National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

B-Cell Lymphomas

Version 1.2018 — February 15, 2018

NCCN.org

Continue

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018 Panel Members
B-Cell Lymphomas

NCCN Guidelines Index
Table of Contents
Discussion

* Andrew D. Zelenetz, MD, PhD/Chair † Þ
Memorial Sloan Kettering Cancer Center

* Leo I. Gordon, MD/Co-Vice Chair ‡ ξ
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Jeremy S. Abramson, MD † ‡
Massachusetts General Hospital Cancer Center

Ranjana H. Advani, MD †
Stanford Cancer Institute

C. Babis Andreadis, MD, MSCE ‡ †
UCSF Helen Diller Family Comprehensive Cancer Center

Nancy Bartlett, MD †
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Paolo Caimi, MD ‡ †
Case Comprehensive Cancer Center/ University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

Julie E. Chang, MD ‡
University of Wisconsin Carbone Cancer Center

Julio C. Chavez, MD †
Moffitt Cancer Center

Beth Christian, MD †
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

Luis E. Fayad, MD ‡ Þ †
The University of Texas MD Anderson Cancer Center

Martha J. Glenn, MD † ‡ Þ ξ
Huntsman Cancer Institute at the University of Utah

Thomas M. Habermann, MD ‡ ξ
Mayo Clinic Cancer Center

Nancy Lee Harris, MD ≠
Massachusetts General Hospital Cancer Center

Francisco Hernandez-Ilizaliturri, MD †
Roswell Park Cancer Institute

Mark S. Kaminski, MD †
University of Michigan Comprehensive Cancer Center

Christopher R. Kelsey, MD §
Duke Cancer Institute

Nadia Khan, MD †
Fox Chase Cancer Center

Susan Krivacic, MPAff ¥
Consultant

Ann S. LaCasce, MD †
Dana-Farber/Brigham and Women's Cancer Center

Amitkumar Mehta MD † ‡ Þ
University of Alabama at Birmingham Comprehensive Cancer Center

Auayporn Nademanee, MD † ‡ ξ
City of Hope Comprehensive Cancer Center

Rachel Rabinovitch, MD §
University of Colorado Cancer Center

Nishitha Reddy, MD ‡ ξ
Vanderbilt-Ingram Cancer Center

Erin Reid, MD ‡
UC San Diego Moores Cancer Center

Stephen D. Smith, MD ‡
Fred Hutchinson Cancer Research Center/ Seattle Cancer Care Alliance

Erin D. Snyder, MD Þ
University of Alabama at Birmingham Comprehensive Cancer Center

Lode J. Swinnen, MB, ChB ‡ ξ
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Julie M. Vose, MD, MBA ‡ ξ
Fred & Pamela Buffett Cancer Center

NCCN
Mary Dwyer, MS
Hema Sundar, PhD

Continue

NCCN Guidelines Panel Disclosures

† Medical oncology
‡ Hematology/Hematology oncology
§ Radiotherapy/Radiation oncology
ξ Bone marrow transplantation
≠ Pathology
Þ Internal medicine
¥ Patient advocacy
* Discussion Writing Committee Member

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018 Table of Contents
B-Cell Lymphomas

NCCN Guidelines Index
Table of Contents
Discussion

Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018 Updates
B-Cell Lymphomas

NCCN Guidelines Index
Table of Contents
Discussion

Updates in Version 1.2018 of the NCCN Guidelines for B-Cell Lymphomas from Version 7.2017 include:

Global changes

- The common bullets related to diagnosis were removed for each subtype and added to a new page, DIAG-1. For each subtype, the diagnosis section is now titled, "Additional Diagnostic Testing."
- Workup, "CBC, differential, platelets" was changed to "CBC with differential."
- Suggested treatment regimen references were updated throughout the guidelines.
- Radioimmunotherapy was clarified as "ibritumomab tiuxetan" throughout the guidelines.

Follicular Lymphoma

FOLL-2

- Workup,
  - "Beta-2-microglobulin" was moved from Essential to Useful in Selected Cases and qualified with "necessary for calculation of FLIPI-2."

FOLL-3

- Stage I, II
  - Non-bulky was replaced and defined with "<7 cm"
  - Bulky was replaced and defined with "≥7 cm"

FOLL-4

- Stage III, IV
  - Indications for treatment
    - ◊ 6th bullet was revised, "Steady *or rapid* progression." Change made throughout the guidelines as appropriate.
- Indication present, "Local ISRT (4–30 Gy) (palliation of locally symptomatic disease)" was revised to "Palliative ISRT" and the dosing was added to NHODG-D 3 of 4. (Also for FOLL-5, NODE-3, and NODE-4)

FOLL-6

- Histologic transformation to DLBCL and minimal or no prior chemotherapy,
  - For CR and PR, "± ISRT if not previously given" was added to HDT/ASCR and HCT. (Also for NODE-5)
  - For PR, ISRT was revised by adding, "for localized residual and/or residual FDG-avid disease not previously irradiated." (Also for NODE-5)
- Footnotes (Also for FOLL-7 and appropriate footnotes on NODE-5)
  - Footnote t was added, "This includes ≥2 of chemoimmunotherapy regimens for indolent or transformed disease. For example, prior treatment with BR and RCHOP."
  - Footnote u was revised, "~~If locoregional transformation, consider adding RT~~. *Consider ISRT for localized presentations, bulky disease, and/or limited osseous disease*."
  - Footnote v was added, "If transformation is co-existing with extensive FL, consider maintenance (see FOLL-5, Optional Extended Therapy)."
  - Footnote w was revised, "If proceeding to an autologous stem cell rescue, consider additional ~~cytoreductive~~ *systemic* therapy ± *ISRT* to induce CR prior to transplant. Axicabtagene ciloleucel is not an appropriate treatment option for patients with a CR."
  - Footnote x was added, "Repeat biopsy should be strongly considered if PET-positive prior to additional therapy. If biopsy negative, follow CR pathway."

FOLL-7

- Histologic transformation to DLBCL after multiple lines of prior therapies,
  - Chemoimmunotherapy was clarified as "second-line therapy" on BCEL-C. (Also for NODE-5)
  - After responsive disease, "± ISRT if not previously given" was added to HDT/ASCR and HCT. (Also for NODE-5)

FOLL-8

- Treatment,
  - "for patients with extensive local disease who are not candidates for excision or ISRT" was added to RCHOP.
  - "Observe" was added after "Excision (preferred)"
- Footnote cc was revised by adding, "Localized disease (stage I,II) is more common than advanced-stage disease (stage III,IV)."
- Footnote dd was revised by adding, "There are no data to support maintenance therapy."

FOLL-B 1 of 4

- First-line Therapy
  - The regimens were separated into "preferred regimens" and "other recommended regimens" and listed in alphabetical order.
  - Bendamustine + rituximab was changed from a category 1 to a category 2A recommendation.
  - RCHOP was changed from a category 1 to a category 2A recommendation.
  - RCVP was changed from a category 1 to a category 2A recommendation.
- First-line Consolidation or Extended Dosing (optional)
  - Ibritumomab tiuxetan was revised by removing "(after induction with chemotherapy or chemoimmunotherapy)."

Continued

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018 Updates
B-Cell Lymphomas

NCCN Guidelines Index
Table of Contents
Discussion

Updates in Version 1.2018 of the NCCN Guidelines for B-Cell Lymphomas from Version 7.2017 include:

FOLL-B 1 of 4

- First-line Therapy for Elderly or Infirm
  - Single-agent alkylators (eg, chlorambucil or cyclophosphamide) ± rituximab was revised to list the recommendations as follows:
    - ◊ Chlorambucil + rituximab
    - ◊ Cyclophosphamide + rituximab
    - ◊ Chlorambucil
    - ◊ Cyclophosphamide
- Footnote d was added, "Prophylaxis for PJP and VZV should be administered, see Supportive Care (NHODG-B). In the GALLIUM study, there was an increased risk of mortality from OI and secondary malignancies in patients receiving bendamustine. Increased risk of mortality occurred over entire treatment program and extending beyond maintenance."

FOLL-B 2 of 4

- Second-line and Subsequent Therapy
  - The regimens were separated into "preferred regimens" and "other recommended regimens."
  - For clarity, "Chemoimmunotherapy (as listed under first-line therapy)" was replaced with the list of first-line regimens.
  - Ibritumomab tiuxetan was changed from a category 1 to a category 2A recommendation.
  - The following regimens were removed:
    - ◊ Fludarabine + rituximab
    - ◊ RFND (rituximab, fludarabine, mitoxantrone, dexamethasone)
- Footnotes
  - Footnote k was added, "Generally, a first-line regimen is not repeated."
  - Footnote l was added, "Prophylaxis for PJP and VZV should be administered, see Supportive Care (NHODG-B)."
  - Footnote m was revised by adding, "Obinutuzumab is preferred in patients with rituximab refractory disease, which includes disease progressing on or within 6 months of prior rituximab therapy."
- Footnotes were removed
  - "Fludarabine-containing regimens negatively impact stem cell mobilization for transplant."
  - "RFND regimen may be associated with stem cell toxicity and secondary malignancies (see Discussion)."

Gastric MALT Lymphoma

MALT-1

- Footnote f was revised, "If IHC for cyclin D1 is positive, FISH for t(11;14) is not necessary*, see MANT-1*."

MALT-2

- Stage I_1, or I_2 or Stage II_1, H. pylori positive, "t(11;18) negative disease" was added.

MALT-3

- Stage was clarified as, *"Stage IIE or II_2 or* Stage IV *(distant nodal, advanced stage)* ~~(advanced-stage disease uncommon)~~."
  - Indication present,
    - ◊ "Induction chemoimmunotherapy" was replaced with a link to "First-line Therapy for Marginal Zone Lymphomas (MZL-A 1 of 2)."
    - ◊ "Locoregional RT for palliation in specific settings" was changed to "Palliative ISRT." Similar change made throughout the guidelines.
  - "Gastric MALT lymphomas with concurrent large cell transformation" was added to the page.

MALT-5

- "Or rituximab" was added to the heading "After RT."
- After relapse, pathway for "See indications for treatment" was added. (Also for MALT-6, NGMLT-3, SPLN-3)

MALT-A

- Staging of Gastric MALT Lymphoma: Comparison of Different Systems
  - Lugano Staging was revised.

Nongastric MALT Lymphoma

NGMLT-2

- Footnotes
  - Footnote k was revised, "~~Treatment of each site may be indicated (eg, bilateral conjunctiva) both at diagnosis and at relapse.~~ *Definitive treatment of multiple sites may be indicated (eg, bilateral orbital disease only) or palliative treatment of symptomatic sites*."
  - Footnote was removed from ISRT, "Dose is site dependent with lower dose reserved for eye involvement."

NGMLT-3

- After local recurrence, after ISRT, "if not previously treated" was added.

Continued

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018 Updates
B-Cell Lymphomas

NCCN Guidelines Index
Table of Contents
Discussion

Updates in Version 1.2018 of the NCCN Guidelines for B-Cell Lymphomas from Version 7.2017 include:

Nodal Marginal Zone Lymphoma

NODE-2

- A new algorithm for Stage I, II was added.

Splenic Marginal Zone Lymphoma

SPLN-2

- Splenomegaly
  - Hepatitis C negative, if cytopenias and symptoms, "preferred" was added to rituximab and "if not responsive to rituximab" was added to "splenectomy."
  - Footnote e was revised, "Pneumococcal, meningococcal, *and hepatitis B* vaccinations should be given at least 2 weeks before splenectomy."

Marginal Zone Lymphomas

MZL-A 1 of 3

- First-line Therapy
  - The regimens were separated into "Preferred regimens" and "other recommended regimens." These were placed in alphabetical order.
  - "Preferred for SMZL" was added to "rituximab (375 mg/m^2 weekly for 4 doses)."
  - The following were added as "other recommended regimens"
    - ◊ Lenalidomide + rituximab as a category 2B recommendation
    - ◊ Ibritumomab tiuxetan as a category 2B recommendation. Corresponding footnotes e and f were added.
- First-line Therapy for Elderly or Infirm
  - Single-agent alkylators (eg, chlorambucil or cyclophosphamide) ± rituximab was revised to list the recommendations as
    - ◊ Chlorambucil + rituximab
    - ◊ Cyclophosphamide + rituximab
    - ◊ Chlorambucil
    - ◊ Cyclophosphamide

MZL-A 2 of 3

- Second-Line and Subsequent Therapy
  - For clarity, "chemoimmunotherapy (as listed under first-line therapy)" was replaced with the list of first-line regimens.
  - Ibritumomab tiuxetan was added as a category 2B recommendation.
  - The following regimens were removed:
    - ◊ Fludarabine + rituximab
    - ◊ RFND (rituximab, fludarabine, mitoxantrone, dexamethasone)
- Footnotes were removed
  - "Fludarabine-containing regimens negatively impact stem cell mobilization for transplant."
  - "RFND regimen may be associated with stem cell toxicity and secondary malignancies (see Discussion)."

Mantle Cell Lymphoma

MANT-1

- Additional Diagnostic Testing, Useful Under Certain Circumstances
  - 1st bullet was revised, "IHC: LEF1 may help distinguish from variant CLL; SOX11 or IGHV sequencing may be useful for determination of *clinically* indolent MCL..." Corresponding footnote d was added, "Most common biomarker for indolent disease: (SOX11- [IGHV mutated. Typical clinical presentation: leukemic non-nodal CLL-like with splenomegaly, low tumor burden, Ki-67 proliferation fraction <10%."
- Workup, Useful Under Certain Circumstances
  - Hepatitis C testing was added.
- Footnote c was revised by removing, "However, it is not used to guide treatment."

MANT-2

- Stage I, II
  - Induction therapy was revised from "See Suggested Regimens (MANT-A) ± RT or RT" to "ISRT or Chemoimmunotherapy (MANT-A, Less aggressive regimens) + ISRT or Chemoimmunotherapy (MANT-A, Less aggressive regimens) or Observe in highly selected cases."
- Footnote was removed, "Clinical trials of adjuvant therapy or for relapsed disease involving high-dose therapy with autologous stem cell rescue or allogeneic hematopoietic cell transplant, immunotherapy with nonmyeloablative stem cell rescue, or evaluation of treatment with new agents are appropriate." (Also for MANT-3)

MANT-4

- After "Evaluate for clinical concern of transformation, "Rebiopsy and evaluate for TP53/del(17p)" was revised as, "Rebiopsy and TP53 sequencing and FISH for del(17p)."

Continued

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018 Updates
B-Cell Lymphomas

NCCN Guidelines Index
Table of Contents
Discussion

Updates in Version 1.2018 of the NCCN Guidelines for B-Cell Lymphomas from Version 7.2017 include:

MANT-A 1 of 4

- Induction therapy
  - For both aggressive and less aggressive therapy, the regimens were separated into "preferred regimens" and "other recommended regimens" and listed in preference order.
  - Aggressive therapy
    - ◊ Footnote was removed, "Oxaliplatin or carboplatin can also be used" and oxaliplatin was added to the regimen RDHAX (rituximab, dexamethasone, cytarabine, oxaliplatin) as an alternative to RDHAP.
    - ◊ HyperCVAD, "(NOTE: There are conflicting data regarding the need for consolidation with HDT/ASCR.)" was added to the bullet.
    - ◊ Bendamustine + rituximab was added as a category 2B recommendation
    - ◊ The following regimens were removed:
      - – CALGB regimen
      - – Sequential RCHOP/RICE
  - Less aggressive therapy
    - ◊ RBAC (rituximab, bendamustine, cytarabine) was added as a category 2B recommendation.
    - ◊ Cladribine + rituximab was removed
- "First-line Consolidation Candidate for HDT/ASCR: High-dose therapy with autologous stem cell rescue + rituximab maintenance (category 1 for rituximab maintenance) and First-line Consolidation Not a Candidate for HDT/ASCR: Rituximab maintenance (category 1 following RCHOP)" were clarified as follows:
  - Consolidation *after aggressive therapy*: High-dose therapy followed by autologous stem cell rescue
  - Maintenance after HDT/ASCR: Maintenance rituximab *every 8 weeks x 3 y* (category 1)
  - *Maintenance after less aggressive therapy*: Rituximab maintenance *every 8 weeks until progression or intolerance* (category 1 for RCHOP; *5 y for modified rituximab-HyperCVAD)*
    - ◊ *NOT appropriate after BR*
    - ◊ *Untested after VR-CAP, RBAC*
- Footnote was removed, "Randomized data with anthracycline-containing regimens suggest an improvement in progression-free survival with the addition of first-line high-dose therapy with autologous stem cell consolidation."

MANT-A 2 of 4

- Second-line therapy
  - Therapies were reorganized first by "Short response duration to prior chemoimmunotherapy (< expected median PFS)" and "Extended response duration to prior chemoimmunotherapy (> expected median PFS)." Then the regimens were separated into "Preferred regimens" and "Other recommended regimens."
  - The following was added,
    - ◊ RCHOP (if not previously given) (category 2B)
    - ◊ VRCAP (if not previously given) (category 2B)
    - ◊ "± rituximab" was added to ibrutinib.
    - ◊ "(if not previously given)" was added to bendamustine ± rituximab
  - The following regimens were removed,
    - ◊ Cladribine + rituximab
    - ◊ FC (fludarabine, cyclophosphamide) ± rituximab
    - ◊ PCR (pentostatin, cyclophosphamide, rituximab)

Continued

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018 Updates
B-Cell Lymphomas

NCCN Guidelines Index
Table of Contents
Discussion

Updates in Version 1.2018 of the NCCN Guidelines for B-Cell Lymphomas from Version 7.2017 include:

Diffuse Large B-Cell Lymphoma

BCEL-1
- Subtypes included
  - "DLBCL with IRF4/MUM1 rearrangement" was added.
  - "EBV-positive DLBCL, *NOS* ~~of the elderly~~" was revised.
- Footnotes
  - Footnote f was added, "fIn the 2018 WHO revision of lymphoma, DLBCL, double hit has been designated in a unique category called high-grade B-cell lymphomas with translocations of MYC and BCL2 and/or BCL6."
  - Footnote was removed, "Burkitt lymphoma intermediate histology or DLBCL CD10+ tumors with very high proliferation >90% with or without Burkitt lymphoma-like features might be considered for more aggressive treatment as per BURK-A."

BCEL-2
- Workup, Useful in Selected Cases
  - 4th bullet was added, "Hepatitis C testing."
  - 6th bullet was revised by adding, "Lumbar puncture, consider if have 4–6 factors according to prognostic model (See BCEL-A 2 of 2), HIV lymphoma, testicular, double expressor lymphoma *(MYC ≥40% and BCL2 ≥50%)*."

BCEL-3
- Stage I, II
  - Nonbulky, first-line therapy, "RCHOP-14 x 4–6 cycles" was added.
  - For nonbulky and bulky, after first-line therapy was revised by adding, "RT planned" and "RT not planned."
- Footnote t was added, "PET/CT scan at interim restaging can lead to increased false positives and should be carefully considered in select cases. If PET/CT scan performed and positive, rebiopsy before changing course of treatment."
- Footnote was removed, "May include high-dose therapy" from clinical trial.

BCEL-4
- Stage I, II, this page now applies only for when RT is planned at the end of first-line chemoimmunotherapy.
- PET/CT scan, "FPS" was added to PET negative for CR and PET positive for PR.
- Follow-up therapy,
  - For PR,
    - Second option was revised, "If PET+ after 6 cycles of RCHOP *or after 4–6 cycles of RCHOP-14*, high-dose therapy..."
    - Third option was revised by removing, "Clinical trial ~~(may include allogeneic stem cell transplant ± RT pre- or post-transplant)~~."
  - No response or progressive disease, "RT in select patients who are not candidates for chemotherapy" was removed.

BCEL-5
- Stage I, II, this page now applies only to end-of-treatment restaging when RT is not planned.
- PET/CT scan "FPS" was added to PET negative for CR and PET positive for PR and Progressive disease.
- After PR, the 2nd option was revised as, "~~Palliative~~ ISRT ~~in select patients who are not chemotherapy candidates~~"

BCEL-6
- Stage III, IV
  - No response or progressive disease, follow-up therapy option was removed, "ISRT in select patients who are not candidates for chemotherapy."
  - End-of-treatment response
    - PET/CT scan "FPS" was added to PET negative for CR and PET positive for PR.
    - After progressive disease, option was removed, "Palliative ISRT in select patients who are not candidates for chemotherapy."

BCEL-7
- Relapsed/refractory disease
  - For patients with intention to proceed to high-dose therapy, "± ISRT" was added to the HCT option under Consolidation/Additional Therapy.
  - For non-candidates for high-dose therapy, after second-line therapy, "Complete response" and "partial response" were added.

BCEL-8
- Follow-up recommendations were added.

BCEL-B 1 of 3
- Primary Mediastinal Large B-Cell Lymphoma
  - 4th bullet was revised, "Role of RT *in first-line therapy* is controversial."
  - 6th bullet, "Pembrolizumab" was added as a relapsed/refractory option.

BCEL-B 3 of 3
- Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type
  - No response (NR) was added to PR after initial therapy
  - Footnote c was added, "These patients are at higher risk for CNS involvement (See BCEL-A 2 of 2); consider CNS prophylaxis according to institutional standards."

Continued

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018 Updates
B-Cell Lymphomas

NCCN Guidelines Index
Table of Contents
Discussion

Updates in Version 1.2018 of the NCCN Guidelines for B-Cell Lymphomas from Version 7.2017 include:

BCEL-C 1 of 4

- First-line Therapy
  - Dose-adjusted EPOCH + rituximab was changed from a category 2B to category 2A recommendation.
  - Very Frail Patients were moved from First-line Therapy for Patients with Poor Left Ventricular Function to Patients >80 y of Age with Comorbidities.
  - Very Frail Patients and Patients >80 y of Age with Comorbidities
    - ◊ RCEPP and RCDOP were added as options.

BCEL-C 2 of 4

- Second-line and Subsequent Therapy (non-candidates for high-dose therapy)
  - "Ibrutinib (non-GCB DLBCL)" was added as an option.

HGBL-1

- The title of the Double hit lymphoma page was changed to "High-Grade B-Cell Lymphomas with Translocations of MYC and BCL2 and/or BCL6 (Double/Triple Hit Lymphoma)."
- A footnote was added to the definition heading, "In the 2018 WHO revision of lymphoma, DLBCL, double hit has been designated in a unique category called high-grade B-cell lymphomas with translocations of MYC and BCL2 and/or BCL6."

Burkitt Lymphoma

BURK-1

- Footnote a was revised from "WHO 2008 classification recognizes that it may not always be possible to distinguish between DLBCL and Burkitt lymphoma. In the setting where it is not possible to distinguish, aggressive therapy per this guideline is appropriate in selected cases. Treatment of double or triple hit tumors is controversial. Optimum regimen has not been identified." to "For treatment of double or triple hit tumors, see HGBL-1. In other cases where it is not possible to distinguish between BL and high-grade lymphoma, therapy per this guideline may be appropriate."

BURK-2

- High risk was defined as "any patient not low risk."
- For both low and high risk, after initial response, the algorithm was extensively revised.

BURK-A

- Induction therapy, "CALGB 10002 regimen" was removed.

AIDS-Related B-cell Lymphomas

AIDS-3

- Burkitt lymphoma
  - The regimens were separated into "Preferred regimens" and "Other recommended regimen."
  - "CDE (cyclophosphamide, doxorubicin, etoposide) + rituximab" was removed as an option.
  - After treatment, the algorithm is directed to "For relapse, see second-line regimens (BURK-A)."
- Diffuse large B-cell lymphoma, HHV8-positive DLBCL, NOS and Primary effusion lymphoma
  - "CDE + rituximab" was removed as an option.

AIDS-4

- Plasmablastic lymphoma
  - "Preferred" was added to "Dose-adjusted EPOCH."
  - 3rd bullet was added, "Consider high-dose therapy with autologous stem cell rescue in first complete remission in select high-risk patients" with a corresponding footnote k, "High-risk features include an age-adjusted IPI higher than 2, presence of MYC gene rearrangement, or *TP53* gene deletion. Note that HIV-negative patients with plasmablastic lymphoma are generally considered to have higher risk disease. Optimization of HIV control with antiretroviral therapy is important."

Continued

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018 Updates
B-Cell Lymphomas

NCCN Guidelines Index
Table of Contents
Discussion

Updates in Version 1.2018 of the NCCN Guidelines for B-Cell Lymphomas from Version 7.2017 include:

Post-Transplant Lymphoproliferative Disorders

PTLD-1

- Subtypes
  - Monomorphic was changed to "Monomorphic (B-cell type)."
  - T-cell PTLD was changed to "Monomorphic PTLD (T-cell type)."
- Footnote c was revised, "~~Refers to B-cell post-transplant lymphomas.~~ *Early lesions are of B-cell type and include plasmacytic hyperplasia, infectious mononucleosis, florid follicular hyperplasia*."

PTLD-2

- Initial response, "Partial response" was added to "persistent or progressive disease." Also for PTLD-3.
- Second-line therapy,
  - Early lesions, after CR was revised by adding, "graft organ function monitoring." Also for polymorphic PTLD on PTLD-3.
  - Monomorphic PTLD (B-cell type), "If chemoimmunotherapy was initial therapy, see BCEL-6" was added as an option.
- Footnotes
  - Footnote e was revised by adding, "RI: Reduction in calcineurin inhibition (cyclosporin and tacrolimus), discontinuation of antimetabolic agents (azathioprine and mycophenolate mofetil), and for critically ill patients all non-glucocorticoid immunosuppression should be discontinued. Response to RI is variable and patients need to be closely monitored; RI should be coordinated with the transplant team."
  - Footnote h was added, "Restage in two to four weeks."

PTLD-A

- Bullet "For CD20 negative monomorphic T-cell post-transplant lymphomas, the above regimens recommended for B-cell post-transplant lymphomas are used without rituximab" was replaced with the list of regimens.

Castleman's Disease

CD-2

- Unicentric CD, Surgically unresectable
  - After primary treatment, if surgically resectable, the choice of "incomplete resection" was added.

CD-3

- Multicentric CD
  - Primary treatment, 2nd bullet was added, "Rituximab (if not candidate for combination therapy)"

Use of Immunophenotyping

NHODG-A 4 of 11

- B-cell neoplasms, small cells
  - After CD5+ and CD23-, the next choices were changed to "Cyclin D1+ *or* t(11;14)+" and "Cyclin D1- *and* t(11;14)-."
  - After CD5-, CD10+, BCL6+, the next choices were changed to "BCL2+ *or* t(14;18)+" and "BCL2- *and* t(14;18)-."

NHODG-A 6 of 11

- After CD10-, an option for "BCL6- and IRF4/MUM1-" was added.

Supportive Care for B-Cell Lymphomas

NHODG-B 3 of 4

- Bullets regarding alemtuzumab were removed.
- Immunizations, a bullet linking to the NCCN Guidelines for Survivorship - General Principles of Immunizations" was added.

NHODG-B 4 of 4

- New page regarding bone health was added.

Principles of Radiation Therapy

NHODG-D 3 of 4

- The general dose guidelines were separated by "definitive treatment" and "palliative treatment."
- For Definitive treatment,
  - "(1.5–2 Gy daily fractions)" was added.
  - MZL, for gastric dosing, "(most commonly uses 1.5 Gy daily fractions)" was added.
  - Early-stage mantle cell lymphoma dose was changed from 30–36 Gy to 24–36 Gy.
  - DLBCL, for RT as primary treatment for refractory or non-candidates for chemotherapy, the dose was changed from 40–55 Gy to 30–55 Gy.
  - The following was added to palliative treatment
    - ◊ Palliative RT (higher doses/fraction typically appropriate)
      - – FL/MZL/MCL: 2 Gy X 2 or 4 Gy X 1 (which may be repeated as needed); doses up to 30 Gy may be appropriate in select circumstances
      - – DLBCL: 24–30 Gy

Special Considerations for the Use of Small-Molecule Inhibitors

NHODG-E 1 of 3

- Information regarding copanlisib was added. Also for NHODG-E 3 of 3.

NHODG-E 2 of 3

- Ibrutinib,
  - 4th bullet, 4th sub-bullet was revised, "Patients with recurrent atrial fibrillation that is not medically controllable should be changed to ~~idelalisib~~ *an alternative agent.*"

DIAGNOSIS

- Excisional or incisional biopsy. An FNA biopsy alone is not generally suitable for the initial diagnosis of lymphoma. A core needle biopsy is not optimal but can be used under certain circumstances. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for *IGHV* and *TCR* gene rearrangements, karyotype, and FISH for major translocations) may be sufficient for diagnosis.
- Histologic grading cannot be performed on an FNA.
- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.

ADDITIONAL DIAGNOSTIC TESTING

- Follicular lymphoma → See FOLL-1
- Gastric MALT lymphoma → See MALT-1
- Nongastric MALT lymphoma → See NGMLT-1
- Nodal marginal zone lymphoma → See NODE-1
- Splenic marginal zone lymphoma → See SPLN-1
- Mantle cell lymphoma → See MANT-1
- Diffuse large B-cell lymphoma → See BCEL-1
- High-grade B-cell lymphomas with translocations of *MYC* and *BCL2* and/or *BCL6* (double hit lymphoma) → See HGBL-1
- Burkitt lymphoma → See BURK-1
- AIDS-related B-cell lymphomas → See AIDS-1
- Lymphoblastic lymphoma → See BLAST-1
- Post-transplant lymphoproliferative disorders → See PTLD-1
- Castleman's disease → See CD-1

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

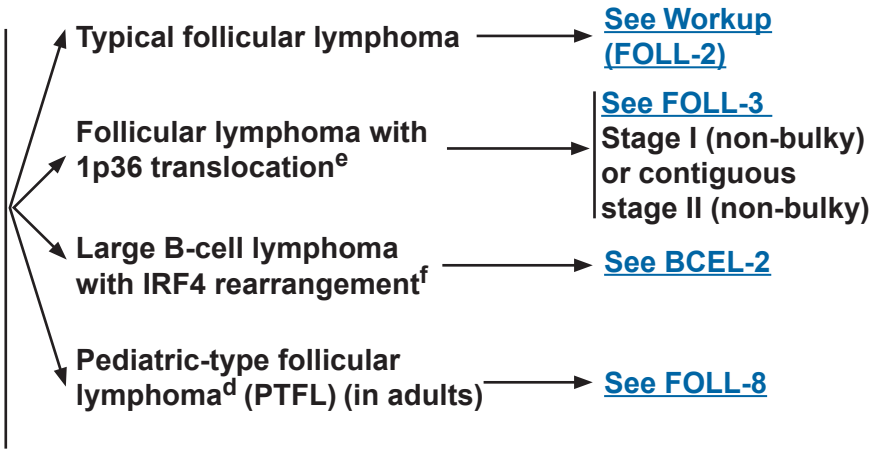
ADDITIONAL DIAGNOSTIC TESTING[a]

ESSENTIAL:

- **Adequate immunophenotyping to establish diagnosis[b,c]**
  - **IHC panel: CD20, CD3, CD5, CD10, BCL2,[d] BCL6, CD21, or CD23, with or without**
  - **Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **Molecular analysis to detect: antigen receptor gene rearrangements; *BCL2* rearrangements[d]**
- **Karyotype or FISH:[e,f] t(14;18); *BCL6*, 1p36, *IRF4/MUM1* rearrangements[d]**
- **IHC panel: Ki-67;[g] IRF4/MUM1 for FL grade 3, cyclin D1**



Germinal center or follicular center cell phenotype type is not equivalent to follicular lymphoma and occurs in Burkitt lymphoma and some DLBCL.

[a]Follicular lymphoma (FL), grade 1-2. FL, grade 3 is an area of controversy. The distinction between follicular grade 3a and 3b has not been shown to have clinical significance to date. However, controversy exists regarding management of FL grade 3. Some may treat FL grade 3a as FL and others may treat it as diffuse large B-cell lymphoma (DLBCL). FL, grade 3b is commonly treated according to the NCCN Diffuse Large B-Cell Lymphoma Guideline (BCEL-1). Any area of DLBCL in a FL of any grade should be diagnosed and treated as a DLBCL.

[b]Typical immunophenotype: CD10+, BCL2+, CD23+/-, CD43-, CD5-, CD20+, BCL6+. Rare cases of follicular lymphoma may be CD10- or BCL2-.

[c]See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).

[d]In young patients with localized disease that lacks BCL2 expression or t(14;18), consider entity of PTFL. Analysis of *BCL6* rearrangement may be useful for evaluating the diagnosis of PTFL.

[e]FL with 1p36 deletions have a predominant diffuse pattern in inguinal nodes, large localized mass, CD23+, typically grade 1-2 and have a good prognosis.

[f]Lymphomas with IRF4 translocations are usually DLBCL but occasionally are purely FL grade 3b and often DLBCL with FL grade 3b. Patients typically present with Waldeyer's ring involvement and are often children/young adults. The tumor is locally aggressive but responds well to chemotherapy +/- RT. These lymphomas do not have a *BCL2* rearrangement and should not be treated as low-grade FL.

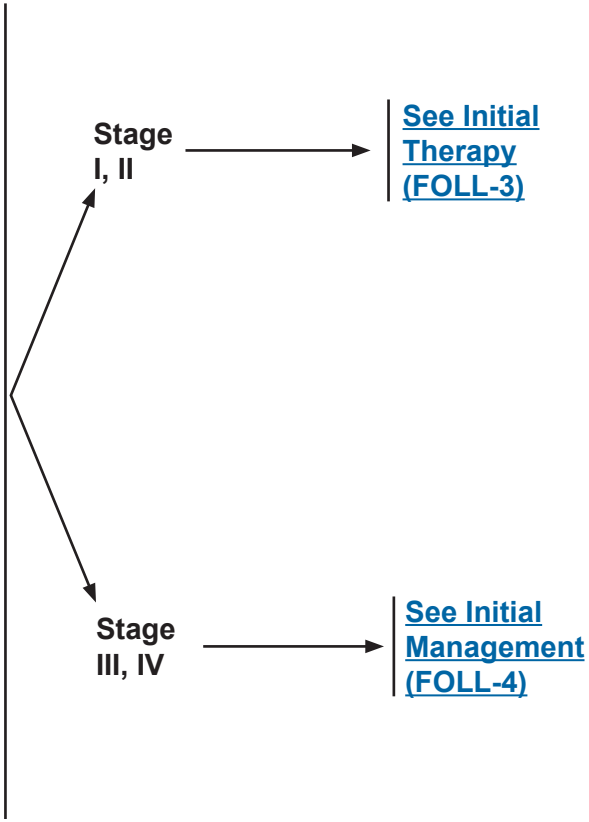
[g]There are reports showing that Ki-67 proliferation fraction of >30% may be associated with a more aggressive clinical behavior, but there is no evidence that this should guide treatment decisions.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

WORKUP

ESSENTIAL:
- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC with differential
- LDH
- Comprehensive metabolic panel
- Hepatitis B testing[h]
- Chest/abdominal/pelvic (C/A/P) CT with contrast of diagnostic quality and/or whole-body PET/CT scan (PET/CT scan essential if RT for stage I, II disease planned)
- Bone marrow biopsy + aspirate to document clinical stage I-II disease[i]
- Pregnancy testing in women of child-bearing age (if chemotherapy or RT planned)

USEFUL IN SELECTED CASES:
- Echocardiogram or MUGA scan if anthracycline or anthracenedione-based regimen is indicated
- Neck CT with contrast
- Beta-2-microglobulin (necessary for calculation of FLIPI-2)
- Uric acid
- SPEP and/or quantitative immunoglobulin levels
- Hepatitis C testing
- Discussion of fertility issues and sperm banking



[a]FL, grade 1-2. FL, grade 3 is an area of controversy. The distinction between follicular grade 3a and 3b has not been shown to have clinical significance to date. However, controversy exists regarding management of FL grade 3. Some may treat FL grade 3a as follicular lymphoma and others may treat it as diffuse large B-cell lymphoma (DLBCL). FL, grade 3b is commonly treated according to the NCCN Diffuse Large B-Cell Lymphoma Guideline (BCEL-1). Any area of DLBCL in a FL of any grade should be diagnosed and treated as a DLBCL.

[h]Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

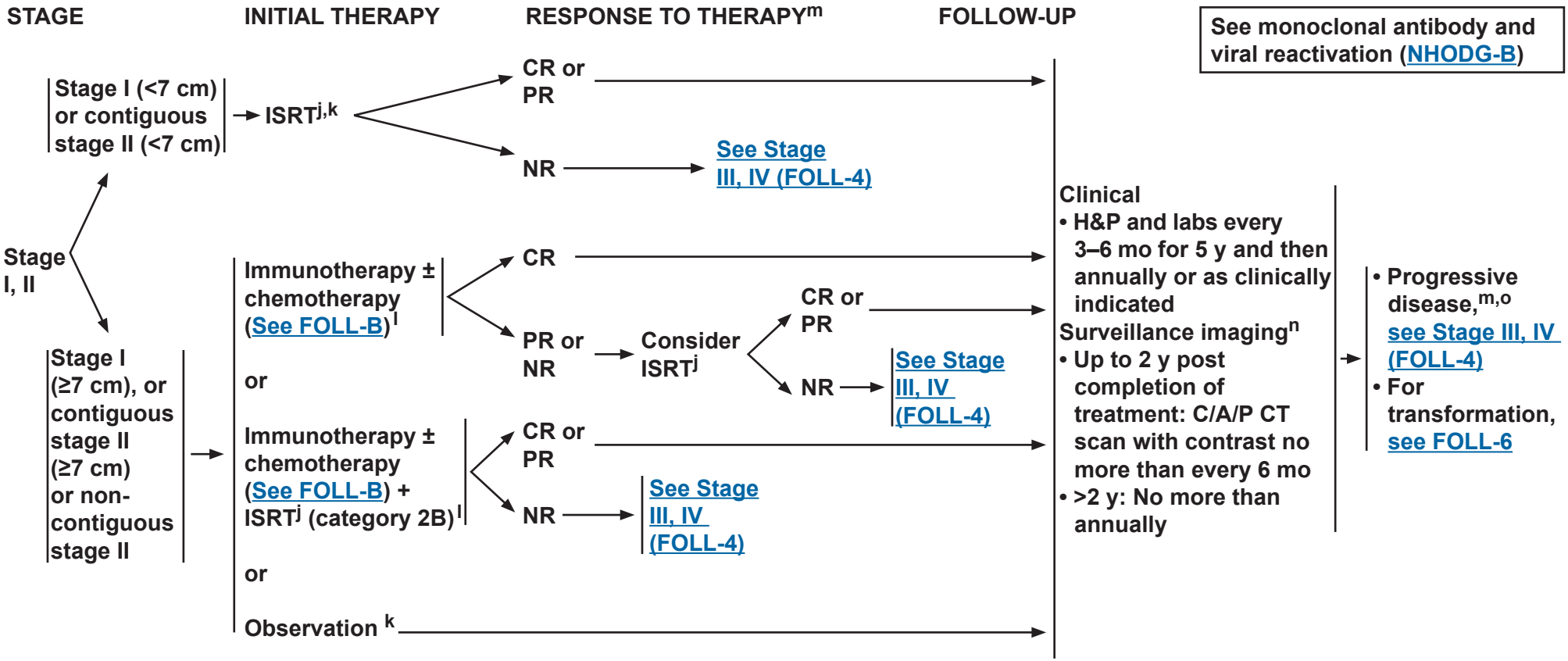
[i]Bilateral or unilateral provided core biopsy is >1.6 cm. If ibritumomab tiuxetan is considered, bilateral cores are recommended and the pathologist should provide the percent of overall cellular elements and the percent of cellular elements involved in the marrow. If observation is initial therapy, bone marrow biopsy may be deferred.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018
Follicular Lymphoma (grade 1-2)

NCCN Guidelines Index
Table of Contents
Discussion



[j] See Principles of Radiation Therapy (NHODG-D).

[k] Observation may be appropriate in circumstances where potential toxicity of involved-site RT (ISRT) outweighs potential clinical benefit.

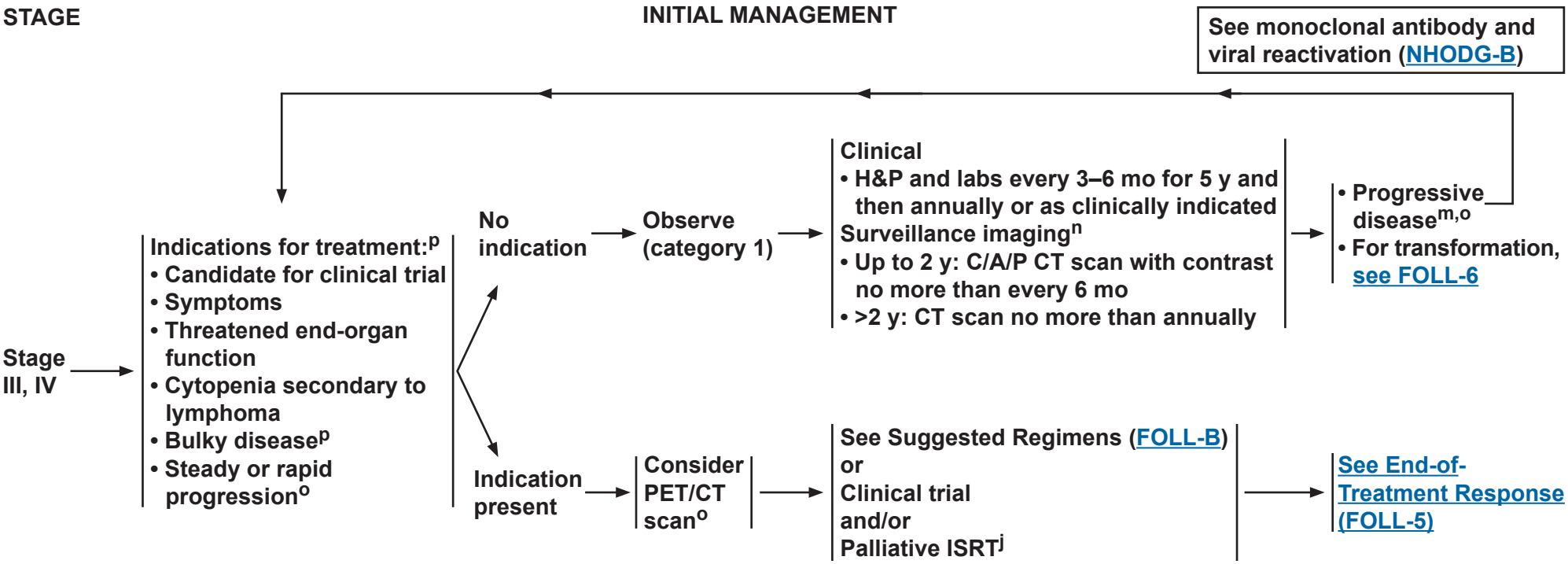
[l] Initiation of chemotherapy or more extended RT can improve failure-free survival (FFS), but has not been shown to improve overall survival. These are options for therapy.

[m] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C). PET/CT scan should be interpreted via the PET Five Point Scale (FPS).

[n] Imaging should be performed whenever there are clinical indications. For surveillance imaging, see Discussion for consensus imaging recommendations.

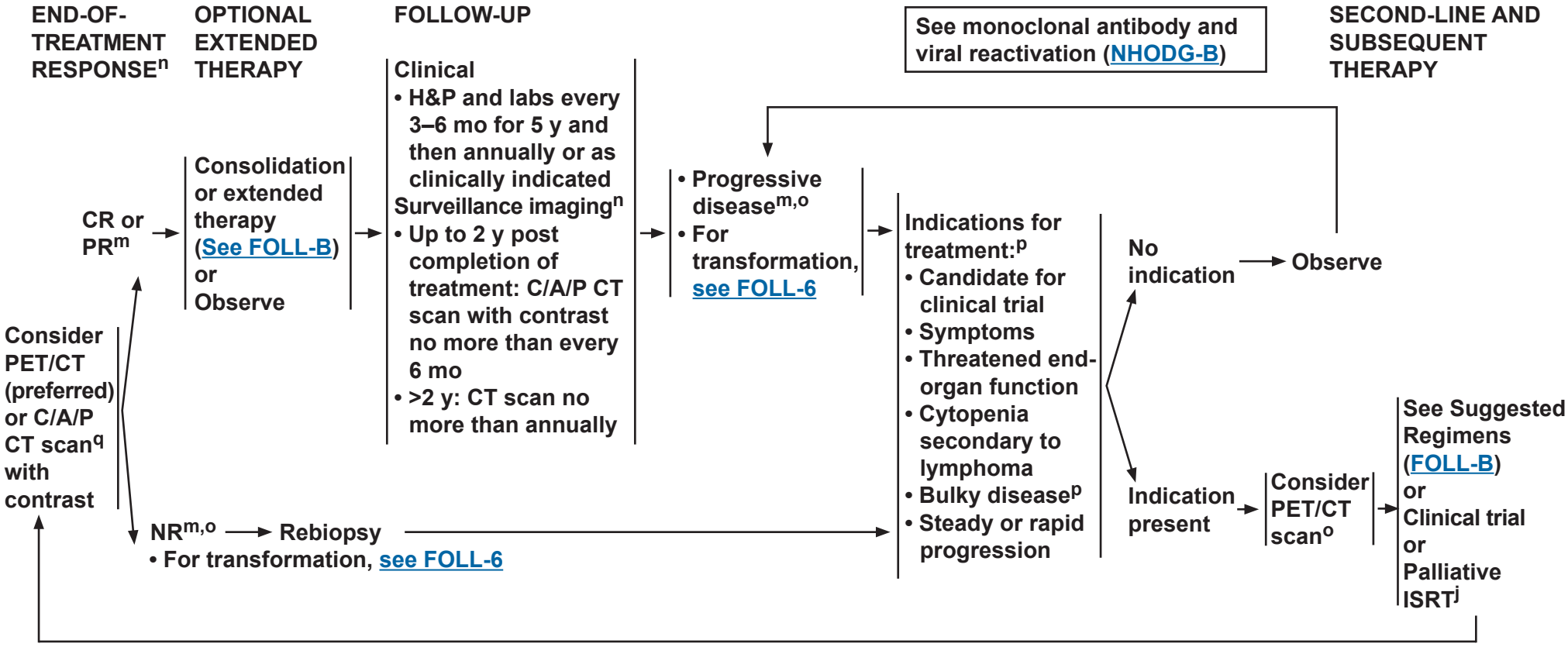
[o] Consider possibility of histologic transformation in patients with progressive disease, especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, or there are new B symptoms. If clinical suspicion of transformation, FDG-PET may help identify areas suspicious for transformation. FDG-PET scan demonstrating marked heterogeneity or sites of intense FDG avidity may indicate transformation, and biopsy should be directed biopsy at the most FDG-avid area. Functional imaging does not replace biopsy to diagnose transformation. If transformation is histologically confirmed, treat with anthracycline-based therapy. See Management of Transformation (FOLL-6).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[j] See Principles of Radiation Therapy (NHODG-D).
[m] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C). PET/CT scan should be interpreted via the PET Five Point Scale (FPS).
[n] Imaging should be performed whenever there are clinical indications. For surveillance imaging, see Discussion for consensus imaging recommendations.
[o] Consider possibility of histologic transformation in patients with progressive disease, especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, or there are new B symptoms. If clinical suspicion of transformation, FDG-PET may help identify areas suspicious for transformation. FDG-PET scan demonstrating marked heterogeneity or sites of intense FDG avidity may indicate transformation, and biopsy should be directed biopsy at the most FDG-avid area. Functional imaging does not replace biopsy to diagnose transformation. If transformation is histologically confirmed, treat with anthracycline-based therapy. See Management of Transformation (FOLL-6).
[p] See GELF criteria (FOLL-A).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[j] See Principles of Radiation Therapy (NHODG-D).

[m] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C). PET/CT scan should be interpreted via the PET Five Point Scale (FPS).

[n] Imaging should be performed whenever there are clinical indications. For surveillance imaging, see Discussion for consensus imaging recommendations.

[o] Consider possibility of histologic transformation in patients with progressive disease, especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, or there are new B symptoms. If clinical suspicion of transformation, FDG-PET may help identify areas suspicious for transformation. FDG-PET scan demonstrating marked heterogeneity or sites of intense FDG avidity may indicate transformation, and biopsy should be directed biopsy at the most FDG-avid area. Functional imaging does not replace biopsy to diagnose transformation. If transformation is histologically confirmed, treat with anthracycline-based therapy. See Management of Transformation (FOLL-6).

[p] See GELF criteria (FOLL-A).

[q] A PET-positive PR is associated with a shortened PFS (See Discussion); however, additional treatment at this juncture has not been shown to change outcome.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

HISTOLOGIC TRANSFORMATION TO DIFFUSE LARGE B-CELL LYMPHOMA[r]

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

Histologic transformation to DLBCL[r]

- **Minimal[s] or no prior chemotherapy** → **Chemoimmunotherapy (anthracycline- or anthracenedione-based regimens preferred unless contraindicated) (See BCEL-C, first-line therapy) ± ISRT[j,u]**
- **After multiple lines of prior therapies[t]** → **See FOLL-7**

Chemoimmunotherapy (anthracycline- or anthracenedione-based regimens preferred unless contraindicated) (See BCEL-C, first-line therapy) ± ISRT[j,u] → **Consider PET/CT[m] (preferred) or C/A/P CT scan with contrast**

Consider PET/CT[m] (preferred) or C/A/P CT scan with contrast

- **CR[m,v]** → **Observation or Clinical trial or High-dose therapy with autologous stem cell rescue (HDT/ASCR) or allogeneic hematopoietic cell transplant (HCT)[y] ± ISRT if not previously given[j,u]**
- **PR[m,w,x]** → **HDT/ASCR or allogeneic HCT[y] ± ISRT if not previously given[j,u] or Axicabtagene ciloleucel (only after ≥2 prior chemoimmunotherapy regimens)[z] or Clinical trial or Ibritumomab tiuxetan or ISRT[j] for localized residual and/or residual FDG-avid disease not previously irradiated or Observation**
- **NR or progressive disease[m]** → **Clinical trial or Ibritumomab tiuxetan or Second-line therapy (See BCEL-C) or Axicabtagene ciloleucel (only after ≥2 prior chemoimmunotherapy regimens)[z] or Best supportive care**

Observation or Clinical trial or High-dose therapy with autologous stem cell rescue (HDT/ASCR) or allogeneic hematopoietic cell transplant (HCT)[y] ± ISRT if not previously given[j,u]

HDT/ASCR or allogeneic HCT[y] ± ISRT if not previously given[j,u] or Axicabtagene ciloleucel (only after ≥2 prior chemoimmunotherapy regimens)[z] or Clinical trial or Ibritumomab tiuxetan or ISRT[j] for localized residual and/or residual FDG-avid disease not previously irradiated or Observation

Clinical trial or Ibritumomab tiuxetan or Second-line therapy (See BCEL-C) or Axicabtagene ciloleucel (only after ≥2 prior chemoimmunotherapy regimens)[z] or Best supportive care

Relapsed or Progressive disease[m] → **See Multiple Prior Therapies (FOLL-7)**

[j] See Principles of Radiation Therapy (NHODG-D).

[m] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C). PET/CT scan should be interpreted via the PET Five Point Scale (FPS).

[r] For pathologic evaluation of histologic transformation, FISH for BCL2 rearrangement [t(14;18)], and *MYC* rearrangements [t(8;14) or variants, t(8;22), t(2;8)].

[s] ISRT alone or one course of single-agent therapy including rituximab.

[t] This includes ≥2 of chemoimmunotherapy regimens for indolent or transformed disease. For example, prior treatment with BR and RCHOP.

[u] Consider ISRT for localized presentations, bulky disease, and/or limited osseous disease.

[v] If transformation is co-existing with extensive FL, consider maintenance (see FOLL-5, Optional Extended Therapy).

[w] If proceeding to an autologous stem cell rescue, consider additional systemic therapy ± ISRT to induce CR prior to transplant. Axicabtagene ciloleucel is not an appropriate treatment option for patients with a CR.

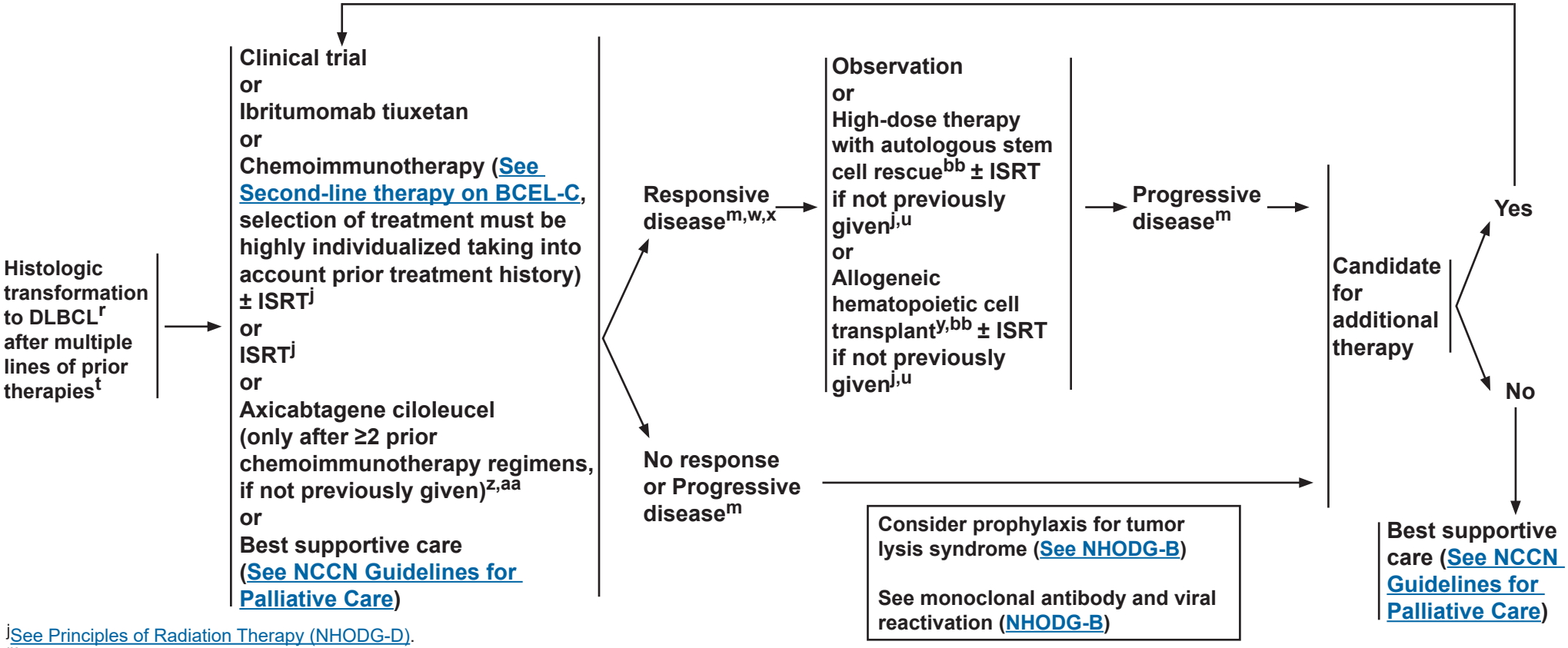
[x] Repeat biopsy should be strongly considered if PET-positive prior to additional therapy. If biopsy negative, follow CR pathway.

[y] Strongly recommend this treatment be given in the context of a clinical trial.

[z] See Guidance for Treatment of Patients with Chimeric Antigen Receptor (CAR) T-Cell Therapy (BCEL-D).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

HISTOLOGIC TRANSFORMATION TO DIFFUSE LARGE B-CELL LYMPHOMA[r]



[j] See Principles of Radiation Therapy (NHODG-D).
[m] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C). PET/CT scan should be interpreted via the PET Five Point Scale (FPS).
[r] For pathologic evaluation of histologic transformation, FISH for *BCL2* rearrangement [t(14;18)], and *MYC* rearrangements [t(8;14) or variants, t(8;22), t(2;8)].
[t] This includes ≥2 of chemoimmunotherapy regimens for indolent or transformed disease. For example, prior treatment with BR and RCHOP.
[u] Consider ISRT for localized presentations, bulky disease, and/or limited osseous disease.
[w] If proceeding to an autologous stem cell rescue, consider additional systemic therapy ± ISRT to induce CR prior to transplant. Axicabtagene ciloleucel is not an appropriate treatment option for patients with a CR.
[x] Repeat biopsy should be strongly considered if PET-positive prior to additional therapy.
[y] Strongly recommend this treatment be given in the context of a clinical trial.
[z] See Guidance for Treatment of Patients with Chimeric Antigen Receptor (CAR) T-Cell Therapy (BCEL-D).
[aa] Patients should have received at least one anthracycline or anthracenedione-based regimen, unless contraindicated.
[bb] Data on transplant after treatment with axicabtagene ciloleucel are not available. HDT/ASCR is not recommended after axicabtagene ciloleucel. Allogeneic HCT could be considered but remains investigational.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PEDIATRIC-TYPE FOLLICULAR LYMPHOMA IN ADULTS

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

PATHOLOGIC AND CLINICAL PRESENTATION[d,cc]

- Pathologic
  - Morphology: expansile follicles, effacement of architecture, absence of diffuse area
  - Expresses: BCL6, CD10, ± IRF4/MUM1 (~20%)
  - Proliferation index (Ki-67/MIB-1) >30%
  - No rearrangement of *BCL2*, *BCL6*, IRF4/MUM1
- Clinical
  - Localized disease (stage I,II)
  - Head and neck (cervical, submandibular, submental, postauricular, or periparotid lymph nodes) or less common inguinal lymph nodes
  - Male sex predominant
  - Younger age than typical FL (though can occur in adults older than age 60)

STAGING WORKUP

- PET/CT scan
- Bone marrow biopsy

→ Stage I,II →

TREATMENT

Excision (preferred) → Observe[dd]
or
ISRT[j]
or
RCHOP for patients with extensive local disease who are not candidates for excision or ISRT

→ Restage with PET/CT

- CR[m] → Observe[dd]
- <CR → See FOLL-5, Progressive disease

[d] In young patients with localized disease that lack BCL2 expression or t(14;18), consider entity of PTFL. Analysis of *BCL6* rearrangement may be useful for evaluating the diagnosis of PTFL.

[j] See Principles of Radiation Therapy (NHODG-D).

[m] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C). PET/CT scan should be interpreted via the PET Five Point Scale (FPS).

[cc] Localized disease (stage I,II) is more common than advanced-stage disease (stage III,IV). If the patient has disease >stage II, it is by definition not PTFL.

[dd] If patients have an excellent prognosis, no surveillance imaging is necessary. There are no data to support maintenance therapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

GELF CRITERIA[a,b]

- Involvement of ≥3 nodal sites, each with a diameter of ≥3 cm
- Any nodal or extranodal tumor mass with a diameter of ≥7 cm
- B symptoms
- Splenomegaly
- Pleural effusions or peritoneal ascites
- Cytopenias (leukocytes <1.0 x 10^9/L and/or platelets <100 x 10^9/L)
- Leukemia (>5.0 x 10^9/L malignant cells)

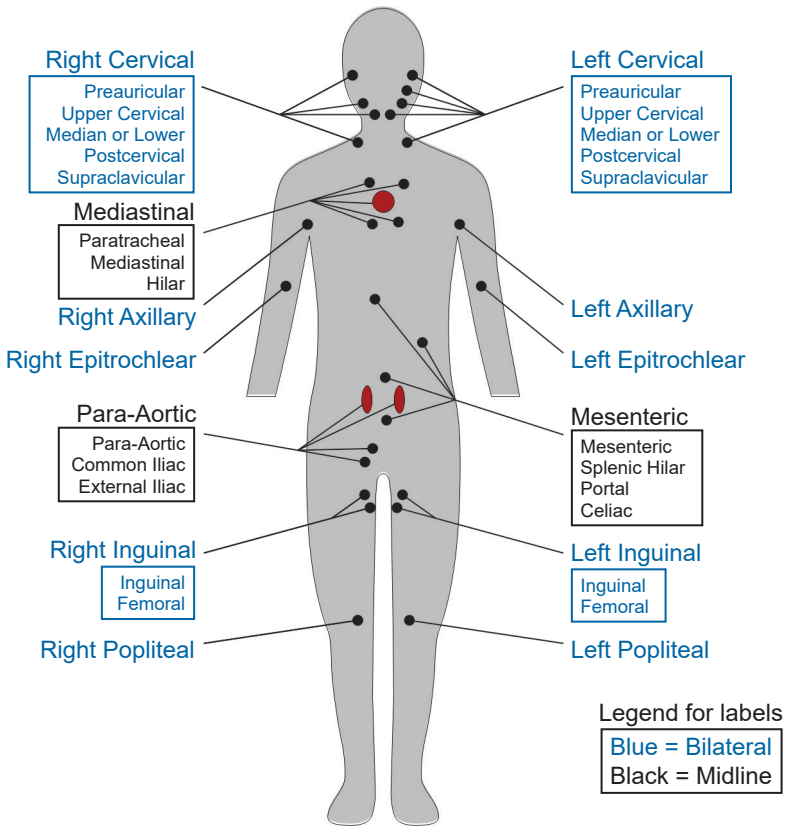
FLIPI - 1 CRITERIA[a,c,d]

Age	≥60 y
Ann Arbor stage	III–IV
Hemoglobin level	<12 g/dL
Serum LDH level	>ULN (upper limit of normal)
Number of nodal sites[d]	≥5

Risk group according to FLIPI chart

	Number of factors
Low	0–1
Intermediate	2
High	≥3

Nodal Areas



Mannequin used for counting the number of involved areas.[e]

[a]This provides useful prognostic information that may be used to guide therapeutic decisions.

[b]Solal-Celigny P, Lepage E, Brousse N, et al. Doxorubicin-containing regimen with or without interferon alfa 2b for advanced follicular lymphomas: final analysis of survival and toxicity in the Groupe d'Etude des Lymphomes Folliculaire 86 trial. J Clin Oncol 1998;16:2332-2338.

[c]This research was originally published in Blood. Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood 2004;104:1258-1265. (c) the American Society of Hematology.

[d]FLIPI-2 (Federico M, Bellei M, Marcheselli L, et al. J Clin Oncol 2009;27:4555-4562) predicts for outcomes after active therapy; see Discussion.

[e]The map is used to determine the number of nodal sites in FLIPI-1 criteria and is different than the conventional Ann Arbor site map.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018
Follicular Lymphoma (grade 1-2)

NCCN Guidelines Index
Table of Contents
Discussion

SUGGESTED TREATMENT REGIMENS[a,b,c]

First-line Therapy

- **Preferred regimens (in alphabetical order)**
  - **Bendamustine[d] + obinutuzumab[e]**
  - **Bendamustine[d] + rituximab**
  - **CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + obinutuzumab[e]**
  - **RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)**
  - **CVP (cyclophosphamide, vincristine, prednisone) + obinutuzumab[e]**
  - **RCVP (rituximab, cyclophosphamide, vincristine, prednisone)**
- **Other recommended regimens (in alphabetical order)**
  - **Lenalidomide + rituximab (category 2B)**
  - **Rituximab (375 mg/m² weekly for 4 doses) (consider for low tumor burden)[f]**

First-line Consolidation or Extended Dosing (optional)

- **Rituximab maintenance 375 mg/m² one dose every 8 wks for 12 doses for patients initially presenting with high tumor burden (category 1)[i]**
- **Obinutuzumab maintenance (1000 mg every 8 weeks for 12 doses)**
- **If initially treated with single-agent rituximab, consolidation with rituximab 375 mg/m² one dose every 8 weeks for 4 doses**
- **Ibritumomab tiuxetan[g,h,j] (category 2B)**

First-line Therapy for Elderly or Infirm (if none of the above are expected to be tolerable in the opinion of treating physician)

- **Rituximab (preferred) (375 mg/m² weekly for 4 doses)**
- **Chlorambucil + rituximab**
- **Cyclophosphamide + rituximab**
- **Chlorambucil**
- **Cyclophosphamide**
- **Ibritumomab tiuxetan[g,h] (category 2B)**

See Second-line and Subsequent Therapy on FOLL-B 2 of 4

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

[a]See references for regimens FOLL-B 3 of 4 and FOLL-B 4 of 4.

[b]The choice of initial therapy requires consideration of many factors, including age, comorbidities, and future treatment possibilities (eg, HDT with SCR). Therefore, treatment selection is highly individualized.

[c]Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.

[d]Prophylaxis for PJP and VZV should be administered, see Supportive Care (NHODG-B). In the GALLIUM study, there was an increased risk of mortality from OI and secondary malignancies in patients receiving bendamustine. Increased risk of mortality occurred over entire treatment program and extending beyond maintenance.

[e]The clinical trial evaluating this regimen included obinutuzumab maintenance. The use without maintenance was an extrapolation of the data.

[f]Rituximab may be appropriate in patients initially observed and with progression of low tumor burden disease not meeting GELF criteria (FOLL-A). Immediate initial therapy with rituximab in patients not meeting GELF criteria has not improved OS (Ardeshna K, et al. Lancet Oncol 2014;15:424-435).

[g]Selection of patients requires adequate marrow cellularity >15% and <25% involvement of lymphoma in bone marrow, and platelets >100,000. In patients with prior autologous stem cell rescue, referral to a tertiary care center is highly recommended for ibritumomab tiuxetan.

[h]If ibritumomab tiuxetan is considered, bilateral cores are recommended and the pathologist should provide the percent of overall cellular elements and the percent of cellular elements involved in the marrow. Karyotype ± FISH for known MDS markers. As of 2010, updates suggest a trend towards an increased risk of MDS with RIT.

[i]This is based on the PRIMA study for patients with high tumor burden treatment with RCVP and RCHOP. There are no data following other regimens.

[j]The full impact of an induction regimen containing rituximab on RIT consolidation is unknown.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS[a,b,c]
(in preference order)

Second-line and Subsequent Therapy

- **Preferred regimens[k]**
  - **Bendamustine[l] + obinutuzumab[m] or rituximab**
  - **CHOP + obinutuzumab[m] or rituximab**
  - **CVP + obinutuzumab[m] or rituximab**
  - **Rituximab**
  - **Lenalidomide ± rituximab**
- **Other recommended regimens**
  - **Ibritumomab tiuxetan[g,h]**
  - **Idelalisib[n] (refractory to both alkylator and rituximab)**
  - **Copanlisib[n] (refractory to at least 2 prior therapies)**
  - **See Second-line Therapy for DLBCL (BCEL-C 2 of 4) without regard to transplantability**

Second-line and Subsequent Therapy for Elderly or Infirm (if none of the therapies are expected to be tolerable in the opinion of treating physician)

- **Rituximab (preferred) (375 mg/m² weekly for 4 doses)**
- **Chlorambucil + rituximab**
- **Cyclophosphamide + rituximab**
- **Chlorambucil**
- **Cyclophosphamide**
- **Ibritumomab tiuxetan[g,h] (category 2B)**

Second-line Consolidation or Extended Dosing (optional)

- **Rituximab maintenance 375 mg/m² one dose every 12 weeks for 2 years (category 1)**
- **Obinutuzumab maintenance for rituximab-refractory disease (1 g every 8 weeks for total of 12 doses)**
- **High-dose therapy with autologous stem cell rescue**
- **Allogeneic hematopoietic cell transplant for highly selected patients**

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

[a]See references for regimens FOLL-B 3 of 4 and FOLL-B 4 of 4.

[b]The choice of initial therapy requires consideration of many factors, including age, comorbidities, and future treatment possibilities (eg, HDT with SCR). Therefore, treatment selection is highly individualized.

[c]Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.

[g]Selection of patients requires adequate marrow cellularity >15% and <25% involvement of lymphoma in bone marrow, and platelets >100,000. In patients with prior autologous stem cell rescue, referral to a tertiary care center is highly recommended for ibritumomab tiuxetan.

[h]If ibritumomab tiuxetan is considered, bilateral cores are recommended and the pathologist should provide the percent of overall cellular elements and the percent of cellular elements involved in the marrow. Karyotype for known MDS markers. As of 2010, updates suggest a trend towards an increased risk of MDS with RIT.

[k]Generally, a first-line regimen is not repeated.

[l]Prophylaxis for PJP and VZV should be administered, see Supportive Care (NHODG-B).

[m]The clinical trial evaluating this regimen included obinutuzumab maintenance. The use without maintenance was an extrapolation of the data. Obinutuzumab is preferred in patients with rituximab refractory disease, which includes disease progressing on or within 6 months of prior rituximab therapy. .

[n]See Special Considerations for the Use of Small-Molecule Inhibitors (NHODG-E).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS
References

First-line Therapy

Bendamustine + rituximab

Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet 2013;381:1203-1210.

Flinn IW, van der Jagt R, Kahl BS, et al. Open-label, randomized, noninferiority study of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of advanced indolent NHL or MCL: the BRIGHT study. Blood 2014;123:2944-2952.

Bendamustine + obinutuzumab

Marcus R, Davies A, Ando K, et al. Obinutuzumab for the first-line treatment of follicular lymphoma. N Engl J Med 2018;377:1331-1344.

RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)

Czuczman MS, Weaver R, Alkuzweny B, et al. Prolonged clinical and molecular remission in patients with low-grade or follicular non-Hodgkin's lymphoma treated with rituximab plus CHOP chemotherapy: 9-year follow-up. J Clin Oncol 2004;22:4711-4716.

Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2005;106:3725-3732.

CHOP + obinutuzumab

Marcus R, Davies A, Ando K, et al. Obinutuzumab for the first-line treatment of follicular lymphoma. N Engl J Med 2018;377:1331-1344.

RCVP (rituximab, cyclophosphamide, vincristine, prednisone)

Marcus R, Imrie K, Solal-Celigny P, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J Clin Oncol 2008;26:4579-4586.

CVP + obinutuzumab

Marcus R, Davies A, Ando K, et al. Obinutuzumab for the first-line treatment of follicular lymphoma. N Engl J Med 2018;377:1331-1344.

Rituximab

Hainsworth JD, Litchy S, Burris HA, III, et al. Rituximab as first-line and maintenance therapy for patients with indolent Non-Hodgkin's lymphoma. J Clin Oncol 2002;20:4261-4267.

Colombat P, Salles G, Brousse N, et al. Rituximab (anti-CD20 monoclonal antibody) as single first-line therapy for patients with follicular lymphoma with a low tumor burden: Clinical and molecular evaluation. Blood 2001;97:101-106.

Martinelli G, Schmitz SF, Utiger U, et al. Long-term follow-up of patients with follicular lymphoma receiving single-agent rituximab at two different schedules in trial SAKK 35/98. J Clin Oncol 2010;28:4480-4484.

Ardeshna KM, Qian W, Smith P, et al. Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial. The Lancet Oncology 2014;15:424-435.

Lenalidomide + rituximab

Martin P, Jung SH, Pitcher B, et al. A phase II trial of lenalidomide plus rituximab in previously untreated follicular non-Hodgkin's lymphoma (NHL): CALGB 50803 (Alliance). Ann Oncol 2018;28:2806-2812.

Fowler N, Davis R, Rawal S, et al. Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: an open-label, phase 2 trial. The Lancet Oncology 2014;15:1311-1318.

Ibritumomab tiuxetan

Scholz CW, Pinto A, Linkesch W, et al. (90)Yttrium-ibritumomab-tiuxetan as first-line treatment for follicular lymphoma: 30 months of follow-up data from an international multicenter phase II clinical trial. J Clin Oncol 2013;31:308-313.

First-line Consolidation or Extended Dosing

Chemoimmunotherapy followed by rituximab maintenance

Salles GA, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): A phase 3, randomised controlled trial. The Lancet 2011;377:42-51.

Salles GA, Seymour JF, Feugier P, et al. Long term follow-up of the PRIMA Study: Half of patients receiving rituximab maintenance remain progression free at 10 years [abstract]. Blood 2018;130 (Suppl 1):Abstract 486.

Extended dosing with rituximab

Ghielmini M, Schmitz SH, Cogliatti SB, et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule. Blood 2004;103:4416-4423.

Obinutuzimab-based chemoimmunotherapy followed by obinutuzumab maintenance

Marcus R, Davies A, Ando K, et al. Obinutuzumab for the first-line treatment of follicular lymphoma. N Engl J Med 2018;377:1331-1344.

Ibritumomab tiuxetan

Morschhauser F, Radford J, Van Hoof A, et al. Phase III trial of consolidation therapy with Yttrium-90–Ibritumomab Tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma. J Clin Oncol 2008;26:5156-5164.

Morschhauser F, Radford J, Van Hoof A, et al. 90Yttrium-ibritumomab tuxetan consolidation of first remission in advanced-stage follicular non-Hodgkin lymphoma: Updated results after a median follow-up of 7.3 years from the international, randomized, phase III first-line indolent trial. J Clin Oncol 2013;31:1977-1983.

Continued

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS
References

Second-line and Subsequent Therapy

Bendamustine + obinutuzumab

Sehn LH, Chua N, Mayer J, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. Lancet Oncol 2018;17:1081-1093.

Copanlisib

Dreyling M, Santoro A, Mollica L, et al. Updated safety and efficacy from the copanlisib CHRONOS-1 trial in patients with relapsed or refractory indolent B-cell lymphoma: Low incidence of late-onset severe toxicities [abstract]. Blood 2018;130 (Suppl 1):2777.

Dreyling M, Santoro A, Mollica L, et al. Phosphatidylinositol 3-kinase inhibition by copanlisib in relapsed or refractory indolent lymphoma. J Clin Oncol 2018;35:3898-3905.

Idelalisib

Gopal A, Kahl B, De Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med 2014;370:1008-1018.

Lenalidomide ± rituximab

Leonard JP, Jung SH, Johnson J, et al. Randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma: CALGB 50401 (Alliance). J Clin Oncol 2015;33:3635-3640.

Witzig TE, Wiernik PH, Moore T, et al. Lenalidomide oral monotherapy produces durable responses in relapsed or refractory indolent non-Hodgkin's Lymphoma. J Clin Oncol 2009;27:5404-5409.

Ibritumomab tiuxetan

Witzig TE, Flinn IW, Gordon LI, et al. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. J Clin Oncol 2002;20:3262-3269.

Witzig TE, Gordon LI, Cabanillas F, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol 2002;20:2453-2463.

Rituximab

McLaughlin P, Grillo-Lopez AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol 1998;16:2825-2833.

Ghielmini M, Schmitz SH, Cogliatti SB, et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule. Blood 2004;103:4416-4423.

Second-line Consolidation or Extended Dosing

Rituximab maintenance

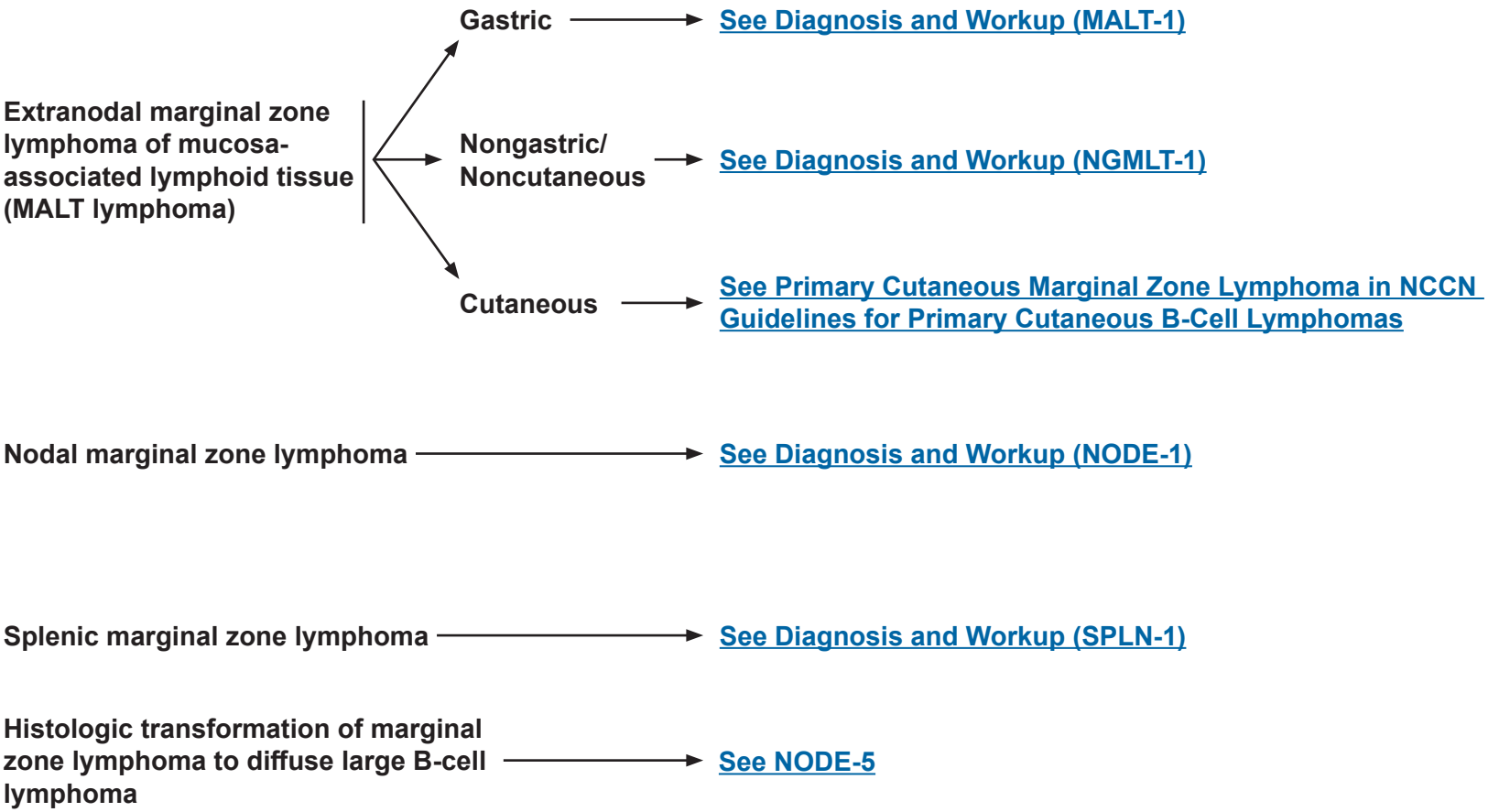
van Oers MHJ, Van Glabbeke M, Giurgea L, et al. Rituximab maintenance treatment of relapsed/resistant follicular non-hodgkin's lymphoma: Long-term outcome of the EORTC 20981 Phase III randomized Intergroup Study. J Clin Oncol 2010;28:2853-2858.

Forstpointer R, Unterhalt M, Dreyling M, et al. Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG). Blood 2006;108:4003-4008.

Obinutuzumab maintenance for rituximab refractory disease

Sehn LH, Chua N, Mayer J, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. Lancet Oncol 2018;17:1081-1093.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ADDITIONAL DIAGNOSTIC TESTING[a,b]

ESSENTIAL:
- Diagnosis of gastric MALT lymphoma requires an endoscopic biopsy and an FNA is never adequate.
- Adequate immunophenotyping to establish diagnosis[c,d]
  - IHC panel: CD20, CD3, CD5, CD10, BCL2, kappa/lambda, CD21 or CD23, cyclin D1,[f] BCL6 with or without
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10
- Helicobacter pylori (H. pylori) stain (gastric), if positive, then PCR or FISH for t(11;18)[e]

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- Molecular analysis to detect: antigen receptor gene rearrangements; *MYD88* mutation status to differentiate WM versus MZL if plasmacytic differentiation present
- Karyotype or FISH: t(1;14); t(3;14); t(11;14);[f] t(11;18)
- FISH or PCR: t(14;18)

→

WORKUP

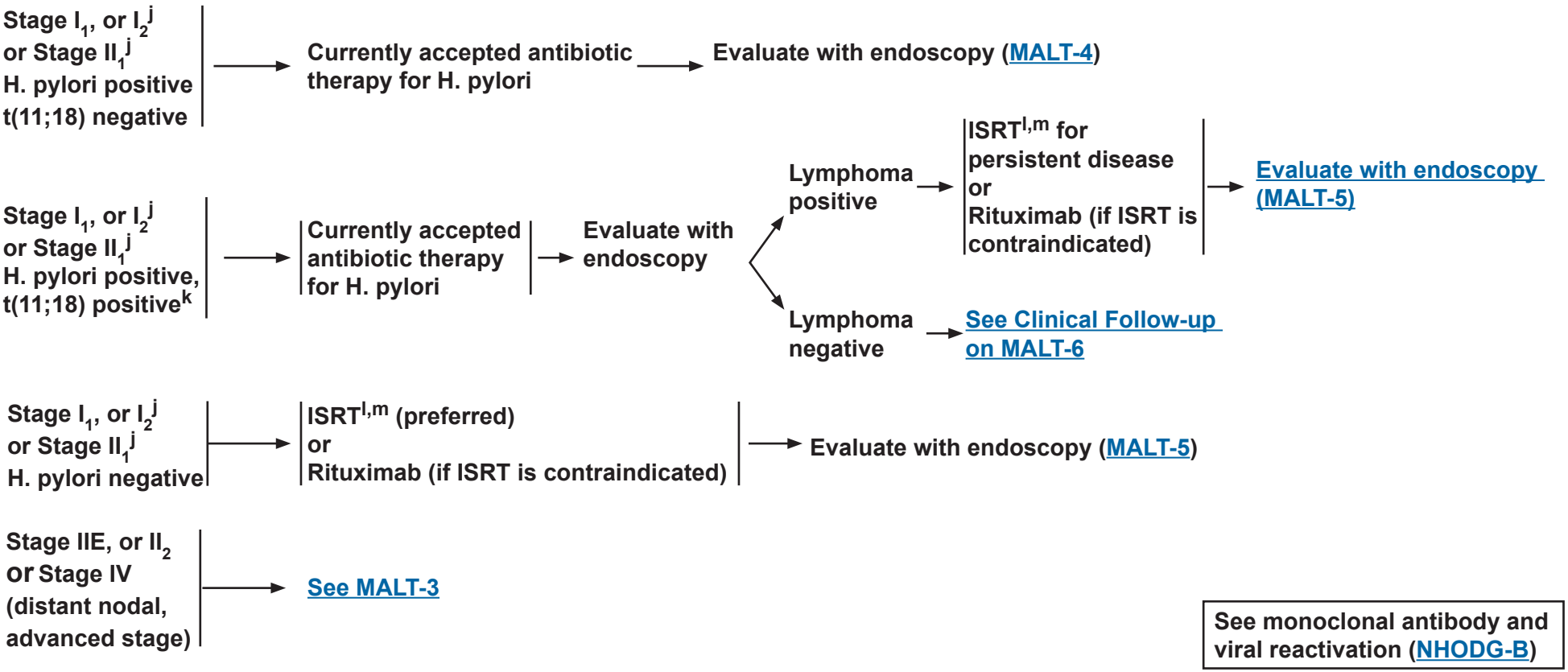
ESSENTIAL:
- Physical exam with attention to nongastric sites (eyes, skin)
- Performance status
- CBC with differential
- Comprehensive metabolic panel
- LDH
- If H. pylori negative by histopathology, then use noninvasive H. pylori testing (stool antigen test or urea breath test)
- Hepatitis B testing[g] if rituximab contemplated
- Hepatitis C testing
- C/A/P CT with contrast of diagnostic quality and/or whole-body PET/CT scan (especially if ISRT anticipated)
- Pregnancy testing in women of child-bearing age (if chemotherapy or RT planned)

USEFUL IN SELECTED CASES:
- Bone marrow biopsy ± aspirate
- Echocardiogram or MUGA scan if anthracycline or anthracenedione-based regimen is indicated
- Endoscopy with ultrasound (if available) with multiple biopsies of anatomical sites[h]
- Discussion of fertility issues and sperm banking
- SPEP

→ See Initial Therapy (MALT-2)

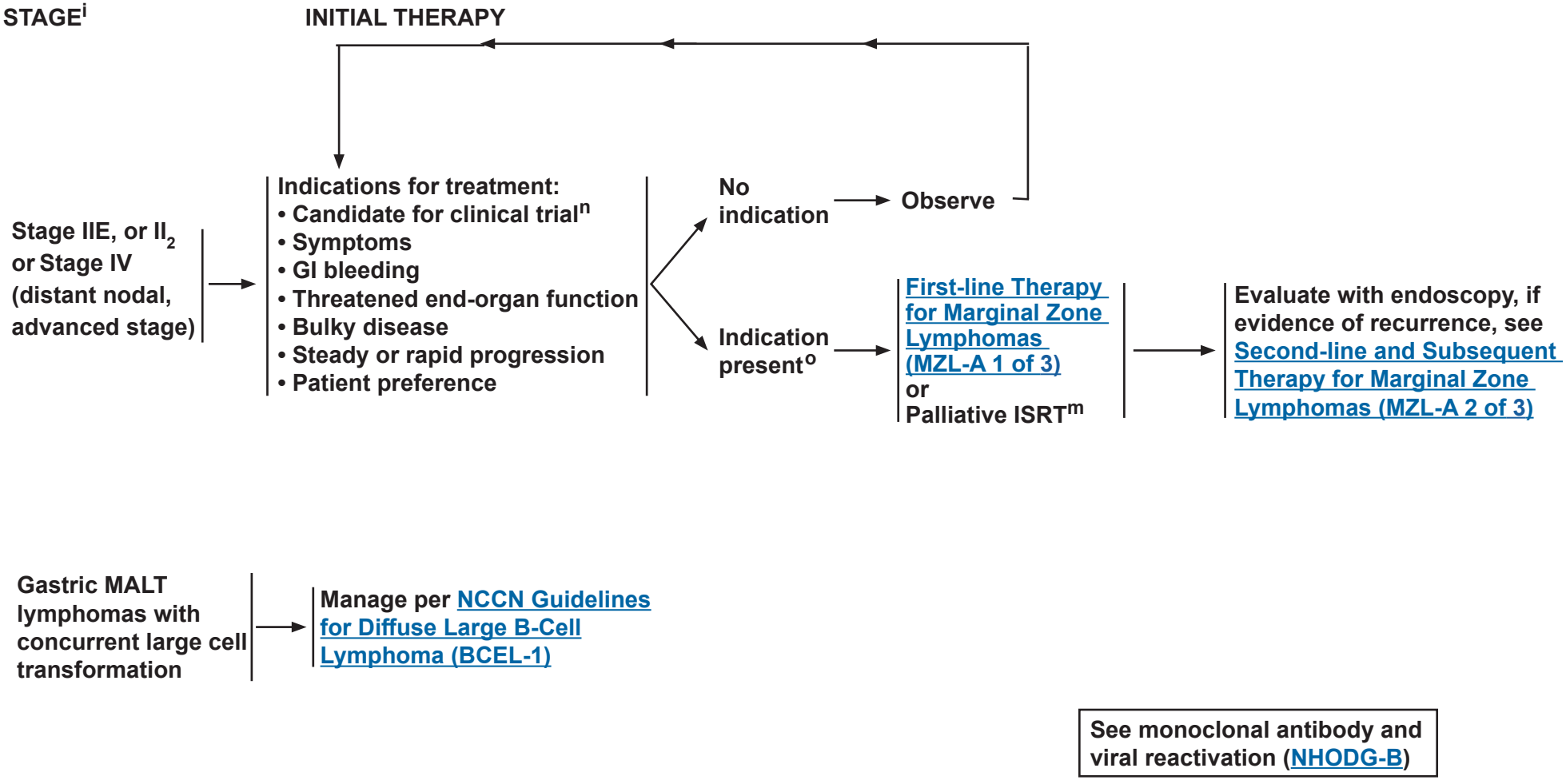
[a]Nondiagnostic atypical lymphoid infiltrates that are H. pylori positive should be rebiopsied to confirm or exclude lymphoma prior to treatment of H. pylori.
[b]Any area of DLBCL should be treated according to the NCCN Guidelines for Diffuse Large B-Cell Lymphoma (BCEL-1).
[c]Typical immunophenotype: CD10-, CD5-, CD20+, cyclin D1-, BCL2- follicles.
[d]See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).
[e]Locally advanced disease is more likely in patients with gastric MALT lymphoma with t(11;18), which is less likely to respond to antibiotics.
[f]If IHC for cyclin D1 is positive, FISH for t(11;14) is not necessary; see MANT-1.
[g]Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.
[h]This is particularly useful for H. pylori-positive cases because the likelihood of tumor response is related to depth of tumor invasion.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[i]See Lugano Staging System for Gastrointestinal Lymphomas (MALT-A).
[j]Involvement of submucosa or regional lymph nodes are much less likely to respond to antibiotic therapy. If there is persistent disease after evaluation, RT may be considered earlier in the course.
[k]t(11;18) is a predictor for lack of tumor response (<5%) to antibiotics. Antibiotics are used in these patients to eradicate the H. plyori infection. These patients should be considered for alternative therapy of the lymphoma. Liu H, Ye H, Ruskone-Fourmestraux A, et al. t(11;18) is a marker for all stage gastric MALT lymphomas that will not respond to H. pylori eradication. Gastroenterology 2002;122:1286-1294.
[l]If H. pylori negative by both histology and serum antibodies, RT is recommended.
[m]See Principles of Radiation Therapy (NHODG-D).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

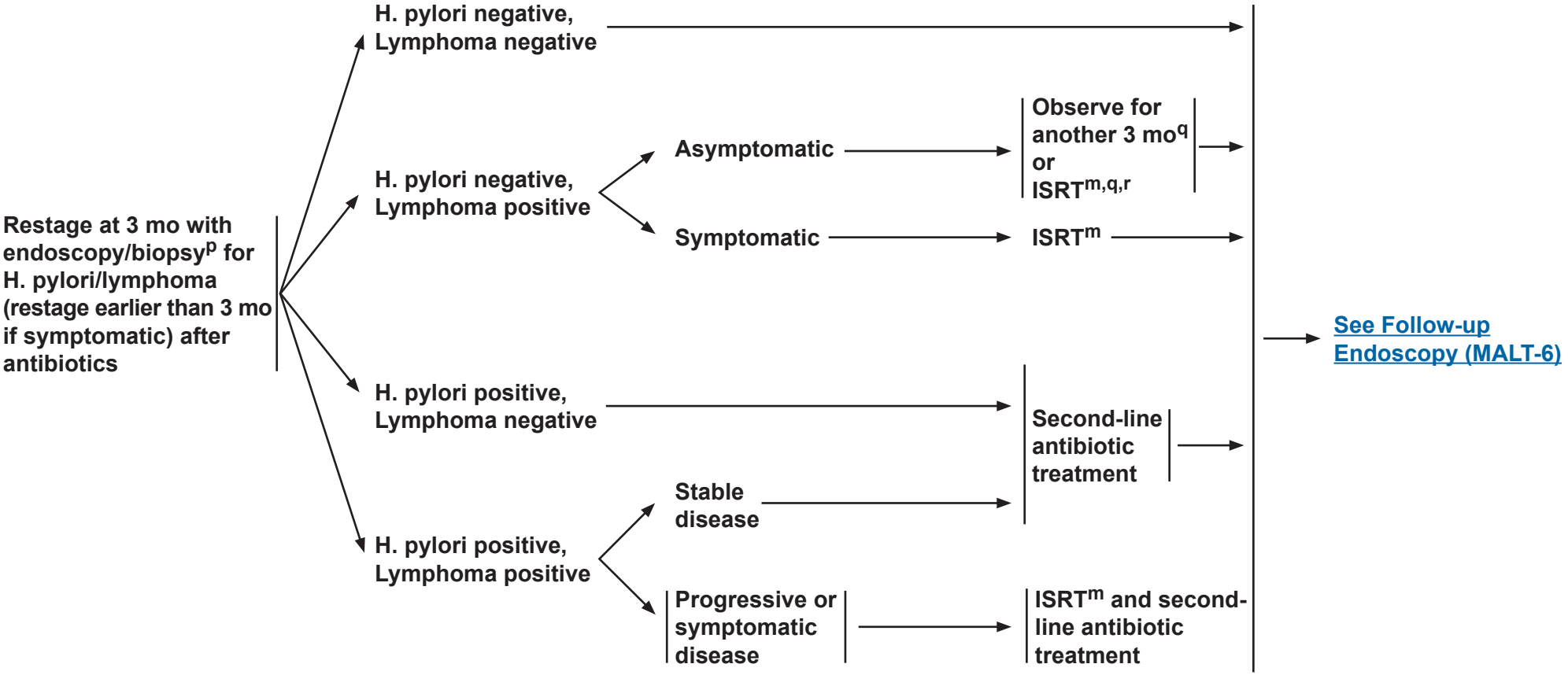


[i]See Lugano Staging System for Gastrointestinal Lymphomas (MALT-A).
[m]See Principles of Radiation Therapy (NHODG-D).
[n]Given incurability with conventional therapy, consider investigational therapy as first line of treatment.
[o]Surgical resection is generally limited to specific clinical situations (ie, life-threatening hemorrhage).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

3-MONTH RESTAGING AND FOLLOW-UP ENDOSCOPY

AFTER ANTIBIOTICS | **ADDITIONAL THERAPY**



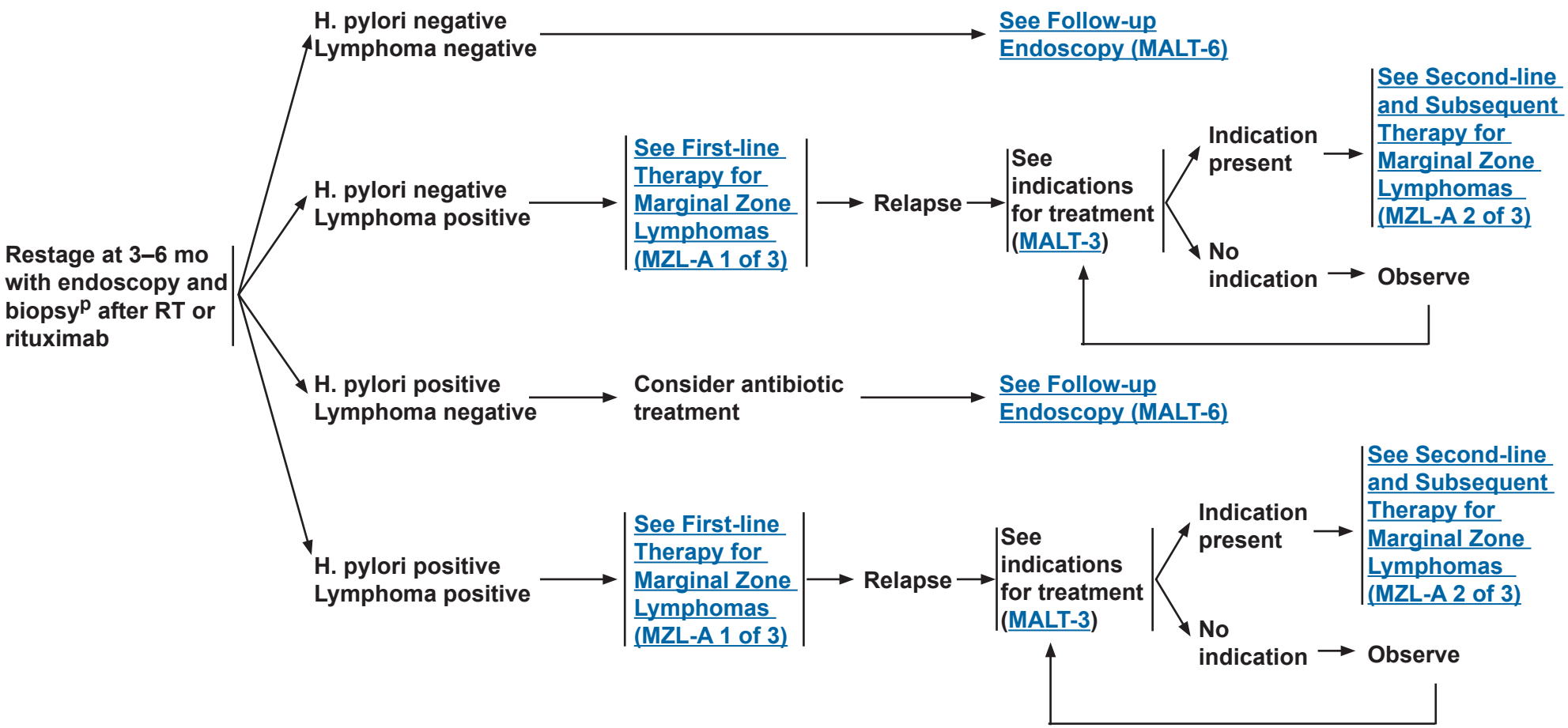
[m] See Principles of Radiation Therapy (NHODG-D).
[p] Biopsy to rule out large cell lymphoma. Any area of DLBCL should be treated according to the NCCN Guidelines for Diffuse Large B-Cell Lymphoma (BCEL-1).
[q] If re-evaluation suggests slowly responding disease or asymptomatic nonprogression, continued observation may be warranted. RT can be considered as early as 3 mo after observation but can be prolonged to 18 mo (category 2B).
[r] If patient originally had clinical Stage I_2 or Stage II_E, early RT should be considered if there is no response to antibiotics.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

3- to 6-MONTH RESTAGING AND FOLLOW-UP ENDOSCOPY

AFTER RT OR RITUXIMAB

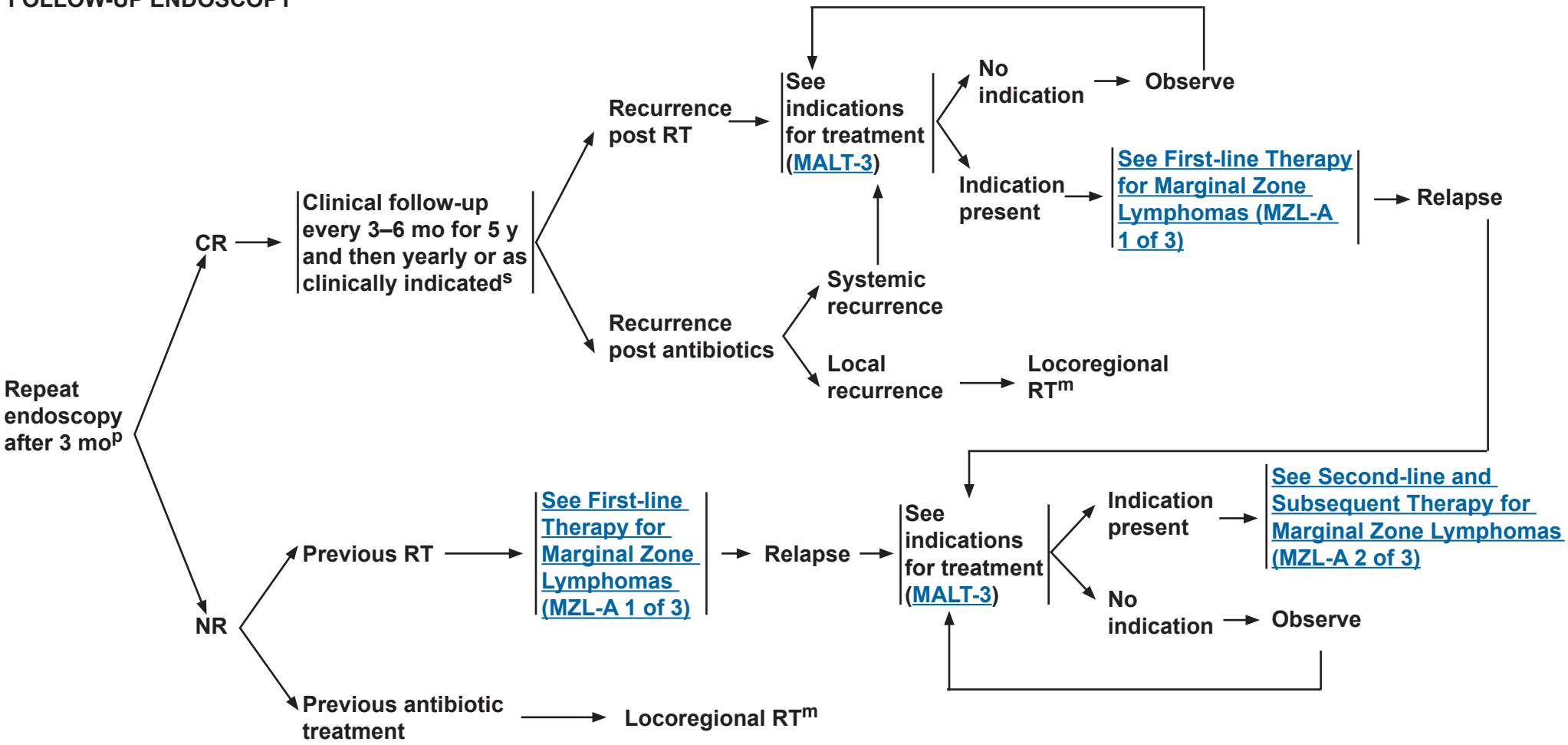
ADDITIONAL THERAPY



[p]Biopsy to rule out large cell lymphoma. Any area of DLBCL should be treated according to the NCCN Guidelines for Diffuse Large B-Cell Lymphoma (BCEL-1).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

FOLLOW-UP ENDOSCOPY



[m] See Principles of Radiation Therapy (NHODG-D).
[p] Biopsy to rule out large cell lymphoma. Any area of DLBCL should be treated according to the NCCN Guidelines for Diffuse Large B-Cell Lymphoma (BCEL-1).
[s] Optimal interval for follow-up endoscopy and imaging is not known. At NCCN Member Institutions, follow-up endoscopy and imaging using the modalities performed during workup is driven by symptoms.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

STAGING OF GASTRIC MALT LYMPHOMA: COMPARISON OF DIFFERENT SYSTEMS

Lugano Staging System for Gastrointestinal Lymphomas		Lugano Modification of Ann Arbor Staging System	TNM Staging System Adapted for Gastric Lymphoma	Tumor Extension
Stage I	Confined to GI tract[a]			
	I_1 = mucosa, submucosa	I_E	T1 N0 M0	Mucosa, submucosa
	I_2 = muscularis propria, serosa	I_E	T2 N0 M0	Muscularis propria
		I_E	T3 N0 M0	Serosa
Stage II	Extending into abdomen			
	II_1 = local nodal involvement	II_E	T1-3 N1 M0	Perigastric lymph nodes
	II_2 = distant nodal involvement	II_E	T1-3 N2 M0	More distant regional lymph nodes
Stage IIE	Penetration of serosa to involve adjacent organs or tissues	II_E	T4 N0 M0	Invasion of adjacent structures
Stage IV[b]	Disseminated extranodal involvement or concomitant supradiaphragmatic nodal involvement		T1-4 N3 M0	Lymph nodes on both sides of the diaphragm/ distant metastases (eg, bone marrow or additional extranodal sites)
		IV	T1-4 N0-3 M1	

Zucca E, Bertoni F, Yahalom J, Isaacson P. Extranodal Marginal Zone B-cell Lymphoma of Mucosa-Associated Lymphoid Tissue (MALT lymphoma) in Armitage et al eds. Non-Hodgkin's Lymphomas. Philadelphia: Lippincott, 2010:242. (http://lww.com)

[a]Single primary or multiple, noncontiguous.
[b]Involvement of multiple extranodal sites in MALT lymphoma appears to be biologically distinct from multiple extranodal involvement in other lymphomas, and these patients may be managed by treating each site separately with excision or RT. In contrast, cases with disseminated nodal involvement appear to behave more like nodal marginal zone lymphoma or like disseminated follicular lymphoma.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ADDITIONAL DIAGNOSTIC TESTING

ESSENTIAL:
- Adequate immunophenotyping to establish diagnosis[c,d]
  - IHC panel: CD20, CD3, CD5, CD10, BCL2, kappa/lambda, CD21 or CD23, cyclin D1 with or without
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- Molecular analysis to detect: antigen receptor gene rearrangements; *MYD88* mutation status to differentiate WM versus MZL if plasmacytic differentiation present; PCR for t(11;18)
- Karyotype or FISH: t(11;18), t(11;14), t(3;14)
- FISH or PCR: t(14;18)

→

WORKUP

ESSENTIAL:
- Physical exam with performance status
- CBC with differential
- Comprehensive metabolic panel
- LDH
- Hepatitis B testing[e] if rituximab contemplated
- Hepatitis C testing
- C/A/P CT and other suspected sites with contrast of diagnostic quality and/or whole-body PET/CT scan
- Pregnancy testing in women of child-bearing age (if chemotherapy or RT planned)

USEFUL IN SELECTED CASES:
- Echocardiogram or MUGA scan if anthracycline or anthracenedione-based regimen is indicated
- Bone marrow biopsy ± aspirate
- Endoscopy with multiple biopsies of anatomical sites[f]
- MRI with contrast for neurological evaluation or if CT with contrast is contraindicated
- Discussion of fertility issues and sperm banking
- SPEP

→ See Initial Therapy (NGMLT-2)

[a]Typical sites of extranodal marginal zone lymphoma other than the stomach include the following: bowel (small and large), breast, head and neck, lung, ocular adnexa, ovary, parotid, prostate, and salivary gland. Infectious agents have been reported to be associated with many nongastric sites, but testing for these infectious organisms is not required for management.

[b]This guideline pertains to noncutaneous; for primary cutaneous marginal zone lymphoma, see NCCN Guidelines for Primary Cutaneous B-Cell Lymphomas.

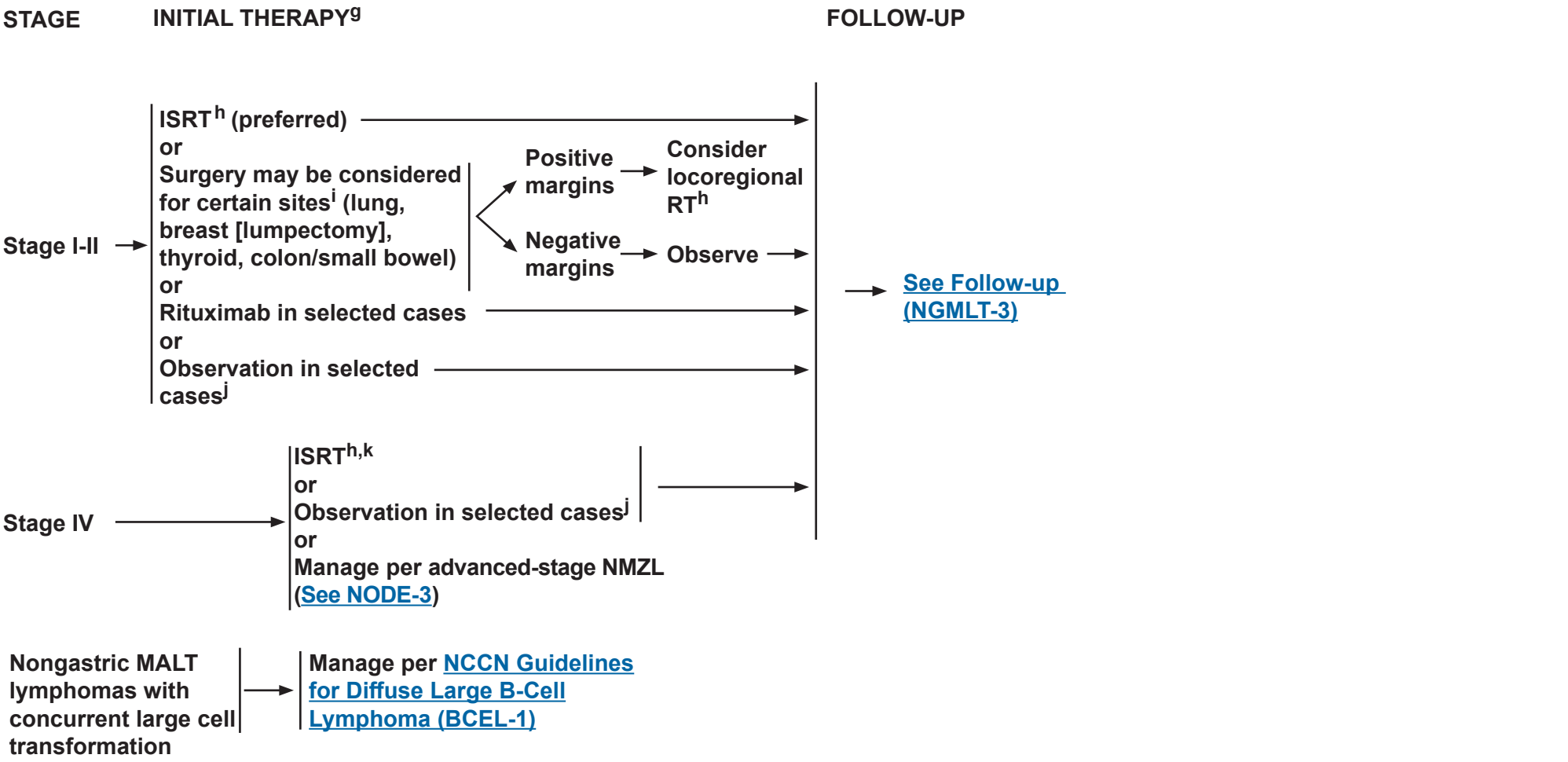
[c]Typical immunophenotype: CD10-, CD5-, CD20+, CD23-/+, CD43-/+, cyclin D1-, BCL2- follicles.

[d]See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-cell and NK/T-cell Neoplasms (NHODG-A).

