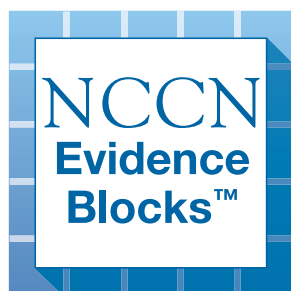


NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

B-cell Lymphomas: Diffuse Large B-Cell Lymphoma and Follicular Lymphoma

NCCN Evidence Blocks™

Version 7.2017 — January 9, 2018



NCCN.org

Continue



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

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

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

Ranjana H. Advani, MD †
Stanford Cancer Institute

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

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

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

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

Julio C. Chavez, MD †
Moffitt Cancer Center

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

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

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

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

Nancy Lee Harris, MD ≠
Massachusetts General Hospital Cancer Center

Francisco Hernandez-Ilizaliturri, MD †
Roswell Park Cancer Institute

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

Christopher R. Kelsey, MD §
Duke Cancer Institute

Nadia Khan, MD
Fox Chase Cancer Center

Susan Krivacic, MPAff ≠
Consultant

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

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

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

Rachel Rabinovitch, MD §
University of Colorado Cancer Center

Nishitha Reddy, MD ‡ §
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 †
University of Alabama at Birmingham
Comprehensive Cancer Center

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

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

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



[NCCN B-cell Lymphoma Panel Members](#)
[NCCN Evidence Blocks Definitions \(EB-1\)](#)

- [Follicular Lymphoma \(FOLL-1\)](#)
- [Diffuse Large B-Cell Lymphoma \(BCEL-1\)](#)
- [Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms \(NHODG-A\)](#)
- [Supportive Care for B-cell Lymphomas \(NHODG-B\)](#)
- [Lugano Response Criteria for Non-Hodgkin's Lymphoma \(NHODG-C\)](#)
- [Principles of Radiation Therapy \(NHODG-D\)](#)
- [Special Considerations for the Use of Small-Molecule Inhibitors \(Ibrutinib and Idelalisib\) \(NHODG-E\)](#)

[Classification and Staging \(ST-1\)](#)

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

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

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

See [NCCN Categories of Evidence and Consensus](#).

[Primary CNS Lymphoma \(See NCCN Guidelines for CNS\)](#)

[Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma \(See NCCN Guidelines for WM/LPL\)](#)

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NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS

5					
4					
3					
2					
1					

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

5					
4	■	■		■	
3	■	■	■	■	■
2	■	■	■	■	■
1	■	■	■	■	■

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)

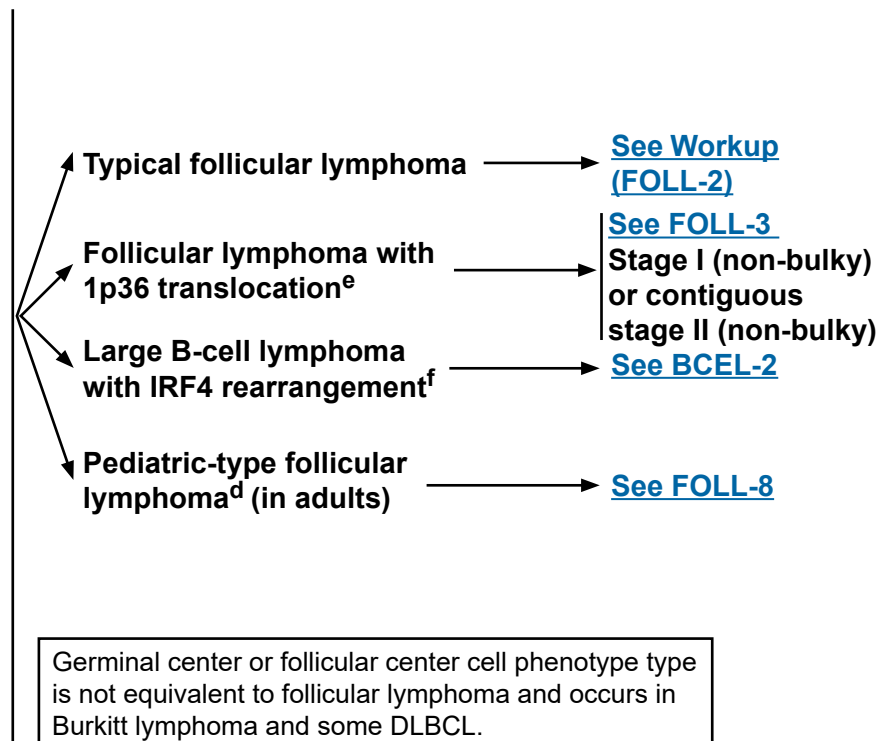
5	Very inexpensive
4	Inexpensive
3	Moderately expensive
2	Expensive
1	Very expensive

**DIAGNOSIS****ESSENTIAL:**

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



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

^bTypical immunophenotype: CD10+, BCL2+, CD23+/-, CD43-, CD5-, CD20+, BCL6+. Rare cases of follicular lymphoma may be CD10- or BCL2-.

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

^dIn young patients with localized disease that lacks BCL2 expression or t(14;18), consider entity of pediatric-type FL. Analysis of BCL6 rearrangement may be useful for evaluating the diagnosis of pediatric-type FL.

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

^fLymphomas 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.

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

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

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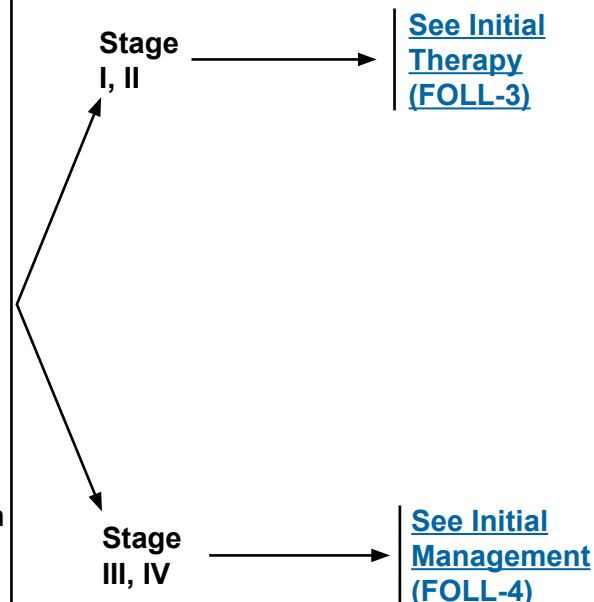
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

**WORKUP****ESSENTIAL:**

- **Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen**
- **Performance status**
- **B symptoms**
- **CBC, differential, platelets**
- **LDH**
- **Beta-2-microglobulin**
- **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 diseaseⁱ**
- **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**
- **Uric acid**
- **Discussion of fertility issues and sperm banking**
- **SPEP and/or quantitative immunoglobulin levels**
- **Hepatitis C testing**



^aFollicular 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 follicular lymphoma and others may treat it as diffuse large B-cell lymphoma (DLBCL). FL, grade 3b is commonly treated according to the [NCCN Diffuse Large B-Cell Lymphoma Guideline \(BCEL-1\)](#). Any area of DLBCL in a FL of any grade should be diagnosed and treated as a DLBCL.

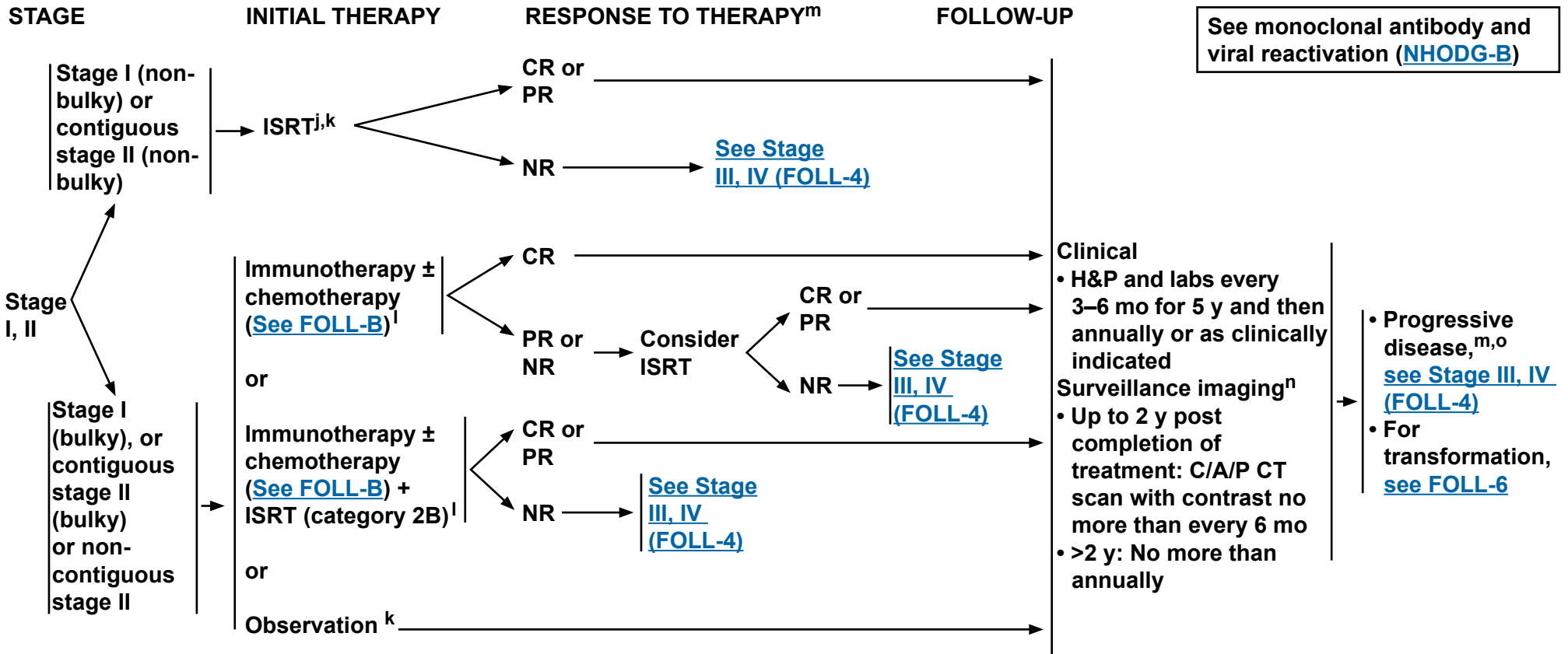
^hHepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check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

ⁱBilateral or unilateral provided core biopsy is >1.6 cm. If radioimmunotherapy 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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See monoclonal antibody and viral reactivation ([NHODG-B](#))

^jSee Principles of Radiation Therapy ([NHODG-D](#)).

^kObservation may be appropriate in circumstances where potential toxicity of involved-site RT (ISRT) outweighs potential clinical benefit.

ⁱInitiation 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.

^mSee Lugano Response Criteria for Non-Hodgkin's Lymphoma ([NHODG-C](#)).

ⁿImaging should be performed whenever there are clinical indications. For surveillance imaging, see Discussion for consensus imaging recommendations.

^oConsider 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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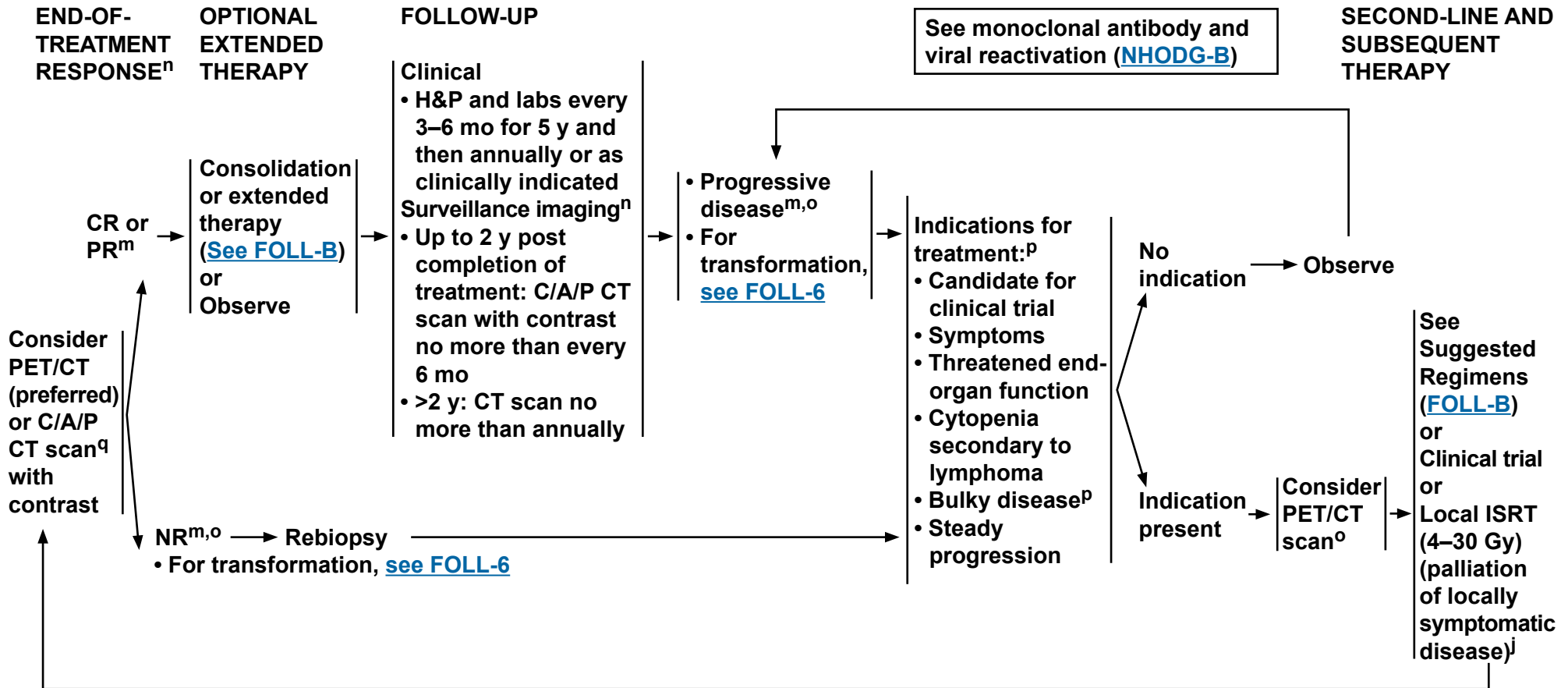
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Follicular Lymphoma^a (grade 1-2)

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^jSee Principles of Radiation Therapy (NHODG-D).

