National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

B-Cell Lymphomas

NCCN Evidence Blocks™

Version 6.2019 — November 26, 2019

NCCN Evidence Blocks™

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*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

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

Paolo F. 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 Rogel 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 National Medical 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

Kenneth B. Roberts, MD §
Yale Cancer Center/Smilow Cancer Hospital

*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

Jakub Svoboda, MD ‡
Abramson Cancer Center at the University of Pennsylvania

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

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

NCCN Guidelines Panel Disclosures

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

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

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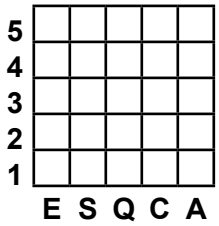
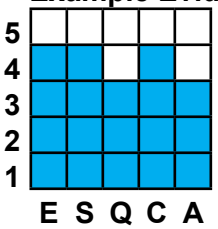
NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Example Evidence Block



E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	**Highly effective:** Cure likely and often provides long-term survival advantage
4	**Very effective:** Cure unlikely but sometimes provides long-term survival advantage
3	**Moderately effective:** Modest impact on survival, but often provides control of disease
2	**Minimally effective:** No, or unknown impact on survival, but sometimes provides control of disease
1	**Palliative:** Provides symptomatic benefit only

Safety of Regimen/Agent

5	**Usually no meaningful toxicity:** Uncommon or minimal toxicities; no interference with activities of daily living (ADLs)
4	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only; little interference with ADLs
3	**Mildly toxic:** Mild toxicity that interferes with ADLs
2	**Moderately toxic:** Significant toxicities often occur but life threatening/fatal toxicity is uncommon; interference with ADLs is frequent
1	**Highly toxic:** Significant toxicities or life threatening/fatal toxicity occurs often; interference with ADLs is usual and severe

Note: For significant chronic or long-term toxicities, score decreased by 1

Quality of Evidence

5	**High quality:** Multiple well-designed randomized trials and/or meta-analyses
4	**Good quality:** One or more well-designed randomized trials
3	**Average quality:** Low quality randomized trial(s) or well-designed non-randomized trial(s)
2	**Low quality:** Case reports or extensive clinical experience
1	**Poor quality:** Little or no evidence

Consistency of Evidence

5	**Highly consistent:** Multiple trials with similar outcomes
4	**Mainly consistent:** Multiple trials with some variability in outcome
3	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome
2	**Inconsistent:** Meaningful differences in direction of outcome between quality trials
1	**Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	**Very inexpensive**
4	**Inexpensive**
3	**Moderately expensive**
2	**Expensive**
1	**Very expensive**

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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 (multiple biopsies preferred) and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry [IHC], flow cytometry, PCR for *IGHV* and *TCR* gene rearrangements, karyotype, and FISH for major translocations[a]) 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

[a]If a high suspicion of a clonal process remains and other techniques have not resulted in a clear identification of a clonal process, then next-generation sequencing (NGS) can be used.

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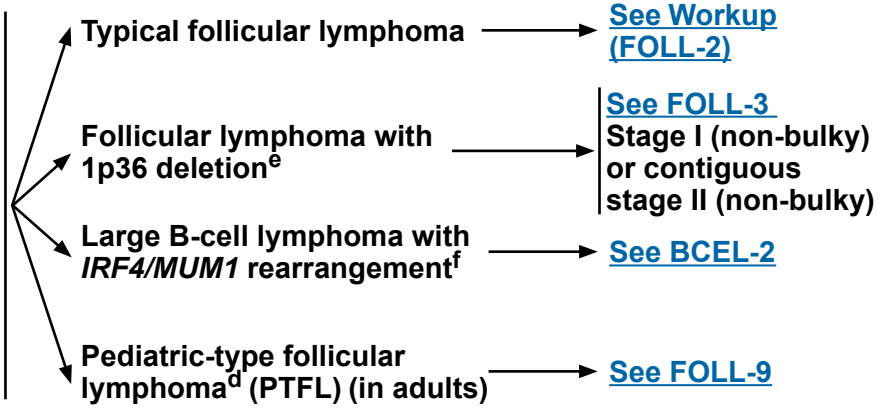
ADDITIONAL DIAGNOSTIC TESTING[a]

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 an 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.

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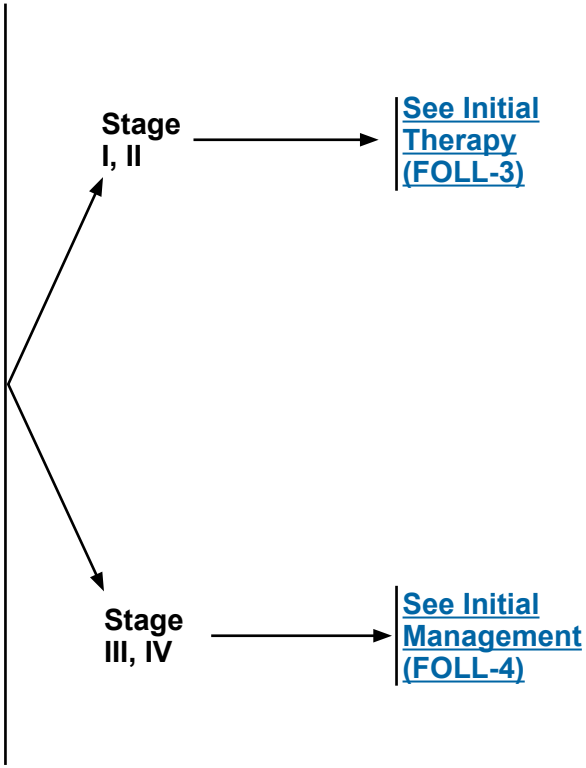
WORKUP[a]

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 an 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]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.

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Follicular Lymphoma (grade 1-2)
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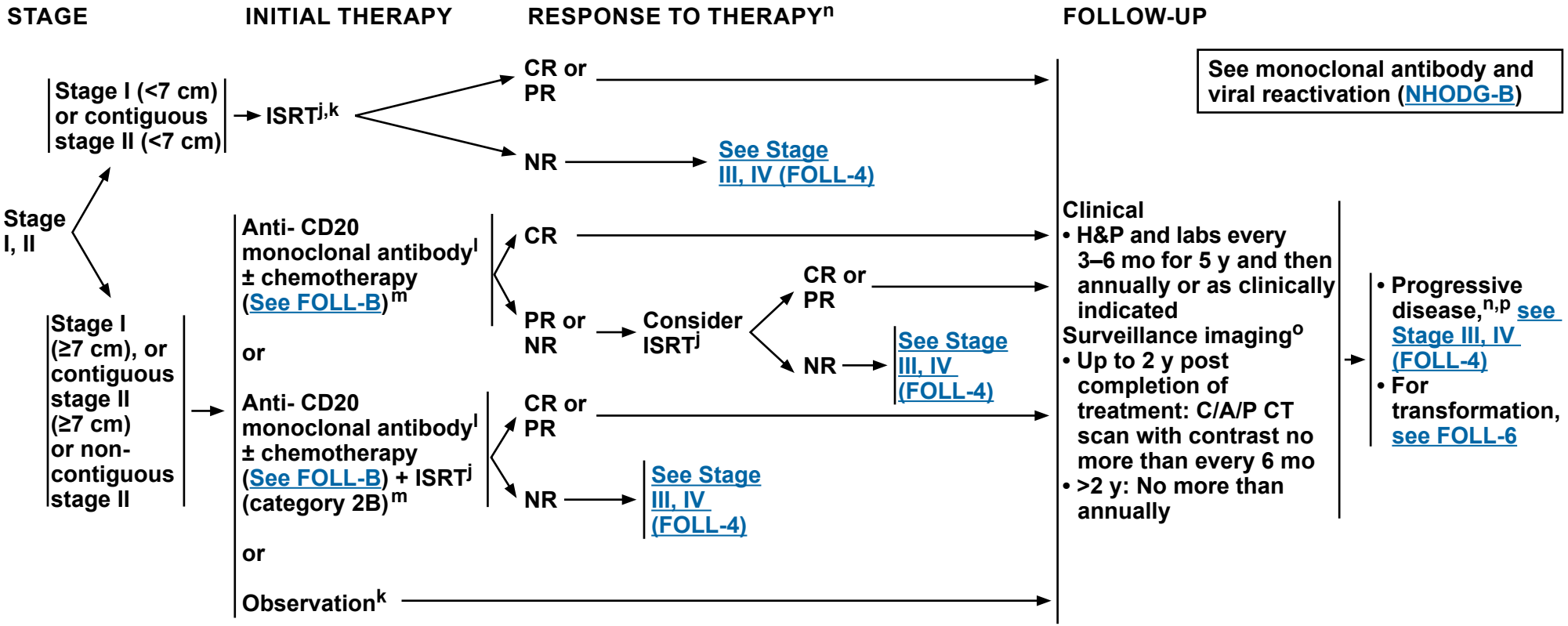

[j] See Principles of Radiation Therapy (NHODG-D).

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

[l] Anti-CD20 monoclonal antibodies include rituximab or obinutuzumab. Obinutuzumab is not indicated as single-agent therapy.

[m] 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.

[n] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C). PET/CT scan should be interpreted via the PET Five Point Scale (5-PS).

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

[p] 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).

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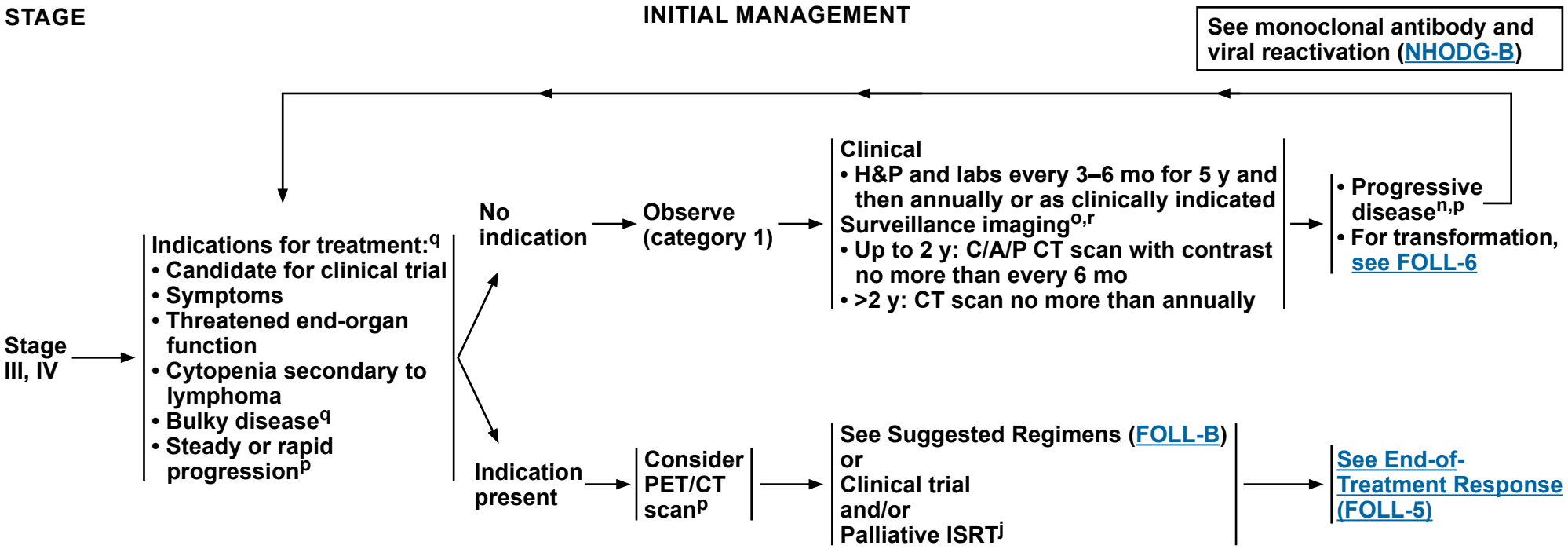

[j] See Principles of Radiation Therapy (NHODG-D).
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[q] See GELF criteria (FOLL-A).
[r] When disease (eg, bone) is only imaged on PET/CT scan, it is appropriate to be used in follow-up.

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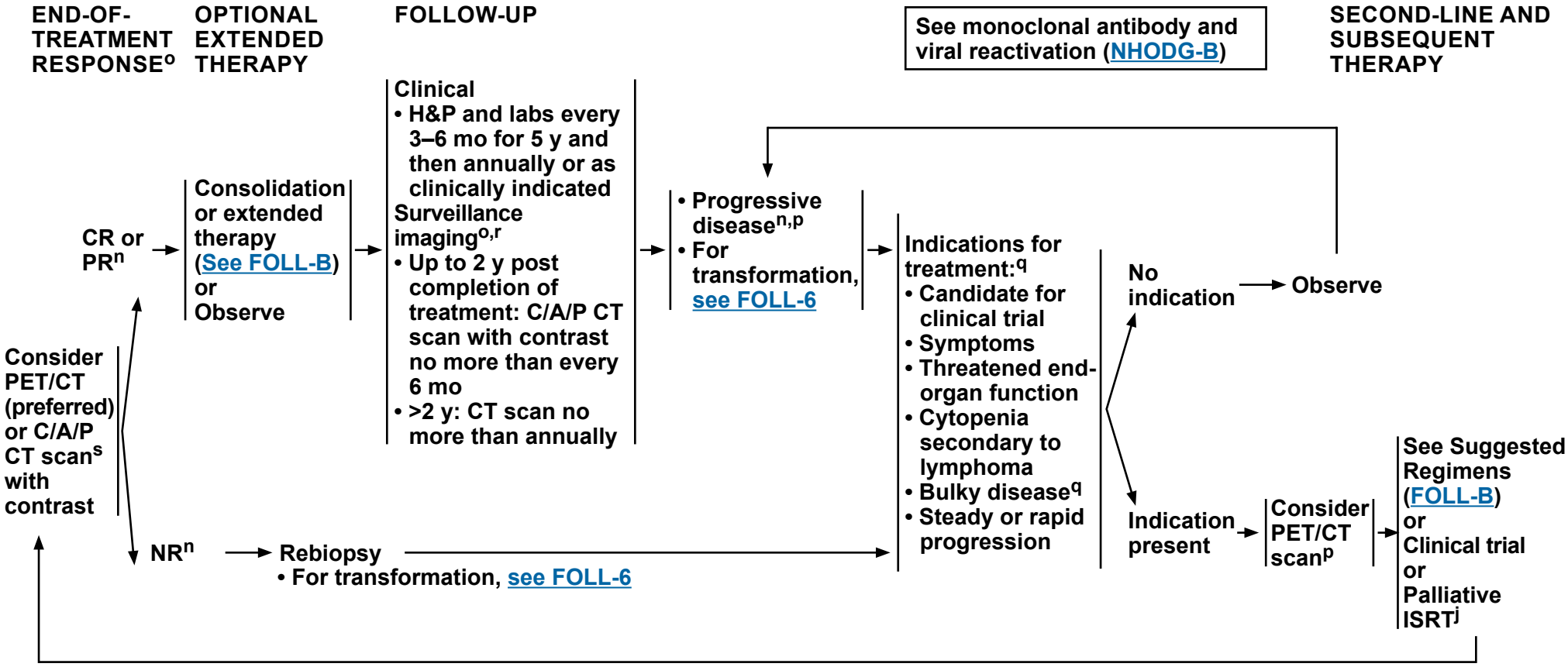

[j] See Principles of Radiation Therapy (NHODG-D).

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

[r] When disease (eg, bone) is only imaged on PET/CT scan, it is appropriate to be used in follow-up.

[s] 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.

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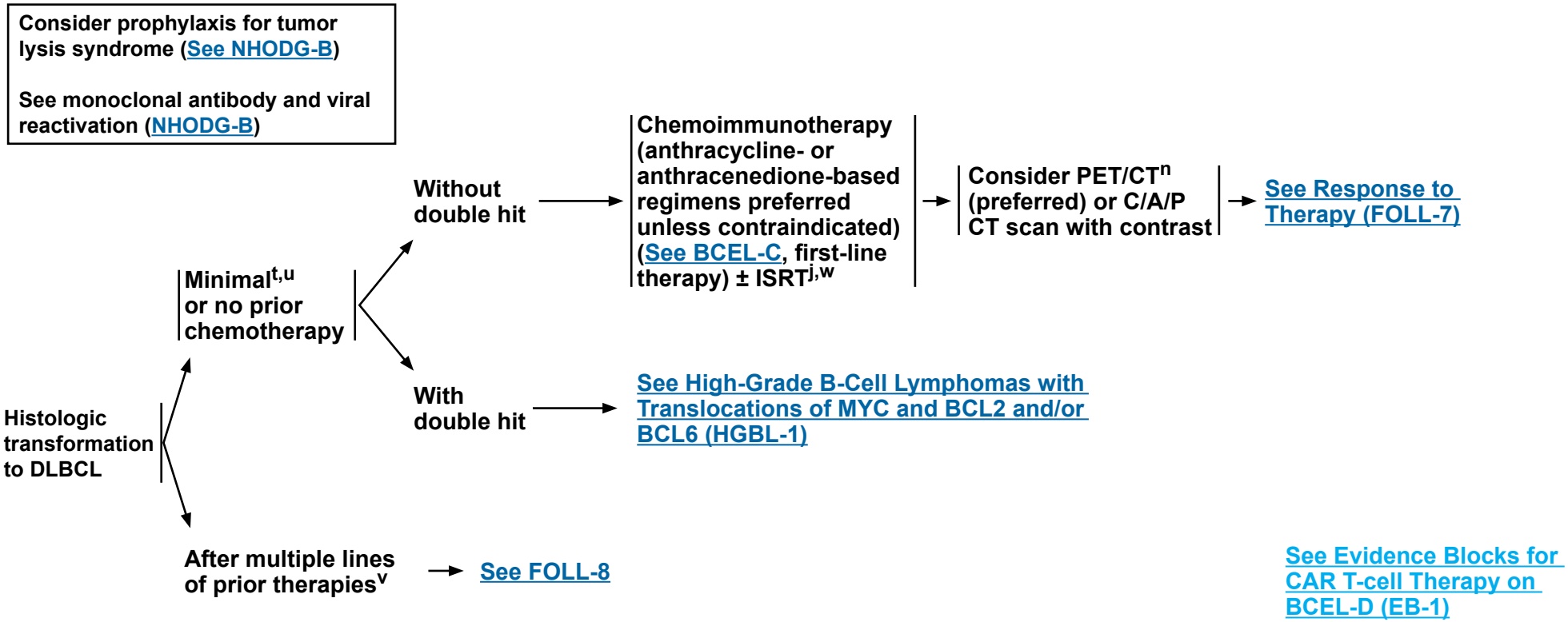
HISTOLOGIC TRANSFORMATION TO DIFFUSE LARGE B-CELL LYMPHOMA

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

See monoclonal antibody and viral reactivation (NHODG-B)



See Evidence Blocks for CAR T-cell Therapy on BCEL-D (EB-1)

[j] See Principles of Radiation Therapy (NHODG-D).
[n] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C). PET/CT scan should be interpreted via the PET Five Point Scale (5-PS).
[t] FISH for BCL2 rearrangement [t(14;18)], and *MYC* rearrangements [t(8;14) or variants, t(8;22), t(2;8)].
[u] ISRT alone or one course of single-agent therapy including rituximab.
[v] This includes ≥2 of chemoimmunotherapy regimens for indolent or transformed disease. For example, prior treatment with BR and RCHOP.
[w] Consider ISRT for localized presentations, bulky disease, and/or limited osseous disease.

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

RESPONSE TO THERAPY

CR[n,x] →
- Observation
- or
- Clinical trial
- or
- High-dose therapy with autologous stem cell rescue (HDT/ASCR) or allogeneic hematopoietic cell transplant (HCT) in selected cases ± ISRT if not previously given[j,w]

PR[n,y,z] →
- HDT/ASCR[y] or allogeneic HCT in selected cases[y] ± ISRT if not previously given[j,w]
- or
- Axicabtagene ciloleucel or tisagenlecleucel (only after ≥2 prior chemoimmunotherapy regimens)[aa,bb]
- 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[n] →
- Clinical trial
- or
- Ibritumomab tiuxetan or Second-line therapy (See BCEL-C)
- or
- Axicabtagene ciloleucel or tisagenlecleucel (only after ≥2 prior chemoimmunotherapy regimens)[aa,bb]
- or
- Best supportive care

Relapsed or progressive disease[n] → **Biopsy[z]** → See Histologic Transformation to DLBCL After Multiple Prior Therapies (FOLL-8)

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

See Evidence Blocks for CAR T-cell Therapy on BCEL-D (EB-1)

[j] See Principles of Radiation Therapy (NHODG-D).
[n] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C). PET/CT scan should be interpreted via the PET Five Point Scale (5-PS).
[t] FISH for BCL2 rearrangement [t(14;18)], and *MYC* rearrangements [t(8;14) or variants, t(8;22), t(2;8)].
[u] ISRT alone or one course of single-agent therapy including rituximab.
[w] Consider ISRT for localized presentations, bulky disease, and/or limited osseous disease.
[x] If transformation is co-existing with extensive FL, consider maintenance (see FOLL-5, Optional Extended Therapy).
[y] If proceeding to transplant, consider additional systemic therapy ± ISRT to induce CR prior to transplant. Axicabtagene ciloleucel or tisagenlecleucel are not appropriate treatment options for patients with a CR.
[z] Repeat biopsy should be strongly considered if PET-positive prior to additional therapy because PET positivity may represent post-treatment inflammation. Patients with a durable response for transformed disease may recur with the original indolent lymphoma. In that case, the management should be as per FOLL-5. If biopsy negative, follow CR pathway.
[aa] See Guidance for Treatment of Patients with Chimeric Antigen Receptor (CAR) T-Cell Therapy (BCEL-D).
[bb] Patients should have received at least one anthracycline or anthracenedione-based regimen, unless contraindicated.

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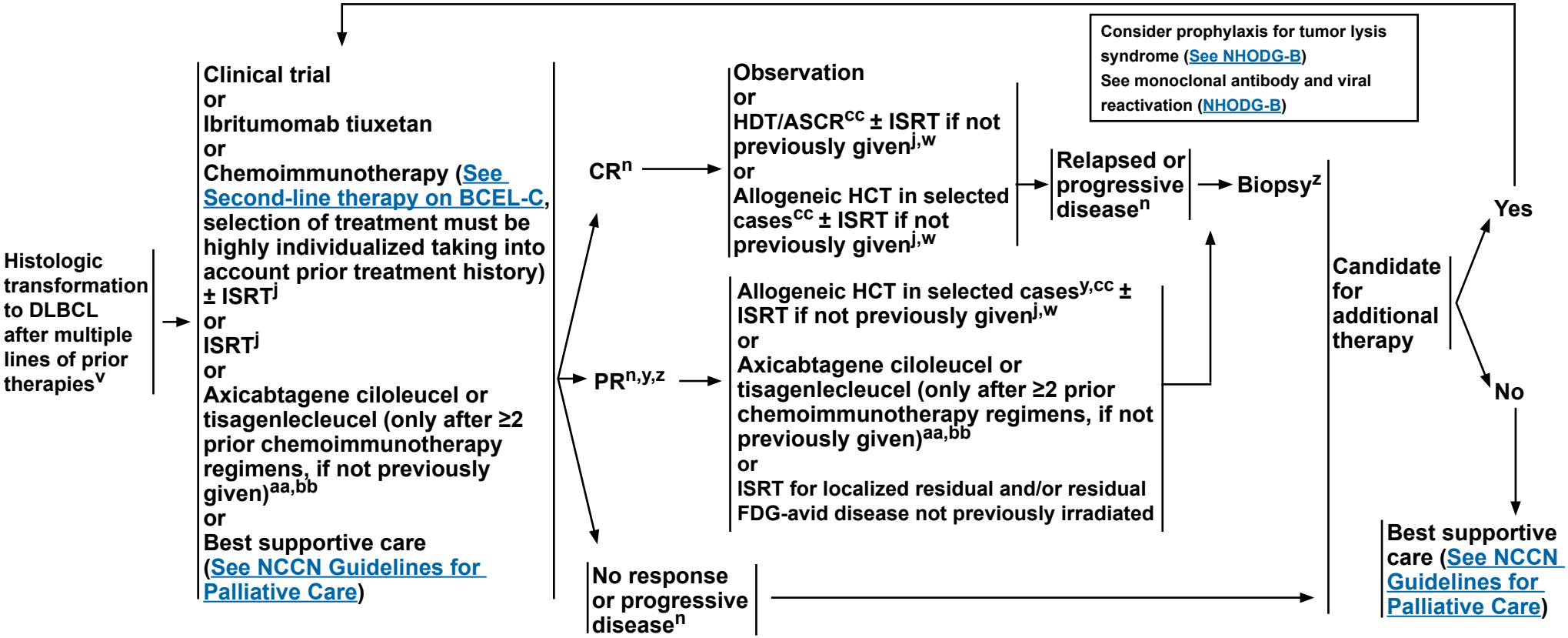
HISTOLOGIC TRANSFORMATION TO DIFFUSE LARGE B-CELL LYMPHOMA



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

[n] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C). PET/CT scan should be interpreted via the PET Five Point Scale (5-PS).

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

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

[y] If proceeding to transplant, consider additional systemic therapy ± ISRT to induce CR prior to transplant. Axicabtagene ciloleucel or tisagenlecleucel are not appropriate treatment options for patients with a CR.

[z] Repeat biopsy should be strongly considered if PET-positive prior to additional therapy because PET positivity may represent post-treatment inflammation. Patients with a durable response for transformed disease may recur with the original indolent lymphoma. In that case, the management should be as per FOLL-5. If biopsy negative, follow CR pathway.

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

[bb] Patients should have received at least one anthracycline or anthracenedione-based regimen, unless contraindicated.

[cc] Data on transplant after treatment with axicabtagene ciloleucel or tisagenlecleucel are not available. HDT/ASCR is not recommended after axicabtagene ciloleucel. Allogeneic HCT could be considered but remains investigational.

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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,ee]

- **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[ff]**

or

ISRT[j]

or

RCHOP for patients with extensive local disease who are not candidates for excision or ISRT

→ **Restage with PET/CT**

- **CR[n]** → **Observe[ff]**
- **<CR** → **See FOLL-5, Progressive disease**

[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.

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

[n] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C). PET/CT scan should be interpreted via the PET Five Point Scale (5-PS).

[ee] 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.

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

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NCCN Guidelines Version 6.2019
Follicular Lymphoma (grade 1-2)
NCCN Evidence Blocks™

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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)

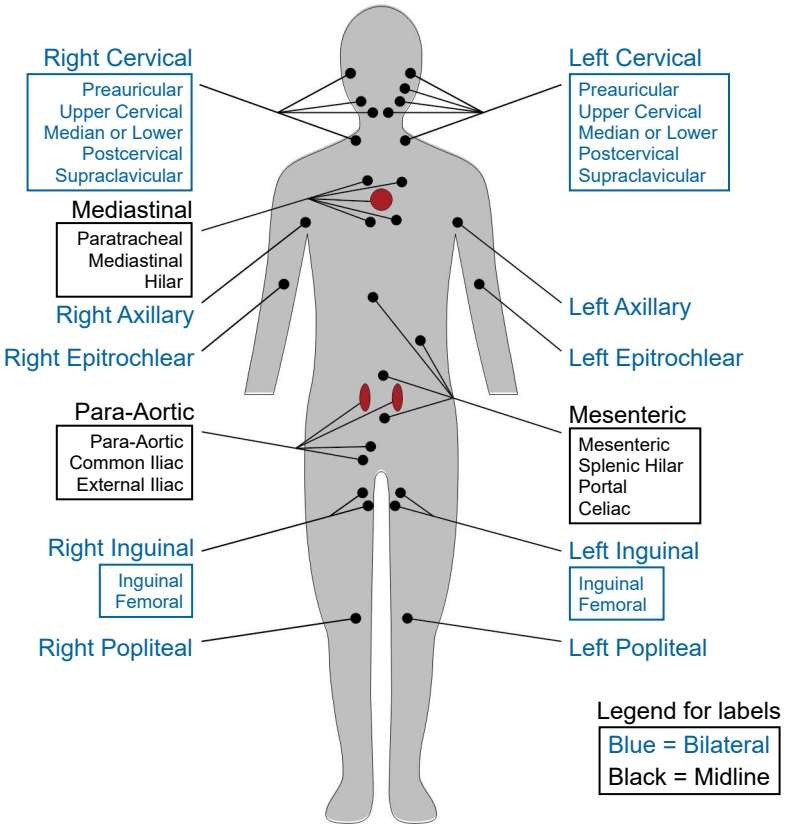
FLIPI - 1 CRITERIA[a,c,d]

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]

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[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.

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NCCN Guidelines Version 6.2019
Follicular Lymphoma (grade 1-2)
NCCN Evidence Blocks™

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Discussion

SUGGESTED TREATMENT REGIMENS[a,b,c]

An FDA-approved biosimilar is an appropriate substitute for rituximab.

See Evidence Blocks on FOLL-B (EB-1)

First-line Therapy

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

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

See Evidence Blocks on FOLL-B (EB-2)

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

First-line Consolidation or Extended Dosing (optional)

- **Rituximab maintenance 375 mg/m² one dose every 8 weeks 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)**

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 on 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 NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections. 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 the 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.

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EVIDENCE BLOCKS FOR FIRST-LINE THERAPY

Preferred Regimens (in alphabetical order)	Stage I-II	Stage III-IV
Bendamustine/obinutuzumab		
Bendamustine/obinutuzumab/ISRT		—
Bendamustine/rituximab		
Bendamustine/rituximab/ISRT		—
CHOP/obinutuzumab		
CHOP/obinutuzumab/ISRT		—
CHOP/rituximab		
CHOP/rituximab/ISRT		—
CVP/obinutuzumab		
CVP/obinutuzumab/ISRT		—
CVP/rituximab		
CVP/rituximab/ISRT		—
Lenalidomide/rituximab		
Lenalidomide/rituximab/ISRT		—

Other Recommended Regimens (in alphabetical order)	Stage I-II	Stage III-IV
Rituximab (for low tumor burden)		
Rituximab/ISRT (for low tumor burden)		—

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EVIDENCE BLOCKS FOR FIRST-LINE THERAPY FOR THE ELDERLY OR INFIRM AND FIRST-LINE CONSOLIDATION THERAPY

First-Line Therapy (Elderly or Infirm)		
	Stage I-II	Stage III-IV
Rituximab		
Rituximab/ISRT		—
Chlorambucil/rituximab		
Chlorambucil/rituximab/ISRT		—
Cyclophosphamide/rituximab		
Cyclophosphamide/rituximab/ISRT		—
Chlorambucil		
Chlorambucil/ISRT		—
Cyclophosphamide		
Cyclophosphamide/ISRT		—
Ibritumomab tiuxetan		

First-Line Consolidation or Extended Dosing	
Rituximab maintenance (375 mg/m^2 one dose every 8 weeks for 12 doses)	
Obinutuzumab maintenance	
Rituximab maintenance (375 mg/m^2 one dose every 8 weeks for 4 doses)	
Ibritumomab tiuxetan	

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SUGGESTED TREATMENT REGIMENS[a,b,c]
(in preference order)
An FDA-approved biosimilar is an appropriate substitute for rituximab.

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]**
  - **PI3K inhibitors (relapsed/refractory after 2 prior therapies)**
    - ◊ **Idelalisib[n]**
    - ◊ **Copanlisib[n]**
    - ◊ **Duvelisib[n]**
  - **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)

See Evidence Blocks on FOLL-B (EB-3)

[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 NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

[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).

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EVIDENCE BLOCKS FOR SECOND-LINE AND SECOND-LINE CONSOLIDATION THERAPY

Second-Line and Subsequent Therapy	
Preferred Regimens	
Bendamustine/obinutuzumab	
Bendamustine/rituximab	
CHOP/obinutuzumab	
RCHOP	
CVP/obinutuzumab	
RCVP	
Rituximab	
Lenalidomide/rituximab	
Lenalidomide	
Other Recommended Regimens	
Ibritumomab tiuxetan	
Idelalisib	
Copanlisib	
Duvelisib	

Second-Line and Subsequent Therapy (Elderly or Infirm)	
Rituximab (375 mg/m^2 weekly for 4 doses)	
Chlorambucil/rituximab	
Cyclophosphamide/rituximab	
Chlorambucil	
Cyclophosphamide	
Ibritumomab tiuxetan	

Second-Line Consolidation or Extended Dosing	
Rituximab maintenance (375 mg/m^2 one dose every 12 wks for 2 years)	
Obinutuzumab maintenance for rituximab-refractory disease (1 g every 8 wks for total of 12 doses)	

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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 2017;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 2017;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 2017;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.

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First-line Consolidation or Extended Dosing

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Obinutuzimab-based chemoimmunotherapy followed by obinutuzumab maintenance

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Continued

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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 2016;17:1081-1093.

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Rituximab

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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.**CAR T-Cell Therapy**

Axicabtagene ciloleucel

Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med 2017;377:2531-2544.

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Second-line Consolidation or Extended Dosing

Rituximab maintenance

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Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

- **Gastric** → See Diagnosis and Workup (MALT-1)
- **Nongastric/ Noncutaneous** → See Diagnosis and Workup (NGMLT-1)
- **Cutaneous** → See Primary Cutaneous Marginal Zone Lymphoma in NCCN Guidelines for Primary Cutaneous B-Cell Lymphomas

Nodal marginal zone lymphoma → See Diagnosis and Workup (NODE-1)

Splenic marginal zone lymphoma → See Diagnosis and Workup (SPLN-1)

Histologic transformation of marginal zone lymphoma to diffuse large B-cell lymphoma → See NODE-5

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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.

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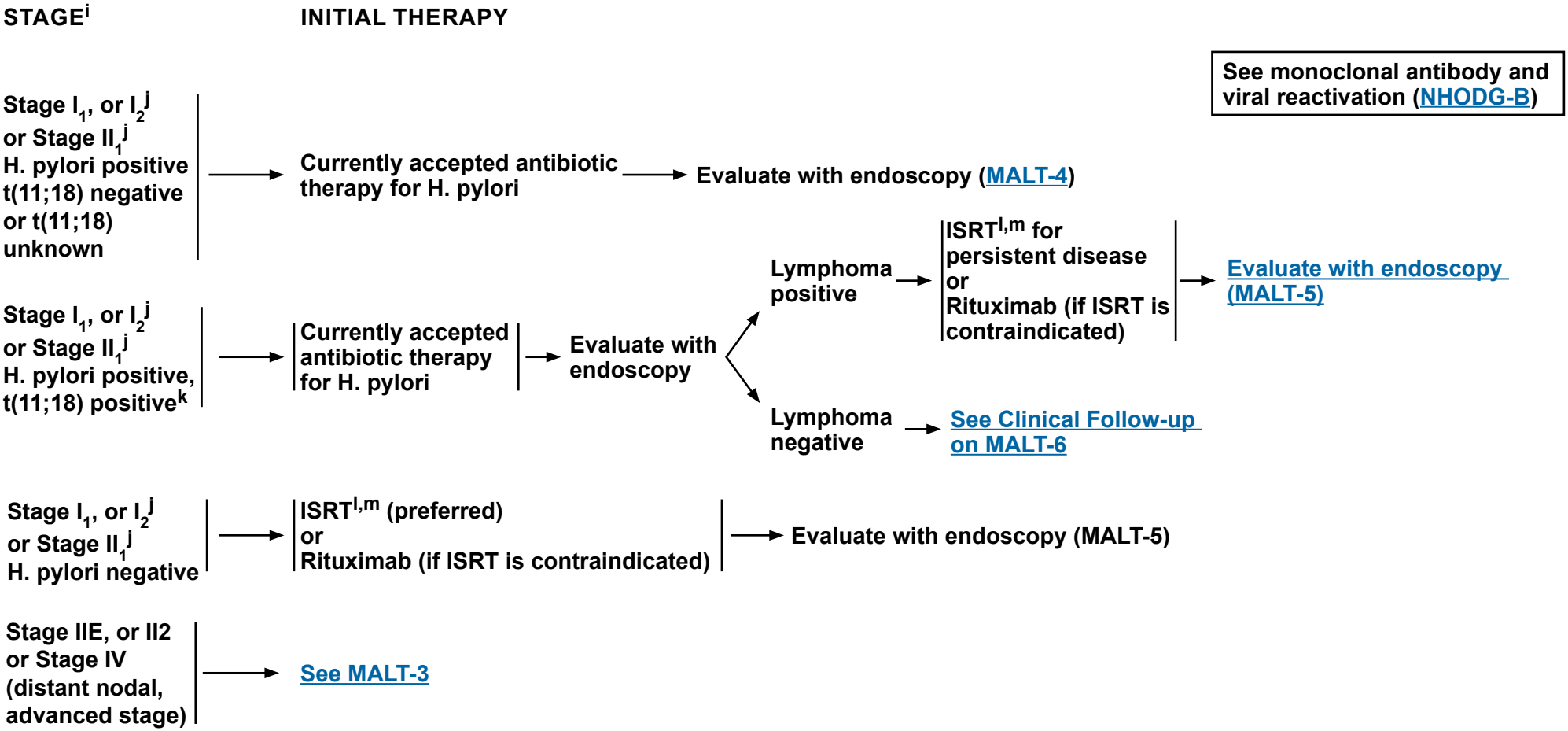

[i]See Lugano Staging System for Gastrointestinal Lymphomas (MALT-A).
[j]Involvement of submucosa or regional lymph nodes are much less likely to respond to antibiotic therapy. If there is persistent disease after evaluation, RT may be considered earlier in the course.
[k]t(11;18) is a predictor for 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).

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STAGE[i] | **INITIAL THERAPY**

See monoclonal antibody and viral reactivation (NHODG-B)

Stage IIE, or II_2 or Stage IV (distant nodal, advanced stage) →

Indications for treatment:
- **Candidate for clinical trial[n]**
- **Symptoms**
- **GI bleeding**
- **Threatened end-organ function**
- **Bulky disease**
- **Steady or rapid progression**
- **Patient preference**

No indication → **Observe**

Indication present[o] → **First-line Therapy for Marginal Zone Lymphomas (MZL-A 1 of 3)** or **Palliative ISRT[m]** → **Evaluate with endoscopy, if evidence of recurrence, see Second-line and Subsequent Therapy for Marginal Zone Lymphomas (MZL-A 2 of 3)**

Gastric MALT lymphomas with concurrent large cell transformation → **Manage per NCCN Guidelines for Diffuse Large B-Cell Lymphoma (BCEL-1)**

[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).

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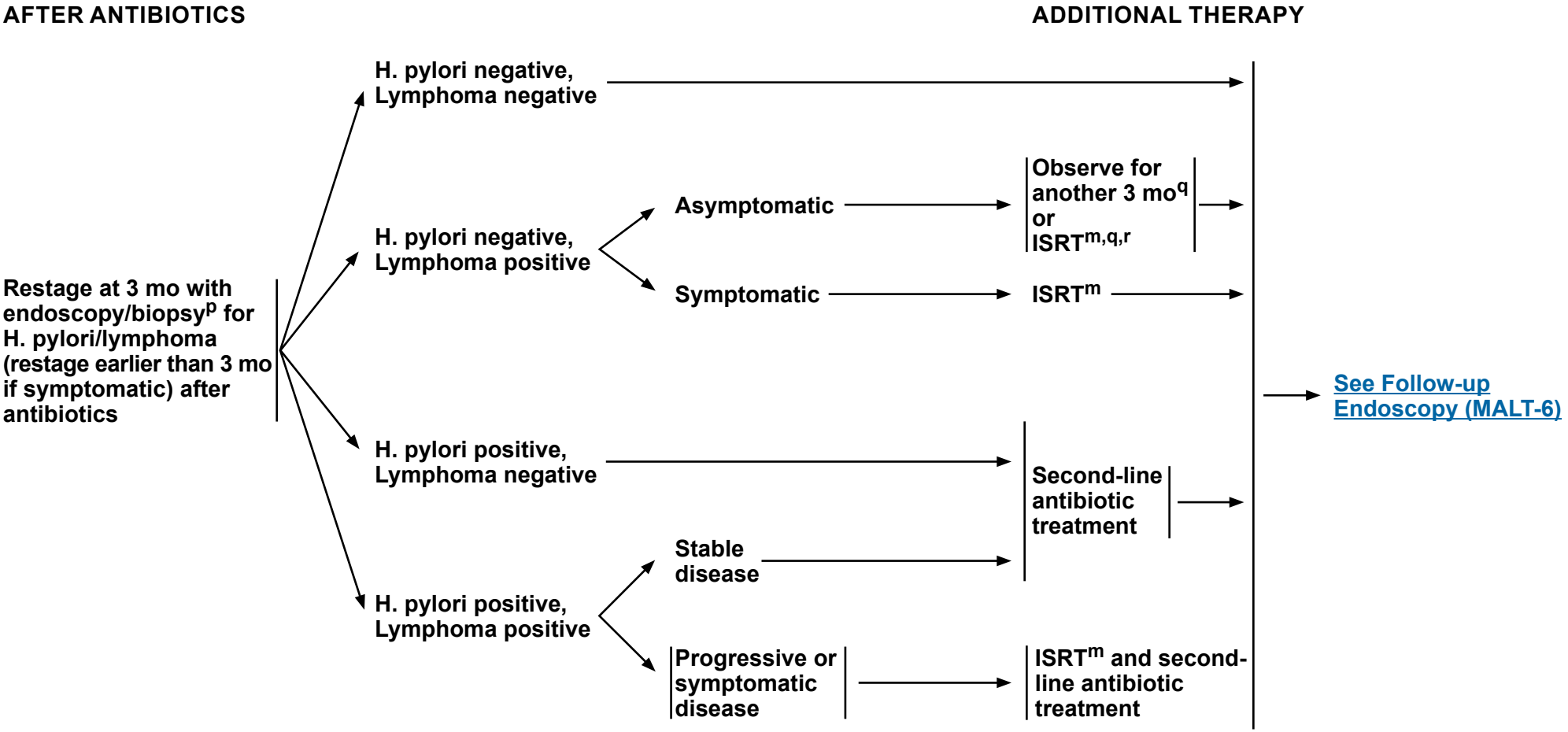
3-MONTH RESTAGING AND FOLLOW-UP ENDOSCOPY



[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).
[q] If re-evaluation suggests slowly responding disease or asymptomatic nonprogression, continued observation may be warranted. Complete responses may be observed as early as 3 months after antibiotic treatment but can take longer to achieve (up to 18 months) (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.

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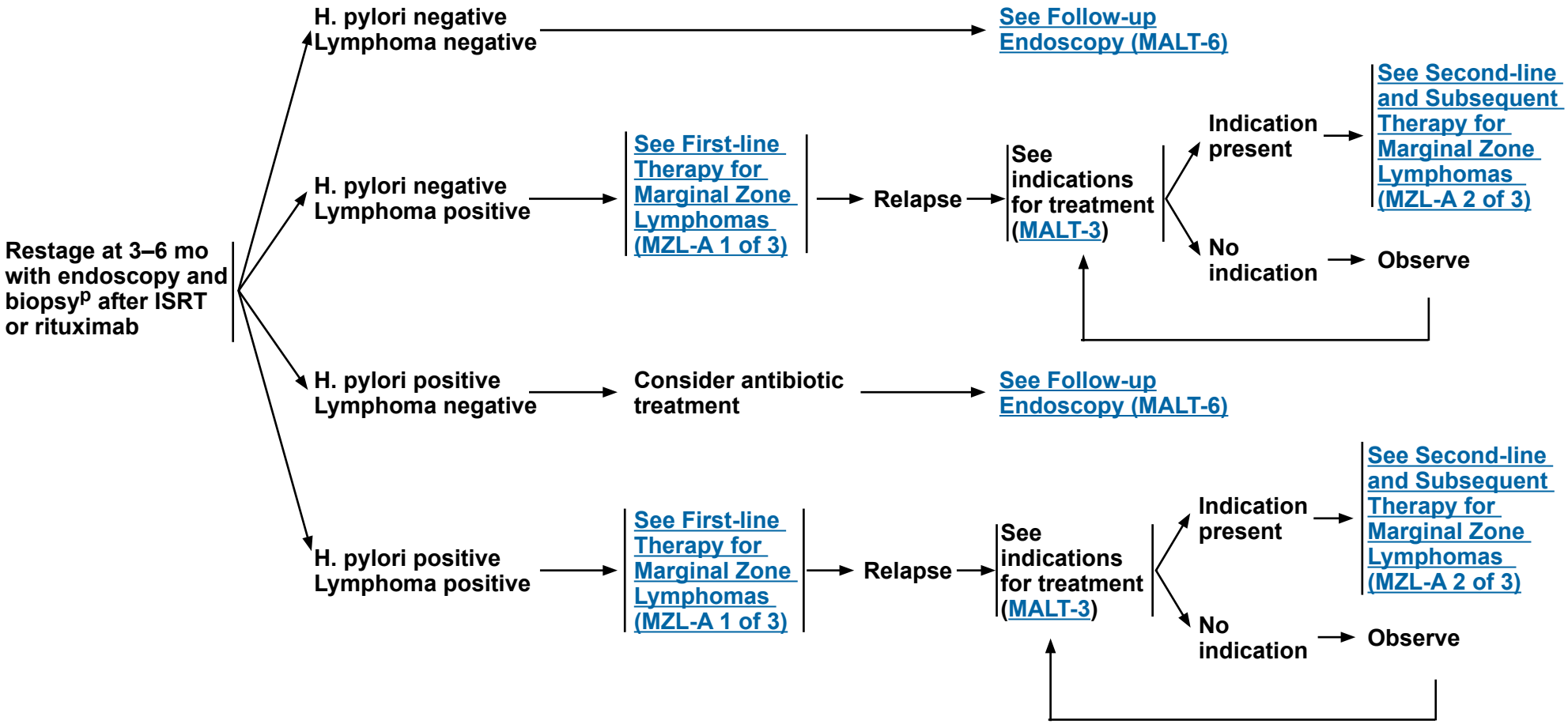
3- TO 6-MONTH RESTAGING AND FOLLOW-UP ENDOSCOPY

AFTER ISRT 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).

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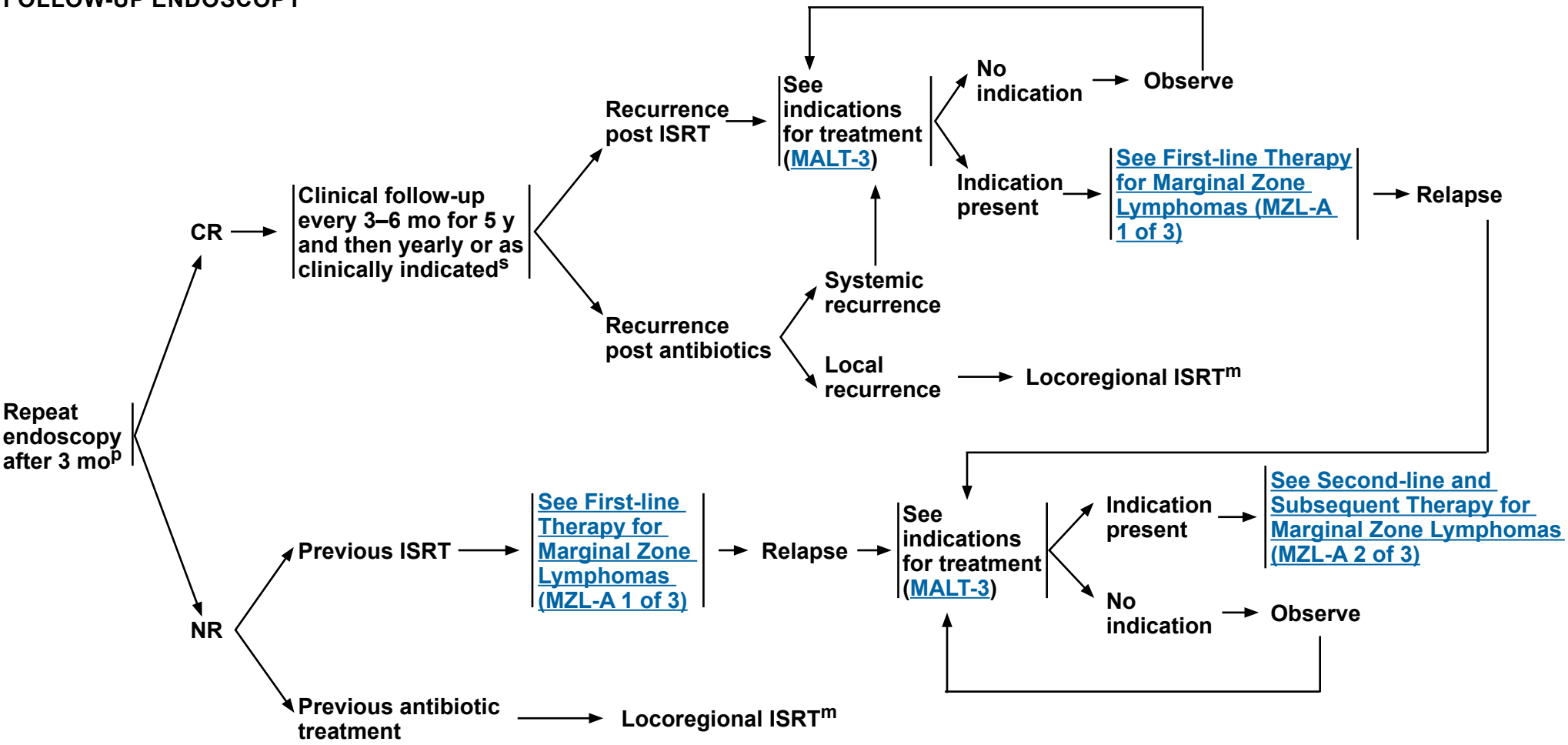
FOLLOW-UP ENDOSCOPY



[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.

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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.

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ADDITIONAL DIAGNOSTIC TESTING[a,b]

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 neurologic 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.

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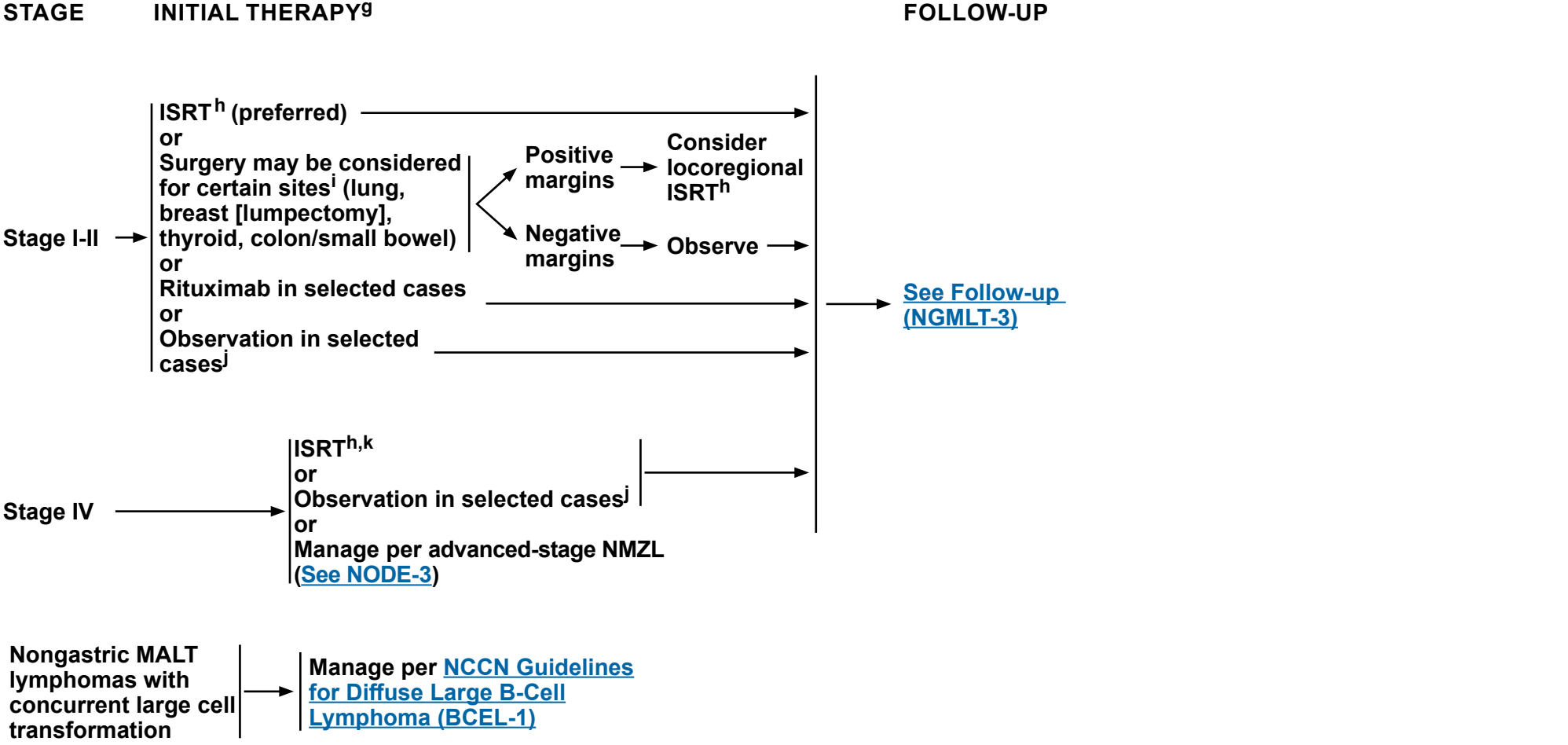

[g]Based on anecdotal responses to antibiotics in ocular and cutaneous marginal zone lymphomas, some physicians will give an empiric course of doxycycline prior to initiating other therapy.
[h]See Principles of Radiation Therapy (NHODG-D).
[i]Surgical excision for adequate diagnosis may be appropriate 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 without evidence of disease elsewhere) or palliative treatment of symptomatic sites.

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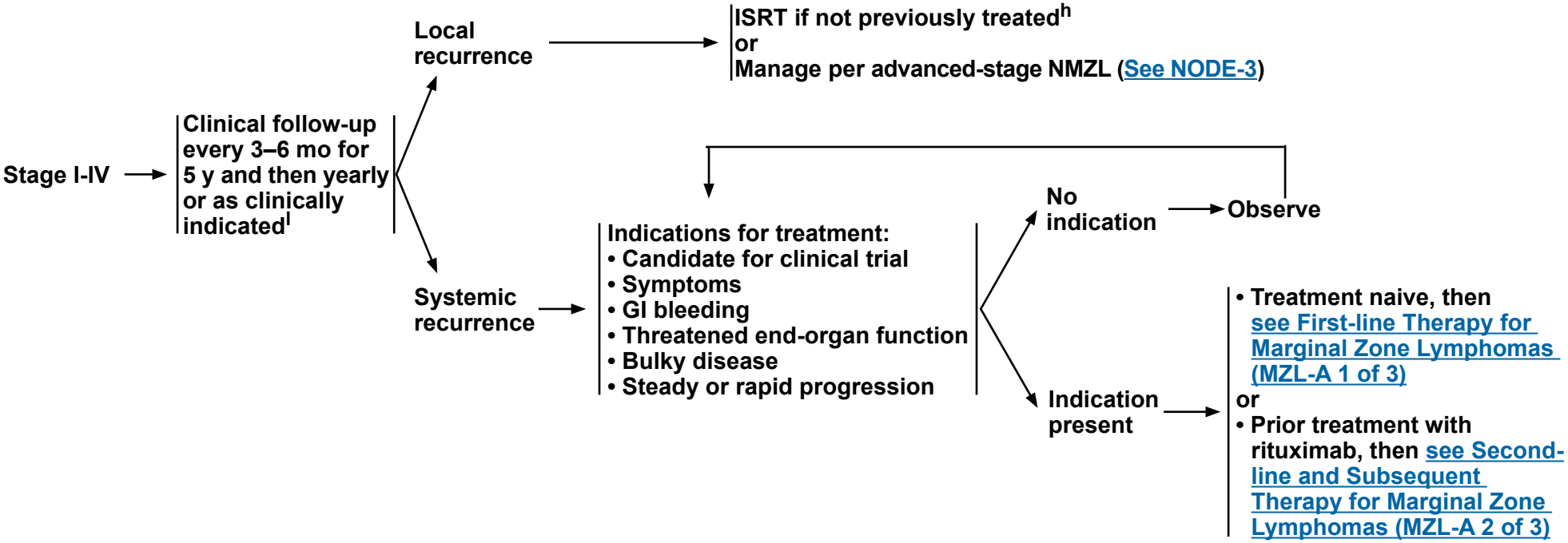
STAGE **FOLLOW-UP**



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

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NCCN Guidelines Version 6.2019
Nodal Marginal Zone Lymphoma
NCCN Evidence Blocks™

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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.

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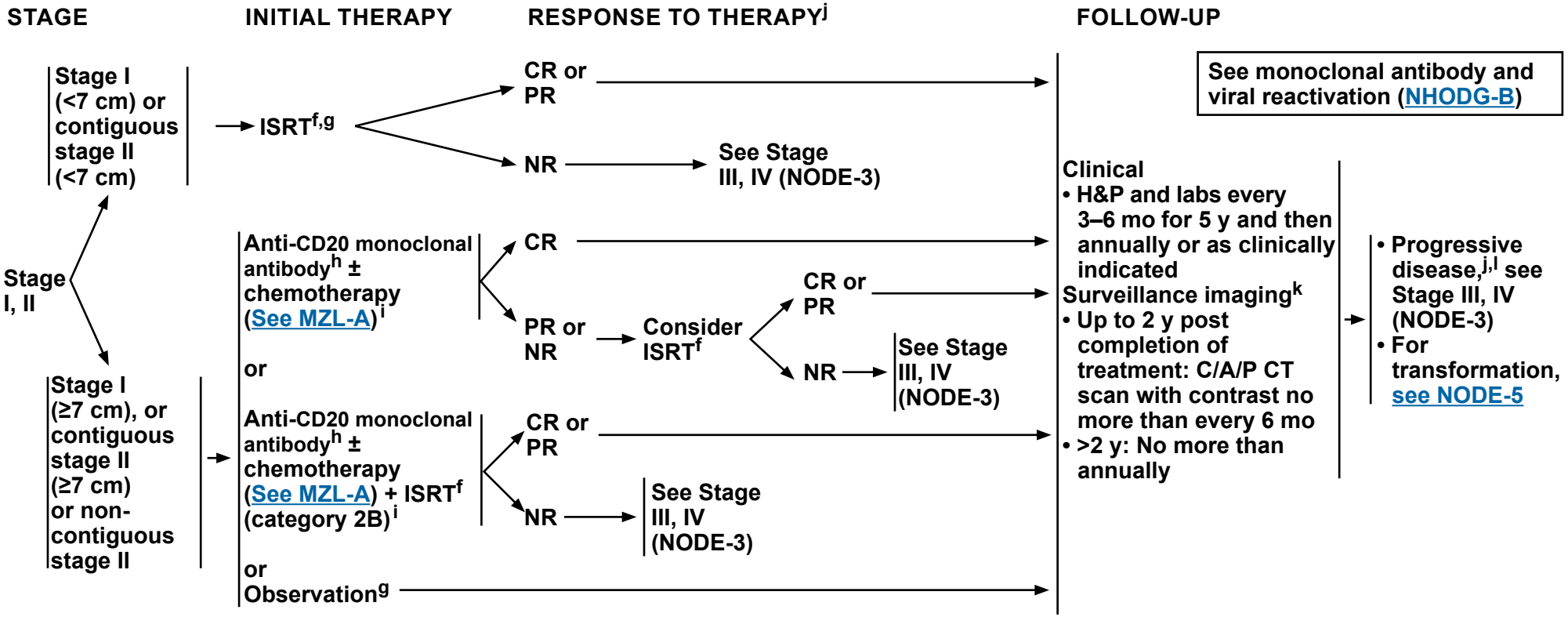

[f] See Principles of Radiation Therapy (NHODG-D).
[g] Observation may be appropriate in circumstances where potential toxicity of ISRT outweighs potential clinical benefit.
[h] Anti-CD20 monoclonal antibodies include rituximab or obinutuzumab. Obinutuzumab is not indicated as single-agent therapy.
[i] Initiation of chemotherapy or more extended RT can improve FFS, but has not been shown to improve overall survival. These are options for therapy.
[j] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[k] Imaging should be performed whenever there are clinical indications. For surveillance imaging, see Discussion for consensus imaging recommendations.
[l] 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).