[e]Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

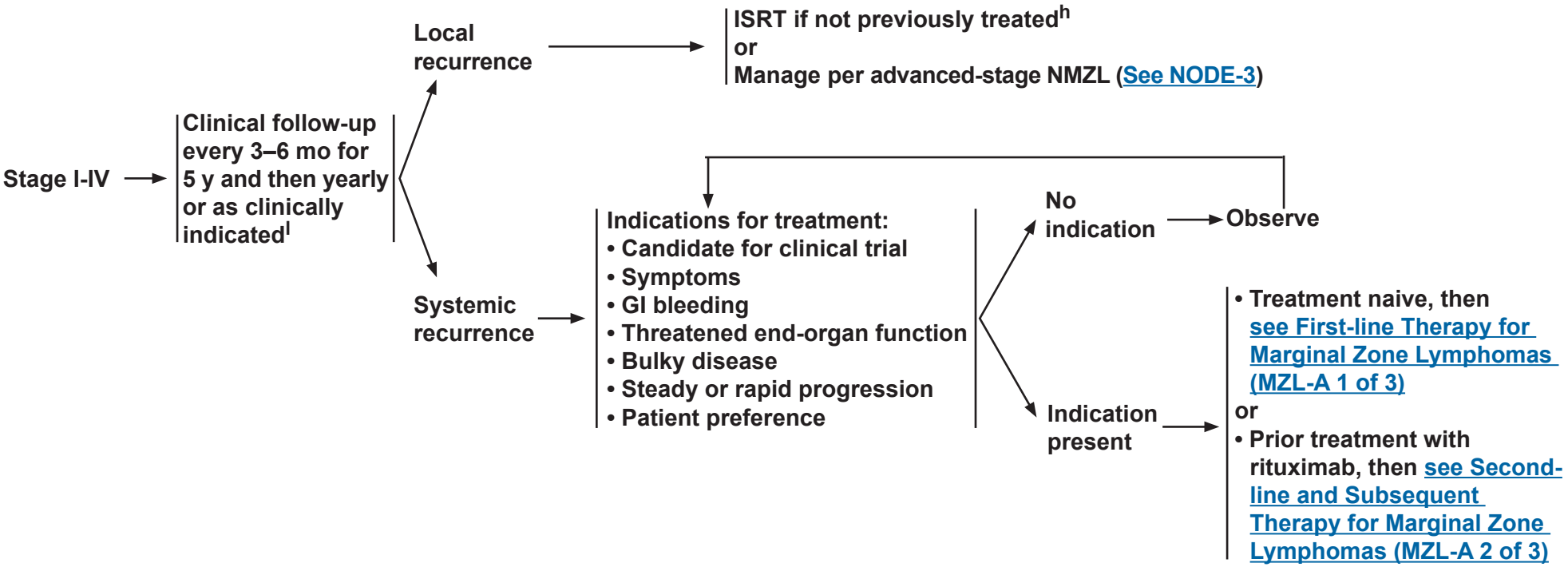
[f]In cases where primary site is thought to be in head/neck or lungs, upper GI endoscopy should be considered.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[g]Based on anecdotal responses to antibiotics in ocular and cutaneous marginal zone lymphomas, some physicians will give an empiric course of doxycycline prior to initiating other therapy.
[h]See Principles of Radiation Therapy (NHODG-D).
[i]Surgical excision for adequate diagnosis may be appropriate treatment for disease.
[j]Observation may be considered for patients whose diagnostic biopsy was excisional, or where RT could result in significant morbidity.
[k]Definitive treatment of multiple sites may be indicated (eg, bilateral orbital disease only) or palliative treatment of symptomatic sites.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[h] See Principles of Radiation Therapy (NHODG-D).
[l] Follow-up includes diagnostic tests and imaging previously used as clinically indicated.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ADDITIONAL DIAGNOSTIC TESTING[a]

ESSENTIAL:

- **Adequate immunophenotyping to establish diagnosis[b,c]**
  - **IHC panel: CD20, CD3, CD5, CD10, BCL2, kappa/lambda, CD21 or CD23, cyclin D1 with or without**
  - **Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10**
- **Pediatric nodal marginal zone lymphoma should be considered with localized disease in a young patient.**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **Molecular analysis to detect: antigen receptor gene rearrangements; *MYD88* mutation status to differentiate WM versus MZL if plasmacytic differentiation present; PCR for t(11;18)**
- **Karyotype or FISH: t(11;18), t(1;14), del(13q), del(7q)**
- **FISH or PCR: t(14;18)**

WORKUP

ESSENTIAL:

- **Physical exam with performance status**
- **CBC with differential**
- **Comprehensive metabolic panel**
- **LDH**
- **Hepatitis B testing[d] if rituximab contemplated**
- **Hepatitis C testing**
- **C/A/P CT or other suspected sites with contrast of diagnostic quality and/or whole-body PET/CT scan**
- **Bone marrow biopsy + aspirate to document clinical stage I-II disease[e]**
- **Evaluation to rule out extranodal primary sites**
  - **Neck nodes: ocular, parotid, thyroid, and salivary gland**
  - **Axillary nodes: lung, breast, and skin**
  - **Mediastinal/hilar nodes: lung**
  - **Abdominal nodes: splenic and GI**
  - **Inguinal/iliac nodes: GI and skin**
- **Pregnancy testing in women of child-bearing age (if chemotherapy or RT planned)**

USEFUL IN SELECTED CASES:

- **Echocardiogram or MUGA scan if anthracycline or anthracenedione-based regimen is indicated**
- **Additional imaging as appropriate**
- **Discussion of fertility issues and sperm banking**
- **SPEP**

Stage I, II
See NODE-2

Stage III, IV
See NODE-3

[a]Nodal MZL is rare and occurs most commonly as spread from extranodal MALT; must also be distinguished from nodal FL, MCL, lymphoplasmacytic lymphoma, and CLL, all of which are more common.

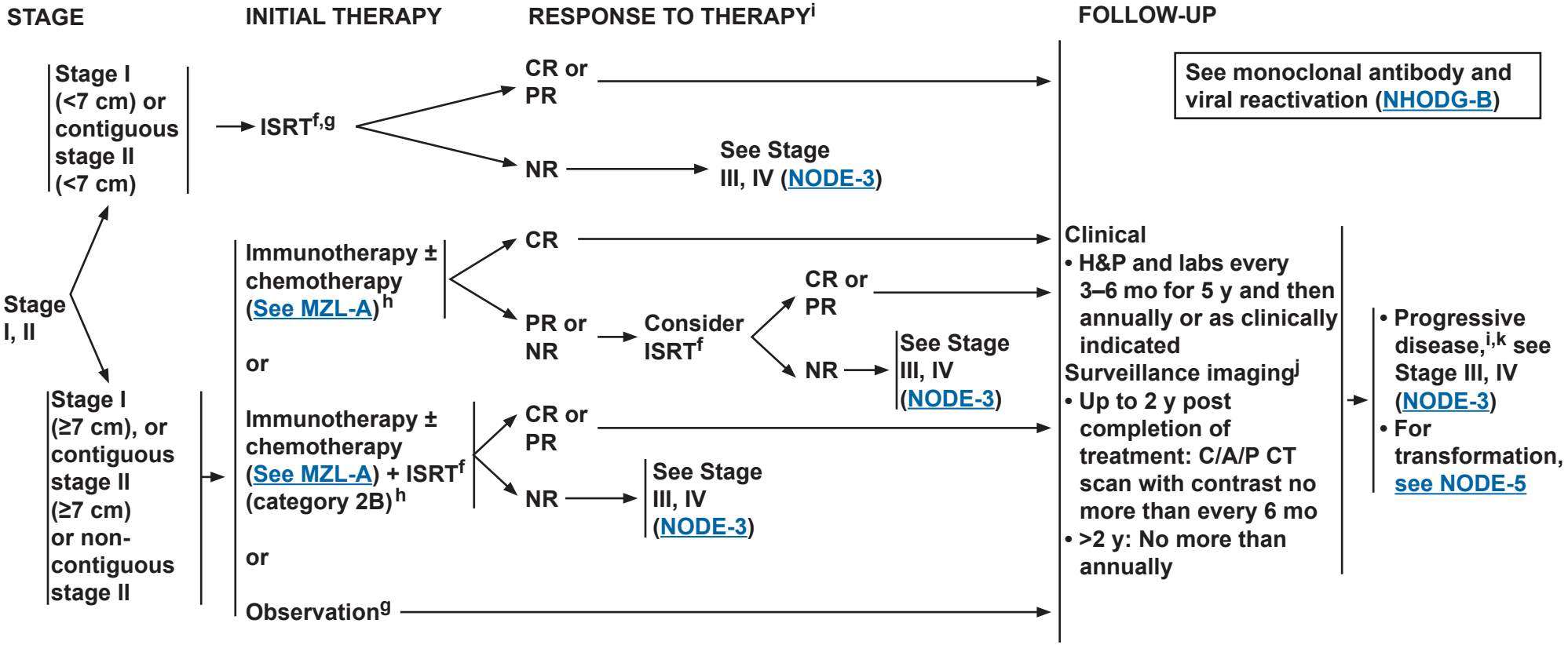
[b]Typical immunophenotype: CD10-, CD5-, CD20+, CD23-/+, CD43-/+ and cyclin D1-, BCL2- follicles.

[c]See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).

[d]Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

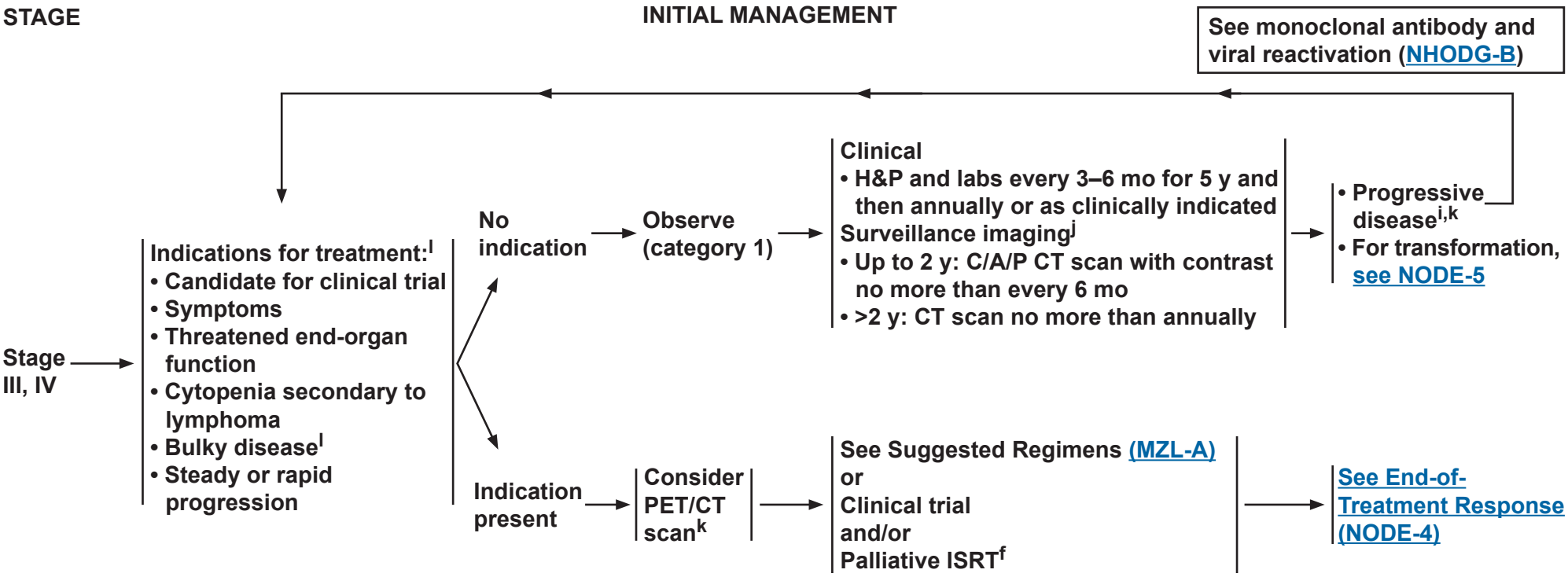
[e]Bilateral or unilateral provided core biopsy is >2 cm. If ibritumomab tiuxetan is considered, bilateral cores are recommended and the pathologist should provide the percent of overall cellular elements and the percent of cellular elements involved in the marrow. If observation is initial therapy, bone marrow biopsy may be deferred.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



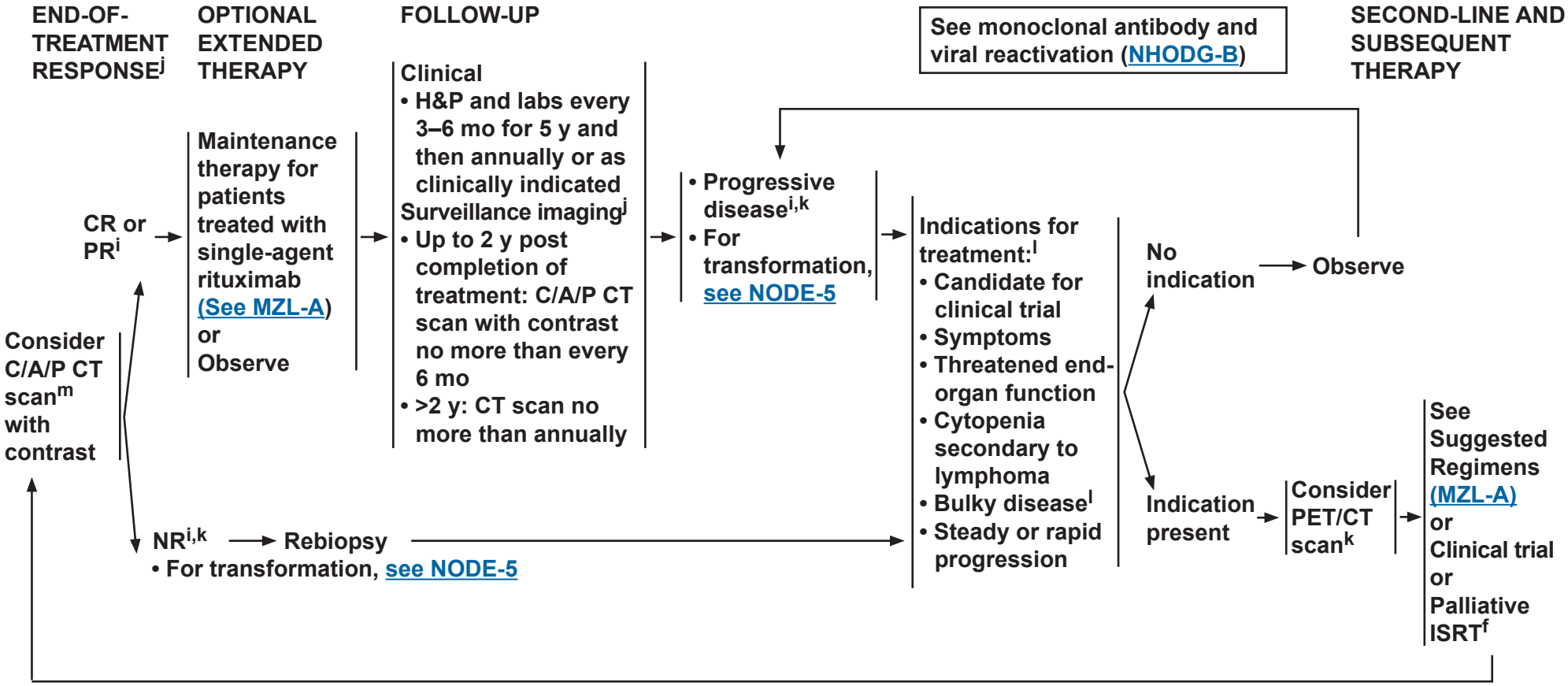
[f] See Principles of Radiation Therapy (NHODG-D).
[g] Observation may be appropriate in circumstances where potential toxicity of involved-site RT (ISRT) outweighs potential clinical benefit.
[h] Initiation of chemotherapy or more extended RT can improve failure-free survival (FFS), but has not been shown to improve overall survival. These are options for therapy.
[i] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[j] Imaging should be performed whenever there are clinical indications.
For surveillance imaging, see Discussion for consensus imaging recommendations.
[k] Consider possibility of histologic transformation in patients with progressive disease, especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, or there are new B symptoms. If clinical suspicion of transformation, FDG-PET may help identify areas suspicious for transformation. FDG-PET scan demonstrating marked heterogeneity or sites of intense FDG avidity may indicate transformation, and biopsy should be directed biopsy at the most FDG-avid area. Functional imaging does not replace biopsy to diagnose transformation. If transformation is histologically confirmed, treat with anthracycline-based therapy. See Management of Transformation (NODE-5).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[f] See Principles of Radiation Therapy (NHODG-D).
[i] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[j] Imaging should be performed whenever there are clinical indications. For surveillance imaging, see Discussion for consensus imaging recommendations.
[k] Consider possibility of histologic transformation in patients with progressive disease, especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, or there are new B symptoms. If clinical suspicion of transformation, FDG-PET may help identify areas suspicious for transformation. FDG-PET scan demonstrating marked heterogeneity or sites of intense FDG avidity may indicate transformation, and biopsy should be directed biopsy at the most FDG-avid area. Functional imaging does not replace biopsy to diagnose transformation. If transformation is histologically confirmed, treat with anthracycline-based therapy. See Management of Transformation (NODE-5).
[l] See GELF criteria (FOLL-A).

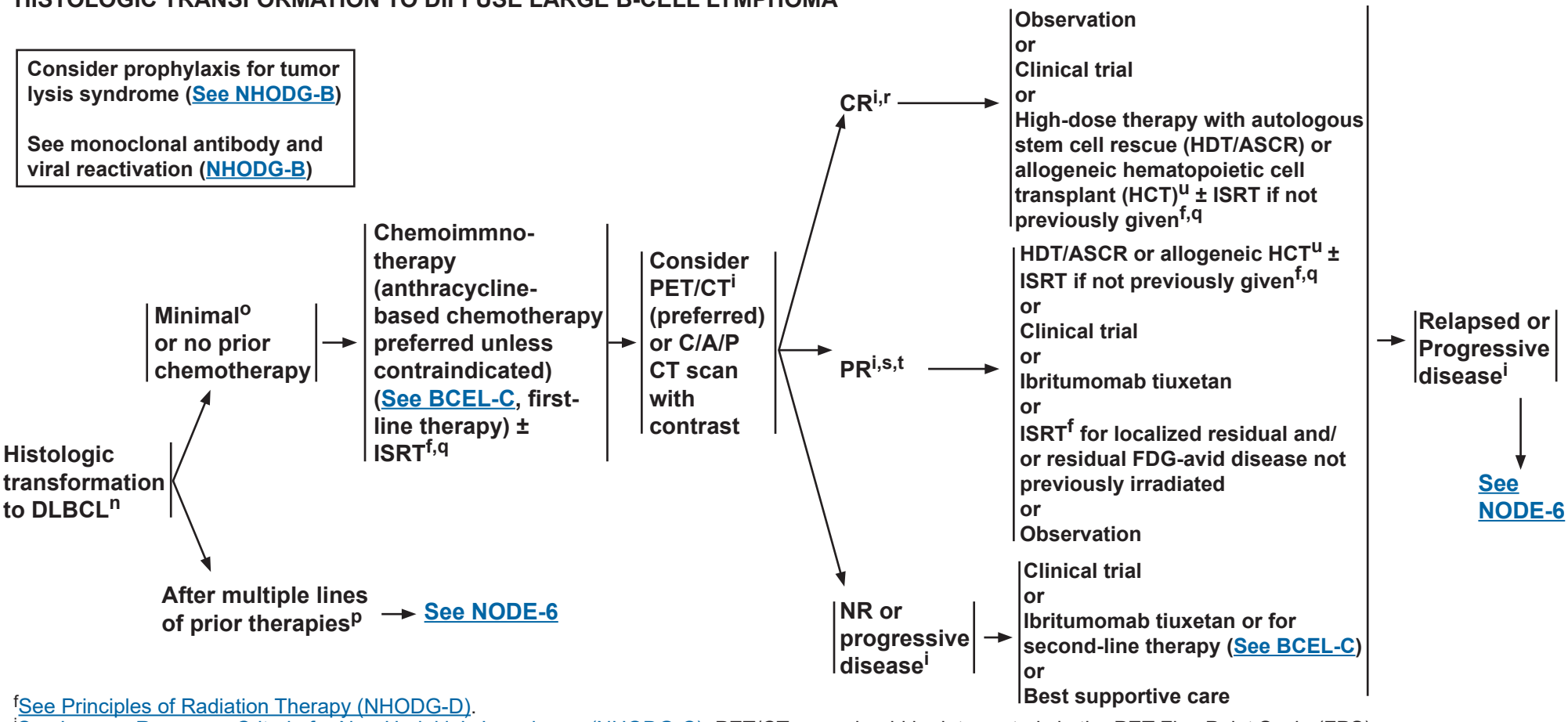
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[f] See Principles of Radiation Therapy (NHODG-D).
[i] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[j] Imaging should be performed whenever there are clinical indications. For surveillance imaging, see Discussion for consensus imaging recommendations.
[k] Consider possibility of histologic transformation in patients with progressive disease, especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, or there are new B symptoms. If clinical suspicion of transformation, FDG-PET may help identify areas suspicious for transformation. FDG-PET scan demonstrating marked heterogeneity or sites of intense FDG avidity may indicate transformation, and biopsy should be directed biopsy at the most FDG avid area. Functional imaging does not replace biopsy to diagnose transformation. If transformation is histologically confirmed, treat with anthracycline-based therapy. See Management of Transformation (NODE-5).
[l] See GELF criteria (FOLL-A).
[m] A PET-positive PR is associated with a shortened PFS (see Discussion); however, additional treatment at this juncture has not been shown to change outcome.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

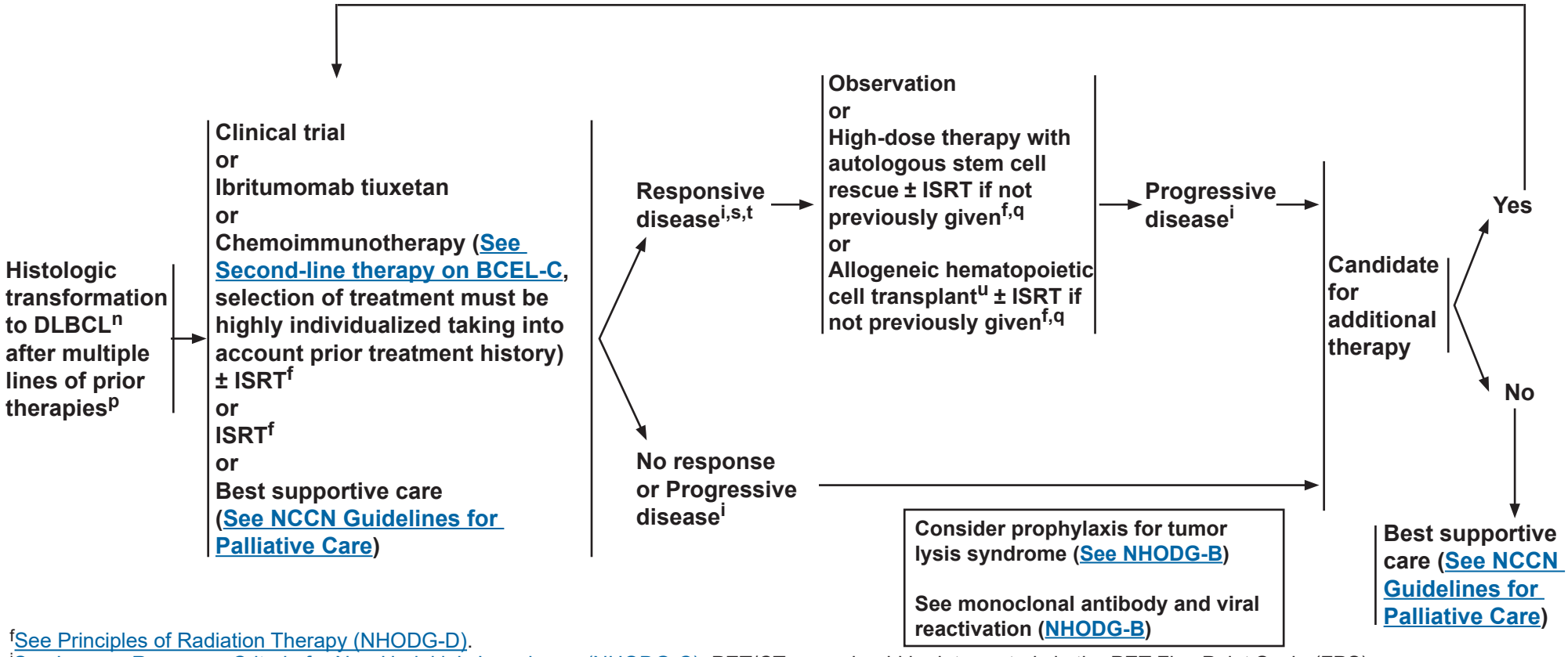
HISTOLOGIC TRANSFORMATION TO DIFFUSE LARGE B-CELL LYMPHOMA



[f] See Principles of Radiation Therapy (NHODG-D).
[i] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C). PET/CT scan should be interpreted via the PET Five Point Scale (FPS).
[n] For pathologic evaluation of histologic transformation, FISH for *BCL2* rearrangement [t(14;18)], and *MYC* rearrangements [t(8;14) or variants, t(8;22), t(2;8)].
[o] ISRT alone or one course of single-agent therapy including rituximab.
[p] This includes ≥2 of chemoimmunotherapy regimens for indolent or transformed disease. For example, prior treatment with BR and RCHOP.
[q] Consider ISRT for localized presentations, bulky disease, and/or limited osseous disease.
[r] If transformation is coexisting with extensive MZL, consider maintenance (see NODE-4, Optional Extended Therapy).
[s] If proceeding to an autologous stem cell rescue, consider additional systemic therapy ± ISRT to induce CR prior to transplant.
[t] Repeat biopsy should be strongly considered if PET-positive prior to additional therapy. If biopsy negative, follow CR pathway.
[u] Strongly recommend this treatment be given in the context of a clinical trial.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

HISTOLOGIC TRANSFORMATION TO DIFFUSE LARGE B-CELL LYMPHOMA[n]



[f]See Principles of Radiation Therapy (NHODG-D).
[i]See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C). PET/CT scan should be interpreted via the PET Five Point Scale (FPS).
[n]For pathologic evaluation of histologic transformation, FISH for *BCL2* rearrangement [t(14;18)], and *MYC* rearrangements [t(8;14) or variants, t(8;22), t(2;8)].
[p]This includes ≥2 of chemoimmunotherapy regimens for indolent or transformed disease. For example, prior treatment with BR and RCHOP.
[q]Consider ISRT for localized presentations, bulky disease, and/or limited osseous disease.
[s]If proceeding to an autologous stem cell rescue, consider additional systemic therapy ± ISRT to induce CR prior to transplant.
[t]Repeat biopsy should be strongly considered if PET-positive prior to additional therapy. If biopsy negative, follow CR pathway.
[u]Strongly recommend this treatment be given in the context of a clinical trial.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ADDITIONAL DIAGNOSTIC TESTING[a]

ESSENTIAL:

- **Adequate immunophenotyping to establish diagnosis[b,c]**
  - **IHC panel: CD20, CD3, CD5, CD10, BCL2, kappa/lambda, CD21 or CD23, cyclin D1, IgD, CD43, annexin A1; with or without**
  - **Cell surface marker analysis by flow cytometry (peripheral blood, bone marrow, or tissue): kappa/lambda, CD19, CD20, CD5, CD23, CD10, CD43, CD103**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **Molecular analysis to detect: antigen receptor gene rearrangements; *MYD88* mutation status to differentiate WM versus MZL if plasmacytic differentiation present; *BRAF* mutation status to differentiate MZL from HCL by IHC or sequencing; PCR for t(11;18)**
- **Karyotype or FISH: CLL panel; t(11;18), t(11;14), del(7q)**
- **FISH or PCR: t(14;18)**

→

WORKUP

ESSENTIAL:

- **Physical exam with performance status**
- **CBC with differential**
- **Comprehensive metabolic panel**
- **LDH**
- **Hepatitis B testing[d] if rituximab contemplated**
- **Hepatitis C testing**
- **C/A/P CT or other suspected sites with contrast of diagnostic quality and/or whole-body PET/CT scan**
- **Bone marrow biopsy ± aspirate**
- **SPEP and/or quantitative immunoglobulin levels**
- **Pregnancy testing in women of child-bearing age (if chemotherapy or RT planned)**

USEFUL IN SELECTED CASES:

- **Additional imaging as appropriate**
- **Discussion of fertility issues and sperm banking**
- **Immunofixation of blood (for elevated immunoglobulins or positive SPEP)**
- **Cryoglobulins**
- **Direct Coombs testing**

→ **See Management (SPLN-2)**

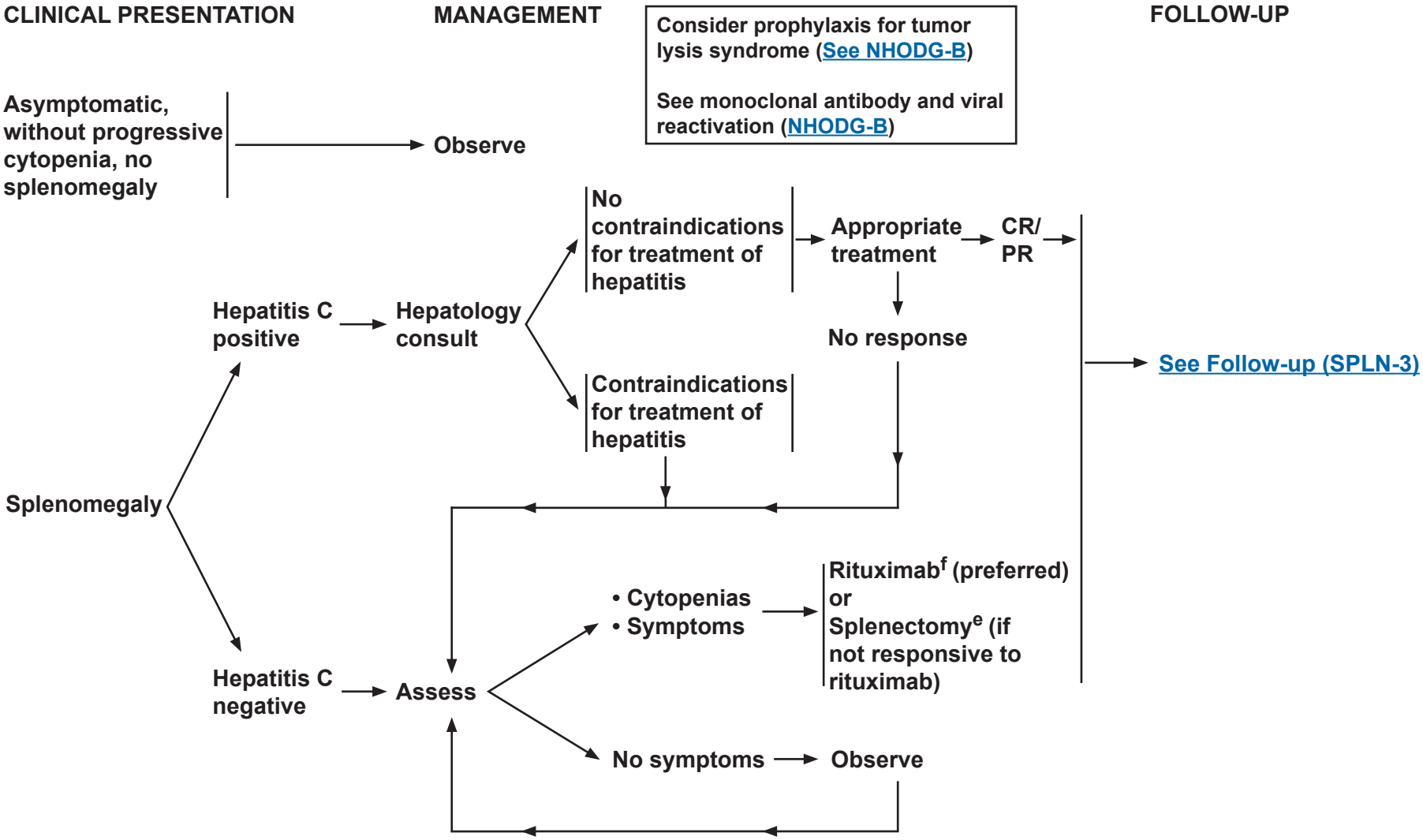
[a]SMZL is most definitively diagnosed at splenectomy, since the immunophenotype is nonspecific and morphologic features on the bone marrow may not be diagnostic. However, the diagnosis of SMZL may be made on the basis of bone marrow ± peripheral blood involvement by small lymphoid cells with immunoglobulin (Ig) light chain restriction that lack characteristic features of other small B-cell neoplasms (CD5, CD10, cyclin D1). Plasmacytoid differentiation with cytoplasmic Ig detectable on paraffin sections may occur. In such cases, the differential diagnosis may include lymphoplasmacytic lymphoma. With a characteristic intrasinusoidal lymphocytic infiltration of the bone marrow, the diagnosis can strongly be suggested on bone marrow biopsy alone, if the immunophenotype is consistent.

[b]Typical immunophenotype: CD10-, CD5-, CD20+, CD23-/+, CD43-/+ and cyclin D1-, BCL2- follicles, annexin A1, CD103- (distinction from hairy cell leukemia) with expression of both IgM and IgD.

[c]See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).

[d]Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

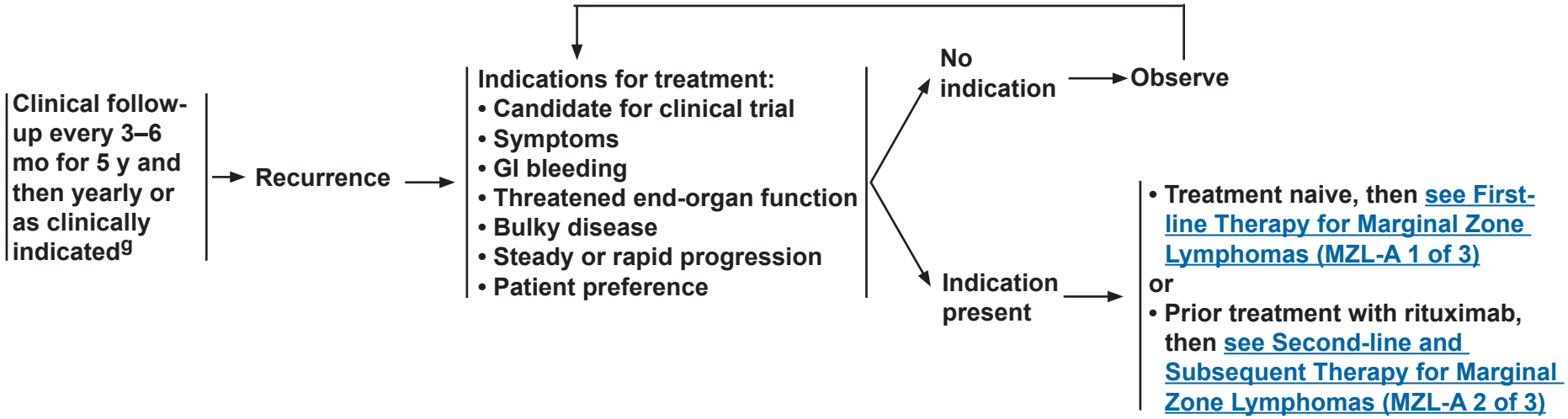


[e]Pneumococcal, meningococcal, and hepatitis B vaccinations should be given at least 2 weeks before splenectomy.

[f]Tsimberidou AM, Catovsky D, Schlette E, et al. Outcomes in patients with splenic marginal zone lymphoma and marginal zone lymphoma treated with rituximab with or without chemotherapy or chemotherapy alone. Cancer 2006;107:125-135.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

FOLLOW-UP



[g]Follow-up includes diagnostic tests and imaging using the same modalities performed during workup as clinically indicated.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS[a,b,c]

First-line Therapy

- **Preferred regimens (in alphabetical order)**
  - **Bendamustine + rituximab**
  - **RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)**
  - **RCVP (rituximab, cyclophosphamide, vincristine, prednisone)**
  - **Rituximab (375 mg/m^2 weekly for 4 doses) (preferred for SMZL)**
- **Other recommended regimens (in alphabetical order)**
  - **Ibritumomab tiuxetan[d,e] (category 2B)**
  - **Lenalidomide + rituximab (category 2B)**

First-line Therapy for Elderly or Infirm (if none of the above is expected to be tolerable in the opinion of treating physician)

- **Rituximab (preferred) (375 mg/m^2 weekly for 4 doses)**
- **Chlorambucil + rituximab**
- **Cyclophosphamide + rituximab**
- **Chlorambucil**
- **Cyclophosphamide**

First-line Extended Therapy (optional)

- **If initially treated with single-agent rituximab, consolidation with rituximab 375 mg/m^2 one dose every 12 weeks**

See Second-line and Subsequent Therapy on MZL-A 2 of 3

For patients with locally bulky or locally symptomatic disease, consider ISRT 4–24 Gy ± additional systemic therapy.

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

[a]See references for regimens MZL-A 3 of 3.
[b]The choice of initial therapy requires consideration of many factors, including age, comorbidities, and future treatment possibilities (eg, HDT with SCR). Therefore, treatment selection is highly individualized.
[c]Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.
[d]Selection of patients requires adequate marrow cellularity >15% and <25% involvement of lymphoma in bone marrow, and platelets >100,000. In patients with prior autologous stem cell rescue, referral to a tertiary care center is highly recommended for ibritumomab tiuxetan.
[e]If ibritumomab tiuxetan is considered, bilateral cores are recommended and the pathologist should provide the percent of overall cellular elements and the percent of cellular elements involved in the marrow. Karyotype ± FISH for known MDS markers. As of 2010, updates suggest a trend towards an increased risk of MDS with RIT.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS[a,b,c]
(in preference order)

Second-line and Subsequent Therapy
- Bendamustine + rituximab
- RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)
- RCVP (rituximab, cyclophosphamide, vincristine, prednisone)
- Rituximab
- Ibrutinib[f]
- Lenalidomide ± rituximab
- Bendamustine + obinutuzumab
- Idelalisib[f] (refractory to both alkylator and rituximab)
- Ibritumomab tiuxetan[d,e] (category 2B)

Second-line and Subsequent Therapy for Elderly or Infirm (if none of the above is expected to be tolerable in the opinion of treating physician)
- Rituximab (preferred) (375 mg/m^2 weekly for 4 doses)
- Chlorambucil + rituximab
- Cyclophosphamide + rituximab
- Chlorambucil
- Cyclophosphamide

Second-line Consolidation or Extended Dosing (optional)
- If treated with bendamustine + obinutuzumab for recurrent disease then obinutuzumab maintenance for rituximab-refractory disease (1 g every 8 wks for total of 12 doses)
- High-dose therapy with autologous stem cell rescue
- Allogeneic hematopoietic cell transplant for highly selected patients

For patients with locally bulky or locally symptomatic disease, consider ISRT 4–24 Gy ± additional systemic therapy.

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

[a]See references for regimens MZL-A 3 of 3.
[b]The choice of initial therapy requires consideration of many factors, including age, comorbidities, and future treatment possibilities (eg, HDT with SCR). Therefore, treatment selection is highly individualized.
[c]Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.
[d]Selection of patients requires adequate marrow cellularity >15% and <25% involvement of lymphoma in bone marrow, and platelets >100,000. In patients with prior autologous stem cell rescue, referral to a tertiary care center is highly recommended for ibritumomab tiuxetan.
[e]If ibritumomab tiuxetan is considered, bilateral cores are recommended and the pathologist should provide the percent of overall cellular elements and the percent of cellular elements involved in the marrow. Karyotype ± FISH for known MDS markers. As of 2010, updates suggest a trend towards an increased risk of MDS with RIT.
[f]See Special Considerations for the Use of Small-Molecule Inhibitors (NHODG-E).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS

References

First-line Therapy

Chlorambucil ± rituximab

Zucca E, Conconi A, Martinelli G, et al. Final results of the IELSG-19 randomized trial of mucosa-associated lymphoid tissue lymphoma: Improved event-free and progression-free survival with rituximab plus chlorambucil versus either chlorambucil or rituximab monotherapy. J Clin Oncol 2018;35:1905-1912.

RCHOP/RCVP/BR

Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet 2013;381:1203-1210.

Flinn IW, van der Jagt R, Kahl BS, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood 2014;123:2944-2952.

Salar A, Domingo-Domenech E, Panizo C, et al. First-line response-adapted treatment with the combination of bendamustine and rituximab in patients with mucosa-associated lymphoid tissue lymphoma (MALT2008-01): a multicentre, single-arm, phase 2 trial. Lancet Haematol 2014;1:e104-111.

Ibritumomab tiuxetan

Lossos IS, Fabregas JC, Koru-Sengul T, et al. Phase II study of (90)Y Ibritumomab tiuxetan in patients with previously untreated marginal zone lymphoma. Leuk Lymphoma 2015;56:1750-1755.

Lenalidomide + rituximab

Fowler NH, Davis RE, Rawal S, et al. Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: an open-label, phase 2 trial. Lancet Oncol 2014;15:1311-1318.

Rituximab (preferred for SMZL)

Tsimberidou AM, Catovsky D, Schlette E, et al. Outcomes in patients with splenic marginal zone lymphoma and marginal zone lymphoma treated with rituximab with or without chemotherapy or chemotherapy alone. Cancer 2006;107:125-135.

Else M, Marin-Niebla A, de la Cruz F, et al. Rituximab, used alone or in combination, is superior to other treatment modalities in splenic marginal zone lymphoma. Br J Haematol 2012;159:322-328.

Kalpadakis C, Pangalis GA, Angelopoulou MK, et al. Treatment of splenic marginal zone lymphoma with rituximab monotherapy: progress report and comparison with splenectomy. Oncologist 2013;18:190-197.

First-line Extended Therapy (optional)

Extended dosing with rituximab

Williams ME, Hong F, Gascoyne RD, et al. Rituximab extended schedule or retreatment trial for low tumour burden non-follicular indolent B-cell non-Hodgkin lymphomas: Eastern Cooperative Oncology Group Protocol E4402. Br J Haematol 2016;173:867-875.

Second-line and Subsequent Therapy

Bendamustine + obinutuzumab

Sehn LH, Chua N, Mayer J, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. Lancet Oncol 2018;17:1081-1093.

Ibritumomab tiuxetan

Vanazzi A, Grana C, Crosta C, et al. Efficacy of (9)(0)Yttrium-ibritumomab tiuxetan in relapsed/refractory extranodal marginal-zone lymphoma. Hematol Oncol 2014;32:10-15.

Ibrutinib

Noy A, de Vos S, Thieblemont C, et al. Targeting Bruton tyrosine kinase with ibrutinib in relapsed/refractory marginal zone lymphoma. Blood 2018;129:2224-2232.

Idelalisib

Gopal A, Kahl B, De Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med 2014;370:1008-1018.

Lenalidomide + rituximab

Witzig TE, Wiernik PH, Moore T, et al. Lenalidomide oral monotherapy produces durable responses in relapsed or refractory indolent non-Hodgkin's Lymphoma. J Clin Oncol 2009;27:5404-5409.

Sacchi S, Marcheselli R, Bari A, et al. Safety and efficacy of lenalidomide in combination with rituximab in recurrent indolent non-follicular lymphoma: final results of a phase II study conducted by the Fondazione Italiana Linfomi. Haematologica 2016;101:e196.

Second-line Consolidation or Extended Dosing (optional)

Obinutuzumab maintenance for rituximab refractory disease

Sehn LH, Chua N, Mayer J, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. Lancet Oncol 2018;17:1081-1093.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ADDITIONAL DIAGNOSTIC TESTING

ESSENTIAL:

- **Adequate immunophenotyping to establish diagnosis[a,b]**
  - **IHC panel: CD20, CD3, CD5, cyclin D1, CD10, CD21, CD23, BCL2, BCL6, Ki-67[c] with or without**
  - **Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **IHC: LEF1 may help distinguish from variant CLL; *SOX11* or I*GHV* sequencing may be useful for determination of clinically indolent[d] MCL; may also help in diagnosis of CCND1- MCL.**
- **Karyotype or FISH: t(11;14), t(14;18), CLL panel**
- **Cell surface marker analysis by flow cytometry: CD200**

WORKUP

ESSENTIAL:

- **Physical exam: Attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen**
- **Performance status**
- **B symptoms**
- **CBC with differential**
- **Comprehensive metabolic panel**
- **LDH**
- **Bone marrow biopsy ± aspirate**
- **C/A/P CT with contrast of diagnostic quality and/or whole-body PET/CT scan**
- **Hepatitis B testing[e] if rituximab contemplated**
- **Echocardiogram or MUGA scan if anthracycline or anthracenedione-based regimen is indicated**
- **Pregnancy testing in women of child-bearing age (if chemotherapy or RT planned)**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **Endoscopy/colonoscopy[f]**
- **Neck CT with contrast**
- **Uric acid**
- **Discussion of fertility issues and sperm banking**
- **Lumbar puncture (for blastic variant or CNS symptoms)**
- **Beta-2-microglobulin**
- **Hepatitis C testing**

See Stage I, II Induction Therapy (MANT-2)

See Stage II bulky, III, IV Induction Therapy (MANT-3)

[a]Typical immunophenotype: CD5+, CD20+, CD43+, CD23-/+, cyclin D1+, CD10-/+. Note: Some cases of MCL may be CD5- or CD23+. If the diagnosis is suspected, cyclin D1 staining or FISH for t(11;14) should be done. There are rare cases of *CCND1*- MCL (<5%) with an otherwise typical immunophenotype.

[b]See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).

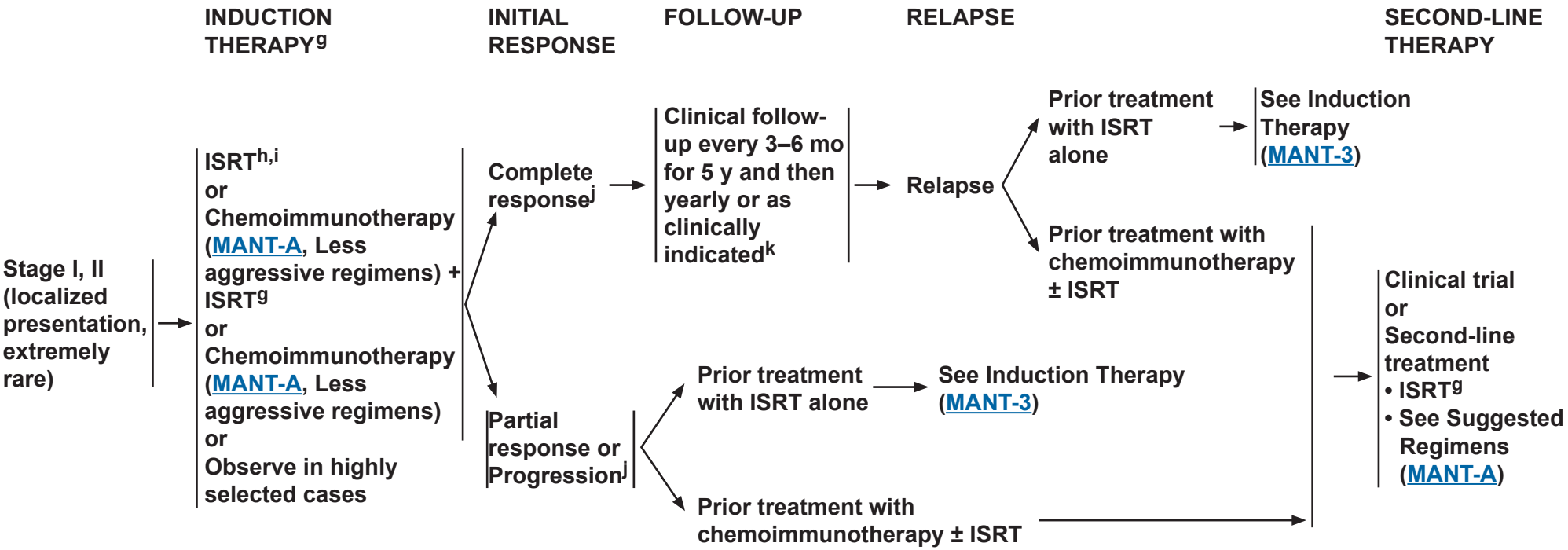
[c]Ki-67 proliferation fraction of <30% in lymph nodes is associated with a more favorable prognosis.

[d]Most common biomarker for indolent disease: SOX11- [IGHV mutated]. Typical clinical presentation: leukemic non-nodal CLL-like with splenomegaly, low tumor burden, Ki-67 proliferation fraction <10%.

[e]Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

[f]Essential for confirmation of stage I-II disease. See Discussion for details.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

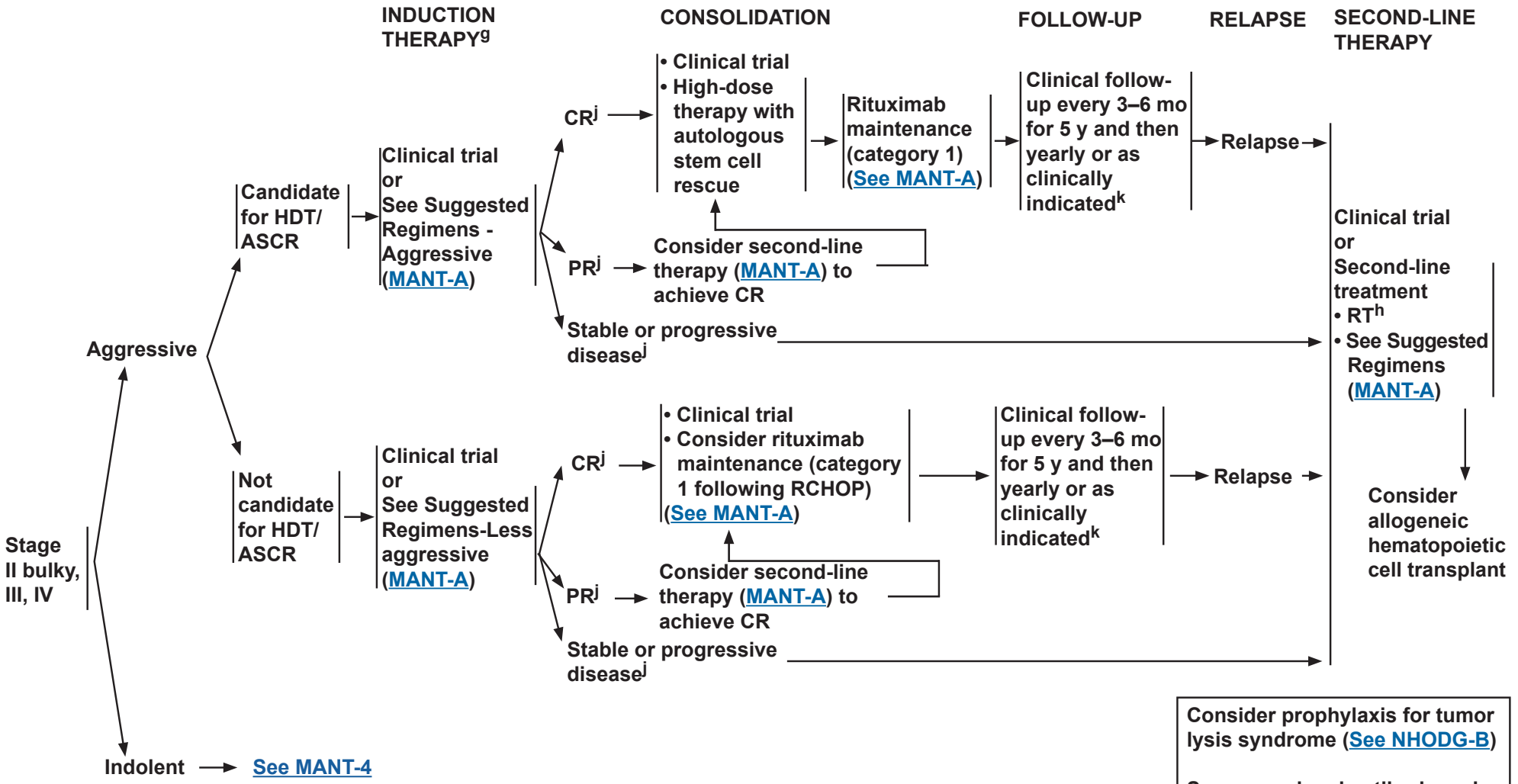


Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

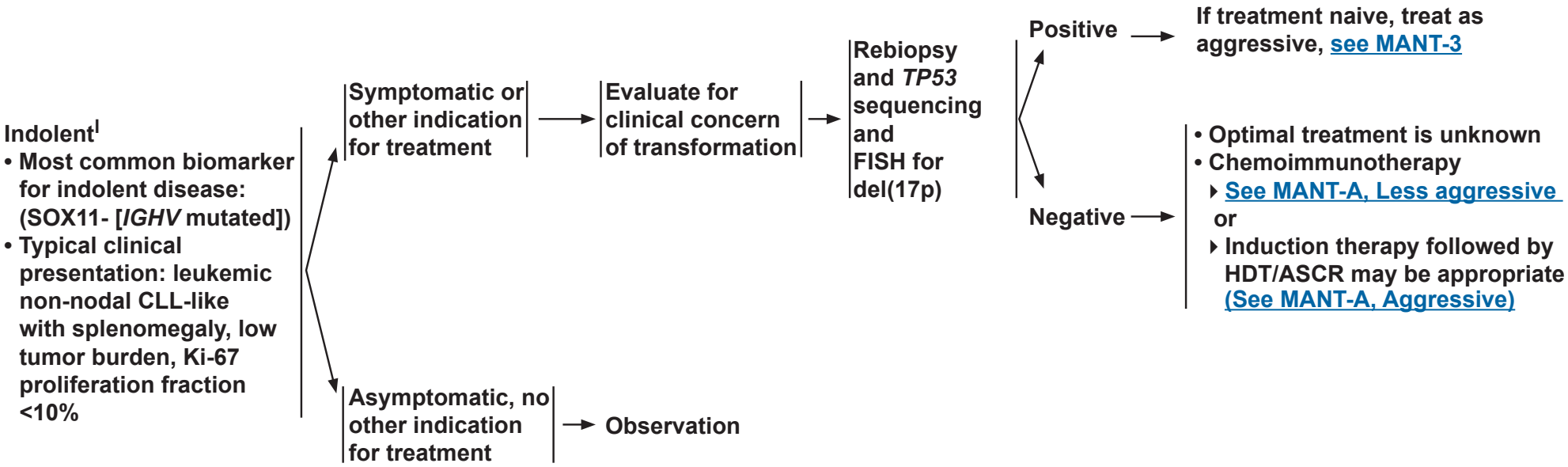
[g]Early referral for high-dose therapy with stem cell rescue is advisable for planning purposes.
[h]See Principles of Radiation Therapy (NHODG-D).
[i]Leitch HA, Gascoyne RD, Chhanabhai M, et al. Limited-stage mantle-cell lymphoma. Ann Oncol 2003;14:1555-1561.
[j]See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[k]Follow-up includes diagnostic tests and imaging using the same modalities performed during workup as clinically indicated.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[g]Early referral for high-dose therapy with stem cell rescue is advisable for planning purposes.
[h]See Principles of Radiation Therapy (NHODG-D).
[j]See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[k]Follow-up includes diagnostic tests and imaging using the same modalities performed during workup as clinically indicated.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

[l]The description represents the most common indolent presentation; however, there are some patients with GI or blood/bone marrow involvement only, which may express SOX11 and have an indolent course.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS[a,b]
(in preference order)

Induction Therapy

- **Aggressive therapy**
  - **Preferred regimens**
    - ◊ **RDHAP or RDHAX (rituximab, dexamethasone, cytarabine, cisplatin/oxaliplatin)**
    - ◊ **Alternating RCHOP/RDHAP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)/(rituximab, dexamethasone, cytarabine, cisplatin)**
    - ◊ **NORDIC regimen (dose-intensified induction immunochemotherapy with rituximab + cyclophosphamide, vincristine, doxorubicin, prednisone [maxi-CHOP]) alternating with rituximab + high-dose cytarabine)**
    - ◊ **HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab[c] (NOTE: There are conflicting data regarding the need for consolidation with HDT/ASCR.)**
  - **Other recommended regimen**
    - ◊ **Bendamustine + rituximab (category 2B)**
- **Less aggressive therapy**
  - **Preferred**
    - ◊ **Bendamustine + rituximab**
    - ◊ **VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone)**
    - ◊ **RCHOP[d]**
    - ◊ **Lenalidomide + rituximab**
    - ◊ **Modified rituximab-HyperCVAD in patients older than 65 y**
  - **Other recommended regimen**
    - ◊ **RBAC (rituximab, bendamustine, cytarabine) (category 2B)**

Consolidation After Aggressive Therapy

- **High-dose therapy followed by autologous stem cell rescue**

Maintenance After HDT/ASCR

- **Maintenance rituximab every 8 weeks x 3 y (category 1)**

Maintenance After Less Aggressive Therapy

- **Rituximab every 8 weeks until progression or intolerance (category 1 for RCHOP; 5 y for modified rituximab-HyperCVAD)**
  - **NOT appropriate after BR**
  - **Untested after VR-CAP, RBAC**

See Second-line Therapy on MANT-A 2 of 4.

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

[a]See references for regimens MANT-A 3 of 4 and MANT-A 4 of 4.
[b]Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.
[c]Rituximab + ibrutinib can be used as a pre-treatment to limit the number of cycles of RHyperCVAD/rituximab maintenance.
[d]There is a randomized trial that demonstrated that RCHOP was not superior to CHOP.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS[a,b]
(in preference order)

Second-line Therapy

- **Short response duration to prior chemoimmunotherapy (< expected median PFS)**
  - **Preferred regimens**
    - ◊ **Acalabrutinib[e,f]**
    - ◊ **Ibrutinib[e] ± rituximab**
    - ◊ **Lenalidomide ± rituximab**
    - ◊ **Venetoclax**
  - **Other recommended regimen**
    - ◊ **Ibrutinib, lenalidomide, rituximab (category 2B)**

- **Extended response duration to prior chemoimmunotherapy (> expected median PFS)**
  - **Preferred regimens**
    - ◊ **Bendamustine ± rituximab (if not previously given)**
    - ◊ **Bortezomib ± rituximab**
  - **Other recommended regimens**
    - ◊ **Small molecule inhibitors as above**
    - ◊ **RCHOP (if not previously given) (category 2B)**
    - ◊ **VRCAP (if not previously given) (category 2B)**
    - ◊ **Bendamustine, bortezomib, and rituximab (category 2B)**
    - ◊ **PEPC (prednisone, etoposide, procarbazine, cyclophosphamide) ± rituximab (category 3)**
    - ◊ **See Second-line Therapy for DLBCL (BCEL-C 2 of 4) without regard to transplantability**

Second-line Consolidation

- **Allogeneic hematopoietic cell transplant (nonmyeloablative or myeloablative)**

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

[a]See references for regimens MANT-A 3 of 4 and MANT-A 4 of 4.
[b]Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.

[e]See Special Considerations for Use of Small-Molecule Inhibitors (NHODG-E).
[f]The phase 2 ACE-LY-004 study excluded patients treated with Bruton's tyrosine kinase (BTK) or BCL-2 inhibitor and concomitant warfarin or equivalent vitamin K antagonists.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS

References

Induction Therapy

Aggressive therapy

HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with methotrexate and cytarabine) + rituximab

Romaguera JE, Fayad L, Rodriguez MA, et al. High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. J Clin Oncol 2005;23:7013-7023.

Merli F, Luminari S, Ilariucci F, et al. Rituximab plus HyperCVAD alternating with high dose cytarabine and methotrexate for the initial treatment of patients with mantle cell lymphoma, a multicentre trial from Gruppo Italiano Studio Linfomi. Br J Haematol 2012;156:346-353.

Nordic trial regimen (Dose-intensified induction immunochemotherapy with rituximab + cyclophosphamide, vincristine, doxorubicin, prednisone [maxi-CHOP] alternating with rituximab + high-dose cytarabine)

Geisler CH, Kolstad A, Laurell A, et al. Long-term progression-free survival of mantle cell lymphoma following intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: A non-randomized phase-II multicenter study by the Nordic Lymphoma Group. Blood 2008;112:2687-2693.

RCHOP/RDHAP

Pott C, Hoster E, Beldjord K, et al. R-CHOP/R-DHAP compared to R-CHOP induction followed by high dose therapy with autologous stem cell transplantation induces higher rates of molecular remission in MCL: Results of the MCL Younger Intergroup Trial of the European MCL Network [abstract]. Blood 2010;116:Abstract 965.

Delarue R, Haioun C, Ribrag V, et al. CHOP and DHAP plus rituximab followed by autologous stem cell transplantation (ASCT) in mantle cell lymphoma (MCL): a phase II study from the GELA. Blood 2013;121:48-53.

RDHAP (rituximab, dexamethasone, cisplatin [oxaliplatin or carboplatin], cytarabine)

Le Gouill S, Thieblemont C, Oberic L, et al. Rituximab after autologous stem-cell transplantation in mantle-cell lymphoma. N Engl J Med 2018;377:1250-1260.

Le Gouill S, Thieblemont C, Oberic L, et al. R-DHA-Oxaliplatin before autologous stem cell transplantation prolongs PFS and OS as compared to R-DHA-carboplatin and R-DHA-cisplatin in patients with mantle cell lymphoma, a subgroup analysis of the LyMa trial [abstract]. Blood 2018;130 (Suppl 1):Abstract 1496.

Less aggressive therapy

Bendamustine + rituximab

Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet 2013;381:1203-1210.

Flinn IW, van der Jagt R, Kahl BS, et al. Open-label, randomized, noninferiority study of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of advanced indolent NHL or MCL: the BRIGHT study. Blood 2014;123:2944-2952.

Bendamustine + rituximab + maintenance rituximab

Rummel, MJ, Balser, Kaiser, U et al. Bendamustine plus rituximab versus fludarabine plus rituximab in patients with relapsed follicular, indolent, or mantle cell lymphomas – 8-year follow-up results of the randomized phase III study NHL 2-2003 on behalf of the StiL (Study Group Indolent Lymphomas, Germany) [abstract]. Blood 2014;124:Abstract 145.

VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone)

Robak T, Huang H, Jin J, et al. Bortezomib-based therapy for newly diagnosed mantle-cell lymphoma. N Engl J Med 2015;372:944-953.

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab

Lenz G, Dreyling M, Hoster E, et al. Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). J Clin Oncol 2005;23:1984-1992.

Kluin-Nelemans HC, Hoster E, Hermine O, et al. Treatment of older patients with mantle-cell lymphoma. N Eng J Med 2012;367:520-531.

Modified HyperCVAD with rituximab maintenance

Kahl BS, Long WL, Eickhoff JC, et al. Maintenance rituximab following induction chemoimmunotherapy may prolong progression-free survival in mantle cell lymphoma: A pilot study from the Wisconsin Oncology Network. Ann Oncol 2006;17:1418-1423.

Lenalidomide + rituximab

Ruan J, Martin P, Shah B, et al. Lenalidomide plus rituximab as initial treatment for mantle-cell lymphoma. N Engl J Med 2015;373:1835-44.

Ruan J, Martin P, Christos PJ, et al. Initial treatment with lenalidomide plus rituximab for mantle cell lymphoma: 5-year follow-up and correlative analysis from a multi-center phase II study [abstract]. Blood 2018;130 (Suppl 1):Abstract 154.

Ibrutinib + rituximab

Wang M, Lee HJ, Thirumurthi S, et al. Chemotherapy-Free Induction with Ibrutinib-Rituximab Followed By Shortened Cycles of Chemo-Immunotherapy Consolidation in Young, Newly Diagnosed Mantle Cell Lymphoma Patients: A Phase II Clinical Trial [abstract]. Blood 2018;128: Abstract 147.

RBAC (rituximab, bendamustine, cytarabine)

Visco C, Finotto S, Zambello R, et al. Combination of rituximab, bendamustine, and cytarabine for patients with mantle-cell non-Hodgkin lymphoma ineligible for intensive regimens or autologous transplantation. J Clin Oncol 2013;31:1442-1449.

Continued

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS
References

First-line Consolidation

High-dose therapy with autologous stem cell rescue

Dreyling M, Lenz G, Hoster E, et al. Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle cell lymphoma: results of a prospective randomized trial of the European MCL Network. Blood 2005;105:2677-2684.

Thieblemont C, Antal D, Lacotte-Thierry L, et al. Chemotherapy with rituximab followed by high-dose therapy and autologous stem cell transplantation in patients with mantle cell lymphoma. Cancer 2005;104:1434-1441.

Ritchie D, Seymour J, Grigg A, et al. The hyper-CVAD–rituximab chemotherapy programme followed by high-dose busulfan, melphalan and autologous stem cell transplantation produces excellent event-free survival in patients with previously untreated mantle cell lymphoma. Ann Hematol 2007;86:101-105.

van 't Veer MB, de Jong D, MacKenzie M, et al. High-dose Ara-C and beam with autograft rescue in R-CHOP responsive mantle cell lymphoma patients. Br J Haematol 2009;144:524-530.

Rituximab maintenance

Kluin-Nelemans HC, Hoster E, Hermine O, et al. Treatment of older patients with mantle-cell lymphoma. N Engl J Med 2012;367:520-531.

Graf S, Stevenson P, Holmberg LA, et al. Maintenance rituximab after autologous stem cell transplantation in patients with mantle cell lymphoma. Ann Oncol 2015;26:2323-2328.

Le Gouill S, Thieblemont C, Oberic L, et al. Rituximab after autologous stem-cell transplantation in mantle-cell lymphoma. N Engl J Med 2018;377:1250-1260.

Hoster E, Kluin-Nelemans H, Hermine O, et al. Rituximab maintenance after first-line immunochemotherapy in mantle cell lymphoma: Long-term follow-up of the randomized European MCL Elderly Trial. Blood 2018;130 (Suppl 1):Abstract 153.

Second-line Therapy

Acalabrutinib

Wang M, Rule S, Zinzani P, et al. Efficacy and safety of acalabrutinib monotherapy in patients with relapsed/refractory mantle cell lymphoma in the phase 2 ACE-LY-004 study. 2018 ASH Meeting Abstracts: Abstract 155.

Bendamustine

Robinson KS, Williams ME, van der Jagt RH, et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell Non-Hodgkin's Lymphoma. J Clin Oncol 2008; 26:4473-4479.

Rummel MJ, Al-Batran SE, Kim S-Z, et al. Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-hodgkin's lymphoma. J Clin Oncol 2005;23:3383-3389.

Bendamustine, bortezomib, and rituximab

Friedberg JW, Vose JM, Kelly JL, et al. The combination of bendamustine, bortezomib, and rituximab for patients with relapsed/refractory indolent and mantle cell non-Hodgkin lymphoma. Blood 2011;117:2807-2812.

Bortezomib

Goy A, Bernstein SH, Kahl BS, et al. Bortezomib in patients with relapsed or refractory mantle cell lymphoma: updated time-to-event analyses of the multicenter phase 2 PINNACLE study. Ann Oncol 2009;20:520-525.

Baiocchi RA, Alinari L, Lustberg ME, et al. Phase 2 trial of rituximab and bortezomib in patients with relapsed or refractory mantle cell and follicular lymphoma. Cancer 2011;117:2442-2451.

Ibrutinib

Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Eng J Med 2013;369:507-516.

Wang ML, Blum KA, Martin P, et al. Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results. Blood 2015;126:739-745.

Dreyling M, Jurczak W, Jerkeman M, et al. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. Lancet 2018;387:770-778.

Ibrutinib, lenalidomide, rituximab

Jerkeman M, Hutchings M, Räty R, et al. Ibrutinib-Lenalidomide-Rituximab in Patients with Relapsed/Refractory Mantle Cell Lymphoma: First Results from the Nordic Lymphoma Group MCL6 (PHILEMON) Phase II Trial [abstract]. Blood 2018;128:Abstract 148.

Lenalidomide

Habermann TM, Lossos IS, Justice G, et al. Lenalidomide oral monotherapy produces a high response rate in patients with relapsed or refractory mantle cell lymphoma. Br J Haematol 2009;145:344-349.

Witzig TE, Vose JM, Zinzani PL, et al. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. Ann Oncol 2011;22:1622-1627.

Goy A, Sinha R, Williams ME, et al. Single-agent lenalidomide in patients with mantle-cell lymphoma who relapsed or progressed after or were refractory to bortezomib: phase II MCL-001 (EMERGE) study. J Clin Oncol 2013;31:3688-3695.

Lenalidomide + rituximab

Wang M, Fayad L, Wagner-Bartak N, et al. Lenalidomide in combination with rituximab for patients with relapsed or refractory mantle-cell lymphoma: a phase 1/2 clinical trial. Lancet Oncol 2012;13:716-723.

PEP-C (prednisone, etoposide, procarbazine, cyclophosphamide) ± rituximab

Coleman M, Martin P, Ruan J, et al. Prednisone, etoposide, procarbazine, and cyclophosphamide (PEP-C) oral combination chemotherapy regimen for recurring/refractory lymphoma: low-dose metronomic, multidrug therapy. Cancer 2008;112:2228-2232.

Venetoclax

Davids MS, Roberts AW, Seymour JF, et al. Phase I first-in-human study of venetoclax in patients with relapsed or refractory non-Hodgkin lymphoma. J Clin Oncol 2018;35:826-833.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ADDITIONAL DIAGNOSTIC TESTING[a]

ESSENTIAL:

- Adequate immunophenotyping to establish diagnosis and GCB versus non-GCB origin[b,c]
  - IHC panel: CD20, CD3, CD5, CD10, CD45, BCL2, BCL6, Ki-67, IRF4/MUM1, MYC with or without
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD3, CD5, CD19, CD10, CD20

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Additional immunohistochemical studies to establish lymphoma subtype
  - IHC panel: cyclin D1, kappa/lambda, CD30, CD138, Epstein-Barr virus in situ hybridization (EBER-ISH), ALK, HHV8, SOX11
- Karyotype or FISH: *MYC, BCL2, BCL6* rearrangements[d]

→

SUBTYPES

- Subtypes included:
  - DLBCL, NOS[e,f]
  - DLBCL coexistent with follicular lymphoma of any grade
  - DLBCL coexistent with gastric MALT lymphoma
  - DLBCL coexistent with nongastric MALT lymphoma
  - Follicular lymphoma grade 3[g]
  - Intravascular large B-cell lymphoma
  - DLBCL associated with chronic inflammation
  - ALK-positive DLBCL[h]
  - EBV-positive DLBCL, NOS
  - T-cell-/histiocyte-rich large B-cell lymphoma
  - DLBCL with *IRF4/MUM1* rearrangement

→ See Workup (BCEL-2)

- Subtypes *not* included:
  - Primary cutaneous B-cell lymphomas (See NCCN Guidelines for Primary Cutaneous B-Cell Lymphomas)
  - Primary DLBCL of the CNS (See NCCN Guidelines for CNS)

Primary Mediastinal Large B-Cell Lymphoma (PMBL), see BCEL-B 1 of 3.
Grey Zone Lymphoma, see BCEL-B 2 of 3.
High-Grade B-Cell Lymphomas with Translocations of *MYC* and *BCL2* and/or *BCL6* (Double/Triple Hit Lymphoma), see HGBL-1.
Primary Cutaneous B-cell Lymphomas, Leg type, see BCEL-B 3 of 3.

[a] See International Prognostic Index (BCEL-A).
[b] Typical immunophenotype: CD20+, CD45+, CD3-; other markers used for subclassification.
[c] See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).
[d] Cases with double expression of MYC and either BCL2 or BCL6 by IHC having a GCB-like immunophenotype should undergo FISH testing for *MYC, BCL2,* and *BCL6* rearrangement.
[e] Germinal center (or follicle center) phenotype is not equivalent to follicular lymphoma and can occur in DLBCL and Burkitt lymphoma. Morphology is required to establish diagnosis.
[f] In the 2018 WHO revision of lymphoma, DLBCL, double hit has been designated in a unique category called high-grade B-cell lymphomas with translocations of *MYC* and *BCL2* and/or *BCL6*.
[g] Controversy exists regarding management of FL grade 3. Some may treat FL grade 3a as follicular lymphoma and others may treat it as DLBCL.
[h] These are most often CD20 negative and rituximab is not necessary.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

WORKUP

ESSENTIAL:

- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC with differential
- LDH
- Comprehensive metabolic panel
- Uric acid
- Whole-body PET/CT scan ± C/A/P CT with contrast of diagnostic quality
- Adequate bone marrow biopsy (>1.6 cm) ± aspirate; bone marrow may not be needed if PET/CT scan negative unless finding of another lymphoma subtype is important for treatment decision
- Calculation of International Prognostic Index (IPI) (See BCEL-A 1 of 2)
- Hepatitis B testing[i]
- Echocardiogram or MUGA scan if anthracycline or anthracenedione-based regimen is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy or RT planned)

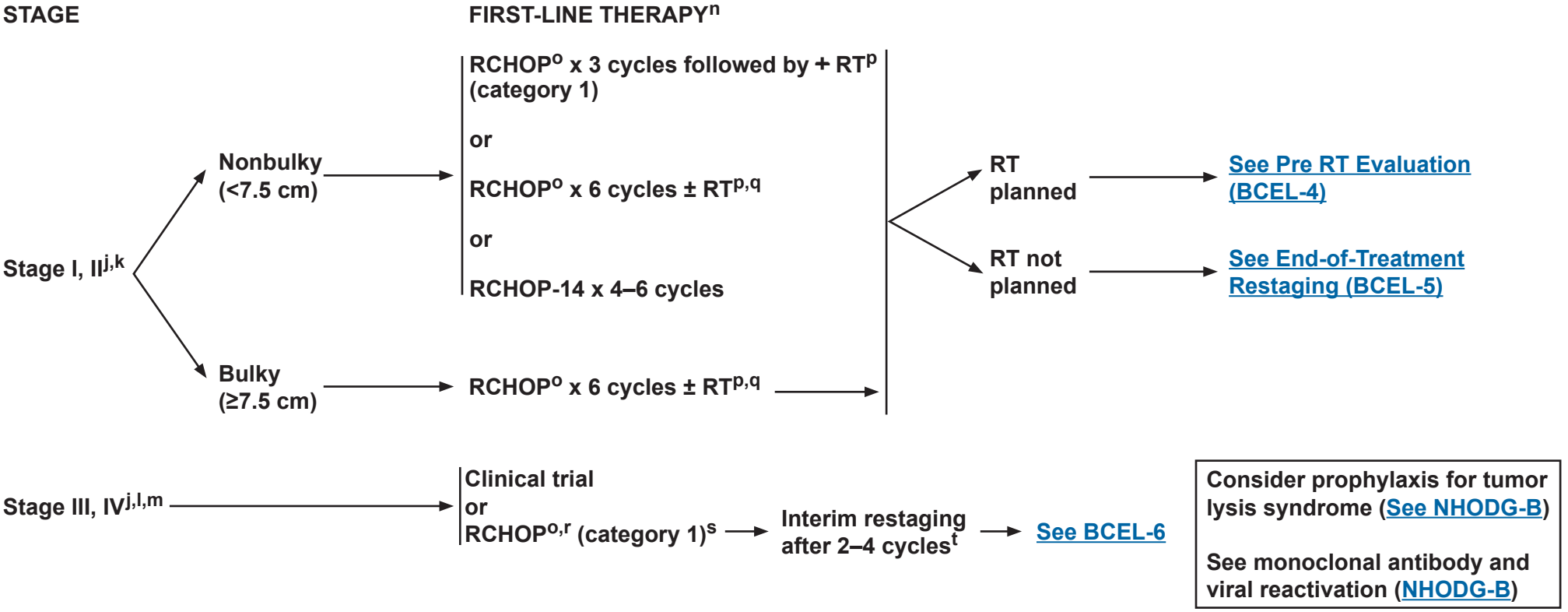
USEFUL IN SELECTED CASES:

- Head CT/MRI with contrast or Neck CT/MRI with contrast
- Discussion of fertility issues and sperm banking
- HIV testing
- Hepatitis C testing
- Beta-2-microglobulin
- Lumbar puncture, consider if have 4–6 factors according to prognostic model (See BCEL-A 2 of 2), HIV lymphoma, testicular, double expressor lymphoma (MYC ≥40% and BCL2 ≥50%)

→ See Induction Therapy (BCEL-3)

[i]Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[j]In testicular lymphoma, after completion of chemotherapy, scrotal RT should be given (25–30 Gy).

[k]In patients who are not candidates for chemotherapy, involved-site radiation therapy (ISRT) is recommended.

[l]In selected cases (4–6 factors according to prognostic model, HIV lymphoma, testicular, double hit lymphoma), there may be an increased risk of CNS events. The optimal management of these events is uncertain, but CNS prophylaxis can be considered with 4–8 doses of intrathecal methotrexate and/or cytarabine, or systemic methotrexate (3–3.5 g/m^2) during the course of treatment. Recent data regarding stage IE DLBCL of the breast have been suggested as a potential risk for CNS disease. See Prognostic Model to Assess the Risk of CNS Disease (BCEL-A 2 of 2).

[m]For systemic disease with concurrent CNS disease, see BCEL-C.

[n]Recommendations are for HIV-negative lymphoma only. For HIV-positive DLBCL, see AIDS-2.

[o]See BCEL-C for regimens used in patients with poor left ventricular function and patients >80 years of age with comorbidities.

[p]See Principles of Radiation Therapy (NHODG-D).

[q]If RT is not used, interim staging after 3–4 cycles of RCHOP is appropriate to confirm response.

[r]Based on current clinical trials, RCHOP is preferable due to reduced toxicities, but other comparable anthracycline-based regimens are also acceptable (see BCEL-C).

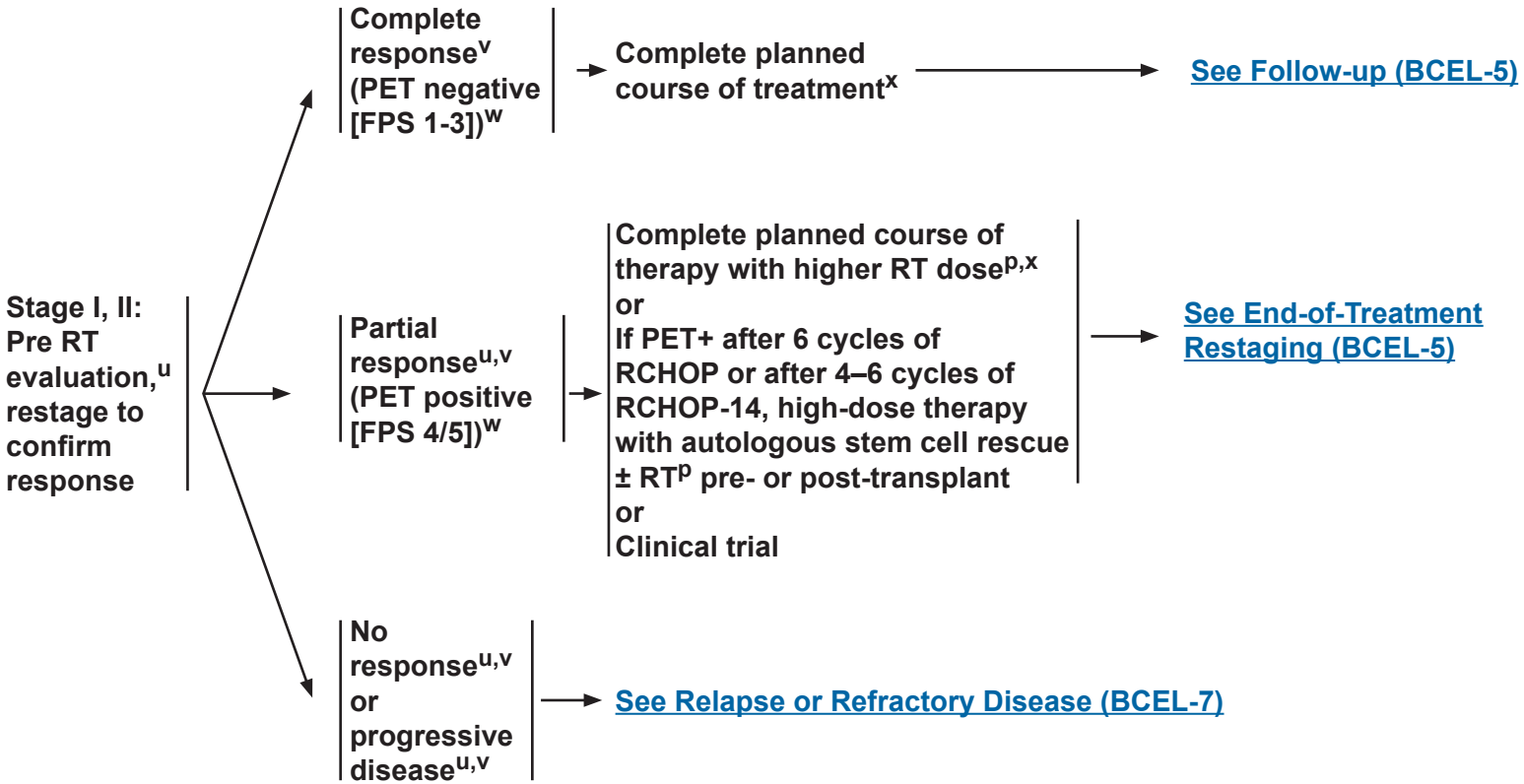
[s]In selected cases, RT to initially bulky sites of disease may be beneficial (category 2B).

[t]PET/CT scan at interim restaging can lead to increased false positives and should be carefully considered in select cases. If PET/CT scan performed and positive, rebiopsy before changing course of treatment.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRE RT EVALUATION
(End of first-line chemoimmunotherapy)

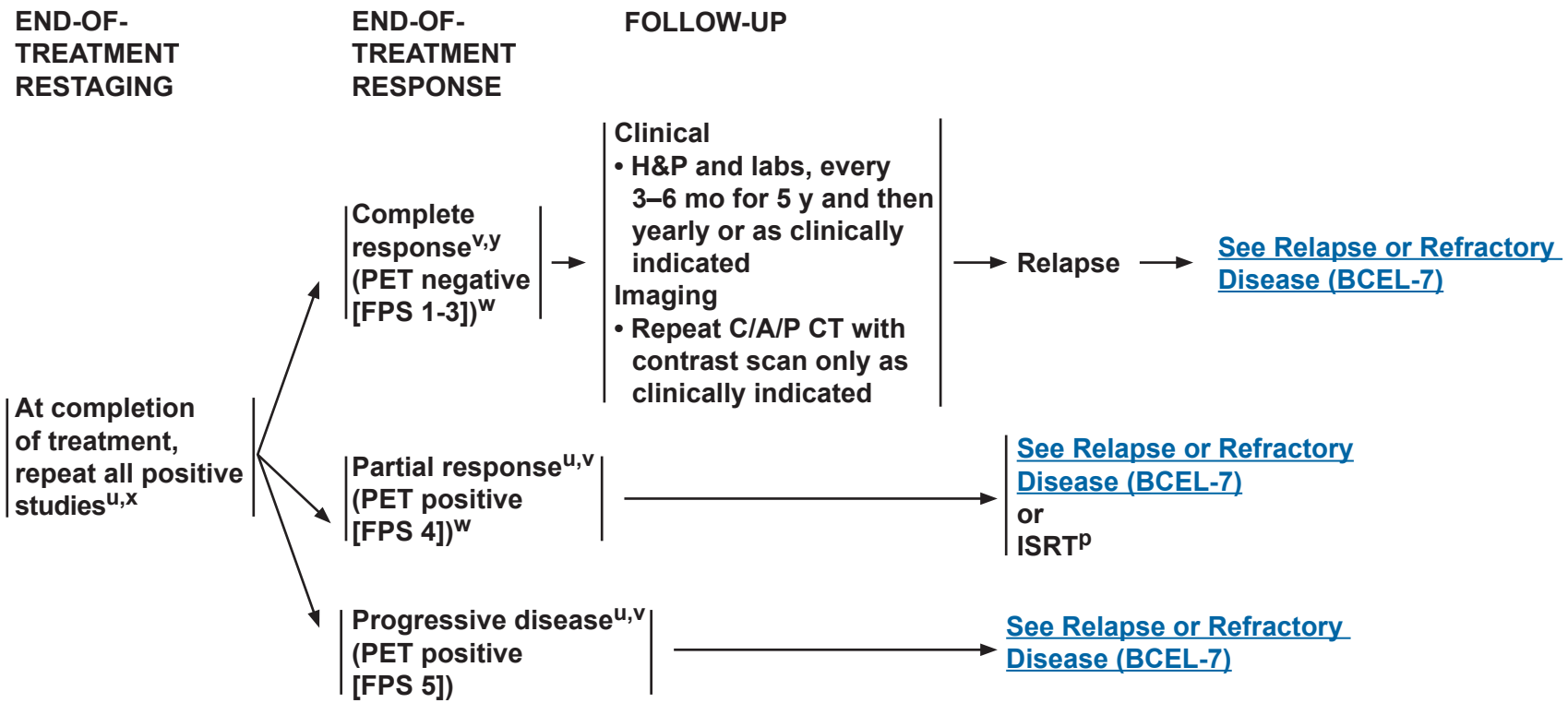
FOLLOW-UP THERAPY



[p] See Principles of Radiation Therapy (NHODG-D).
[u] Repeat biopsy should be strongly considered if PET-positive prior to additional therapy. If biopsy negative, follow PET-negative guideline.
[v] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[w] PET/CT scan should be interpreted via the PET Five Point Scale (FPS) (See NHODG-C 3 of 3).
[x] The optimum timing of end-of-treatment PET/CT is unknown; however, waiting a minimum of 8 weeks after RT to repeat PET/CT scan is suggested. False positives may occur due to posttreatment changes.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

STAGE I, II



[p] See Principles of Radiation Therapy (NHODG-D).

[u] Repeat biopsy should be strongly considered if PET-positive prior to additional therapy. If biopsy negative, follow PET-negative guideline.

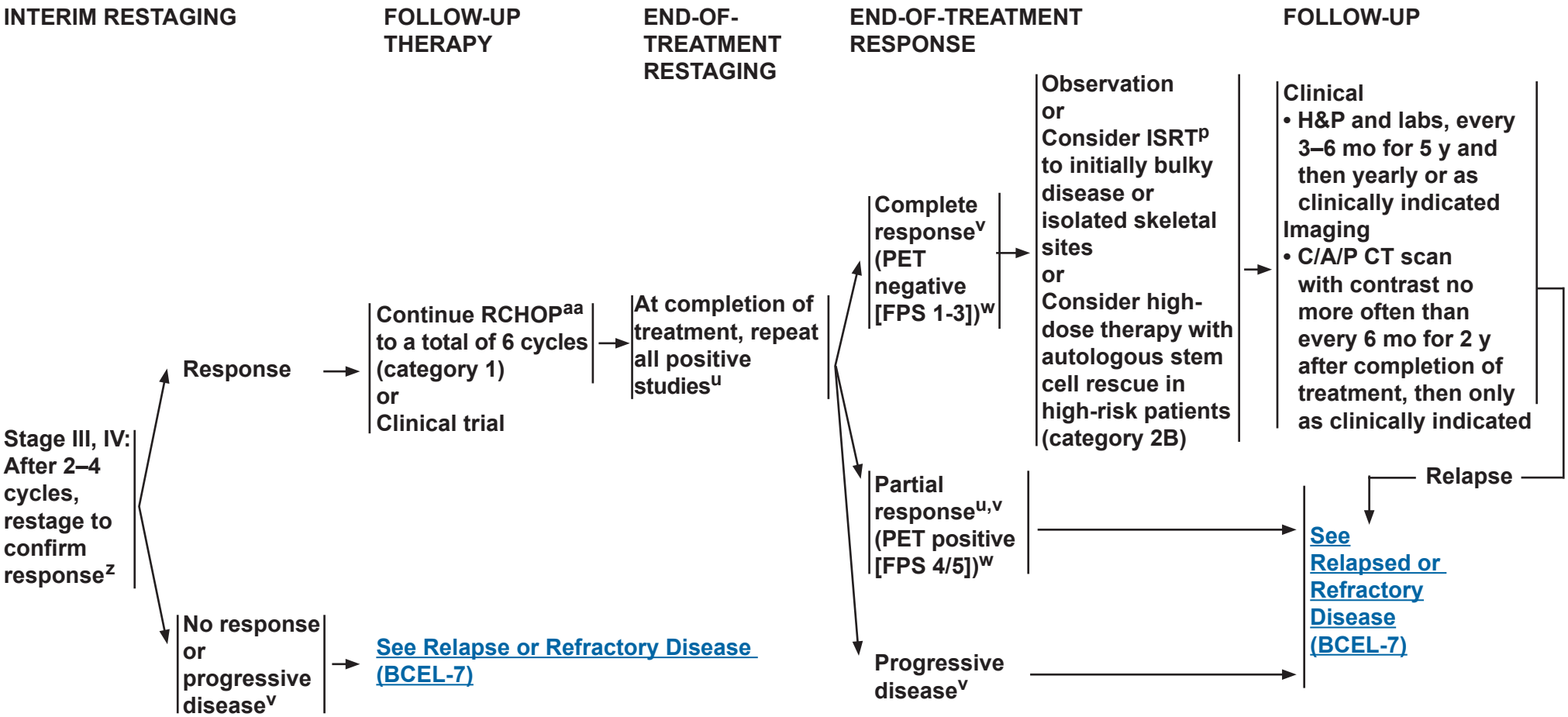
[v] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).

[w] PET/CT scan should be interpreted via the PET Five Point Scale (FPS) (See NHODG-C 3 of 3).

[x] The optimum timing of end-of-treatment PET/CT is unknown; however, waiting a minimum of 8 weeks after RT to repeat PET/CT scan is suggested. False positives may occur due to posttreatment changes.

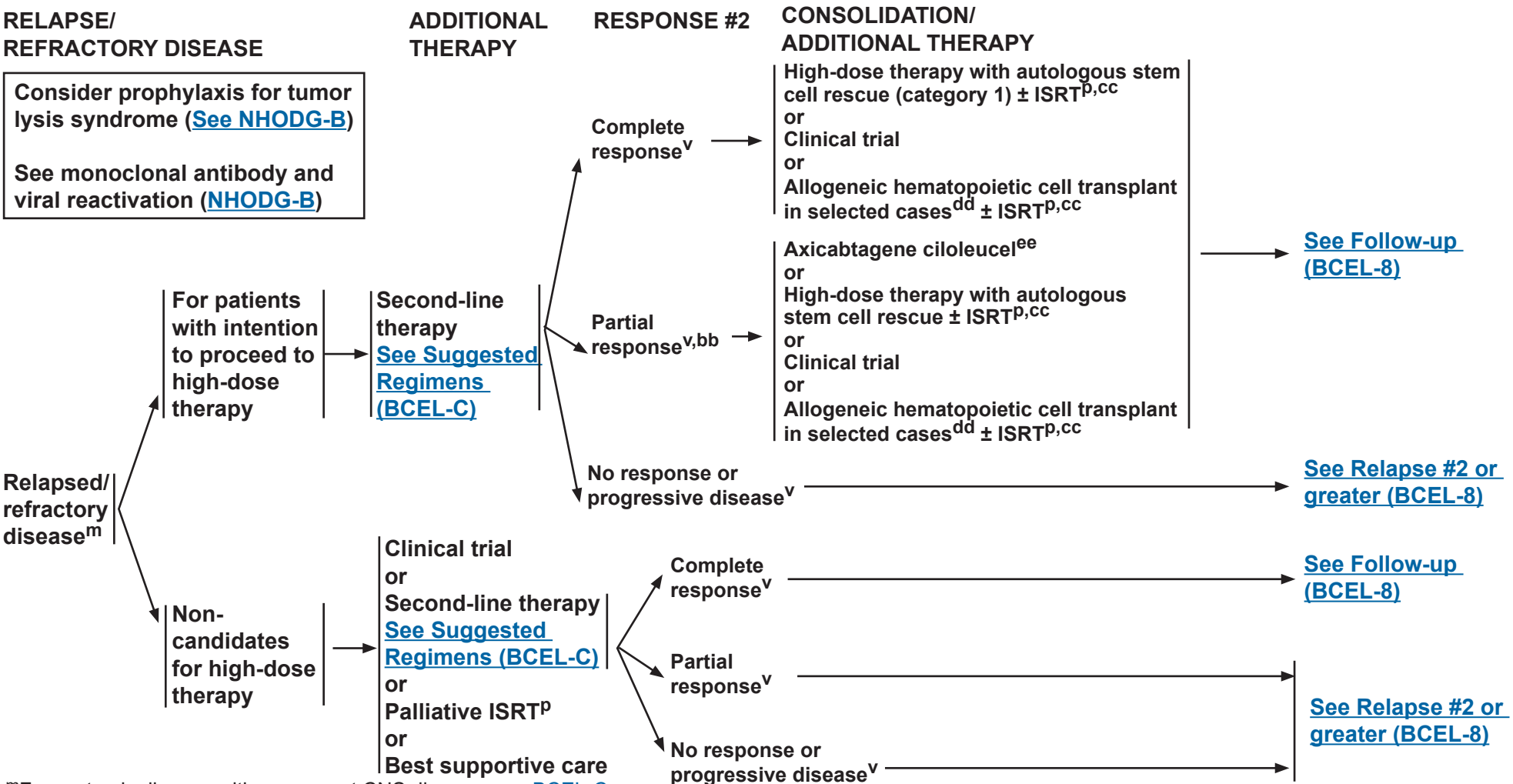
[y] Patients in first remission may be candidates for consolidation trials including high-dose therapy with autologous stem cell rescue.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[p] See Principles of Radiation Therapy (NHODG-D).
[u] Repeat biopsy should be strongly considered in PET-positive prior to additional therapy. If biopsy negative, follow PET-negative guideline.
[v] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[w] PET/CT scan should be interpreted via the PET Five Point Scale (See NHODG-C 3 of 3).
[z] PET/CT scan at interim restaging can lead to increased false positives and should be carefully considered in select cases. If PET/CT scan performed and positive, rebiopsy before changing course of treatment.
[aa] For other regimens, see BCEL-C.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[m]For systemic disease with concurrent CNS disease, see BCEL-C.
[p]See Principles of Radiation Therapy (NHODG-D).
[v]See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[bb]Some NCCN Member Institutions require a complete metabolic response in order to proceed to high-dose therapy with autologous stem cell rescue.
[cc]Additional RT can be given before or after transplant to sites of previous positive disease.
[dd]Selected cases include mobilization failures and persistent bone marrow involvement.
[ee]See Guidance for Treatment of Patients with Chimeric Antigen Receptor (CAR) T-Cell Therapy (BCEL-D).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

FOLLOW-UP

RELAPSE #2 OR GREATER

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

Follow-up after treatment for relapsed/refractory disease[m]

→

- **Clinical: H&P and labs, every 3–6 mo for 5 y and then yearly or as clinically indicated**
- **Imaging: C/A/P CT scan with contrast no more often than every 6 mo for 2 y after completion of treatment, then only as clinically indicated**

→

Relapse or Progression of disease[v]

→

Axicabtagene ciloleucel[ee] (if not previously given)
or
Clinical trial
or
Alternative second-line therapy[ff] (See BCEL-C)
or
Palliative ISRT[p]
or
Best supportive care

[m]For systemic disease with concurrent CNS disease, see BCEL-C.
[p]See Principles of Radiation Therapy (NHODG-D).
[v]See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).

[ee]See Guidance for Treatment of Patients with Chimeric Antigen Receptor (CAR) T-Cell Therapy (BCEL-D).
[ff]Patients who progress after three successive regimens are unlikely to derive additional benefit from currently utilized combination chemotherapy regimens, except for patients with a long disease-free interval.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

INTERNATIONAL PROGNOSTIC INDEX[a]

ALL PATIENTS:	INTERNATIONAL INDEX, ALL PATIENTS:	
• Age >60 years	• Low	0 or 1
• Serum LDH > normal	• Low-intermediate	2
• Performance status 2–4	• High-intermediate	3
• Stage III or IV	• High	4 or 5
• Extranodal involvement >1 site		

AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX[a]

PATIENTS ≤60 YEARS:	INTERNATIONAL INDEX, PATIENTS ≤60 YEARS:	
• Stage III or IV	• Low	0
• Serum LDH > normal	• Low-intermediate	1
• Performance status 2–4	• High-intermediate	2
	• High	3

STAGE-MODIFIED INTERNATIONAL PROGNOSTIC INDEX[b]

STAGE I or II PATIENTS:	INTERNATIONAL INDEX, STAGE I or II PATIENTS:	
• Age >60 years	• Low	0 or 1
• Serum LDH > normal	• High	2–4
• Performance status 2–4		
• Stage II or IIE		

NCCN-IPI[c]

		Risk group	
Age, years		• Low	0–1
>40 to ≤60	1	• Low-intermediate	2–3
>60 to <75	2	• High-intermediate	4–5
≥75	3	• High	≥6
LDH, normalized			
>1 to ≤3	1		
>3	2		
Ann Arbor stage III-IV	1		
Extranodal disease*	1		
Performance status ≥2	1		

*Disease in bone marrow, CNS, liver/GI tract, or lung.

[a]The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-hodgkin's lymphoma. N Engl J Med1993; 329:987-994.
[b]Miller TP, Dahlberg S, Cassady JR. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med 1998;339:21-26.
[c]This research was originally published in *Blood*. Zhou Z, Sehn LH, Rademaker AW, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. Blood 2014;123:837-842. © the American Society of Hematology

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Back to Workup (BCEL-2)

Prognostic Model to Assess the Risk of CNS Disease[d,e]

- **Age >60 years**
- **Serum LDH > normal**
- **Performance status >1**
- **Stage III or IV**
- **Extranodal involvement >1 site**
- **Kidney or adrenal gland involvement**

Low risk	**0–1**
Intermediate-risk	**2–3**
High-risk	**4–6**

[d]Schmitz N, Zeynalova S, Nickelsen M, et al. A new prognostic model to assess the risk of CNS disease in patients with aggressive B-cell lymphoma [abstract]. Hematol Oncol 2013;31 (Suppl. 1):96-150; Abstract 047.
[e]Savage K, et al Validation of a prognostic model to assess the risk of CNS disease in patients with aggressive B-cell lymphoma [abstract]. Blood 2014;124:Abstract 394.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Primary Mediastinal Large B-Cell Lymphoma

- **Primary mediastinal large B-cell lymphoma (PMBL) can be defined as a clinical entity presenting with primary site of disease in mediastinum with or without other sites and has histology of DLBCL. PMBL overlaps with grey zone lymphomas that have intermediate features between Hodgkin lymphoma and PMBL and have unique diagnostic characteristics.**
  See Grey Zone Lymphoma (BCEL-B 2 of 3).

- **Clinical pathologic correlation is required to establish diagnosis.**

- **Optimal first-line therapy is more controversial than other subtypes of NHL; however, treatment regimens include (in order of preference):[a]**
  - **Dose-adjusted EPOCH-R ([etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin] + rituximab)[b] x 6 cycles**
    - **For persistent focal disease, RT can be added.**
  - **RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) x 6 cycles + RT**
  - **RCHOP x 4 cycles followed by ICE (ifosfamide, carboplatin, etoposide)[c] x 3 cycles ± RT (category 2B)**

- **Role of RT in first-line therapy is controversial. If PET/CT scan was negative at the end of treatment and initial disease was non-bulky, observation may be considered.**

- **Residual mediastinal masses are common. PET/CT scan is essential post-treatment. Biopsy of PET/CT scan positive mass is recommended if additional systemic treatment is contemplated.**

- **Relapsed/refractory therapy**
  - **see BCEL-7**
  - **Pembrolizumab**

[a]Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.

[b]Dunleavy K, Pittaluga S, Maeda LS, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. N Engl J Med 2013;368:1408-1416.

[c]Moskowitz C, Hamlin PA, Jr., Maragulia J, et al. Sequential dose-dense RCHOP followed by ICE consolidation (MSKCC protocol 01-142) without radiotherapy for patients with primary mediastinal large B-cell lymphoma [abstract]. Blood 2010;116:Abstract 420.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Grey Zone Lymphoma[a,b,c]
(intermediate between DLBCL and classical HL)

Synonyms
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma (CHL)
- Large B-cell lymphoma with Hodgkin features
- Hodgkin-like anaplastic large cell lymphoma

Clinical Presentation
- Present with large anterior mediastinal mass with or without supraclavicular lymph nodes
  - More common in males, presenting between 20–40 y
- Non-mediastinal grey zone lymphoma is more likely compared to mediastinal cases to occur in older individuals and typically have higher risk features, more advanced-stage disease, and higher IPI.[d]

Morphology
- Pleomorphic cells in a diffusely fibrous stroma
- Typically larger and more pleomorphic than in PMBL, sometimes resembling lacunar or Hodgkin-like cells
- Necrosis without neutrophilic infiltrate is frequent

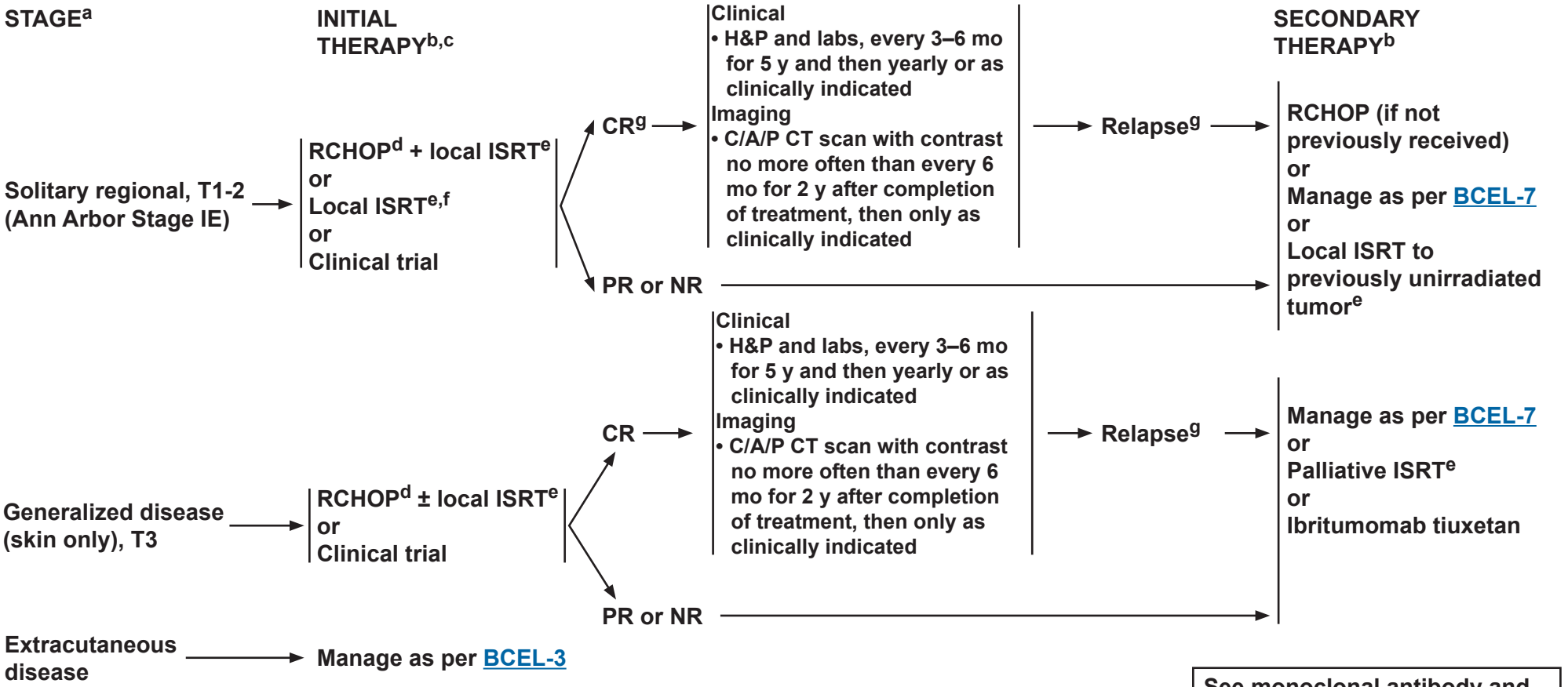
Immunophenotype
- Often transitional features between CHL and PMBL
- CD45 often positive; CD30, CD15, CD20, CD79a frequently positive
- EBV -
- PAX5, BOB.1, OCT-2 are often positive, BCL6 variable
- CD10, ALK are negative
- If morphology closer to PMBL, or absence of CD20, CD15+ would suggest the diagnosis of grey zone lymphoma
- If morphology closer to CHL, CD20 strong positivity and other B-cell markers and absence of CD15 would suggest grey zone lymphoma.

Prognosis and Treatment[e]
- A worse prognosis than either CHL or PMBL has been suggested.
- While there is no consensus on the treatment, aggressive large B-cell lymphoma regimens are preferred.
- If the tumor cells are CD20+, the addition of rituximab to the chemotherapy treatment should be considered.
- Data suggest that the use of rituximab-anthracycline-based chemotherapy as in other B-cell lymphomas (See BCEL-C) is helpful. If localized disease, then RT is preferred.
- There is no ostensible difference in outcome between mediastinal and non-mediastinal grey zone lymphoma.

[a]Dunleavy K, Pittaluga S, Tay K, et al. Comparative clinical and biological features of primary mediastinal B-cell lymphoma (PMBL) and mediastinal grey zone lymphoma (MGZL) [abstract]. Blood 2009;114:Abstract 106.
[b]Jaffe ES, Stein H, Swerdlow SH, et al. B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:267-268.
[c]Quintanilla-Martinez L, de Jong D, de Mascarel A, et al. Gray zones around diffuse large B cell lymphoma. Conclusions based on the workshop of the XIV meeting of the European Association for Hematopathology and the Society of Hematopathology in Bordeaux, France. J Hematop 2009;2:211-236.
[d]Evens AM, Kanakry JA, Sehn LH, et al. Gray zone lymphoma with features intermediate between classical Hodgkin lymphoma and diffuse large B-cell lymphoma: Characteristics, outcomes, and prognostication among a large multicenter cohort. Am J Hematol 2015;90:778-783.
[e]Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRIMARY CUTANEOUS DIFFUSE LARGE B-CELL LYMPHOMA, LEG TYPE



See monoclonal antibody and viral reactivation (NHODG-B)

[a]For TNM Classification of Cutaneous Lymphoma other than MF/SS (See NCCN Guidelines for T-Cell Lymphomas and Cutaneous B-Cell Lymphoma).
[b]Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.
[c]These patients are at higher risk for CNS involvement (See BCEL-A 2 of 2); consider CNS prophylaxis according to institutional standards.
[d]For patients who cannot tolerate anthracyclines, see BCEL-C for regimens for patients with poor left ventricular function.
[e]See Principles of Radiation Therapy (NHODG-D).
[f]For patients not able to tolerate chemotherapy.
[g]PET/CT (strongly preferred) or C/A/P CT with contrast at the end-of-treatment to assess response. It can be repeated if there is clinical suspicion of progressive disease.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS[a,b]
(in alphabetical order)

First-line Therapy
- RCHOP (rituximab,[c] cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)
- Dose-dense RCHOP 14[c] (category 3)
- Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab

First-line Therapy for Patients with Poor Left Ventricular Function[d,e,f]
- RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine)
- RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, prednisone)
- DA-EPOCH[g] (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab
- RCEOP (rituximab, cyclophosphamide, etoposide, vincristine, prednisone)
- RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, prednisolone)

First-line Therapy for Very Frail Patients and Patients >80 Years of Age with Comorbidities[f]
- RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine)
- RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, prednisone)
- R-mini-CHOP
- RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, prednisolone)

First-line Consolidation (optional)
- Lenalidomide maintenance (category 2B) for patients 60–80 y of age
- Age-adjusted IPI high-risk disease: High-dose therapy with autologous stem cell rescue (category 2B)

Concurrent Presentation with CNS Disease
- Parenchymal: 3 g/m^2 or more of systemic methotrexate given on Day 15 of a 21-day RCHOP cycle that has been supported by growth factors.
- Leptomeningeal: IT methotrexate/cytarabine, consider Ommaya reservoir placement and/or systemic methotrexate (3–3.5 g/m^2)

See Second-line Therapy on BCEL-C 2 of 4.

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

[a]See references for regimens BCEL-C 3 of 4 and BCEL-C 4 of 4.
[b]Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.
[c]In RCHOP-14 and RCHOP-21, may consider increasing dose of rituximab to 500 mg/m^2 in men >60 y.
[d]Inclusion of any anthracycline or anthracenedione in patients with impaired cardiac functioning should have more frequent cardiac monitoring.
[e]There are limited published data regarding the use of these regimens; however, they are used at NCCN Member Institutions for the first-line treatment of DLBCL for patients with poor left ventricular function.
[f]There are limited data for treatment of early-stage disease with these regimens; however, short-course chemotherapy + RT for stage I-II disease is practiced at NCCN Member Instituions.
[g]If upward dose adjustment is necessary, doxorubicin should be maintained at base dose and not increased.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS[a,b]
(in alphabetical order)

Second-line and Subsequent Therapy[d,h,i] (intention to proceed to high-dose therapy)
- DHAP (dexamethasone, cisplatin, cytarabine) ± rituximab
- ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± rituximab
- GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab
- GemOx (gemcitabine, oxaliplatin) ± rituximab
- ICE (ifosfamide, carboplatin, etoposide) ± rituximab
- MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± rituximab

Second-line and Subsequent Therapy[d,h,i] (non-candidates for high-dose therapy)
- Bendamustine ± rituximab
- Brentuximab vedotin for CD30+ disease (category 2B)
- CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) ± rituximab - PO and IV
- CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± rituximab
- DA-EPOCH ± rituximab
- GDP ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab
- GemOx ± rituximab
- Gemcitabine, vinorelbine ± rituximab (category 3)
- Ibrutinib[j] (non-GCB DLBCL)
- Lenalidomide ± rituximab (non-GCB DLBCL)
- Rituximab

See First-line Therapy on BCEL-C 1 of 4.