^mSee Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).

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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).

^pSee GELF criteria (FOLL-A).

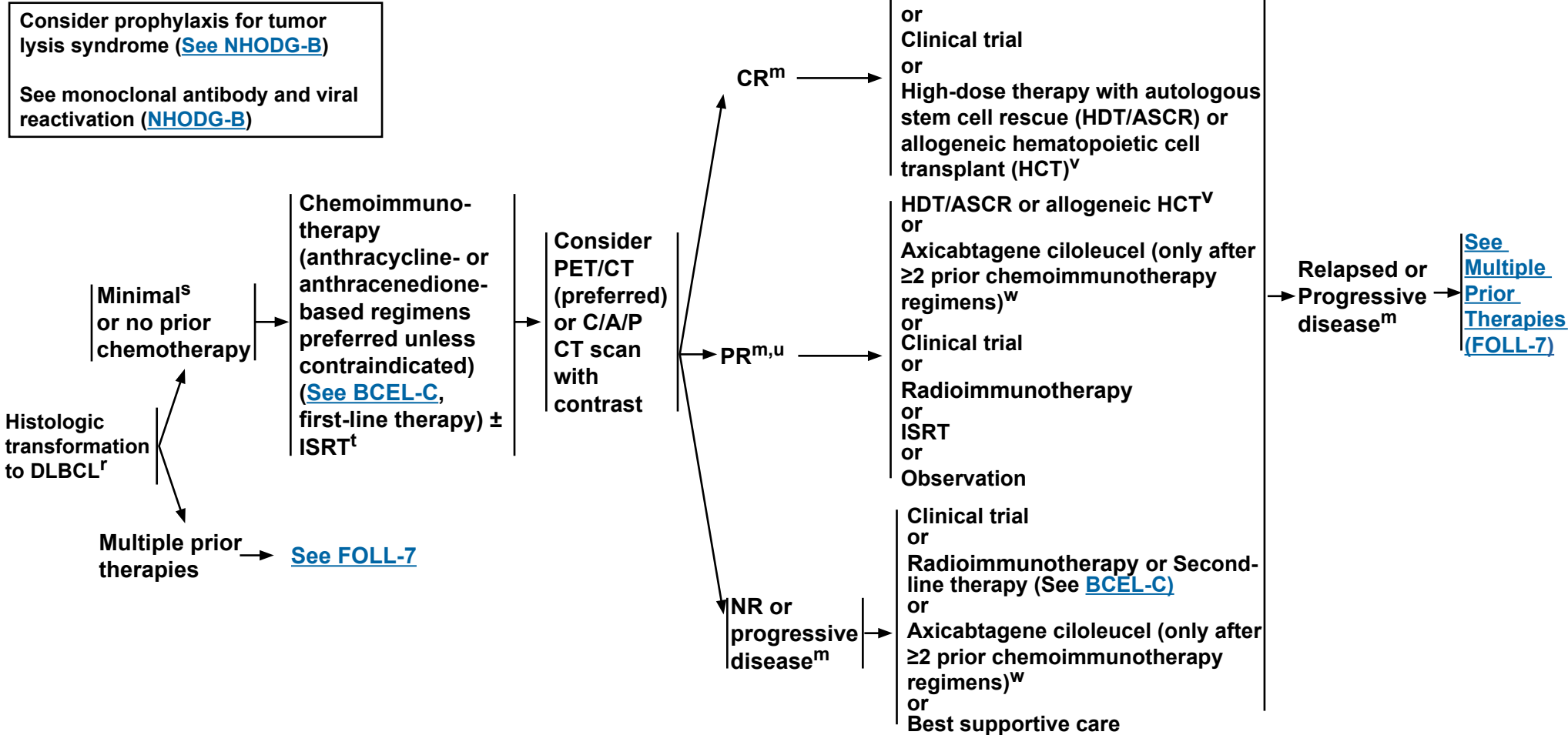
^qA PET-positive PR is associated with a shortened PFS (See Discussion); however, additional treatment at this juncture has not been shown to change outcome.

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HISTOLOGIC TRANSFORMATION TO DIFFUSE LARGE B-CELL LYMPHOMA^r



^mSee [Lugano Response Criteria for Non-Hodgkin's Lymphoma \(NHODG-C\)](#).

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

^sInvolvement-site RT alone or one course of single-agent therapy including rituximab.

^tIf locoregional transformation, consider adding RT.

^uIf proceeding to an autologous stem cell rescue, consider additional cytoreductive therapy to induce CR prior to transplant. Axicabtagene ciloleucel is not an appropriate treatment option for patients with a CR.

^vStrongly recommend this treatment be given in the context of a clinical trial.

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

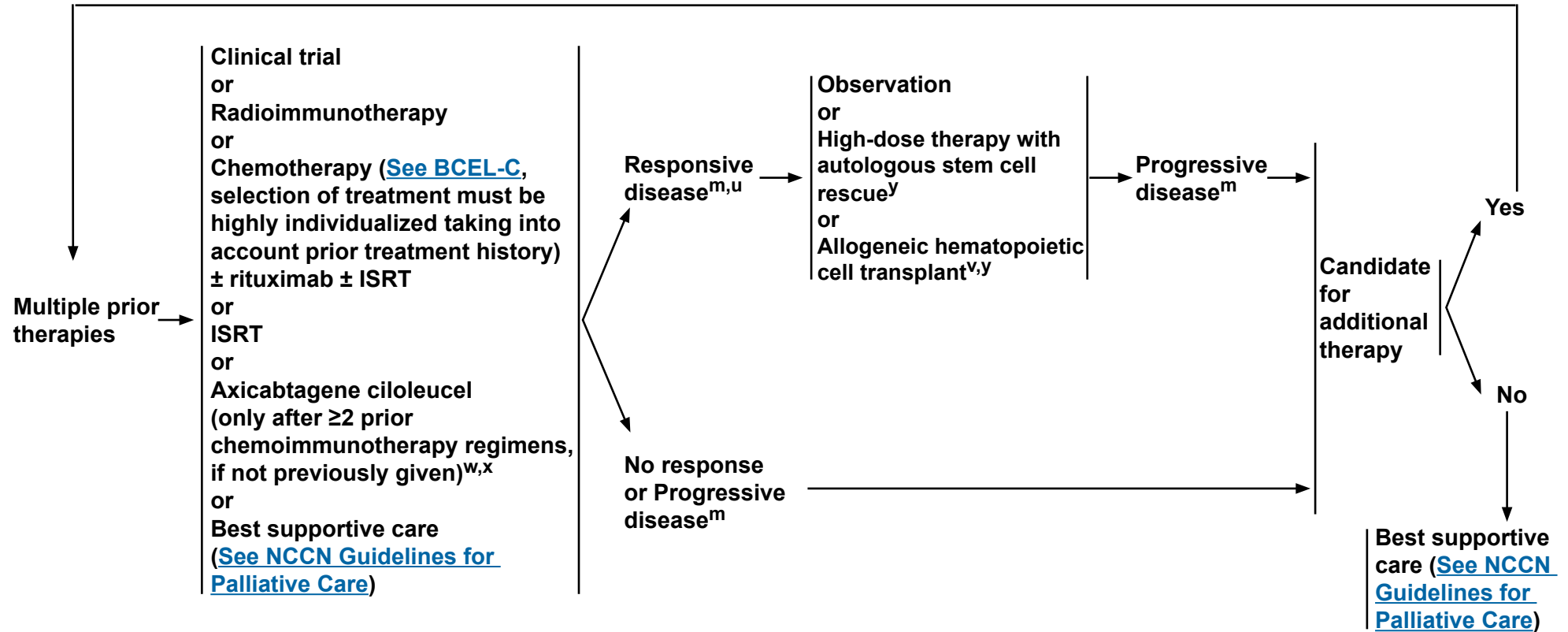
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HISTOLOGIC TRANSFORMATION TO DIFFUSE LARGE B-CELL LYMPHOMA^f



^mSee [Lugano Response Criteria for Non-Hodgkin's Lymphoma \(NHODG-C\)](#).

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

^uIf proceeding to an autologous stem cell rescue, consider additional cytoreductive therapy to induce CR prior to transplant. Axicabtagene ciloleucel is not an appropriate treatment option for patients with a CR.

^vStrongly recommend this treatment be given in the context of a clinical trial.

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

^xPatients should have received at least one anthracycline or anthracenedione-based regimen, unless contraindicated.

^yData on transplant after treatment with axicabtagene ciloleucel are not available. HDT/ASCR is not recommended after axicabtagene ciloleucel. Allogeneic HCT could be considered but remains investigational.

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

See monoclonal antibody and viral reactivation ([NHODG-B](#))

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PEDIATRIC-TYPE FOLLICULAR LYMPHOMA IN ADULTS

PATHOLOGIC AND CLINICAL PRESENTATION^d

- Pathologic
 - ▶ Morphology: expansile follicles, effacement of architecture, absence of diffuse area
 - ▶ Expresses: BCL6, CD10, ±MUM1/IRF4 (~20%)
 - ▶ Proliferation index (Ki-67/MIB-1) >30%
 - ▶ No rearrangement of BCL2, BCL6, MUM1/IRF4
- Clinical
 - ▶ Localized disease (stage I)>> Advanced stage (III/IV)
 - ▶ 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 even over age 60)

STAGING WORKUP

- PET/CT scan
- Bone marrow biopsy

Stage I,II^z

TREATMENT

Excision (preferred) or ISRT or RCHOP

Restage post-RT or chemotherapy with PET/CT

CR^m → Observe^{aa}

<CR → [See FOLL-5, progressive disease](#)

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

See monoclonal antibody and viral reactivation ([NHODG-B](#))

^dIn young patients with localized disease that lack BCL2 expression or t(14;18), consider entity of pediatric-type FL.

Analysis of BCL6 rearrangement may be useful for evaluating the diagnosis of pediatric-type FL.

^m[See Lugano Response Criteria for Non-Hodgkin's Lymphoma \(NHODG-C\).](#)

^zIf the patient has disease >Stage II, it is by definition not PTFL.

^{aa}Patients have an excellent prognosis, no surveillance imaging is necessary.

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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 10⁹/L and/or platelets <100 x 10⁹/L)
- Leukemia (>5.0 x 10⁹/L malignant cells)

FLIPI - 1 CRITERIA^{a,c,d}

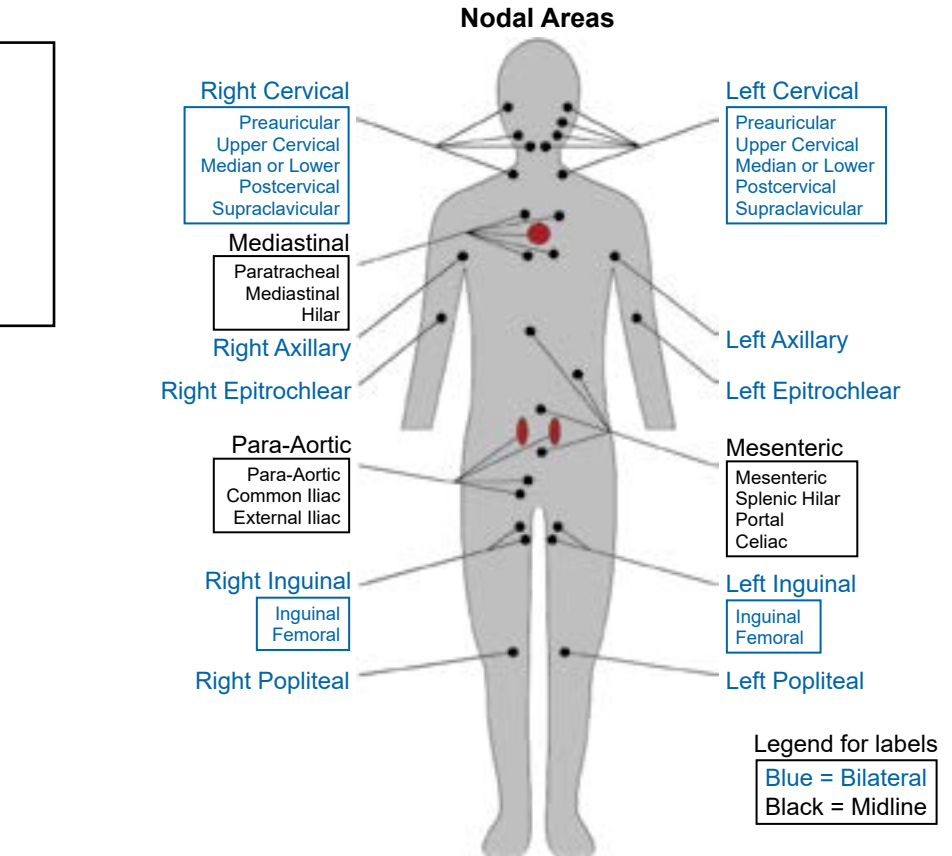
Age	≥60 y
Ann Arbor stage	III-IV
Hemoglobin level	<12 g/dL
Serum LDH level	>ULN (upper limit of normal)
Number of nodal sites ^d	≥5

Risk group according to FLIPI chart

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

^aThis provides useful prognostic information that may be used to guide therapeutic decisions.