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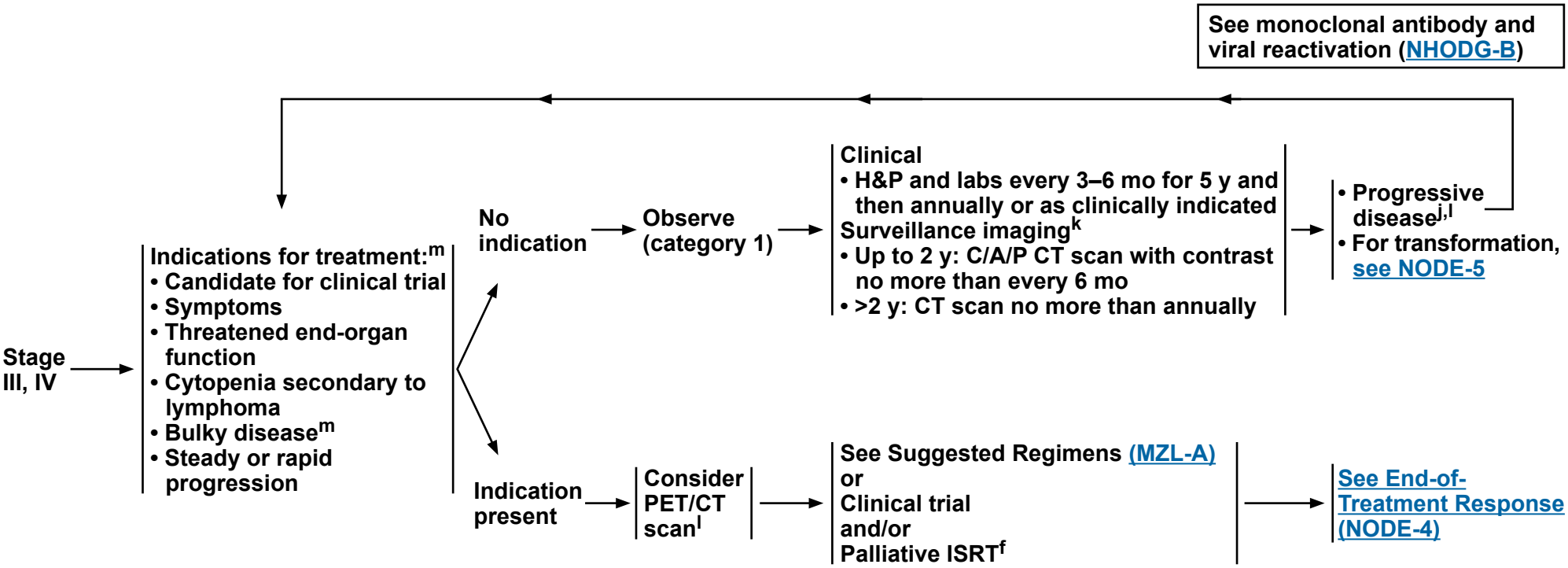

[f] See Principles of Radiation Therapy (NHODG-D).
[j] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[k] Imaging should be performed whenever there are clinical indications. For surveillance imaging, see Discussion for consensus imaging recommendations.
[l] Consider possibility of 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).
[m] See GELF criteria (FOLL-A).

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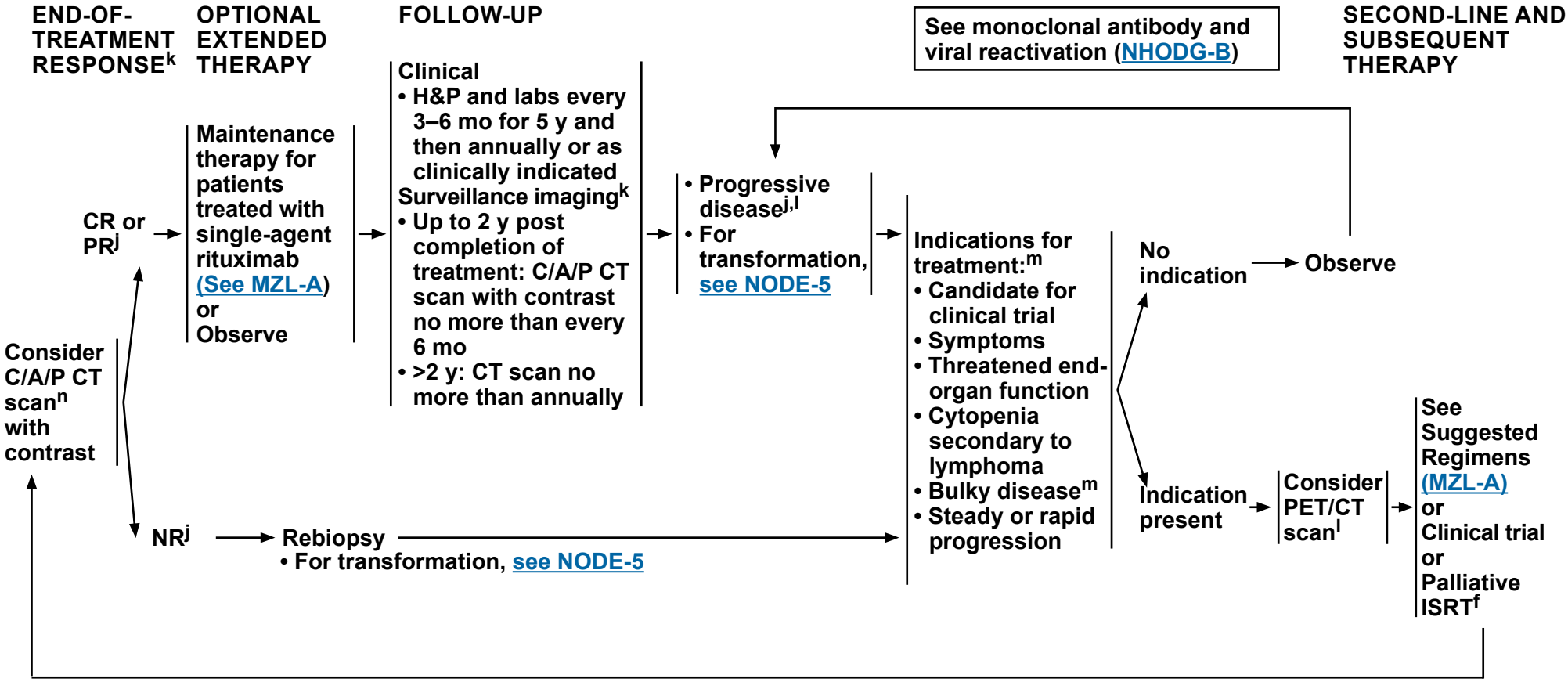

[f] See Principles of Radiation Therapy (NHODG-D).
[j] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[k] Imaging should be performed whenever there are clinical indications. For surveillance imaging, see Discussion for consensus imaging recommendations.
[l] Consider possibility of 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).
[m] See GELF criteria (FOLL-A).
[n] 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.

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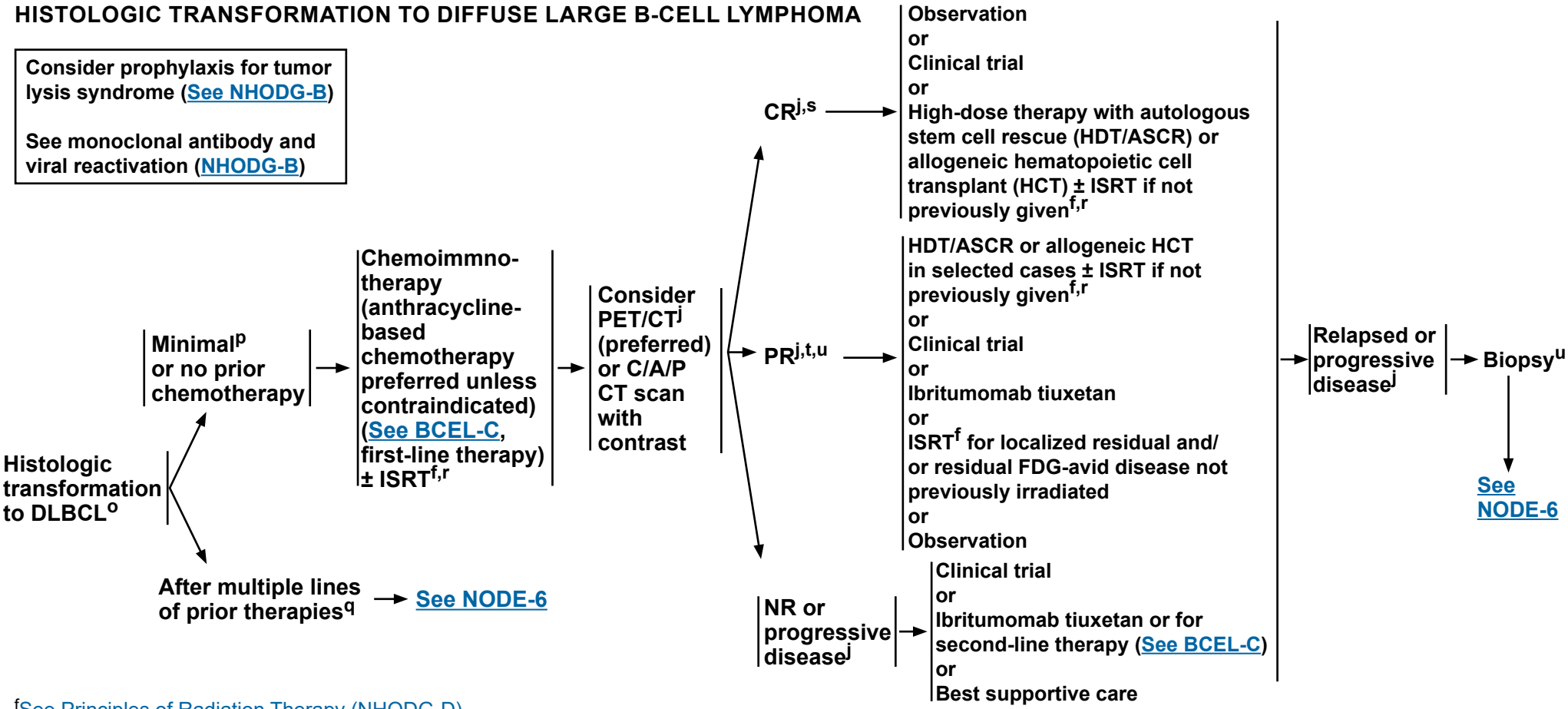
HISTOLOGIC TRANSFORMATION TO DIFFUSE LARGE B-CELL LYMPHOMA



[f]See Principles of Radiation Therapy (NHODG-D).
[j]See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C). PET/CT scan should be interpreted via the PET Five Point Scale (5-PS).
[o]FISH for *BCL6* rearrangement and *MYC* rearrangements.
[p]ISRT alone or one course of single-agent therapy including rituximab.
[q]This includes ≥2 of chemoimmunotherapy regimens for indolent or transformed disease. For example, prior treatment with BR and RCHOP.
[r]Consider ISRT for localized presentations, bulky disease, and/or limited osseous disease.
[s]If transformation is coexisting with extensive MZL, consider maintenance (see NODE-4, Optional Extended Therapy).
[t]If proceeding to an autologous stem cell rescue, consider additional systemic therapy ± ISRT to induce CR prior to transplant.
[u]Repeat biopsy should be strongly considered if PET-positive prior to additional therapy, because PET positivity may represent post-treatment inflammation. Patients with a durable response for transformed disease may recur with the original indolent lymphoma. In that case, the management should be as per NODE-4. If biopsy negative, follow CR pathway.

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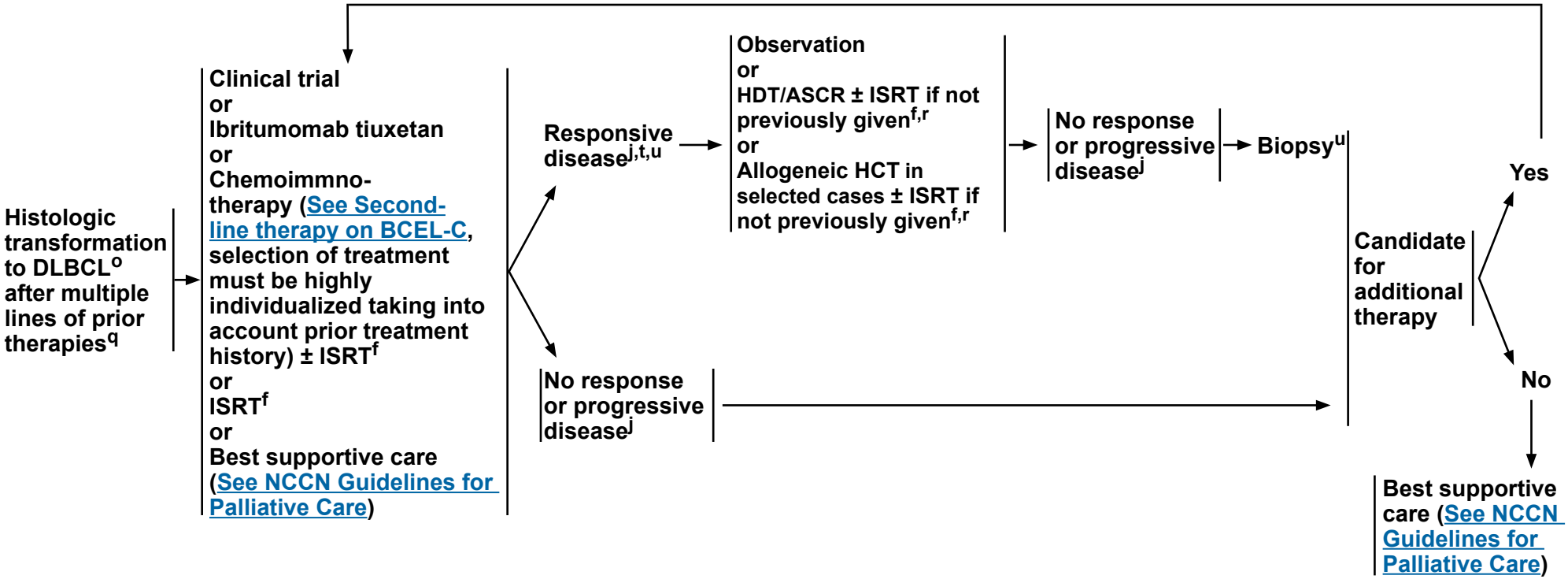
HISTOLOGIC TRANSFORMATION TO DIFFUSE LARGE B-CELL LYMPHOMA

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

See monoclonal antibody and viral reactivation (NHODG-B)



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

[j] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C). PET/CT scan should be interpreted via the PET Five Point Scale (5-PS).

[o] FISH for *BCL6* rearrangement and *MYC* rearrangements.

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

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

[t] If proceeding to an autologous stem cell rescue, consider additional systemic therapy ± ISRT to induce CR prior to transplant.

[u] Repeat biopsy should be strongly considered if PET-positive prior to additional therapy because PET positivity may represent post-treatment inflammation. Patients with a durable response for transformed disease may recur with the original indolent lymphoma. In that case, the management should be as per NODE-4. If biopsy negative, follow CR pathway.

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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, and 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.

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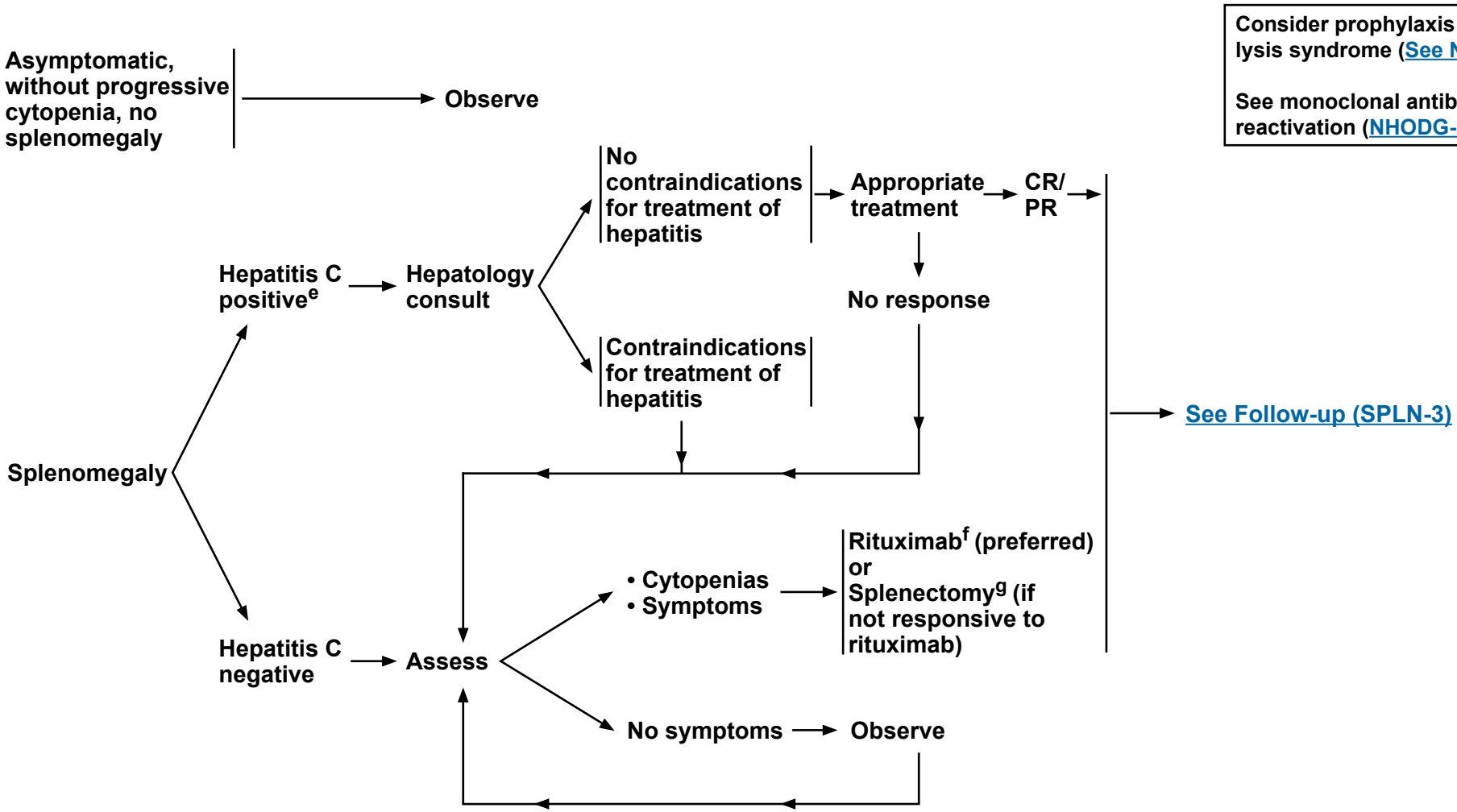

[e]If there is hepatic involvement and hepatitis C positive, treat with an appropriate regimen for hepatitis C.
[f]Tsimberidou AM, Catovsky D, Schlette E, et al. Outcomes in patients with splenic marginal zone lymphoma and marginal zone lymphoma treated with rituximab with or without chemotherapy or chemotherapy alone. Cancer 2006;107:125-135.
[g]Pneumococcal, meningococcal, and hepatitis B vaccinations should be given at least 2 weeks before splenectomy.

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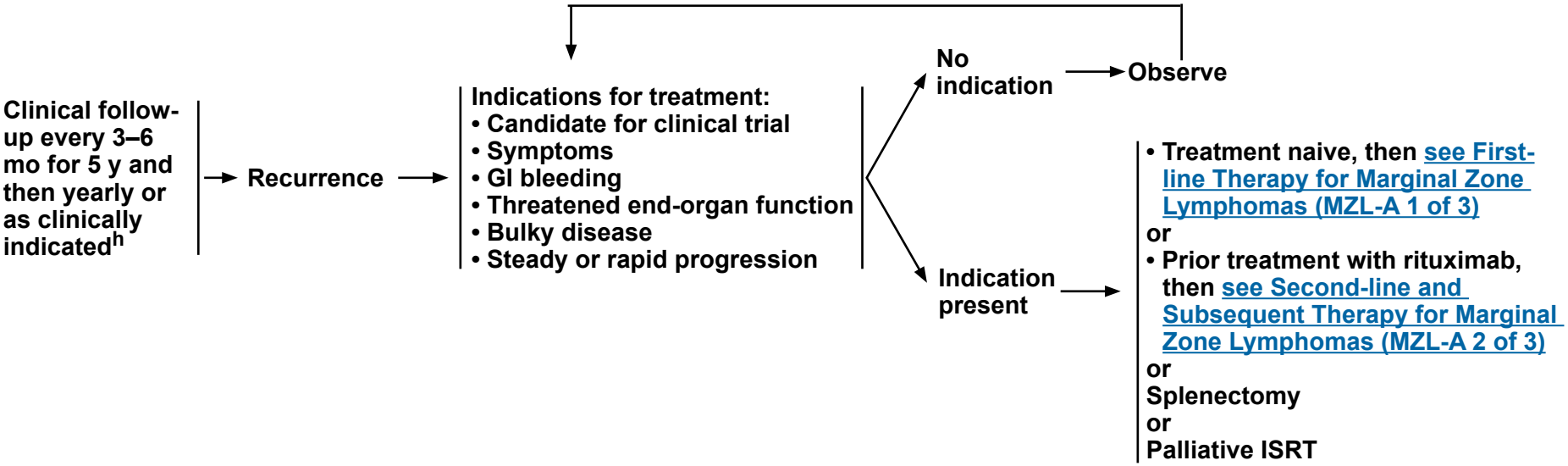
FOLLOW-UP



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

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SUGGESTED TREATMENT REGIMENS[a,b,c]
An FDA-approved biosimilar is an appropriate substitute for rituximab.

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

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.

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SUGGESTED TREATMENT REGIMENS[a,b,c]
(in preference order)
An FDA-approved biosimilar is an appropriate substitute for rituximab.

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
- PI3K inhibitors (relapsed/refractory after 2 prior therapies)
  - Copanlisib[f]
  - Duvelisib[f]
  - Idelalisib[f]
- 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 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 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).

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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 2017;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. Long-term results of a phase 2 study of rituximab and bendamustine for mucosa-associated lymphoid tissue lymphoma. Blood 2017;130:1772-1774.

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 2016;17:1081-1093.

Copanlisib

Dreyling M, Panayiotidis P, Egyed M, et al. Efficacy of copanlisib monotherapy in patients with relapsed or refractory marginal zone lymphoma: subset analysis from the CHRONOS-1 trial [abstract]. Blood 2017;130:Abstract 4053.

Duvelisib

Flinn IW, Miller CB, Ardeshna KM, et al. DYNAMO: A phase II study of duvelisib (IPI-145) in patients with refractory indolent non-Hodgkin lymphoma. J Clin Oncol 2019; 37:912 922.

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 2017;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 2016;17:1081-1093.

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Mantle Cell Lymphoma
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ADDITIONAL DIAGNOSTIC TESTING

ESSENTIAL:
- **Adequate immunophenotyping to establish diagnosis[a,b]**
  - **IHC panel: CD20, CD3, CD5, cyclin D1, CD10, CD21, CD23, BCL2, BCL6, TP53, 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**
- ***TP53* sequencing (patients with typical MCL with an expected aggressive clinical course or particularly if upfront transplant anticipated)[e]**

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[f] 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[g]**
- **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]*TP53* mutation has been associated with poor prognosis in patients treated with conventional therapy, including transplant. Clinical trial is strongly suggested for these patients.

[f]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.

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

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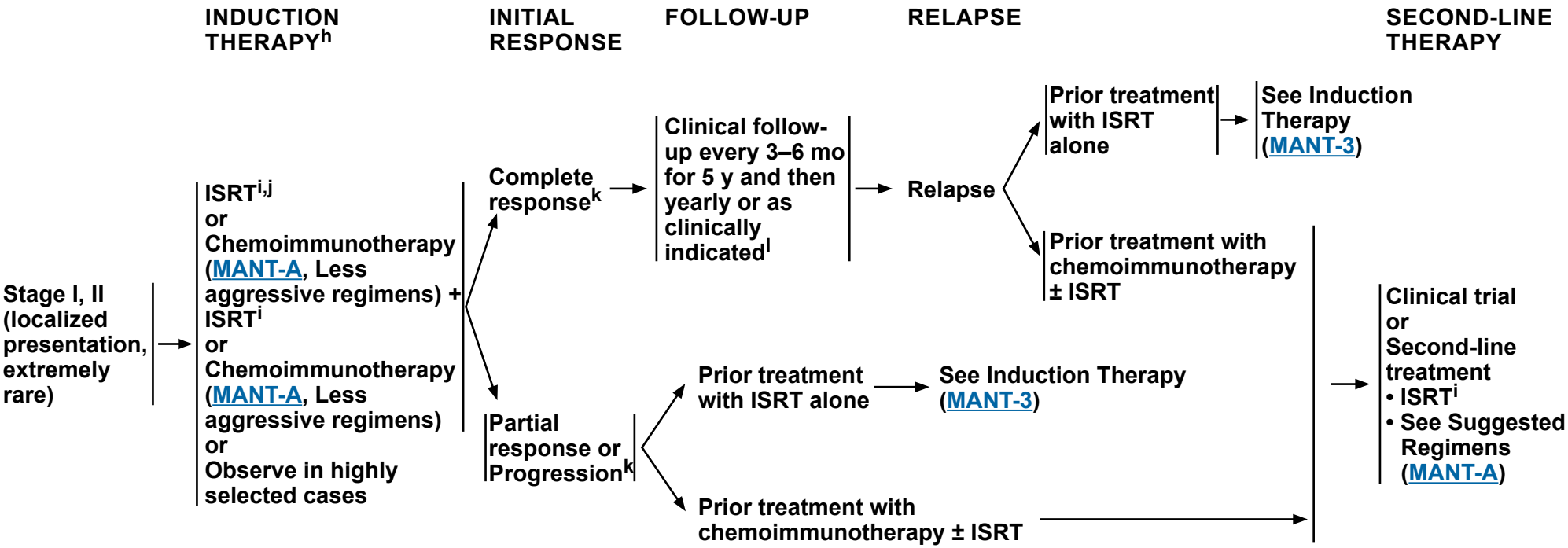

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

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

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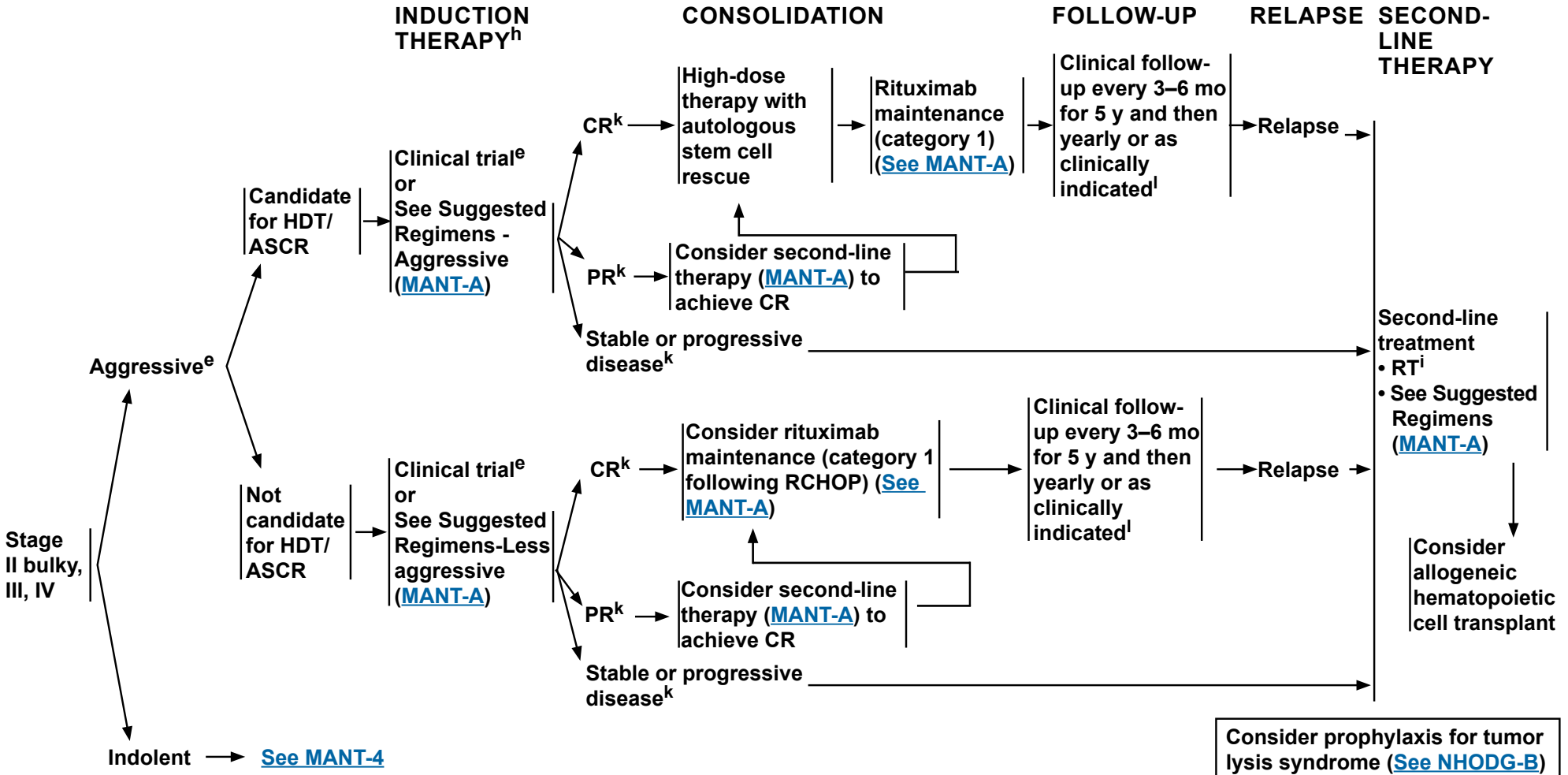

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

[e] *TP53* mutation has been associated with poor prognosis in patients treated with conventional therapy, including transplant. Clinical trial is strongly suggested for these patients.
[h] Early referral for high-dose therapy with stem cell rescue is advisable for planning purposes.
[i] See Principles of Radiation Therapy (NHODG-D).
[k] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[l] Follow-up includes diagnostic tests and imaging using the same modalities performed during workup as clinically indicated.

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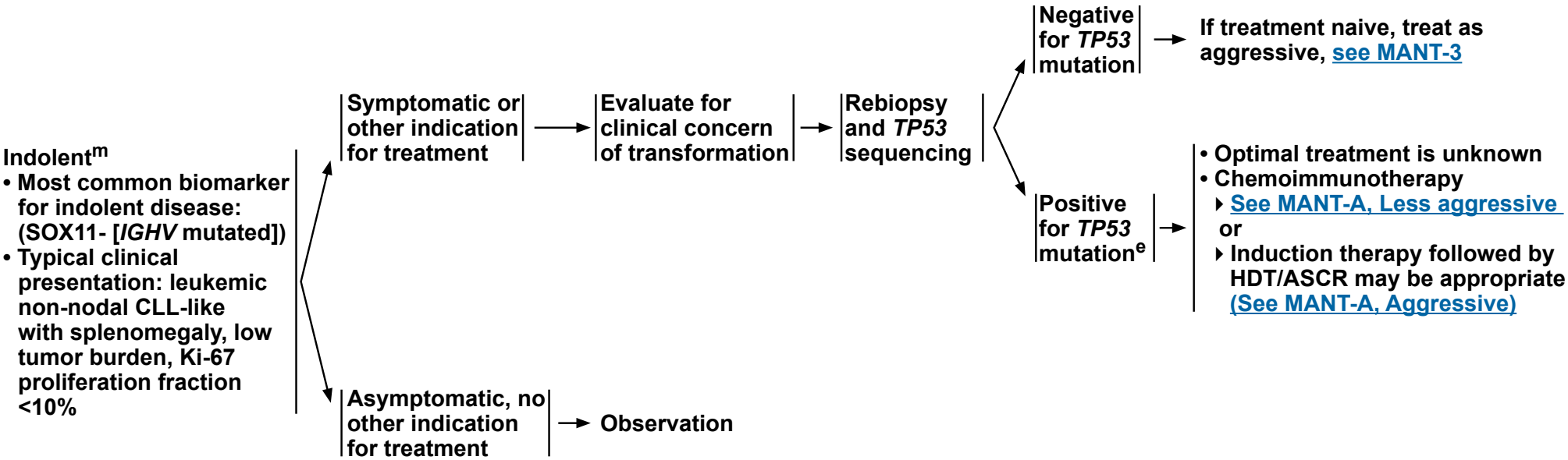
Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)



[e] *TP53* mutation has been associated with poor prognosis in patients treated with conventional therapy, including transplant. Clinical trial is strongly suggested for these patients.

[m] 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.

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SUGGESTED TREATMENT REGIMENS[a,b]

An FDA-approved biosimilar is an appropriate substitute for rituximab.

Induction Therapy

- **Aggressive therapy**
  - **Preferred regimens**
    - ◊ **RDHA (rituximab, dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or 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)**

Maintenance After Less Aggressive Therapy

- **Rituximab every 8 weeks until progression or intolerance (category 1 following RCHOP; 2–5 y following modified rituximab-HyperCVAD)**
  - **Prospective trial data suggest no benefit after BR**
  - **Untested after VR-CAP, RBAC**

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

Consolidation After Aggressive Therapy

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

See Evidence Blocks on MANT-A (EB-1)

Maintenance After HDT/ASCR

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

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. Wang ML, Lee H, Thirumurthi S, et al. Hematological Oncology 2017;35:142-143.
[d]There is a randomized trial that demonstrated that RCHOP was not superior to CHOP.

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EVIDENCE BLOCKS FOR INDUCTION THERAPY FOR STAGE II BULKY, III, OR IV MCL

Aggressive Therapy	
Preferred Regimens	
Rituximab, dexamethasone, cytarabine (RDHA)/cisplatin/ oxaliplatin	
Rituximab, dexamethasone, cytarabine (RDHA)/carboplatin	
Alternating RCHOP/RDCHAP	
NORDIC regimen (dose-intensified chemoimmunotherapy with rituximab, cyclophosphamide, vincristine, doxorubicin, prednisone) alternating with rituximab + high-dose cytarabine	
HyperCVAD/rituximab	
Other Recommended Regimens	
Bendamustine/rituximab	

Maintenance After HDT/ASCR	
Rituximab maintenance	

Less Aggressive Therapy	
Preferred Regimens	
Bendamustine/rituximab	
VR-CAP	
RCHOP	
Lenalidomide/rituximab	
Modified HyperCVAD/rituximab	
Other Recommended Regimens	
RBAC (rituximab, bendamustine, cytarabine)	

Maintenance After Less Aggressive Therapy	
Rituximab maintenance	

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SUGGESTED TREATMENT REGIMENS[a,b]
An FDA-approved biosimilar is an appropriate substitute for rituximab.

Second-line Therapy

- **Short response duration to prior chemoimmunotherapy (< expected median PFS)**
  - **Preferred regimens (in alphabetical order)**
    - ◊ **BTK inhibitors[e]**
      - – **Acalabrutinib[f]**
      - – **Ibrutinib ± rituximab**
      - – **Zanubrutinib**
    - ◊ **Lenalidomide ± rituximab**
    - ◊ **Venetoclax[e]**
  - **Other recommended regimens**
    - ◊ **Ibrutinib,[e] lenalidomide, rituximab (category 2B)**
    - ◊ **Venetoclax + ibrutinib (category 2B)[e]**

- **Extended response duration to prior chemoimmunotherapy (> expected median PFS)**
  - **Preferred regimens (in alphabetical order)**
    - ◊ **Bendamustine ± rituximab (if not previously given)**
    - ◊ **Bortezomib ± rituximab**
  - **Other recommended regimens (in alphabetical order by category)**
    - ◊ **Small molecule inhibitors as above (category 2B for zanubrutinib)[e]**
    - ◊ **Bendamustine, bortezomib, and rituximab (category 2B)**
    - ◊ **PEPC (prednisone, etoposide, procarbazine, cyclophosphamide) ± rituximab (category 2B)**
    - ◊ **RCHOP (if not previously given) (category 2B)**
    - ◊ **VRCAP (if not previously given) (category 2B)**
    - ◊ **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)**

See Evidence Blocks on MANT-A (EB-2)

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.

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EVIDENCE BLOCKS FOR SECOND-LINE THERAPY

Short Response Duration to Prior Chemoimmunotherapy (<Expected Median PFS)	
Preferred Regimens	
BTK Inhibitors	
Acalabrutinib	
Ibrutinib	
Ibrutinib/rituximab	
Zanubrutinib	*
Lenalidomide	
Lenalidomide/rituximab	
Venetoclax	
Other Recommended Regimens	
Ibrutinib/lenalidomide/rituximab	
Venetoclax/ibrutinib	

Extended Response Duration to Prior Chemoimmunotherapy (>Expected Median PFS)	
Preferred Regimens	
Bendamustine	
Bendamustine/rituximab	
Bortezomib	
Bortezomib/rituximab	
Other Recommended Regimens	
Small Molecule Inhibitors	
Acalabrutinib	*
Ibrutinib	*
Venetoclax	*
Venetoclax/ibrutinib	*
Zanubrutinib	*
Bendamustine/bortezomib/rituximab	
RCHOP (if not previously given)	
VR-CAP (if not previously given)	
PEPC (prednisone, etoposide, procarbazine, cyclophosphamide)	
PEPC/rituximab	

*Evidence Block development in progress

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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.

Eskelund CW, Kolstad A, Jerkeman M, et al. 15-year follow-up of the Second Nordic Mantle Cell Lymphoma trial (MCL2): prolonged remissions without survival plateau. Br J Haematol 2016;175:410-418.

RCHOP/RDHAP

Hermine O, Hoster E, Walewski J, et al. Addition of high-dose cytarabine to immunochemotherapy before autologous stem-cell transplantation in patients aged 65 years or younger with mantle cell lymphoma (MCL Younger): a randomised, open-label, phase 3 trial of the European Mantle Cell Lymphoma Network. Lancet 2016;388:565-575.

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 2017;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 2017;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, Knauf W, Goerner M, et al. Two years rituximab maintenance vs. observation after first-line treatment with bendamustine plus rituximab (B-R) in patients with mantle cell lymphoma: First results of a prospective, randomized, multicenter phase II study (a subgroup study of the StiL NHL7-2008 MAINTAIN trial) [abstract]. J Clin Oncol 2016;34:Abstract 7503.

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

Robak T, Jin J, Pylypenko H, et al. Frontline bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) versus rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in transplantation-ineligible patients with newly diagnosed mantle cell lymphoma: final overall survival results of a randomised, open-label, phase 3 study. Lancet Oncol 2018;19:1449-1458.

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 P, et al. Five-year follow-up of lenalidomide plus rituximab as initial treatment for mantle cell lymphoma. Blood 2018;132:2016-2025.

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.

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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 2017;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 2017;130 (Suppl 1):Abstract 153.

Second-line Therapy

Acalabrutinib

Wang M, Rule S, Zinzani PL, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. Lancet 2018;391:659-667.

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, 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 2016;387:770-778.

Rule S, Jurczak W, Jerkeman M, et al. Ibrutinib versus temsirolimus: 3-year follow-up of patients with previously treated mantle cell lymphoma from the phase 3, international, randomized, open-label RAY study. Leukemia 2018;32:1799-1803.

Ibrutinib + rituximab

Wang ML, Lee H, Chuang H, et al. Ibrutinib in combination with rituximab in relapsed or refractory mantle cell lymphoma: a single-centre, open-label, phase 2 trial. Lancet Oncol 2016;7:48-56.

Ibrutinib, lenalidomide, and rituximab

Jerkeman M, Eskelund C, Hutchings M, et al. Ibrutinib, lenalidomide, and rituximab in relapsed or refractory mantle cell lymphoma (PHILEMON): a multicentre, open-label, single-arm, phase 2 tria. Lancet Haematol 2018(3):e109-e116.

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.

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.

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.

Trneny M, Lamy T, Walewski J, et al. Lenalidomide versus investigator's choice in relapsed or refractory mantle cell lymphoma (MCL-002; SPRINT): a phase 2, randomised, multicentre trial. Lancet Oncol 2016;17:319-331

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. Low-dose metronomic, multidrug therapy with the PEP-C oral combination chemotherapy regimen for mantle cell lymphoma. Leuk Lymphoma 2008;49:447-450.

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 2017s;35:826-833.

Venetoclax + ibrutinib

Tam C, Anderson M, Pott C, et al. Ibrutinib plus venetoclax for the treatment of mantle-cell lymphoma. N Engl J Med 2018;378:1211-1223.

Zanubrutinib

Song Y, Zhou K, Zou D, et al. Zanubrutinib in patients with relapsed/refractory mantle cell lymphoma [abstract]. Hematological Oncology 2019;37:45-46.

Tam CS, Wang M, Simpson D, et al. Updated safety and efficacy data in the phase 1 trial of patients with mantle cell lymphoma (mcl) treated with bruton tyrosine kinase (BTK) inhibitor zanubrutinib (BGB-3111) [abstract]. Hematological Oncology 2019;37:245-247.

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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 (EBV-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 marginal zone lymphoma (PCMZL) and primary cutaneous follicle center lymphoma (PCFCL) (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.
- High-grade B-cell lymphomas, NOS; see HGNOS-1.
- Primary cutaneous diffuse large B-cell lymphomas, leg type; see BCEL-B 3 of 3.
- DLBCL arising from CLL (Richter's transformation) (See NCCN Guidelines for CLL/SLL)

[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 2017 revised WHO classification of lymphomas, 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.

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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 for patients with 4–6 factors according to prognostic model (See BCEL-A 2 of 2), HIV lymphoma, testicular lymphoma, high-grade B-cell lymphomas (HGBL) with translocations of *MYC* and *BCL2* and/or *BCL6,* or HGBL, NOS**

→ 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.

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STAGE

FIRST-LINE THERAPY[n]

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

See monoclonal antibody and viral reactivation (NHODG-B)

Stage I, II[j,k]

- **Nonbulky (<7.5 cm)** →
  - **RCHOP[o] x 3 cycles followed by ISRT[p] (category 1)**
  - **or**
  - **RCHOP[o] x 6 cycles ± ISRT[p,q]**
  - **or**
  - **RCHOP-14 x 4–6 cycles ± ISRT[p,q]**
- **Bulky (≥7.5 cm)** → **RCHOP[o] x 6 cycles ± ISRT[p,q]**

→
- **ISRT planned** → **See Pre RT Evaluation (BCEL-4)**
- **ISRT not planned** → **See End-of-Treatment Restaging (BCEL-5)**

Stage III, IV[j,l,m] → **Clinical trial or RCHOP[o,r] (category 1)[s]** → **Interim restaging after 2–4 cycles[t]** → **See BCEL-6**

[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, ISRT is recommended.
[l] 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, very frail patients, 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.

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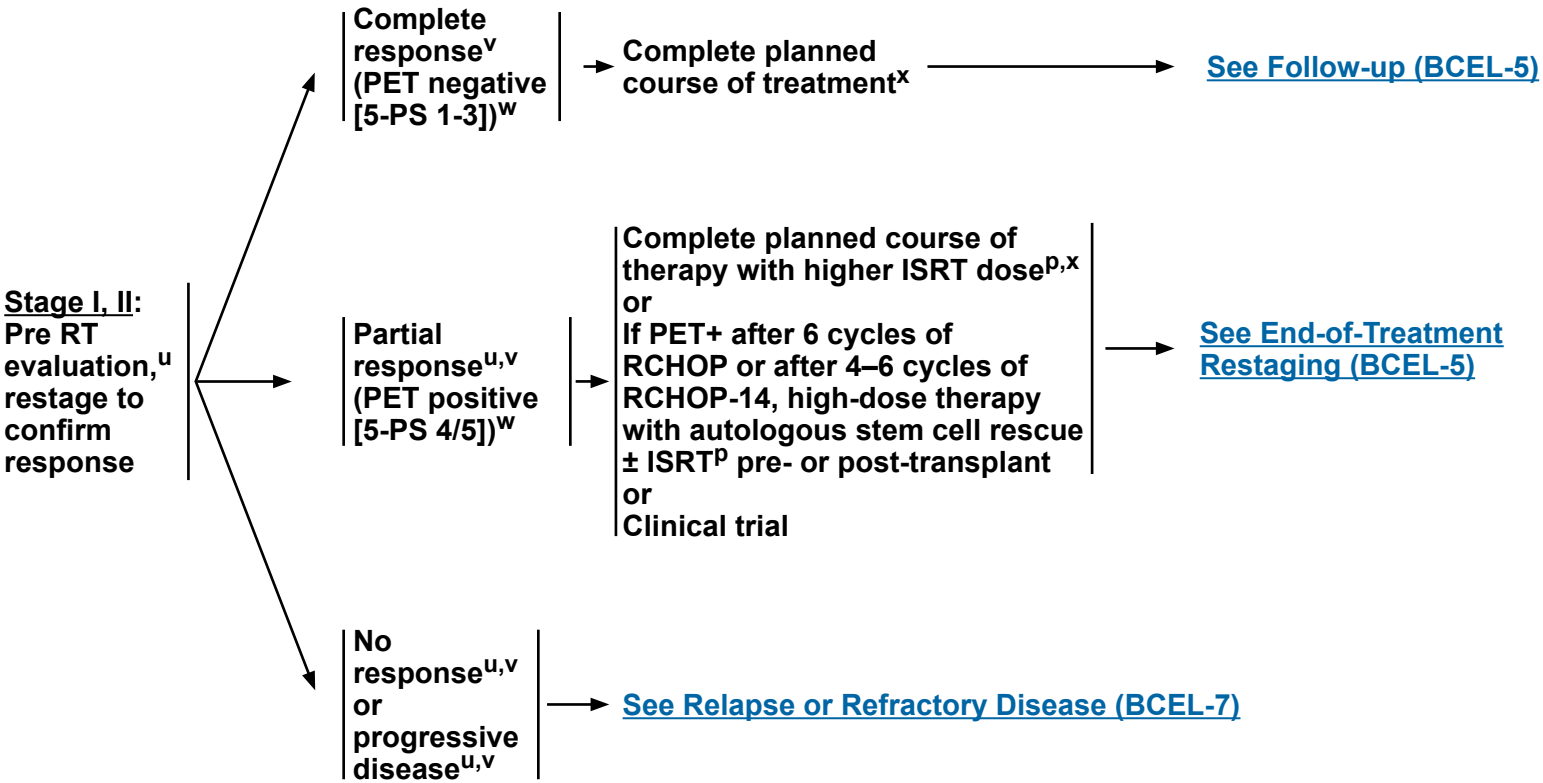
PRE RT EVALUATION
(End of first-line chemoimmunotherapy)

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 (5-PS) (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.

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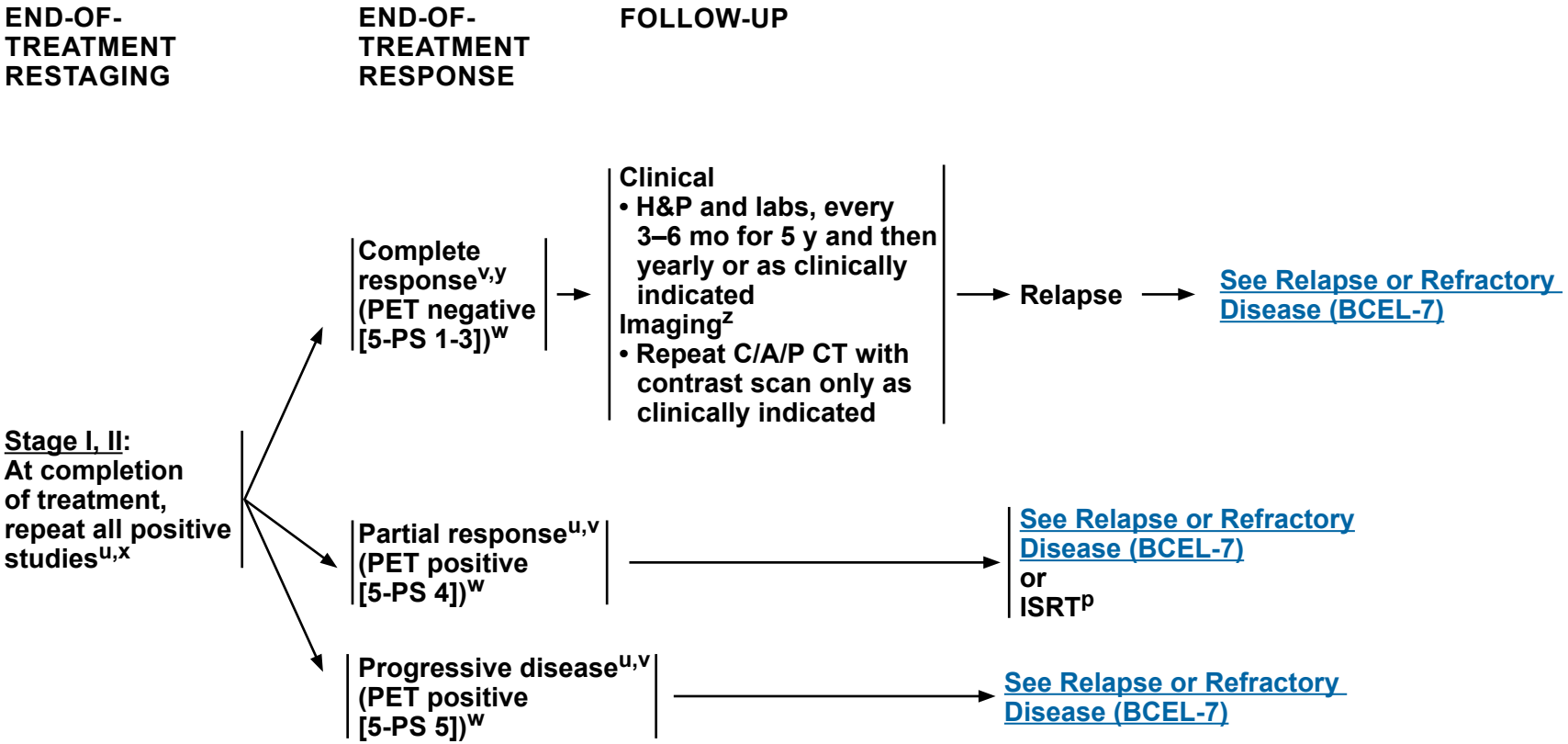

[p] See Principles of Radiation Therapy (NHODG-D).
[u] Repeat biopsy should be strongly considered if PET-positive prior to additional therapy. If biopsy negative, follow PET-negative guideline.
[v] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[w] PET/CT scan should be interpreted via the PET Five Point Scale (5-PS) (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.
[z] When disease (eg, bone) is only imaged on PET/CT scan, it is appropriate to be used in follow-up.

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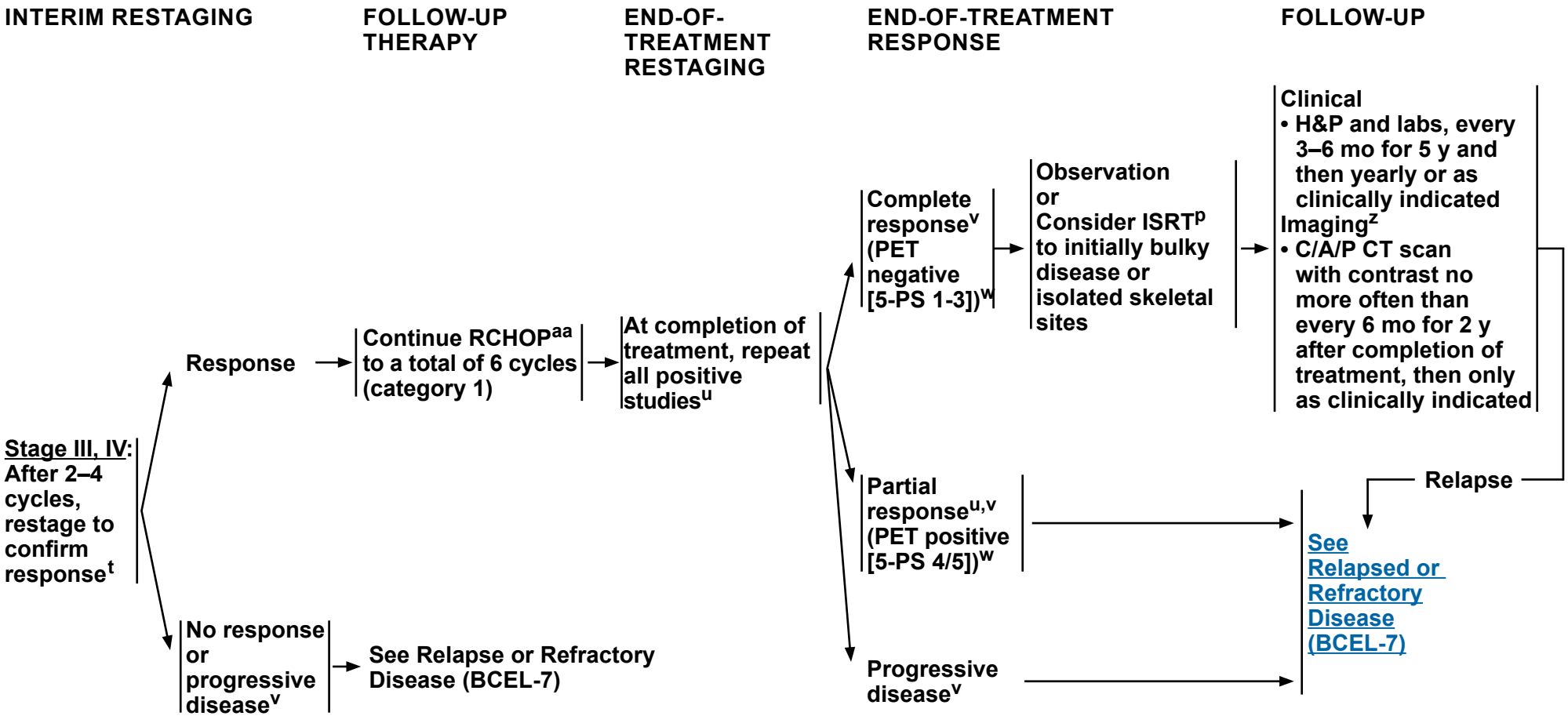

[p] See Principles of Radiation Therapy (NHODG-D).
[t] PET/CT scan at interim restaging can lead to increased false positives and should be carefully considered in select cases. If PET/CT scan performed and positive, rebiopsy before changing course of treatment.
[u] Repeat biopsy should be strongly considered 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] When disease (eg, bone) is only imaged on PET/CT scan, it is appropriate to be used in follow-up.
[aa] For other regimens, see BCEL-C.

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NCCN Guidelines Version 6.2019
Diffuse Large B-Cell Lymphoma
NCCN Evidence Blocks™

NCCN Guidelines Index
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Discussion

RELAPSE/ REFRACTORY DISEASE | **ADDITIONAL THERAPY** | **RESPONSE #2** | **CONSOLIDATION/ADDITIONAL THERAPY**

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

See monoclonal antibody and viral reactivation (NHODG-B)

Relapsed/ refractory disease

For patients with intention to proceed to transplant → **Second-line therapy See Suggested Regimens (BCEL-C)**

Non-candidates for transplant → **Clinical trial or Second-line therapy See Suggested Regimens (BCEL-C) or Palliative ISRT[p] or Best supportive care**

Complete response[v] → **High-dose therapy with autologous stem cell rescue (category 1) ± ISRT[p,cc] or Clinical trial or Allogeneic hematopoietic cell transplant in selected cases[dd] ± ISRT[p,cc]**

Partial response[v,bb] → **Axicabtagene ciloleucel or tisagenlecleucel[ee,ff] or High-dose therapy with autologous stem cell rescue ± ISRT[p,cc] or Clinical trial or Allogeneic hematopoietic cell transplant in selected cases[dd] ± ISRT[p,cc]**

→ **See Follow-up (BCEL-8)**

See Evidence Blocks for CAR T-cell Therapy on BCEL-D (EB-1)

No response or progressive disease[v] → **See Relapse #2 or greater (BCEL-8)**

Complete response[v] → **See Follow-up (BCEL-8)**

Partial response[v,gg] → **See Relapse #2 or greater (BCEL-8)**

No response or progressive disease[v] → **See Relapse #2 or greater (BCEL-8)**

[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).
[ff] Tisagenlecleucel is not FDA-approved for relapsed/refractory primary mediastinal large B-cell lymphoma.
[gg] Repeat biopsy should be strongly considered if PET-positive prior to additional therapy, because PET positivity may represent post-treatment inflammation. If biopsy negative, follow CR pathway.