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

[a]See references for regimens BCEL-C 3 of 4 and BCEL-C 4 of 4.
[b]Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.
[d]Inclusion of any anthracycline or anthracenedione in patients with impaired cardiac functioning should have more frequent cardiac monitoring.
[h]If additional anthracycline is administered after a full course of therapy, careful cardiac monitoring is essential. Dexrazoxane may be added as a cardioprotectant.
[i]Rituximab should be included in second-line therapy if there is relapse after a reasonable remission (>6 mo); however; rituximab should often be omitted in patients with primary refractory disease.
[j]See Special Considerations for Use of Small-Molecule Inhibitors (NHODG-E).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS
References

First-line Therapy

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab with RT

Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-hodgkin's lymphoma. N Engl J Med 1998;339:21-26.

Horning SJ, Weller E, Kim K, et al. Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-hodgkin's lymphoma: Eastern Cooperative Oncology Group Study 1484. J Clin Oncol 2004;22:3032-3038.

Persky DO, Unger JM, Spier CM, et al. Phase II study of rituximab plus three cycles of CHOP and involved-field radiotherapy for patients with limited-stage aggressive B-cell lymphoma: Southwest Oncology Group Study 0014. J Clin Oncol 2008;26:2258-2263.

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab

Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood 2010;116:2040-2045.

Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 2005;23:4117-4126.

Pfreundschuh M, Trumper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol 2006;7:379-391.

Dose-dense CHOP 14 + rituximab

Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). Lancet Oncol 2008;9:105-116.

Cunningham D, Hawkes EA, Jack A, et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. Lancet 2013;381:1817-1826.

Lamy T, Damaj G, Soubeyran P, et al. R-CHOP 14 with or without radiotherapy in nonbulky limited-stage diffuse large B-cell lymphoma. Blood 2018;131:174-181.

Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab

Purroy N, Bergua J, Gallur L, et al. Long-term follow-up of dose-adjusted EPOCH plus rituximab (DA-EPOCH-R) in untreated patients with poor prognosis large B-cell lymphoma. A phase II study conducted by the Spanish PETHEMA Group. Br J Haematol 2015;169:188-198.

Wilson WH, Dunleavy K, Pittaluga S, et al. Phase II study of dose-adjusted EPOCH and rituximab in untreated diffuse large B-cell lymphoma with analysis of germinal center and post-germinal center biomarkers. J Clin Oncol 2008;26:2717-2724.

Wilson WH, Jung SH, Porcu P, et al. A Cancer and Leukemia Group B multi-center study of DA-EPOCH-rituximab in untreated diffuse large B-cell lymphoma with analysis of outcome by molecular subtype. Haematologica 2012;97:758-765.

First-line Therapy for Patients with Poor Left Ventricular Function

CDOP (cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone) + rituximab

Martino R, Perea G, Caballero MD, et al. Cyclophosphamide, pegylated liposomal doxorubicin (Caelyx), vincristine and prednisone (CCOP) in elderly patients with diffuse large B-cell lymphoma: Results from a prospective phase II study. Haematologica 2002;87:822-827.

Zaja F, Tomadini V, Zaccaria A, et al. CHOP-rituximab with pegylated liposomal doxorubicin for the treatment of elderly patients with diffuse large B-cell lymphoma. Leuk Lymphoma 2006;47:2174-2180.

RCEOP (rituximab, cyclophosphamide, etoposide, vincristine, prednisone)

Moccia A, Schaff K, Hoskins P, et al. R-CHOP with etoposide substituted for doxorubicin (R-CEOP): Excellent outcome in diffuse large B cell lymphoma for patients with a contraindication to anthracyclines [abstract]. Blood 2009;114:Abstract 408.

RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, and prednisolone)

Fields PA, Townsend W, Webb A, et al. De novo treatment of diffuse large B-cell lymphoma with rituximab, cyclophosphamide, vincristine, gemcitabine, and prednisolone in patients with cardiac comorbidity: a United Kingdom National Cancer Research Institute trial. J Clin Oncol 2014;32:282-287.

First-line Therapy for Elderly Patients (age >80 years)

R-mini-CHOP

Peyrade F, Jardin F, Thieblemont C, et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. Lancet Oncol 2011;12:460-468.

First-line Consolidation

Thieblemont C, Tilly H, Gomes da Silva M, et al. Lenalidomide maintenance compared with placebo in responding elderly patients with diffuse large B-cell lymphoma treated with first-line rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol 2018;35:2473-2481.

Stiff PJ, Unger JM, Cook JR, et al. Autologous transplantation as consolidation for aggressive non-Hodgkin's lymphoma. N Engl J Med 2013;369:1681-1690.

Continued

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS
References

Second-line and Subsequent Therapy

Bendamustine ± rituximab

Weidmann E, Kim SZ, Rost A, et al. Bendamustine is effective in relapsed or refractory aggressive non-Hodgkin's lymphoma. Ann Oncol 2002;13:1285-1289.

Vacirca JL, Acs PI, Tabbara IA, et al. Bendamustine combined with rituximab for patients with relapsed or refractory diffuse large B cell lymphoma. Ann Hematol 2014;93:403-409.

Ohmachi K, Niitsu N, Uchida T, et al. Multicenter phase II study of bendamustine plus rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol 2013;31:2103-2109.

Brentuximab vedotin

Jacobsen ED, Sharman JP, Oki Y, et al. Brentuximab vedotin demonstrates objective responses in a phase 2 study of relapsed/refractory DLBCL with variable CD30 expression. Blood 2015;125:1394-1402.

DHAP (dexamethasone, cisplatin, cytarabine) ± rituximab

Velasquez WS, Cabanillas F, Salvador P, et al. Effective salvage therapy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone (DHAP). Blood 1988;71:117-122.

Mey UJ, Orlopp KS, Flieger D, et al. Dexamethasone, high-dose cytarabine, and cisplatin in combination with rituximab as salvage treatment for patients with relapsed or refractory aggressive non-Hodgkin's lymphoma. Cancer Invest 2006;24:593-600.

Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 2010;28:4184-4190.

ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± rituximab

Velasquez WS, McLaughlin P, Tucker S, et al. ESHAP - an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. J Clin Oncol 1994;12:1169-1176.

Martin A, Conde E, Arnan M, et al. R-ESHAP as salvage therapy for patients with relapsed or refractory diffuse large B-cell lymphoma: the influence of prior exposure to rituximab on outcome. A GEL/TAMO study. Haematologica 2008;93:1829-1836.

GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab

Crump M, Baetz T, Couban S, et al. Gemcitabine, dexamethasone, and cisplatin in patients with recurrent or refractory aggressive histology B-cell non-Hodgkin lymphoma: a Phase II study by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG). Cancer 2004;101:1835-1842.

GDP (gemcitabine, dexamethasone, carboplatin) ± rituximab

Gopal AK, Press OW, Shustov AR, et al. Efficacy and safety of gemcitabine, carboplatin, dexamethasone, and rituximab in patients with relapsed/refractory lymphoma: a prospective multi-center phase II study by the Puget Sound Oncology Consortium. Leuk Lymphoma 2010;51:1523-1529.

CAR T-Cell Therapy (Axicabtagene ciloleucel)

Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-vell therapy in refractory large B-cell lymphoma. N Engl J Med 2018:Epub ahead of publication.

Neelapu SS, Locke FL, Bartlett NL, et al. Long-term follow-up ZUMA-1: A pivotal trial of axicabtagene ciloleucel (Axi-Cel; KTE-C19) in patients with refractory aggressive non-Hodgkin lymphoma [abstract] (NHL). Blood 2018;130:Abstract 578.

GemOX (gemcitabine, oxaliplatin) ± rituximab

Lopez A, Gutierrez A, Palacios A, et al. GEMOX-R regimen is a highly effective salvage regimen in patients with refractory/relapsing diffuse large-cell lymphoma: a phase II study. Eur J Haematol 2008;80:127-132.

Corazzelli G, Capobianco G, Arcamone M, et al. Long-term results of gemcitabine plus oxaliplatin with and without rituximab as salvage treatment for transplant-ineligible patients with refractory/relapsing B-cell lymphoma. Cancer Chemother Pharmacol 2009;64:907-916.

El Gnaoui T, Dupuis J, Belhadj K, et al. Rituximab, gemcitabine and oxaliplatin: An effective salvage regimen for patients with relapsed or refractory B-cell lymphoma not candidates for high-dose therapy. Ann Oncol 2007;18:1363-1368.

Gemcitabine, vinorelbine, rituximab

Papageorgiou ES, Tsirigotis P, Dimopoulos M, et al. Combination chemotherapy with gemcitabine and vinorelbine in the treatment of relapsed or refractory diffuse large B-cell lymphoma: a phase-II trial by the Hellenic Cooperative Oncology Group. Eur J Hematol 2005;75:124-129.

Xiros N, Economopoulos T, Valsami S, et al. Rituximab in combination with vinorelbine/gemcitabine chemotherapy in patients with primary refractory or early relapsed T cell rich B cell lymphoma. A pilot study. Leuk Res 2003;27:1097-1099.

Ibrutinib

Wilson WH, Young RM, Schmitz R, et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. Nat Med 2015;21:922-926.

ICE (ifosfamide, carboplatin, etoposide) ± rituximab

Zelenetz AD, Hamlin P, Kewalramani T, et al. Ifosfamide, carboplatin, etoposide (ICE)-based second-line chemotherapy for the management of relapsed and refractory aggressive non-Hodgkin's lymphoma. Ann Oncol 2003;14[suppl 1]:i5-10.

Kewalramani T, Zelenetz AD, Nimer SD, et al. Rituximab and ICE (RICE) as second-line therapy prior to autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. Blood 2004;103:3684-8.

Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 2010;28:4184-4190.

Lenalidomide ± rituximab

Witzig TE, Vose JM, Zinzani PL, et al. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. Ann Oncol 2011;22:1622-1627.

Wiernik PH, Lossos IS, Tuscano JM, et al. Lenalidomide monotherapy in relapsed or refractory aggressive Non-Hodgkin's lymphoma. J Clin Oncol 2008;26:4952-4957.

Wang M, Fowler N, Wagner-Bartak N, et al. Oral lenalidomide with rituximab in relapsed or refractory diffuse large cell, follicular, and transformed lymphoma: a phase II clinical trial. Leukemia 2013;27:1902-1909.

CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) ± rituximab

Chao NJ, Rosenberg SA, and Horning SJ. CEPP(B): An effective and well-tolerated regimen in poor-risk, aggressive non-Hodgkin's lymphoma. Blood 1990;76:1293-1298.

EPOCH + rituximab

Gutierrez M, Chabner BA, Pearson D, et al. Role of a doxorubicin-containing regimen in relapsed and resistant lymphomas: An 8-year follow-up study of EPOCH. J Clin Oncol 2000;18:3633-3642.

Jermann M, Jost LM, Taverna C, et al. Rituximab-EPOCH, an effective salvage therapy for relapsed, refractory or transformed B-cell lymphomas: Results of a phase II study. Ann Oncol 2004;15:511-516.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

GUIDANCE FOR TREATMENT OF PATIENTS WITH CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY

AXICABTAGENE CILOLEUCEL

- **Patient selection**
  - **Axicabtagene ciloleucel is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL, NOS; primary mediastinal large B-cell lymphoma; high grade B-cell lymphoma; and DLBCL arising from follicular lymphoma.[a]**
  - **Clinical trials excluded patients who are ECOG PS ≥2, have CNS involvement, or have serious infections. Patients must have adequate organ and marrow function. Clinical judgment is required.**
  - **Health care facilities that dispense and administer axicabtagene ciloleucel must be enrolled and comply with the Risk Evaluation and Mitigation Strategies (REMS) requirements.[a] See REMS for axicabtagene ciloleucel.**

- **Cytokine release syndrome (CRS) management[a] (See Table 1 (BCEL-D 2 of 3) for the grading and management of CRS)**
  - **Median time to onset was 2 days (range: 1–12 days). Median duration was 7 days (range: 2–58 days).**
  - **Manifestations of CRS include fever, hypotension, tachycardia, hypoxia, and chills. Serious events may include atrial fibrillation and ventricular tachycardia, cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome.**

- **Neurologic toxicity management[a] (See Table 2 (BCEL-D 3 of 3) for the grading and management of neurologic toxicities)**
  - **Median time to onset was 4 days (range: 1–43 days). Median duration was 17 days.**
  - **The most common neurologic toxicities included encephalopathy, headache, tremor, dizziness, aphasia, delirium, insomnia, and anxiety. Serious events including leukoencephalopathy and seizures occurred with axicabtagene ciloleucel. Fatal and serious cases of cerebral edema have occurred in patients treated with axicabtagene ciloleucel.**

- **Prolonged cytopenias[a]**
  - **Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and axicabtagene ciloleucel infusion.**

- **Hypogammaglobulinemia[a]**
  - **B-cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment with axicabtagene ciloleucel.**

[a]Prescribing information for axicabtagene ciloleucel is available at: https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM581226.pdf.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

GUIDANCE FOR TREATMENT OF PATIENTS WITH CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY

AXICABTAGENE CILOLEUCEL

Table 1. CRS Grading and Management Guidance[a]

CRS Grade[b]	Tocilizumab[d]	Corticosteroids
Grade 1 Symptoms require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgia, malaise).	N/A	N/A
Grade 2 Symptoms require and respond to moderate intervention. Oxygen requirement <40% FiO_2 or hypotension responsive to fluids or low-dose of one vasopressor or Grade 2 organ toxicity[c]	Administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab.
Grade 3 Symptoms require and respond to aggressive intervention. Oxygen requirement ≥40% FiO_2 or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis.	Per Grade 2	Administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (eg, 10 mg intravenously every 6 hours). Continue corticosteroid use until the event is Grade 1 or less, then taper over 3 days.
Grade 4 Life-threatening symptoms. Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD) or Grade 4 organ toxicity (excluding transaminitis).	Per Grade 2	Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improvement is seen, then manage as above.

[a]Prescribing information for axicabtagene ciloleucel is available at: https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM581226.pdf.

[b]Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124:188-195.

[c]See Table 2 for Neurologic Toxicity Grading and Management Guidance (BCEL-D 3 of 3).

[d]Refer to the prescribing information for tocilizumab for details.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

GUIDANCE FOR TREATMENT OF PATIENTS WITH CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY

AXICABTAGENE CILOLEUCEL

Table 2. Neurologic Toxicity Grading and Management Guidance[a]

Grading Assessment	Concurrent CRS[d]	No Concurrent CRS
Grade 1 **Mild symptoms**	See Table 1 for the management of CRS	Observe
	Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis.	
Grade 2 **Moderate symptoms: limiting instrumental activities of daily living (ADL)**	Administer tocilizumab per Table 1 for management of Grade 2 CRS. If no improvement within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenously every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.
	Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis.	
Grade 3 **Severe symptoms: Limiting self-care ADL**	Administer tocilizumab per Table 1 for management of Grade 2 CRS. In addition, administer dexamethasone 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.
	Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis.	
Grade 4 **Life-threatening consequences; urgent intervention indicated**	Administer tocilizumab per Table 1 for management of Grade 2 CRS. Administer methylprednisolone 1000 mg intravenously per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenously per day for 2 more days; if improvement is seen, then manage as above.	Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improvement is seen, then manage as above.
	Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis.	

See Table 1 for CRS Grading and Management Guidance (BCEL-D 2 of 3).

[a]Prescribing information for axicabtagene ciloleucel is available at: https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM581226.pdf.

[d]Refer to the prescribing information for tocilizumab for details.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Definition[a]

- **High-grade B-cell lymphomas (HGBLs) with translocations of *MYC* and *BCL2* and/or *BCL6* as detected by FISH or standard cytogenetics) are known as "double-hit" lymphomas. If all three are rearranged, they are referred to as "triple-hit" lymphomas.**
- **Vast majority are germinal center B-cell–like lymphomas.**

Clinical Presentation

- **Often present with poor prognostic parameters, such as elevated LDH, bone marrow and CNS involvement, and a high IPI score.**

Treatment[b]

- **Clinical trial is recommended.**
- **While the standard of care is not established, the following regimens have been used at NCCN Member Institutions:**
  - **DA-EPOCH-R**
  - **RHyper-CVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine)**
  - **R-CODOX-M/R-IVAC (rituximab-cyclophosphamide, vincristine, doxorubicin with methotrexate/ifosfamide, etoposide, and cytarabine)**
- **RCHOP has been associated with inferior outcomes.**
- **Consider consolidation with high-dose therapy with autologous stem cell rescue. While its role is not established, this is done at some NCCN Member Institutions.**
- **These patients are at higher risk for CNS involvement (See BCEL-A 2 of 2); consider CNS prophylaxis according to institutional standards.**
- **Relapsed/refractory disease, see BCEL-7.**

[a]In the 2018 WHO revision of lymphoma, DLBCL, double hit has been designated in a unique category called high-grade B-cell lymphomas (HGBLs) with translocations of *MYC* and *BCL2* and/or *BCL6*.

[b]Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.

References:

Petrich A, Gandhi M, Jovanovic B, et al. Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. Blood 2014;124:2354-2361.

Dunleavy K, Fanale M, LaCasce A, et al. Preliminary report of a multicenter prospective phase II study of DA-EPOCH-R in MYC-rearranged aggressive B-cell lymphoma [abstract]. Blood 2014: Abstract 395.

Johnson NA, Slack GW, Savage KJ et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol 2012;30:3452-3459.

Green TM, Young KH, Visco C, et al. Immunohistochemical double-hit score is a strong predictor of outcome in patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol 2012;30:3460-3467.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ADDITIONAL DIAGNOSTIC TESTING[a,b]

ESSENTIAL:
- Adequate immunophenotyping to establish diagnosis[c,d,e]
  - IHC panel: CD45, CD20, CD3, CD10, Ki-67, BLC2, BCL6, TdT with or without
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD20, CD3, CD5, CD19, CD10, TdT
- Karyotype ± FISH: t(8;14) or variants; *MYC* rearrangement[f]

USEFUL UNDER CERTAIN CIRCUMSTANCES
- FISH: *BCL2*; *BCL6* rearrangements
- EBER-ISH

WORKUP

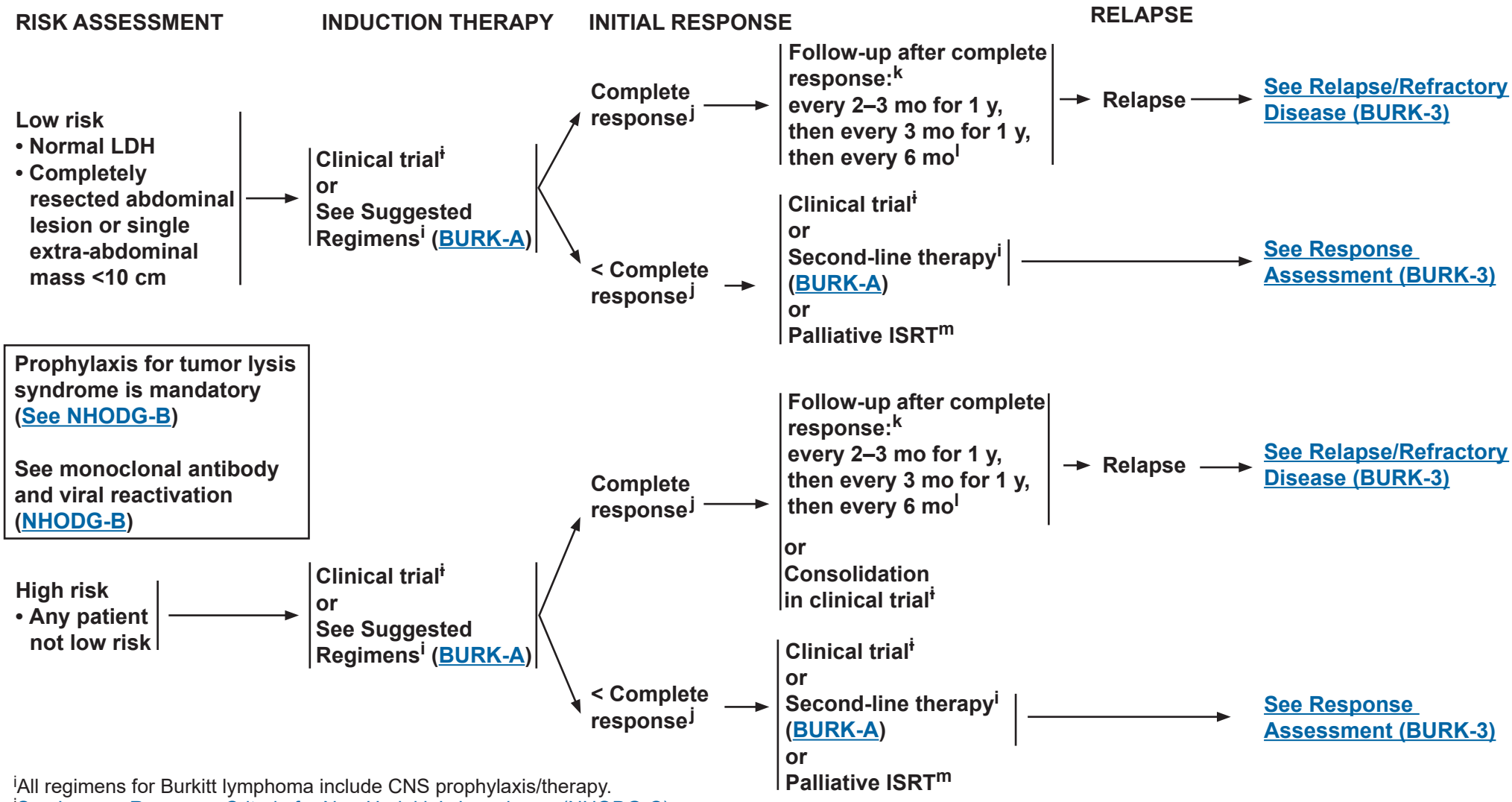
ESSENTIAL:
- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC with differential
- LDH
- Comprehensive metabolic panel
- Uric acid
- C/A/P CT with contrast of diagnostic quality
- Lumbar puncture
- Flow cytometry of cerebrospinal fluid
- Unilateral or bilateral bone marrow biopsy ± aspirate
- HIV testing (if positive, see AIDS-1)
- Hepatitis B testing[g]
- Echocardiogram or MUGA scan if anthracycline or anthracenedione-based regimen is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy or RT planned)

USEFUL IN SELECTED CASES:
- Neck CT with contrast
- Discussion of fertility issues and sperm banking
- Brain MRI with and without contrast
- Whole-body PET/CT scan[h]

See Risk Assessment and Induction Therapy (BURK-2)

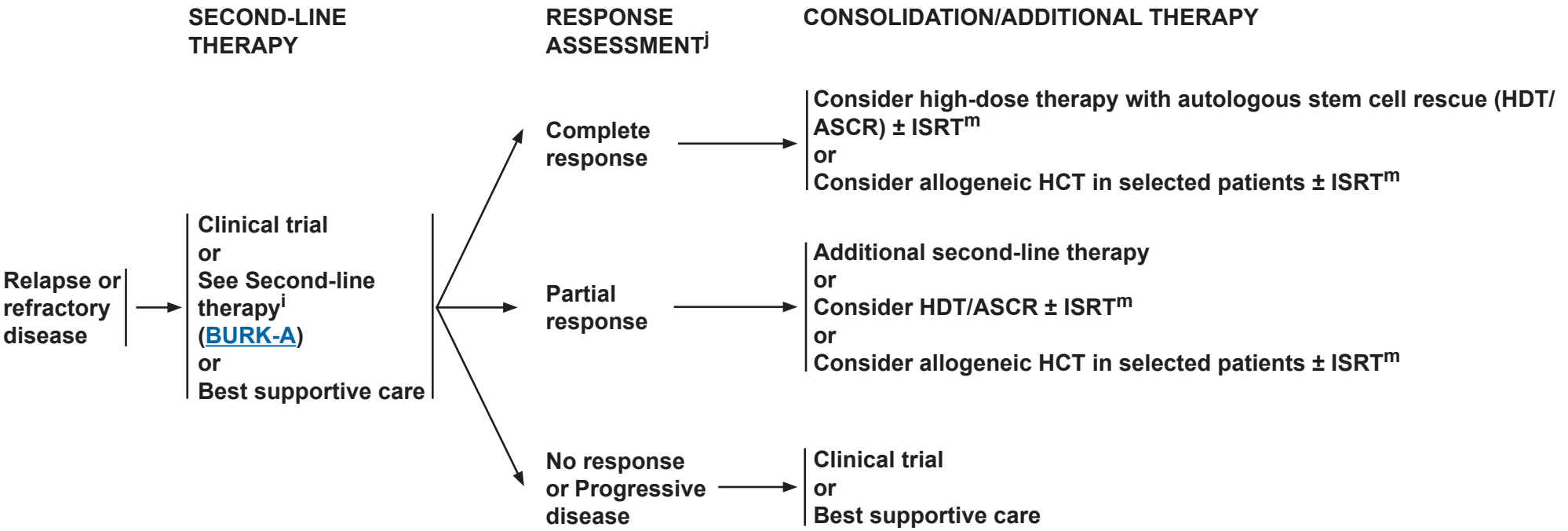
[a]For treatment of double or triple hit tumors, see HGBL-1. In other cases where it is not possible to distinguish between BL and high-grade lymphoma, therapy per this guideline ~~is~~ may be appropriate.
[b]This disease is complex and curable; it is preferred that treatment occur at centers with expertise in the management of the disease.
[c]Typical immunophenotype: sIg+, CD10+, Cd20+, TdT-, Ki-67+ (≥95%), BCL2-, BCL6+, simple karyotype with *MYC* rearrangement as sole abnormality.
[d]See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).
[e]If flow cytometry initially performed, IHC for selected markers (BCL2 and Ki-67) can supplement the flow results.
[f]There is an uncommon variant of BL without *MYC* rearrangement but with 11q aberration. Optimum management of this rare subtype is undefined, though it is most often treated like typical BL.
[g]Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.
[h]Initiation of therapy should not be delayed in order to obtain a PET/CT scan.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[i] All regimens for Burkitt lymphoma include CNS prophylaxis/therapy.
[j] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[k] Repeat C/A/P CT scan with contrast only as clinically indicated.
[l] Relapse after 2 y is rare; therefore, follow-up should be individualized according to patient characteristics.
[m] See Principles of Radiation Therapy (NHODG-D).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



Prophylaxis for tumor lysis syndrome is mandatory (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

[i]All regimens for Burkitt lymphoma include CNS prophylaxis/therapy.
[j]See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[m]See Principles of Radiation Therapy (NHODG-D).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS[a,b,*]
(in alphabetical order)

Prophylaxis for tumor lysis syndrome is mandatory (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

CHOP is not adequate therapy.

Induction Therapy

Low Risk- Combination Regimens

- **CODOX-M (original or modified) (cyclophosphamide, doxorubicin, vincristine with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate) ± rituximab (3 cycles)**
- **Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab (minimum 3 cycles with one additional cycle beyond CR) (regimen includes intrathecal methotrexate) (Data are for patients without CNS disease.)**
- **HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine + rituximab (regimen includes intrathecal therapy)**

High Risk- Combination Regimens

- **CODOX-M (original or modified) (cyclophosphamide, doxorubicin, vincristine with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate) alternating with IVAC (ifosfamide, cytarabine, etoposide, and intrathecal methotrexate) ± rituximab**
- **Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab (for high-risk patients not able to tolerate aggressive treatments) (regimen includes intrathecal methotrexate) (Data are for patients without CNS disease.)**
- **HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine + rituximab (regimen includes intrathecal therapy)**

Second-line Therapy (select patients with reasonable remission)

While no definitive second-line therapies exist, there are limited data for the following regimens:

- **Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab (minimum 3 cycles with one additional cycle beyond CR) (regimen includes intrathecal methotrexate) (Data are for patients without CNS disease.)**
- **RICE (rituximab, ifosfamide, carboplatin, etoposide); intrathecal methotrexate if have not received previously**
- **RIVAC (rituximab, ifosfamide, cytarabine, etoposide); intrathecal methotrexate if have not received previously**
- **RGDP (rituximab, gemcitabine, dexamethasone, cisplatin)**
- **High-dose cytarabine + rituximab**

[a]See references for regimens BURK-A 2 of 2.
[b]All regimens for Burkitt lymphoma include CNS prophylaxis/therapy.

*Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS

References

Low- and High-Risk Combination Regimens

CODOX-M (original or modified) (cyclophosphamide, doxorubicin, vincristine with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate) with (for high-risk) or without (for low-risk) alternating IVAC (ifosfamide, cytarabine, etoposide, and intrathecal methotrexate ± rituximab)

LaCasce A, Howard O, Lib S, et al. Modified magrath regimens for adults with Burkitt and Burkitt-like lymphoma: preserved efficacy with decreased toxicity. Leuk Lymphoma 2004;45:761-767.

Mead GM, Sydes MR, Walewski J, et al. An international evaluation of CODOX-M and CODOX-M alternating with IVAC in adult Burkitt's lymphoma: results of United Kingdom Lymphoma Group LY06 study. Ann Oncol 2002;13:1264-1274.

Barnes JA, Lacasce AS, Feng Y, et al. Evaluation of the addition of rituximab to CODOX-M/IVAC for Burkitt's lymphoma: a retrospective analysis. Ann Oncol 2011;22:1859-1864.

Evens AM, Carson KR, Kolesar J, et al. A multicenter phase II study incorporating high-dose rituximab and liposomal doxorubicin into the CODOX-M/IVAC regimen for untreated Burkitt's lymphoma. Ann Oncol 2013;24:3076-3081.

Dose-adjusted EPOCH plus rituximab (regimen includes IT methotrexate)

Dunleavy K, Pittaluga S, Shovlin M, et al. Low-intensity therapy in adults with Burkitt's lymphoma. N Engl J Med 2013;369:1915-1925.

Roschewski M, Dunleavy K, Abramson JS, et al. Risk-adapted therapy in adults with Burkitt lymphoma: Results of NCI 9177, a multicenter prospective phase II study of DA-EPOCH-R [abstract]. Blood 2018;130 (Suppl 1):Abstract 188.

HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine + rituximab

Thomas DA, Faderl S, O'Brien S, Bueso-Ramos C, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer 2006;106:1569-1580.

Thomas DA, Kantarjian HM, Cortes J, et al. Long-term outcome after hyper-CVAD and rituximab chemoimmunotherapy for Burkitt (BL) or Burkitt-like (BLL) leukemia/lymphoma and mature B-cell acute lymphocytic leukemia (ALL) [abstract]. Blood 2008;112:Abstract 1929.

Second-line Therapy

RICE (rituximab, ifosfamide, carboplatin, etoposide)

Griffin TC, Weitzman S, Weinstein H, et al. A study of rituximab and ifosfamide, carboplatin, and etoposide chemotherapy in children with recurrent/refractory B-cell (CD20+) non-Hodgkin lymphoma and mature B-cell acute lymphoblastic leukemia: A report from the Children's Oncology Group. Pediatr Blood Cancer 2009;52:177-181.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ADDITIONAL DIAGNOSTIC TESTING

ESSENTIAL:

- **Adequate immunophenotyping to establish diagnosis[a] and subclassification (DLBCL, Burkitt, Plasmablastic, Primary effusion lymphoma [PEL])**
  - **IHC panel: CD45, CD20, CD3, CD10, BCL2, BCL6, Ki-67, CD138, kappa/lambda, HHV8 LANA,[b] CD30 for PEL, with or without**
  - **Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD3, CD5, CD19, CD10, CD20**
- **EBER-ISH**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **Molecular analysis to detect: antigen receptor gene rearrangements; *BCL2*; *BCL6*; *MYC* rearrangements**
- **Karyotype or FISH: *BCL2*; *BCL6*; *MYC***

→ See Workup (AIDS-2)

[a] See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).
[b] HHV8 can also be detected by PCR.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

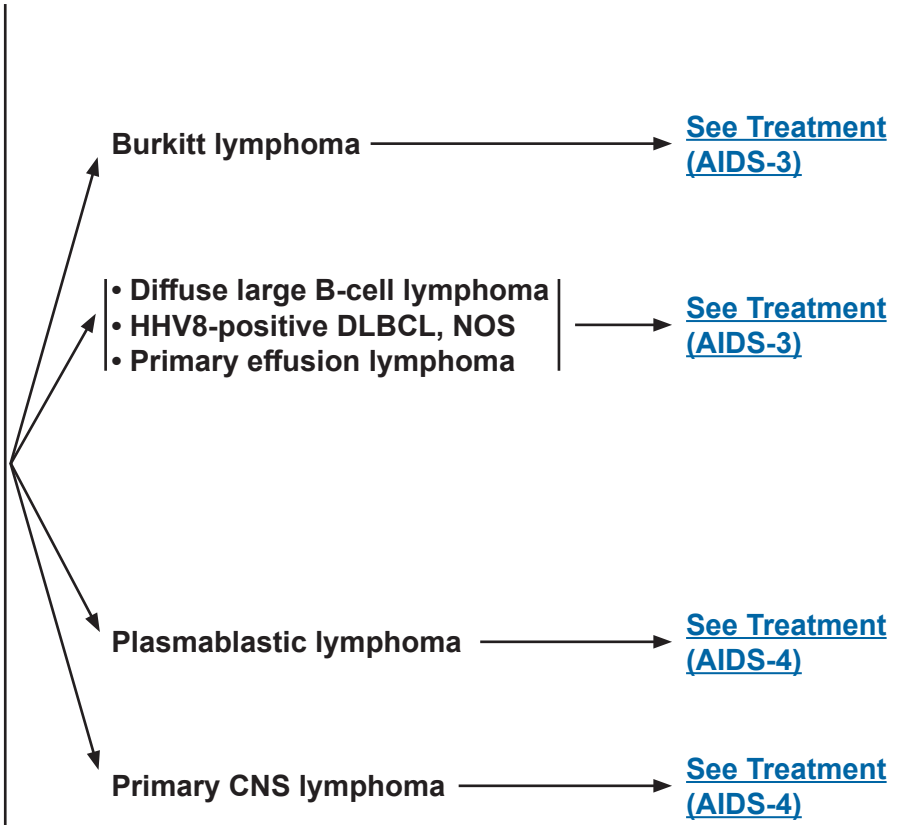
WORKUP

ESSENTIAL

- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC with differential
- LDH
- Comprehensive metabolic panel
- Uric acid, phosphate
- C/A/P CT with contrast of diagnostic quality and/or whole-body PET/CT scan
- Bone marrow biopsy ± aspirate
- CD4 count
- Lumbar puncture, except for PEL and early-stage DLBCL
- HIV viral load
- Hepatitis B testing[c]
- Hepatitis C testing[d]
- Echocardiogram or MUGA scan if anthracycline or anthracenedione-based regimen is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy or RT planned)

USEFUL IN SELECTED CASES:

- UGI/barium enema/endoscopy
- Neck CT with contrast
- Plain bone radiographs and bone scan
- Discussion of fertility issues and sperm banking
- Beta-2-microglobulin
- Brain MRI with contrast, or head CT with contrast
- EBV viral load
- Quantitative immunoglobulins



[c]Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.
[d]Hepatitis C antibody and if positive, viral load and consult with hepatologist.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

TREATMENT[e]

Antiretrovirals (ARVs) can be administered safely with chemotherapy but consultation with an HIV specialist or pharmacist is important to optimize compatibility. With continued development of new ARVs, effective alternatives are often available to patients when the existing ARVs are expected to affect metabolism of or share toxicities with chemotherapy. In general, avoidance of zidovudine, cobicistat, and ritonavir is strongly recommended. Concurrent ART is associated with higher CR rates (Barta et al. Blood 2013,122:3251-3262).

Burkitt lymphoma →

- **Suggested regimens:[f,g]**
  - **Preferred regimens**
    - ◊ **CODOX-M/IVAC (modified): cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate alternating with ifosfamide, etoposide, high-dose cytarabine ± rituximab**
    - ◊ **Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab[h]**
  - **Other recommended regimen**
    - ◊ **HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab**
- **If CD4 <50, maximize supportive care**
- **GCSF for all patients**

→ **For relapse, see second-line regimens (BURK-A)**

- **Diffuse large B-cell lymphoma**
- **HHV8-positive DLBCL, NOS**
- **Primary effusion lymphoma**

→

- **Suggested regimens:[f,g]**
  - **Dose-adjusted EPOCH + rituximab[h] (preferred)**
  - **CHOP + rituximab**
- **GCSF for all patients**
- **Intrathecal therapy (IT)[i]**
- **If CD20-, rituximab is not indicated**
- **If CD4 <50, maximize supportive care**

→ **For relapse, see BCEL-7**

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

[e] See Supportive Care (AIDS-A).
[f] See references for regimens (AIDS-B).
[g] Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.
[h] For dose-adjusted EPOCH + rituximab dosing, see Sparano J, et al. Blood 2010;115:3008-3016.
[i] Prophylactic IT methotrexate is used at some NCCN Member Institutions for all patients with HIV-associated DLBCL. At other NCCN Member Institutions, patients receive IT methotrexate in selective settings (4–6 factors according to prognostic model, HIV lymphoma, testicular, double hit lymphoma). See Prognostic Model to Assess the Risk of CNS Disease (BCEL-A 2 of 2).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

TREATMENT[e]

ARVs can be administered safely with chemotherapy but consultation with an HIV specialist or pharmacist is important to optimize compatibility. With continued development of new ARVs, effective alternatives are often available to patients when the existing ARVs are expected to affect metabolism of or share toxicities with chemotherapy. In general, avoidance of zidovudine, cobicistat, and ritonavir is strongly recommended. Concurrent ART is associated with higher CR rates (Barta et al. Blood 2013,122:3251-3262).

Plasmablastic lymphoma[j] →

- **Standard CHOP is not adequate therapy**
- **Suggested regimens:[f]**
  - **Dose-adjusted EPOCH (preferred)**
  - **CODOX-M/IVAC (modified)**
  - **HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine)**
- **Consider high-dose therapy with autologous stem cell rescue in first complete remission in select high-risk patients[k]**

Primary CNS lymphoma →

- **Initiate ART, if not already receiving**
- **Even with poorly controlled HIV and/or marginal performance status, consider high-dose methotrexate**
- **For select patients with good performance status on ART, see NCCN Guidelines for CNS - Primary CNS Lymphoma**
- **Consider RT alone for palliation of patients who are not candidates for systemic therapy**
- **Best supportive care (See NCCN Guidelines for Palliative Care)**

See monoclonal antibody and viral reactivation (NHODG-B)

[e] See Supportive Care (AIDS-A).
[f] See references for regimens (AIDS-B).
[j] Management can also apply to HIV-negative plasmablastic lymphoma.
[k] High-risk features include an age-adjusted IPI higher than 2, presence of *MYC* gene rearrangement or *TP53* gene deletion. Note that HIV-negative patients with plasmablastic lymphoma are generally considered to have higher risk disease. Optimization of HIV control with antiretroviral therapy is important.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUPPORTIVE CARE

- **Increased risk of infectious complications mitigated with improved HIV control and aggressive infection prophylaxis:**
  - **Patients not on ART at diagnosis may initiate ART during staging period, or alternately initiate after first cycle of chemotherapy. All ART initiation or changes should be done in consultation with an HIV specialist.**
  - **ARVs can be administered safely with chemotherapy but consultation with an HIV specialist or pharmacist is important to optimize compatibility. With continued development of new ARVs, effective alternatives are often available to patients when the existing ARVs are expected to affect metabolism of or share toxicities with chemotherapy. In general, avoidance of zidovudine, cobicistat, and ritonavir is strongly recommended.**
- **Required for all:**
  - **Growth factor support: begin 24–48 hours after chemotherapy and continue past nadir recovery of blood counts of each cycle**
  - **PJP prophylaxis: Continue until CD4 recovered to >200 post completion of chemotherapy**
  - **Gram-negative rods: Quinolone prophylaxis or equivalent during period of neutropenia**
  - **MAC prophylaxis for CD4 <100**
- **Strongly consider**
  - **Fungal: Azole antifungals should be held 24 hours prior to through 24 hours post chemotherapy with CYP3A4 metabolism**
  - **VZV/HSV prophylaxis**
- **Strongly encourage consultation with infectious disease specialist for febrile neutropenia in context of extensive prophylaxis as well as for refractory diarrhea.**

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS
References

CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate alternating with ifosfamide, etoposide, high-dose cytarabine) ± rituximab

Wang ES, Straus DJ, Teruya-Feldstein J, et al. Intensive chemotherapy with cyclophosphamide, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine (CODOX-M/IVAC) for human immunodeficiency virus-associated Burkitt lymphoma. Cancer 2003;98:1196-1205.

Barnes JA, LaCasce AS, Feng Y, et al. Evaluation of the addition of rituximab to CODOX-M/IVAC for Burkitt's lymphoma: A retrospective analysis. Ann Oncol 2011; 22:1859-1864.

Noy A, Lee JY, Cesarman E, et al. AMC 048: modified CODOX-M/IVAC-rituximab is safe and effective for HIV-associated Burkitt lymphoma. Blood 2015;126:160-166.

Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)

Little RF, Pittaluga S, Grant N, et al. Highly effective treatment of acquired immunodeficiency syndrome-related lymphoma with dose-adjusted EPOCH: impact of antiretroviral therapy suspension and tumor biology. Blood 2003;101:4653-4659.

Dose-adjusted EPOCH + rituximab

Barta SK, Lee JY, Kaplan LD, et al. Pooled analysis of AIDS malignancy consortium trials evaluating rituximab plus CHOP or infusional EPOCH chemotherapy in HIV-associated non-Hodgkin lymphoma. Cancer 2012;118:3977-3983.

Bayraktar UD, Ramos JC, Petrich A, et al. Outcome of patients with relapsed/refractory acquired immune deficiency syndrome-related lymphoma diagnosed 1999-2008 and treated with curative intent in the AIDS Malignancy Consortium. Leuk Lymphoma 2012;53:2383-2389.

Sparano, JA, Lee, JY, Kaplan, L D, et al. Rituximab plus concurrent infusional EPOCH chemotherapy is highly effective in HIV-associated B-cell non-Hodgkin lymphoma. Blood 2010;115:3008-3016.

CDE + rituximab

Spina M, Jaeger U, Sparano JA, et al. Rituximab plus infusional cyclophosphamide, doxorubicin, and etoposide in HIV-associated non-Hodgkin lymphoma: Pooled results from 3 phase 2 trials. Blood 2005;105:1891-1897.

Spina M, Simonelli C, Vaccher E, et al. Long-term follow-up of rituximab and infusional cyclophosphamide, doxorubicin, and etoposide (CDE) in combination with HAART in HIV related Non-Hodgkin's Lymphomas (NHL). Blood 2008;112:Abstract 1467.

HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) ± rituximab

Cortes J, Thomas D, Rios A, et al. Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone and highly active antiretroviral therapy for patients with acquired immunodeficiency syndrome-related Burkitt lymphoma/leukemia. Cancer 2002;94:1492-1499.

Thomas DA, Faderl S, O'Brien S, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer 2006;106:1569-1580.

Thomas DA, Kantarjian HM, Faderl S, et al. Hyper-CVAD and rituximab for de novo Burkitt lymphoma/leukemia [abstract]. Blood 2011;118:Abstract 2698.

CHOP + rituximab

Boue F, Gabarre J, Gisselbrecht C, et al. Phase II trial of CHOP plus rituximab in patients with HIV-associated non-Hodgkin's lymphoma. J Clin Oncol 2006;24:4123-4128.

Ribera JM, Oriol A, Morgades M, et al. Safety and efficacy of cyclophosphamide, adriamycin, vincristine, prednisone and rituximab in patients with human immunodeficiency virus-associated diffuse large B-cell lymphoma: results of a phase II trial. Br J Haematol 2008;140:411-419.

Rituximab and CD4 counts

Sparano JA, Lee JY, Kaplan LD et al. Rituximab plus concurrent infusional EPOCH chemotherapy is highly effective in HIV-associated B-cell non-Hodgkin lymphoma. Blood 2010;115:3008-3016.

Kaplan LD, Lee JY, Ambinder RF, et al. Rituximab does not improve clinical outcome in a randomized phase 3 trial of CHOP with or without rituximab in patients with HIV-associated non-Hodgkin lymphoma: AIDS-Malignancies Consortium Trial 010. Blood 2005;106:1538-1543.

Barta SK, Xue X, Wang D, et al. Treatment factors affecting outcomes in HIV-associated non-Hodgkin lymphomas: a pooled analysis of 1546 patients. Blood 2013;122:3251-3262.

Barta SK, Lee JY, Kaplan LD, et al. Pooled analysis of AIDS malignancy consortium trials evaluating rituximab plus CHOP or infusional EPOCH chemotherapy in HIV-associated non-Hodgkin lymphoma. Cancer 2012;118:3977-3983.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ADDITIONAL DIAGNOSTIC TESTING[a,b]

ESSENTIAL:

- **Adequate immunophenotyping to establish diagnosis[c]**
  - **IHC panel: CD45, CD19, CD20, CD79a, CD3, CD2, CD5, CD7, TdT, CD1a, CD10, cyclin D1 with or without**
  - **Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD3, CD5, CD4, CD7, CD8, CD19, CD20, CD10, TdT, CD13, CD33, CD1a, cytoplasmic CD3, CD22, myeloperoxidase**
- **Karyotype ± FISH: *MYC*; t(9;22); t(8;14), and variants or PCR for *BCR-ABL***

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **Additional immunohistochemical studies to establish lymphoma subtype**
  - **Paraffin panel: CD22, CD4, CD8, cyclin D1**
- **Molecular analysis to detect: antigen receptor gene rearrangements**

→

WORKUP

ESSENTIAL:

- **Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen**
- **Performance status**
- **B symptoms**
- **CBC with differential**
- **LDH**
- **Comprehensive metabolic panel**
- **Uric acid, phosphate**
- **C/A/P CT with contrast of diagnostic quality**
- **Lumbar puncture**
- **Flow cytometry of cerebrospinal fluid**
- **Bilateral or unilateral bone marrow biopsy ± aspirate with flow and cytogenetics**
- **Hepatitis B testing[d]**
- **Echocardiogram or MUGA scan if anthracycline or anthracenedione-based regimen is indicated**
- **Pregnancy testing in women of child-bearing age (if chemotherapy or RT planned)**

USEFUL IN SELECTED CASES:

- **Brain MRI with contrast**
- **Discussion of fertility issues and sperm banking**
- **Beta-2-microglobulin**
- **Whole-body PET/CT scan[e]**

→ **See NCCN Guidelines for Acute Lymphoblastic Leukemia**

[a]The lymphoblastic lymphoma (LL) category comprises two diseases, T-cell LL (LL-T; 90%) and B-cell LL (LL-B; 10%), which corresponds to T-ALL and B-ALL, respectively, with presentations in extramedullary sites.

[b]This disease is complex and curable; it is preferred that treatment occur at centers with expertise in the management of the disease.

[c]Typical immunophenotype: *LL-B*: sIg-, CD10+/-, CD19+, CD20-/+, TdT+. *LL-T*: sIg-, CD10-, CD19/20-, CD3-/+, CD4/8+/+, CD1a+/-, TdT+, CD2+, CD7+ cytoplasmic CD3+, sCD3-/+.

[d]Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

[e]Initiation of therapy should not be delayed in order to obtain a PET/CT scan.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018
Post-Transplant Lymphoproliferative Disorders

NCCN Guidelines Index
Table of Contents
Discussion

ADDITIONAL DIAGNOSTIC TESTING

ESSENTIAL:
- Adequate immunophenotyping to establish diagnosis
  - IHC panel: CD3, CD5, CD10, BCL6, BCL2, IRF4/MUM1, CD20, CD79a, PAX5, Ki-67, kappa, lambda with or without
  - Cell surface marker analysis by flow cytometry: CD3, CD5, CD7, CD4, CD8, CD19, CD20, CD10, kappa, lambda
- Epstein-Barr virus evaluation by EBV-LMP1 or EBER-ISH (if EBV-LMP1 negative, EBER-ISH is recommended)

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- Additional immunophenotyping
  - IHC panel: CD15, CD30, CD45, CD7, CD4, CD8, ALK, TIA-1, Granzyme B, CD57, CD56, CD138
  - Cell surface marker analysis by flow cytometry: CD138, cytoplasmic kappa and lambda, CD30, CD57, CD56, CD16, CD25, CD52.
- Molecular analysis to detect: *IGHV* gene rearrangements
- *BCL6* gene mutation analysis[a]
- EBV by southern blot

WORKUP

ESSENTIAL:
- Performance status
- Albumin
- Immunosuppressive regimen
- LDH, electrolytes, BUN, creatinine
- CBC with differential
- Hepatitis B testing[b]
- C/A/P CT with contrast and/or whole-body PET/CT scan
- Pregnancy testing in women of child-bearing age (if chemotherapy or RT planned)

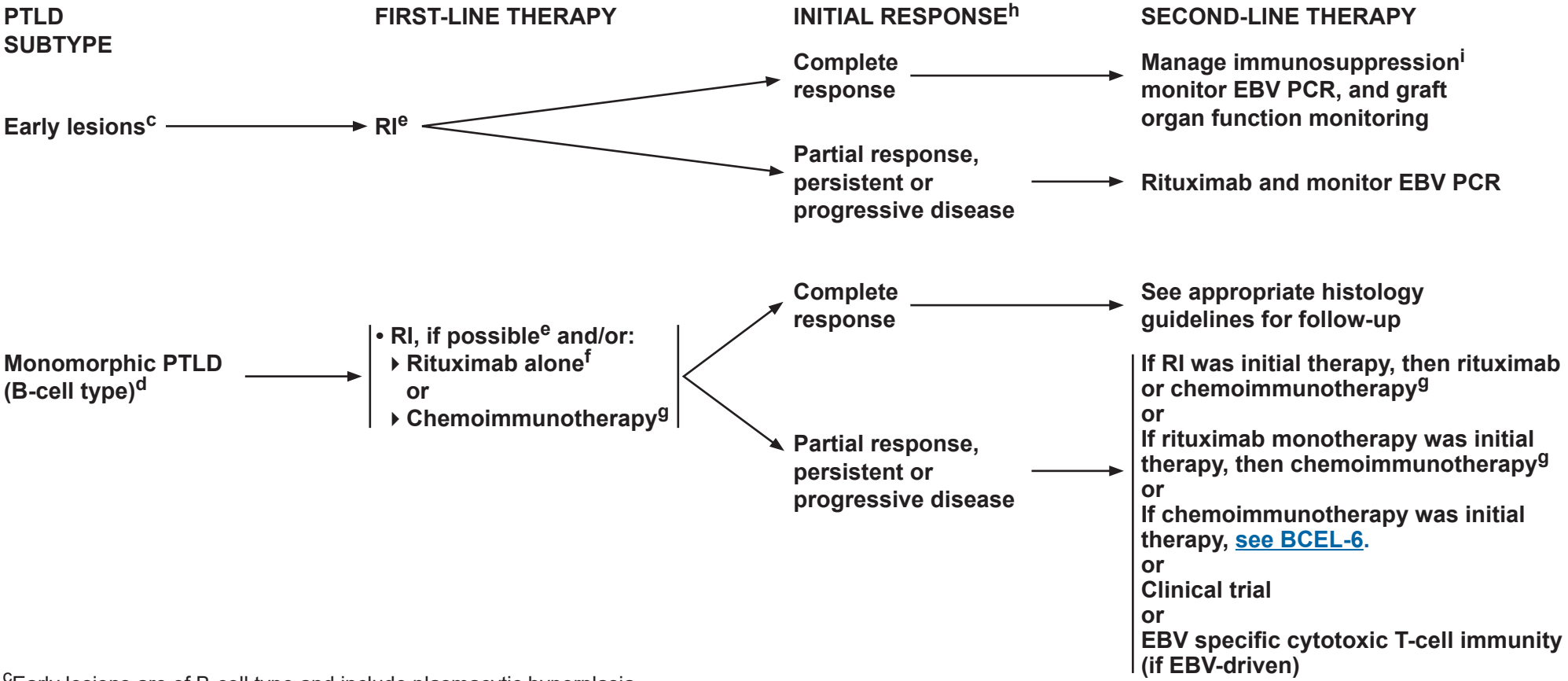
USEFUL IN SELECTED CASES:
- Echocardiogram or MUGA scan if treatment includes regimens containing anthracyclines or anthracenediones
- Bone marrow evaluation
- Brain MRI with and without contrast
- EBV PCR
- CMV PCR
- EBV serology for primary versus reactivation

PTLD SUBTYPE

- Early lesions[c] → See First-line Therapy (PTLD-2)
- Monomorphic[e] PTLD (B-cell type) → See First-line Therapy (PTLD-2)
- Polymorphic[e] PTLD → See First-line Therapy (PTLD-3)
- Monomorphic PTLD (T-cell type) →
  - Other than reduction of immunosuppression (RI), there are no established treatments.
  - Treatment with multiagent T-cell regimens may be considered (see Suggested Regimens PTLD-A); however, autotransplant may not be appropriate.
- Classical Hodgkin lymphoma PTLD → See NCCN Guidelines for Hodgkin Lymphoma

[a] *BCL6* positivity has been associated with a poor response to reduction in immunosuppressive therapy.
[b] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.
[c] Early lesions are of B-cell type and include plasmacytic hyperplasia, infectious mononucleosis, florid follicular hyperplasia.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

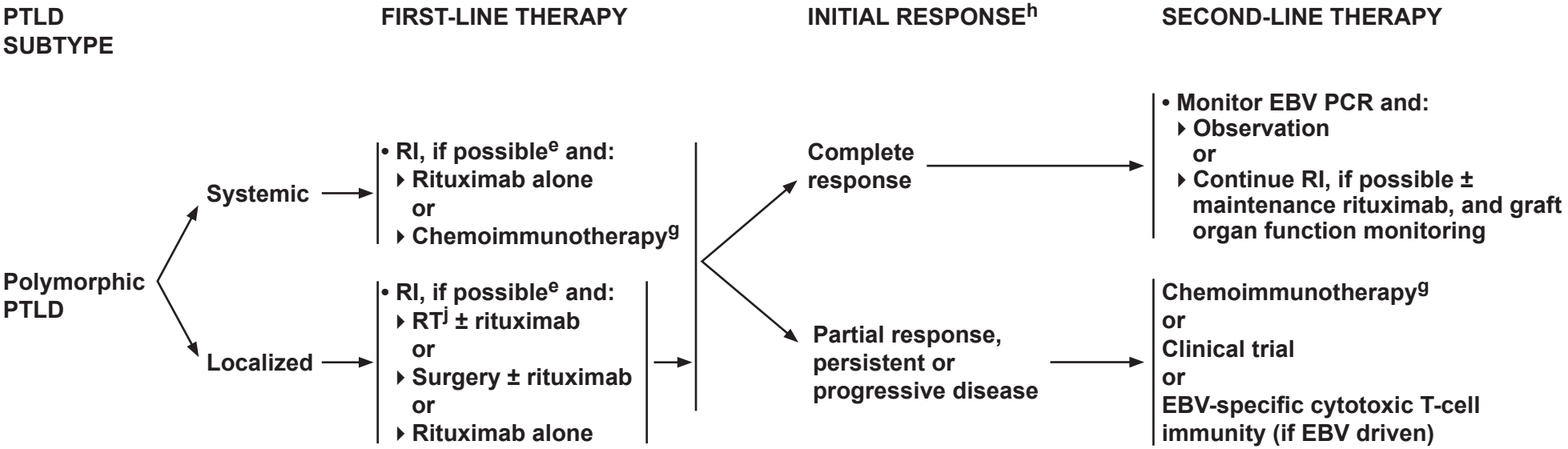


[c]Early lesions are of B-cell type and include plasmacytic hyperplasia, infectious mononucleosis, florid follicular hyperplasia.
[d]Treatment is based on the unique histology.
[e]Response to RI is variable and patients need to be closely monitored; RI should be coordinated with the transplant team. RI: Reduction in calcineurin inhibition (cyclosporin and tacrolimus), discontinuation of antimetabolic agents (azathioprine and mycophenolate mofetil), and for critically ill patients all non-glucocorticoid immunosuppression should be discontinued. Response to RI is variable and patients need to be closely monitored; RI should be coordinated with the transplant team.
[f]As part of a step-wise approach in patients who are not highly symptomatic or cannot tolerate chemotherapy secondary to comorbidity.

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

[g]Concurrent or sequential chemoimmunotherapy, See Suggested Treatment Regimens (PTLD-A).
[h]Restage in two to four weeks.
[i]Re-escalation of immunosuppressive therapy should be individualized, taking into account the extent of initial RI and the nature of the organ allograft. These decisions should be made in conjunction with the transplant team.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

[e]Response to RI is variable and patients need to be closely monitored; RI should be coordinated with the transplant team. RI: Reduction in calcineurin inhibition (cyclosporin and tacrolimus), discontinuation of antimetabolic agents (azathioprine and mycophenolate mofetil), and for critically ill patients all non-glucocorticoid immunosuppression should be discontinued. Response to RI is variable and patients need to be closely monitored; RI should be coordinated with the transplant team.

[g]Concurrent or sequential chemoimmunotherapy, See Suggested Treatment Regimens (PTLD-A).
[h]Restage in two to four weeks.
[j]See Principles of Radiation Therapy (NHODG-D).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS[a]
(in alphabetical order)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

Monomorphic PTLD (B-cell type) and Polymorphic PTLD
Concurrent chemoimmunotherapy

- **RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)**
- **For frail patients who cannot tolerate anthracycline, no specific regimen has been identified but options may include:[b]**
  - **RCVP (rituximab, cyclophosphamide, vincristine, prednisone)**
  - **RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine)**
  - **RCEOP (rituximab, cyclophosphamide, etoposide, vincristine, prednisone)**

Sequential chemoimmunotherapy

- **Rituximab 375 mg/m^2 weekly x 4 weeks[c]**
  - **Restage with PET/CT scan**
    - ◊ **If PET/CT scan negative, rituximab 375 mg/m^2 every 3 weeks x 4 cycles**
    - ◊ **If PET/CT scan positive, CHOP-21 every 3 weeks x 4 cycles**

Monomorphic PTLD (T-cell type)

- **CHOP**
- **CHOEP**
- **For frail patients who cannot tolerate anthracycline, no specific regimen has been identified but options may include:**
  - **CVP**
  - **CEPP**
  - **CEOP**

[a]Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.
[b]There are no published data regarding the use of these regimens; however, they are used at NCCN Member Institutions for the treatment of PTLD.
[c]Trappe R, Oertel S, Leblond V, et al. Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicentre phase 2 PTLD-1 trial. Lancet Oncol 2012;13:196-206.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ADDITIONAL DIAGNOSTIC TESTING[a,b,c]

ESSENTIAL:
- Adequate immunophenotyping to establish diagnosis
  - IHC panel: kappa/lambda, CD20, CD3, CD5, CD138, HHV8
  - EBER-ISH

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- Molecular analysis to detect: immunoglobulin and *TCR* gene rearragements
- IHC: Ki-67 index; Ig heavy chains,[d] CD10, BCL2, BCL6, cyclin D1, CD21, or CD23, CD38, IRF4/MUM1, PAX5
- Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10

→

WORKUP[e]

ESSENTIAL:
- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Performance status
- Assess for criteria for active disease[f]
- CBC with differential
- Comprehensive metabolic panel
- LDH, CRP, ESR
- Beta-2-microglobulin, serum protein electrophoresis and urine electrophoresis with immunofixation, serum light chains, quantitative immunoglobulins
- HIV ELISA, HHV8 DNA titer by PCR, Hepatitis B testing,[g] EBV DNA titer by PCR
- Whole-body PET/CT scan (preferred) or C/A/P CT with contrast of diagnostic quality
- Pregnancy testing in women of child-bearing age (if chemotherapy or RT planned)

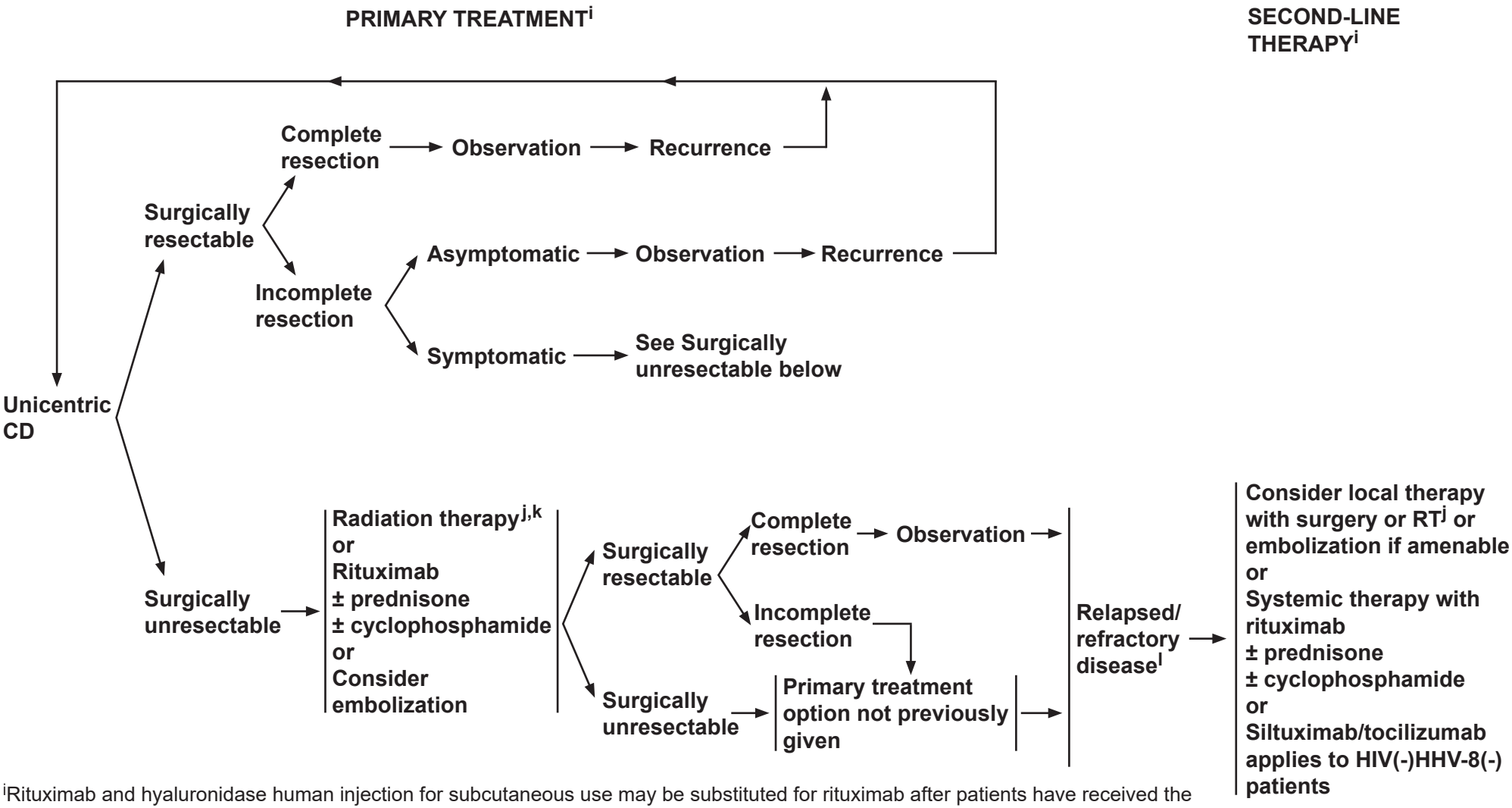
USEFUL UNDER CERTAIN CIRCUMSTANCES
- If HHV8 or HIV positive, screening for concurrent Kaposi's sarcoma is strongly recommended
- Bone marrow biopsy + aspirate
- Neck CT with contrast
- Echocardiogram or MUGA scan if anthracycline or anthracenedione-based regimen is indicated
- sIL6, sIL10, VEGF, uric acid, ferritin[h]
- Hepatitis C testing
- Discussion of fertility issues and sperm banking

→ Unicentric CD → See CD-2

→ Multicentric CD → See CD-3

[a]For AIDS-related lymphoma associated with Castleman's disease, see AIDS-1. For DLBCL-associated with CD in non-HIV patients, see BCEL-1.
[b]There are 2 variants – hyaline vascular (virtually always unicentric, HHV8-) and plasma cell (may be multicentric, often HHV8+, +/- HIV+).
[c]Two types of DLBCL are associated with the HHV8+ PC type: plasmablastic (EBV-) and "germinotropic" (EBV+).
[d]In plasma cell variant HHV8+, plasmablasts are IgM lambda while normal plasma cells are IgG or A polytypic.
[e]If concurrent polyneuropathy and monoclonal plasma cell disorder, a workup for POEMS syndrome is recommended.
[f]See Criteria for Active Disease (CD-A).
[g]Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.
[h]Measurement of acute phase reactants maybe helpful in monitoring therapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



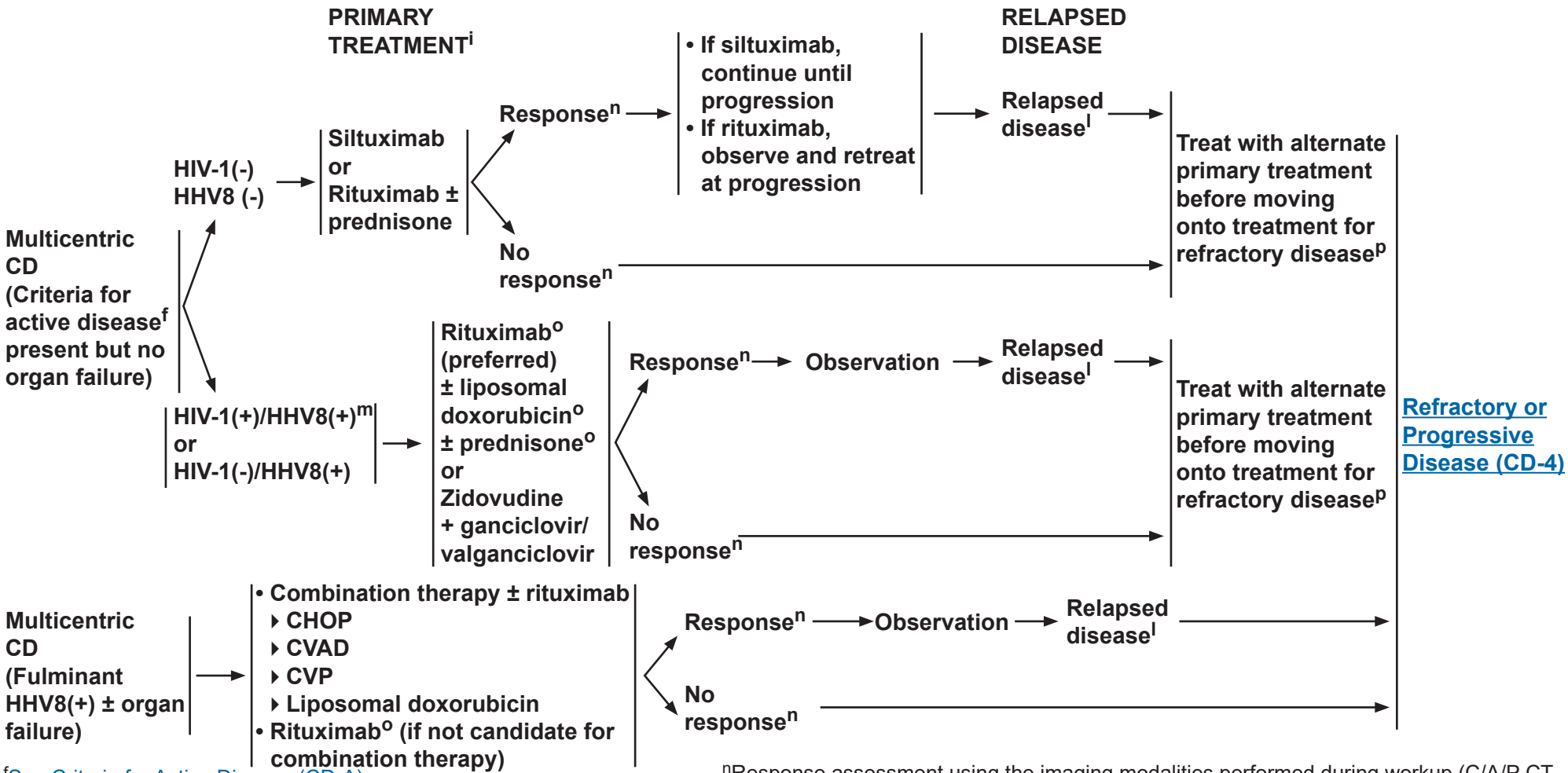
[i]Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.

[j]See Principles of Radiation Therapy (NHODG-D).

[k]Patients with non-bulky disease may be observed after RT.

[l]Encourage biopsy to rule out transformation to DLBCL or concomitant development of other malignancies or opportunistic infections.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[f] See Criteria for Active Disease (CD-A).

[i] Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.

[l] Encourage biopsy to rule out transformation to DLBCL or concomitant development of other malignancies or opportunistic infections.

[m] All HIV+ patients should be on combination antiretroviral therapy (cART).

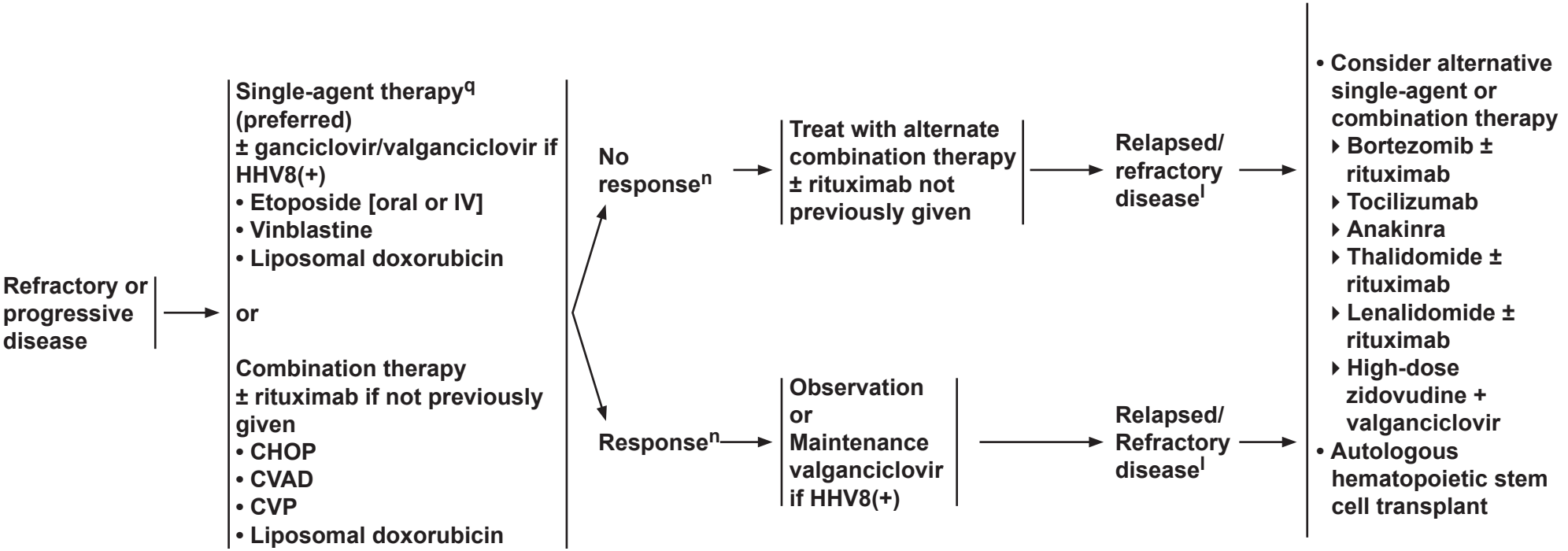
[n] Response assessment using the imaging modalities performed during workup (C/A/P CT with contrast or PET/CT).

[o] Occult Kaposi sarcoma (KS) is prevalent in HIV/HHV8+ MCD and may flare after rituximab or prednisone. Consider baseline imaging and direct visualization to screen for pulmonary ± GI KS as well as concurrent KS-directed therapy (ie, addition of liposomal doxorubicin).

[p] Rituximab ± prednisone may repeat without limit if progression ≥6 months after completion of rituximab.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

REFRACTORY OR PROGRESSIVE DISEASE[i]



[i]Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.l
[l]Encourage biopsy to rule out transformation to DLBCL or concomitant development of other malignancies or opportunistic infections.
[n]Response assessment using the imaging modalities performed during workup (C/A/P CT with contrast or PET/CT).
[q]Single-agent therapy is preferred for asymptomatic patients with no organ failure; combination therapy is preferred for patients with fulminant disease and organ failure.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CRITERIA FOR ACTIVE DISEASE[a]

- **Fever**
- **Increased serum C-reactive protein level >20 mg/L in the absence of any other etiology**
- **At least three of the following other MCD-related symptoms:**
  - **Peripheral lymphadenopathy**
  - **Enlarged spleen**
  - **Edema**
  - **Pleural effusion**
  - **Ascites**
  - **Cough**
  - **Nasal obstruction**
  - **Xerostomia**
  - **Rash**
  - **Central neurologic symptoms**
  - **Jaundice**
  - **Autoimmune hemolytic anemia**

[a]Gérard L, Bérezné A, Galicier L, et al. Prospective study of rituximab in chemotherapy-dependent human immunodeficiency virus-associated multicentric Castleman's disease: ANRS 117 CastlemaB Trial. J Clin Oncol 2007;25:3350-3356.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

USE OF IMMUNOPHENOTYPING/GENETIC TESTING IN DIFFERENTIAL DIAGNOSIS OF MATURE B-CELL AND NK/T-CELL NEOPLASMS[a] (TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)

GENERAL PRINCIPLES

- Morphology ± clinical features drive both the choice and the interpretation of special studies.
- Differential diagnosis is based on morphology ± clinical setting.
- Begin with a broad panel appropriate to morphologic diagnosis, limiting panel of antibodies based on the differential diagnosis.
  - Avoid "shotgun" panels of unnecessary antibodies unless a clinically urgent situation warrants.
- Add antigens in additional panels, based on initial results.
- Follow with genetic studies as needed.
- Return to clinical picture if immunophenotype + morphology are not specific.

Continued on next page (NHODG-A 2 of 11)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

USE OF IMMUNOPHENOTYPING/GENETIC TESTING IN DIFFERENTIAL DIAGNOSIS OF MATURE B-CELL AND NK/T-CELL NEOPLASMS[a] (TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)

B-cell antigens positive[b,c] (CD19, CD20, CD79a, PAX5)

- Morphology
  - Cytology
    - ◊ Small cells
    - ◊ Medium-sized cells
    - ◊ Large cells
  - Pattern
    - ◊ Diffuse
    - ◊ Nodular, follicular, mantle, marginal
    - ◊ Sinuses
- Clinical
  - Age (child, adult)
  - Location
    - ◊ Nodal
    - ◊ Extranodal, specific site
- Immunophenotype
  - Naïve B cells: CD5, CD23
  - GCB cells: CD10, BCL6
  - FDC: CD21, CD23
  - Post-GCB cells: IRF4/MUM1, CD138
  - Immunoglobulin heavy and light chains (surface, cytoplasmic, class switch, light chain type)
  - Oncogene products: BCL2, cyclin D1, MYC, BCL6, ALK
  - Viruses: EBV, HHV8
  - Other: CD43, Ki-67
- Genetic testing
  - BCL2, BCL6, CCND1, MYC, ALK, MYD88, BRAF, IG rearrangement

T- or NK/T-cell antigens positive[b,c] (CD2, CD3, CD5, CD7) [and B-cell antigens negative]

- Morphology
  - Anaplastic vs. non-anaplastic
  - Epidermotropic
- Clinical
  - Age (child, adult)
  - Location
    - ◊ Cutaneous
    - ◊ Extranodal noncutaneous (specific site)
    - ◊ Nodal
- Immunophenotype
  - CD30, ALK*, CD56, ßF1, cytotoxic granule proteins
  - CD4, CD8, CD5, CD7, TCRαß, TCRγδ, CD1a, TdT
  - Follicular T-cells: CD10, BCL6, CD57, PD1/CD279
  - Viruses: EBV, HTLV1 (clonal)
- Genetic testing
  - ALK, TCR, HTLV1

*Always do ALK if CD30+

See Initial Morphologic, Clinical, and Immunophenotypic Analysis (NHODG-A 3 of 11)

[a]These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.

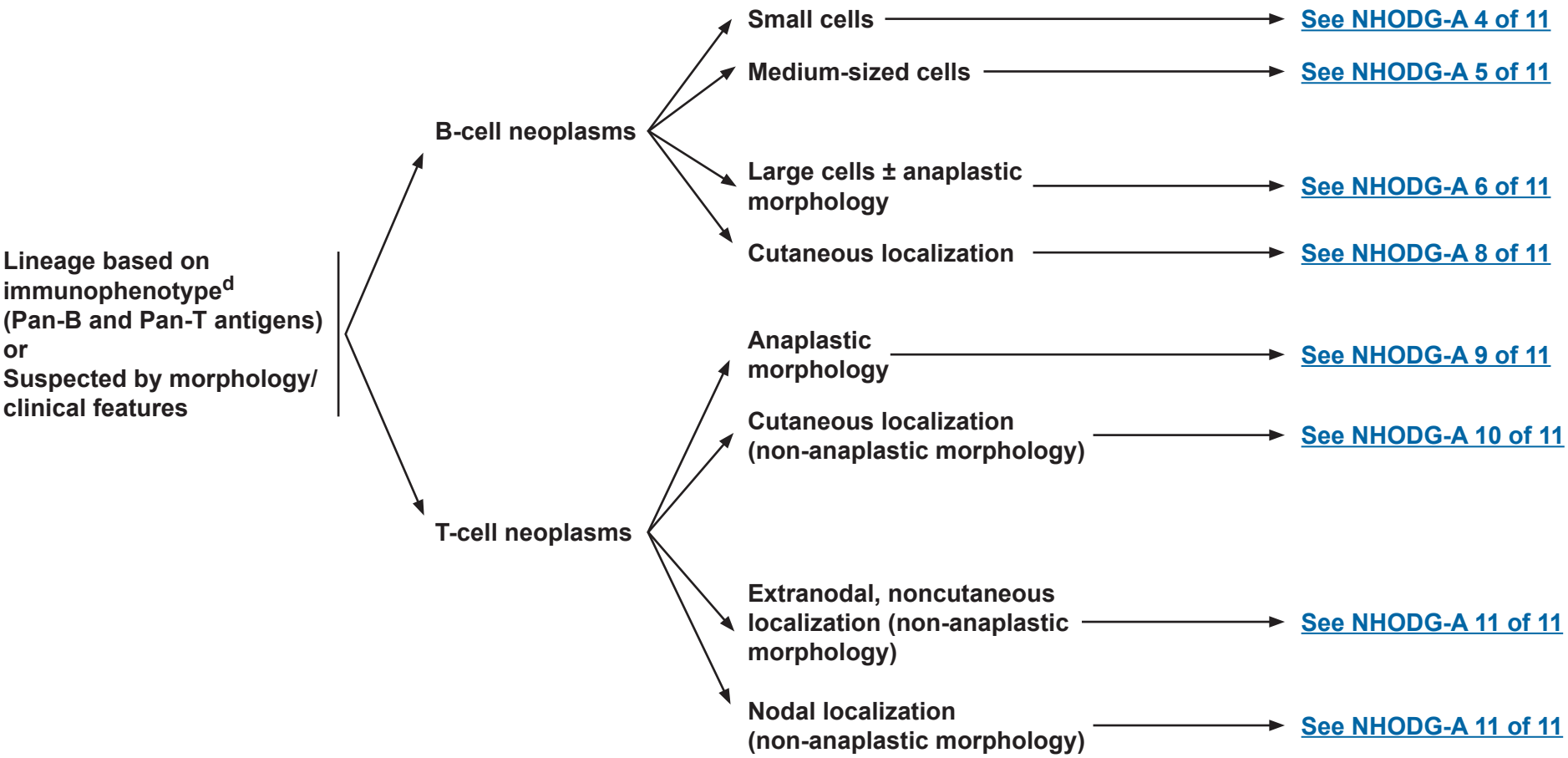
[b]Some lymphoid neoplasms may lack pan leukocyte (CD45), pan-B, and pan-T antigens. Selection of additional antibodies should be based on the differential diagnosis generated by morphologic and clinical features (eg, plasma cell myeloma, ALK+ DLBCL, plasmablastic lymphoma, anaplastic large cell lymphoma, NK-cell lymphomas).

[c]Usually 1 Pan-B (CD20) and 1 Pan-T (CD3) markers are done unless a terminally differentiated B-cell or a specific PTCL is suspected.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

USE OF IMMUNOPHENOTYPING/GENETIC TESTING IN DIFFERENTIAL DIAGNOSIS OF MATURE B-CELL AND NK/T-CELL NEOPLASMS[a] (TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)

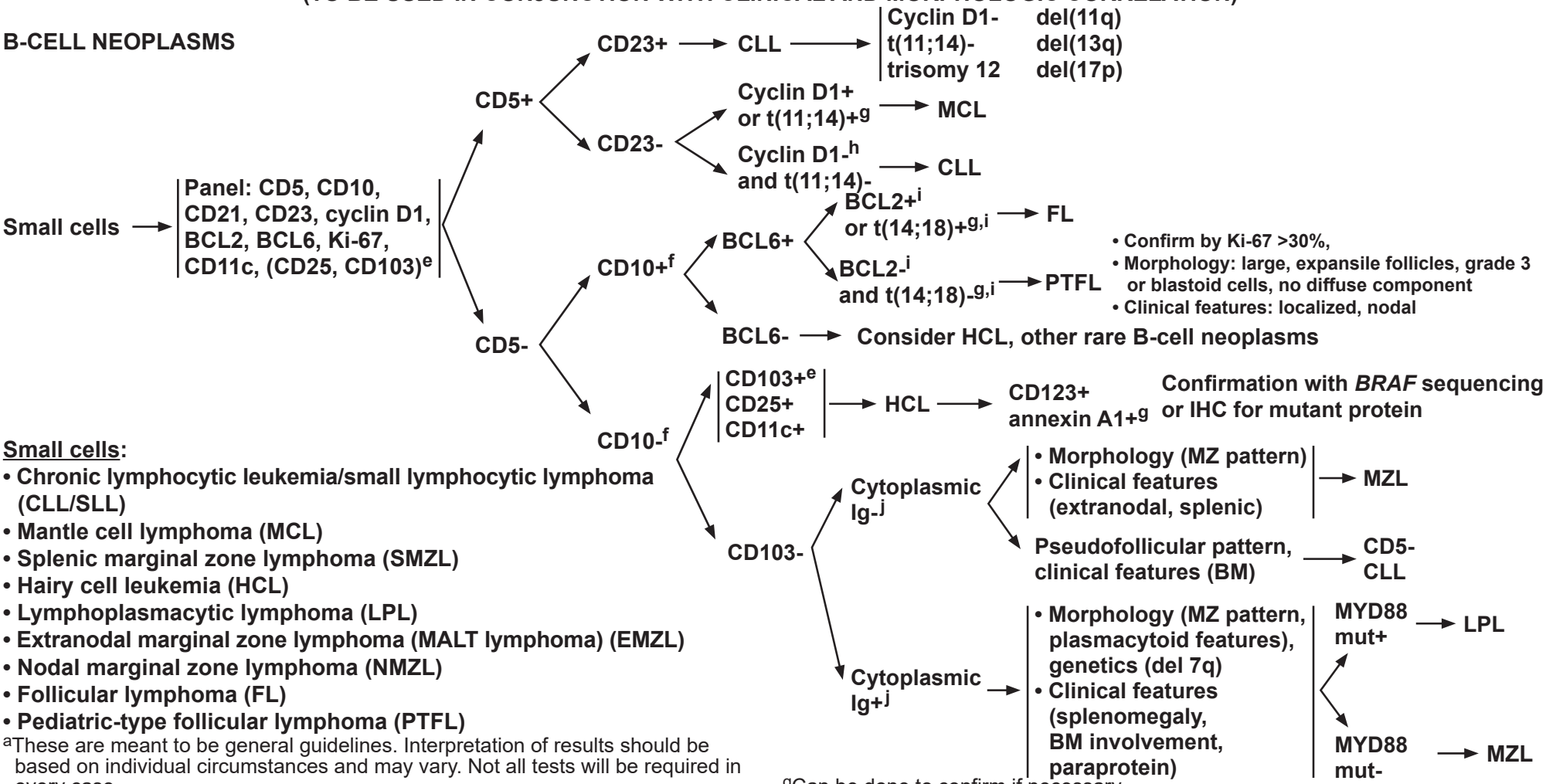
INITIAL MORPHOLOGIC, CLINICAL, AND IMMUNOPHENOTYPIC ANALYSIS



[a]These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.
[d]Initial panel will often include additional markers based on morphologic differential diagnosis and clinical features.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

USE OF IMMUNOPHENOTYPING/GENETIC TESTING IN DIFFERENTIAL DIAGNOSIS OF MATURE B-CELL AND NK/T-CELL NEOPLASMS[a] (TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)



Small cells:

- Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)
- Mantle cell lymphoma (MCL)
- Splenic marginal zone lymphoma (SMZL)
- Hairy cell leukemia (HCL)
- Lymphoplasmacytic lymphoma (LPL)
- Extranodal marginal zone lymphoma (MALT lymphoma) (EMZL)
- Nodal marginal zone lymphoma (NMZL)
- Follicular lymphoma (FL)
- Pediatric-type follicular lymphoma (PTFL)

[a]These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.

[e]Flow cytometry on blood or bone marrow done only if HCL is in differential diagnosis by morphology.

[f]Rare cases of HCL may be CD10+ or CD5+ and some cases of FL are CD10-. BCL6 is a useful discriminate if needed (rarely). Rare cases of MCL are CD5-.

[g]Can be done to confirm if necessary.

[h]Rare cases of cyclin D1 and t(11;14) negative MCL have been reported. This diagnosis should be made with extreme caution and with expert consultation.

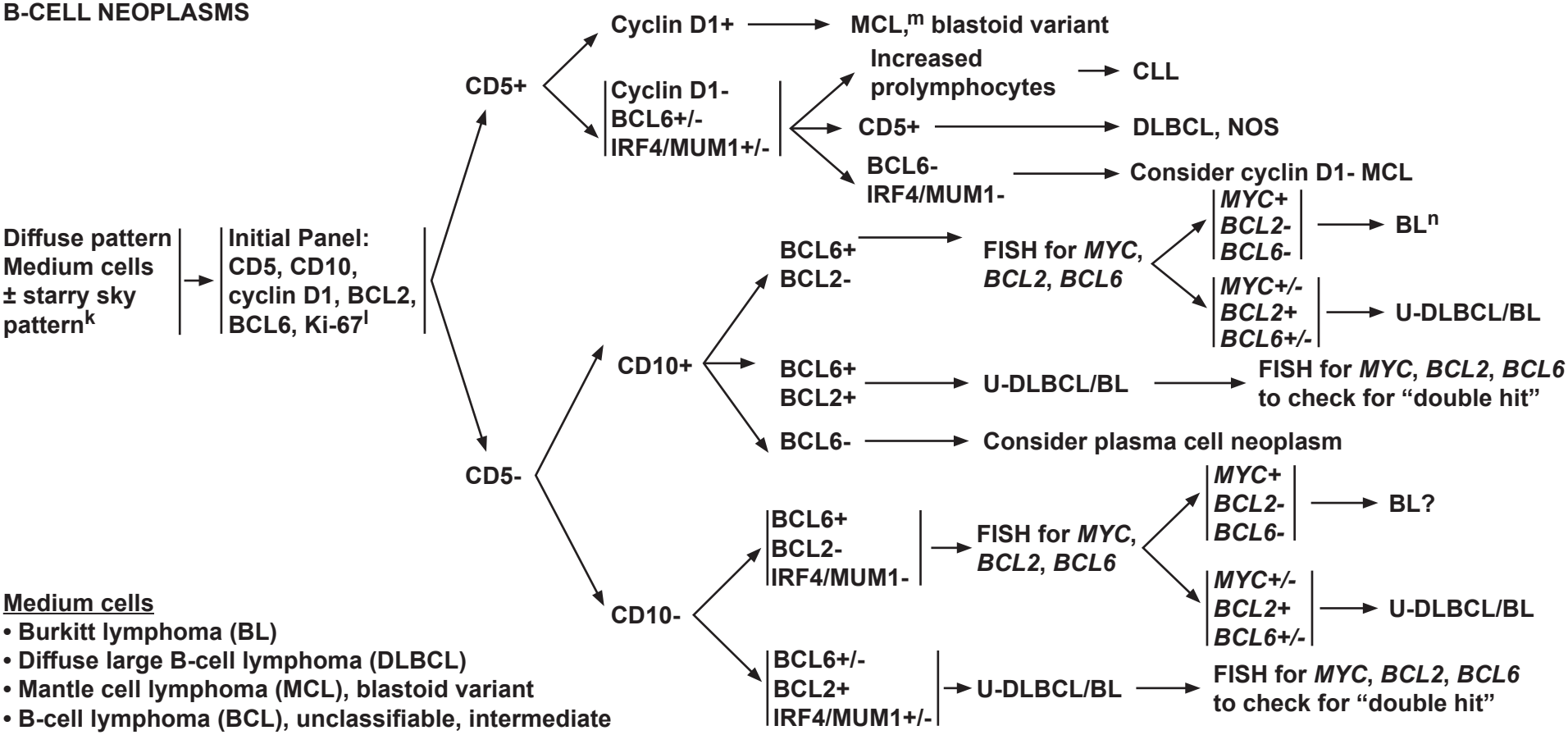
[i]85% of follicular lymphoma will be BCL2+ or t(14;18)+.

[j]Kappa and lambda light chains; IgG, IgM, and IgA may be helpful.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

USE OF IMMUNOPHENOTYPING/GENETIC TESTING IN DIFFERENTIAL DIAGNOSIS OF MATURE B-CELL AND NK/T-CELL NEOPLASMS[a] (TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)

B-CELL NEOPLASMS



Medium cells

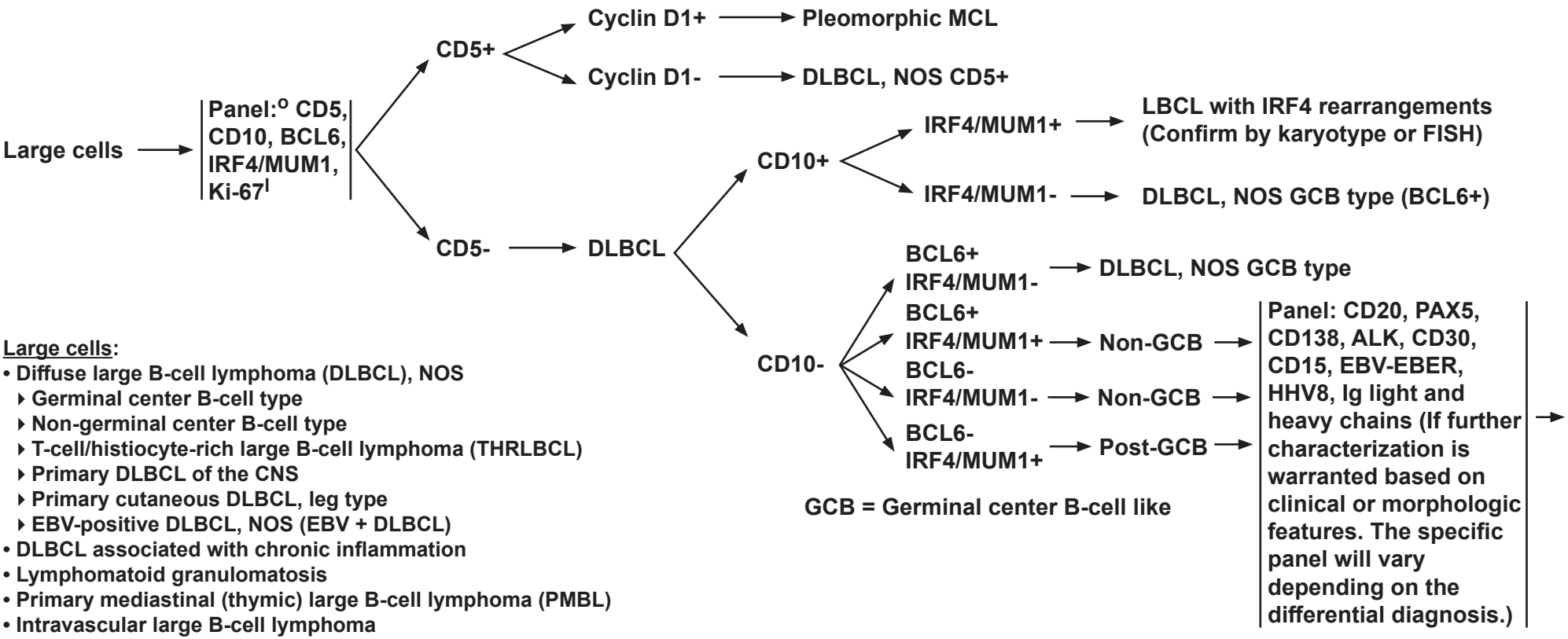
- **Burkitt lymphoma (BL)**
- **Diffuse large B-cell lymphoma (DLBCL)**
- **Mantle cell lymphoma (MCL), blastoid variant**
- **B-cell lymphoma (BCL), unclassifiable, intermediate between DLBCL and BL (U-DLBCL/BL)**

[a]These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.
[k]Starry sky pattern is typically present in BL and frequently in U-DLBCL/BL.
[l]Ki-67 is a prognostic factor in some lymphomas (eg, mantle cell and is typically >90% in Burkitt lymphoma). It is not useful in predicting the presence of MYC rearrangement or in classification.
[m]Rare MCL may be cyclin D1-.
[n]Rare BL may lack detectable MYC rearrangement. Correlation with morphology and clinical features is essential.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

USE OF IMMUNOPHENOTYPING/GENETIC TESTING IN DIFFERENTIAL DIAGNOSIS OF MATURE B-CELL AND NK/T-CELL NEOPLASMS[a] (TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)

B-CELL NEOPLASMS



Large cells:

- Diffuse large B-cell lymphoma (DLBCL), NOS
  - Germinal center B-cell type
  - Non-germinal center B-cell type
  - T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL)
  - Primary DLBCL of the CNS
  - Primary cutaneous DLBCL, leg type
  - EBV-positive DLBCL, NOS (EBV + DLBCL)
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma (PMBL)
- Intravascular large B-cell lymphoma
- ALK-positive large B-cell lymphoma
- Plasmablastic lymphoma
- HHV8+ Large B-cell lymphoma NOS
- Large B-cell Lymphoma (LBCL) with IRF4 rearrangement
- Primary effusion lymphoma
- B-cell lymphoma, unclassifiable, intermediate between DLBCL (U-DLBCL) and classical Hodgkin lymphoma (CHL)
- Mantle cell lymphoma (MCL), pleomorphic variant

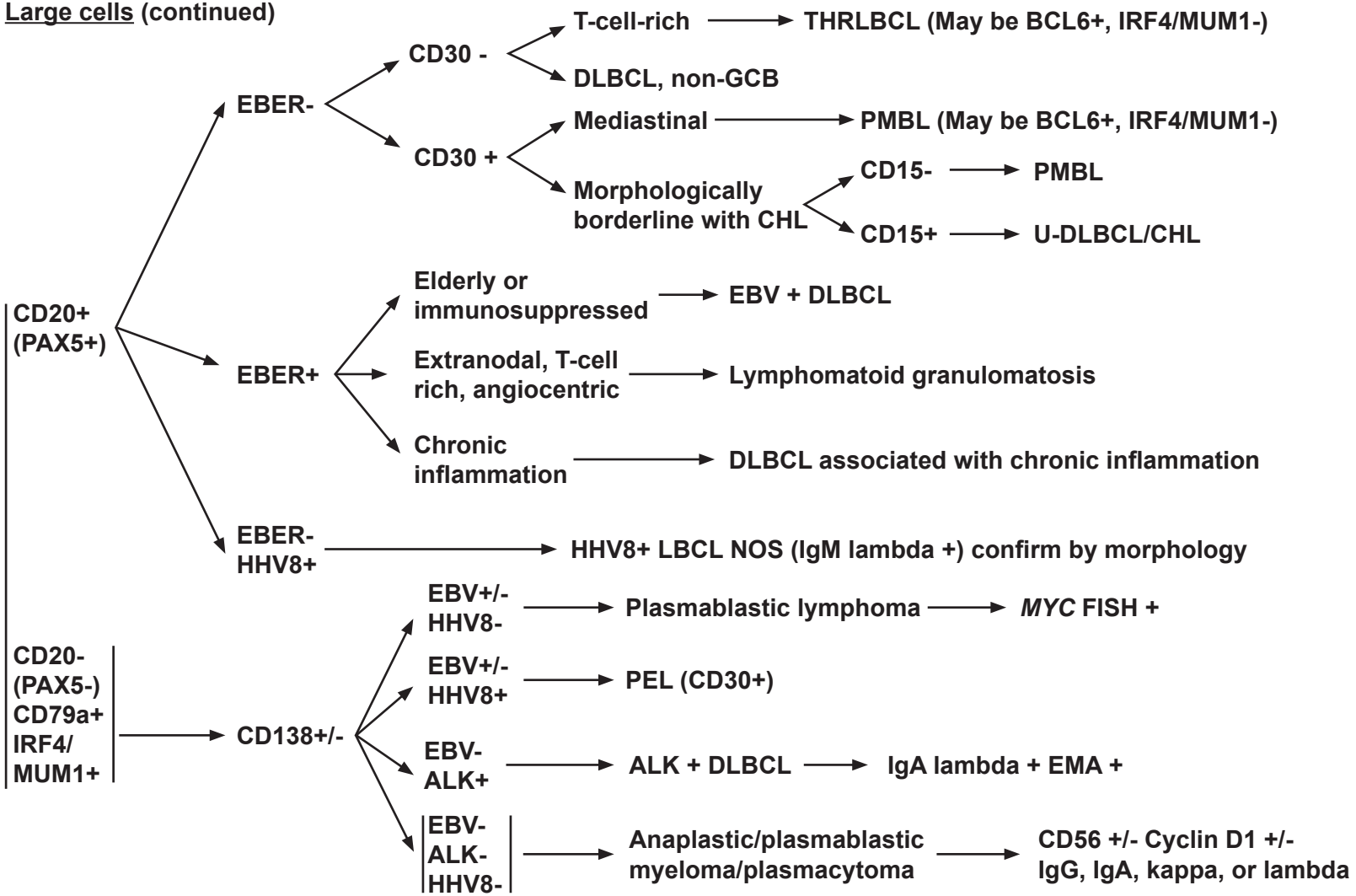
Continued

[a]These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.
[l]Ki-67 is a prognostic factor in some lymphomas (eg, mantle cell and is typically >90% in Burkitt lymphoma). It is not useful in predicting the presence of MYC rearrangement or in classification.
[o]CD5 is included to identify pleomorphic MCL; if CD5 is positive, cyclin D1 staining is done to confirm or exclude MCL.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

USE OF IMMUNOPHENOTYPING/GENETIC TESTING IN DIFFERENTIAL DIAGNOSIS OF MATURE B-CELL AND NK/T-CELL NEOPLASMS[a] (TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)

Large cells (continued)



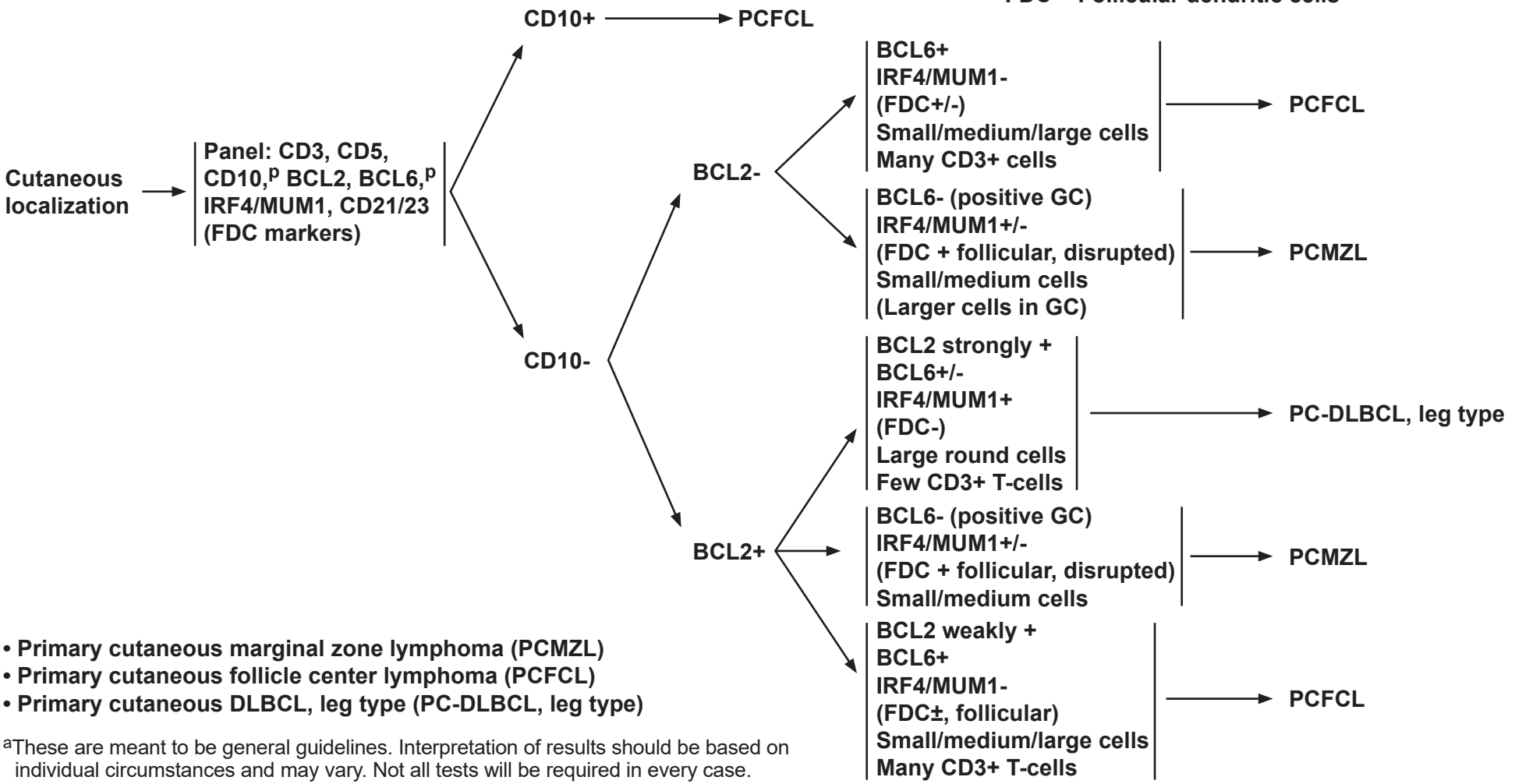
[a]These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

USE OF IMMUNOPHENOTYPING/GENETIC TESTING IN DIFFERENTIAL DIAGNOSIS OF MATURE B-CELL AND NK/T-CELL NEOPLASMS[a] (TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)

B-CELL NEOPLASMS

FDC = Follicular dendritic cells

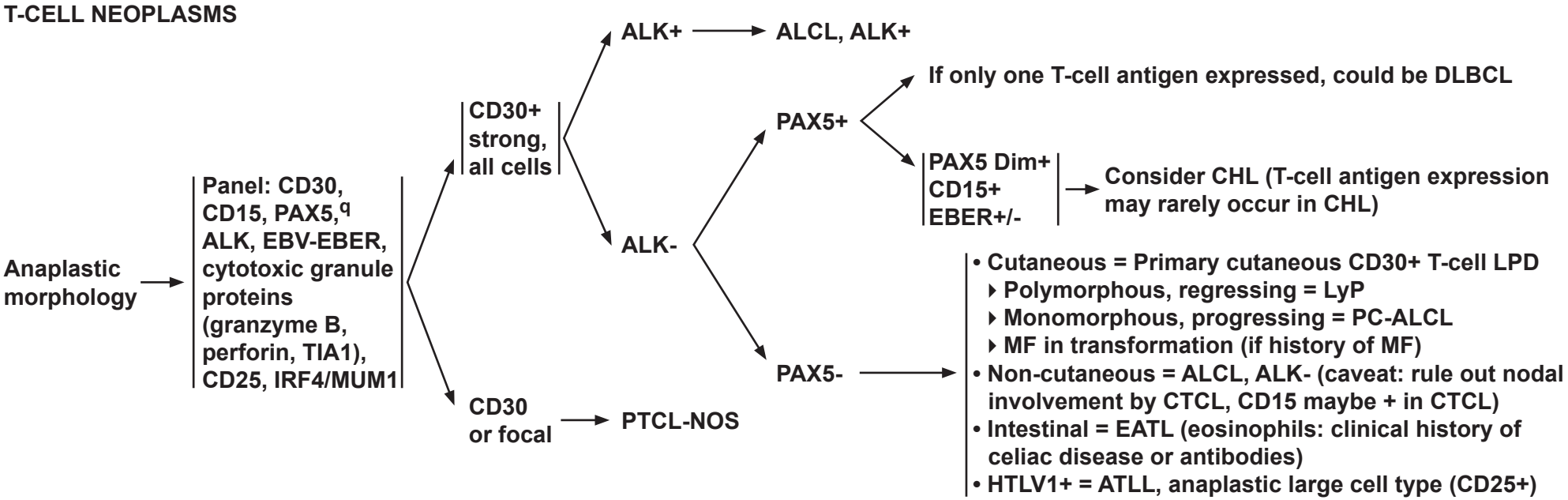


- **Primary cutaneous marginal zone lymphoma (PCMZL)**
- **Primary cutaneous follicle center lymphoma (PCFCL)**
- **Primary cutaneous DLBCL, leg type (PC-DLBCL, leg type)**

[a]These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.
[p]These are assessed both in follicles (if present) and in intrafollicular/diffuse areas. CD10+ BCL6 + germinal centers are present in PCMZL, while both follicular and interfollicular/diffuse areas (tumor cells) are positive for BCL6+/- CD10 in PCFCL.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

USE OF IMMUNOPHENOTYPING/GENETIC TESTING IN DIFFERENTIAL DIAGNOSIS OF MATURE B-CELL AND NK/T-CELL NEOPLASMS[a] (TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)



Anaplastic morphology

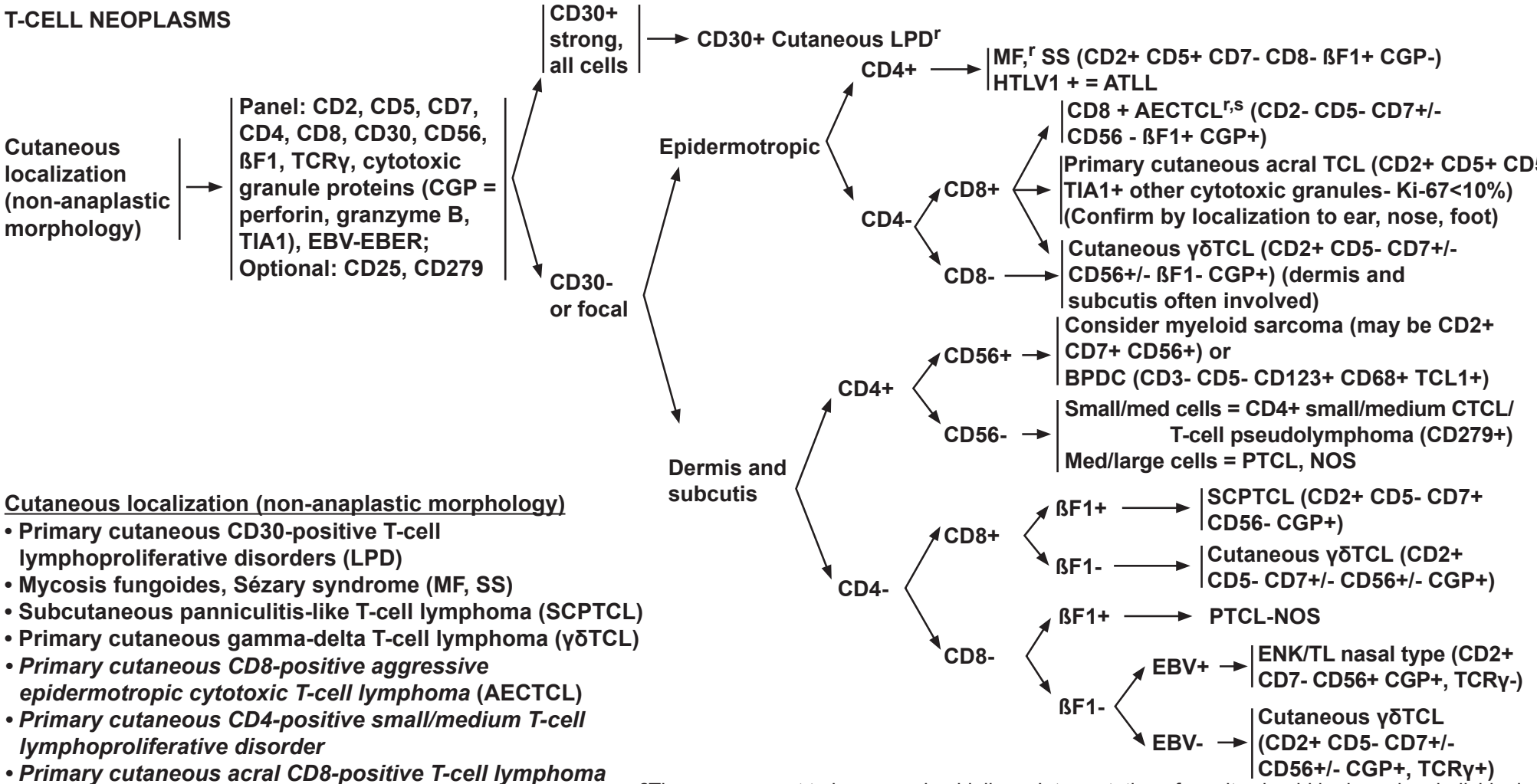
- Anaplastic large cell lymphoma (ALCL), ALK positive
- Anaplastic large cell lymphoma (ALCL), ALK negative
- Adult T-cell leukemia/lymphoma (ATLL), anaplastic large cell type
- Enteropathy-associated T-cell lymphoma (EATL)
- Primary cutaneous CD30-positive T-cell lymphoproliferative disorders
  - Lymphomatoid papulosis (LyP)
  - Primary cutaneous anaplastic large cell lymphoma (PC-ALCL)

[a]These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.