^bSolal-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.



Mannequin used for counting the number of involved areas.^e

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^cThis 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.

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

^eThe 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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**SUGGESTED TREATMENT REGIMENS^{a,b,*}**
(in preference order)**First-line Therapy**

- Bendamustine + rituximab (category 1)
- Bendamustine + obinutuzumab^c
- RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)
- CHOP + obinutuzumab^c
- RCVP (rituximab, cyclophosphamide, vincristine, prednisone) (category 1)
- CVP + obinutuzumab^c
- Rituximab (375 mg/m² weekly for 4 doses) (consider for low tumor burden)^d
- Lenalidomide + rituximab (category 2B)

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

- Rituximab (preferred) (375 mg/m² weekly for 4 doses)
- Single-agent alkylators (eg, chlorambucil or cyclophosphamide) ± rituximab
- Radioimmunotherapy^{e,f} (category 2B)

See Evidence Blocks on FOLL-B (EB-1)^aSee references for regimens [FOLL-B 3 of 4](#) and [FOLL-B 4 of 4](#).^bThe 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.^cThe clinical trial evaluating this regimen included obinutuzumab maintenance. The use without maintenance was an extrapolation of the data.^dRituximab 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).^eSelection 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 radioimmunotherapy.**First-line Consolidation or Extended Dosing (optional)**

- Rituximab maintenance 375 mg/m² one dose every 8 wks for 12 doses for patients initially presenting with high tumor burden (category 1)^g
- 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
- Radioimmunotherapy (after induction with chemotherapy or chemoimmunotherapy)^{e,f,h} (category 2B)

[See Second-line and Subsequent Therapy on FOLL-B 2 of 4](#)**Consider prophylaxis for tumor lysis syndrome (See NHODG-B)**
See monoclonal antibody and viral reactivation (NHODG-B)^{*}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 ibrutinomab tiuxetan.^fIf radioimmunotherapy 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. Cytogenetics ± FISH for known MDS markers. As of 2010, updates suggest a trend towards an increased risk of MDS with RIT.^gThis is based on the PRIMA study for patients with high tumor burden treatment with RCVP and RCHOP. There are no data following other regimens.^hThe full impact of an induction regimen containing rituximab on RIT consolidation is unknown.**Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.****All recommendations are category 2A unless otherwise indicated.****Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**



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Follicular Lymphoma^a (grade 1-2)

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	E	S	Q	C	A

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

First-Line Therapy

	Stage I-II	Stage III-IV
Bendamustine + rituximab		
Bendamustine + rituximab + ISRT		—
Bendamustine + obinutuzumab		
Bendamustine + obinutuzumab + ISRT		—
RCHOP		
RCHOP + ISRT		—
CHOP + obinutuzumab		
CHOP + obinutuzumab + ISRT		—
RCVP		
RCVP + ISRT		—
CVP + obinutuzumab		
CVP + obinutuzumab + ISRT		—
Rituximab (for low tumor burden)		
Rituximab + ISRT (for low tumor burden)		—
Lenalidomide + rituximab		
Lenalidomide + rituximab + ISRT		—

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		—
Radioimmunotherapy		

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)	
Radioimmunotherapy	

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

All recommendations are category 2A unless otherwise indicated.

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

**SUGGESTED TREATMENT REGIMENS^{a,b,*}**
(in preference order)**Second-line and Subsequent Therapy**

- Chemoimmunotherapy (as listed under first-line therapy)
- Rituximab
- Lenalidomide ± rituximab
- Bendamustine + obinutuzumab
- Radioimmunotherapy^{e,f} (category 1)
- Idelalisibⁱ (refractory to both alkylator and rituximab)
- Copanlisibⁱ (refractory to at least 2 prior therapies)
- Fludarabine^j + rituximab
- RFND^{j,k} (rituximab, fludarabine, mitoxantrone, dexamethasone)
- [See Second-line Therapy for DLBCL \(BCEL-C 2 of 4\)](#) without regard to transplantability

Second-line Consolidation or Extended Dosing (optional)

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

[See Evidence Blocks on FOLL-B \(EB-2\)](#)**Consider prophylaxis for tumor lysis syndrome ([See NHODG-B](#))
See monoclonal antibody and viral reactivation ([NHODG-B](#))**^aSee references for regimens [FOLL-B 3 of 4](#) and [FOLL-B 4 of 4](#).^bThe 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.^eSelection 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 radioimmunotherapy.

*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.

^fIf radioimmunotherapy 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. Cytogenetics ± FISH for known MDS markers. As of 2010, updates suggest a trend towards an increased risk of MDS with RIT.ⁱ[See Special Considerations for the Use of Small-Molecule Inhibitors \(NHODG-E\)](#).^jFludarabine-containing regimens negatively impact stem cell mobilization for transplant.^kRFND regimen may be associated with stem cell toxicity and secondary malignancies (see Discussion).**Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page [EB-1](#).****All recommendations are category 2A unless otherwise indicated.****Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

5		E = Efficacy of Regimen/Agent
4		S = Safety of Regimen/Agent
3		Q = Quality of Evidence
2		C = Consistency of Evidence
1		A = Affordability of Regimen/Agent
	E S Q C A	

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

Second-Line Therapy

Bendamustine + rituximab	
Bendamustine + obinutuzumab	
RCHOP	
CHOP + obinutuzumab	
RCVP	
CVP + obinutuzumab	
Rituximab	
Lenalidomide + rituximab	
Lenalidomide	
Radioimmunotherapy	
Idelalisib	
Copanlisib	
Fludarabine + rituximab	
Fludarabine, mitoxantrone, dexamethasone, and rituximab	

CEOP	
CEOP + rituximab	
CEPP	
CEPP + rituximab	
DHAP	
DHAP + rituximab	
Dose-adjusted EPOCH	
Dose-adjusted EPOCH + rituximab	
ESHAP	
ESHAP + rituximab	
GDP	
GDP + rituximab	

Gemcitabine and vinorelbine	
Gemcitabine, dexamethasone, and carboplatin	
Gemcitabine, dexamethasone, and carboplatin + rituximab	
Gemcitabine, vinorelbine, and rituximab	
GemOx	
GemOx + rituximab	
ICE	
ICE + rituximab	
MINE	
MINE + rituximab	

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)	

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page [EB-1](#).
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

**SUGGESTED TREATMENT REGIMENS****References****First-line Therapy****Bendamustine + rituximab**

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

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

Bendamustine + obinutuzumab

Marcus RE, Davies AJ, Ando K, et al. Obinutuzumab-Based Induction and Maintenance Prolongs Progression-Free Survival (PFS) in Patients with Previously Untreated Follicular Lymphoma: Primary Results of the Randomized Phase 3 GALLIUM Study [abstract]. *Blood* 2017;128:Abstract 6.

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 RE, Davies AJ, Ando K, et al. Obinutuzumab-Based Induction and Maintenance Prolongs Progression-Free Survival (PFS) in Patients with Previously Untreated Follicular Lymphoma: Primary Results of the Randomized Phase 3 GALLIUM Study [abstract]. *Blood* 2017;128:Abstract 6.

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 RE, Davies AJ, Ando K, et al. Obinutuzumab-Based Induction and Maintenance Prolongs Progression-Free Survival (PFS) in Patients with Previously Untreated Follicular Lymphoma: Primary Results of the Randomized Phase 3 GALLIUM Study [abstract]. *Blood* 2017;128:Abstract 6.

Rituximab

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

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

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

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

Lenalidomide + rituximab

Martin P, Jung S-H, Johnson JL, et al. CALGB 50803 (Alliance): A phase II trial of lenalidomide plus rituximab in patients with previously untreated follicular lymphoma [abstract]. *J Clin Oncol* 2014;32:Abstract 8521.

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

Radioimmunotherapy

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

First-line Consolidation or Extended Dosing**Chemoimmunotherapy followed by rituximab maintenance**

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

Salles G, Seymour JF, Feugier P, et al. Updated 6 year follow-up of the PRIMA study confirms the benefit of 2-year rituximab maintenance in follicular lymphoma patients responding to frontline immunochemotherapy [abstract]. *Blood* 2013;122:Abstract 509.

Extended dosing with rituximab

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

Obinutuzumab-based chemoimmunotherapy followed by obinutuzumab maintenance

Marcus RE, Davies AJ, Ando K, et al. Obinutuzumab-Based Induction and Maintenance Prolongs Progression-Free Survival (PFS) in Patients with Previously Untreated Follicular Lymphoma: Primary Results of the Randomized Phase 3 GALLIUM Study [abstract]. *Blood* 2017;128:Abstract 6.

Radioimmunotherapy (after induction with chemotherapy or chemoimmunotherapy)

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

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

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page [EB-1](#).

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

[Continued on next page](#)

**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* 2017;17:1081-1093.

Copanlisib

Dreyling M, Santoro A, Leppä S, et al. Copanlisib in patients with relapsed or refractory indolent B-cell lymphoma: primary results of the pivotal Chronos-1 study [abstract]. AARC Meeting 2017; Abstract CT149.

Fludarabine + rituximab

Czuczman MS, Koryzna A, Mohr A, et al. Rituximab in combination with fludarabine chemotherapy in low-grade of follicular lymphoma. *J Clin Oncol* 2005;23:694-704.

Idelalisib

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

Lenalidomide ± rituximab

Leonard JP, Jung SH, Johnson J, et al. Randomized Trial of Lenalidomide Alone Versus Lenalidomide Plus Rituximab in Patients With Recurrent Follicular Lymphoma: CALGB 50401 (Alliance). *J Clin Oncol*. 2015;33:3635-3640.

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

Radioimmunotherapy

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

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

Rituximab

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

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

RFND (rituximab, fludarabine, mitoxantrone, dexamethasone)

McLaughlin P, Hagemeister FB, Rodriguez MA, et al. Safety of fludarabine, mitoxantrone, and dexamethasone combined with rituximab in the treatment of stage IV indolent lymphoma. *Semin Oncol* 2000;27:37-41.

Second-line Consolidation or Extended Dosing**Rituximab maintenance**

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

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

Obinutuzumab maintenance for rituximab refractory disease

Sehn LH, Chua N, Mayer J, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. *Lancet Oncol* 2017;17:1081-1093.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page [EB-1](#).

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**DIAGNOSIS^{a,b}****ESSENTIAL:**

- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis.
- Adequate immunophenotyping to establish diagnosis and GCB versus non-GCB origin^{c,d}
 - ▶ IHC panel: CD20, CD3, CD5, CD10, CD45, BCL2, BCL6, Ki-67, IRF4/MUM1, MYC with or without
 - ▶ Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD3, CD5, CD19, CD10, CD20

USEFUL UNDER CERTAIN CIRCUMSTANCES:

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

^aBurkitt lymphoma intermediate histology or DLBCL CD10+ tumors with very high proliferation >90% with or without Burkitt lymphoma-like features might be considered for more aggressive treatment as per [BURK-A](#).

^b[See International Prognostic Index \(BCEL-A\)](#).

^cTypical immunophenotype: CD20+, CD45+, CD3-; other markers used for subclassification.

SUBTYPES

- Subtypes included:
 - ▶ DLBCL, NOS^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 of the elderly
 - ▶ T-cell-/histiocyte-rich large B-cell lymphoma
- Subtypes *not* included:
 - ▶ Primary cutaneous B-cell lymphomas ([See NCCN Guidelines for Primary Cutaneous B-Cell Lymphomas](#))
 - ▶ Primary DLBCL of the CNS ([See NCCN Guidelines for CNS](#))

Primary Mediastinal Large B-Cell Lymphoma (PMBL), [see BCEL-B 1 of 4](#).

Grey Zone Lymphoma, [see BCEL-B 2 of 4](#).

Double Hit Lymphomas, [see BCEL-B 3 of 4](#).

Primary Cutaneous B-cell Lymphomas, Leg type, [see BCEL-B 4 of 4](#).

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

^eCases 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.

^fGerminal 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.

^gControversy exists regarding management of FL grade 3. Some may treat FL grade 3a as follicular lymphoma and others may treat it as DLBCL.

^hThese are most often CD20 negative and rituximab is not necessary.

→ [See Workup \(BCEL-2\)](#)

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page [EB-1](#).

All recommendations are category 2A unless otherwise indicated.