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FOLLOW-UP

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

→

- **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**

→

Partial response[gg] or Relapse or Progression of disease[v]

→

RELAPSE #2 OR GREATER

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

See Evidence Blocks for CAR T-cell Therapy on BCEL-D (EB-1)

[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] Tisagenlecleucel is not FDA-approved for relapsed/refractory primary mediastinal large B-cell lymphoma.
[gg] Repeat biopsy should be strongly considered if PET-positive prior to additional therapy, because PET positivity may represent post-treatment inflammation. If biopsy negative, follow CR pathway.
[hh] 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.

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INTERNATIONAL PROGNOSTIC INDEX[a]

ALL PATIENTS:
- Age >60 years
- Serum LDH > normal
- Performance status 2–4
- Stage III or IV
- Extranodal involvement >1 site

INTERNATIONAL INDEX, ALL PATIENTS:	
• Low	0 or 1
• Low-intermediate	2
• High-intermediate	3
• High	4 or 5

AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX[a]

PATIENTS ≤60 YEARS:
- Stage III or IV
- Serum LDH > normal
- Performance status 2–4

INTERNATIONAL INDEX, PATIENTS ≤60 YEARS:	
• Low	0
• Low-intermediate	1
• High-intermediate	2
• High	3

STAGE-MODIFIED INTERNATIONAL PROGNOSTIC INDEX[b]

STAGE I OR II PATIENTS:
- Age >60 years
- Serum LDH > normal
- Performance status 2–4
- Stage II or IIE

INTERNATIONAL INDEX, STAGE I OR II PATIENTS:	
• Low	0 or 1
• High	2–4

NCCN-IPI[c]

Age, years	
>40 to ≤60	1
>60 to <75	2
≥75	3
LDH, normalized	
>1 to ≤3	1
>3	2
Ann Arbor stage III-IV	1
Extranodal disease*	1
Performance status ≥2	1

Risk Group	
• Low	0–1
• Low-intermediate	2–3
• High-intermediate	4–5
• High	≥6

*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

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Back to Workup (BCEL-2)

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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**	**or kidney or adrenal gland involvement**

[d]Schmitz N, Zeynalova S, Nickelsen M, et al. CNS International Prognostic Index: A risk model for CNS relapse in patients with diffuse large B-cell lymphoma treated with R-CHOP. J Clin Oncol 2016;34:3150-3156.

[e]There may be an increased risk of CNS events in selected patients with 4–6 risk factors according to the above prognostic model, HIV lymphoma, testicular lymphoma, high-grade B-cell lymphomas (HGBLs) with translocations of *MYC* and *BCL2* and/or *BCL6*; HGBL, NOS; or kidney or adrenal involvement. The optimal management of CNS 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 suggest that stage IE DLBCL of the breast is a potential risk factor for CNS disease.

Back to Workup (BCEL-2)

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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,b]**
  - **Dose-adjusted EPOCH-R ([etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin] + rituximab)[c] 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) ± rituximab[d] 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[d]**

[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]An FDA-approved biosimilar is an appropriate substitute for rituximab.
[c]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.
[d]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.
[e]Zinzani PL, Ribrag V, Moskowitz CH, et al. Safety and tolerability of pembrolizumab in patients with relapsed/refractory primary mediastinal large B-cell lymphoma. Blood 2017;130:267-270.

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GREY ZONE LYMPHOMA[a]
(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.[b]

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 is 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[c]
- 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.[d]
- 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]Pilichowska M, Pittaluga S, Ferry JA, et al. Clinicopathologic consensus study of gray zone lymphoma with features intermediate between DLBCL and classical HL. Blood Adv 2017;1:2600-2609; Wilson WH, Pittaluga S, Nicolae A, et al. A prospective study of mediastinal gray-zone lymphoma. Blood 2014;124:1563-1569; Swerdlow SH CE, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, ed. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th ed. Lyon: IARC; 2017.; 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.
[b]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.
[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]An FDA-approved biosimilar is an appropriate substitute for rituximab.

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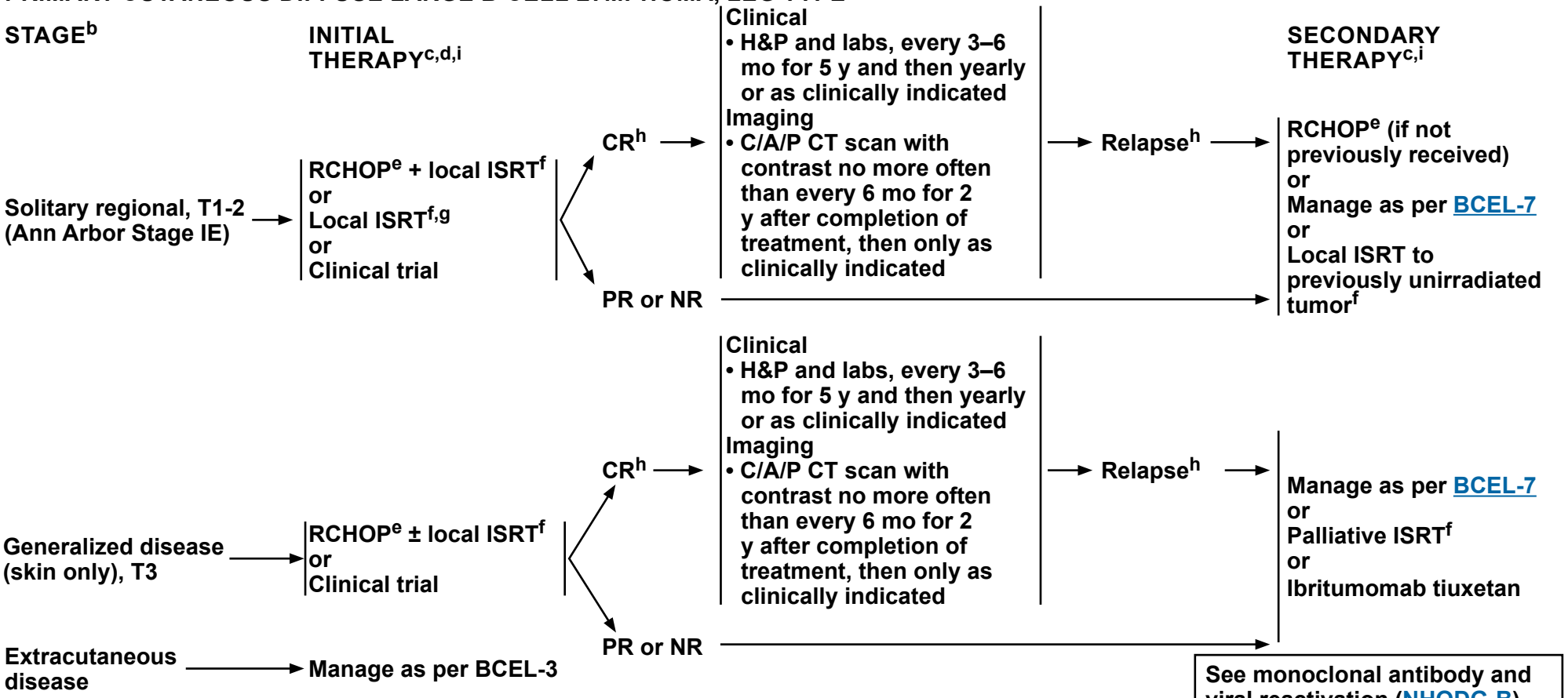
PRIMARY CUTANEOUS DIFFUSE LARGE B-CELL LYMPHOMA, LEG TYPE[a]



[a]Expert hematopathologist review is essential to confirm diagnosis of primary cutaneous DLBCL, Leg type.
[b]For TNM Classification of Cutaneous Lymphoma other than MF/SS (See NCCN Guidelines for T-Cell Lymphomas and Primary Cutaneous Lymphomas).
[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]These patients are at higher risk for CNS involvement (See BCEL-A 2 of 2); consider CNS prophylaxis according to institutional standards.
[e]For patients who cannot tolerate anthracyclines, see BCEL-C for regimens for patients with poor left ventricular function.
[f]See Principles of Radiation Therapy (NHODG-D).
[g]For patients not able to tolerate chemotherapy.
[h]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.
[i]An FDA-approved biosimilar is an appropriate substitute for rituximab.

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

An FDA-approved biosimilar is an appropriate substitute for rituximab.

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[e,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

Concurrent Presentation with CNS Disease[h]
- Parenchymal: 3 g/m² 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. Systemic methotrexate (3–3.5 g/m²) can be given in combination with RCHOP or as consolidation after RCHOP + IT methotrexate/cytarabine

See Evidence Blocks on BCEL-C (EB-1)

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/m² 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, very frail patients, and patients >80 years of age with comorbidities.
[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.
[h]Concurrent high-dose methotrexate with dose-adjusted EPOCH can result in unacceptable toxicities.

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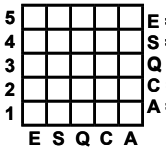
NCCN Guidelines Version 6.2019
Diffuse Large B-Cell Lymphoma
NCCN Evidence Blocks™



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

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EVIDENCE BLOCKS FOR FIRST-LINE THERAPY

Stage I-II		
	Non-bulky disease	Bulky disease
RCHOP x 3 cycles + RT		—
RCHOP x 6 cycles		
RCHOP x 6 cycles + RT		
RCHOP 14 x 4-6 cycles		—
RCHOP 14 x 4-6 cycles + RT		—

Patients with Poor Left Ventricular Function	
RCEPP/RT	
RCDOP/RT	
DA-EPOCH/rituximab/RT	
RCEOP/RT	
RGCVP/RT	
Very Frail Patients and Patients >80 Years of Age with Comorbidities	
RCEPP/RT	
RCDOP/RT	
R-mini-CHOP/RT	
RGCVP/RT	
First-line Consolidation for Patients 60–80 Years of Age	
Lenalidomide maintenance	

Stage III-IV	
RCHOP	
Dose-dense RCHOP 14	
Dose-adjusted EPOCH/rituximab	

Patients with Poor Left Ventricular Function	
RCEPP	
RCDOP	
DA-EPOCH/rituximab	
RCEOP	
RGCVP	
Very Frail Patients and Patients >80 Years of Age with Comorbidities	
RCEPP	
RCDOP	
R-mini-CHOP	
RGCVP	
Concurrent Presentation with CNS Disease*	
Parenchymal: Systemic methotrexate	
Leptomeningeal: IT methotrexate/cytarabine	
Leptomeningeal: Systemic methotrexate	

*Incorporated as part of treatment of plan as outlined in BCEL-C (1 of 4).

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SUGGESTED TREATMENT REGIMENS[a,b]
(in alphabetical order)
An FDA-approved biosimilar is an appropriate substitute for rituximab.

Second-line and Subsequent Therapy[d,i,j] (intention to proceed to transplant)
- **DHAP (dexamethasone, cisplatin, cytarabine) ± rituximab**
- **DHAX (dexamethasone, cytarabine, oxaliplatin) ± 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,i,j] (non-candidates for transplant)
- **Bendamustine ± rituximab[k] (category 2B)**
- **Bendamustine, rituximab and polatuzumab vedotin-piiq (after ≥ 2 prior therapies)[k,l]**
- **Brentuximab vedotin for CD30+ disease**
- **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[m] (non-GCB DLBCL)**
- **Lenalidomide ± rituximab (non-GCB DLBCL)**
- **Rituximab**

See Evidence Blocks on BCEL-C (EB-2)

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.
[i]If additional anthracycline is administered after a full course of therapy, careful cardiac monitoring is essential. Dexrazoxane may be added as a cardioprotectant.
[j]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.
[k]In patients intended to receive CAR T-cell therapy, bendamustine should be used with caution unless immediately prior to CAR T-cell therapy, since it could impact the success of the patient's T-cell collection.
[l]Bendamustine, rituximab and polatuzumab vedotin-piiq is indicated for the treatment of adult patients with relapsed or refractory DLBCL and HGBL with translocations of *MYC* and *BCL2* and/or *BCL6* after ≥2 prior therapies.
[m]See Special Considerations for Use of Small-Molecule Inhibitors (NHODG-E).

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EVIDENCE BLOCKS FOR SECOND-LINE AND SUBSEQUENT THERAPY

Candidates for HDT/ASCR	
DHAP	
DHAP/rituximab	
DHAX	
DHAX/rituximab	
ESHAP	
ESHAP/rituximab	
GDP	
GDP/rituximab	
GemOx	
GemOx/rituximab	
ICE	
ICE/rituximab	
MINE	
MINE/rituximab	

Non-Candidates for HDT/ASCR	
Bendamustine	
Bendamustine/rituximab	
Bendamustine, rituximab and polatuzumab vedotin-piiq (after ≥ 2 prior therapies)	
Brentuximab vedotin for CD30+ disease	
CEPP	
CEPP/rituximab	
CEOP	
CEOP/rituximab	
DA-EPOCH	
DA-EPOCH/rituximab	

Non-Candidates for HDT/ASCR	
GDP	
GDP/rituximab	
Gemcitabine/dexamethasone/ carboplatin	
Gemcitabine/dexamethasone/ carboplatin/rituximab	
GemOx	
GemOx/rituximab	
Gemcitabine/vinorelbine	
Gemcitabine/vinorelbine/ rituximab	
Ibrutinib (non-GCB DLBCL)	
Lenalidomide (non-GCB DLBCL)	
Lenalidomide/rituximab (non-GCB DLBCL)	
Rituximab	

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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.

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.

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 2017;35:2473-2481.

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.

Bendamustine, rituximab and polatuzumab vedotin-piiq

Sehn LH, Herrera AF, Matasar MJ, et al. Polatuzumab vedotin (Pola) plus bendamustine (B) with rituximab (R) or obinutuzumab (G) in relapsed/refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL): Updated results of a phase (Ph) Ib/II study [abstract]. Blood 2018;132: Abstract 1683.

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

Continued

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SUGGESTED TREATMENT REGIMENS
REFERENCES

Second-line and Subsequent Therapy (continued)

CAR T-Cell Therapy

Axicabtagene ciloleucel

Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med 2017;377:2531-2544.

Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol 2019;20:31-42.

Tisagenlecleucel

Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med 2019;380:45-56.

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.

DHAP (dexamethasone, cisplatin, cytarabine) ± rituximab

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, 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.

DHAX (dexamethasone, cytarabine, oxaliplatin) ± rituximab

Lignon J, Sibon D, Madelaine I, et al. Rituximab, dexamethasone, cytarabine, and oxaliplatin (R-DHAX) is an effective and safe salvage regimen in relapsed/refractory B-cell non-Hodgkin lymphoma. Clin Lymphoma Myeloma Leuk 2010;10):262-9.

Rigacci L, Fabbri A, Puccini B, et al. Oxaliplatin-based chemotherapy (dexamethasone, high-dose cytarabine, and oxaliplatin)+/-rituximab is an effective salvage regimen in patients with relapsed or refractory lymphoma. Cancer 2010;116:4573-4579.

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.

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 or carboplatin) ± rituximab

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.

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.

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.

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.

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

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, 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

Lenalidomide ± rituximab

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.

Czuczman MS, Trneny M, Davies A, et al. A phase 2/3 multicenter, randomized, open-label study to compare the efficacy and safety of lenalidomide versus investigator's choice in patients with relapsed or refractory diffuse large B-cell lymphoma. Clin Cancer Res 2017;23:4127-4137.

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

Axicabtagene ciloleucel[a]

- **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]**
  - **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 - See CAR T-Cell-Related Toxicities in the NCCN Guidelines for Management of Immunotherapy-Related Toxicities**
- **Neurologic toxicity management - See CAR T-Cell-Related Toxicities in the NCCN Guidelines for Management of Immunotherapy-Related Toxicities**
- **Prolonged cytopenias**
  - **Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and axicabtagene ciloleucel infusion.**
- **Hypogammaglobulinemia**
  - **B-cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment with axicabtagene ciloleucel.**

Tisagenlecleucel[b]

- **Patient selection**
  - **Tisagenlecleucel 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 and high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.[b]**
  - **Health care facilities that dispense and administer tisagenlecleucel must be enrolled and comply with the REMS requirements.[b] See REMS for tisagenlecleucel.**
- **CRS management - See CAR T-Cell-Related Toxicities in the NCCN Guidelines for Management of Immunotherapy-Related Toxicities**
- **Neurologic toxicity management - See CAR T-Cell-Related Toxicities in the NCCN Guidelines for Management of Immunotherapy-Related Toxicities**
- **Prolonged cytopenias**
  - **Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and tisagenlecleucel infusion.**
- **Hypogammaglobulinemia**
  - **B-cell aplasia and hypogammaglobulinemia can occur in patients with a complete remission after tisagenlecleucel infusion.**

[a]Prescribing information for axicabtagene ciloleucel is available at: https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM581226.pdf.
[b]Prescribing information for tisagenlecleucel is available at: https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM573941.pdf.

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EVIDENCE BLOCKS FOR CAR T-CELL THERAPY

Histologic Transformation of FL to DLBCL (FOLL-6, FOLL-7)	
Axicabtagene ciloleucel	
Tisagenlecleucel	

Relapsed/Refractory DLBCL (BCEL-7, BCEL-8)						
	Partial Response After Second-Line Therapy		No Response or Progressive Disease After Second-Line Therapy		Second Relapse or Greater	
Regimens	Candidates for HDT/ASCR	Non-Candidates for HDT/ASCR	Candidates for HDT/ASCR	Non-Candidates for HDT/ASCR	Candidates for HDT/ASCR	Non-Candidates for HDT/ASCR
Axicabtagene ciloleucel						
Tisagenlecleucel						

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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.**
- **The 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,c]

- **Clinical trial is recommended.**
- **While the standard of care is not established, the following induction regimens have been used at NCCN Member Institutions:**
  - **DA-EPOCH-R**
  - **Potentially toxic regimens; performance status and comorbidities should be considered**
    - **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 2017 revised WHO classification of lymphomas, DLBCL, double hit has been designated in a unique category called HGBL 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.

[c]An FDA-approved biosimilar is an appropriate substitute for rituximab.

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 MA, Abramson JS, et al. Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) in untreated aggressive diffuse large B-cell lymphoma with MYC rearrangement: a prospective, multicentre, single-arm phase 2 study. Lancet Haematol 2018;5:e609-e617.

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.

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Definition

- **HGBL, NOS include cases that appear blastoid or cases intermediate between DLBCL and BL, but which lack an *MYC* and *BCL2* and/or *BCL6* rearrangement.**
- **They exclude patient with translocations of *MYC* and *BCL2* and/or *BCL6* or clear DLBCL.**

Clinical Presentation

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

Treatment[a,b]

- **Clinical trial is recommended.**
- **For early-stage disease, consider consolidative RT for localized disease.**
- **While the standard of care is not established, the following induction regimens have been used at NCCN Member Institutions:**
  - **RCHOP**
  - **DA-EPOCH-R**
  - **Potentially toxic regimens; performance status and comorbidities should be considered**
    - **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)**
- **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.**
- **For Relapsed/refractory disease, see BCEL-7.**

[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]An FDA-approved biosimilar is an appropriate substitute for rituximab.

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ADDITIONAL DIAGNOSTIC TESTING[a,b]

ESSENTIAL:
- **Adequate immunophenotyping to establish diagnosis[c,d,e]**
  - **IHC panel: CD45, CD20, CD3, CD10, Ki-67, BCL2, 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 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.

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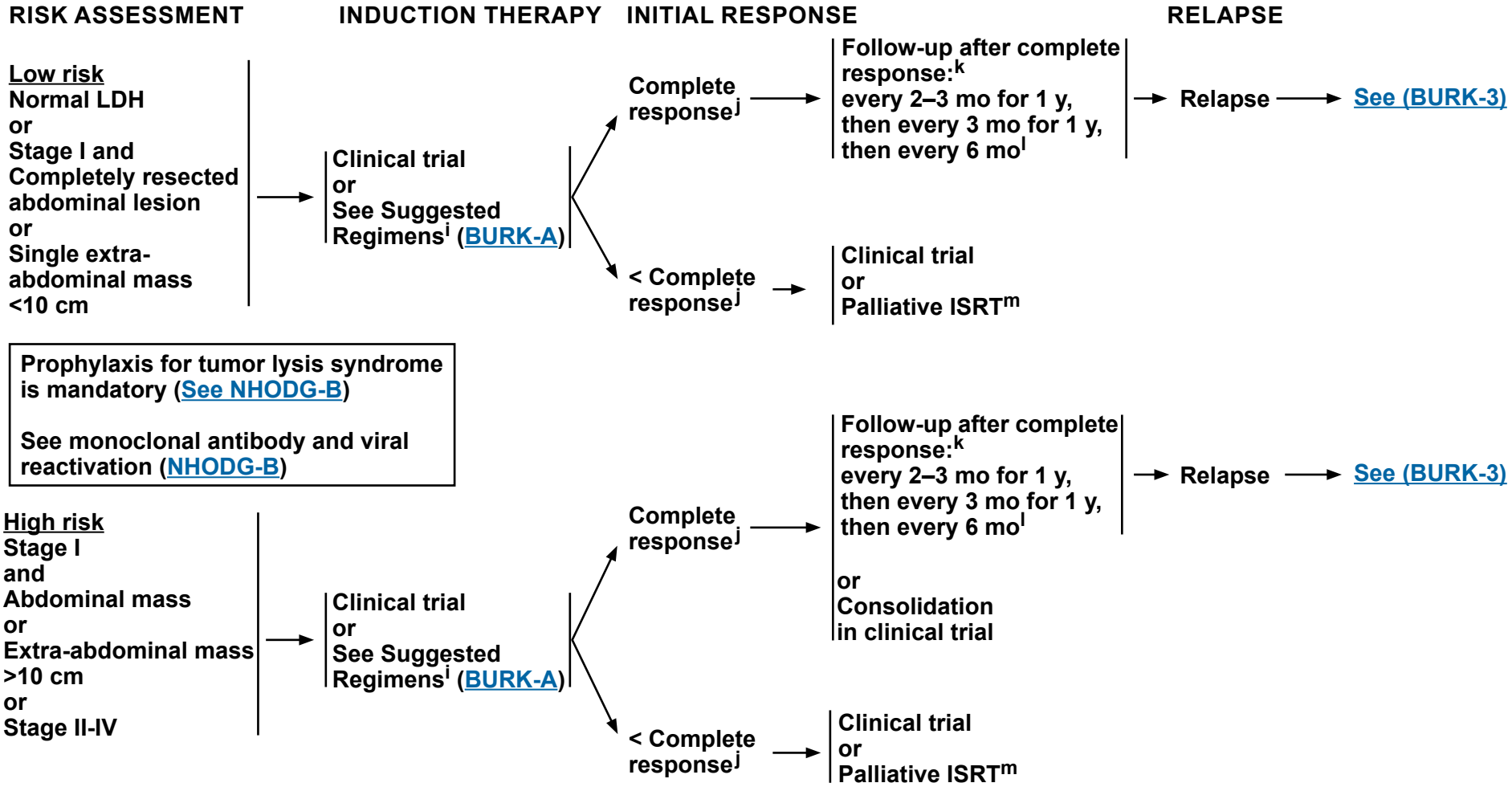

[i]All regimens for Burkitt lymphoma include CNS prophylaxis/therapy.
[j]See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[k]Repeat C/A/P CT scan with contrast only as clinically indicated.
[l]Relapse after 2 y is rare; therefore, follow-up should be individualized according to patient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

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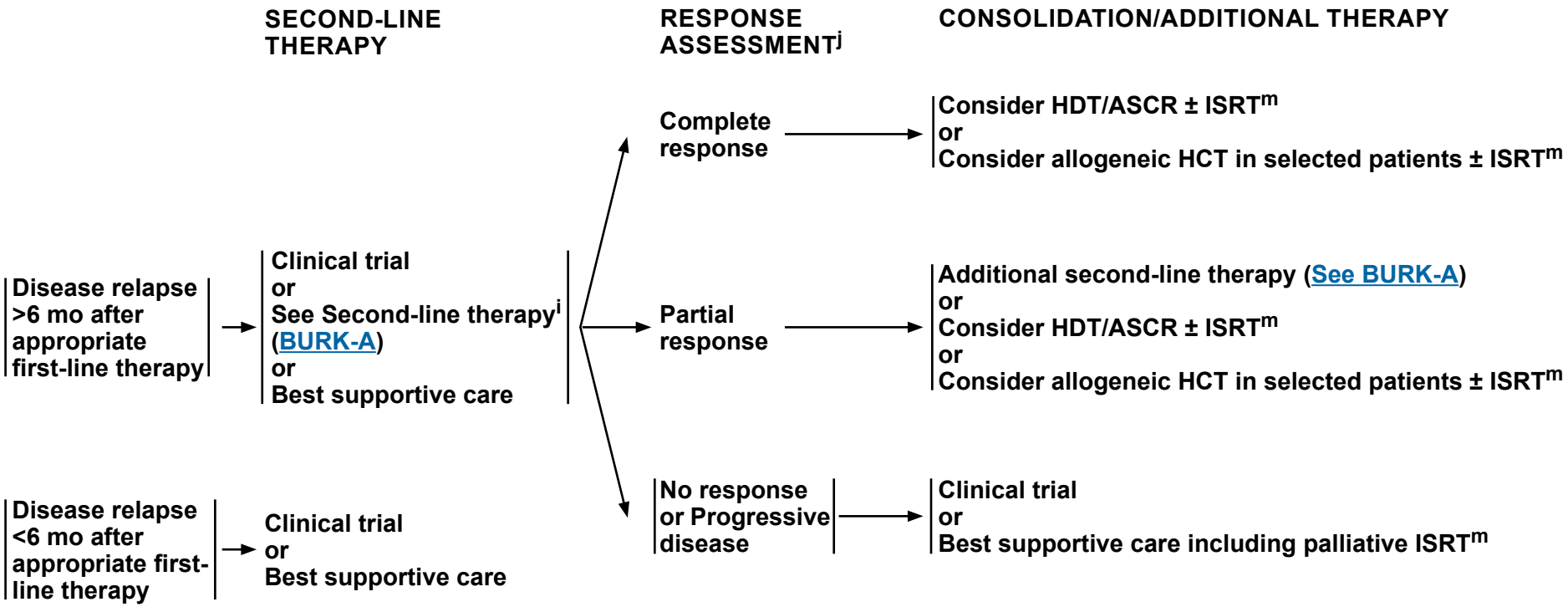

Prophylaxis for tumor lysis syndrome is mandatory (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

See Evidence Blocks on BURK-A (EB-1)

[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).

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

An FDA-approved biosimilar is an appropriate substitute for rituximab.

CHOP is not an adequate therapy.

Induction Therapy

Low Risk

- **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

- **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 (for patients with disease relapse >6 mo after appropriate first-line therapy)

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**

See Evidence Blocks on BURK-A (EB-1)

Prophylaxis for tumor lysis syndrome is mandatory (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

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

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EVIDENCE BLOCKS FOR BURKITT LYMPHOMA

Induction Therapy for Low-Risk Burkitt Lymphoma	
CODOX-M (3 cycles)	
CODOX-M/rituximab (3 cycles)	
Dose-adjusted EPOCH/rituximab (minimum 3 cycles with one additional cycle beyond CR; regimen includes intrathecal methotrexate)	
HyperCVAD/rituximab (regimen includes intrathecal therapy)	

Induction Therapy for High-Risk Burkitt Lymphoma	
CODOX-M alternating with IVAC	
CODOX-M alternating with IVAC/rituximab	
Dose-adjusted EPOCH/rituximab (regimen includes intrathecal methotrexate)	
HyperCVAD/rituximab (regimen includes intrathecal therapy)	

Second-Line Therapy (for Patients with Disease Relapse >6 Mo After Appropriate First-Line Therapy)	
Dose-adjusted EPOCH/rituximab (minimum 3 cycles with one additional cycle beyond CR; regimen includes intrathecal methotrexate)	
High-dose cytarabine/rituximab	
RGDP (rituximab, gemcitabine, dexamethasone, cisplatin)	
RICE (rituximab, ifosfamide, carboplatin, etoposide)/intrathecal methotrexate	
RIVAC (rituximab, ifosfamide, cytarabine, etoposide)/intrathecal methotrexate	

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SUGGESTED TREATMENT REGIMENS
REFERENCES

Induction therapy

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 2017;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, Faderl S, et al. Hyper-CVAD and rituximab for de novo Burkitt lymphoma/leukemia [abstract]. Blood 2011;118:Abstract 2698.

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.

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ADDITIONAL DIAGNOSTIC TESTING

ESSENTIAL:

- **Adequate immunophenotyping to establish diagnosis[a] and subclassification (eg, DLBCL, Burkitt lymphoma, plasmablastic lymphoma, 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.

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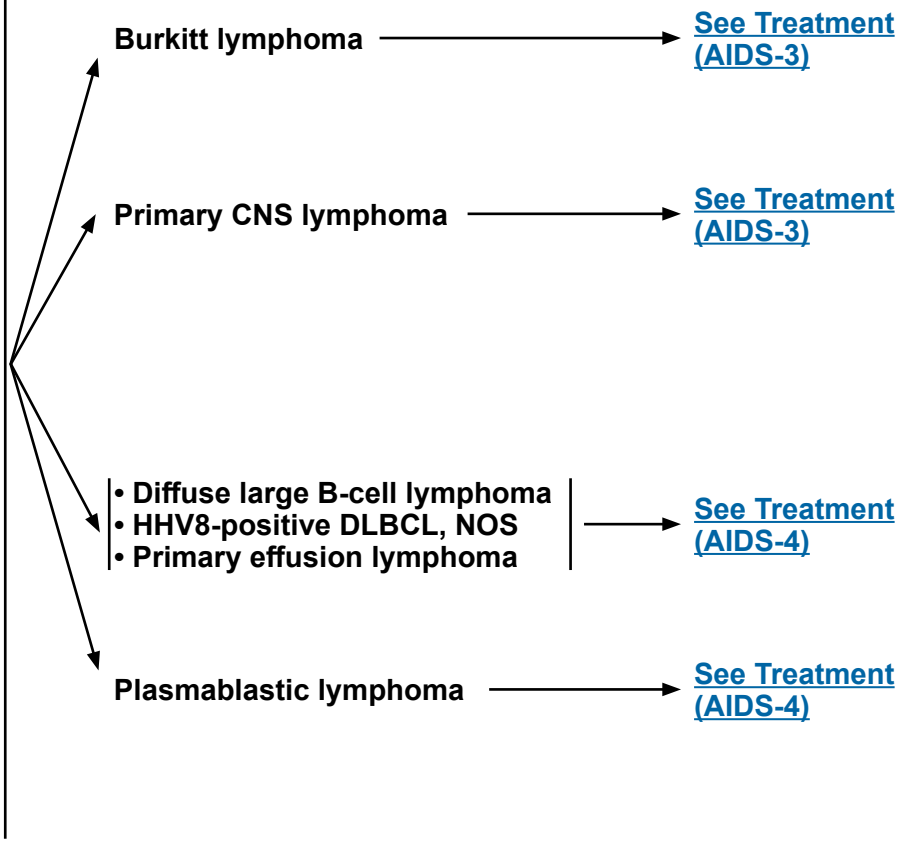
WORKUP

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
- 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.

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TREATMENT

Antiretroviral therapy (ART) can be administered safely with chemotherapy but consultation with an HIV specialist or pharmacist is important to optimize compatibility. With continued development of new ARTs, effective alternatives are often available to patients when the existing ARTs 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). For principles of concurrent HIV management and supportive care, see the NCCN Guidelines for Cancer in People Living with HIV.[e]

Burkitt lymphoma →

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

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

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 the 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)**

[e]In the NCCN Guidelines for Cancer in People Living with HIV, see the Principles of HIV Management While Undergoing Cancer Therapy; Principles of Systemic Therapy and Drug-Drug Interactions; and Principles of Supportive Care.
[f]See references for regimens (AIDS-A).
[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]An FDA-approved biosimilar is an appropriate substitute for rituximab.
[i]For R-EPOCH dosing, see 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.

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TREATMENT

ART can be administered safely with chemotherapy but consultation with an HIV specialist or pharmacist is important to optimize compatibility. With continued development of new ARTs, effective alternatives are often available to patients when the existing ARTs 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). For principles of supportive care, see the NCCN Guidelines for Cancer in People Living with HIV.[e]

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

→

- Suggested regimens:[f,g,h]
  - R-EPOCH[j] (preferred) → For relapse, see BCEL-7
  - CHOP + rituximab
- GCSF for all patients
- Intrathecal (IT) therapy[k]
- If CD20-, rituximab is not indicated
- If CD4 <50, maximize supportive care and monitor closely for cytopenias and infections while administering lymphoma therapy

Plasmablastic lymphoma[l] →

- Standard CHOP is not adequate therapy
- Suggested regimens:[f]
  - EPOCH (preferred)[j]
  - 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[m]
- IT therapy[k]

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

[e] In the NCCN Guidelines for Cancer in People Living with HIV, see the Principles of HIV Management While Undergoing Cancer Therapy; Principles of Systemic Therapy and Drug-Drug Interactions; and Principles of Supportive Care.

[f] See references for regimens (AIDS-A).

[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] An FDA-approved biosimilar is an appropriate substitute for rituximab.

[j] See Recommendations for EPOCH ± Rituximab Dose Adjustments for Non-Burkitt Lymphomas (AIDS-B).

[k] CNS prophylaxis indicated if double-hit lymphoma or lymphomatous involvement of bone marrow, testes, sinuses, or epidural regions. The specific regimen is at the discretion of the primary oncologist but should include 4–6 doses of therapy (IT cytarabine or IT methotrexate). If a patient presents with positive CSF or leptomeningeal involvement, intrathecal therapy should be administered twice weekly until CSF is negative, then weekly x 1 month, then monthly x 6 months. Although the specific regimen may vary, a suggested regimen is: cytarabine 50 mg + methotrexate 12 mg + hydrocortisone 50 mg. (See Prognostic Model to Assess the Risk of CNS Disease (BCEL-A 2 of 2).

[l] Management can also apply to HIV-negative plasmablastic lymphoma.

[m] 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.

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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.

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.

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

Ramos J, Sparano J, Rudek M, et al. Safety and preliminary efficacy of vorinostat with R-EPOCH in high-risk HIV-associated non-Hodgkin's lymphoma (AMC-075). Clin Lymphoma Myeloma Leuk 2018;18:180-190.

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.

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RECOMMENDATIONS FOR EPOCH ± RITUXIMAB DOSE ADJUSTMENTS FOR NON-BURKITT LYMPHOMAS[1]

EPOCH ± rituximab dosing recommendations for cycle 1:

- **Rituximab (if CD20-positive) 375 mg/m² IV on Day 1**
- **Etoposide 50 mg/m²/day continuous IV infusion for 4 days (96 hours)**
- **Doxorubicin 10 mg/m²/day continuous IV infusion for 4 days (96 hours)**
- **Vincristine 0.4 mg/m²/day continuous IV infusion for 4 days (96 hours)**
- **Day 5 cyclophosphamide dosing**
  - **If baseline CD4 count is >200 cells/mm³, start cyclophosphamide at 750 mg/m²**
  - **If baseline CD4 count is 50–200 cells/mm³, start cyclophosphamide at 375 mg/m²**
  - **For baseline CD4 counts <50 cells/mm³, doses of cyclophosphamide above 187.5 mg/m² have not been published. For cycle 1, consider a starting dose of 187.5 mg/m² and consider initial therapy with EPOCH alone with the addition of rituximab in future cycles if the EPOCH is tolerated and/or CD4 count has improved with concurrent antiretroviral therapy.**
- **Prednisone 60 mg/m²/day for 5 days.**

EPOCH Dose Modifications for Subsequent Cycles Based on Cytopenias (Non-Burkitt Lymphomas)[1]	
Event	**Action**
ANC nadir on any cycle <500/mm³ on 2 nonconsecutive days at least 3 days apart and/or platelet nadir <25,000/mm³ in the previous cycle	**Reduce cyclophosphamide dose by 187 mg/m²**
ANC nadir <500/mm³ x ≥3 days or platelets <25,000/mm³ x ≥3 days, AND patient was receiving no cyclophosphamide in the previous cycle	**Reduce doxorubicin and etoposide by 25% of the full dose**
ANC nadir ≥500/mm³ AND platelet nadir ≥50,000/mm³ in the previous cycle	**Increase cyclophosphamide dose by 187 mg/m² each cycle to a maximum dose of 750 mg/m²**

[1]For R-EPOCH dosing for non-Burkitt lymphomas, see Ramos J, Sparano J, Rudek M, et al. Safety and preliminary efficacy of vorinostat with R-EPOCH in high-risk HIV-associated non-Hodgkin's lymphoma (AMC-075). Clin Lymphoma Myeloma Leuk 2018;18:180-190. This is an ongoing clinical trial and the utility of adding vorinostat to R-EPOCH has not yet been established.

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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.

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NCCN Guidelines Version 6.2019
Post-Transplant Lymphoproliferative Disorders
NCCN Evidence Blocks™

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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 (EBV) 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
- History of therapy for transplant
- 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 for cell-free plasma EBV DNA marker
- CMV PCR
- EBV serology for primary versus reactivation

PTLD SUBTYPE[c]

- Early lesions[d] → See First-line Therapy (PTLD-2)
- Monomorphic PTLD (B-cell type) → See First-line Therapy (PTLD-2)
- Polymorphic PTLD → See First-line Therapy (PTLD-3)
- Monomorphic PTLD (T-cell type) →
  - Other than reduction of immunosuppression (RI), there are no established treatments.
  - Consider treatment with multiagent regimens (see Suggested Regimens PTLD-A); autologous HCT 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] Indolent small B-cell lymphomas arising in transplant recipients are not included among PTLDs, with the exception of EBV-positive marginal zone lymphomas.
[d] Early lesions are of B-cell type and include plasmacytic hyperplasia, infectious mononucleosis, and florid follicular hyperplasia.

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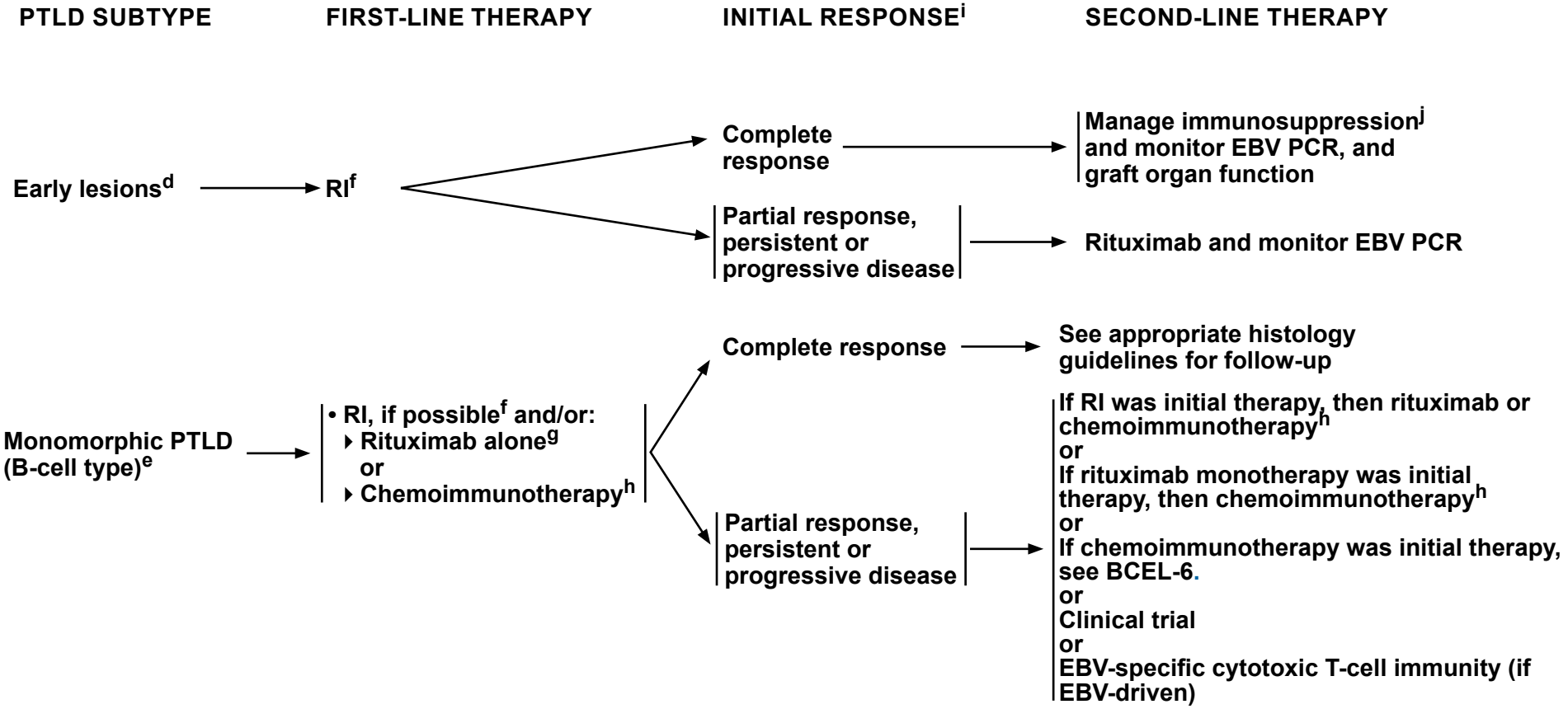

[d]Early lesions are of B-cell type and include plasmacytic hyperplasia, infectious mononucleosis, and florid follicular hyperplasia.
[e]Treatment is based on the unique histology.
[f]Response to RI is variable and patients need to be closely monitored; RI should be coordinated with the transplant team. 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.
[g]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)

[h]For concurrent or sequential chemoimmunotherapy, see Suggested Treatment Regimens (PTLD-A).
[i]Restage in two to four weeks.
[j]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.

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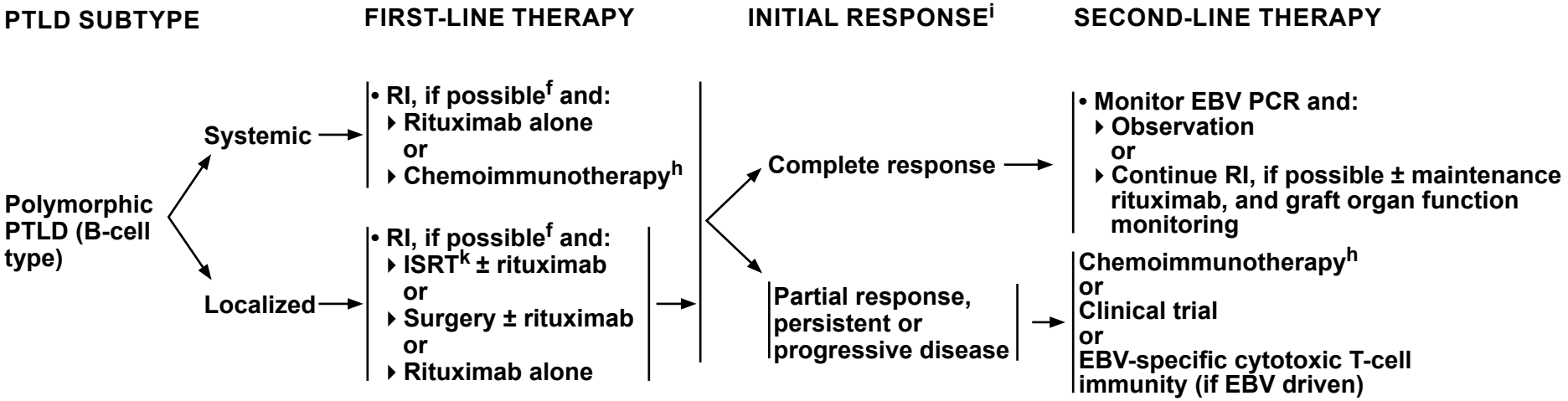

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

[f]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.
[h]For concurrent or sequential chemoimmunotherapy, see Suggested Treatment Regimens (PTLD-A).
[i]Restage in two to four weeks.
[k]See Principles of Radiation Therapy (NHODG-D).

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SUGGESTED TREATMENT REGIMENS[a]
(in alphabetical order)
An FDA-approved biosimilar is an appropriate substitute for rituximab.

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]**
  - **RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine)**
  - **RCEOP (rituximab, cyclophosphamide, etoposide, vincristine, prednisone)**
  - **RCVP (rituximab, cyclophosphamide, vincristine, prednisone)**

Sequential chemoimmunotherapy
- **Rituximab 375 mg/m^2 weekly x 4 weeks (on days 1, 8, 15, and 22)[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 + G-CSF (on days 50, 72, 94, and 116) 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**
  - **CEOP**
  - **CEPP**

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

[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.

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NCCN Guidelines Version 6.2019
Castleman's Disease
NCCN Evidence Blocks™

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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 rearrangements
- 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, SPEP 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 Castelman's disease** → See CD-2

→ **Multicentric Castelman's disease** → See CD-3

[a]For AIDS-related lymphoma associated with Castleman's disease, see AIDS-1. For DLBCL-associated with Castelman's disease 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.

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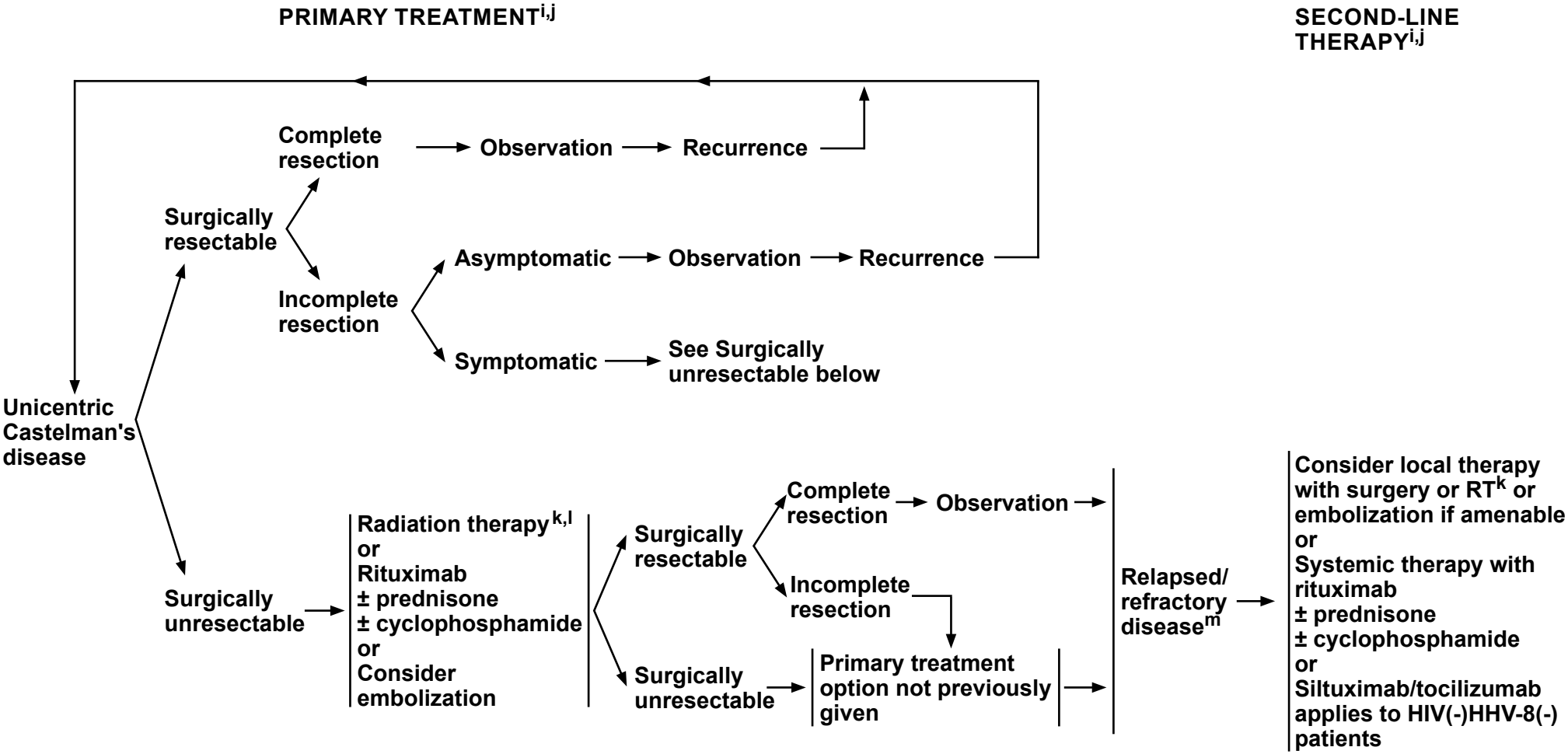

[i]Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.
[j]An FDA-approved biosimilar is an appropriate substitute for rituximab.
[k]See Principles of Radiation Therapy (NHODG-D).
[l]Patients with non-bulky disease may be observed after RT.
[m]Encourage biopsy to rule out transformation to DLBCL or concomitant development of other malignancies or opportunistic infections.

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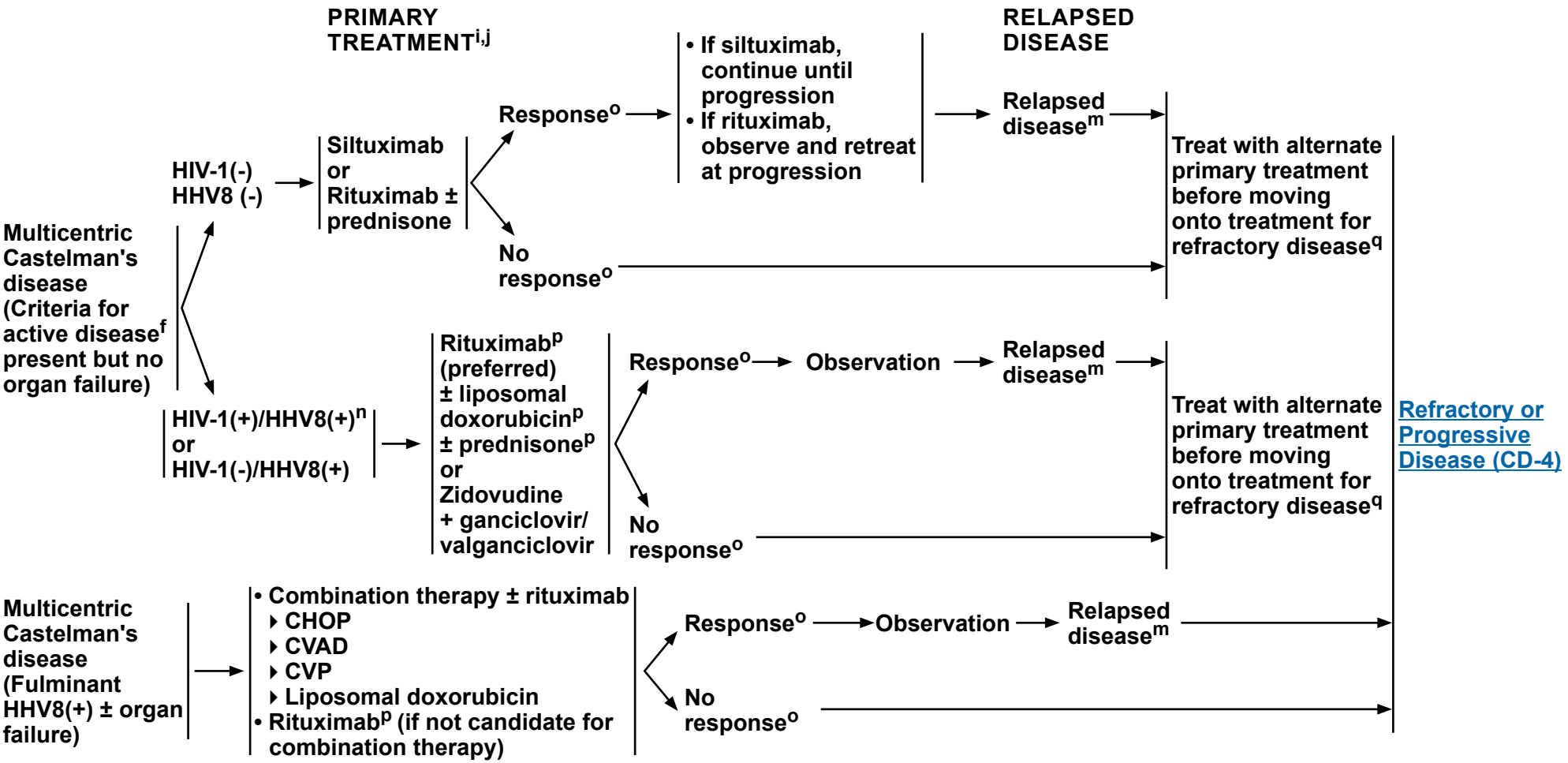

[f] See Criteria for Active Disease (CD-A).

[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.

[j] An FDA-approved biosimilar is an appropriate substitute for rituximab.

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

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

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

[p] 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).

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

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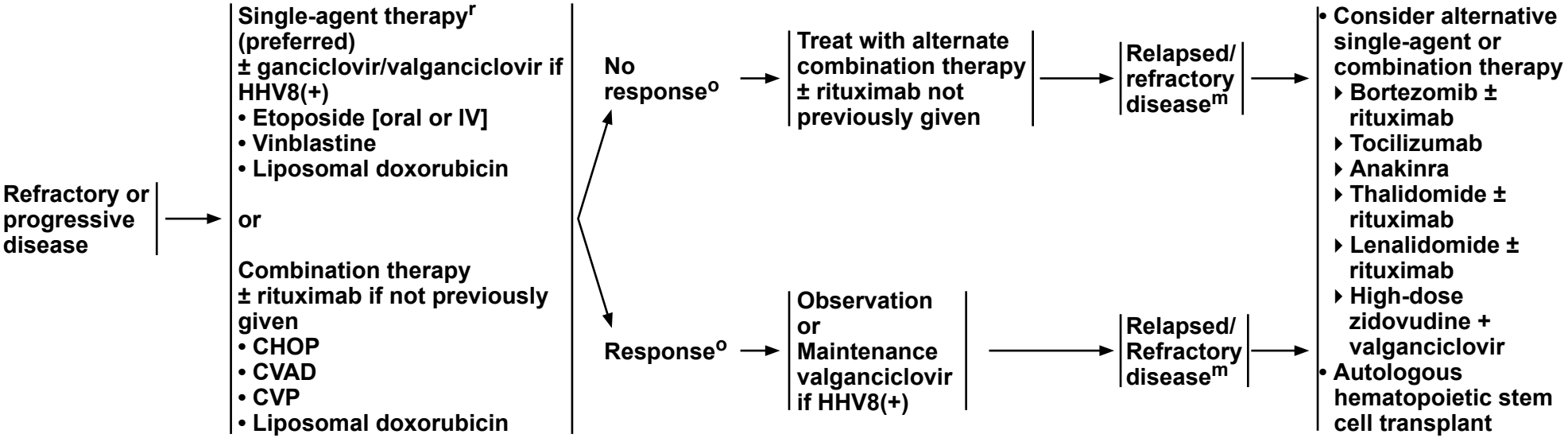
REFRACTORY OR PROGRESSIVE DISEASE[i,j]



[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]An FDA-approved biosimilar is an appropriate substitute for rituximab.
[m]Encourage biopsy to rule out transformation to DLBCL or concomitant development of other malignancies or opportunistic infections.
[o]Response assessment using the imaging modalities performed during workup (C/A/P CT with contrast or PET/CT).
[r]Single-agent therapy is preferred for asymptomatic patients with no organ failure; combination therapy is preferred for patients with fulminant disease and organ failure.

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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.

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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

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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.

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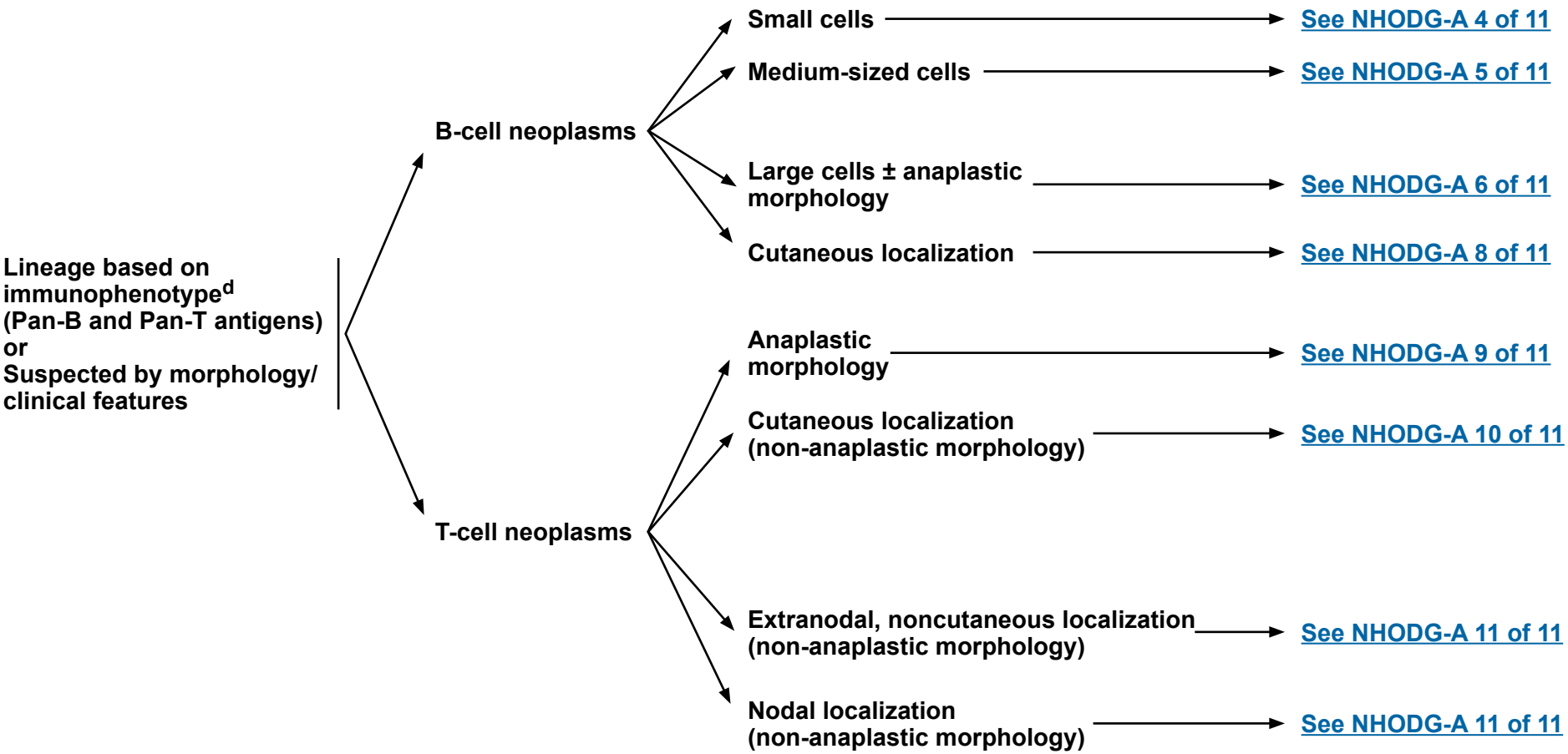
INITIAL MORPHOLOGIC, CLINICAL, AND IMMUNOPHENOTYPIC ANALYSIS



[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.