[q]Rare T-cell lymphomas may be CD20+ or PAX5+. Assessment of other Pan-T and -B markers is essential. The expression of multiple markers of 1 lineage and only 1 of the other lineages supports lineage assignment. PCR analysis may be required to determine lineage in such cases.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

USE OF IMMUNOPHENOTYPING/GENETIC TESTING IN DIFFERENTIAL DIAGNOSIS OF MATURE B-CELL AND NK/T-CELL NEOPLASMS[a] (TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)



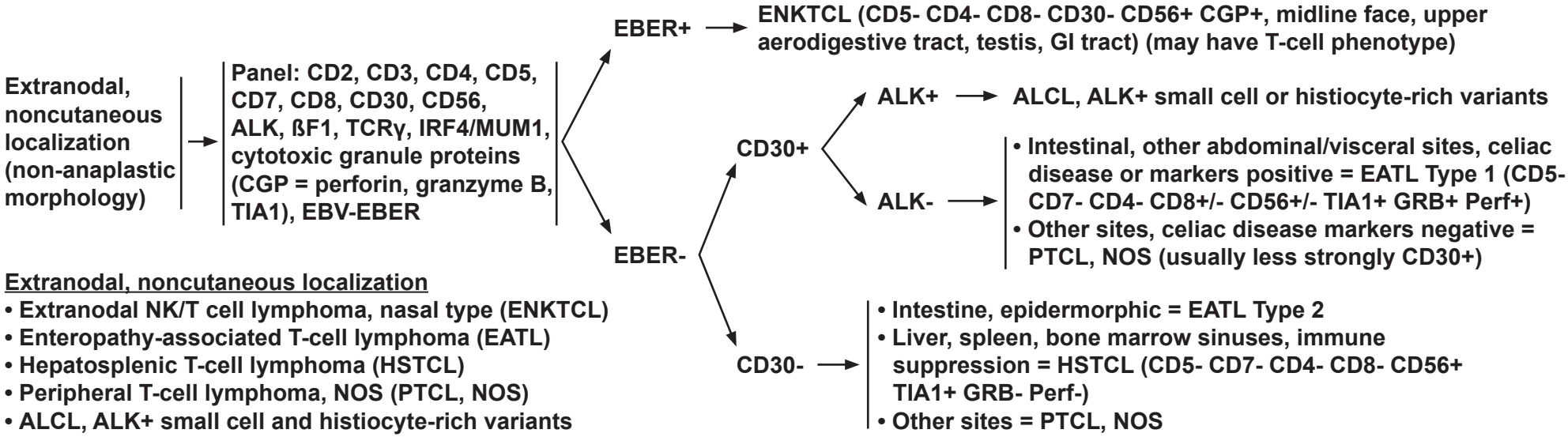
Cutaneous localization (non-anaplastic morphology)

- Primary cutaneous CD30-positive T-cell lymphoproliferative disorders (LPD)
- Mycosis fungoides, Sézary syndrome (MF, SS)
- Subcutaneous panniculitis-like T-cell lymphoma (SCPTCL)
- Primary cutaneous gamma-delta T-cell lymphoma (γδTCL)
- *Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma* (AECTCL)
- *Primary cutaneous CD4-positive small/medium T-cell lymphoproliferative disorder*
- *Primary cutaneous acral CD8-positive T-cell lymphoma*
- Extranodal NK/T-cell lymphoma, nasal type
- Peripheral T-cell lymphoma, NOS (PTCL, NOS)
- Blastic plasmacytoid dendritic cell (BPDC) neoplasm

[a]These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.
[r]A minority of MF cases can be CD30+, CD4-, CD8+/-, and TIA1+. ATLL may also be CD30+.
[s]AECTCL has distinctive morphology and clinical presentation.

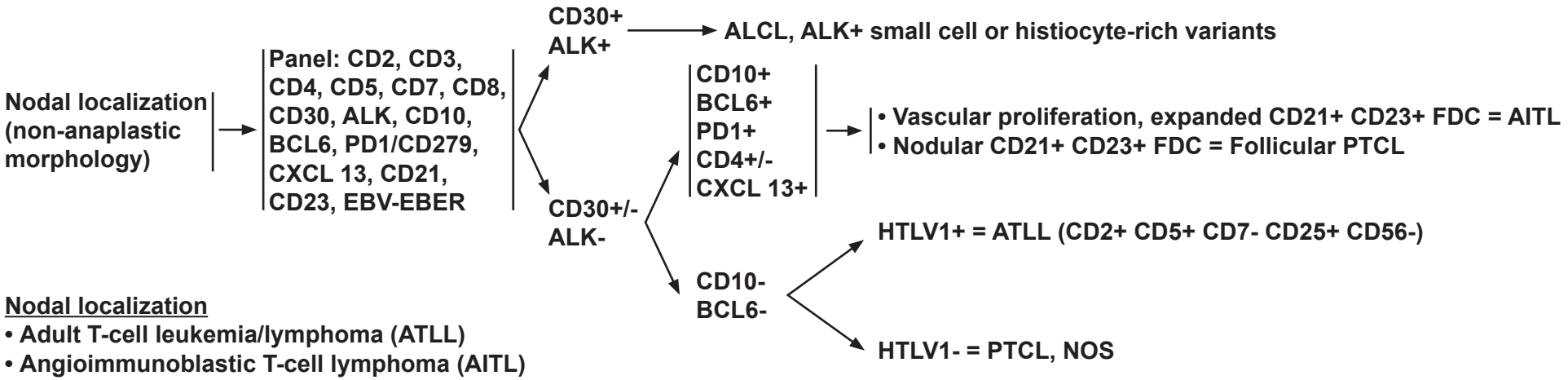
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

USE OF IMMUNOPHENOTYPING/GENETIC TESTING IN DIFFERENTIAL DIAGNOSIS OF MATURE B-CELL AND NK/T-CELL NEOPLASMS[a] (TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)



Extranodal, noncutaneous localization

- Extranodal NK/T cell lymphoma, nasal type (ENKTCL)
- Enteropathy-associated T-cell lymphoma (EATL)
- Hepatosplenic T-cell lymphoma (HSTCL)
- Peripheral T-cell lymphoma, NOS (PTCL, NOS)
- ALCL, ALK+ small cell and histiocyte-rich variants



Nodal localization

- Adult T-cell leukemia/lymphoma (ATLL)
- Angioimmunoblastic T-cell lymphoma (AITL)
- Peripheral T-cell lymphoma, NOS (PTCL, NOS)
- ALCL, ALK+ small cell and histiocyte-rich variants

[a]These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUPPORTIVE CARE FOR B-CELL LYMPHOMAS

Tumor Lysis Syndrome (TLS)

- Laboratory hallmarks of TLS:
  - High potassium
  - High uric acid
  - High phosphorous
  - Low calcium

- Symptoms of TLS:
  - Nausea and vomiting, shortness of breath, irregular heartbeat, clouding of urine, lethargy, and/or joint discomfort.

- High-risk features:
  - Histologies of Burkitt lymphoma and lymphoblastic lymphoma; occasionally patients with DLBCL and CLL
  - Spontaneous TLS
  - Elevated WBC
  - Bone marrow involvement
  - Pre-existing elevated uric acid
  - Ineffectiveness of allopurinol
  - Renal disease or renal involvement by tumor

- Treatment of TLS:
  - TLS is best managed if anticipated and treatment is started prior to chemotherapy.
  - Centerpiece of treatment includes:
    - ◊ Rigorous hydration
    - ◊ Management of hyperuricemia
    - ◊ Frequent monitoring of electrolytes and aggressive correction (essential)
  - First-line and at retreatment for hyperuricemia
    - ◊ Allopurinol beginning 2–3 days prior to chemotherapy and continued for 10–14 days
      or
      Rasburicase is indicated for patients with any of the following risk factors:
      - Presence of any high-risk feature
      - Urgent need to initiate therapy in a high-bulk patient
      - Situations where adequate hydration may be difficult or impossible
      - Acute renal failure
    - ◊ One dose of rasburicase is frequently adequate. Doses of 3–6 mg are usually effective.[a] Redosing should be individualized.
  - If TLS is untreated, its progression may cause acute kidney failure, cardiac arrhythmias, seizures, loss of muscle control, and death.

Continued

[a]There are data to support that fixed-dose rasburicase is very effective in adult patients.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUPPORTIVE CARE FOR B-CELL LYMPHOMAS

For other immunosuppressive situations, see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

Monoclonal Antibody Therapy and Viral Reactivation

Anti-CD20 Antibody Therapy

Hepatitis B virus (HBV):

- **Hepatitis B surface antigen (HBsAg) and Hepatitis B core antibody (HBcAb) testing for all patients receiving anti-CD20 antibody therapy**
  - **Quantitative hepatitis B viral load by PCR and surface antibody only if one of the screening tests is positive**
- **Note: Patients receiving IV immunoglobulin (IVIG) may be HBcAb-positive as a consequence of IVIG therapy.**
- **Prophylactic antiviral therapy with entecavir is recommended for any patient who is HBsAg-positive and receiving anti-lymphoma therapy. If there is active disease (PCR+), it is considered treatment/management and not prophylactic therapy. In cases of HBcAb positivity, prophylactic antiviral therapy is preferred; however, if there is a concurrent high-level hepatitis B surface antibody, these patients may be monitored with serial hepatitis B viral load.**
  - **Entecavir is preferred based on Huang YH, et al. J Clin Oncol 2013;31:2765-2772; Huang H et al. JAMA 2014;312:2521-2530.**
  - **Avoid lamivudine due to risks of resistance development.**
  - **Other antivirals including adefovir, telbivudine, and tenofovir are proven active treatments and are acceptable alternatives.**
  - **Monitor hepatitis B viral load with PCR monthly through treatment and every 3 months thereafter**
    - **◊ If viral load is consistently undetectable, treatment is considered prophylactic**
    - **◊ If viral load fails to drop or previously undetectable PCR becomes positive, consult hepatologist and discontinue anti-CD20 antibody therapy**
  - **Maintain prophylaxis up to 12 mo after oncologic treatment ends**
    - **◊ Consult with hepatologist for duration of therapy in patient with active HBV**

Hepatitis C virus (HCV):

- **New evidence from large epidemiology studies, molecular biology research, and clinical observation supports an association of HCV and B-cell NHL. Recently approved direct-acting antiviral agents (DAA) for chronic carriers of HCV with genotype 1 demonstrated a high rate of sustained viral responses.**
  - **Low-grade B-cell NHL**
    - **◊ According to the American Association for the Study of Liver Diseases, combined therapy with DAA should be considered in asymptomatic patients with HCV genotype 1 since this therapy can result in regression of lymphoma.**
  - **Aggressive B-cell NHL**
    - **◊ Patients should be initially treated with chemoimmunotherapy regimens according to NCCN Guidelines for NHL.**
    - **◊ Liver functional tests and serum HCV RNA levels should be closely monitored during and after chemoimmunotherapy for development of hepatotoxicity.**
    - **◊ Antiviral therapy should be considered in patients in complete remission after completion of lymphoma therapy.**

Anti-CD20 Antibody Therapy and Brentuximab Vedotin

Progressive multifocal leukoencephalopathy (PML):

- **Caused by the JC virus and is usually fatal.**
  - **Diagnosis made by PCR of CSF and in some cases brain biopsy.**
- **No known effective treatment.**
- **Clinical indications may include changes in behavior such as confusion, dizziness or loss of balance, difficulty talking or walking, and vision problems.**

Continued

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUPPORTIVE CARE FOR B-CELL LYMPHOMAS

Rare Complications of Monoclonal Antibody Therapy

- Rare complications such as mucocutaneous reactions including paraneoplastic pemphigus, Steven-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis can occur. Expert consultation with dermatology is recommended.

Rituximab Rapid Infusion

- If no infusion reactions were experienced with prior cycle of rituximab, a rapid infusion over 90 minutes can be used.

Renal Dysfunction Associated with Methotrexate

- Consider use of glucarpidase if significant renal dysfunction and methotrexate levels are >10 microM beyond 42 to 48 hours. Leucovorin remains a component in the treatment of methotrexate toxicity and should be continued for at least 2 days following glucarpidase administration. However, be aware that leucovorin is a substrate for glucarpidase, and therefore should not be administered within two hours prior to or following glucarpidase.

Immunizations

- See NCCN Guidelines for Survivorship - General Principles of Immunizations.

Continued

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUPPORTIVE CARE FOR B-CELL LYMPHOMAS

Bone Health: Recommendations for Patients Who Have Received Steroid-Containing Regimens[a,b,c,d]
(in addition to standard recommendations for screening)

- ***Evaluation***
  - Vitamin D, 25-OH level
  - Post-treatment bone mineral density (BMD) evaluation (1 year following therapy)
    - ◊ Greatest risk in women with chemotherapy-induced premature menopause
      - – If osteopenic (T score between -1.1 and -2.4):
    - ◊ Use Fracture Risk Assessment Tool (FRAX) to determine if drug therapy is necessary (https://www.sheffield.ac.uk/FRAX/)
      - ▪ 20% risk for any major osteoporotic fracture or 3% risk for hip fracture are the thresholds where drug therapy is recommended
      - – If T-score -2 to -2.4 (at any site) or ongoing glucocorticoid exposure repeat BMD every 1–2 years, as long as risk factors persist.[e]
      - – If T-score -1.5 to -1.9 (at any site) with no risk factors, repeat BMD in 5 years[e]

- ***Therapy***
  - If vitamin D 25-OH is deficient, then replete
    - ◊ In lymphoma patients with current elevations in 1,25-dihydroxyvitamin D, deficient 25(OH)D levels should not be aggressively replaced.
  - Calcium intake from food (plus supplements if necessary) should be commensurate with Institute of Medicine recommendations except in cases of lymphoma-induced hypercalciuria/hypercalcemia due to excessive 1,25-dihydroxyvitamin D production.
    - ◊ In patients receiving corticosteroid-containing chemotherapy regimens, adequate calcium intake is of paramount importance since corticosteroids block calcium absorption and increase fracture risk.[f]
  - Patients with osteoporotic bone mineral density, with a history of hip or vertebral fractures, or with asymptomatic vertebral compression deformity (as seen on CT scan or other imaging) should be started on therapy as per National Osteoporosis Foundation (NOF) guidelines; referral to an endocrinologist with expertise on bone health is recommended.
    - ◊ In appropriate women with premature menopause, hormone replacement therapy (HRT) up until the expected time of natural menopause, or raloxifene could be considered.
    - ◊ Bisphosphonates should be used as first-line pharmacologic treatment for osteoporosis.
    - ◊ In patients who cannot tolerate or whose symptoms do not improve with bisphosphonate therapy, denosumab is an effective alternative medication to prevent osteoporotic fractures.
      - – Teriparatide is contraindicated in patients with a history of radiotherapy; also, theoretical concerns in patients with a recent history of cancer exist.

[a]Crandall CJ, Newberry SJ, Diamant A, et al. Comparative effectiveness of pharmacologic treatments to prevent fractures: an updated systematic review. Ann Intern Med 2014;161:711-723.
[b]MacLean C, Newberry S, Maglione M, et al. Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. Ann Intern Med 2008;148:197-213.
[c]Cummings SR, San Martin J, McClung MR, et al.; FREEDOM Trial. Denosumab for prevention of fractures in postmenopausal women with osteoporosis [published correction appears in N Engl J Med. 2009; 361(19):1914]. N Engl J Med 2009;361:756-765.
[d]Paccou L, Merlusca I, Henry-Desailly A, et al. Alterations in bone mineral density and bone turnover markers in newly diagnosed adults with lymphoma receiving chemotherapy: a 1-year prospective pilot study. Ann Oncol 2014; 25:481-486.
[e]https://www.uptodate.com/contents/screening-for-osteoporosis?source=see_link
[f]Van Staa TP, Leufkens HG, Abenhaim L, et al. Use of oral corticosteroids and risk of fractures. June, 2000. J Bone Miner Res. 2005 Aug;20(8):1487-1494.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

LUGANO RESPONSE CRITERIA FOR NON-HODGKIN'S LYMPHOMA

PET should be done with contrast-enhanced diagnostic CT and can be done simultaneously or at separate procedures.

Response	Site	PET-CT (Metabolic response)	CT (Radiologic response)
Complete response	Lymph nodes and extralymphatic sites	Score 1, 2, 3[a] with or without a residual mass on 5 point scale (5-PS)[b,c]	All of the following: Target nodes/nodal masses must regress to ≤1.5 cm in longest transverse diameter of a lesion (LDi) No extralymphatic sites of disease
	Non-measured lesion	Not applicable	Absent
	Organ enlargement	Not applicable	Regress to normal
	New Lesions	None	None
	Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminatem and flow cytometry IHC negative
Partial response	Lymph nodes and extralymphatic sites	Score 4 or 5[b] with reduced uptake compared with baseline. No new progressive lesions. At interim these findings suggest responding disease. At end of treatment these findings may indicate residual disease.	All of the following: ≥50% decrease in SPD of up to 6 target measureable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5mm x 5mm as the default value. When no longer visible, 0x0 mm For a node >5 mm x 5mm, but smaller than normal, use actual measurement for calculation
	Non-measured lesion	Not applicable	Absent/normal, regressed, but no increase
	Organ enlargment	Not applicable	Spleen must have regressed by >50% in length beyond normal
	New Lesions	None	None
	Bone Marrow	Residual uptake higher than update in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the content of a nodal response, consider further evaluation with biopsy, or an interval scan.	Not applicable

Footnotes on NHODG-C 3 of 3

Continued

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

LUGANO RESPONSE CRITERIA FOR NON-HODGKIN'S LYMPHOMA

PET should be done with contrast-enhanced diagnostic CT and can be done simultaneously or at separate procedures.

Response	Site	PET-CT (Metabolic response)	CT (Radiologic response)
No response or stable disease	Target nodes/ nodal masses, extranodal lesions	Score 4 or 5[b] with no significant change in FDG uptake from baseline at interim or end of treatment. No new or progressive lesions.	<50% decrease from baseline in SPD of up to 6 dominant, measureable nodes and extranodal sites; no criteria for progressive disease are met
	Non-measured lesion	Not applicable	No increase consistent with progression
	Organ enlargement	Not applicable	No increase consistent with progression
	New Lesions	None	None
	Bone marrow	No change from baseline	Not applicable
Progressive disease	Individual target nodes/ nodal masses, extranodal lesions	Score 4 or 5[b] with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment[e]	Requires at least one of the following PPD progression: An individual node/lesion must be abnormal with: LDi >1.5 cm and Increase by ≥50% from PPD nadir and An increase in LDi or SDi from nadir 0.5cm for lesions ≤2 cm 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline. If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
	Non-measured lesion	None	New or clear progression of preexisting nonmeasured lesions
	New Lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered[e]	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
	Bone Marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Footnotes on NHODG-C 3 of 3

Continued

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

LUGANO RESPONSE CRITERIA FOR NON-HODGKIN'S LYMPHOMA

Footnotes

[a]Score 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider score 3 as an inadequate response (to avoid under-treatment).
[b]See PET Five Point Scale (5-PS).
[c]It is recognized that in Waldeyer's ring or extranodal sites with high physiological uptake or with activation within spleen or marrow, e.g. with chemotherapy or myeloid colony stimulating factors, uptake may be greater than normal mediastinum and/or liver. In this circumstance, CMR may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiological uptake.
[d]FDG-avid lymphomas should have response assessed by PET-CT. Diseases that can typically be followed with CT alone include CLL/SLL and marginal zone lymphomas.
[e]False-positive PET scans may be observed related to infectious or inflammatory conditions. Biopsy of affected sites remains the gold standard for confirming new or persistent disease at end of therapy.

PET Five Point Scale (5-PS)

1	**No uptake above background**
2	**Uptake ≤ mediastinum**
3	**Uptake > mediastinum but ≤ liver**
4	**Uptake moderately > liver**
5	**Uptake markedly higher than liver and/or new lesions**
X	**New areas of uptake unlikely to be related to lymphoma**

SPD – sum of the product of the perpendicular diameters for multiple lesions
LDi – Longest transverse diameter of a lesion
SDi – Shortest axis perpendicular to the LDi
PPD – Cross product of the LDi and perpendicular diameter

Measured dominant lesions – Up to 6 of the largest dominant nodes, nodal masses and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body, and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs, e.g., liver, spleen, kidneys, lungs, etc, gastrointestinal involvement, cutaneous lesions of those noted on palpation.
Non-measured lesions – Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant, measurable or which do not meet the requirements for measurability, but are still considered abnormal. As well as truly assessable disease which is any site of suspected disease that would be difficult to follow quantitiatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses and other lesions that cannot be confirmed and followed by imaging.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF RADIATION THERAPY[a]

- **Treatment with photons, electrons, or protons may all be appropriate, depending on clinical circumstances.**
- **Advanced radiation therapy technologies such as IMRT, breath hold or respiratory gating, image-guided therapy, or proton therapy may offer significant and clinically relevant advantages in specific instances to spare important organs at risk such as the heart (including coronary arteries and valves), lungs, kidneys, spinal cord, esophagus, bone marrow, breasts, stomach, muscle/soft tissue, and salivary glands and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control. Achieving highly conformal dose distributions is especially important for patients who are being treated with curative intent or who have long life expectancies following therapy.**
- **The demonstration of significant dose-sparing for these organs at risk reflects best clinical practice.**
- **In mediastinal lymphoma, the use of 4D-CT for simulation and the adoption of strategies to deal with respiratory motion such as inspiration breath-hold techniques, and image-guided RT during treatment delivery is also important.**
- **Since the advantages of these techniques include tightly conformal doses and steep gradients next to normal tissues, target definition and delineation and treatment delivery verification require careful monitoring to avoid the risk of tumor geographic miss and subsequent decrease in tumor control. Image guidance may be required to provide this assurance.**
- **Randomized studies to test these concepts are unlikely to be done since these techniques are designed to decrease late effects, which take 10+ years to evolve. In light of that, the modalities and techniques that are found to best reduce the doses to the organs at risk (OAR) in a clinically meaningful way without compromising target coverage should be considered.**

Continued

[a]See references on NHODG-D 4 of 4.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF RADIATION THERAPY[a]

Volumes:

- **Involved-site radiation therapy (ISRT) for nodal disease**
  - ISRT is recommended as the appropriate field for NHL. Planning for ISRT requires modern CT-based simulation and planning capabilities. Incorporating other modern imaging like PET and MRI often enhances treatment volume determination.
  - ISRT targets the site of the originally involved lymph node(s). The volume encompasses the original suspicious volume prior to chemotherapy or surgery. Yet, it spares adjacent uninvolved organs (like lungs, bone, muscle, or kidney) when lymphadenopathy regresses following chemotherapy.
  - The pre-chemotherapy or pre-biopsy gross tumor volume (GTV) provides the basis for determining the clinical target volume (CTV). Concerns for questionable subclinical disease and uncertainties in original imaging accuracy or localization may lead to expansion of the CTV and are determined individually using clinical judgment.
  - For indolent NHL, often treated with RT alone, larger fields should be considered. For example, the CTV definition for treating follicular lymphoma with radiation therapy alone will be greater than that employed for DLBCL with similar disease distribution being treated with combined modality therapy.
  - Possible movement of the target by respiration as determined by 4D-CT or fluoroscopy (internal target volume- ITV) should also influence the final CTV.
  - The planning treatment volume (PTV) is an additional expansion of the CTV that accounts only for setup variations (see ICRU definitions).
  - The OAR should be outlined for optimizing treatment plan decisions.
  - The treatment plan is designed using conventional, 3-D conformal, or IMRT techniques using clinical treatment planning considerations of coverage and dose reductions for OAR.

- **ISRT for extranodal disease**
  - Similar principles as for ISRT nodal sites (see above).
  - For most organs and particularly for indolent disease, the whole organ comprises the CTV (eg, stomach, salivary gland, thyroid). For other organs, including orbit, breast, lung, bone, localized skin, and in some cases when RT is consolidation after chemotherapy, partial organ RT may be appropriate.
  - For most NHL subtypes no radiation is required for uninvolved lymph nodes.

Continued

[a]See references on NHODG-D 4 of 4.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF RADIATION THERAPY[a]

General Dose Guidelines:

Definitive treatment (1.5–2.0 Gy daily fractions)

- **Follicular lymphoma: 24–30 Gy**
- **Marginal zone lymphoma:**
  - **Gastric: 30 Gy (most commonly uses 1.5 Gy daily fractions)**
  - **Other extranodal sites: 24–30 Gy**
  - **Nodal MZL: 24–30 Gy**
- **Early-stage mantle cell lymphoma: 24–36 Gy**
- **DLBCL**
  - **Consolidation after chemotherapy CR: 30–36 Gy**
  - **Complimentary after PR: 40–50 Gy**
  - **RT as primary treatment for refractory or non-candidates for chemotherapy: 30–55 Gy**
  - **In combination with stem cell transplantation: 20–36 Gy, depending on sites of disease and prior RT exposure**

Palliative RT (higher doses/fraction typically appropriate)

- **FL/MZL/MCL: 2 Gy X 2 or 4 Gy X 1 (which may be repeated as needed); doses up to 30 Gy may be appropriate in select circumstances**
- **DLBCL: 24–30 Gy**

[a]See references on NHODG-D 4 of 4.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF RADIATION THERAPY

REFERENCES

Charpentier AM, Conrad T, Sykes J, et al. Active breathing control for patients receiving mediastinal radiation therapy for lymphoma: Impact on normal tissue dose. Pract Radiat Oncol 2014;4:174-180.

Filippi AR, Ragona R, Fusella M, et al. Changes in breast cancer risk associated with different volumes, doses, and techniques in female Hodgkin lymphoma patients treated with supra-diaphragmatic radiation therapy. Pract Radiat Oncol 2013;3:216-222.

Girinsky T, Pichenot C, Beaudre A, et al. Is intensity-modulated radiotherapy better than conventional radiation treatment and three-dimensional conformal radiotherapy for mediastinal masses in patients with Hodgkin's disease, and is there a role for beam orientation optimization and dose constraints assigned to virtual volumes? Int J Radiat Oncol Biol Phys 2006;64:218-226.

Goda JS, Gospodarowicz M, Pintilie M, et al. Long-term outcome in localized extranodal mucosa-associated lymphoid tissue lymphomas treated with radiotherapy. Cancer 2010;116:3815-3824.

Haas RL, Poortmans P, de Jong D, et al. High response rates and lasting remissions after low-dose involved field radiotherapy in indolent lymphomas, J Clin Oncol 2003;21: 2474-2480.

Held G et al., Role of RT to bulky disease in aggressive B-cell lymphoma. J Clin Oncol 2014;32:1112-1118.

Held G et al., Impact of rituximab and RT on outcome of aggressive B-cell lymphoma and skeletal involvement. J Clin Oncol 2013;31:4115-4122.

Hoppe RT. Treatment strategies in limited stage follicular lymphoma. Best Pract Res Clin Haematol 2011;24:179-186.

Hoppe BS, Flampouri S, Su Z, et al. Effective dose reduction to cardiac structures using protons compared with 3DCRT and IMRT in mediastinal Hodgkin lymphoma. Int J Radiat Oncol Biol Phys 2012;84:449-455.

Horning SJ, Weller E, Kim K, et al. Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-Hodgkin's lymphoma: Eastern Cooperative Oncology Group study 1484. J Clin Oncol 2004;22:3032-3038.

Hoskin PJ, Díez P, Williams M, et al. Recommendations for the use of radiotherapy in nodal lymphoma. Clin Oncol (R Coll Radiol) 2013;25:49-58.

Hoskin PJ, Kirkwood AA, Popova B et al. 4 Gy versus 24 Gy radiotherapy for patients with indolent lymphoma (FORT): a randomised phase 3 non-inferiority trial. Lancet Oncol 2014;15:457-463.

Illidge T, Specht L, Yahalom J, et al. Modern radiation therapy for nodal non-Hodgkin lymphoma-target definition and dose guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys 2014 1;89:49-58.

Jang JW, Brown JG, Mauch PM, Ng AK. Four-dimensional versus 3-dimensional computed tomographic planning for gastric mucosa associated lymphoid tissue lymphoma. Pract Radiat Oncol 2013;3:124-129.

Li J, Dabaja B, Reed V, et al. Rationale for and preliminary results of proton beam therapy for mediastinal lymphoma. Int J Radiat Oncol Biol Phys 2011;81(1):167-174.

Lowry L, Smith P, Qian W, et al. Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: a randomised phase III trial. Radiother Oncol 2011;100:86-92

Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med 1998;339:21-26.

Nieder C, Schill S, Kneschaurek P, Molls M. Inflence of different treatment techniques on radiation dose to the LAD coronary artery. Radiat Oncol 2007;2:20.

Petersen P, Gospodarowicz M, Tsang R, et al. Long-term outcome in stage I and II follicular lymphoma following treatment with involved field radiation therapy alone. J Clin Oncol 2004;22:Abtract 6521.

Wirth A, Gospodarowicz M, Aleman BM, et al. Long-term outcome for gastric marginal zone lymphoma treated with radiotherapy: a retrospective, multi-centre, International Extranodal Lymphoma Study Group study. Ann Oncol 2013;24:1344-1351.

Xu LM, Li YX, Fang H, et al. Dosimetric evaluation and treatment outcome of intensity modulated radiation therapy after doxorubicin-based chemotherapy for primary mediastinal large B-cell lymphoma. Int J Radiat Oncol Biol Phys 2013;85:1289-1295.

Yahalom J, Illidge T, Specht L, Hoppe RT, et al. Modern Radiation Therapy for Extranodal Lymphomas: Field and Dose Guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys 2015;92:11-31.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SPECIAL CONSIDERATIONS FOR THE USE OF SMALL-MOLECULE INHIBITORS[1]

ACALABRUTINIB

- **Dosage: The recommended dose of acalabrutinib is 100 mg PO approximately every 12 hours**
- **Grade ≥3 bleeding events were observed in 2% of patients on acalabrutinib. The mechanism is not well understood. Acalabrutinib may increase the risk of hemorrhage in patients receiving anti-platelet or anticoagulant therapies. The phase 2 ACE-LY-004 study excluded patients on concomitant warfarin or equivalent vitamin K antagonists. Patients should be monitored for signs of bleeding. Consider the benefit-risk of withholding acalabrutinib for 3–7 days pre-and post-surgery depending on the type of surgery and risk of bleeding.**
- **Atrial fibrillation and flutter of any grade was reported in 3% of patients and atrial fibrillation grade 3 was reported in 1% of patients. Monitor for atrial fibrillation and flutter and manage as appropriate.**

COPANLISIB

- **The recommended dose of copanlisib is 60 mg administered as a 1-hour IV infusion on Days 1, 8, and 15 of a 28-day treatment cycle on an intermittent schedule (3 weeks on and 1 week off).**
- **Serious adverse reactions including infections, hyperglycemia, hypertension, neutropenia, and severe cutaneous reactions have been observed in patients treated with copanlisib.**
  - **Infection: Monitor patients for signs and symptoms of infection prior to and during treatment. Copanlisib should be withheld for grade ≥ infection until resolution.**
  - **Pneumocystis jiroveci pneumonia (PJP): Consider PJP prophylaxis for patients at risk before initiating copanlisib. Copanlisib should be withheld in patients with suspected PJP infection of any grade. If confirmed, treat infection until resolution, then resume copanlisib at previous dose with concomitant PJP prophylaxis.**
  - **Neutropenia: Monitor blood counts at least weekly during treatment with copanlisib. Interrupt copanlisib, reduce dose, or discontinue copanlisib depending on the severity and persistence of neutropenia.**
  - **Hyperglycemia: Patients with diabetes mellitus should only be treated with copanlisib following adequate glucose control and should be monitored closely. Interrupt copanlisib, reduce dose, or discontinue copanlisib depending on the severity and persistence of hyperglycemia.**
  - **Hypertension: Optimal blood pressure control should be achieved before starting each copanlisib infusion. Monitor blood pressure pre- and post-infusion. Interrupt copanlisib, reduce dose, or discontinue copanlisib depending on the severity and persistence of hypertension.**

Continued

[1]Please refer to package insert for full prescribing information and monitoring for adverse reactions, available at www.fda.gov.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SPECIAL CONSIDERATIONS FOR THE USE OF SMALL-MOLECULE INHIBITORS[1]

IBRUTINIB

- Dosage
  - MCL: The recommended dose of ibrutinib is 560 mg PO daily, continuous and should be continued until time of progression.
- Lymphocytosis
  - MCL: Upon initiation of ibrutinib, transient increase in absolute lymphocyte counts occurred in 33% of patients. The onset of isolated lymphocytosis occurs during the first few weeks of ibrutinib therapy and resolves by a median of 8 weeks.
- Grade >2 bleeding events were observed in 6% of patients on ibrutinib; the mechanism is not well understood. Consider the benefit-risk of ibrutinib in patients requiring anti-platelet or anticoagulant therapies. Clinical trials excluded patients on concurrent warfarin. Ibrutinib should be held 3 days before and after a minor surgical procedure and 7 days before and after a major surgical procedure. Ibrutinib should not be given concomitantly with warfarin.
- New-onset atrial fibrillation was reported in 6%–9%, associated with ibrutinib administration.[2]
  - Consider non-warfarin anticoagulation
  - Monitor carefully
  - Consider switching to alternate therapy
  - Patients with recurrent atrial fibrillation that is not medically controllable should be changed to an alternative agent.
- Hypertension associated with ibrutinib has been uncommonly reported as a basis for discontinuation and should be mananged with anti-hypertensives as appropriate. Ibrutinib should only be discontinued for uncontrollable hypertension.

IDELALISIB

- The recommended dose of idelalisib is 150 mg PO twice daily, per prescribing recommendations.
- Fatal and/or serious hepatotoxicity, severe diarrhea or colitis, pneumonitis, and intestinal perforation have been observed in patients treated with idelalisib.
  - Hepatotoxicity: Monitor hepatic function prior to and during treatment. Interrupt (if ALT/AST > 5 x ULN [upper limit of normal]) and when resolved may resume at a reduced dose (100 mg PO twice daily).
  - Diarrhea or colitis: Monitor for the development of severe diarrhea or colitis. Interrupt until resolution and then reduce or discontinue idelalisib. Severe diarrhea and colitis can be managed with systemic or nonabsorbable steroids.
  - Pneumonitis: Monitor for pulmonary symptoms and bilateral interstitial infiltrates. Discontinue idelalisib.
  - Intestinal perforation: Discontinue idelalisib if intestinal perforation is suspected.
- CMV: Monitor per institutional guidelines or consult with infectious disease specialist.

Continued

[1]Please refer to package insert for full prescribing information and monitoring for adverse reactions, available at www.fda.gov.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SPECIAL CONSIDERATIONS FOR THE USE OF SMALL-MOLECULE INHIBITORS[1]

Co-administration with CYP3A inhibitors and inducers

- **Acalabrutinib**
  - **Avoid concomitant use of strong CYP3A inhibitors or inducers.**
  - **For strong CYP3A inhibitors used short-term, interrupt acalabrutinib during the duration of inhibitor use.**
  - **For concomitant use with a moderate CYP3A inhibitor, reduce acalabrutinib dose to 100 mg once daily.**
  - **If concomitant use with a strong CYP3A inducer cannot be avoided, increase acalabrutinib dose to 200 mg twice daily.**

- **Copanlisib**
  - **Avoid concomitant use of strong CYP3A inhibitors or inducers.**
  - **If concomitant use with strong CYP3A inhibitors cannot be avoided, reduce the copanlisib dose to 45 mg.**

- **Ibrutinib**
  - **Avoid concomitant use of strong and moderate CYP3A inhibitors. Consider alternative agents with less CYP3A inhibition.**
    - **For strong CYP3A inhibitors used short-term (eg, antifungals and antibiotics for 7 days or less; eg, ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin), consider interrupting ibrutinib during the duration of inhibitor use. Avoid strong CYP3A inhibitors that are needed chronically.**
    - **If a moderate CYP3A inhibitor must be used, reduce ibrutinib dose to 140 mg.**
    - **Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of ibrutinib toxicity**
  - **Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, St. John's Wort). Consider alternative agents with less CYP3A induction.**

- **Idelalisib**
  - **Avoid concomitant use of strong CYP3A inhibitors or inducers.**
  - **Patients taking concomitant strong CYP3A4 inhibitors should be monitored more closely for signs of idelalisib toxicity.**

[1]Please refer to package insert for full prescribing information and monitoring for adverse reactions, available at www.fda.gov.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Classification

Table 1

WHO Classification of the Mature B-Cell, T-Cell, and NK-Cell Neoplasms (2016)

Mature B-Cell Neoplasms

- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- Monoclonal B-cell lymphocytosis
- B-cell prolymphocytic leukemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- *Splenic lymphoma/leukemia, unclassifiable**
  - *Splenic diffuse red pulp small B-cell lymphoma**
  - *Hairy cell leukemia-variant**
- Lymphoplasmacytic lymphoma
  - Waldenström's macroglobulinemia
- Monoclonal gammopathy of undetermined significance (MGUS), IgM
- Mu heavy chain disease
- Gamma heavy chain disease
- Alpha heavy chain disease
- Monoclonal gammopathy of undetermined significance (MGUS), IgG/A
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extraosseous plasmacytoma
- Monoclonal immunoglobulin deposition diseases
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodal marginal zone lymphoma
  - *Pediatric nodal marginal zone lymphoma**
- Follicular lymphoma
  - In situ follicular neoplasia
  - Duodenal-type follicular lymphoma
- Pediatric-type follicular lymphoma
- *Large B-cell lymphoma with IRF4 rearrangement*
- Primary cutaneous follicle center lymphoma
- Mantle cell lymphoma
  - In situ mantle cell neoplasia
- Diffuse large B-cell lymphoma (DLBCL), NOS
  - Germinal center B-cell type
  - Activated B-cell type
- T-cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the central nervous system (CNS)
- Primary cutaneous DLBCL, leg type
- EBV-positive DLBCL, NOS
- *EBV*-positive *mucocutaneous ulcer**
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK-positive large B-cell lymphoma
- Plasmablastic lymphoma
- Primary effusion lymphoma
- *HHV8*-positive *DLBCL, NOS**
- Burkitt lymphoma
- *Burkitt-like lymphoma with 11q aberration**
- High-grade B-cell lymphoma, with *MYC* and B*CL2* and/or *BCL6* rearrangements
- High-grade B-cell lymphoma, NOS
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

*Provisional entities are listed in italics.

Continued on next page

Classification

Table 1 continued

WHO Classification of the Mature B-Cell, T-Cell, and NK-Cell Neoplasms (2016)

Mature T-Cell and NK-Cell Neoplasms

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- *Chronic lymphoproliferative disorder of NK-cells**
- Aggressive NK-cell leukemia
- Systemic EBV-positive T-cell lymphoma of childhood
- Hydroa vacciniforme–like lymphoproliferative disorder
- Adult T-cell leukemia/lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma*
- *Indolent T-cell lymphoproliferative disorder of the GI tract**
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30-positive T-cell lymphoproliferative disorders
  - Lymphomatoid papulosis
  - Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous gamma-delta T-cell lymphoma
- *Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma**
- *Primary cutaneous acral CD8-positive T-cell lymphoma**
- *Primary cutaneous CD4-positive small/medium T-cell lymphoproliferative disorder**
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- *Follicular T-cell lymphoma**
- *Nodal peripheral T-cell lymphoma with TFH phenotype**
- Anaplastic large-cell lymphoma, ALK positive
- Anaplastic large-cell lymphoma, ALK negative
- *Breast implant–associated anaplastic large-cell lymphoma**

Hodgkin Lymphoma

- Nodular lymphocyte-predominant Hodgkin lymphoma
- Classical Hodgkin lymphoma
  - Nodular sclerosis classical Hodgkin lymphoma
  - Lymphocyte-rich classical Hodgkin lymphoma
  - Mixed cellularity classical Hodgkin lymphoma
  - Lymphocyte-depleted classical Hodgkin lymphoma

Posttransplant Lymphoproliferative Disorders (PTLD)

- Plasmacytic hyperplasia PTLD
- Infectious mononucleosis-like PTLD
- Florid follicular hyperplasia PTLD
- Polymorphic PTLD
- Monomorphic PTLD (B- and T/NK-cell types)
- Classical Hodgkin lymphoma PTLD

Histiocytic and dendritic cell neoplasms

- Histiocytic sarcoma
- Langerhans cell histiocytosis
- Langerhans cell sarcoma
- Indeterminate dendritic cell tumor
- Interdigitating dendritic cell sarcoma
- Follicular dendritic cell sarcoma
- Fibroblastic reticular cell tumor
- Disseminated juvenile xanthogranuloma
- Erdheim-Chester disease

*Provisional entities are listed in italics.

Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD, Jaffe ES. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2018;127:2375-2390.

Staging

**Lugano Modification of Ann Arbor Staging System*
(for primary nodal lymphomas)**

Stage	Involvement	Extranodal (E) status
Limited		
Stage I	**One node or a group of adjacent nodes**	**Single extranodal lesions without nodal involvement**
Stage II	**Two or more nodal groups on the same side of the diaphragm**	**Stage I or II by nodal extent with limited contiguous extranodal involvement**
Stage II bulky**	**II as above with "bulky" disease**	**Not applicable**
Advanced		
Stage III	**Nodes on both sides of the diaphragm**	**Not applicable**
	Nodes above the diaphragm with spleen involvement	
Stage IV	**Additional non-contiguous extralymphatic involvement**	**Not applicable**

*Extent of disease is determined by PET/CT for avid lymphomas, and CT for non-avid histologies
Note: Tonsils, Waldeyer's ring, and spleen are considered nodal tissue
**Whether II bulky is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

Categorization of A versus B has been removed from the Lugano Modification of Ann Arbor Staging.

 Cheson B, Fisher R, Barrington S, et al. Recommendations for Initial Evaluation, Staging and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma – the Lugano Classification. J Clin Oncol 2014;32:3059-3067.

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated on 05/03/16

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

NCCN Categories of Preference

Preferred intervention: Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.

Other recommended intervention: Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.

Useful in certain circumstances: Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Table of Contents

Overview

Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of lymphoproliferative disorders originating in B-lymphocytes, T-lymphocytes or natural killer (NK) cells NK/T-cell lymphomas are very rare. In 2015, an estimated 71,850 people will be diagnosed with NHL and there will be approximately 19,790 deaths due to the disease; cases of chronic lymphocytic leukemia (CLL) are estimated separately.[1] NHL is the seventh leading site of new cancer cases among men and women, accounting for 4% of new cancer cases and 3% of cancer-related deaths.[1]. In a prospectively collected data from the National Cancer Data Base, diffuse large B-cell lymphoma (DLBCL; 32.5%), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL; 18.6%), follicular lymphoma (FL; 17.1%), marginal zone lymphomas (MZL; 8.3%), mantle cell lymphoma (MCL; 4.1%) and peripheral T-cell lymphoma not-otherwise-specified (PTCL-NOS; 1.7%) were the major subtypes of NHL diagnosed in the United States between 1998-2011.[2]

The incidence of NHL has increased dramatically between 1970 and 1995; the increase has moderated since the mid-90s. This increase has been attributed partly to the human immunodeficiency virus (HIV) epidemic and the development of AIDS-related NHL. However, much of the increase in incidence has been observed in patients in their sixth and seventh decades; a large part of this increase incidence has paralleled a major decrease in mortality from other causes. The median age of individuals with NHL has risen in the last two decades.[3] As a result, patients with NHL may also have significant comorbid conditions, which complicate treatment options.

The National Comprehensive Cancer Network (NCCN®) Guidelines (NCCN Guidelines®) were developed as a result of meetings convened by a multidisciplinary panel of NHL experts, with the aim to provide recommendations for diagnostic workup, treatment, and surveillance strategies for the most common subtypes of NHL, in addition to a general discussion on the classification systems used in NHL and supportive care considerations.

The most common B-cell Lymphoma subtypes that are covered in these NCCN Guidelines are listed below:

- Follicular lymphoma (FL)
- Marginal Zone lymphomas (MZL)
  - Gastric MALT lymphoma
  - Non gastric MALT lymphoma
  - Nodal MZL
  - Splenic MZL
- Mantle cell lymphoma (MCL)
- Diffuse large B-cell lymphoma (DLBCL)
- Burkitt lymphoma (BL)
- AIDS-related B-cell lymphoma
- Post-Transplant Lymphoproliferative Disorders
- Castleman's Disease

Classification

In 1956, Rappaport et al. proposed a lymphoma classification that was based on the pattern of cell growth (nodular or diffuse), and size and shape of the tumor cells.[4,5] This classification, though widely used in the Unites states, quickly became outdated with the discovery and the existence of distinct types of lymphocytes (B, T and NK). The Kiel classification became the first and most significant classification that applied this new information to the classification of lymphomas.[6-8] According to the Kiel classification, the lymphomas were divided into low-grade and high-grade based on the histological features. This

classification was widely used in Europe. The use of different classification systems in clinical studies made it difficult to compare results from clinical studies. Hence, the International Working Formulation (IWF) for NHLs was developed to standardize the classification of lymphomas.

International Working Formulation Classification

The IWF classified NHL into three major categories as low, intermediate and high grade, based on the morphology and natural history.[9] This classification divided DLBCL into intermediate and high grade groups. However, these distinctions were not reproducible. Since this classification did not include immunophenotyping, the categories were not reproducible.[10] In addition, after this classification was published many new diseases were described that were not included in the IWF classification.

Revised European American Classification

In 1994, the International Lymphoma Study Group (ILSG) developed the REAL classification, which classified lymphomas based on the cell of origin (B, T, or NK) and included morphology, immunophenotype, genetic and clinical features to define diseases.[11] In 1997, the International Lymphoma Classification Project performed a clinical evaluation of the Revised European American Classification (REAL) classification in a cohort of 1,403 cases of NHL.[12,13] The diagnosis of NHL was confirmed in 1,378 (98.2%) of the cases. This study identified the thirteen most common histological types, comprising about 90% of the cases of NHL in the United States. The findings were as follows: DLBCL, 31%; follicular lymphoma (FL), 22%; small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL), 6%; mantle cell lymphoma (MCL), 6%; peripheral T-cell lymphoma (PTCL), 6%; and mucosa associated lymphoid tissue (MALT) lymphoma, 5%. The remaining subtypes each occurred in less than 2% of cases. Importantly, in the United States more than 50% of cases of lymphoma are either DLBCL or FL. The study investigators concluded that the REAL classification can be readily applied and identifies clinically distinctive types of NHL.

World Health Organization Classification

In 2001, the World Health Organization (WHO) updated the classification of hematopoietic and lymphoid neoplasms.[14,15] The 2001 WHO classification applied the principles of REAL classification and represented the first international consensus on classification of hematologic malignancies. The REAL/WHO classification of NHL includes many entities not recognized by the IWF.[14,15] After consideration of cell of origin (B, T, or NK), the classification subdivides lymphomas into those derived from precursor lymphocytes versus those derived from mature lymphocytes. The classification is further refined based on immunophenotype, genetic, and clinical features. These considerations have aided in defining active treatment for specific subtypes of lymphoma.

In 2008, the International T-cell lymphoma Project evaluated the WHO classification of T-cell lymphoma in a cohort of 1,314 cases of PTCL and natural killer/T-cell lymphomas (NKTCL). The diagnosis of PTCL or NKTCL was confirmed in 1,1,53 cases (88%). The most common subtypes were PTCL-not otherwise specified (NOS; 25.9%), angioimmunoblastic lymphoma (18.5%), NKTCL (10.4%), adult T-cell leukemia/lymphoma (ATLL; 9.6%), anaplastic large cell lymphoma (ALCL), ALK-positive (6.6%) and ALCL, ALK-negative (5.5%).[16] The findings of this study validated the utility of the WHO classification for defining subtypes of T-cell lymphomas.

The WHO classification was updated again in September 2008 to add new diseases and subtypes that have been recognized in the past decade, and to better define some of the heterogeneous and ambiguous categories based on the recent advances.[17] Genetic features, detected by cytogenetics or fluorescence in-situ hybridization (FISH) are increasingly important in defining specific NHL subtypes. In addition, detection of viruses, particularly Epstein-Barr virus, HHV8 and HTLV1, is often necessary to establish a specific diagnosis.

2008 WHO Classification of Mature B-cell Lymphomas

Follicular Lymphoma

In FL, pathological grading according to the number of centroblasts is considered to be a clinical predictor of outcome. In the 2001 WHO classification, three grades were recommended: FL1, FL2, and FL3; FL3 could be optionally stratified into 3A (centrocytes still present) or 3B (sheets of centroblasts). However, clinical outcomes for patients with FL1 and FL2 do not differ and this classification was deemed unreliable. Therefore, in the updated 2008 WHO classification, these grades are grouped under a single grade (FL1-2). Hans et al reported that there was no difference in survival outcomes between patients with Grade 3A and 3B FL, whereas patients with FL3 with more than 50% diffuse component have an inferior survival similar to the survival of those with DLBCL.[18] FL3B with cytogenetic abnormalities of BCL6 (at 3q27) are thought to be genetically more akin to germinal center type DLBCL than FL1-3A, and is associated with a more aggressive clinical course. Patients with FL3B with BCL2 translocation appear to have a clinical course similar to patients with FL1-3A.[19] Since FL3B is rare, the clinical behavior of FL3 in most studies is based mainly on FL3A cases. The 2008 WHO classification mandates stratifying FL3 into either 3A or 3B. FL is thus still divided into three grades (FL1-2, FL3A and FL3B) based on the number of centroblasts. Any diffuse areas in FL should be given a separate diagnosis of DLBCL, if it meets the criteria for FL3A or 3B. Pediatric-type FL, primary intestinal FL, other extranodal FLs and follicular lymphoma “in situ” (FLIS) are the other variants that are included under FL.

Pediatric-type follicular lymphoma: Pediatric-type FL is considered a rare variant of FL in the 2008 WHO classification and is generally characterized by lack of *BCL2* rearrangement and t(14,18), which constitute the genetic hallmark of conventional FL seen in adults.[20-24] Pediatric-type FL has a better prognosis than adult FL and is often cured with minimal therapy.

Primary intestinal follicular lymphoma: FL of the gastrointestinal tract is a recently described entity, which is common in the small intestine with the vast majority of cases occurring in the duodenum. The morphology, immunophenotype, and genetic features are similar to those of nodal FL. However, most patients have clinically indolent and localized disease. Survival appears to be excellent even without treatment.

*Other extranodal follicular lymphoma***:** In many of the other extranodal sites, the morphology, immunophenotype, and genetic features are similar to those of nodal FL. Patients usually have localized disease and systemic relapses are rare.

Follicular Lymphoma “in situ”: FLIS is characterized by the preservation of the lymph node architecture, with the incidental finding of focal strongly positive staining for BCL2 (restricted to germinal centers) and CD10 in the involved follicles, and the detection of t(14;18) by FISH.[21,25-27] FLIS has been reported in patients with prior FL or concurrent FL (at other sites), as well as in individuals with no known history of FL.[21,25,26] The occurrence of FLIS in the general population appears to be rare.

Primary Cutaneous Follicle Center Lymphoma (PC-FCL)

This is a new category in the 2008 classification and is defined as a tumor of neoplastic follicle center cells, including centrocytes and variable numbers of centroblasts, with a follicular, follicular and diffuse or a diffuse growth pattern. PC-FCL is the most common B-cell lymphoma of the skin and it is classified as a distinct entity in the EORTC classification of cutaneous lymphomas.[28] Gene expression profiling studies have also provided evidence in support of this classification.[29] PC-FCL presents as a solitary or localized skin lesion on the scalp, forehead or the trunk. It is characterized by an indolent course and rarely disseminates to extracutaneous sites. PC-FCL is consistently BCL6-positive, may be CD10-positive in cases with a follicular growth pattern. BCL2 is often either negative or dim (predominantly seen in cases with a follicular growth pattern). PC-FCL has an excellent prognosis with a 5-year survival rate of 95%.[28,30] PC-FCL must be distinguished from primary cutaneous DLBCL, leg type, which is not always possible histologically, and can be identified by expression of IRF4/MUM1, is strongly BCL2+ and has a more unfavorable prognosis.[31,32]

Diffuse Large B-cell Lymphomas

Some of the new categories of DLBCL are defined by extranodal primary sites and the association with viruses such as EBV or HHV8. Two borderline categories have also been included to incorporate cases in which it is not possible to distinguish between adult Burkitt lymphoma (BL) and DLBCL, and primary mediastinal large B-cell lymphoma (PMBL) and nodular sclerosis classical Hodgkin lymphoma (NSCHL). The ALK-positive DLBCL, plasmablastic lymphoma and primary effusion lymphoma are considered as distinct entities. The 2008 classification also has new category of large B-cell lymphoma arising in HHV8-associated multicentric Castleman's disease.

DLBCL, Not Otherwise Specified (NOS)

The 2008 classification has included DLBCL, NOS as a new category to include germinal center B-cell (GCB) subtype, activated B-cell (ABC) subtype as well as other DLBCL cases that do not belong to any of the four specific subtypes (T-cell/histiocyte rich large B-cell lymphoma, primary CNS DLBCL, primary cutaneous DLBCL ("leg type") or EBV+ DLBCL of the elderly).

Gene expression profiling (GEP) has been used to identify distinct subtypes of DLBCL: GCB) subtype, ABC subtype, PMBL, and type 3 which includes cases that cannot be classified as GCB, ABC, or PMBL subtypes.[33] GEP is not yet recommended for routine clinical use. Immunostaining algorithms have been developed to differentiate between GCB and ABC subtypes using a combination of CD10, BCL6, IRF4/MUM1, GCET1, FOXP1, and LMO2.[34-36] GCB subtype is associated with an improved outcome compared to non-GCB subtype.[36-38] However, at the present time, the upfront standard of care remains the same for both GCB and non-GCB subtypes.

B-cell Lymphoma, Intermediate between BL and DLBCL

BL is characterized by t(8;14), which results in the juxtaposition of *MYC* gene from chromosome 8 with the immunoglobulin heavy chain variable (*IGHV*) region on chromosome14 and variant translocations involving *MYC* and the immunoglobulin light chain genes.[39] Nevertheless, *MYC* translocations also occur in DLBCL. GEP studies have confirmed that the distinction between BL and DLBCL is not reliably reproducible with the use of the current criteria of morphology, immunophenotype, and genetic abnormalities.[40,41] Mature aggressive B-cell lymphomas without a molecular BL signatures (non-mBL) with *MYC* rearrangements[41] as well as those with both t(8;14) and t(14;18) translocations are associated with a poor prognosis.[42]

This provisional category replaces the “Atypical Burkitt Lymphoma” that was included in the 2001 WHO classification. The new category includes lymphomas with features of both DLBCL and BL, but or biological and clinical reasons should not be diagnosed as DLBCL or BL. Lymphomas in this provisional category include those that are morphologically intermediate between BL and DLBCL with immunophenotype suggestive of BL (CD10-positive, BCL6-positive, BCL2-negative and IRF4/MUM1-negative or weakly positive), lymphomas that are morphologically similar to BL but are strongly BCL2-positive and those with *MYC* rearrangement in addition to *BCL2* and/or *BCL6* rearrangements by FISH or standard cytogenetics (“double hit”) and complex karyotypes.

B-cell Lymphoma Intermediate between PMBL and NSCHL

PMBL has been recognized as a subtype of DLBCL based on its distinctive clinical and morphological features. NSCHL is the most common form of HL. Both tumors occur in the mediastinum and affect adolescents and young adults. GEP studies strongly support a relationship between PMBL and CHL. About a third of the genes that were more highly expressed in PMBL were also characteristically expressed in CHL cells.[43] Traverse-Glehen, et al., reported borderline cases with biologic and morphologic features of both CHL and B-cell NHL, known as "mediastinal gray zone lymphomas".[44]

This provisional category includes lymphomas with overlapping features between CHL and DLBCL, especially PBML. Those cases that morphologically resemble NSCHL have a strong expression of CD20 and other B-cell associated markers. Those cases that resemble PBML may have dim or no expression of CD20, strong expression of CD30 and CD15. These lymphomas have a more aggressive course and poorer outcome than either CHL or PBML.

Primary Cutaneous DLBCL, Leg Type (PC-DLBCL)

PC-DLBCL, leg type, is an unusual form of DLBCL composed of large transformed B cells most commonly arising on the leg (85-90%) although it can arise at other sites (10-15%).[30] These tumors arise from post-germinal center B-cell with expression of CD20, IRF4/MUM1, FOXP1, and BCL2; many cases express BCL6 and lack expression of CD10.[30,45,46] These tumors can disseminate to non-cutaneous sites, including the CNS. Studies have reported the development of extracutaneous relapse in 17-47% of patients with PC-DLBCL.[30,47,48] In a study in patients with PC-DLBCL (N=60), CNS was the most common site of visceral progression, occurring in 27% of patients with extracutaneous relapse (or in 12% of all patients on this study).[47] The high frequency of extracutaneous relapse in PC-DLBCL results in a poorer prognosis than the other cutaneous B-cell lymphomas, especially when the presentation involves multiple cutaneous lesions.[47]

Role of PET Scans

Response Assessment

The International Working Group (IWG) published the guidelines for response criteria for lymphoma in 1999.[49] These response criteria are based on the reduction in the size of the enlarged lymph node as measured by CT scan and the extent of bone marrow involvement that is determined by bone marrow aspirate and biopsy.[49] These guidelines were revised in 2007 by the International Harmonization Project to incorporate IHC, flow cytometry and 18-flourodeoxyglucose (FDG)-positron emission tomography (PET) scans in the definition of response for lymphoma.[50] In the revised guidelines, the response category of complete response uncertain (CRu) was essentially eliminated because residual masses were defined as a partial response (PR) or a complete response (CR) based on the result of a PET scan.

The response is categorized as CR, PR, stable disease (SD) and relapsed disease or progressive disease (PD).

In 2014, revised response criteria, known as the Lugano criteria, were introduced for staging and response assessment using PET-CT scans.[51,52] PET-CT is recommended for initial staging of all FDG-avid lymphomas. The use of 5-point scale (5-PS) is recommended for the interpretation and reporting of PET-CT scans. The 5-PS is based on the visual assessment of FDG uptake in the involved sites relative to that of the mediastinum and the liver.[53-55] A score of 1 denotes no abnormal FDG-avidity, while a score of 2 represents uptake less than the mediastinum. A score of 3 denotes uptake greater than the mediastinum but less than the liver, while scores of 4 and 5 denote uptake greater than the liver, and greater than the liver with new sites of disease, respectively. Different clinical trials have considered scores of either 1-2 or 1-3 to be PET-negative, while scores of 4-5 are universally considered PET-positive. A score of 4 on an interim or end of treatment restaging scan may be consistent with a partial response if the FDG-avidity has declined from initial staging, while a score of 5 denotes progressive disease.

However, the application of PET-CT to response assessment is limited to histologies where there is reliable FDG uptake in active tumor and the revised response criteria have thus far only been validated for DLBCL and Hodgkin lymphoma. The application of the revised response criteria to other histologies requires validation and the original IWG guidelines should be used. Of note, the Lugano response criteria may not be applicable for several of the tumor subtypes included in the NCCN Guidelines. Tumor specific response criteria are included in the guidelines for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), hairy cell leukemia (HCL), mycosis fungoides/Sezary syndrome (MF/SS), adult T-cell leukemia/lymphoma (ATLL), and T-cell-prolymphocytic leukemia (T-PLL).

Staging

PET-CT scans are now employed for initial staging, restaging and end of treatment response assessment in the majority of patients with NHL.[56] In a meta-analysis study, PET showed a high positivity and specificity when used for the staging and restaging of patients with lymphoma.[57] PET is nearly universally positive at diagnosis in Hodgkin lymphoma, DLBCL, and follicular lymphoma,[58] about 90% in T-cell lymphoma[59] and nodal MZL but less sensitive for extra-nodal MZL.[60] However, a number of benign conditions including sarcoid, infection, and inflammation can result in false-positive PET scans, complicating the interpretation. Lesions smaller than 1 cm are not reliably visualized with PET scans. Although PET scans may detect additional disease sites at diagnosis, the clinical stage is modified only in 15-20% of patients and a change in treatment in only 8% of patients. PET scans are now virtually always performed as combined PET-CT scans.

PET-CT has distinct advantages in both staging and restaging compared to full-dose diagnostic CT or PET alone.[61,62] In a retrospective study, PET-CT performed with low-dose non-enhanced CT was found to be more sensitive and specific than the routine contrast-enhanced CT in the evaluation of lymph node and organ involvement in patients with Hodgkin disease or high-grade NHL.[62] Preliminary results of another recent prospective study (47 patients; patients who had undergone prior diagnostic CT were excluded) showed a good correlation between low-dose unenhanced PET-CT and full-dose enhanced PET-CT in the evaluation of lymph nodes and extranodal disease in lymphomas.[61] PET-CT is particularly important for staging before consideration of RT and baseline PET-CT will aid in

the interpretation of post-treatment response evaluation based on the 5-PS as described above.[52]

PET-CT is recommended for initial staging of FDG-avid lymphomas. PET should be done with contrast-enhanced diagnostic CT. Staging imaging with CT is recommended for lymphomas that are minimally FDG-avid (CLL/SLL, marginal zone lymphomas, HCL, cutaneous B-cell lymphomas, MF/SS, CD30+ cutaneous lymphomas and T-cell large granular lymphocytic leukemia), except in selected circumstances. FDG-avid lymphomas should have response assessed by PET-CT using the 5-PS. False-positive PET scans may be observed related to infectious or inflammatory conditions. Biopsy of affected sites remains the gold standard for confirming new or persistent disease at end of therapy.

Principles of Radiation Therapy

Radiation therapy (RT) can be delivered with photons, electrons or protons, depending upon clinical circumstances. Advanced RT techniques emphasize tightly conformal doses and steep gradients next to normal tissues. Therefore, target definition and delineation and treatment delivery verification require careful monitoring to avoid the risk of missing geographic location of the tumor and subsequent decrease in tumor control. Image guidance may be required to facilitate target definition. Preliminary results from single-institution studies have shown that significant dose reduction to organs at risk (OAR; eg, lungs, heart, breasts, kidneys, spinal cord, esophagus, carotid artery, bone marrow, stomach, muscle, soft tissue and salivary glands) can be achieved with advanced RT planning and delivery techniques such as 4D-CT simulation, intensity-modulated RT (IMRT), image-guided RT, respiratory gating or deep inspiration breath hold.[63-66] These techniques offer significant and clinically relevant advantages in specific instances to spare OAR and decrease the risk for normal tissue damage and late effects without compromising the primary goal of local tumor control.[67-70] In mediastinal lymphoma, the use of 4D-CT simulation and the adoption of strategies to deal with respiratory motion such as inspiration breath-hold techniques, and image guided RT during treatment delivery is also important.

Randomized prospective studies to test these concepts are unlikely to be done since these techniques are designed to decrease late effects, which usually develop ≥ 10 years after completion of treatment. Therefore, the guidelines recommend that RT delivery techniques that are found to best reduce the doses to the OAR in a clinically meaningful manner without compromising target coverage should be considered.

Involved-site RT (ISRT) is intended to limit radiation exposure to adjacent uninvolved organs (such as lungs, bone, muscle, or kidney) when lymphadenopathy regresses following chemotherapy, thus minimizing the potential long term complications. Extended-field RT (EFRT) and involved-field RT (IFRT) techniques have now been replaced by ISRT, in an effort to restrict the size of the RT fields to smaller volumes.[71,72] ISRT targets the initially involved nodal and extra-nodal sites detectable at presentation.[71,72] Larger RT fields should be considered for limited stage indolent NHL, often treated with RT alone.[71]

Treatment planning for ISRT requires the use of CT-based simulation. The incorporation of additional imaging techniques such as PET and MRI often enhances the treatment planning. The OAR should be outlined for optimizing treatment plan decisions. The treatment plan is designed using conventional, 3D conformal, or IMRT techniques using clinical treatment planning considerations of coverage and dose reductions for OAR.[71]

The principles of ISRT are similar for both nodal and extranodal disease. The gross tumor volume (GTV) defined by radiological imaging prior to biopsy, chemotherapy or surgery provides the basis for determining the clinical target volume (CTV).[73] Possible movement of the target by respiration as determined by 4D-CT or fluoroscopy should also influence the final CTV. The presence of suspected subclinical disease and uncertainties in original imaging accuracy or localization may lead to the expansion of the CTV. The planning treatment volume (PTV) is an additional expansion of the CTV that accounts only for setup variations.

In the case of extranodal disease, particularly for indolent lymphoma, in most cases, the whole organ comprises the CTV (eg, stomach, salivary gland, and thyroid). For other organs, including orbit, breast, lung, bone, localized skin, and in some cases when RT is consolidation after chemotherapy, partial organ RT may be appropriate. No radiation is required for uninvolved lymph nodes for most NHL subtypes.

The general dose guidelines for individual subtypes of NHL are outlines in the “Principles of RT” section of the guidelines.

Diagnosis

In all cases of NHL, the most important first step is an accurate pathologic diagnosis. The basic pathological evaluation is the same in each Guidelines (by tumor subtype), although some further evaluation may be useful in certain circumstances to clarify a particular diagnosis; these are outlined in the pathological evaluation of the individual Guidelines.

An incisional or excisional lymph node biopsy is recommended to establish the diagnosis of NHL. Core needle biopsy is discouraged unless the clinical situation dictates that this is the only safe means of obtaining diagnostic tissue. Fine needle aspiration (FNA) biopsy is widely used in the diagnosis of malignant neoplasms, but its role in the diagnosis of lymphoma is still controversial.[74,75] Since the revised REAL/WHO classification is based on both morphology and immunophenotyping, FNA alone is not acceptable as a reliable diagnostic tool for NHL. However, its use in combination with ancillary techniques may provide precise diagnosis thereby obviating the need for a more invasive biopsy in highly selected circumstances. Recent studies have shown that the diagnostic accuracy of FNA improves significantly when it is used in combination with IHC and flow cytometry.[76-78]

In the NCCN Guidelines, FNA alone is not suitable for an initial diagnosis of NHL, though it may be sufficient to establish relapse. However, in certain circumstances, when a lymph node is not easily accessible, a combination of core biopsy and FNA in conjunction with appropriate ancillary techniques [PCR for *IGHV* and/or T-cell receptor (*TCR*) gene rearrangements; FISH for major translocations; immunophenotypic analysis] may be sufficient for diagnosis. This is particularly true for the diagnosis of CLL. In other entities presenting in leukemic phase, such as FL or MCL, a biopsy is still preferred to clarify histological subtype.

Immunophenotypic analysis is essential for the differentiation of various subtypes of NHL to establish the proper diagnosis. It can be performed by flow cytometry and/or IHC; the choice depends on the antigens as well as the expertise and resources available to the hematopathologist. In some cases flow cytometry and IHC are complementary diagnostic tools.[79] Cytogenetic or molecular genetic analysis may be necessary under certain circumstances to identify the specific chromosomal translocations that are characteristic of some NHL subtypes or to establish clonality.

After the publication of the 2008 WHO Classification, the NHL Guidelines panel developed a series of algorithms for the use of immunophenotyping in the diagnosis of mature lymphoid neoplasms. These algorithms were developed to provide guidance for surgical pathologists as well as an aid to the clinician in the interpretation of pathology reports and they should be used in conjunction with clinical and pathological correlation. See *Immunophenotyping/Genetic Testing* in the guidelines.

Workup

Essential workup procedures include a complete physical exam with particular attention to node bearing areas and the size of liver and spleen, symptoms present, performance status, laboratory studies including CBC, serum lactate dehydrogenase (LDH), hepatitis B virus testing (see below), comprehensive metabolic panel, and CT chest/abdominal/pelvic with oral and intravenous contrast (unless co-existent renal insufficiency). MUGA scan or echocardiograms are recommended when anthracyclines and anthracenedione containing regimens are used. Due the risk of hepatitis B reactivation, the panel has included hepatitis B testing (hepatitis B surface antigen and hepatitis B core antibody) as part of essential workup prior to initiation of treatment in all patients who will receive anti CD20 monoclonal antibody-based regimens. Furthermore, hepatitis B reactivation has been reported with chemotherapy alone and testing should be considered in anyone with a risk factor (e.g. blood transfusion, IV drug abuse) or if from a region with a non-negligible prevalence of hepatitis B infection (see *"Hepatitis B Reactivation"* in the Supportive Care section below). Hepatitis C testing is needed in high-risk patients and patients with splenic marginal zone lymphoma.

Optional procedures (depending on specific lymphoma type) include beta-2-microglobulin, CT or PET-CT scans, endoscopic ultrasound (gastric MALT lymphoma), head CT or brain MRI and lumbar puncture to analyze cerebrospinal fluid (MCL and DLBCL). Discussion of fertility issues and sperm banking should be addressed in the appropriate circumstances.[80]

Bone marrow biopsy with or without aspirate is essential in all cases where treatment is considered; however, there are circumstances where it may be deferred. Bone marrow biopsy is usually included in the workup for all patients with NHL with the exception of SLL/CLL when there is a clonal lymphocytosis identified by flow cytometry. Bone marrow involvement occurs in 39% of low-grade, 36% of intermediate grade and 18% of high-grade lymphomas. Bone marrow involvement was associated with significantly shorter survivals in patients with intermediate or high-grade lymphomas.[81] In a retrospective analysis, the incidence of bone marrow involvement and the parameters predicting bone marrow involvement were analyzed in 192 patients with stage I and II in DLBCL.[82] Overall incidence of BM involvement was 3.6%. The authors concluded that bone marrow biopsy may be safely omitted in selected patients with early stage DLBCL.[82] In cutaneous B-cell lymphomas, bone marrow biopsy is essential for PC-DLBCL, leg type, since this is an aggressive lymphoma that will probably require systemic treatment, whereas the role of bone marrow biopsy in the PC-FCL and PC-MZL subtypes is less clear. Recent studies have indicated that bone marrow biopsy is an essential component of staging in patients with PC-FCL first presenting in the skin, whereas it appears to have limited value in patients with MZL presenting in the skin, and may be considered only in selected cases.[83,84]

In the NCCN Guidelines, bone marrow biopsy with or without aspirate is included as part of essential workup for all lymphomas. However, in patients with low bulk indolent disease with radiographic clinical stage III disease, an initial staging bone marrow evaluation can be deferred if observation is recommended as it will not change the clinical recommendations. However, in the evaluation of potentially early stage indolent lymphoma (stage I or II), bone marrow biopsy is essential; some panel members advocate bilateral core biopsies in this situation.[85] Bilateral cores are recommended if radioimmunotherapy is considered.

Supportive Care

Supportive care remains an important component of managing patients with NHL, particularly during active therapy. Supportive care measures for NHL may include (but are not limited to) management of infectious complications, management of tumor lysis syndrome, and use of myeloid growth factors or blood product transfusions. These measures may help to maximize the benefit of NHL therapy for patients by enhancing tolerability, reducing treatment-related toxicities, and ensuring timely delivery of planned treatment courses. Patients with hematologic malignancies are at increased risk for infectious complications due to profound immunosuppression stemming from myelosuppressive therapy and/or the underlying malignancy. For example, reactivation of latent viruses may occur in the setting of significant immunosuppression in patients with NHL.

Viral Reactivation and Infections

Hepatitis B Virus Reactivation

Hepatitis B virus (HBV) reactivation has been reported in patients treated with chemotherapy with or without immunotherapy agents.[86] HBV carriers with lymphoid malignancies have a high risk of HBV reactivation and disease,[87] especially those treated with anti-CD20 monoclonal antibodies (e.g., rituximab, ofatumumab).[86] Cases of liver failure and death associated with HBV reactivation have occurred in patients receiving rituximab-containing regimens.[86]

Testing for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) can determine the HBV status of an individual. Because of the widespread use of the hepatitis B vaccine, hepatitis B surface antibody (HBsAb) positivity is of limited value; however, in rare cases, HBsAb levels can help to guide therapy. Patients with malignancies who are positive for either HBsAg or HBcAb are at risk for HBV reactivation with cytotoxic chemotherapy; approximately 20% to 50% of patients with HBsAg positivity and 3% to 45% with HBcAb positivity develop HBV reactivation.[88-97] False-negative HBsAg results may occur in chronic liver disease; therefore, patients with a history of hepatitis in need of chemotherapy should be assessed by viral load measurement.[98] HBsAb positivity is generally equated with protective immunity, although reactivated HBV disease may occur in the setting of significant immunosuppression in HBcAb-positive individuals.[95,99] In patients with B-cell lymphoid malignancies treated with rituximab-containing regimens, HBV reactivation was observed in patients with HBcAb positivity (with or without HBsAb positivity), even among those who were HBsAg negative prior to initiation of treatment.[90,96,97] A recent meta-analysis and evaluation of the FDA safety reports concerning HBV reactivation in patients with lymphoproliferative disorders reported that HBcAb positivity was correlated with increased incidence of rituximab-associated HBV reactivation.[89] Vaccination against HBV should be strongly considered In HBV-naïve patients (i.e., negative for HBsAg, HBsAb, and HBcAb).[95,100]

Recommended strategies for the management of HBV reactivation in patients with hematologic malignancies undergoing immunosuppressive therapy include upfront antiviral prophylaxis or pre-emptive therapy. Prophylactic approaches involve treating patients who are HBsAg-positive or HBcAb-positive with prophylactic antiviral therapy, regardless of viral load or presence of clinical manifestations of HBV reactivation. The alternative strategy of pre-emptive therapy involves close surveillance with a highly sensitive quantitative assay for HBV, combined with antiviral therapy upon a rising HBV DNA load.[95] Antiviral prophylaxis with lamivudine has been shown to reduce the risks for HBV reactivation in HBsAg-positive patients with hematologic malignancies treated with immunosuppressive cytotoxic agents.[87,101-104] A small randomized study in HBsAg-positive patients with lymphoma (N=30) showed that antiviral prophylaxis with lamivudine was superior to deferred pre-emptive therapy (i.e., antivirals given at the time of serological evidence of HBV reactivation based on viral DNA in serum samples).[101] HBV reactivation occurred in 53% of patients in the deferred therapy arm compared with none in the prophylaxis arm. In a meta-analysis of clinical trials evaluating the benefit of lamivudine prophylaxis in HBsAg-positive lymphoma patients treated with immunosuppressive regimens, prophylaxis resulted in significant reductions in HBV reactivation (risk ratio=0.21; 95% CI, 0.13–0.35) and a trend for reduced HBV-related deaths (risk ratio=0.68; 95% CI, 0.19–2.49) compared with no prophylaxis.[104]

Recent studies have shown entecavir to be more effective than lamivudine in preventing rituximab-associated HBV reactivation.[105-107]

The results of a randomized controlled trial showed that entecavir prophylaxis (before initiation of chemotherapy to 3 months after completion of chemotherapy) was more effective in preventing HBV-reactivation than the control (initiation of entecavir therapy at the time of HBV reactivation and HBsAg reverse seroconversion after chemotherapy).[105] The cumulative HBV reactivation rates at months 6, 12, and 18 after chemotherapy were 8%, 11.2%, and 25.9%, respectively, in the control group, and 0%, 0%, and 4.3% in the entecavir prophylaxis (*P* = .019). In another prospective study that compared the efficacy of antiviral prophylaxis with entecavir (n= 61) and lamivudine (n= 60) in HBsAg-positive patients with newly diagnosed DLBCL treated with R-CHOP chemoimmunotherapy, entecavir was associated with significantly lower rates of HBV reactivation (6.6% vs 30.0%, *P* =.001), HBV-related hepatitis (0% vs 13.3%, *P* =.003) and disruption of chemotherapy (1.6% vs 18.3%, *P* =.002).[107]

Although prophylaxis with lamivudine has been evaluated in the setting of immunosuppressive anti-tumor therapy (as mentioned above), the optimal antiviral strategy remains unclear. Concerns over the development of resistance to lamivudine exist.[108-112] Adefovir combined with lamivudine has been evaluated in patients with lamivudine-resistant HBV infections.[113] Tenofovir has demonstrated superior antiviral efficacy compared with adefovir in randomized double-blind phase III studies in patients with chronic HBV infection, and may be the preferred agent in this setting, however, limited data are available regarding its use in patients with cancer.[114] Entecavir and telbivudine have also been evaluated in randomized open-label studies with adefovir as the comparator in patients with chronic HBV infection, and both agents have shown improved antiviral activity compared with adefovir.[115,116]

The panel recommends HBsAg and HBcAb testing for all patients planned for treatment with anti-CD20 monoclonal antibody-containing regimens. In individuals who test positive for HBsAg and/or HBcAb, baseline quantitative PCR for HBV DNA should be obtained to determine viral load. However, a negative baseline PCR does not preclude the possibility of reactivation. Patients receiving intravenous

immunoglobulin (IVIG) may be HBcAb positive as a consequence of IVIG therapy, although HBV viral load monitoring is recommended.[117]

Prophylactic antiviral therapy with entecavir is recommended for patients who are HBsAg positive and undergoing anti-lymphoma therapy. Lamivudine prophylaxis should be avoided due to the risks for the development of resistance. For patients who are HBsAg negative but HBcAb positive, antiviral prophylaxis with entecavir is also the preferred approach; however, if these patients concurrently have high levels of HBsAb, they may be monitored with serial measurements of HBV viral load and treated with pre-emptive antivirals upon increasing viral load. During the treatment period, viral load should be monitored monthly with PCR and then every 3 months after completion of treatment. If viral load is consistently undetectable, prophylaxis with antivirals should be continued. If viral load fails to drop or a previously undetectable PCR becomes positive, consultation with a hepatologist and discontinuation of anti-CD20 antibody therapy is recommended.

As mentioned above, several antiviral agents are available for prophylactic measures. The optimal choice will be driven by institutional standards or recommendation from hepatology or infectious disease consultant. The appropriate duration of prophylaxis remains undefined, but the panel recommended that surveillance and antiviral prophylaxis should be continued for up to 12 months after the completion of oncologic treatment.[95]

Hepatitis C Virus-associated B-cell NHL

Case-control studies have demonstrated a strong association between seropositivity for hepatitis C virus (HCV) and development of NHL, particularly for B-cell lymphomas.[118-126] In large population-based or multicenter case-control studies, prevalence of HCV seropositivity was consistently increased among patients with B-cell histologies, including DLBCL and marginal zone lymphomas.[120,121,124,126] A retrospective study in patients with HCV infection (N=3209) showed that the cumulative incidence of developing malignant lymphomas was significantly higher among patients with persistent HCV infection compared with those who had sustained virologic response (SVR) to interferon-containing therapy (15-year incidence rate 2.6% vs. 0%; *P*=0.016).[127] Based on multivariate analysis, persistent HCV infection remained a significant independent factor associated with development of malignant lymphomas. This study suggested that achievement of SVR with interferon-based therapy may reduce the incidence of malignant lymphoma in patients with HCV infection.[127] Several published reports suggested that treatment with antivirals (typically, interferon with or without ribavirin) led to regression of NHLs in HCV-positive patients, which provide additional evidence for the involvement of HCV infection in the pathogenesis of lymphoproliferative diseases.[128-134] In a retrospective study in patients with NHL (N=343; indolent and aggressive histologies) who achieved a CR after chemotherapy, the subgroup of HCV-positive patients treated with antivirals (interferon and ribavirin; n=25) had significantly longer disease-free survival compared with HCV-positive patients who did not receive antiviral therapy (n=44); the probability of relapse-free survival at 5-year follow up was 76% and 55%, respectively.[133] In addition, none of the patients with a SVR to antivirals (n=0 of 8) relapsed compared with 29% who did not respond to antivirals (n=5 of 17).

In a multicenter retrospective study from a large series of HCV-positive patients with indolent NHL, antiviral therapy (interferon or pegylated interferon, with or without ribavirin), resulted in HCV-RNA clearance was achieved in 80% of patients who received first-line antivirals (n=100) and in 67% of those who received antivirals as second-line therapy after failure of initial treatment (n=34).[134] Patients in this analysis did not require immediate treatment for their lymphoma. The ORR for

patients treated with antiviral in the first-line setting was 77% (44% CR and 33% PR) and the ORR for patients treated with antiviral in the second-line setting was 85% (56% CR and 29% PR). In the group of patients who received antivirals in first line, hematologic response was significantly associated with achievement of HCV-RNA clearance. Thus, in HCV-positive patients with indolent NHL not requiring immediate anti-tumor therapy with chemoimmunotherapy regimens, initial treatment with interferon (with or without ribavirin) appeared to induce lymphoma regression in a high proportion of patients. In HCV-positive patients with NHL who achieve a remission with anti-tumor therapy, subsequent treatment with antivirals may be associated with lower risk of disease relapse.

The optimal management of HCV-positive patients with NHL remains to be defined. Patients with indolent NHL and HCV seropositivity may benefit from antiviral treatment as initial therapy, as demonstrated in several reports.[128,130,132,134,135] In patients with aggressive NHL, an earlier analysis of pooled data from GELA clinical studies (prior to the rituximab era) suggested that HCV seropositivity in patients with DLBCL was associated with significantly decreased survival outcomes, due, in part, to severe hepatotoxicity among those with HCV infection.[136] Subsequent studies in the rituximab era showed that HCV seropositivity was not predictive of outcomes in terms of PFS or OS in patients with DLBCL.[137,138] However, the incidence of hepatotoxicity with chemoimmunotherapy was higher among HCV-positive patients, confirming the observation made from the GELA studies.

The treatment of chronic HCV infection has improved with the advent of newer antiviral agents, especially those that target carriers of HCV genotype 1. Direct acting antiviral agents (DAA) administered in combination with standard antivirals (pegylated interferon and ribavirin) have shown significantly higher rates of SVR compared with standard therapy alone in chronic carriers of HCV genotype 1.[139-142] Telaprevir and boceprevir are DAAs that were recently approved by the FDA for the treatment (in combination with pegylated interferon and ribavirin) of patients with HCV genotype 1 infection. The updated guidelines for the management of HCV infection from the American Association for the Study of Liver Diseases (AASLD) recommended that DAAs be incorporated into standard antiviral therapy for patients infected with HCV genotype 1.[143]

The panel recommends initial antiviral therapy in asymptomatic patients with HCV-positive low-grade B-cell NHL. For those with HCV genotype 1, triple antiviral therapy with inclusion of DAAs should be considered as per AASLD guidelines. Patients with HCV-positive aggressive B-cell NHL should initially be treated with appropriate chemoimmunotherapy regimens according to the NCCN Guidelines for NHL. Liver function and serum HCV RNA levels should be closely monitored during and after chemoimmunotherapy for development of hepatotoxicity. Antiviral therapy should then be considered in patients who achieve a CR after completion of chemoimmunotherapy.

Cytomegalovirus Reactivation

Cytomegalovirus (CMV) reactivation may occur among patients with lymphoproliferative malignancies receiving alemtuzumab therapy, and occurs most frequently between 3 to 6 weeks after initiation of therapy when T-cell counts reach a nadir. CMV reactivation is a well-documented infectious complication in patients receiving treatment with alemtuzumab, occurring in up to 25% of treated patients. Current management practices for prevention of CMV reactivation include the use of prophylactic ganciclovir (oral or IV) if CMV viremia is present prior to alemtuzumab therapy, or pre-emptive use of these drugs when the viral load is found to be increasing during therapy.

Patients with hematologic malignancies treated with alemtuzumab-containing regimens should be closely monitored and managed for potential development of CMV reactivation. To this end, periodic monitoring for the presence of CMV antigens using quantitative polymerase chain reaction (PCR) assays is an effective management approach. The panel recommends routine surveillance for CMV viremia (every 2–3 weeks) during the treatment course with alemtuzumab and for 2 months following completion of alemtuzumab treatment.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a rare but serious and usually fatal CNS infection caused by reactivation of the latent JC polyoma virus. Cases of PML generally occur in severely immunocompromised individuals, as in the case of patients with AIDS. Patients with hematologic malignancies who have profound immunosuppression (due to the underlying disease and/or immunosuppressive therapies) are also at risk of developing PML. In a report of 57 cases from the Research on Adverse Drug Events and Reports project, 52 patients with lymphoproliferative disorders developed PML after treatment with rituximab and other treatments which included hematopoietic stem cell transplantation or chemotherapy with purine analogs or alkylating agents.[144] Median time from last rituximab dose to PML diagnosis was 5.5 months. Median time to death after PML diagnosis was 2 months. The case fatality rate was 90%.[144] The use of rituximab may be associated with an increased risk of PML in immunocompromised patients with lymphoproliferative malignancies.[145] PML has been reported with rituximab treatment (usually in combination with chemotherapy regimens) in patients with CLL/SLL or other types of NHL. Patients with low CD4+ T-cells prior to or during anti-tumor treatment with rituximab-containing regimens may be particularly susceptible to PML.[144,146,147] Patients with NHL receiving treatment with another anti-CD20 monoclonal antibody ofatumumab,[148] or the anti-CD30 antibody-drug conjugate brentuximab vedotin, may also be at potential risk for PML.[149-151]

Development of PML is clinically suspected based on neurological signs and symptoms that may include confusion, motor weakness or poor motor coordination, visual changes, and/or speech changes.[144] PML is usually diagnosed with PCR of cerebrospinal fluid (CSF) or in some cases, by analysis of brain biopsy material. There is no effective treatment for PML. Patients should be carefully monitored for the development of any neurological symptoms. There is currently no consensus on pretreatment evaluations that can be undertaken to predict for the subsequent development of PML.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is a potentially serious complication of anticancer therapy characterized by metabolic and electrolyte abnormalities caused by the abrupt release of intracellular contents into the peripheral blood resulting from cellular disintegration induced by anticancer therapy. It is usually observed within 12 to 72 hours after start of chemotherapy.[152] Untreated TLS can induce profound metabolic changes resulting in cardiac arrhythmias, seizures, loss of muscle control, acute renal failure, and even death.

Cairo and Bishop have classified TLS into laboratory TLS and clinical TLS. Laboratory TLS is defined as a 25% increase in the levels of serum uric acid, potassium, or phosphorus or a 25% decrease in calcium levels.[153] Clinical TLS refers to laboratory TLS with clinical toxicity that requires intervention. Clinical complications may include renal insufficiency, cardiac arrhythmia, or seizures. The four primary electrolyte abnormalities of TLS are hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia. Symptoms associated with

TLS may include nausea and vomiting, diarrhea, seizures, shortness of breath, or cardiac arrhythmias. The risk factors for TLS include bone marrow involvement, bulky tumors that are chemosensitive, rapidly proliferative or aggressive hematologic malignancies, an elevated leukocyte count or pretreatment LDH, pre-existing elevated uric acid, renal disease or renal involvement of tumor. Patients diagnosed with lymphoblastic lymphoma or Burkitt lymphoma are at a higher risk of developing TLS. Occasionally, patients with bulky presentation of DLBCL and patients with CLL and high white blood cell count may experience TLS at a moderately high frequency.

TLS is best managed if anticipated and when treatment is started prior to chemotherapy. The cornerstone of TLS management is hydration and the management of hyperuricemia. Allopurinol (xanthine oxidase inhibitor) and rasburicase (recombinant urate oxidase) are highly effective for the management of hyperuricemia. Allopurinol is a xanthine analog and a competitive inhibitor of xanthine oxidase, thereby blocking conversion of purine metabolites to uric acid. Allopurinol will decrease the formation of uric acid production and has been shown to reduce the incidence of uric-acid uropathy.[154] Since the drug inhibits new uric acid formation rather than reduce existing uric acid, it can take several days for elevated levels of uric acid to normalize after the initiation of treatment, which may delay the start of chemotherapy. Furthermore, allopurinol may lead to the accumulation of xanthine crystals in renal tubules leading to acute obstructive uropathy. Allopurinol will also reduce clearance of 6-mercaptopurine and high-dose methotrexate. Rasburicase is a recombinant urate oxidase, which catalyzes the oxidation of uric acid to a highly soluble non-toxic metabolite that is readily excreted. It has been shown to be safe and highly effective in the prevention and treatment of chemotherapy-induced hyperuricemia in both children and adults with hematologic malignancies.[155] In an international compassionate use trial in patients at risk for TLS during chemotherapy (N=280 enrolled), rasburicase (0.20 mg/kg/day IV for 1–7 days) resulted in uric acid response in all evaluable patients (n=219; adults, n=97).[155] Among the subgroup of adults with hyperuricemia (n=27), mean uric acid levels decreased from pretreatment levels of 14.2 mg/dL to 0.5 mg/dL 24 to 48 hours after administration of last dose of rasburicase. Among adult patients at risk for TLS (but without baseline hyperuricemia; n=70), mean uric acid levels decreased from 4.8 mg/dL to 0.4 mg/dL.[155] The GRAAL1 trial evaluated the efficacy and safety of rasburicase (0.20 mg/kg/day IV for 3–7 days, started on day 0 or day 1 of chemotherapy) for the prevention and treatment of hyperuricemia in adult patients with aggressive NHL during induction chemotherapy (N=100).[156] Prior to chemotherapy, 66% of patients had elevated lactate dehydrogenase (LDH) levels and 11% had elevated uric acid levels (>7.56 mg/dL). Uric acid levels were normalized and maintained within normal ranges during chemotherapy in all patients. Uric acid levels decreased within 4 hours after the first injection of rasburicase. In addition, serum creatinine levels and other metabolites were also controlled with the administration of rasburicase.[156]

A prospective, multicenter randomized phase III trial compared the efficacy and safety of rasburicase and allopurinol in adult patients with hematological malignancies at high or potential risk for TLS (N=275).[157] Patients were randomized to receive treatment with rasburicase alone (0.20 mg/kg/day IV for days 1–5; n=92), rasburicase combined with allopurinol (rasburicase 0.20 mg/kg/day IV for days 1–3; allopurinol 300 mg/day PO for days 3–5; n=92) or allopurinol alone (300 mg/day PO for days 1–5; n=91). The rate of uric acid response (defined as plasma uric acid levels ≤7.5 mg/dL for all measurements from days 3–5) was 87% for rasburicase, 78% for rasburicase combined with allopurinol and 66% for allopurinol.[157] The incidence of clinical TLS was similar across treatment arms, occurring in 3%, 3%

and 4% of patients, respectively. The incidence of laboratory TLS was 21%, 27%, and 41%, respectively, with significantly lower incidence observed in the rasburicase arm compared with allopurinol (*P* =.003). The response rate with rasburicase was superior to allopurinol in the overall study population (87% vs. 66%, as above; *P* =.001) as well as in patients with high risk TLS (89% vs. 68%; *P* =.001) and in patients with baseline hyperuricemia (90% vs. 53%; *P* =.015). The median time to control for serum uric acid in hyperuricemic patients was 4 hours for rasburicase, 4 hours for rasburicase combined with allopurinol and 27 hours for allopurinol.[157] Potential hypersensitivity to study regimen was reported in 4% of patients in the rasburicase arm and 1% in the combination arm; no anaphylaxis or grade 4 hypersensitivity reactions were reported in this trial.[157] However, rasburicase can induce anaphylactic reactions. Other adverse reactions include methemoglobinemia and severe hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. A single fixed dose of rasburicase (6 mg)[158,159] or a single weight-based dose of rasburicase (0.05–0.15 mg/kg)[160,161] has been shown to be effective in the management of uric acid levels in adult patients with hyperuricemia or with high-risk factors for TLS. A recent phase II randomized trial compared the efficacy of rasburicase administered as a single dose (0.15 mg/kg, followed by additional days of dosing as needed) versus rasburicase (0.15 mg/kg/day) given for 5 days in adult patients at high risk or potential risk for TLS (N=80 treated).[162] The median pretreatment uric acid level was 8.5 mg/dL for high-risk patients (n=40) and 5.6 mg/dL for potential risk patients (n=40). Nearly all treated patients (99%) showed normalization of uric acid levels within 4 hours after the first dose of rasburicase; levels of uric acid were undetectable (<0.7 mg/dL) in 84% of patients.[162] In the single-dose rasburicase arm, 85% of patients had sustained uric acid response compared with 98% of patients in the 5-day rasburicase arm. Among high-risk patients within the single-dose arm, 6 patients received a second dose of rasburicase to achieve uric acid response.[162]

Allopurinol should be administered prior to the initiation of chemotherapy. Rasburicase is indicated in cases where the uric acid level remains elevated despite treatment with allopurinol or in patients with renal insufficiency. Electrolytes and renal function should be monitored every 6 to 8 hours with appropriate interventions for hyperkalemia and hyperphosphatemia. Careful clinical monitoring will help to preempt complications, and in many cases, admission to ICU may be appropriate. Cardiac monitoring or serial ECG may be beneficial to identify early electrolyte-related cardiac abnormalities. Dialysis may be necessary in cases of anuric acute renal failure.

The NCCN Guidelines recommend allopurinol or rasburicase as first-line and at retreatment of hyperuricemia. Allopurinol be started 2−3 days prior to chemotherapy and continued for 10−14 days. Rasburicase is recommended for patients with any of the following risk factors: presence of any high risk feature (i.e., Burkitt lymphoma or lymphoblastic lymphomas; spontaneous TLS; elevated WBC count; elevated uric acid levels; bone marrow involvement; renal disease or renal involvement by tumor); bulky disease requiring immediate therapy; patients in whom adequate hydration is not possible; allopurinol is ineffective; or acute renal failure. A single dose is adequate in most cases; repeat dosing should be given on an individual basis.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5-29. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25559415.

2. Al-Hamadani M, Habermann TM, Cerhan JR, et al. Non-Hodgkin lymphoma subtype distribution, geodemographic patterns, and survival in the US: A longitudinal analysis of the National Cancer Data Base from 1998 to 2011. Am J Hematol 2015;90:790-795. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26096944.

3. Groves FD, Linet MS, Travis LB, Devesa SS. Cancer surveillance series: non-Hodgkin's lymphoma incidence by histologic subtype in the United States from 1978 through 1995. J Natl Cancer Inst 2000;92:1240-1251. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10922409.

4. Hicks EB, Rappaport H, Winter WJ. Follicular lymphoma; a re-evaluation of its position in the scheme of malignant lymphoma, based on a survey of 253 cases. Cancer 1956;9:792-821. Available at: http://www.ncbi.nlm.nih.gov/pubmed/13356265.

5. Rappaport H. Tumors of the hematopoietic system. In: Atlas of Tumor Pathology Series (ed I). Washington, DC: Armed Forces Institute of Pathology; 1966.

6. Bennetta MH, Farrer-Brown G, Henry K, et al. Classification of non-Hodgkin's lymphomas. Lancet 1974;2:405-408. Available at: http://www.ncbi.nlm.nih.gov/pubmed/4136882.

7. Lennert K. Malignant lymphomas other than Hodgkin's disease. New York: Springer-Verlag 1978.

8. Lennert K, Feller A. Histopathology of Non-Hodgkin's Lymphomas (ed 2nd Edition). Berlin: Springer-Verlag; 1992.

9. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: summary and description of a working formulation for clinical usage. The Non-Hodgkin's Lymphoma Pathologic Classification Project. Cancer 1982;49:2112-2135. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6896167.

10. Classification of non-Hodgkin's lymphomas. Reproducibility of major classification systems. NCI non-Hodgkin's Classification Project Writing Committee. Cancer 1985;55:91-95. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3965089.

11. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994;84:1361-1392. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8068936.

12. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 1997;89:3909-3918. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9166827.

13. Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. J Clin Oncol 1998;16:2780-2795. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9704731.

14. Harris NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. J Clin Oncol 1999;17:3835-3849. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10577857.

15. Jaffe ES, Harris. N.L., Stein H, Vardiman JW. WHO classification of tumours. Pathology and genetics of tumours of haematopoietic and lymphoid tissues Lyon: IARC; 2001.

16. Vose J, Armitage J, Weisenburger D. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical

outcomes. J Clin Oncol 2008;26:4124-4130. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18626005.

17. Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (4th ed). Lyon, France: International Agency for Research on Cancer; ; 2008.

18. Hans CP, Weisenburger DD, Vose JM, et al. A significant diffuse component predicts for inferior survival in grade 3 follicular lymphoma, but cytologic subtypes do not predict survival. Blood 2003;101:2363-2367. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12424193.

19. Katzenberger T, Ott G, Klein T, et al. Cytogenetic alterations affecting BCL6 are predominantly found in follicular lymphomas grade 3B with a diffuse large B-cell component. Am J Pathol 2004;165:481-490. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15277222.

20. Lorsbach RB, Shay-Seymore D, Moore J, et al. Clinicopathologic analysis of follicular lymphoma occurring in children. Blood 2002;99:1959-1964. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11877266.

21. Harris NL, Swerdlow SH, Jaffe ES, et al. Follicular lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:220-226.

22. Oschlies I, Salaverria I, Mahn F, et al. Pediatric follicular lymphoma--a clinico-pathological study of a population-based series of patients treated within the Non-Hodgkin's Lymphoma--Berlin-Frankfurt-Munster (NHL-BFM) multicenter trials. Haematologica 2010;95:253-259. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19679882.

23. Louissaint A, Jr., Ackerman AM, Dias-Santagata D, et al. Pediatric-type nodal follicular lymphoma: an indolent clonal proliferation in children and adults with high proliferation index and no BCL2 rearrangement. Blood 2012;120:2395-2404. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22855608.

24. Liu Q, Salaverria I, Pittaluga S, et al. Follicular lymphomas in children and young adults: a comparison of the pediatric variant with usual follicular lymphoma. Am J Surg Pathol 2013;37:333-343. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23108024.

25. Cong P, Raffeld M, Teruya-Feldstein J, et al. In situ localization of follicular lymphoma: description and analysis by laser capture microdissection. Blood 2002;99:3376-3382. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11964306.

26. Sotomayor EA, Shah IM, Sanger WG, Mark HF. In situ follicular lymphoma with a 14;18 translocation diagnosed by a multimodal approach. Exp Mol Pathol 2007;83:254-258. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17482162.

27. Carbone A, Gloghini A, Santoro A. In situ follicular lymphoma: pathologic characteristics and diagnostic features. Hematol Oncol 2012;30:1-7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21560142.

28. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005;105:3768-3785. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15692063.

29. Hoefnagel JJ, Dijkman R, Basso K, et al. Distinct types of primary cutaneous large B-cell lymphoma identified by gene expression profiling. Blood 2005;105:3671-3678. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15308563.

30. Senff NJ, Hoefnagel JJ, Jansen PM, et al. Reclassification of 300 primary cutaneous B-Cell lymphomas according to the new WHO-EORTC classification for cutaneous lymphomas: comparison with previous classifications and identification of prognostic markers. J Clin Oncol 2007;25:1581-1587. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17353548.

31. Grange F, Bekkenk M, Wechsler J, et al. Prognostic factors in primary cutaneous large B-cell lymphomas: a European multicenter

study. J Clin Oncol 2001;19:3602-3610. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11504742.

32. Willemze R, Meijer CJ, Sentis HJ, et al. Primary cutaneous large cell lymphomas of follicular center cell origin. A clinical follow-up study of nineteen patients. J Am Acad Dermatol 1987;16:518-526. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3546419.

33. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 2000;403:503-511. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10676951.

34. Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood 2004;103:275-282. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14504078.

35. Choi WWL, Weisenburger DD, Greiner TC, et al. A new immunostain algorithm classifies diffuse large B-cell lymphoma into molecular subtypes with high accuracy. Clin Cancer Res 2009;15:5494-5502. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19706817.

36. Meyer PN, Fu K, Greiner TC, et al. Immunohistochemical methods for predicting cell of origin and survival in patients with diffuse large B-cell lymphoma treated with rituximab. J Clin Oncol 2011;29:200-207. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21135273.

37. Nyman H, Adde M, Karjalainen-Lindsberg ML, et al. Prognostic impact of immunohistochemically defined germinal center phenotype in diffuse large B-cell lymphoma patients treated with immunochemotherapy. Blood 2007;109:4930-4935. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17299093.

38. Fu K, Weisenburger DD, Choi WWL, et al. Addition of rituximab to standard chemotherapy improves the survival of both the germinal center B-cell-like and non-germinal center B-cell-like subtypes of diffuse large B-cell lymphoma. J Clin Oncol 2008;26:4587-4594. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18662967.

39. Ferry JA. Burkitt's lymphoma: clinicopathologic features and differential diagnosis. Oncologist 2006;11:375-383. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16614233.

40. Dave SS, Fu K, Wright GW, et al. Molecular diagnosis of Burkitt's lymphoma. N Engl J Med 2006;354:2431-2442. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16760443.

41. Hummel Ml, Bentink S, Berger H, et al. A biologic definition of Burkitt's lymphoma from transcriptional and genomic profiling. N Engl J Med 2006;354:2419-2430. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16760442.

42. Macpherson N, Lesack D, Klasa R, et al. Small noncleaved, non-Burkitt's (Burkitt-Like) lymphoma: cytogenetics predict outcome and reflect clinical presentation. J Clin Oncol 1999;17:1558-1567. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10334544.

43. Rosenwald A, Wright G, Leroy K, et al. Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to Hodgkin lymphoma. J Exp Med 2003;198:851-862. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12975453.

44. Traverse-Glehen A, Pittaluga S, Gaulard P, et al. Mediastinal gray zone lymphoma: the missing link between classic Hodgkin's lymphoma and mediastinal large B-cell lymphoma. Am J Surg Pathol 2005;29:1411-1421. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16224207.

45. Hoefnagel JJ, Mulder MMS, Dreef E, et al. Expression of B-cell transcription factors in primary cutaneous B-cell lymphoma. Mod Pathol 2006;19:1270-1276. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16778825.

46. Kodama K, Massone C, Chott A, et al. Primary cutaneous large B-cell lymphomas: clinicopathologic features, classification, and prognostic factors in a large series of patients. Blood 2005;106:2491-2497. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15947086.

47. Grange F, Beylot-Barry M, Courville P, et al. Primary cutaneous diffuse large B-cell lymphoma, leg type: clinicopathologic features and prognostic analysis in 60 cases. Arch Dermatol 2007;143:1144-1150. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17875875.

48. Zinzani PL, Quaglino P, Pimpinelli N, et al. Prognostic factors in primary cutaneous B-cell lymphoma: the Italian Study Group for Cutaneous Lymphomas. J Clin Oncol 2006;24:1376-1382. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16492713.

49. Cheson BD, Horning SJ, Coiffier B, et al. Report of an International Workshop to standardize response criteria for Non-Hodgkin's Lymphomas. J Clin Oncol 1999;17:1244-1253. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10561185.

50. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579-586. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17242396.

51. Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of Imaging in the Staging and Response Assessment of Lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25113771.

52. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32:3059-3068. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25113753.

53. Barrington SF, Qian W, Somer EJ, et al. Concordance between four European centres of PET reporting criteria designed for use in multicentre trials in Hodgkin lymphoma. Eur J Nucl Med Mol Imaging 2010;37:1824-1833. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20505930.

54. Meignan M, Gallamini A, Haioun C, Polliack A. Report on the Second International Workshop on interim positron emission tomography in lymphoma held in Menton, France, 8-9 April 2010. Leuk Lymphoma 2010;51:2171-2180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21077737.

55. Meignan M, Gallamini A, Itti E, et al. Report on the Third International Workshop on Interim Positron Emission Tomography in Lymphoma held in Menton, France, 26-27 September 2011 and Menton 2011 consensus. Leuk Lymphoma 2012;53:1876-1881. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22432519.

56. Seam P, Juweid ME, Cheson BD. The role of FDG-PET scans in patients with lymphoma. Blood 2007;110:3507-3516. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17709603.

57. Isasi CR, Lu P, Blaufox MD. A metaanalysis of 18F-2-deoxy-2-fluoro-D-glucose positron emission tomography in the staging and restaging of patients with lymphoma. Cancer 2005;104:1066-1074. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16047335.

58. Trotman J, Fournier M, Lamy T, et al. Positron emission tomography-computed tomography (PET-CT) after induction therapy is highly predictive of patient outcome in follicular lymphoma: analysis of PET-CT in a subset of PRIMA trial participants. J Clin Oncol 2011;29:3194-3200. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21747087.

59. Feeney J, Horwitz S, Gonen M, Schoder H. Characterization of T-cell lymphomas by FDG PET/CT. AJR Am J Roentgenol 2010;195:333-340. Available at: http://www.ncbi.nlm.nih.gov/entrez/20651187.

60. Hoffmann M, Kletter K, Becherer A, et al. 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) for staging and follow-up

of marginal zone B-cell lymphoma. Oncology 2003;64:336-340. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12759529.

61. Rodriguez-Vigil B, Gomez-Leon N, Pinilla I, et al. PET/CT in lymphoma: prospective study of enhanced full-dose PET/CT versus unenhanced low-dose PET/CT. J Nucl Med 2006;47:1643-1648. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17015900.

62. Schaefer NG, Hany TF, Taverna C, et al. Non-Hodgkin lymphoma and Hodgkin disease: coregistered FDG PET and CT at staging and restaging--do we need contrast-enhanced CT? Radiology 2004;232:823-829. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15273335.

63. Li YX, Wang H, Jin J, et al. Radiotherapy alone with curative intent in patients with stage I extranodal nasal-type NK/T-cell lymphoma. Int J Radiat Oncol Biol Phys 2012;82:1809-1815. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21470789.

64. Hoppe BS, Flampouri S, Su Z, et al. Effective dose reduction to cardiac structures using protons compared with 3DCRT and IMRT in mediastinal Hodgkin lymphoma. Int J Radiat Oncol Biol Phys 2012;84:449-455. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22386373.

65. Jang JW, Brown JG, Mauch PM, Ng AK. Four-dimensional versus 3-dimensional computed tomographic planning for gastric mucosa associated lymphoid tissue lymphoma. Pract Radiat Oncol 2013;3:124-129. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24674315.

66. Xu LM, Li YX, Fang H, et al. Dosimetric evaluation and treatment outcome of intensity modulated radiation therapy after doxorubicin-based chemotherapy for primary mediastinal large B-cell lymphoma. Int J Radiat Oncol Biol Phys 2013;85:1289-1295. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23245279.

67. Girinsky T, Pichenot C, Beaudre A, et al. Is intensity-modulated radiotherapy better than conventional radiation treatment and three-dimensional conformal radiotherapy for mediastinal masses in patients with Hodgkin's disease, and is there a role for beam orientation optimization and dose constraints assigned to virtual volumes? Int J Radiat Oncol Biol Phys 2006;64:218-226. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16169675.

68. Nieder C, Schill S, Kneschaurek P, Molls M. Influence of different treatment techniques on radiation dose to the LAD coronary artery. Radiat Oncol 2007;2:20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17547777.

69. Filippi AR, Ragona R, Fusella M, et al. Changes in breast cancer risk associated with different volumes, doses, and techniques in female Hodgkin lymphoma patients treated with supra-diaphragmatic radiation therapy. Pract Radiat Oncol 2013;3:216-222. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24674367.

70. Charpentier AM, Conrad T, Sykes J, et al. Active breathing control for patients receiving mediastinal radiation therapy for lymphoma: Impact on normal tissue dose. Pract Radiat Oncol 2014;4:174-180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24766684.

71. Illidge T, Specht L, Yahalom J, et al. Modern radiation therapy for nodal non-Hodgkin lymphoma-target definition and dose guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys 2014;89:49-58. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24725689.

72. Yahalom J, Illidge T, Specht L, et al. Modern radiation therapy for extranodal lymphomas: field and dose guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys 2015;92:11-31. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25863750

http://www.redjournal.org/article/S0360-3016(15)00050-4/pdf.

73. Hoskin PJ, Diez P, Williams M, et al. Recommendations for the use of radiotherapy in nodal lymphoma. Clin Oncol (R Coll Radiol)

2013;25:49-58. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22889569.

74. Hehn ST, Grogan TM, Miller TP. Utility of fine-needle aspiration as a diagnostic technique in lymphoma. J Clin Oncol 2004;22:3046-3052. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15284254.

75. Meda BA, Buss DH, Woodruff RD, et al. Diagnosis and subclassification of primary and recurrent lymphoma. The usefulness and limitations of combined fine-needle aspiration cytomorphology and flow cytometry. Am J Clin Pathol 2000;113:688-699. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10800402.

76. Dong HY, Harris NL, Preffer FI, Pitman MB. Fine-needle aspiration biopsy in the diagnosis and classification of primary and recurrent lymphoma: a retrospective analysis of the utility of cytomorphology and flow cytometry. Mod Pathol 2001;14:472-481. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11353059.

77. Jeffers MD, Milton J, Herriot R, McKean M. Fine needle aspiration cytology in the investigation on non-Hodgkin's lymphoma. J Clin Pathol 1998;51:189-196. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9659258.