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

**WORKUP****ESSENTIAL:**

- **Physical exam:** attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- **Performance status**
- **B symptoms**
- **CBC, differential, platelets**
- **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 testingⁱ**
- **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**
- **Lumbar puncture, consider if have 4–6 factors according to prognostic model (See [BCEL-A 2 of 2](#)), HIV lymphoma, testicular, double expressor lymphoma**
- **Beta-2-microglobulin**

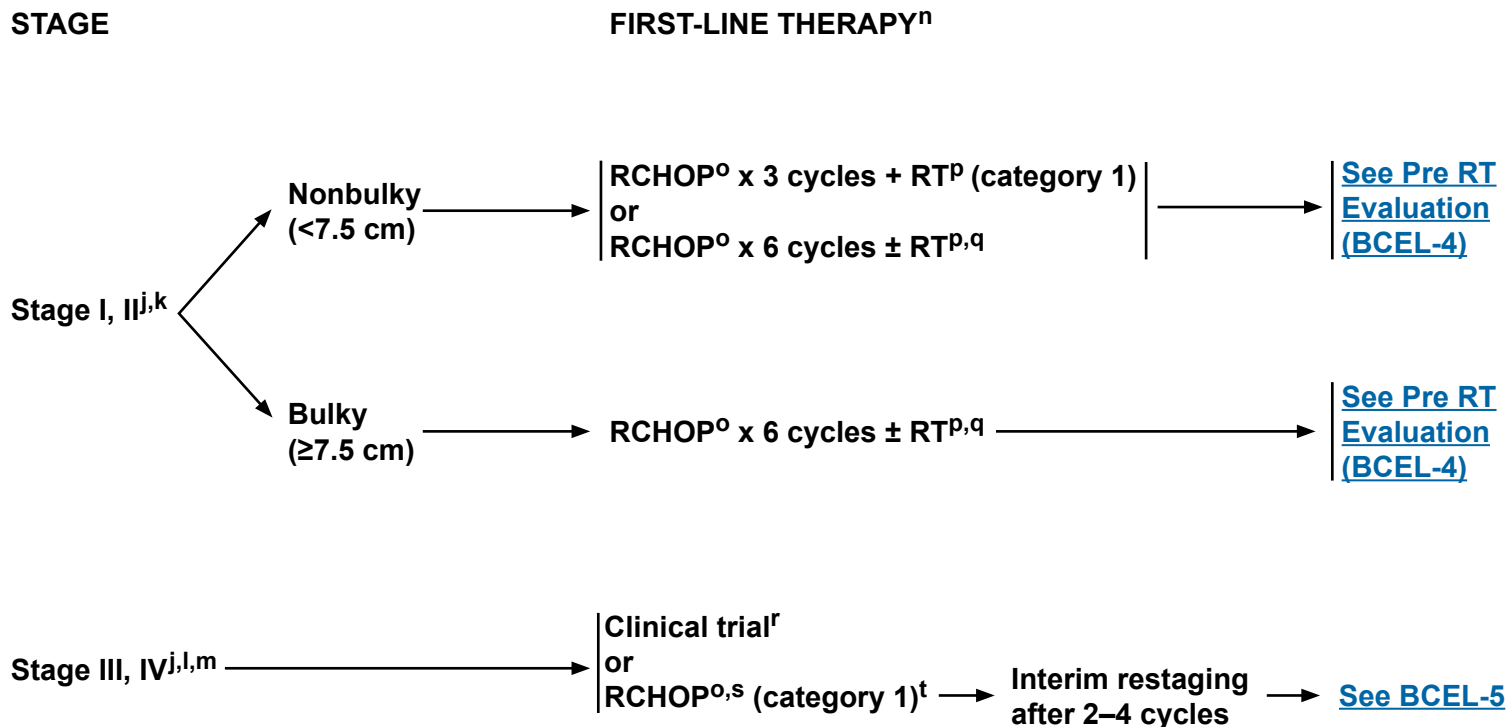
→ [See Induction Therapy \(BCEL-3\)](#)

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

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page [EB-1](#).

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

See monoclonal antibody and viral reactivation (NHODG-B)

^jIn testicular lymphoma, after completion of chemotherapy, scrotal RT should be given (25–30 Gy).

^kIn patients who are not candidates for chemotherapy, involved-site radiation therapy (ISRT) is recommended.

^lIn selected cases (4–6 factors according to prognostic model, HIV lymphoma, testicular, double hit lymphoma), there may be an increased risk of CNS events. The optimal management of these events is uncertain, but CNS prophylaxis can be considered with 4–8 doses of intrathecal methotrexate and/or cytarabine, or systemic methotrexate (3–3.5 g/m²) during the course of treatment. Recent data regarding stage IE DLBCL of the breast have been suggested as a potential risk for CNS disease. [See Prognostic Model to Assess the Risk of CNS Disease \(BCEL-A 2 of 2\)](#).

^mFor systemic disease with concurrent CNS disease, [see BCEL-C](#).

ⁿRecommendations are for HIV-negative lymphoma only.

For HIV-positive DLBCL, [see AIDS-2](#).

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

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

^qIf RT is not used, interim staging after 3–4 cycles of RCHOP is appropriate to confirm response.

^rMay include high-dose therapy.

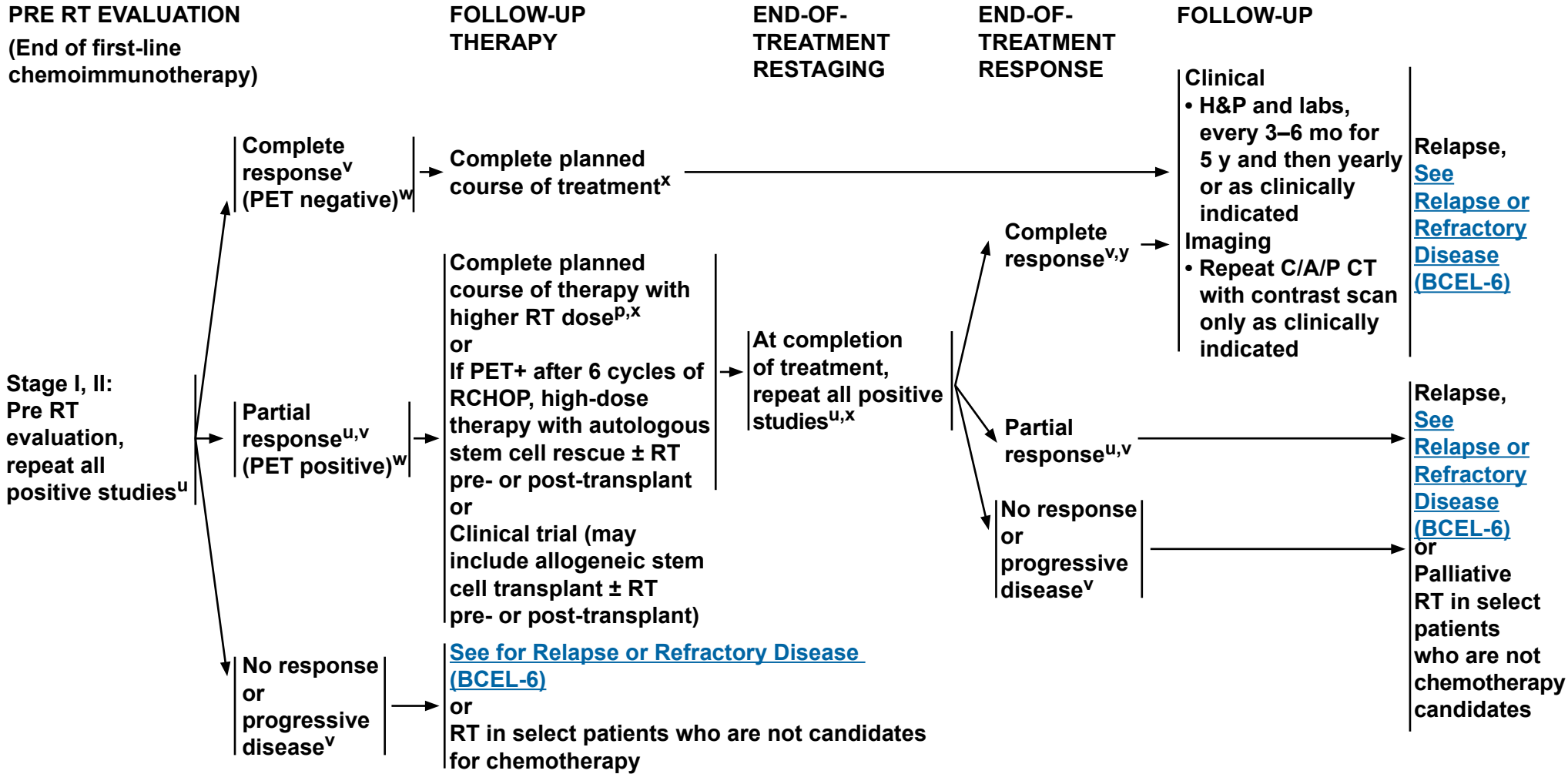
^sBased on current clinical trials, RCHOP is preferable due to reduced toxicities, but other comparable anthracycline-based regimens are also acceptable ([see BCEL-C](#)).

^tIn selected cases, RT to initially bulky sites of disease may be beneficial (category 2B).

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^pSee Principles of Radiation Therapy (NHODG-D).

^uRepeat biopsy should be strongly considered if PET-positive prior to additional therapy. If biopsy negative, follow PET-negative guideline.

^vSee Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).

^wPET/CT scan should be interpreted via the PET Five Point Scale (See NHODG-C 3 of 3).

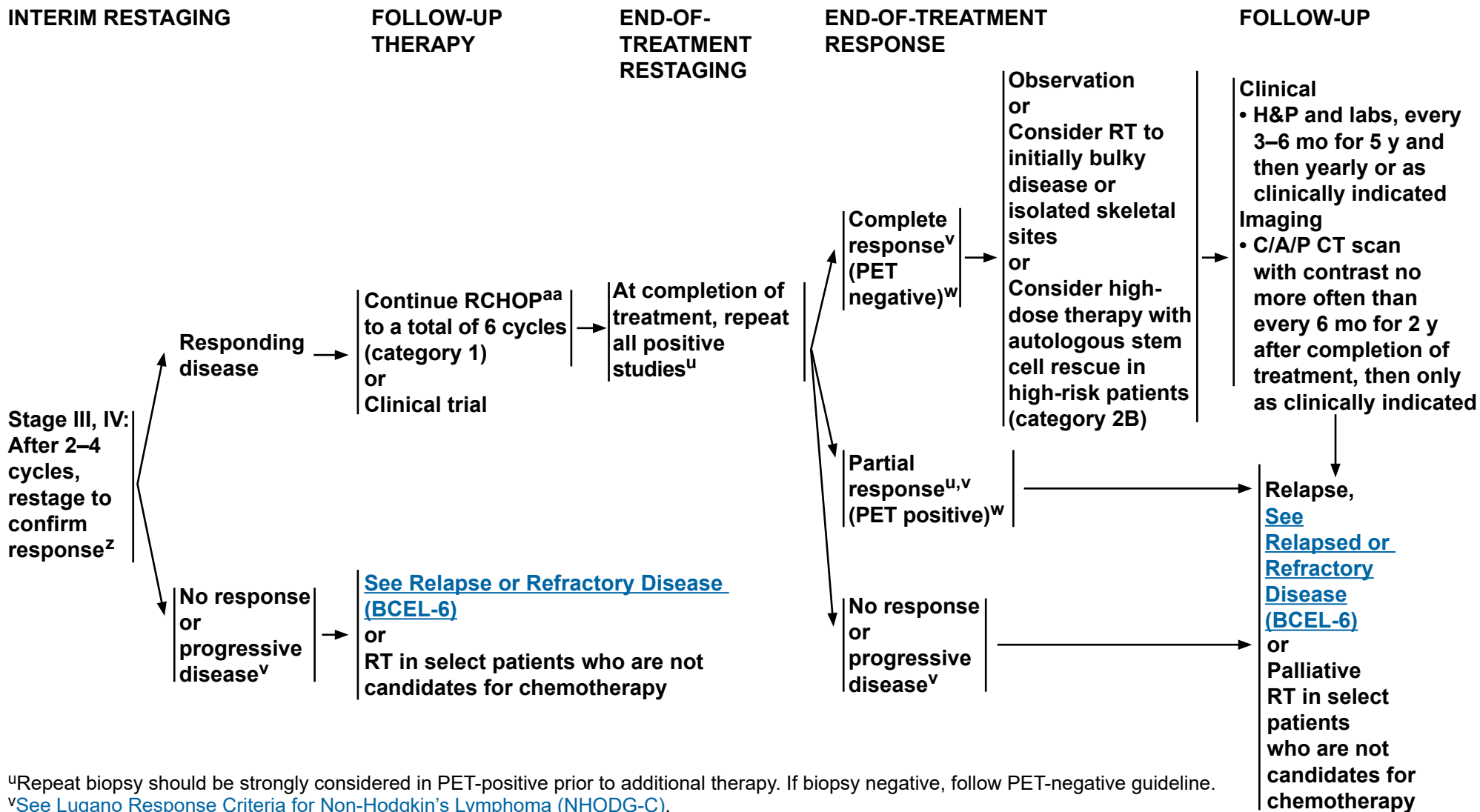
^xThe optimum timing of end-of-treatment PET/CT is unknown; however, waiting a minimum of 8 weeks after RT to repeat PET/CT scan is suggested. False positives may occur due to posttreatment changes.

^yPatients in first remission may be candidates for consolidation trials including high-dose therapy with autologous stem cell rescue.

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All recommendations are category 2A unless otherwise indicated.

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



^uRepeat biopsy should be strongly considered in PET-positive prior to additional therapy. If biopsy negative, follow PET-negative guideline.

^vSee [Lugano Response Criteria for Non-Hodgkin's Lymphoma \(NHODG-C\)](#).