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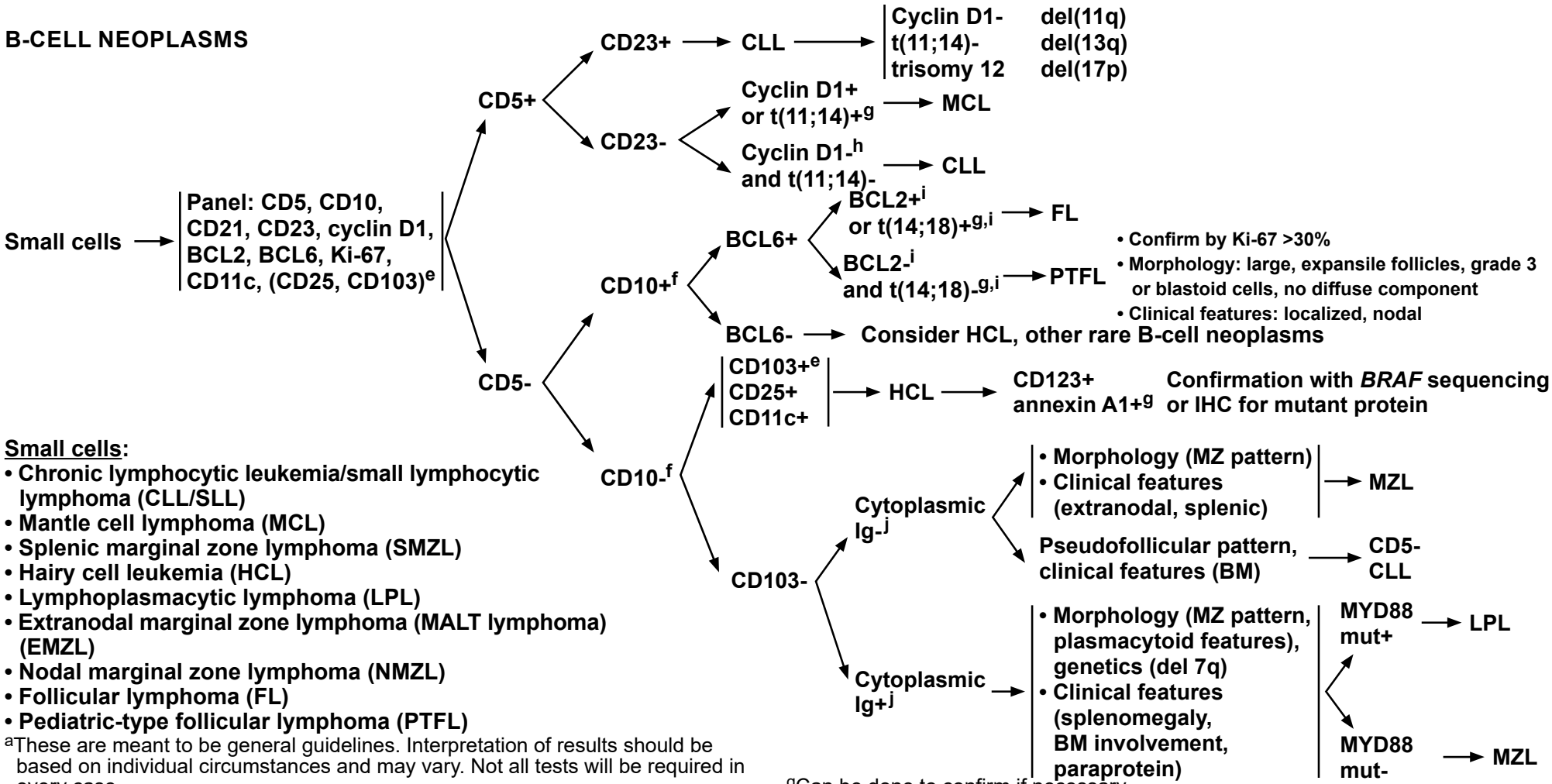

Small cells:
- Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)
- Mantle cell lymphoma (MCL)
- Splenic marginal zone lymphoma (SMZL)
- Hairy cell leukemia (HCL)
- Lymphoplasmacytic lymphoma (LPL)
- Extranodal marginal zone lymphoma (MALT lymphoma) (EMZL)
- Nodal marginal zone lymphoma (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.

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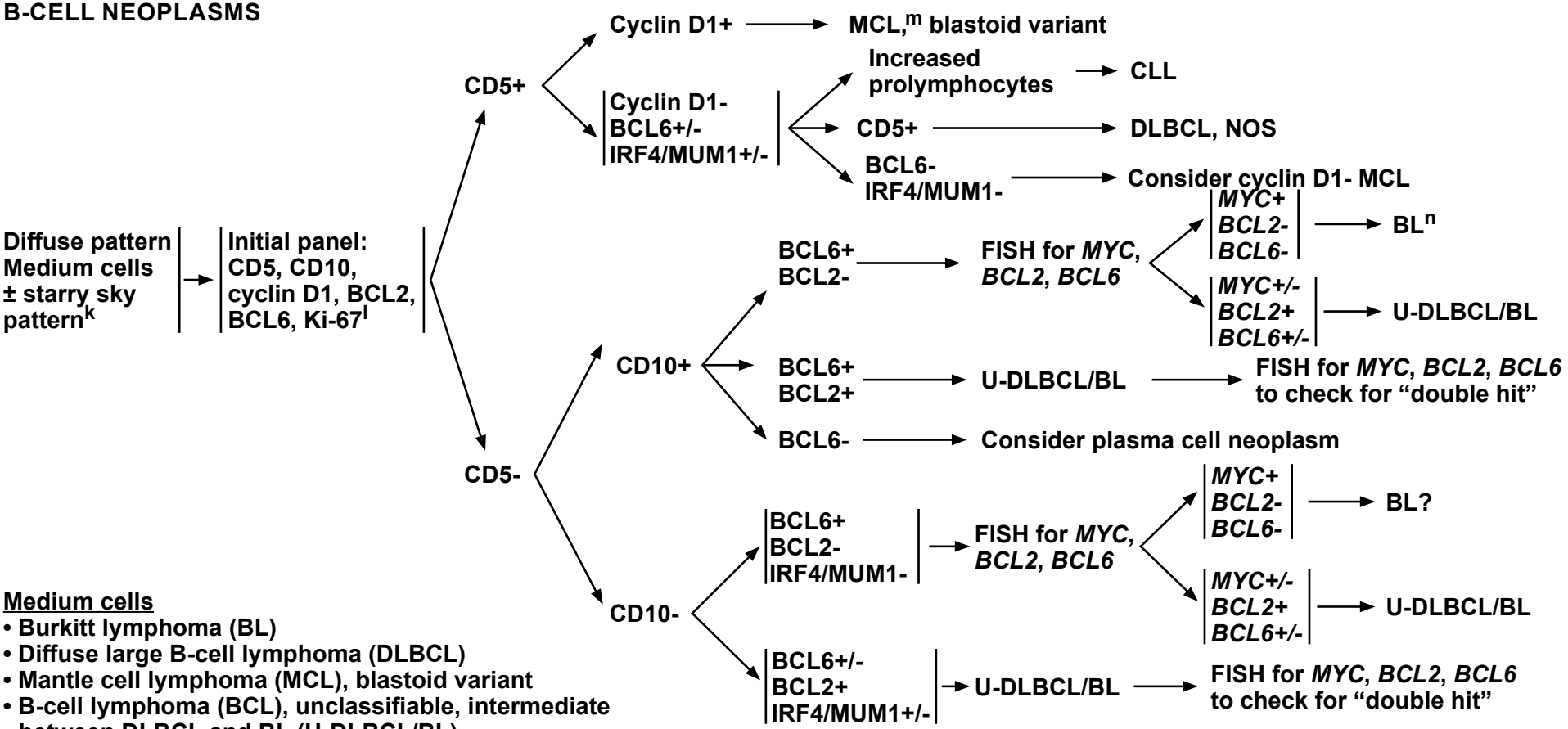
B-CELL NEOPLASMS



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.

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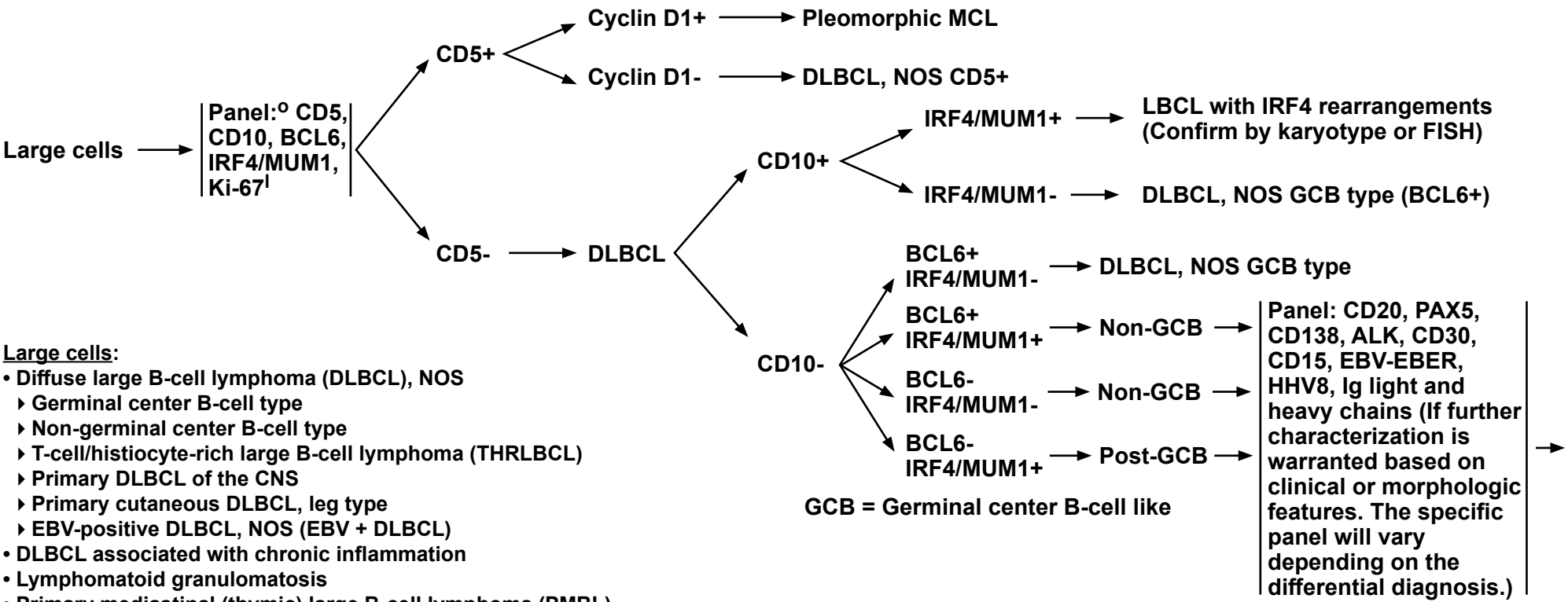
B-CELL NEOPLASMS



GCB = Germinal center B-cell like

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.

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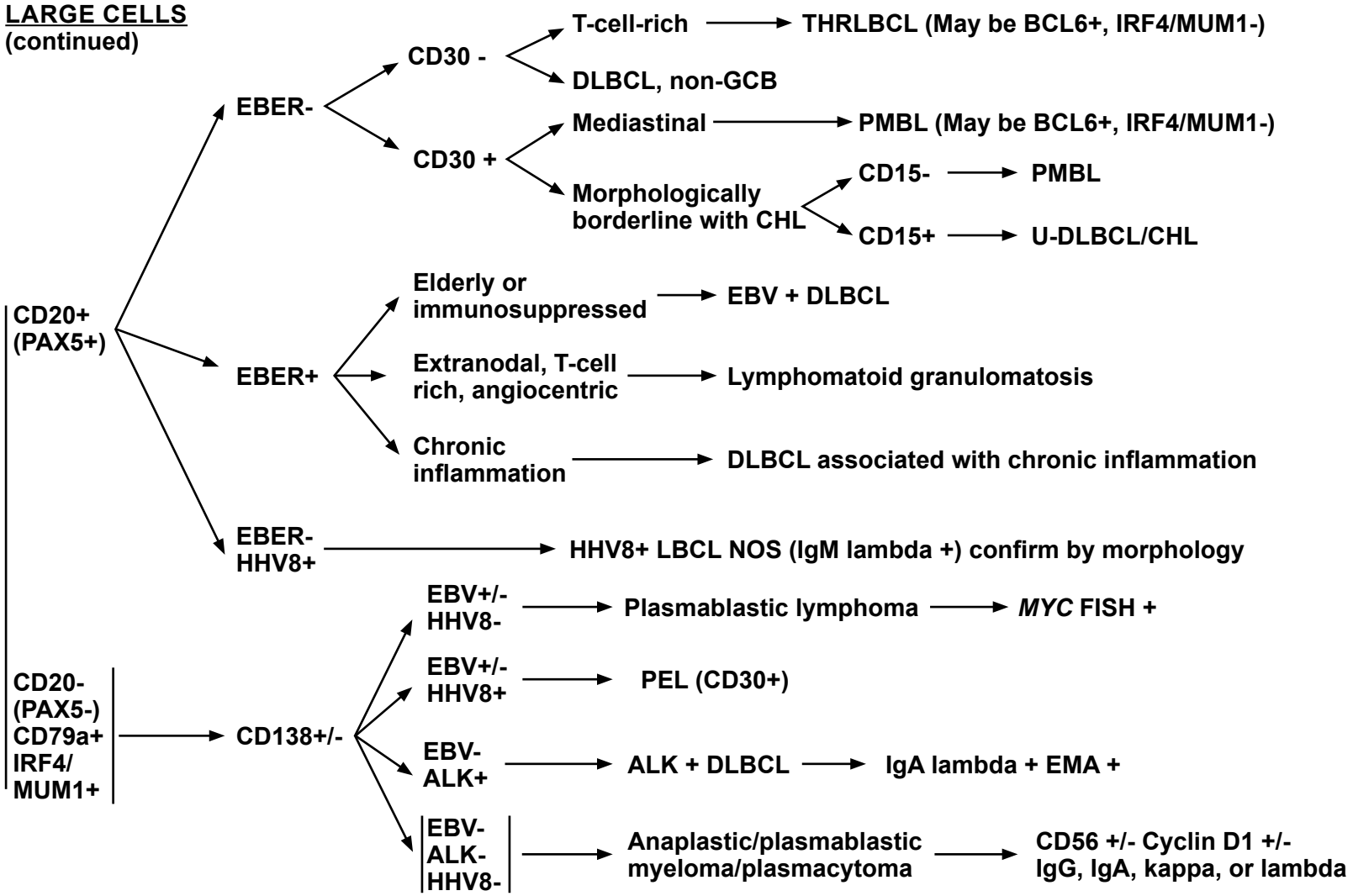

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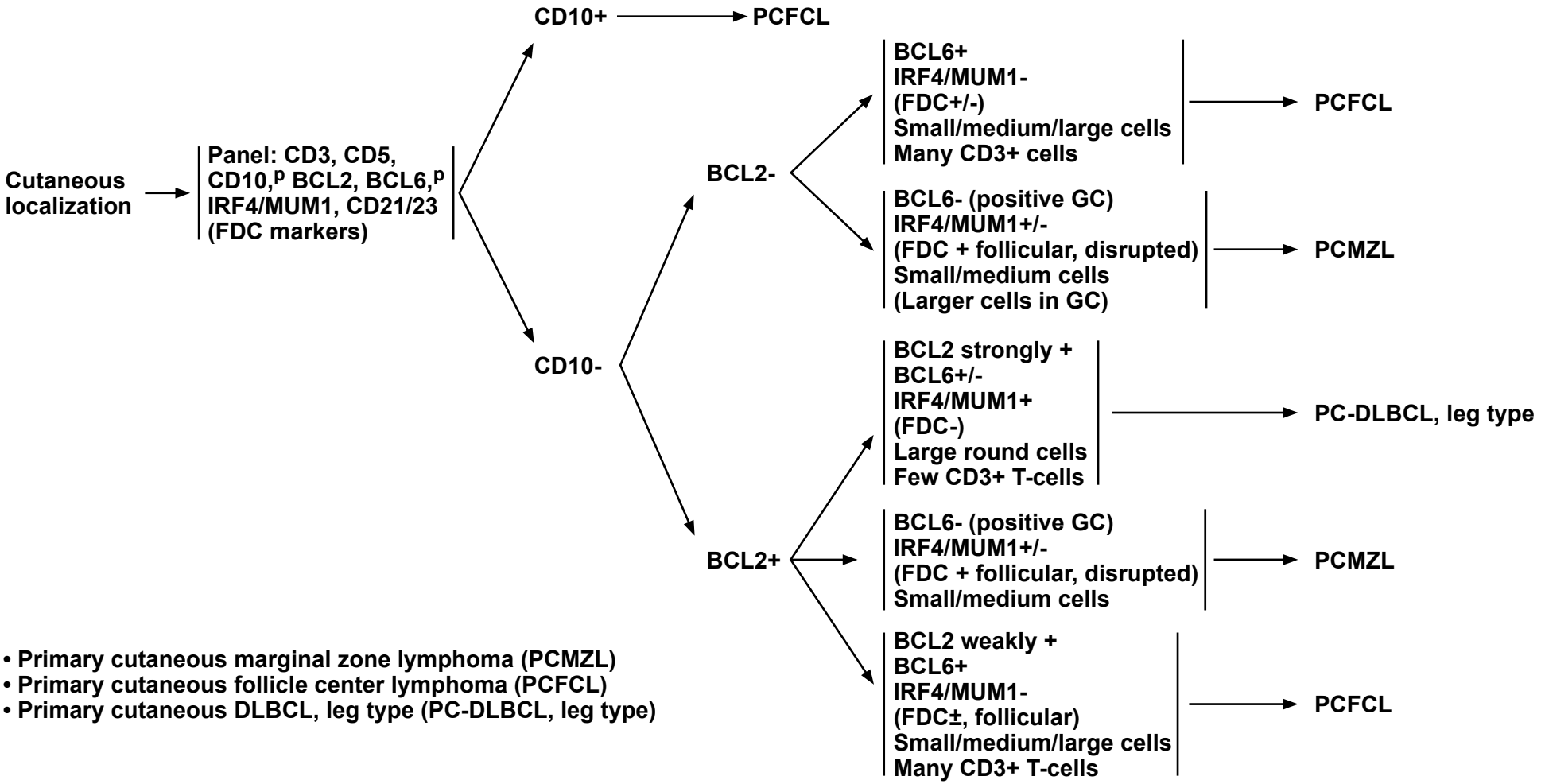
B-CELL NEOPLASMS

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.

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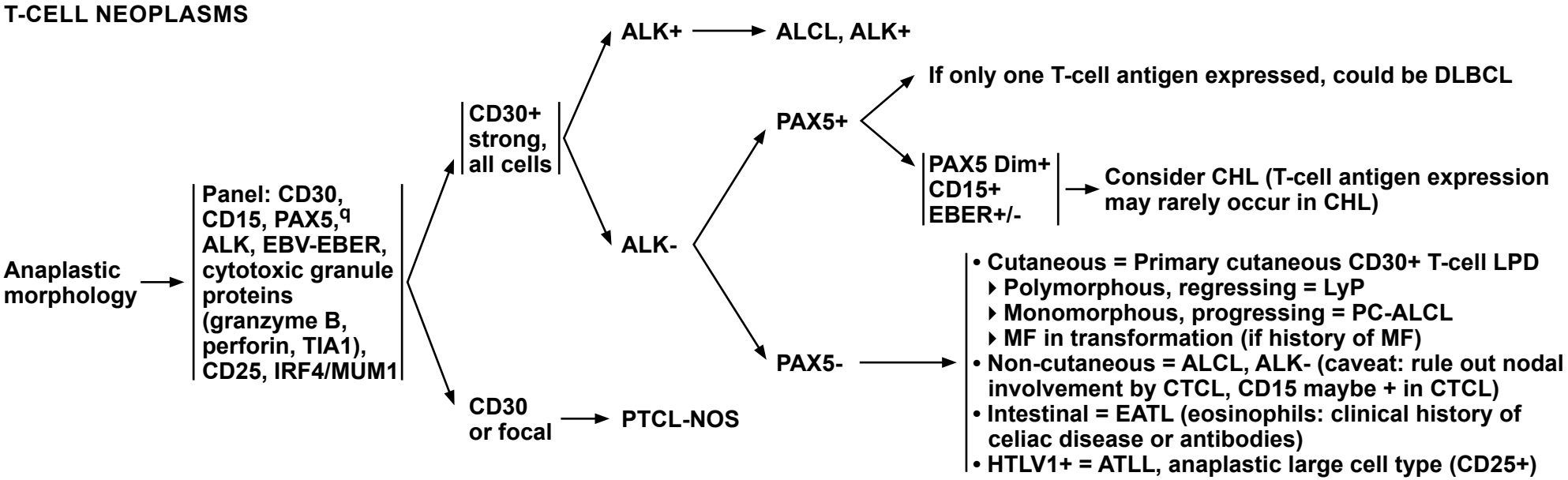

Anaplastic morphology

- 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.

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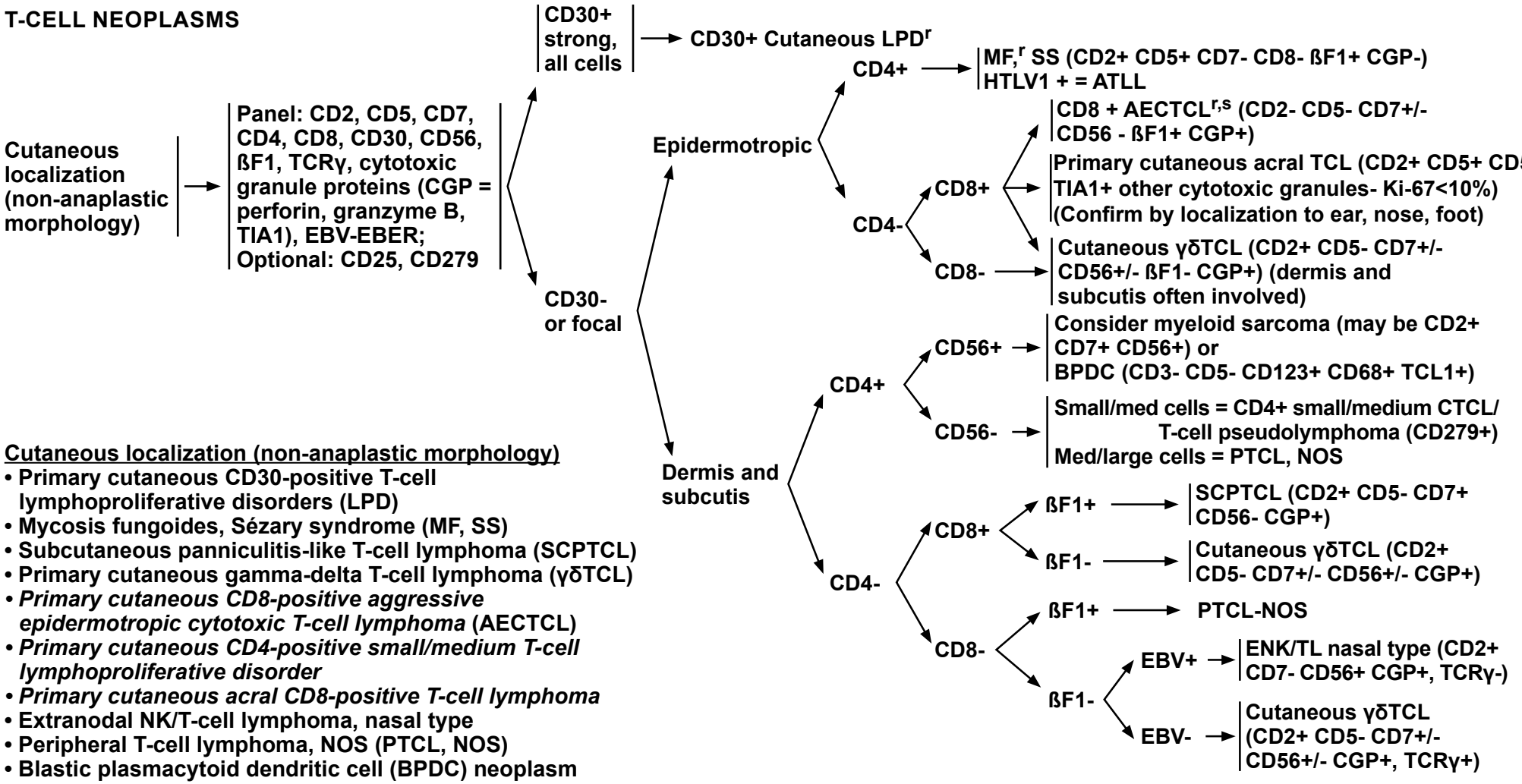

Cutaneous localization (non-anaplastic morphology)

- 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.

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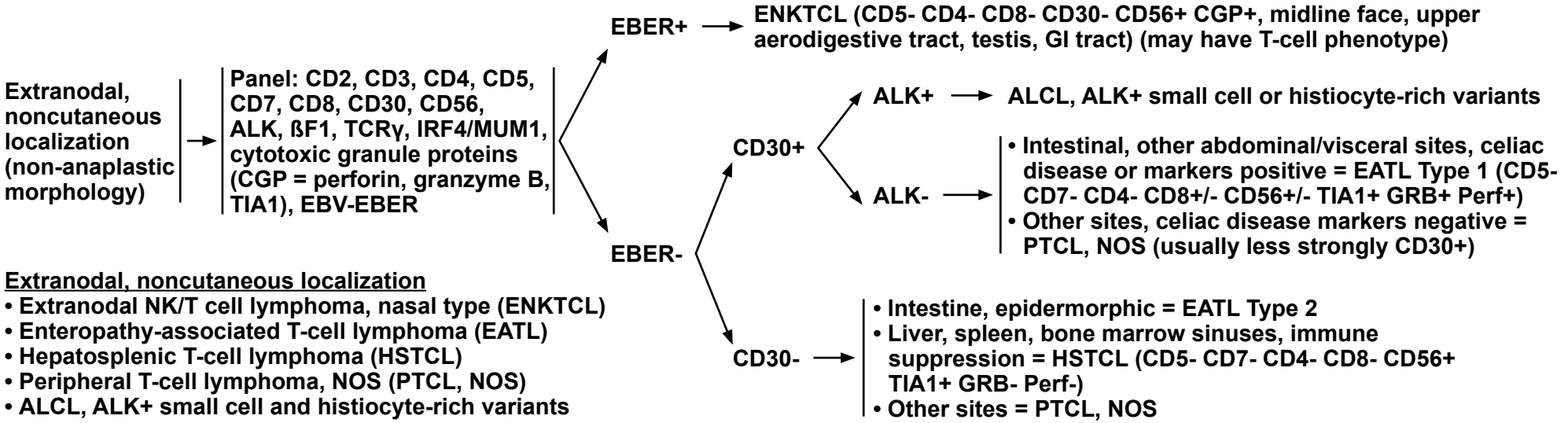
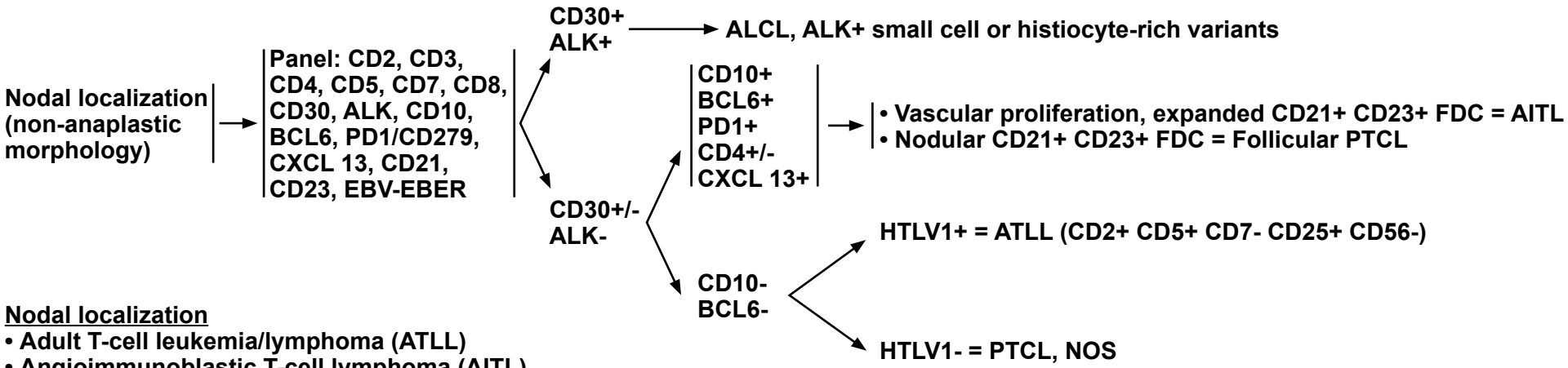


Extranodal, noncutaneous localization

- 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.

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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.

- TLS features:
  - Consider TLS prophylaxis for patients with the following risk factors:
    - ◊ Histologies of Burkitt lymphoma and lymphoblastic lymphoma; occasionally DLBCL
    - ◊ Spontaneous TLS
    - ◊ Elevated WBC
    - ◊ Bone marrow involvement
    - ◊ Pre-existing elevated uric acid
    - ◊ Ineffectiveness/intolerance 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:
    - ◊ Vigorous hydration
    - ◊ Management of hyperuricemia
    - ◊ Frequent monitoring of electrolytes and aggressive correction (essential)
  - First-line and at retreatment for hyperuricemia
    - ◊ Allopurinol or febuxostat if intolerant to allopurinol beginning 2–3 days prior to chemotherapy and continued for 10–14 days
      or
      Rasburicase (doses of 3 to 6 mg are usually effective.[a] One dose of rasburicase is frequently adequate. Re-dosing should be individualized) is indicated for patients with any of the following risk factors:
      - Urgent need to initiate therapy in a high-bulk patient
      - Situations where adequate hydration may be difficult or impossible
      - Acute renal failure
  - If TLS is untreated, its progression may cause acute kidney failure, cardiac arrhythmias, seizures, loss of muscle control, and death.

[a]There are data to support that fixed-dose rasburicase is very effective in adult patients.

Continued

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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.**

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SUPPORTIVE CARE FOR B-CELL LYMPHOMAS[b]

Rare Complications of Monoclonal Antibody Therapy

- **Rare complications such as mucocutaneous reactions including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis can occur. Expert consultation with dermatology is recommended.**
- **Re-challenge with the same monoclonal antibody is not recommended in patients experiencing rare complications to chosen anti-CD20 monoclonal antibody (rituximab, obinutuzumab, or ofatumumab). An alternative anti-CD20 monoclonal antibody (obinutuzumab or ofatumumab) could be used for patients with intolerance to rituximab, regardless of histology. It is unclear that the use of alternative anti-CD20 monoclonal antibody poses the same risk of recurrence.**

Rituximab Rapid Infusion

- **If no infusion reactions were experienced with prior cycle of rituximab, a rapid infusion over 90 minutes can be used.**

Rituximab-Related Neutropenia

- **Usually delayed in onset weeks to months after last exposure**
- **Occurs in up to 10% of patients**
- **Can be severe, but usually not presenting with infections**
- **Can be initially observed for spontaneous recovery, but if prolonged a short course of G-CSF is indicated**
- **IVIG has been anecdotally successful in patients refractory to G-CSF**

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.**

[b]Supportive care measures specific to rituximab include both rituximab as well rituximab biosimilars.

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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 National Academy 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 in 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. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009;361:756-765. [published correction appears in N Engl J Med. 2009; 361(19):1914].
[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. J Bone Miner Res 2005;20:1487-1494.

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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)[d]
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 5 mm x 5 mm as the default value. When no longer visible, 0x0 mm For a node >5 mm x 5 mm, 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

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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)[d]
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 0.5 cm 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

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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 quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses and other lesions that cannot be confirmed and followed by imaging.

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PRINCIPLES OF RADIATION THERAPY

General Principles[a]

- **Treatment with photons, electrons, or protons may all be appropriate, depending on clinical circumstances.**
- **Advanced radiation therapy technologies such as IMRT/VMAT, breath hold or respiratory gating, and/or 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 as it reduces the risk of late complications from normal tissue damage. This is especially important for patients being treated with curative intent or who have long life expectancies following therapy.**
- **In mediastinal lymphoma, the use of 4D-CT or breath-hold techniques for simulation, the adoption of strategies to deal with respiratory motion such as inspiration breath-hold techniques, and image-guided RT during treatment delivery are also important. Breath-hold techniques have been shown to decrease incidental dose to the heart and lungs in many disease presentations.**
- **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.**

[a]See references on NHODG-D 4 of 4.

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PRINCIPLES OF RADIATION THERAPY[a]

Volumes

- **ISRT for nodal disease (see Illidge T, et al. Int J Radiat Oncol Biol Phys 2014;89:49-58)**
  - **ISRT is recommended as the appropriate field for NHL. Planning for ISRT requires modern CT-based simulation and treatment 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 extent of disease suspicious volume prior to chemotherapy or surgery. However, it spares adjacent uninvolved organs (eg, lungs, bone, muscle, 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 treatment volumes should be considered to encompass potential microscopic disease in adjacent lymph nodes or the immediate vicinity. 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).**
  - **Organs at risk should be outlined for optimizing treatment plan decisions.**
  - **The treatment plan can be designed using conventional, 3-D conformal, or IMRT/VMAT and proton therapy techniques using clinical treatment planning considerations of coverage and normal tissue avoidance.**

- **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.**

[a]See references on NHODG-D 4 of 4.

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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; PR: 36–50 Gy**
    - **Complementary 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/Burkitt lymphoma: 24–30 Gy**
  - **AIDS-related B-cell lymphomas and PTLD: Treated based on underlying histologic subtype and treatment intent (curative vs. palliative)**

[a]See references on NHODG-D 4 of 4.

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PRINCIPLES OF RADIATION THERAPY
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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
- **Toxicity**
  - 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

- **Dosage**
  - 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).
- **Toxicity**
  - 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.

[1]Please refer to package insert for full prescribing information and monitoring for adverse reactions, available at www.fda.gov.

Continued

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SPECIAL CONSIDERATIONS FOR THE USE OF SMALL-MOLECULE INHIBITORS[1]

Duvelisib

- **Dosage**
  - The recommended dose of duvelisib is 25 mg PO twice daily, per prescribing recommendations.
- **Lymphocytosis**
  - Upon initiation of duvelisib, transient increase in absolute lymphocyte count is expected in most patients, which does not signify disease progression. This onset of isolated lymphocytosis occurs during the first few weeks of duvelisib therapy and may persist for several weeks on treatment.
- **Toxicity**
  - Hepatotoxicity: Monitor hepatic function prior to and during treatment. Interrupt if ALT/AST >5 x ULN (upper limit of normal) and when resolved resume at the same dose (25 mg twice daily) for first occurrence or at a reduced dose (15 mg twice daily) for subsequent occurrence. Discontinue duvelisib if ALT/AST > 20 × ULN.
  - Diarrhea or colitis: Monitor for the development of severe diarrhea or colitis. Initiate supportive therapy with antidiarrheal agents as appropriate. In case of severe diarrhea or colitis, interrupt duvelisib until resolution and then resume at a reduced dose (15 mg twice daily) or discontinue duvelisib. Severe diarrhea and colitis can be managed with enteric acting steroids (eg, budesonide) or systemic steroids.
  - Pneumonitis without suspected infectious cause: Interrupt duvelisib and treat with systemic steroid therapy for grade 2. If pneumonitis recovers to grade 0 or 1, duvelisib may be resumed at reduced dose (15 mg twice daily). Discontinue duvelisib if non-infectious pneumonitis recurs or patient does not respond to steroid therapy or for severe (grade 3) or life threatening pneumonitis.
  - Cutaneous reactions: Monitor closely and initiate supportive care with emollients, antihistamines (for pruritus), or topical steroids. In case of severe cutaneous reactions, interrupt duvelisib until resolution and initiate supportive care with emollients, antihistamines (for pruritus), or topical steroids. Resume at a reduced dose (15 mg twice daily). If severe cutaneous reaction does not improve, worsens, or recurs, discontinue duvelisib.
  - Infections: PJP prophylaxis with sulfamethoxazole/trimethoprim or equivalent.
  - CMV reactivation: Consider prophylactic antivirals to prevent CMV infection including CMV reactivation.

Ibrutinib

- **Dosage**
  - MCL, DLBCL: 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.
- **Toxicity**
  - 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.
    - ◊ 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.

[1]Please refer to package insert for full prescribing information and monitoring for adverse reactions, available at www.fda.gov.

Continued

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SPECIAL CONSIDERATIONS FOR THE USE OF SMALL-MOLECULE INHIBITORS[1]

Idelalisib

- Dosage
  - The recommended dose of idelalisib is 150 mg PO twice daily, per prescribing recommendations.
- Toxicity
  - Hepatotoxicity: Monitor hepatic function prior to and during treatment. Interrupt (if ALT/AST > 5 x ULN) 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.
- Infections: PJP prophylaxis with sulfamethoxazole/ trimethoprim or equivalent.
- CMV: Monitor per institutional guidelines or consult with infectious disease specialist.

Venetoclax

- Dosage
  - The recommended single-agent dose for venetoclax is 400 mg (higher dose for insufficient response).
  - Initiate venetoclax at 20 mg for one week and gradually escalate to target dose of 400 mg PO daily over 5 weeks to reduce the risk of TLS.
  - TLS: See Tumor Lysis Syndrome (NHODG-B 1 of 4)
- Toxicity
  - Consider the use of neutrophil growth factors for neutropenia according to standard guidelines.

Zanubrutinib

- Dosage
  - The recommended dose of zanubrutinib is 160 mg orally twice daily or 320 mg orally once daily, per prescribing recommendations.
- Toxicity
  - Hemorrhage: Grade 3 or higher bleeding events including intracranial and gastrointestinal hemorrhage, hematuria, and hemothorax have been reported in 2% of patients treated with zanubrutinib monotherapy. Bleeding events of any grade, including purpura and petechiae, occurred in 50% of patients treated with zanubrutinib monotherapy. Consider the benefit-risk of withholding zanubrutinib for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.
  - Cytopenias: Grade 3 or 4 cytopenias, including neutropenia (27%), thrombocytopenia (10%), and anemia (8%) based on laboratory measurements, were reported in patients treated with zanubrutnib monotherapy.
  - Cardiac arrhythmias: Atrial fibrillation and atrial flutter have occurred in 2% of patients treated with zanubrutinib monotherapy. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher events were reported in 0.6% of patients treated with zanubrutinib monotherapy.
- Infections: Grade 3 or higher infections occurred in 23% of patients treated with zanubrutinib monotherapy. Consider prophylaxis for herpes simplex virus, pneumocystis jiroveci pneumonia, and other infections according to standard of care in patients who are at increased risk for infections.

Continued

[1]Please refer to package insert for full prescribing information and monitoring for adverse reactions, available at www.fda.gov.

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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.**
- **Duvelisib**
  - **Avoid concomitant use of strong CYP3A inducers.**
  - **Patients taking concomitant strong CYP3A4 inhibitors should be monitored more closely for signs of duvelisib toxicity. Reduce dose to 15 mg twice daily when co-administered with strong CYP3A4 inhibitors.**
  - **Monitor for signs of toxicities when coadministering with sensitive CYP3A substrates.**
- **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.**
- **Venetoclax**
  - **Avoid concomitant use of strong CYP3A inhibitors or inducers.**
- **Zanubrutinib**
  - **Modify dose with strong CYP3A inhibitors. Interrupt dose as recommended for adverse reactions.**
  - **Modify dose with moderate CYP3A inhibitors. Modify dose as recommended for adverse reactions.**
  - **Avoid concomitant use with moderate or strong CYP3A inducers.**

[1]Please refer to package insert for full prescribing information and monitoring for adverse reactions, available at www.fda.gov.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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Classification

Table 1

WHO Classification of the Mature B-Cell, T-Cell, and NK-Cell Neoplasms (2017)

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 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

Swerdlow SH CE, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, ed. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th ed. Lyon: IARC; 2017.

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Classification

***Table 1 (*continued)**

WHO Classification of the Mature B-Cell, T-Cell, and NK-Cell Neoplasms (2017)

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.

Continued

Swerdlow SH CE, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, ed. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th ed. Lyon: IARC; 2017.

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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.

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Discussion

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 indicated.

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

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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 2019, an estimated 74,200 people will be diagnosed with NHL and there will be approximately 19,970 deaths due to the disease.[1] NHL is the seventh leading site of new cancer cases among men and women, accounting for 4% to 5% of new cancer cases and 3% to 4% of cancer-related deaths.[1] In prospectively collected data from the National Cancer Database, diffuse large B-cell lymphoma (DLBCL; 32%), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL; 19%), follicular lymphoma (FL; 17%), marginal zone lymphoma (MZL; 8%), mantle cell lymphoma (MCL; 4%), and peripheral T-cell lymphoma not otherwise specified (PTCL-NOS; 2%) were the major subtypes of NHL diagnosed in the United States between 1998 and 2011.[2]

The incidence of NHL has increased dramatically between 1970 and 1995; the increase has moderated since the mid-1990s. This increase has been attributed partly to the human immunodeficiency virus (HIV) epidemic and the development of acquired immunodeficiency virus (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 (MZLs)
  - 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 lymphomas
- Post-transplant lymphoproliferative disorders
- Castleman's disease

Classification

The 2001 World Health Organization (WHO) classification of hematopoietic and lymphoid neoplasms represented the first international consensus on classification of hematologic malignancies. 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 was further refined based on immunophenotype, genetic, and clinical features to aid in defining active treatment for specific subtypes of lymphoma.

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 (EBV), HHV8, and HTLV1, is often necessary to establish a specific

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diagnosis. The WHO classification was revised in 2008 and 2017 to include new disease entities and better define some of the heterogeneous and ambiguous subtypes, based on the evolving genetic and molecular landscape of various subtypes of NHL.[4,5]

Revisions to the 2008 and 2017 WHO classifications are discussed under the respective subtypes of B-cell lymphomas.

Diagnosis

An accurate pathologic diagnosis of the subtype is the most important first step in the management of B-cell lymphomas. The basic pathologic evaluation is the same for each subtype, although some further evaluation may be useful in certain circumstances to clarify a particular diagnosis; these are outlined in the pathologic evaluation of the individual Guidelines.

An incisional or excisional lymph node biopsy is recommended to establish the diagnosis of B-cell lymphomas. Fine-needle aspiration (FNA) biopsy alone is not generally suitable for the initial diagnosis of lymphoma.[6,7] Recent studies have shown that the diagnostic accuracy of FNA improves significantly when it is used in combination with immunohistochemistry (IHC) and flow cytometry.[8-10] A core needle biopsy is not optimal but can be used under certain circumstances when a clinical situation dictates that this is the only safe means of obtaining diagnostic tissue. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core needle biopsy (multiple biopsies preferred) and FNA biopsies in conjunction with appropriate ancillary techniques (IHC, flow cytometry, karyotype and fluorescence in situ hybridization [FISH] for major translocations and molecular analysis for immunoglobulin heavy chain variable [*IGHV*] and T-cell receptor [*TCR*] gene rearrangements) may be sufficient for the differential diagnosis. Hematopathology review of all slides (with at least one paraffin block representative of the tumor) is recommended. Rebiopsy should be done if consult material is nondiagnostic.

IHC 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.[11] 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.

The NCCN 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 pathologic correlation. See "*Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms"* in the algorithm.

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, and laboratory studies including complete blood count (CBC), serum lactate dehydrogenase (LDH), hepatitis B virus (HBV) testing (see below), comprehensive metabolic panel, and CT chest/abdominal/pelvic with oral and intravenous contrast (unless coexistent renal insufficiency). Multigated acquisition (MUGA) scan or echocardiograms are recommended when anthracyclines and anthracenedione-containing regimens are used.

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HBV reactivation (resulting in liver failure and death) has been reported in patients treated with anti-CD20 monoclonal antibody (MAB)-based regimens.[12] HBV carriers with lymphoid malignancies have a high risk of HBV reactivation and disease, especially those treated with anti-CD20 MAB-based regimens.[13] The panel has included testing for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) as part of essential workup prior to initiation of treatment in all patients who will receive anti-CD20 MAB-based regimens. See *Hepatitis B virus Reactivation* in the *Supportive Care* section.

Large population-based or multicenter case-control studies have demonstrated a strong association between seropositivity for hepatitis C virus (HCV) and the development of B-cell lymphomas.[14-21] The prevalence of HCV seropositivity was consistently increased among patients with DLBCL and MZL.[14,15,19,20] HCV testing is needed in high-risk patients and in patients with splenic MZL. See *Hepatitis C Virus-associated B-Cell Lymphomas* in the *Supportive Care* section.

Optional workup procedures (depending on specific lymphoma type) include beta-2-microglobulin, CT or PET/CT scans, endoscopic ultrasound, head CT, or brain MRI and lumbar puncture to analyze cerebrospinal fluid (CSF). Discussion of fertility issues and sperm banking should be addressed in the appropriate circumstances.[22]

Role of PET Scans

Staging

PET has a high positivity and specificity when used for the staging and restaging of lymphoma.[23] PET is nearly universally positive at diagnosis in DLBCL, FL, and nodal MZL, but less sensitive for extranodal MZL.[24,25] However, a number of benign conditions including sarcoid, infection, and inflammation can result in false-positive PET scans, complicating the interpretation. Lesions <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% to 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.[26,27] In a retrospective study, PET/CT performed with low-dose non-contrast-enhanced CT was found to be more sensitive and specific than contrast-enhanced CT for the evaluation of lymph node and organ involvement in patients with Hodgkin lymphoma or high-grade NHL.[26] Preliminary results of a prospective study (47 patients; patients who had undergone prior diagnostic CT were excluded) also showed a good correlation between low-dose non-contrast-enhanced PET/CT and full-dose contrast-enhanced PET/CT for the evaluation of lymph nodes and extranodal disease in lymphomas.[27]

PET/CT should be done with contrast-enhanced diagnostic CT and is recommended for initial staging and restaging of all FDG-avid lymphomas.[28,29] PET/CT is particularly important for staging before consideration of radiation therapy (RT) and baseline PET/CT will aid in the interpretation of post-treatment response evaluation based on the 5-point scale (5-PS) as described below.[29]

Response Assessment

The guidelines for response criteria for lymphoma were first published in 1999 by the International Working Group (IWG).[30] 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.[30] These guidelines were revised in 2007 by the International Harmonization Project to incorporate IHC, flow cytometry, and PET scans in the definition of response for lymphoma.[31] In the revised guidelines, the response is categorized as

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complete response (CR), partial response (PR), stable disease (SD), and relapsed disease or progressive disease (PD) based on the result of a PET scan. The response category of complete response uncertain (CRu) was essentially eliminated.

In 2014, revised response criteria, known as the Lugano criteria, were introduced for response assessment using PET/CT scans according to the 5-PS.[28,29] The 5-PS is based on the visual assessment of fluorodeoxyglucose (FDG) uptake in the involved sites relative to that of the mediastinum and the liver.[32-34] 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 to 2 or 1 to 3 to be PET-negative, but a score of 1 to 3 is now widely considered to be PET negative. Scores of 4 to 5 are universally considered PET-positive. A score of 4 on an interim or end-of-treatment restaging scan may be consistent with a PR if the FDG avidity has declined from initial staging, while a score of 5 denotes PD.

However, the application of PET/CT to response assessment is limited to FDG-avid lymphomas 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. 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

RT can be delivered with photons, electrons, or protons, depending upon clinical circumstances.[35] 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 (OARs; 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.[36-39] These techniques offer significant and clinically relevant advantages in specific instances to spare OARs and reduce the risk of late complications from normal tissue damage. This is especially important for patients being treated with curative intent or who have long life expectancies following therapy.[40-43] 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 recommended as the appropriate field for NHL as it limits the radiation exposure to adjacent uninvolved organs (such as

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lungs, bone, muscle, or kidney) when lymphadenopathy regresses following chemotherapy, thus minimizing the potential long-term complications.[44,45] ISRT targets the initially involved nodal and extranodal sites detectable at presentation.[44,45] Larger RT fields should be considered for limited-stage indolent NHL, often treated with RT alone.[44]

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 OARs 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.[44]

The principles of ISRT are similar for both nodal and extranodal disease. The gross tumor volume (GTV) defined by radiologic imaging prior to biopsy, chemotherapy, or surgery provides the basis for determining the clinical target volume (CTV).[46] 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 outlined in the *Principles of Radiation Therapy* section of the algorithm.

Biosimilars

A biosimilar is a biological product that is highly similar to the FDA approved reference biological product with the exception of minor differences in clinically inactive components and no clinically meaningful differences in safety, purity, or potency.[47]

Pharmacokinetic (drug exposure) and pharmacodynamic (response) studies in the appropriate patient population are essential to demonstrate the efficacy and safety of the biosimilar.[48] Biosimilars require only one clinical trial to demonstrate equivalent safety and efficacy in the most sensitive indication for the reference biological product. If the mechanism of action, pharmacokinetics, and pharmacodynamics are similar, the biosimilar may be approved for all of the same indications as the reference biological product and can be substituted for the reference biological product.[48] Extrapolation of clinical and safety data from one indication to other approved indications is a key concept in the development of biosimilars that potentially provides substantial cost savings in oncology care, as biosimilars are typically more affordable than their reference products. Extrapolation should only be considered for indications where the mechanism of action is identical to that studied in the pivotal trial.

In November 2018, the FDA approved rituximab-abbs as the first biosimilar to rituximab for the following indications: 1) relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL as a single agent; 2) previously untreated follicular, CD20-positive, B-cell NHL in combination with first-line chemotherapy and, in patients achieving a CR or PR to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy; and 3) non-progressing (including SD), low-grade, CD20-positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine and prednisone (CVP) chemotherapy.

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In July 2019, the FDA approved rituximab-pvvr as the second biosimilar to rituximab for all of the same indications as rituximab-abbs. In addition, rituximab-pvvr is also approved for previously untreated DLBCL, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens.

The approval of these two biosimilars is based on a review of evidence that included extensive structural and functional characterization, animal study data, human pharmacokinetic data, clinical immunogenicity data, and other clinical data demonstrating that the efficacy and safety profiles of rituximab-abbs and rituximab-pvvr are comparable to that of the reference biologic product (rituximab).[49-51]

The efficacy, pharmacokinetics, and safety of rituximab-abbs (as a single agent and in combination with CVP chemotherapy) in comparison to rituximab was evaluated in 2 phase III randomized trials in patients with previously untreated low-burden FL (258 patients were randomized in the trial that evaluated rituximab-abbs as a single agent and 140 patients were enrolled in the trial that evaluated rituximab-abbs in combination with CVP).[49,50] The efficacy and safety profile of rituximab-abbs were comparable to that of the reference biologic product (rituximab), although the incidences of grade 3 neutropenia were higher with rituximab-abbs in both studies.

The efficacy, pharmacokinetics, and safety of rituximab-pvvr as a single agent was evaluated in a phase III randomized trial in patients with previously untreated low-burden FL (394 patients were randomized to rituximab-pvvr or the reference biologic product). The efficacy, safety and immunogenicity, pharmacokinetics and pharmacodynamics of rituximab-pvvr were comparable to that of the reference biologic product (rituximab) up to 26 weeks.[51]

Rituximab-abbs is an FDA-approved biosimilar without an extrapolation to all of the indications as that of the reference biological product (rituximab) for NHL. Therefore, initially, the panel consensus was to include rituximab-abbs as an appropriate substitute for rituximab only for patients with indolent lymphomas (FL and MZL) as per the FDA approval. Rituximab-pvvr, however, is approved for all of the same indications as the reference biological product (rituximab), although the safety and efficacy of rituximab-pvvr was established only in patients with FL. Based on this approval, the panel consensus was to include an FDA-approved biosimilar (eg. rituximab-abbs or rituximab-pvvr) as an appropriate substitute for rituximab (for use as a single agent or in combination with chemotherapy) in all subtypes of B-cell lymphomas.

Alternating between the biosimilar and the reference product is acceptable without the intervention of a health care provider only if a biosimilar is designated as interchangeable since such a substitution will not result in higher toxicity or diminished efficacy.[47] However, alternating between the biosimilar and reference product is not recommended, if the biosimilar is not designated as interchangeable. Rituximab-abbs and rituximab-pvvr have not been approved as interchangeable biological products. Therefore, during a single course of therapy, the patient should remain on the same product that was used to initiate treatment (rituximab or rituximab-abbs or rituximab-pvvr) throughout the course of the treatment.

Supportive Care

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is a potentially serious complication of anticancer therapy characterized by metabolic and electrolyte abnormalities caused by the disintegration of malignant cells by anticancer therapy and rapid release of intracellular contents into peripheral blood. It is usually observed within 12 to 72 hours after start of chemotherapy.[52]

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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.[53] Clinical TLS refers to laboratory TLS with clinical toxicity that requires intervention. Hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia are the primary electrolyte abnormalities associated with TLS. Clinical symptoms may include nausea and vomiting, diarrhea, seizures, shortness of breath, renal insufficiency, or cardiac arrhythmias. Untreated TLS can induce profound metabolic changes resulting in cardiac arrhythmias, seizures, loss of muscle control, acute renal failure, and even death. The cornerstone of TLS management is hydration and the management of hyperuricemia. Allopurinol, febuxostat, and rasburicase are highly effective for the management of hyperuricemia.

Allopurinol is a xanthine analog and a competitive inhibitor of xanthine oxidase, thereby blocking the conversion of purine metabolites to uric acid and decreasing the formation of uric acid production.[54] 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 allopurinol, which may delay the start of chemoimmunotherapy. 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.[55-57] In a prospective, multicenter, randomized phase III trial that compared the efficacy and safety of rasburicase and allopurinol in adult patients with hematologic malignancies at high or potential risk for TLS (275 patients were randomized to receive rasburicase alone [0.20 mg/kg/d IV for days 1–5; n = 92], rasburicase combined with allopurinol [rasburicase 0.20 mg/kg/d IV for days 1–3; allopurinol 300 mg/d PO for days 3–5; n = 92], or allopurinol alone [300 mg/d PO for days 1–5; n = 91]), rasburicase was superior to allopurinol in the overall study population as well as in patients at high-risk for TLS.[57] 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 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. 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. 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). 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.[57] However, rasburicase can induce anaphylactic reactions. Other adverse reactions include methemoglobinemia and severe hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

There are data to suggest that single fixed dose (6 mg or 3 mg) or single weight-based dose of rasburicase (0.05–0.15 mg/kg) are effective in adult patients with hyperuricemia or high-risk factors for TLS.[58-63] In the phase II randomized trial that 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/d) given for 5 days in 80 adult patients at high risk or potential risk for TLS, nearly all treated

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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.[63] 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). 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.

In a randomized trial that compared the efficacy and safety of febuxostat and allopurinol in 346 adult patients with hematologic malignancies at intermediate or high risk for TLS, one fixed dose of febuxostat achieved a significantly superior serum uric acid control in comparison to allopurinol with comparable renal function preservation and safety profile.[64]

TLS is best managed if anticipated and when treatment is started prior to chemoimmunotherapy. Histologies of Burkitt lymphoma, lymphoblastic lymphoma and occasionally DLBCL, 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 are considered as risk factors for developing TLS.[65] TLS prophylaxis should be considered for patients with any of these risk factors. Frequent monitoring of electrolytes and aggressive correction is essential. The NCCN Guidelines recommend allopurinol or febuxostat (if intolerant to allopurinol) or rasburicase as first-line and at retreatment of hyperuricemia. Allopurinol should be started 2 to 3 days prior to the initiation of chemotherapy and continued for 10 to 14 days. Rasburicase is recommended for patients with any of the following risk factors: bulky disease requiring immediate therapy; patients in whom adequate hydration is not possible; or acute renal failure. A single dose is adequate in most cases; repeat dosing should be given on an individual basis.

Hepatitis B Virus Reactivation

Testing for HBsAg and HBcAb can determine the HBV status of an individual. Because of the widespread use of the hepatitis B vaccine, 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.[66-75] 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.[76] HBsAb positivity is generally equated with protective immunity, although reactivated HBV disease may occur in the setting of significant immunosuppression in HBcAb-positive individuals.[73,77] In patients with B-cell lymphomas 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.[68,74,75] A 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.[67] Vaccination against HBV should be strongly considered in HBV-naïve patients (ie, negative for HBsAg, HBsAb, and HBcAb).[73,78]

Recommended strategies for the management of HBV reactivation in patients with hematologic malignancies undergoing immunosuppressive therapy include upfront antiviral prophylaxis or pre-emptive therapy. Antiviral prophylaxis involves treating patients who are HBsAg-positive or HBcAb-positive with antiviral therapy, regardless of viral load or presence

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of clinical manifestations of HBV reactivation. Pre-emptive therapy involves close surveillance with a highly sensitive quantitative assay for HBV, combined with antiviral therapy given at the time of serological evidence of HBV reactivation based upon a rising HBV DNA load.[73]

Lamivudine has been shown to reduce the risks for HBV reactivation in HBsAg-positive patients with hematologic malignancies treated with immunosuppressive cytotoxic agents.[13,79-81] A small randomized study in 30 HBsAg-positive patients with lymphoma showed that antiviral prophylaxis with lamivudine was superior to deferred pre-emptive therapy.[79] 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 and a trend for reduced HBV-related deaths compared with no prophylaxis.[81]

Entecavir has been shown to be more effective than lamivudine in preventing rituximab-associated HBV reactivation.[82,83] In one randomized controlled trial, 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 reversed seroconversion after chemotherapy).[82] The cumulative HBV reactivation rates at months 6, 12, and 18 after chemotherapy were 8%, 11%, and 26%, respectively, in the control group, and 0%, 0%, and 4% 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 (7% vs. 30%, *P* = .001), HBV-related hepatitis (0% vs. 13%, *P* = .003), and disruption of chemotherapy (2% vs. 18%, *P* = .002) than lamivudine.[83]

The panel recommends HBsAg and HBcAb testing for all patients planned for treatment with anti-CD20 MAB-containing regimens. In individuals who test positive for HBsAg and/or HBcAb, baseline quantitative polymerase chain reaction (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.[84]

Entecavir prophylaxis is recommended for patients who are HBsAg positive and receiving anti-lymphoma therapy.[82,83] Entecavir prophylaxis is also the preferred approach for patients who are HBsAg negative but HBcAb positive; 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. Lamivudine should be avoided due to the risks for the development of resistance.[85-87] Other antivirals such as adefovir, telbivudine, and tenofovir have also demonstrated antiviral efficacy in patients with chronic HBV infection and are acceptable alternatives.[88-91]

The optimal choice of prophylactic antiviral therapy will be driven by institutional standards or recommendation from hepatology or an 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.[73] 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

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hepatologist and discontinuation of anti-CD20 antibody therapy is recommended.