78. Zeppa P, Marino G, Troncone G, et al. Fine-needle cytology and flow cytometry immunophenotyping and subclassification of non-Hodgkin lymphoma: a critical review of 307 cases with technical suggestions. Cancer 2004;102:55-65. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14968418.

79. Dunphy CH. Applications of flow cytometry and immunohistochemistry to diagnostic hematopathology. Arch Pathol Lab Med 2004;128:1004-1022. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15335254

80. Howell SJ, Shalet SM. Fertility preservation and management of gonadal failure associated with lymphoma therapy. Curr Oncol Rep 2002;4:443-452. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12162920.

81. Conlan MG, Bast M, Armitage JO, Weisenburger DD. Bone marrow involvement by non-Hodgkin's lymphoma: the clinical significance of morphologic discordance between the lymph node and bone marrow. Nebraska Lymphoma Study Group. J Clin Oncol 1990;8:1163-1172. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1694234.

82. Lim ST, Tao M, Cheung YB, et al. Can patients with early-stage diffuse large B-cell lymphoma be treated without bone marrow biopsy? Ann Oncol 2005;16:215-218. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15668272.

83. Kim YH, Willemze R, Pimpinelli N, et al. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110:479-484. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17339420.

84. Senff N, Kluin-Nelemans H, Willemze R. Results of bone marrow examination in 275 patients with histological features that suggest an indolent type of cutaneous B-cell lymphoma. Br J Haematol 2008;142:52-56. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18422781.

85. Juneja SK, Wolf MM, Cooper IA. Value of bilateral bone marrow biopsy specimens in non-Hodgkin's lymphoma. J Clin Pathol 1990;43:630-632. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2401730.

86. FDA Drug Safety Communication: Boxed Warning and new recommendations to decrease risk of hepatitis B reactivation with the immune-suppressing and anti-cancer drugs Arzerra (ofatumumab) and Rituxan (rituximab); September 25, 2013. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM369436.pdf.

87. Yeo W, Chan PKS, Ho WM, et al. Lamivudine for the prevention of hepatitis B virus reactivation in hepatitis B s-antigen seropositive cancer patients undergoing cytotoxic chemotherapy. J Clin Oncol 2004;22:927-934. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14990649.

88. Borentain P, Colson P, Coso D, et al. Clinical and virological factors associated with hepatitis B virus reactivation in HBsAg-negative and anti-HBc antibodies-positive patients undergoing chemotherapy and/or autologous stem cell transplantation for cancer. J Viral Hepat 2010;17:807-815. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20002298.

89. Evens AM, Jovanovic BD, Su YC, et al. Rituximab-associated hepatitis B virus (HBV) reactivation in lymphoproliferative diseases: meta-analysis and examination of FDA safety reports. Ann Oncol 2011;22:1170-1180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21115603.

90. Fukushima N, Mizuta T, Tanaka M, et al. Retrospective and prospective studies of hepatitis B virus reactivation in malignant lymphoma with occult HBV carrier. Ann Oncol 2009;20:2013-2017. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19561036.

91. Ji D, Cao J, Hong X, et al. Low incidence of hepatitis B virus reactivation during chemotherapy among diffuse large B-cell lymphoma patients who are HBsAg-negative/ HBcAb-positive: a multicenter retrospective study. Eur J Haematol 2010;85:243-250. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20491883.

92. Koo YX, Tan DS, Tan IB, et al. Hepatitis B virus reactivation and role of antiviral prophylaxis in lymphoma patients with past hepatitis B virus infection who are receiving chemoimmunotherapy. Cancer 2010;116:115-121. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19899164.

93. Lalazar G, Rund D, Shouval D. Screening, prevention and treatment of viral hepatitis B reactivation in patients with haematological malignancies. Br J Haematol 2007;136:699-712. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17338776.

94. Lau GK, Leung YH, Fong DY, et al. High hepatitis B virus (HBV) DNA viral load as the most important risk factor for HBV reactivation in patients positive for HBV surface antigen undergoing autologous hematopoietic cell transplantation. Blood 2002;99:2324-2330. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11895763.

95. Liang R. How I treat and monitor viral hepatitis B infection in patients receiving intensive immunosuppressive therapies or undergoing hematopoietic stem cell transplantation. Blood 2009;113:3147-3153. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19144986.

96. Matsue K, Kimura S, Takanashi Y, et al. Reactivation of hepatitis B virus after rituximab-containing treatment in patients with CD20-positive B-cell lymphoma. Cancer 2010;116:4769-4776. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20597091.

97. Yeo W, Chan TC, Leung NW, et al. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. J Clin Oncol 2009;27:605-611. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19075267.

98. Brechot C, Degos F, Lugassy C, et al. Hepatitis B virus DNA in patients with chronic liver disease and negative tests for hepatitis B surface antigen. N Engl J Med 1985;312:270-276. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2981408.

99. Dhedin N, Douvin C, Kuentz M, et al. Reverse seroconversion of hepatitis B after allogeneic bone marrow transplantation: a retrospective study of 37 patients with pretransplant anti-HBs and anti-HBc. Transplantation 1998;66:616-619. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9753342.

100. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology 2007;45:507-539. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17256718.

101. Lau GKK, Yiu HHY, Fong DYT, et al. Early is superior to deferred preemptive lamivudine therapy for hepatitis B patients undergoing chemotherapy. Gastroenterology 2003;125:1742-1749. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14724827.

102. Rossi G, Pelizzari A, Motta M, Puoti M. Primary prophylaxis with lamivudine of hepatitis B virus reactivation in chronic HbsAg carriers with lymphoid malignancies treated with chemotherapy. Br J Haematol 2001;115:58-62. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11722410.

103. Tsutsumi Y, Tanaka J, Kawamura T, et al. Possible efficacy of lamivudine treatment to prevent hepatitis B virus reactivation due to rituximab therapy in a patient with non-Hodgkin's lymphoma. Ann Hematol 2004;83:58-60. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14513286.

104. Ziakas PD, Karsaliakos P, Mylonakis E. Effect of prophylactic lamivudine for chemotherapy-associated hepatitis B reactivation in lymphoma: a meta-analysis of published clinical trials and a decision tree addressing prolonged prophylaxis and maintenance. Haematologica 2009;94:998-1005. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19454492.

105. Huang YH, Hsiao LT, Hong YC, et al. Randomized controlled trial of entecavir prophylaxis for rituximab-associated hepatitis B virus reactivation in patients with lymphoma and resolved hepatitis B. J Clin Oncol 2013;31:2765-2772. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23775967.

106. Kim SJ, Hsu C, Song YQ, et al. Hepatitis B virus reactivation in B-cell lymphoma patients treated with rituximab: analysis from the Asia Lymphoma Study Group. Eur J Cancer 2013;49:3486-3496. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23910494.

107. Huang H, Li X, Zhu J, et al. Entecavir vs lamivudine for prevention of hepatitis B virus reactivation among patients with untreated diffuse large B-cell lymphoma receiving R-CHOP chemotherapy: a randomized clinical trial. JAMA 2014;312:2521-2530. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25514302.

108. Allen MI, Deslauriers M, Andrews CW, et al. Identification and characterization of mutations in hepatitis B virus resistant to lamivudine. Lamivudine Clinical Investigation Group. Hepatology 1998;27:1670-1677. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9620341.

109. Gauthier J, Bourne EJ, Lutz MW, et al. Quantitation of hepatitis B viremia and emergence of YMDD variants in patients with chronic hepatitis B treated with lamivudine. J Infect Dis 1999;180:1757-1762. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10558928.

110. Law JK, Ali JA, Harrigan PR, et al. Fatal postlymphoma chemotherapy hepatitis B reactivation secondary to the emergence of a YMDD mutant strain with lamivudine resistance in a noncirrhotic patient. Am J Hematol 2006;81:969-972. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16937392.

111. Picardi M, Pane F, Quintarelli C, et al. Hepatitis B virus reactivation after fludarabine-based regimens for indolent non-Hodgkin's lymphomas: high prevalence of acquired viral genomic mutations. Haematologica 2003;88:1296-1303. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14607759.

112. Schnepf N, Sellier P, Bendenoun M, et al. Reactivation of lamivudine-resistant occult hepatitis B in an HIV-infected patient undergoing cytotoxic chemotherapy. J Clin Virol 2007;39:48-50. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17368969.

113. Peters MG, Hann Hw H, Martin P, et al. Adefovir dipivoxil alone or in combination with lamivudine in patients with lamivudine-resistant chronic hepatitis B. Gastroenterology 2004;126:91-101. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14699491.

114. Marcellin P, Heathcote EJ, Buti M, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Engl J Med 2008;359:2442-2455. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19052126.

115. Chan HL, Heathcote EJ, Marcellin P, et al. Treatment of hepatitis B e antigen positive chronic hepatitis with telbivudine or adefovir: a randomized trial. Ann Intern Med 2007;147:745-754. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17909201.

116. Leung N, Peng C-Y, Hann H-W, et al. Early hepatitis B virus DNA reduction in hepatitis B e antigen-positive patients with chronic hepatitis B: A randomized international study of entecavir versus adefovir. Hepatology 2009;49:72-79. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19065670.

117. Arnold DM, Crowther MA, Meyer RM, et al. Misleading hepatitis B test results due to intravenous immunoglobulin administration: implications for a clinical trial of rituximab in immune thrombocytopenia. Transfusion 2010;50:2577-2581. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20576011.

118. Arcaini L, Burcheri S, Rossi A, et al. Prevalence of HCV infection in nongastric marginal zone B-cell lymphoma of MALT. Ann Oncol 2007;18:346-350. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17071937.

119. Arcaini L, Merli M, Volpetti S, et al. Indolent B-cell lymphomas associated with HCV infection: clinical and virological features and role of antiviral therapy. Clin Dev Immunol 2012;2012:638185. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22956970.

120. de Sanjose S, Benavente Y, Vajdic CM, et al. Hepatitis C and non-Hodgkin lymphoma among 4784 cases and 6269 controls from the International Lymphoma Epidemiology Consortium. Clin Gastroenterol Hepatol 2008;6:451-458. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18387498.

121. Engels EA, Chatterjee N, Cerhan JR, et al. Hepatitis C virus infection and non-Hodgkin lymphoma: results of the NCI-SEER multi-center case-control study. Int J Cancer 2004;111:76-80. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15185346.

122. Gisbert JP, Garcia-Buey L, Pajares JM, Moreno-Otero R. Prevalence of hepatitis C virus infection in B-cell non-Hodgkin's lymphoma: systematic review and meta-analysis. Gastroenterology 2003;125:1723-1732. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14724825.

123. Mele A, Pulsoni A, Bianco E, et al. Hepatitis C virus and B-cell non-Hodgkin lymphomas: an Italian multicenter case-control study. Blood 2003;102:996-999. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12714514.

124. Nieters A, Kallinowski B, Brennan P, et al. Hepatitis C and risk of lymphoma: results of the European multicenter case-control study EPILYMPH. Gastroenterology 2006;131:1879-1886. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17087949.

125. Schollkopf C, Smedby KE, Hjalgrim H, et al. Hepatitis C infection and risk of malignant lymphoma. Int J Cancer 2008;122:1885-1890. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18271005.

126. Spinelli JJ, Lai AS, Krajden M, et al. Hepatitis C virus and risk of non-Hodgkin lymphoma in British Columbia, Canada. Int J Cancer 2008;122:630-633. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17935132.

127. Kawamura Y, Ikeda K, Arase Y, et al. Viral elimination reduces incidence of malignant lymphoma in patients with hepatitis C. Am J Med 2007;120:1034-1041. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18060923.

128. Hermine O, Lefrere F, Bronowicki JP, et al. Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus

infection. N Engl J Med 2002;347:89-94. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12110736.

129. Kelaidi C, Rollot F, Park S, et al. Response to antiviral treatment in hepatitis C virus-associated marginal zone lymphomas. Leukemia 2004;18:1711-1716. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15284859.

130. Tursi A, Brandimarte G, Torello M. Disappearance of gastric mucosa-associated lymphoid tissue in hepatitis C virus-positive patients after anti-hepatitis C virus therapy. J Clin Gastroenterol 2004;38:360-363. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15087696.

131. Gisbert JP, Garcia-Buey L, Pajares JM, Moreno-Otero R. Systematic review: regression of lymphoproliferative disorders after treatment for hepatitis C infection. Aliment Pharmacol Ther 2005;21:653-662. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15771751.

132. Vallisa D, Bernuzzi P, Arcaini L, et al. Role of anti-hepatitis C virus (HCV) treatment in HCV-related, low-grade, B-cell, non-Hodgkin's lymphoma: a multicenter Italian experience. J Clin Oncol 2005;23:468-473. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15659492.

133. La Mura V, De Renzo A, Perna F, et al. Antiviral therapy after complete response to chemotherapy could be efficacious in HCV-positive non-Hodgkin's lymphoma. J Hepatol 2008;49:557-563. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18678434.

134. Arcaini L, Vallisa D, Rattotti S, et al. Antiviral treatment in patients with indolent B-cell lymphomas associated with HCV infection: a study of the Fondazione Italiana Linfomi. Ann Oncol 2014;25:1404-1410. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24799461.

135. Pellicelli AM, Marignani M, Zoli V, et al. Hepatitis C virus-related B cell subtypes in non Hodgkin's lymphoma. World J Hepatol 2011;3:278-284. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22125661.

136. Besson C, Canioni D, Lepage E, et al. Characteristics and outcome of diffuse large B-cell lymphoma in hepatitis C virus-positive patients in LNH 93 and LNH 98 Groupe d'Etude des Lymphomes de l'Adulte programs. J Clin Oncol 2006;24:953-960. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16418500.

137. Ennishi D, Maeda Y, Niitsu N, et al. Hepatic toxicity and prognosis in hepatitis C virus-infected patients with diffuse large B-cell lymphoma treated with rituximab-containing chemotherapy regimens: a Japanese multicenter analysis. Blood 2010;116:5119-5125. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20823454.

138. Nishikawa H, Tsudo M, Osaki Y. Clinical outcome in diffuse large B-cell lymphoma with hepatitis C virus infection in the rituximab era: a single center experience. Oncol Rep 2012;28:835-840. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22736295.

139. Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1207-1217. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21449784.

140. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011;364:2405-2416. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21696307.

141. McHutchison JG, Everson GT, Gordon SC, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. N Engl J Med 2009;360:1827-1838. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19403902.

142. Poordad F, McCone J, Jr., Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1195-1206. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21449783.

143. Ghany MG, Nelson DR, Strader DB, et al. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology 2011;54:1433-1444. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21898493.

144. Carson KR, Evens AM, Richey EA, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. Blood 2009;113:4834-4840. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19264918.

145. FDA Prescribing Information for Rituxan® (rituximab). 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/103705s5414lbl.pdf.

146. Hopfinger G, Plessl A, Grisold W, et al. Progressive multifocal leukoencephalopathy after rituximab in a patient with relapsed follicular lymphoma and low IgG levels and a low CD4+ lymphocyte count. Leuk Lymphoma 2008;49:2367-2369. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19052987.

147. Yokoyama H, Watanabe T, Maruyama D, et al. Progressive multifocal leukoencephalopathy in a patient with B-cell lymphoma during rituximab-containing chemotherapy: case report and review of the literature. Int J Hematol 2008;88:443-447. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18855101.

148. Arzerra (ofatumumab) Injection:Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER). September 2013. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm372685.htm.

149. von Geldern G, Pardo CA, Calabresi PA, Newsome SD. PML-IRIS in a patient treated with brentuximab. Neurology 2012;79:2075-2077. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23115213.

150. Wagner-Johnston ND, Bartlett NL, Cashen A, Berger JR. Progressive multifocal leukoencephalopathy in a patient with Hodgkin lymphoma treated with brentuximab vedotin. Leuk Lymphoma 2012;53:2283-2286. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22424602.

151. Carson KR, Newsome SD, Kim EJ, et al. Progressive multifocal leukoencephalopathy associated with brentuximab vedotin therapy: a report of 5 cases from the Southern Network on Adverse Reactions (SONAR) project. Cancer 2014;120:2464-2471. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24771533.

152. Coiffier B, Altman A, Pui C, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol 2008;26:2767-2778. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18509186.

153. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol 2004;127:3-11. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15384972.

154. Krakoff IH, Meyer RL. Prevention of hyperuricemia in leukemia and lymphoma: use of alopurinol, a xanthine oxidase inhibitor. . JAMA 1965;193:1-6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14297704.

155. Bosly A, Sonet A, Pinkerton CR, et al. Rasburicase (recombinant urate oxidase) for the management of hyperuricemia in patients with cancer: report of an international compassionate use study. Cancer 2003;98:1048-1054. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12942574.

156. Coiffier B, Mounier N, Bologna S, et al. Efficacy and safety of rasburicase (recombinant urate oxidase) for the prevention and treatment of hyperuricemia during induction chemotherapy of aggressive non-Hodgkin's lymphoma: results of the GRAAL1 (Groupe d'Etude des Lymphomes de l'Adulte Trial on Rasburicase Activity in

Adult Lymphoma) study. J Clin Oncol 2003;21:4402-4406. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14581437.

157. Cortes J, Moore JO, Maziarz RT, et al. Control of plasma uric acid in adults at risk for tumor lysis syndrome: efficacy and safety of rasburicase alone and rasburicase followed by allopurinol compared with allopurinol alone-results of a multicenter phase III study. J Clin Oncol 2010;28:4207-4213. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20713865.

158. McDonnell AM, Lenz KL, Frei-Lahr DA, et al. Single-dose rasburicase 6 mg in the management of tumor lysis syndrome in adults. Pharmacotherapy 2006;26:806-812. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16716134.

159. Vines AN, Shanholtz CB, Thompson JL. Fixed-dose rasburicase 6 mg for hyperuricemia and tumor lysis syndrome in high-risk cancer patients. Ann Pharmacother 2010;44:1529-1537. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20841516.

160. Campara M, Shord SS, Haaf CM. Single-dose rasburicase for tumour lysis syndrome in adults: weight-based approach. J Clin Pharm Ther 2009;34:207-213. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19250141.

161. Knoebel RW, Lo M, Crank CW. Evaluation of a low, weight-based dose of rasburicase in adult patients for the treatment or prophylaxis of tumor lysis syndrome. J Oncol Pharm Pract 2011;17:147-154. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20332174.

162. Vadhan-Raj S, Fayad LE, Fanale MA, et al. A randomized trial of a single-dose rasburicase versus five-daily doses in patients at risk for tumor lysis syndrome. Ann Oncol 2012;23:1640-1645. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22015451.

This discussion is being updated to correspond with the newly updated algorithm. Last updated 10/28/2014.

Follicular Lymphoma

Diagnosis

FL is the most common subtype of indolent NHL, and accounts for about 22% of all newly diagnosed cases of NHL.[1] About 90% of the cases have a t(14;18) translocation, which juxtaposes *BCL2* with the *IgH* locus resulting in the deregulated expression of BCL2.

Immunophenotyping using IHC and/or flow cytometry for cell surface marker analysis is required to establish a diagnosis. FL has a characteristic immunophenotype, which includes CD20+, CD10+, BCL2+, CD23+/-, CD43-, CD5-, CCND1- and BCL6+. Occasional cases of FL may be CD10- or BCL2-. The diagnosis is easily established on histological grounds, but immunophenotyping is encouraged to distinguish FL from a nodular MCL or SLL. Low-grade FL with a high proliferation index (as determined by Ki-67 immunostaining) has been shown to be associated with an aggressive clinical behavior. There is no evidence, however, that high Ki-67 should guide the selection of therapy.[2,3] Molecular genetic analysis to detect *BCL2* rearrangement, cytogenetics or FISH to identify t(14;18), and immunohistochemistry for Ki-67 may be useful under certain circumstances. In patients with BCL2-negative localized disease, the diagnosis of pediatric-type FL may be considered.

The Follicular Lymphoma International Prognostic Index (FLIPI) is a prognostic scoring system based on age, Ann Arbor stage, and number of nodal sites involved, hemoglobin levels and serum LDH levels.[4] The FLIPI was developed based on a large set of retrospective data from patients with FL, and established three distinct prognostic groups with 5-year survival outcomes ranging from 52.5% to 91% (in the pre-rituximab era).[4] In the National LymphoCare study, which analyzed the treatment options and outcomes of 2,728 patients with newly diagnosed FL, FLIPI was able to categorize patients into three distinct prognostic groups.[5] In a more recent study conducted by the International Follicular Lymphoma Prognostic Factor Project, a prognostic model (FLIPI-2) was developed based on prospective collection of data from patients with newly diagnosed FL treated in the era of rituximab-containing chemoimmunotherapy regimens.[6] The final prognostic model included age, hemoglobin levels, longest diameter of largest involved lymph node, beta-2 microglobulin levels, and bone marrow involvement. FLIPI-2 was highly predictive of treatment outcomes, and separated patients into three distinct risk groups with 3-year progression-free survival (PFS) rates ranging from 51% to 91%, and OS rates ranging from 82% to 99%; the FLIPI-2 also defined distinct risk groups among the subgroup of patients treated with rituximab-containing regimens, with a PFS rate ranging from 57% to 89%.[6] Thus, FLIPI-2 may be useful for assessing prognosis in patients receiving active therapy with rituximab-based treatments. Both the FLIPI-1 and FLIPI-2 predict for prognosis, but these index scores have not yet been established as a means of selecting treatment options. Most recently, a simpler prognostic index incorporating only the baseline serum beta 2-microglobulin and LDH levels has been devised, which appears to be as predictive of outcomes as the FLIPI-1 and FLIPI-2 indices, and is easier to apply.[7,8]

In-situ Involvement of Follicular Lymphoma-like Cells of Unknown Significance (Follicular Lymphoma “in situ”)

The presence of FL-like B-cells in the germinal centers of morphologically reactive lymph nodes (initially called “in situ localization of FL” or “follicular lymphoma in situ”[FLIS]) was first described a decade ago.[9,10] These cases are characterized by the preservation of

the lymph node architecture, with the incidental finding of focal strongly positive staining for BCL2 (restricted to germinal centers) and CD10 in the involved follicles, and the detection of t(14;18) by FISH. [9-12]

Cases of FLIS have been reported in patients with prior FL or concurrent FL (at other sites), as well as in individuals with no known history of FL.[9-11] The occurrence of FLIS in the general population appears to be rare. Based on data from a consecutive series of unselected surgical samples of reactive lymph nodes from patients (N=132; 1294 samples), the prevalence of FLIS was 2.3%.[13] Development of (or progression to) overt lymphoma in patients found to have FLIS has been reported, although this appears to be uncommon (5–6%).[14,15] The significance or potential for malignancy of FLIS in patients without known FL remains unclear. These cases may potentially represent the tissue counterpart of circulating B-cells with t(14;18), or may represent a very early lesion with t(14;18) but without other genetic abnormalities that lead to overt lymphoma.[10,14,16] The WHO classification recommends that a diagnosis of FL not be made in such cases, but that the report should suggest evaluation for the presence of FL elsewhere, and possibly close follow-up.

Pediatric-type Follicular Lymphoma

Pediatric-type FL is considered a rare variant of FL in the 2008 WHO classification,[10] and has been reported to comprise less than 2% of childhood NHLs.[17-20] In published studies, the median age at diagnosis of pediatric FL was approximately 11 years, and the large majority of cases were stage I or II at diagnosis with a predilection for localized nodal involvement in the head and neck region.[18-22] Histologically, pediatric FL cases tend to be associated with large expansive follicles with a “starry sky” pattern, high histologic grade (grade 3), and a high proliferation index.[20-22] Expression of BCL-2 protein may be observed in approximately 40% to 50% of cases, and expression of Bcl-6 protein can be seen in the majority of cases.[19-22]

Importantly, the pediatric variant of FL is generally characterized by lack of *BCL2* rearrangement and t(14,18), which constitute the genetic hallmark of conventional FL cases seen in adults.[10,19-22] Rearrangement of *BCL6* is also typically absent in pediatric-type FL.[20,21] Expression of BCL-2 protein (by IHC) has been reported in approximately half of the cases of FL without *BCL2* rearrangement or t(14,18), as mentioned above.[20-22] Pediatric FL without *BCL2* rearrangements tend to be associated with localized disease with an indolent course and favorable prognosis, with only rare instances of disease progression or relapse.[19-22] In a recent analysis of FL cases in younger patients (age <40 years; n=27), a highly indolent pediatric-type FL was identified based on the lack of *BCL2* rearrangement concurrent with a high proliferation index (defined as ki-67 ≥ 30%).[21] These cases without *BCL2* rearrangement but with high proliferation index (n=21) were all stage I disease and none showed disease progression or relapse. In contrast, the remaining cases (n=6) with *BCL2* rearrangement and/or low proliferation index (defined as ki-67 <30%) all patients had stage III or IV disease, and 83% of these patients experienced disease progression or recurrence. Cases of indolent pediatric-type FL were also found among a separate cohort of adult patients; similar to the finding from the younger cohort of patients, adult patients without *BCL2* rearrangement but with high proliferation index (n=13) all had stage I disease, and none had progressed or relapsed after a median follow-up time of 61 months.[21] This study showed that pediatric-type FL characterized by lack of *BCL2* rearrangement, early-stage disease, and an indolent disease course can be diagnosed in adults. Cases of pediatric-type FL have primarily been managed with chemotherapy (with or without RT), excision only (with or without RT), and more

recently, chemoimmunotherapy with generally favorable outcomes and prognosis.[19,21,23]

Workup

The diagnostic workup for FL is similar to the workup for other lymphomas. The initial workup for newly diagnosed patients should include a thorough physical examination with attention to node-bearing areas, and evaluation of performance status and constitutional symptoms. Laboratory assessments should include CBC with differential and a comprehensive metabolic panel, in addition to measurements of serum lactate dehydrogenase (LDH) levels and serum beta-2 microglobulin. HBV testing is recommended due to increased risks of viral reactivation when chemoimmunotherapy regimens are being considered for treatment. Measurement of uric acid and hepatitis C testing may be useful for certain cases.

The majority of patients with FL will present with disseminated disease. The approach to therapy differs dramatically between patients with localized and those with disseminated disease. Bone marrow biopsy with aspirate is essential for documenting clinical stage I-II disease. Adequate trephine biopsy (specimen ≥1.6 cm)[24,25] should be obtained for initial staging evaluation, along with bone marrow aspiration. If radioimmunotherapy is considered, bilateral core biopsy is recommended; in such instances, the pathologist should provide the percent of overall cellular elements and the percent of cellular elements involved in the marrow. Bone marrow biopsy can be deferred if observation is the initial option.

The majority of the NCCN Member Institutions routinely employ chest, abdominal and pelvic CT as part of the diagnostic evaluation. CT scan of the neck may also assist in defining the extent of local disease. In patients presenting with what appears to be localized disease, a PET scan may be helpful in identifying occult sites of disease or if there is concern about histologic transformation.[26] PET does not replace histologic confirmation of the diagnosis; however, if there are sites with discordant high FDG-avidity, these represent the most likely sites of transformation. For patients being considered for treatment regimens containing anthracyclines or anthracenediones, a MUGA scan or echocardiogram should be obtained.

Treatment Options for Stage I-II FL

The NCCN Guidelines for FL apply to patients with grade FL1-2. Cases of FL3A and FL3B are commonly treated according to treatment recommendations for DLBCL.

Involved-site radiotherapy (ISRT) remains the current standard of care for patients with early-stage FL. Results from studies with long-term follow up showed favorable outcomes with RT in these patients.[27-30] In patients with stage I or II low-grade FL initially treated with involved- or extended-field RT, the median overall survival (OS) was about 14 years; 15-year OS rate was 40% and the 15-year relapse-free survival (RFS) or progression-free survival (PFS) was also about 40%.[29,30] In both of these studies, 41% of patients had stage I disease. The 15-year PFS outcomes were influenced by factors such as disease stage (66% for stage I vs. 26% for stage II disease) and maximal tumor size (49% for tumors < 3 cm vs. 29% for ≥ 3 cm). The OS rate was not significantly different between extended-field RT compared with IFRT (49% vs. 40%, respectively).[30] Long-term outcomes from another study of RT in patients with early-stage grade 1-2 FL (with or without chemotherapy) reported a median OS of 19 years and a 15-year OS rate of 62%.[28] In this study, the majority of patients (74%) had stage I disease and 24% had received chemotherapy with RT, which may have resulted in the higher OS rate reported compared with the aforementioned studies. In a

recent study of patients with limited stage FL (grade 1 to 3A) treated with IFRT or reduced IFRT (RT of involved nodes only), the 10-year PFS and OS rates were 49% and 66%, respectively.[27] The reduction in radiation field size did not impact PFS or OS outcomes. Observation alone has been evaluated in patients with early-stage FL for whom toxicities related to IFRT were a concern. In a retrospective analysis of patients with stage I-II disease, carefully selected patients (requirement of large abdominal radiation field, advanced age, concern for xerostomia or patient refusal) who did not receive immediate treatment had comparable outcomes to those who were treated with RT.[31]

Sequential combination treatment with RT and chemotherapy has also been evaluated in patients with early-stage FL. In a prospective study of 44 patients with stage I-II low-grade NHL, the addition of cyclophosphamide, vincristine, prednisone, and bleomycin (COP-bleomycin) or CHOP-bleomycin to RT resulted in a 5-year failure-free survival (FFS) rate and OS rate of 74% and 89%, respectively.[32] The combination treatment appeared to improve failure-free survival but did not impact OS in patients with early-stage disease.[32] In a small prospective randomized study of RT alone compared with RT with adjuvant CHOP in patients with stage I low- or intermediate-grade NHL (n=44), the addition of adjuvant CHOP to RT did not improve relapse-free survival (RFS) or OS in the subgroup of patients with early-stage low-grade NHL.[33]

In a prospective analysis based on data from the National LymphoCare study registry, outcomes with different first-line management approaches were evaluated in the subgroup of patients (rigorously staged with bone marrow biopsy and complete imaging studies) with stage I FL (n=206).[34] First-line management strategies included observation only (i.e., “watch and wait”) in 17%, RT only in 27%, rituximab monotherapy in 12%, rituximab combined with chemotherapy (chemoimmunotherapy) in 28%, and combined modality with RT (typically involved chemoimmunotherapy prior to RT) in 13%. With a median follow up of 57 months, the median PFS with RT alone was 72 months; median PFS had not been reached with the other management approaches. After adjusting for tumor grade, LDH level and presence of B symptoms, treatment with chemoimmunotherapy or combined modality with RT improved PFS compared with RT alone (HRs of 0.36 and 0.11 respectively).[34] PFS outcomes did not differ between RT alone, observation alone and rituximab monotherapy. With the current follow up time, no differences in OS outcomes were observed between the various management approaches.[34] The study investigators suggested that the ‘standard’ approach of treating early-stage symptomatic FL with RT alone may be challenged in the current era of diverse therapeutic strategies.

A recent multicenter retrospective analysis evaluated outcomes in 145 patients with stage I or II FL who were managed with six different first-line treatment options (observation (i.e., “watchful waiting”), chemotherapy alone, RT alone, RT combined with chemotherapy, rituximab monotherapy and rituximab combined with chemotherapy (chemoimmunotherapy).[35] The median age was 55 years; 58% had stage I disease and 42% had stage II disease. Bulky disease was present in 15% of patients. For patients who received active therapy, the CR rates were 57% for single-agent rituximab, 69% for chemotherapy alone, 75% for chemoimmunotherapy, 81% for RT alone and 95% for RT combined with chemotherapy.[35] PFS rate at 7.5 years was highest with chemoimmunotherapy (60%) compared with other management options (19% with RT alone, 23% with chemotherapy alone, 26% with RT combined with chemotherapy and 26% for observation only; *P* =.00135). However, no significant differences were observed in OS at 7.5 years across the different approaches (66% with

RT alone, 74% with chemotherapy alone, 67% with RT combined with chemotherapy, 72% with observation only, and 74% with chemoimmunotherapy).[35]

Treatment Options for Stage II (bulky) and Stage III-IV

Despite therapeutic advances that have improved outcomes, FL is generally considered a chronic disease characterized by multiple recurrences with current therapies. Several prospective randomized trials have failed to demonstrate a survival advantage with immediate treatment versus a "watch and wait" approach in patients with advanced stage, low tumor burden (or asymptomatic) FL.[36-38] These studies used chemotherapy regimens for the immediate treatment arm, as the studies were conducted prior to the standard incorporation of rituximab in FL therapy.

A randomized phase III intergroup trial evaluated the role of immediate treatment with rituximab (with or without additional rituximab maintenance) versus watchful waiting in patients with advanced stage, asymptomatic FL (n=462).[39] The primary endpoint of this trial was time to initiation of new therapy from randomization. Results from an interim analysis of this trial showed that immediate treatment with rituximab resulted in significantly longer median time to initiation of new therapy compared with observation alone (not reached at 4 years vs. 33 months; P <.001); median PFS was also significantly longer with rituximab compared with observation (not reached vs. approximately 24 months; P < .001). The endpoint chosen for this trial, however, is rather controversial considering that one arm of the trial involved initiation of early therapy; a more justifiable endpoint for this study could have been "time to initiation of second therapy". Moreover, no differences in OS were observed between the study arms.[39] Further follow up is needed to evaluate whether immediate treatment with rituximab has an impact on time to second-line therapy.

In a more recent randomized phase III trial conducted by ECOG (E4402 study; RESORT), patients with low tumor burden FL (by GELF criteria) were treated with standard doses of rituximab, of which responding patients were then randomized to receive immediate maintenance with rituximab (n=140) or retreatment with rituximab upon progression (n=134).[40] The primary endpoint of this trial was time to treatment failure (TTF). Results from a planned interim analysis showed that at a median follow up of 3.8 years, median TTF was similar between the maintenance arm and retreatment arm (3.9 years vs. 3.6 years). Time to initiation of cytotoxic therapy was longer with maintenance rituximab compared with retreatment (95% vs. 86% remained free of cytotoxic therapy at 3 years), but both approaches delayed the initiation of cytotoxic therapy compared with historical "watch and wait" approaches in a similar population.[40] Evaluation of OS outcomes will require further follow up.

In a recent analysis based on data from the F2-study registry of the International Follicular Lymphoma Prognostic Factor Project, outcomes were evaluated in a cohort of patients with low-tumor burden FL who were initially managed by a "watch and wait" approach (n=107).[41] All of the patients in this cohort were asymptomatic, and 84% had stage III or IV disease. With a median follow up of 64 months, the median time observed without treatment was 55 months. Fifty-four patients (50%) required therapy, and among these patients, 71% received first-line treatment with rituximab-containing regimens. Multivariate analysis showed that involvement of more than 4 nodal areas was a significant independent predictor of shorter time to initiation of treatment. In order to assess whether an initial "watch and wait" approach would have negative effects on treatment efficacy during subsequent treatment,

outcomes in this cohort were compared with those of patients from the F2-study registry who had low-tumor burden, asymptomatic FL, but were initially treated with rituximab-containing regimens (n=242).[41] The endpoint for the comparison was freedom from treatment failure (FFTF), which was defined as the time from diagnosis to one of the following events: progression during treatment, initiation of salvage therapy, relapse, or death from any cause. In the "watch and wait" cohort, initiation of first-line therapy was not considered an event for FFTF. The 4-year FFTF was 79% in the "watch and wait" cohort compared with 69% in the cohort initially treated with rituximab-containing regimens; the difference was not significant after adjusting for differences in baseline disease factors between the cohorts. In addition, the 5-year OS was similar (87% vs. 88%, respectively).[41] The investigators concluded that "watch and wait" remained a valid strategy even in the rituximab era, for the management of patients with prognostically favorable, low-tumor burden FL,

Collectively, findings from the above studies suggest that outside of clinical trials, observation is still the standard practice for patients with advanced stage low tumor burden FL. In the clinical practice setting, treatment should only be initiated when a patient presents with indications for treatment (based on GELF criteria).

Rituximab has demonstrated single-agent activity in previously untreated patients, as well in those with relapsed or refractory disease.[42-44] The addition of rituximab to combination chemotherapy regimens has consistently been associated with increased ORR, response duration and PFS outcomes.[45-49] In addition, some studies have demonstrated OS benefit with the addition of rituximab; a recent meta-analysis has confirmed the benefit in OS despite what is still limited follow up for FL.[50]

Long-term follow-up data from a multicenter phase II trial demonstrated the safety and efficacy of rituximab combined with CHOP chemotherapy (R-CHOP) in patients with relapsed or newly diagnosed indolent NHL.[46] The ORR rate was 100% with 87% of patients achieving a CR or CRu. The median time to progression and the duration of response was 82 months and 83.5 months respectively. The superiority of R-CHOP to CHOP as first-line therapy was established in a prospective randomized phase III study conducted by the German Low-Grade Lymphoma Study Group (GLSG) in previously untreated patients with advanced-stage FL (N=428). R-CHOP was associated with a 60% reduction in the relative risk for treatment failure, significantly prolonged time to treatment failure, higher ORR (but no difference in CR rate) and prolonged duration of remission.[47] OS analysis was complicated by a second randomization (for patients age <60 years), which included high-dose therapy followed by autologous stem cell rescue (HDT/ASCR). Outcomes were not significantly different with and without rituximab, in patients who received consolidation with HDT/ASCR. However, in patients who received interferon maintenance (who did not undergo HDT/ASCR), duration of remission was significantly improved with R-CHOP followed by interferon compared with CHOP/interferon (median not reached vs. 26 months). In addition, among the subgroup of older patients (age ≥60 years) who received interferon maintenance (as these patients were not eligible for HDT/ASCR), R-CHOP/interferon was associated with significantly improved 4-year PFS rate (62% vs. 28%) and OS rate (90% vs. 81%) compared with CHOP/interferon.[51]

In a randomized phase III study, addition of rituximab to CVP chemotherapy (R-CVP; n=162) compared with CVP (n=159) significantly improved outcome in patients with previously untreated FL, with no significant increase in toxicity.[48] At a median follow-up of

53 months, R-CVP was associated with improved ORR (81% vs. 57%), CR/CRu rate (41% vs. 10%), median time to progression (34 months vs. 15 months) and 4-year OS rate (83% vs. 77%).[49]

The addition of rituximab to fludarabine or fludarabine-based combination has also been evaluated in various clinical studies.[52-55] In a phase II study, rituximab combined with fludarabine (FR) was evaluated in patients with previously untreated or relapsed low-grade or follicular NHL (n=40; 68% previously untreated).[52] The ORR was 90% with 80% of patients achieving a CR. With a median follow-up time of 44 months, the median response duration, time to progression and OS had not been reached. The probability of OS at 50 months was estimated to be 80%. No significant differences in response or OS outcomes were noted between previously untreated and relapsed patients.[52] In a prospective randomized phase III trial (n=147; 128 evaluable patients), the combination of rituximab and FCM (fludarabine, cyclophosphamide, mitoxantrone; R-FCM) was associated with superior outcomes compared with FCM in patients with relapsed or refractory FL and MCL.[53] R-FCM resulted in significantly higher ORR (79% vs. 58%; *P*=0.01), higher CR rates (33% vs. 13%; *P* =.005), improved median PFS (16 months vs. 10 months; *P* =.038) and improved median OS (not reached at 3 years vs. 24 months; *P*=0.003) compared with FCM alone. In addition, among the subgroup of patients with FL (n=65), R-FCM was associated with significantly improved median PFS (not reached at 3 years vs. 21 months; *P* =.014); median OS (not reached in either treatment arm) was not significantly different.[53] In a randomized trial from the MD Anderson Cancer Center (MDACC), concurrent administration of rituximab with FND regimen (fludarabine, mitoxantrone and dexamethasone; R-FND) resulted in a significantly higher 3-year FFS rate (84% vs. 59% for sequential arm) in the subset of patients with FL.[54] In a subsequent report from the MDACC that included an analysis of this study (concurrent or sequential inclusion of rituximab with FND) in patients with FL (n=151), the median FFS and OS had not been reached at a median follow up of 3.3 years; the 5-year FFS rate and OS rate with the regimen was 60% and 95%, respectively.[56] The combination of rituximab with fludarabine and mitoxantrone (R-FM) was evaluated in a phase II trial in patients with relapsed/refractory FL with high tumor burden (based on GELF criteria; n=50).[57] None of the patients were previously treated with rituximab, fludarabine or mitoxantrone. The ORR with this regimen was 84% (CR/CRu in 68%). The 3-year PFS rate and OS rate was 47% and 66%, respectively.[57]

The incorporation of rituximab to chemotherapy regimens has become a widely accepted standard of care for first-line therapy for patients with FL. However, no head-to-head randomized studies have shown superiority of one chemoimmunotherapy regimen over another with regards to OS outcomes. A report from the prospective, multicenter observational National LymphoCare Study based on the data collected from a large population of previously untreated patients with FL in the U.S. (n=2,738) showed that rituximab-containing chemoimmunotherapy was used in 52% of patients.[5] Among these patients, the most commonly employed regimens included R-CHOP (55%), R-CVP (23%) and rituximab with fludarabine-based regimens (R-Flu; 15.5%). In a recent analysis of patients treated with these rituximab-containing regimens in the National LymphoCare Study, 2-year PFS rates were similar between patients treated with R-CHOP, R-CVP or R-Flu (78% vs. 72% vs. 76%).[58] The 2-year OS rate showed significant differences, however (94% vs. 88% vs. 91%, respectively), with OS benefits observed for R-CHOP compared with R-CVP; this benefit with R-CHOP was more apparent in the subgroup of patients with poor-risk FLIPI scores.[58]

The phase III randomized trial of the Italian Lymphoma group (FOLL-05 Trial) evaluated the efficacy of three chemoimmunotherapy regimens (R-CVP, R-CHOP and R-FM) as first-line therapy in patients with advanced stage FL (n=534).[59] The primary endpoint of this study was time to treatment failure (TTF). The 3-year TTF rate was 46% for patients randomized to R-CVP, 62% for R-CHOP (*P* =.003 versus R-CVP) and 59% with R-FM (*P*=0.006 versus R-CVP), after a median follow up of 34 months. The 3-year PFS was 52%, 68%, and 63%, respectively (*P* =.011). No significant differences were observed between treatment arms for ORR or CR rates. The 3-year OS rate was 95% for all patients in this study.[59] Grade 3 or 4 neutropenia was more common in the R-FM arm, occurring in 64% of patients, compared with 28% with R-CVP and 50% with R-CHOP. The incidence of secondary malignancies was also more common with R-FM (8%) than with R-CVP (2%) or R-CHOP (3%).[59] Although these studies suggest a potential advantage of R-CHOP over R-CVP, both regimens are considered standard first-line therapies, and the selection of the optimal therapy would mainly depend on individual patient factors.

Fludarabine-based chemoimmunotherapy regimens may not be an ideal treatment option in the front-line setting because of the stem cell toxicity and increased risks for secondary malignancies associated with such regimens.[60-62] This may be of particular concern for younger patients with FL who may be candidates for autologous stem cell transplantation in the future. Prior exposure to fludarabine has been associated with poorer mobilization of peripheral blood stem cells in patients with lymphoma.[45,60-62]

Bendamustine, an alkylating agent with a purine-like benzimidazole ring component, has been shown to have low or incomplete cross-resistance with other alkylating agents due to its unique cytotoxic properties. Bendamustine (as a single agent or in combination with rituximab) has shown promising results with acceptable toxicity in patients with newly diagnosed as well as heavily pretreated relapsed or refractory indolent or mantle cell histologies or transformed NHL.[63-68] A multicenter randomized open-label phase III study conducted by the StiL (Study Group Indolent Lymphomas) compared rituximab combined with bendamustine (BR) with R-CHOP as first-line treatment in patients with advanced follicular, indolent, and mantle cell lymphomas (n=514).[69] The primary endpoint of this study was PFS, which was significantly longer with BR compared with R-CHOP (median 69.5 months vs. 31 months; hazard ratio=0.58, 95% CI 0.44–0.74; *P* <.0001). Median PFS was significantly longer with BR in the subgroup of patients with FL (n=279; not reached vs. 41 months; *P* =.0072). The ORR was similar between treatment arms (93% with BR; 91% with R-CHOP), although the CR rate was significantly higher in the BR arm (40% vs. 30%; *P*=.021).[69] With a median follow up of 45 months, no significant difference in OS was observed between treatment arms, and median OS has not been reached in either arm. The BR regimen was associated with a lower incidence of serious adverse events compared with R-CHOP (19% vs. 29%). In addition, BR was associated with less frequent grade 3 or 4 neutropenia (29% vs. 69%) or infections (any grade; 37% vs. 50%). Erythema (16% vs. 9%) and allergic skin reactions (15% vs. 6%) were more common with BR compared with R-CHOP. The incidence of secondary malignancies was similar, with 20 cases (8%) in the BR arm and 23 cases (9%) with R-CHOP.[69]

Another ongoing multicenter randomized open-label phase III study is evaluating the efficacy and safety of the BR regimen compared with R-CHOP/R-CVP in patients with previously untreated indolent NHL or mantle cell lymphoma (BRIGHT Study).[70] Among evaluable patients (N=419), the CR rate (assessed by an independent review committee) with BR was not inferior to R-CHOP/R-CVP (31% vs. 25%). The CR

rate in the subgroup of patients with indolent NHL was 27% and 23%, respectively. BR was associated with less grade 3 or 4 neutropenia (by laboratory assessment: 44% vs. 70%) but more infusion-related reactions (6% vs. 4%) compared with R-CHOP/R-CVP. Fatal adverse events occurred in 6 patients (3%) in the BR arm and 1 patient (<1%) in the R-CHOP/R-CVP arm.[70] In a phase II multicenter study, BR resulted in an ORR of 92% (CR in 41%) in patients with relapsed or refractory indolent and mantle cell lymphomas (N=67).[67] The median duration of response and PFS were 21 months and 23 months, respectively. Outcomes were similar for patients with indolent or mantle cell histologies.[67]

Bendamustine combined with rituximab and the proteasome inhibitor bortezomib (BVR) has been evaluated in two recent phase II studies in patients with relapsed and/or refractory FL.[63,64] In a study of 30 patients with relapsed/refractory indolent or mantle cell lymphoma (16 patients had FL; high-risk FLIPI, 56%; median 4 prior therapies), BVR regimen was associated with an ORR of 83% (CR in 52%).[64] The ORR was 93% among the subgroup of patients with FL and 75% for the subgroup with rituximab-refractory disease (n=10). The 2-year PFS rate was 47% and the median PFS for all patients was approximately 22 months. Serious adverse events were reported in 8 patients, which included 1 death due to sepsis.[64] In another study (VERTICAL) that evaluated a different BVR combination regimen in patients with relapsed/refractory FL (n=73; high-risk FLIPI, 38%; median 2 prior therapies), the ORR (among n=60 evaluable) was 88% (CR in 53%).[63] The median duration of response was 12 months. Among the subgroup of patients refractory to prior rituximab (n=20 evaluable), the ORR was 95%. The median PFS for all patients on the study was 15 months. Serious adverse events were reported in 34% of patients; the most common grade 3 or 4 adverse events were myelotoxicities, fatigue, peripheral neuropathy, and gastrointestinal symptoms.[63]

The immunomodulating agent lenalidomide (a thalidomide analog indicated for the treatment of multiple myeloma and myelodysplastic syndromes), with or without rituximab, has also been evaluated in the treatment of both patients with previously untreated and relapsed/refractory indolent NHL. In a phase II trial of patients with relapsed/refractory indolent NHL (n=43; median 3 prior therapies), single-agent lenalidomide induced an ORR of 23% (CR /CRu in 7%).[71] Among the subgroup of patients with FL (n=22), the ORR was 27%. The median duration of response was longer than 16.5 months, and has not been reached. Median PFS for all patients was 4.4 months.[71] An ongoing randomized phase II trial is assessing the activity of lenalidomide alone compared with lenalidomide in combination with rituximab (CALGB 50401 study) in patients with recurrent FL (N=94; n=89 evaluable).[72] The ORR with lenalidomide alone was 49% (CR in 13%) and with the combination regimen was 75% (CR in 32%). With a median follow up of 1.5 years, median EFS was significantly longer with the combination (2 years vs. 1.2 years; *P*=.0063). Approximately 19% of patients in each arm discontinued therapy due to adverse events. Grade 3 or 4 adverse events were reported in a similar proportion of patients in the monotherapy and combination arms (49% vs. 52%; grade 4 in 9% in each arm). The most common grade 3 or 4 toxicities included neutropenia (16% vs. 19%), fatigue (9% vs. 14%), and thrombosis (16% vs. 4%).[72] The combination of lenalidomide and rituximab was also evaluated in a phase II study in patients with previously untreated indolent NHL (N=110; n=103 evaluable).[73] Among the subgroup of patients with FL (n=46), the ORR was 98% (CR/CRu in 87%) and the 2-year PFS was 89%. In patients with FL who had a positive PET scan prior to therapy (n=45), 93% achieved PET-negative response after treatment. Grade 3 or greater

neutropenia was common, and occurred in 40% of patients overall. Thrombosis was reported in 3 patients (3%).[73]

Radioimmunotherapy (RIT) with the radio-labelled monoclonal antibodies ^{90}Y-ibritumomab tiuxetan[74-78] and ^{131}I-tositumumab[79-82] has been evaluated in patients with newly diagnosed, as well as those with relapsed, refractory or histologically transformed FL. In an international phase II trial, ^{90}Y-ibritumomab when used as a first-line therapy in older patients (age >50 years) with stage III or IV FL (N=59; median age 66 years, range 51–83 years) resulted in an ORR of 87% (CR in 41%, CRu in 15%) at 6 months after therapy.[78] After a median follow-up of approximately 31 months, the median PFS was 26 months and median OS has not been reached. The most common toxicities with first-line ^{90}Y-ibritumomab included grade 3 or 4 thrombocytopenia (48%; grade 4 in 7%) and neutropenia (32%; grade 4 in 17%). No grade 3 or 4 non-hematologic toxicities were reported. Grade 2 infections occurred in 20% and grade 2 GI toxicities in 10% of patients.[78] In a randomized phase III study in patients with relapsed or refractory low-grade, follicular or transformed lymphoma (n=143), ^{90}Y-ibritumomab tiuxetan also produced statistically and clinically significant higher ORR (80% vs. 56%) and CR rate (30% vs. 16%) compared with rituximab alone.[75] At a median follow-up of 44 months, median TTP (15 vs.10 months) and duration of response (17 vs. 11 months) were longer for patients treated with ^{90}Y-ibritumomab compared with rituximab.[76]

Initial treatment with a single one-week course of ^{131}I-tositumomab induced prolonged clinical and molecular remissions in patients with advanced FL (N=76).[79] After a median follow-up of 10 years, the median duration of response was 6 years. For the 57 patients with a CR, median PFS was almost 11 years.[83] Ten-year PFS and OS rates were approximately 40% and 82%, respectively. Secondary malignancies were reported in 11 patients (14%) during this long-term follow-up period, and 1 patient (1%) developed MDS about 8 years after therapy.[83] A single course of ^{131}I-tositumumab was significantly more efficacious than the last qualifying chemotherapy in extensively pretreated patients with refractory, low-grade, or transformed NHL (n=60).[81] The final results of the study demonstrated that ^{131}I-tositumumab resulted in long-term durable CRs. Among the 12 patients who achieved a CR, the median duration of response was nearly 10 years; among the 5 patients who continued in CR (lasting ≥10 years), none had received prior rituximab therapy.[84]

Phosphatidylinositol 3-kinase (PI3K) plays a central role in the normal B-cell development and function.[85] PI3Kδ signaling pathways are frequently hyperactive in B-cell neoplasms. Idelalisib, the isoform-selective oral inhibitor of PI3K-delta, has demonstrated promising clinical activity in phase I studies in patients with indolent NHL.[86] The safety and efficacy of idelalisib in patients with relapsed indolent NHL was evaluated in a phase II multicenter single arm study.[87] In this study, 122 patients with indolent NHL (72 patients with FL, 28 patients with SLL and 15 patients with MZL) that had not responded to previous treatment with rituximab and an alkylating agent were treated with idelalisib (150 mg oral, BID) until disease progression or patient withdrawal from the study.[87] Majority of the patients (89%) had stage III or IV disease. Among patients with FL, 79% of patients were of intermediate-risk or high-risk, based on FLIPI scores and 17% of patients had FL grade 3a. The primary end point of the study was the ORR. The median duration of treatment with idelalisib was 6.6 months. Idelalisib resulted in tumor reductions in 90% of the patients, with an ORR of 57% (6% CR and 50% PR). Response rates were similar across all subtypes of indolent NHL. The median duration of response, median PFS and OS were 12.5 months, 11.0 months and 20.3 months, respectively. At 48 weeks, 47% of the

patients remained progression-free. The median follow-up was 9.7 months. The most common adverse events of grade 3 or higher were neutropenia (27%), elevations in aminotransferase levels (13%), diarrhea (13%), and pneumonia (7%). Fatal and/or serious hepatotoxicity, severe diarrhea or colitis, pneumonitis, and intestinal perforation have been observed in patients treated with idelalisib.[88] See *"Special Considerations for the use of BCR Inhibitors"* in the guidelines for monitoring and management of adverse reactions associated with idelalisib.

Based on the results of this study, idelalisib (150 mg oral, BID) was recently approved by the FDA for the treatment of relapsed FL that has not responded to at least two prior systemic therapies. The NCCN Guidelines have included idelalisib as an option for second-line therapy for patients with relapsed or refractory FL.

First-line Consolidation with RIT

First-line chemotherapy followed by RIT with ^{90}Y-ibritumomab[89-92] or ^{131}I-tositumumab[93-96] has also been evaluated in several phase II studies.

In the international phase III trial (First-line Indolent Trial; FIT), patients with advanced stage FL responding to first-line induction therapy (n=414) were randomized to receive ^{90}Y-ibritumomab or no further treatment (observation only).[91] After a median follow-up of 7.3 years, the estimated 8-year PFS was 41% with ^{90}Y-ibritumomab tiuxetan consolidation and 22% with observation only, with a median PFS of 4.1 years versus 1.1 years, respectively (*P* <.001).[97] No significant difference in OS was observed between treatment arms. The incidence of secondary malignancies was higher in the consolidation arm compared with the observation arm (13% vs. 7%), but the difference was not statistically significant. MDS/AML occurred more frequently in the consolidation arm (3% vs. <1%), with a significantly increased actuarial 8-year incidence rate (4.2% vs. 0.6%; *P* <.042). The median time from randomization to second malignancies was 58 months. The FIT study included only a small number of patients (14%) who received rituximab in combination with chemotherapy as induction.[91,97] Among these patients, the estimated 8-year PFS rate was 56% with ^{90}Y-ibritumomab consolidation and 45% with observation alone; the median PFS was greater than 7.9 years and 4.9 years, respectively. The difference in PFS outcomes was not significant in this subgroup; however, the trial was not statistically powered to detect differences in subgroups based on induction therapies.[97] Since only a small proportion of patients enrolled in the FIT trial received rituximab-containing induction therapy, the effects of RIT consolidation following rituximab-containing regimens cannot be fully evaluated.

In the Southwest Oncology Group (SWOG S9911) trial, CHOP followed by ^{131}I-tositumomab resulted in an ORR of 91%, including a 69% CR rate in patients with previously untreated, advanced FL (n=90).[95] After a median follow-up of 5 years, the estimated 5-year PFS rate and OS rate was 67% and 87%, respectively.[94] In a historical comparison, these results were more favorable than those reported for CHOP alone. In a multicenter phase II study, CVP chemotherapy followed by ^{131}I-tositumomab resulted in an ORR of 100% with a 93% CR rate in untreated patients with FL (n=30). The 5-year PFS rate and OS rate was 56% and 83%, respectively.[96]

The phase III randomized Intergroup study by the SWOG/CALGB (S0016) evaluated the role of RIT consolidation with ^{131}I-tositumumab (CHOP-RIT) following first-line therapy in patients with advanced stage FL.[7] In this study, 554 patients were randomized to first-line therapy with 6 cycles of R-CHOP or 6 cycles of CHOP followed by consolidation with ^{131}I-tositumumab (CHOP-RIT).[7] After a median follow-up time of 4.9

years, the estimated 2-year PFS (76% vs. 80%) and OS (97% vs. 93%) rates were not significantly different between R-CHOP and CHOP-RIT. Median time to progression has not yet been reached for either study arm. Both the ORR (84% in each arm) and CR rates (40% vs. 45%, respectively) were also similar between treatment arms. CHOP-RIT was associated with a higher incidence of grade 3 or 4 thrombocytopenia (18% vs. 2%) but fewer febrile neutropenia (10% vs. 16%) compare with R-CHOP. The incidences of secondary malignancies (9% vs. 8%) and AML/MDS (1% vs. 3%) were not different between R-CHOP and CHOP-RIT.[7]

An ongoing trial (SWOG study S0801) is evaluating whether R-CHOP with RIT consolidation and with maintenance rituximab will provide improved efficacy outcomes. Data from this trial are awaited to assess the role of RIT consolidation in patients with FL treated with rituximab-containing induction.

First-line Consolidation with Maintenance Rituximab

Several studies have reported that prolonged administration of rituximab (or rituximab maintenance) significantly improved EFS in chemotherapy-naïve patients responding to initial rituximab induction, although this benefit did not translate to OS advantage.[98-100] In a study that evaluated maintenance rituximab compared with retreatment with rituximab upon progression in patients with chemotherapy-treated indolent lymphomas responsive to rituximab therapy (n=90 randomized), maintenance rituximab significantly improved PFS compared with the retreatment approach (31 months vs. 7 months; *P*=0.007).[101] However, retreatment with rituximab at progression provided the same duration of benefit from rituximab as did maintenance rituximab (31 months vs. 27 months).[101] Therefore, either approach (maintenance or retreatment at progression) appeared to be beneficial for this patient population. The randomized phase III study from ECOG (E1496) demonstrated a PFS benefit with rituximab maintenance in patients with advanced indolent lymphoma responding to first-line chemotherapy with CVP (n=311; FL, n=282).[102] The 3-year PFS rate was 68% for maintenance rituximab compared with 33% for observation for all patients with advanced indolent lymphoma with response or stable disease after CVP chemotherapy. For the subgroup of patients with FL, the corresponding PFS rates were 64% and 33%, respectively; the 3-year OS rate was not significantly different in patients with FL (91% vs. 86%, respectively).[102]

The phase III randomized PRIMA trial prospectively evaluated the role of rituximab maintenance in patients responding to first-line chemotherapy in combination with rituximab.[103] In this study, patients with FL responding to first-line chemoimmunotherapy (R-CVP, R-CHOP or R-FCM) were randomized to observation only or rituximab maintenance for 2 years (n=1018). After a median follow-up of 36 months, the 3-year PFS rate was 75% in the rituximab maintenance arm and 58% in the observation arm (*P* =.0001). Two years after randomization,71.5% of patients in the rituximab maintenance arm were in CR/CRu compared with 52% in the observation group.[103] However, no significant difference was observed in OS between the two groups. Based on multivariate analysis, induction therapy with R-CHOP or R-FCM was one of the independent factors associated with improved PFS, suggesting that R-CVP induction was not as beneficial in this study. Longer follow up is needed to evaluate the effect of rituximab maintenance on OS.

Second-line Consolidation with Maintenance Rituximab

Rituximab maintenance following second-line therapy has also been evaluated in patients with relapsed/refractory disease. Two large randomized trials have demonstrated a PFS advantage with rituximab maintenance over observation for patients treated with

chemoimmunotherapy induction.[104-106] In a prospective phase III randomized study by the GLSG, rituximab maintenance after second- line treatment with R-FCM significantly prolonged duration of response in the subgroup of patients with recurring or refractory FL (n=81); median PFS with rituximab maintenance was not reached compared with 26 months in the observation arm (*P* =.035).[104] In a phase III randomized Intergroup trial (EORTC 20981) in patients with relapsed or resistant FL (n=334), responding to CHOP or R-CHOP induction therapy, maintenance rituximab significantly improved median PFS (3.7 years vs. 1.3 years; *P* <.001) compared with observation alone.[105,106] This PFS benefit was observed regardless of the induction therapy employed (CHOP or R-CHOP). With a median follow-up of 6 years, the 5-year OS rate was not significantly different between study arms (74% vs. 64%, respectively).[106]

Hematopoietic Stem Cell Transplantation (HSCT) After Induction

HDT/ASCR has been shown to prolong OS and PFS in patients with relapsed or refractory disease.[107-109] The GELA recently conducted a retrospective analysis of patients treated with chemotherapy alone in the first-line setting and found that EFS and survival after relapse were superior for patients treated with rituximab-containing regimens compared to chemotherapy only-based HDT/ASCR in relapsed or refractory FL.[110] The combination of rituximab-based second-line therapy followed by HDT/ASCR resulted in favorable survival rates after relapse, which was 90% at 5 years. Allogeneic HSCT is associated with high treatment-related mortality (TRM) rates (about 30-40% for myeloablative and 25% for nonmyeloablative allogeneic HSCT).[111,112] In a recent report from IBMTR, both myeloablative and nonmyeloablative HSCT resulted in similar TRM rates; however, nonmyeloablative allogeneic HSCT was associated with an increased risk of disease progression.[113]

Imaging Studies for FL

Imaging studies using CT or PET-CT scans are important components of diagnostic workup, interim restaging, and post-treatment assessments in patients with lymphomas. For patients with FL, CT scans of the chest, abdominal and pelvic regions are considered essential for diagnostic workup. The use of PET-CT is considered optional or useful in selected patients with FL during workup or for post-treatment assessment. Although PET-CT is now considered a standard part of post-treatment response evaluation in patients with aggressive NHLs or Hodgkin lymphoma, its role in patients with indolent lymphomas is less certain.

Several studies have reported on the potential usefulness of PET imaging in patients with indolent lymphomas, and documented the ability of this modality to detect lesions with high sensitivity (94–98%) and specificity (88–100%).[114-117] Studies have also suggested that PET/CT scans may be more accurate than CT scans alone in detecting disease.[116,118,119] In addition, post-treatment PET/CT scans have demonstrated prognostic utility in patients with indolent lymphomas. Several studies have shown that PET status (i.e., PET-positivity or PET-negativity at the end of induction therapy) was associated with PFS outcomes. In these studies, PET-negativity was associated with a longer PFS compared to PET-positivity.[114,119,120] In a retrospective study in patients with FL treated with R-CHOP, PET/CT imaging was found to be more accurate than CT imaging in detecting both nodal and extranodal lesions at staging and in assessing response to treatment.[120] Post-treatment PET/CT-negativity was associated with more favorable PFS outcomes; median PFS was 48 months among PET/CT-negative cases compared with 17 months for positive cases (*P* <.001).[120] An exploratory retrospective analysis of the prognostic value of post-induction PET/CT scans was conducted based on data obtained

from the PRIMA trial of patients with FL. In this trial, patients with previously untreated FL treated with rituximab-containing chemoimmunotherapy were randomized to rituximab maintenance (for 2 years) or observation only.[103] Among patients with a post-induction PET/CT scan (n=122), those with a positive PET/CT scan had a significantly inferior PFS rate compared with those who were PET negative (33% vs. 71% at 42 months; *P* <.001).[121] The median PFS was 20.5 months and not reached, respectively. Among the patients randomized to observation (n=57), PET/CT status remained significantly predictive of PFS outcomes. In this group, the 42-months PFS rate was 29% for PET/CT-positive patients compared with 68% in PET/CT-negative cases; median PFS was 30 months and 52 months, respectively.[103] Among the patients randomized to rituximab maintenance (n=47), PET/CT positivity was associated with inferior (but not statistically significant) PFS outcomes compared with PET/CT-negative cases (56% vs. 77% at 41 months); median PFS has not yet been reached in either the PET/CT-positive or PET/CT-negative subgroups. Moreover, PET/CT status was also associated with OS outcomes in this exploratory analysis. Patients who were PET/CT-positive after induction therapy had significantly inferior OS compared with PET/CT-negative patients (78.5% vs. 96.5% at 42 months; *P* =.001).[103]

In a recent prospective study, the prognostic value of PET imaging was evaluated in patients with high-tumor burden FL treated with first-line therapy with 6 cycles of R-CHOP (n=121; no maintenance rituximab administered).[122] PET scans were performed after 4 cycles of R-CHOP (interim PET) and at the end of treatment (final PET), and all scans were centrally reviewed. A positive PET was defined as Deauville score 4 or higher. Among patients with an interim PET scan (n=111), 76% had a PET-negative response. Among patients with a final PET (n=106), 78% had a PET-negative response.[122] At the end of treatment, nearly all patients (98%) who achieved a CR based on IWC also achieved a PET-negative response. Interim PET was associated with significantly higher 2-year PFS (86% for PET negative vs. 61% for positive; *P*=0.0046) but no significant difference in terms of OS. Final PET-negativity was associated with both significantly higher 2-year PFS (87% vs. 51%; *P* <.001) and higher OS (100% vs. 88%; *P*=0.013).[122] These studies suggest that post-treatment imaging studies may have a role as a predictive factor for survival outcomes in patients with FL. Further prospective studies are warranted to determine whether interim and/or end-of-treatment PET scans have a role in guiding post-induction therapeutic interventions.

PET scans may be useful in detecting transformation in patients with indolent NHL. Standard FDG uptake values (SUV) on PET have been reported to be higher among transformed than non-transformed cases of indolent lymphomas.[116] High SUVs on PET imaging should raise the suspicion of transformation to aggressive lymphoma, and can be used to direct the optimal site of biopsy for histological confirmation.[123]

Little data exist on the potential role of follow-up surveillance imaging for detection of relapse in patients with indolent NHL. In an early retrospective study, patients with stage I to stage III FL with a CR after induction were evaluated with clinical, laboratory and imaging studies during routine follow up (n=257).[124] Patients underwent CT scans of the abdomen and/or pelvis during follow-up visits. Follow up was typically performed every 3 to 6 months for the first 5 years of treatment, and then annually thereafter. The median follow-up time was 80 months (range, 13–209 months). Relapse was detected in 78 patients, with the majority of relapses (77%) occurring within the first 5 years of treatment.[124] Eleven of the relapses were detected with abdominal and/or pelvic CT scans alone. Thus, in this analysis, 4% of patients with

an initial CR had recurrence determined by routine surveillance with CT scans.[124] A more recent prospective study evaluated the role of surveillance PET scans in patients with lymphomas (Hodgkin lymphoma and NHL) with a CR after induction.[125] PET scans were performed every 6 months for the first 2 years after completion of induction, then annually thereafter. In the cohort of patients with indolent NHL (n=78), follow-up PET scans detected true relapses in 10% of patients (8 of 78) at 6 months, 12% (8 of 68) at 12 months, 9% (5 of 56) at 18 months, 9% (4 of 47) at 24 months, 8% (3 of 40) at 36 months and 6% (2 of 34) at 48 months.[125] Among 13 patients who were PET-positive without a corresponding abnormality on CT scan, relapse was documented in 8 of these patients by biopsy. Of the 47 patients with PET-positive relapses, 38 patients were detected on CT and 30 patients were detected clinically at the same time as the PET. It is unclear whether this earlier detection of relapse in a proportion of patients translates to improved outcomes.

In the absence of evidence demonstrating improved survival outcomes with early PET detection of relapse, PET scans are not recommended for routine surveillance in patients who have achieved a CR after treatment.

NCCN Recommendations for Treatment of Stage I-II Disease

Involved-site radiotherapy (ISRT; 24–30 Gy, with an additional 6 Gy in selected patients with bulky disease) is the preferred treatment option for patients with stage I or contiguous stage II disease. In selected cases where toxicity of ISRT outweighs the potential clinical benefit, observation may be appropriate. Alternate treatment options include immunotherapy with or without chemotherapy with or without RT. Because chemotherapy added to RT was not shown to provide relapse-free survival benefit, chemotherapy plus RT is included in the NCCN Guidelines with a category 2B recommendation.

For patients with a PR following initial immunotherapy with or without chemotherapy (but without RT), additional treatment with ISRT should be considered. Otherwise, for patients with a clinical PR (following ISRT) or CR, clinical follow-up with a complete physical exam and laboratory assessment should be performed every 3 to 6 months for the first 5 years, and then annually (or as clinically indicated) thereafter. Surveillance imaging with CT scans can be performed no more than every 6 months up to the first 2 years following completion of treatment, and then no more than annually (or as clinically indicated) thereafter. Patients with no response to initial therapy should be managed in the same manner as patients with advanced disease, as described below.

NCCN Recommendations for Treatment of Stage II (bulky) and Stage III-IV Disease

As previously mentioned, treatment for patients with advanced-stage FL in the clinical practice setting should only be initiated when indicated by the GELF criteria. The modified criteria used to determine treatment initiation include: symptoms attributable to FL (not limited to B-symptoms); threatened end-organ function; cytopenia secondary to lymphoma; bulky disease (single mass >7 cm or 3 or more masses >3 cm), splenomegaly; and steady progression over at least 6 months. Treatment decisions should also consider the patient's preference; however, patients opting for immediate treatment in the absence of a clinical indication should be referred to an appropriate clinical trial. The selection of treatment should be highly individualized according to the patient's age, extent of disease, presence of comorbid conditions, and the goals of therapy. When choosing an initial therapy, care should be given to avoid excessively myelotoxic regimens in patients who may subsequently be candidates for HDT/ASCR. Chemoimmunotherapy

regimens (containing rituximab) frequently used in the management of FL may be associated with risks for reactivation of HBV, which can lead to hepatitis and hepatic failure. Therefore, prior to initiation of therapy, HBV testing (including HBsAg and HBcAb testing) should be performed for all patients; viral load should be monitored routinely for patients with positive test results. In addition, the use of empiric antiviral therapy or upfront prophylaxis should be incorporated into the treatment plan.

First-line Therapy

In the absence of an appropriate clinical trial, patients with indications for treatment should be treated with systemic therapy. In selected cases such as the elderly frail patient who would not tolerate chemotherapy, ISRT (4 Gy) may be used for local palliation. Asymptomatic patients, especially those older than 70 years of age, should be observed.[38]

Based on the reported data, rituximab in combination with bendamustine, CHOP or CVP chemotherapy for first-line therapy in patients with advanced FL are all category 1 recommendations. In the absence of a randomized trial showing superior OS with R-CHOP versus R-CVP, either of these regimens can be considered appropriate in the first-line setting. The BR regimen has been shown to have less toxicity and a superior PFS compared to R-CHOP in a randomized phase III study; however, the OS outcomes were not significantly different. Furthermore, we have limited data on the risk of secondary MDS/AML after bendamustine. Data from a limited subset of patients suggests that peripheral blood stem cells can be collected after both BR and R-CHOP; additional data are needed to confirm this finding. Other suggested regimens include rituximab either as a single agent or in combination with fludarabine-based chemotherapy. As discussed earlier, the use of fludarabine-containing regimens may not be ideal in the first-line setting for younger, physically fit patients (who may be candidates for future HDT/HSCR) because of the stem cell toxicity and risks for secondary malignancies. Thus, the use of regimens such as R-FND in the first-line setting is included as a category 2B recommendation. RIT is included as a category 3 option due to the absence of additional data from randomized studies. ISRT (4–30 Gy) with or without systemic therapy can be considered for palliation in patients with locally bulky or symptomatic disease if they are unable to tolerate systemic therapy.

Single-agent rituximab is the preferred first-line therapy for elderly or infirm patients. Single-agent cyclophosphamide had equivalent OS and CR rates compared to cyclophosphamide-based combination chemotherapy.[126] The NCCN Guidelines have also included RIT, alkylating agent-based chemotherapy (cyclophosphamide or chlorambucil) with or without rituximab, as alternative options for elderly or infirm patients.

First-line Consolidation or Extended Dosing

Patients with CR or PR to first-line therapy can either be observed or can be treated with optional consolidation or extended therapy. Based on the results of the PRIMA study,[103] maintenance therapy with rituximab (one dose every 8 weeks) up to 2 years is recommended (category 1) for patients responding to first-line chemoimmunotherapy. Based on the results of the FIT trial,[91,97] RIT is recommended (category 1) for patients who received first-line chemotherapy.

As of February 2014, ^{131}I-tositumumab has been discontinued and will no longer be available for the treatment of patients with FL.

For patients receiving consolidation therapy, clinical follow-up with a complete physical exam and laboratory assessment should be performed every 3 to 6 months for the first 5 years, and then annually

(or as clinically indicated) thereafter. Surveillance imaging with CT scans can be performed no more than every 6 months up to the first 2 years following completion of treatment, and then no more than annually (or as clinically indicated) thereafter.

Second-line Therapy for Relapsed or Progressive Disease

Frequently, patients will benefit from a second period of observation after progressing from first-line therapy. Thus, treatment for relapsed or progressive disease is based on the modified GELF criteria as in first-line therapy. Progressive disease should be histologically documented to exclude transformation, especially in the presence of raising LDH levels, disproportional growth in one area, development of extranodal disease or development of new constitutional symptoms. Areas of high SUV, especially in values in excess of 13.1, should raise suspicion for the presence of transformation. However, a positive PET/CT scan does not replace a biopsy; rather, results of the PET/CT scan should be used to direct a biopsy to enhance the diagnostic yield from the biopsy. For patients requiring second-line therapy or treatment for disease unresponsive to first-line regimens, the options include chemoimmunotherapy regimens used for first-line treatment, BVR (bendamustine, bortezomib, rituximab), fludarabine combined with rituximab, FCM-R regimen (category 1) or RIT (category 1) or any of the second-line regimens used for patients with DLBCL. Based on the recent FDA approval, idelalisib is also included as an option for second-line therapy.

As of February 2014, ^{131}I-tositumumab has been discontinued and will no longer be available for the treatment of patients with FL.

Second-line Consolidation or Extended Dosing

For patients in remission after second-line therapy, optional maintenance therapy with rituximab (one dose every 12 weeks for 2 years) can be recommended (category 1). However, the NCCN Guidelines panel recognizes that the efficacy of maintenance rituximab in the second-line setting would likely be impacted by a patient's response to first-line maintenance with rituximab. If a patient progressed during or within 6 months of first-line maintenance with rituximab, the clinical benefit of maintenance in the second-line setting is likely very minimal. HDT/ASCR is an appropriate consolidative therapy for patients with second or third remission. Allogeneic HSCT may also be considered for highly selected patients. For patients receiving consolidation therapy, clinical follow-up with a complete physical exam and laboratory assessment should be performed every 3 to 6 months for the first 5 years, and then annually (or as clinically indicated) thereafter. Surveillance imaging with CT scans can be performed no more than every 6 months up to the first 2 years following completion of treatment, and then no more than annually (or as clinically indicated) thereafter.

Histological Transformation to DLBCL

In patients with FL, histological transformation to DLBCL is generally associated with a poor clinical outcome. Histological transformation to DLBCL occurs at an annual rate of approximately 3% for 15 years and the risk of transformation falls after that time, for reasons that remain unclear.[127] In a multivariate analysis, advanced stage disease at diagnosis was the only predictor of future transformation. The median OS after transformation has been reported to be less than 2 years.[127] However, patients with limited disease with no previous exposure to chemotherapy may have the favorable outcomes similar to *de novo* DLBCL.[128] The 5-year OS rate for patients with limited extent transformation was 66% compared with 19% for those with advanced disease (P<0.0001).[127]

In cases where the patient has had multiple prior therapies, the prognosis is much poorer and enrollment in an appropriate clinical trial is the preferred option. In the absence of a suitable clinical trial, treatment options include RIT, chemotherapy with or without rituximab, ISRT or best supportive care. HDT/ASCR or allogeneic HSCT can be considered as consolidation therapy for patients in remission after initial treatment. In a multicenter cohort study (172 patients) conducted by the Canadian blood and bone marrow transplant group, HDT/ASCR was associated with better outcomes than rituximab-based chemotherapy alone for patients aggressive histological transformation.[129] The 5-year OS after transformation was 65%, 61% and 46% respectively for patients treated with HDT/ASCR, rituximab-containing chemotherapy and allogeneic SCT. The corresponding 5-year PFS rates after transformation were 55%, 40% and 46% respectively.

If the patient has had minimal (ISRT alone or one course of single- agent therapy including rituximab) or no prior chemotherapy, anthracycline-based chemotherapy with rituximab, with or without RT is included as a treatment option. Enrollment in clinical trial is recommended for all patients following initial therapy. Patients responding to initial treatment (with a PR or CR) could also be considered for consolidation therapy with HDT/ASCR or allogeneic HSCT. Alternatively, patients with CR to initial therapy may be observed and RIT may be considered for those with PR. Patients with no response or progressive disease following initial therapy should be treated with RIT, palliative therapy or best supportive care.

References

1. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 1997;89:3909-3918. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9166827.

2. Koster A, Tromp HA, Raemaekers JM, et al. The prognostic significance of the intra-follicular tumor cell proliferative rate in follicular lymphoma. Haematologica 2007;92:184-190. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17296567.

3. Wang SA, Wang L, Hochberg EP, et al. Low histologic grade follicular lymphoma with high proliferation index: morphologic and clinical features. Am J Surg Pathol 2005;29:1490-1496. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16224216.

4. Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood 2004;104:1258-1265. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15126323.

5. Friedberg JW, Taylor MD, Cerhan JR, et al. Follicular lymphoma in the United States: first report of the national LymphoCare study. J Clin Oncol 2009;27:1202-1208. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19204203.

6. Federico M, Bellei M, Marcheselli L, et al. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. J Clin Oncol 2009;27:4555-4562. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19652063.

7. Press OW, Unger JM, Rimsza LM, et al. Phase III randomized intergroup trial of CHOP plus rituximab compared with CHOP chemotherapy plus (131)iodine-tositumomab for previously untreated follicular non-Hodgkin lymphoma: SWOG S0016. J Clin Oncol 2013;31:314-320. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23233710.

8. Press OW, Unger JM, Rimsza LM, et al. A comparative analysis of prognostic factor models for follicular lymphoma based on a phase III trial of CHOP-rituximab versus CHOP + 131iodine--tositumomab. Clin Cancer Res 2013;19:6624-6632. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24130072.

9. Cong P, Raffeld M, Teruya-Feldstein J, et al. In situ localization of follicular lymphoma: description and analysis by laser capture microdissection. Blood 2002;99:3376-3382. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11964306.

10. Harris NL, Swerdlow SH, Jaffe ES, et al. Follicular lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:220-226.

11. Sotomayor EA, Shah IM, Sanger WG, Mark HF. In situ follicular lymphoma with a 14;18 translocation diagnosed by a multimodal approach. Exp Mol Pathol 2007;83:254-258. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17482162.

12. Carbone A, Gloghini A, Santoro A. In situ follicular lymphoma: pathologic characteristics and diagnostic features. Hematol Oncol 2012;30:1-7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21560142.

13. Henopp T, Quintanilla-Martinez L, Fend F, Adam P. Prevalence of follicular lymphoma in situ in consecutively analysed reactive lymph nodes. Histopathology 2011;59:139-142. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21771030.

14. Jegalian AG, Eberle FC, Pack SD, et al. Follicular lymphoma in situ: clinical implications and comparisons with partial involvement by follicular lymphoma. Blood 2011;118:2976-2984. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21768298.

15. Pillai RK, Surti U, Swerdlow SH. Follicular lymphoma-like B-cells of uncertain significance (in situ follicular lymphoma) may infrequently

progress, but precedes follicular lymphoma, is associated with other overt lymphomas and mimics follicular lymphoma in flow cytometric studies. Haematologica 2013;98:1571-1580. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23831923.

16. Bonzheim I, Salaverria I, Haake A, et al. A unique case of follicular lymphoma provides insights to the clonal evolution from follicular lymphoma in situ to manifest follicular lymphoma. Blood 2011;118:3442-3444. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21940830.

17. Frizzera G, Murphy SB. Follicular (nodular) lymphoma in childhood: a rare clinical-pathological entity. Report of eight cases from four cancer centers. Cancer 1979;44:2218-2235. Available at: http://www.ncbi.nlm.nih.gov/pubmed/389411.

18. Ribeiro RC, Pui CH, Murphy SB, et al. Childhood malignant non-Hodgkin lymphomas of uncommon histology. Leukemia 1992;6:761-765. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1640726.

19. Lorsbach RB, Shay-Seymore D, Moore J, et al. Clinicopathologic analysis of follicular lymphoma occurring in children. Blood 2002;99:1959-1964. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11877266.

20. Oschlies I, Salaverria I, Mahn F, et al. Pediatric follicular lymphoma--a clinico-pathological study of a population-based series of patients treated within the Non-Hodgkin's Lymphoma--Berlin-Frankfurt-Munster (NHL-BFM) multicenter trials. Haematologica 2010;95:253-259. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19679882.

21. Louissaint A, Jr., Ackerman AM, Dias-Santagata D, et al. Pediatric-type nodal follicular lymphoma: an indolent clonal proliferation in children and adults with high proliferation index and no BCL2 rearrangement. Blood 2012;120:2395-2404. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22855608.

22. Liu Q, Salaverria I, Pittaluga S, et al. Follicular lymphomas in children and young adults: a comparison of the pediatric variant with usual follicular lymphoma. Am J Surg Pathol 2013;37:333-343. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23108024.

23. Kumar R, Galardy PJ, Dogan A, et al. Rituximab in combination with multiagent chemotherapy for pediatric follicular lymphoma. Pediatr Blood Cancer 2011;57:317-320. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21462303.

24. Bain BJ. Bone marrow trephine biopsy. J Clin Pathol 2001;54:737-742. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11577117.

25. Bishop PW, McNally K, Harris M. Audit of bone marrow trephines. J Clin Pathol 1992;45:1105-1108. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1479037.

26. Schoder H, Noy A, Gonen M, et al. Intensity of 18fluorodeoxyglucose uptake in positron emission tomography distinguishes between indolent and aggressive non-Hodgkin's lymphoma. J Clin Oncol 2005;23:4643-4651. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15837966.

27. Campbell BA, Voss N, Woods R, et al. Long-term outcomes for patients with limited stage follicular lymphoma: involved regional radiotherapy versus involved node radiotherapy. Cancer 2010;116:3797-3806. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20564082.

28. Guadagnolo BA, Li S, Neuberg D, et al. Long-term outcome and mortality trends in early-stage, Grade 1-2 follicular lymphoma treated with radiation therapy. Int J Radiat Oncol Biol Phys 2006;64:928-934. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16243446.

29. Mac Manus MP, Hoppe RT. Is radiotherapy curative for stage I and II low-grade follicular lymphoma? Results of a long-term follow-up study of patients treated at Stanford University. J Clin Oncol

1996;14:1282-1290. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8648385.

30. Wilder RB, Jones D, Tucker SL, et al. Long-term results with radiotherapy for Stage I-II follicular lymphomas. Int J Radiat Oncol Biol Phys 2001;51:1219-1227. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11728680.

31. Advani R, Rosenberg S, Horning S. Stage I and II follicular non-Hodgkin's lymphoma: long-term follow-up of no initial therapy. J Clin Oncol 2004;22:1454-1459. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15024027.

32. McLaughlin P, Fuller L, Redman J, et al. Stage I-II low-grade lymphomas: a prospective trial of combination chemotherapy and radiotherapy. Ann Oncol 1991;2 Suppl 2:137-140. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1710918.

33. Yahalom J, Varsos G, Fuks Z, et al. Adjuvant cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy after radiation therapy in stage I low-grade and intermediate-grade non-Hodgkin lymphoma. Results of a prospective randomized study. Cancer 1993;71:2342-2350. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8453557.

34. Friedberg JW, Byrtek M, Link BK, et al. Effectiveness of first-line management strategies for stage I follicular lymphoma: analysis of the National LymphoCare Study. J Clin Oncol 2012;30:3368-3375. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22915662.

35. Michallet AS, Lebras LL, Bauwens DD, et al. Early stage follicular lymphoma: what is the clinical impact of the first-line treatment strategy? J Hematol Oncol 2013;6:45. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23816219.

36. Young RC, Longo DL, Glatstein E, et al. The treatment of indolent lymphomas: watchful waiting v aggressive combined modality treatment. Semin Hematol 1988;25:11-16. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2456618.

37. Brice P, Bastion Y, Lepage E, et al. Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 1997;15:1110-1117. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9060552.

38. Ardeshna KM, Smith P, Norton A, et al. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. Lancet 2003;362:516-522. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12932382.

39. Ardeshna K, Qian W, Smith P, et al. An Intergroup randomized trial of rituximab versus a watch and wait strategy in patients with stage II, III, IV, asymptomatic, non-bulky follicular lymphoma (grades 1, 2 and 3a). A preliminary analysis [abstract] Blood 2010;116:Abstact 6. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/6.

40. Kahl BS, Hong F, Williams ME, et al. Results of Eastern Cooperative Oncology Group Protocol E4402 (RESORT): A Randomized Phase III Study Comparing Two Different Rituximab Dosing Strategies for Low Tumor Burden Follicular Lymphoma [abstract]. Blood 2011;118:Abstract LBA-6. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/118/21/LBA-6 .

41. Solal-Celigny P, Bellei M, Marcheselli L, et al. Watchful waiting in low-tumor burden follicular lymphoma in the rituximab era: results of an F2-study database. J Clin Oncol 2012;30:3848-3853. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23008294.

42. Colombat P, Salles G, Brousse N, et al. Rituximab (anti-CD20 monoclonal antibody) as single first-line therapy for patients with

follicular lymphoma with a low tumor burden: clinical and molecular evaluation. Blood 2001;97:101-106. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11133748.

43. Witzig TE, Vukov AM, Habermann TM, et al. Rituximab therapy for patients with newly diagnosed, advanced-stage, follicular grade I non-Hodgkin's lymphoma: a phase II trial in the North Central Cancer Treatment Group. J Clin Oncol 2005;23:1103-1108. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15657404.

44. McLaughlin P, Grillo-Lopez AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol 1998;16:2825-2833. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9704735.

45. Czuczman MS, Grillo-Lopez AJ, White CA, et al. Treatment of patients with low-grade B-cell lymphoma with the combination of chimeric anti-CD20 monoclonal antibody and CHOP chemotherapy. J Clin Oncol 1999;17:268-276. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10458242.

46. Czuczman MS, Weaver R, Alkuzweny B, et al. Prolonged clinical and molecular remission in patients with low-grade or follicular non-Hodgkin's lymphoma treated with rituximab plus CHOP chemotherapy: 9-year follow-up. J Clin Oncol 2004;22:4711-4716. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15483015.

47. Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2005;106:3725-3732. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16123223.

48. Marcus R, Imrie K, Belch A, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood 2005;105:1417-1423. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15494430.

49. Marcus R, Imrie K, Solal-Celigny P, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J Clin Oncol 2008;26:4579-4586. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18662969.

50. Schulz H, Bohlius JF, Trelle S, et al. Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis. J Natl Cancer Inst 2007;99:706-714. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17470738.

51. Buske C, Kneba M, Lengfelder E, et al. Front - line combined immuno-chemotherapy (R-CHOP) significantly improves the time to treatment failure and overall survival in elderly patients with advanced stage follicular lymphoma - results of a prospective randomized trial of the german low grade lymphoma study group (GLSG) [abstract] Blood 2006;108:Abstract 482. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/108/11/482.

52. Czuczman MS, Koryzna A, Mohr A, et al. Rituximab in combination with fludarabine chemotherapy in low-grade or follicular lymphoma. J Clin Oncol 2005;23:694-704. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15681517.

53. Forstpointner R, Dreyling M, Repp R, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2004;104:3064-3071. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15284112.

54. McLaughlin P, Hagemeister FB, Rodriguez MA, et al. Safety of fludarabine, mitoxantrone, and dexamethasone combined with rituximab in the treatment of stage IV indolent lymphoma. Semin Oncol 2000;27:37-41. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11225999.

55. Zinzani PL, Pulsoni A, Perrotti A, et al. Fludarabine plus mitoxantrone with and without rituximab versus CHOP with and without rituximab as front-line treatment for patients with follicular lymphoma. J Clin Oncol 2004;22:2654-2661. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15159414.

56. Liu Q, Fayad L, Cabanillas F, et al. Improvement of overall and failure-free survival in stage IV follicular lymphoma: 25 years of treatment experience at The University of Texas M.D. Anderson Cancer Center. J Clin Oncol 2006;24:1582-1589. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16575009.

57. Morschhauser F, Mounier N, Sebban C, et al. Efficacy and safety of the combination of rituximab, fludarabine, and mitoxantrone for rituximab-naive, recurrent/refractory follicular non-Hodgkin lymphoma with high tumor burden: a multicenter phase 2 trial by the Groupe d'Etude des Lymphomes de l'Adulte (GELA) and Groupe Ouest Est des Leucemies et Autres Maladies du Sang (GOELAMS). Cancer 2010;116:4299-4308. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20549824.

58. Nastoupil L, Sinha R, Byrtek M, et al. A Comparison of the Effectiveness of First-Line Chemoimmunotherapy Regimens for Follicular Lymphoma (FL) Used in the United States [abstract]. Blood 2011;118:Abstract 97. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/118/21/97.

59. Federico M, Luminari S, Dondi A, et al. R-CVP Versus R-CHOP Versus R-FM for the Initial Treatment of Patients With Advanced-Stage Follicular Lymphoma: Results of the FOLL05 Trial Conducted by the Fondazione Italiana Linfomi. J Clin Oncol 2013;31:1506-1513. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23530110.

60. Kalaycio M, Rybicki L, Pohlman B, et al. Risk factors before autologous stem-cell transplantation for lymphoma predict for secondary myelodysplasia and acute myelogenous leukemia. J Clin Oncol 2006;24:3604-3610. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16877727.

61. Ketterer N, Salles G, Moullet I, et al. Factors associated with successful mobilization of peripheral blood progenitor cells in 200 patients with lymphoid malignancies. Br J Haematol 1998;103:235-242. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9792315.

62. Micallef IN, Apostolidis J, Rohatiner AZ, et al. Factors which predict unsuccessful mobilisation of peripheral blood progenitor cells following G-CSF alone in patients with non-Hodgkin's lymphoma. Hematol J 2000;1:367-373. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11920216.

63. Fowler N, Kahl BS, Lee P, et al. Bortezomib, Bendamustine, and Rituximab in Patients With Relapsed or Refractory Follicular Lymphoma: The Phase II VERTICAL Study. J Clin Oncol 2011;29:3389-3395. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21810687.

64. Friedberg JW, Vose JM, Kelly JL, et al. The combination of bendamustine, bortezomib, and rituximab for patients with relapsed/refractory indolent and mantle cell non-Hodgkin lymphoma. Blood 2011;117:2807-2812. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21239695.

65. Friedberg JW, Cohen P, Chen L, et al. Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin's lymphoma: results from a phase II multicenter, single-agent study. J Clin Oncol 2008;26:204-210. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18182663.

66. Kahl BS, Bartlett NL, Leonard JP, et al. Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin

lymphoma: results from a multicenter study. Cancer 2010;116:106-114. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19890959.

67. Robinson KS, Williams ME, van der Jagt RH, et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma. J Clin Oncol 2008;26:4473-4479. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18626004.

68. Rummel MJ, Kaiser U, Balser C, et al. Bendamustine plus rituximab versus fludarabine plus rituximab in patients with relapsed follicular, indolent and mantle cell lymphomas - final results of the randomized phase III study NHL 2-2003 on behalf of the StiL (Study Group Indolent Lymphomas, Germany) [abstract]. Blood 2010;116:Abstract 856. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/856.

69. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet 2013;381:1203-1210. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23433739.

70. Flinn IW, Van der Jagt RH, Kahl BS, et al. An Open-Label, Randomized Study of Bendamustine and Rituximab (BR) Compared with Rituximab, Cyclophosphamide, Vincristine, and Prednisone (R-CVP) or Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) in First-Line Treatment of Patients with Advanced Indolent Non-Hodgkin's Lymphoma (NHL) or Mantle Cell Lymphoma (MCL): The Bright Study [abstract]. Blood 2012;120:Abstract 902. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/120/21/902.

71. Witzig TE, Wiernik PH, Moore T, et al. Lenalidomide oral monotherapy produces durable responses in relapsed or refractory indolent non-Hodgkin's Lymphoma. J Clin Oncol 2009;27:5404-5409. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19805688.

72. Leonard J, Jung S-H, Johnson JL, et al. CALGB 50401: A randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma [abstract]. J Clin Oncol 2012;30:Abstract 8000. Available at: http://meeting.ascopubs.org/cgi/content/abstract/30/15_suppl/8000.

73. Fowler NH, Neelapu SS, Hagemeister FB, et al. Lenalidomide and Rituximab for Untreated Indolent Lymphoma: Final Results of a Phase II Study [abstract]. Blood 2012;120:Abstract 901. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/120/21/901.

74. Witzig TE, Flinn IW, Gordon LI, et al. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. J Clin Oncol 2002;20:3262-3269. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12149300.

75. Witzig TE, Gordon LI, Cabanillas F, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol 2002;20:2453-2463. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12011122.

76. Gordon LI, Witzig T, Molina A, et al. Yttrium 90-labeled ibritumomab tiuxetan radioimmunotherapy produces high response rates and durable remissions in patients with previously treated B-cell lymphoma. Clin Lymphoma 2004;5:98-101. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15453924.

77. Scholz CW, Pinto A, Linkesch W, et al. 90Yttrium ibritumomab tiuxetan as first line treatment for follicular lymphoma. first results from an international phase II clinical trial [abstract]. Blood 2010;116:Abstract 593. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/593.

78. Scholz CW, Pinto A, Linkesch W, et al. (90)Yttrium-ibritumomab-tiuxetan as first-line treatment for follicular lymphoma: 30 months of follow-up data from an international

multicenter phase II clinical trial. J Clin Oncol 2013;31:308-313. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23233718.

79. Kaminski MS, Tuck M, Estes J, et al. 131I-tositumomab therapy as initial treatment for follicular lymphoma. N Engl J Med 2005;352:441-449. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15689582.

80. Vose JM, Wahl RL, Saleh M, et al. Multicenter phase II study of iodine-131 tositumomab for chemotherapy-relapsed/refractory low-grade and transformed low-grade B-cell non-Hodgkin's lymphomas. J Clin Oncol 2000;18:1316-1323. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10715303.

81. Kaminski MS, Zelenetz AD, Press OW, et al. Pivotal study of iodine I 131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. J Clin Oncol 2001;19:3918-3328. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11579112.

82. Horning SJ, Younes A, Jain V, et al. Efficacy and safety of tositumomab and iodine-131 tositumomab (Bexxar) in B-cell lymphoma, progressive after rituximab. J Clin Oncol 2005;23:712-719. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15613695.

83. Kaminski MS, Tuck M, Estes J, et al. Tositumomab and iodine I-131 tositumomab for previously untreated, advanced-stage, follicular lymphoma: median 10 year follow-up results [abstract]. Blood 2009;114:Abstract 3759. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/114/22/3759.

84. Kaminski MS, Zelenetz AD, Press OW, et al. Tositumomab and I 131 Tositumomab achieves complete remissions lasting > 10 years in patients with chemotherapy-refractory low-grade and transformed B-cell lymphomas [abstract]. Blood 2010;116:Abstract 3960. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/3960.

85. Pauls SD, Lafarge ST, Landego I, et al. The phosphoinositide 3-kinase signaling pathway in normal and malignant B cells: activation mechanisms, regulation and impact on cellular functions. Front Immunol 2012;3:224. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22908014.

86. Lannutti BJ, Meadows SA, Herman SE, et al. CAL-101, a p110delta selective phosphatidylinositol-3-kinase inhibitor for the treatment of B-cell malignancies, inhibits PI3K signaling and cellular viability. Blood 2011;117:591-594. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20959606.

87. Gopal AK, Kahl BS, de Vos S, et al. PI3Kdelta inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med 2014;370:1008-1018. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24450858.

88. Full prescribing information for idelalisib. 2014 Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206545lbl.pdf.

89. Hainsworth JD, Spigel DR, Markus TM, et al. Rituximab plus short-duration chemotherapy followed by Yttrium-90 Ibritumomab tiuxetan as first-line treatment for patients with follicular non-Hodgkin lymphoma: a phase II trial of the Sarah Cannon Oncology Research Consortium. Clin Lymphoma Myeloma 2009;9:223-228. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19525191.

90. Jacobs SA, Swerdlow SH, Kant J, et al. Phase II trial of short-course CHOP-R followed by 90Y-ibritumomab tiuxetan and extended rituximab in previously untreated follicular lymphoma. Clin Cancer Res 2008;14:7088-7094. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18981007.

91. Morschhauser F, Radford J, Van Hoof A, et al. Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular

lymphoma. J Clin Oncol 2008;26:5156-5164. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18854568.

92. Zinzani PL, Tani M, Pulsoni A, et al. Fludarabine and mitoxantrone followed by yttrium-90 ibritumomab tiuxetan in previously untreated patients with follicular non-Hodgkin lymphoma trial: a phase II non-randomised trial (FLUMIZ). Lancet Oncol 2008;9:352-358. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18342572.

93. Leonard JP, Coleman M, Kostakoglu L, et al. Abbreviated chemotherapy with fludarabine followed by tositumomab and iodine I 131 tositumomab for untreated follicular lymphoma. J Clin Oncol 2005;23:5696-5704. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16110029.

94. Press OW, Unger JM, Braziel RM, et al. Phase II trial of CHOP chemotherapy followed by tositumomab/iodine I-131 tositumomab for previously untreated follicular non-Hodgkin's lymphoma: five-year follow-up of Southwest Oncology Group Protocol S9911. J Clin Oncol 2006;24:4143-4149. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16896003.

95. Press OW, Unger JM, Braziel RM, et al. A phase 2 trial of CHOP chemotherapy followed by tositumomab/iodine I 131 tositumomab for previously untreated follicular non-Hodgkin lymphoma: Southwest Oncology Group Protocol S9911. Blood 2003;102:1606-1612. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12738671.

96. Link BK, Martin P, Kaminski MS, et al. Cyclophosphamide, vincristine, and prednisone followed by tositumomab and iodine-131-tositumomab in patients with untreated low-grade follicular lymphoma: eight-year follow-up of a multicenter phase II study. J Clin Oncol 2010;28:3035-3041. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20458031.

97. Morschhauser F, Radford J, Van Hoof A, et al. 90Yttrium-Ibritumomab Tiuxetan Consolidation of First Remission in Advanced-Stage Follicular Non-Hodgkin Lymphoma: Updated Results After a Median Follow-Up of 7.3 Years From the International, Randomized, Phase III First-Line Indolent Trial. J Clin Oncol 2013;31:1977-1983. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23547079.

98. Ghielmini M, Schmitz SH, Cogliatti SB, et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule. Blood 2004;103:4416-4423. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14976046.

99. Martinelli G, Hsu Schmitz SF, Utiger U, et al. Long-term follow-up of patients with follicular lymphoma receiving single-agent rituximab at two different schedules in trial SAKK 35/98. J Clin Oncol 2010;28:4480-4484. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20697092.

100. Taverna CJ, Bassi S, Hitz F, et al. Rituximab maintenance treatment for a maximum of 5 years in follicular lymphoma: safety analysis of the randomized phase III trial SAKK 35/03. Blood 2010;116:1802. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/1802.

101. Hainsworth JD, Litchy S, Shaffer DW, et al. Maximizing therapeutic benefit of rituximab: maintenance therapy versus re-treatment at progression in patients with indolent non-Hodgkin's lymphoma--a randomized phase II trial of the Minnie Pearl Cancer Research Network. J Clin Oncol 2005;23:1088-1095. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15657401.

102. Hochster H, Weller E, Gascoyne RD, et al. Maintenance rituximab after cyclophosphamide, vincristine, and prednisone prolongs progression-free survival in advanced indolent lymphoma: results of the randomized phase III ECOG1496 Study. J Clin Oncol 2009;27:1607-1614. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19255334.

103. Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. Lancet 2011;377:42-51. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21176949.

104. Forstpointner R, Unterhalt M, Dreyling M, et al. Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG). Blood 2006;108:4003-4008. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16946304.

105. van Oers MHJ, Klasa R, Marcus RE, et al. Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: results of a prospective randomized phase 3 intergroup trial. Blood 2006;108:3295-3301. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16873669.

106. van Oers MHJ, Van Glabbeke M, Giurgea L, et al. Rituximab maintenance treatment of relapsed/resistant follicular non-Hodgkin's lymphoma: long-term outcome of the EORTC 20981 phase III randomized intergroup study. J Clin Oncol 2010;28:2853-2858. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20439641.

107. Freedman AS, Neuberg D, Mauch P, et al. Long-term follow-up of autologous bone marrow transplantation in patients with relapsed follicular lymphoma. Blood 1999;94:3325-3333. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10552941.

108. Rohatiner AZS, Nadler L, Davies AJ, et al. Myeloablative therapy with autologous bone marrow transplantation for follicular lymphoma at the time of second or subsequent remission: long-term follow-up. J Clin Oncol 2007;25:2554-2559. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17515573.

109. Schouten HC, Qian W, Kvaloy S, et al. High-dose therapy improves progression-free survival and survival in relapsed follicular non-Hodgkin's lymphoma: results from the randomized European CUP trial. J Clin Oncol 2003;21:3918-3927. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14517188.

110. Sebban C, Brice P, Delarue R, et al. Impact of rituximab and/or high-dose therapy with autotransplant at time of relapse in patients with follicular lymphoma: a GELA study. J Clin Oncol 2008;26:3614-3620. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18559872.

111. Peniket AJ, Ruiz de Elvira MC, Taghipour G, et al. An EBMT registry matched study of allogeneic stem cell transplants for lymphoma: allogeneic transplantation is associated with a lower relapse rate but a higher procedure-related mortality rate than autologous transplantation. Bone Marrow Transplant 2003;31:667-678. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12692607.

112. van Besien K, Loberiza FR, Bajorunaite R, et al. Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. Blood 2003;102:3521-3529. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12893748.

113. Hari P, Carreras J, Zhang M-J, et al. Allogeneic transplants in follicular lymphoma: higher risk of disease progression after reduced-intensity compared to myeloablative conditioning. Biol Blood Marrow Transplant 2008;14:236-245. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18215784.

114. Bishu S, Quigley JM, Bishu SR, et al. Predictive value and diagnostic accuracy of F-18-fluoro-deoxy-glucose positron emission tomography treated grade 1 and 2 follicular lymphoma. Leuk Lymphoma 2007;48:1548-1555. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17701586.

115. Blum RH, Seymour JF, Wirth A, et al. Frequent impact of [18F]fluorodeoxyglucose positron emission tomography on the staging and management of patients with indolent non-Hodgkin's lymphoma.

Clin Lymphoma 2003;4:43-49. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12837154.

116. Karam M, Novak L, Cyriac J, et al. Role of fluorine-18 fluoro-deoxyglucose positron emission tomography scan in the evaluation and follow-up of patients with low-grade lymphomas. Cancer 2006;107:175-183. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16721817.

117. Wohrer S, Jaeger U, Kletter K, et al. 18F-fluoro-deoxy-glucose positron emission tomography (18F-FDG-PET) visualizes follicular lymphoma irrespective of grading. Ann Oncol 2006;17:780-784. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16497824.

118. Janikova A, Bolcak K, Pavlik T, et al. Value of [18F]fluorodeoxyglucose positron emission tomography in the management of follicular lymphoma: the end of a dilemma? Clin Lymphoma Myeloma 2008;8:287-293. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18854283.

119. Zinzani PL, Musuraca G, Alinari L, et al. Predictive role of positron emission tomography in the outcome of patients with follicular lymphoma. Clin Lymphoma Myeloma 2007;7:291-295. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17324337.

120. Le Dortz L, De Guibert S, Bayat S, et al. Diagnostic and prognostic impact of 18F-FDG PET/CT in follicular lymphoma. Eur J Nucl Med Mol Imaging 2010;37:2307-2314. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20717826.

121. Trotman J, Fournier M, Lamy T, et al. Positron emission tomography-computed tomography (PET-CT) after induction therapy is highly predictive of patient outcome in follicular lymphoma: analysis of PET-CT in a subset of PRIMA trial participants. J Clin Oncol 2011;29:3194-3200. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21747087.

122. Dupuis J, Berriolo-Riedinger A, Julian A, et al. Impact of [18F]Fluorodeoxyglucose Positron Emission Tomography Response Evaluation in Patients With High-Tumor Burden Follicular Lymphoma Treated With Immunochemotherapy: A Prospective Study From the Groupe d'Etudes des Lymphomes de l'Adulte and GOELAMS. J Clin Oncol 2012;30:4317-4322. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23109699.

123. Noy A, Schoder H, Gonen M, et al. The majority of transformed lymphomas have high standardized uptake values (SUVs) on positron emission tomography (PET) scanning similar to diffuse large B-cell lymphoma (DLBCL). Ann Oncol 2009;20:508-512. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19139176.

124. Oh YK, Ha CS, Samuels BI, et al. Stages I-III follicular lymphoma: role of CT of the abdomen and pelvis in follow-up studies. Radiology 1999;210:483-486. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10207433.

125. Zinzani PL, Stefoni V, Tani M, et al. Role of [18F]fluorodeoxyglucose positron emission tomography scan in the follow-up of lymphoma. J Clin Oncol 2009;27:1781-1787. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19273712.

126. Peterson BA, Petroni GR, Frizzera G, et al. Prolonged single-agent versus combination chemotherapy in indolent follicular lymphomas: a study of the cancer and leukemia group B. J Clin Oncol 2003;21:5-15. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12506163.

127. Al-Tourah AJ, Gill KK, Chhanabhai M, et al. Population-based analysis of incidence and outcome of transformed non-Hodgkin's lymphoma. J Clin Oncol 2008;26:5165-5169. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18838711.

128. Yuen AR, Kamel OW, Halpern J, Horning SJ. Long-term survival after histologic transformation of low-grade follicular lymphoma. J Clin Oncol 1995;13:1726-1733. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7602362.

129. Villa D, Crump M, Panzarella T, et al. Autologous and allogeneic stem-cell transplantation for transformed follicular lymphoma: a report of the Canadian blood and marrow transplant group. J Clin Oncol 2013;31:1164-1171. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23401459.

This discussion is being updated to correspond with the newly updated algorithm. Last updated 10/28/2014.

Marginal Zone Lymphomas

Marginal zone lymphomas (MZLs) are a group of B-cell malignancies thought to originate from B lymphocytes that are normally present in the marginal zone of lymphoid follicles that can be found in the spleen, lymph nodes, and mucosal lymphoid tissues.[1,2] Three distinct subtypes of MZLs exist, which include extranodal MZL of mucosa-associated lymphoid tissue (MALT lymphoma), nodal MZL, and splenic MZL.[3-5] MZLs comprise about 10% of all non-Hodgkin's lymphomas (NHLs), with MALT lymphomas being the most common subtype (occurring in 7-8% of NHLs); nodal MZLs occur in <2% and splenic MZLs in <1% of NHLs.[6] Recent analysis from the SEER database suggested that survival outcomes were more favorable for patients with MALT lymphoma (5-year relative survival 89%) compared with those with splenic MZL (80%) or nodal MZL (76.5%).[7]

The etiology of MZLs has been associated with chronic immune stimulation due to infectious pathogens or inflammation; infection with *Helicobacter pylori (H. Pylori)* has been implicated in cases of gastric MALT lymphoma, and other pathogens such as *Chlamydia psittaci, Campylobacter jejuni, Borrelia burgdorferi*, and hepatitis C virus (HCV) have also been implicated in the putative pathogenesis of MZLs.[1,4] Positive HCV serology has been associated with MZLs (primarily splenic MZL) in about 30% of cases.[8,9] In addition, HCV positivity has also been reported in about 35% of patients with non-gastric MALT lymphomas.[10]

Since MZL are also characterized by clinical and pathological features that overlap with Waldenström's Macroglobulinemia/lymphoplasmacytic lymphoma (WM/LPL), it can be difficult to distinguish WM/LPL from MZLs in selected circumstances.[11] Recent studies have confirmed that the MYD88 L265P somatic mutation which is widely prevalent in patients with WM/LPL could be useful in differentiating WM/LPL from other B-cell malignancies with overlapping clinical and pathological features.[12-14] In a retrospective study that analyzed the immunoglobulin heavy chain variable (*IGHV*) gene sequences and MYD88 mutation status in a series of 123 patients with a diagnosis of MZLs and WM/LPL, MYD88 mutation was found in 67% of patients with WM/LPL (18 of 27) compared to 4% of patients with splenic MZLs (2 out of 53), 7% of patients with MALT lymphomas (2 out of 28) and 0% of patients with nodal MZLs.[13] *IGHV* analysis clearly distinguished splenic MZLs and WM/LPL. Splenic MZLs were characterized by overrepresentation of *IGHV1-2* gene rearrangements with low or intermediate mutation rates whereas WM/LPL was associated with overrepresentation of *IGHV3-23* rearrangements and high mutation rates.[13] In selected circumstances when plasmacytic differentiation is present, MYD88 mutational analysis should be considered to differentiate MZLs from WM/LPL.

The following sections provide a brief summary of the diagnosis, workup, and treatment recommendations for the three subtypes of MZL: MALT lymphomas (gastric and non-gastric), nodal MZL, and splenic MZL.

MALT Lymphomas

In MALT lymphomas, the gastrointestinal (GI) tract is the most common site of involvement (about 50% of MALT lymphomas) and within the GI tract, the stomach is the most common primary site (80-80% of gastric MALT lymphomas).[4,15,16] Common non-gastric sites of involvement in MALT lymphomas include the orbit (7-12%), lung (8-14%), and skin (9-12%).[15-17] MALT lymphomas tend to be indolent, with similar long-term outcomes reported between gastric and non-gastric subtypes.