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

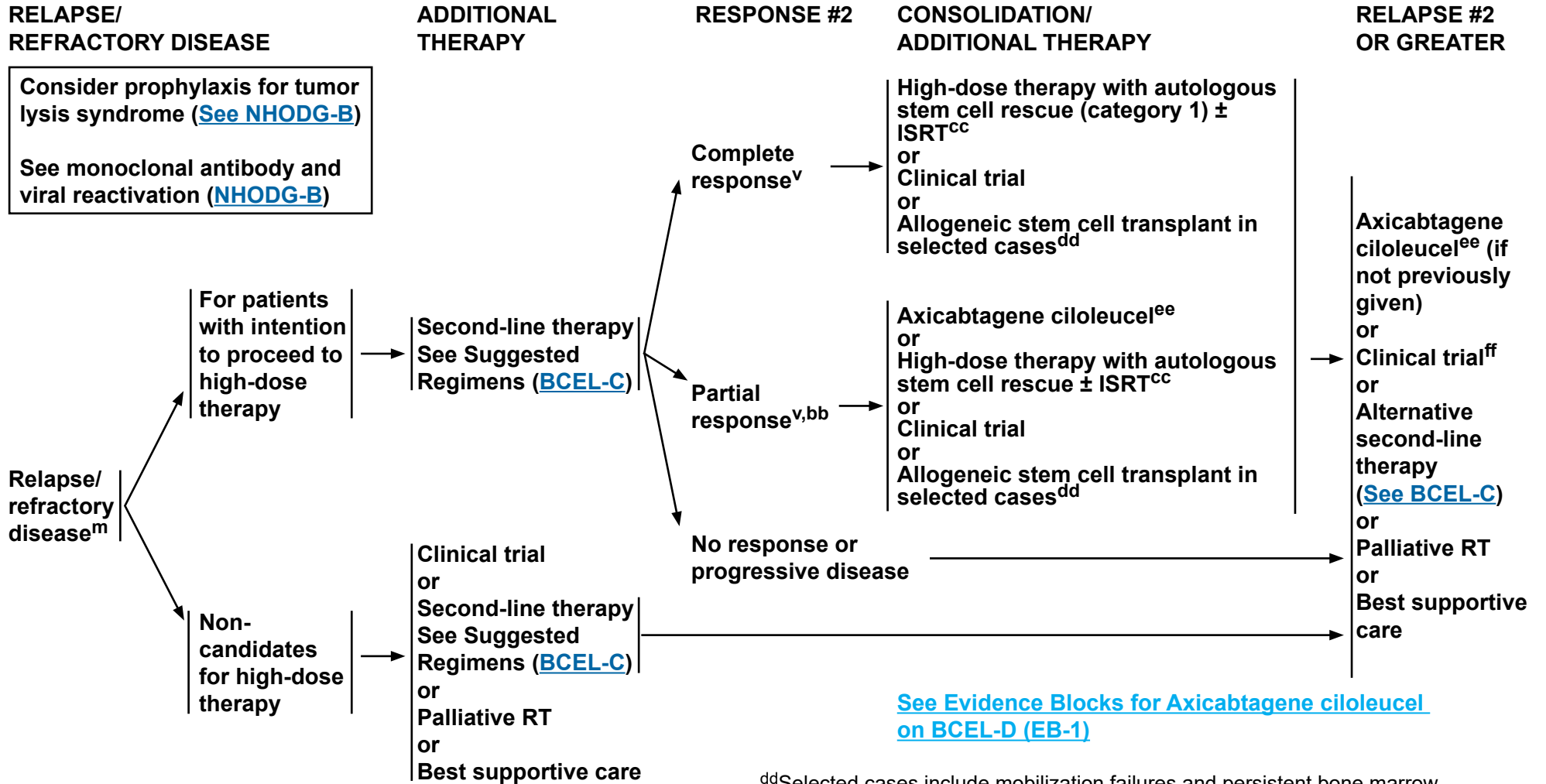
^zPET/CT scan at interim restaging can lead to increased false positives and should be carefully considered in select cases. If PET/CT scan performed and positive, rebiopsy before changing course of treatment.

^{aa}For other regimens, [see BCEL-C](#).

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

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



^mFor systemic disease with concurrent CNS disease, [see BCEL-C](#).

^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 high-dose therapy with stem cell rescue 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}Clinical trials or individual regimens: Patients who progress after three successive regimens are unlikely to derive additional benefit from currently utilized combination chemotherapy regimens, except for patients with a long disease-free interval.

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

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



NCCN Guidelines Version 7.2017

Diffuse Large B-Cell Lymphoma

NCCN Evidence Blocks™

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-ADJUSTED 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.

^aThe International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-hodgkin's lymphoma. N Engl J Med 1993; 329:987-994.

^bMiller 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.

^cThis research was originally published in *Blood*. Zhou Z, Sehn LH, Rademaker AW, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. *Blood* 2014;123:837-842. © the American Society of Hematology

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

All recommendations are category 2A unless otherwise indicated.

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

[Back to Workup \(BCEL-2\)](#)



Prognostic Model to Assess the Risk of CNS Disease^{a,b}

• Age >60 years	Low risk	0–1
• Serum LDH > normal	Intermediate-risk	2–3
• Performance status >1	High-risk	4–6
• Stage III or IV		
• Extranodal involvement >1 site		
• Kidney or adrenal gland involvement		

^aSchmitz N, Zeynalova S, Nickelsen M, et al. A new prognostic model to assess the risk of CNS disease in patients with aggressive B-cell lymphoma [abstract]. *Hematol Oncol* 2013;31 (Suppl. 1):96-150; Abstract 047.

^bSavage K, et al Validation of a prognostic model to assess the risk of CNS disease in patients with aggressive B-cell lymphoma [abstract]. *Blood* 2014;124:Abstract 394.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page [EB-1](#).

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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 \(BCEL-B 2 of 4\)](#).
- **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):**
 - ▶ **Dose-adjusted EPOCH-R ([etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin] + rituximab)^a 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)^b x 3 cycles ± RT (category 2B)**
- **Role of RT 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 disease, see [BCEL-6](#).**

*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.

^aDunleavy 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.

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

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page [EB-1](#).

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**Grey Zone Lymphoma^{a,b,c,*}**
(intermediate between DLBCL and classical HL)**Synonyms**

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

Clinical Presentation

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

Morphology

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

Immunophenotype

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

Prognosis and Treatment

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

*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.

^aDunleavy K, Pittaluga S, Tay K, et al. Comparative clinical and biological features of primary mediastinal B-cell lymphoma (PMBL) and mediastinal grey zone lymphoma (MGZL) [abstract]. Blood 2009;114:Abstract 106.

^bJaffe ES, Stein H, Swerdlow SH, et al. B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:267-268.

^cQuintanilla-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.

^dEvens 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.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page [EB-1](#).

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

**Double Hit Lymphomas*****Definition**

- **Double Hit (Double Rearrangements):**
 - ▶ DLBCL or HGB-NOS (intermediate between DLBCL and BL) with *MYC* rearrangement plus *BCL2* and/or *BCL6* rearrangements (as detected by FISH or standard cytogenetics) are known as "double-hit" lymphomas (if all three are rearranged, they are referred to as "triple-hit" lymphomas).
 - ▶ Vast majority are germinal center B-cell–like lymphomas

Clinical Presentation

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

Treatment

- Clinical trial is recommended.
- While the standard of care is not established, the following regimens have been used at NCCN Member Institutions:
 - ▶ DA-EPOCH-R
 - ▶ RHyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab
 - ▶ 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-6](#).

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

References:

- Petrich A, Gandhi M, Jovanovic B, et al. Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. *Blood* 2014;124:2354-2361.
- Dunleavy K, Fanale M, LaCasce A, et al. Preliminary report of a multicenter prospective phase II study of DA-EPOCH-R in MYC-rearranged aggressive B-cell lymphoma [abstract]. *Blood* 2014: Abstract 395.
- Johnson NA, Slack GW, Savage KJ et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J Clin Oncol* 2012;30:3452-3459.
- Green TM, Young KH, Visco C, et al. Immunohistochemical double-hit score is a strong predictor of outcome in patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J Clin Oncol* 2012;30:3460-3467.

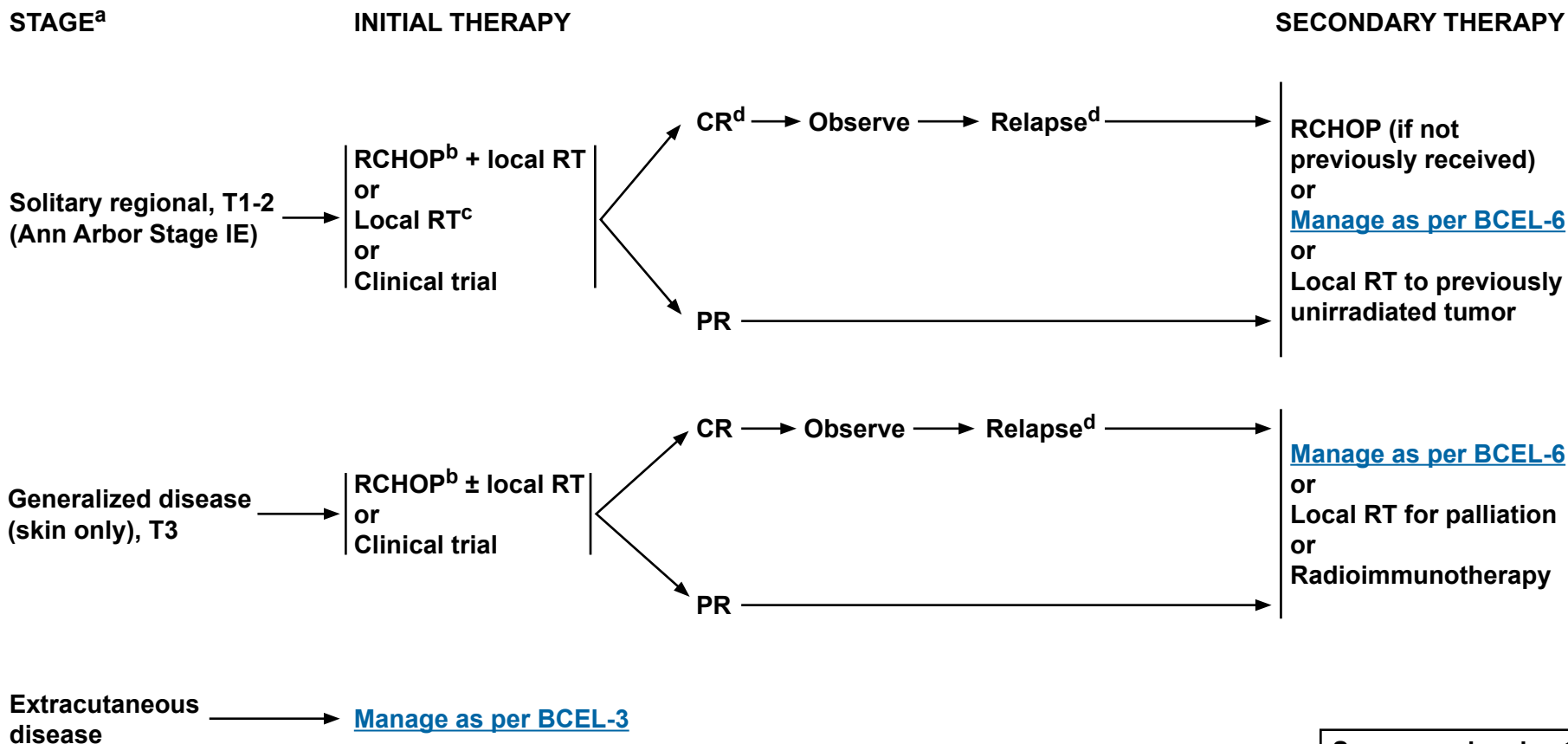
Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page [EB-1](#).

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PRIMARY CUTANEOUS DIFFUSE LARGE B-CELL LYMPHOMA, LEG TYPE*



See monoclonal antibody and viral reactivation ([NHODG-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.

^aFor TNM Classification of Cutaneous Lymphoma other than MF/SS (See NCCN Guidelines for T-Cell Lymphomas and Cutaneous B-Cell Lymphoma).

^bFor patients who cannot tolerate anthracyclines, see [BCEL-C](#) for regimens for patients with poor left ventricular function.

^cFor patients not able to tolerate chemotherapy.

^d 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.

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**SUGGESTED TREATMENT REGIMENS^{a,*}**
(in alphabetical order)**First-line Therapy**

- **RCHOP (rituximab,^b cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)**
- **Dose-dense RCHOP 14^b (category 3)**
- **Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab (category 2B)**

First-line Therapy for Patients with Poor Left Ventricular Function or Very Frail^{c,d,e}

- **RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine)**
- **RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, prednisone)**
- **DA-EPOCH^f (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab**
- **RCEOP (rituximab, cyclophosphamide, etoposide, vincristine, prednisone)**
- **RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, prednisolone)**

Patients >80 Years of Age with Comorbidities^e

- **R-mini-CHOP**
- **RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, prednisolone)**

First-line Consolidation (optional)

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

Concurrent Presentation with CNS Disease

- **Parenchymal: 3 g/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 and/or systemic methotrexate (3–3.5 g/m²)**

*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.

^aSee references for regimens [BCEL-C 3 of 4](#) and [BCEL-C 4 of 4](#).

^bIn RCHOP-14 and RCHOP-21, may consider increasing dose of rituximab to 500 mg/m² in men >60 y.