Hepatitis C Virus-associated B-Cell Lymphomas

As noted earlier, large population-based or multicenter case-control studies have demonstrated a strong association between seropositivity for HCV and development of B-cell lymphomas.[14-21] The prevalence of HCV seropositivity was consistently increased among patients with DLBCL and MZL.[14,15,19,20] A retrospective study in patients with HCV infection 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 3% vs. 0%; *P* = .016).[17] 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.[17]

Several published reports suggested that treatment with antivirals (typically interferon with or without ribavirin) led to regression of NHLs in HCV-positive patients, which provides additional evidence for the involvement of HCV infection in the pathogenesis of lymphoproliferative diseases.[92-98] 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.[97] In addition, none of the patients with an 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 being 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).[98] 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 NHL in HCV-positive patients remains to be defined. Patients with indolent NHL may benefit from antiviral treatment as initial therapy, as demonstrated in several reports.[92,94,96,98,99] 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.[100] 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.[101,102] However, the incidence of hepatotoxicity with chemoimmunotherapy was higher among HCV-positive patients, confirming the observation made from the GELA studies.

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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.[103-106] Telaprevir and boceprevir are DAA 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 DAA be incorporated into standard antiviral therapy for patients infected with HCV genotype 1.[107]

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 for the development of hepatotoxicity during and after chemoimmunotherapy. Antiviral therapy should then be considered in patients who achieve a CR after completion of chemoimmunotherapy.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a rare but serious and usually fatal CNS infection caused by reactivation of the latent JC polyomavirus. PML generally occurs in severely immunocompromised individuals, as in the case of patients with AIDS and in patients with low CD4+ T-cells prior to or during anti-lymphoma treatment.[108-110] PML has been reported in patients with NHL receiving treatment with rituximab (usually in combination with chemotherapy) or brentuximab vedotin.[108,111]

In a report of 57 patients 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.[108] Median time from last rituximab dose to PML diagnosis was 6 months. Median time to death after PML diagnosis was 2 months, with a case fatality rate of 90%.

PML is clinically suspected based on neurologic signs and symptoms that may include confusion, motor weakness or poor motor coordination, visual changes, and/or speech changes.[108] PML is usually diagnosed with PCR of 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 neurologic symptoms. There is currently no consensus on pretreatment evaluations that can be undertaken to predict for the subsequent development of PML.

Management of anti-CD20 Monoclonal Antibody Therapy Intolerance

Rare complications such as mucocutaneous reactions including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis can occur in patients treated with anti-CD20 MAB. Expert consultation with a dermatologist is recommended.

Re-challenge with the same anti-CD20 MAB is not recommended in patients experiencing the aforementioned complications to chosen anti-CD20 MAB (rituximab, obinutuzumab, or ofatumumab). There are data supporting the use of ofatumumab in patients experiencing intolerance to rituximab.[112,113] An alternative anti-CD20 MAB (obinutuzumab or ofatumumab) could be used for patients with intolerance to rituximab, regardless of histology. However, it is unclear if such a substitution poses the same risk of recurrence.

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Rituximab and hyaluronidase human injection for subcutaneous use is approved by the FDA for the treatment of patients with previously untreated and relapsed/refractory FL and previously untreated DLBCL, only for patients who have received at least one full dose of intravenous rituximab. The FDA approval was based on the results of two large phase III randomized trials that confirmed the non-inferiority for subcutaneous rituximab (1400 mg SC dose) compared with intravenous rituximab (375 mg/m^2) when used in combination with chemotherapy (CHOP or CVP) in patients with previously untreated FL (SABRINA study)[114] or DLBCL (MabEase study).[115]

The guidelines recommend that rituximab and hyaluronidase human injection for subcutaneous use may be substituted for intravenous rituximab after patients have received the first full dose of rituximab by intravenous infusion. Switching to subcutaneous rituximab is not recommended until a full intravenous dose of rituximab is successfully administered without experiencing severe adverse reactions. This substitution with subcutaneous rituximab is also not recommended for intravenous rituximab used in combination with ibritumomab tiuxetan.

Management of Bone Health in Patients Receiving Steroid-Containing Regimens

Steroid-containing systemic therapy regimens have been associated with increased risk of fractures and treatment-induced bone loss in patients with NHL.[116-118] The risk of treatment-induced bone loss is higher among young women with chemotherapy-induced premature menopause and older patients receiving chemotherapy.[119,120] In addition, patients with newly diagnosed NHL are also at risk of low bone mineral density (BMD), which may worsen during treatment with steroid-based systemic therapy.[121]

Evaluation of vitamin D levels and post-treatment BMD evaluation using a fracture risk assessment tool is recommended for patients receiving steroid-based systemic therapy.[122,123] Referral to an endocrinologist with expertise on bone health and initiation of treatment as per National Osteoporosis Foundation guidelines is recommended for patients with osteoporotic BMD, with a history of hip or vertebral fractures, or with asymptomatic vertebral compression deformity (as seen on imaging studies).[124]

Adequate calcium intake is of paramount importance since corticosteroids block calcium absorption and increase the risk of fracture. Raloxifene or hormone replacement therapy up until the expected time of natural menopause could be considered in appropriate women with premature menopause. The use of bisphosphonates (pamidronate and zoledronic acid) has been shown to effectively stabilize BMD, prevent bone loss, and reduce the risk of new vertebral fractures in patients with NHL.[125,126] Bisphosphonates should be used as first-line pharmacologic treatment for osteoporosis. Denosumab is an effective alternative option to prevent osteoporotic fractures in patients who cannot tolerate or whose symptoms do not improve with bisphosphonate therapy.[127]

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Follicular Lymphoma

Overview

Follicular lymphoma (FL) is the most common subtype of indolent non-Hodgkin's lymphoma (NHL), and accounts for about 22% of all newly diagnosed cases of NHL.[1] About 90% of patients have a t(14;18) translocation, which juxtaposes *BCL2* with the *IGH* locus resulting in the deregulated expression of BCL2. Pathologic grading according to the number of centroblasts is considered to be a clinical predictor of outcome. Clinical outcomes for patients with FL1 and FL2 do not differ and this classification has been deemed unreliable. Therefore, in the WHO classification, FL1 and FL2 are grouped under a single grade (FL1-2). The WHO classification mandates stratifying FL3 into either 3A (centrocytes still present) or 3B (sheets of centroblasts).[2] Thus, FL is divided into three grades (FL1-2, FL3A, and FL3B) based on the number of centroblasts.

FL1-2 should be managed according to the treatment recommendations for FL. However, controversy exists regarding management of FL grade 3. There is no difference in survival outcomes between patients with FL3A and FL3B. However, FL3 with >50% diffuse component has an inferior survival outcome similar to that of diffuse large B-cell lymphoma (DLBCL).[3] FL3B with BCL2 translocation appears to have a clinical course similar to FL1-3A, whereas FL3B with cytogenetic abnormalities of BCL6 is thought to be genetically more akin to germinal center type and is associated with a more aggressive clinical course.[4] Since FL3B is rare, the clinical behavior of FL3 in most studies is based mainly on FL3A cases. Some may treat FL3A as FL and others may treat it as DLBCL. FL3B is commonly treated according to the treatment recommendations for DLBCL. Any area of DLBCL in a FL of any grade should be diagnosed and treated as a DLBCL.

FL with predominantly diffuse pattern is characterized by the absence the t(14;18) translocation, presence of 1p36 deletion, frequent inguinal lymph node involvement, uniform CD23 expression, and low clinical stage.[5,6] FL with 1p36 deletion is typically grade 1–2 and has a good prognosis. It should be managed according to treatment recommendations for FL.

Large B-cell lymphoma (LBCL) with *IRF4* rearrangement, which occurs most commonly in children and young adults, is considered as a new distinct provisional entity in the 2017 WHO classification.[2] These lymphomas are characterized by strong expression of IRF4/MUM1, and may have a follicular, follicular and diffuse, or pure diffuse growth pattern resembling FL3B or DLBCL.[7] Patients typically present with Waldeyer's ring involvement and/or cervical lymph nodes and locally aggressive disease that responds well to chemotherapy with or without radiation therapy (RT). LBCL with *IRF4* rearrangement should be managed according to treatment recommendations for DLBCL.

Pediatric-type FL (PTFL) is considered as a definite entity in the 2017 WHO classification, since it is a biologically and clinically distinct indolent lymphoma and can also occur in adults.[2] PTFL is generally characterized by lack of *BCL2* rearrangement and t(14,18), which constitute the genetic hallmark of conventional FL cases seen in adults and *BCL6* rearrangement is also typically absent in PTFL.[8-11] *MAP2K1* and *TNFRSF14* mutations are the most frequent genetic alterations found in PTFL.[12-14] The diagnosis and management of PTFL in adults is discussed on MS-18.

In the 2017 WHO classification, FL in situ (with the presence of FL-like B-cells in the germinal centers of morphologically reactive lymph nodes) has been renamed as in situ follicular neoplasia (ISFN).[2] It 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 fluorescence in situ hybridization (FISH).[15-17] ISFN has been

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reported in patients with prior FL or concurrent FL (at other sites), as well as in individuals with no known history of FL and the prevalence of ISFN in the general population has been reported to be 2%.[15,16,18] Although uncommon (5%–6%), the development of or progression to overt lymphoma has been reported in patients reported to have ISFN.[19,20] The significance or potential for malignancy of ISFN 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.[19,21] 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.

FL of the gastrointestinal tract (primary intestinal FL) 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. 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.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for B-Cell Lymphomas an electronic search of the PubMed database was performed to obtain key literature in FL published since the previous Guidelines update using the following search terms: follicular lymphoma and indolent lymphoma. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[22]

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 data from key PubMed articles deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). 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 at www.NCCN.org.

Diagnosis

Immunophenotyping using immunohistochemistry (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 histologic grounds, but immunophenotyping is encouraged to distinguish FL from a nodular mantle cell lymphoma (MCL) or small lymphocytic lymphoma (SLL). Molecular genetic analysis to detect *BCL2* rearrangement; karyotype or FISH to identify t(14;18) and *BCL6, 1p36,* and *IRF4/MUM1* gene rearrangements; and IHC for Ki-67 and IRF4/MUM1 for FL grade 3, cyclin D1 may be useful under certain circumstances. Low-grade FL with a high proliferation index (≥30% as determined by Ki-67 immunostaining) has been shown to be associated with an aggressive clinical behavior.[23,24] There is no evidence, however, that high Ki-67 should guide the selection of therapy.

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The Follicular Lymphoma International Prognostic Index (FLIPI) is a prognostic scoring system that divides patients into three distinct prognostic groups. FLIPI1 is based on age, Ann Arbor stage, and number of nodal sites involved; hemoglobin level; and serum lactate dehydrogenase (LDH) level.[25] FLIPI1 was developed in the pre-rituximab era but it has been shown to retain its prognostic significance in the modern chemoimmunotherapy era also.[26] FLIPI-2 was developed based on prospective collection of data from patients with newly diagnosed FL treated in the rituximab era and is based on age, hemoglobin level, longest diameter of largest involved lymph node, beta-2 microglobulin level, and bone marrow involvement.[27] FLIPI-2 was highly predictive of treatment outcomes, and separated patients into three distinct risk groups with 5-year progression-free survival (PFS) rates of 79%, 51%, and 20% for patients at low-risk, intermediate-risk and high-risk, respectively (P < .00001). The FLIPI-2 also defined distinct risk groups among the subgroup of patients treated with rituximab-containing regimens, with 5-year PFS rates of 98%, 88%, and 77% for patients at low-risk, intermediate-risk and high-risk, respectively (P < .0001).[27] Thus, FLIPI-2 may be useful for assessing prognosis in patients receiving active therapy with rituximab-based regimens. A simpler prognostic index incorporating only the baseline serum beta 2-microglobulin and LDH levels has been developed, which is easier to apply and also appears to be as predictive of outcomes as the FLIPI-1 and FLIPI-2 indices.[28]

Although these index scores predict for prognosis, they have not yet been established as a means of selecting treatment options.

Workup

The initial workup 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 LDH levels. Hepatitis B virus (HBV) testing prior to initiation of treatment is recommended for all patients who will receive anti-CD20 monoclonal antibody (MAB) based regimens due to increased risk of HBV reactivation. Measurement of uric acid, serum beta-2 microglobulin (necessary for calculation of FLIPI-2), and hepatitis C testing may be useful for certain cases.

Bone marrow biopsy with aspirate is essential to document clinical stage I–II disease. Adequate trephine biopsy (specimen ≥1.6 cm) should be obtained for initial staging evaluation, along with bone marrow aspiration.[29,30] However, in patients with low burden indolent lymphoma with radiographic clinical stage III disease, an initial staging bone marrow evaluation can be deferred if observation is the initial option as it will not change the clinical recommendations. 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.

Chest/abdomen/pelvic CT with contrast of diagnostic quality and/or whole-body PET/CT scan are recommended as part of initial diagnostic workup. PET/CT scan is essential if RT is planned for stage I-II disease. CT scan of the neck may also assist in defining the extent of local disease. Multigated acquisition (MUGA) scan or echocardiogram is recommended for patients being considered for treatment regimens containing anthracyclines.

Role of PET/CT in FL

Diagnosis and Workup

PET/CT scans are more accurate than CT scans alone in the detection of disease in patients with indolent lymphomas and several studies have reported high sensitivity (94%–98%) and specificity (88%–100%) for PET/CT scans for indolent lymphomas.[31-34]

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PET scans may also be useful in identifying occult sites of disease and detecting histologic transformation of FL to DLBCL.[32,35,36] Standard fluorodeoxyglucose (FDG) uptake values (SUVs) on PET have been reported to be higher among transformed than non-transformed cases of indolent lymphomas.[32] PET scans do not replace histologic confirmation of the diagnosis; however, if there are sites with discordantly high FDG avidity, these represent the most likely sites of histologic transformation. High SUVs on PET scan should raise the suspicion of histologic transformation to DLBCL, and can be used to direct the optimal site of biopsy for histologic confirmation.[36]

Post-treatment Response Evaluation

The prognostic utility of post-treatment PET scans (PET negativity was associated with a longer PFS compared to PET positivity) has also been demonstrated in several studies.[34,37-42]

In a retrospective study in patients with FL treated with RCHOP, 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.[39] 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).[39]

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.[40] 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). The median PFS was 21 months and not reached, respectively. Among the patients randomized to observation, the 42-month 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. 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 negativity (56% vs. 77% at 41 months); median PFS has not yet been reached in either the PET/CT-positive or PET/CT-negative subgroups. 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 (79% vs. 97% at 42 months; P = .001).

The prognostic value of PET imaging in patients with high-tumor-burden FL treated with first-line therapy with 6 cycles of RCHOP (n = 121; no rituximab maintenance administered) was also evaluated in a prospective study.[41] PET scans were performed after 4 cycles of RCHOP (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.[41] At the end of treatment, nearly all patients (98%) who achieved a CR based on International Working Group (IWG) response criteria also achieved a PET-negative response. Interim PET was associated with significantly higher 2-year PFS (86% for PET negative vs. 61% for PET-positive; P = .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 = .013).[41]

These studies suggest that post-treatment imaging studies may have a role as a predictive factor for survival outcomes in patients with FL. End-of-treatment PET/CT scan is now considered a standard part of post-treatment response evaluation in patients with indolent lymphomas.

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Further prospective studies are warranted to determine whether interim PET scans have a role in guiding post-induction therapeutic interventions.

Surveillance

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).[43] 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 was 80 months. Relapse was detected in 78 patients, with the majority of relapses (77%) occurring within the first 5 years of treatment.[43] 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.[43]

The role of surveillance PET scans in patients with lymphomas (Hodgkin lymphoma and NHL) with a CR after induction was also evaluated in a prospective study.[44] 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 at 6 months, 12% at 12 months, 9% at 18 months, 9% at 24 months, 8% at 36 months, and 6% at 48 months. Among 13 patients who were PET-positive without a corresponding abnormality on CT scan, relapse was documented by biopsy in 8 patients. 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.

Stage I–II FL

RT is an effective treatment option for patients with stage I-II disease resulting in long-term disease control rates of >90% with the 10-year PFS and OS rates ranging from 40% to 59% and 58% to 86%, respectively.[45-49] The 15-year PFS outcomes were influenced by 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 involved-filed RT (49% vs. 40%, respectively) and the reduction in radiation field (RT of involved nodes only) did not impact PFS or OS outcomes.[48,49] A more recent multicenter retrospective study conducted by the International Lymphoma Radiation Oncology Group also established RT alone (≥24 Gy) as a potentially curative treatment option for patients with untreated stage I to II FL (512 patients staged by PET/CT; 410 patients had stage I disease).[50] After a median follow-up of 52 months, the 5-year freedom-from-progression (FFP) and OS rates were 69% and 96% for the entire study population. The 5-year FFP rate was 74% for patients with stage I FL compared to 49% for those with stage II FL ($P < .0001$).

The addition of systemic therapy (rituximab, chemotherapy, or chemoimmunotherapy) to involved-field RT (IFRT) has been shown to improve failure-free survival (FFS) and PFS but did not impact OS in patients with early-stage disease.[51-58]

Long-term outcomes from a 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%.[53] In this study, the majority of patients (74%) had stage I disease and 24% had received chemotherapy with RT,

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which may have resulted in the higher OS rate reported compared with the other studies. In a small prospective randomized study of RT alone compared with RT with 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.[51] The results of a multicenter observation study (n = 94) showed that the addition of rituximab to involved-site RT (ISRT) significantly prolongs PFS in patients with stage I–II disease.[57] The 10-year PFS rates were 65% and 51%, respectively ($P < .05$), for patients treated with rituximab + RT and RT alone. However, the OS rates were not significantly different between the treatment groups. In the phase III randomized trial of the Trans-Tasman Radiation Oncology Group (TROG 99.03) that evaluated IFRT vs. IFRT followed by CVP (cyclophosphamide, vincristine, and prednisone) plus rituximab (RCVP) in 150 patients with early-stage FL, at a median follow-up of 10 years, IFRT followed by RCVP was associated with superior PFS compared to IFRT alone.[58] The 10-year PFS rates were 59% and 41%, respectively. However, the 10-year OS rate was not significantly different between the treatment arms (95% and 87%, respectively).

In retrospective studies that have evaluated the outcomes of patients with stage I–II FL with various treatment approaches (observation, RT, rituximab monotherapy, chemoimmunotherapy, and combined modality with RT), no differences in OS outcomes were observed between the various management approaches.[59,60] Carefully selected patients (requirement of large abdominal radiation field, advanced age, concern for xerostomia, or patient refusal) with stage I–II disease who did not receive immediate treatment had comparable outcomes to those who were treated with RT.[61] Observation may be appropriate in circumstances where potential toxicity of ISRT outweighs potential clinical benefit.

Treatment of Stage I (<7 cm) or Contiguous Stage II (<7 cm) FL

ISRT (24–30 Gy) is recommended for patients with non-bulky disease. No further treatment is necessary for patients achieving CR or PR to ISRT. Clinical follow-up with a complete history and physical exam and laboratory assessment is recommended 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 thereafter.

Patients with disease not responding to ISRT should be managed as described for stage III or IV disease.

Treatment of Stage I (≥7 cm) or Contiguous Stage II (≥7 cm), or Non-Contiguous Stage II FL

Anti-CD20 monoclonal antibody (MAB) with or without chemotherapy with or without ISRT is recommended for patients with bulky disease (stage I or contiguous stage II) or non-contiguous stage II disease. The addition of ISRT is included with a category 2B recommendation. Clinical follow-up with a complete history and physical exam, laboratory assessment, and surveillance imaging (as described above) are recommended for patients with CR or PR after completion of treatment.

Patients with non-responsive disease should be managed as described below for stage III or IV disease.

Treatment of Stage III–IV FL

Several prospective randomized trials conducted in the pre-rituximab era have failed to demonstrate a survival benefit with immediate treatment versus watchful waiting in patients with advanced stage, low-tumor-burden or asymptomatic FL.[62-64] Results from more recent studies have shown that although immediate treatment with rituximab monotherapy results in

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significantly longer median time to initiation of new therapy compared watchful waiting, it does not improve OS.[65-67]

In an analysis of the data from the F2-study registry of the International Follicular Lymphoma Prognostic Factor Project, outcomes in a cohort of patients with asymptomatic, advanced stage, low-tumor-burden FL who were initially managed by a "watch and wait" approach (n = 107) were compared with the outcomes of patients who had low-tumor-burden, asymptomatic FL, but were initially treated with rituximab-containing regimens (n = 242).[65] 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 second-line 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 rate was 79% in the "watch and wait" cohort compared to 69% in the cohort of patients 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 rates were similar (87% vs. 88%, respectively).

The role of immediate treatment with rituximab (with or without additional rituximab maintenance) versus watchful waiting in patients with advanced stage, asymptomatic low-tumor-burden FL was evaluated in a randomized phase III intergroup trial (187 patients were assigned to watchful waiting; 192 patients were assigned to maintenance rituximab; and 84 patients were assigned to the induction therapy with rituximab, though this arm was closed early).[66] The primary endpoint of this trial was time to initiation of new treatment from randomization. Long-term follow-up data showed that there was a significant difference in the percentage of patients not needing new treatment at 3 years between the watchful waiting group and rituximab maintenance group (46% vs. 88%; $P < .0001$) or rituximab induction group (46% vs. 78%; $P < .0001$), suggesting that rituximab monotherapy should be considered for patients with asymptomatic, advanced-stage, low-tumor-burden FL. However, no differences in OS were observed between the study arms. After a median follow-up of 50 months for the 3-arm study, the 3-year OS rates were 94%, 97%, and 96%, respectively, for the watchful waiting group, rituximab maintenance group, and induction rituximab group. The endpoint chosen for this trial, however, is also 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."

A recent report from the National LymphoCare Study that compared the outcomes of patients with stage II–IV FL who were managed with watchful waiting (n = 386), rituximab monotherapy (n = 296), or rituximab plus chemotherapy (n = 1072) as initial management strategy also confirmed that there was no significant difference in OS between the 3 different management strategies.[67] With a median follow-up of 8 years, the estimated 8-year OS rates were 74%, 67%, and 72%, respectively, for the watchful waiting group, rituximab monotherapy group, and rituximab plus chemotherapy group.

Collectively, findings from clinical studies suggest that immediate initial therapy with rituximab in patients not meeting the modified GELF criteria does not improve OS and outside the context of clinical trials, observation is still the standard practice for patients with advanced stage low-tumor-burden FL.[65-67] Treatment should only be initiated when a patient presents with indications for treatment (based on the modified 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. Suggested treatment regimens for first-line therapy are discussed below. Patients achieving CR

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or PR to first-line therapy can either be observed or treated with optional consolidation or extended therapy. Options are discussed under "*First-line Consolidation Therapy* or *Extended Dosing.*

The NCCN B-Cell Lymphomas Panel stratified all the regimens into 3 categories (based on the evidence, efficacy, toxicity, preexisting comorbidities, and in some cases access to certain agents): preferred regimens, other recommended regimens, and useful under certain circumstances.

First-line Therapy: Preferred Regimens

Chemoimmunotherapy with anti-CD20 Monoclonal Antibody (obinutuzumab or rituximab)

Bendamustine, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CVP (cyclophosphamide, vincristine, and prednisone) with obinutuzumab or rituximab and lenalidomide + rituximab are included as preferred regimens, based on the results from phase III randomized trials (discussed below).

The multicenter randomized phase III study (StiL NHL1) that compared bendamustine and rituximab (BR) and RCHOP as first-line treatment for patients with indolent and MCLs showed that BR was superior to RCHOP in terms of PFS in all histologic subtypes.[68,69] At a median follow-up of 45 months, the median PFS was 69 months and 31 months *(P* < .0001), respectively, for BR and RCHOP.[68] The ORR was similar between treatment arms (93% with BR; 91% with RCHOP), although the CR rate was significantly higher in the BR arm (40% vs. 30%; *P* = .021). BR was associated with less frequent grade 3 or 4 neutropenia (29% vs. 69%) or infections (any grade; 37% vs. 50%), whereas erythema (16% vs. 9%) and allergic skin reactions (15% vs. 6%) were more common with BR compared with RCHOP. The incidence of secondary malignancies was similar (8% with BR and 9% with RCHOP). However, the OS outcomes were not significantly different between treatment arms, even after long-term follow-up; the estimated 10-year survival rates were 71% and 66%, respectively, for BR and RCHOP.[69]

Another randomized phase III study (BRIGHT) demonstrated that BR was noninferior to RCHOP or RCVP (in terms of PFS) as first-line treatment of patients with indolent or MCL (224 patients were randomized to receive BR and 223 patients were randomized to receive RCHOP or RCVP).[70] At a median follow up of 5 years, the 5-year PFS rate for the overall study population was 66% and 56% (P = .0025), for BR and RCHOP/RCVP, respectively. The 5-year OS rate was not statistically different between the treatment groups and the incidence of opportunistic infections and secondary malignancies were slightly higher in patients treated with BR.[70]

The phase III randomized trial (GALLIUM trial) compared the efficacy and safety of obinutuzumab compared to rituximab when used in combination with chemotherapy (bendamustine, CHOP, or CVP) in patients with previously untreated advanced stage FL (1202 patients were randomized [1:1] to receive obinutuzumab or rituximab in combination with chemotherapy).[71] Patients with disease responding to induction chemoimmunotherapy received maintenance treatment with the same antibody for up to 2 years. However, this trial was not designed to compare the chemotherapy regimens. After a median follow-up of 34 months, a planned interim analysis showed that obinutuzumab-based chemoimmunotherapy was associated with significantly longer PFS and lower risk of progression and relapse than rituximab-based chemoimmunotherapy. The estimated 3-year PFS rates were 80% and 73%, respectively. However, response rates at the end of induction treatment were not significantly different between the two groups (88% for the obinutuzumab-based chemoimmunotherapy and 87% for rituximab-based chemoimmunotherapy) and OS was similar in both groups. In addition, grade 3 to 5 adverse events were higher with obinutuzumab than with rituximab (infections, 20% vs. 16%; neutropenia,

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46% vs. 39%; and infusion-related reactions, 12% vs. 7%) and bendamustine was associated with higher rates of grade 3 to 5 infections and secondary cancers. Non-relapse-related fatal adverse events were also more common with bendamustine (6% in the obinutuzumab group and 4% in the rituximab group) than with CHOP or CVP (2% for both regimens when used in combination with obinutuzumab or rituximab).

The panel acknowledged that chemoimmunotherapy with anti-CD20 monoclonal antibody (obinutuzumab or rituximab) is an appropriate first-line therapy for patients with advanced stage FL requiring treatment. However, in the absence of data from randomized trials showing significant OS benefit for one chemoimmunotherapy regimen over another, the panel concluded that the available data are not strong enough to designate obinutuzumab-based chemoimmunotherapy as superior to rituximab-based chemoimmunotherapy. The panel consensus was to list all of the chemoimmunotherapy regimens as preferred regimens with category 2A recommendation.

The selection of a chemoimmunotherapy regimen 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 may be associated with risks for HBV reactivation, 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. In the GALLIUM study, there was an increased risk of mortality from opportunistic infections and secondary malignancies in patients receiving bendamustine, and the rates of severe infections were also higher with bendamustine than CHOP or CVP during the maintenance and follow-up phases.[71] The panel recommends that prophylaxis for pneumocystis jirovecii pneumonia (PJP) and varicella zoster virus (VZV) should be administered for patients receiving bendamustine.

Lenalidomide + Rituximab

In phase II studies, lenalidomide + rituximab has demonstrated activity in patients with previously untreated FL resulting in an ORR of 95% to 98% and 2-year PFS rates of 86% to 89%.[72,73]

The results from the multicenter, international, randomized phase III study (RELEVANCE) showed that the efficacy of lenalidomide + rituximab was similar to that of chemotherapy + rituximab in patients with previously untreated advanced stage FL.[74] In this study, 1030 patients were randomized to receive lenalidomide + rituximab (n = 513) or chemotherapy + rituximab (investigator's choice of one the 3 regimens: RCHOP, RCVP, or BR; n = 517) followed by maintenance therapy with rituximab. The ORR (84% for lenalidomide + rituximab and 89% for chemotherapy + rituximab), CR rate at 120 weeks (48% and 53%, respectively; *P* = .13), and the interim 3-year PFS rate (77% and 78%, respectively) were similar in the two treatment groups. Lenalidomide + rituximab was associated with lower rates of grade 3 or 4 neutropenia (32% vs. 50%) and febrile neutropenia of any grade (2% vs. 7%) than chemotherapy + rituximab. Grade 3 or 4 cutaneous reactions were higher with lenalidomide + rituximab (7% vs. 1%).

Although the RELEVANCE trial (which was designed as a superiority trial) did not show that lenalidomide + rituximab was superior to chemotherapy + rituximab in terms of efficacy, this trial confirmed lenalidomide + rituximab as an effective alternative to chemoimmunotherapy for patients with previously untreated FL.[74] Based on the results of this study, the panel consensus was to included lenalidomide + rituximab as an option for preferred regimen with a category 2A recommendation.

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First-line Therapy: Other Recommended Regimens

Rituximab

Rituximab has been shown to induce high complete molecular response rate in patients with low burden FL and also has demonstrated single-agent activity in patients with previously untreated advanced stage FL.[75-77] Rituximab should be considered as a first-line treatment for patients with low burden disease.

First-line Consolidation or Extended Therapy

Several studies have reported that prolonged administration of rituximab (or rituximab maintenance) significantly improved event-free survival (EFS) in chemotherapy-naïve patients responding to initial rituximab induction, although this benefit did not translate to OS advantage.[78-81]

The phase III randomized trial (E4402 study; RESORT) compared rituximab maintenance versus rituximab retreatment in patients with previously untreated low burden FL responding to rituximab induction therapy.[82] In this study, 289 patients were randomized to receive maintenance with rituximab or rituximab retreatment. Patients receiving rituximab retreatment were eligible for re-treatment at each disease progression until treatment failure. The primary endpoint of this trial was TTF. At a median follow-up of 5 years, the estimated TTF was similar for patients receiving rituximab maintenance and rituximab re-treatment (4 years for both treatment arms; *P* = .54). The 3-year freedom from cytotoxic therapy was 95% and 84%, respectively, for those receiving rituximab maintenance and rituximab re-treatment (*P* = .03). These results suggest that rituximab retreatment provides comparable disease control to rituximab maintenance in patients with low burden FL.

The phase III randomized PRIMA trial evaluated the role of rituximab maintenance in patients with FL responding to first-line chemoimmunotherapy.[83] In this study, patients with FL responding to first-line chemoimmunotherapy (RCVP, RCHOP, or RFCM) 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% of patients in the rituximab maintenance arm were in CR/CRu compared with 52% in the observation group. However, no significant difference was observed in OS between the two groups. Based on multivariate analysis, induction therapy with RCHOP or RFCM was one of the independent factors associated with improved PFS, suggesting that RCVP induction was not as beneficial in this study. Long-term follow-up data confirmed that rituximab maintenance is associated with significant PFS benefit over observation.[84] At 10 years, the estimated PFS rate was 51% in the rituximab maintenance arm and 35% in the observation arm. The OS estimates were identical (80%) in both treatment arms. The benefit of rituximab maintenance for PFS was significant irrespective of quality of response to chemoimmunotherapy.

The GALLIUM trial (discussed above) demonstrated that obinutuzumab-based chemoimmunotherapy followed by obinutuzumab maintenance resulted in significantly longer PFS than rituximab-based chemoimmunotherapy followed by rituximab maintenance.[71] But the OS was not significantly different between the two treatment approaches.

Patients achieving CR or PR to first-line therapy can either be observed or treated with optional consolidation or extended therapy:

- Rituximab maintenance (one dose every 8 weeks up to 2 years) is included as an option with a category 1 recommendation for patients with high tumor burden treated with RCVP and RCHOP based on the PRIMA study.[83,84] There are not enough data to support the use of rituximab maintenance in patients achieving CR after first-line therapy with BR. In a multicenter real-world analysis that evaluated maintenance rituximab versus observation following first-line treatment with BR, rituximab maintenance was associated

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with a significant improvement in PFS only in patients achieving PR but not in patients achieving CR.[85]

- Obinutuzumab maintenance is included with a category 2A recommendation based on the results of the GALLIUM trial.[71]
- Consolidation with rituximab should be considered if initially treated with single-agent rituximab.
- Ibritumomab tiuxetan is included with a category 2B recommendation based on the results of the First-line Indolent Trial (FIT).[86] Since this trial included only a small number of patients (14%) who received rituximab in combination with chemotherapy as induction therapy, the effects of consolidation with radioimmunotherapy (RIT) following rituximab-containing regimens cannot be fully evaluated.

Clinical follow-up with a complete physical exam and laboratory assessment (every 3–6 months for the first 5 years, and then annually [or as clinically indicated]) is recommended. 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 and Subsequent Therapy

Frequently, patients with disease relapse or progression of disease (POD) after first-line therapy will benefit from a second period of observation. Considerations and indications for treatment of relapsed/refractory or progressive disease include, among other factors, the modified GELF criteria, which include: symptoms attributable to FL (not limited to B symptoms); threatened end-organ function; significant cytopenia secondary to lymphoma; bulky disease; splenomegaly; and steady progression over at least 6 months.

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, should raise suspicion for the presence of transformation.[36] However, a positive PET/CT scan does not replace a biopsy; rather, the results of the PET/CT scan should be used to direct the optimal site of biopsy for histologic confirmation to enhance the diagnostic yield from the biopsy.

POD ≤24 months of diagnosis and failure to achieve EFS at 12 months (EFS12) after initial treatment with chemoimmunotherapy have been identified as prognostic indicators of poor survival.[87-89] In the National LymphoCare Study, the 5-year OS rate was 50% for patients with POD ≤2 years after first-line therapy with RCHOP compared with 90% for those with POD >2 years.[87] In a population-based analysis of relative survival of patients with FL compared to age-and-sex-matched controls (from U.S. and French data sets), the group of patients achieving EFS12 following initial management had similar OS outcomes compared to age-and-sex-matched general populations, whereas patients who failed to achieve EFS12 had lower subsequent OS.[88]

Alternate non–cross-resistant chemoimmunotherapy regimens or the combination of lenalidomide and rituximab are options for second-line therapy for patients with relapsed/refractory disease. Duration of response to first-line therapy is an important factor in the selection of second-line therapy. Rituximab monotherapy may be appropriate for patients with late relapse as well, particularly if disease burden is low. Patients with POD ≤2 years after first-line therapy should be considered for treatment with lenalidomide-based regimens, novel approaches including clinical trials or referral for the consideration of HDT/ASCR.[90-92]

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Preferred Regimens

Chemoimmunotherapy with Anti-CD20 Monoclonal Antibody

The BR regimen has also demonstrated efficacy with acceptable toxicity in patients with relapsed or refractory indolent lymphomas.[93-95] In a randomized phase III study of 230 patients with relapsed or refractory indolent lymphoma or MCL (114 patients assigned to BR and 105 patients assigned to fludarabine plus rituximab [FR]), BR was more effective than FR in terms of PFS.[95] At a median follow-up of 96 months, the median PFS was 34 months and 12 months, respectively, for BR and FR.

Obinutuzumab-based chemoimmunotherapy has also been evaluated in patients with relapsed or refractory FL.[96-98]

The safety and efficacy of CHOP plus obinutuzumab in patients with relapsed or refractory FL was demonstrated in a randomized study (56 patients were randomized to obinutuzumab in combination with CHOP or FC [fludarabine and cyclophosphamide]).[96] The ORRs were 96% and 93%, respectively, for patients treated with CHOP plus obinutuzumab and FC plus obinutuzumab. The corresponding CR rates were 39% and 50%, respectively. In the CHOP plus obinutuzumab group, 25% of patients with rituximab-refractory disease achieved CR and in the FC plus obinutuzumab, 30% achieved CR. All of the patients with rituximab-refractory disease achieved at least PR. FC plus obinutuzumab was associated with more adverse events than CHOP plus obinutuzumab.

The phase III randomized trial (GADOLIN) compared bendamustine + obinutuzumab versus bendamustine monotherapy in patients with rituximab-refractory indolent lymphoma (413 patients; 335 patients had FL; 164 patients were randomized to bendamustine + obinutuzumab; 171 patients were randomized to bendamustine monotherapy).[97,98] Patients without POD in the bendamustine + obinutuzumab group received obinutuzumab maintenance. After a median follow-up of 32 months, the median PFS was significantly longer with bendamustine + obinutuzumab than with bendamustine monotherapy (25 months vs. 14 months; $P <$ .001) in patients with FL.[100] The median OS was not reached in the bendamustine + obinutuzumab group compared to 54 months for the bendamustine group. The most frequent grade ≥3 adverse events were neutropenia (33% for bendamustine plus obinutuzumab vs. 26% for bendamustine monotherapy), thrombocytopenia (11% vs.16%), anemia (8% vs. 10%), and infusion-related reactions (11% vs. 6%).

Given the concerns for increased incidences of opportunistic infections and secondary malignancies in patients treated with BR as first-line therapy,[71,99] BR is not recommended as an option for second-line therapy if it was previously used as first-line therapy.

Rituximab

Rituximab has also demonstrated single-agent activity in patients with relapsed or refractory disease resulting in a response rate of 48%.[100]

Lenalidomide with or without Rituximab

In a phase II trial of patients with relapsed/refractory indolent NHL (n = 43), single-agent lenalidomide induced an ORR of 23% (7% CR).[101] The ORR was 27% among the subgroup of 22 patients with FL. The median duration of response was longer than 16 months, and has not been reached. Median PFS for all patients was 4 months.

In the randomized phase II trial that evaluated the activity of lenalidomide monotherapy compared with lenalidomide plus rituximab (CALGB 50401 study) in patients with recurrent FL (n = 91), the ORR was significantly higher for patients receiving lenalidomide + rituximab than for those receiving lenalidomide monotherapy (76% vs. 53%; P = .029).[102] With a median follow-up of 2.5 years, the median time to progression was 2 years and 1 year, respectively, for lenalidomide + rituximab and lenalidomide monotherapy. The incidences of grade ≥3 adverse events were similar in both treatment arms (53% for lenalidomide plus rituximab

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vs. 58% for lenalidomide monotherapy). However, lenalidomide alone was associated with more treatment failures, with 22% of patients discontinuing treatment due to adverse events. The most common grade 3 or 4 toxicities included neutropenia (20% vs. 16%), fatigue (13% vs. 9%), and thrombosis (4% vs. 16%).

In the multicenter, double-blind, randomized phase III study (AUGMENT; n = 358; 295 patients had FL), lenalidomide + rituximab was superior to rituximab monotherapy in terms of PFS in all histologic subtypes of previously treated indolent lymphomas except MZL.[103] At median follow-up of 28 months, the median PFS was 39 months for lenalidomide + rituximab compared to 14 months for rituximab monotherapy (P < .0001) in the subgroup of patients with previously treated FL. The ORRs were 80% (35% CR) and 55% (20% CR), respectively (P < .0001). The estimated 2-year OS rates were 95% and 86%, respectively for lenalidomide + rituximab and rituximab monotherapy. Infections (63% vs. 49%), cutaneous reactions (32% vs. 12%), constipation (26% vs. 14%), thrombocytopenia (15% vs. 4%), and tumor flare reaction (11% vs. 1%) were more common with lenalidomide + rituximab with neutropenia (50% vs. 13%) and leukopenia (7% vs. 2%) being the most common grade 3 or 4 toxicities.

Other Recommended Regimens

Ibritumomab Tiuxetan

In a randomized phase III study of 143 patients with relapsed or refractory low-grade, follicular, or transformed lymphoma, ^{90}Y-ibritumomab tiuxetan produced a statistically and clinically significant higher ORR (80% vs. 56%) and CR rate (30% vs. 16%) compared with rituximab alone.[104] 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.[105]

Phosphatidylinositol 3-kinase (PI3K) Inhibitors

Idelalisib, copanlisib, and duvelisib have shown promising results in the treatment of relapsed/refractory disease after 2 prior therapies.[106-110] Idelalisib and copanlisib have also been shown to be effective for high-risk patients with disease relapse ≤2 years after first-line therapy.[109,111]

Based on the recent FDA approvals, idelalisib, copanlisib, and duvelisib are included as options for relapsed/refractory disease after 2 prior therapies. Evidence from clinical trials supporting this recommendation are discussed below.

Idelalisib

In a phase II multicenter, single-arm study of 125 patients with rituximab- and alkylating agent-refractory indolent NHL (72 patients had FL), idelalisib resulted in tumor reductions in 90% of the patients, with an ORR of 57% (6% CR).[106] The median duration of response and the median PFS were 13 months and 11 months, respectively. In a post hoc subgroup analysis of 72 patients with FL, the ORR was 56% (14% CR; 42% PR) and the overall disease control rate was 87%.[107] The PFS rate at 12 months and the estimated OS rate at 24 months were 43% and 70%, respectively. Grade ≥3 or greater toxicities included neutropenia (27%), thrombocytopenia (6%), elevated alanine transaminase (ALT) (13%), diarrhea (13%), and pneumonia (7%). In a post hoc analysis, the median PFS was 8 months for patients with POD within 12 months compared to 14 months for those with POD between 12 months and 24 months.[111] The ORR, however, was not significantly different between the 2 groups (71% and 45%, respectively, for patients with POD within 12 months and those with POD between 12 months and 24 months; P = .18).

Copanlisib

In a phase II study (CHRONOS-1) of 142 patients with relapsed/refractory indolent NHL after ≥2 prior lines of therapy, copanlisib resulted in an ORR

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of 59% in the subgroup of 104 patients with FL (14% CR; 44% PR) and the median duration of response was 12 months. The median PFS and OS were 11 months and not reached, respectively.[108] The 2-year follow-up data also confirmed these results. The ORR was 61% (20% CR; 39% PR) and the median PFS and OS were 13 months and 43 months, respectively.[109] Among the 98 patients with FL and POD within 24 months, the ORR was 60% (22% CR; 38% PR), which was not significantly different from ORR of 59% for patients with POD after 24 months; however, the CR rate was higher in the POD <24 months group (22%) compared with 18% in the POD >24 months group.[109] Grade ≥3 toxicities included neutropenia (24%), thrombocytopenia (7%), hyperglycemia (41%), hypertension (24%), pneumonia (15%), and diarrhea (5%).

Duvelisib

In the phase II study (DYNAMO) evaluating the safety and efficacy of duvelisib in 129 patients with indolent NHL refractory to both rituximab and chemotherapy or radioimmunotherapy (RIT) , duvelisib resulted in an ORR of 47% (42% for the subgroup of patients with FL).[110] The estimated median duration of response and median PFS were 10 months and 9.5 months, respectively. Grade ≥3 toxicities included neutropenia (25%), anemia (15%), thrombocytopenia (12%), and diarrhea (15%).

Second-line Consolidation or Extended Dosing

Two large randomized trials have demonstrated a PFS advantage with rituximab maintenance over observation following second-line therapy.[112,113]

In a prospective phase III randomized study by the GLSG, rituximab maintenance after second-line treatment with RFCM 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).[112]

In a phase III randomized Intergroup trial (EORTC 20981) in patients with relapsed or resistant FL (n = 334) responding to CHOP or RCHOP induction therapy, rituximab maintenance significantly improved median PFS (4 years vs. 1 year; *P* < .001) compared with observation alone.[113] This PFS benefit was observed regardless of the induction therapy employed (CHOP or RCHOP). With a median follow-up of 6 years, the 5-year OS rate was not significantly different between study arms (74% vs. 64%, respectively).[113]

In the GADOLIN study (discussed above), obinutuzumab maintenance following second-line therapy with bendamustine plus obinutuzumab improved PFS in patients with rituximab-refractory FL.[97,98]

In a randomized study that evaluated the benefit of rituximab maintenance versus rituximab retreatment at progression in patients with indolent lymphomas previously treated with chemotherapy (n = 114), rituximab maintenance significantly improved PFS compared with rituximab retreatment (31 months vs. 7 months; *P* = .007).[114] However, the duration of benefit was similar in both treatment groups (31 months vs. 27 months). Therefore, either approach (maintenance or rituximab retreatment at progression) could be beneficial for this patient population.

Patients achieving CR or PR to second-line or subsequent therapy can either be observed or treated with optional consolidation or extended therapy.

- Rituximab maintenance (one dose every 12 weeks up to 2 years) is included with a category 1 recommendation.[112,113] However, the panel recognizes that the efficacy of rituximab maintenance in the second-line setting would likely be impacted by a patient's response to first-line maintenance with rituximab. The clinical benefit of rituximab maintenance in the second-line setting is likely

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very minimal in patients with POD during or within 6 months of first-line maintenance with rituximab.

- Obinutuzumab maintenance (1 g every 8 weeks for a total of 12 doses) is preferred for patients with rituximab refractory disease, which includes POD on or within 6 months of prior rituximab therapy.[97,98]

HDT/ASCR is an appropriate consolidative therapy for patients with second or third remission. HDT/ASCR as consolidation therapy has been shown to prolong OS and PFS in patients with relapsed or refractory disease.[115-119] Allogeneic hematopoietic cell transplant (HCT) results in lower relapse rates than HDT/ASCR, but it is associated with high transplant-related mortality (TRM) rate.[119-121] Allogeneic HCT may also be considered for highly selected patients.

Clinical follow-up with a complete physical exam and laboratory assessment (every 3 to 6 months for the first 5 years, and then annually [or as clinically indicated]) is recommended. 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.

Suggested Treatment Regimens for Elderly or Infirm Patients

As discussed earlier, rituximab monotherapy has demonstrated single-agent activity in patients with previously untreated low burden FL and advanced stage FL as well as in patients with relapsed/refractory disease.[75,76,100] In a retrospective study of 75 patients with newly diagnosed FL, chlorambucil + rituximab resulted in an ORR of 97% (75% CR). The 5-year EFS and OS rates were 71% and 98%, respectively.[122] Single-agent cyclophosphamide was associated with similar OS and CR rates compared with cyclophosphamide-based combination chemotherapy.[123]

In an international phase II trial of 59 patients with stage III or IV FL (age >50 years; median age 66 years), ^{90}Y-ibritumomab tiuxetan when used as a first-line therapy resulted in an ORR of 87% (41% CR) at 6 months after therapy.[124] After a median follow-up of 31 months, the median PFS was 26 months and median OS had not been reached. The most common toxicities 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.

Rituximab monotherapy is the preferred treatment option for untreated as well as relapsed/refractory disease in elderly or infirm patients who are not able to tolerate any of the chemoimmunotherapy regimens recommended for first-line therapy. Ibritumomab tiuxetan and alkylating agent-based chemotherapy (cyclophosphamide or chlorambucil) with or without rituximab are included as alternative options. Ibritumomab tiuxetan is included with a category 2B recommendation. Selection of patients requires adequate marrow cellularity (>15%), <25% of bone marrow involvement, and platelet count >100,000. Referral to a tertiary care center is highly recommended for patients treated with prior ASCR.

Histologically Transformed Follicular Lymphoma

Histologic transformation of FL to DLBCL occurs in approximately 15% of patients with an estimated annual rate of 2% to 3% and is generally associated with a poor clinical outcome.[125-127] In a pooled analysis of French and U.S. cohorts of patients with newly diagnosed FL, histologically transformed FL (TFL) after diagnosis was the leading cause death (77 of 140 deaths).[128] Recent studies that have evaluated the outcomes of patients with TFL in the rituximab era have reported improved survival in a subset of patients (eg, histologic transformation after early-stage FL and patients with no previous exposure to chemotherapy or rituximab prior to histologic transformation).[127,129,130]

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Risk Factors

Advanced stage FL, high-risk FLIPI and IPI scores at diagnosis, elevated LDH, and B symptoms at diagnosis have been reported as risk factors for histologic transformation to DLBCL.[125-127,129,131,132]

Early initiation of treatment at diagnosis relative to observation has been suggested to decrease the risk of transformation in some studies.[127,129,131] However, in the randomized phase III intergroup trial that evaluated the role of immediate treatment with rituximab versus observation in patients with advanced stage, asymptomatic, low tumor burden FL, the trial also addressed whether early intensive rituximab therapy would change the risk of histologic transformation. No difference in time to transformation or incidence of histologic transformation was detected between the 3 groups, after a median follow-up of almost 4 years.[66]

Treatment Options

There are no data from randomized studies to support the optimal treatment for patients with TFL, since clinical trials have often excluded this group of patients. Results from retrospective cohort studies suggest that rituximab monotherapy or in combination with anthracycline-based chemotherapy is associated with improved OS.[127,129,132] RIT has also been shown to induce high response rates and durable remissions in patients with TFL.[105,133]

In a series that reported the outcomes of 60 patients with biopsy-proven TFL, RCHOP was the most common treatment for TFL (n = 35; 59%) associated with a median OS of 50 months.[127] At a median follow-up of 60 months, the 5-year OS rate was 66% for patients with TFL treated with RCHOP, which was similar to the outcome of patients with de novo DLBCL treated with RCHOP in the validation cohort (5-year OS rate of 73%). In the National LymphoCare Study that included 147 pathologically confirmed and 232 clinically suspected cases of TFL, the majority of patients were treated with rituximab-based therapy (26% of patients received rituximab monotherapy and 35% received chemotherapy with rituximab).[129] At a median follow-up of 7 years, the median PFS and OS were 12 months and 60 months, respectively, for patients with biopsy-proven histologic transformation to DLBCL. In another study that evaluated the outcomes of patients with FL who had histologic transformation after response to first-line chemoimmunotherapy in the PRIMA trial, the majority of patients with TFL received chemoimmunotherapy regimens recommended for DLBCL with a 5-year OS rate of 48% to 50%.[132]

HDT/ASCR as consolidation therapy has been evaluated only in retrospective studies[134-141] with some series reporting survival benefit for patients who did proceed to transplant.[137,139,141] Allogeneic HCT has been shown to benefit selected patients with disease relapse following HDT/ASCR, but is also associated with significant TRM.[137,138,140,142] However, it should be noted that the efficacy of HDT/ASCR or allogeneic HCT in patients with TFL has not been confirmed in prospective controlled studies.

Histologic Transformation After Minimal Or No Prior Therapy

Anthracycline-based chemoimmunotherapy (with regimens recommended for first-line therapy for DLBCL, unless contraindicated) with or without ISRT is recommended for TFL without double-hit cytogenetics.[4,5] Histologic transformation to high-grade B-cell lymphomas (HGBL) with translocations of *MYC* with either *BCL2* or *BCL6*, also called double- or triple-hit lymphoma, occurs in about 24% of cases and has been associated with an inferior survival compared to TFL without double-hit cytogenetics (2-year survival rates of 50% and 73%, respectively).[143] TFL with double-hit cytogenetics should be managed with more aggressive chemoimmunotherapy regimens as recommended for HGBL with translocations of *MYC* and *BCL2* and/or *BCL6*.

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Consolidation therapy with HDT/ASCR with or without ISRT (if not previously given) or observation are included as treatment options for patients achieving CR or PR to initial treatment.[137,139,141] If transformation is coexisting with extensive FL, rituximab maintenance should be considered for patients achieving CR. Additional systemic therapy ± ISRT to induce CR should be considered for patients achieving PR, if proceeding to transplant. Repeat biopsy should be strongly considered prior to additional therapy for patients with PET-positive PR because PET positivity may represent post-treatment inflammation. Allogeneic HCT should be considered only in selected patients.

RIT with ibritumomab tiuxetan or ISRT (for localized residual disease and/or residual FDG-avid disease not previously irradiated) are included as alternative treatment options for patients achieving PR.[105,133] RIT with ibritumomab tiuxetan or best supportive care are recommended for patients with non-responsive or progressive disease.[105,133] Based on the FDA approval, chimeric antigen receptor (CAR) T-cell therapy (axicabtagene ciloleucel or tisagenlecleucel) is included as an option for patients who have received ≥2 prior chemoimmunotherapy regimens for indolent or transformed disease.[144-146]

Histologic Transformation After Multiple Lines of Prior Therapies

Enrollment in an appropriate clinical trial is the preferred option. In the absence of a suitable clinical trial, treatment options include chemoimmunotherapy (with regimens recommended for second-line therapy for DLBCL) with or without ISRT, RIT with ibritumomab tiuxetan, ISRT, or best supportive care.[132,105,133] Based on the FDA approval, CAR T-cell therapy (axicabtagene ciloleucel or tisagenlecleucel) is included as an option for patients who have received ≥2 prior chemoimmunotherapy regimens for indolent or transformed disease.[144-146]

Consolidation therapy with HDT/ASCR with or without ISRT (if not previously given) or observation are included as treatment options for patients achieving CR.[137,139,141] Allogeneic HCT should be considered only in selected patients.

For patients achieving PR to initial therapy of TFL, treatment options include second-line regimens for DLBCL, allogeneic HCT with or without ISRT (only in the context of a clinical trial), CAR T-cell therapy (axicabtagene ciloleucel or tisagenlecleucel for patients who have received ≥2 prior chemoimmunotherapy regimens for indolent or transformed disease) if not previously given, or ISRT for localized residual disease and/or residual FDG-avid disease not previously irradiated. However, it should be noted that data on the efficacy of transplant in patients who have received CAR T-cell therapy are not available. HDT/ASCR is not recommended after CAR T-cell therapy. Allogeneic HCT could be considered but remains investigational.

Patients with non-responsive or progressive disease can be treated with any of the treatment options (not received previously), if they are candidates for additional therapy.

Pediatric-type Follicular Lymphoma in Adults

PTFL is generally characterized by lack of *BCL2* rearrangement and t(14,18), and *BCL6* rearrangement is also typically absent in PTFL.[2] BCL2 expression may be observed in approximately 40% to 50% of cases, and BCL6 expression can be seen in the majority of cases.[8-11]

Histologically, PTFL is associated with large expansive follicles with a “starry sky” pattern, effacement of architecture, absence of diffuse area, high histologic grade (grade 3), and a high proliferation index.[9-11] In young patients with BCL2-negative localized disease, the diagnosis of PTFL may be considered. Analysis of *BCL6* rearrangement may be useful for evaluating the diagnosis of PTFL.

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In adult patients without *BCL2* rearrangement but with high proliferation index, PTFL has a highly indolent disease course (stage I disease with no disease progression or relapse) compared to PTFL with *BCL2* rearrangement and/or low proliferation index (Ki-67 <30%; stage III or IV disease and majority of patients experience disease progression or recurrence).[10]

PTFL without *BCL2* rearrangements is generally associated with favorable prognosis with only rare instances of disease progression or relapse and is primarily managed with excision (preferred) or ISRT. RCHOP is recommended for patients with extensive local disease who are not candidates for excision or ISRT.[147]

Restaging with PET/CT is recommended for patients treated with ISRT or RCHOP. No further treatment is necessary following excision or CR to ISRT or RCHOP. There are no data to support maintenance therapy. If patients have an excellent prognosis, no surveillance imaging is necessary. Patients with less responsive disease (<CR) should be managed as described for progressive FL.

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Marginal Zone Lymphomas

Marginal zone lymphomas (MZLs) originate in the marginal zone of lymphoid follicles found in the mucosa-associated lymphoid tissues (MALT), spleen, and lymph nodes.[1] Extranodal MZLs of MALT (MALT lymphomas), nodal MZL (NMZL), and splenic MZL (SMZL) are the three distinct subtypes of MZLs. In a Surveillance, Epidemiology, and End Results (SEER) database analysis that assessed the incidence rates (IRs) of different subtypes of MZLs in the United States (2001–2009), NMZL and extranodal MZL were diagnosed in 4,081 (IR = 5.7) and 8,821 (IR = 12.3) individuals, respectively.[2] The most common sites were stomach (IR = 3.8), spleen (IR = 1.6), ocular adnexa (IR = 1.4), and lung, skin, and salivary glands (IR = 0.9–1.0).

The etiology of MZLs has been associated with chronic immune stimulation due to infectious agents or inflammation. Helicobacter pylori (*H. pylori*) has been implicated in the pathogenesis of gastric MALT lymphoma and other infectious agents such as Chlamydia psittaci (*C. psittaci*), Campylobacter jejuni (*C. jejuni*), and Borrelia burgdorferi (*B. burgdorferi*) have also been implicated in the pathogenesis of MZLs.[3] MZLs are also characterized by a high prevalence of hepatitis C virus (HCV) infection and HCV seroprevalence has been reported in about 22% to 35% of patients with NMZL, SMZL, and nongastric MALT lymphomas.[4,5]

MZLs are also characterized by clinical and pathologic features that overlap with Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma (WM/LPL).[6] Recent studies have confirmed that the *MYD88* L265P somatic mutational analysis could be useful in differentiating WM/LPL from other B-cell malignancies with overlapping clinical and pathologic features.[7-10] In a retrospective analysis 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 SMZL (2 out of 53), 7% of patients with MALT lymphomas (2 out of 28), and 0% of patients with NMZL.[8] Immunoglobulin heavy chain variable (*IGHV)* gene sequencing clearly distinguished SMZL and WM/LPL. SMZL was 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.[8] In selected circumstances when plasmacytic differentiation is present, *MYD88* mutational analysis should be considered to differentiate MZLs from WM/LPL.[7-10]

The NCCN Guidelines provide recommendations for the diagnosis, workup, and treatment for MALT lymphomas, NMZL, and SMZL.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for B-Cell Lymphomas an electronic search of the PubMed database was performed to obtain key literature in MZLs published since the previous Guidelines update, using the following search terms: MALT lymphoma, gastric MALT lymphoma, nongastric MALT lymphoma, nodal marginal zone lymphoma and splenic marginal zone lymphoma. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes 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 data from key PubMed articles deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

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The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

MALT Lymphomas

The gastrointestinal (GI) tract is the most common site of involvement with the stomach being the most common primary site in gastric MALT lymphomas; salivary/parotid glands, skin, ocular adnexa, head and neck, lung, thyroid, and breast are the other common sites of involvement in nongastric MALT lymphoma.[2] Bone marrow involvement has been reported in about 15% to 20% of MALT lymphomas.[12,13]

Although MALT lymphomas are localized in most patients, about a third of patients present with disseminated disease and localized disease is more frequently observed with gastric subtype than with nongastric subtype.[12,13] MALT lymphomas tend to be indolent, with similar long-term outcomes reported between gastric and nongastric subtypes and between patients with disseminated and localized disease.[12,14] More recent retrospective data, however, reported higher progression-free survival (PFS) outcomes in patients with gastric MALT lymphomas and in patients with localized disease.[15]

t(11;18), t(1;14), t(14;18), and t(3;14) are the most common genetic alterations implicated in the pathogenesis of MALT lymphomas.[16] t(11;18), resulting in the formation of the chimeric fusion gene, *API2-MALT1*, is frequently detected in gastric and pulmonary MALT lymphomas.[17,18] t(1;14) results in the overexpression of BCL10 protein and occurs in 1% to 2% of MALT lymphomas, usually detected in MALT lymphomas of the stomach, lung, and skin.[19] The presence of both t(11;18) and BCL10 overexpression is associated with locally advanced disease, which is less likely to respond to *H. pylori* eradication with antibiotic therapy.[20] t(14;18) results in the deregulated expression of *MALT1* gene and has been reported to occur in 15% to 20% of MALT lymphomas, most frequently detected in MALT lymphomas of the liver, skin, ocular adnexa, and the salivary gland.[18,21] t(3;14) results in the upregulation of the *FOXP1* gene and is associated with the MALT lymphomas of thyroid, ocular adnexa, and skin.[22] The clinical significance of t(14;18) and t (3;14) is unknown.