In a retrospective analysis of data from patients with MALT lymphomas (N=108), the 10-year overall survival (OS) was not different between patients with gastric MALT lymphoma and non-gastric lymphoma (75% vs. 77%).[16] However, in this analysis, gastric MALT lymphoma was associated with longer time to progression (TTP) from start of treatment than non-gastric presentations (median TTP 8.9 years vs. 4.9 years; *P*=0.01).[16] In a more recent retrospective study in patients with MALT lymphomas (N=98), gastric MALT lymphoma was associated with higher 3-year progression-free survival (PFS) compared with non-gastric cases (95% vs. 82%).[18] In another retrospective study of patients with non-gastric MALT lymphomas (N=180), the 5-year progression-free survival (PFS) and OS was 60% and 90%, respectively.[17] Although disease is localized in most patients with MALT lymphomas, about a third of patients present with disseminated disease; localized disease is more frequently observed with gastric MALT lymphomas than with non-gastric cases.[17,19] Bone marrow involvement has been reported in about 15 to 20% of MALT lymphomas.[15,17,19] In a retrospective analysis of patients with MALT lymphomas (N=158), similar long-term survival was observed between patients with disseminated and localized disease (10-year OS rate 80% in both cases).[19] Recent retrospective data, however, reported decreased PFS outcomes in patients with advanced MALT lymphomas compared with localized disease (3-year PFS rate 73% vs. 94%).[18]

A variety of chromosomal translocations have been implicated in the pathogenesis of MALT lymphomas.[20] t(11;18) is the most common translocation resulting in the formation of the chimeric fusion gene, *API2-MALT1* and is frequently detected in gastric and pulmonary MALT lymphomas.[21,22] t(1;14) results in the overexpression of BCL10 protein and it occurs in 1% to 2% of MALT lymphomas.[23] This translocation has been detected in MALT lymphomas of the stomach, lung and skin. Both t(11;18) and BCL10 overexpression are associated with locally advanced disease, which is less likely to respond to *H. Pylori* eradication with antibiotic therapy.[24] t(14;18) results in the deregulated expression of *MALT1* gene and has been reported to occur in 15% to 20% of MALT lymphomas.[22,25] It is most frequently detected in MALT lymphomas of the liver, skin, ocular adnexa and the salivary gland. t(3;14) results in the upregulation of *FOXP1* gene and is associated with the MALT lymphomas of thyroid, ocular adnexa and skin.[26] The clinical significance of t(14;18) and t (3;14) is unknown.

Gastric MALT Lymphoma

Diagnosis

Common clinical features of gastric MALT lymphoma include symptoms of dyspepsia, reflux, abdominal pain, nausea, or weight loss.[1] An endoscopic biopsy is required to establish the diagnosis of gastric MALT lymphoma, as a fine-needle aspiration is not adequate for diagnosis. Endoscopy may reveal erythema, erosions or ulcerations.[1] Adequate hematopathology review of biopsy material and immunophenotyping are needed to establish a diagnosis. The recommended markers for an immunohistochemistry (IHC) panel includes CD20, CD3, CD5, CD10, CD21 or CD23, kappa/lambda, CCND1, BCL2, and BCL6; the recommended markers for flow cytometry analysis include CD19, CD20, CD5, CD23, and CD10. The typical immunophenotype for MALT lymphoma is CD5-, CD10-, CD20+, CD23-/+, CD43 -/+, cyclin D1-, and BCL2 follicles-.

H. pylori infection has a critical role in the pathogenesis of gastric MALT lymphomas and its eradication can lead to tumor remission.[1,27,28] Therefore, staining for detection of *H. pylori* should be performed. However, *H. Pylori* infection is not evident in approximately 5-10% of patients with gastric MALT lymphomas and the translocation t(11;18)

was reported to occur at a high frequency in *H. pylori*-negative patients with gastric MALT lymphomas.[29] This chromosomal abnormality has been associated with disseminated disease and resistance to antibiotic treatment in patients with gastric MALT lymphoma.[30,31] Molecular analysis by PCR or FISH for the evaluation of t(11;18) is recommended. In some cases, molecular analysis for the detection of antigen receptor gene rearrangements and cytogenetic or FISH evaluation for t(3;14), t(1;14) and t(14;18), may also be useful.

Workup

The initial workup for patients with gastric MALT lymphoma is similar to the workup for other NHLs. A comprehensive physical examination should be performed with attention to non-gastric sites such as the eyes and skin, and performance status should be assessed. Laboratory evaluations should include a complete blood count with differentials and platelets, comprehensive metabolic panel, and measurement of serum LDH levels. Evaluation of bone marrow biopsy, with or without aspirates, may be useful under certain circumstances. Special aspects of the workup for gastric MALT lymphoma include direct endoscopic assessment of the GI tract and additional evaluation of the tumor specimen for the presence of *H.pylori.* If the *H.pylori* infection status is negative based on histopathology evaluation, other non-invasive testing methods may be employed to confirm negative status (i.e., stool antigen test, urea breath test, or blood antibody test) or to establish non-invasive surrogates for upper GI endoscopy. Non-diagnostic atypical lymphoid infiltrates that are *H.pylori* positive should be re-biopsied to confirm or exclude lymphoma prior to treatment of *H.pylori*. Testing for HBV is indicated for patients being considered for treatment with rituximab-containing regimens due to the risk of viral reactivation. Testing for HCV may be useful in selected cases, and given its association with other MZLs and demonstrated importance as a therapeutic target, HCV testing should be performed.

Appropriate imaging studies include CT scan with contrast of diagnostic quality for the chest, abdomen and pelvis. At some NCCN institutions, endoscopic ultrasound (EUS) is used to complement conventional endoscopy at the time of the initial workup and at follow-up. EUS also provides information regarding the depth of involvement in the gastric wall which provides essential information for some of the currently used staging systems; it also helps to distinguish benign lymphoid aggregates from lymphoma associated with *H. pylori* infection.[32] In addition, EUS staging is also useful in predicting the efficacy of *H. Pylori* eradication therapy.[33,34] EUS with multiple biopsies of anatomic sites is particularly useful for H. pylori-positive patients because the likelihood of tumor response to antibiotic therapy is related to depth of tumor invasion. A MUGA scan/echocardiogram should be performed if the patient is being considered for treatment with regimens containing anthracycline or anthracenedione.

Staging can remain a challenge, as it is not standardized for MALT lymphomas; because CT scans may not be optimal for the detection of occult extranodal disease, it is unknown whether staging for MALT lymphomas should follow standard staging systems (e.g., Ann Arbor system) used for nodal-type lymphomas.[1,2] Several different staging systems have been used for gastric MALT lymphomas. The widely used Lugano Staging System for GI lymphomas is a modification of the original Ann Arbor stating system.[35] In the Lugano Staging, stage I refers to disease confined to the GI tract (single primary or multiple non-contiguous lesions; in Stage I_1, the infiltration is limited to mucosa with or without submucosa involvement, and in Stage I_2, infiltration is present in the muscularis propria, serosa or both. Stage II refers to disease extending into the abdomen from the primary GI site; in Stage

II_1, local (perigastric) lymph nodes are involved, and in Stage II_2, distant lymph nodes are involved. Stage IIE refers to lymphoma penetration of serosa to involve adjacent organs or tissues; if both the lymph nodes and adjacent organs are involved, the above subscripts (1 or 2) for lymph node involvement may be added to the designation. Ann Arbor stage III has been removed, and stage IV in the Lugano Staging refers to disseminated extranodal involvement or concomitant supradiaphragmatic nodal involvement. The TNM staging system corresponds to the staging in gastric cancer and the depth of the lymphoma infiltration is measured by EUS. Involvement of multiple extranodal sites in MALT lymphoma appears to be biologically distinct from multiple extranodal involvements in other lymphomas, and these patients may be managed by treating each site separately with excision or RT or with rituximab. By contrast, cases with disseminated nodal involvement appear to behave more like nodal MZL or like disseminated follicular lymphoma (FL).

Treatment Options Based on Clinical Stage

The treatment approach for gastric MALT lymphomas depends on the *H. pylori* infection status and disease stage. *H.pylori* infection plays a central role in the pathogenesis of some cases of gastric MALT lymphoma. The efficacy of antibiotic therapy for the treatment for gastric MALT lymphoma has been evaluated in a number of retrospective and prospective studies.[36-43] In these studies, *H.pylori* eradication with antibiotic therapy resulted in lymphoma regression in 70-95% of patients with localized disease. In studies with long-term follow up, the 5-year OS rate with *H.pylori* eradication therapy was 90-95%, with a 5-year disease-free survival (DFS) or event-free survival (EFS) rate of 75-80%.[38,40,42] However, there is increasing evidence that late relapses can occur after antibiotic treatment and a long duration of follow-up is appropriate. If there is evidence of t(11;18), t(1;14) or t(14;18), treatment of the *H.pylori* infection with antibiotics may be ineffective; these patients should be considered for alternative therapy, though a trial of antibiotics is still warranted in some patients.[30] *H.pylori* eradication therapy generally comprises a proton pump inhibitor (e.g., omeprazole or other agents such as lansoprazole or rabeprazole) along with a combination of antibiotics including clarithromycin and amoxicillin (or metronidazole for patients allergic to penicillin).[1]

Radiation therapy (RT) has been evaluated in patients with both gastric and non-gastric MALT lymphomas. In a retrospective study of patients who received treatment for localized MALT lymphomas (N=103; lymphoma of the stomach, n=17), the CR rate was 99% in the group of patients treated with involved field RT (IFRT; dose range 30-35 Gy) only (n=85).[44] The 5-year DFS and OS rates were 77% and 98%, respectively. The median follow up for patients treated with RT alone was 4.9 years. Among the patients with gastric MALT lymphoma or primary involvement of the thyroid, none had relapsed at the time of last follow up (failure-free survival rate 100%).[44] Long-term outcomes from this study with a median follow up of 7 years showed that patients with localized MALT lymphoma who received IFRT alone (n=144; dose range 25-35 Gy) had an estimated 10-year relapse-free rate and OS rate of 74% and 89%, respectively.[45] The estimated 10-year cancer-specific OS rate was 98%. Similar to the previous report,[44] outcomes were more favorable for patients with gastric or thyroid MALT lymphoma (n=46); the 10-year relapse-free rate for these patients was 89% compared with 68% for patients with lymphomas in other sites (*P*=0.004).[45]

In another retrospective study in patients with localized gastric MALT lymphoma (N=115), initial therapy with RT alone (n=56) resulted in a CR rate of 96% and a 10-year cancer-specific OS rate of 94%.[46] Several studies suggested that RT may preclude the need for surgical

resection and that surgery does not offer an advantage over other treatment modalities. In the randomized controlled study in patients with localized gastric MALT lymphomas (N=241), the 10-year EFS rates for the groups randomized to treatment with surgery (n=80), RT (n=78), and chemotherapy (n=83) were 52%, 52%, and 87%, respectively (P<0.01).[47] The median follow up in this study was 7.5 years. The 10-year OS rate was not significantly different between the groups treated with surgery, RT or chemotherapy (80% vs. 75% vs. 87%, respectively).[47] In an analysis of registry data from a German multicenter study in patients with localized gastric lymphomas, outcomes were compared between patients treated with RT alone and those treated with combined surgery and RT.[48] In the subgroup of patients with indolent gastric lymphomas (gastric MALT lymphomas, n=151), extended field RT (total dose 30 Gy followed by 10 Gy boost) alone resulted in an EFS and OS rate of 88% and 93%, respectively, after a median of 42 months of observation. These outcomes were not significantly different from those of patients with gastric MALT lymphomas who received combined modality therapy with surgery and RT (EFS and OS rates 72% and 82.5%, respectively).[48] This study had also included patients with gastric MALT lymphomas who experienced treatment failure with *H. pylori* eradication therapy. In a small study that evaluated RT alone (median total dose 30 Gy; range, 28.5-43.5 Gy) in patients with gastric MALT lymphoma without evidence of *H. pylori* or with persistent disease after *H. pylori* eradication therapy (N=17), the CR rate was 100% and the EFS rate was 100% after a median follow up of 27 months.[49] Long-term follow up data from other studies suggest that RT is an effective treatment modality in gastric MALT lymphoma after failure with *H. pylori* eradication therapy.[42,46] In the subgroup of patients with gastric MALT lymphomas who were unresponsive to *H. pylori* eradication therapy and underwent second-line therapy with RT (n=10) or single-agent chemotherapy with cyclophosphamide (n=12), the CR rate was 80% and 83%, respectively; the estimated 3-year OS (from start of second-line therapy) was 90% and 88%, respectively.[42] In a retrospective analysis of data from patients who received RT following treatment failure with *H. pylori* eradication therapy (n=35), the CR rate was 89% and the 5-year cause-specific OS rate was 93%.[46]

Immunotherapy with the anti-CD20 monoclonal antibody rituximab has also been evaluated in the clinical setting of failure with *H. pylori* eradication therapy. A prospective study evaluated the activity of standard-dose rituximab in patients with gastric MALT lymphoma (N=27) relapsed/refractory to *H. pylori* eradication therapy or not eligible for eradication therapy (i.e., *H. pylori* negative disease).[50] The majority of patients (81%) had stage I or II_1 disease (Lugano Staging System). The ORR with rituximab was 77% with a CR rate of 46%; at a median follow up of 28 months from start of treatment, all patients were alive and 54% of patients were disease free.[50]

Chemotherapy (single agent or combination regimens) has been evaluated in patients with MALT lymphomas. In an early study of single-agent therapy with the alkylating agents chlorambucil or cyclophosphamide (given orally for 12-24 months) in patients with primarily gastric MALT lymphoma (N=24; advanced stage, n=7), CR was achieved in 75% of patients.[51] In a prospective study that evaluated the purine analog cladribine in patients with MALT lymphoma (N=27; gastric lymphoma, n=19), CR was achieved in 84% of patients.[52] Patients with *H. pylori* positive localized gastric disease underwent eradication therapy and were only enrolled if unresponsive to *H. pylori* eradication treatment. All patients with gastric MALT lymphoma treated with cladribine (n=18) achieved a CR whereas only 43% with non-gastric lymphoma achieved a CR. At a median follow up of 80 months, 84% of patients remained alive.[53] DFS at 6.7 years was 68.5% for all patients, and was higher for patients with gastric MALT lymphoma

compared with those with extra-gastric lymphoma (78.5% vs. 33%).[53] Combination chemotherapy with mitoxantrone, chlorambucil and prednisone (MCP) was retrospectively evaluated in patients with primarily advanced MALT lymphoma (N=15; gastric lymphoma, n=5 only).[54] Among the 5 patients with gastric MALT lymphoma (all were stage I or II), the MCP regimen induced a response in all patients, including a CR in 3 patients who had failed prior *H. pylori* eradication therapy, and a CR in 1 patient who received concurrent *H. pylori* eradication therapy. None of the patients have relapsed after a median follow up of 16 months.[54]

Several studies have evaluated chemoimmunotherapy combination regimens that incorporate rituximab in the treatment of MALT lymphomas.

A retrospective study evaluated rituximab combined with cyclophosphamide, doxorubicin (or mitoxantrone), vincristine, and prednisone (R-CHOP/R-CNOP) in patients with relapsed MALT lymphoma (N=26).[55] CR was achieved in 77% of patients. All patients were alive after a median follow up of 19 months, with 22 patients having ongoing remission.[55] A phase II study evaluated the chemoimmunotherapy combination of fludarabine and rituximab in patients with previously untreated MALT lymphoma (N=22; gastric lymphoma, n=12).[56] Among evaluable patients with gastric MALT lymphoma (n=11), the CR rate was 100% and the 2-year PFS rate was 100%. Another phase II study evaluated a different purine analog cladribine in combination with rituximab in patients with MALT lymphoma (N=40; gastric lymphoma, n=21).[57] The ORR was 81% with CR in 58% of patients. After a median follow up of 17 months, 88% of patients were alive. In the subgroup with gastric MALT, the ORR was 86% with a CR in 76% of patients.[57]

In a non-randomized observational study in patients with gastric MALT lymphoma (N=49), chlorambucil combined with rituximab resulted in improved remission rates at week 25 compared with rituximab alone (93% vs. 81%); interestingly, this apparent benefit with the combined regimen over rituximab alone was observed in the subgroup with t(11;18) (remission rate at week 25: 100% vs.66%) but not among t(11;18)-negative patients (66% vs. 92%).[58]

The international randomized IELSG-19 trial evaluated the combination of chlorambucil with rituximab in comparison to chlorambucil alone in patients with MALT lymphoma not previously treated with systemic anticancer therapy.[59] Eligible patients included those who were not responding to or not suitable for local therapy. Final data analysis was conducted in patients treated with chlorambucil alone (n=113) and chlorambucil combined with rituximab (n=114). The combination regimen resulted in higher CR rates (78% vs. 65%) and improved 5-year EFS (68% vs. 50%; *P*=0.002), while the ORR (90% vs. 87%), 5-year PFS (71% vs. 62%) and OS rate (89% in both arms) were not significantly different.[59]

A multicenter phase II trial is investigating the combination of bendamustine and rituximab in patients with previously untreated MALT lymphoma (N=60; gastric lymphoma, n=20).[60] After 3 cycles of combination therapy, the ORR was 100% and CR rate was 76%; gastric lymphoma was associated with a higher CR rate compared with non-gastric disease (90% vs. 64%). The CR rate after completion of treatment was 98%, with most patients (85%) requiring only 4 or fewer cycles of therapy to achieve a CR. After a median follow up of 16 months, all patients remain relapse free and 1 patient died due to neurologic causes.[60]

The proteasome inhibitor bortezomib was evaluated in a phase II study in patients with relapsed/refractory MALT lymphoma (N=32; gastric lymphoma, n=14; median 2 prior therapies).[61] Among evaluable patients (n=29), the ORR was 48% with a CR rate of 31%. After a median follow up of 24 months, 5 patients died, including 2 deaths due to disease progression.[61]

Although chemotherapy regimens may be active in patients with MALT lymphomas, long-term data from a larger group of patients are needed to evaluate their role in the management of localized disease. The international randomized LY03 trial of chlorambucil versus observation following *H. pylori* eradication in patients with localized gastric MALT lymphoma (N=110) showed no difference between study arms with regards to recurrence/progression rate, PFS, or OS outcomes.[62] Therefore, in the absence of data showing benefits with chemotherapy, localized gastric MALT lymphoma should be treated with *H. pylori* eradication therapy or RT, as appropriate. Chemotherapy regimens may be considered for patients with relapsed/refractory disease following RT or for those with advanced, systemic disease.[63]

NCCN Recommendations for Stage I-II

Antibiotic therapy in combination with a proton pump inhibitor to block gastric acid secretion is recommended for *H. Pylori*-positive. Patients who are *H. Pylori*-positive with t(11;18) could also be treated with antibiotic therapy to eradicate H. Pylori infection. However, since t(11;18) is a predictor for lack of response to antibiotic therapy, these patients should be considered for alternative therapy for lymphoma as described for patients who are *H. pylori*-negative. ISRT is the preferred treatment option for patients with *H. pylori* negative disease (negative status confirmed by both histology and blood antibody test). Rituximab is an option for patients with contraindications to RT.[50]

Patients treated with antibiotic therapy for *H. pylori* eradication should be restaged with endoscopy and biopsy after 3 months following therapy. Patients with stage IE2 or stage IIE disease with involvement of submucosa or regional lymph nodes are much less likely to respond to antibiotic therapy. In symptomatic patients after antibiotic therapy, restaging can be done earlier than 3 months and RT may be considered earlier. Patients with responsive disease (*H. pylori* negative and lymphoma negative) can be observed. Patients who are *H. pylori* negative with persistent or recurrent lymphoma are treated with RT, if they are symptomatic. Asymptomatic patients can be observed for another 3 months; alternatively, locoregional RT can be considered as early as 3 months after observation but observation can be prolonged for up to 18 months (category 2B). If the patient initially had clinical stage I_2 or stage IIE disease, early RT should be considered if the lymphoma does not regress with antibiotic therapy. Patients with persistent *H. pylori* and regressing or stable lymphoma are treated with second-line antibiotics. Lastly, patients who are *H. pylori* positive with progressive or symptomatic lymphoma should be treated with RT and second-line antibiotics.

Patients treated with initial RT should be restaged with endoscopy and biopsy after 3-6 months following RT. Patients with responsive disease (*H. pylori* negative and lymphoma negative) can be observed. Antibiotic treatment can be considered for patients with persistent *H. pylori* and regressing lymphoma. However, patients with persistent lymphoma (regardless of presence of *H. pylori*) following RT should be managed according to recommendations for FL contained in these NCCN Guidelines for NHL.

Following observation or additional therapy with antibiotic therapy or RT (as discussed above), patients are again evaluated with endoscopy and biopsy after 3 months. The biopsy should rule out

evidence of large-cell transformation. Any area of DLBCL should be treated according to recommendations for DLBCL in the NCCN Guidelines for NHL. For patients with a CR, clinical follow-up with physical examination and laboratory assessment should be performed every 3-6 months for 5 years and then yearly thereafter (or as clinically indicated). The optimal interval for follow-up endoscopy and imaging is not known. At the present time, follow-up endoscopy and imaging at NCCN institutions are performed as clinically indicated based on symptoms. Patients with no response to second-line RT or recurrence following an initial CR should be treated with systemic therapy according to the guidelines for FL. Locoregional RT is indicated for patients with no response to second-line antibiotic therapy.

NCCN Recommendations for Stage III or IV

In patients with advanced stage disease (which is uncommon), treatment is similar to that described for patients with advanced stage FL. As with FL, asymptomatic patients without indications for treatment are monitored without therapy. The decision to treat is guided by end-organ dysfunction or the presence of symptoms (such as GI bleeding, early satiety), bulky disease at presentation, steady progression of disease, or patient preference. For patients with indications for treatment, enrollment in clinical trial is recommended given the incurability of advanced disease with conventional regimens. In the absence of suitable clinical trials, treatment may include chemoimmunotherapy or locoregional RT (30 Gy). Surgical resection is generally limited to specific clinical situations such as life-threatening hemorrhage. Although disease control is excellent with total gastrectomy, the long-term morbidity has precluded routine surgical resection. If there is evidence of recurrence (by endoscopy) following initial induction therapy, patients should be managed according to the FL guidelines.

Non-gastric MALT Lymphomas

MALT lymphomas can arise from a large number of non-gastric sites such as the bowel (small and large), breast, lung, ocular adnexa, ovary, prostate, parotid, salivary glands and other head and neck regions.[17] The most common sites of presentation include the parotid and salivary glands (18-26%), skin (12-26%), conjunctiva/orbit (7-14%), head and neck (11%), lung (8-9%), thyroid (6%) and breast (2-3%).[17,64] Infectious pathogens (e.g., *Chlamydia psittaci, Campylobacter jejuni*) have been associated with MALT lymphomas of non-gastric sites[4] but testing for these pathogens is not required for disease workup or management.

Diagnosis

Adequate hematopathology review of biopsy materials and immunophenotyping are needed to establish a diagnosis. The recommended markers for an IHC panel include CD20, CD3, CD5, CD10, CD21 or CD23, kappa/lambda, CCND1, and BCL2; the recommended markers for flow cytometry analysis include CD19, CD20, CD5, CD23, and CD10. The typical immunophenotype for MALT lymphoma is CD5-, CD10-, CD20+, CD23-/+, CD43 -/+, cyclin D1-, BCL2-. Molecular analysis to detect antigen receptor gene rearrangement or t(11;18) may be useful in certain cases. In addition, cytogenetics or FISH for t(11;18) t(3;14), t(11;14) and t(14;18) may also be considered under certain circumstances.

Workup

The workup for non-gastric MALT lymphoma is similar to the workup for other NHLs. A comprehensive physical examination should be performed and performance status should be assessed. Laboratory evaluations should include a complete blood count with differentials and platelets, comprehensive metabolic panel, and measurement of serum LDH levels. Evaluation of bone marrow biopsy, with or without aspirates, may be useful for patients with multifocal disease. In addition,

endoscopy with multiple biopsies of anatomical sites may be useful in selected cases. Appropriate imaging studies include CT scan (with contrast of diagnostic quality) of the chest, abdomen and pelvis. A MUGA scan/echocardiogram should be performed if the patient is being considered for treatment with regimens containing anthracycline or anthracenedione. Testing for hepatitis B virus is indicated for patients being considered for treatment with rituximab-containing regimens due to the risk of viral reactivation with chemoimmunotherapy. Testing for HCV may be useful in selected cases.

Treatment Options

As discussed above in the section for 'Gastric MALT Lymphomas', RT alone has been shown to be an effective treatment strategy for both localized gastric and non-gastric MALT lymphomas. In the long-term follow up from a retrospective study in patients with localized MALT lymphomas treated with RT with or without chemotherapy (N=167; non-gastric lymphomas, n=142), the group who received IFRT alone (n=144; dose range 25-35 Gy; 25 Gy for orbit) had an estimated 10-year relapse-free rate and OS rate of 74% and 89%, respectively.[45] The 10-year relapse-free rates for patients with primary involvement of the thyroid (n=21), salivary gland (n=28), and orbital adnexa (n=71) were 95%, 68%, and 67%, respectively.[45]

Other treatment modalities such as chemotherapy (alone or with RT) or surgery (alone or with RT and/or chemotherapy) have been evaluated. In a retrospective study in patients with non-gastric MALT lymphomas (N=180; Ann Arbor stage IV in 27%), patients were treated with chemotherapy (n=78; with or without RT), RT alone (n=41), or surgery (n=68; with or without RT and/or chemotherapy).[17] More than half of patients with early-stage disease were treated with RT (55%; with or without other therapies), including RT alone in 30%; surgery or systemic chemotherapy (with or without other therapies, in both cases) was employed in 42% (surgery alone in 17%) and 31%, respectively. Among patients with advanced disease (stage IV), the large majority were treated with systemic chemotherapy (75.5%; with or without other therapies); RT alone was used in only 4% of these patients. Surgery (with or without other therapies) was employed in 26.5% of patients with advanced disease, including 10% who received surgery alone.[17] Among evaluable patients (n=174), the ORR to treatment was 93% with a CR rate of 77%. Among patients who received chemotherapy, the ORR and CR rates were 92% and 72%, respectively. After a median follow up of 3.4 years, the estimated 5-year PFS and OS rates were 60% and 90%, respectively. The 5-year PFS and OS rates were both 100% for the subgroup of patients with primary involvement in the conjunctiva (n=18) and thyroid (n=10). In patients with primary disease in the orbit (n=13), however, the corresponding outcomes were 23% and 80%, respectively. For patients with primary disease in the salivary gland (n=46), the 5-year PFS and OS rates were 67% and 97%; for the patients with primary disease in the skin (n=22), the corresponding rates were 53% and 100%, respectively.[17]

In another retrospective study in patients with non-gastric MALT lymphomas (N=208; Ann Arbor stage III-IV in 44%), patients were treated with chemotherapy alone (45%; about half received single-agent alkylating agent while other received combination therapy), surgery (21%), or RT (19%).[64] The ORR to treatment was 90% with a CR rate of 73%. The ORR among patients treated with chemotherapy, RT, or surgery were 65%, 76%, and 90%, respectively. After a median follow up of 2.7 years, the median EFS rate was 2.4 years; the estimated 5-year EFS and OS rates were 37% and 83%, respectively.[64] Among patients with primary disease in the skin (n=55), the 5-year EFS and OS rates were 44% and 100%, respectively. Among patients with primary disease in the salivary glands (n=38), the 5-year EFS and OS rates

were 30% and 86%, respectively; for patients with disease in the orbit/conjunctiva (n=30), the corresponding rates were 49% and 100%, respectively. As would be expected, 5-year OS rates were significantly higher among patients with Ann Arbor stage I-II disease compared with those with stage III-IV disease (94% vs. 69%; *P*=0.001). On multivariate analysis, bone marrow involvement was the only significant independent predictor of inferior outcomes for both EFS and OS.[64]

Rituximab either alone or in combination with chemotherapy has also been evaluated in patients with previously untreated or relapsed non-gastric MALT lymphoma. The IELSG evaluated the clinical activity of single agent rituximab in a phase II study in patients with untreated as well as relapsed MALT lymphomas (35 patients; 15 patients with gastric MALT lymphoma and 20 patients with non-gastric MALT lymphoma).[65] Among patients with non-gastric MALT lymphoma, treatment with rituximab resulted in an ORR of 80% (55% CR and 25% PR). For the entire study population, the ORR was significantly higher in the chemotherapy-naive patients than in previously treated patients (87% and 45% respectively; P = .03).

A phase II study evaluated the chemoimmunotherapy combination of fludarabine and rituximab in patients with previously untreated MALT lymphoma (N=22).[56] In the primary non-gastric MALT subgroup (n=10), the ORR was 100% with a CR rate of 80%; PFS at 2 years was 89% in this subgroup. Another phase II study evaluated a different purine analog cladribine in combination with rituximab in patients with MALT lymphoma (N=40).[57] In the subgroup with primary non-gastric MALT (n=19), the ORR was 74% with a CR in 37% of patients. The CR rate was lower than that reported for the subgroup with primary gastric MALT (76%).[57]

In the international randomized IELSG-19 trial that compared chlorambucil alone with the combination of chlorambucil and rituximab in patients with MALT lymphoma not previously treated with systemic anticancer therapy, CR rates, EFS, PFS, and OS rates were not significantly different between patients with primary gastric and non-gastric lymphoma in either treatment arm.[59] In the multicenter phase II trial that investigated the combination of bendamustine with rituximab in patients with previously untreated patients with MALT lymphoma (N=60), the CR rate was 64% in the subgroup of patients with primary non-gastric lymphoma (n=35).[60]

NCCN Recommendations

ISRT (24-30 Gy) is the preferred treatment for patients with stage I-II disease. RT dose is site dependent, with lower doses usually reserved for orbital involvement. Rituximab is included as an option for selected patients. RT or observation is appropriate for patients with extranodal involvement. Based on anecdotal responses to antibiotics in ocular and cutaneous MZLs, some physicians may give an empiric course of doxycycline prior to initiating other therapy. Observation may be considered for patients whose diagnostic biopsy was excisional or in whom RT or systemic treatment could result in significant morbidity. For patients with stage I-II disease, surgical excision for adequate diagnosis may be appropriate treatment for certain sites of disease (e.g., lung, thyroid, colon, small intestine, and breast). If there is no residual disease following surgery, patients can be observed; for patients with positive margins post-surgery, locoregional RT should be considered.

Clinical follow-up (including repeat diagnostic tests and imaging based on the site of disease and as clinically indicated) should be conducted every 3-6 months for 5 years and then annually thereafter (or as clinically indicated). Local recurrence following primary treatment may be treated with RT or managed according to recommendations for

advanced-stage FL. Systemic recurrence should be managed according to the recommendations for advanced FL, as should patients presenting with stage III-IV disease (extranodal disease and multiple nodal sites) at diagnosis. MALT lymphomas coexistent with large-cell lymphoma should be managed according to the recommendations for DLBCL.

Nodal Marginal Zone Lymphoma

In patients with nodal MZL, peripheral lymphadenopathy is present in nearly all cases (>95%); thoracic or abdominal lymph nodes may also be involved in about 50% of cases.[15,66] In addition, involvement of MZL in the bone marrow and peripheral blood may be seen in about 30-40% and 10% of cases, respectively.[15,66] Although advanced-stage disease is observed in about two-thirds of newly diagnosed nodal MZL, most tumors are non-bulky and B symptoms are present in only about 15% of cases.[15,66] The disease course of nodal MZL tends to be indolent, but long-term outcomes appear less favorable compared with MALT lymphomas. In a retrospective analysis of data from patients with MZL, the OS rate was lower in the subgroup of patients with nodal MZL (n=14) compared with those with MALT lymphoma (n=62)(56% vs. 81%); the 5-year failure-free survival rate was also lower among patients with nodal MZL (28% vs. 65%).[15] In a separate retrospective study in patients with non-MALT-type MZL (N=124), the median TTP (from start of treatment) and median OS was 1.3 years and 5.5 years, respectively, among the subgroup of patients with nodal MZL (n=37).[66]

Diagnosis

Adequate hematopathology review of biopsy materials and immunophenotyping are needed to establish a diagnosis. Nodal MZL is rare and occurs most commonly as disseminated disease from extranodal MALT lymphoma. The recommended markers for an IHC panel include CD20, CD3, CD5, CD10, CD21 or CD23, kappa/lambda, CCND1, and BCL2; the recommended markers for flow cytometry include CD19, CD20, CD5, CD23, and CD10. The typical immunophenotype for nodal MZLs is CD5-, CD10-, CD20+, CD23-/+, CD43 -/+, cyclin D1-, BCL2-. Pediatric nodal MZL should be considered with located disease in young patients. Molecular analysis to detect antigen receptor gene rearrangement or t (11; 18) (by PCR) may be useful in certain cases. In addition, cytogenetics or FISH for t(11;18) t(3;14), t(11;14) , t(14;18), del(13q) and del(7q) may also be considered under certain circumstances.

Workup

The workup for nodal MZLs is similar to the workup for other NHL subtypes. A comprehensive physical examination should be performed and performance status should be assessed. Laboratory evaluations should include a complete blood count with differentials and platelets, comprehensive metabolic panel, and measurement of serum LDH levels. Evaluation of bone marrow biopsy with aspirates should be performed to document clinical stage I-II disease. Bone marrow biopsy may be deferred until treatment is indicated, however. Appropriate imaging studies include CT scan (with contrast of diagnostic quality) of the chest, abdomen and pelvis. Nodal MZL occurs primarily in the lymph nodes, although involvements of additional extranodal sites are common. The diagnosis of nodal MZL requires careful evaluation to rule out extranodal sites of primary disease and must be distinguished from nodal FL, MCL, lymphoplasmacytic lymphoma and CLL, all of which are more common. A MUGA scan/echocardiogram should be performed if the patient is being considered for treatment with regimens containing anthracycline or anthracenedione. Testing for hepatitis B virus is indicated for patients being considered for treatment with rituximab-containing regimens due to the risk of viral reactivation with chemoimmunotherapy. Testing for hepatitis C virus may be useful in select cases.

NCCN Recommendations

The panel recommends that patients with nodal MZL be managed according to the recommendations for FL in the NCCN Guidelines for NHL.

Splenic Marginal Zone Lymphoma

Splenic MZL is characterized by the presence of splenomegaly in all cases, which may become symptomatic when massive or when associated with cytopenias.[2,5,66] Peripheral lymph nodes are generally not involved while splenic hilar lymph nodes are often involved[2,5]; involvement of thoracic or abdominal lymph nodes may also be seen in about a third of patients with splenic MZL.[8,66] In addition, bone marrow involvement is present in the majority of patients (about 85%) and involvement of peripheral blood occurs in 30-50% of patients.[2,8,66] Although most patients with splenic MZL present with advanced-stage disease, the disease course is generally indolent. Among the subgroup of patients with splenic MZL (n=59) in a retrospective study in patients with non-MALT-type MZL, the median TTP (from start of treatment) and median OS was 6.9 years and 9.1 years, respectively.[66] Similarly, in a retrospective review of data from patients with splenic MZL (N=81), the median OS was 10.5 years.[67]

Diagnosis

Adequate hematopathology review of biopsy materials and immunophenotyping are needed to establish a diagnosis. The diagnosis of splenic MZL requires bone marrow involvement with or without peripheral blood involvement by small lymphoid cells with immunoglobulin (Ig) light chain restriction that lack characteristic features of other small B-cell neoplasms (CD5, CD10, cyclin D1).[68] The recommended markers for an IHC panel include CD20, CD3, CD5, CD10, CD21 or CD23, CD43, kappa/lambda, IgD, CCND1, BCL2, and annexin A1; the recommended markers for flow cytometry analysis include CD19, CD20, CD5, CD23, CD10, CD43, and CD103. The typical immunophenotype for splenic MZL is CD5-, CD10-, CD20+, CD23-/+, CD43-, cyclin D1-, BCL2 follicles-, annexinA1-, CD103-,and with expression of both IgM and IgD. This lymphoma is distinguished from CLL by the absence of CD5 expression, strong CD20 expression and variable CD23 expression, and from hairy cell leukemia (HCL) by the absence of CD103 expression.

Splenic MZL is most definitively diagnosed at splenectomy, since the immunophenotype is nonspecific and morphologic features on the bone marrow may not be diagnostic. However in a patient with splenomegaly (small or no M component) and a characteristic intra sinusoidal lymphocytic infiltration of the bone marrow, the diagnosis can strongly be suggested on bone marrow biopsy, if the immunophenotype is consistent. Plasmacytoid differentiation with cytoplasmic Ig detectable on paraffin sections may occur. In such cases, the differential diagnosis may include LPL. *MYD88* and *BRAF* mutation status can be useful in selected cases for differentiating splenic MZLs from WM/LPL and HCL respectively.[13,69,70] Conventional and real-time allele-specific polymerase chain reaction (AS-PCR) for *MYD88 (L265P)* has been reported to be an useful test to differentiate WM from non-IgM LPL and other B-cell lymphomas with overlapping clinical and pathological features.[71]

Workup

The initial workup for splenic MZL is similar to the other indolent lymphomas. A comprehensive physical examination should be performed and performance status should be assessed. Laboratory evaluations should include a complete blood count with differentials and platelets, comprehensive metabolic panel, and measurement of serum LDH levels. Serum protein electrophoresis (SPEP) and/or measurement of quantitative immunoglobulin levels should be performed. If elevated immunoglobulins or monoclonal immunoglobulin is detected, further

characterization by immunofixation of blood may be useful. Evaluation of bone marrow biopsy with or without aspirates should be performed.

Appropriate imaging studies include CT scan (with contrast of diagnostic quality) of the chest, abdomen and pelvis. A MUGA scan/echocardiogram should be performed if the patient is being considered for treatment with regimens containing anthracycline or anthracenedione. Testing for HCV is an essential part of initial workup. Hepatitis C has been associated with and implicated in the pathogenesis of splenic MZL and should be evaluated for all patients suspected of having this diagnosis.[72] Testing for HBV is indicated for patients being considered for treatment with rituximab-containing regimens due to the risk of viral reactivation. Other useful evaluations may include cryoglobulin testing for detection of abnormal proteins frequently associated with hepatitis C, and direct Coombs test for evaluation of autoimmune hemolytic anemia.

Treatment Options

As previously mentioned, HCV infection may be associated with some cases of MZLs. In a retrospective study in patients with MZLs, positive HCV serology was detected in 35% of the group of patients with splenic MZL.[8] Antiviral therapy with interferon (IFN)-alfa, with or without ribavirin, has been shown to induce virologic and hematologic responses in patients with HCV-positive MZLs, including in those with splenic disease.[8,73-75] A recent retrospective study evaluated the activity of antiviral therapy with IFN or pegylated-IFN, with or without ribavirin (84% received ribavirin), in a large series of patients with HCV-positive indolent B-cell NHLs (N=94; splenic MZL histology, n=30 [32%]).[76] Among the patients who received antiviral treatment as first-line therapy (n=76; splenic MZL, n=24), the ORR and CR rate was 77% and 47%, respectively, and a sustained virologic response was observed in 78% of patients. The median duration of response was 23 months after a median follow up of 3.3 years. The 5-year PFS and OS rate was 78% and 94%, respectively.[76]

For patients with splenic MZL with negative HCV serology, various treatment modalities including splenectomy, single-agent chemotherapy, combination chemotherapy, immunotherapy with rituximab, and/or chemoimmunotherapy (rituximab combined with chemotherapy) have been evaluated. About 20% to 25% of patients may be observed without initiating treatment at diagnosis, in the absence of disease symptoms or cytopenias.[67,77] Splenectomy alone can result in an ORR of 80% to 90%, with a median OS of 93 months reported in retrospective series.[77,78] Splenectomy with adjuvant chemotherapy (e.g., CHOP-like regimens, alkylating agents, purine analogs) resulted in CR rates of about 50%, with median OS of 107.5 months (about 9 years).[78,79] In retrospective studies, splenectomy with or without chemotherapy have demonstrated favorable outcomes with a median OS exceeding 10 years and a 10-year OS rate of about 75%.[67,78] In a retrospective series of patients with splenic MZL (N=30) treated with splenectomy (followed by alkylating agent-based or anthracycline-based chemotherapy in the majority of patients) or chemotherapy alone with CHOP-like regimens and/or antiviral therapy for HCV positivity, the ORR and CR rates were 93% and 48%, respectively.[8] The median EFS was 3.3 years and the estimated 3-year OS rate was 75%.

Treatment of splenic MZL with purine analog agents (e.g., pentostatin, cladribine) alone resulted in CR rates of about 20%.[80-82] In a small phase II prospective study in patients with splenic MZL (N=16; previously treated, n=13), single-agent therapy with pentostatin induced an ORR of 68% with a CR in 23% of patients; after a median follow up of 35 months, the median PFS and OS was 18 months and 40 months, respectively.[81] In a retrospective analysis of patients with splenic MZL

(N=50), the subgroup of patients treated with cladribine alone (n=12) had a CR rate of 21%, with a 4-year PFS rate of 52%.[80] In another retrospective study in patients with splenic MZL (N=70), the patients treated with chemotherapy alone (n=11; purine analog regimens, n=10) had a CR rate of 18%, and a 3-year FFS rate of 45%; the 3-year OS rate was 55%.[82]

The anti-CD20 monoclonal antibody rituximab has also been evaluated as both monotherapy and in combination with chemotherapy in patients with splenic MZL. In retrospective series, rituximab alone (with or without maintenance rituximab) has shown high response rates (ORR 90% to 100%; CR/CRu rates 40% to 85%) with durable remissions.[82-84] In a retrospective series of patients with splenic MZL who received rituximab alone (n=26), the ORR and CR/CRu rates were 88% and 42%, respectively.[82] The 3-year FFS and OS rates were 86% and 95%, respectively. Combination therapy with rituximab and chemotherapy appears to provide benefits over purine analog therapy alone. In a small subgroup of patients who received rituximab combined with chemotherapy (n=6), the CR/CRu rate was 33% and both the 3-year FFS and OS rates were 100%.[82] A retrospective study compared outcomes of patients with splenic MZL treated with cladribine alone (n=12) versus cladribine with rituximab (n=38).[80] The combination regimen of cladribine and rituximab resulted in significantly higher CR rate (62.5% vs. 21%; *P*=0.004) and 4-year PFS rate (83% vs. 52%; *P*=0.04) compared with cladribine alone. After a median follow up of 45 months, the 4-year PFS rate for all patients was 67% and the estimated 6-year OS rate was 89%.[80] In a recent retrospective study that assessed treatment with rituximab in patients with splenic MZL (N=43), rituximab alone or in combination resulted in an ORR of 100% with a CR in 79% of patients.[85] This CR rate compared favorably to the 30% CR observed in patients treated with chemotherapy alone (n=10). Moreover, single-agent rituximab resulted in similar CR rates compared with rituximab-based combination (90% vs. 79%), and was associated with less toxicity. The 3-year DFS was more favorable with rituximab-containing therapy (79%) compared with splenectomy alone (29%) or chemotherapy alone (25%). The 3-year OS with rituximab was 98%.[85]

NCCN Recommendations

Asymptomatic patients with no splenomegaly or progressive cytopenia can be observed until indications for treatment develop. Patients presenting with splenomegaly should be treated depending on their HCV serology status. Hepatology evaluation is recommended for patients with HCV positivity. For patients without contradictions for treatment of hepatitis, appropriate treatment with antiviral therapy should be initiated. In addition, patients requiring treatment for symptomatic splenomegaly can be further managed with splenectomy or rituximab therapy. Patients with contraindications should be managed as described below for patients with HCV-negative disease.

Patients who are HCV-negative can be observed if they are asymptomatic. Patients who are symptomatic (cytopenias or symptoms of splenomegaly, weight loss, early satiety or abdominal pain) should be treated with splenectomy or rituximab. Pneumococcal and meningococcal vaccination should be given at least 2 weeks before splenectomy. Patients should be monitored on a regular basis following treatment. Clinical follow up (including repeat diagnostic tests and imaging studies, as clinically indicated) should be performed every 3-6 months for 5 years and then annually or as clinically indicated thereafter. Patients with evidence of disease progression should be managed according to the recommendations for advanced-stage FL in the NCCN Guidelines.

References

1. Kahl B, Yang D. Marginal zone lymphomas: management of nodal, splenic, and MALT NHL. Hematology Am Soc Hematol Educ Program 2008:359-364. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19074110.

2. Thieblemont C. Clinical presentation and management of marginal zone lymphomas. Hematology Am Soc Hematol Educ Program 2005:307-313. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16304396.

3. Campo E, Pileri SA, Jaffe ES, et al. Nodal marginal zone lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:218-219.

4. Isaacson PG, Chott A, Nakamura S, et al. Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). In: Swerdlow SH, Campo E, Harris NL, et al. eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:214-217. Available at:

5. Isaacson PG, Thieblemont C, Piris MA, et al. Splenic B-cell marginal zone lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:185-187.

6. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 1997;89:3909-3918. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9166827.

7. Olszewski AJ, Castillo JJ. Survival of patients with marginal zone lymphoma: Analysis of the Surveillance, Epidemiology, and End Results database. Cancer 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22893605.

8. Arcaini L, Paulli M, Boveri E, et al. Splenic and nodal marginal zone lymphomas are indolent disorders at high hepatitis C virus seroprevalence with distinct presenting features but similar morphologic and phenotypic profiles. Cancer 2004;100:107-115. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14692030.

9. Mele A, Pulsoni A, Bianco E, et al. Hepatitis C virus and B-cell non-Hodgkin lymphomas: an Italian multicenter case-control study. Blood 2003;102:996-999. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12714514.

10. Arcaini L, Burcheri S, Rossi A, et al. Prevalence of HCV infection in nongastric marginal zone B-cell lymphoma of MALT. Ann Oncol 2007;18:346-350. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17071937.

11. Berger F, Traverse-Glehen A, Felman P, et al. Clinicopathologic features of Waldenstrom's macroglobulinemia and marginal zone lymphoma: are they distinct or the same entity? Clin Lymphoma 2005;5:220-224. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15794852.

12. Treon SP, Xu L, Yang G, et al. MYD88 L265P somatic mutation in Waldenstrom's macroglobulinemia. N Engl J Med 2012;367:826-833. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22931316.

13. Gachard N, Parrens M, Soubeyran I, et al. IGHV gene features and MYD88 L265P mutation separate the three marginal zone lymphoma entities and Waldenstrom macroglobulinemia/lymphoplasmacytic lymphomas. Leukemia 2013;27:183-189. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22944768.

14. Varettoni M, Arcaini L, Zibellini S, et al. Prevalence and clinical significance of the MYD88 (L265P) somatic mutation in Waldenstrom's macroglobulinemia and related lymphoid neoplasms. Blood 2013;121:2522-2528. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23355535.

15. Nathwani BN, Anderson JR, Armitage JO, et al. Marginal zone B-cell lymphoma: A clinical comparison of nodal and mucosa-associated lymphoid tissue types. Non-Hodgkin's Lymphoma Classification Project. J Clin Oncol 1999;17:2486-2492. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10561313.

16. Thieblemont C, Bastion Y, Berger F, et al. Mucosa-associated lymphoid tissue gastrointestinal and nongastrointestinal lymphoma behavior: analysis of 108 patients. J Clin Oncol 1997;15:1624-1630. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9193362.

17. Zucca E, Conconi A, Pedrinis E, et al. Nongastric marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. Blood 2003;101:2489-2495. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12456507.

18. Ueda K, Terui Y, Yokoyama M, et al. Non-gastric advanced mucosa-associated lymphoid tissue (MALT) lymphoma has worse prognosis than gastric MALT lymphoma even when treated with rituximab-containing chemotherapy. Leuk Lymphoma 2013;54 1928-1933. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23216271.

19. Thieblemont C, Berger F, Dumontet C, et al. Mucosa-associated lymphoid tissue lymphoma is a disseminated disease in one third of 158 patients analyzed. Blood 2000;95:802-806. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10648389.

20. Farinha P, Gascoyne RD. Molecular pathogenesis of mucosa-associated lymphoid tissue lymphoma. J Clin Oncol 2005;23:6370-6378. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16155022.

21. Auer IA, Gascoyne RD, Connors JM, et al. t(11;18)(q21;q21) is the most common translocation in MALT lymphomas. Ann Oncol 1997;8:979-985. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9402171.

22. Murga Penas EM, Hinz K, Roser K, et al. Translocations t(11;18)(q21;q21) and t(14;18)(q32;q21) are the main chromosomal abnormalities involving MLT/MALT1 in MALT lymphomas. Leukemia 2003;17:2225-2229. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12931213.

23. Willis TG, Jadayel DM, Du MQ, et al. Bcl10 is involved in t(1;14)(p22;q32) of MALT B cell lymphoma and mutated in multiple tumor types. Cell 1999;96:35-45. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9989495.

24. Liu H, Ye H, Dogan A, et al. T(11;18)(q21;q21) is associated with advanced mucosa-associated lymphoid tissue lymphoma that expresses nuclear BCL10. Blood 2001;98:1182-1187. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11493468.

25. Streubel B, Lamprecht A, Dierlamm J, et al. T(14;18)(q32;q21) involving IGH and MALT1 is a frequent chromosomal aberration in MALT lymphoma. Blood 2003;101:2335-2339. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12406890.

26. Streubel B, Vinatzer U, Lamprecht A, et al. T(3;14)(p14.1;q32) involving IGH and FOXP1 is a novel recurrent chromosomal aberration in MALT lymphoma. Leukemia 2005;19:652-658. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15703784.

27. Wotherspoon AC. Gastric lymphoma of mucosa-associated lymphoid tissue and Helicobacter pylori. Annu Rev Med 1998;49:289-299. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9509264.

28. Isaacson PG, Spencer J. Gastric lymphoma and Helicobacter pylori. Important Adv Oncol 1996:111-121. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8791131.

29. Ye H, Liu H, Raderer M, et al. High incidence of t(11;18)(q21;q21) in Helicobacter pylori-negative gastric MALT lymphoma. Blood

2003;101:2547-2550. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12517817.

30. Liu H, Ye H, Ruskone-Fourmestraux A, et al. T(11;18) is a marker for all stage gastric MALT lymphomas that will not respond to H. pylori eradication. Gastroenterology 2002;122:1286-1294. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11984515.

31. Morgner A, Bayerdorffer E, Neubauer A, Stolte M. Helicobacter pylori associated gastric B cell MALT lymphoma: predictive factors for regression. Gut 2001;48:290-292. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11171813.

32. Pavlick AC, Gerdes H, Portlock CS. Endoscopic ultrasound in the evaluation of gastric small lymphocytic mucosa-associated lymphoid tumors. J Clin Oncol 1997;15:1761-1766. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9164183.

33. Sackmann M, Morgner A, Rudolph B, et al. Regression of gastric MALT lymphoma after eradication of Helicobacter pylori is predicted by endosonographic staging. MALT Lymphoma Study Group. Gastroenterology 1997;113:1087-1090. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9322502.

34. Nakamura S, Matsumoto T, Suekane H, et al. Predictive value of endoscopic ultrasonography for regression of gastric low grade and high grade MALT lymphomas after eradication of Helicobacter pylori. Gut 2001;48:454-460. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11247887.

35. Rohatiner A, d'Amore F, Coiffier B, et al. Report on a workshop convened to discuss the pathological and staging classifications of gastrointestinal tract lymphoma. Ann Oncol 1994;5:397-400. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8075046.

36. Stathis A, Chini C, Bertoni F, et al. Long-term outcome following Helicobacter pylori eradication in a retrospective study of 105 patients with localized gastric marginal zone B-cell lymphoma of MALT type. Ann Oncol 2009;20:1086-1093. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19193705.

37. Steinbach G, Ford R, Glober G, et al. Antibiotic treatment of gastric lymphoma of mucosa-associated lymphoid tissue. An uncontrolled trial. Ann Intern Med 1999;131:88-95. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10419446.

38. Wundisch T, Thiede C, Morgner A, et al. Long-term follow-up of gastric MALT lymphoma after Helicobacter pylori eradication. J Clin Oncol 2005;23:8018-8024. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16204012.

39. Chen L, Lin J, Tai J, et al. Long-term results of anti-Helicobacter pylori therapy in early-stage gastric high-grade transformed MALT lymphoma. J Natl Cancer Inst 2005;97:1345-1353. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16174856.

40. Andriani A, Miedico A, Tedeschi L, et al. Management and long-term follow-up of early stage H. pylori-associated gastric MALT-lymphoma in clinical practice: an Italian, multicentre study. Dig Liver Dis 2009;41:467-473. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18945654.

41. Montalban C, Santon A, Boixeda D, et al. Treatment of low grade gastric mucosa-associated lymphoid tissue lymphoma in stage I with Helicobacter pylori eradication. Long-term results after sequential histologic and molecular follow-up. Haematologica 2001;86:609-617. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11418369.

42. Nakamura S, Matsumoto T, Suekane H, et al. Long-term clinical outcome of Helicobacter pylori eradication for gastric mucosa-associated lymphoid tissue lymphoma with a reference to second-line treatment. Cancer 2005;104:532-540. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15937928.

43. Wotherspoon AC, Doglioni C, Diss TC, et al. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid

tissue type after eradication of Helicobacter pylori. Lancet 1993;342:575-577. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8102719.

44. Tsang RW, Gospodarowicz MK, Pintilie M, et al. Localized mucosa-associated lymphoid tissue lymphoma treated with radiation therapy has excellent clinical outcome. J Clin Oncol 2003;21:4157-4164. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14615444.

45. Goda JS, Gospodarowicz M, Pintilie M, et al. Long-term outcome in localized extranodal mucosa-associated lymphoid tissue lymphomas treated with radiotherapy. Cancer 2010;116:3815-3824. Available at: http://www.ncbi.nlm.nih.gov/PubMed/20564130.

46. Vrieling C, de Jong D, Boot H, et al. Long-term results of stomach-conserving therapy in gastric MALT lymphoma. Radiother Oncol 2008;87:405-411. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18343513.

47. Aviles A, Nambo MJ, Neri N, et al. Mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach: results of a controlled clinical trial. Med Oncol 2005;22:57-62. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15750197.

48. Koch P, Probst A, Berdel WE, et al. Treatment results in localized primary gastric lymphoma: data of patients registered within the German multicenter study (GIT NHL 02/96). J Clin Oncol 2005;23:7050-7059. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16129843.

49. Schechter NR, Portlock CS, Yahalom J. Treatment of mucosa-associated lymphoid tissue lymphoma of the stomach with radiation alone. J Clin Oncol 1998;16:1916-1921. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9586910.

50. Martinelli G, Laszlo D, Ferreri AJM, et al. Clinical activity of rituximab in gastric marginal zone non-Hodgkin's lymphoma resistant to or not eligible for anti-Helicobacter pylori therapy. J Clin Oncol 2005;23:1979-1983. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15668468.

51. Hammel P, Haioun C, Chaumette MT, et al. Efficacy of single-agent chemotherapy in low-grade B-cell mucosa-associated lymphoid tissue lymphoma with prominent gastric expression. J Clin Oncol 1995;13:2524-2529. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7595703.

52. Jager G, Neumeister P, Brezinschek R, et al. Treatment of extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type with cladribine: a phase II study. J Clin Oncol 2002;20:3872-3877. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12228207.

53. Jager G, Neumeister P, Quehenberger F, et al. Prolonged clinical remission in patients with extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue type treated with cladribine: 6 year follow-up of a phase II trial. Ann Oncol 2006;17:1722-1723. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16766585.

54. Wohrer S, Drach J, Hejna M, et al. Treatment of extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) with mitoxantrone, chlorambucil and prednisone (MCP). Ann Oncol 2003;14:1758-1761. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14630681.

55. Raderer M, Wohrer S, Streubel B, et al. Activity of rituximab plus cyclophosphamide, doxorubicin/mitoxantrone, vincristine and prednisone in patients with relapsed MALT lymphoma. Oncology 2006;70:411-417. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17220639.

56. Salar A, Domingo-Domenech E, Estany C, et al. Combination therapy with rituximab and intravenous or oral fludarabine in the first-line, systemic treatment of patients with extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue type.

Cancer 2009;115:5210-5217. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19672998.

57. Troch M, Kiesewetter B, Willenbacher W, et al. Rituximab plus subcutaneous cladribine in patients with extranodal marginal zone B-cell lymphoma of the mucosa associated lymphoid tissue-Lymphoma: a phase II study by the Arbeitsgemeinschaft Medikamentose Tumortherapie. Haematologica 2013;98:264-268. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22983582.

58. Levy M, Copie-Bergman C, Amiot A, et al. Rituximab and chlorambucil versus rituximab alone in gastric mucosa-associated lymphoid tissue lymphoma according to t(11;18) status: a monocentric non-randomized observational study. Leuk Lymphoma 2013;54:940-944. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22978684.

59. Zucca E, Conconi A, Laszlo D, et al. Addition of Rituximab to Chlorambucil Produces Superior Event-Free Survival in the Treatment of Patients With Extranodal Marginal-Zone B-Cell Lymphoma: 5-Year Analysis of the IELSG-19 Randomized Study. J Clin Oncol 2013;31:565-572. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23295789.

60. Salar A, Domingo-Domenech E, Panizo C, et al. Final Results of a Multicenter Phase II Trial with Bendamustine and Rituximab As First Line Treatment for Patients with MALT Lymphoma (MALT-2008-01) [abstract]. Blood 2012;120:Abstract 3691. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/120/21/3691.

61. Conconi A, Martinelli G, Lopez-Guillermo A, et al. Clinical activity of bortezomib in relapsed/refractory MALT lymphomas: results of a phase II study of the International Extranodal Lymphoma Study Group (IELSG). Ann Oncol 2011;22:689-695. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20810546.

62. Hancock BW, Qian W, Linch D, et al. Chlorambucil versus observation after anti-Helicobacter therapy in gastric MALT lymphomas: results of the international randomised LY03 trial. Br J Haematol 2009;144:367-375. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19036078.

63. Zucca E, Dreyling M. Gastric marginal zone lymphoma of MALT type: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21 Suppl 5:v175-176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20555074.

64. Arcaini L, Burcheri S, Rossi A, et al. Nongastric marginal-zone B-cell MALT lymphoma: prognostic value of disease dissemination. Oncologist 2006;11:285-291. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16549813.

65. Conconi A, Martinelli G, Thieblemont C, et al. Clinical activity of rituximab in extranodal marginal zone B-cell lymphoma of MALT type. Blood 2003;102:2741-2745. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12842999.

66. Berger F, Felman P, Thieblemont C, et al. Non-MALT marginal zone B-cell lymphomas: a description of clinical presentation and outcome in 124 patients. Blood 2000;95:1950-1956. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10706860.

67. Thieblemont C, Felman P, Berger F, et al. Treatment of splenic marginal zone B-cell lymphoma: an analysis of 81 patients. Clin Lymphoma 2002;3:41-47. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12141954.

68. Franco V, Florena AM, Iannitto E. Splenic marginal zone lymphoma. Blood 2003;101:2464-2472. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12446449.

69. Blombery P, Wong SQ, Hewitt CA, et al. Detection of BRAF mutations in patients with hairy cell leukemia and related lymphoproliferative disorders. Haematologica 2012;97:780-783. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22133769.

70. Arcaini L, Zibellini S, Boveri E, et al. The BRAF V600E mutation in hairy cell leukemia and other mature B-cell neoplasms. Blood 2012;119:188-191. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22072557.

71. Xu L, Hunter ZR, Yang G, et al. MYD88 L265P in Waldenstrom macroglobulinemia, immunoglobulin M monoclonal gammopathy, and other B-cell lymphoproliferative disorders using conventional and quantitative allele-specific polymerase chain reaction. Blood 2013;121:2051-2058. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23321251.

72. Weng WK, Levy S. Hepatitis C virus (HCV) and lymphomagenesis. Leuk Lymphoma 2003;44:1113-1120. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12916862.

73. Hermine O, Lefrere F, Bronowicki JP, et al. Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection. N Engl J Med 2002;347:89-94. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12110736.

74. Kelaidi C, Rollot F, Park S, et al. Response to antiviral treatment in hepatitis C virus-associated marginal zone lymphomas. Leukemia 2004;18:1711-1716. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15284859.

75. Vallisa D, Bernuzzi P, Arcaini L, et al. Role of anti-hepatitis C virus (HCV) treatment in HCV-related, low-grade, B-cell, non-Hodgkin's lymphoma: a multicenter Italian experience. J Clin Oncol 2005;23:468-473. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15659492.

76. Arcaini L, Vallisa D, Merli M, et al. Hematolgical response to antiviral treatment in 94 patients with indolent B-cell lymphomas associated with hepatitis C virus infection: a study of the Fondazione Italiana Linfomi (FIL) [abstract]. Ann Oncol 2011;22 (Suppl 4):Abstract 138. Available at: http://annonc.oxfordjournals.org/content/22/suppl_4/iv128.

77. Iannitto E, Ambrosetti A, Ammatuna E, et al. Splenic marginal zone lymphoma with or without villous lymphocytes. Hematologic findings and outcomes in a series of 57 patients. Cancer 2004;101:2050-2057. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15389479.

78. Milosevic R, Todorovic M, Balint B, et al. Splenectomy with chemotherapy vs surgery alone as initial treatment for splenic marginal zone lymphoma. World J Gastroenterol 2009;15:4009-4015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19705496.

79. Chacon JI, Mollejo M, Munoz E, et al. Splenic marginal zone lymphoma: clinical characteristics and prognostic factors in a series of 60 patients. Blood 2002;100:1648-1654. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12176884.

80. Cervetti G, Galimberti S, Sordi E, et al. Significant efficacy of 2-CdA with or without rituximab in the treatment of splenic marginal zone lymphoma (SMZL). Ann Oncol 2010;21:851-854. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19825880.

81. Iannitto E, Minardi V, Calvaruso G, et al. Deoxycoformycin (pentostatin) in the treatment of splenic marginal zone lymphoma (SMZL) with or without villous lymphocytes. Eur J Haematol 2005;75:130-135. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16000129.

82. Tsimberidou AM, Catovsky D, Schlette E, et al. Outcomes in patients with splenic marginal zone lymphoma and marginal zone lymphoma treated with rituximab with or without chemotherapy or chemotherapy alone. Cancer 2006;107:125-135. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16700034.

83. Bennett M, Sharma K, Yegena S, et al. Rituximab monotherapy for splenic marginal zone lymphoma. Haematologica 2005;90:856-858. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15951303.

84. Kalpadakis C, Pangalis GA, Dimopoulou MN, et al. Rituximab monotherapy is highly effective in splenic marginal zone lymphoma.

Hematol Oncol 2007;25:127-131. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17514771.

85. Else M, Marin-Niebla A, de la Cruz F, et al. Rituximab, used alone or in combination, is superior to other treatment modalities in splenic marginal zone lymphoma. Br J Haematol 2012;159:322-328. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23016878.

This discussion is being updated to correspond with the newly updated algorithm. Last updated 10/28/2014.

Mantle Cell Lymphoma

Diagnosis

Mantle cell lymphoma (MCL) comprises about 6% of all newly diagnosed cases of NHL.[1] MCL can be readily distinguished from other small lymphocytic lymphomas due to the widespread availability of appropriated diagnostic reagents.[2] The diagnosis can be established by histological examination in combination with immunohistochemistry (IHC) with a profile consisting of CD5+, CD10-/+, CD20+, CD23-/+, CD43+, and cyclin D1+. Some cases of MCL may be CD5- or CD23+. MCL is characterized by the reciprocal chromosomal translocation t(11;14), resulting in the overexpression of cyclin D1 and the diagnosis of MCL generally requires the expression of cyclin D1.[3] However, cyclin D1-negative MCL cases with otherwise typical immunophenotype can be observed, though rare (<5% of cases).[4,5] Recent gene expression profiling data suggest that cyclin D1 expression may not be required for the molecular signature of MCL; in these rare cases of MCL negative for cyclin D1 and t(11;14), over-expression of cyclin D2 or cyclin D3 may be observed.[6,7] IHC for cyclin D2 or cyclin D3 is not helpful in establishing the diagnosis of cyclin D1-negative MCL as these proteins are also expressed in other B-cell malignancies. A recent study of cyclin D1-negative MCL showed rearrangements involving the *CCND2* gene in 55% of cases, which was associated with high expression of cyclin D2 mRNA.[8] Gene expression and miRNA profiling showed that the genomic signatures of cyclin D1-negative MCL cases were similar to those of cyclin D1-positive cases.[5,6,8] Nuclear overexpression of the transcription factor SOX11 is observed in nearly all cases of MCL, regardless of cyclin D1 expression level, and may potentially aid in differentiating cyclin D1-negative MCL cases from other B-cell lymphomas.[9-11] The pathologic features and clinical characteristics of cyclin D1-negative MCL appear to be similar to those of cyclin D1-positive cases.[6,8] Thus, in the absence of data suggesting otherwise, cases of cyclin D1-negative MCL should not be managed differently than cyclin D1-positive cases.

Currently available reagents for IHC evaluation of cyclin D1 are robust and yield good staining; however, in some cases, molecular analysis of *CCND1* rearrangements or cytogenetics or FISH for the translocation t(11;14), juxtaposing the cyclin D1 locus with the IgH locus, can be helpful for diagnosis.[12] In certain cases, cytogenetics or FISH for t(14;18) and a FISH panel for chronic lymphocytic leukemia (CLL) may also be useful. In addition, Ki-67 should be included in the IHC panel for initial diagnostic workup. Ki-67 proliferation index of less than 30% has been associated with a more favorable prognosis.[13-17] However, this should not be used to guide treatment decisions at this time.

In-Situ Involvement of Mantle Cell Lymphoma-like Cells of Unknown Significance (Mantle Cell Lymphoma "In Situ")

The presence of MCL-like B-cells in the mantle zones of morphologically reactive lymph nodes ("MCL in situ") has been described in several case reports (including in patients with lymphoid hyperplasia).[18,19] Cases of "MCL in situ" have been characterized by preservation of the lymph node architecture and presence of cyclin D1-positive B-cells restricted to the mantle zones with minimal expansion of the mantle zone (and with only minimal or no spread of cyclin D1-positive cells in the interfollicular area).[18-21] More recently, an unusual case of "MCL in situ" was reported that showed a scattering of cyclin D1-positive cells in the germinal centers (but not the mantle zones) of a lymph node specimen retrospectively evaluated several years prior to the diagnosis of symptomatic MCL.[22]

The occurrence of "MCL in situ" in studies of reactive lymph nodes was very rare.[20,23] In an analysis of a consecutive series of unselected surgical samples of reactive lymph nodes from patients without a history of lymphoma (n=131; 1292 samples), no cases of "MCL in situ" were identified.[23] Development of overt MCL in patients found to have "MCL in situ" has been reported, although this appears to be very uncommon.[20] The significance or potential for malignancy of "MCL in situ" in patients without known MCL remains uncertain. These cases appear to have a very indolent course with long-term survival even without treatment intervention.[20,21] It is therefore important to distinguish cases of "MCL in situ" from cases of overt MCL with a mantle zone pattern. In patients with the former in whom overt MCL can be excluded based on a thorough evaluation (e.g., biopsy of additional suspicious nodes, physical examination, peripheral blood flow cytometry, CT scan of neck, chest, abdomen, and pelvis) close follow-up may still be warranted.[24] Similar to "follicular lymphoma in situ", the WHO classification recommends that a diagnosis of MCL not be made in such cases.

Workup

The workup for MCL is similar to the workup for many indolent lymphomas and certain aggressive lymphomas. The initial workup for newly diagnosed MCL should include a thorough physical examination with attention to node-bearing areas, and evaluation of performance status and constitutional symptoms. Laboratory assessments should include standard blood work including CBC with differential and a comprehensive metabolic panel, in addition to measurements of serum lactate dehydrogenase (LDH). Patients with high tumor burden and elevated LDH should be assessed for spontaneous tumor lysis syndrome, including measurements of uric acid level. Measurement of serum beta-2-microglobulin levels may also be useful in some circumstances. HBV testing is recommended due to increased risks of viral reactivation when immunotherapy regimens are being considered for treatment. MCL is a systemic disease with frequent involvement of the bone marrow, gastrointestinal (GI) tract and may also present with a leukemic phase. For this reason, both the peripheral blood and bone marrow must be carefully evaluated for the presence of malignant cells. Adequate trephine biopsy should be obtained for initial staging evaluation, with or without bone marrow aspiration. Chest, abdominal, and pelvic CT scans are routinely performed. PET-CT scan and CT scan of the neck may be helpful in selected cases. In patients with the blastic variant or for patients presenting with CNS symptoms, a lumbar puncture should be performed to evaluate the cerebral spinal fluid for potential disease involvement.

GI involvement has been reported in 15% to 30% of patients with MCL. In two prospective studies, the frequency of GI tract involvement in patients with MCL was higher than that reported in the literature.[25,26] Salar et al reported upper or lower GI tract involvement in 92% of patients at diagnosis. In the study by Romaguera et al., MCL was histologically present in the lower and upper GI tract in 88% and 43% of patients, respectively.[25] In this report, 26% of patients presented with GI symptoms at the time of diagnosis. Despite the high frequency of GI tract involvement (which was primarily observed at the microscopic level), the use of endoscopy with biopsies led to changes in clinical management in only 4% of patients.[25] The NCCN Guidelines panel does not recommend endoscopy or colonoscopy as part of routine initial workup, but suggests that it may be useful in certain circumstances. However, endoscopic or colonoscopic evaluation of the GI tract is necessary for confirmation of stage I-II disease and for response assessment to initial therapy.

Treatment Options based on Clinical Stage

Generally, MCL is thought to possess the worst characteristics of both indolent and aggressive NHL subtypes owing to the incurability of disease with conventional chemotherapy and a more aggressive disease course.[27]

Stage I-II

Few patients present with localized MCL and the available published literature on management is retrospective and anecdotal. In a retrospective analysis of patients with limited bulk, early-stage (stage IA or IIA) MCL (n=26), inclusion of RT with or without chemotherapy was associated with significantly improved progression-free survival (PFS) at 5 years (68% vs. 11%; *P* =.002) and a trend towards improved overall survival (OS).[28]

Stage II (bulky) and Stage III-IV

Several regimens have shown significant activity in newly diagnosed patients with MCL, but none of these regimens are curative in patients with advanced disease.

In a database analysis from a single-center cohort (n=111), Martin et al reported that treatment with regimens including R-CHOP or R-CVP could yield survival outcomes similar to that achieved with more intensive approaches.[29] The median OS from diagnosis was 85 months, and the 5-year OS rate was 66%. Among patients with available data on treatment regimens (n=75), the majority (70%) had received CHOP-like therapy with or without rituximab, with only 7% having received more intensive first-line therapies (R-hyper-CVAD and/or high-dose therapy with autologous stem cell rescue [HDT/ASCR]).[29]

However, a more recently published analysis from the NCCN Oncology Outcomes Database suggested that median PFS remained 3-4 years despite the use of aggressive regimens in patients with MCL (n=167).[30] This analysis reported superior PFS outcomes with R-hyper-CVAD alone or with rituximab-containing regimens (e.g., R-CHOP) followed by HDT/ASCT, compared with R-CHOP alone, in the first-line setting for younger patients (<65 years of age) with MCL.[30]

Aggressive First-Line Therapy

Rituximab used in combination with hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; alternating with high-dose methotrexate and cytarabine) [R-hyper-CVAD] has resulted in favorable PFS and OS outcomes.[31-34]

In a phase II study in previously untreated patients with MCL (n=97), R-hyper-CVAD produced 3-year failure-free survival (FFS) and OS rates of 64% and 82%, respectively, with a median follow-up time of 40 months.[31] After 10 years of follow-up, the median OS had not been reached and the median time to failure (TTF) was 4.6 years for all patients. Among patients 65 years or younger, the median OS had not been reached and the median TTF was 5.9 years. In the multivariate analysis pre-treatment serum levels of beta-2- microglobulin, IPI score and MIPI score were predictive of both OS and TTF.[32] FFS and OS rates were 43% and 60%, respectively; among patients 65 years or younger, the corresponding survival rates were 52% and 68%, respectively.

In the Italian study (60 evaluable patients), R-hyper-CVAD resulted in an overall response rate of 83% with a CR rate of 72%. The 5-year PFS and OS rates were 61% and 73%, respectively.[33] However, this regimen was associated with substantial toxicity.

In the SWOG 0213 study, R-hyper-CVAD induced CR/CRu in 58% of previously untreated patients (age <70 years) with MCL (n=49).[34] With a

median follow-up of 4.8 years, the median PFS and OS was 4.8 years (5.5 years for those ≤ 65 years) and 6.8 years respectively. The 2-year PFS and OS rates were 63% and 76%, respectively.

Less Aggressive First-Line Therapy

In the earlier studies, the addition of rituximab to CHOP chemotherapy was associated with high response rates but did not translate to prolonged PFS or OS.[35,36] A phase III randomized trial in the German Low Grade Lymphoma study group evaluated R CHOP versus CHOP alone in previously untreated patients (age ≤65 years) with advanced stage MCL (n=122).[36] In this study, R CHOP was significantly superior to CHOP in terms of ORR (94% vs. 75%), CR rate (34% vs 7%) and median time to treatment failure (21 months vs. 14 months). However, no differences were observed between treatment arms for PFS or OS outcomes.[36]

Other non-aggressive regimens have also been evaluated in clinical trials. The combination of bendamustine with rituximab (BR regimen) was investigated in a randomized phase III study of the StiL (Study Group Indolent Lymphomas), which compared BR versus R-CHOP as first-line therapy in patients with advanced follicular, indolent, and mantle cell lymphomas (514 evaluable patients; MCL histology comprised 18% of patients).[37] The ORR was similar in both arms (93% with BR vs. 91% with R-CHOP), although the CR rate was significantly higher in the BR arm (40% vs. 30%; *P* =.021). With a median follow-up time of 45 months, the BR arm was associated with significantly longer median PFS (primary endpoint) compared with R-CHOP (69.5 months vs. 31.2 months; HR=0.58, 95% CI 0.44–0.74; *P* <.0001); however. OS outcomes were not significantly different between treatment arms. Among the subgroup of patients with MCL histology, median PFS was also significantly higher with BR compared with R-CHOP (35 months vs. 22 months; HR=0.49, 95% CI 0.28–0.79; *P* =.0044).[37] The BR regimen was associated with less frequent serious adverse events (19% vs. 29%) and less grade 3-4 hematologic toxicities compared with R-CHOP. Grade 3-4 neutropenia was reported in 29% in the BR arm and 69% with R-CHOP. Peripheral neuropathy (all grades) was less frequent in the BR arm (7% vs. 29%). Infectious complications (all grades) were also less frequent with BR compared with R-CHOP (37% vs. 50%). Fatal sepsis occurred in 1 patient in the BR arm and 5 patients in the R-CHOP arm. The BR regimen was more frequently associated with skin toxicities (all grades) including erythema (16% vs. 9%) and allergic reactions (15% vs. 6%) compared with R-CHOP.[37] Although this phase III randomized trial showed superior PFS outcomes with the BR regimen compared with R-CHOP, there may be limitations given that data from more than half of the patients in this trial were censored prior to the minimum follow-up period.

The combination of bendamustine and rituximab with the addition of cytarabine was evaluated in a phase II study in older patients with MCL (age ≥ 65 years; not eligible for intensive regimens or HDT/ASCR).[38] Among enrolled patients (n=40; median age 70 years), 50% were previously untreated, 93% had stage III/IV disease and 49% had high-risk MIPI scores. Patients with relapsed/refractory disease (n=20) had all previously received rituximab-containing therapies.[38] Among previously untreated patients, the ORR was 100% and the 2-year PFS rate was 95%. Among relapsed/refractory patients, the ORR was 70% and the 2-year PFS was 70%. The most common grade 3 or 4 toxicities included transient thrombocytopenia (87%) and febrile neutropenia (12%).[38]

Cladribine, alone or in combination with rituximab, has shown activity in patients with previously untreated MCL.[39-41] In trials conducted by the North Central Cancer Treatment group, the ORR and median PFS for single agent cladribine were 81% (42% CR) and 14 months,

respectively, for previously untreated patients (n=26); the combination of cladribine and rituximab as initial therapy (n=29) resulted in an ORR of 66% (52% CR) and median PFS of 12 months.[39] In a small trial in patients with previously untreated and pretreated MCL (n=12), cladribine alone induced an ORR of 58% (25% CR) with a median time to progression of 19 months.[40] In a recent retrospective study in patients with previously untreated MCL (n=31), cladribine combined with rituximab yielded an ORR of 87% (61% CR/CRu) with a median PFS and OS of 37.5 months and 85 months, respectively.[41] It should be noted that in this study, the majority of responding patients had received post-induction maintenance therapy with rituximab.

Bortezomib is a proteasome inhibitor with activity in patients with relapsed or refractory MCL[42-44] and is currently approved for this indication. A phase III randomized study evaluated the safety and efficacy of bortezomib in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) vs. R-CHOP in patients with newly diagnosed MCL who are not candidates for HDT/ASCR.[45] In this study, 487 patients were randomized to R-CHOP (n = 244) or VR-CAP (n = 243). The majority of patients had stage IV disease (74%) and 54% of patients had an IPI ≥3. At a median follow-up of 40 months, median progression free survival with VR-CAP was 24.7 months compared to 14.4 months for R-CHOP, which was statistically significant ($P < .001$). VR-CAP was also associated with improvements in median time to progression (30.5 vs 16.1 months; $P < .001$) and CR (CR + CRu) rate (48% vs. 41%).[45] The median duration of response (CR + CRu) was 42 months and 18 months, respectively. The 4-year OS rate was higher with VR-CAP (64% vs. 54% for R-CHOP), but the benefit was not significant. The incidences of grade ≥3 adverse events, although slightly higher with VR-CAP (93% compared to 84% with R-CHOP), were manageable. Based on the results of this study, the FDA approved the use of bortezomib (in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone) for the initial treatment of patients with MCL. The NCCN Guidelines have included VR-CAP as an option for induction therapy for patients with newly diagnosed MCL (stage II-IV).

First-Line Consolidation Therapy

HDT/ASCR as first-line consolidation has demonstrated promising outcomes in a number of studies.[46-52]

In a prospective study of sequential frontline CHOP/DHAP followed by HDT/ASCR in patients with MCL (n=28; n=23 proceeded to transplant), the 3-year event-free survival (EFS) and OS rates were 83% and 90%, respectively.[48] Median OS was not reached after a median follow up of almost 48 months. In a randomized trial conducted by the European MCL Network, patients (age ≤65 years) with advanced stage MCL (n=122) in remission after CHOP-like chemotherapy were randomized to HDT/ASCR or maintenance with interferon alfa.[49] In this study, HDT/ASCR was associated with a significantly longer median PFS compared with interferon alfa maintenance (39 months vs. 17 months; P=0.011) The 3-year OS rates were 83% and 77%, respectively, and were not significantly different between consolidation arms.[49]

In a study conducted by the MD Anderson Cancer Center, HDT/ASCR in patients with MCL (n=33) in first remission following treatment with hyper-CVAD resulted in 5-year disease-free survival and OS rates of 42% and 77%, respectively.[47] In particular, the subgroup of patients with low serum beta-2 microglobulin levels appeared to benefit most, with a 5-year OS rate of 100% (compared with 22% for patients with elevated beta-2 microglobulin).[47] In an analysis of long-term outcomes from patients with MCL treated at the MD Anderson Cancer Center (including

the 33 patients reported in the earlier study above), the subgroup of patients treated primarily with hyper-CVAD (with or without rituximab) followed by HDT/ASCR in first remission (n=50) showed a median PFS of 42 months and a median OS of 93 months.[51]

In a small prospective study that evaluated R-hyper-CVAD followed by HDT/ASCR in patients with previously untreated MCL (n=13; 12 patients proceeded to transplant), the 3-year EFS and OS rate was 92% for both endpoints.[50] These results with R-hyper-CVAD appear favorable relative to induction with R-CHOP.

In a phase II study that evaluated R-CHOP induction followed by HDT/ASCR in patients with previously untreated MCL (n=87; 61 patients proceeded to transplant), the 4-year failure-free survival and OS rates were 36% and 66%, respectively.[52]

In another study, patients with MCL treated with hyper-CVAD or CHOP (with or without rituximab, in either regimen) followed by HDT/ASCR in first remission (n=36) had 3-year PFS and OS rates of 63% and 93%, respectively.[53] Induction with hyper-CVAD resulted in a higher 3-year PFS rate compared with CHOP (81% vs. 44%), although the difference was not statistically significant. The 3-year OS rate was similar between induction regimens (94% vs. 92%, respectively).[53] Disease status at transplant was the most significant factor affecting survival following HDT/ASCR.[53,54] Patients in first remission (CR or PR) at the time of transplant had improved survival outcomes compared with those with relapsed or refractory disease. As mentioned above, among patients transplanted in first remission, hyper-CVAD (with or without rituximab) induction was associated with an improved PFS outcome compared with CHOP (with or without rituximab) in non-randomized studies.[53]

Several different induction regimens incorporating rituximab in combination with dose intensified anthracycline-based[16,55,56] or cladribine-based chemotherapy[57-59] followed by HDT/ASCR have shown promising efficacy in relatively young newly diagnosed patients with MCL.

In the Nordic MCL trial, induction therapy with rituximab and dose intensified CHOP (maxi-CHOP) alternating with high-dose cytarabine resulted in an ORR and CR rate of 96% and 54%, respectively, in previously untreated patients (age ≤65 years) with MCL (n=160).[55] Responding patients were eligible to proceed with HDT/ASCR. The 6-year PFS and OS rates were 66% and 70%, respectively, with no relapses occurring after a median follow up of approximately 4 years (at the time of the initial report).[55] Further follow up from this study with a median observation time of 6.5 years showed median EFS of 7.4 years; median OS exceeded 10 years.[60] Late relapses were reported in 6 patients, who experienced disease progression more than 5 years after the end of therapy. In the multivariate analysis from this study, the international MCL Prognostic Index (MIPI) and ki-67 expression level were the only independent predictors of survival outcomes.[60] However, in this trial, patients were monitored by disease-specific primers for molecular relapse (MRD), and those who relapsed received rituximab as re-induction but were not considered to have relapsed unless there was morphologic evidence of relapse.

The Cancer and Leukemia Group B (CALGB 59909 trial) reported that rituximab in combination with methotrexate and augmented CHOP followed by HDT/ASCR was safe and effective in patients with newly diagnosed MCL (n=78).[56] At a median follow-up of 4.7 years, the 5-year PFS and OS rates were 56% and 64%, respectively.[56]

In newly diagnosed patients with MCL (n=88 evaluable), sequential chemotherapy (CHOP followed by ICE) with or without rituximab followed by consolidation with HDT/ASCR was associated with a superior PFS compared with RIT followed by CHOP (4-year PFS rate: 65% vs. 26%); the 4-year OS rate was 84% for both treatment groups.[16] This study also demonstrated the prognostic significance of the proliferation index on PFS outcomes. Moreover, among the subgroup of patients with a proliferation index <30%, HDT/ASCR resulted in superior PFS compared with RIT-CHOP (5-year PFS rate: 82% vs. 24%).[16]

In the phase III randomized Intergroup trial conducted by the European MCL Network, sequential treatment with 3 cycles each of R-CHOP and R-DHAP followed by HDT/ASCR (using high-dose cytarabine containing myeloablative regimen) induced higher remission rates compared with 6 cycles of R-CHOP followed by HDT/ASCR (using myeloablative radiochemotherapy) in patients (age ≤ 65 years) with advanced stage MCL (391 evaluable patients).[57] The clinical CR rate was 39% and 26%, respectively; median time to treatment failure (TTF) was not reached in the R-CHOP/R-DHAP arm compared with 49 months in the R-CHOP arm, after a median follow up of 27 months. The rate of molecular remission (MRD-negative status in peripheral blood or bone marrow) was significantly higher in the R-CHOP/R-DHAP arm compared with R-CHOP (73% vs. 32%). Achievement of molecular remission in the bone marrow after induction was associated with significantly improved 2-year PFS outcomes in the combined treatment arms.[57] Final analysis from this trial (455 evaluable patients) confirmed that R-CHOP/R-DHAP induction was associated with higher CR rate (36% vs. 25%) and CR/CRu rate (54% vs. 40%) compared with R-CHOP.[58] After HDT/ASCR, the CR rates were similar between treatment arms (61% vs. 63%), although R-CHOP/R-DHAP was associated with longer remission duration (84 months vs. 49 months; *P*=.0001). After a median follow up of 51 months, median TTF was significantly longer in the R-CHOP/R-DHAP arm compared with the R-CHOP arm (88 months vs. 46 months; *P*=.038).[58] Moreover, median OS was longer in the R-CHOP/R-DHAP arm (not reached vs. 82 months; *P*=.045). The investigators concluded that an induction regimen containing high-dose cytarabine in addition to R-CHOP resulted in improved outcomes, and suggested that these regimens followed by HDT/ASCR may define a new standard for the treatment of younger patients (<65 years of age) with MCL.[58]

In a phase II multicenter trial of the French cooperative group GELA, induction with 3 cycles each of R-CHOP and R-DHAP resulted in an ORR of 95% with CR in 57% of patients (age ≤65 years) with previously untreated MCL (n=60).[59] Patients went on to receive HDT/ASCR on this study. After a median follow up of 67 months, the median EFS was 83 months and median OS has not been reached; the 5-year OS was 75%.[59]

Post-induction Maintenance Therapy

Maintenance therapy with rituximab may provide extended disease control for patients who are not physically fit or not eligible to undergo aggressive first-line treatment regimens and HDT/ASCR.[61-63]

In a small phase II pilot study in previously untreated patients (n=22), a less intensive, modified R-hyper-CVAD regimen (without methotrexate or cytarabine, and with modifications to dose schedule of vincristine and steroids) followed by rituximab maintenance for 5 years resulted in a median PFS of 37 months with median OS not reached; the use of rituximab maintenance appeared to prolong PFS with acceptable toxicity.[61]

In a subsequent study that incorporated the proteasome inhibitor bortezomib into the modified R-hyper-CVAD (VcR-CVAD regimen) followed by rituximab maintenance in patients with previously untreated MCL (n=30), the CR/CRu rate was 77%.[62] After a median follow up of 42 months, median PFS and OS had not been reached. The 3-year PFS rate was 63% and OS rate was 86%. This VcR-CVAD regimen with maintenance rituximab was further evaluated in a larger phase II ECOG trial (E1405) in patients with previously untreated MCL (n=75).[64] The ORR in this trial was 95% with CR in 68% of patients. Following induction therapy, patients proceeded with maintenance rituximab (n=44) or consolidation with stem cell transplantation (SCT) off protocol (n=22). After a median follow up of 4.5 years, the 3-year PFS and OS rates were 72% and 88% respectively. No differences in PFS or OS were observed between patients who went on to receive rituximab maintenance or SCT.[64]

The European MCL Network recently conducted a phase III randomized trial in older patients (age >60 years not eligible for HDT/ASCR) with previously untreated MCL (n=560; 485 patients evaluable for response) to evaluate induction with R-FC (rituximab, fludarabine and cyclophosphamide) versus R-CHOP, with a second randomization to maintenance with rituximab every 2 months (until relapse; thus, there was no set duration of maintenance rituximab) versus interferon-alfa (given until progression in both arms).[63] Response after induction therapy with R-CHOP and R-FC was similar (CR rate: 34% vs. 40%; CR/CRu rate: 49% vs.53%; ORR: 86% vs. 78%, respectively), but more patients progressed during R-FC than with R-CHOP (14% vs. 5%). Median duration of response was similar between R-FC and R-CHOP arms (37 months vs. 36 months). OS (from start of induction) was significantly longer with R-CHOP compared with R-FC (Median OS: 67 months vs. 40 months; 4-year OS: 62% vs. 47%; *P*=0.005).[63] Grade 3-4 hematologic toxicities occurred more frequently with R-FC induction. Among the patients who responded to induction and underwent second randomization (n=316), median remission duration was significantly improved with rituximab maintenance compared with interferon alfa (75 months vs. 27 months; *P* <.001). After a median follow up of 42 months, OS outcomes were not significantly different between the two maintenance arms (4-year OS: 79% with rituximab vs. 67% with interferon alfa).[63] However, in the subgroup of patients treated with R-CHOP induction (n=184), median OS (from end of induction) was significantly longer with rituximab maintenance compared with interferon alfa (not reached vs. 64 months; 4-year OS: 87% vs. 63%; *P*=0.005). Moreover, grade 3-4 hematologic toxicities occurred more frequently with interferon alfa. Rituximab was associated with more frequent grade 1-2 infections.[63] This study suggests that for patients who are not candidates for HDT/ASCR as part of first-line therapy, R-CHOP induction followed by rituximab maintenance may offer the best chance to prolong remission duration. Given the positive outcomes reported in this study (with median duration of response exceeding 6 years with rituximab maintenance and a 4-year OS rate of 87% in patients treated with R-CHOP and rituximab maintenance), it is unknown whether first-line consolidation with HDT/ASCR provides an advantage over rituximab maintenance in patients of any age. At the present time, no data are available from randomized studies that would allow direct comparison of outcomes with these two different consolidation approaches.

Relapsed or Refractory Disease

Second-line Therapy

The treatment of patients with relapsed/refractory MCL remains a major challenge, as CR rates are generally low (<30%) and response durations are limited with available regimens.[65]

Bortezomib is a proteasome inhibitor with activity in patients with relapsed or refractory MCL,[42-44] and is currently approved for the treatment of patients with MCL that has relapsed after at least one prior therapy. FDA approval of this agent was based on data from the pivotal phase II PINNACLE trial of single-agent bortezomib in patients with relapsed/refractory MCL (n=155; 141 evaluable patients).[42] In this trial, bortezomib induced an ORR of 33% (CR in 8%), with a median duration of response of 9 months.[42] Median time to progression (in all patients) was 6 months. Longer follow-up data also confirmed these initial findings; after a median follow-up time of 26 months, the median OS in all patients was 23.5 months and was 35 months in responding patients.[66] Small studies have reported promising activity of bortezomib combined with rituximab in heavily pretreated patients with relapsed/refractory MCL.[67,68] In addition, bortezomib in combination with R-hyper-CVAD, with (as discussed above) or without rituximab maintenance, is under investigation in previously untreated patients with MCL.[62,69]

Cladribine has shown activity as a single agent in patients with relapsed MCL.[39,40] In the trial conducted by the North Central Cancer Treatment group, the ORR and median PFS for patients with recurrent MCL (n=25) were 46% (21% CR) and 5 months, respectively.[39]

Fludarabine-based combination regimens, with or without rituximab, have also shown activity in patients with relapsed or refractory MCL.[70-72] Results from a small pilot trial in patients with newly diagnosed and relapsed MCL (20 evaluable patients) showed that the combination of fludarabine, mitoxantrone and rituximab (FMR) induced a CR rate of 90%, with a median duration of CR of 17 months.[71] In patients with MCL (n=66) treated as part of a prospective randomized phase III study of the GLSG, the addition of rituximab to the combination of fludarabine, cyclophosphamide and mitoxantrone (FCM) [R-FCM regimen], produced higher ORR (58% vs. 46%) and CR rates (29% vs. 0%) compared with FCM alone.[72,73] This trial included a second randomization to rituximab maintenance versus observation in patients who responded to therapy. In the subgroup of patients with MCL who received R-FCM induction (n=47), rituximab maintenance resulted in a higher proportion of patients in remission beyond 2 years compared with observation only (45% vs. 9%; *P*=0.049); the median duration of remission was similar between maintenance and observation arms (14 months vs. 12 months).[73]

Fludarabine combined with rituximab (FR) was evaluated as part of a phase III randomized trial from StiL that compared FR versus BR in patients with relapsed/refractory follicular or indolent lymphoma or MCL (208 evaluable patients; MCL histology in about 20%).[74] Following a protocol amendment, maintenance therapy with rituximab was also added in both treatment arms (n=40 only). The FR regimen resulted in an ORR and CR rate of 52.5% and 16%, respectively, which was significantly inferior to response rates with BR (ORR 83.5%; CR rate 38.5%). The median PFS with FR was 11 months, which was also significantly shorter compared with a median of 30 months observed with the BR regimen (*P* <.0001).[74] However, no difference in median OS was observed between treatment arms after a median observation time of 33 months.

Bendamustine, as a single agent or in combination with rituximab (BR), has shown promising results with acceptable toxicity in patients with heavily pretreated patients with relapsed or refractory indolent or mantle cell histologies as well as aggressive lymphomas.[74,75] In a phase II multicenter study, BR resulted in an ORR of 92% (41% CR) in patients with relapsed or refractory indolent lymphomas and MCL (n=67).[75] The median duration of response and PFS was 21 months and 23 months, respectively. Outcomes were similar for patients with indolent or mantle

cell histologies. For the subgroup of patients with MCL histology (n=12), the ORR was 92% (42% CR; 17% CRu) and the median duration of response was 19 months.[75] As discussed above, the phase III randomized trial from StiL showed superiority of the BR regimen compared with FR in patients with relapsed/refractory follicular or indolent lymphoma or MCL (208 evaluable patients; MCL histology in about 20%), with an ORR of 83.5% (38.5% CR) and median PFS of 30 months.[74] In a small multicenter phase II study that evaluated the combination of bendamustine and rituximab with bortezomib in patients with relapsed/refractory indolent lymphomas or MCL (29 evaluable patients; MCL histology, n=7), the ORR was 83% (52% CR) and the 2-year PFS rate was 47%.[76] The ORR among the small subgroup of patients with MCL was 71%. Based on these results, this combination regimen is currently being evaluated in randomized trials conducted by the US cooperative groups.

Lenalidomide is an immunomodulating agent that has been evaluated as a single agent in patients with relapsed or refractory aggressive NHL in two phase II studies (NHL-002 and NHL-003).[77-79] In the subset analysis of patients with MCL (n=15) in the NHL-002 study, the ORR was 53% (20% CR).[78] The median duration of response and PFS were 14 months and 6 months, respectively. The subset analysis of patients with MCL (n=54) enrolled in the larger confirmatory study (NHL-003) also showed similar results with an ORR of 43% (17% CR).[79] An updated analysis from the NHL-003 study showed that in the relapsed/refractory MCL subgroup (n=57), the ORR with single-agent lenalidomide was 35% (12% CR/CRu) by independent central review at a median follow up of 12 months.[80] The ORR by investigator review was 44% (21% CR/CRu). By central review, the median duration of response was 16 months and the median PFS was approximately 9 months.[80] Additional phase II studies are specifically evaluating the role of single-agent lenalidomide in patients with relapsed/refractory MCL. In a phase II study in patients with relapsed/refractory MCL (n=26), lenalidomide (including low-dose lenalidomide maintenance in responding patients) resulted in an ORR of 31% with a median response duration of 22 months.[81] The median PFS was only 4 months. However, among the patients who received maintenance lenalidomide (n=11), the median PFS was 15 months.[81]. In a larger multicenter phase II study (MCL-001) in patients who relapsed after or were refractory to bortezomib (n=134; median 4 prior therapies), lenalidomide as single agent resulted in an ORR of 28% (7.5% CR/CRu) by independent central review.[82] All patients were previously treated with rituximab-containing regimens, and all had relapsed or were refractory to bortezomib. The median duration of response was 16.6 months. The median PFS and OS were was 4 months and 19 months respectively. In the larger studies, the most common grade 3 or 4 toxicities with lenalidomide were myelosuppression (neutropenia in 43%-46% and thrombocytopenia in 28%-30%).[80,82] Lenalidomide combined with rituximab is also under clinical evaluation. In a phase I/II study of a combination regimen with lenalidomide and rituximab in patients with relapsed/refractory MCL (36 evaluable patients), the ORR was 53% (31% CR).[83] The median duration of response was 18 months, and the median PFS (for all patients in the phase II portion) was 14 months. In an updated analysis of this study (n=52), the ORR was 57% (36% CR) among patients treated in the phase II portion (n=44); median duration of response was 19 months.[84] The median PFS was 11 months and median OS was 24 months. The most common grade 3 or 4 toxicities included neutropenia (66%) and thrombocytopenia (23%).[84]

Ibrutinib is a small-molecule inhibitor of Bruton's tyrosine kinase (BTK) involved in the B-cell signalling pathway and has shown promising activity in patients with B-cell malignancies.[85] In a phase I

dose-escalation study in patients with relapsed and/or refractory B-cell malignancies (n=56; follicular lymphoma, 29%; CLL/SLL, 29%; MCL, 16%), ibrutinib given in a continuous or intermittent dosing schedule (until progression) resulted in an ORR of 60% (CR in 16%) among evaluable patients (n=50).[85] The median PFS was approximately 14 months. Among the subgroup of patients with MCL (n=9), response was observed in 7 patients, including a CR in 3 patients. Treatment with ibrutinib was well tolerated even with prolonged dosing (> 6 months), with no dose-limiting toxicities and no significant myelosuppression; grade 3 or 4 adverse events were uncommon.[85] The fixed dose of 560 mg daily given continuously was well tolerated and resulted in full occupancy of the BTK target; thus, the recommended phase II dose was established as 560 mg daily. The results of a multicenter phase II study evaluating ibrutinib (560 mg continuous daily dosing until progression) in patients with relapsed or refractory MCL (n=115; median 3 prior therapies, range 1–5), including in patients previously treated with bortezomib have been published.[86] The large majority of patients had received prior rituximab-containing regimens (89%) and 45% were refractory to last therapy before study enrollment. Most patients had advanced disease (72%) and 49% had high-risk disease based on MIPI scores.[86] Among 111 evaluable patients, the estimated median follow up was 15 months at the time of analysis. The ORR was 68% with a CR in 21% of patients. The median duration of response was 17.5 months. Among the subgroup of patients who were previously treated with bortezomib (n=48), the ORR was 67% with a CR in 23%. The response rates appeared to increase with longer duration of therapy. The estimated median PFS for all treated patients was approximately 14 months. Median OS has not yet been reached; the estimated OS rate at 18 months was 58%. The most common grade 3 or greater adverse events included neutropenia (16%), thrombocytopenia (11%), anemia (10%), pneumonia (6%), diarrhea (6%), fatigue (5%) and dyspnea (5%).[86] This study showed durable responses with single-agent ibrutinib with a favorable toxicity profile. The use of ibrutinib has been known to result in an initial transient lymphocytosis which resolves by a median of 8 weeks after initiation of ibrutinib.[87] Ibrutinib treatment has also been associated with grade ≥ 3 bleeding events in 5% of patients.[87] The benefit and risk of ibrutinib should be considered in patients requiring anti-platelet or anticoagulant therapies. See *"Special Considerations for the use of BCR Inhibitors"* in the guidelines for monitoring and management of adverse reactions associated with ibrutinib.

Based on these data, ibrutinib (560 mg orally, once daily) was recently approved by the FDA for the treatment of patients with MCL who received at least one prior therapy.

Second-Line Consolidation Therapy

In patients with relapsed/refractory indolent NHL, allogeneic stem cell transplant (SCT) has resulted in decreased rates of disease recurrence compared with HDT/ASCR, but at the cost of a higher treatment-related mortality (TRM) rate.[88,89]

In an effort to reduce the TRM associated with allogeneic SCT, the use of reduced-intensity conditioning (RIC) regimens has been explored. In a study that evaluated allogeneic SCT using conventional myeloablative conditioning or RIC in patients with relapsed/refractory NHL (n=25), RIC (fludarabine-based regimens) was associated with a decreased TRM rate (17% vs. 54%) and increased event-free survival (50% vs. 23%) and OS (67% vs. 23%) rates at 1 year compared with myeloablative regimens.[90] A multicenter retrospective study of RIC allogeneic SCT in patients with relapsed/refractory low-grade NHL (n=73) also reported promising long-term outcomes with RIC (primarily using fludarabine-based regimens); in this study, the 3-year EFS and OS

rates were 51% and 56%, respectively.[91] Although the 3-year relapse rate appeared low at 10%, the TRM rate was high, with a 3-year cumulative incidence of 40%.[91] Allogeneic SCT using RIC has been evaluated as a consolidation strategy for patients in remission following treatment for relapsed/refractory MCL.[51,92,93] In patients with relapsed MCL treated with RIC allogeneic SCT (n=18), the 3-year PFS rate and estimated 3-year OS rate was 82% and 85.5%, respectively; the majority of patients in this study (89%) had chemosensitive disease.[92] In another study, RIC allogeneic SCT was evaluated in patients with relapsed/refractory MCL (n=33); 42% of these patients had failed prior HDT/ASCR.[93] The 2-year disease-free survival and OS rates were 60% and 65%, respectively. The 2-year relapse rate was 9%; moreover, with a median follow up of nearly 25 months, none of the patients transplanted in a CR (n=13) experienced disease relapse.[93] The 2-year TRM rate in this study was 24%. In an analysis of patients with MCL treated with SCT at the MD Anderson Cancer Center, the subgroup of patients with relapsed/refractory disease treated with RIC allogeneic SCT (n=35) had favorable long-term outcomes.[51] Most of these patients (62%) were transplanted in remission (31% in second remission). The analysis reported a median PFS of 60 months, and 6-year PFS and OS rates of 46% and 53%, respectively. The TRM rates at 3 months and 1 year were 0% and 9%, respectively.[51]

NCCN Recommendations for Stage I-II

Recommendations for First-line Therapy and Follow-up

Outside of a clinical trial, the NCCN Guidelines panel recommends RT (30-36 Gy) alone or combination chemoimmunotherapy with or without RT. These recommendations are based on treatment principles in the absence of more definitive clinical data.

For patients with a CR, clinical follow up should be conducted every 3-6 months for the first 5 years, and then on a yearly basis or as clinically indicated. If the patient received initial treatment with chemoimmunotherapy with or without RT, and relapses after an initial CR (or the initial response is a PR or disease progression on first-line therapy), the patient should be treated with second-line therapy regimens recommended for stage II (bulky) or stage III-IV disease (see sections below). If the patient received initial treatment with RT alone and relapses after achieving a CR (or the initial response is a PR or disease progression with RT alone), then the patient can be treated with first-line induction therapy (comprising chemoimmunotherapy regimens) recommended for stage II (bulky) and stage III-IV disease.

NCCN Recommendations for Stage II (bulky) and Stage III-IV

Recommendations for First-line Therapy and Follow-up

In the absence of standard management for patients with advanced disease, patients should be referred for participation in prospective clinical trials. Similar to the management of patients with indolent lymphomas, patients with MCL often require highly individualized courses of care. The majority of patients with MCL will have advanced stage disease and require systemic therapy. However, in highly selected patients with asymptomatic disease, close observation with deferred therapy is a reasonable option, especially for those with good performance status and lower risk scores on standard IPI.[94]

The standard treatment regimen for MCL is not yet established. There are no prospective randomized studies comparing the various aggressive induction regimens for MCL, although some randomized data exist for less intensive first-line treatment options (as previously discussed). Given the role of rituximab in the treatment of CD20-positive NHL, it is reasonable to consider rituximab-containing regimens for management of advanced MCL. Based on the available data, the NCCN Guideline panel has included the following regimens for initial induction therapy:

Aggressive Therapy

All regimens listed below (except for hyper-CVAD + rituximab) included first-line consolidation with HDT/ASCR in published reports.

- Hyper-CVAD + rituximab[32-34]
- Dose-intensified CHOP [maxi-CHOP] alternating with rituximab + high-dose cytarabine (NORDIC regimen)[55]
- Rituximab and methotrexate with augmented CHOP (CALGB regimen)[56]
- Sequential R-CHOP and R-ICE[16]
- Alternating R-CHOP and R-DHAP[57]

Less aggressive therapy:

- Bendamustine + rituximab[37]
- Bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP)[45]
- Cladribine + rituximab[39,41]
- CHOP + rituximab (R-CHOP)[29,36]
- Modified Hyper-CVAD with rituximab maintenance in patients older than 65 years[61]

For patients with a CR to first-line therapy, participation in a clinical trial or HDT/ASCR is recommended for eligible patients (see section below). For patients with a CR, clinical follow up should be conducted every 3-6 months for the first 5 years, and then on a yearly basis or as clinically indicated. For patients with only a PR to first-line therapy, additional therapy (see second-line therapy regimens below) may be considered in an effort to improve the quality of a response. If the patient achieves a CR (or improved PR) with additional therapy, consolidation with HDT/ASCR may be considered for eligible patients, as discussed above. For patients who relapse after achieving a remission to first-line therapy, or for patients who experience disease progression during initial therapy, participation in clinical trials is preferred. In the absence of suitable clinical trials, second-line treatment options can be considered.

Recommendations for First-line Consolidation Therapy

The panel recommends consolidation with HDT/ASCR for eligible patients in remission following first-line therapy, although no studies have compared maintenance rituximab with HDT/ASCR for patients in first CR. In general, patients will receive an aggressive induction regimen prior to consolidation; however, less aggressive induction therapy followed by consolidation with HDT/ASCR or maintenance rituximab may also result in good long-term outcome.

For patients who are not candidates for HDT/ASCR, and who are in remission after first-line therapy with R-CHOP, maintenance treatment with rituximab (every 8 weeks until disease progression) is recommended (category 1)[63]

Recommendations for Second-line Therapy

The optimal approach to relapsed or refractory disease remains to be defined. Patients with relapsed disease following CR to induction therapy or those who obtain only a PR to induction therapy or those with progressive disease are appropriate candidates for clinical trials involving HDT/ASCR or allogeneic HSCT, immunotherapy with nonmyeloablative stem cell rescue or treatment with new agents. Based on the recent FDA approval, the panel has included ibrutinib as an option for second-line therapy for patients with relapsed or refractory disease.[86] Alternatively, in the absence of an appropriate clinical trial, these patients can be treated with second-line chemotherapy regimens (with or without rituximab) recommended for patients with DLBCL or any of the following regimens:

- Bendamustine ± rituximab[74]
- Bortezomib ± rituximab[66,67]
- Cladribine ± rituximab[39,40]
- FC (fludarabine, cyclophosphamide) ± rituximab[70]
- FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab)[72]
- FMR (fludarabine, mitoxantrone, rituximab)[71]
- Lenalidomide ± rituximab[82,95]
- PCR (pentostatin, cyclophosphamide, rituximab)
- PEPC (prednisone, etoposide, procarbazine, cyclophosphamide) ± rituximab[96]

Allogeneic transplantation (with myeloablative or reduced intensity conditioning) is an appropriate option for patients with relapsed or refractory disease that is in remission following second-line therapy.[51,92,93]

References

1. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 1997;89:3909-3918. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9166827.

2. Fisher RI, Dahlberg S, Nathwani BN, et al. A clinical analysis of two indolent lymphoma entities: mantle cell lymphoma and marginal zone lymphoma (including the mucosa-associated lymphoid tissue and monocytoid B-cell subcategories): a Southwest Oncology Group study. Blood 1995;85:1075-1082. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7849295.

3. Yatabe Y, Suzuki R, Tobinai K, et al. Significance of cyclin D1 overexpression for the diagnosis of mantle cell lymphoma: a clinicopathologic comparison of cyclin D1-positive MCL and cyclin D1-negative MCL-like B-cell lymphoma. Blood 2000;95:2253-2261. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10733493.

4. Hartmann EM, Campo E, Wright G, et al. Pathway discovery in mantle cell lymphoma by integrated analysis of high-resolution gene expression and copy number profiling. Blood 2010;116:953-961. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20421449.

5. Iqbal J, Shen Y, Liu Y, et al. Genome-wide miRNA profiling of mantle cell lymphoma reveals a distinct subgroup with poor prognosis. Blood 2012;119:4939-4948. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22490335.

6. Fu K, Weisenburger DD, Greiner TC, et al. Cyclin D1-negative mantle cell lymphoma: a clinicopathologic study based on gene expression profiling. Blood 2005;106:4315-4321. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16123218.

7. Wlodarska I, Dierickx D, Vanhentenrijk V, et al. Translocations targeting CCND2, CCND3, and MYCN do occur in t(11;14)-negative mantle cell lymphomas. Blood 2008;111:5683-5690. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18391076.

8. Salaverria I, Royo C, Carvajal-Cuenca A, et al. CCND2 rearrangements are the most frequent genetic events in cyclin D1(-) mantle cell lymphoma. Blood 2013;121:1394-1402. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23255553.

9. Chen YH, Gao J, Fan G, Peterson LC. Nuclear expression of sox11 is highly associated with mantle cell lymphoma but is independent of t(11;14)(q13;q32) in non-mantle cell B-cell neoplasms. Mod Pathol 2010;23:105-112. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19801969.

10. Mozos A, Royo C, Hartmann E, et al. SOX11 expression is highly specific for mantle cell lymphoma and identifies the cyclin D1-negative subtype. Haematologica 2009;94:1555-1562. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19880778.

11. Zeng W, Fu K, Quintanilla-Fend L, et al. Cyclin D1-negative blastoid mantle cell lymphoma identified by SOX11 expression. Am J Surg Pathol 2012;36:214-219. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22251940.

12. Avet-Loiseau H, Garand R, Gaillard F, et al. Detection of t(11;14) using interphase molecular cytogenetics in mantle cell lymphoma and atypical chronic lymphocytic leukemia. Genes Chromosomes Cancer 1998;23:175-182. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9739021.

13. Determann O, Hoster E, Ott G, et al. Ki-67 predicts outcome in advanced-stage mantle cell lymphoma patients treated with anti-CD20 immunochemotherapy: results from randomized trials of the European MCL Network and the German Low Grade Lymphoma Study Group. Blood 2008;111:2385-2387. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18077791.

14. Garcia M, Romaguera JE, Inamdar KV, et al. Proliferation predicts failure-free survival in mantle cell lymphoma patients treated with rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with rituximab plus

high-dose methotrexate and cytarabine. Cancer 2009;115:1041-1048. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19170236.

15. Hsi ED, Jung S, Lai R, et al. Ki67 and PIM1 expression predict outcome in mantle cell lymphoma treated with high dose therapy, stem cell transplantation and rituximab: a Cancer and Leukemia Group B 59909 correlative science study. Leuk Lymphoma 2008;49:2081-2090. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19021050.

16. Schaffel R, Hedvat CV, Teruya-Feldstein J, et al. Prognostic impact of proliferative index determined by quantitative image analysis and the International Prognostic Index in patients with mantle cell lymphoma. Ann Oncol 2010;21:133-139. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20019090.