^cInclusion of any anthracycline or anthracenedione in patients with impaired cardiac functioning should have more frequent cardiac monitoring.

^dThere 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.

^eThere 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 Institutions.

^fIf upward dose adjustment is necessary, doxorubicin should be maintained at base dose and not increased.

[See Evidence Blocks on BCEL-C \(EB-2\)](#)
[See Second-line Therapy on BCEL-C 2 of 4.](#)

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

See monoclonal antibody and viral reactivation ([NHODG-B](#))

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page [EB-1](#).

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5		E = Efficacy of Regimen/Agent
4		S = Safety of Regimen/Agent
3		Q = Quality of Evidence
2		C = Consistency of Evidence
1		A = Affordability of Regimen/Agent
	E S Q C A	

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		

Patients with Poor Left Ventricular Function or Very Frail	
RCEPP + RT	
RCDOP + RT	
DA-EPOCH + rituximab + RT	
RCEOP + RT	
RGCVP + RT	
Patients >80 Years of Age with Comorbidities	
R-mini-CHOP + RT	
RGCVP + RT	

First-line Consolidation for Patients 60–80 Years of Age

Lenalidomide maintenance	
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Stage III-IV

RCHOP	
Dose-dense RCHOP 14	
Dose-adjusted EPOCH + rituximab	

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

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**SUGGESTED TREATMENT REGIMENS^{a,*}**
(in alphabetical order)**Second-line and Subsequent Therapy^{c,g,h} (intention to proceed to high-dose therapy)**

- DHAP (dexamethasone, cisplatin, cytarabine) ± rituximab
- ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± rituximab
- GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab
- GemOx (gemcitabine, oxaliplatin) ± rituximab
- ICE (ifosfamide, carboplatin, etoposide) ± rituximab
- MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± rituximab

Second-line and Subsequent Therapy^{c,g,h} (non-candidates for high-dose therapy)

- Bendamustine ± rituximab
- Brentuximab vedotin for CD30+ disease (category 2B)
- CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) ± rituximab - PO and IV
- CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± rituximab
- DA-EPOCH ± rituximab
- GDP ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab
- GemOx ± rituximab
- Gemcitabine, vinorelbine ± rituximab (category 3)
- Lenalidomide ± rituximab (non-GCB DLBCL)
- Rituximab

See First-line Therapy on [BCEL-C 1 of 4](#).

[See Evidence Blocks on BCEL-C \(EB-2\)](#)

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

See monoclonal antibody and viral reactivation ([NHODG-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.

^aSee references for regimens [BCEL-C 3 of 4](#) and [BCEL-C 4 of 4](#).

^cInclusion of any anthracycline or anthracenedione in patients with impaired cardiac functioning should have more frequent cardiac monitoring.

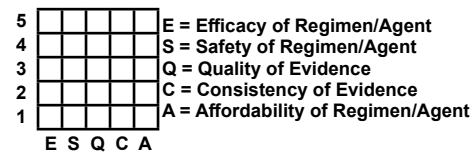
^gIf additional anthracycline is administered after a full course of therapy, careful cardiac monitoring is essential. Dexrazoxane may be added as a cardioprotectant.

^hRituximab 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.

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EVIDENCE BLOCKS FOR SECOND-LINE AND SUBSEQUENT THERAPY

Candidates for HDT/ASCR

DHAP	
DHAP + rituximab	
ESHAP	
ESHAP + rituximab	
GDP	
GDP + rituximab	
GemOx	
GemOx + rituximab	
ICE	
ICE + rituximab	
MINE	
MINE + rituximab	

Non-Candidates for HDT/ASCR

Bendamustine	
Bendamustine + rituximab	
Brentuximab vedotin for CD30+ disease	
CEPP	
CEPP + rituximab	
CEOP	
CEOP + rituximab	
DA-EPOCH	
DA-EPOCH + rituximab	
GDP	
GDP + rituximab	

Gemcitabine/dexamethasone/ carboplatin	
Gemcitabine/dexamethasone/ carboplatin + rituximab	
GemOx	
GemOx + rituximab	
Gemcitabine/vinorelbine	
Gemcitabine/vinorelbine + rituximab	
Lenalidomide	
Lenalidomide + rituximab	
Rituximab	

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

**SUGGESTED TREATMENT REGIMENS****References****First-line Therapy****CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab with RT**

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

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

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

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

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

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

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

Dose-dense CHOP 14 + rituximab

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

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

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

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

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

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

First-line Therapy for Patients with Poor Left Ventricular Function

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

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

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

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

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

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

First-line Therapy for Elderly Patients (age >80 years)**R-mini-CHOP**

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

First-line Consolidation

Thieblemont C, Tilly H, Gomes da Silva M, et al. Lenalidomide Maintenance Compared With Placebo in Responding Elderly Patients With Diffuse Large B-Cell Lymphoma Treated With First-Line Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone. *J Clin Oncol* 2017;35:2473-2481.
Stiff PJ, Unger JM, Cook JR, et al. Autologous transplantation as consolidation for aggressive non-Hodgkin's lymphoma. *N Engl J Med* 2013;369:1681-1690.

[Continued on next page](#)

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page [EB-1](#).

All recommendations are category 2A unless otherwise indicated.

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

**SUGGESTED TREATMENT REGIMENS****References****Second-line and Subsequent Therapy****Bendamustine ± rituximab**

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

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

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

Brentuximab vedotin

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

DHAP (dexamethasone, cisplatin, cytarabine) ± rituximab

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

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

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

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

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

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

GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab

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

GDP (gemcitabine, dexamethasone, carboplatin) ± rituximab

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

GemOX (gemcitabine, oxaliplatin) ± rituximab

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

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

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

Gemcitabine, vinorelbine, rituximab

Papageorgiou ES, Tsigotis 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.

ICE (ifosfamide, carboplatin, etoposide) ± rituximab

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

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

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

Lenalidomide ± rituximab

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

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

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

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

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

EPOCH + rituximab

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

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

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page [EB-1](#).

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**GUIDANCE FOR TREATMENT OF PATIENTS WITH CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY****AXICABTAGENE CILOLEUCEL****• Patient selection**

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

• Cytokine release syndrome (CRS) management^a ([See Table 1 \(BCEL-D 2 of 3\) for the grading and management of CRS](#))

- ▶ Median time to onset was 2 days (range: 1–12 days). Median duration was 7 days (range: 2–58 days).
- ▶ Manifestations of CRS include fever, hypotension, tachycardia, hypoxia, and chills. Serious events may include atrial fibrillation and ventricular tachycardia, cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome.

• Neurologic toxicity management^a ([See Table 2 \(BCEL-D 3 of 3\) for the grading and management of neurologic toxicities](#))

- ▶ Median time to onset was 4 days (range: 1–43 days). Median duration was 17 days.
- ▶ The most common neurologic toxicities included encephalopathy, headache, tremor, dizziness, aphasia, delirium, insomnia, and anxiety. Serious events including leukoencephalopathy and seizures occurred with axicabtagene ciloleucel. Fatal and serious cases of cerebral edema have occurred in patients treated with axicabtagene ciloleucel.

• Prolonged cytopenias^a

- ▶ Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and axicabtagene ciloleucel infusion.

• Hypogammaglobulinemia^a

- ▶ B-cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment with axicabtagene ciloleucel.

^aPrescribing information for axicabtagene ciloleucel is available at: <https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM581226.pdf>.

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**GUIDANCE FOR TREATMENT OF PATIENTS WITH CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY****AXICABTAGENE CILOLEUCEL****Table 1. CRS Grading and Management Guidance^a**

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

^aPrescribing information for axicabtagene ciloleucel is available at: <https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM581226.pdf>.

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

^cSee Table 2 for Neurologic Toxicity Grading and Management Guidance (BCEL-D 3 of 3).

^dRefer to the prescribing information for tocilizumab for details.

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**GUIDANCE FOR TREATMENT OF PATIENTS WITH CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY****AXICABTAGENE CILOLEUCEL****Table 2. Neurologic Toxicity Grading and Management Guidance^a**

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

See Table 1 for CRS Grading and Management Guidance (BCEL-D 2 of 3).^aPrescribing information for axicabtagene ciloleucel is available at: <https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM581226.pdf>.^dRefer to the prescribing information for tocilizumab for details.**Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.****All recommendations are category 2A unless otherwise indicated.****Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**



NCCN Guidelines Version 7.2017

Diffuse Large B-Cell Lymphoma

NCCN Evidence Blocks™

5					E = Efficacy of Regimen/Agent
4					S = Safety of Regimen/Agent
3					Q = Quality of Evidence
2					C = Consistency of Evidence
1					A = Affordability of Regimen/Agent
	E	S	Q	C	A

EVIDENCE BLOCKS FOR CAR T-CELL THERAPY (AXICABTAGENE CILOLEUCEL) RELAPSED/REFRACTORY DISEASE

	Candidates for HDT/ASCR	Non-Candidates for HDT/ASCR
Axicabtagene ciloleucel (partial response after second-line therapy)		—
Axicabtagene ciloleucel (no response or progressive disease after second-line therapy)		—
Axicabtagene ciloleucel (second relapse or greater)		

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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 on next page \(NHODG-A 2 of 11\)](#)

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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)**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, βF1, cytotoxic granule proteins
 - ▶ CD4, CD8, CD5, CD7, TCRαβ, 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 \(NHODG-A 3 of 11\)](#)^aThese 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.^bSome 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).^cUsually 1 Pan-B (CD20) and 1 Pan-T (CD3) markers are done unless a terminally differentiated B-cell or a specific PTCL is suspected.**Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.**

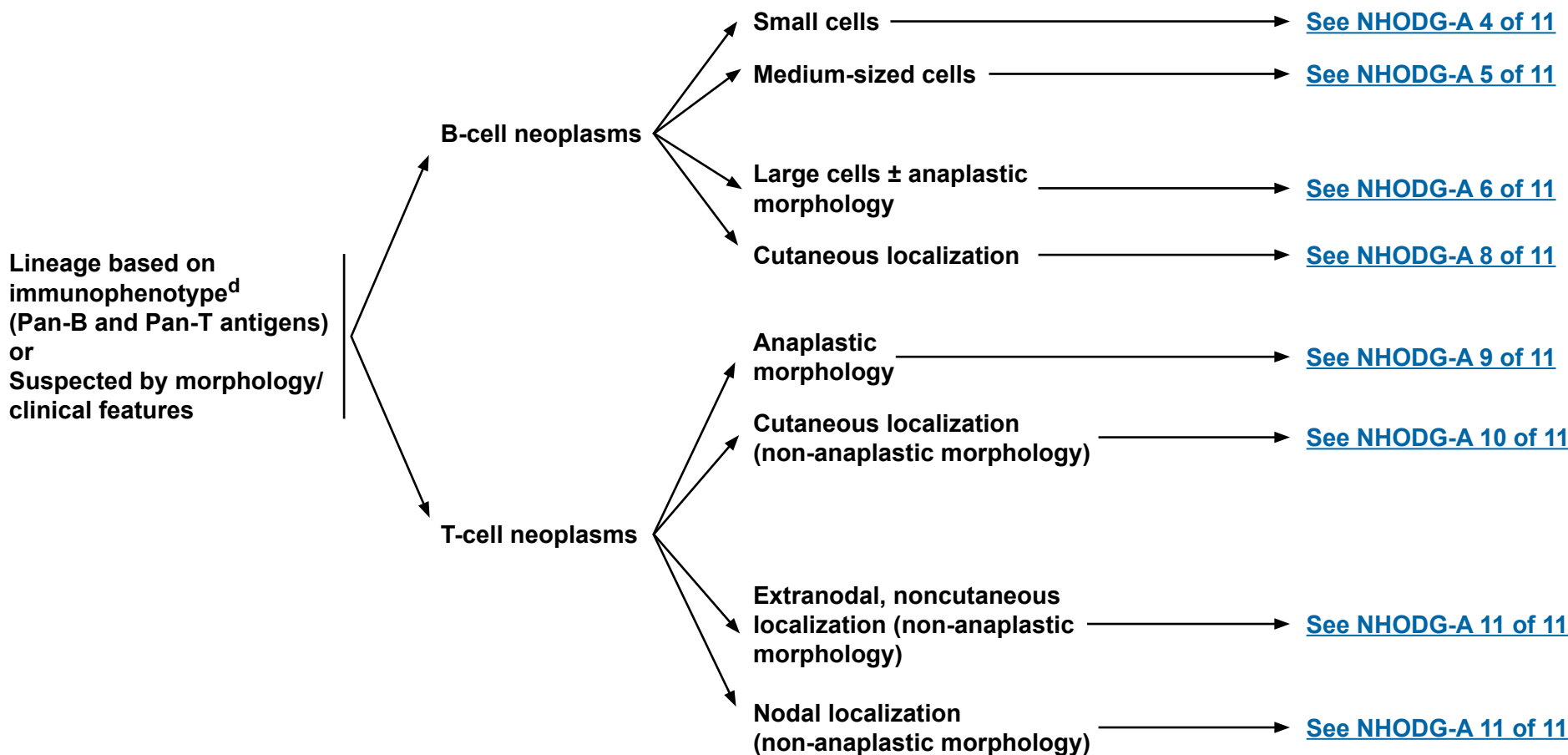
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USE OF IMMUNOPHENOTYPING/GENETIC TESTING IN DIFFERENTIAL DIAGNOSIS OF MATURE B-CELL AND NK/T-CELL NEOPLASMS^a
(TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)