Gastric MALT Lymphoma

Diagnosis

An endoscopic biopsy is required to establish the diagnosis of gastric MALT lymphoma, as fine-needle aspiration (FNA) is not adequate for diagnosis. Endoscopy may reveal erythema, erosions, or ulcerations.[23] Adequate hematopathology review of biopsy material and immunophenotyping are needed to establish a diagnosis. The recommended markers for an immunohistochemistry (IHC) panel include 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.[23-25] Therefore, staining for detection of *H. pylori* should be performed. However, *H. pylori* infection is not evident in approximately 5% to 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.[26] This chromosomal abnormality has been associated with disseminated disease and resistance to antibiotic treatment in patients with gastric MALT lymphoma.[27,28] Molecular analysis by polymerase chain reaction (PCR) or fluorescence in situ hybridization (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.

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Workup

A comprehensive physical examination should be performed with attention to nongastric sites such as the eyes and skin, and performance status should be assessed. Laboratory evaluations should include a complete blood count (CBC) with differentials and platelets, comprehensive metabolic panel, and measurement of serum lactate dehydrogenase (LDH) levels. Evaluation of bone marrow biopsy, with or without aspirates, may be useful under certain circumstances. Testing for HCV should be performed for all patients and testing for hepatitis B virus (HBV) is indicated for patients being considered for treatment with rituximab-containing regimens due to the risk of viral reactivation. Appropriate imaging studies include chest/abdomen/pelvis CT scan with contrast of diagnostic quality and/or whole body PET/CT (especially if involved-site radiation therapy [ISRT] is anticipated). A multigated acquisition (MUGA) scan/echocardiogram should be performed if the patient is being considered for treatment with regimens containing anthracycline or anthracenedione.

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 histopathologic evaluation, other noninvasive testing methods may be employed to confirm negative status (ie, stool antigen test, urea breath test, blood antibody test). Nondiagnostic atypical lymphoid infiltrates that are *H. pylori* positive should be rebiopsied to confirm or exclude lymphoma prior to treatment of *H. pylori*. At some NCCN Member Institutions, endoscopic ultrasound (EUS) is used to complement conventional endoscopy at the time of the initial workup and at follow-up. EUS 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.[29]

In addition, EUS staging is also useful in predicting the efficacy of *H. pylori* eradication therapy.[30,31] 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.

Staging

It is unknown whether staging for MALT lymphomas should follow the standard Ann Arbor staging systems used for nodal lymphomas. The widely used Lugano staging system for GI lymphomas is a modification of the original Ann Arbor staging system.[32] Ann Arbor stage III has been removed. The TNM staging system corresponds to the staging in gastric cancer and the depth of the lymphoma infiltration is measured by EUS. Stage I refers to disease confined to the GI tract (single primary or multiple non-contiguous lesions (stage I_1, the infiltration is limited to mucosa or submucosa and in stage I_2, infiltration is present in the muscularis propria, serosa, or both). Stage II refers to disease extending into the abdomen (stage II_1, localized nodal involvement [perigastric lymph nodes] and in stage II_2, distant nodal involvement). Stage IIE refers to penetration of serosa to involve adjacent organs or tissues; subscripts (1 or 2) may be added to the designation if both the lymph nodes and adjacent organs are involved. Stage IV refers to disseminated extranodal involvement or concomitant supradiaphragmatic nodal involvement, and cases with disseminated nodal involvement appear to behave more like NMZL or follicular lymphoma (FL).

Treatment

H. pylori infection plays a central role in the pathogenesis of localized gastric MALT lymphoma and the treatment approach depends on the *H. pylori* infection status. In retrospective and prospective clinical studies, *H. pylori* eradication with antibiotic therapy resulted in lymphoma regression in 70% to 95% of patients with localized disease.[33-40] In a multicenter cohort follow-up study of 420 patients with gastric MALT lymphoma, the response rate was 77% for *H. pylori* eradication therapy and the estimated

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10-year freedom from treatment failure (FFTF), overall survival (OS), and event-free survival (EFS) rates were 90%, 95%, and 86%, respectively.[40] The presence of t(11;18) and *H. pylori*-negativity and submucosal invasion were independent predictors of resistance to *H. pylori* eradication. *H. pylori* eradication therapy generally comprises a proton pump inhibitor (eg, 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).[23]

Long-term follow-up data from clinical studies suggest that RT is an effective treatment modality in gastric MALT lymphoma after failure with *H. pylori* eradication therapy or as an initial treatment for patients with *H. pylori*-negative disease.[41-46]

In the randomized controlled study of 241 patients with localized gastric MALT lymphomas, after a median follow-up of 8 years, the 10-year EFS rates were 52%, 52%, and 87%, respectively, for patients treated with surgery, RT, and chemotherapy ($P < .01$).[41] The 10-year OS rate was not significantly different between the treatment groups (80% vs. 75% vs. 87%, respectively). In an analysis of registry data from a German multicenter study in patients with localized gastric lymphomas, extended-field RT (30 Gy followed by 10 Gy boost) alone resulted in an EFS and OS rate of 88% and 93%, respectively, in the subgroup of patients with gastric MALT lymphomas.[42] These outcomes were not significantly different from patients with gastric MALT lymphomas who received combined modality therapy with surgery and RT (EFS and OS rates of 72% and 83%, respectively).[42] This study had also included patients with gastric MALT lymphomas who experienced treatment failure with *H. pylori* eradication therapy. In a retrospective study of 192 patients with localized (stage I–II) MALT lymphomas, the complete response (CR) rate was 99% in the group of patients treated with involved-field RT (IFRT) (30–35 Gy) alone.[44] After a median follow-up of 7 years, the estimated 10-year relapse-free survival (RFS) rate, disease-free survival (DFS) rate, and OS rate were 76%, 68%, and 87%, respectively. Patients with thyroid and gastric MALT lymphomas had better outcome than patients with MALT lymphomas diagnosed at other sites ($P = .004$). The 10-year RFS rate was 95% for thyroid, 92% for stomach, 68% for salivary glands, and 67% for orbit. In a recent prospective randomized study, reduced-dose RT (25 Gy) was also effective for the treatment of *H. pylori*-negative stage I–II disease or *H. pylori*-positive disease that is refractory to *H. pylori* eradication therapy.[46] The presence of the t(11,18) translocation was a predictor for persistent lymphoma after *H. pylori* eradication therapy.

Rituximab has demonstrated activity in patients not eligible for eradication therapy (*H. pylori*-negative disease) or in those with gastric MALT lymphoma relapsed or refractory to *H. pylori* eradication therapy.[47,48] In a prospective study of 27 patients with relapsed/refractory disease or *H. pylori*-negative disease (majority of patients [81%] had stage I or II_1 disease), rituximab resulted in an overall response rate (ORR) of 77% (46% CR). At a median follow-up of 28 months from start of treatment, all patients were alive and 54% of patients were disease free.[47] In a retrospective study that evaluated treatment options for patients with persistent disease despite *H. pylori* eradication therapy or *H. pylori*-negative disease (n = 106; 28 patients were treated with rituximab), rituximab resulted in an ORR of 73% (64% CR).[48] After a median follow- up of 5 years, the 5-year PFS and OS rates were 70% and 95%, respectively.

Stage I–II

H. Pylori-positive Stage I_1, or I_2 or Stage II_1 Disease

Antibiotic therapy to eradicate the *H. Pylori* infection is recommended, regardless of t(11;18) status. However, it should be noted that t(11;18) is a predictor for lack of response to antibiotic therapy.[28,40] Patients with

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involvement of submucosa or regional lymph nodes are also much less likely to respond to antibiotic therapy.[40]

Evaluation with endoscopy and biopsy is recommended after 3 months following antibiotic therapy. In symptomatic patients after antibiotic therapy, restaging can be done earlier than 3 months. Clinical follow-up every 3 to 6 months for 5 years and then yearly or as clinically indicated is recommended for patients with disease responding to initial antibiotic therapy (*H. pylori* negative and lymphoma negative). There is increasing evidence that late relapses can occur after antibiotic treatment and a long duration of follow-up is appropriate.

For patients with t(11;18)-negative disease or t(11;18) status unknown, ISRT is recommended for those who are *H. pylori* negative with persistent lymphoma.[41-44,46] Alternatively, asymptomatic patients can be observed for another 3 months. CRs may be observed as early as 3 months after antibiotic treatment but can take longer to achieve (up to 18 months). If re-evaluation suggests slowly responding disease or asymptomatic nonprogression, continued observation may be warranted (category 2B). Second-line antibiotic treatment is recommended for patients with persistent *H. pylori* and regressing or stable lymphoma. Lastly, patients who are *H. pylori* positive with progressive or symptomatic lymphoma should be treated with ISRT and second-line antibiotics.

Follow-up endoscopy is recommended after 3 months following completion of treatment (ISRT or second-line antibiotic treatment). Biopsy is recommended to rule out evidence of diffuse large B-cell lymphoma (DLBCL). Any area of DLBCL should be treated according to recommendations for DLBCL. Clinical follow-up every 3 to 6 months for 5 years and then yearly thereafter (or as clinically indicated) is recommended for patients with a CR. The optimal interval for follow-up endoscopy and imaging is not known. Follow-up endoscopy and imaging at NCCN Member Institutions are performed as clinically indicated based on symptoms. Locoregional RT is indicated for patients with no response to second-line antibiotic therapy and chemoimmunotherapy is recommended for patients with no response to ISRT.

For patients with t(11;18)-positive disease, those with persistent lymphoma after antibiotic therapy should be treated with ISRT or rituximab (if ISRT is contraindicated).[41-44,46,47] Evaluation with endoscopy and biopsy is recommended after 3 to 6 months following ISRT or rituximab. Clinical follow-up every 3 to 6 months for 5 years and then yearly or as clinically indicated is recommended for patients with responsive disease (*H. pylori* negative and lymphoma negative). Antibiotic treatment can be considered for patients with persistent *H. pylori* and regressing lymphoma. However, patients with persistent lymphoma (regardless of *H. pylori status*) following ISRT or rituximab should be managed with chemoimmunotherapy.

Suggested treatment regimens for first-line therapy are discussed in *Chemoimmunotherapy for Marginal Zone Lymphomas*.

H. pylori Negative Stage I_1, or I_2 or Stage II_1 Disease

ISRT is preferred for *H. pylori*-negative disease and rituximab is an option for patients with contraindications to ISRT.[41-44,46,47] Evaluation with endoscopy and biopsy is recommended after 3 to 6 months following ISRT or rituximab. Additional treatment options are similar to that described above for patients with t(11;18)-positive disease.

Treatment for Relapsed Disease

Locoregional ISRT is recommended for local recurrence following antibiotic therapy. Treatment for recurrence following ISRT or systemic recurrence following antibiotic therapy is based on the presence of indications for treatment. Asymptomatic patients without indications for treatment are observed. Chemoimmunotherapy is recommended for patients with indications for treatment.

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Suggested treatment regimens for second-line therapy are discussed in the section *Chemoimmunotherapy for Marginal Zone Lymphomas*.

Stage IIE, II$_2$, or IV

In patients with distant nodal, advanced stage disease (which is uncommon), treatment is similar to that described for patients with advanced stage FL. Asymptomatic patients without indications for treatment are observed. 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. Chemoimmunotherapy or palliative ISRT is recommended for patients with indications for treatment. Suggested treatment regimens for first-line therapy are discussed in *Chemoimmunotherapy for Marginal Zone Lymphomas*. 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.

Evaluation with endoscopy is recommended after completion of treatment. Recurrent disease should be managed with treatment regimens for second-line therapy as discussed in *Chemoimmunotherapy for Marginal Zone Lymphomas*.

Nongastric MALT Lymphomas

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-, and 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 nongastric MALT lymphoma is similar to the workup for other non-Hodgkin's lymphomas (NHLs). A comprehensive physical examination should be performed and performance status should be assessed. Laboratory evaluations should include a CBC 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. Upper GI endoscopy should be considered where primary site is thought to be in head/neck or lungs.[49] Testing for HCV should be performed for all patients and testing for HBV is indicated for patients being considered for treatment with rituximab-containing regimens due to the risk of viral reactivation. Infectious pathogens such as *C. jejuni and C. psittaci* have been associated with nongastric MALT lymphomas, but testing for these pathogens is not required for disease workup or management.[3]

Appropriate imaging studies include chest/abdomen/pelvis CT scan with contrast of diagnostic quality and/or whole body PET/CT. A MUGA scan/echocardiogram should be performed if the patient is being considered for treatment with regimens containing anthracycline or anthracenedione. MRI with contrast should be done for neurologic evaluation or if CT with contrast is contraindicated.

Treatment

ISRT is an effective initial treatment for patients with nongastric MALT lymphoma.[44,45,50] In a retrospective study of 167 patients with localized MALT lymphomas treated with RT with or without chemotherapy

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(nongastric MALT lymphoma, n = 142), the group who received IFRT alone (n = 144; dose range 25–35 Gy; 25 Gy for orbit) had an estimated 10-year RFS rate and OS rate of 74% and 89%, respectively.[44] The 10-year RFS rates for patients with primary involvement of the thyroid, salivary gland, and orbital adnexa were 95%, 68%, and 67%, respectively. In another retrospective study of 208 patients with nongastric MALT lymphomas (Ann Arbor stage III–IV in 44%), the ORR among patients treated with chemotherapy, RT, or surgery were 65%, 76%, and 90%, respectively.[50] After a median follow-up of 3 years, the estimated 5-year EFS and OS rates were 37% and 83%, respectively. The 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* = .001). On multivariate analysis, bone marrow involvement was the only significant independent predictor of inferior EFS and OS.[50]

Rituximab has demonstrated activity in patients with nongastric MALT lymphoma.[51-53] 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; 20 patients with nongastric MALT lymphoma).[51] Among patients with nongastric MALT lymphoma, treatment with rituximab resulted in an ORR of 80% (55% CR and 25% partial response [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).

ISRT (24–30 Gy) is the preferred treatment for patients with stage I–II disease and is also recommended for patients presenting with stage IV disease.[44,45,50] In patients with stage IV disease, definitive treatment of multiple sites and palliative treatment of symptomatic sites may be indicated. RT dose is site dependent, with lower doses usually reserved for orbital involvement. Based on anecdotal responses to antibiotics in ocular and cutaneous MZLs, some physicians may give an empiric course of doxycycline prior to initiating therapy. Observation may be considered for patients whose diagnostic biopsy was excisional or in whom RT could result in significant morbidity.

Rituximab is an option for selected patients with stage I–II disease.[51-53] Surgical excision may be appropriate treatment for certain extranodal sites (e., lung, thyroid, colon, small intestine, breast) in patients with stage I–II disease.[13] Observation is recommended if there is no residual disease following surgery and locoregional RT should be considered for patients with positive surgical margins.

Clinical follow-up (including repeat diagnostic tests and imaging based on the site of disease and as clinically indicated) should be conducted every 3 to 6 months for 5 years and then annually thereafter (or as clinically indicated). Local recurrence may be treated with ISRT (if not previously received) or managed according to recommendations for advanced-stage NMZL. In patients with systemic recurrence, observation is recommended for patients without any indications for treatment. Chemoimmunotherapy is recommended for patients with indications for treatment. Suggested treatment regimens for first-line therapy (for treatment-naïve patients) or second-line therapy (in patients who have received prior treatment with rituximab) are discussed in *Chemoimmunotherapy for Marginal Zone Lymphomas*.

Nodal Marginal Zone Lymphoma

In patients with NMZL, peripheral lymphadenopathy is present in nearly all cases (>95%); thoracic or abdominal lymph nodes may also be involved in about 50% of cases and involvement of bone marrow and peripheral blood may be seen in about 30% to 40% and 10% of cases, respectively.[54,55] Although about two-thirds of patients with newly diagnosed NMZL present with advanced-stage disease, most tumors are non-bulky and B symptoms are present in only about 15% of patients.[54,55] NMZL has an indolent

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disease course, but long-term survival outcomes appear less favorable compared with MALT lymphomas.[54,56] In a retrospective analysis of data from patients with MZL, the OS rate (56% vs. 81%) and 5-year failure-free survival rate (28% vs. 65%) were lower in the subgroup of patients with NMZL compared with those with MALT lymphoma.[54] A SEER database analysis also reported more favorable 5-year survival outcomes for patients with MALT lymphoma (89%) compared to those with SMZL (80%) or NMZL (77%).[56] A more recent cohort analysis has reported more favorable survival outcomes for 56 patients with NMZL treated in the rituximab era (the majority of patients [79%] presented with advanced-stage disease).[57] After a median follow-up of 38 months, the PFS was 42 months and the estimated OS at 120 months after diagnosis was 72%.

Diagnosis

Adequate hematopathology review of biopsy materials and immunophenotyping are needed to establish a diagnosis. NMZL 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 NMZL is CD5-, CD10-, CD20+, CD23-/+, CD43 -/+, cyclin D1-, and BCL2-. Pediatric NMZL 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

NMZL occurs primarily in the lymph nodes, although involvements of additional extranodal sites are common.[54,55] The diagnosis of NMZL requires careful evaluation to rule out extranodal sites of primary disease and must be distinguished from nodal FL, mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), and WM/LPL. A comprehensive physical examination should be performed and performance status should be assessed. Laboratory evaluations should include a CBC 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. Testing for HCV should be performed for all patients, and testing for HBV is indicated for patients being considered for treatment with rituximab-containing regimens due to the risk of viral reactivation.

Appropriate imaging studies include chest/abdomen/pelvis CT scan with contrast of diagnostic quality and/or whole body PET/CT. A MUGA scan/echocardiogram should be performed if the patient is being considered for treatment with regimens containing anthracycline or anthracenedione.

First-line Treatment

Stage I–II

ISRT (24–30 Gy) is recommended for patients with non-bulky stage I–II disease. Clinical follow-up (complete history and physical exam and laboratory assessment is recommended every 3–6 months for the first 5 years, and then annually thereafter or as clinically indicated) is recommended for patients achieving CR or PR. 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 thereafter. Patients with disease not responding to ISRT should be managed as described for stage III or IV disease.

Anti-CD20 monoclonal antibody (MAB) with or without chemotherapy with or without ISRT is recommended for patients with bulky disease (stage I or contiguous stage II) or non-contiguous stage II disease. The addition of

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ISRT is included with a category 2B recommendation. Observation may be appropriate in circumstances where potential toxicity of ISRT outweighs potential clinical benefit. Clinical follow-up with a complete history and physical exam, laboratory assessment, and surveillance imaging (as described above) is recommended for patients with CR or PR after completion of treatment. Patients with non-responsive disease should be managed as described below for stage III or IV disease.

Stage III–IV

Observation is recommended for patients with no indications for treatment. Treatment should only be initiated when a patient presents with indications for treatment (based on the modified 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.

Suggested regimens for first-line therapy are discussed in *Chemoimmunotherapy for Marginal Zone Lymphomas*.

First-line Consolidation or Extended Therapy

Observation is recommended for patients achieving CR or PR to first-line therapy.

Rituximab maintenance (single-dose rituximab every 3 months until treatment failure) or retreatment with rituximab (rituximab weekly x 4 at the time of each progression until treatment failure) was evaluated in an exploratory sub-study in patients with low-tumor-burden, non-follicular, indolent B-cell NHL responding to induction therapy with single-agent rituximab.[58] The ORR after induction therapy with rituximab was 40% (52% for patients with MZL). After a median of 4 years from randomization, maintenance rituximab significantly improved time to treatment failure (TTTF) compared to rituximab retreatment (5 years and 1 year respectively; P = .012). Consolidation with rituximab (375 mg/m^2 one dose every 12 weeks) is recommended for patients initially treated with single-agent rituximab.

Second-line and Subsequent Therapy

Frequently, patients with disease relapse or progression of disease after first-line therapy will benefit from a second period of observation. Considerations and indications for treatment of relapsed/refractory or progressive disease include, among other factors, the modified GELF criteria, which include: symptoms attributable to MZL (not limited to B symptoms); threatened end-organ function; significant cytopenia secondary to lymphoma; bulky disease; splenomegaly; and steady progression over at least 6 months.

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 standardized uptake value (SUV) 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.

Suggested regimens for second-line therapy are discussed under *Chemoimmunotherapy for Marginal Zone Lymphomas*.

Second-line Consolidation or Extended Dosing

Obinutuzumab maintenance (1 g every 8 weeks for a total of 12 doses) is included as an option for patients with rituximab-refractory disease treated with bendamustine + obinutuzumab based on the results of the GADOLIN study.[59]

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High-dose therapy followed by autologous stem cell rescue (HDT/ASCR) has been associated with survival benefit in patients with relapsed or refractory disease.[60-62] HDT/ASCR is included as an option for consolidative therapy for patients with disease responding to second-line therapy. Allogeneic hematopoietic cell transplant (HCT) may also be considered for highly selected patients.[61,63]

Splenic Marginal Zone Lymphoma

SMZL is characterized by the presence of splenomegaly in all cases, which may become symptomatic when massive or when associated with cytopenias.[55,64] Peripheral lymph nodes are generally not involved while splenic hilar lymph nodes are often involved.[64] Involvement of thoracic or abdominal lymph nodes may also be seen in about a third of patients with SMZL.[55] In addition, bone marrow involvement is present in the majority of patients (about 85%) and involvement of peripheral blood occurs in 30% to 50% of patients.[55,64] The disease course of SMZL is generally indolent, although most patients present with advanced-stage disease. In a retrospective study that evaluated the clinical outcomes of 124 patients with non-MALT–type MZL, the median time to progression (TTP) and median OS were 7 years and 9 years, respectively, for the subgroup of 59 patients with SMZL.[55] In a cohort analysis of 64 patients with SMZL treated in the rituximab era, the estimated median PFS and OS were 53 months and 156 months, respectively, after a median follow-up of 38 months.[65]

Diagnosis

Adequate hematopathology review of biopsy materials and immunophenotyping are needed to establish a diagnosis. The diagnosis of SMZL 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 (ie, CD5, CD10, cyclin D1). 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 SMZL 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.

SMZL 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 WM/LPL. *MYD88* mutation analysis [7-10] and *BRAF* mutation analysis can be useful in selected cases for differentiating SMZL from WM/LPL and HCL, respectively.

Workup

The initial workup for SMZL 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 CBC with differentials and platelets, comprehensive metabolic panel, and measurement of serum LDH levels. Serum protein electrophoresis (SPEP) and/or measurement of quantitative Ig levels should be performed. If elevated Ig or monoclonal Ig is detected, further characterization by immunofixation of blood may be useful. Evaluation of bone marrow biopsy with or without aspirates should be performed. Testing for HCV should be performed for all patients and testing for HBV is

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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.

Appropriate imaging studies include chest/abdomen/pelvis CT scan with contrast of diagnostic quality and/or whole body PET/CT. A MUGA scan/echocardiogram should be performed if the patient is being considered for treatment with regimens containing anthracycline or anthracenedione.

Treatment

Asymptomatic patients with no splenomegaly or progressive cytopenias can be observed until indications for treatment develop.[66,67] Patients presenting with splenomegaly should be treated depending on their HCV serology status.

Hepatology evaluation is recommended for patients with HCV-positive disease and appropriate antiviral therapy should be initiated for patients without contradictions for treatment of hepatitis. Interferon (IFN)-based antiviral therapy has been shown to induce virologic and hematologic responses in patients with HCV-positive MZLs.[68-73] In a retrospective series of 134 patients with HCV-positive indolent B-cell NHLs (36 patients with SMZL), among the patients who received antiviral therapy with IFN or pegylated-IFN, with or without ribavirin as first-line therapy (n = 100; 23 patients with SMZL), the ORR and CR rates were 77% (65% for patients with SMZL) and 47%, respectively, and a sustained virologic response was observed in 78% of patients. The median duration of response was 33 months. After a median follow-up of 4 years, the 5-year PFS and OS rates were 63% and 92%, respectively. IFN-free antiviral therapy with a combination of direct-acting antivirals (DAAs) has also been reported to be effective, resulting in high lymphoproliferative disease response rates in patients with HCV-positive MZLs.[74] Patients with no response to antiviral therapy or contraindications for treatment of hepatitis should be managed as described below for patients with HCV-negative disease.

Patients with HCV-negative disease can be observed if they are asymptomatic. Rituximab monotherapy (with or without maintenance rituximab) is associated with high response rates with durable remissions and is the preferred treatment for patients who are symptomatic (cytopenias or symptoms of splenomegaly, weight loss, early satiety, or abdominal pain).[75-79] In a retrospective study that assessed treatment with rituximab in 43 patients with SMZL, rituximab monotherapy resulted in an ORR of 100% with a CR in 79% of patients and was associated with less toxicity.[77] The 3-year DFS was more favorable with rituximab-containing therapy, with or without splenectomy (79%) compared with splenectomy alone (29%) or chemotherapy alone (25%).[77] In this small retrospective study, patients who underwent splenectomy had a higher likelihood of attaining a CR with rituximab (100%) than those who did not undergo splenectomy (67%).

Splenectomy is recommended if the disease is not responsive to rituximab. In retrospective studies, splenectomy with or without chemotherapy has demonstrated favorable outcomes with a median OS exceeding 10 years and a 10-year OS rate of 61% to 84%.[4,67,80-84] 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 to 6 months for 5 years and then annually or as clinically indicated thereafter. In patients with recurrence, observation is recommended for patients without any indications for treatment. Splenectomy, ISRT, or chemoimmunotherapy are recommended for patients with indications for treatment. Suggested

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treatment regimens for first-line therapy (for treatment-naïve patients) or second-line therapy (in patients who have received prior treatment with rituximab) are discussed in *Chemoimmunotherapy for Marginal Zone Lymphomas*.

Chemoimmunotherapy for Marginal Zone Lymphomas

The NCCN B-Cell Lymphomas Panel stratified all the regimens into 3 categories (based on the evidence, efficacy, toxicity, preexisting comorbidities, and in some cases access to certain agents): preferred regimens, other recommended regimens, and useful under certain circumstances.

First-line Therapy: Preferred Regimens

Chemoimmunotherapy with anti-CD20 monoclonal antibody

Bendamustine + rituximab (BR), RCHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), or RCVP (cyclophosphamide, vincristine, prednisone) are included as preferred regimens.

In the multicenter randomized phase III study (StiL NHL1) that included 67 patients with MZL, BR was superior to RCHOP in terms of PFS in all histologic subtypes of indolent lymphomas except MZL (P =.32).[85,86] The phase III randomized study (BRIGHT) also showed that BR was noninferior to RCHOP or RCVP in terms of PFS in patients with previously untreated indolent lymphoma or MCL.[87,88] This study included 46 patients with MZL (28 patients were randomized to BR and 18 patients were randomized to RCHOP or RCVP). The ORRs in the subgroup of patients with MZL were 92% (20% CR) and 71% (24% CR), for BR and RCHOP/RCVP, respectively.[87]

BR and RCVP have also demonstrated efficacy as first-line therapy in small clinical studies that have evaluated these regimens specifically in patients with MZL.[89-94] In a multicenter phase II trial (MALT 2008-01) of 60 patients with previously untreated MALT lymphoma (20 patients with gastric MALT lymphoma; 34 patients with nongastric MALT lymphoma), after 3 cycles of treatment, BR resulted in an ORR of 100% (75% CR) and the CR rates were significantly higher for patients with gastric MALT lymphoma (90% vs. 62%; P = .023).[89] After completion of 6 cycles, the ORR and CR rates were 100% and 98%, respectively, with no significant differences according to primary site of disease. After a median observation of 82 months, the 7-year EFS rate was 88% for all patients (90% for patients with gastric MALT lymphoma and 84% for those with nongastric MALT lymphoma). In a phase II study (BRISMA) of 56 patients with SMZL treated with BR as first-line therapy, the ORR and CR rates were 91% and 73%, respectively. The 3-year PFS and OS rates were 90% and 96%, respectively.[92] In a phase II study of 40 patients with advanced-stage MZL, RCVP resulted in an ORR of 88% (60% CR).[93] After a median follow-up of 38 months, the estimated 3-year PFS and OS rates were 59% and 95%, respectively. RCVP regimen is also effective for the treatment of patients ineligible for *H. pylori* eradication therapy or those with gastric MALT lymphoma that is resistant to *H. pylori* eradication therapy.[94]

In the clinical trial that evaluated the efficacy and safety of obinutuzumab compared to rituximab when used in combination with chemotherapy (bendamustine, CHOP, or CVP) in patients with previously untreated advanced-stage MZL (195 patients), after a median follow-up of 38 months, there were no clinically relevant differences in ORR and PFS between the study arms.[95] However, grade 3 to 5 adverse events were higher with obinutuzumab than with rituximab. Obinutuzumab-based chemoimmunotherapy is not recommended as first-line therapy for patients with MZL.

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Rituximab

As discussed earlier, rituximab monotherapy has demonstrated activity in MALT lymphomas [47,48,51-53] and SMZL.[75-79] It is the preferred initial treatment for patients with SMZL.

First-line Therapy: Other Recommended Regimens

Ibritumomab tiuxetan and lenalidomide + rituximab are included with a category 2B recommendation.

Ibritumomab Tiuxetan

In a phase II study of 16 patients with previously untreated MZL, ibritumomab tiuxetan resulted in an ORR of 88% (50% CR; 31% PR).[96] With a median follow-up of 66 months, the median PFS was 48 months and the median OS was not reached. The 5-year PFS and OS rates were 40% and 72%, respectively.

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

Lenalidomide + Rituximab

In the phase II trial that evaluated lenalidomide + rituximab in patients with untreated, advanced-stage, indolent lymphoma (n = 110; 30 patients with MZL), the ORR was 89% (67% CR; 22% PR) and the median PFS was 54 months among the subgroup of patients with MZL.[97]

Lenalidomide monotherapy or in combination with rituximab also has demonstrated activity in patients with MALT lymphoma, resulting in ORRs of 61% (33% CR; 28% PR) and 80% (54% CR; 26% PR), respectively.[98,99]

Second-line and Subsequent Therapy

Alternate non–cross-resistant chemoimmunotherapy with anti-CD20 MAB (bendamustine with obinutuzumab or rituximab, RCHOP, or RCVP),[59,100,101] lenalidomide ± rituximab,[102,103] rituximab monotherapy,[51] or ibritumomab tiuxetan[104] are included as options for relapsed/refractory disease. Ibrutinib and phosphatidylinositol 3-kinase (PI3K) inhibitors (idelalisib, copanlisib, and duvelisib) have shown promising activity in the treatment of relapsed or refractory MZL.[105-108] Ibrutinib is also FDA approved for the treatment of relapsed/refractory MZL.

Bendamustine + Obinutuzumab

The GADOLIN study (413 patients: 47 patients had MZL; 28 patients were randomized to bendamustine + obinutuzumab; 19 patients were randomized to bendamustine monotherapy) confirmed that the combination of bendamustine + obinutuzumab followed by obinutuzumab maintenance significantly prolongs PFS compared to bendamustine monotherapy in patients with rituximab-refractory indolent NHL.[59] After a median follow-up of 32 months, the median PFS was significantly longer with bendamustine + obinutuzumab than with bendamustine monotherapy for the overall intent-to-treat study population (26 months vs. 14 months; $P < .001$).

Lenalidomide + Rituximab

In the MAGNIFY trial that is evaluating lenalidomide + rituximab followed by maintenance therapy in patients with relapsed/refractory indolent NHL (155 patients; 27 patients with MZL), induction therapy with lenalidomide + rituximab resulted in an ORR of 55% (45% CR) in the subgroup of patients with MZL.[103]

In the multicenter, double-blind, randomized phase III study (AUGMENT) that compared lenalidomide + rituximab versus rituximab monotherapy in patients with relapsed/refractory indolent lymphoma (n = 358; 63 patients had MZL), although the ORRs were higher with lenalidomide + rituximab

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(64% [29% CR; 35% PR]) compared to rituximab monotherapy (44% [13% CR; 31% PR]) in the subgroup of patients with MZL, PFS improvements favored lenalidomide + rituximab all the histologic subtypes of indolent lymphomas except MZL (HR:1.0; 95% CI, 0.47–2.13).[109] After a median follow-up of 28 months, the estimated 2-year OS rates were 82% and 94%, respectively for lenalidomide + rituximab and rituximab monotherapy for the subgroup of patients with MZL.

Ibrutinib

In a multicenter phase II study of 60 patients with relapsed or refractory MZL (after prior therapy with an anti-CD20 MAB-based regimen), ibrutinib resulted in an ORR of 48% (3% CR and 45% PR).[105] After a median follow-up of 19 months, the median PFS was 14 months. The median PFS by subtype was 14 months for extranodal MZL, 19 months for SMZL, and 8 months for NMZL. The median OS has not been reached and the 18-month estimated OS rate was 81%. Infections (19%), anemia (14%), pneumonia (8%), and fatigue (6%) were the most common grade ≥3 adverse events.

PI3K Inhibitors

In a post hoc analysis that evaluated the safety and efficacy of idelalisib in the subset of 21 patients with MZL (enrolled in 2 clinical studies that evaluated idelalisib in patients with relapsed/refractory indolent NHL), ibrutinib resulted in an ORR of 33% and 47%. The median PFS was 7 months.[106]

In the subset analysis from the CHRONOS-1 trial (142 patients with relapsed/ refractory indolent NHL after ≥2 prior lines of therapy; 23 patients has MZL), copanlisib resulted in an ORR of 70% (13% CR).[107] After a median duration of treatment of 23 weeks, 85% of patients were estimated to be in response at 9 months.

In the phase II study (DYNAMO) evaluating the safety and efficacy of duvelisib in 129 patients with indolent NHL refractory to both rituximab and chemotherapy or radioimmunotherapy, duvelisib resulted in an ORR of 47% (39% for the subgroup of patients with MZL [n = 18]).[108] The estimated median duration of response and median PFS were 10 months and 9.5 months, respectively.

Based on these results, idelalisib, copanlisib, and duvelisib are included as options for relapsed/refractory disease after 2 prior therapies.

Ibritumomab Tiuxetan

Ibritumomab tiuxetan also has demonstrated clinical activity in patients with relapsed or refractory extranodal MZL.[104] In a small study of 30 patients, ibritumomab tiuxetan resulted in an ORR of 90% (77% CR; 13% PR). After a median follow-up of 5 years, 12 patients were still in CR. Ibritumomab tiuxetan is included as an option with a category 2B recommendation.

Suggested Treatment Regimens for Elderly or Infirm Patients

Rituximab monotherapy is the preferred treatment option for untreated as well as relapsed/refractory disease in elderly or infirm patients. Ibritumomab tiuxetan and alkylating agent-based chemotherapy (cyclophosphamide or chlorambucil) with or without rituximab are included as alternative options.[110-112]

In a study that evaluated chlorambucil + rituximab versus rituximab monotherapy in 49 patients with gastric MALT lymphoma, chlorambucil + rituximab was more efficient than rituximab alone in patients with t(11;18)-positive disease, whereas rituximab alone is as efficient as chlorambucil + rituximab in patients with t(11;18)-negative disease.[110] In the international randomized IELSG-19 trial that evaluated the combination of chlorambucil + rituximab versus chlorambucil or rituximab monotherapy in patients with MALT lymphoma not previously treated with

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systemic anticancer therapy, the addition of rituximab to chlorambucil resulted in significantly better EFS.[111] At a median follow-up of 7 years, the 5-year EFS rate was 68% for chlorambucil + rituximab compared to 51% and 50%, respectively, for chlorambucil and rituximab monotherapy. The 5-year OS rate was not significantly different between the treatment arms. Cyclophosphamide + rituximab was effective in the treatment of SMZL in frail patients not fit for splenectomy resulting in an ORR of 87% with a median PFS of 20 months.[112]

Histologically Transformed Marginal Zone Lymphoma

Histologic transformation of MZL to DLBCL occurs at an annual rate of approximately 3% to 5% across all subtypes and is generally associated with a poor clinical outcome.[113,114] High-risk IPI scores, elevated LDH, and B symptoms; disease involvement in multiple mucosal sites and >4 nodal sites at the time of diagnosis of MZL; and failure to achieve CR after initial treatment have been reported as risk factors for histologic transformation to DLBCL.[113-116]

Treatment Options

Histologically transformed MZL is usually managed with chemoimmunotherapy regimens recommended for DLBCL. However, there are no data from randomized studies to support the optimal treatment, since clinical trials have often excluded this group of patients.

Anthracycline-based chemoimmunotherapy (with regimens recommended for first-line therapy for DLBCL, unless contraindicated) with or without ISRT is recommended for patients who have received minimal (ISRT alone or one course of single agent therapy including rituximab) or no chemotherapy prior to transformation. Observation or consolidation therapy with HDT/ASCR or allogeneic HCT (in selected patients), with or without ISRT (if not previously given), are included as treatment options for patients achieving CR or PR. Alternatively, patients achieving PR may be treated with ibritumomab tiuxetan or ISRT for localized residual disease and/or residual FDG-avid disease not previously irradiated. Ibritumomab tiuxetan, second-therapy regimens recommended for DLBCL, or best supportive care are included as options for patients with non-responsive or progressive disease.

Enrollment in an appropriate clinical trial is the preferred option for patients who have received multiple prior therapies prior to transformation. In the absence of a suitable clinical trial, treatment options include ibritumomab tiuxetan, ISRT chemoimmunotherapy (with regimens for second-line therapy for DLBCL) with or without ISRT, or best supportive care. Observation or consolidation therapy with HDT/ASCR or allogeneic HCT (in selected patients), with or without ISRT (if not previously given), are included as treatment options for patients with disease responding to initial treatment. Patients with nonresponsive or progressive disease can be treated with any of the initial treatment options (not received previously), if they are candidates for additional therapy.

HDT/ASCR and allogeneic HCT may be reasonable treatment options for selected patients with histologically transformed MZL.[117] The efficacy of HDT/ASCR or allogeneic HCT has not been confirmed in prospective controlled studies. Additional systemic therapy ± ISRT to induce CR prior to transplant should be considered for patients achieving PR. Repeat biopsy should be strongly considered if PET positive prior to initiating additional therapy. If transformation is coexisting with extensive MZL, rituximab maintenance should be considered for patients achieving CR.

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Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) comprises about 3% of all newly diagnosed cases of non-Hodgkin's lymphomas (NHL).[1] MCL is thought to possess the unfavorable characteristics of both indolent and aggressive NHL subtypes owing to the incurability of disease with conventional chemotherapy and a typically more aggressive disease course compared to indolent lymphomas.[2] MCL is characterized by the reciprocal chromosomal translocation t(11;14), juxtaposing the cyclin D1 locus with the immunoglobulin heavy chain (*IGH*) gene locus, resulting in the overexpression of cyclin D1 and the diagnosis of MCL generally requires the expression of cyclin D1.[3]

Cyclin D1-negative MCL with otherwise typical immunophenotype has also been reported, though rare (<5% of cases).[4,5] In the rare instances of MCL negative for cyclin D1 and t(11;14), overexpression of cyclin D2 or cyclin D3 may be observed.[6,7] Immunohistochemistry (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 profiling (GEP) and miRNA profiling showed that the genomic signatures of cyclin D1-negative MCL were similar to those of cyclin D1-positive MCL.[5,6,8] The pathologic features and clinical characteristics of cyclin D1-negative MCL appear to be similar to those of cyclin D1-positive MCL.[6,8] Thus, in the absence of data suggesting otherwise, cyclin D1-negative MCL should not be managed differently than cyclin D1-positive MCL.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for B-Cell Lymphomas an electronic search of the PubMed database was performed to obtain key literature in MCL published since the previous Guidelines update. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[9]

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 data from key PubMed articles deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). 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 at www.NCCN.org.

Diagnosis

The diagnosis can be established by histologic examination in combination with IHC with a profile consisting of CD5+, CD10-/+, CD20+, CD23-/+, CD43+, and cyclin D1+. Some cases of MCL may be CD5- or CD23+. 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 fluorescence in situ hybridization (FISH) for t(11;14) can be helpful for diagnosis.[10] 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.[11-15] However, this should not be used to guide treatment decisions at this time. Nuclear overexpression of the

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transcription factor SOX11 is observed in nearly all cases of MCL, regardless of cyclin D1 expression level. Immunoglobulin heavy chain variable (*IGHV*) g*ene* sequencing or IHC for SOX11 potentially aid in differentiating cyclin D1-negative MCL cases from other B-cell lymphomas.[16-18]

TP53 mutation is associated with poor prognosis in patients treated with conventional therapy, including hematopoietic cell transplantation (HCT). In an analysis that evaluated the prognostic effect of the most common genomic alterations in 183 patients with MCL treated in clinical trials, *TP53* mutations were significantly associated with Ki-67 >30%, blastoid morphology, and inferior responses to both induction chemotherapy and high-dose chemotherapy.[19] *TP53* sequencing would be useful to identify patients with typical MCL with an expected aggressive clinical course, particularly if upfront HCT is anticipated.

GEP studies have identified an indolent, leukemic, and non-nodal MCL subtype that is largely *IGHV* mutated and mostly SOX11-negative, with peripheral blood, bone marrow and splenic involvement, low tumor burden and, a Ki-67 proliferation fraction <10%.[20-22] This description represents the most common indolent presentation; however, there are some patients with gastrointestinal (GI) or blood/bone marrow involvement only, which may express SOX11 and have an indolent course. The 2017 WHO classification also recognizes the two MCL subtypes with different clinicopathologic and molecular features: the usual MCL subtype (nodal or extranodal) that is SOX11+ and *IGHV* unmutated with an aggressive clinical course; and indolent (leukemic and non-nodal) subtype.[23]

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).[24,25] "MCL in situ" is 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).[24-26] An unusual presentation with 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 has also been reported.[27] "MCL in situ" is now known as "in situ mantle cell neoplasia" (ISMCN).

The occurrence of ISMCN in studies of reactive lymph nodes is very rare.[26,28] 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 ISMCN were identified.[28] Development of overt MCL in patients found to have ISMCN has been reported, although this appears to be very uncommon.[26] The significance or potential for malignancy of ISMCN in patients without known MCL remains uncertain. These cases appear to have a very indolent course with long-term survival even without treatment intervention.[26] It is therefore important to distinguish cases of ISMCN 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 (eg, 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.[29] Similar to "follicular lymphoma in situ", the WHO classification recommends that a diagnosis of MCL not be made in such cases.

Workup

The initial workup 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

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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. 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/abdomen/pelvic CT with contrast of diagnostic quality and/or whole-body PET/CT scan are recommended as part of initial diagnostic workup. CT scan of the neck with contrast 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. Multigated acquisition (MUGA) scan or echocardiogram is recommended for patients being considered for treatment regimens containing anthracyclines or anthracenediones.

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.[30,31] 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, and 26% of patients presented with GI symptoms at the time of diagnosis.[30] 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.[30] Salar et al reported upper or lower GI tract involvement in 38% and 54% of patients, respectively, at diagnosis.[30] 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.

Stage I–II

Few patients present with localized MCL and the available published literature on the management of localized disease is retrospective and anecdotal. In a retrospective analysis of 26 patients with limited bulk, early-stage (stage IA or IIA) MCL, radiation therapy (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).[32]

In the absence of a suitable clinical trial, involved-site RT (ISRT) (30–36 Gy) or chemoimmunotherapy with or without ISRT are included as options for induction therapy. 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 International Prognostic Index (IPI).[33,34] These recommendations are based on treatment principles in the absence of more definitive clinical data.

For patients with a complete response (CR), clinical follow-up should be conducted every 3 to 6 months for the first 5 years, and then on a yearly basis or as clinically indicated. Treatment options for patients with a partial response (PR) or disease progression after induction therapy are similar to that of disease relapse as described below. Disease relapse after an initial CR to chemoimmunotherapy with or without ISRT should be managed with second-line therapy regimens recommended for stage II (bulky) or stage III–IV disease (see sections below). Disease relapse after an initial CR to ISRT alone should be managed with first-line induction therapy with

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chemoimmunotherapy regimens recommended for stage II (bulky) and stage III-IV disease.

Stage II (bulky) and Stage III–IV

While some investigators have suggested that treatment with less aggressive regimens could yield survival outcomes similar to that achieved with more aggressive regimens, others have reported superior survival outcomes with more aggressive regimens.[35,36] In a single-center cohort analysis of 111 patients with newly diagnosed MCL, among the 75 patients with available data on treatment regimens, the majority of patients (70%) had received CHOP-like regimen with or without rituximab and only 7% of patients had received rituximab in combination with hyperCVAD (R-hyperCVAD; rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone; alternating with high-dose methotrexate and cytarabine) and/or high-dose therapy with autologous stem cell rescue (HDT/ASCR).[35] The median OS from diagnosis was 85 months, and the 5-year OS rate was 66%. An analysis from the NCCN Oncology Outcomes Database (n = 167) reported superior PFS outcomes with R-hyperCVAD alone or with rituximab-containing regimens (eg, RCHOP) followed by HDT/ASCR, compared with RCHOP alone, in the first-line setting for patients <65 years of age.[36] However, the median PFS remained 3 to 4 years despite the use of aggressive regimens.

The standard treatment regimen for induction therapy is not yet established. There are no prospective randomized studies comparing the various aggressive regimens, although some randomized data exist for less aggressive regimens. The NCCN B-Cell Lymphomas Panel stratified the regimens for initial induction therapy into 3 categories (based on the available evidence, efficacy, toxicity, preexisting comorbidities, and in some cases access to certain agents): preferred regimens, other recommended regimens, and useful under certain circumstances.

Aggressive Disease

The majority of patients have advanced stage aggressive MCL, requiring systemic therapy. Induction therapy with aggressive regimens is recommended for patients who are candidates for HDT/ASCR, whereas induction therapy with less aggressive regimens is recommended for those who are not candidates for HDT/ASCR. *TP53* mutation has been associated with poor prognosis in patients treated with conventional therapy, including HCT.[19] Participation in prospective clinical trials is strongly suggested for these patients.

Indolent Disease

Among patients with indolent MCL (*IGHV* mutated and mostly SOX11-negative with leukemic and non-nodal presentation [as described earlier]),[20-22] observation is a reasonable option for patients with asymptomatic disease with no indications for treatment. For patients with symptomatic disease or other indications for treatment, induction therapy with aggressive regimens is recommended for those without *TP53* mutation. Optimal management is unknown for those with *TP53* mutation. These patients could be treated with induction therapy followed by HDT/ASCR or less aggressive regimens.

Aggressive Induction Therapy: Preferred Regimens

Rituximab, Dexamethasone, Cytarabine and Platinum (carboplatin, cisplatin, or oxaliplatin)

In a phase III trial randomized trial that evaluated the role of rituximab maintenance after HDT/ASCR in patients <66 years (discussed below), induction chemoimmunotherapy with rituximab, dexamethasone, and cytarabine (RDHA) with a platinum agent (carboplatin, cisplatin, or oxaliplatin) resulted in an overall response rate (ORR) of 89% (77% CR).[37] HDT/ASCR following induction therapy was performed in 257 patients, resulting in a CR rate of 65%. In a subsequent analysis that evaluated the prognostic impact of carboplatin, cisplatin, or oxaliplatin on survival outcomes, the PFS and OS were identical for all three regimens

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(RDHA-carboplatin, RDHA-cisplatin, and RDHA-oxaliplatin) but there was a trend towards improved PFS and OS with RDHA-oxaliplatin.[38] In the intent-to-treat population, the 4-year PFS and OS rates were 87% and 92% for RDHA-oxaliplatin compared to 65% and 76%, respectively, for the combined RDHA-carboplatin and RDHA-cisplatin group.

Alternating RCHOP and RDHAP (rituximab, dexamethasone, cytarabine, and cisplatin)

In the phase III randomized Intergroup trial conducted by the European-MCL Network (497 patients ≤65 years of age with advanced stage MCL were randomized to receive 6 cycles of RCHOP followed by HDT/ASCR using myeloablative radiochemotherapy or 6 cycles of alternating RCHOP and RDHAP followed by HDT/ASCR using high-dose cytarabine-containing myeloablative regimen), alternating RCHOP and RDHAP induction was associated with higher remission rates compared with RCHOP.[39] After a median follow-up of 6 years, the ORR (94% vs. 90%; *P* = .14;) and CR rates (38% vs. 25%; *P* = .0016) after induction therapy were higher for alternating RCHOP/R-DHAP than with RCHOP. The median time to treatment failure (TTF) was significantly longer in the RCHOP/RDHAP arm compared with the RCHOP arm (not reached vs. 9 years; *P* = .038) and the 5-year OS rates were 76% and 69%, respectively (*P* = .12). After HDT/ASCR, the ORR (98% vs. 97%) and CR rates (63% vs. 61%), were similar between treatment arms, although RCHOP/RDHAP was associated with longer remission duration (84 months vs. 49 months; *P* = .0001). These results suggest that induction therapy with alternating RCHOP/RDHAP is associated with improved outcomes, in patients <65 years.

In a phase II multicenter trial of the French cooperative group GELA (n = 60), induction therapy with 3 cycles each of RCHOP and RDHAP resulted in an ORR of 95% with CR in 57% of patients (age ≤65 years) with previously untreated MCL.[40] Patients went on to receive HDT/ASCR on this study. After a median follow-up of 67 months, the median event-free survival (EFS) was 83 months and median OS has not been reached; the 5-year OS was 75%.[40]

Dose-intensified RCHOP (maxi-CHOP) Alternating with High-Dose Cytarabine

In the Nordic MCL2 study (n = 160), induction therapy with dose-intensified RCHOP (maxi-CHOP) alternating with high-dose cytarabine resulted in an ORR and CR rate of 96% and 54%, respectively, in patients ≤65 years of age with previously untreated MCL.[41] Patients with responding disease were eligible to proceed to HDT/ASCR. The ORR and 6-year PFS and OS rates were 96% (54% CR), 66%, and 70%, respectively, with no relapses occurring after a median follow-up of approximately 4 years (at the time of the initial report). After a median follow-up of 11 years, the median PFS and OS were 9 years and 13 years, respectively, for all the intent-to-treat patient population.[42] The median OS was not reached and median PFS was 11 years for the 145 patients who proceeded to HDT/ASCR. The OS and PFS were significantly better for patients who had achieved CR to induction therapy than those who achieved PR (*P* = .0038 for OS; *P* < .0001 for PFS). However, a continuous pattern of relapse and an excess mortality were observed even after prolonged remission (late relapses were reported in 6 patients, who experienced disease relapse more than 10 years after the end of therapy).[42] In the multivariate analysis, the MCL IPI (MIPI) and Ki-67 expression level were the only independent predictors of survival outcomes.[42,43] However, in this trial, patients were monitored by disease-specific primers for molecular relapse, and those with disease relapse received rituximab as re-induction but were not considered to have disease relapse unless there was morphologic evidence of disease relapse.

HyperCVAD + Rituximab

R-hyperCVAD has resulted in favorable PFS and OS outcomes in patients with previously untreated MCL.[44-47]

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In a phase II study of 97 patients with previously untreated with MCL, R-hyperCVAD produced 3-year failure-free survival (FFS) and OS rates of 64% and 82%, respectively, with a median follow-up time of 40 months.[44] After 10 years of follow-up, the median OS had not been reached and the median TTF was 5 years for all patients. Among patients ≤65 years, the median OS had not been reached and the median TTF was 6 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.[45] 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 ORR of 83% with a CR rate of 72%. The 5-year PFS and OS rates were 61% and 73%, respectively.[46] However, this regimen was associated with substantial toxicity.

In the SWOG 0213 study of 49 patients with previously untreated MCL (age <70 years), R-hyper-CVAD induced CR/CRu in 58% of patients.[47] With a median follow-up of 5 years, the median PFS and OS were 5 years (6 years for those ≤65 years) and 7 years, respectively. The 2-year PFS and OS rates were 63% and 76%, respectively.

Rituximab + ibrutinib has been used as a pre-treatment to limit the number of cycles of R-HyperCVAD and rituximab maintenance in young patients.[48]

Aggressive Induction Therapy: Other Recommended Regimen

Bendamustine + rituximab is included as an option with a category 2B recommendation based on the results from 2 phase III randomized studies (discussed below)..[49,50]

Consolidation After Aggressive Induction Therapy

HDT/ASCR as first-line consolidation has demonstrated promising outcomes in a number of studies.[51-58]

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 (DFS) and OS rates of 42% and 77%, respectively.[52] 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).[52] In a randomized trial conducted by the European-MCL Network, patients ≤65 years of age with advanced stage MCL (n = 122) in remission after CHOP-like chemotherapy were randomized to HDT/ASCR or maintenance with interferon alfa.[53] In this study, HDT/ASCR was associated with a significantly longer median PFS compared with interferon alfa maintenance (39 months vs. 17 months; *P* = .011) The 3-year OS rates were 83% and 77%, respectively, and were not significantly different between consolidation arms.[53] In an analysis of long-term outcomes from patients with MCL treated at the MD Anderson Cancer Center, the median PFS and OS were 42 months and 93 months, respectively, for the subgroup of patients treated primarily with hyper-CVAD (with or without rituximab) followed by HDT/ASCR in first remission (n = 50).[57]

Rituximab maintenance after HDT/ASCR has been associated with survival benefit.[37,59,60]

In a phase III randomized trial, rituximab maintenance after HDT/ASCR prolonged EFS, PFS, and OS compared to observation in patients <66 years.[37] In this trial involving 299 patients, 279 patients received induction chemoimmunotherapy with RDHA with a platinum agent (carboplatin, cisplatin, or oxaliplatin) resulting in an ORR of 89% (77% CR). HDT/ASCR

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was performed in 257 patients following induction therapy. Among these 257 patients, 240 patients were randomized to receive rituximab maintenance or observation after HDT/ASCR. After a median follow-up of 50 months, the 4-year EFS, PFS, and OS rates were 79%, 83%, and 89%, respectively, for patients assigned to rituximab maintenance. The corresponding survival rates were 61%, 64%, and 80%, respectively, for patients assigned to observation. The results of a more recent study also confirmed the survival benefit of rituximab maintenance in patients with newly diagnosed MCL treated with Nordic MCL regimen followed by HDT/ASCR.[60] After a median follow-up of 4 years, the estimated 5-year PFS and OS rates were both 83% for patients assigned to rituximab maintenance. The corresponding survival rates were 63% and 79%, respectively, for patients assigned to observation.

The panel recommends consolidation with HDT/ASCR for eligible patients in CR following induction therapy with aggressive regimens, although no studies have compared maintenance rituximab with HDT/ASCR for patients in first CR. Rituximab maintenance following HDT/ASCR is included with a category 1 recommendation.[37,59,60] For patients with only a PR to first-line therapy, additional treatment with second-line therapy regimens 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.

Less Aggressive Induction Therapy: Preferred Regimens

Bendamustine + Rituximab

The efficacy of bendamustine and rituximab (BR) as first-line therapy for MCL was established in 2 randomized phase III studies.[49,50]

The randomized phase III study of the StiL (Study Group Indolent Lymphomas) compared BR versus RCHOP as first-line therapy in patients with advanced follicular, indolent, and mantle cell lymphomas (514 evaluable patients; MCL histology comprised 18% of patients).[49] With a median follow-up time of 45 months, the BR regimen was associated with significantly longer median PFS (primary endpoint) compared with RCHOP (70 months vs. 31 months; $P < .0001$). However, OS outcomes were not significantly different between treatment arms and ORR was similar in both arms (93% with BR vs. 91% with RCHOP), although the CR rate was significantly higher in the BR arm (40% vs. 30%; $P = .021$). Among the subgroup of patients with MCL, the median PFS was significantly higher with BR compared with RCHOP (35 months vs. 22 months; $P = .0044$).[49] The BR regimen was associated with less frequent serious adverse events (19% vs. 29%) and less grade 3–4 hematologic toxicities compared with RCHOP. Grade 3–4 neutropenia (29% vs. 69%), peripheral neuropathy (all grades; 7% vs. 29%), and infectious complications (all grades; 37% vs. 50%) were less frequent with BR compared with RCHOP was less frequent in the BR arm. Fatal sepsis occurred in 1 patient in the BR arm and 5 patients in the RCHOP arm. Skin toxicities (all grades) including erythema (16% vs. 9%) and allergic reactions (15% vs. 6%) were more frequent with BR than with RCHOP.[49] Although this phase III randomized trial showed superior PFS outcomes with the BR regimen compared with RCHOP, 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.

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Another randomized phase III study (BRIGHT) demonstrated that BR was noninferior to RCHOP or RCVP (in terms of PFS) as first-line treatment of patients with indolent or MCL (224 patients were randomized to receive BR and 223 patients were randomized to receive RCHOP or RCVP).[50] At a median follow up of 5 years, the corresponding 5-year PFS rate for the overall study population was 66% and 56% (P = .0025), for BR and RCHOP/RCVP, respectively.[50] The 5-year OS rate was not statistically different between the treatment groups and the incidences of vomiting and drug hypersensitivity reactions, opportunistic infections and secondary malignancies were significantly higher in patients treated with BR.

Bortezomib, Rituximab, Cyclophosphamide, Doxorubicin, and Prednisone (VR-CAP)

A phase III randomized study evaluated the safety and efficacy of bortezomib in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) versus RCHOP in patients with newly diagnosed MCL who are not candidates for HDT/ASCR.[61] In this study, 487 patients were randomly assigned to VR-CAP or RCHOP; 268 patients (140 patients in the VR-CAP group and 128 patients in the RCHOP group) were included in the final follow-up analysis. The majority of patients had stage IV disease (74%) and 54% of patients had an IPI ≥3. After median follow-up of 82, the median OS was significantly longer for patients in the VR-CAP group than in the RCHOP group (91 months vs. 56 months; *P* = .001). The incidences of grade ≥3 adverse events, although slightly higher with VR-CAP (93% compared to 84% with RCHOP), were manageable.