17. Tiemann M, Schrader C, Klapper W, et al. Histopathology, cell proliferation indices and clinical outcome in 304 patients with mantle cell lymphoma (MCL): a clinicopathological study from the European MCL Network. Br J Haematol 2005;131:29-38. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16173960.

18. Koletsa T, Markou K, Ouzounidou S, et al. In situ mantle cell lymphoma in the nasopharynx. Head Neck 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23280758.

19. Richard P, Vassallo J, Valmary S, et al. "In situ-like" mantle cell lymphoma: a report of two cases. J Clin Pathol 2006;59:995-996. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16935977.

20. Carvajal-Cuenca A, Sua LF, Silva NM, et al. In situ mantle cell lymphoma: clinical implications of an incidental finding with indolent clinical behavior. Haematologica 2012;97:270-278. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22058203.

21. Swerdlow SH, Campo E, Seto M, Muller-Hermelink HK. Mantle cell lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:229-232.

22. Edlefsen KL, Greisman HA, Yi HS, et al. Early lymph node involvement by mantle cell lymphoma limited to the germinal center: report of a case with a novel "follicular in situ" growth pattern. Am J Clin Pathol 2011;136:276-281. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21757601.

23. Adam P, Schiefer AI, Prill S, et al. Incidence of preclinical manifestations of mantle cell lymphoma and mantle cell lymphoma in situ in reactive lymphoid tissues. Mod Pathol 2012;25:1629-1636. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22790016.

24. Carbone A, Santoro A. How I treat: diagnosing and managing "in situ" lymphoma. Blood 2011;117:3954-3960. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21224472.

25. Romaguera JE, Medeiros LJ, Hagemeister FB, et al. Frequency of gastrointestinal involvement and its clinical significance in mantle cell lymphoma. Cancer 2003;97:586-591. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12548600.

26. Salar A, Juanpere N, Bellosillo B, et al. Gastrointestinal involvement in mantle cell lymphoma: a prospective clinic, endoscopic, and pathologic study. Am J Surg Pathol 2006;30:1274-1280. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17001159.

27. Teodorovic I, Pittaluga S, Kluin-Nelemans JC, et al. Efficacy of four different regimens in 64 mantle-cell lymphoma cases: clinicopathologic comparison with 498 other non-Hodgkin's lymphoma subtypes. European Organization for the Research and Treatment of Cancer Lymphoma Cooperative Group. J Clin Oncol 1995;13:2819-2826. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7595744.

28. Leitch HA, Gascoyne RD, Chhanabhai M, et al. Limited-stage mantle-cell lymphoma. Ann Oncol 2003;14:1555-1561. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14504058.

29. Martin P, Chadburn A, Christos P, et al. Intensive treatment strategies may not provide superior outcomes in mantle cell lymphoma:

overall survival exceeding 7 years with standard therapies. Ann Oncol 2008;19:1327-1330. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18349031.

30. Lacasce AS, Vandergrift JL, Rodriguez MA, et al. Comparative outcome of initial therapy for younger patients with mantle cell lymphoma: an analysis from the NCCN NHL Database. Blood 2012;119:2093-2099. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22234679.

31. Romaguera JE, Fayad L, Rodriguez MA, et al. High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. J Clin Oncol 2005;23:7013-7023. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16145068.

32. Romaguera JE, Fayad LE, Feng L, et al. Ten-year follow-up after intense chemoimmunotherapy with Rituximab-HyperCVAD alternating with Rituximab-high dose methotrexate/cytarabine (R-MA) and without stem cell transplantation in patients with untreated aggressive mantle cell lymphoma. Br J Haematol 2010;150:200-208. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20528872.

33. Merli F, Luminari S, Ilariucci F, et al. Rituximab plus HyperCVAD alternating with high dose cytarabine and methotrexate for the initial treatment of patients with mantle cell lymphoma, a multicentre trial from Gruppo Italiano Studio Linfomi. Br J Haematol 2012;156:346-353. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22145911.

34. Bernstein SH, Epner E, Unger JM, et al. A phase II multicenter trial of hyperCVAD MTX/Ara-C and rituximab in patients with previously untreated mantle cell lymphoma; SWOG 0213. Ann Oncol 2013;24:1587-1593. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23504948.

35. Howard OM, Gribben JG, Neuberg DS, et al. Rituximab and CHOP induction therapy for newly diagnosed mantle-cell lymphoma: molecular complete responses are not predictive of progression-free survival. J Clin Oncol 2002;20:1288-1294. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11870171.

36. Lenz G, Dreyling M, Hoster E, et al. Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). J Clin Oncol 2005;23:1984-1992. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15668467.

37. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet 2013;381:1203-1210. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23433739.

38. Visco C, Finotto S, Zambello R, et al. Combination of rituximab, bendamustine, and cytarabine for patients with mantle-cell non-Hodgkin lymphoma ineligible for intensive regimens or autologous transplantation. J Clin Oncol 2013;31:1442-1449. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23401442.

39. Inwards DJ, Fishkin PA, Hillman DW, et al. Long-term results of the treatment of patients with mantle cell lymphoma with cladribine (2-CDA) alone (95-80-53) or 2-CDA and rituximab (N0189) in the North Central Cancer Treatment Group. Cancer 2008;113:108-116. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18470909.

40. Rummel MJ, Chow KU, Jager E, et al. Treatment of mantle-cell lymphomas with intermittent two-hour infusion of cladribine as first-line therapy or in first relapse. Ann Oncol 1999;10:115-117. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10076731.

41. Spurgeon SE, Pindyck T, Okada C, et al. Cladribine plus rituximab is an effective therapy for newly diagnosed mantle cell lymphoma. Leuk

Lymphoma 2011;52:1488-1494. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21623691.

42. Fisher RI, Bernstein SH, Kahl BS, et al. Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. J Clin Oncol 2006;24:4867-4874. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17001068.

43. Belch A, Kouroukis CT, Crump M, et al. A phase II study of bortezomib in mantle cell lymphoma: the National Cancer Institute of Canada Clinical Trials Group trial IND.150. Ann Oncol 2007;18:116-121. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16971665.

44. O'Connor OA, Moskowitz C, Portlock C, et al. Patients with chemotherapy-refractory mantle cell lymphoma experience high response rates and identical progression-free survivals compared with patients with relapsed disease following treatment with single agent bortezomib: results of a multicentre phase 2 clinical trial. British Journal of Haematology 2009;145:34-39. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19220284.

45. Cavalli F, Rooney B, Pei L, et al. Randomized phase 3 study of rituximab, cyclophosphamide, doxorubicin, and prednisone plus vincristine (R-CHOP) or bortezomib (VR-CAP) in newly diagnosed mantle cell lymphoma (MCL) patients (pts) ineligible for bone marrow transplantation (BMT) [abstract]. J Clin Oncol 2014;32 (15_suppl):Abstract 8500. Available at: http://meeting.ascopubs.org/cgi/content/abstract/32/15_suppl/8500.

46. Khouri IF, Romaguera J, Kantarjian H, et al. Hyper-CVAD and high-dose methotrexate/cytarabine followed by stem-cell transplantation: an active regimen for aggressive mantle-cell lymphoma. J Clin Oncol 1998;16:3803-3809. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9850025.

47. Khouri IF, Saliba RM, Okoroji GJ, et al. Long-term follow-up of autologous stem cell transplantation in patients with diffuse mantle cell lymphoma in first disease remission: the prognostic value of beta2-microglobulin and the tumor score. Cancer 2003;98:2630-2635. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14669282.

48. Lefrere F, Delmer A, Suzan F, et al. Sequential chemotherapy by CHOP and DHAP regimens followed by high-dose therapy with stem cell transplantation induces a high rate of complete response and improves event-free survival in mantle cell lymphoma: a prospective study. Leukemia 2002;16:587-593. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11960337.

49. Dreyling M, Lenz G, Hoster E, et al. Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: results of a prospective randomized trial of the European MCL Network. Blood 2005;105:2677-2684. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15591112.

50. Ritchie DS, Seymour JF, Grigg AP, et al. The hyper-CVAD-rituximab chemotherapy programme followed by high-dose busulfan, melphalan and autologous stem cell transplantation produces excellent event-free survival in patients with previously untreated mantle cell lymphoma. Ann Hematol 2007;86:101-105. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17089127.

51. Tam CS, Bassett R, Ledesma C, et al. Mature results of the M. D. Anderson Cancer Center risk-adapted transplantation strategy in mantle cell lymphoma. Blood 2009;113:4144-4152. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19168784.

52. van 't Veer MB, de Jong D, MacKenzie M, et al. High-dose Ara-C and beam with autograft rescue in R-CHOP responsive mantle cell lymphoma patients. Br J Haematol 2009;144:524-530. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19036081.

53. Till BG, Gooley TA, Crawford N, et al. Effect of remission status and induction chemotherapy regimen on outcome of autologous stem cell transplantation for mantle cell lymphoma. Leuk Lymphoma

2008;49:1062-1073. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18452065.

54. Vandenberghe E, Ruiz de Elvira C, Loberiza FR, et al. Outcome of autologous transplantation for mantle cell lymphoma: a study by the European Blood and Bone Marrow Transplant and Autologous Blood and Marrow Transplant Registries. Br J Haematol 2003;120:793-800. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12614212.

55. Geisler CH, Kolstad A, Laurell A, et al. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. Blood 2008;112:2687-2693. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18625886.

56. Damon LE, Johnson JL, Niedzwiecki D, et al. Immunochemotherapy and autologous stem-cell transplantation for untreated patients with mantle-cell lymphoma: CALGB 59909. J Clin Oncol 2009;27:6101-6108. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19917845.

57. Pott C, Hoster E, Beldjord K, et al. R-CHOP/R-DHAP compared to R-CHOP induction followed by high dose therapy with autologous stem cell transplantation induces higher rates of molecular remission in MCL: results of the MCL younger intergroup trial of the European MCL Network [abstract]. Blood 2010;116:Abstract 965. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/965.

58. Hermine O, Hoster E, Walewski J, et al. Alternating Courses of 3x CHOP and 3x DHAP Plus Rituximab Followed by a High Dose ARA-C Containing Myeloablative Regimen and Autologous Stem Cell Transplantation (ASCT) Increases Overall Survival When Compared to 6 Courses of CHOP Plus Rituximab Followed by Myeloablative Radiochemotherapy and ASCT in Mantle Cell Lymphoma: Final Analysis of the MCL Younger Trial of the European Mantle Cell Lymphoma Network (MCL net) [abstract]. Blood 2012;120:Abstract 151. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/120/21/151.

59. Delarue R, Haioun C, Ribrag V, et al. CHOP and DHAP plus rituximab followed by autologous stem cell transplantation in mantle cell lymphoma: a phase 2 study from the Groupe d'Etude des Lymphomes de l'Adulte. Blood 2013;121:48-53. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22718839.

60. Geisler CH, Kolstad A, Laurell A, et al. Nordic MCL2 trial update: six-year follow-up after intensive immunochemotherapy for untreated mantle cell lymphoma followed by BEAM or BEAC + autologous stem-cell support: still very long survival but late relapses do occur. Br J Haematol 2012;158:355-362. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22640180.

61. Kahl BS, Longo WL, Eickhoff JC, et al. Maintenance rituximab following induction chemoimmunotherapy may prolong progression-free survival in mantle cell lymphoma: a pilot study from the Wisconsin Oncology Network. Ann Oncol 2006;17:1418-1423. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16766582.

62. Chang JE, Peterson C, Choi S, et al. VcR-CVAD induction chemotherapy followed by maintenance rituximab in mantle cell lymphoma: a Wisconsin Oncology Network study. Br J Haematol 2011;155:190-197. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21848883.

63. Kluin-Nelemans HC, Hoster E, Hermine O, et al. Treatment of older patients with mantle-cell lymphoma. N Engl J Med 2012;367:520-531. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22873532.

64. Chang JE, Li H, Smith MR, et al. Phase II study of VcR-CVAD with maintenance rituximab for untreated mantle cell lymphoma: an Eastern Cooperative Oncology Group Study (E1405). Blood 2014;123:1665-1673. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24458437.

65. Goy A, Kahl B. Mantle cell lymphoma: the promise of new treatment options. Crit Rev Oncol Hematol 2011;80:69-86. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21168343.

66. Goy A, Bernstein SH, Kahl BS, et al. Bortezomib in patients with relapsed or refractory mantle cell lymphoma: updated time-to-event analyses of the multicenter phase 2 PINNACLE study. Ann Oncol 2009;20:520-525. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19074748.

67. Baiocchi RA, Alinari L, Lustberg ME, et al. Phase 2 trial of rituximab and bortezomib in patients with relapsed or refractory mantle cell and follicular lymphoma. Cancer 2011;117:2442-2451. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21157957.

68. Lamm W, Kaufmann H, Raderer M, et al. Bortezomib combined with rituximab and dexamethasone is an active regimen for patients with relapsed and chemotherapy-refractory mantle cell lymphoma. Haematologica 2011;96:1008-1014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21486866.

69. Romaguera JE, Fayad LE, McLaughlin P, et al. Phase I trial of bortezomib in combination with rituximab-HyperCVAD alternating with rituximab, methotrexate and cytarabine for untreated aggressive mantle cell lymphoma. Br J Haematol 2010;151:47-53. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20735402.

70. Cohen BJ, Moskowitz C, Straus D, et al. Cyclophosphamide/fludarabine (CF) is active in the treatment of mantle cell lymphoma. Leuk Lymphoma 2001;42:1015-1022. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11697618.

71. Levine AM, Tulpule A, Smith L, et al. Results of a pilot trial of fludarabine, mitoxantrone and Rituxan in mantle cell lymphoma [abstract]. Blood 2005;106:Abstract 945. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/106/11/945.

72. Forstpointner R, Dreyling M, Repp R, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2004;104:3064-3071. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15284112.

73. Forstpointner R, Unterhalt M, Dreyling M, et al. Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG). Blood 2006;108:4003-4008. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16946304.

74. Rummel MJ, Kaiser U, Balser C, et al. Bendamustine plus rituximab versus fludarabine plus rituximab in patients with relapsed follicular, indolent and mantle cell lymphomas - final results of the randomized phase III study NHL 2-2003 on behalf of the StiL (Study Group Indolent Lymphomas, Germany) [abstract]. Blood 2010;116:Abstract 856. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/856.

75. Robinson KS, Williams ME, van der Jagt RH, et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma. J Clin Oncol 2008;26:4473-4479. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18626004.

76. Friedberg JW, Vose JM, Kelly JL, et al. The combination of bendamustine, bortezomib, and rituximab for patients with relapsed/refractory indolent and mantle cell non-Hodgkin lymphoma. Blood 2011;117:2807-2812. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21239695.

77. Wiernik PH, Lossos IS, Tuscano JM, et al. Lenalidomide monotherapy in relapsed or refractory aggressive non-Hodgkin's lymphoma. J Clin Oncol 2008;26:4952-4957. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18606983.

78. Habermann TM, Lossos IS, Justice G, et al. Lenalidomide oral monotherapy produces a high response rate in patients with relapsed or refractory mantle cell lymphoma. Br J Haematol 2009;145:344-349. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19245430.

79. Reeder CB, Witzig TE, Zinzani PL, et al. Efficacy and safety of lenalidomide oral monotherapy in patients with relapsed or refractory mantle-cell lymphoma: Results from an international study (NHL-003) [abstract]. J Clin Oncol 2009;27:Abstract 8569. Available at: http://meeting.ascopubs.org/cgi/content/abstract/27/15S/8569.

80. Zinzani PL, Vose JM, Czuczman MS, et al. Phase II Multicenter Study of the Safety and Efficacy of Single-Agent Lenalidomide in Subjects with Relapsed/Refractory Mantle Cell Lymphoma: Long-Term Follow-up Analysis of the NHL-003 Study [abstract]. Blood 2012;120:Abstract 2738. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/120/21/2738.

81. Eve HE, Carey S, Richardson SJ, et al. Single-agent lenalidomide in relapsed/refractory mantle cell lymphoma: results from a UK phase II study suggest activity and possible gender differences. Br J Haematol 2012;159:154-163. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22881386.

82. Goy A, Sinha R, Williams ME, et al. Single-agent lenalidomide in patients with mantle-cell lymphoma who relapsed or progressed after or were refractory to bortezomib: phase II MCL-001 (EMERGE) study. J Clin Oncol 2013;31:3688-3695. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24002500.

83. Wang L, Fayad L, Hagemeister FB, et al. A phase I/IIstudy of lenalidomide in combination with rituximab in relapsed/refractory mantle cell lymphoma [abstract]. Blood 2009;114:Abstract 2719. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/114/22/2719.

84. Wang M, Fayad L, Wagner-Bartak N, et al. Lenalidomide in combination with rituximab for patients with relapsed or refractory mantle-cell lymphoma: a phase 1/2 clinical trial. Lancet Oncol 2012;13:716-723. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22677155.

85. Advani RH, Buggy JJ, Sharman JP, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. J Clin Oncol 2013;31:88-94. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23045577.

86. Wang ML, Rule S, Martin P, et al. Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma. N Engl J Med 2013;369:507-516. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23782157.

87. Full prescribing information for ibrutinib. 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/205552lbl.pdf.

88. Hosing C, Saliba RM, McLaughlin P, et al. Long-term results favor allogeneic over autologous hematopoietic stem cell transplantation in patients with refractory or recurrent indolent non-Hodgkin's lymphoma. Ann Oncol 2003;14:737-744. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12702528.

89. van Besien K, Loberiza FR, Bajorunaite R, et al. Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. Blood 2003;102:3521-3529. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12893748.

90. Bertz H, Illerhaus G, Veelken H, Finke J. Allogeneic hematopoetic stem-cell transplantation for patients with relapsed or refractory lymphomas: comparison of high-dose conventional conditioning versus fludarabine-based reduced-intensity regimens. Ann Oncol 2002;13:135-139. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11863095.

91. Vigouroux S, Michallet M, Porcher R, et al. Long-term outcomes after reduced-intensity conditioning allogeneic stem cell transplantation for low-grade lymphoma: a survey by the French Society of Bone

Marrow Graft Transplantation and Cellular Therapy (SFGM-TC). Haematologica 2007;92:627-634. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17488686.

92. Khouri IF, Lee MS, Saliba RM, et al. Nonablative allogeneic stem-cell transplantation for advanced/recurrent mantle-cell lymphoma. J Clin Oncol 2003;21:4407-4412. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14645431.

93. Maris MB, Sandmaier BM, Storer BE, et al. Allogeneic hematopoietic cell transplantation after fludarabine and 2 Gy total body irradiation for relapsed and refractory mantle cell lymphoma. Blood 2004;104:3535-3542. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15304387.

94. Martin P, Chadburn A, Christos P, et al. Outcome of deferred initial therapy in mantle-cell lymphoma. J Clin Oncol 2009;27:1209-1213. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19188674.

95. Witzig TE, Vose JM, Zinzani PL, et al. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. Ann Oncol 2011;22:1622-1627. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21228334.

96. Coleman M, Martin P, Ruan J, et al. Prednisone, etoposide, procarbazine, and cyclophosphamide (PEP-C) oral combination chemotherapy regimen for recurring/refractory lymphoma: low-dose metronomic, multidrug therapy. Cancer 2008;112:2228-2232. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18338745.

This discussion is being updated to correspond with the newly updated algorithm. Last updated on 05/03/16

Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphomas (DLBCL) are the most common lymphoid neoplasms in adults, accounting for approximately 32.5% of NHLs diagnosed annually.[1] DLBCL NOS, follicular lymphoma (grade 3 only), DLBCL coexistent with a low-grade lymphoma of any kind (e.g., follicular lymphoma, gastric MALT or non-gastric MALT lymphoma), intravascular large B-cell lymphoma, DLBCL associated with chronic inflammation, ALK-positive DLBCL, EBV-positive DLBCL in older patients and T-cell/histiocyte rich large B-cell lymphoma are also managed according to the DLBCL guidelines.

Gene expression profiling (GEP) has revealed significant heterogeneity within DLBCL.[2] However, incorporation of this information into treatment algorithms awaits further investigation. Immunohistochemical markers such as CD10, BCL6, and IRF4/MUM1 have been reported to recapitulate the GEP in classifying DLBCL into 2 different subtypes: germinal center B-cell (GCB) subtype (CD10+, or BCL6+, IRF4/MUM1-) and non-GCB subtype (CD10-, IRF4/MUM1+ or BCL6-, IRF4/MUM1-).[3] See "Use of Immunophenotyping/Genetic Testing in the Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A, Page 6)" in the guidelines. Immunohistochemical algorithms including GCET1, FOXP1, and LMO2 in addition to CD10, BCL6 and IRF4/MUM1 have also been proposed.[4,5] *MYC* gene rearrangements have been reported in 5-8% of patients with DLBCL, and often correlate with GCB phenotype.[6-8] GCB subtype is associated with an improved outcome compared to non-GCB subtype in patients treated with R-CHOP. Ongoing randomized clinical trials are exploring whether the addition of novel targeted agents to R-CHOP will selectively improve the outcome in patients with non-GCB DLBCL.[9,10] Presently, the upfront standard of care remains the same for both GCB and non-GCB subtypes.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for Non-Hodgkin's Lymphomas an electronic search of the PubMed database was performed to obtain key literature in "Diffuse large B-cell lymphoma" published between June 2014 and October 2015 using the following search terms: diffuse large B-cell lymphoma, aggressive B-cell lymphoma, primary mediastinal B- cell lymphoma, double-hit lymphoma, gray zone lymphoma. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[11]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 108 citations and their potential relevance was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN webpage.

Diagnosis

Adequate immunophenotyping is required to establish the diagnosis and to determine GCB versus non-GCB origin. The typical immunophenotype is CD20+, CD45+, and CD3-. The recommended immunophenotyping panel includes CD20, CD3, CD5, CD10, CD45, BCL2, BCL6, Ki-67, IRF4/MUM1 and MYC. Patients with GCB-like immunophenotype along with the expression of MYC and either BCL2 or BCL6 by IHC should undergo FISH or karyotype testing for the detection of *MYC, BCL2*, and *BCL6* gene rearrangements. Additional markers such as CD138, CD30, cyclin D1, ALK1, SOX11, EBV and HHV-8 may be useful under certain circumstances to establish the subtype. SOX11 positivity may be useful in differentiating rare cases of cyclin D1-negative pleomorphic or blastoid MCL from CD5-positive DLBCL.[12,13]

Workup

The initial workup for newly diagnosed patients with DLBCL should include a thorough physical examination with attention to node-bearing areas, and evaluation of performance status (PS) and constitutional symptoms. Laboratory assessments should include standard blood work including CBC with differential, a comprehensive metabolic panel, and measurements of serum lactate dehydrogenase (LDH). Patients with high tumor burden and elevated LDH should be assessed for spontaneous tumor lysis syndrome (TLS), including measurements of uric acid, potassium, phosphorous, calcium, and renal function. HBV testing (surface antigen, surface antibody, and core antibody) is recommended especially if rituximab-based treatment regimens are being considered due to increased risks of viral reactivation,[14] though viral reactivation has also been described after chemotherapy alone without rituximab. HIV testing and serum beta-2-microglobulin levels would be useful in selected patients.

PET-CT scans have a more clear-cut role in selected patients with DLBCL than in other lymphoid neoplasms. PET scans are particularly informative in the initial staging where upstaging resulting in altered therapy occurs about 9% of the time, and for response assessment after treatment because they can distinguish residual fibrotic masses from masses containing viable tumor.[15] PET-CT scan ± chest/abdominal/pelvic CT with contrast of diagnostic quality is recommended for initial workup. As PET scans have now been incorporated into the response criteria, a baseline PET scan is necessary for optimal interpretation of post-treatment PET scans. PET-CT has also been reported to be accurate and complementary to bone marrow biopsy for the detection of bone marrow involvement in patients with newly diagnosed DLBCL.[16,17] Bone marrow biopsy may not be needed if there is clearly positive marrow uptake by PET-CT. Bone marrow biopsy may also be omitted in the absence of any skeletal uptake on the staging PET/CT scan, unless finding another lymphoma subtype (discordant low-grade lymphoma) would be considered important for treatment decisions.

The staging workup is designed to identify all sites of known disease and determine prognosis with known clinical risk factors. International Prognostic Index (IPI) identifies specific groups of patients who are more or less likely to be cured with standard therapy.[18,19] IPI scores are based on patient's age, stage of disease, serum LDH level, PS, and the number of extranodal sites. In patients who are 60 years or younger, the prognostic factors include tumor stage, PS, and serum LDH level. Zhou et al reported an enhanced IPI (NCCN-IPI) to stratify patients with newly diagnosed DLBCL into 4 different risk groups (low, low-intermediate, high-intermediate, and high) based on their clinical features (age, LDH, sites of involvement, Ann Arbor stage, ECOG PS).[20] This analysis included 1650 patients identified in NCCN database that were diagnosed with DLBCL between 2000 and 2010 and treated with

rituximab-based therapy. The NCCN-IPI discriminated patients in the low- and high-risk subgroups better (5-year OS rate 96% vs 33%) than the IPI (5 year OS rate 90% vs 54%). The NCCN-IPI was also validated using an independent cohort of 1138 patients from the British Columbia Cancer Agency. While the IPI, revised IPI (R-IPI), and NCCN-IPI predict clinical outcome with high accuracy, R-IPI and NCCN-IPI could also identify a specific subgroup of patients with very good prognosis (3-year progression-free survival [PFS] and overall survival [OS] of 100%).[21]

Elevated LDH, ≥2 extranodal sites and involvement of specific sites (the testes, paranasal sinus and bone marrow) are associated with increased risk for developing central nervous system (CNS) relapse.[22-24] The German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL) recently proposed a prognostic model to predict the risk of CNS relapse incorporating the 5 clinical factors (age > 60 years, LDH > normal, stage III or IV, ECOG PS >1, and involvement of the kidney or adrenal gland) and this model was validated in an independent cohort of 1597 patients by Savage et al.[25,26] This prognostic model separated patients into three risk categories based on the rate of developing CNS disease at 2 years: low-risk (0 or 1 risk factor; rate of CNS disease ≤1%), intermediate-risk (2 or 3 factors; rate of CNS disease 2–10%) and high-risk group (4 or 5 factors; rate of CNS disease at 17.0%). In both datasets, involvement of the kidney or adrenal gland was highly associated with CNS relapse. Lumbar puncture should be considered in patients with 4-6 risk factors identified in the DSHNHL prognostic model, the presence of ≥2 extranodal sites plus elevated LDH, involvement of testes, HIV-associated lymphoma, or double hit lymphoma. The diagnostic yield is improved if flow cytometric analysis of cerebrospinal fluid is undertaken.

Treatment

Treatment options for DLBCL differ between patients with localized (Ann Arbor stage I-II) and advanced (Ann Arbor stage III-IV) disease. Prognosis is extremely favorable for patients with no adverse risk factors (elevated LDH, stage II bulky disease, older than 60 years or ECOG PS ≥ 2). Patients with advanced disease should be enrolled in clinical trials, whenever possible.

Stage I-II

In the SWOG 8736 study, 3 cycles of CHOP followed by involved field radiation therapy (IFRT) produced significantly better progression-free survival (PFS; 5-year estimated PFS: 77% vs. 64% for CHOP alone) and OS (82% vs. 72% for CHOP alone) than 8 cycles of CHOP alone in patients with localized aggressive NHL;[27] however, this difference disappeared with further follow-up. The benefit of CHOP (3 cycles) followed by IFRT (5-year OS of 95%) in patients with limited-stage DLBCL (60 years or younger with no adverse risk factors) was also confirmed in a series from the British Columbia Cancer Agency.[28] Another randomized trial (ECOG 1484 study) showed that the addition of RT to CHOP (8 cycles) prolonged disease-free survival (DFS) in patients with limited stage DLBCL who had achieved complete remission (CR) to CHOP alone (6-year DFS was 73% for IFRT and 56% for observation).[29] In the a GELA study (LNH 93-4), however, the addition of RT to 4 cycles of CHOP did not provide any advantage over 4 cycles of CHOP alone for the treatment of older patients with low-risk localized aggressive lymphoma. The estimated 5-year event-free survival (EFS) was not different between the two groups (61% and 64%, respectively) and the 5-year estimated OS rates were 68% and 72%, respectively.[30] However, in this study, administration of RT was markedly delayed and 12% of patients on the RT arm did not receive RT.

The efficacy of the addition of rituximab to CHOP (R-CHOP) and IFRT has also been reported in patients with limited stage DLBCL. In the SWOG 0014 study that evaluated 3 cycles of R-CHOP followed by IFRT in patients with at least one adverse factor (non-bulky stage II disease, age > 60 years, ECOG PS 2, or elevated serum LDH) as defined by the stage-modified IPI (N=60), the 4-year PFS rate was 88%, after a median follow-up of 5 years; the corresponding 4-year OS rate was 92%.[31] In historical comparison, these results were favorable relative to the survival rates for patients treated without rituximab (4-year PFS and OS were 78% and 88%, respectively). A phase III trial (MabThera International Trial [MInT]) compared 6 cycles of CHOP-like chemotherapy to 6 cycles of CHOP-like chemotherapy plus rituximab.[32,33] All patients were younger than 60 years of age and had 0-1 IPI risk factors. Three quarters of patients had limited stage disease, and RT was included for all extranodal sites of disease or any site >7.5 cm. The trial found a benefit to rituximab-based chemotherapy with a 6-year OS rate of 90.1%% versus 80% (P = .0004). The 6-year EFS rate (74.3% vs. 55.8%; P < .0001) and PFS rate (80.2% vs. 63.9%; P < .0001) were also significantly higher for patients assigned to chemotherapy plus rituximab compared to chemotherapy alone.[33]

Abbreviated course R-CHOP with RT is also associated with reduced short-term toxicity compared to 6-8 cycles of R-CHOP alone. A SEER-Medicare database analysis of a large cohort of older patients with stage I-II DLBCL confirmed that 3 cycles of R-CHOP with RT and 6-8 cycles of R-CHOP alone have similar OS; however, 3 cycles of R-CHOP with RT was associated with significantly lower risk of second-line therapy and lower incidences of neutropenia including those requiring hospitalization.[34] The study suggested better upfront disease control and less toxicity with abbreviated RCHOP with RT.

In the two GELA studies, intensified chemotherapy [ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone) followed by consolidation with methotrexate, etoposide, ifosfamide and cytarabine] with or without rituximab was found to be superior to CHOP with or without rituximab (3 cycles) plus RT in patients with low-risk early-stage disease.[35,36] However, this regimen was also associated with significant toxicity and includes vindesine, which is not available in the United States.

Stage III-IV

R-CHOP-21 chemotherapy is the standard treatment for patients with advanced stage DLBCL based on the results of the GELA study (LNH98-5) that demonstrated the addition of rituximab to CHOP-21 improved PFS and OS in older patients with advanced DLBCL. In this study, older patients (age 60–80 years; N=399) were randomized to receive 8 cycles of R-CHOP or CHOP.[37-39] Long-term follow-up of this study showed that PFS (36.5% vs. 20%), DFS (64% vs. 43%), and OS (43.5% vs. 28%) rates were significantly in favor of R-CHOP at a median follow-up of 10 years.[40] These findings have been confirmed in three additional randomized trials including the MInT (6 cycles of R-CHOP or CHOP) which extended the findings to young patients with 0 or 1 risk factors according to the IPI.[32,33] The Dutch HOVON and Nordic Lymphoma Group study (8 cycles of R-CHOP-14 or CHOP-14) and the ECOG/CALGB study confirmed the findings in patients older than 60 years.[41,42] The ECOG/CALGB 9703 study also showed that maintenance rituximab in first CR offered no clinical benefit to patients who received R-CHOP as their induction therapy.[42]

The DSHNHL studies demonstrated that 6 cycles of dose dense CHOP (CHOP-14) as first-line therapy was superior to 6 cycles of CHOP-21, prior to the introduction of rituximab.[43-45] In the RICOVER 60-trial, older patients (age 61–80 years) were randomized to receive

6 or 8 cycles CHOP-14 with or without 8 cycles of rituximab.[46,47] RT was administered to sites of initial bulky disease with or without extranodal involvement. The addition of rituximab to 6 or 8 cycles of CHOP-14 (R-CHOP-14) significantly improved clinical outcomes compared with CHOP-14 alone. With a median observation time of 82 months, EFS was significantly improved after R-CHOP-14 (*P* <.001) compared with CHOP-14. OS rate was also significantly improved in patients treated with R-CHOP-14. No difference in clinical benefit but increased toxicity was seen in patients treated with 8 cycles compared with 6 cycles of therapy.[47] The investigators concluded that 6 cycles of R-CHOP-14 in combination with 8 doses of rituximab should be the preferred regimen in this patient population.

The role of IFRT following CR (evaluated by CT criteria) to initial bulky sites ≥7.5 cm or extranodal involvement was evaluated in the RICOVER-noRTh trial (an amendment to the RICOVER-60 trial).[48] In this study, 164 patients with stage III-IV disease were treated with 6 cycles of R-CHOP-14 (best arm of the RICOVER-60 trial) but RT to bulky sites or extranodal involvement was omitted. The 3-year PFS and OS rates were significantly inferior, compared to the corresponding survival rates in patients from the RICOVER-60 trial treated with same chemoimmunotherapy with RT to bulky sites.[48] The study was therefore discontinued. Similarly, subgroup analyses of the MInT and RICOVER-60 trial showed that patients with skeletal involvement significantly benefitted from RT to sites of skeletal involvement.[49] Although retrospective subgroup analyses may be subjected selection biases, the benefit of RT held up on multivariate analysis in both studies and may be considered.

Two randomized trials have compared R-CHOP-21 with dose-dense R-CHOP-14.[50,51] A large phase III randomized trial involving 1080 patients with newly diagnosed DLBCL found no significant difference in either PFS or OS at a median follow up of 46 months.[50] The 2-year OS rate was 82.7% in the R-CHOP-14 arm and 80.8% in the R-CHOP-21 arm (*P* = ·3763). The corresponding 2-year PFS rates were 75·4% and 74·8%, respectively (*P* =·5907). Toxicity was similar, except for a lower rate of grade 3 or 4 neutropenia in the R-CHOP-14 arm (31% vs. 60%), reflecting the fact that all patients in the R-CHOP-14 arm received primary growth factor prophylaxis with G-CSF whereas no primary prophylaxis was given with R-CHOP-21.[50] Notably, there was no difference in outcome between GCB-like and non-GCB-like DLBCL by IHC in this large prospective study. The phase III LNH03-6B GELA study compared 8 cycles of R-CHOP-14 with R-CHOP-21 in 602 older patients (age 60–80 years) with untreated DLBCL. After a median follow-up of 56 months, no significant differences between R-CHOP-14 and R-CHOP-21 were observed in terms of 3-year EFS (56% vs. 60%; *P* =.7614), PFS (60% vs. 62%) or OS rates (69% vs 72%).[51] Grade 3 or 4 neutropenia were observed more frequently in the R-CHOP-14 arm (74% compared to 64% in the R-CHOP 21 arm) despite a higher proportion of patients having received G-CSF (90%) compared with patients in the R-CHOP-21 arm (66%).

The results of the dense-R-CHOEP trial showed that doubling the number of rituximab (375 mg/m^2) infusions (from 6 to 12) administered with 8 x CHOEP-14 did not result in a significant improvement of EFS and OS in aaIPI2 patients with DLBCL.[52] After a median follow-up of 24 months, the 2-year EFS and OS rates were 69% and 82% respectively. The corresponding survival rates in patients treated with 8 x CHOEP-14 with 6 infusions of rituximab in the R-MegaCHOEP study were 71% and 85% respectively [53] The lack of improvement in survival rates could be attributed to more aggressive chemotherapy (CHOP vs. CHOEP), different timing of rituximab infusions and

differences in the pharmacokinetic profile of younger and older patients. There was an improvement in EFS and OS rates in patients with aaIPI 3; however, it was not statistically significant because this group had only 11 patients.

Collectively, these studies suggest that R-CHOP-21 remains the standard treatment regimen for patients with newly diagnosed DLBCL with no improvement in outcome observed for dose-dense therapy in the rituximab era.

Multiple randomized trials (RICOVER 60, NHL-B2, MInT, and the MegaCHOEP trials) have demonstrated superior outcomes in women relative to men, particularly in older adults with older women benefiting more from the addition of rituximab than men.[54] This could be explained by a slower clearance rate of rituximab in older women. Based on these data, a prospective non-randomized trial evaluated R-CHOP with rituximab dose of 500 mg/m^2 in men over the age of 60 with DLBCL and demonstrated that the serum levels and OS rates improved compared to historical data in older men treated with rituximab dose of 375mg/m^2, and similar to older women treated with rituximab dose of 375 mg/m^2.[55] Based on these data, a rituximab dose of 500 mg/m^2 may be considered in older men (under the age of 80 years) treated with R-CHOP. A randomized clinical trial is ongoing.

Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) plus rituximab (DA-EPOCH-R) has shown significant activity in patients with untreated DLBCL.[56,57] In a multicenter phase II CALGB study, DA-EPOCH-R (6–8 cycles) was evaluated in patients with previously untreated DLBCL (n=69; 48 patients with DLBCL).[56] IPI score was high-intermediate risk in 19% and high risk in 21% of patients. After a median follow up of 62 months, the 5-year TTP was 81% and OS was 84% in all patients. The 5-year TTP rates among patients with low/low-intermediate, high-intermediate, and high risk IPI were 87%, 92%, and 54%, respectively (*P* =.0085); the 5-year OS in these subgroups were 95%, 92%, and 43%, respectively (*P*<.001).[56] The TTP rate was significantly higher in the subgroup with GCB phenotype compared with non-GCB phenotype (100% vs. 67%; *P*=.008); the GC phenotype was also associated with a higher 5-year OS rate (94% vs. 68%; *P* =.04). High tumor proliferation index (Ki-67 ≥60%) was associated with significantly decreased TTP and OS only for the subgroup with non-GCB phenotype. Febrile neutropenia occurred in 36% (grade 4 in 7%) and no significant grade 4 non-hematologic toxicities were observed. The most common grade 3 non-hematologic toxicities included neuropathies (25%), fatigue (16%), and arrhythmia (6%).[56] In another multi-institutional study that assessed the safety and efficacy of DA-EPOCH-R in patients with untreated large B-cell lymphomas and poor prognosis (IPI > 1; n = 81; DLBCL, n = 68; primary mediastinal DLBCL, n = 6) and follicular lymphoma grade 3b, n = 7), DA-EPOCH-R produced a CR rate of 80·2%.[57] After a median follow-up time of 64 months, 10-year EFS and OS rates were 47·8% and 63·6%, respectively.[57]

An ongoing phase III randomized study (CALGB 50303) is evaluating DA-EPOCH-R compared with R-CHOP in untreated patients with DLBCL. Pending results of that study, there is insufficient evidence to recommend DA-EPOCH-R as standard initial therapy for patients with newly diagnosed DLBCL except in highly selected circumstances such as poor left-ventricular function, B-cell lymphoma unclassifiable with intermediate features between DLBCL and Burkitt lymphoma, double-hit lymphomas, and primary mediastinal B-cell lymphoma (PMBL).

Patients older than 80 years have not been represented in prospective clinical trials of R-CHOP and are usually not appropriate candidates for full-dose therapy. To address this, the GELA study group

conducted a multicenter single-arm prospective phase II study evaluating the safety and efficacy of a decreased dose of CHOP with a conventional dose of rituximab (R-mini-CHOP) in 149 patients older than 80 years with DLBCL.[58] After a median follow-up of 20 months, the median OS and PFS were 29 months and 21 months respectively. The 2-year OS and PFS rates were 59% and 47% respectively. An update with extended follow-up reports the 4-year PFS and OS rates to be 41% and 49%, respectively.[59] Grade ≥3 neutropenia was the most frequent hematological toxicity observed in 59 patients. The guidelines have included R-miniCHOP as a treatment option for patients older than 80 years.

Role of HDT/ASCR

In the randomized GELA LNH87-2 study, patients with DLBCL in first CR after induction therapy received consolidation therapy with either sequential chemotherapy or HDT/ASCR.[60] Although no difference in outcome was prospectively observed in this trial, a retrospective subset analysis of patients with aaIPI high/intermediate- or high-risk disease (n=236), found that HDT/ASCR resulted in significantly improved outcomes compared with sequential chemotherapy with regards to both 8-year disease-free survival rate (55% vs. 39%; *P*=0.02) and 8-year OS rate (64% vs. 49%; *P*=0.04) in the high-intermediate/high-risk subset.[60] This study was performed prior to rituximab-based induction chemoimmunotherapy.

In the SWOG 9704 trial, 253 patients with high-intermediate/high IPI were randomized to receive 3 cycles of R-CHOP or HDT/ASCR, following initial remission with 5 cycles of CHOP or R-CHOP induction.[61] The 2-year PFS rate was significantly higher with HDT/ASCR compared with chemoimmunotherapy alone (69% vs. 55%; *P*=0.005); the 2-year OS rates were not significantly different (74% vs. 71%, respectively; *P* = .30). In an exploratory subset analysis, HDT/ASCR was associated with an OS benefit for high-risk patients. In this subgroup, the 2-year OS rates were 82% and 63% respectively, for patients treated with HDT/ASCR and chemoimmunotherapy. Notably, in this study a third of the patients did not receive rituximab as part of their induction regimen.

The role of upfront HDT/ASCR has also been evaluated in prospective studies.[53,62,63] In the French GOELAMS 075 study, patients aged ≤60 years with DLBCL (N=286 evaluable) were randomized to receive 8 cycles of R-CHOP-14 or HDT with rituximab (R-HDT) followed by ASCR.[62] The 3-year PFS rate and OS rates were 76% and 83%, respectively, with no significant differences between treatment arms.[62] In a randomized trial of the German High-Grade NHL Study Group, patients aged ≤60 years with aggressive lymphomas (N=262 evaluable) were treated with 8 cycles of CHOEP-14 (cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone) combined with 6 doses of rituximab (R-CHOEP-14) or 4 cycles of MegaCHOEP combined with 6 doses of rituximab and followed by ASCR (R-MegaCHOEP).[53] No significant differences were observed between the R-CHOEP-14 and R-MegaCHOEP arms for PFS (3-year rate: 74% vs. 70%, respectively) or OS outcomes (3-year rate: 85% vs. 77%, respectively). Among patients with high/intermediate aaIPI (score of 2), EFS (75.5% vs. 63.5%; *P* = .0509) and OS rates (91% vs. 77.1%; *P* = .01) were significantly better with R-CHEOP-14 compared with R-MegaCHOEP.[53]

In the randomized DLCL04 trial of the Italian Lymphoma Foundation, patients aged ≤65 years with DLBCL, 399 patients were randomized to receive rituximab-containing first-line regimens (8 cycles of R-CHOP-14 or 6 cycles of R-MegaCHOP-14) with or without HDT/ASCR.[63] The 3-year PFS rate was significantly higher in the HDT/ASCR groups compared with the non-HDT/ASCR groups (70% vs. 59%; *P*=.010), but the 3-year OS rate was not significantly different between the two

groups (81% and 78% respectively; *P* = .556). In addition, no significant differences were observed in the 3-year PFS rates between the two rituximab-based first-line regimens.

The above studies, overall, found no benefit to upfront HDT/ASCR as compared with first-line rituximab-based chemoimmunotherapy, except in high-risk IPI patients, but this remains controversial since this finding emerged only on a retrospective subset analysis involving a small number of patients. Presently, first-line consolidation with HDT/ASCR is recommended only in selected high risk patients (category 2B), or in the context of a clinical trial.

NCCN Recommendations

R-CHOP (3 cycles) with ISRT or R-CHOP (6 cycles) with or without ISRT is recommended for patients with non-bulky (<7.5 cm) stage I or II disease.[31,33] Patients with bulky disease (≥ 7.5 cm) may be treated more effectively with R-CHOP (6 cycles) with or without locoregional RT (category 1).[33] Regarding the addition RT, it is important to consider the results from the RICOVER-noRTh trial that showed a significant advantage to adding RT to initial bulky sites ≥7.5 cm.[48] R-mini-CHOP may be substituted for patients over the age of 80 to improve chemotherapy tolerability[58,59] and ISRT alone is recommended for patients who are not candidates for any chemotherapy. See "Principles of Radiation Therapy" in the guidelines for the ISRT dose recommendations.

R-CHOP-21 for a total of 6 cycles (category 1) is recommended for patients with stage III-IV disease.[33,41,42] In selected patients, RT to bulky sites may be beneficial (category 2B). In patients with bulky disease or impaired renal function, initial therapy should include monitoring and prophylaxis for TLS. R-CHOP-21 for a total of 6 cycles is the preferred regimen due to reduced toxicities. Other comparable anthracycline-based regimens may also be used. Suggested alternate regimens include DA-EPOCH-R (category 2B)[56,57] or dose-dense R-CHOP-14 (category 3).[50,51] Participation in clinical trials is recommended, if available.

Inclusion of any anthracycline or anthracenedione in patients with impaired cardiac function should include more frequent cardiac monitoring. The following regimens are used at NCCN Member Institutions for the first-line treatment of DLBCL in very frail patients or those with poor left ventricular function, based on limited published data.

- R-miniCHOP (for frail patients over 80 years of age)[58,59]
- RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine)
- RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone)[64-66]
- DA-EPOCH-R[56,57]
- RCEOP (rituximab, cyclophosphamide, etoposide, vincristine, and prednisone)[67]
- RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, and prednisolone)[68]

For concurrent presentation of CNS disease with parenchymal involvement, systemic methotrexate (≥3 g/m^2) should be incorporated as part of the treatment plan. Intrathecal methotrexate/cytarabine and/or 3 to 3.5 g/m^2 systemic methotrexate should be incorporated as part of the treatment plan for concurrent presentation of CNS disease with leptomeningeal involvement. Ommaya reservoir placement should be considered in patients with leptomeningeal disease. When administering high dose methotrexate, patients must be pretreated with hydration and alkalinization of the urine, and then receive leucovorin

rescue beginning 24 hours after the initiation of methotrexate infusion. Renal and hepatic function must be monitored. Adequate recovery of blood counts should be confirmed prior to initiating the next cycle of R CHOP.

Patients with risk factors for CNS involvement (age > 60 years, elevated LDH, stage III or IV, ECOG PS > 1, extranodal sites >1, kidney or adrenal gland involvement) should be considered for CNS prophylaxis.[22-26] The method by which prophylaxis should be given is controversial. Intrathecal methotrexate given at least once per systemic treatment cycle has been used for many years. More recent retrospective studies have suggested that high-dose IV methotrexate-based prophylaxis may be associated with a lower incidence of CNS relapses.[69-72] Systemic methotrexate with leucovorin rescue has been safely incorporated into R-CHOP-21, with methotrexate administered on day 15 of the 21-day R-CHOP cycle.[69] However, other reports suggest that CNS prophylaxis is insufficient to prevent CNS relapse.[73,74] The NCCN Guidelines currently recommend CNS prophylaxis with 4 to 8 doses of intrathecal methotrexate and/or cytarabine, or 3-3.5 g/m^2 of systemic methotrexate.

Response Assessment

Interim restaging is performed to identify patients whose disease has not responded to or has progressed on induction therapy. A negative PET scan after 2 to 4 cycles of induction therapy has been associated with favorable outcomes in several studies.[75-78] In patients with aggressive lymphoma (N=90) treated with first-line anthracycline-based induction chemoimmunotherapy with rituximab (41% of patients), those with a negative PET scan (n=54) after 2 cycles of induction therapy had significantly higher 2-year EFS rate (82% vs. 43%; *P* <.001) and OS rate (90% vs. 61%; *P* =.006) compared with those with a positive PET scan (n=36).[77] In another study, among patients with aggressive lymphoma (N=103) treated with first-line CHOP or CHOP-like regimens (with rituximab in 49% of cases), the 5-year EFS rates were significantly higher for those with a negative PET scan (n=77) compared to patients with a positive PET scan (n=22) following 4 cycles of induction therapy (80% vs. 36%; *P* < .0001).[78]

However, interim PET scans can produce false positive results and some patients treated with chemoimmunotherapy have a favorable long-term outcome despite a positive interim PET scan. In a prospective study that evaluated the significance of interim PET scans in patients with DLBCL (after 4 cycles of accelerated R-CHOP), only 5 of 37 patients with a positive interim PET scan had a biopsy demonstrating persistent disease; PFS outcome in patients who were interim PET-positive, biopsy-negative was identical to that in patients with a negative interim PET scan.[79] A retrospective analysis of 88 newly diagnosed patients with DLBCL treated with 6-8 cycles of R-CHOP also reported only a minor difference in the 2-year PFS rates between patients with a positive interim PET scan and a negative interim PET scan; the 2 year PFS rates were 72% and 85% respectively (*P* = .0475).[80] Conversely, the end-of-treatment PET scan was highly predictive of PFS; the 2-year PFS rate was 64% for patients with a final positive PET scan compared to 83% for those with a final negative PET scan (P <.001).

More recent reports have also confirmed the limited prognostic value of interim PET scans in patients with DLBCL treated with R-CHOP.[81-84] In a prospective study that evaluated the predictive value of interm PET scans after 2 cycles of R-CHOP in 138 evaluable patients, the 2-year EFS rate was significantly shorter for patients with a positive interim PET-scan compared to those with a negative interim PET scan (48% vs. 74%; *P* = .004); however, the 2-year OS was not significantly different between the two groups (88% vs. 91%; *P* = .46).[83]

Therefore, interim PET imaging is not recommended to be used to guide changes in therapy. If treatment modifications are considered based on interim PET scan results, a repeat biopsy of residual masses should be strongly considered to confirm PET-positivity prior to additional therapy. If the biopsy is negative, the planned course of treatment as recommended for PET-negative guidelines should be completed. Patients should undergo evaluation prior to receiving RT, including all positive studies. If RT is not planned, interim restaging after 3–4 cycles of R-CHOP is appropriate to confirm response. End of treatment restaging is performed upon completion of treatment. The optimal time to end of treatment restaging is not known. However, the panel recommends waiting for 6-8 weeks after completion of therapy before repeating PET scans.

Response assessment by PET-CT should be done according to the 5-point scale (5-PS).[16,85] The 5-PS is based on the visual assessment of FDG uptake in the involved sites relative to that of the mediastinum and the liver.[86-88] A score of 1 denotes no abnormal FDG-avidity, while a score of 2 represents uptake less than the mediastinum. A score of 3 denotes uptake greater than the mediastinum but less than the liver, while scores of 4 and 5 denote uptake greater than the liver, and greater than the liver with new sites of disease, respectively. Different clinical trials have considered scores of either 1-2 or 1-3 to be PET-negative, while scores of 4-5 are universally considered PET-positive. A score of 4 on an interim or end of treatment restaging scan may be consistent with a partial response if the FDG-avidity has declined from initial staging, while a score of 5 denotes progressive disease.

Follow-up

Considerable debate remains with the routine use of imaging for surveillance in patients who achieve a CR after induction therapy. Although positive scans can help to identify patients with early asymptomatic disease relapse, false positive cases remain common and problematic, and may lead to unnecessary radiation exposure for patients as well as increased healthcare costs. In a study that evaluated the use of surveillance CT scans (at 3 and 12 months after completion of chemotherapy) in patients with DLBCL who achieved a CR with induction chemotherapy (N=117), 35 patients relapsed, and only 6% of these relapses were detected by follow-up CT scan in asymptomatic patients; 86% of cases of relapse were associated with development of new symptoms or signs of relapse.[89] The investigators therefore concluded that routine surveillance with CT scans had limited value in the detection of early relapse in patients with a CR following induction therapy. In a retrospective study evaluating the use of surveillance imaging in patients with relapsed aggressive lymphoma who had a CR to initial chemotherapy (N=108), 20% of relapses were detected by imaging in asymptomatic patients.[90] In the remaining 80% of cases, relapse was identified by clinical signs and/or symptoms. Moreover, the cases of relapse detected by imaging were more likely to represent a population of patients with low-risk disease based on age-adjusted IPI at the time of relapse.[90] Thus, routine imaging during remission may help to identify patients with more limited disease at the time of relapse, but has not been shown to improve ultimate outcome.

In a prospective study that evaluated the role of PET scans (at 6, 12, 18, and 24 months after completion of induction therapy) in patients with a CR after induction therapy for lymphomas, surveillance using PET scans was found to be useful for detecting early relapse.[91] Among the cohort of patients with aggressive lymphomas in this study (n=183), follow-up PET scans detected true relapses in 10% of patients at 6 months, 5% at 12 months, and 11% at 18 months; the rate of false-positive scans was low, at 1% (including cohorts of patients with

indolent and aggressive NHL).[91] Inconclusive PET scans were obtained in 4% of patients (8 out of 183), 6 of those had confirmed relapse based on biopsy evaluation. In a retrospective study that evaluated the use of follow-up PET/CT scan in patients with DLBCL who achieved a CR after induction therapy (N=75), follow-up PET/CT scan detected relapse in 27 patients, of which 23 patients had confirmed relapse based on biopsy evaluation; thus, the positive predictive value of PET/CT scan for detecting relapse was 0.85.[92] In this study, patient age (>60 years) and the presence of clinical signs of relapse were significant predictors of disease relapse.

Data from more recent retrospective studies also suggest that routine surveillance with PET or CT scans is of limited utility in the detection of relapse in majority of patients with DLBCL.[93-95] A study comparing the performance of surveillance PET scans in patients with DLBCL treated with CHOP alone versus R-CHOP, found higher false positive results in patients treated with R-CHOP (77% vs. 26%; P < .001).[93] Another study reported a positive predictive value of 56% for surveillance PET-CT scans in patients IPI score <3 compared with 80% for patients with IPI score ≥3, suggesting that surveillance PET-CT has a very limited role in the majority of patients in CR after primary therapy.[94] Another multi-institutional retrospective study evaluated the utility of surveillance scans in two independent prospectively enrolled cohorts of patients with DLBCL treated with anthracycline-based chemoimmunotherapy.[95] In one cohort (n = 680; 552 patients entered post- treatment observation), post treatment surveillance scans detected DLBCL relapse prior to clinical manifestations only in 1.6% of patients (9 out of 552 patients) during a planned follow-up visit. In another cohort (n = 261; 222 patients entered post-treatment observation), surveillance imaging detected asymptomatic relapse only in 1.8% of patients (4 out of 222 patients). A population-based study of patients from the Danish and Swedish lymphoma registries also showed that imaging-based surveillance strategy had no impact on survival for patients DLBCL in first complete remission.[96]

A multi-institutional retrospective study evaluated the EFS at 24 months (EFS24) in two independent prospectively enrolled cohorts of 767 patients with DLBCL treated with anthracycline-based chemoimmunotherapy.[97] Patients who achieved EFS24 had an OS equivalent to that of the age-matched and sex-matched general population (*P* = .25). This was also confirmed in another data set that included 820 patients from a GELA LNH2003B program and the hospital-based registry in France (*P* = .71). These data indicate that EFS24 should be useful for developing strategies for post-therapy surveillance, patient counseling, and as an end point in clinical studies for patients with DLBCL.

In the absence of evidence demonstrating an improved outcome favoring routine surveillance imaging for the detection of relapse, the NCCN Guidelines do not recommend the use of PET or CT for routine surveillance for patients with stage I-II disease who have achieved a CR to initial therapy. For patients with stage III-IV disease who achieve remission to initial therapy, the NCCN Guidelines recommend CT scans no more than once every 6 months for up to 2 years after completion of treatment, with no ongoing routine surveillance imaging after that time, unless it is clinically indicated. When surveillance imaging is performed, CT scan is preferred over PET/CT for the majority of patients. PET/CT may be preferable is for patients with primarily osseous presentations, with the caveat that bone remodeling may also be FDG-avid, so a biopsy is recommended for PET positive sites prior to instituting second line therapy.

Interim and End of Treatment Response Evaluation for Stage I-II

When the treatment plan involves RT, restaging should be done after completion of first-line chemoimmunotherapy prior to initiation of RT as the dose of RT will be influenced by the result (see *"Principles of RT"* in the Guidelines). If interim restaging demonstrates CR (PET-negative), the planned course of treatment with same dose of RT is completed. If the interim restaging demonstrates a PR (PET-positive), treatment with a higher dose of RT (see Guidelines section on "Principles of RT") is appropriate. It is appropriate to enroll patients with an interim PR on a clinical trial. At the present time, there is no data to suggest that a PR with persistent PET positivity after 3 cycles should prompt a change in treatment. If the PET scan is positive after 6 cycles of RCHOP, the patient can proceed to second-line therapy followed by HDT/ASCR with or without RT. Patients with primary refractory or progressive disease are managed as refractory or relapsed disease. After end of treatment restaging, follow-up at regular intervals (every 3–6 months for 5 years and then annually or as clinically indicated thereafter) is recommended for patients with CR. In these patients, follow-up CT scans are recommended only if clinically indicated. Patients with PR and those with no response to treatment or progressive disease are treated as described for relapsed or refractory disease. Palliative RT is recommended for selected patients who are not candidates for chemoimmunotherapy.

Interim and End of Treatment Response Evaluation for Stage III-IV

If interim staging (after 2–4 cycles of R-CHOP-21) demonstrates a CR and PR, the planned course of R-CHOP to a total of 6 cycles is completed. End of treatment restaging is performed upon completion of treatment. After end of treatment restaging, observation is preferred for patients with CR. RT to initially bulky disease (category 2B) or first-line consolidation with HDT/ASCR can be considered in selected high-risk patients (category 2B).[60,61] Patients in CR are followed up at regular intervals (every 3–6 months for 5 years and then annually or as clinically indicated thereafter). In these patients, follow-up imaging CT scans should be performed no more than every 6 months for 2 years after completion of therapy, and then only as clinically indicated thereafter. Patients with PR (after completion of initial therapy) and those with no response to treatment or progressive disease are treated as described below for relapsed or refractory disease. Palliative RT is recommended for selected patients who are not candidates for chemoimmunotherapy.

Relapsed or Refractory Disease

The role of HDT/ASCR in patients with relapsed or refractory disease was demonstrated in an international randomized phase III trial (PARMA study).[98] In this study, patients with DLBCL responding to induction DHAP (dexamethasone, cisplatin and cytarabine) chemotherapy after first or second relapse (N=109) were randomized to receive additional DHAP chemotherapy plus RT or RT plus HDT/ASCR. The 5-year EFS rate was significantly higher among the transplant group compared with the non-transplant group (46% vs. 12%; *P*=.001), as was the 5-year OS (53% vs. 32%; *P*=.038).[98] This study was performed prior to the availability of rituximab. A recent retrospective analysis based on data from the EBMT registry evaluated the role of HDT/ASCR in patients achieving a second CR after salvage therapy (N=470).[99] In this analysis, 25% of patients had received rituximab-based therapy prior to ASCR. The 5-year DFS and OS was 48% and 63% after ASCR for all patients. The median DFS after ASCR was 51 months, which was significantly longer than the duration of first CR (11 months; *P*<.001). The longer DFS with ASCR compared with first CR was also significant in the subgroup of patients previously treated with rituximab (median not reached vs. 10 months;

P<.001) and the subgroup who relapsed within 1 year of first-line therapy (median 47 months vs. 6 months; *P*<.001).[99]

The efficacy of second-line therapy is predicted by the second-line age-adjusted IPI.[100,101] Furthermore, pre-transplantation PET scans have been identified as predictive factors following HDT/ ASCR.[102,103] PET positivity before transplant and chemoresistance are associated with a poor outcome.[104,105] The results of studies from the GEL-TAMO group and ABMTR suggested that HDT/ASCR should be considered for patients who do not achieve a CR but who are still sensitive to chemotherapy.[106-108]

Rituximab as a single agent is modestly active in patients with relapsed or refractory DLBCL and is reserved for the frail older patient.[109] Several chemotherapy regimens (with or without rituximab) such as DHAP (dexamethasone, cisplatin and cytarabine), ESHAP (etoposide, methylprednisolone, cytarabine and cisplatin), ICE (ifosfamide, carboplatin and etoposide), MINE (mesna, ifosfamide, mitoxantrone and etoposide), EPOCH and CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) have been evaluated in patients with relapsed or refractory DLBCL.[110-118] In an outpatient setting, rituximab in combination with ICE (R-ICE) produced an ORR of 71% (25% CR) and an estimated 1-year EFS rate and OS rate of 60% and 72%, respectively, in patients with refractory B-cell lymphoma (N=28).[114] In a phase II study, R-ICE regimen produced a CR rate of 53% in patients with relapsed or refractory DLBCL (N=34), which was significantly better than historical controls treated with ICE alone (27%).[115]

An international randomized intergroup study (CORAL study; N=477) evaluated second-line therapy of relapsed or refractory DLBCL with R-ICE versus R-DHAP, followed by ASCR in all chemosensitive patients.[119,120] No significant difference in outcome was found between treatment arms. The overall response rates were 63% after R-ICE and 64% after R-DHAP. The 4-year EFS rate was 26% with R-ICE compared with 34% with R-DHAP (*P = .2*) and the 4-year OS rate was 43% and 51%, respectively (*P = .3*).[120] Notably, patients relapsing less than 1 year after initial R-CHOP therapy had a particularly poor outcome with 3-year PFS of 23%. Moreover, the subgroup of patients with *MYC* gene rearrangement (with or without concurrent in *BCL2* and/or *BCL6* gene rearrangements) had poor outcomes regardless of treatment arm.[121] The 4-year PFS was 18% among patients with *MYC* gene rearrangements compared with 42% in those without (*P*=.032); 4-year OS was 29% and 62%, respectively (*P*=.011). Among patients with *MYC* gene rearrangements, the 4-year PFS was 17% with R-DHAP and 19% with R-ICE; OS was 26% and 31%, respectively.[121] Novel approaches are needed for these poor-risk patients. Interestingly, a subgroup analysis from the CORAL study (Bio-CORAL) showed that for patients with a GCB phenotype (based on Hans algorithm), R-DHAP resulted in improved PFS (3-year PFS 52% vs. 31% with R-ICE).[122] This difference was not observed among patients with non-GCB phenotype (3-year PFS 32% with R-DHAP vs. 27% with R-ICE).[122] R-DHAP and R-ICE are acceptable options for patients with relapsed or refractory DLBCL.

The CORAL study was also designed to evaluate the role of rituximab maintenance (every 2 months for 1 year) following ASCR. Among the patients randomized post-ASCR to rituximab maintenance or observation (n=242), the 4-year EFS after ASCR was similar between randomized groups: 52% with rituximab versus 53% with observation.[120] The proportion of patients with progression or relapse was similar between randomized groups. In addition, the 4-year OS was not statistically different (61% and 65%, respectively). Serious adverse events were more frequent in the rituximab maintenance arm. Given

that this study showed no benefit with rituximab maintenance compared with observation post-ASCR, maintenance therapy cannot be recommended in this setting.[120]

Gemcitabine-based chemotherapy regimens such as GDP (gemcitabine, dexamethasone, cisplatin) and GemOx (gemcitabine and oxaliplatin),[123-128] bendamustine and rituximab (BR) [129-132] and lenalidomide (with or without rituximab) [133-137] have also been evaluated in patients with relapsed or refractory DLBCL.

GemOx in combination with rituximab (R-GemOx) was evaluated in patients with relapsed or refractory DLBCL who are not eligible for transplant.[124,126,127] In a pilot study of 46 patients with relapsed or refractory B-cell lymphoma, the majority of whom (72%) had DLBCL, R-GemOx resulted in an ORR of 83% and half of the patients achieved a CR.[124] The 2-year EFS and OS rates in this study were 43% and 66%, respectively. In a subsequent multicenter phase II study that included 49 patients with relapsed or refractory DLBCL, R-GemOx resulted in an ORR of 61% (44% CR and 17% PR).[127] The 5-year PFS and OS rates were 12.8% and 13.9%, respectively.

In a small dose-escalation study of patients with relapsed/refractory aggressive NHL (N=9; DLBCL, n=5), BR regimen resulted in PR in 1 patient (90 mg/m^2 dose of bendamustine; n=3) while the same combination with 120 mg/ m^2 dose of bendamustine (n=6) resulted in CR in 5 patients and a PR in 1 patient.[130] In a recent phase II study of the BR regimen (bendamustine dose 120 mg/m^2) in patients with relapsed/refractory DLBCL (N=59; median age 67 years), the ORR was 63% with a CR in 37% of patients.[131] Patients had received 1 to 3 prior therapies, and were not considered suitable for (or have undergone) ASCR. Nearly all patients (97%) had received prior therapy with rituximab-based regimens.[131] The median PFS was approximately 7 months. The most common grade 3 or 4 toxicities were neutropenia (76%) and thrombocytopenia (22%).[131] In older patients with relapsed/refractory DLBCL (59 patients; median age 74 years; 48 evaluable patients), the BR regimen (with bendamustine dose 120 mg/m^2) resulted in an ORR of 45.8% (15.3% CR; 30.5% PR).[132] The median duration of response and median PFS were 17.3 months and 3.6 months, respectively. Myelosuppression was the most common grade 3 or 4 toxicity.

Lenalidomide monotherapy has been shown to induce an ORR of 28% in patients with relapsed or refractory DLBCL.[133,134] Data from retrospective analysis suggest that the response rates are higher in patients with non-GCB DLBCL versus GCB-DLBCL (ORR: 52.9% vs. 8.7%; *P* = .006; CR rate: 23.5% versus 4.3%).[135] In a multicenter randomized study, 102 patients with relapsed/refractory DLBCL (≥2 prior therapies or ineligible for stem cell transplantation; GCB-DLBCL, n=48; non-GCB DLBCL, n=54) were randomized to lenalidomide monotherapy or single-agent investigator's choice.[138] Lenalidomide resulted in improved ORR, PFS and OS in patients with non-GCB subtype compared to those with GCB subtype. In another phase II trial, 45 patients with relapsed or refractory DLBCL (n=32), transformed large cell lymphoma (n=9) or follicular lymphoma grade 3 (n=4), lenalidomide in combination with rituximab induced ORR in 33% of patients.[136] The median response duration, PFS and OS were 10.2 months, 3.7 months and 10.7 months, respectively.[136] Myelosuppression was the most common grade 3 or 4 toxicity.

Brentuximab vedotin, a CD30-directed antibody-drug conjugate, has demonstrated activity in patients with relapsed or refractory CD30-positive lymphomas. A phase 2, open-label study evaluated the efficacy of brentuximab vedotin in relapsed or refractory CD30-positive NHL.[139] In a planned subset analysis that included 49 patients with

DLBCL, the ORR was 44% (17% CR) with a median duration of 16.6 months. Although there was no statistical correlation between the response and the level of CD30 expression, all patients with responding disease had quantifiable CD30 by IHC.

Brentuximab vedotin (for CD30-positive DLBCL), lenalidomide ± rituximab (for non-GCB-DLBCL) and bendamustine ± rituximab are included as options for patients with relapsed or refractory DLBCL who are not candidates for HDT/ASCR.

NCCN Recommendations

All patients with relapsed or refractory DLBCL should be considered for enrollment in available clinical trials. HDT/ASCR is the treatment of choice for patients with relapsed or refractory DLBCL that is chemosensitive at relapse. Patients who are candidates for HDT/ASCR should be treated with second-line chemotherapy, with or without rituximab (depending on whether the patient is deemed to be refractory to prior rituximab regimens). Suggested regimens (with or without rituximab) include the following:

- DHAP (dexamethasone, cisplatin, cytarabine)
- ESHAP (methylprednisolone, etoposide, cytarabine, cisplatin)
- GDP (gemcitabine, dexamethasone, cisplatin)
- ICE (ifosfamide, carboplatin and etoposide)
- MINE (mitoxantrone, ifosfamide, mesna, etoposide)

Patients with CR or PR to second-line therapy should be considered for further consolidation with HDT/ASCR (category 1 for patients with CR) with or without RT.[98,99] ISRT before HDT/ASCR has been shown to result in good local disease control and improved outcome.[140] Additional RT can be given to limited sites with prior positive disease before or after ASCR. Pertinent clinical trials, including the option of allogeneic stem cell transplantation, may also be considered.

Patients who are not eligible for HDT/ASCR should be treated in the context of a clinical trial. Alternatively, in the absence of suitable clinical trials, patients can also be treated single agent rituximab or the following chemotherapy regimens (with or without rituximab).

- Bendamustine
- Brentuximab vedotin for CD30+ disease (category 2B)
- CEPP
- CEOP (cyclophosphamide, etoposide, vincristine, prednisone)
- DA-EPOCH
- GDP
- Gemcitabine, dexamethasone, carboplatin
- GemOx
- Lenalidomide (non-GCB DLBCL)

Patients with disease relapse following HDT/ASCR should be treated in the context of a clinical trial or treatment should be individualized. However, those with progressive disease after three successive regimens are unlikely to derive additional benefit from currently available chemotherapy regimens, except for patients who have experienced a long disease-free interval.

Primary Mediastinal Large B-cell Lymphoma

PMBL is a distinct subtype of NHL that can be histologically indistinguishable from DLBCL that tends to occur in young adults with a median age of 35 years with a slight female predominance.[141,142] PMBL arises from thymic B-cells with initial local regional spread to supraclavicular, cervical, hilar nodes and into the mediastinum and

lung.[141] Widespread extranodal disease is uncommon at initial diagnosis, present in approximately one quarter of patients, but can be more common at recurrence.[142] Clinical symptoms related to rapid growth of a mediastinal mass include superior vena cava (SVC) syndrome, pericardial and pleural effusions.

GEP has indicated that PMBL is distinct from DLBCL; the pattern of gene expression in PMBL is more similar to classical Hodgkin lymphoma (CHL).[143,144] PMBL expresses B-cell antigens and lacks surface immunoglobulins. PMBL is CD19+, CD20+, CD22+, CD21-, IRF4/MUM1+ and CD23+ with a variable expression of BCL2 and BCL6. CD30 is weakly and heterogeneously expressed in more than 80% of cases and CD15 is occasionally present.[142] CD10 positivity is seen in 8-32% cases. PMBL is also characterized by a low expression of HLA I or II molecules. There have been rare cases of mediastinal gray zone lymphomas with combined features of PMBL and CHL. Cytogenetic abnormalities that are common in PMBL include gains in chromosome 9p24 (involving the *JAK2* in 50–75% of patients) and chromosome 2p15 (involving the *c-REL*, encoding a member of the NF-κB family of transcription factors) and loss in chromosomes 1p, 3p, 13q, 15q, and 17p.[142] Age-adjusted IPI is of limited value in determining the prognosis of PMBL at diagnosis.[141,145,146] In a retrospective analysis of 141 patients from MSKCC, ≥2 extranodal sites and the type of initial therapy were predictors of outcome for EFS, whereas only the initial therapy was a predictor for OS.[145]

In retrospective analyses, intensive chemotherapy regimens have appeared more effective than CHOP[146-148] and the addition of IFRT has been associated with improved PFS; however, these studies were conducted in the pre-rituximab era.[149,150] The results of subsequent retrospective studies suggest that although the addition of rituximab to MACOP-B (methotrexate, leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin) or VACOP-B (etoposide, leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin) did not appear to result in significant differences in clinical outcomes, its addition to CHOP improves outcome in patients with PMBL.[151-155] In an analysis of the subgroup of patients with PMBL (N=87) from the randomized MInT study, which evaluated CHOP-like regimens with or without rituximab, the addition of rituximab significantly improved the CR rate (80% vs. 54% without rituximab; *P*=.015) and 3-year EFS rate (78% vs. 52%; *P*=.012), but not the OS rate (89% vs. 78%; *P* = .158).[152] The MInT study, however, only included young low-risk patients with IPI scores 0-1. In a recent follow-up report with a median observation time of 62 months in patients with PMBL, the increase in EFS with rituximab remained significant at 5 years (79% vs. 47%; *P*=.011).[154] The 5-year PFS was also significantly increased in the rituximab arm (90% vs. 60%; *P*=.006); 5-year OS was not significantly different (90% vs. 78%), but was similar to OS outcomes in patients with DLBCL in this study (92% with rituximab vs. 81% without; *P*<.001).[154] In a retrospective analysis of 95 consecutive patients treated with chemotherapy (VACOP-B or CHOP) with and without rituximab, the 5-year PFS and OS rates were 79% and 97% for patients treated with rituximab-based chemotherapy compared with 58% and 88%, respectively for those treated with chemotherapy alone. The 5-year PFS rates in patients treated with R-VACOP-B, R-CHOP, VACOP-B, and CHOP were 83%, 69%, 62%, and 20%, respectively.[155] Sequential dose dense R-CHOP followed by ICE consolidation (without RT) was also highly effective in patients with PMBL, with similar outcomes to the above analysis with R-chemotherapy from the MInT study.[156] At a median follow up for surviving patients at 3 years, the OS and PFS rates were 88% and 78%, respectively.[156] A retrospective analysis of 63 patients with PMBL treated with R-CHOP found a 21% rate of primary induction failure, with adverse predictors of outcome being advanced

stage and high-risk IPI scores, suggesting that R-CHOP may not be the optimal chemotherapy backbone in PMBL, particularly for high-risk patients.[157]

DA-EPOCH-R has also been evaluated in small cohorts of patients with PMBL.[158,159] A small prospective NCI study of the DA-EPOCH-R without RT demonstrated an encouraging 91% EFS at a median follow-up of 4 years. In a subsequent prospective phase II study from the NCI, DA-EPOCH-R (6–8 cycles) and filgrastim, without RT, was evaluated in 51 patients with previously untreated PMBL.[158] Stage IV disease was present in 29% of patients. After treatment with DA-EPOCH-R, 2 patients showed persistent focal disease and 1 patient had disease progression; 2 of these patients required mediastinal RT while 1 patient was observed after excision biopsy. At a median follow up of 63 months, EFS and OS rates were 93% and 97%, respectively. Grade 4 neutropenia and thrombocytopenia occurred in 50% and 6% of treatment cycles, respectively. Hospitalization for febrile neutropenia occurred in 13% of cycles.[158] This study showed that DA-EPOCH-R is a highly effective regimen in patients with PMBL and obviates the need for RT in the large majority of patients. A single institution retrospective analysis also showed that R-CHOP/R-VACOP-B with RT and DA-EPOCH-R without RT result in excellent outcomes in patients with stage I-II PMBL.[159]

The role of consolidation RT remains unclear. A few studies have evaluated the utility of PET scans (based on the 5-PS) to identify patients at high-risk of progression who could be considered for RT after completion of chemotherapy.[160,161] However, these findings need to be confirmed in larger prospective randomized trials.

In the absence of randomized trials, optimal first-line treatment for patients with PMBL is more controversial than other subtypes of NHL. However, based on the available data, the following regimens are included as options for first-line therapy.

- R-CHOP (6 cycles) ± RT
- DA-EPOCH-R (6 cycles)[158] + RT only for persistent PET-positive local disease
- R-CHOP (4 cycles) followed by ICE (3 cycles)[156] with or without RT (category 2B)

Post-treatment PET-CT is considered essential; if PET-CT is negative at the end of treatment and initial disease was non-bulky, patients may be observed. Residual mediastinal masses are common. For patients initially treated with R-CHOP, consolidation with RT should be considered, particularly if increased FDG-activity persists in the primary tumor. For patients who are PET-CT negative after more intensive therapies (e.g., DA-EPOCH-R), observation may be appropriate. If PET-CT is positive, biopsy is recommended before additional treatment is contemplated.

Grey Zone Lymphoma

Grey zone lymphomas, a provisional diagnostic category included in the 2008 WHO classification, refer to a group of lymphomas with features intermediate between DLBCL and classical Hodgkin lymphoma (cHL).[154,162-165] Other synonyms include large B-cell lymphoma with Hodgkin features or Hodgkin-like anaplastic large cell lymphoma. The morphology of grey zone lymphomas is characterized by sheet-like growth of pleomorphic cells in a diffusely fibrous stroma; cells are typically larger and more pleomorphic than those in PMBL, and may sometimes resemble lacunar or Hodgkin-like cells.[164] Necrosis without neutrophilic infiltration is frequently present.[154,162,164] Patients with gray zone lymphomas may present with mediastinal or non-mediastinal disease. Mediastinal grey zone lymphomas are more commonly seen in

young adult males between the ages of 20 to 40 years and are characterized by the presence of a large anterior mediastinal mass with or without supraclavicular lymph node involvement.[162,163,165] Non-mediastinal gray zone lymphomas occur in older patients, have a higher incidence of bone marrow involvement, more than one extranodal disease, advanced stage disease and high-risk IPI score than mediastinal grey zone lymphomas.[166] In a retrospective multicenter analysis of 112 patients with grey zone lymphomas, mediastinal presentations were found in 43% of patients, while 57% presented with non-mediastinal grey zone lymphomas. [166]

The immunophenotype is atypical, often showing transitional features between PMBL and CHL. In general, CD45 is often positive, and CD15, CD20, CD30, and CD79a are also frequently positive. CD10 and ALK are usually negative. B-cell transcription factors such as PAX5, BOB.1, and OCT-2 are often positive.[162,164,167] BCL6 is variably expressed. EBV is more often negative.[162,163] If the morphology more closely resembles PMBL, absence of CD20, or CD15 positivity, would be suggestive of grey zone lymphoma. If the morphology more closely resembles cHL, strong CD20 expression (and/or other B-cell markers) and absence of CD15 would be suggestive of grey zone lymphoma.[162] A study that evaluated epigenetic changes based on DNA methylation analysis of microdissected tumor cells from patients with mediastinal grey zone lymphomas, PMBL, cHL, and DLBCL showed distinct methylation signatures (hypomethylated and hypermethylated sites) of CpG targets between PMBL and cHL..[168] The methylation profiles of patients with grey zone lymphoma were intermediate to those of PMBL and cHL, but distinct from patients with DLBCL. Among 235 CpG targets that were identified as being differentially methylated between the lymphomas, 22 targets could be used to readily distinguish between PMBL and CHL cHL, with grey zone lymphomas showing an overlap of both signatures. The investigators concluded that the unique epigenetic signature of mediastinal grey zone lymphomas provide validation of its classification as a separate disease entity in the 2008 WHO classification.[168]

The treatment of patients with grey zone lymphomas poses a challenge, as these lymphomas appear to be associated with a worse prognosis compared with PMBL or cHL..[164,167,169] In a prospective study that evaluated 6 to 8 cycles of DA-EPOCH-R in a small group of patients with mediastinal grey zone lymphoma (n=24), the EFS and OS were 62% and 74%, respectively, at the median follow-up of 59 months.[170] With a median follow-up of 5 years, the EFS (62% vs 93%; *P* = .0005) and OS (74% vs 97%; *P* = .0012), were significantly lower for patients with mediastinal grey zone lymphoma compared to patients with PMBL (n = 51) enrolled in the same study. In a multicenter retrospective analysis of gray zone lymphoma (that did not have central pathology review), patients treated with CHOP-like regimens with or without rituximab had superior outcomes compared to subjects treated with ABVD, with 2 year PFS rates of 52% and 22%, respectively.[166]

Patients with grey zone lymphomas are best managed in cancer centers with experience in treating this type of lymphoma, preferably in the context of clinical trials where appropriate. No standard of care or consensus exists for the management of patients with grey zone lymphomas, although patients are typically treated with multiagent chemotherapy regimens used for patients with DLBCL. The addition of rituximab is generally suggested for tumors expressing CD20. In the absence of suitable clinical trials, R-CHOP-21 or DA-EPOCH-R should be considered. Given the apparent inferior outcomes among gray zone lymphomas treated with traditional chemotherapy regimens, consolidative RT should be strongly considered for patients with limited stage disease amenable to RT.

Double-hit lymphomas

DLBCL or high-grade B-cell lymphoma unclassifiable (intermediate between DLBCL and BL) with *MYC* gene rearrangement in addition to *BCL2* and/or *BCL6* gene rearrangements by FISH or standard cytogenetics are known as double-hit lymphomas (DHL). Immunohistochemical staining can also identify DLBCL with dual expression of both MYC and BCL2 proteins, known as double-expressing DLBCL (DEL).[171,172] These patients have an inferior prognosis compared to those with DLBCL as a whole, but not to the same magnitude as patients with true DHL on the basis of gene rearrangements. FISH for *MYC, BCL2,* and *BCL6* gene rearrangements is recommended for those with expression of MYC and either BCL2 or BCL6 by IHC, and a GCB-like immunophenotype. Nearly all DHL are GCB-DLBCL and are characterized by highly aggressive clinical behavior and overlapping pathologic features with DLBCL, Burkitt lymphoma (BL) and B-cell lymphoblastic lymphoma/leukemia (B-LBL).[173] DHL have been observed in 2% to 11% of newly diagnosed patients with DLBCL.

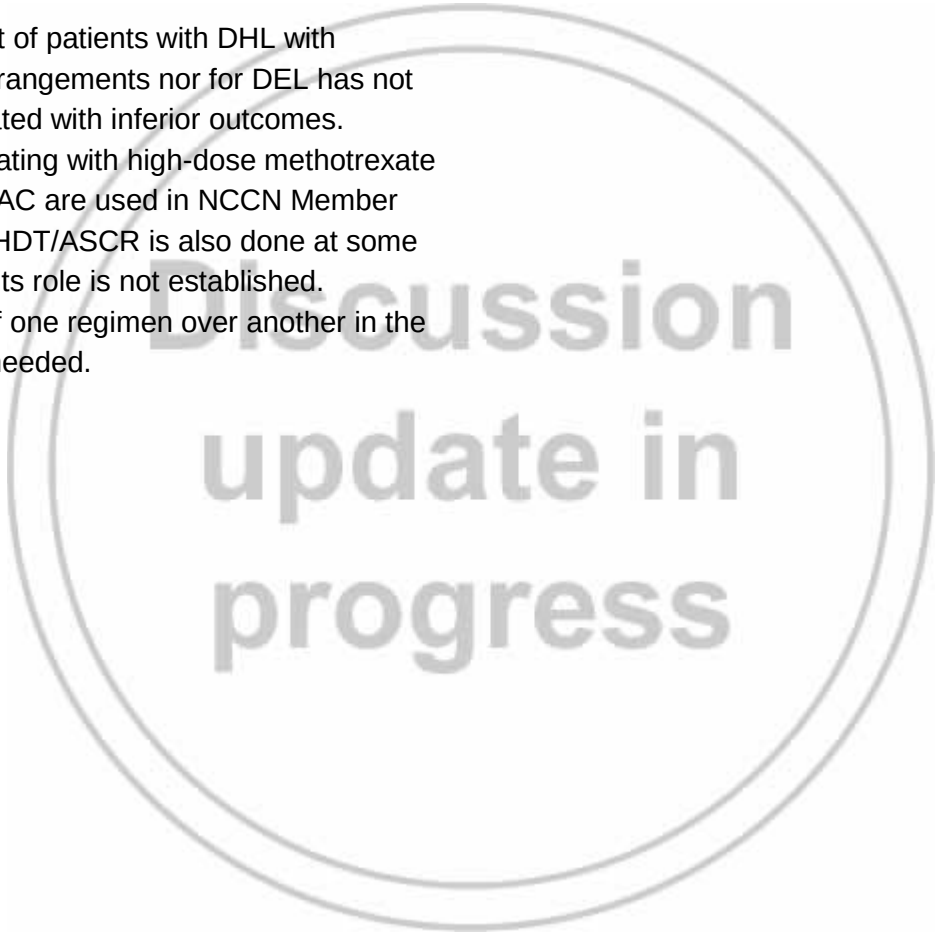
DHL are highly aggressive with very poor clinical outcomes, even with rituximab-based chemoimmunotherapy or intensive therapy with stem cell transplantation.[171,172,174,175] In a series of 193 patients with DLBCL uniformly treated with standard R-CHOP, the median OS (13 months vs. 95 months) and PFS (6 months vs. 95 months), 3-year PFS rate (46% vs. 65%: *P*=.012) and 3-year OS rate (46% vs. 75%; *P*=.002) were significantly lower in patients with DHL compared with those without DHL.[171] In another study with a longer follow-up, 5-year PFS and OS were 18% and 27%, respectively, in patients with double-hit DLBCL treated with R-CHOP.[172] These studies have also shown that high expressions of both MYC and BCL2 protein levels (assessed by IHC but not *MYC* or *BCL2* expression alone) were associated with significantly inferior outcomes after treatment with R-CHOP.[171,172] In the multivariate analysis that included IPI score and cell of origin, concurrent *MYC/BCL2* expression remained a significant independent predictor of poorer PFS and OS after R-CHOP.[171,172]

Data from retrospective studies suggest that more intensive chemotherapy regimens may result in better outcomes.[176-178] In a multicenter retrospective analysis of 106 patients (77% of patients had DHL characterized by *MYC* and *BCL2* gene rearrangements), treatment with intensive regimens such as DA-EPOCH-R, R-HyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone) or R-CODOX-M/IVAC (rituximab, cyclophosphamide, doxorubicin, vincristine, methotrexate/ifosfamide, etoposide, high dose cytarabine) resulted in superior complete remissions and PFS compared to R-CHOP.[176] A recent meta-analysis compared survival outcomes in patients with DHL treated with more aggressive regimens including R-HyperCVAD, R-CODOX-M/IVAC or R-EPOCH versus standard-dose regimens (R-CHOP) in the first-line setting.[179] The median PFS for the R-CHOP, DA-EPOCH-R and other dose intensive regimens was 12.1, 22.2, and 18.9 months, respectively. DA-EPOCH-R significantly reduced the risk of progression compared with R-CHOP; however, OS was not significantly different across treatment approaches.

DA-EPOCH-R is being evaluated in a prospective phase II study of 52 patients with newly diagnosed with DLBCL or B-cell lymphoma unclassifiable with features intermediate between DLBCL and BL).[180] All patients had a *MYC* gene rearrangement. *BCL2* gene rearrangement and BCL2 overexpression were identified in 45% and 56% of patients respectively. Preliminary reports from this study showed that PFS and OS were 79% and 77% respectively for all patients, at a median follow-up of 14 months. PFS was 87% and 64% in cases that were FISH positive (double-hit) and IHC positive for BCL2 respectively.[180]

Additional prospective studies are needed to evaluate the efficacy of DA-EPOCH-R as well as other regimens and stem cell transplantation strategies in patients with DHL. Alternative treatment strategies are needed to improve outcomes in this poor-risk patient population.

The standard of care for the treatment of patients with DHL with concurrent *MYC* and *BCL2* gene rearrangements nor for DEL has not been established. R-CHOP is associated with inferior outcomes. DA-EPOCH-R, R-HyperCVAD (alternating with high-dose methotrexate and cytarabine) or R-CODOX-M/R-IVAC are used in NCCN Member Institutions for the treatment of DHL. HDT/ASCR is also done at some NCCN Member Institutions; however its role is not established. Currently, no data supports the use of one regimen over another in the setting of DEL, and clinical trials are needed.



References

1. Al-Hamadani M, Habermann TM, Cerhan JR, et al. Non-Hodgkin lymphoma subtype distribution, geodemographic patterns, and survival in the US: A longitudinal analysis of the National Cancer Data Base from 1998 to 2011. Am J Hematol 2015;90:790-795. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26096944.

2. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 2000;403:503-511. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10676951.

3. Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood 2004;103:275-282. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14504078.

4. Choi WWL, Weisenburger DD, Greiner TC, et al. A new immunostain algorithm classifies diffuse large B-cell lymphoma into molecular subtypes with high accuracy. Clin Cancer Res 2009;15:5494-5502. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19706817.

5. Meyer PN, Fu K, Greiner TC, et al. Immunohistochemical methods for predicting cell of origin and survival in patients with diffuse large B-cell lymphoma treated with rituximab. J Clin Oncol 2011;29:200-207. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21135273.

6. Savage KJ, Johnson NA, Ben-Neriah S, et al. MYC gene rearrangements are associated with a poor prognosis in diffuse large B-cell lymphoma patients treated with R-CHOP chemotherapy. Blood 2009;114:3533-3537. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19704118.

7. Barrans S, Crouch S, Smith A, et al. Rearrangement of MYC is associated with poor prognosis in patients with diffuse large B-cell lymphoma treated in the era of rituximab. J Clin Oncol 2010;28:3360-3365. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20498406.

8. Tzankov A, Xu-Monette ZY, Gerhard M, et al. Rearrangements of MYC gene facilitate risk stratification in diffuse large B-cell lymphoma patients treated with rituximab-CHOP. Mod Pathol 2014;27:958-971. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24336156.

9. Nowakowski GS, LaPlant B, Macon WR, et al. Lenalidomide combined with R-CHOP overcomes negative prognostic impact of non-germinal center B-cell phenotype in newly diagnosed diffuse large B-Cell lymphoma: a phase II study. J Clin Oncol 2015;33:251-257. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25135992.

10. Wilson WH, Young RM, Schmitz R, et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. Nat Med 2015;21:922-926. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26193343.

11. U.S. National Library of Medicine Key MEDLINE® Indicators Available at: http://www.nlm.nih.gov/bsd/bsd_key.html.

12. Mozos A, Royo C, Hartmann E, et al. SOX11 expression is highly specific for mantle cell lymphoma and identifies the cyclin D1-negative subtype. Haematologica 2009;94:1555-1562. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19880778.

13. Zeng W, Fu K, Quintanilla-Fend L, et al. Cyclin D1-negative blastoid mantle cell lymphoma identified by SOX11 expression. Am J Surg Pathol 2012;36:214-219. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22251940.

14. FDA Drug Safety Communication: Boxed Warning and new recommendations to decrease risk of hepatitis B reactivation with the immune-suppressing and anti-cancer drugs Arzerra (ofatumumab) and Rituxan (rituximab); September 25, 2013. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM369436.pdf.

15. Juweid ME. FDG-PET/CT in lymphoma. Methods Mol Biol 2011;727:1-19. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21331925.

16. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32:3059-3068. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25113753.

17. Adams HJ, Kwee TC, de Keizer B, et al. FDG PET/CT for the detection of bone marrow involvement in diffuse large B-cell lymphoma: systematic review and meta-analysis. Eur J Nucl Med Mol Imaging 2014;41:565-574. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24281821.

18. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med 1993;329:987-994. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8141877.

19. Sehn LH, Berry B, Chhanabhai M, et al. The revised international prognostic index (R-IPI) is a better predictor of outcome than the standard ipi for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood 2006;109:1857-1861. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17105812.

20. Zhou Z, Sehn LH, Rademaker AW, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. Blood 2014;123:837-842. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24264230.

21. El-Galaly TC, Villa D, Alzahrani M, et al. Outcome prediction by extranodal involvement, IPI, R-IPI, and NCCN-IPI in the PET/CT and rituximab era: A Danish-Canadian study of 443 patients with diffuse-large B-cell lymphoma. Am J Hematol 2015;90:1041-1046. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26260224.

22. Zucca E, Conconi A, Mughal TI, et al. Patterns of outcome and prognostic factors in primary large-cell lymphoma of the testis in a survey by the International Extranodal Lymphoma Study Group. J Clin Oncol 2003;21:20-27. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12506165.

23. Laskin JJ, Savage KJ, Voss N, et al. Primary paranasal sinus lymphoma: natural history and improved outcome with central nervous system chemoprophylaxis. Leuk Lymphoma 2005;46:1721-1727. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16263574.

24. Shimazu Y, Notohara K, Ueda Y. Diffuse large B-cell lymphoma with central nervous system relapse: prognosis and risk factors according to retrospective analysis from a single-center experience. Int J Hematol 2009;89:577-583. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19353238.

25. Schmitz N, Zeynalova S, Nickelsen M, et al. A new prognosticmodel to assess the risk of CNS disease in patients with aggressive B-cell lymphoma. Hematological Oncology 2013;31(Suppl 1):Abstract 047. Available at: http://dx.doi.org/10.1002/hon.2057.

26. Savage KJ, Zeynalova S, Kansara RR, et al. Validation of a prognostic model to assess the risk of CNS disease in patients with aggressive B-cell lymphoma [abstract]. Blood 2014;124:Abstract 394. Available at: http://www.bloodjournal.org/content/124/21/394.abstract.

27. Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med 1998;339:21-26. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9647875.

28. Shenkier TN, Voss N, Fairey R, et al. Brief chemotherapy and involved-region irradiation for limited-stage diffuse large-cell lymphoma: an 18-year experience from the British Columbia Cancer Agency. J Clin Oncol 2002;20:197-204. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11773170.

29. Horning SJ, Weller E, Kim K, et al. Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-Hodgkin's lymphoma: Eastern Cooperative Oncology Group study 1484. J Clin Oncol 2004;22:3032-3038. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15210738.

30. Bonnet C, Fillet G, Mounier N, et al. CHOP alone compared with CHOP plus radiotherapy for localized aggressive lymphoma in elderly patients: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 2007;25:787-792. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17228021.

31. Persky DO, Unger JM, Spier CM, et al. Phase II study of rituximab plus three cycles of CHOP and involved-field radiotherapy for patients with limited-stage aggressive B-cell lymphoma: Southwest Oncology Group study 0014. J Clin Oncol 2008;26:2258-2263. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18413640.

32. Pfreundschuh M, Trumper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol 2006;7:379-391. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16648042.

33. Pfreundschuh M, Kuhnt E, Trumper L, et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. Lancet Oncol 2011;12:1013-1022. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21940214.

34. Odejide OO, Cronin AM, Davidoff AJ, et al. Limited stage diffuse large B-cell lymphoma: comparative effectiveness of treatment strategies in a large cohort of elderly patients. Leuk Lymphoma 2015;56:716-724. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24913508.

35. Reyes F, Lepage E, Ganem G, et al. ACVBP versus CHOP plus radiotherapy for localized aggressive lymphoma. N Engl J Med 2005;352:1197-1205. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15788496.

36. Recher C, Coiffier B, Haioun C, et al. Intensified chemotherapy with ACVBP plus rituximab versus standard CHOP plus rituximab for the treatment of diffuse large B-cell lymphoma (LNH03-2B): an open-label randomised phase 3 trial. Lancet 2011;378:1858-1867. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22118442.

37. Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 1993;328:1002-1006. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7680764.

38. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002;346:235-242. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11807147.

39. Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 2005;23:4117-4126. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15867204.

40. Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood 2010;116:2040-2045. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20548096.

41. Sonneveld P, van Putten W, Holte H, et al. Intensified CHOP with rituximab for intermediate or high-risk Non-hodgkin's lymphoma: interim analysis of a randomized phase III trial in elderly patients by the Dutch

HOVON and Nordic Lymphoma Groups [abstract]. Blood 2005;106:Abstract 16. Available at: http://www.bloodjournal.org/content/106/11/16.

42. Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol 2006;24:3121-3127. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16754935.

43. Blayney DW, LeBlanc ML, Grogan T, et al. Dose-intense chemotherapy every 2 weeks with dose-intense cyclophosphamide, doxorubicin, vincristine, and prednisone may improve survival in intermediate- and high-grade lymphoma: a phase II study of the Southwest Oncology Group (SWOG 9349). J Clin Oncol 2003;21:2466-2473. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12829664.

44. Halaas JL, Moskowitz CH, Horwitz S, et al. R-CHOP-14 in patients with diffuse large B-cell lymphoma: feasibility and preliminary efficacy. Leuk Lymphoma 2005;46:541-547. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16019482.

45. Pfreundschuh M, Trumper L, Kloess M, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL. Blood 2004;104:634-641. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15016643.

46. Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). Lancet Oncol 2008;9:105-116. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18226581.

47. Pfreundschuh M, Ziepert M, Zeynalova S, et al. Six versus eight cycles of biweekly CHOP-14 with or without R in elderly patients (pts) with aggressive CD20+ B-cell lymphomas: Seven-year FU of the RICOVER-60 trial of the DSHNHL [abstract]. J Clin Oncol 2011;29:Abstract 8029. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/8029.

48. Held G, Murawski N, Ziepert M, et al. Role of radiotherapy to bulky disease in elderly patients with aggressive B-cell lymphoma. J Clin Oncol 2014;32:1112-1118. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24493716.

49. Held G, Zeynalova S, Murawski N, et al. Impact of rituximab and radiotherapy on outcome of patients with aggressive B-cell lymphoma and skeletal involvement. J Clin Oncol 2013;31:4115-4122. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24062391.

50. Cunningham D, Hawkes EA, Jack A, et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. Lancet 2013;381:1817-1826. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23615461.

51. Delarue R, Tilly H, Mounier N, et al. Dose-dense rituximab-CHOP compared with standard rituximab-CHOP in elderly patients with diffuse large B-cell lymphoma (the LNH03-6B study): a randomised phase 3 trial. Lancet Oncol 2013;14:525-533. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23578722.

52. Schmitz N, Nickelsen M, Ziepert M, et al. Optimization of Rituximab for Treatment of DLBCL in Young, High-Risk Patients-Results of the Dense-R-CHOEP Trial of the German High-Grade Lymphoma Study Group. Blood 2015;126:474-474. Available at: http://www.bloodjournal.org/content/126/23/474.abstract.

53. Schmitz N, Nickelsen M, Ziepert M, et al. Conventional chemotherapy (CHOEP-14) with rituximab or high-dose chemotherapy (MegaCHOEP) with rituximab for young, high-risk patients with aggressive B-cell lymphoma: an open-label, randomised, phase 3 trial (DSHNHL 2002-1). Lancet Oncol 2012;13:1250-1259. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23168367.

54. Pfreundschuh M, Muller C, Zeynalova S, et al. Suboptimal dosing of rituximab in male and female patients with DLBCL. Blood 2014;123:640-646. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24297867.

55. Pfreundschuh M, Held G, Zeynalova S, et al. Increased rituximab (R) doses and effect on risk of elderly male patients with aggressive CD20+ B-cell lymphomas: Results from the SEXIE-R-CHOP-14 trial of the DSHNHL [abstract]. J Clin Oncol 2014;32 (15_suppl):Abstract 8501. Available at: http://meeting.ascopubs.org/cgi/content/abstract/32/15_suppl/8501.

56. Wilson WH, Jung SH, Porcu P, et al. A Cancer and Leukemia Group B multi-center study of DA-EPOCH-rituximab in untreated diffuse large B-cell lymphoma with analysis of outcome by molecular subtype. Haematologica 2012;97:758-765. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22133772.

57. Purroy N, Bergua J, Gallur L, et al. Long-term follow-up of dose-adjusted EPOCH plus rituximab (DA-EPOCH-R) in untreated patients with poor prognosis large B-cell lymphoma. A phase II study conducted by the Spanish PETHEMA Group. Br J Haematol 2015;169:188-198. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25521006.

58. Peyrade F, Jardin F, Thieblemont C, et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. Lancet Oncol 2011;12:460-468. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21482186.

59. Peyrade F, Fain O, Fabiani B, et al. Long-term follow-up of the GELA LNH 03-7B study: A prospective phase II study of 150 patients over 80 years with diffuse large B-cell lymphoma (DLBCL) treated with RminiCHOP [abstract]. J Clin Oncol 2013;31(15_suppl):Abstract 8536. Available at: http://meeting.ascopubs.org/cgi/content/abstract/31/15_suppl/8536.

60. Haioun C, Lepage E, Gisselbrecht C, et al. Survival benefit of high-dose therapy in poor-risk aggressive non-Hodgkin's lymphoma: final analysis of the prospective LNH87-2 protocol--a groupe d'Etude des lymphomes de l'Adulte study. J Clin Oncol 2000;18:3025-3030. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10944137.

61. Stiff PJ, Unger JM, Cook JR, et al. Autologous transplantation as consolidation for aggressive non-Hodgkin's lymphoma. N Engl J Med 2013;369:1681-1690. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24171516.

62. Le Gouill S, Milpied NJ, Lamy T, et al. First-line rituximab (R) high-dose therapy (R-HDT) versus R-CHOP14 for young adults with diffuse large B-cell lymphoma: Preliminary results of the GOELAMS 075 prospective multicenter randomized trial [abstract]. J Clin Oncol 2011;29:Abstract 8003. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/8003.

63. Vitolo U, Chiappella A, Brusamolino E, et al. Rituximab Dose-Dense Chemotherapy Followed by Intensified High-Dose Chemotherapy and Autologous Stem Cell Transplantation (HDC+ASCT) Significantly Reduces the Risk of Progression Compared to Standard Rituximab Dose-Dense Chemotherapy As First Line Treatment in Young Patients with High-Risk (aa-IPI 2-3) Diffuse Large B-Cell Lymphoma (DLBCL): Final Results of Phase III Randomized Trial DLCL04 of the Fondazione Italiana Linfomi (FIL)[absttract]. Blood 2012;120:Abstract 688. Available at: http://www.bloodjournal.org/content/120/21/688.

64. Martino R, Perea G, Caballero MD, et al. Cyclophosphamide, pegylated liposomal doxorubicin (Caelyx), vincristine and prednisone (CCOP) in elderly patients with diffuse large B-cell lymphoma: results from a prospective phase II study. Haematologica 2002;87:822-827. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12161358.

65. Visani G, Guiducci B, D'Adamo F, et al. Cyclophosphamide, pegylated liposomal doxorubicin, vincristine and prednisone (CDOP) plus rituximab is effective and well tolerated in poor performance status elderly patients with non-Hodgkin's lymphoma. Leuk Lymphoma

2005;46:477-479. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15621843.

66. Zaja F, Tomadini V, Zaccaria A, et al. CHOP-rituximab with pegylated liposomal doxorubicin for the treatment of elderly patients with diffuse large B-cell lymphoma. Leuk Lymphoma 2006;47:2174-2180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17071492.

67. Moccia AA, Schaff K, Hoskins P, et al. R-CHOP with etoposide substituted for doxorubicin (R-CEOP): excellent outcome in diffuse large b cell lymphoma for patients with a contraindication to anthracyclines [abstract]. Blood 2009;114:Abstract 408. Available at: http://www.bloodjournal.org/content/114/22/408.

68. Fields PA, Townsend W, Webb A, et al. De novo treatment of diffuse large B-cell lymphoma with rituximab, cyclophosphamide, vincristine, gemcitabine, and prednisolone in patients with cardiac comorbidity: a United Kingdom National Cancer Research Institute trial. J Clin Oncol 2014;32:282-287. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24220559.

69. Abramson JS, Hellmann M, Barnes JA, et al. Intravenous methotrexate as central nervous system (CNS) prophylaxis is associated with a low risk of CNS recurrence in high-risk patients with diffuse large B-cell lymphoma. Cancer 2010;116:4283-4290. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20564149.

70. Holte H, Leppa S, Bjorkholm M, et al. Dose-densified chemoimmunotherapy followed by systemic central nervous system prophylaxis for younger high-risk diffuse large B-cell/follicular grade 3 lymphoma patients: results of a phase II Nordic Lymphoma Group study. Ann Oncol 2013;24:1385-1392. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23247661.

71. Cheah CY, Herbert KE, O'Rourke K, et al. A multicentre retrospective comparison of central nervous system prophylaxis strategies among patients with high-risk diffuse large B-cell lymphoma. Br J Cancer 2014;111:1072-1079. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25072255.

72. Ferreri AJ, Bruno-Ventre M, Donadoni G, et al. Risk-tailored CNS prophylaxis in a mono-institutional series of 200 patients with diffuse large B-cell lymphoma treated in the rituximab era. Br J Haematol 2015;168:654-662. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25312994.

73. Kumar A, Vanderplas A, LaCasce AS, et al. Lack of benefit of central nervous system prophylaxis for diffuse large B-cell lymphoma in the rituximab era: findings from a large national database. Cancer 2012;118:2944-2951. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22006274.

74. Tomita N, Takasaki H, Ishiyama Y, et al. Intrathecal methotrexate prophylaxis and central nervous system relapse in patients with diffuse large B-cell lymphoma following rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone. Leuk Lymphoma 2015;56:725-729. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24913502.

75. Mikhaeel NG, Timothy AR, O'Doherty MJ, et al. 18-FDG-PET as a prognostic indicator in the treatment of aggressive Non-Hodgkin's Lymphoma-comparison with CT. Leuk Lymphoma 2000;39:543-553. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11342337.

76. Spaepen K, Stroobants S, Dupont P, et al. Early restaging positron emission tomography with (18)F-fluorodeoxyglucose predicts outcome in patients with aggressive non-Hodgkin's lymphoma. Ann Oncol 2002;13:1356-1363. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12196360.

77. Haioun C, Itti E, Rahmouni A, et al. [18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in aggressive lymphoma: an early prognostic tool for predicting patient outcome. Blood 2005;106:1376-1381. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15860666.

78. Dupuis J, Itti E, Rahmouni A, et al. Response assessment after an inductive CHOP or CHOP-like regimen with or without rituximab in 103 patients with diffuse large B-cell lymphoma: integrating 18fluorodeoxyglucose positron emission tomography to the International Workshop Criteria. Ann Oncol 2009;20:503-507. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19074215.

79. Moskowitz CH, Schoder H, Teruya-Feldstein J, et al. Risk-adapted dose-dense immunochemotherapy determined by interim FDG-PET in advanced-stage diffuse large B-cell lymphoma. J Clin Oncol 2010;28:1896-1903. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20212248.

80. Pregno P, Chiappella A, Bello M, et al. Interim 18-FDG-PET/CT failed to predict the outcome in diffuse large B-cell lymphoma patients treated at the diagnosis with rituximab-CHOP. Blood 2012;119:2066-2073. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22234681.

81. Carr R, Fanti S, Paez D, et al. Prospective international cohort study demonstrates inability of interim PET to predict treatment failure in diffuse large B-cell lymphoma. J Nucl Med 2014;55:1936-1944. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25429159.

82. Dabaja BS, Vanderplas AM, Crosby-Thompson AL, et al. Radiation for diffuse large B-cell lymphoma in the rituximab era: analysis of the National Comprehensive Cancer Network lymphoma outcomes project. Cancer 2015;121:1032-1039. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25492236.

83. Mamot C, Klingbiel D, Hitz F, et al. Final Results of a Prospective Evaluation of the Predictive Value of Interim Positron Emission Tomography in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP-14 (SAKK 38/07). J Clin Oncol 2015;33:2523-2529. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26150440.

84. Swinnen LJ, Li H, Quon A, et al. Response-adapted therapy for aggressive non-Hodgkin's lymphomas based on early [18F] FDG-PET scanning: ECOG-ACRIN Cancer Research Group study (E3404). Br J Haematol 2015;170:56-65. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25823885.

85. Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of Imaging in the Staging and Response Assessment of Lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25113771.

86. Barrington SF, Qian W, Somer EJ, et al. Concordance between four European centres of PET reporting criteria designed for use in multicentre trials in Hodgkin lymphoma. Eur J Nucl Med Mol Imaging 2010;37:1824-1833. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20505930.

87. Meignan M, Gallamini A, Haioun C, Polliack A. Report on the Second International Workshop on interim positron emission tomography in lymphoma held in Menton, France, 8-9 April 2010. Leuk Lymphoma 2010;51:2171-2180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21077737.

88. Meignan M, Gallamini A, Itti E, et al. Report on the Third International Workshop on Interim Positron Emission Tomography in Lymphoma held in Menton, France, 26-27 September 2011 and Menton 2011 consensus. Leuk Lymphoma 2012;53:1876-1881. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22432519.

89. Guppy AE, Tebbutt NC, Norman A, Cunningham D. The role of surveillance CT scans in patients with diffuse large B-cell non-Hodgkin's lymphoma. Leuk Lymphoma 2003;44:123-125. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12691151.

90. Liedtke M, Hamlin PA, Moskowitz CH, Zelenetz AD. Surveillance imaging during remission identifies a group of patients with more favorable aggressive NHL at time of relapse: a retrospective analysis of a uniformly-treated patient population. Ann Oncol 2006;17:909-913. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16672295.

91. Zinzani PL, Stefoni V, Tani M, et al. Role of [18F]fluorodeoxyglucose positron emission tomography scan in the follow-up of lymphoma. J Clin Oncol 2009;27:1781-1787. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19273712.

92. Petrausch U, Samaras P, Haile SR, et al. Risk-adapted FDG-PET/CT-based follow-up in patients with diffuse large B-cell lymphoma after first-line therapy. Ann Oncol 2010;21:1694-1698. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20139151.

93. Avivi I, Zilberlicht A, Dann EJ, et al. Strikingly high false positivity of surveillance FDG-PET/CT scanning among patients with diffuse large cell lymphoma in the rituximab era. Am J Hematol 2013;88:400-405. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23423884.

94. Cheah CY, Hofman MS, Dickinson M, et al. Limited role for surveillance PET-CT scanning in patients with diffuse large B-cell lymphoma in complete metabolic remission following primary therapy. Br J Cancer 2013;109:312-317. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23807169.

95. Thompson CA, Ghesquieres H, Maurer MJ, et al. Utility of routine post-therapy surveillance imaging in diffuse large B-cell lymphoma. J Clin Oncol 2014;32:3506-3512. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25267745.

96. El-Galaly TC, Jakobsen LH, Hutchings M, et al. Routine Imaging for Diffuse Large B-Cell Lymphoma in First Complete Remission Does Not Improve Post-Treatment Survival: A Danish-Swedish Population-Based Study. J Clin Oncol 2015;33:3993-3998. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26438115.

97. Maurer MJ, Ghesquieres H, Jais JP, et al. Event-free survival at 24 months is a robust end point for disease-related outcome in diffuse large B-cell lymphoma treated with immunochemotherapy. J Clin Oncol 2014;32:1066-1073. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24550425.

98. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med 1995;333:1540-1545. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7477169.

99. Mounier N, Canals C, Gisselbrecht C, et al. High-dose therapy and autologous stem cell transplantation in first relapse for diffuse large B cell lymphoma in the rituximab era: an analysis based on data from the European Blood and Marrow Transplantation Registry. Biol Blood Marrow Transplant 2012;18:788-793. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22005647.

100. Hamlin PA, Zelenetz AD, Kewalramani T, et al. Age-adjusted International Prognostic Index predicts autologous stem cell transplantation outcome for patients with relapsed or primary refractory diffuse large B-cell lymphoma. Blood 2003;102:1989-1996. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12676776.