INITIAL MORPHOLOGIC, CLINICAL, AND IMMUNOPHENOTYPIC ANALYSIS



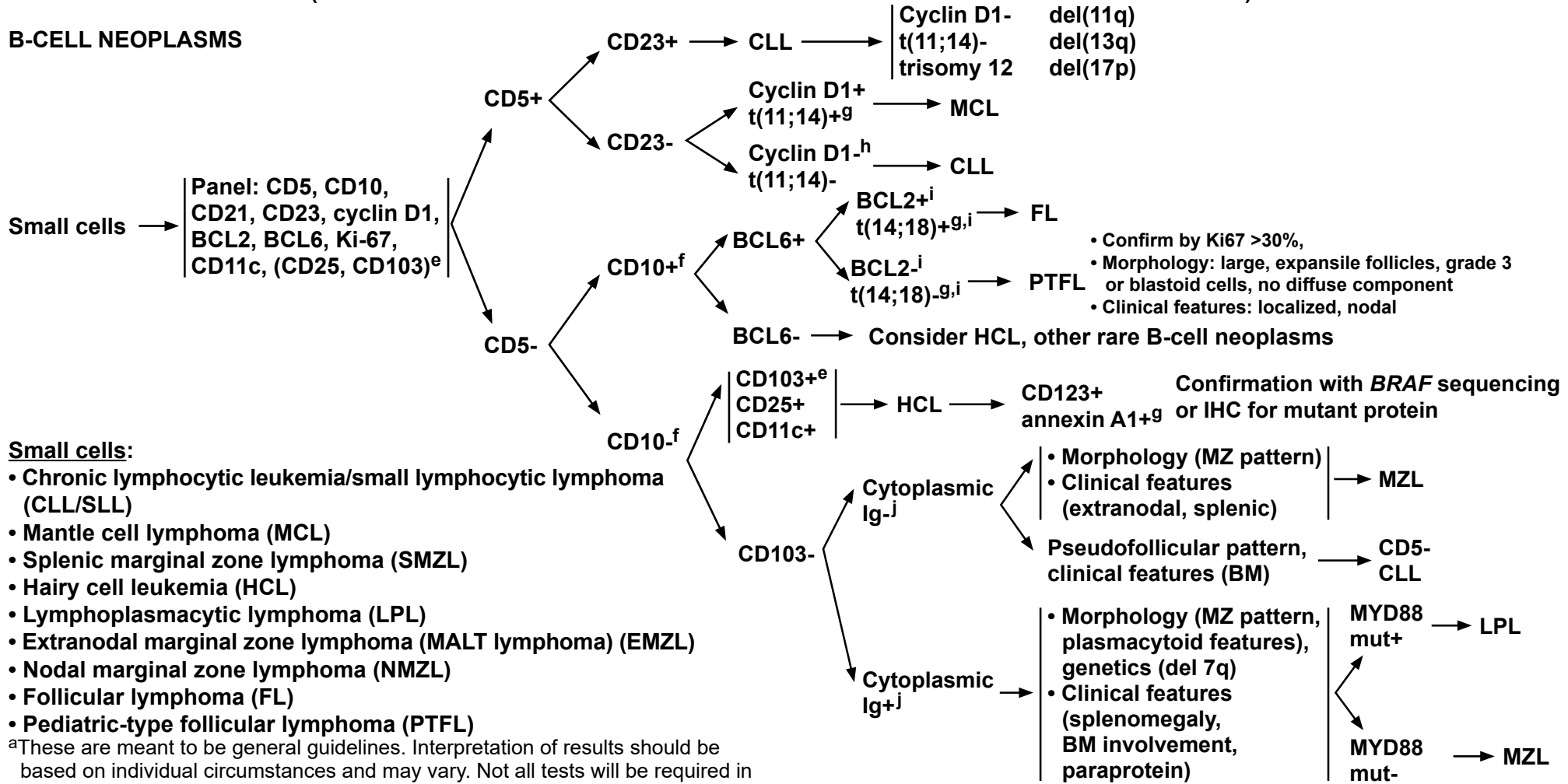
^aThese are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.

^dInitial panel will often include additional markers based on morphologic differential diagnosis and clinical features.

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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)

B-CELL NEOPLASMS



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)

^aThese 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.

^eFlow cytometry on blood or bone marrow done only if HCL is in differential diagnosis by morphology.

^fRare cases of HCL may be CD10+ or CD5+ and some cases of FL are CD10-. BCL6 is a useful discriminant if needed (rarely). Rare cases of MCL are CD5-.

^gCan be done to confirm if necessary.

^hRare 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.

ⁱ85% of follicular lymphoma will be BCL2+ or t(14;18)+.

^jKappa and lambda light chains; IgG, IgM, and IgA may be helpful.

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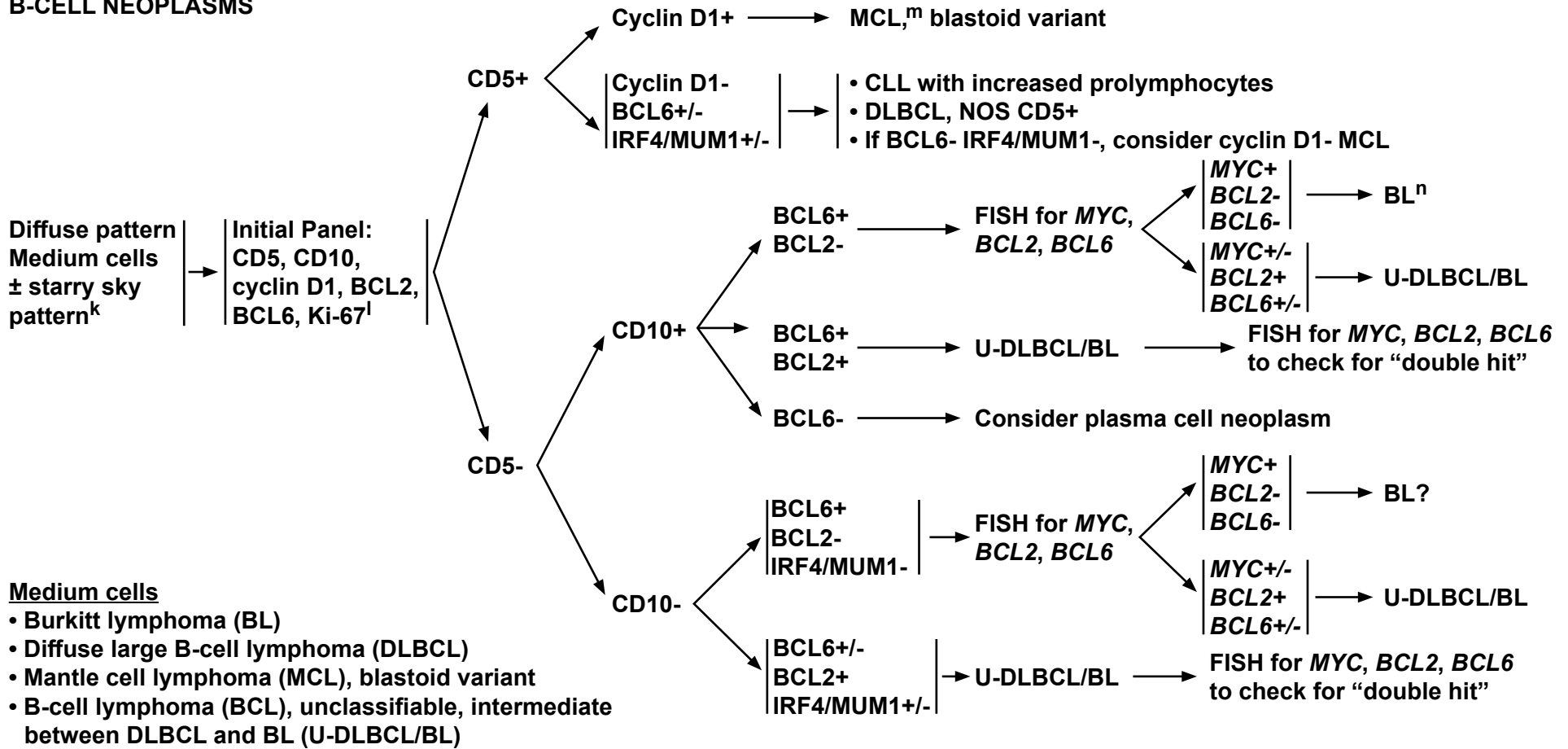
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(TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)

B-CELL NEOPLASMS



^aThese 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.

^kStarry sky pattern is typically present in BL and frequently in U-DLBCL/BL.

^lKi-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.

^mRare MCL may be cyclin D1-.

ⁿRare BL may lack detectable MYC rearrangement. Correlation with morphology and clinical features is essential.

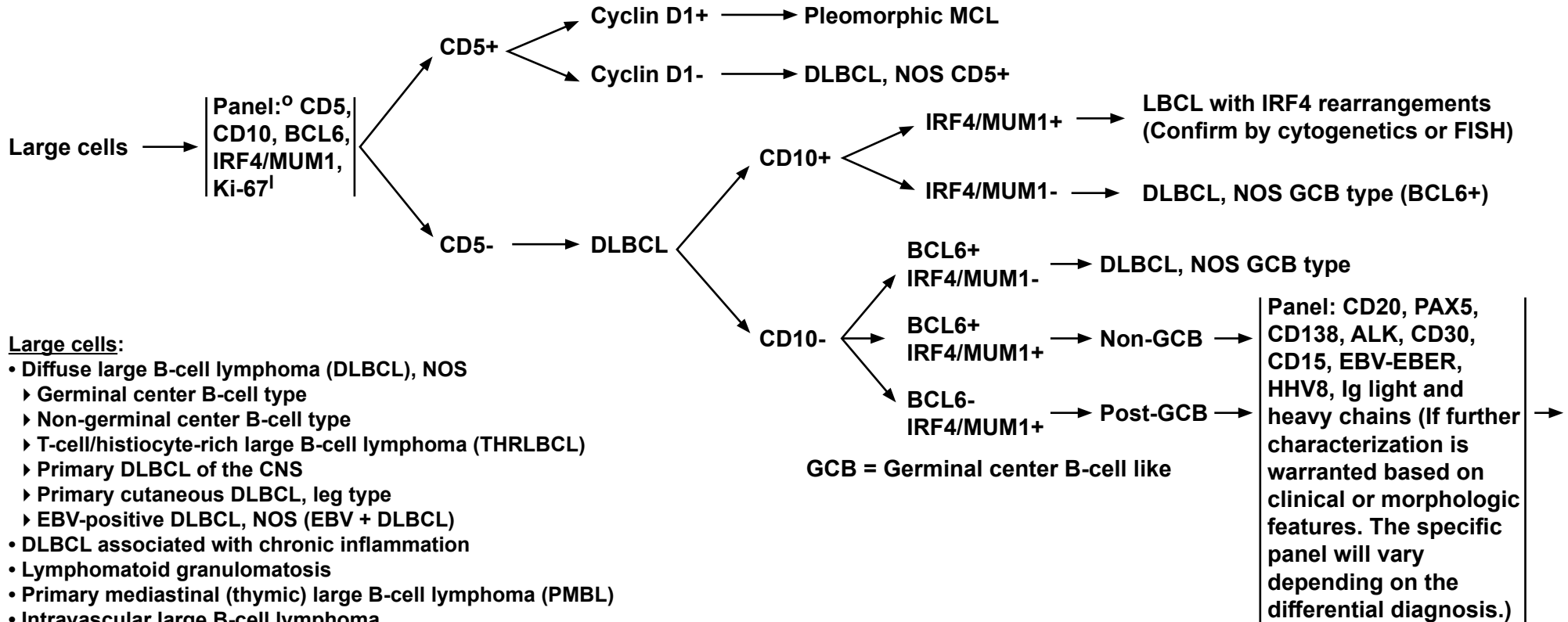
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(TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)

B-CELL NEOPLASMS



[Continued on next page](#)

^aThese 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.

^lKi-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.

^oCD5 is included to identify pleomorphic MCL; if CD5 is positive, cyclin D1 staining is done to confirm or exclude MCL.