RCHOP

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.[62,63] In a phase III randomized trial by the European-MCL Network that evaluated rituximab maintenance following induction therapy with R-FC (rituximab, fludarabine, and cyclophosphamide) or RCHOP in patients >60 years with previously untreated MCL not eligible for HDT/ASCR (n = 560; 485 patients evaluable for response), RCHOP was associated with significantly longer median OS (67 months vs. 40 months) and significantly higher 4-year OS rate (62% and 47%, respectively; *P* = .005) than R-FC, although response rates (ORR; 86% vs.78%; CR; 34% vs. 40%) and median duration of response (37 months vs. 36 months) were similar for both regimens.[64] Grade 3–4 hematologic toxicities occurred more frequently with R-FC induction.

Lenalidomide + Rituximab

In a multicenter phase II study that evaluated lenalidomide plus rituximab as induction and maintenance therapy for patients with previously untreated MCL (n=38), at the median follow-up of 30 months, lenalidomide plus rituximab resulted in an ORR of 87% (61% CR).[65] At a median follow-up of 64 months, the 3-year PFS and OS rates were 80% and 90%, respectively, with the 5-year estimated PFS and OS of 64% and 77%, respectively.[66]

Modified HyperCVAD + Rituximab

In a small phase II pilot study of 22 patients with previously untreated MCL, 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.[67]

In a phase II study (E1405), the addition of bortezomib to the modified R-hyper-CVAD (VcR-CVAD regimen) resulted in an ORR of 95% (68% CR) in patients with previously untreated MCL (n = 75).[68] Following induction therapy, patients proceeded with maintenance rituximab (n = 44) or consolidation with HCT 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.

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No differences in PFS or OS were observed between patients who went on to receive rituximab maintenance or SCT.

Modified R-hyperCVAD is included as an option for patients >65 years.

Less Aggressive Induction Therapy: Other Recommended Regimen

RBAC (rituximab, bendamustine, and cytarabine)

In a phase II study that included 20 patients ≥65 years with previously untreated MCL not eligible for HDT/ASCR, the RBAC regimen was well tolerated resulting in an ORR of 100% (95% CR).[69] After a median follow-up of 26 months, the 2-year PFS rate was 95%.

Maintenance Rituximab After Less Aggressive Induction Therapy

In the aforementioned phase III randomized trial that evaluated induction therapy R-FC versus RCHOP, patients with disease responding to induction therapy (n = 316) underwent second randomization to receive maintenance therapy (given until progression) with either rituximab or interferon.[64] The 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).[64] However, in the subgroup of 184 patients treated with RCHOP induction therapy, the 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%; $P = .005$). Moreover, grade 3–4 hematologic toxicities occurred more frequently with interferon alfa. Rituximab was associated with more frequent grade 1–2 infections.[64] Long-term follow-up data also confirmed that rituximab maintenance after RCHOP induction is associated with substantially prolonged PFS and OS in older patients who are not candidates for HDT/ASCR.[70] At a median follow-up of 7 years, after response to RCHOP, the 5-year PFS rates were 51% and 22%, respectively ($P < .0001$) for patients randomized to rituximab maintenance and interferon. The corresponding 5-year OS rates were 79% and 59%, respectively ($P = .0026$).

This study suggests that RCHOP followed by rituximab maintenance as part of induction therapy may offer the best chance to prolong remission duration for patients who are not candidates for HDT/ASCR.[64,70] 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 RCHOP 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.

Rituximab maintenance (every 8 weeks until disease progression) is recommended for patients who are not candidates for HDT/ASCR, and who are in remission after induction therapy with less aggressive regimens (category 1 following RCHOP).[64,70] Rituximab maintenance following induction therapy with modified R-hyper-CVAD regimen has also been reported to provide extended disease control for patients who are not physically fit or not eligible to undergo aggressive first-line treatment regimens and HDT/ASCR.[67,68,71] Data from a prospective, randomized phase II trial suggest that there is no benefit to rituximab maintenance after induction therapy with the BR regimen.[72] Rituximab maintenance following induction therapy VR-CAP and RBAC has not been evaluated in clinical trials.

Second-line Therapy

The optimal approach to relapsed or refractory disease remains to be defined. Duration of response to prior chemoimmunotherapy is an

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important factor in the selection of second-line therapy. Treatment with regimens containing small-molecule inhibitors or lenalidomide (with or without rituximab) should be considered for patients with early relapse (short response duration to prior chemoimmunotherapy), whereas alternate non–cross-resistant chemoimmunotherapy regimens (not previously given) would be more appropriate for patients with late relapse (extended response duration to prior chemoimmunotherapy).

See *Special Considerations for the Use of Small-Molecule Inhibitors* in the algorithm for monitoring and management of adverse reactions associated with small-molecule inhibitors (ibrutinib, acalabrutinib and venetoclax).

Short Response Duration to Prior Chemoimmunotherapy (< expected median PFS)

Preferred Regimens

Bruton Tyrosine Kinase Inhibitors

Acalabrutinib

In a phase II study of 124 patients with relapsed or refractory MCL, at a median follow-up of 15 months, acalabrutinib resulted in an ORR of 81% (40% CR).[73] The 12-month PFS and OS rates were 67% and 87%, respectively. Long-term follow-up (>24 months) also confirmed these initial findings.[74] The median PFS was 20 months and the estimated 24-month OS rate was 72%. Headache (38%), diarrhea (36%), fatigue (28%), cough (22%), bleeding (22%), and myalgia (21%) were the most common grade 1 or 2 adverse events. Anemia (10%), neutropenia (10%), pneumonia (6%), and infections (15%) were the most common grade 3 or 4 adverse events.

Ibrutinib ± Rituximab

Ibrutinib, either as monotherapy or in combination with rituximab results in durable responses with a favorable toxicity profile in patients with relapsed or refractory MCL.[75-77] In the multicenter phase II study of 111 patients with relapsed or refractory MCL after a median of 3 prior therapies, after a median follow-up of 27 months, ibrutinib monotherapy resulted in an ORR of 67% (23% CR) with a median duration of response of 18 months.[75] The 24-month PFS and OS rates were 31% and 47%, respectively. A phase III randomized trial (RAY) compared ibrutinib (n = 139) and temsirolimus (n = 141) in patients with relapsed or refractory MCL.[76] The ORR was 77% for ibrutinib and 47% for temsirolimus ($P < .0001$). After a median follow-up of 39 months, the median PFS was significantly longer with ibrutinib (16 months vs. 6 months) and there was also a trend toward improved OS in patients randomized to receive ibrutinib (30 months vs. 24 months; $P = .06$). Diarrhea (33%), fatigue (24%), and cough (23%) were the most common adverse events of any grade in the ibrutinib group. Thrombocytopenia (56%), anemia (44%), and diarrhea (31%) were the most common adverse events in the temsirolimus group. The rate of grade ≥3 bleeding events (9% vs. 5%) and atrial fibrillation (5% vs. 1%) were higher with ibrutinib.

In another phase II study of 50 patients with relapsed or refractory MCL after a median of 3 prior therapies, at a median follow-up of 47 months, ibrutinib in combination with rituximab resulted in a CR of 58% and the median PFS was 43 months.[77] Blastoid morphology, high-risk MIPI score, and high Ki-67 were associated with inferior survival.

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. Ibrutinib treatment has also been associated with grade ≥3 bleeding events and atrial fibrillation. The benefit and risk of ibrutinib should be considered in patients requiring anti-platelet or anticoagulant therapies.

Zanubrutinib

In November 2019, the FDA granted accelerated approval of zanubrutinib (selective and irreversible BTK inhibitor) for the treatment of

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relapsed or refractory MCL after at least one prior therapy. This approval is based on the efficacy results (ORR as the primary end point) from two multicenter single-arm clinical trials (phase II study, 86 patients with relapsed or refractory MCL and phase I study, 48 patients [37 patients with relapsed or refractory MCL]).[78,79] Zanubrutinib (160 mg BID given until disease progression or unacceptable toxicity) resulted in an ORR of 85% (77% CR) and 87% (30% CR) in these two trials, respectively. With a median follow-up of 14 to 16 months, treatment discontinuation due to progressive disease was reported in 22% and 33% of patients, respectively. The median PFS was 17 months and 15 months, respectively. Neutropenia (16%), anemia (6%), lung infection (6%), thrombocytopenia (5%) and hypertension (3.5%) were the most common grade 3 adverse events; major hemorrhage (serious or grade 3 bleeding or CNS bleeding of any grade) was reported in 2% of patients.[78]

Lenalidomide With or Without Rituximab

Lenalidomide monotherapy has demonstrated efficacy in patients with relapsed or refractory MCL in multiple multicenter phase II studies.[80-82]

In the multicenter MCL-001 (EMERGE) study that evaluated the safety and efficacy of lenalidomide in relapsed or refractory MCL in patients who had received prior bortezomib (n = 134), lenalidomide resulted in an ORR of 28% (7.5% CR/CRu) by independent central review.[80] The median duration of response was 17 months. The median PFS and OS were 4 months and 19 months, respectively. The most common grade 3 or 4 toxicities were neutropenia (43%), thrombocytopenia (28%), anemia (11%), pneumonia (8%), and fatigue (7%).

In the multicenter MCL-002 (SPRINT) study, 254 patients with relapsed/refractory MCL ineligible for intensive chemotherapy or HCT were randomized to receive lenalidomide (n = 170) or investigator's choice monotherapy (n = 84).[81] At a median follow-up of 16 months, lenalidomide significantly improved PFS compared with investigator's choice monotherapy (9 months vs. 5 months; *P* = .004). Neutropenia without increased risk of infection (73% vs. 34%), thrombocytopenia (18% vs. 28%), leucopenia (8% vs. 11%), and anemia (8% vs. 7%) were the most common grade 3–4 adverse events.

Lenalidomide plus rituximab is also well tolerated and effective for patients with relapsed or refractory MCL. In a phase I/II study of 52 patients with relapsed or refractory MCL, lenalidomide in combination with rituximab resulted in an ORR of 57% (36% CR).[83] The median duration of response, PFS, and OS were 19 months, 11 months, and 24 months, respectively. The most common grade 3 or 4 toxicities included neutropenia (66%) and thrombocytopenia (23%).

Venetoclax

This recommendation is based on the results from a phase I study that demonstrated the safety and efficacy of venetoclax in relapsed or refractory NHL (106 patients; 28 patients had MCL).[84] Venetoclax resulted in responses across all NHL subtypes (ORR of 44%) and the estimated median PFS for all patients was 6 months. The ORR (75%; CR, 21%) and median PFS (14 months) were higher for patients with MCL than other NHL subtypes. The estimated 12-month OS was 70% for all patients and 82% for those with MCL.

Patients with high tumor burden, particularly those with MCL, are at increased risk for tumor lysis syndrome (TLS) and may be best managed with a starting dose of 20 mg daily for one week, and gradually escalate to target dose of 400 mg daily over 5 weeks to reduce the risk of TLS.

Other Recommended Regimens

Ibrutinib, Lenalidomide, and Rituximab

The panel has included this regimen with a category 2B recommendation based on the preliminary report from a multicenter phase II study of 50 patients with relapsed or refractory MCL in which the combination of

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ibrutinib, lenalidomide, and rituximab resulted in an ORR of 76% (56% CR; 20% PR) at a median follow-up of 18 months.[85]

Venetoclax + Ibrutinib

The panel has included the combination of venetoclax + ibrutinib as an option with a category 2B recommendation based on the results of a phase II study that showed improved outcomes in patients with MCL and poor prognostic factors (eg, *TP53* aberrations and high-risk prognostic score).[86] In this study, the CR rate of 42% as assessed by CT scan at 16 weeks was higher than the historical CR rate of 9% with ibrutinib monotherapy ($P < .001$) and 78% of patients with responding disease were estimated to have an ongoing response at 15 months.

Extended Response Duration to Prior Chemoimmunotherapy (> expected median PFS)

Preferred Regimens

Bendamustine ± Rituximab (if not previously given)

Bendamustine, as a single agent or in combination with rituximab (BR), has also shown promising results with acceptable toxicity in patients with relapsed or refractory MCL.[87,88]

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).[87] The median duration of response and PFS was 21 months and 23 months, respectively. The ORR was 92% (42% CR) and the median duration of response was 19 months for the subgroup of patients with MCL (n = 12).[87]

The phase III randomized trial from StiL demonstrated superiority of the BR regimen over fludarabine and rituximab in patients with relapsed/refractory follicular or indolent lymphoma or MCL (219 evaluable patients; MCL histology in about 20%).[88] At a median follow-up of 96 months, the median PFS was 34 months and 12 months, respectively, for BR and fludarabine plus rituximab ($P < .0001$).

Bortezomib ± Rituximab

Bortezomib is a proteasome inhibitor with activity in patients with relapsed or refractory MCL and is currently approved for this indication.[89,90] In the pivotal phase II PINNACLE trial (n = 155; 141 evaluable patients), bortezomib induced an ORR of 33% (CR in 8%), with a median duration of response of 9 months.[89] 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 24 months (35 months in patients with responding disease).[90]

The efficacy of bortezomib + rituximab in patients with heavily pretreated relapsed or refractory MCL was demonstrated in a phase II study (11 patients with FL and 14 patients with MCL).[91] The ORR was 40% in all 25 patients (29% in patients with MCL). The estimated 2-year PFS rate was 24% for all patients and 60% in patients with responding disease.

Other Recommended Regimens

The panel has included prednisone, etoposide, procarbazine, and cyclophosphamide (PEP-C) oral combination chemotherapy regimen and bendamustine, bortezomib, and rituximab options with a category 2B recommendation.[92,93] In a single-center study of 22 patients with heavily pretreated MCL, PEP-C regimen was well tolerated resulting in an ORR of 82% (46% CR; 36% PR).[92] The efficacy of bendamustine, bortezomib, and rituximab was established in a multicenter phase 2 study of 30 patients (7 patients with MCL),[93] and this regimen is currently being evaluated in a larger randomized trial.

Small-molecule inhibitors (as listed above for patients with short response duration to prior chemoimmunotherapy; category 2B for zanubrutinib),

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RCHOP (if not previously given), and VR-CAP (if not previously given) are included as alternate options.

Second-Line Consolidation Therapy

Allogeneic HCT using reduced-intensity conditioning (RIC) has been evaluated as a consolidation strategy for patients in remission following treatment for relapsed/refractory MCL.[57,94-96]

In an analysis of patients with MCL treated with HCT at the MD Anderson Cancer Center, the subgroup of patients with relapsed/refractory disease treated with RIC allogeneic stem cell transplant (SCT) (n = 35) had favorable long-term outcomes.[57] Most of these patients (62%) received HCT after achieving remission (31% in second remission). The median PFS was 60 months, and the 6-year PFS and OS rates were 46% and 53%, respectively. The transplant-related mortality (TRM) rates at 3 months and 1 year were 0% and 9%, respectively.[57]

In a small study of 18 patients with relapsed MCL treated with allogeneic HCT using RIC, the 3-year PFS rate and estimated 3-year OS rate were 82% and 86%, respectively; the majority of patients in this study (89%) had chemosensitive disease.[94] In another study that evaluated allogeneic SCT using RIC in 33 patients with relapsed/refractory MCL (42% of these patients had failed prior HDT/ASCR), the 2-year DFS and OS rates were 60% and 65%, respectively.[95] The 2-year relapse rate and the 2-year TRM rate were 9% and 24% respectively; moreover, with a median follow-up of nearly 25 months, none of the 13 patients who received HCT after achieving CR experienced disease relapse.

The results of another retrospective analysis (70 patients; 35 in CR, 20 in PR, and 15 in stable or progressive disease) suggest that allogeneic HCT using RIC may be an effective therapy in patients with relapsed or refractory disease that is chemosensitive disease at time of HCT.[96] At a median follow-up of 24 months, the 2-year EFS and OS rates were 50% and 53%, respectively. Disease status at transplantation was the only significant predictor of EFS and OS.

Remission duration after autologous HCT has been identified as the only significant predictor of outcome following allogeneic HCT in patients with relapsed MCL.[97] Longer remission duration (>12 months) after autologous HCT was associated with significantly better outcomes compared to early relapse (within 1 year after autologous HCT) or primary refractory disease.

Allogeneic HCT (with myeloablative conditioning or RIC) should be considered for patients with relapsed or refractory disease that is in remission following second-line therapy.

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Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphomas (DLBCL) are the most common lymphoid neoplasms in adults, accounting for approximately 30% of non-Hodgkin's lymphomas (NHLs) diagnosed annually.[1] DLBCL not otherwise specified (NOS), follicular lymphoma (FL; grade 3 only), DLBCL coexistent with a low grade lymphoma of any kind (e.g., FL, gastric MALT lymphoma, or non-gastric MALT lymphoma), intravascular large B-cell lymphoma, DLBCL-associated with chronic inflammation, anaplastic lymphoma kinase (ALK)-positive DLBCL, Epstein-Barr virus (EBV)-positive DLBCL in older patients, and T-cell/histiocyte-rich large B-cell lymphoma are also managed according to the DLBCL guidelines.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for B-cell Lymphomas an electronic search of the PubMed database was performed to obtain key literature in DLBCL published since the previous Guidelines update, using the following search terms: diffuse large B-cell lymphoma, aggressive B-cell lymphoma, primary mediastinal B- cell lymphoma, grey zone lymphoma and high grade B-cell lymphoma. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[2]

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 data from key PubMed articles deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). 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 at www.NCCN.org.

Diagnosis

Gene expression profiling (GEP) has identified distinct subtypes within DLBCL NOS based on cell of origin (COO): germinal center B-cell (GCB) subtype and activated B-cell (ABC) subtype.[3,4] Notably, GEP is not currently available in the clinic and remains utilized only in the context of clinical trials. Immunohistochemistry (IHC) algorithms have been developed as surrogates for GEP to assign COO in clinical practice and can generally assign tumors as GCB or non-GCB. The term non-GCB is used when classified by IHC because specific IHC markers for activated B-cells are not routinely available, and thus the non-GCB category is more heterogeneous than true ABC DLBCL when assigned by GEP. The most commonly used IHC algorithms include CD10, BCL6, and IRF4/MUM1 to classify DLBCL into GCB (CD10+; or BCL6+, IRF4/MUM1-) and non-GCB (CD10-, IRF4/MUM1+; or BCL6-, IRF4/MUM1-).[5] IHC algorithms including GCET1, FOXP1, and LMO2 in addition to CD10, BCL6 and IRF4/MUM1 have been proposed.[6-8]

GCB DLBCL is associated with an improved outcome compared to ABC DLBCL in patients treated with R-CHOP, and ongoing randomized clinical trials are exploring whether the addition of novel targeted agents to R-CHOP will selectively improve the outcome in patients with ABC DLBCL.[9-11] Presently, the upfront standard of care remains the same for both GCB and ABC subtypes.

In the 2017 WHO classification, double-hit/triple-hit lymphomas (DHL/THL) that harbor *MYC* and *BCL2* and/or *BCL6* translocations have been included in a unique category called high-grade B-cell lymphomas (HGBL)

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with translocations of *MYC* and *BCL2* and/or *BCL6*.[4] This subtype is distinct from DLBCL with dual expression of both MYC and BCL2 by IHC but are negative for rearrangements, the so called double expressing lymphomas (DEL). These lymphomas have an inferior prognosis compared to DLBCL as a whole, but not to the same magnitude as true double-hit lymphomas on the basis of gene rearrangements, and do not currently warrant therapy different from typical cases of DLBCL.

Adequate immunophenotyping is required to establish the diagnosis as well as to aid in risk stratification. The IHC panel includes CD20, CD3, CD5, CD10, CD45, BCL2, BCL6, Ki-67, IRF4/MUM1 and MYC. Patients with 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. *MYC* gene rearrangements have been reported in 5% to 8% of patients with DLBCL, and often correlate with GCB phenotype and higher risk of progression.[12-15] Additional markers such as CD138, CD30, cyclin D1, ALK1, SOX11, HHV-8 and EBV in situ hybridization (EBV-ISH) 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 mantle cell lymphoma (MCL) from CD5-positive DLBCL.[16,17]

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 complete blood count (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. Hepatitis B virus (HBV) testing prior to initiation of treatment is recommended for all patients who will receive anti-CD20 monoclonal antibody (MAB)-based regimens due to increased risk of HBV reactivation. Human immunodeficiency virus (HIV) testing, hepatitis C virus (HCV) testing and measurement of serum beta-2-microglobulin levels would be useful in selected patients.

PET/CT scans are essential for the initial staging of DLBCL 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.[18] Whole body PET/CT scan ± chest/abdomen/pelvic CT with contrast of diagnostic quality is recommended for initial workup. 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.[19,20] 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) and the revised IPI (R-IPI) identify specific groups of patients who are more or less likely to be cured with standard therapy.[21,22] IPI scores are based on patient's age, stage of disease, serum LDH level, ECOG PS, and the number of extranodal sites. In patients who are ≤60 years, an age-adjusted IPI uses the prognostic factors of stage, ECOG PS, and serum LDH level.[20] An NCCN-IPI has also been developed based on the outcome data from NCCN Member Institutions, and can stratify patients with newly diagnosed DLBCL into 4 different risk groups (low, low-intermediate, high-intermediate, and high) based on quantification of

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age, LDH, sites of involvement, Ann Arbor stage and ECOG PS).[23] This analysis included 1650 patients identified in the 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 overall survival [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.[23] While the 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 OS of 100%).[24]

Stage I-II

In the SWOG 0014 study that evaluated 3 cycles of R-CHOP followed by involved-field RT (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%.[25] In historical comparison, these results were favorable relative to the survival rates for patients treated without rituximab (4-year PFS and OS rates 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.[26] 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% versus 80% (P = .0004). The 6-year event-free survival (EFS) rate (74% vs. 56%; P < .0001) and PFS rate (80% vs. 64%; P < .0001) were also significantly higher for patients assigned to chemotherapy plus rituximab compared to chemotherapy alone.[26] The results from the RICOVER-noRTh trial also showed a significant advantage to adding RT to initial bulky sites ≥7.5 cm.[27]

R-CHOP (3 cycles) with RT is also associated with reduced short-term toxicity compared to 6-8 cycles of R-CHOP alone. In a SEER-Medicare database analysis of a large cohort of older patients with stage I-II DLBCL, while both treatment options had similar OS, 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.[28]

The results of a prospective randomized trial showed that R-CHOP-14 was not inferior to R-CHOP-14 plus RT in patients with non-bulky limited-stage DLBCL.[29] In this trial, 334 patients were randomized to receive R-CHOP-14 alone (n = 165) or R-CHOP-14 plus RT (n=169). Patients with 0 IPI risk factors received 4 cycles while patients with ≥1 risk factor received 6. After a median follow-up of 64 months, the 5-year EFS (89% and 92%, respectively; P = .18) and OS (92% and 96% respectively) were not statistically significantly different between the R-CHOP-14 alone and R-CHOP-14 plus RT arms.

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.[30,31] However, this regimen was also associated with significant toxicity and includes vindesine, which is not available in the United States.

R-CHOP (3 cycles) followed by involved site RT (ISRT) (category 1) or R-CHOP (6 cycles) or R-CHOP-14 (4–6 cycles) with or without ISRT are included as first-line therapy options for patients with non-bulky (<7.5 cm) disease.[25,26,29] R-CHOP (6 cycles) with or without ISRT is recommended for patients with bulky disease (≥ 7.5 cm).[26,27] R-mini-CHOP (decreased

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dose of CHOP with a conventional dose of rituximab) may be substituted for very frail patients and patients >80 years of age with comorbidities to improve tolerability.[32,33] In a prospective single arm phase II study by the GELA study group that evaluated the safety and efficacy of R-mini-CHOP in 149 patients with >80 years, the 4-year PFS and OS rates were 41% and 49%, respectively.[33] Grade ≥3 neutropenia was the most frequent hematological toxicity observed in 59 patients.

Patients with primary testicular DLBCL are at increased risk of central nervous system (CNS) and contralateral scrotal recurrence, even when presenting with stage I disease. Inclusion of methotrexate for CNS prophylaxis as well as scrotal RT (25–30 Gy) after completion of chemoimmunotherapy is therefore recommended.[34] ISRT alone for DLBCL is associated with a high rate of relapse and is only recommended for patients who are not candidates for any chemotherapy.

Stage III-IV

The efficacy of R-CHOP-21 in patients with advanced stage DLBCL has been demonstrated in multiple randomized trials.[26,35-38] The GELA study (LNH98-5), evaluated 8 cycles of R-CHOP versus CHOP in older patients (age 60–80 years; n=399).[35] At a median follow-up of 10 years, the 10-year PFS (37% vs. 20%), disease-free survival (DFS) (64% vs. 43%), and OS (44% vs. 28%) rates were significantly higher for R-CHOP.[36] The MInT study (6 cycles of R-CHOP or CHOP) extended these findings to younger patients with 0 or 1 risk factors according to the IPI.[26] 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.[37,38] 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.[38]

The RICOVER 60-trial showed that the addition of rituximab to 6 or 8 cycles of CHOP-14 (R-CHOP-14) also significantly improved clinical outcomes compared with CHOP-14 alone.[39,40] In this trial, older patients (age 61–80 years) were randomized to receive CHOP-14 (6 or 8 cycles) with or without 8 cycles of rituximab. RT was administered to sites of initial bulky disease with or without extranodal involvement. With a median follow-up of 78 months, R-CHOP-14 was associated with significantly improved EFS and OS compared to CHOP-14 (P <.001).[40] While there was no difference in clinical benefit, increased toxicity was seen in patients treated with 8 cycles compared with 6 cycles of therapy. 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.

Two randomized trials that have compared R-CHOP-21 with R-CHOP-14 showed that while both treatment options are associated with similar OS and PFS, R-CHOP-14 was associated with significantly higher rates of grade 3 or 4 neutropenia.[41,42] In the phase III randomized trial of 1080 patients with newly diagnosed DLBCL, at a median follow up of 46 months, the 2-year OS rates were 83% and 81% respectively for R-CHOP-14 and R-CHOP-21 (P = .38).[41] The corresponding 2-year PFS rates were 75% for both treatment arms (P =.59). Notably, there was no difference in outcome between GCB-like and non-GCB-like DLBCL by IHC in this large prospective study. 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 given with R-CHOP-21.[41] In the phase III LNH03-6B GELA study which compared R-CHOP-14 (8 cycles) 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 were observed in terms of 3-year EFS (56% vs. 60%; P =.76), PFS (60% vs. 62%) or OS rates (69% vs 72%) between R-CHOP-14 and R-CHOP-21.[42] Grade 3 or 4 neutropenia was

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more frequent 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 R-MegaCHOEP study reported that the 3-year PFS and OS rates of were 74% and 85% respectively, in young, high-risk patients with DLBCL treated with 8 x CHOEP-14 with 6 infusions of rituximab.[43] The results of the dense-R-MegaCHOEP 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 patients with age-adjusted IPI of 2.[44] After a median follow-up of 24 months, the 2-year EFS and OS rates were 69% and 82% respectively. The results of the PETAL trial also confirmed that the addition of 2 more doses of rituximab to 6 x R-CHOP (6 vs 8 doses of rituximab) did not improve outcome.[45]

Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab; DA-EPOCH-R) has shown significant activity in patients with untreated DLBCL with 5-year and 1-year OS rates of 84% and 64%, respectively in a phase II trial.[46,47] A phase III randomized trial (CALGB 50303) evaluated DA-EPOCH-R versus R-CHOP in untreated patients with DLBCL.[48] In this study, 524 patients were randomly assigned to 6 cycles of R-CHOP (n = 223) or DA-EPOCH-R (n = 232). The ORR was 89% in both arms, and after a median follow-up of 5 years, there were no statistically significant differences in the 2-year PFS (79% vs. 76%; *P* = .65) or 2-year OS rates (87% and 86%; *P* = .42) between the R-CHOP and DA-EPOCH-R. In addition, R-CHOP also had a more favorable safety and tolerability profile. DA-EPOCH-R was associated with a significantly increased risk of cytopenias and neuropathy.

Collectively, available data from clinical trials discussed above suggest that R-CHOP administered on a 21 day schedule remains the standard treatment regimen for the majority of patients with newly diagnosed DLBCL.

R-CHOP for a total of 6 cycles (category 1) is the preferred regimen for patients with stage III-IV disease due to reduced toxicities compared to other regimens.[26,35-38] In selected patients, RT to bulky sites may be beneficial (category 2B). DA-EPOCH-R (category 2B)[46,47] or dose-dense R-CHOP-14 (category 3) [41,42] are included as alternative regimens in selected patients. DA-EPOCH-R may be preferred for patients with primary mediastinal large B-cell lymphoma (PMBL) or with HGBL with translocations of *MYC* and *BCL2* and/or *BCL6* (DHL/THL). There is no evidence to suggest that an intensified regimen is better in patients with DLBCL and IHC expression of MYC and BCL2 without chromosomal rearrangements (DEL), for whom standard R-CHOP remains preferred.

R-mini-CHOP may be substituted for very frail patients and for patients >80 years of age with comorbidities to improve tolerability.[32,33] In patients with bulky disease or impaired renal function, initial therapy should include monitoring and prophylaxis for TLS.

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.[49] This could be explained by a slower clearance rate of rituximab in older women. 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.[50] Rituximab 500 mg/m^2 was associated with better serum levels and improved OS rates in male patients compared to historical data in older men treated with rituximab 375mg/m^2. In a planned subgroup analysis, rituximab 500 mg/m^2 was associated with improved PFS (*P* = .039) with a trend toward better OS (*P* = .076) but was also not more toxic than 375 mg/m^2 rituximab in elderly male patients. Based on these data, a rituximab dose of 500 mg/m^2 may

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be considered in men >60 years of age treated with R-CHOP. A randomized clinical trial is ongoing.

Prediction and Management of CNS Disease

Age >60 years, elevated LDH, ≥2 extranodal sites and involvement of specific extranodal sites (bone marrow, testes, kidney, adrenal gland and paranasal) have been associated with increased risk for developing CNS relapse.[51] Stage IE primary DLBCL of the breast has also been identified as a potential risk factor for CNS relapse.[52,53]

The German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL) has proposed a prognostic model (CNS-IPI) to predict the risk of CNS relapse incorporating the 6 clinical factors (age > 60 years, LDH > normal, ECOG PS >1, stage III or IV disease, extranodal involvement >1 and involvement of the kidney and/or adrenal gland).[54]

The CNS-IPI separated patients into three risk groups based on the rate of developing CNS disease at 2 years: low-risk (0 or 1 risk factor; rate of CNS disease 0.6%), intermediate-risk (2 or 3 risk factors; rate of CNS disease 3%) and high-risk group (4 to 6 risk factors; rate of CNS disease at 10%).[54] In the multivariate analysis, age >60 years, elevated LDH, ECOG PS >1, and stage III or IV disease were identified as the most significant predictors of CNS relapse. Although involvement of >1 extranodal site was not a significant predictor of CNS relapse, it was retained in the final CNS-IPI for the ease of application. Among the specific extranodal sites, only the involvement of the kidney or adrenal gland were significantly associated with CNS relapse or progression. In another international multicenter retrospectively analysis of 1532 patients with DLBCL treated with chemoimmunotherapy, there was a strong correlation between absolute number of extranodal sites and risk of CNS relapse. The 3-year cumulative incidence of CNS relapse was 15% for patients with >2 extranodal sites compared with 3% for those with ≤2 extranodal sites (P < 0.001).[55]

There may be an increased risk of CNS relapse in patients with 4 to 6 risk factors according to CNS-IPI; HIV-associated lymphoma; testicular lymphoma; HGBL with translocations of *MYC* and *BCL2* and/or *BCL6* (DHL/THL); HGBL, NOS; or kidney or adrenal involvement. Lumbar puncture should be considered for these patients, particularly if neurologic symptoms are present. The diagnostic yield is improved if flow cytometric analysis of cerebrospinal fluid is undertaken.

CNS prophylaxis should be considered for patients with risk factors for CNS disease but the optimal method 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.[56-59] 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.[56] However, other reports suggest that CNS prophylaxis is insufficient to prevent CNS relapse.[60,61] The NCCN Guidelines currently recommend CNS prophylaxis with 4 to 8 doses of intrathecal methotrexate and/or cytarabine, or systemic methotrexate (3–3.5 g/m^2). In selected patients, systemic methotrexate (3–3.5 g/m^2) may also be given as consolidation after R-CHOP + intrathecal methotrexate/cytarabine.

For concurrent presentation with systemic and CNS DLBCL, systemic methotrexate (≥3.5 g/m^2) should be incorporated as part of the treatment plan on day 15 of a 21-day R-CHOP cycle that has been supported by growth factors) for parenchymal involvement. Intrathecal methotrexate/cytarabine and/or systemic methotrexate (3–3.5 g/m^2) should be incorporated as part of the treatment plan for leptomeningeal involvement. Ommaya reservoir placement should be considered in

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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 as well as methotrexate clearance must be monitored. Adequate recovery of blood counts should be confirmed prior to initiating the next cycle of R-CHOP.

Role of HDT/ASCR

Several studies have evaluated high-dose therapy and autologous stem cell rescue (HDT/ASCR) as consolidation therapy for patients in first CR after induction therapy.[62-65]

In the randomized GELA LNH87-2 study (performed in pre-rituximab era), patients with DLBCL in first CR after induction therapy received consolidation therapy with either sequential chemotherapy or HDT/ASCR.[62] Although no difference in outcome was prospectively observed in this trial, a retrospective subset analysis of 236 patients with age-adjusted IPI of 2 (high-intermediate) or 3 (high-risk), found that HDT/ASCR resulted in significantly improved outcomes compared with sequential chemotherapy with regards to both 8-year DFS rate (55% vs. 39%; *P* =.02) and 8-year OS rate (64% vs. 49%; *P* =.04) in the high-intermediate/high-risk subset.[62]

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.[63] The 3-year PFS rate and OS rates were 76% and 83%, respectively, with no significant differences between treatment arms.[63]

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.[64] The 2-year PFS rate was significantly higher with HDT/ASCR compared with chemoimmunotherapy alone (69% vs. 55%; *P* =.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.

In the randomized DLCL04 trial of the Italian Lymphoma Foundation, 399 patients with DLBCL (aged ≤65 years) 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.[65] After a median follow-up of 72 months, the 2-year failure-free survival rate was significantly higher in the HDT/ASCR group compared with the non-HDT/ASCR groups (71% vs. 62%; *P* =.012), but the 5-year OS rate was not different between the two groups (78% and 77% respectively; *P* = .91). In addition, grade ≥3 hematologic toxicities were higher in the transplant group (92% compared to 68%).

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. HDT/ASCR is therefore not routinely recommended.

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 significantly higher EFS and OS rates in several studies.[66-69] However, interim PET scans can produce false positive results and many patients

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treated with chemoimmunotherapy have a favorable long-term outcome despite a positive interim PET scan.[70,71] In one prospective study, the PFS in patients who were interim PET-positive, biopsy-negative (after 4 cycles of accelerated R-CHOP) was identical to that in patients with a negative interim PET scan.[70] A retrospective analysis 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 after treatment with 6 to 8 cycles of R-CHOP (72% and 85% respectively; *P* = .0475).[71] 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.[72-75] 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).[74] The results of the PETAL trial showed that a positive interim PET scan (change in SUVmax of <66%) was associated with significantly inferior EFS and OS, although PET-based treatment intensification did not improve outcome in patients with DLBCL treated with R-CHOP.[76]

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 2 to 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 to 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).[19,77] The 5-PS is based on the visual assessment of fluorodeoxyglucose (FDG) uptake in the involved sites relative to that of the mediastinum and the liver.[78-80] 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 to 2 or 1 to 3 to be PET-negative, but a score of 1 to 3 is now widely considered to be PET negative. Scores of 4 to 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.

Interim and End-of-Treatment Response Evaluation for Stage I–II

When the treatment plan involves ISRT, restaging should be done after completion of first-line chemoimmunotherapy prior to initiation of ISRT as the dose of RT will be influenced by the result (see *Principles of Radiation Therapy* in the algorithm).

If interim restaging demonstrates CR (PET-negative), the planned course of treatment with the same dose of RT is completed. If the interim restaging demonstrates a PR (PET-positive), treatment with a higher dose of RT is appropriate. It is appropriate to enroll patients with an interim PR on a clinical trial. At the present time, there are no data to suggest that a PR with persistent PET positivity after 3 cycles should prompt a change in

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treatment. If the PET scan is positive after 6 cycles of R-CHOP or R-CHOP-14, the patient can proceed to 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) demonstrates a CR or 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.

The role of ISRT 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).[27] In this study, 164 patients with stage III-IV disease were treated with 6 cycles of R-CHOP-14 and 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 the same chemoimmunotherapy with RT to bulky sites.[27] 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.[81] Although retrospective subgroup analyses may be subjected selection biases, the benefit of RT held up on multivariate analysis in both studies.

After end of treatment restaging, observation is preferred for patients with CR. ISRT to initially bulky disease or isolated skeletal sites can be considered for patients with CR.[27,81] Lenalidomide maintenance as first-line consolidation therapy for patients 60 to 80 years of age is included with a category 2B recommendation based on the results of the phase III randomized ReMARC trial which showed that lenalidomide maintenance for 24 months significantly prolonged PFS in elderly patients with DLBCL achieving CR or PR to R-CHOP induction therapy, but without impact on OS.[82]

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.

Follow-up

Considerable debate remains regarding 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 and invasive procedures 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 117 patients with DLBCL who achieved a CR with induction chemotherapy, 35 patients relapsed, and only 6% of these relapses were detected by follow-up CT scan in

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asymptomatic patients; 86% of cases of relapse were associated with development of new symptoms or signs of relapse.[83] 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 108 patients with relapsed aggressive lymphoma who had a CR to initial chemotherapy, 20% of relapses were detected by imaging in asymptomatic patients.[84] 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.[84] 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.[85] 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).[85] 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 75 patients with DLBCL who achieved a CR after induction therapy, 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.[86] 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 the majority of patients with DLBCL.[87-89] 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).[87] Another study reported a positive predictive value of 56% for surveillance PET/CT scans in patients with an IPI score <3 compared with 80% for patients with an IPI score ≥3, suggesting that surveillance PET/CT has a very limited role in the majority of patients in CR after primary therapy.[88] Another multiinstitutional retrospective study evaluated the utility of surveillance scans in two independent prospectively enrolled cohorts of patients with DLBCL treated with anthracycline-based chemoimmunotherapy.[89] In one cohort (n = 680; 552 patients entered post- treatment observation), post treatment surveillance scans detected DLBCL relapse prior to clinical manifestations only in 2% of 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 2% of 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.[90]

A multiinstitutional 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.[91] 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

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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 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.

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) in the pre-rituximab era.[92] 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).[92] A recent retrospective analysis based on data from the EBMT registry evaluated the role of HDT/ASCR in patients achieving a second CR after second-line therapy (N=470).[93] 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).[93]

Outcomes of relapsed/refractory DLBCL differ based on the response to initial therapy, timing of relapse and opportunity to undergo HDT/ASCR. In a population based study of 1039 patients treated with anthracycline-based chemoimmunotherapy, 244 patients (23%) had relapsed disease that was subsequently re-treated.[94] Across all therapies, the 4-year OS rate was 28% and 51% for patients who underwent HDT/ASCR. The 4-year OS rate was 47% for patients with disease relapse after 12 months from initial diagnosis whereas the 4-year OS rate was 13% for those with a transient or no response to initial therapy. Pre-transplantation PET scans have been identified as predictive factors in patients undergoing HDT/ASCR, with positive PET scans following second-line therapy predicting poor outcomes following HDT/ASCR.[95-97] The results of studies from the GELTAMO 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.[98-100]

Effective second line regimens for patients who are candidates for HDT/ASCR include R-ICE (rituximab, ifosfamide, carboplatin and etoposide),[101-103] R-DHAP (rituximab, dexamethasone, cytarabine and cisplatin),[103,104] R-DHAX (rituximab, dexamethasone, cytarabine and oxaliplatin)[105,106] or R-GDP (gemcitabine, dexamethasone, cisplatin or carboplatin).[101-103,107,108] The efficacy of second-line therapy is predicted by the second-line age-adjusted IPI.[109,110]

In the international randomized intergroup study (CORAL study) that evaluated second-line chemoimmunotherapy (R-ICE vs. R-DHAP)

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followed by ASCR in 469 patients with chemosensitive relapsed or refractory DLBCL no significant difference in outcome was found between treatment arms.[103] The overall response rates (ORRs) were 63% after R-ICE and 64% after R-DHAP. After a median follow-up of 44 months, 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*).[103] Notably, patients relapsing less than 1 year after initial R-CHOP therapy had a particularly poor outcome with 3-year PFS of 23%. 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).[111] This difference was not observed among patients with non-GCB phenotype (3-year PFS 32% with R-DHAP vs. 27% with R-ICE).[111] 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.[112] 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.[112]

The CORAL study was also designed to evaluate the role of rituximab maintenance (every 2 months for 1 year) following ASCR. Among the 242 patients randomized after ASCR to rituximab maintenance or observation, the 4-year EFS rate was similar between the two groups: 52% with rituximab versus 53% with observation.[103] The proportion of patients with progression or relapse was also similar between the two groups. In addition, the 4-year OS rate was also 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 following ASCR, maintenance therapy cannot be recommended in this setting. [103 103 103 103 103 102]

In a randomized study of 619 patients with relapsed/refractory aggressive lymphoma (419 patients with relapsed/refractory DLBCL randomized to receive GDP [gemcitabine, dexamethasone, cisplatin] or DHAP), GDP was non-inferior to DHAP in terms of ORR (45% vs. 44%) and transplantation rate (52% vs. 49).[107] After a median follow-up of 53 months, no differences were detected in EFS (*P* =.95) or OS (*P* = .78) between GDP and DHAP. Treatment with GDP was associated with less toxicity (*P* < .001).

Second-line combination chemotherapy is recommended for patients with an intention to proceed to transplant. Rituximab should be included if there is disease relapse after reasonable remission period (>6 months) and biopsy demonstrates continued CD20 expression; however; rituximab should often be omitted in patients with primary refractory disease. Consolidation therapy with HDT/ASCR (category 1 for patients with CR) with or without RT is recommended for patients with CR or PR to second-line therapy, if they are candidates for transplant.[92,93] ISRT before HDT/ASCR has been shown to result in good local disease control and improved outcome.[113] Additional RT can be given to limited sites with prior positive disease before or after HDT/ASCR. Allogeneic HCT should be considered in selected patients with mobilization failures and persistent bone marrow involvement or lack of adequate response to second line therapy, though patients should be in CR or near CR at the time of transplant.

Patients who are not candidates for transplant should ideally be treated in the context of a clinical trial. Standard options include gemcitabine-based regimens with or without rituximab,[114-116] bendamustine ± rituximab,[117-119] or brentuximab vedotin if CD30 positive.[120] Lenalidomide with or without rituximab,[9,10] and ibrutinib[11] are appropriate options at relapse, particularly

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for patients with non-GCB DLBCL. Based on the results of the phase II randomized clinical trial that evaluated bendamustine + rituximab (BR) versus polatuzumab vedotin + BR, bendamustine ± rituximab is included with a category 2B recommendation.

Patients who are not candidates for transplant with PR to second-line therapy or those with progressive or refractory disease to second-line therapy (regardless of transplant eligibility) or those with disease relapse following HDT/ASCR or allogeneic HCT should be managed with third-line systemic therapy, palliative ISRT or best supportive care. Repeat biopsy should be strongly considered prior to additional therapy for patients who are non-candidates for transplant achieving PET-positive PR to second-line therapy because PET positivity may represent post-treatment inflammation.

However, patients with progressive disease after ≥2 prior lines of systemic therapy regimens are unlikely to derive additional benefit from currently available systemic therapy options, except for patients who have experienced a long disease-free interval. The results of a multicenter retrospective study (SCHOLAR-1) showed that outcomes are consistently poor among patients with refractory DLBCL.[121] In this study that evaluated the outcome of 636 patients with refractory DLBCL (defined as progressive or stable disease as best response at any point during chemotherapy [>4 cycles of first-line or 2 cycles of later-line therapy] or disease relapse at ≤12 months from HDT/ASCR), the pooled ORR was 26% (7% CR) to the next line of therapy, and the median OS was 6 months.[121] The response rates were much lower for patients with primary refractory disease or refractory disease after second-line or subsequent therapy (20% and 26%, respectively) compared to those with disease relapse ≤12 months from HDT/ASCR. Data from recent clinical trials (discussed below) suggest that chimeric antigen receptor (CAR) T-cell therapy represents an improved treatment option for this group of patients.

Recently, FDA granted accelerated approval of polatuzumab vedotin (anti-CD79b antibody-drug conjugate) in combination with bendamustine and rituximab (BR) for the treatment relapsed or refractory DLBCL after ≥2 prior lines of therapies. This approval is based on the results from the phase II randomized trial that evaluated polatuzumab vedotin + BR (n=40) versus BR (n =40) in patients with relapsed or refractory DLBCL ineligible for HDT/ASCR.[122] At a median follow-up of 22 months, the ORR were 45% and 18%, for polatuzumab vedotin + BR and BR, respectively. The CR rates were significantly higher for polatuzumab vedotin + BR compared with BR alone (40% vs 18%; *P* =.026). The median PFS (8 months vs. 2 months; *P* < .0001) and OS (12 months vs. 5 months; *P* = .0023) were also significantly longer for polatuzumab vedotin + BR compared with BR. Polatuzumab vedotin + BR was also associated with survival benefit regardless of COO (GCB vs. non-GCB) and double expressor status (MYC and BCL2 overexpression), although the biomarker sample sizes were small. In patients with non-GCB subtype (14 patients in the polatuzumab vedotin + BR arm; 16 patients in the BR arm), the median PFS and OS were 11 months and 14 months, respectively for polatuzumab vedotin + BR. The corresponding median PFS and OS were 3 months and 4 months, respectively for BR. In patients with MYC and BCL2 overexpression (9 patients in the polatuzumab vedotin + BR arm; 6 patients in the BR arm), the median PFS and OS were 7 months and 13 months, respectively for polatuzumab vedotin + BR. The corresponding median PFS and OS were <1 month and 4 months for BR. Polatuzumab vedotin + BR is an appropriate treatment option for patients with relapsed or refractory DLBCL (after ≥2 prior lines of therapies) ineligible for HDT/ASCR.

CAR T-Cell Therapy

Axicabtagene ciloleucel and tisagenlecleucel are anti-CD19 CAR T-cell therapies that are FDA-approved for the treatment of adult patients with relapsed/refractory DLBCL, HGBL and transformed follicular lymphoma

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(TFL) after ≥2 prior systemic therapy regimens, based on the results of the ZUMA-1 and JULIET trials (discussed below).[123-125] Axicabtagene ciloleucel is also approved for relapsed or refractory PMBL after ≥2 prior systemic therapy regimens.

The multicenter phase II study (ZUMA-1) evaluated axicabtagene ciloleucel in patients with refractory DLBCL (n=81), TFL (n = 30) or PMBL (n = 8).[123] Eligible patients had an absolute neutrophil count >1,000 cells/μL, an absolute lymphocyte count greater than >100 cells/μL, a platelet count >75,000 cells/μL, adequate organ function, no central CNS involvement, and no active infection. In the primary analysis that included 101 patients (78 patients with disease refractory ≥2 lines of prior therapy and 21 patients with disease relapse after HDT/ASCR) that were evaluated 6 months after the infusion of axicabtagene ciloleucel, the ORR was 82% (54% CR and 28% PR). With a median follow-up of 15 months, the estimated PFS rate at 15 months and the OS rate at 18 months were 41% and 52%, respectively. The ORRs were 81% (49% CR; 32% PR) and 83% (71% CR; 12% PR), respectively for the subgroup of patients with DLBCL and TFL or PMBL. The 2-year follow-up data also confirmed these initial findings.[124] After a median follow-up of 27 months, 39% of patients remained in ongoing remission, and 51% remained alive. The median duration of response was 11 months and the median PFS was 6 months.

The multicenter phase II study (JULIET) evaluated tisagenlecleucel in patients with relapsed/refractory DLBCL (after at least two lines of therapy, including rituximab and an anthracycline) and TFL.[125] Patients who had been previously treated with anti CD19 CAR T-cell therapy or an allogeneic HCT and those with PMBL, or active CNS involvement were excluded. In this study, 115 patients received infusion with tisagenlecleucel. Among the 93 patients included in the efficacy analysis with ≥3 months of follow-up or had discontinued participation in the study before 3 months, the best ORR was 52% (40% CR; 12% PR). The estimated PFS rate at 12 months was 83% for patients who had a CR or PR at 3 months. The estimated OS rate at 12 months was 49% for all patients and 90% for those with a CR.

Axicabtagene ciloleucel and tisagenlecleucel result in responses across all subgroups, including DHL/THL, GCB and non-GCB subtypes, and patients with either relapsed or primary refractory disease. CD19 expression levels did not correlate with response. The NCCN Guidelines recommend CAR T-cell therapy (axicabtagene ciloleucel or tisagenlecleucel) for patients achieving PR following second-line therapy (regardless of their eligibility for transplant) and for those with disease relapse after achieving CR to second-line therapy or progressive disease., Bendamustine should be used with caution (unless immediately prior to CAR T-cell therapy) in patients intended to receive CAR T-cell therapy, since it could impact the success of the patient's T-cell collection.

Guidance for the Treatment of Patients with CAR T-Cell Therapy

Axicabtagene ciloleucel and tisagenlecleucel should only be dispensed and administered in health care facilities that are enrolled in and comply with the Risk Evaluation and Mitigation Strategies (REMS) requirements.

Cytokine-release syndrome (CRS) and neurologic toxicity (also known as CAR-T-cell-related encephalopathy syndrome [CRES]) are the most frequent life-threatening toxicities associated with CAR T-cell therapy. In the ZUMA-1 trial, CRS and neurologic toxicity of any grade were reported in 93% and 64% of patients respectively.[123,124] The median time from infusion to onset of symptoms was 2 days and 5 days respectively, with the median duration of 8 days and 17 days, respectively. Grade ≥3 CRS and neurologic events occurred in 13% and 28% of the patients, respectively. Pyrexia (11%), hypoxia (9%), and hypotension (9%) were the most common symptoms of grade ≥3 CRS. The median time to the onset of CRS was 2 days after infusion and the median time until resolution was 8 days. Encephalopathy (21%), confusional state (9%), aphasia (7%), and

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somnolence (7%) were the most common grade ≥3 neurologic events. The incidence of grade ≥3 CRS and neurologic events decreased over the course of the study (occurring in 12% and 31% of patients respectively after a median follow-up of 15 months). In the JULIET trial, CRS and neurologic toxicity of any grade were reported in 58% and 21% of patients respectively.[125] Grade ≥3 CRS and neurologic events occurred in 22% and 12% of patients respectively. The median time from infusion to onset of symptoms was 2 days and 6 days respectively, with the median duration of 7 days and 14 days, respectively. Notably, different toxicity scales were used for the grading of CRS in the ZUMA-1 and JULIET trials (grade 3 CRS in JULIET was similar to grade 2 in ZUMA-1), so while rates of any CRS can be compared, the rates specifically of severe (grade 3 or 4) CRS cannot be directly compared with accuracy.

The anti-interleukin-6 (IL-6) receptor monoclonal antibody tocilizumab is highly effective for the management of CRS, inducing rapid reversal of symptoms in most patients.[126] Tocilizumab is approved for the treatment of CRS occurring after CAR-T-cell therapy and its use has not been shown to have any impact on the efficacy of CAR-T-cell therapy, in terms of response rates or duration of response. Corticosteroids are also an important adjunctive treatment for CRS, in concert with tocilizumab. Corticosteroids are preferred for the management of neurologic toxicity if not associated with CRS whereas tocilizumab in combination with corticosteroids is recommended for management of CRS occurring in tandem with neurologic toxicity.[126] The use of corticosteroids for the management of toxicities associated with CAR T-cell therapy did not impact the efficacy of CAR T-cell therapy, although their use has been to shown to impair T-cell function. CRS and neurologic toxicity should be managed based on the toxicity grade as outlined in the *Management of CAR T-Cell-Related Toxicities* section of the NCCN Guidelines for the Management of Immunotherapy-Related Toxicities.

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.[127,128] PMBL arises from thymic B-cells with initial locoregional spread to supraclavicular, cervical, hilar nodes and into the mediastinum and lung.[127] Widespread extranodal disease is uncommon at initial diagnosis, present in approximately one quarter of patients, but can be more common at recurrence.[128] Clinical symptoms may be related to rapid growth of a mediastinal mass include superior vena cava (SVC) syndrome, pericardial effusions 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).[129,130] PMBL expresses B-cell antigens and lacks surface immunoglobulin. 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.[128] 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.[128] Age-adjusted IPI is of limited value in determining the prognosis of PMBL at diagnosis.[127,131,132] In a retrospective analysis of 141 patients, ≥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.[131]

In retrospective analyses from the pre-rituximab era, intensive chemotherapy regimens have appeared more effective than CHOP and

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the addition of IFRT has been associated with improved PFS.[132-136] The results of subsequent retrospective studies suggest that the addition of rituximab to CHOP improves outcome in patients with PMBL.[137-141]

In a subgroup analysis of 87 patients with PMBL from the MInT study, 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).[138] The MInT study, however, only included young low-risk patients with IPI scores 0-1. In a more recent retrospective analysis that evaluated the outcome of 80 patients with PMBL treated with a CHOP-based regimen with and without rituximab, the 5-year PFS (95% vs. 67%; *P* =.001) and OS (92% vs. 72%; *P*=.001) rates were significantly higher in the rituximab arm.[139] In multivariate analysis, only the addition of rituximab to induction chemotherapy and CR after first line therapy had a beneficial effect on both PFS and OS. In another 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%, respectively for patients treated with rituximab-based chemotherapy compared with 58% and 88%, respectively for those treated with chemotherapy alone.[141] 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.

A more recent retrospective analysis of 63 patients with PMBL treated with R-CHOP reported 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.[142] 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.[143] At a median follow up for surviving patients at 3 years, the OS and PFS rates were 88% and 78%, respectively.[143]

DA-EPOCH-R has also been evaluated in small cohorts of patients with PMBL.[144-147] A prospective phase II study from the NCI 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.[144] In this study DA-EPOCH-R for 6 cycles and filgrastim, without RT, was evaluated in 51 patients with previously untreated PMBL. 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. In a multicenter retrospective analysis that assessed the outcome of 156 patients with PMBL treated with DA-EPOCH-R (38 children and 118 adults; all patients received at least one cycle of DA-EPOCH-R. RT was administered in 15% of patients). At a median follow-up of 23 months, the estimated 3-year EFS and OS rates were 86% and 95%, respectively. Negative PET at end-of-treatment was associated with improved EFS (95% vs. 55%, *P* < ·001).[146] In another multi-center cohort analysis of 132 patients with PMBL (56 patients were treated with R-CHOP and 76 patients were treated with DA-EPOCH-R), both R-CHOP and DA-EPOCH-R were associated with excellent 2-year OS rates (89% and 91% respectively).[147] While DA-EPOCH-R resulted in higher CR rates than R-CHOP, patients treated with DA-EPOCH-R were more likely to experience short-term treatment-related toxicities but were spared long-term risks associated with mediastinal RT.

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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: DA-EPOCH-R (6 cycles)[144] + RT only for persistent PET-positive local disease; R-CHOP (6 cycles) +/- RT; or R-CHOP (4 cycles) followed by ICE with or without rituximab (3 cycles) with or without RT (category 2B).[143]

Post-treatment PET/CT is considered essential; 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. If PET/CT is negative at the end of treatment after more intensive therapies (e.g., DA-EPOCH-R) and initial disease was non-bulky, observation may be appropriate. If PET/CT is positive, biopsy is recommended before additional treatment is contemplated.

Relapsed or refractory disease should be managed as described above for DLBCL. However, outcomes of second-line therapy followed by HDT/ASCR remains undefined in patients with relapsed or refractory PMBL. Retrospective analyses that evaluated the outcomes of patients with relapsed/refractory PMBL have reported OS rates of 67% to 68% and PFS rates of 57% in patients undergoing HDT/ASCR after second-line therapy.[148,149] In a multivariate analysis, incomplete response to initial therapy, advanced Ann Arbor stage at disease progression, and failure to achieve a ≥PR after second-line therapy were independently associated with inferior EFS and OS.[149]

Pembrolizumab (a humanized anti–PD-1 monoclonal antibody) has demonstrated promising activity resulting in an ORR of 41% after a median follow-up of 11 months in a cohort of 18 patients with relapsed/refractory PMBL enrolled in the KEYNOTE-013 study (a multicenter, international trial evaluating the safety and efficacy of pembrolizumab in patients with hematologic malignancies).[150] Pembrolizumab is FDA-approved for the treatment of relapsed or refractory PMBL after ≥2 prior lines of therapy. As discussed above, CAR T-cell therapy with axicabtagene ciloleucel is also approved for relapsed or refractory PMBL after ≥2 prior systemic therapy regimens.[123,124]

Grey Zone Lymphomas

Grey zone lymphoma, officially known in the 2017 WHO classification as B-cell lymphoma unclassifiable with features intermediate between DLBCL and CHL,[4] refers to lymphomas with overlapping pathologic features between CHL and PMBL, and with a poorer clinical outcome than either CHL or PMBL.[151-155] In 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, the methylation profiles of patients with grey zone lymphoma were intermediate to those of PMBL and CHL, but distinct from patients with DLBCL.[156] 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, with grey zone lymphomas showing an overlap of both signatures. This unique epigenetic signature of mediastinal grey zone lymphomas provide validation of its classification as a separate disease entity in the WHO classification.[4,156]

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; necrosis without neutrophilic infiltration is frequently present.[4,153] Mediastinal grey zone lymphomas with biologic and morphologic features of both CHL and DLBCL, 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.[151,152,154]

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Non-mediastinal grey zone lymphomas occur in older patients, have a higher incidence of bone marrow involvement, include more than one extranodal disease, and have advanced stage disease and higher risk IPI score than mediastinal grey zone lymphomas.[157] 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.[157]

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; BCL6 is variably expressed and EBV is more often negative.[151-153,155] If the morphology more closely resembles PMBL, dim or no expression of CD20 and strong expression of CD30 and CD15 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.[4]

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.[151,153,158] 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. 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.[157] DA-EPOCH-R has also been associated with improved clinical outcomes.[159,160] 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.[159] With a median follow-up of 5 years, the EFS (62% vs 93%; *P* = .0005) and OS (74% vs 97%; *P* = .001), were significantly lower for patients with mediastinal grey zone lymphoma compared to patients with PMBL (n = 51) enrolled in the same study.