101. Lerner RE, Thomas W, Defor TE, et al. The International Prognostic Index assessed at relapse predicts outcomes of autologous transplantation for diffuse large-cell non-Hodgkin's lymphoma in second complete or partial remission. Biol Blood Marrow Transplant 2007;13:486-492. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17382255.

102. Derenzini E, Musuraca G, Fanti S, et al. Pretransplantation positron emission tomography scan is the main predictor of autologous stem cell transplantation outcome in aggressive B-cell non-Hodgkin lymphoma. Cancer 2008;113:2496-2503. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18833583.

103. Spaepen K, Stroobants S, Dupont P, et al. Prognostic value of pretransplantation positron emission tomography using fluorine 18-fluorodeoxyglucose in patients with aggressive lymphoma treated with high-dose chemotherapy and stem cell transplantation. Blood 2003;102:53-59. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12609836.

104. Trneny M, Bosly A, Bouabdallah K, et al. Independent predictive value of PET-CT pre transplant in relapsed and refractory patients with CD20 diffuse large B-cell lymphoma (DLBCL) included in the CORAL study [abstract]. Blood 2009;114:Abstract 881. Available at: http://www.bloodjournal.org/content/114/22/881.

105. Hoppe BS, Moskowitz CH, Zhang Z, et al. The role of FDG-PET imaging and involved field radiotherapy in relapsed or refractory diffuse large B-cell lymphoma. Bone Marrow Transplant 2009;43:941-948. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19139730.

106. Vose JM, Zhang MJ, Rowlings PA, et al. Autologous transplantation for diffuse aggressive Non-hodgkin's lymphoma in patients never achieving remission: a report from the autologous Blood and Marrow Transplant Registry. J Clin Oncol 2001;19:406-413. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11208832.

107. Caballero MD, Pérez-Simón JA, Iriondo A, et al. High-dose therapy in diffuse large cell lymphoma: results and prognostic factors in 452 patients from the GEL-TAMO Spanish Cooperative Group. Annals of Oncology 2003;14:140-151. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12488306.

108. Rodriguez J, Caballero MD, Gutierrez A, et al. Autologous stem-cell transplantation in diffuse large B-cell non-Hodgkin's lymphoma not achieving complete response after induction chemotherapy: the GEL/TAMO experience. Annals of Oncology 2004;15:1504-1509. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15367411.

109. Coiffier B, Haioun C, Ketterer N, et al. Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: a multicenter phase II study. Blood 1998;92:1927-1932. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9731049.

110. Mey UJ, Orlopp KS, Flieger D, et al. Dexamethasone, high-dose cytarabine, and cisplatin in combination with rituximab as salvage treatment for patients with relapsed or refractory aggressive non-Hodgkin's lymphoma. Cancer Invest 2006;24:593-600. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16982464.

111. Velasquez WS, McLaughlin P, Tucker S, et al. ESHAP--an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. J Clin Oncol 1994;12:1169-1176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8201379.

112. Joyce RM, Regan M, Ottaway J, et al. A phase I-II study of rituximab, ifosfamide, mitoxantrone and etoposide (R-IME) for B cell non-Hodgkin's lymphoma prior to and after high-dose chemotherapy and autologous stem cell transplantation (HDC-ASCT). Ann Oncol 2003;14 Suppl 1:21-27. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12736227.

113. Zelenetz AD, Hamlin P, Kewalramani T, et al. Ifosfamide, carboplatin, etoposide (ICE)-based second-line chemotherapy for the management of relapsed and refractory aggressive non-Hodgkin's lymphoma. Ann Oncol 2003;14 Suppl 1:i5-10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12736224.

114. Vose J, Sneller V. Outpatient regimen rituximab plus ifosfamide, carboplatin and etoposide (R-ICE) for relapsed non-Hodgkin's lymphoma. Ann Oncol 2003;14 Suppl 1:17-20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12736226.

115. Kewalramani T, Zelenetz AD, Nimer SD, et al. Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. Blood 2004;103:3684-3688. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14739217.

116. Gutierrez M, Chabner BA, Pearson D, et al. Role of a doxorubicin-containing regimen in relapsed and resistant lymphomas: an 8-year follow-up study of EPOCH. J Clin Oncol 2000;18:3633-3642. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11054436.

117. Jermann M, Jost LM, Taverna C, et al. Rituximab-EPOCH, an effective salvage therapy for relapsed, refractory or transformed B-cell lymphomas: results of a phase II study. Ann Oncol 2004;15:511-516. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14998858.

118. Chao NJ, Rosenberg SA, Horning SJ. CEPP(B): an effective and well-tolerated regimen in poor-risk, aggressive non-Hodgkin's lymphoma. Blood 1990;76:1293-1298. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2207307.

119. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era J Clin Oncol 2010;28:4184-4190. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20660832.

120. Gisselbrecht C, Schmitz N, Mounier N, et al. Rituximab Maintenance Therapy After Autologous Stem-Cell Transplantation in Patients With Relapsed CD20+ Diffuse Large B-Cell Lymphoma: Final Analysis of the Collaborative Trial in Relapsed Aggressive Lymphoma. J Clin Oncol 2012;30:4462-4469. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23091101.

121. Cuccuini W, Briere J, Mounier N, et al. MYC+ diffuse large B-cell lymphoma is not salvaged by classical R-ICE or R-DHAP followed by BEAM plus autologous stem cell transplantation. Blood 2012;119:4619-4624. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22408263.

122. Thieblemont C, Briere J, Mounier N, et al. The germinal center/activated B-cell subclassification has a prognostic impact for response to salvage therapy in relapsed/refractory diffuse large B-cell lymphoma: a bio-CORAL study. J Clin Oncol 2011;29:4079-4087. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21947824.

123. Crump M, Baetz T, Couban S, et al. Gemcitabine, dexamethasone, and cisplatin in patients with recurrent or refractory aggressive histology B-cell non-Hodgkin lymphoma: a Phase II study by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG). Cancer 2004;101:1835-1842. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15386331.

124. El Gnaoui T, Dupuis J, Belhadj K, et al. Rituximab, gemcitabine and oxaliplatin: an effective salvage regimen for patients with relapsed or refractory B-cell lymphoma not candidates for high-dose therapy. Ann Oncol 2007;18:1363-1368. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17496309.

125. Lopez A, Gutierrez A, Palacios A, et al. GEMOX-R regimen is a highly effective salvage regimen in patients with refractory/relapsing diffuse large-cell lymphoma: a phase II study. Eur J Haematol 2008;80:127-132. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18005385.

126. Corazzelli G, Capobianco G, Arcamone M, et al. Long-term results of gemcitabine plus oxaliplatin with and without rituximab as salvage treatment for transplant-ineligible patients with refractory/relapsing B-cell lymphoma. Cancer Chemother Pharmacol 2009;64:907-916. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19219604.

127. Mounier N, El Gnaoui T, Tilly H, et al. Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II Lymphoma Study Association trial. Haematologica 2013;98:1726-1731. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23753028.

128. Crump M, Kuruvilla J, Couban S, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. J Clin Oncol 2014;32:3490-3496. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25267740.

129. Weidmann E, Kim SZ, Rost A, et al. Bendamustine is effective in relapsed or refractory aggressive non-Hodgkin's lymphoma. Ann Oncol 2002;13:1285-1289. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12181253.

130. Ogura M, Ando K, Taniwaki M, et al. Feasibility and pharmacokinetic study of bendamustine hydrochloride in combination with rituximab in relapsed or refractory aggressive B cell non-Hodgkin's lymphoma(6). Cancer Sci 2011;102:1687-1692. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21624007.

131. Ohmachi K, Niitsu N, Uchida T, et al. Multicenter Phase II Study of Bendamustine Plus Rituximab in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma. J Clin Oncol 2013;31:2103-2109. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23650408.

132. Vacirca JL, Acs PI, Tabbara IA, et al. Bendamustine combined with rituximab for patients with relapsed or refractory diffuse large B cell lymphoma. Ann Hematol 2014;93:403-409. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23955074.

133. Wiernik PH, Lossos IS, Tuscano JM, et al. Lenalidomide monotherapy in relapsed or refractory aggressive non-Hodgkin's lymphoma. J Clin Oncol 2008;26:4952-4957. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18606983.

134. Witzig TE, Vose JM, Zinzani PL, et al. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. Ann Oncol 2011;22:1622-1627. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21228334.

135. Hernandez-Ilizaliturri FJ, Deeb G, Zinzani PL, et al. Higher response to lenalidomide in relapsed/refractory diffuse large B-cell lymphoma in nongerminal center B-cell-like than in germinal center B-cell-like phenotype. Cancer 2011;117:5058-5066. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21495023.

136. Wang M, Fowler N, Wagner-Bartak N, et al. Oral Lenalidomide with rituximab in relapsed or refractory diffuse large cell, follicular, and transformed lymphoma: a phase II clinical trial. Leukemia 2013;27:1902-1909. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23545991.

137. Zinzani PL, Vose JM, Czuczman MS, et al. Long-term follow-up of lenalidomide in relapsed/refractory mantle cell lymphoma: subset analysis of the NHL-003 study. Ann Oncol 2013;24:2892-2897. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24030098.

138. Czuczman MS, Davies A, Linton KM, et al. A Phase 2/3 Multicenter, Randomized Study Comparing the Efficacy and Safety of Lenalidomide Versus Investigator's Choice in Relapsed/Refractory DLBCL. Blood 2014;124:628-628. Available at: http://www.bloodjournal.org/content/124/21/628.abstract.

139. Jacobsen ED, Sharman JP, Oki Y, et al. Brentuximab vedotin demonstrates objective responses in a phase 2 study of relapsed/refractory DLBCL with variable CD30 expression. Blood 2015;125:1394-1402. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25573987.

140. Hoppe BS, Moskowitz CH, Filippa DA, et al. Involved-field radiotherapy before high-dose therapy and autologous stem-cell rescue in diffuse large-cell lymphoma: long-term disease control and toxicity. J Clin Oncol 2008;26:1858-1864. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18332466.

141. Cazals-Hatem D, Lepage E, Brice P, et al. Primary mediastinal large B-cell lymphoma. A clinicopathologic study of 141 cases compared with 916 nonmediastinal large B-cell lymphomas, a GELA ("Groupe d'Etude des Lymphomes de l'Adulte") study. Am J Surg Pathol 1996;20:877-888. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8669537.

142. Faris JE, LaCasce AS. Primary mediastinal large B-cell lymphoma. Clin Adv Hematol Oncol 2009;7:125-133. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19367254.

143. Rosenwald A, Wright G, Leroy K, et al. Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to Hodgkin

lymphoma. J Exp Med 2003;198:851-862. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12975453.

144. Savage KJ, Monti S, Kutok JL, et al. The molecular signature of mediastinal large B-cell lymphoma differs from that of other diffuse large B-cell lymphomas and shares features with classical Hodgkin lymphoma. Blood 2003;102:3871-3879. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12933571.

145. Hamlin PA, Portlock CS, Straus DJ, et al. Primary mediastinal large B-cell lymphoma: optimal therapy and prognostic factor analysis in 141 consecutive patients treated at Memorial Sloan Kettering from 1980 to 1999. Br J Haematol 2005;130:691-699. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16115124.

146. Savage KJ, Al-Rajhi N, Voss N, et al. Favorable outcome of primary mediastinal large B-cell lymphoma in a single institution: the British Columbia experience. Ann Oncol 2006;17:123-130. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16236753.

147. Todeschini G, Secchi S, Morra E, et al. Primary mediastinal large B-cell lymphoma (PMLBCL): long-term results from a retrospective multicentre Italian experience in 138 patients treated with CHOP or MACOP-B/VACOP-B. Br J Cancer 2004;90:372-376. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14735179.

148. Zinzani PL, Martelli M, Bertini M, et al. Induction chemotherapy strategies for primary mediastinal large B-cell lymphoma with sclerosis: a retrospective multinational study on 426 previously untreated patients. Haematologica 2002;87:1258-1264. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12495899.

149. De Sanctis V, Finolezzi E, Osti MF, et al. MACOP-B and involved-field radiotherapy is an effective and safe therapy for primary mediastinal large B cell lymphoma. Int J Radiat Oncol Biol Phys 2008;72:1154-1160. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18472357.

150. Mazzarotto R, Boso C, Vianello F, et al. Primary mediastinal large B-cell lymphoma: results of intensive chemotherapy regimens (MACOP-B/VACOP-B) plus involved field radiotherapy on 53 patients. A single institution experience. Int J Radiat Oncol Biol Phys 2007;68:823-829. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17379431.

151. Zinzani PL, Stefoni V, Finolezzi E, et al. Rituximab combined with MACOP-B or VACOP-B and radiation therapy in primary mediastinal large B-cell lymphoma: a retrospective study. Clin Lymphoma Myeloma 2009;9:381-385. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19858058.

152. Rieger M, Osterborg A, Pettengell R, et al. Primary mediastinal B-cell lymphoma treated with CHOP-like chemotherapy with or without rituximab: results of the Mabthera International Trial Group study. Ann Oncol 2011;22:664-670. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20724576.

153. Vassilakopoulos TP, Pangalis GA, Katsigiannis A, et al. Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone with or without radiotherapy in primary mediastinal large B-cell lymphoma: the emerging standard of care. Oncologist 2012;17:239-249. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22282906.

154. Witzens-Harig M, Ho AD, Kuhnt E, et al. Primary Mediastinal B Cell Lymphoma Treated with CHOP-Like Chemotherapy with or without Rituximab: 5-Year Results of the Mabthera International Trial Group (MInT) Study [abstract]. Blood 2012;120:Abstract 1612. Available at: http://www.bloodjournal.org/content/120/21/1612.

155. Avigdor A, Sirotkin T, Kedmi M, et al. The impact of R-VACOP-B and interim FDG-PET/CT on outcome in primary mediastinal large B cell lymphoma. Ann Hematol 2014;93:1297-1304. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24595734.

156. Moskowitz C, Hamlin PA, Jr., Maragulia J, et al. Sequential dose-dense RCHOP followed by ICE consolidation (MSKCC protocol

01-142) without radiotherapy for patients with primary mediastinal large B-cell lymphoma[abstract]. Blood 2010;116:Abstract 420. Available at: http://www.bloodjournal.org/content/116/21/420.

157. Soumerai JD, Hellmann MD, Feng Y, et al. Treatment of primary mediastinal B-cell lymphoma with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone is associated with a high rate of primary refractory disease. Leuk Lymphoma 2014;55:538-543. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23734654.

158. Dunleavy K, Pittaluga S, Maeda LS, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. N Engl J Med 2013;368:1408-1416. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23574119.

159. Binkley MS, Hiniker SM, Wu S, et al. A single-institution retrospective analysis of outcomes for stage I-II primary mediastinal large B-cell lymphoma treated with immunochemotherapy with or without radiotherapy. Leuk Lymphoma 2015:1-5. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26159046.

160. Martelli M, Ceriani L, Zucca E, et al. [18F]fluorodeoxyglucose positron emission tomography predicts survival after chemoimmunotherapy for primary mediastinal large B-cell lymphoma: results of the International Extranodal Lymphoma Study Group IELSG-26 Study. J Clin Oncol 2014;32:1769-1775. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24799481.

161. Pinnix CC, Dabaja B, Ahmed MA, et al. Single-institution experience in the treatment of primary mediastinal B cell lymphoma treated with immunochemotherapy in the setting of response assessment by 18fluorodeoxyglucose positron emission tomography. Int J Radiat Oncol Biol Phys 2015;92:113-121. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25863759.

162. Jaffe ES, Stein H, Swerdlow SH, et al. B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:267-268.

163. Quintanilla-Martinez L, de Jong D, de Mascarel A, et al. Gray zones around diffuse large B cell lymphoma. Conclusions based on the workshop of the XIV meeting of the European Association for Hematopathology and the Society of Hematopathology in Bordeaux, France. J Hematop 2009;2:211-236. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20309430.

164. Hoeller S, Copie-Bergman C. Grey zone lymphomas: lymphomas with intermediate features. Adv Hematol 2012;2012:460801. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22548066.

165. Gualco G, Natkunam Y, Bacchi CE. The spectrum of B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma: a description of 10 cases. Mod Pathol 2012;25:661-674. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22222636.

166. Evens AM, Kanakry JA, Sehn LH, et al. Gray zone lymphoma with features intermediate between classical Hodgkin lymphoma and diffuse large B-cell lymphoma: Characteristics, outcomes, and prognostication among a large multicenter cohort. Am J Hematol 2015;90:778-783. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26044261.

167. Traverse-Glehen A, Pittaluga S, Gaulard P, et al. Mediastinal gray zone lymphoma: the missing link between classic Hodgkin's lymphoma and mediastinal large B-cell lymphoma. Am J Surg Pathol 2005;29:1411-1421. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16224207.

168. Eberle FC, Rodriguez-Canales J, Wei L, et al. Methylation profiling of mediastinal gray zone lymphoma reveals a distinctive signature with elements shared by classical Hodgkin's lymphoma and primary mediastinal large B-cell lymphoma. Haematologica 2011;96:558-566. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21454882.

169. Garcia JF, Mollejo M, Fraga M, et al. Large B-cell lymphoma with Hodgkin's features. Histopathology 2005;47:101-110. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15982329.

170. Wilson WH, Pittaluga S, Nicolae A, et al. A prospective study of mediastinal gray-zone lymphoma. Blood 2014;124:1563-1569. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25024303.

171. Green TM, Young KH, Visco C, et al. Immunohistochemical double-hit score is a strong predictor of outcome in patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol 2012;30:3460-3467. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22665537.

172. Johnson NA, Slack GW, Savage KJ, et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol 2012;30:3452-3459. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22851565.

173. Snuderl M, Kolman OK, Chen YB, et al. B-cell lymphomas with concurrent IGH-BCL2 and MYC rearrangements are aggressive neoplasms with clinical and pathologic features distinct from Burkitt lymphoma and diffuse large B-cell lymphoma. Am J Surg Pathol 2010;34:327-340. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20118770.

174. Le Gouill S, Talmant P, Touzeau C, et al. The clinical presentation and prognosis of diffuse large B-cell lymphoma with t(14;18) and 8q24/c-MYC rearrangement. Haematologica 2007;92:1335-1342. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18024371.

175. Aukema SM, Siebert R, Schuuring E, et al. Double-hit B-cell lymphomas. Blood 2011;117:2319-2331. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21119107.

176. Petrich AM, Gandhi M, Jovanovic B, et al. Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. Blood 2014;124:2354-2361. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25161267.

177. Oki Y, Noorani M, Lin P, et al. Double hit lymphoma: the MD Anderson Cancer Center clinical experience. Br J Haematol 2014;166:891-901. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24943107.

178. Sun H, Savage KJ, Karsan A, et al. Outcome of Patients With Non-Hodgkin Lymphomas With Concurrent MYC and BCL2 Rearrangements Treated With CODOX-M/IVAC With Rituximab Followed by Hematopoietic Stem Cell Transplantation. Clin Lymphoma Myeloma Leuk 2015;15:341-348. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25656914.

179. Howlett C, Snedecor SJ, Landsburg DJ, et al. Front-line, dose-escalated immunochemotherapy is associated with a significant progression-free survival advantage in patients with double-hit lymphomas: a systematic review and meta-analysis. Br J Haematol 2015;170:504-514. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25907897.

180. Dunleavy K, Fanale M, LaCasce A, et al. Preliminary report of a multicenter prospective phase ii study of DA-EPOCH-R in MYC-rearranged aggressive b-cell lymphoma [abstract]. Blood 2014;124:Abstract 395. Available at: http://www.bloodjournal.org/content/124/21/395.abstract.

This discussion is being updated to correspond with the newly updated algorithm. Last updated 10/28/2014.

Burkitt Lymphoma

BL is a rare and aggressive B-cell tumor typically involving extranodal disease sites. In the WHO Classification, three clinical variants of BL are described: endemic, sporadic, and immunodeficiency-associated BL.[1] The endemic variant is the most common form of childhood malignancy occurring in equatorial Africa and the majority of cases are associated with Epstein-Barr virus (EBV) infection. Sporadic BL accounts for 1% to 2% of all adult lymphomas in the US and Western Europe, and can be associated with EBV infection in about 30% of cases.[1-3] Immunodeficiency-associated BL occurs mainly in patients infected with HIV, in some posttransplant patients and in individuals with congenital immunodeficiency. A recent analysis from the NCI SEER database reported improved survival outcomes in patients with BL diagnosed during the last decade (N=1922; year of diagnosis 2002–2008).[4] The 5-year survival estimate was 56% compared with 43% in patients diagnosed prior to 2002. Thus, durable remission may be possible in approximately 60% of patients with BL.

Diagnosis

Adequate immunophenotyping by flow cytometry analysis or immunohistochemistry (IHC) is needed to establish the diagnosis of BL. Flow cytometry analysis should include the following markers: CD5, CD10, CD19, CD20, CD45, TDT, and kappa/lambda. The IHC panel should include the following: CD3, CD10, CD20, CD45, TdT, Ki-67, BCL2, and BCL6. If immunophenotyping is performed using flow cytometry first, then IHC using selected markers (Ki-67 and BCL2) can supplement the findings from flow cytometry. EBV encoded RNA in situ hybridization (EBER ISH) may be useful to evaluate for EBV infection status in some cases.

The typical immunophenotype of BL is sIg+, CD10+, CD19+, CD20+, CD22+, TdT-, Ki67+ (>95%), BCL2-, BCL6+, and simple karyotype with *MYC* rearrangement. Translocations involving the *MYC* gene are detected in nearly all cases of BL. Most cases (80%) of classical BL are characterized by t(8;14) which results in the juxtaposition of *MYC* gene from chromosome 8 with the *IgH* region on chromosome14.[5] Other variants with *MYC* rearrangements [t(8;22) or t(2;8)] are less common. Some cases of DLBCL are also associated with an overexpression of *MYC*. Therefore, establishing the diagnosis of BL can be challenging using routine cytogenetic analysis. FISH using a break apart probe or long segment PCR are more reliable for the detection of t(8;14) and its variants.[6] Gene expression profiling also has been reported as an accurate, quantitative method for distinguishing BL from DLBCL.[7,8] However, this technique is not yet recommended for widespread clinical use. Cytogenetic analysis (with or without FISH) for detection of t(8;14) or variants should be performed in all cases with evaluation of *BCL2 or BCL6* gene rearrangements under certain circumstances.

The 2008 WHO lymphoma classification eliminates atypical BL. For cases without typical morphology or immunophenotype, a provisional category has been introduced, “B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL”.[9,10] These are aggressive lymphomas with substantial heterogeneity in terms of morphology, immunophenotype, and genetic features.[9,11] Survival outcomes in patients with these lymphomas are poor, with a median survival of 9 months (and a 5-year survival rate of only 30%) reported in a retrospective analysis (N=39).[11] This group of lymphomas also includes cases that harbor both *MYC* and *BCL2* (and/or *BCL6*) translocations, the so-called “double-hit” lymphomas.[9,10] Such cases of “double-hit” lymphomas have a highly aggressive disease course with poor prognosis; case series have reported a median overall survival

(OS) time of 4 to 6 months among patients with "double-hit" lymphomas.[12-14] The optimal management of patients with "double-hit" or "triple-hit" (involving *BCL6* translocation in addition to *MYC* and *BCL2* translocations)[12] lymphomas has not been identified. Further discussions concerning "double-hit" lymphomas are included under the section for DLBCL of the NCCN Guidelines for NHL.

Workup

The initial diagnostic workup includes a detailed physical examination (with special attention to the node bearing areas, liver and spleen) and CT scans of the chest, abdomen and pelvis. CT scan of the neck may be useful in certain cases. Adult patients with BL commonly present with bulky abdominal masses, B symptoms, and laboratory evidence of tumor lysis; in addition, bone marrow involvement (up to 70% of cases) and leptomeningeal CNS involvement (up to 40% of cases) may also be common findings at the time of diagnosis. Brain MRI may be useful under certain circumstances (e.g., if CNS involvement is suspected at time of diagnosis due to neurological signs or symptoms). PET or integrated PET-CT scans are not recommended for routine use, since it is unlikely that findings of PET or PET-CT would alter therapy for patients with newly diagnosed BL. If the treatment includes an anthracycline-containing regimen, cardiac evaluation with MUGA scan or echocardiogram is recommended, particularly for older patients.

Evaluations of bone marrow aspirates, biopsy, lumbar puncture and flow cytometry of cerebrospinal fluid are essential. In these highly aggressive lymphomas, as in DLBCLs, the serum LDH level has prognostic significance. These tumors exhibit a high degree of cellular proliferation, as determined by Ki-67 expression levels. Because BL is frequently associated with HIV infection, HIV serology should be part of the diagnostic workup for these diseases (for cases with positive HIV serology, see recommendations for AIDS-related B-cell lymphoma in the NCCN Guidelines for NHL). In addition, testing for hepatitis B virus (HBV) should be performed, as chemoimmunotherapy regimens (often used in the treatment of BL) are associated with increased risks for HBV reactivation. Patients with serum LDH levels within normal ranges and with complete resection of abdominal lesions (or single extra-nodal mass < 10 cm) are generally considered to have low-risk disease; all other patients should be considered as high-risk cases.

Treatment Options

BL is curable in a significant subset of patients when treated with dose- intensive, multiagent chemotherapy regimens that also incorporates CNS prophylaxis. It is important to note that CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or similar regimens are not considered adequate therapy for the management of BL. In a recent population-based analysis of data from patients with BL (HIV-negative BL; N=258) from a Swedish/Danish registry, CHOP (or CHOP with etoposide) regimens resulted in a 2-year OS of only 39% compared with approximately 70% to 80% with more intensive multiagent chemotherapy regimens.[15] Thus, for patients with BL who can tolerate aggressive therapies, intensive multiagent chemotherapy may offer the best chance for durable disease control. About 60% to 90% of pediatric and young adult patients with BL achieve durable remission if treated appropriately.[16] However, the survival of older adults with BL appears to be less favorable, compared with younger patients.[17] Although the SEER database suggests that older adults (patients aged >40 years) represent about 60% of BL cases (with about 30% aged >60 years), this patient population is underrepresented in published clinical trials.[16,17] It is preferred that patients with BL receive treatment at centers with expertise in the management of this highly aggressive disease.

Most contemporary regimens used in adult patients have been developed from the pediatric protocols, and include intensive multiagent chemotherapy along with CNS prophylaxis with systemic and/or intrathecal chemotherapy. Tumor lysis syndrome is more common in patients with BL and should be managed as outlined under "Tumor Lysis Syndrome" in the Supportive Care section of the Guidelines and Discussion.

CODOX-M (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate), alternating with IVAC (ifosfamide, etoposide and high dose cytarabine) is a highly effective regimen developed by Magrath et al.[18] Both cycles included intrathecal chemotherapy (cytarabine or methotrexate) for CNS prophylaxis in addition to high-dose systemic cytarabine and methotrexate. In the updated results obtained with 4 cycles of CODOX-M/IVAC protocol given to previously untreated patients (n=55, BL or Burkitt-like lymphoma; n=11, DLBCL), the 1-year event-free survival (EFS) rate was 85%.[19]

In an international phase II study, Mead et al established the value of a modified CODOX-M/IVAC regimen in adults with BL (N=52 evaluable).[20] Low-risk patients (n=12) received modified CODOX-M (3 cycles) and high-risk patients (n=40) received modified CODOX-M and IVAC (alternating cycles for 4 cycles). In low-risk patients, 2-year EFS and OS rates were 83% and 81%, respectively, compared with 60% and 70%, respectively, for high- risk patients.[20] The efficacy of the modified CODOX-M/IVAC regimen in high-risk BL (n=42) was confirmed in a subsequent trial, which reported 2-year progression-free survival (PFS) and OS rates of 62% and 64%, respectively.[21] Modified CODOX-M regimen with or without alternating IVAC was also effective and well tolerated in older patients with BL or Burkitt-like lymphoma (N=14)[22] and in patients with HIV-associated BL (n=8).[23]

More recently, the addition of the anti-CD20 monoclonal antibody rituximab has been investigated in combination with CODOX-M/IVAC, given that most cases of BL are CD20-positive. In a small study that evaluated CODOX-M/IVAC with or without rituximab in patients with BL or B-cell lymphoma unclassifiable (N=15), the 5-year PFS and OS rates were 87% for both outcome measures.[24] In a larger retrospective study in patients with BL (N=80) treated with CODOX-M/IVAC with or without rituximab, the 3-year EFS and OS rates with rituximab were 74% and 77%, respectively; the 3-year EFS and OS rates without the addition of rituximab was 61% and 66%, respectively.[25] Although a trend for improvement in outcomes with the addition of rituximab was observed, the differences were not statistically significant. In another recent retrospective study that evaluated outcomes with different regimens in patients with BL (N=258), 2-year OS with CODOX-M/IVAC (with or without rituximab) was 69%.[15]

The hyper-CVAD regimen (hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with methotrexate and cytarabine, including intrathecal methotrexate) developed by the MD Anderson Cancer Center, has also been evaluated in patients with Burkitt-lymphoma/leukemia (N=26).[26] With this regimen, complete remission (CR) was achieved in 81% of patients and the 3-year OS rate was 49%; OS rate was higher among patients aged 60 years or younger (77% vs. 17% for patients older than 60 years).[26] In a phase II trial in HIV-negative patients with newly diagnosed BL or B-ALL (N=31), the addition of rituximab to the hyper-CVAD regimen (R-hyper-CVAD) induced CR in 86% of patients; the 3-year EFS and disease-free survival rates were 80% and 88%, respectively.[27] The 3-year OS rates were similar among the elderly and younger patients (89% vs. 88%).[27] In the updated report (n = 57; 30 patients non-HIV BL and 27 patients with B-ALL) , with a median follow up of 62 months, the 5-year OS rate with R-hyper-CVAD was

74%; the corresponding OS rates in patients younger than 60 years and those older than 60 years were 72% and 70%, respectively.[28] In a historical comparison with patients treated with hyper-CVAD alone (corresponding 5-year OS rates 50%, 70%, and 19%, respectively), outcomes were superior with the R-hyper-CVAD regimen. The results of this study showed that the addition of rituximab to hyper-CVAD improved long-term outcomes in patients with BL or B-ALL, particularly in the older patient subgroup. In a recent retrospective study that evaluated outcomes with different regimens in patients with BL (N=258), the 2-year OS rate was one of the highest with the use of hyper-CVAD (with or without rituximab), at 83%.[15]

The CALGB 9251 study evaluated the efficacy of intensive multiagent chemotherapy with and without cranial radiation for central nervous system (CNS) prophylaxis in adult patients with Burkitt leukemia or lymphoma.[29] Given the severe neurotoxicity, the protocol was amended after the first 52 of 92 patients were enrolled. The 3-year EFS rate was 52% in the cohort of patients who received intensive CNS prophylaxis (cranial RT and 12 doses of triple intrathecal chemotherapy) compared to 45% in those who received only 6 doses of intrathecal chemotherapy and cranial irradiation (the latter for high-risk patients only).[29] The subsequent CALGB 10002 study investigated the addition of rituximab and growth factor support to the above CALGB 9251 regimen, and without the use of prophylactic CNS irradiation.[30] Among patients with previously untreated BL or Burkitt-like lymphoma/leukemia (N=103 evaluable), 82% achieved a CR and 7% had a partial remission (PR). The 4-year EFS and OS rates were 74% and 78%, respectively; as would be expected, these survival outcomes were more favorable among the subgroup of patients with low-risk IPI scores (4-year EFS and OS rates 86% and 90%, respectively) compared with those with high-risk IPI scores (55% and 55%, respectively).

A recent prospective study (30 patients with perviously untreated BL) evaluated the standard dose-adjusted EPOCH with rituximab (DA-EPOCH-R) in HIV-negative patients (n = 19) and a lower-dose short-course regimen with a double dose of rituximab (SC-EPOCH-RR) in HIV-positive patients (n =11).[31] At a median follow up of 86 months, the FFP and OS rates with DA-EPOCH-R were 95% and 100%, respectively. The highly favorable outcomes seen in this study may reflect the inclusion of more low-risk patients compared to other studies, with approximately 53% of all patients (37% in the DA-EPOCH-R group) presenting with normal LDH levels.

A prospective multicenter study from the German study group evaluated the efficacy and safety of a new short-intensive regimen combined with rituximab in patients with CD20-positive BL and Burkitt leukemia (N=363).[32] The regimen comprised multiagent chemotherapy with high-dose methotrexate, high-dose cytarabine, cyclophosphamide, etoposide, ifosfamide and corticosteroids, combined with rituximab. Patients also received triple intrathecal therapy with methotrexate, cytarabine, and dexamethasone. Among the patients with BL (n=229), the CR rate with this regimen was 91%; at a median follow up of more than 7 years, the PFS and OS rates in the BL subgroup were 83% and 88%, respectively.[32] Frequent grade 3 or 4 toxicities among patients with BL included neutropenia (64%), mucositis (31%), and infections (23%). These outcomes appear highly promising, with a manageable toxicity profile.[32]

Several studies have evaluated the role of hematopoietic stem cell transplantation (HSCT) in patients with BL. The Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) demonstrated the feasibility of intensive high-dose induction chemotherapy (prednisone, cyclophosphamide, doxorubicin, etoposide and mitoxantrone, without high-dose methotrexate or high-dose cytarabine) followed by

consolidation with BEAM and autologous HSCT in untreated adults with BL, Burkitt-like lymphoma, or B-ALL.[33] Among the patients with BL/Burkitt-like lymphoma (n=27), CR was achieved in 81% of patients with a PR in 11%; the 5-year EFS and OS rates were 73% and 81%, respectively.[33] In a recent analysis of outcomes with HSCT (autologous or allogeneic transplant) in patients with BL from the CIBMTR database (N=241), the 5-year PFS and OS rates with autologous HSCT at first remission were 78% and 83%, respectively.[34] These outcomes with autologous HSCT were similar to findings from the above HOVON study, and appeared to compare favorably to the 5-year PFS and OS rates with allogeneic HSCT in first remission, which were 50% and 53%, respectively. Not surprisingly, patients who underwent HSCT with less than a first remission had poorer outcomes regardless of transplant type. The 5-year PFS and OS rates with autologous HSCT in those without a first remission were 27% and 31%, respectively; the corresponding rates with allogeneic HSCT without first remission were only 19% and 20%, respectively. For patients in a second remission, autologous HSCT resulted in a 5-year PFS of 44%.[34] An earlier retrospective analysis from the CIBMTR database in patients with relapsed or refractory BL (children and adolescents age ≤ 18 years; n=41) showed similar 5-year EFS outcomes between autologous and allogeneic HSCT (27% vs. 31%).[35] As would be expected, EFS rates were lower among patients who were not in CR at the time of transplant.

The management of patients with B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL, as well as those patients with “double-hit” B-cell lymphoma has not been well studied. Patients with “double-hit” lymphomas have very poor prognosis, with a median OS of only 4 to 6 months with chemotherapy combinations (e.g., CHOP, CODOX-M/IVAC, hyper-CVAD, EPOCH), with or without the incorporation of rituximab.[12,14,21,36] Therefore, these patients are best managed in the context of clinical trials evaluating novel targeted agents.

NCCN Recommendations

Induction Therapy

Participation in clinical trials is recommended for all patients. As mentioned earlier, CHOP or CHOP-like therapy is not adequate for the treatment of BL. The NCCN Guidelines panel recommends the following regimens for induction therapy, which should also include adequate CNS prophylaxis with systemic and/or intrathecal chemotherapy with methotrexate and/or cytarabine:

- CALGB 10002 regimen
- CODOX-M/IVAC (original or modified) with or without addition of rituximab
- Dose-adjusted EPOCH with rituximab (DA-EPOCH-R)
- Hyper-CVAD with rituximab (R-hyper-CVAD)

Patients with CR to induction therapy should be followed up every 2 to 3 months for 1 year then every 3 months for the next 1 year and then every 6 months thereafter. Disease relapse after 2 years is rare following CR to induction therapy, and follow up should be individualized according to patient characteristics. Consolidation therapy in the context of a clinical trial may be considered for high-risk patients with CR to induction therapy. Patients with less than CR to induction therapy should be treated in the context of a clinical trial. In the absence of suitable clinical trials palliative RT may be considered appropriate.

Relapsed or Refractory Disease

Patients with relapsed or refractory disease should be treated in the context of a clinical trial. Second-line chemotherapy with rituximab-containing regimens followed by high-dose therapy and

autologous HSCT or allogeneic HSCT (if donor available) may be considered in selected patients with a reasonable remission duration following induction therapy. However, the treatment options remain undefined for patients who relapse after first-line therapy.

The guidelines have included DA-EPOCH-R, IVAC combined with rituximab (R-IVAC). R-GDP (gemcitabine, dexamethasone, cisplatin, combined with rituximab), R-ICE (ifosfamide, carboplatin, etoposide, combined with rituximab), and high-dose cytarabine as options for second-line therapy. However, it should be noted that these suggestions are based on very limited, retrospective studies with only a few patients. For instance, the R-ICE regimen was evaluated in a small group of pediatric patients with relapsed BL and B-ALL (n=14), which resulted in CR in 29% and PR in 36% of patients.[37]

The best options for patients requiring second-line therapy for relapsed/refractory disease are investigational treatments in the context of clinical trials. In the absence of suitable clinical trials or for patients unlikely to benefit from additional intensive multiagent chemotherapy regimens, best supportive care should be considered appropriate.

References

1. Leoncini L, Raphael M, Stein H, et al. Burkitt lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:262-264.

2. Blum KA, Lozanski G, Byrd JC. Adult Burkitt leukemia and lymphoma. Blood 2004;104:3009-3020. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15265787.

3. Aldoss I, Weisenburger D, Fu K, et al. Adult Burkitt lymphoma: advances in diagnosis and treatment. Oncology (Williston Park) 2008;22:1508-1517. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19133605.

4. Costa LJ, Xavier AC, Wahlquist AE, Hill EG. Trends in survival of patients with Burkitt lymphoma/leukemia in the USA: an analysis of 3691 cases. Blood 2013;121:4861-4866. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23641015.

5. Ferry JA. Burkitt's lymphoma: clinicopathologic features and differential diagnosis. Oncologist 2006;11:375-383. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16614233.

6. Burmeister T, Schwartz S, Horst HA, et al. Molecular heterogeneity of sporadic adult Burkitt-type leukemia/lymphoma as revealed by PCR and cytogenetics: correlation with morphology, immunology and clinical features. Leukemia 2005;19:1391-1398. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15973450.

7. Dave SS, Fu K, Wright GW, et al. Molecular diagnosis of Burkitt's lymphoma. N Engl J Med 2006;354:2431-2442. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16760443.

8. Hummel Ml, Bentink S, Berger H, et al. A biologic definition of Burkitt's lymphoma from transcriptional and genomic profiling. N Engl J Med 2006;354:2419-2430. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16760442.

9. Kluin PM, Raphael M, Harris NL, et al. B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:265-266.

10. Hasserjian RP, Ott G, Elenitoba-Johnson KS, et al. Commentary on the WHO classification of tumors of lymphoid tissues (2008): "Gray zone" lymphomas overlapping with Burkitt lymphoma or classical Hodgkin lymphoma. J Hematop 2009. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19669187.

11. Perry AM, Crockett D, Dave BJ, et al. B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and burkitt lymphoma: study of 39 cases. Br J Haematol 2013. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23600716.

12. Tomita N, Tokunaka M, Nakamura N, et al. Clinicopathological features of lymphoma/leukemia patients carrying both BCL2 and MYC translocations. Haematologica 2009;94:935-943. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19535347.

13. Johnson NA, Savage KJ, Ludkovski O, et al. Lymphomas with concurrent BCL2 and MYC translocations: the critical factors associated with survival. Blood 2009;114:2273-2279. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19597184.

14. Snuderl M, Kolman OK, Chen YB, et al. B-cell lymphomas with concurrent IGH-BCL2 and MYC rearrangements are aggressive neoplasms with clinical and pathologic features distinct from Burkitt lymphoma and diffuse large B-cell lymphoma. Am J Surg Pathol 2010;34:327-340. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20118770.

15. Wasterlid T, Brown PN, Hagberg O, et al. Impact of chemotherapy regimen and rituximab in adult Burkitt lymphoma: a retrospective population-based study from the Nordic Lymphoma Group. Ann Oncol

2013;24:1879-1886. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23446093.

16. Perkins AS, Friedberg JW. Burkitt lymphoma in adults. Hematology Am Soc Hematol Educ Program 2008:341-348. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19074108.

17. Kelly JL, Toothaker SR, Ciminello L, et al. Outcomes of patients with Burkitt lymphoma older than age 40 treated with intensive chemotherapeutic regimens. Clin Lymphoma Myeloma 2009;9:307-310. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19717381.

18. Magrath I, Adde M, Shad A, et al. Adults and children with small non-cleaved-cell lymphoma have a similar excellent outcome when treated with the same chemotherapy regimen. J Clin Oncol 1996;14:925-934. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8622041.

19. Adde M, Shad A, Venzon D, et al. Additional chemotherapy agents improve treatment outcome for children and adults with advanced B-cell lymphomas. Semin Oncol 1998;25:33-39; discussion 45-48. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9578060.

20. Mead GM, Sydes MR, Walewski J, et al. An international evaluation of CODOX-M and CODOX-M alternating with IVAC in adult Burkitt's lymphoma: results of United Kingdom Lymphoma Group LY06 study. Ann Oncol 2002;13:1264-1274. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12181251.

21. Mead GM, Barrans SL, Qian W, et al. A prospective clinicopathologic study of dose-modified CODOX-M/IVAC in patients with sporadic Burkitt lymphoma defined using cytogenetic and immunophenotypic criteria (MRC/NCRI LY10 trial). Blood 2008;112:2248-2260. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18612102.

22. Lacasce A, Howard O, Lib S, et al. Modified Magrath regimens for adults with Burkitt and Burkitt-like lymphomas: preserved efficacy with decreased toxicity. Leuk Lymphoma 2004;45:761-767. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15160953.

23. Wang ES, Straus DJ, Teruya-Feldstein J, et al. Intensive chemotherapy with cyclophosphamide, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine (CODOX-M/IVAC) for human immunodeficiency virus-associated Burkitt lymphoma. Cancer 2003;98:1196-1205. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12973843.

24. Maruyama D, Watanabe T, Maeshima AM, et al. Modified cyclophosphamide, vincristine, doxorubicin, and methotrexate (CODOX-M)/ifosfamide, etoposide, and cytarabine (IVAC) therapy with or without rituximab in Japanese adult patients with Burkitt lymphoma (BL) and B cell lymphoma, unclassifiable, with features intermediate between diffuse large B cell lymphoma and BL. Int J Hematol 2010;92:732-743. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21120644.

25. Barnes JA, Lacasce AS, Feng Y, et al. Evaluation of the addition of rituximab to CODOX-M/IVAC for Burkitt's lymphoma: a retrospective analysis. Ann Oncol 2011;22:1859-1864. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21339382.

26. Thomas DA, Cortes J, O'Brien S, et al. Hyper-CVAD program in Burkitt's-type adult acute lymphoblastic leukemia. J Clin Oncol 1999;17:2461-2470. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10561310.

27. Thomas DA, Faderl S, O'Brien S, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer 2006;106:1569-1580. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16502413.

28. Thomas DA, Kantarjian HM, Faderl S, et al. Hyper-CVAD and Rituximab for De Novo Burkitt Lymphoma/Leukemia [abstract]. Blood 2011;118:Abstract 2698. Available at:

http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;118/21/2698.

29. Rizzieri DA, Johnson JL, Niedzwiecki D, et al. Intensive chemotherapy with and without cranial radiation for Burkitt leukemia and lymphoma: final results of Cancer and Leukemia Group B Study 9251. Cancer 2004;100:1438-1448. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15042678.

30. Rizzieri DA, Johnson JL, Byrd JC, et al. Improved efficacy using rituximab and brief duration, high intensity chemotherapy with filgrastim support for Burkitt or aggressive lymphomas: cancer and Leukemia Group B study 10 002. Br J Haematol 2014;165:102-111. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24428673.

31. Dunleavy K, Pittaluga S, Shovlin M, et al. Low-intensity therapy in adults with Burkitt's lymphoma. N Engl J Med 2013;369:1915-1925. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24224624.

32. Hoelzer D, Walewski J, Dohner H, et al. Substantially Improved Outcome of Adult Burkitt Non-Hodgkin Lymphoma and Leukemia Patients with Rituximab and a Short-Intensive Chemotherapy; Report of a Large Prospective Multicenter Trial [abstract]. Blood 2012;120:Abstract 667. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/120/21/667.

33. van Imhoff GW, van der Holt B, MacKenzie MA, et al. Short intensive sequential therapy followed by autologous stem cell transplantation in adult Burkitt, Burkitt-like and lymphoblastic lymphoma. Leukemia 2005;19:945-952. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15800666.

34. Maramattom LV, Hari PN, Burns LJ, et al. Autologous and allogeneic transplantation for burkitt lymphoma outcomes and changes in utilization: a report from the center for international blood and marrow transplant research. Biol Blood Marrow Transplant 2013;19:173-179. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23200705.

35. Gross TG, Hale GA, He W, et al. Hematopoietic stem cell transplantation for refractory or recurrent non-Hodgkin lymphoma in children and adolescents. Biol Blood Marrow Transplant 2010;16:223-230. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19800015.

36. Le Gouill S, Talmant P, Touzeau C, et al. The clinical presentation and prognosis of diffuse large B-cell lymphoma with t(14;18) and 8q24/c-MYC rearrangement. Haematologica 2007;92:1335-1342. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18024371.

37. Griffin TC, Weitzman S, Weinstein H, et al. A study of rituximab and ifosfamide, carboplatin, and etoposide chemotherapy in children with recurrent/refractory B-cell (CD20+) non-Hodgkin lymphoma and mature B-cell acute lymphoblastic leukemia: a report from the Children's Oncology Group. Pediatr Blood Cancer 2009;52:177-181. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18816698.

This discussion is being updated to correspond with the newly updated algorithm. Last updated 09/06/2013.

AIDS-Related B-Cell Lymphoma

Overview

AIDS-related lymphoma is usually an AIDS-defining diagnosis in patients infected by the human immunodeficiency virus (HIV). Systemic lymphoma accounts for 70% to 90% of cases of HIV-associated lymphoma, while primary CNS lymphoma accounts for the remaining 10% to 30% of cases.[1-3] The distribution of systemic versus primary CNS lymphoma (PCNSL) may vary depending upon differences in factors such as geographic regions, time period covered and referral patterns of the institutions, between published reports. Burkitt lymphoma (BL) and diffuse large B-cell lymphomas (DLBCL) are the most common forms of systemic HIV-associated lymphoma.[2,3] In systemic cases of HIV-associated lymphomas, the BL histology is generally associated with a higher CD4+ cell count at diagnosis compared with DLBCL; cases of PCNSL is associated with much lower CD4+ count levels relative to systemic cases.[1,2]

Prior to the development of highly active antiretroviral therapy (HAART), HIV-associated lymphomas often presented with widespread, extra nodal disease, B symptoms, CNS involvement, and poor prognosis.[3] With the routine use of combination antiviral therapy in the HAART era, the prognosis of patients diagnosed with HIV-related NHL has improved, primarily for those with systemic lymphomas. In an early assessment of the shift in prognosis of patients with HIV-associated lymphomas between the pre-HAART (1993-1994) and HAART (1997-1998) eras, median overall survival (OS) improved from approximately 6 months in the pre-HAART years compared with 21 months in the HAART era for patients with systemic lymphomas; patients with PCNSL, however, continued to have poor prognosis, with a median OS less than 3 months during both periods.[2] In a recent report from the COHERE (Collaboration of Observational HIV Epidemiological Research Europe) study evaluating outcomes of patients with HIV-associated lymphomas treated in the HAART era (1998-2006), the 1-year OS rates among patients with systemic lymphoma and PCNSL were 66% and 54%, respectively.[1] Although survival outcomes appear to be improving with contemporary therapies, outcomes for patients with PCNSL remain poor. Moreover, survival rates for patients with HIV-associated lymphomas remain low compared with patients with lymphomas unassociated with HIV infection; in a recent study, the 2-year OS rate for patients with HIV-associated lymphomas treated in the HAART era (1996-2005) was 41% compared with 70% in lymphoma patients without HIV infections.[4] Studies suggest that the improvement in prognosis observed with systemic HIV-associated lymphoma apply primarily to HIV-associated DLBCL but less to BL histology. In a study that investigated differences in outcomes by lymphoma histology and treatment era, median OS improved from 8 months (pre-HAART years: 1982-1996) to 38 months (HAART years: 1997-2003) among patients with HIV-associated DLBCL; contrastingly, OS outcomes remained poor (median 6 months to 5 months) during the same period among patients with HIV-associated BL.[5] BL histology appears to be associated with poorer survival outcomes among patients with HIV-associated lymphoma, even in the HAART era.[4,5]

Plasmablastic lymphoma (PBL) and primary effusion lymphoma (PEL) are two forms of lymphoma seen more commonly associated with HIV compared to lymphoma in patients without HIV infections. PEL accounts for less than 5% of HIV-associated lymphoma cases, most often occurring in the pleural, pericardial, and abdominal cavities.[6,7] PELs are associated with human herpes virus 8 (HHV8) infection and many are also co-infected with Epstein Barr virus (EBV). PBL is

another unique large B-cell lymphoma that mainly involves the jaw and oral cavity of HIV-infected patients.[8,9] Multicentric Castleman's disease (MCD) is prevalent in HIV-infected individuals, and has also been associated with HHV8 infection and increased incidence of lymphoma in HIV infected patients.[10]

Diagnosis

The diagnostic evaluation of HIV-associated lymphoma is not different from the non-HIV-associated disease. The major factor is to distinguish between BL and DLBCL. Hodgkin lymphoma and indolent lymphoma are seen in patients with HIV infection at an incidence higher than in the general population, but are much less common than BL or DLBCL.

Workup

The diagnostic evaluation and workup are as outlined in the NCCN Guidelines section for BL. However, all patients (without regard to histology) should have a lumbar puncture to rule out CNS involvement. In addition, baseline values for CD4 counts and HIV viral load should be obtained.

Treatment

Optimal management of HIV-associated lymphoma is not established. However, several key factors have emerged as being important to improve outcome. In general, studies have demonstrated that early introduction of HAART therapy is associated with superior outcomes. This has allowed for the administration of more dose-intense chemotherapy regimens and a reduction in treatment-associated toxicity.[11-13]

In prospective phase II studies, combination chemotherapy regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or CDE (cyclophosphamide, doxorubicin and etoposide) given with concomitant HAART,[13-15] have proven to be active and tolerable in patients with HIV-associated lymphoma. The CHOP regimen has been shown to induce CR rates of 30% to 48%, with a median OS of approximately 25 months in patients with HIV-associated lymphomas.[14-16] The CDE regimen from the ECOG 1494 study demonstrated a CR rate of 45% with a 2-year OS of 43% in patients with HIV-associated lymphomas.[13] In a phase I/II study, combination therapy with CDOP (cyclophosphamide, liposomal doxorubicin, vincristine and prednisone) given with concomitant HAART showed high response rates (88% overall) in patients with HIV-associated lymphoma (N=24; DLBCL or variant in 79% of patients).[17] Liposomal doxorubicin was given at doses ranging from 40 to 80 mg/m^2, with fixed doses of the other three drugs. The CR rate with this regimen was 75%, and the median duration of CR was 16+ months; the OS rate at 1 year after start of therapy was 58%.[17] Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin) is another combination chemotherapy regimen that has been evaluated in patients with HIV-associated lymphoma. In a phase II study in previously untreated patients with HIV-associated NHL (N=39; 79% DLBCL; 18% BL), treatment with dose-adjusted EPOCH resulted in a ORR of 87% with a CR in 74% of patients.[18] At a median follow up of 53 months, progression-free survival (PFS) and OS rates were 73% and 60%, respectively. Only 2 of the patients with a CR experienced disease recurrence at last follow up (for a disease-free survival [DFS] rate of 92%). OS outcomes were decreased among the patients with low baseline CD4 counts (≤ 100/mcL) compared with those with higher CD4 counts (16% vs. 87%). Multivariate analysis using a Cox proportional hazard model showed that low CD4 counts and CNS

involvement were the only significant factors associated with decreased OS.[18]

With the advent and wide availability of the anti-CD20 monoclonal antibody rituximab, the safety and efficacy of this immunotherapy agent in combination with chemotherapy has also been evaluated in clinical trials for patients with HIV-associated lymphomas. In the randomized phase III trial conducted by the AIDS Malignancies Consortium (AMC 010 study) in patients with HIV-associated NHL (N=150; 80% DLBCL; 9% BL), the addition of rituximab to CHOP (R-CHOP) was associated with improved CR rates (CR + unconfirmed CR [CRu]) compared with CHOP alone (58% vs. 47%); the median PFS was similar between treatment groups (10 months vs. 9 months) but both the median time to progression (29 months vs. 20 months) and OS (32 months vs. 25 months) were longer with R-CHOP.[16] These outcomes were not significantly different between treatment arms, however, and the R-CHOP combination was associated with increased risks of serious infections (including infection-related deaths in 14% of patients), particularly in patients with CD4+ counts of less than 50/mcL. It should also be noted that in this study, 35 patients randomized to the R-CHOP arm had received maintenance rituximab following initial R-CHOP.[16] In subsequent phase II trials, 6 cycles of the R-CHOP regimen showed CR/CRu rates of 69% to 77% in patients with HIV-associated NHL (majority with DLBCL histology), with manageable toxicities.[19,20] Infection-related deaths (regardless of attribution to study treatment) were reported in 2% to 9% of patients on these studies. In one study, the 2-year OS rate was 75%.[19] In the other study, the 3-year OS rate was 56% and the 3-year DFS rate among patients with a CR (measured from the time of documented CR) was 77%.[20] Rituximab in combination with infusional CDE (R-CDE) was also shown to be feasible and effective with an acceptable toxicity level in patients with HIV-associated lymphomas. In a phase II study in patients with primarily HIV-associated DLBCL histology (N=74; 72% DLBCL; 28% BL), the CR rate with R-CDE was 70% with a 5-year OS rate of 56% and time-to-treatment-failure rate of 52%; among patients with a CR (measured from the time of documented CR), the 5-year DFS rate was 81%.[21,22] Infection-related deaths occurred in 8% of patients; 3% were considered related to study treatment. Rituximab was also evaluated in combination with infusional CDOP (R-CDOP) with concomitant antiretroviral therapy in a recent multicenter phase II trial (AMC 047 study) in patients with HIV-associated NHL (N=40; DLBCL in 98% of cases).[23] The ORR was 67.5% with a CR in 47.5%. The 1-year PFS and OS rates were 61% and 70%, respectively; the 2-year PFS and OS were 52% and 62%, respectively. Infectious complications were reported in 40% of patients (grade 4 in 5%) but no infection-related deaths occurred.[23] This may in part be explained by the fact that patients received concomitant HAART and those with low CD4 counts (≤ 100/mcL at baseline or during anti-tumor therapy) received antimicrobial prophylaxis. Factors such as decreased CD4 counts or increased HIV viral load did not appear to influence treatment response.[23] These results with the R-CDOP regimen, however, appeared less favorable compared with the EPOCH regimen discussed earlier (74% CR; 60% OS at median 53 months follow up)[18] or the EPOCH-R regimen (91% CR; 68% OS at median 5 years follow up),[24] discussed below.

The CODOX-M/IVAC regimen (cyclophosphamide, doxorubicin and high-dose methotrexate, alternating with ifosfamide, etoposide and high-dose cytarabine) with or without rituximab, is commonly used in the management of patients with BL. Retrospective studies suggest that this regimen may be applicable in patients with HIV-associated BL cases.[25,26] In a small retrospective analysis that included a subgroup of patients with HIV-associated BL treated with CODOX-M/IVAC (n=8), the CR rate was 63% with a 2-year event-free survival rate of 60%.[26]

In a recent retrospective study of CODOX-M/IVAC with or without rituximab in patients with BL (N=80), similar outcomes were observed between the subgroup of patients with HIV infection (n=14) and those without HIV infection (n=66).[25] The CR rates among patients with and without HIV infection were 93% and 88%, respectively; the 3-year PFS rate was 68% for both subgroups, and the 3-year OS rate was 68% and 72%, respectively. [25] This retrospective analysis also suggested that in the overall patient cohort, no significant differences in outcomes were observed with the addition of rituximab to CODOX-M/IVAC, although a trend toward improved 3-year PFS rate (74% vs. 61%) and OS rate (77% vs. 66%) with the addition of rituximab was noted. Among the small subgroup of patients with HIV-associated BL who received CODOX-M/IVAC with rituximab (n=10), 1 patient (10%) died due to a treatment-related infectious complication.[25]

The EPOCH regimen in combination with rituximab (EPOCH-R) has been shown to be effective and tolerable in patients with HIV-associated lymphomas.[24,27,28] In a study of dose-adjusted EPOCH with rituximab (DA-EPOCH-R) in patients with BL (N=23; including HIV-associated BL, n=8), the CR rate was 100% and both the PFS and OS rates at median 27 months of follow up was 100%.[27] More recently, the EPOCH-R regimen was evaluated using a short course of EPOCH with dose-dense rituximab in patients with HIV-associated DLBCL (N=33).[24] The CR rate with this regimen was 91%, and the PFS and OS rates were 84% and 68%, respectively, at a median follow up of 5 years.[24] In this study, the addition of rituximab did not appear to cause serious infection-related complications or deaths. The AMC 034 randomized trial evaluated the use of the EPOCH regimen in combination with sequential versus concurrent rituximab in patients with HIV-associated lymphomas (N=106; 75% DLBCL; 25% BL, BL-like).[28] The CR rate was 73% and 55% of patients in the concurrent (n=48 evaluable) and sequential (n=53 evaluable) arms, respectively; the 2-year PFS rate (66% vs. 63%) and OS rate (70% vs. 67%) were similar between treatment arms.[28] Toxicity was comparable in the 2 treatment arms, although the concurrent regimen was associated with a higher incidence of treatment-related deaths among the patients with a baseline CD4+ count of less than 50/mcL. Overall, treatment-related deaths occurred in 5 patients (10%) in the concurrent arm (n=3 due to infections) and 4 patients (7%) in the sequential arm (n=3 due to infections). The authors concluded that concurrent EPOCH-R was an effective regimen for HIV-associated lymphoma, which merits further evaluation. The investigators from the aforementioned AMC trials (AMC 010 and AMC 034)[16,28] recently conducted a pooled analysis that included patients with HIV-associated NHL treated in the R-CHOP or EPOCH-R protocols (N=150 total).[29] The analysis was intended to evaluate patient/disease factors and treatment factors associated with outcomes. Factors such as low age-adjusted IPI score and baseline CD4 count 100/mcL or greater were significantly associated with improved CR rate, EFS and OS outcomes. Among the patients who were treated with concurrent EPOCH-R, both EFS and OS were significantly improved compared with R-CHOP (after adjusting for aaIPI and CD4 counts). The incidence of treatment-related deaths were higher in patients with low baseline CD4 counts (<50/mcL) compared with those with higher CD4 counts (37% vs. 6%; P<0.01).[29] The hyper-CVAD regimen (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine) with or without rituximab has also demonstrated high CR rates (64–92%) and a median OS of 12 months in patients with HIV-associated BL/leukemia and Burkitt-like lymphoma.[30,31]

The treatment of relapsed or refractory HIV-associated lymphomas remains a challenge, with autologous HSCT being the only potentially curative strategy, A recent retrospective analysis evaluated outcomes

in patients with relapsed or refractory HIV-associated lymphoma treated with curative intent at AMC sites (13 sites, N=88).[32] The lymphoma diagnosis was NHL in the majority of patients (89%; the remainder had Hodgkin lymphoma [HL]). The most commonly used second-line regimens were ICE (ifosfamide, carboplatin and etoposide, 39%), dose adjusted EPOCH (19%) and ESHAP (etoposide, methylprednisone, cytarabine and cisplatin, 12.5%). Among the subgroup of patients with NHL, the ORR was 31% and the 1-year OS rate was 37%. Patients with a BL histology (n=12) appeared to have the worse outcomes with an ORR of 17% (compared with 33% in non-BL NHL) and a 1-year OS rate of only 12% (compared with 41.5% in non-BL NHL; *P*=0.005).[32] Among all patients (both NHL and HL), those with primary refractory disease (n=54) had significantly decreased ORR (24% vs. 56%; *P*=0.003) and decreased 1-year OS (31% vs. 59%; *P*=0.022) compared with those with relapsed disease. Baseline CD4 counts did not influence OS outcomes. Subsequent treatment with autologous HSCT was associated with improved 1-year OS (63% vs. 37%) compared with no transplant. However, for patients who experienced a response (CR or PR) after second-line therapy, no difference in 1-year OS was observed based on HSCT (87.5% with HSCT vs. 82% with no transplant).[32] For patients with relapsed/refractory HIV-associated NHL who can tolerate curative treatment regimens, autologous HSCT may offer the best chance for disease control. Although this retrospective analysis suggests that some patients may experience durable remission without HSCT, longer follow up data are needed.

PBL was associated with a poor prognosis in the pre-HAART era. In the HAART era, prognosis has improved with the use of intensive chemotherapy regimens along with HAART. The outcome of the HIV-positive patients with PBL treated at the Memorial Sloan-Kettering Cancer Center was reported to compare favorably to reports in the literature.[33] Among 6 patients treated with anthracycline-based multiagent chemotherapy in conjunction with HAART, 5 patients were alive and diseases free with a median follow-up of 22 months.[33] However, only limited data exist on the treatment approach for patients with PBL.

PCNSL is associated with severe immunosuppression and an overall poor prognosis. In retrospective analyses, patients with PCNSL treated with HAART and RT had a more favorable outcome.[34,35]

NCCN Recommendations

The NCCN Guidelines recommend the use of HAART and growth factor (e.g., G-CSF) support along with full-dose chemotherapy regimens. Any change in antiviral therapy should be made in consultation with an infectious disease specialist. Patients on antiretrovirals with persistently low CD4+ count of less than 50 to 100/mcL tend to have a poorer prognosis and higher risk of infection when being treated with rituximab-containing regimens.[16,21,28] Therefore, omission of rituximab is strongly suggested for these patients due to the higher risk of serious infectious complications. CNS prophylaxis with intrathecal methotrexate is used at some NCCN institutions for all patients, whereas at other NCCN institutions, only the patients with HIV-associated DLBCL with selected high-risk features (e.g., involvement of 2 or more extranodal sites with elevated LDH, bone marrow involvement, or other high-risk site involvement such as epidural, testicular or paranasal sinuses) receive upfront prophylaxis.

Recommended treatment regimens for patients with HIV-associated BL include dose-adjusted EPOCH with rituximab (DA-EPOCH-R), CODOX-M/IVAC (with or without rituximab), CDE with rituximab, or hyper-CVAD with rituximab. Recommended treatment options for

patients with HIV-associated DLBCL include rituximab in combination with chemotherapy regimens such as dose-adjusted EPOCH, CDE or CHOP. The panel recommended DA-EPOCH-R as the preferred regimen for the treatment of HIV-associated BL and DLBCL. Patients with lymphoma associated with MCD and PEL can also be treated with the same regimens as described for patients with DLBCL. Since most cases of PEL are CD20-negative, the addition of rituximab to the chemotherapy regimen is not indicated.

The NCCN Guidelines recommend CODOX-M/IVAC, EPOCH or hyper-CVAD regimens for patients with PBL, with the realization that only limited data are available on the management of these patients at this time. High-dose methotrexate, RT or antiretroviral therapy can be considered for patients with PCNSL. Selected patients with good performance status receiving HAART may also be treated as per the NCCN Guidelines for Primary CNS Lymphoma.

References

1. Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study group. Prognosis of HIV-associated non-hodgkin lymphoma in patients starting combination antiretroviral therapy. AIDS 2009;23:2029-2037. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19531926.

2. Besson C, Goubar A, Gabarre J, et al. Changes in AIDS-related lymphoma since the era of highly active antiretroviral therapy. Blood 2001;98:2339-2344. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11588028.

3. Levine AM, Seneviratne L, Espina BM, et al. Evolving characteristics of AIDS-related lymphoma. Blood 2000;96:4084-4090. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11110677.

4. Chao C, Xu L, Abrams D, et al. Survival of non-Hodgkin lymphoma patients with and without HIV infection in the era of combined antiretroviral therapy. AIDS 2010;24:1765-1770. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20453630.

5. Lim ST, Karim R, Nathwani BN, et al. AIDS-related Burkitt's lymphoma versus diffuse large-cell lymphoma in the pre-highly active antiretroviral therapy (HAART) and HAART eras: significant differences in survival with standard chemotherapy. J Clin Oncol 2005;23:4430-4438. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15883411.

6. Boulanger E, Gerard L, Gabarre J, et al. Prognostic factors and outcome of human herpesvirus 8-associated primary effusion lymphoma in patients with AIDS. J Clin Oncol 2005;23:4372-4380. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15994147.

7. Nador RG, Cesarman E, Chadburn A, et al. Primary effusion lymphoma: a distinct clinicopathologic entity associated with the Kaposi's sarcoma-associated herpes virus. Blood 1996;88:645-656. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8695812.

8. Delecluse HJ, Anagnostopoulos I, Dallenbach F, et al. Plasmablastic lymphomas of the oral cavity: a new entity associated with the human immunodeficiency virus infection. Blood 1997;89:1413-1420. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9028965.

9. Dong HY, Scadden DT, de Leval L, et al. Plasmablastic lymphoma in HIV-positive patients: an aggressive Epstein-Barr virus-associated extramedullary plasmacytic neoplasm. Am J Surg Pathol 2005;29:1633-1641. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16327436.

10. Mylona EE, Baraboutis IG, Lekakis LJ, et al. Multicentric Castleman's disease in HIV infection: a systematic review of the literature. AIDS Rev 2008;10:25-35. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18385778.

11. Cheung MC, Pantanowitz L, Dezube BJ. AIDS-related malignancies: emerging challenges in the era of highly active antiretroviral therapy. Oncologist 2005;10:412-426. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15967835.

12. Mounier N, Spina M, Gisselbrecht C. Modern management of non-Hodgkin lymphoma in HIV-infected patients. Br J Haematol 2007;136:685-698. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17229246.

13. Sparano JA, Lee S, Chen MG, et al. Phase II trial of infusional cyclophosphamide, doxorubicin, and etoposide in patients with HIV-associated non-Hodgkin's lymphoma: an Eastern Cooperative Oncology Group Trial (E1494). J Clin Oncol 2004;22:1491-1500. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15084622.

14. Ratner L, Lee J, Tang S, et al. Chemotherapy for human immunodeficiency virus-associated non-Hodgkin's lymphoma in combination with highly active antiretroviral therapy. J Clin Oncol 2001;19:2171-2178. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11304769.

15. Weiss R, Mitrou P, Arasteh K, et al. Acquired immunodeficiency syndrome-related lymphoma: simultaneous treatment with combined cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy and highly active antiretroviral therapy is safe and improves survival--results of the German Multicenter Trial. Cancer 2006;106:1560-1568. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16502436.

16. Kaplan LD, Lee JY, Ambinder RF, et al. Rituximab does not improve clinical outcome in a randomized phase 3 trial of CHOP with or without rituximab in patients with HIV-associated non-Hodgkin lymphoma: AIDS-Malignancies Consortium Trial 010. Blood 2005;106:1538-1543. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15914552.

17. Levine AM, Tulpule A, Espina B, et al. Liposome-encapsulated doxorubicin in combination with standard agents (cyclophosphamide, vincristine, prednisone) in patients with newly diagnosed AIDS-related non-Hodgkin's lymphoma: results of therapy and correlates of response. J Clin Oncol 2004;22:2662-2670. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15226333.

18. Little RF, Pittaluga S, Grant N, et al. Highly effective treatment of acquired immunodeficiency syndrome-related lymphoma with dose-adjusted EPOCH: impact of antiretroviral therapy suspension and tumor biology. Blood 2003;101:4653-4659. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12609827.

19. Boue F, Gabarre J, Gisselbrecht C, et al. Phase II trial of CHOP plus rituximab in patients with HIV-associated non-Hodgkin's lymphoma. J Clin Oncol 2006;24:4123-4128. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16896005.

20. Ribera JM, Oriol A, Morgades M, et al. Safety and efficacy of cyclophosphamide, adriamycin, vincristine, prednisone and rituximab in patients with human immunodeficiency virus-associated diffuse large B-cell lymphoma: results of a phase II trial. Br J Haematol 2008;140:411-419. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18162120.

21. Spina M, Jaeger U, Sparano JA, et al. Rituximab plus infusional cyclophosphamide, doxorubicin, and etoposide in HIV-associated non-Hodgkin lymphoma: pooled results from 3 phase 2 trials. Blood 2005;105:1891-1897. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15550484.

22. Spina M, Simonelli C, Vaccher E, et al. Long-term follow-up of rituximab and infusional cyclophosphamide, doxorubicin, and etoposide (CDE) in combination with HAART in HIV related Non-hodgkin's lymphomas (NHL)[abstract]. Blood 2008;112:Abstract 1467. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/112/11/1467.

23. Levine AM, Noy A, Lee JY, et al. Pegylated liposomal doxorubicin, rituximab, cyclophosphamide, vincristine, and prednisone in AIDS-related lymphoma: AIDS Malignancy Consortium Study 047. J Clin Oncol 2013;31:58-64. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23169503.

24. Dunleavy K, Little RF, Pittaluga S, et al. The role of tumor histogenesis, FDG-PET, and short-course EPOCH with dose-dense rituximab (SC-EPOCH-RR) in HIV-associated diffuse large B-cell lymphoma. Blood 2010;115:3017-3024. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20130244.

25. Barnes JA, Lacasce AS, Feng Y, et al. Evaluation of the addition of rituximab to CODOX-M/IVAC for Burkitt's lymphoma: a retrospective analysis. Ann Oncol 2011;22:1859-1864. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21339382.

26. Wang ES, Straus DJ, Teruya-Feldstein J, et al. Intensive chemotherapy with cyclophosphamide, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine (CODOX-M/IVAC) for human immunodeficiency virus-associated Burkitt lymphoma. Cancer 2003;98:1196-1205. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12973843.

27. Dunleavy K, Little RF, Pittaluga S. A prospective study of dose-adjusted (DA) EPOCH with rituximab in adult with newly diagnosed Burkitt lymphoma: A regimen with high efficacy and low toxicity. Annals of Oncology 2008;19 (suppl_4):iv83-84 Available at: http://annonc.oxfordjournals.org/content/19/suppl_4.

28. Sparano JA, Lee JY, Kaplan LD, et al. Rituximab plus concurrent infusional EPOCH chemotherapy is highly effective in HIV-associated B-cell non-Hodgkin lymphoma. Blood 2010;115:3008-3016. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20023215.

29. Barta SK, Lee JY, Kaplan LD, et al. Pooled analysis of AIDS malignancy consortium trials evaluating rituximab plus CHOP or infusional EPOCH chemotherapy in HIV-associated non-Hodgkin lymphoma. Cancer 2012;118:3977-3983. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22180164.

30. Cortes J, Thomas D, Rios A, et al. Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone and highly active antiretroviral therapy for patients with acquired immunodeficiency syndrome-related Burkitt lymphoma/leukemia. Cancer 2002;94:1492-1499. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11920506.

31. Thomas DA, Kantarjian HM, Cortes J, et al. Long-term outcome after hyper-CVAD and rituximab chemoimmunotherapy for Burkitt (BL) or Burkitt-like (BLL) leukemia/lymphoma and mature B-cell acute lymphocytic leukemia (ALL) [abstract]. Blood 2008;112:Abstract 1929. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/112/11/1929.

32. Bayraktar UD, Ramos JC, Petrich A, et al. Outcome of patients with relapsed/refractory acquired immune deficiency syndrome-related lymphoma diagnosed 1999-2008 and treated with curative intent in the AIDS Malignancy Consortium. Leuk Lymphoma 2012;53:2383-2389. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22642936.

33. Teruya-Feldstein J, Chiao E, Filippa DA, et al. CD20-negative large-cell lymphoma with plasmablastic features: a clinically heterogenous spectrum in both HIV-positive and -negative patients. Ann Oncol 2004;15:1673-1679. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15520070.

34. Newell ME, Hoy JF, Cooper SG, et al. Human immunodeficiency virus–related primary central nervous system lymphoma. Cancer 2004;100:2627-2636. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15197806.

35. Diamond C, Taylor TH, Im T, et al. Highly active antiretroviral therapy is associated with improved survival among patients with AIDS-related primary central nervous system non-Hodgkin's lymphoma. Curr HIV Res 2006;4:375-378. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16842088.

This discussion is being updated to correspond with the newly updated algorithm. Last updated 09/06/2013.

Post-Transplant Lymphoproliferative Disorders

Post-transplant lymphoproliferative disorders (PTLD) are a heterogeneous group of lymphoid neoplasms associated with immunosuppression following solid organ transplantation (SOT) or allogeneic hematopoietic stem cell transplantation (HSCT).[1-4] PTLD following autologous HSCT is very rare. The majority of PTLD following both allogeneic HSCT and SOT are of B cell origin, and are usually associated with the Epstein Barr virus (EBV).[2,5-8] Although rare, PTLD of T cell or NK cell origin can also occur (EBV-associated in approximately 30% of cases), and tend to occur late (median 6 years post transplant in one series).[9] EBV-negative PTLD has been shown to be a late serious complication of transplantation, and tend to occur later (>2 years) after SOT than EBV-positive disease.[10-12] Gene expression profiling studies have shown that EBV negative PTLD are biologically distinct from their EBV associated counterparts.[13,14] PTLD following HSCT are usually of donor origin, whereas PTLD following SOT are of recipient origin in the majority of cases, with a minority of donor derived cases that often involve the grafted organ.[2,3,15-20]

The incidence of PTLD following allogeneic HSCT ranges from about 1% to 3% with a slightly higher incidence in patients who are recipients of cord blood transplant.[1,21-24] The large majority of these PTLD occur early, within 6 to 12 months of transplant.[1,21-23] The incidence of PTLD following SOT ranges from about 1% to 10% depending upon the type of organ transplant.[2,25-28] Small bowel transplant appears to be associated with the highest incidence of PTLD, at about 20%.[2,29] More than 50% of PTLD cases following SOT are diagnosed beyond 12 months from the time of transplant.[26,28,30,31] The incidence of PTLD is generally higher among pediatric patients compared with adults.[2,8,21,29,31]

Median survival following a diagnosis of PTLD (after SOT) ranges from about 10 to 32 months.[8,26,28,32,33] Survival outcomes for PTLD occurring after allogeneic HSCT are poor.[21]

Factors such as EBV and cytomegalovirus (CMV) serology status (of the recipient and the donor), age, type of organ transplant, type of immunosuppressive agents (likely correlated with degree of immunosuppression), and time from transplant, contribute to variations in the risks for developing PTLD.[2,34-37] In patients undergoing allogeneic HSCT, factors associated with increased risks for PTLD included T-cell depletion of the allograft, unrelated or HLA-mismatched grafts, and anti-T-cell therapy (e.g., antithymocyte globulin [ATG] or anti-CD3 monoclonal antibody) for prophylaxis or treatment of graft-versus-host disease (GVHD).[1,20-23] In recipients of SOT, factors associated with increased risks for PTLD included the type of organ transplant (e.g., highest risks in bowel, lung, heart/lung transplants), EBV serology mismatch (i.e., negative recipient/positive donor), CMV serology mismatch (i.e., negative recipient/positive donor), HLA mismatch, and anti-T-cell therapy (e.g., ATG or OKT3) for prevention or treatment of graft rejection.[2,10,31,36-38] Moreover, the use of tacrolimus (compared with cyclosporin) as primary immunosuppressive therapy appeared to increase the risk of PTLD in SOT recipients.[31,38-40] Although CMV disease has also been associated with risks for EBV-positive PTLD, the correlation between CMV infection and development of PTLD is unclear.[37,41,42] In patients with PTLD following SOT, factors such as older age, poor performance status, elevated lactate dehydrogenase (LDH), organ dysfunction, multiple involved lymph nodes, and multi organ involvement were identified as prognostic factors for poorer survival.[7,32,43,44]

The diagnosis and classification of PTLD can be challenging given the nonspecific clinical presentation, and heterogeneity in histopathologic

and immunophenotypic presentations. Moreover, subtypes of PTLD may overlap within the same individual. In the 2008 WHO classification, PTLD are classified into 4 major categories: early lesions, monomorphic PTLD, polymorphic PTLD and classical Hodgkin lymphoma (cHL) type PTLD.[3] Early lesions typically develop within a year of transplantation and are more common in transplant recipients who are EBV naive.[45] Early lesions consist of 2 histological subtypes, plasmacytic hyperplasia and infectious mononucleosis like PTLD.[3] Monomorphic histologies appear to be the most common subtype of PTLD,[28,30,46,47] and resemble one of the B-cell lymphomas (except for indolent lymphomas) or T-cell/NK cell lymphomas seen in immunocompetent individuals. EBV serology status can vary according to lineage; most monomorphic B-cell PTLD are EBV positive whereas most T-cell PTLD are EBV negative.[9,45] Monomorphic B-cell PTLD most commonly resembles diffuse large B cell lymphoma (DLBCL), but some lesions, although less common, can resemble Burkitt lymphoma, plasma cell myeloma or plasmacytoma.[3] Polymorphic PTLD is mostly EBV positive, and can be either polyclonal or monoclonal; this represents the most common type of PTLD among children. cHL-type PTLD is almost always EBV-positive, and is the least common of the PTLD categories.[3]

Diagnosis

Histopathology and adequate immunophenotyping are essential to confirm the diagnosis of PTLD.[3,48,49] Immunophenotyping should include both B-cell and T-cell (as well as NK cell) associated markers. Among B-cell PTLD, expression of BCL6, MUM1 and CD138 can be useful in distinguishing between the histological subtypes of PTLD.[50,51] BCL6 expression was detected in cases of monomorphic PTLD (71% of centroblastic DLBCL), whereas it was consistently absent in polymorphic PTLD. MUM1 was preferentially expressed in 92% of polymorphic PTLD.[50] Overall, BCL6−, MUM1+ and CD138− phenotype is associated most frequently with polymorphic PTLD; BCL6+, MUM1+/ − and CD138− is mostly associated with monomorphic PTLD.[50,51] The recommended panel for immunohistochemistry (IHC) includes the following markers: CD3, CD5, CD10, BCL6, BCL2, IRF4/MUM1, CD20, CD79a, PAX5, Ki67, and kappa, lambda light chains.. Cell surface markers CD3, CD5, CD7, CD4, CD8, CD19, CD20, CD10, and kappa, lambda are recommended for flow cytometric analysis. Under certain circumstances, the following additional markers may be useful for an IHC panel: CD15, CD30, CD45, CD7, CD4, CD8, ALK, TIA-1, granzyme B, CD57, CD56, and CD138. In addition, the following markers for flow cytometry may also be useful under certain situations: CD138, CD30, CD57, CD56, CD16, CD25, CD52, and cytoplasmic kappa or lambda.

Evaluation of EBV infection status is another essential component of the diagnostic workup. EBV can be detected by either IHC for latent membrane protein 1 (LMP 1) or EBV encoded RNA in situ hybridization (EBER ISH). EBER ISH is more sensitive than immunohistochemistry,[48] and is recommended if EBV-LMP-1 is negative. If immunostaining for EBV-LMP 1 is positive, EBER ISH is not required. Under certain circumstances, EBV evaluation by Southern blot may also be useful.

Immunoglobulin heavy chain (IGH) gene mutations are seen in the majority of B-cell PTLD cases, with the exception of early lesions.[45,51,52] Genetic alterations in MYC, NRAS and TP53 are seen only in monomorphic PTLD.[45,53] BCL6 mutations have been associated with shorter survival and poor response to therapy.[54] In certain situations, molecular genetic analysis to detect IGH rearrangements and BCL6 gene mutations could be useful.

Workup

The initial workup for PTLD should include a physical examination and evaluation of performance status. Laboratory assessments should include standard blood work including CBC with differential and a metabolic panel (to include albumin, electrolytes, BUN, and creatinine), in addition to measurements of serum LDH levels. Bone marrow evaluations may be useful in selected cases. Prior history of immunosuppressive therapy should also be assessed. CT scans of chest, abdomen and pelvis should be performed. PET CT scan and brain MRI may be useful in selected cases. In addition, MUGA scan/echocardiogram may be useful in cases where treatment with anthracycline or anthracenedione-containing regimens is being considered. Hepatitis B virus (HBV) testing should be performed prior to initiation of treatment with immunotherapy (with or without chemotherapy) given the potential risks for viral reactivation with such regimens. Evaluation of EBV viral load by quantitative PCR can aid in the diagnosis as well as monitoring of treatment responses in patients with PTLD. Plasma or peripheral blood mononuclear cells (PBMC) are useful for measuring EBV viral load, although some studies have shown that viral load in plasma is more sensitive than PBMC in the diagnosis of PTLD.[55-57] EBV serology to assess primary infection versus reactivation may be useful. As previously mentioned, CMV infection has also been associated with an increased risk of PTLD in EBV seronegative patients.[37,41] Thus, PCR for the measurement of EBV and CMV can be useful for selected patients.

Treatment

While guidelines have been published, the optimal treatment for PTLD is not well defined due to the lack of randomized controlled trials and the heterogeneity of the disease.[58] Published reports of treatment for PTLD have included reduction in immunosuppression (RI), use of antiviral agents, single-agent treatment with rituximab, chemotherapy, and/or chemoimmunotherapy regimens; treatment approaches are largely dependent on the PTLD subtype. In general, RI remains the initial step in the management of nearly all cases of PTLD.[2,44,58,59] In a prospective phase II study that evaluated a sequential approach to therapy (i.e., RI first, then interferon-alfa for less than complete remission (CR), then multiagent chemotherapy if less than CR to interferon) for adults with PTLD following SOT (N=20; n=16 evaluable), RI alone resulted in only one partial remission (PR).[60] The remaining patients experienced either disease progression or graft rejection. One patient achieved a CR with interferon, and among patients eligible for multiagent chemotherapy, 67% achieved a CR. Rituximab was not evaluated as part of this study.[60] The role of antiviral therapy is controversial since the majority of PTLD are associated with latent EBV. Replicating EBV DNA has been reported in about 40% of EBV associated lymphoproliferative disorders in immunocompromised patients.[61,62] Antiviral drugs targeting EBV replication may be beneficial in this subset of patients with early or polymorphic PTLD.[63]

Several phase II studies and retrospective analyses have confirmed the efficacy of rituximab monotherapy in the treatment of patients with B-cell PTLD.[64-70] In a prospective multicenter phase II study in patients with PTLD after SOT (N=46; n=43 evaluable), rituximab induced responses in 44% of patients (CR in 28%) with a 1-year overall survival (OS) rate of 67%.[65] Another prospective multicenter phase II study demonstrated that extended treatment with rituximab (e.g., 2 courses of rituximab) induced a high rate of CR (60.5%; including patients treated with a second course) in patients with PTLD after SOT (N=38) without increasing toxicity.[71] Among the patients who could not achieve a CR with rituximab alone and subsequently received rituximab combined with chemotherapy (R-CHOP or R-EPOCH; n=8), 6 patients achieved a

CR (75%). At a median follow up of 27.5 months, the event-free survival and OS rates were 42% and 47%, respectively.[71] In a multicenter retrospective analysis of data from patients with PTLD following SOT (N=80), all patients had received initial RI, and 74% were treated with rituximab with or without chemotherapy.[67] The 3-year progression-free survival (PFS) and OS rates for all patients were 57% and 62%, respectively. Inclusion of rituximab as part of initial therapy significantly improved both 3-year PFS (70% vs. 21%) and OS (73% vs. 33%) rates compared with the group who did not receive rituximab.[67]

Anthracycline based chemotherapy with or without rituximab has also been effective in the treatment of patients with PTLD.[43,66,72-75] In a retrospective analysis, CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) induced an overall response rate (ORR) of 65% (CR in 50%) in patients with PTLD after SOT (N=26) who were unresponsive to RI alone.[43] With a median follow up of nearly 9 years, the median OS was 14 months. Treatment-related mortality rate was high, at 31%.[43] Chemotherapy and RI, with or without rituximab has also been reported to induce durable CR with reduced risk of graft impairment when used as first line treatment.[76,77]

As mentioned above, rituximab with or without chemotherapy was shown to improve outcomes in patients with PTLD in a retrospective study.[67] More recently, a prospective multicenter phase II study evaluated the role of sequential chemoimmunotherapy with rituximab (4 weekly doses) followed by CHOP-21 (4 cycles) combined with G-CSF in patients with PTLD who failed initial RI (N=74; n=70 evaluable).[78] The large majority of patients presented with monomorphic histology (primarily DLBCL), and 44% of cases were EBV positive. The ORR with rituximab (n=70) was 60% (CR in 20%), which improved to 90% (CR in 68%) in the patients who received subsequent CHOP chemotherapy following rituximab (n=59). Median response duration has not yet been reached. The median PFS and OS were 4 years and 6.6 years, respectively; the 5-year PFS and OS rates were 50% and 55%, respectively.[78] The most common grade 3 or 4 toxicities included leukopenia (68%) and infectious events (41%). Treatment-related mortality associated with CHOP was reported in 11% of patients.[78] This trial was amended to introduce a risk-stratified treatment strategy based upon initial response to rituximab, whereby low-risk patients (defined as those achieving CR after initial rituximab) received consolidation with rituximab monotherapy and high-risk patients (defined as non-CR after initial rituximab) received chemoimmunotherapy with R-CHOP-21 (4 cycles) combined with G-CSF.[79] Among the patients enrolled in the risk-stratified protocol (N=91; n=80 evaluable), the ORR was 93% (CR in 78%). The CR rate after initial rituximab alone was 27%. In this low-risk group (who subsequently received rituximab consolidation; n=23), the rate of relapse after a median follow up of more than 3 years was 13%. Among patients with progressive disease after initial rituximab (n=23), sequential therapy with R-CHOP resulted in CR in 65%; this CR rate was higher than that of patients with progressive disease (following initial rituximab) who received sequential CHOP in the original study protocol (CR in 27%).[79] The 3-year OS with the risk-stratified approach was 70%, which compared favorably to the OS rate of 61% (although not statistically different) with the original protocol. This risk-stratified sequential treatment strategy spared the need for chemotherapy in low-risk PTLD patients, while incorporating a more effective chemoimmunotherapy regimen (R-CHOP) in high-risk patients.[79]

Adoptive immunotherapy using autologous or allogeneic EBV specific cytotoxic T lymphocytes (EBV CTLs) has been investigated in several studies.[80-85] In small studies, the use of autologous EBV-CTLs has been shown to prevent the occurrence of PTLD in SOT recipients who were

considered at high risk for developing PTLD.[80,85] In patients who underwent allogeneic HSCT, the use of allogeneic EBV-CTLs successfully prevented PTLD in all patients (N=39).[84] In a subsequent study that evaluated the effectiveness of allogeneic EBV-CTLs in a larger series of patients (including those reported in the earlier Rooney et al, 1998 study) who underwent allogeneic HSCT (N=114), EBV-CTLs prevented PTLD in all patients (n=101) and induced a durable CR in 85% of patients in the subgroup with existing PTLD (n=13).[83] This study also showed that during long-term follow up, functional EBV-CTLs persisted up to 9 years. A prospective multicenter phase II study evaluated allogeneic EBV-CTLs in the treatment of patients with PTLD that failed conventional therapy (N=33).[82] The majority of patients (94%) had received SOT; the remaining patients had undergone allogeneic HSCT. All patients had RI as part of initial therapy for PTLD, and some patients had also received treatment with rituximab, anti-virals, or chemotherapy. The ORR at 6 months was 52% (CR in 42%). The OS rate at 6 months was 79%.[82] Results from this study suggest that immunotherapy with EBV-CTLs may be a promising strategy in patients with PTLD who fail conventional treatments. However, further prospective studies are needed to better define the role of adoptive immunotherapy in the prevention and management of PTLD.

NCCN Recommendations

First-line Treatment and Initial Response

Treatment options for PTLD depend on the histological subtype and should be individualized. RI, if possible, should be a part of the initial treatment approach for all patients with PTLD. It should be noted that response to RI is variable, and patients should be closely monitored during RI. Importantly, RI should be initiated and managed in coordination with the transplant team in order to minimize risks for graft rejection.

For patients with early lesions, first-line management could involve RI alone. For patients who achieve a CR with this approach, re-escalation of immunosuppressive should be individualized, taking into account the extent of initial RI and the nature of the organ allograft; these decisions should be made in conjunction with the transplant team.[35,60,86] EBV viral load can be monitored by PCR assays. Patients with early lesions who have persistent or progressive disease with RI alone should be managed with second-line therapy options (see section below).

For patients with localized polymorphic PTLD, treatment should include RI, if possible, along with RT with or without rituximab, surgery with or without rituximab, or rituximab alone. For patients with systemic polymorphic PTLD, the NCCN Guidelines panel recommends RI, if possible, along with rituximab alone or rituximab as part of a chemoimmunotherapy regimen (concurrent or sequential combination). In patients with (systemic or localized) polymorphic PTLD who achieve a CR with initial therapy, the patient should either be observed or continue RI (if possible) with or without rituximab maintenance. Patients who have persistent or progressive disease with initial therapy should be managed with second-line treatment options (see section below).

The treatment approach for patients with monomorphic PTLD should be based on the standard treatment regimens used for the unique histology. The treatment options include RI, if possible, and/or rituximab alone or rituximab as part of a chemoimmunotherapy regimen (concurrent or sequential regimen); rituximab alone should only be considered as part of a step-wise approach to treatment in patients who are not highly symptomatic or in those who cannot tolerate chemotherapy due to comorbid conditions. Patients who achieve a CR with initial therapy should undergo surveillance/follow up according to the Guidelines specific for the histology. Patients who have persistent or

progressive disease with initial therapy should be managed with second-line treatment options (see section below).

Second line Treatment

Treatment options in the second-line setting are dependent on the response to initial treatment and the histological subtype. For patients with early lesions who have persistent or progressive disease with RI alone, rituximab is recommended as second-line therapy.

For polymorphic PTLD, chemoimmunotherapy or EBV CTL infusion (if EBV positive) are included as options for patients who experience persistent or progressive disease with initial therapy. Participation in a suitable clinical trial, where available, should also be considered in this setting.

For patients with monomorphic PTLD with persistent or progressive disease with initial therapy, second line treatment options are dependent on prior therapy. Rituximab or chemoimmunotherapy regimens are options for patients who received RI alone as initial treatment, whereas patients who received single-agent rituximab as initial therapy should be treated with chemoimmunotherapy. In both situations, other options include participation in a suitable clinical trial, if available, or incorporation of EBV CTL infusion (if EBV positive).

References

1. Curtis RE, Travis LB, Rowlings PA, et al. Risk of lymphoproliferative disorders after bone marrow transplantation: a multi-institutional study. Blood 1999;94:2208-2216. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10498590.

2. Jacobson CA, LaCasce AS. Lymphoma: risk and response after solid organ transplant. Oncology (Williston Park) 2010;24:936-944. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21138175.

3. Swerdlow SH, Webber SA, Chadburn A, Ferry JA. Post-transplant lymphoproliferative disorders. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008.

4. Wagner H-J, Rooney CM, Heslop HE. Diagnosis and treatment of posttransplantation lymphoproliferative disease after hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2002;8:1-8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11846351.

5. Berg LC, Copenhaver CM, Morrison VA, et al. B-cell lymphoproliferative disorders in solid-organ transplant patients: detection of Epstein-Barr virus by in situ hybridization. Hum Pathol 1992;23:159-163. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1310951.

6. Leblond V, Sutton L, Dorent R, et al. Lymphoproliferative disorders after organ transplantation: a report of 24 cases observed in a single center. J Clin Oncol 1995;13:961-968. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7707124.

7. Leblond V, Dhedin N, Mamzer Bruneel MF, et al. Identification of prognostic factors in 61 patients with posttransplantation lymphoproliferative disorders. J Clin Oncol 2001;19:772-778. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11157030.

8. Morrison VA, Dunn DL, Manivel JC, et al. Clinical characteristics of post-transplant lymphoproliferative disorders. Am J Med 1994;97:14-24. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8030652.

9. Herreman A, Dierickx D, Morscio J, et al. Clinicopathological characteristics of posttransplant lymphoproliferative disorders of T-cell origin: single-center series of nine cases and meta-analysis of 147 reported cases. Leuk Lymphoma 2013. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23402267.

10. Knight JS, Tsodikov A, Cibrik DM, et al. Lymphoma after solid organ transplantation: risk, response to therapy, and survival at a transplantation center. J Clin Oncol 2009;27:3354-3362. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19451438.

11. Leblond V, Davi F, Charlotte F, et al. Posttransplant lymphoproliferative disorders not associated with Epstein-Barr virus: a distinct entity? J Clin Oncol 1998;16:2052-2059. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9626203.

12. Nelson BP, Nalesnik MA, Bahler DW, et al. Epstein-Barr virus-negative post-transplant lymphoproliferative disorders: a distinct entity? Am J Surg Pathol 2000;24:375-385. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10716151.

13. Craig FE, Johnson LR, Harvey SA, et al. Gene expression profiling of Epstein-Barr virus-positive and -negative monomorphic B-cell posttransplant lymphoproliferative disorders. Diagn Mol Pathol 2007;16:158-168. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17721324.

14. Morscio J, Dierickx D, Ferreiro JF, et al. Gene Expression Profiling Reveals Clear Differences Between EBV-Positive and EBV-Negative Posttransplant Lymphoproliferative Disorders. Am J Transplant 2013. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23489474.

15. Chadburn A, Suciu-Foca N, Cesarman E, et al. Post-transplantation lymphoproliferative disorders arising in solid organ transplant recipients

are usually of recipient origin. Am J Pathol 1995;147:1862-1870. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7495309.

16. Gulley ML, Swinnen LJ, Plaisance KT, Jr., et al. Tumor origin and CD20 expression in posttransplant lymphoproliferative disorder occurring in solid organ transplant recipients: implications for immune-based therapy. Transplantation 2003;76:959-964. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14508361.

17. Peterson MR, Emery SC, Yung GL, et al. Epstein-Barr virus-associated posttransplantation lymphoproliferative disorder following lung transplantation is more commonly of host origin. Arch Pathol Lab Med 2006;130:176-180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16454557.

18. Petit B, Le Meur Y, Jaccard A, et al. Influence of host-recipient origin on clinical aspects of posttransplantation lymphoproliferative disorders in kidney transplantation. Transplantation 2002;73:265-271. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11821742.

19. Weissmann DJ, Ferry JA, Harris NL, et al. Posttransplantation lymphoproliferative disorders in solid organ recipients are predominantly aggressive tumors of host origin. Am J Clin Pathol 1995;103:748-755. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7785662.

20. Zutter MM, Martin PJ, Sale GE, et al. Epstein-Barr virus lymphoproliferation after bone marrow transplantation. Blood 1988;72:520-529. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2840986.

21. Baker KS, DeFor TE, Burns LJ, et al. New malignancies after blood or marrow stem-cell transplantation in children and adults: incidence and risk factors. J Clin Oncol 2003;21:1352-1358. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12663726.

22. Landgren O, Gilbert ES, Rizzo JD, et al. Risk factors for lymphoproliferative disorders after allogeneic hematopoietic cell transplantation. Blood 2009;113:4992-5001. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19264919.

23. Micallef IN, Chhanabhai M, Gascoyne RD, et al. Lymphoproliferative disorders following allogeneic bone marrow transplantation: the Vancouver experience. Bone Marrow Transplant 1998;22:981-987. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9849695.

24. Omar H, Hagglund H, Gustafsson-Jernberg A, et al. Targeted monitoring of patients at high risk of post-transplant lymphoproliferative disease by quantitative Epstein-Barr virus polymerase chain reaction. Transpl Infect Dis 2009;11:393-399. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19497070.

25. Di Benedetto F, Lauro A, Masetti M, et al. Outcomes after adult isolated small bowel transplantation: experience from a single European centre. Dig Liver Dis 2005;37:240-246. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15788207.

26. Kremer BE, Reshef R, Misleh JG, et al. Post-transplant lymphoproliferative disorder after lung transplantation: a review of 35 cases. J Heart Lung Transplant 2012;31:296-304. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22112992.

27. Taylor AL, Marcus R, Bradley JA. Post-transplant lymphoproliferative disorders (PTLD) after solid organ transplantation. Crit Rev Oncol Hematol 2005;56:155-167. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15979320.

28. Wudhikarn K, Holman CJ, Linan M, et al. Post-transplant lymphoproliferative disorders in lung transplant recipients: 20-yr experience at the University of Minnesota. Clin Transplant 2011;25:705-713. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21077949.

29. Nalesnik M, Jaffe R, Reyes J, et al. Posttransplant lymphoproliferative disorders in small bowel allograft recipients.

Transplant Proc 2000;32:1213. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10995914.

30. Muti G, Cantoni S, Oreste P, et al. Post-transplant lymphoproliferative disorders: improved outcome after clinico-pathologically tailored treatment. Haematologica 2002;87:67-77. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11801467.

31. Opelz G, Dohler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. Am J Transplant 2004;4:222-230. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14974943.

32. Ghobrial IM, Habermann TM, Ristow KM, et al. Prognostic factors in patients with post-transplant lymphoproliferative disorders (PTLD) in the rituximab era. Leuk Lymphoma 2005;46:191-196. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15621801.

33. Oton AB, Wang H, Leleu X, et al. Clinical and pathological prognostic markers for survival in adult patients with post-transplant lymphoproliferative disorders in solid transplant. Leuk Lymphoma 2008;49:1738-1744. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18798108.

34. Post-transplantation lymphoproliferative disorder and OKT3. N Engl J Med 1991;324:1437-1439. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2020303.

35. Swinnen LJ. Transplantation-related lymphoproliferative disorder: a model for human immunodeficiency virus-related lymphomas. Semin Oncol 2000;27:402-408. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10950366.

36. Swinnen LJ, Costanzo-Nordin MR, Fisher SG, et al. Increased incidence of lymphoproliferative disorder after immunosuppression with the monoclonal antibody OKT3 in cardiac-transplant recipients. N Engl J Med 1990;323:1723-1728. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2100991.

37. Walker RC, Marshall WF, Strickler JG, et al. Pretransplantation assessment of the risk of lymphoproliferative disorder. Clin Infect Dis 1995;20:1346-1353. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7620022.

38. Caillard S, Dharnidharka V, Agodoa L, et al. Posttransplant lymphoproliferative disorders after renal transplantation in the United States in era of modern immunosuppression. Transplantation 2005;80:1233-1243. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16314791.

39. Cao S, Cox KL, Berquist W, et al. Long-term outcomes in pediatric liver recipients: comparison between cyclosporin A and tacrolimus. Pediatr Transplant 1999;3:22-26. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10359027.

40. Younes BS, McDiarmid SV, Martin MG, et al. The effect of immunosuppression on posttransplant lymphoproliferative disease in pediatric liver transplant patients. Transplantation 2000;70:94-99. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10919581.

41. Manez R, Breinig MC, Linden P, et al. Posttransplant lymphoproliferative disease in primary Epstein-Barr virus infection after liver transplantation: the role of cytomegalovirus disease. J Infect Dis 1997;176:1462-1467. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9395355.

42. Stevens SJ, Verschuuren EA, Pronk I, et al. Frequent monitoring of Epstein-Barr virus DNA load in unfractionated whole blood is essential for early detection of posttransplant lymphoproliferative disease in high-risk patients. Blood 2001;97:1165-1171. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11222357.

43. Choquet S, Trappe R, Leblond V, et al. CHOP-21 for the treatment of post-transplant lymphoproliferative disorders (PTLD) following solid organ transplantation. Haematologica 2007;92:273-274. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17296588.

44. Tsai DE, Hardy CL, Tomaszewski JE, et al. Reduction in immunosuppression as initial therapy for posttransplant lymphoproliferative disorder: analysis of prognostic variables and long-term follow-up of 42 adult patients. Transplantation 2001;71:1076-1088. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11374406.

45. Tsao L, Hsi ED. The clinicopathologic spectrum of posttransplantation lymphoproliferative disorders. Arch Pathol Lab Med 2007;131:1209-1218. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17683183.

46. Dierickx D, Tousseyn T, Sagaert X, et al. Single-center analysis of biopsy-confirmed posttransplant lymphoproliferative disorder: incidence, clinicopathological characteristics and prognostic factors. Leuk Lymphoma 2013. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23442063.

47. Majhail NS. Secondary cancers following allogeneic haematopoietic cell transplantation in adults. Br J Haematol 2011;154:301-310. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21615719.

48. Harris NL, Ferry JA, Swerdlow SH. Posttransplant lymphoproliferative disorders: summary of Society for Hematopathology Workshop. Semin Diagn Pathol 1997;14:8-14. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9044505.

49. Parker A, Bowles K, Bradley JA, et al. Diagnosis of post-transplant lymphoproliferative disorder in solid organ transplant recipients - BCSH and BTS Guidelines. Br J Haematol 2010;149:675-692. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20408847.

50. Capello D, Cerri M, Muti G, et al. Molecular histogenesis of posttransplantation lymphoproliferative disorders. Blood 2003;102:3775-3785. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12907442.

51. Capello D, Rossi D, Gaidano G. Post-transplant lymphoproliferative disorders: molecular basis of disease histogenesis and pathogenesis. Hematol Oncol 2005;23:61-67. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16216037.

52. Capello D, Cerri M, Muti G, et al. Analysis of immunoglobulin heavy and light chain variable genes in post-transplant lymphoproliferative disorders. Hematol Oncol 2006;24:212-219. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16897790.

53. Knowles DM, Cesarman E, Chadburn A, et al. Correlative morphologic and molecular genetic analysis demonstrates three distinct categories of posttransplantation lymphoproliferative disorders. Blood 1995;85:552-565. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7812011.

54. Cesarman E, Chadburn A, Liu YF, et al. BCL-6 gene mutations in posttransplantation lymphoproliferative disorders predict response to therapy and clinical outcome. Blood 1998;92:2294-2302. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9746767.

55. Ryan JL, Fan H, Swinnen LJ, et al. Epstein-Barr Virus (EBV) DNA in plasma is not encapsidated in patients with EBV-related malignancies. Diagn Mol Pathol 2004;13:61-68. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15167006.

56. Wagner HJ, Wessel M, Jabs W, et al. Patients at risk for development of posttransplant lymphoproliferative disorder: plasma versus peripheral blood mononuclear cells as material for quantification of Epstein-Barr viral load by using real-time quantitative polymerase chain reaction. Transplantation 2001;72:1012-1019. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11579293.

57. Tsai DE, Douglas L, Andreadis C, et al. EBV PCR in the diagnosis and monitoring of posttransplant lymphoproliferative disorder: results of a two-arm prospective trial. Am J Transplant 2008;8:1016-1024. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18312608.

58. Parker A, Bowles K, Bradley JA, et al. Management of post-transplant lymphoproliferative disorder in adult solid organ transplant recipients - BCSH and BTS Guidelines. Br J Haematol 2010;149:693-705. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20408848.

59. Reshef R, Vardhanabhuti S, Luskin MR, et al. Reduction of immunosuppression as initial therapy for posttransplantation lymphoproliferative disorder. Am J Transplant 2011;11:336-347. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21219573.

60. Swinnen LJ, LeBlanc M, Grogan TM, et al. Prospective study of sequential reduction in immunosuppression, interferon alpha-2B, and chemotherapy for posttransplantation lymphoproliferative disorder. Transplantation 2008;86:215-222. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18645482.

61. Fan H, Kim SC, Chima CO, et al. Epstein-Barr viral load as a marker of lymphoma in AIDS patients. J Med Virol 2005;75:59-69. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15543571.

62. Katz BZ, Raab-Traub N, Miller G. Latent and replicating forms of Epstein-Barr virus DNA in lymphomas and lymphoproliferative diseases. J Infect Dis 1989;160:589-598. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2551973.

63. Hanto DW, Frizzera G, Gajl-Peczalska KJ, et al. Epstein-Barr virus-induced B-cell lymphoma after renal transplantation: acyclovir therapy and transition from polyclonal to monoclonal B-cell proliferation. N Engl J Med 1982;306:913-918. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6278307.

64. Blaes AH, Peterson BA, Bartlett N, et al. Rituximab therapy is effective for posttransplant lymphoproliferative disorders after solid organ transplantation: results of a phase II trial. Cancer 2005;104:1661-1667. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16149091.

65. Choquet S, Leblond V, Herbrecht R, et al. Efficacy and safety of rituximab in B-cell post-transplantation lymphoproliferative disorders: results of a prospective multicenter phase 2 study. Blood 2006;107:3053-3057. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16254143.

66. Elstrom RL, Andreadis C, Aqui NA, et al. Treatment of PTLD with rituximab or chemotherapy. Am J Transplant 2006;6:569-576. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16468968.

67. Evens AM, David KA, Helenowski I, et al. Multicenter analysis of 80 solid organ transplantation recipients with post-transplantation lymphoproliferative disease: outcomes and prognostic factors in the modern era. J Clin Oncol 2010;28:1038-1046. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20085936.

68. Jain AB, Marcos A, Pokharna R, et al. Rituximab (chimeric anti-CD20 antibody) for posttransplant lymphoproliferative disorder after solid organ transplantation in adults: long-term experience from a single center. Transplantation 2005;80:1692-1698. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16378063.

69. Milpied N, Vasseur B, Parquet N, et al. Humanized anti-CD20 monoclonal antibody (Rituximab) in post transplant B-lymphoproliferative disorder: a retrospective analysis on 32 patients. Ann Oncol 2000;11 Suppl 1:113-116. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10707791.

70. Oertel SHK, Verschuuren E, Reinke P, et al. Effect of anti-CD 20 antibody rituximab in patients with post-transplant lymphoproliferative disorder (PTLD). Am J Transplant 2005;5:2901-2906. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16303003.

71. Gonzalez-Barca E, Domingo-Domenech E, Capote FJ, et al. Prospective phase II trial of extended treatment with rituximab in patients with B-cell post-transplant lymphoproliferative disease. Haematologica 2007;92:1489-1494. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18024397.

72. Buadi FK, Heyman MR, Gocke CD, et al. Treatment and outcomes of post-transplant lymphoproliferative disease: a single institution study. Am J Hematol 2007;82:208-214. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17022049.

73. Buell JF, Gross TG, Hanaway MJ, et al. Chemotherapy for posttransplant lymphoproliferative disorder: the Israel Penn International Transplant Tumor Registry experience. Transplant Proc 2005;37:956-957. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15848588.

74. Fohrer C, Caillard S, Koumarianou A, et al. Long-term survival in post-transplant lymphoproliferative disorders with a dose-adjusted ACVBP regimen. Br J Haematol 2006;134:602-612. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16889621.

75. Orjuela M, Gross TG, Cheung Y-K, et al. A pilot study of chemoimmunotherapy (cyclophosphamide, prednisone, and rituximab) in patients with post-transplant lymphoproliferative disorder following solid organ transplantation. Clin Cancer Res 2003;9:52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14506193.

76. Taylor AL, Bowles KM, Callaghan CJ, et al. Anthracycline-based chemotherapy as first-line treatment in adults with malignant posttransplant lymphoproliferative disorder after solid organ transplantation. Transplantation 2006;82:375-381. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16906036.

77. Trappe R, Hinrichs C, Appel U, et al. Treatment of PTLD with rituximab and CHOP reduces the risk of renal graft impairment after reduction of immunosuppression. Am J Transplant 2009;9:2331-2337. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19663889.

78. Trappe R, Oertel S, Leblond V, et al. Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicentre phase 2 PTLD-1 trial. Lancet Oncol 2012;13:196-206. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22173060.

79. Trappe RU, Dierickx D, Reinke P, et al. Interim analysis of the largest prospective trial to date in adult CD20-positive post-transplant lymphoproliferative disorder (PTLD): Introducing risk-stratified sequential treatment (RSST) [abstract]. J Clin Oncol 2012;30:Abstract 8030. Available at: http://meeting.ascopubs.org/cgi/content/abstract/30/15_suppl/8030.

80. Comoli P, Labirio M, Basso S, et al. Infusion of autologous Epstein-Barr virus (EBV)-specific cytotoxic T cells for prevention of EBV-related lymphoproliferative disorder in solid organ transplant recipients with evidence of active virus replication. Blood 2002;99:2592-2598. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11895798.

81. Haque T, Wilkie GM, Taylor C, et al. Treatment of Epstein-Barr-virus-positive post-transplantation lymphoproliferative disease with partly HLA-matched allogeneic cytotoxic T cells. Lancet 2002;360:436-442. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12241714.

82. Haque T, Wilkie GM, Jones MM, et al. Allogeneic cytotoxic T-cell therapy for EBV-positive posttransplantation lymphoproliferative disease: results of a phase 2 multicenter clinical trial. Blood 2007;110:1123-1131. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17468341.

83. Heslop HE, Slobod KS, Pule MA, et al. Long-term outcome of EBV-specific T-cell infusions to prevent or treat EBV-related lymphoproliferative disease in transplant recipients. Blood 2010;115:925-935. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19880495.

84. Rooney CM, Smith CA, Ng CY, et al. Infusion of cytotoxic T cells for the prevention and treatment of Epstein-Barr virus-induced lymphoma in

allogeneic transplant recipients. Blood 1998;92:1549-1555. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9716582.

85. Savoldo B, Goss JA, Hammer MM, et al. Treatment of solid organ transplant recipients with autologous Epstein Barr virus-specific cytotoxic T lymphocytes (CTLs). Blood 2006;108:2942-2949. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16835376.

86. Swinnen LJ. Diagnosis and treatment of transplant-related lymphoma. Ann Oncol 2000;11 Suppl 1:45-48. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10707778.