Patients with grey zone lymphomas are best managed in cancer centers with experience in treating this type of lymphoma. In the absence of suitable clinical trials, R-CHOP-21 or DA-EPOCH-R should be considered for initial therapy. 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.

High-Grade B-Cell Lymphomas with translocations of *MYC* and *BCL2* and/or *BCL6*

HGBL with translocations of *MYC* and *BCL2* and/or *BCL6* have been observed in 2% to 11% of newly diagnosed patients with DLBCL. The vast majority are GCB-DLBCL and are characterized by highly aggressive clinical behavior and overlapping pathologic features with DLBCL, B-cell lymphoblastic lymphoma/leukemia (B-LBL) and Burkitt lymphoma (BL).[161] FISH for *MYC, BCL2,* and *BCL6* gene rearrangements is recommended for those with expression of MYC and either BCL2 or BCL6 by IHC.

IHC will also identify DLBCL with dual expression of both MYC and BCL2 proteins without associated rearrangements (double expressing lymphomas; DEL), which also have an inferior prognosis.[162,163] In a series of 193 patients with DLBCL uniformly treated with standard R-CHOP, the 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 DEL compared with those without protein expression of MYC and BCL2.[162] In another study with a longer follow-up, 5-year PFS and OS were 18% and 27%,

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respectively, in patients with DHL/THL and DEL treated with R-CHOP.[163] MYC or BCL2 expression alone has not been associated with a worse outcome.[162,163] In a 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.[162,163]

Data from retrospective studies suggest that more intensive chemoimmunotherapy regimens may result in better outcomes in patients with DHL/THL.[164-166] In a multicenter retrospective analysis of 106 patients with DHL/THL, treatment with intensive regimens such as DA-EPOCH-R, R-HyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone) or R-CODOX-M/IVAC (rituximab, cyclophosphamide, doxorubicin, vincristine, methotrexate/ifosfamide, etoposide, and high dose cytarabine) resulted in superior CR and PFS compared to R-CHOP.[164] A meta-analysis compared survival outcomes in patients with double-hit cytogenetics treated with more aggressive regimens including R-HyperCVAD, R-CODOX-M/IVAC or R-EPOCH versus R-CHOP in the first-line setting.[167] The median PFS for the R-CHOP, DA-EPOCH-R and other dose intensive regimens was 12, 22, and 19 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 was evaluated in a prospective phase II study of 53 patients with untreated aggressive B-cell lymphoma with *MYC* gene rearrangement (19 patients had confirmed *MYC* rearrangement alone and 24 patients also had rearrangement of *BCL2, BCL6*, or both [double-hit]). After a median follow-up of 56 months, 48-month EFS and OS rates were 71% and 77%, respectively for all patients.[168] 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 HGBL with translocations of *MYC* and *BCL2* and/or *BCL6.* Alternative treatment strategies are needed to improve outcomes in this poor-risk patient population.

The standard of care for the treatment of patients with HGBL with translocations of *MYC* and *BCL2* and/or *BCL6* 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 HGBL with translocations of *MYC* and *BCL2* and/or *BCL6.* CNS prophylaxis should be considered according to institutional standards since these patients are at higher risk for CNS involvement.[164,165] Consolidation with HDT/ASCR is done at some NCCN Member Institutions; however its role is not established. Consolidative RT has also been reported to result in improved PFS among patients with a CR to chemotherapy.[169] Currently, no data supports the use of any regimen other than R-CHOP for DEL, and additional clinical trials are needed.

Relapsed/refractory disease should be managed as described for DLBCL. However, limited data are available regarding the outcome of relapsed/refractory disease following HDT/ASCR or allogeneic HCT in patients with HGBL with translocations of *MYC* and *BCL2* and/or *BCL6* or DEL.[170,171] Polatuzumab vedotin + BR is an appropriate treatment option for patients with relapsed or refractory HGBL with translocations of *MYC* and *BCL2* and/or *BCL6* (after ≥2 prior lines of therapies) ineligible for HDT/ASCR.[122] CAR T-cell therapy (axicabtagene ciloleucel or tisagenlecleucel) is FDA approved for the treatment of relapsed/refractory HGBL after ≥2 prior systemic therapy regimens.[123-125]

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Burkitt Lymphoma

Burkitt Lymphoma (BL) is a rare and aggressive B-cell lymphoma typically involving extranodal disease sites. Endemic, sporadic, and immunodeficiency-associated BL are the three clinical variants of BL that are described in the WHO classification.[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 United States and Western Europe, and can be associated with EBV infection in about 30% of cases.[2] Immunodeficiency-associated BL occurs mainly in patients infected with human immunodeficiency virus (HIV), in individuals with congenital immunodeficiency, and in some patients following hematopoietic cell transplant (HCT). An analysis from the NCI SEER database reported improved survival outcomes in patients with BL diagnosed during the last decade (1922 patients diagnosed between 2002 and 2008).[3] The estimated 5-year survival rate was 56% compared with 43% in patients diagnosed prior to 2002. Thus, durable remission may be possible in approximately 60% of patients with BL.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for B-Cell Lymphomas an electronic search of the PubMed database was performed to obtain key literature in BL published since the previous Guidelines update. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[4]

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 data from key PubMed articles deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). 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 at www.NCCN.org.

Diagnosis

Adequate immunophenotyping using immunohistochemistry (IHC) with or without flow cytometry analysis is essential to establish the diagnosis of BL. The typical immunophenotype of BL is sIg+, CD10+, CD19+, CD20+, CD22+, TdT-, Ki67+ (>95%), BCL2-, BCL6+, and simple karyotype with *MYC* rearrangement as sole abnormality. The IHC panel should include the following: CD3, CD10, CD20, CD45, TdT, Ki-67, BCL2, and BCL6. Flow cytometry analysis should include the following markers: CD5, CD10, CD19, CD20, CD45, TDT, and kappa/lambda. 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.

By definition, classical BL is characterized by *MYC* gene rearrangement as the sole cytogenetic abnormality[(due to t(8;14) in 80% of cases, or its variants, t(2;8) and t(8:22) in the remaining 20% of cases], which results in the juxtaposition of *MYC* gene on chromosome 8 with the immunoglobulin heavy chain variable (*IGHV*) region on chromosome 14 or the immunoglobulin light chain genes.[5] Cytogenetic analysis (with or without fluorescence in situ hybridization [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. FISH using a

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break-apart probe, or long-segment PCR, are more reliable for the detection of t(8;14) and its variants, and are often utilized to detect these rearrangements.[6]

There are other mature aggressive B-cell lymphomas with morphologic, immunophenotypic, and/or molecular features similar to BL that do not meet this strict definition.[7,8] Recent studies have identified a molecularly distinct subset of B-cell lymphomas with morphologic and clinical features of BL, characterized by deregulation of *11q* gene but lacking *MYC* rearrangements.[9-12] In the 2017 WHO classification, these are included as a provisional entity designated as Burkitt-like lymphoma with *11q* aberration.[1] These subset of lymphomas have a clinical course similar to BL, but the optimum management of this rare subtype is undefined, though it is most often treated like typical BL.

As discussed above, *MYC* translocations are detected in all cases of BL, but *MYC* translocations also occur in diffuse large B-cell lymphoma (DLBCL) and in a subset of B-cell lymphomas with features intermediate between BL and DLBCL.[13] Double-hit or triple-hit lymphomas that harbor both *MYC* and *BCL2* and/or *BCL6* translocations have a highly aggressive disease course with poor prognosis (median survival of 4–6 months) and the optimal management has not been identified.[14-18] In the 2017 classification, these lymphomas have been included in a unique category called high-grade B-cell lymphomas (HGBL) with translocations of *MYC* and *BCL2* and/or *BCL6.*[1]

B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL was added as a provisional category in the 2008 WHO l classification to include the following subsets of B-cell lymphomas with features intermediate between BL and DLBCL: lymphomas with features of both DLBCL and BL, that cannot be diagnosed as DLBCL or BL for biological and clinical reasons; lymphomas that are morphologically intermediate between BL and DLBCL include lymphomas with immunophenotype suggestive of BL (CD10 positive, BCL6 positive, BCL2 negative, and IRF4/MUM1 negative or weakly positive); and lymphomas that are morphologically similar to BL but are strongly BCL2 positive.[19] These lymphomas often present with poor prognostic factors (eg, elevated lactate dehydrogenase [LDH], bone marrow and CNS involvement, and a high International Prognostic Index [IPI]) and are associated with poor survival outcomes (median survival of 9 months and a 5-year survival rate of only 30%).[13] In the 2017 WHO classification, the provisional category of BCLU has been eliminated and lymphomas that appear blastoid or lymphomas with features intermediate between DLBCL and BL but lack a *MYC* and *BCL2* and/or *BCL6* rearrangement are placed in the new category, HGBL, NOS.[1]

Workup

The initial diagnostic workup includes a detailed physical examination (with special attention to the node-bearing areas, liver, and spleen) and chest/abdomen/pelvic CT with contrast of diagnostic quality. 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 central nervous system (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 (eg, if CNS involvement is suspected at time of diagnosis due to neurologic 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. Multigated acquisition (MUGA) scan or echocardiogram is recommended, particularly for older patients, if the treatment includes an anthracycline-based regimen.

Evaluations of bone marrow aspirate and biopsy, lumbar puncture, and flow cytometry of cerebrospinal fluid are essential. In these highly

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aggressive lymphomas, as in DLBCLs, the serum LDH level has prognostic significance. 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 lymphomas). In addition, hepatitis B virus (HBV) testing prior to initiation of treatment is recommended for all patients who will receive anti-CD20 monoclonal antibody (MAB)-based regimens due to increased risk of HBV reactivation.

Induction Therapy

BL is curable in a significant subset of patients when treated with dose-intensive, multiagent chemotherapy regimens that also incorporate CNS prophylaxis. About 60% to 90% of pediatric and young adult patients with BL achieve durable remission if treated appropriately.[20] However, the survival of older adults with BL appears to be less favorable, compared with younger patients.[21] 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.[20,21]

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 algorithm.

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. Results from retrospective analyses have shown that more intensive multiagent chemotherapy regimens such as hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine, including intrathecal methotrexate) or CODOX-M/IVAC (cyclophosphamide, doxorubicin, and high-dose methotrexate, alternating with ifosfamide, etoposide, and high-dose cytarabine) are associated with more favorable outcomes than CHOP or CHOP plus etoposide.[22,23] In a population-based analysis of data from 258 patients with HIV-negative BL from a Swedish/Danish registry, the 2-year overall survival (OS) rate was only 39% for CHOP or CHOP with etoposide compared with 83%, and 69%, respectively, for hyper-CVAD and CODOX-M/IVAC.[22]

Thus, for patients with BL who can tolerate aggressive therapies, intensive multiagent chemotherapy may offer the best chance for durable disease control. Data from clinical trials that have evaluated induction therapy with more intensive multiagent chemotherapy regimens are discussed below.

CODOX-M/IVAC (originally published in 1998) is a highly effective regimen with a 1-year event-free survival (EFS) rate of 85% in pediatric and adult patients with previously untreated BL or Burkitt-like lymphoma.[24,25] Patients with high-risk disease received 4 alternating treatments (ABAB) of CODOX-M (A) and IVAC (B), and those with low-risk disease received 3 cycles of CODOX-M. Both cycles included intrathecal chemotherapy (cytarabine or methotrexate) for CNS prophylaxis in addition to high-dose systemic cytarabine and methotrexate.

Subsequent phase II and retrospective studies have confirmed the efficacy of this regimen, and a “modified” regimen (inclusion of rituximab and dose-modified to decrease toxicity).[15,26-29]

The efficacy of modified CODOX-M/IVAC regimen (modified slightly with vincristine dose capped at 2 mg) in adult patients with BL was confirmed in an international phase II study (n =52; 12 patients had low-risk disease; 40 patients had high-risk disease).[26] The overall 2-year EFS and OS rates were 65% and 73%, respectively. The 2-year EFS and OS rates were 83%

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and 81%, respectively, for patients with low-risk disease. The corresponding survival rates were 60% and 70%, respectively, for those with high- risk disease.[26] Subsequent reports showed that lowering the dose of systemic methotrexate to 3 g/m^2 from the originally reported 7 g/m^2 maintained the efficacy and was also associated with decreased toxicity, with a 2-year progression-free survival (PFS) rate of 62% to 64% and 2-year OS rate of 71%.[15,27] Another small study that evaluated modified CODOX-M/IVAC (reducing the dose of methotrexate to 3 g/m^2) with or without rituximab in 15 patients with BL or B-cell lymphoma unclassifiable, also reported 5-year PFS and OS rates of 87%.[28]

The addition of rituximab to modified CODOX-M/IVAC was evaluated in a retrospective study of 80 patients with BL.[29] There was a trend for improvement in outcomes with the addition of rituximab but the differences were not statistically significant. The 3-year PFS and OS rates with rituximab were 74% and 77%, respectively; the 3-year PFS and OS rates without the addition of rituximab were 61% and 66%, respectively.

An additional modification of CODOX-M/IVAC utilizing liposomal doxorubicin instead of doxorubicin, plus rituximab, has also been shown to be effective in patients with newly diagnosed classic BL.[30,31] In a phase II trial of 25 patients, this modified CODOX-M/IVAC regimen resulted in an overall response rate of (ORR) of 100% (92% CR).[31] At 34-month median follow-up, the 2-year PFS and OS rates for all patients were 80% and 84%, respectively (PFS and OS rates were both 100% for patients with low-risk BL and the corresponding survival rates were 76% and 81%, respectively, for those with high-risk BL). The 2-year PFS and OS rates for high-risk, HIV-negative patients were 84% and 89%, respectively.

The hyper-CVAD regimen is also effective, resulting in CR rates of 81% and a 3-year OS rate of 49% in patients with BL or leukemia.[32] The OS rate was higher among patients ≤60 years (77% vs. 17% for patients >60 years). The results of a phase II study (57 patients; 30 patients with non-HIV BL and 27 patients with B-ALL) showed that the addition of rituximab to hyper-CVAD (R-hyper-CVAD) improved long-term outcomes in patients with newly diagnosed BL or B-ALL, particularly in the older patient subgroup.[33,34] R-hyper-CVAD induced complete response (CR) in 86% of patients and the 5-year OS rate was 74%, with a median follow-up of 62 months.[34] The 5-year OS rates were 72% and 70%, respectively, in patients <60 years and those >60 years. These survival outcomes were superior in historical comparison with patients treated with hyper-CVAD alone.

Dose-adjusted EPOCH with rituximab (DA-EPOCH-R) also resulted in highly favorable outcomes in patients with previously untreated BL. In a prospective study that evaluated DA-EPOCH-R in HIV-negative patients (n = 19) and a short course of EPOCH with dose-dense rituximab (SC-EPOCH-RR) in HIV-positive patients (n =11), at a median follow-up of 86 months, the freedom-from-progression (FFP) and OS rates with DA-EPOCH-R were 95% and 100%, respectively.[35] 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 risk-adapted treatment approach with DA-EPOCH-R was validated in a subsequent multicenter phase II trial (n = 113).[36] Low-risk patients received 2 cycles of DA-EPOCH-R without intrathecal therapy followed by PET and one more cycle, if interim PET was negative. High-risk patients with no CNS involvement received 2 cycles of DA-EPOCH-R without intrathecal therapy followed by PET and 4 additional cycles of DA-EPOCH-R, unless interim PET showed progression. After a median follow-up of 36 months, the PFS, FFP, and OS rates were 86%, 92% and 86%, respectively.

A large, prospective, multicenter study from the German study group evaluated the efficacy and safety of a short-intensive multiagent

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chemotherapy regimen (including high-dose methotrexate, high-dose cytarabine, cyclophosphamide, etoposide, ifosfamide, and corticosteroids) combined with rituximab in patients with BL (n = 225) and Burkitt leukemia (n = 138).[37] Patients also received triple intrathecal therapy with methotrexate, cytarabine, and dexamethasone. The CR rate was 88% for the total cohort. At a median follow-up of >7 years, the PFS and OS rates were 71% and 80%, respectively. The diagnosis of BL versus Burkitt-like lymphoma had no influence on outcome. These outcomes appear highly promising, with a manageable toxicity profile. The results of a more recent randomized phase III trial (n = 260) from the French lymphoma study group (GELA) also showed that the addition of rituximab to short intensive chemotherapy is associated with improved EFS in adults with BL.[38] With a median follow-up of 38 months, the 3-year EFS rates were significantly higher for patients treated with rituximab and dose-dense chemotherapy than for patients treated with dose-dense chemotherapy alone (75% vs. 62%; *P* =.024).

Several studies have evaluated the role of HCT 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 HCT in untreated BL, Burkitt-like lymphoma, or B-ALL.[39] Among the patients with BL/Burkitt-like lymphoma (n = 27), CR was achieved in 81% of patients with a partial response (PR) in 11%; the 5-year EFS and OS rates were 73% and 81%, respectively.[39] In a recent analysis of outcomes with HCT (autologous or allogeneic transplant) in patients with BL from the CIBMTR database (N = 241), the 5-year PFS and OS rates with autologous HCT at first remission were 78% and 83%, respectively.[40] These outcomes with autologous HCT were similar to findings from the above HOVON study, and appeared to compare favorably to the 5-year PFS and OS rates with allogeneic HCT in first remission, which were 50% and 53%, respectively. Not surprisingly, patients who underwent HCT with less than a first remission had poorer outcomes regardless of transplant type. The 5-year PFS and OS rates with autologous HCT in those without a first remission were 27% and 31%, respectively; the corresponding rates with allogeneic HCT without first remission were only 19% and 20%, respectively. For patients in a second remission, autologous HCT resulted in a 5-year PFS of 44%.[40] 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 HCT (27% vs. 31%).[41] As would be expected, EFS rates were lower among patients who were not in CR at the time of transplant.

NCCN Recommendations

It is preferred that patients with BL receive treatment at centers with expertise in the management of this highly aggressive disease. 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.[22,23] The management of patients with B-cell lymphomas with features intermediate between BL and DLBCL (now included in the new category, HGBL, NOS) as well as those patients with double-hit or triple-hit lymphomas (HGBL with translocations of *MYC* and *BCL2* and/or *BCL6)* has not been well studied. Therefore, these patients are best managed in the context of clinical trials evaluating novel targeted agents.

Patients with either of the following clinical characteristics are generally considered to have low-risk disease: normal serum LDH or stage I disease and a completely resected abdominal lesion or a single extra-abdominal mass <10 cm. All other patients should be considered as having high-risk disease.

CODOX-M (original or modified) ± rituximab (3 cycles), DA-EPOCH-R (3 cycles with one more additional cycle for patients achieving CR), and

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hyper-CVAD + rituximab are included as options for patients with low-risk BL.

CODOX-M/IVAC (original or modified) with or without rituximab, DA-EPOCH-R (for patients not able to tolerate aggressive treatments), and R-hyper-CVAD are included as options for patients with high-risk BL.

Adequate CNS prophylaxis with systemic and/or intrathecal chemotherapy with methotrexate and/or cytarabine is recommended with all regimens.

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 involved-site radiation therapy (ISRT) may be considered appropriate.

Relapsed or Refractory Disease

Patients with relapsed or refractory disease should be treated in the context of a clinical trial. In the absence of suitable clinical trials, selected patients with a reasonable remission duration following induction therapy may be managed with second-line therapy using multiagent chemotherapy regimens.

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 are included as options for second-line therapy. However, it should be noted that treatment options remain undefined for patients who relapse after first-line therapy and 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.[42]

Consolidation with high-dose therapy and autologous stem cell rescue (HDT/ASCR) or allogeneic HCT (if donor available) may be considered for selected patients achieving a CR or PR to second-line therapy. Clinical trial or best supportive care including palliative ISRT are recommended for patients with disease not responding to second-line therapy or those with progressive disease.

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AIDS-Related B-Cell Lymphomas

Non-Hodgkin's lymphomas (NHL), Kaposi sarcoma (KS) and lung cancer are the most common cancer types diagnosed in people living with human immunodeficiency virus (HIV) in the United States and the incidences of cancer in this patient population is expected to shift substantially through 2030, with the largest declines projected for NHL and KS.[1,2]

Diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), and primary central nervous system lymphoma (PCNSL) are the most common subtypes of NHL in people living with HIV.[3] The distribution of systemic lymphomas versus PCNSL may vary between published reports depending upon the different factors such as geographic regions, time period covered and referral patterns of the institutions. The incidences of Hodgkin lymphoma (HL) and indolent lymphoma are also elevated in people living with HIV, but are much less common than BL or DLBCL.[3] Plasmablastic lymphoma (PBL) and primary effusion lymphoma (PEL) are the less common forms of systemic lymphomas, accounting for less than 5% of lymphomas in people living with HIV.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for B-Cell Lymphomas an electronic search of the PubMed database was performed to obtain key literature in AIDS-related lymphomas published since the previous Guidelines update, using the following search terms: AIDS-related lymphomas or HIV-associated lymphomas or HIV-positive lymphomas. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[4]

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 26 citations and their potential relevance was examined. The data from key PubMed articles deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). 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 at www.NCCN.org.

Prognosis

The routine use of antiretroviral therapy (ART) has improved the prognosis of patients with HIV-associated lymphomas and the pathologic spectrum of lymphomas in people living with HIV has also changed in the era of ART, with a drastic decrease in the incidence of PBL and a much lower incidence of systemic HIV-associated lymphomas.[5,6] Nevertheless, HIV continues to be independently associated with increased risk of death among patients with HIV-associated lymphomas even in the ART era in the United States, and the association varies by lymphoma subtype.[7-9] Increased incidence of lymphoma due to unmasking immune reconstitution inflammatory syndrome soon after receiving ART has also been described in people living with HIV.[10]

In a report from the COHERE (Collaboration of Observational HIV Epidemiological Research Europe) study that evaluated the outcomes of patients with HIV-associated lymphomas treated in the ART era (1998-2006), the 1-year OS rates among patients with systemic lymphoma and PCNSL were 66% and 54%, respectively.[8] In large cohort

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study that evaluated the trends in presentation and survival of lymphoma a large HIV-infected cohort, the 5-year survival rates were 50%, 44%, 23% and 43% respectively for DLBCL, BL, PCNSL and other NHLsubtypes.[3] Older age, lymphoma occurrence during antiretroviral therapy, lower CD4 count at lymphoma diagnosis, higher HIV RNA and histologic category were identified as independent risk factors for mortality. In a recent analysis that evaluated the characteristics and outcomes of DLBCL in HIV-infected patients in the era of ART, the 2-year OS and progression-free survival (PFS) were both 75% after treatment with RCHOP; PFS after treatment with RCHOP did not differ from that of the HIV-negative counterparts.[11]

PCNSL in people with HIV may have a better prognosis and is actually curable with less intensive chemotherapy regimens when used along with immune reconstitution.[12-15] Immune reconstitution with ART administered along with high-dose methotrexate or radiation therapy (RT) is associated with improved survival outcomes in patients with HIV-associated PCNSL, even among those with a history of opportunistic infections, limited access to healthcare and medical non-adherence.[14]

PBL is an aggressive CD20-negative large B-cell lymphoma that mainly involves the jaw and oral cavity in people living with HIV and is also associated with EBV infection.[16,17] The prognosis of PBL has improved in the ART era even in patients with higher stage disease and more extranodal involvement, with some case series reporting favorable outcomes for patients with HIV-associated PBL treated with anthracycline-based multiagent chemotherapy in conjunction with ART.[18-20] In a cohort study of 61 patients with PBL, age (<50 years of age) and early stage disease (stage I/II disease) were identified as prognostic factors for favorable survival outcomes.[19] EBV-positive status was associated with a better event-free survival (EFS) compared to EBV-negative status. In a case series of 12 patients with newly diagnosed PBL treated exclusively in the ART era at the AIDS Malignancy Consortium (AMC) sites, at a median follow up of 73 weeks, the 1-year survival rate was 67% with no reported deaths in the follow up period after one year.[20] However, other studies suggest that the prognosis of patients with HIV-associated PBL remains poor even in the ART era.[21-24] In the German AIDS-related-Lymphoma-Cohort-Study, the 2-year OS rate for patients with PBL was 43% compared to the 2-year OS rates of 69% and 63% respectively for patients with BL and DLBCL.[23] PBL histology, international prognostic index (IPI) and bone marrow involvement were identified as independent predictors of mortality.

PEL is characterized by neoplastic effusions in body cavities without detectable tumor masses (occurring most often in the pleural, pericardial, and abdominal cavities) and is associated with Kaposi sarcoma-associated herpesvirus (KSHV), otherwise known as human herpes virus 8 (HHV8) and it may also be co-infected with Epstein Barr virus (EBV).[25,26] PEL has a poor survival compared to HIV-associated DLBCL or BL, even in the ART era. In a study that analyzed the outcomes of 10,769 patients with HIV-associated lymphomas identified in the National Cancer Data Base, the estimated 5-year OS rates were 42%, 45%, 22% and 28% respectively for DLBCL, BL, PCNSL, and PEL.[27] Poor performance status, advanced stage disease and absence of ART prior to the diagnosis of PEL have been identified as prognostic factors for shorter survival.[28,29] The use of ART with chemotherapy is essential to improve the outcomes of PEL.

Diagnosis

The major factor in the diagnostic evaluation of HIV-associated lymphoma is to distinguish between different subtypes. Adequate immunophenotyping using immunohistochemistry (IHC) with or without flow cytometry analysis is essential to establish the diagnosis of the subtype of HIV-associated lymphomas.[30] Epstein-Barr virus (EBV)-encoded RNA in situ hybridization (EBER-ISH) is recommended

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for all patients since EBV is the most commonly found oncogenic virus in patients HIV-associated lymphomas.[31] HHV8/KHSV testing would be useful to confirm the diagnosis of PEL since this oncogenic virus is implicated in the pathogenesis of PEL.[25,26]

Workup

The diagnostic evaluation and workup are as outlined in the NCCN Guidelines section for HIV-associated lymphomas. 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. Among the systemic HIV-associated lymphomas, BL is generally associated with a higher CD4+ cell count at diagnosis compared with DLBCL. PCNSL, PBL and PEL are particularly associated with low CD4+ count levels.

Initial Treatment

Several key factors have emerged as being important to improve the outcome in patients with HIV-associated lymphomas. The introduction of ART has allowed for the administration of more dose-intense chemotherapy regimens and a reduction in treatment-associated toxicity. In addition, the use of concurrent ART is also associated with superior outcomes (improved CR rates, a trend towards improved OS and faster immune recovery).[32-37]

In prospective phase II studies, several combination chemotherapy regimens (with or without rituximab) given with concomitant ART, have been proven to be active and tolerable in patients with HIV-associated lymphomas. In a pooled analysis of 1546 patients with HIV-associated lymphomas included in prospective clinical trials, initial therapy with more dose-intense regimens and the use of rituximab resulted in higher CR rates; the use of rituximab was also associated improved PFS and OS.[35]

EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab

In the AMC 034 trial, patients with HIV-associated aggressive B-cell NHL were randomized to receive infusional EPOCH regimen either concurrently with rituximab or followed sequentially by rituximab (106 patients with HIV-associated lymphomas;75% DLBCL; 25% BL, BL-like).[38] The complete response (CR) rate was 73% and 55%, respectively for concurrent and sequential rituximab. The 2-year PFS rate (66% vs. 63%) and OS rate (70% vs. 67%) were similar between treatment arms. Toxicity was comparable in the 2 treatment arms, although the use of concurrent rituximab was associated with a higher incidence of treatment-related deaths among the patients with a baseline CD4+ count <50/mcL. Overall, treatment-related deaths occurred in 5 patients (10%) in the concurrent rituximab arm and 4 patients (7%) in the sequential rituximab arm. In this trial, ART was given concurrently with EPOCH or delayed until chemotherapy completion per investigator choice. Although the use of concurrent ART was not associated with improved survival outcomes compared to delayed use of ART, concurrent use of ART was associated with faster immune recovery (CD4 counts higher than baseline 6 months after EPOCH and decrease in HIV viral load during chemotherapy).[37]

In a pooled analysis that included 150 patients with HIV-associated NHL treated in the AMC trials (AMC 010 and AMC 034), low age-adjusted IPI score and baseline CD4 count ≥100/mcL were significantly associated with improved CR rate, EFS and OS outcomes.[39] Among the patients who were treated with concurrent EPOCH-R, both EFS and OS were significantly improved compared with RCHOP (after adjusting for aaIPI and CD4 counts). The incidence of treatment-related deaths were higher in patients with baseline CD4 counts <50/mcL compared with those with higher CD4 counts (37% vs. 6%; P<0.01).[39]

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Dose-adjusted EPOCH (DA-EPOCH) is also effective resulting in an ORR of 87% with a CR rate of 74% in patients with untreated HIV-associated NHL (n = 39; 79% DLBCL; 18% BL).[40] At a median follow up of 53 months, PFS and OS rates were 73% and 60%, respectively. The disease-free survival (DFS) rate was 92% with only 2 of the patients with a CR experiencing disease recurrence at last follow up). The OS outcomes were decreased among the patients with low baseline CD4 counts (≤ 100/mcL) compared with those with higher CD4 counts (16% vs. 87%). In a multivariate analysis, low CD4 counts and CNS involvement were the only significant factors associated with decreased OS.[40]

In a more recent phase II study, a short course of EPOCH with dose-dense rituximab (SC-EPOCH-RR) was shown to effective resulting in a CR rate of 91% in patients with HIV-associated DLBCL (n = 33). At a median follow up of 5 years, the PFS and OS rates were 84% and 68%, respectively.[41] In this study, the addition of rituximab did not appear to cause serious infection-related complications or deaths. The safety and efficacy of SC-EPOCH-RR in patients with low-risk HIV-associated BL was demonstrated in a subsequent prospective study that included 11 patients with HIV-associated BL.[42] At a median follow-up of 86 months, the rates of freedom from progression and OS were 100% and 90%, respectively for patients treated with SC-EPOCH-RR. This regimen was also associated with lower incidences of fever and neutropenia than DA-EPOCH-R.

The safety and preliminary efficacy of vorinostat in combination with EPOCH-R regimen in patients with high-risk HIV-associated NHL (with at least one of the following high-risk characteristics: age-adjusted IPI 2–3, Ki-67 80%, non-germinal center B-cell (GCB) DLBCL, non-Burkitt B-cell NHL) was established in a phase I study and the utility of adding vorinostat to EPOCH-R regimen is being evaluated in a phase II randomized trial.[43] The result of a retrospective study showed that the addition of bortezomib to EPOCH is also safe and effective as a front-line treatment for HIV-associated PBL but this has to be confirmed in a prospective study.[44]

CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone with or without rituximab

CHOP regimen has been shown to induce CR rates of 30% to 48%, with a median OS of approximately 25 months and the addition of rituximab has been associated with improved CR rates in patients with HIV-associated lymphomas.[45-49]

In the randomized phase III trial (AMC 010 study) of 150 patients with HIV-associated NHL (80% DLBCL; 9% BL), the addition of rituximab to CHOP (RCHOP) was associated with improved CR rates (58% vs. 47%) as well as longer median time to progression (29 months vs. 20 months) and longer median OS (32 months vs. 25 months) compared with CHOP alone.[46] The median PFS was similar between treatment groups (10 months vs. 9 months). It should also be noted that in this study, 35 patients randomized to the RCHOP arm had received maintenance rituximab following initial RCHOP.[46] However, clinical trials evaluating maintenance rituximab in non-HIV patients did not show survival benefit. In addition, in the aforementioned clinical trial, all deaths due to infection occurred during the maintenance phase.[46] Therefore, the use of maintenance rituximab is not recommended for patients with HIV-associated lymphomas. In subsequent phase II trials, 6 cycles of the RCHOP resulted in CR/CRu rates of 69% to 77%, with 2-year OS and 3-year OS rates of 75% and 56%, respectively, in patients with HIV-associated NHL (majority with DLBCL), with manageable toxicities.[48,49]

Liposomal doxorubicin or pegylated liposomal doxorubicin in combination with cyclophosphamide, vincristine and prednisone (CDOP) has also been shown to be effective in patients with HIV-associated lymphoma.[50,51] In a multicenter phase II trial (AMC 047 study) of 40

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patients with HIV-associated NHL (DLBCL in 98% of cases), infusional CDOP (with pegylated liposomal doxorubicin) in combination with rituximab (RCDOP), resulted in an ORR of 68% (48% CR). 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. This may in part be explained by the fact that patients received concomitant ART 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. However, these results, however, appeared less favorable compared with the EPOCH regimen.

CODOX-M/IVAC regimen (cyclophosphamide, doxorubicin and high-dose methotrexate, alternating with ifosfamide, etoposide and high-dose cytarabine) with or without rituximab

The CODOX-M/IVAC regimen (cyclophosphamide, doxorubicin and high-dose methotrexate, alternating with ifosfamide, etoposide and high-dose cytarabine) with or without rituximab, commonly used in the management of patients with BL is also effective in patients with HIV-associated BL.[52-56]

In one retrospective study that evaluated CODOX-M/IVAC with or without rituximab in 80 patients with BL, the CR rates (93% and 88%, respectively) 3-year PFS (68% for both subgroups) and 3-year OS rates (68% and 72%, respectively) were similar among patients with and without HIV infection. There was a trend toward improved 3-year PFS rate (74% vs. 61%) and OS rate (77% vs. 66%) with the addition of rituximab.[53] The AMC 048 trial prospectively evaluated modified CODOX-M/IVAC with rituximab in 34 patients with HIV-associated BL (2 patients had low-risk disease; 32 patients had high-risk disease).[56] Patients with low-risk disease were treated with 3 cycles of rituximab and CODOX-M (R-CODOX-M) whereas all other patients with high-risk disease were treated with R-CODOX-M/IVAC. The median follow-up was 26 months. The 1-year PFS and OS rates were 69% and 72%, respectively; the 2-year OS rate was 69%.

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

The hyperCVAD regimen (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine) with or without rituximab has demonstrated efficacy in the treatment of *de novo* BL/leukemia and incorporation of rituximab was associated with improved disease-related outcomes particularly for the older subset of patients.[57,58] HyperCVAD regimen given in combination with ART has also been shown to be effective in patients with HIV-associated BL/leukemia and Burkitt-like lymphoma resulting in CR rates of 64–92% and a median OS of 12 months.[59]

NCCN Recommendations

The NCCN Guidelines recommend the use of ART and growth factor support along with full-dose chemotherapy with or without rituximab. Patients on ART with persistently low CD4+ count of less than 50 to 100/mcL tend to have a poorer prognosis, higher risk of infection and cytopenias.[38,46,60] Therefore, omission of rituximab is strongly suggested for these patients due to the higher risk of serious infectious complications. Maximizing supportive care and close monitoring for cytopenias and infections is recommended while administering lymphoma therapy for this groups of patients.

ART can be administered safely with chemotherapy. However, certain antiviral drugs can interfere with the metabolism of cancer therapies, commonly by CYP3A4 inhibition (protease inhibitors) or CYP3A4 induction (non-nucleoside reverse transcriptase inhibitors).[61,62] Therefore, effective alternatives for the existing ART should be considered to

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minimize toxicities and drug-drug interactions when anticipated. In general, avoidance of zidovudine, cobicistat, and ritonavir is strongly recommended. Any change in antiviral therapy should be made in consultation with an infectious disease specialist.

CODOX-M/IVAC (with or without rituximab), EPOCH-R and hyperCVAD with rituximab are recommended for patients with HIV-associated BL. EPOCH or CHOP in combination with rituximab is recommended for patients with HIV-associated DLBCL. EPOCH-R is included as the preferred regimen for the treatment of HIV-associated BL and DLBCL. CNS prophylaxis with intrathecal methotrexate or intrathecal cytarabine is indicated for patients with HIV-associated DLBCL with selected high-risk features (e.g., double-hit lymphoma, 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).

Patients with lymphoma associated with HHV8-positive DLBCL, NOS and PEL can also be treated with the same regimens as described for patients with HIV-associated DLBCL. Since most cases of PEL are CD20-negative, the addition of rituximab to the chemotherapy s not indicated.

CODOX-M/IVAC, EPOCH or hyper-CVAD are recommended for patients with PBL, with the realization that only limited data are available on the management of these patients at this time.[18,21,63] A CD4 count of >100/µL at diagnosis, chemosensitive disease and CR to first-line chemotherapy were associated with better outcomes.[21,63] Consolidation with high-dose therapy followed by autologous stem cell rescue (HDT/ASCR) can be considered following CR after initial therapy for patients with high-risk features (age-adjusted IPI >2, presence of *MYC* gene rearrangement or *TP53* deletion).[64,65]

Immune reconstitution with ART along with the use of high-dose methotrexate should be considered for patients with PCNSL.[12-15] RT should be reserved for patients who are not able to tolerate systemic therapy or for those with disease that is refractory to systemic therapy. Selected patients with good performance status receiving ART may also be treated as per the NCCN Guidelines for Primary CNS Lymphoma.

Relapsed/Refractory Disease

In a recent multicenter study that evaluated the risk factors and incidence of relapse in a large cohort of patients with HIV-associated lymphomas (after achieving CR to first-line treatment), unclassifiable histology, advanced stage disease, no concomitant ART during chemotherapy and the use of R-CHOP-based regimens were independently associated with higher risk of relapse in patients with BL.[36]

Bortezomib in combination with ICE (ifosfamide, carboplatin and etoposide) + rituximab is an effective second-line therapy for patients with relapsed/refractory HIV-associated lymphomas.[66] Brentuximab vedotin has also been shown to be effective in patients with PEL (albeit in case reports).[67] Additional prospective studies are warranted to confirm these findings.

HDT/ASCR is associated with favorable survival outcome in patients with chemosensitive relapsed/refractory disease, similar to the HIV-seronegative population.[68-74]

In a retrospective analysis that evaluated the outcomes of 88 patients with relapsed or refractory HIV-associated lymphomas treated with curative intent at 13 AMC sites, ICE (39%), DA-EPOCH (19%) and ESHAP (etoposide, methylprednisone, cytarabine and cisplatin, 13%) were the most commonly used second-line regimens.[71] The ORR was 31% and the 1-year OS rate was 37% for the entire study population. Baseline CD4 counts did not influence OS outcomes. Subsequent

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treatment with autologous hematopoietic cell transplant (HCT) was associated with improved 1-year OS (63% vs. 37%) compared with no HCT. There was no difference in 1-year OS rate based on HCT (88% with HCT vs. 82% with no transplant) for patients who experienced a response (CR or PR) after second-line therapy. The response rate and survival outcomes were better for patients with non-BL histology than that of patients with BL histology. The ORR and 1-year OS rate were 33% and 42% respectively for patients with non-BL histology compared to 17% and 12% respectively for those with BL histology. Patients with primary refractory disease (n=54) had significantly decreased ORR (24% vs. 56%; *P* =.003) and decreased 1-year OS (31% vs. 59%; *P* =.022) compared with those with relapsed disease.

In a phase II study of 43 patients with chemosensitive, relapsed or refractory HIV-associated lymphoma, at a median follow-up of 25 months, autologous HCT was associated with an estimated 1-year and 2-year OS rates of 87% and 82%, respectively.[72] The estimated 2-year PFS rate and the 1-year transplant related mortality rates were 80% and 5%, respectively. A matched population of control patients from the CIBMTR data registry revealed that these outcomes did not differ statistically from that of non–HIV-infected patients.

In a more recent retrospective study that evaluated the outcome of patients with HIV-associated lymphomas (n = 118; DLBCL, 47%, HL, 24%, BL, 18%, and PEL, 7%) following autologous HCT in the rituximab and ART era, at a median follow-up of 4 years, the 3-year non-relapse mortality, incidence of relapse, PFS and OS rates were 10%, 27%, 63% and 66%, respectively.[74] In the multivariate analysis, disease status less than PR at the time of transplant was a significant predictor of unfavorable PFS and OS.

These results suggest that HDT/ASCR should be considered for patients with chemosensitive relapsed or refractory HIV-associated lymphomas if they are candidates for transplant.

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Post-Transplant Lymphoproliferative Disorders

Post-transplant lymphoproliferative disorders (PTLD) are a heterogeneous group of lymphomas that occur after solid organ transplant (SOT) or allogeneic hematopoietic cell transplant (HCT) that are related to immunosuppression and the Epstein-Barr virus (EBV).[1] PTLD following SOT are of recipient origin in the majority of cases, often involving the grafted organ, whereas PTLD following allogeneic HCT are usually of donor origin.[2-9]

The incidence of PTLD following SOT varies significantly depending on the transplanted organ (kidney transplants, 0.8% to 3%; pancreatic transplants, 0.5% to 5%; liver transplants, 1% to 6%; heart transplants, 2.0% to 8%; lung transplants, 3% to 10%; and multiorgan and intestinal transplants, ≤20%).[1] The incidence of PTLD following allogeneic HCT varies depending on the on the degree of human leucocyte antigen (HLA) matching and the need for T-cell depletion protocol prior to transplantation.[4,5,9] Thus, the incidence of PTLD is the highest following haploidentical allogeneic HCT especially in cases of selective T-cell depletion (>20%) followed by cases of unrelated donors (4% to 10%), umbilical-cord transplants (4% to 5%), and matched, related donors (1% to 3%).

About 50% of PTLD following SOT are considered late-onset PTLD (diagnosed >1 year after transplant) and are more likely EBV-negative.[10-15] Gene expression profiling studies have also shown that EBV-negative PTLD are clinically and biologically distinct from EBV-positive PTLD.[16-20] EBV-negative PTLD are more likely to be of germinal center B-cell (GCB) type and EBV-positive PTLD are usually of non-GCB type.[17,21]

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for B-Cell Lymphomas an electronic search of the PubMed database was performed to obtain key literature in PTLD published since the previous Guidelines update. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[22]

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 data from key PubMed articles deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). 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 at www.NCCN.org.

Risk factors for developing PTLD

EBV serology mismatch (recipient EBV-negative and donor EBV-positive), type of transplanted organ (highest risks for multiorgan, bowel, lung, heart/lung transplants), intensity of induction immunosuppression, and the type of immunosuppression are considered as established risk factors for developing PTLD.[23-30] The risk is higher among children compared with adults, because primary EBV infection in EBV-negative organ recipients is the most common driver in children.[30-37]

Unrelated or HLA-mismatched allografts, the use of anti-thymocyte globulin (ATG) or anti-CD3 monoclonal antibody (MAB) for the prevention or treatment of graft-versus-host disease (GVHD), and T-cell depletion of the allograft are associated with increased risks for PTLD in patients

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undergoing allogeneic HCT.[4,5,34] The use of ATG or anti-CD3 MAB (OKT3), calcineurin inhibition with tacrolimus as primary immunosuppressive therapy along with the use of azathioprine and new agents (eg. belatacept in EBV-negative transplant recipients) are associated with increased risks for developing PTLD following SOT.[25,29] In an analysis of 523 patients who underwent heart transplant, switching from calcineurin inhibitor-based immunosuppression to sirolimus-based immunosuppression was associated with decreased rates of malignancies following heart transplant.[38]

Risk factors for surviving PTLD

Older age, poor performance status (Eastern Cooperative Oncology performance score of ≥2), elevated lactate dehydrogenase (LDH), organ dysfunction, multiple involved lymph nodes, multi organ involvement, graft organ involvement, central nervous system (CNS) involvement, number of extranodal sites (one versus more than one), the type of organ transplanted, hypoalbuminemia, the International Prognostic Factor Index (IPI), and comorbidities have been identified as prognostic factors for poor survival in patients with PTLD following SOT.[39-43] In the PTLD-1 trial, the IPI, lung transplants, and inadequate response to rituximab induction therapy were associated with a worse prognosis.[44]

Classification

In the 2017 WHO classification, PTLD are classified into 6 subclasses: 3 early lesions (nondestructive PTLD), monomorphic PTLD (B-cell, T-cell and NK cell type), polymorphic PTLD, and classical Hodgkin lymphoma (CHL) PTLD.[45]

Early lesions consist of 3 histologic subtypes: plasmacytic hyperplasia PTLD, infectious mononucleosis PTLD, and florid follicular hyperplasia PTLD. Early lesions typically develop within a year of transplantation and are EBV-positive in almost all cases.[46]

Monomorphic PTLD appear to be the most common subtype of PTLD and the majority are of B-cell origin with diffuse large B cell lymphoma (DLBCL) being the most frequent subtype.[21,37] Although uncommon, Burkitt lymphoma (BL),[47-50] plasma cell myeloma or plasmacytoma[51-55] have also been reported. Indolent B-cell lymphomas arising in transplant recipients are not included among PTLD, with the exception of EBV-positive marginal zone lymphomas. Monomorphic PTLD of T-cell or natural killer (NK)-cell origin (although very rare) tend to occur later (after a median of 6 years following transplant in one series).[56,57] Peripheral T-cell lymphoma, not-otherwise specified (PTCL, NOS) is the most prevalent subtype followed by anaplastic large cell lymphoma (ALCL) and hepatosplenic T-cell lymphoma (HSTCL).[57] From a pathology perspective, monomorphic PTLD cannot be distinguished from lymphomas with a similar lineage and cell of origin in immunocompetent patients suggesting that the subclassification of these types should be the same.

Polymorphic PTLD are mostly EBV positive, and can be either polyclonal or monoclonal. These are the most common type of PTLD among children and are characterized by a mixed lymphoproliferation consisting of immunoblasts, plasma cells, and intermediate-sized lymphoid cells. Immunohistochemistry (IHC) will show a variable mixtures of B-cells and T-cells. However, subdividing polymorphic PTLD is not indicated in the WHO classification since this does not reliably predict clinical behavior.[46]

CHL PTLD is almost always EBV-positive, and is the least common of the four PTLD categories.[58]

Diagnosis

The clinical presentation of PTLD is heterogeneous and is characterized by a high incidence of extranodal disease which may involve the gastrointestinal tract in (20% to 30%), solid allografts (10% to 15%), and CNS (5% to 20%). The diagnosis of PTLD can be challenging given the

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nonspecific clinical presentation, and heterogeneity in histopathologic and immunophenotypic presentations. Histopathology and adequate immunophenotyping are essential to confirm the diagnosis of PTLD.[59,60] Among B-cell PTLD, expression of BCL6, MUM1 and CD138 can be useful in distinguishing between the histological subtypes of PTLD.[61,62] BCL6 expression was detected in most 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.[61] Overall, BCL6−, MUM1+ and CD138− phenotype is associated most frequently with polymorphic PTLD; BCL6+, MUM1+/− and CD138− is mostly associated with monomorphic PTLD.[61,62]

The recommended IHC panel 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.

Up to 50% of PTLD cases that develop after SOT are not associated with EBV.[13] Although an association with EBV is not required for the diagnosis of PTLD, evaluation of EBV infection status is an 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 IHC, 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 variable (*IGHV*) gene mutations are seen in the majority of B-cell PTLD, with the exception of early lesions.[46,62,63] Genetic alterations in *MYC, NRAS* and *TP53* are seen only in monomorphic PTLD and *BCL6* mutations (present in 43% of the polymorphic PTLD) have been associated with shorter survival and poor response to therapy.[46,64,65] In certain situations, molecular analysis to detect *IGHV* rearrangements and *BCL6* 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 complete blood count (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. The history of immunosuppression treatment with the transplant course must be assessed. Chest/abdomen/pelvis CT with contrast of diagnostic quality and/or whole-body PET/CT scan are recommended as part of initial diagnostic workup. Brain MRI may be useful in selected cases, especially when CNS involvement is suspected. In addition, multigated acquisition (MUGA) scan or echocardiogram is recommended for patients being considered for treatment regimens containing anthracyclines or anthracenediones. 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.

SOT and HCT recipients who develop PTLD have a higher EBV viral load than transplant recipients without PTLD.[66] Evaluation of EBV viral load by quantitative polymerase-chain-reaction (PCR) amplification of EBV DNA can aid in the diagnosis as well as monitoring of treatment responses in patients with PTLD.[66-69] The reported positive and negative predictive

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values for this approach have varied significantly for SOT (28% to 100% and 75% to 100%, respectively) and HCT (25% to 40% and 67% to 86%, respectively) recipients.[70-72] 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, especially in patients with EBV-positive disease.[68,73,74] In recent studies, cell-free plasma EBV DNA was a better marker than EBV DNA from peripheral blood mononuclear cells.[70,71] EBV serology to assess primary infection versus reactivation may be useful. CMV infection has been associated with risks for EBV-positive PTLD.[24,75] Thus, EBV PCR for the measurement of cell-free plasma EBV DNA marker and CMV PCR can be useful for selected patients.

Treatment

Treatment approaches are largely dependent on the PTLD subtype.[76] Published reports have included reduction in immunosuppression (RI), antiviral therapy, rituximab monotherapy, chemotherapy, and/or chemoimmunotherapy regimens. The optimal treatment for PTLD is not well defined due to the lack of randomized controlled trials and the heterogeneity of the disease.

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.[77-79] Antiviral drugs targeting EBV replication may be beneficial in the subset of patients with early or polymorphic PTLD.[80,81]

Reduction in immunosuppression

RI remains the initial step in the management of nearly all cases of PTLD. RI leads to regression of PTLD in 20% to 80% of patients with polyclonal and monoclonal PTLD.[82-84] EBV-negative disease is less responsive to RI, but responses have been reported.[21,37] In a prospective phase II study that evaluated a sequential approach (RI first, then interferon-alfa for less than complete response (CR), then multiagent chemotherapy if less than CR to interferon) in 16 eligible patients with PTLD following SOT, RI resulted in one partial response (PR).[85]

Rituximab monotherapy

The efficacy of rituximab monotherapy in the treatment of patients with B-cell PTLD has been confirmed in phase II studies and retrospective analyses.[43,86-91] In a prospective multicenter phase II study of 43 eligible patients with PTLD after SOT, rituximab monotherapy resulted in an overall response rate (ORR) of 44% (28% CR) with a 1-year overall survival (OS) rate of 67%.[87] A prospective multicenter phase II study of 38 patients with PTLD after SOT demonstrated that risk-adapted extended treatment with 4 additional doses of rituximab increased the CR rate from 34% to 61% without increasing toxicity.[92] Among the patients who could not achieve a CR with rituximab monotherapy and subsequently received rituximab in combination with chemotherapy (R-CHOP or R-EPOCH; n=8), 6 patients achieved a CR (75%). At a median follow up of 28 months, the event-free survival (EFS) and OS rates were 42% and 47%, respectively.[92]

The results of a multicenter retrospective analysis (80 patients with PTLD following SOT) suggests that the inclusion of rituximab as part of initial therapy significantly improved both progression-free survival (PFS) and OS.[43] All patients initially underwent RI, and 74% were treated with rituximab with or without chemotherapy. The 3-year PFS and OS rates for all patients were 57% and 62%, respectively. The 3-year PFS and OS rates were 70% and 73% respectively for patients who received rituximab-based therapy as part of initial treatment compared to 21% and 33%, respectively for those who did not receive rituximab-based therapy.

Chemotherapy with or without rituximab

Anthracycline-based chemotherapy with or without rituximab has also been effective in the treatment of patients with PTLD[88,93-97] In a

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retrospective analysis of 26 patients with PTLD after SOT with disease unresponsive to RI alone, CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) induced an ORR of 65% (50% CR).[95] With a median follow up of nearly 9 years, the median OS was 14 months. Treatment-related mortality rate was high, at 31%.[95] 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.[98,99]

Sequential Chemoimmunotherapy

The prospective multicenter phase II study (PTLD-1) demonstrated the safety and efficacy of sequential chemoimmunotherapy (4 weekly doses of rituximab followed by 4 cycles of CHOP-21) with G-CSF in patients with PTLD after failure with initial RI (n =74; 70 evaluable patients).[100] The large majority of patients presented with monomorphic PTLD (primarily DLBCL), and 44% were EBV positive. The ORR with rituximab was 60% (20% CR), which improved to 90% (68% CR) in the patients who received CHOP chemotherapy following rituximab. The 5-year PFS and OS rates were 50% and 55%, respectively.[100] 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.

A risk-stratified treatment strategy based upon initial response to rituximab was evaluated in a subsequent prospective, international, multicenter phase II trial. In this trial, 152 patients with PTLD after SOT unresponsive to RI received induction therapy with 4 weekly doses of rituximab.[101] Low-risk patients (defined as those achieving CR after initial rituximab) received consolidation with rituximab monotherapy on days 50, 72, 94, and 116. High-risk patients (defined as non-CR after initial rituximab) received chemoimmunotherapy with R-CHOP-21 (4 cycles) combined with G-CSF. *Pneumocystis jirovecii* prophylaxis was recommended. Among the 126 patients enrolled in the risk-stratified protocol, the ORR was 88% (70% CR). The estimated 3-year OS rate was 70%, which compared favorably to the OS rate of 61%. The treatment related mortality was 8% and the median OS was 6.6 years. The estimated 3-year time-to progression (TTP) was 89% for patients with low-risk group treated with rituximab consolidation and response to rituximab remained a prognostic factor for OS despite the risk stratification. This risk-stratified sequential treatment strategy obviates the need for chemoimmunotherapy for low-risk patients achieving a CR to rituximab, while incorporating a more effective chemoimmunotherapy regimen (R-CHOP) for high-risk patients.[44,101]

Other indications for chemotherapy include specific histologic subtypes, such as PTCL, NOS, BL, CHL, and other uncommon lymphomas. These must be managed with treatment approaches associated with improved outcomes in the specific histologic subtypes. In a retrospective multiinstitutional analysis of 84 patients with primary CNS PTLD, 93% of patients received RI.[102] Additional first-line therapy included high-dose methotrexate (48%), high-dose cytarabine (33%), brain radiotherapy (24%), and/or rituximab (44%). The ORR was 60%. At a median follow-up of 42 months, the 3-year PFS and OS rates were 32% and 43%, respectively.

Retransplantation after diagnosis and treatment of PTLD

Retransplantation after diagnosis and treatment of PTLD is feasible in selected patients with PTLD following SOT.[83,103] Waiting for at least one year from the control of PTLD to retransplantation is recommended to minimize risk of PTLD recurrence.[83] In a French cohort study of 52 patients with kidney transplants who underwent 55 retransplantation, the median time elapsed from PTLD to retransplantation was 90 months and only one patient developed PTLD recurrence after retransplantation.[103]

Adoptive immunotherapy with EBV-specific cytotoxic T-lymphocytes

Adoptive immunotherapy with autologous or allogeneic EBV-specific cytotoxic T-lymphocytes (EBV-CTL) may be a promising strategy in patients with PTLD after failure of conventional treatments.[104-108] A prospective multicenter phase II study evaluated allogeneic EBV-CTL in

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the treatment of 33 patients with PTLD that failed conventional therapy.[107] The majority of patients (94%) had received SOT. All patients had RI as part of initial therapy for PTLD, and some patients had also received rituximab monotherapy, anti-viral therapy, or chemotherapy. The ORR and OS rate at 6 months were 52% (42% CR) and 79%, respectively. In a study that evaluated the effectiveness of allogeneic EBV-CTL in 114 patients who underwent allogeneic HSCT, EBV-CTL prevented PTLD in 101 patients and induced a durable CR in 85% of patients in the subgroup with existing PTLD (n=13).[108] This study also showed that during long-term follow up, functional EBV-CTL persisted up to 9 years.

Further prospective studies are needed to better define the role of adoptive immunotherapy in the prevention and management of PTLD.

NCCN Recommendations

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.[82-84] Initial management strategies include reduction of calcineurin inhibition (cyclosporin or tacrolimus) by 50% and discontinuation of antimetabolic agents (azathioprine or mycophenolate mofetil). Discontinuation of all non-steroidal immunosuppression should be considered in patients who are critically ill with extensive and life-threatening disease. The response to RI is 20% to 80% in polyclonal or monoclonal cases, and patients should be closely monitored during RI. Graft monitoring is essential to allow for early detection of allograft rejection. Importantly, RI should be initiated and managed in coordination with the transplant team in order to minimize risks for graft rejection. In contrast to the staging of lymphoma in immunocompetent patients, restaging should be performed at 2 to 4 weeks in patients receiving RI as the only treatment option, since responses occur very early. Additional treatment options are necessary (as described below based on the subtype) for patients who have not achieved a CR or those with persistent or progressive disease after initial RI.

CHL PTLD should be managed as described in the NCCN Guidelines for Hodgkin Lymphoma. In a cohort study of 192 patients with CHL-like PTLD identified in the Scientific Registry of Transplant Recipients (SRTR), among the 145 patients treated with chemotherapy, most of the patients received regimens specific for CHL, and the use of CHL-specific chemotherapy was associated with improved OS and disease-specific survival.[58]

Early lesions

RI alone is an appropriate first-line therapy for patients with early lesions. For patients who achieve a CR, 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. Graft organ function and EBV viral load should be monitored.

Rituximab is recommended as second-line therapy for patients with persistent or progressive disease after RI. EBV viral load should be monitored by PCR.

Monomorphic PTLD

Treatment options include RI and/or rituximab monotherapy[43,86-91] or chemoimmunotherapy for patients with B-cell type.[88,93-97] A risk stratified approach (as described above) could be used for patients achieving CR to rituximab monotherapy.[44,92,100,101] Rituximab monotherapy 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 chemoimmunotherapy due to the presence of comorbid conditions. In addition, RI is effective in plasmacytic PTLD with responses ranging from 33% to 75% in small series.[51,53,54] Patients who achieve a CR with initial

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therapy should undergo surveillance/follow up according to the NCCN Guidelines for B-Cell Lymphoma specific for the B-cell lymphoma subtype.

Second-line therapy options for patients with persistent or progressive disease are dependent on initial therapy. Rituximab or chemoimmunotherapy are recommended for patients who received RI alone as initial treatment, whereas patients who received rituximab monotherapy should be treated with chemoimmunotherapy. Patients who received chemoimmunotherapy as initial treatment should be managed as described for relapsed or refractory DLBCL. Other options include participation in a suitable clinical trial, if available, or adoptive immunotherapy with EBV-specific cytotoxic T-lymphocytes (if EBV positive).[104-108] Future strategies and other therapies have been reviewed.[1]

There are no established treatment options (other than RI) for patients with T-cell subtype. Treatment with anthracycline-based multiagent chemotherapy regimens recommended for T-cell lymphomas could be considered.

Polymorphic PTLD

RI along with rituximab monotherapy [43,86-91] or chemoimmunotherapy[88,93-97] are recommended for patients with systemic disease. RI along with involved-site radiation therapy (ISRT) with or without rituximab or surgery with or without rituximab, or rituximab monotherapy is recommended for patients with localized disease. A risk stratified approach (as described above) could be used for patients achieving CR to rituximab monotherapy.[44,92,100,101]

Observation or continuation of RI with or without rituximab maintenance is recommended for patients who achieve a CR. Chemoimmunotherapy or adoptive immunotherapy with EBV-specific cytotoxic T-lymphocytes (if EBV positive) are included as options for patients with persistent or progressive disease.[104-108] Participation in a suitable clinical trial, where available, should also be considered.

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