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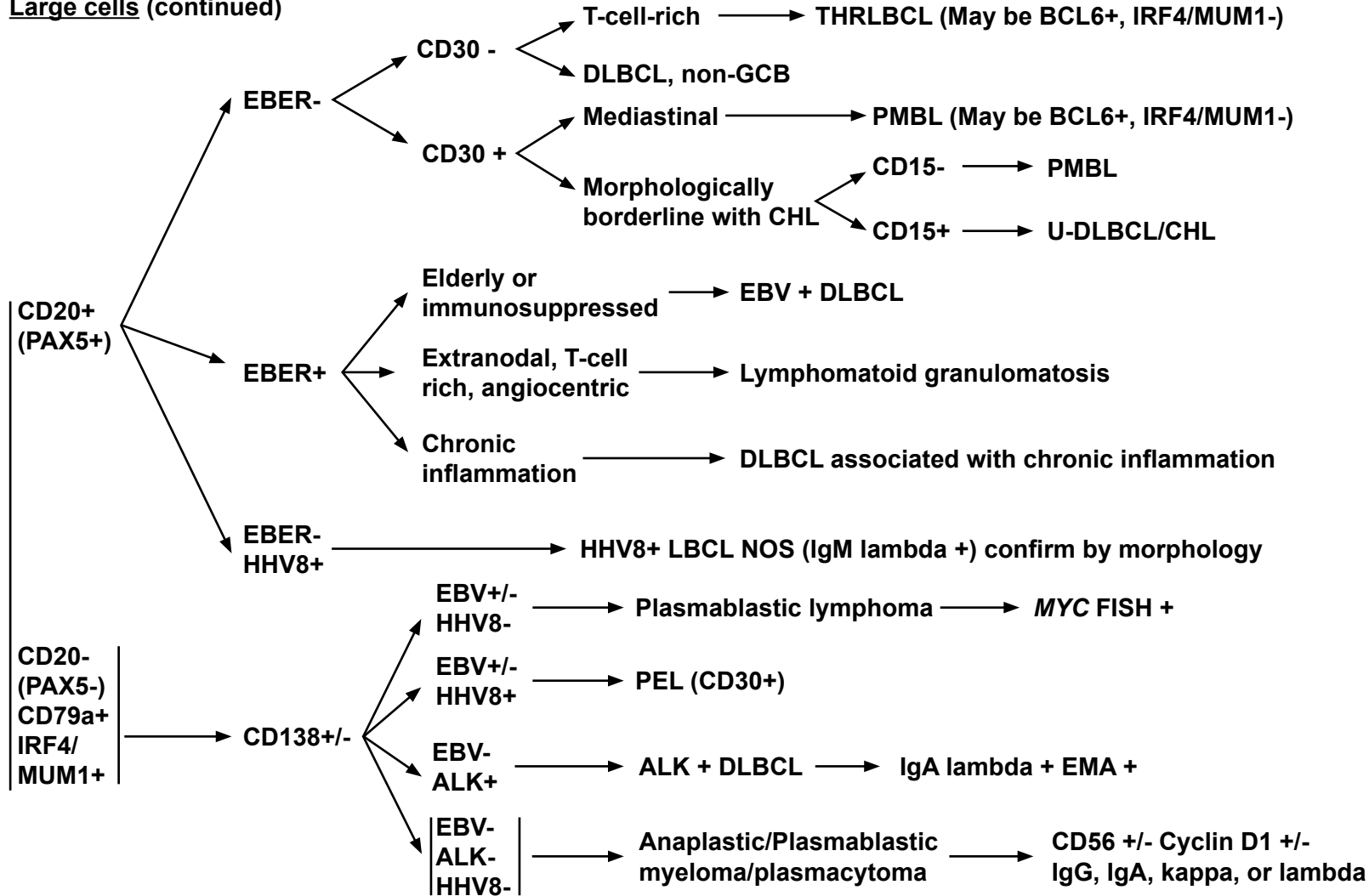
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USE OF IMMUNOPHENOTYPING/GENETIC TESTING IN DIFFERENTIAL DIAGNOSIS OF MATURE B-CELL AND NK/T-CELL NEOPLASMS^a
(TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)

Large cells (continued)

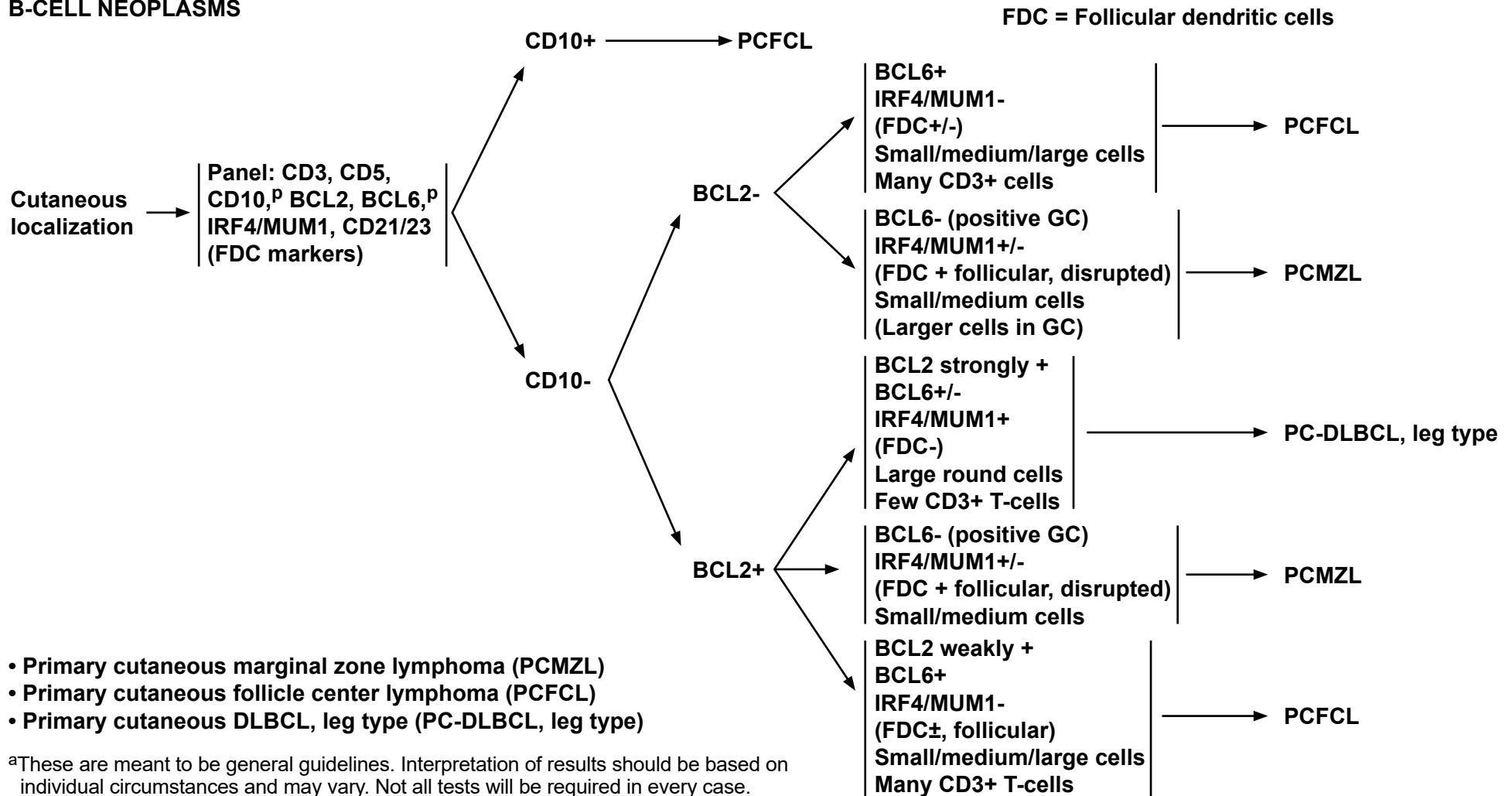


^aThese are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.

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(TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)

B-CELL NEOPLASMS



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

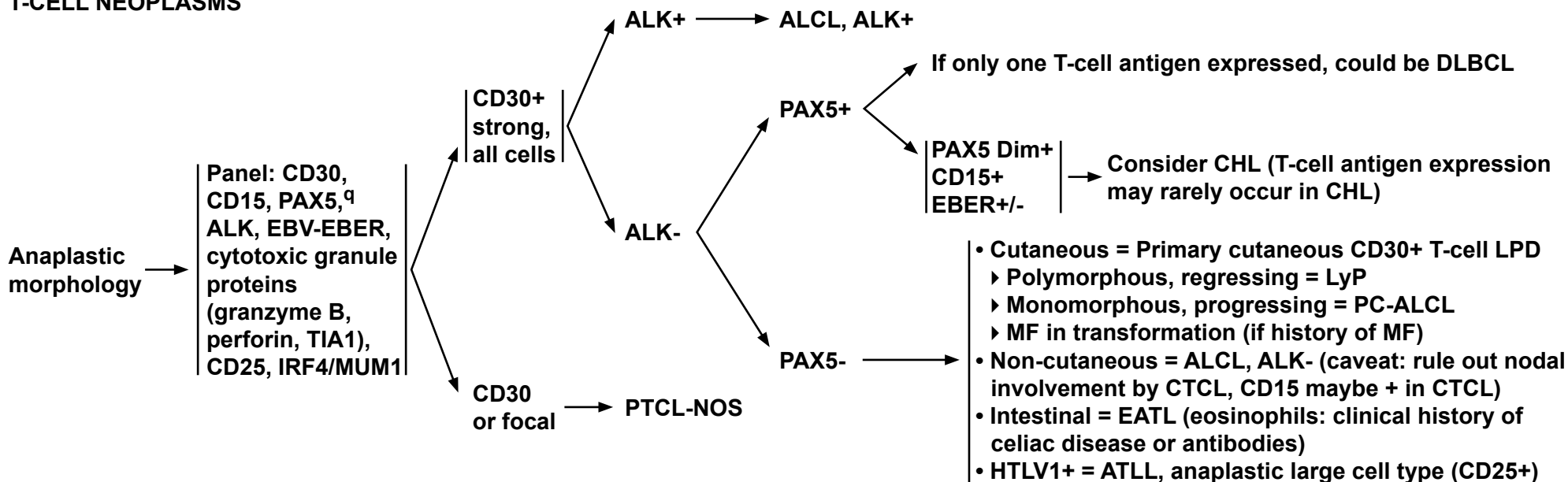
^aThese are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.
^PThese are assessed both in follicles (if present) and in intrafollicular/diffuse areas. CD10+ BCL6 + germinal centers are present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

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(TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)

T-CELL NEOPLASMS



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)

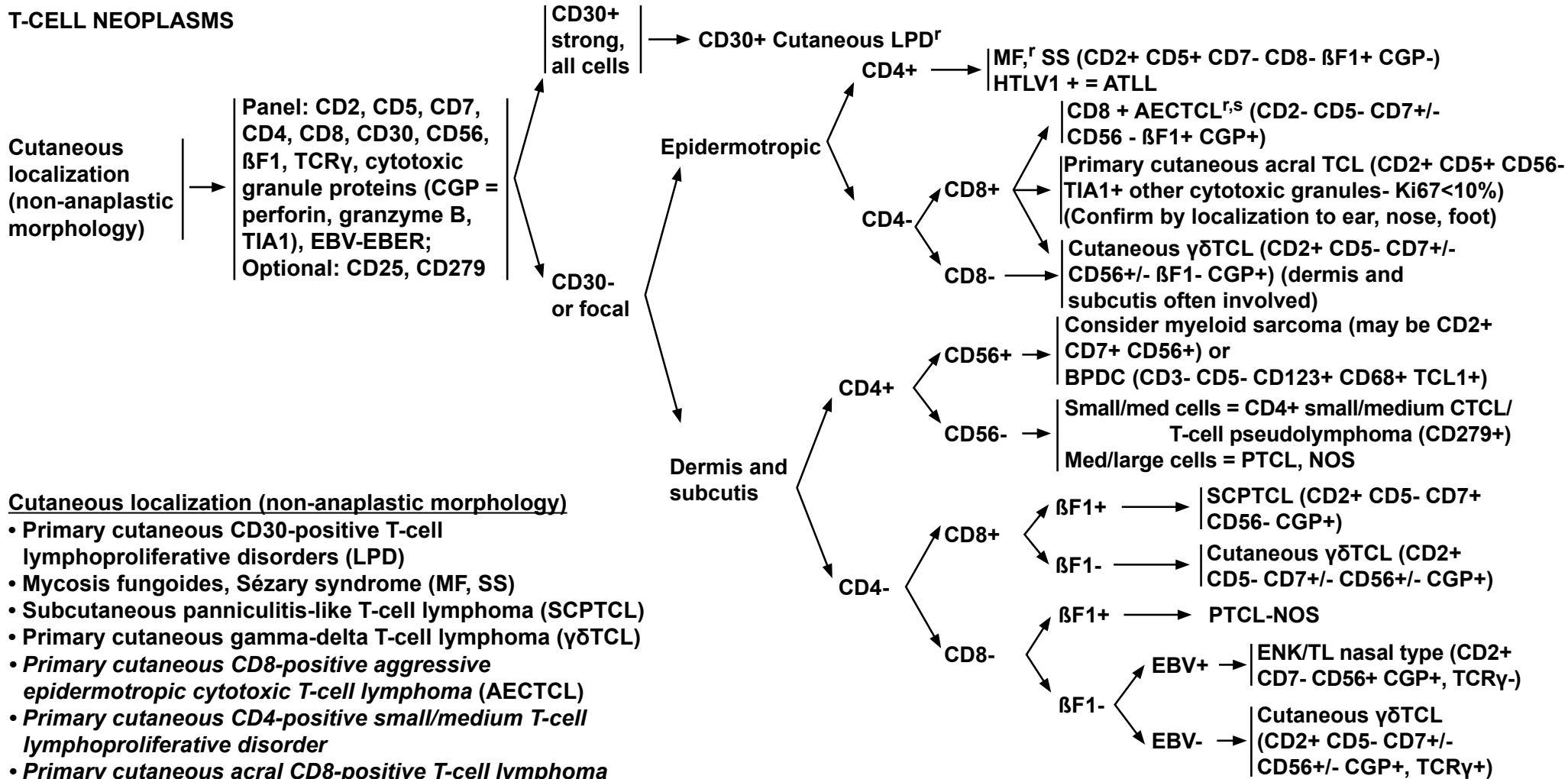
^aThese are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.

^qRare 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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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)

T-CELL NEOPLASMS



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
- Blastic plasmacytoid dendritic cell (BPDC) neoplasm

^aThese 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.

^rA minority of MF cases can be CD30+, CD4-, CD8+/-, and TIA1+. ATLL may also be CD30+.

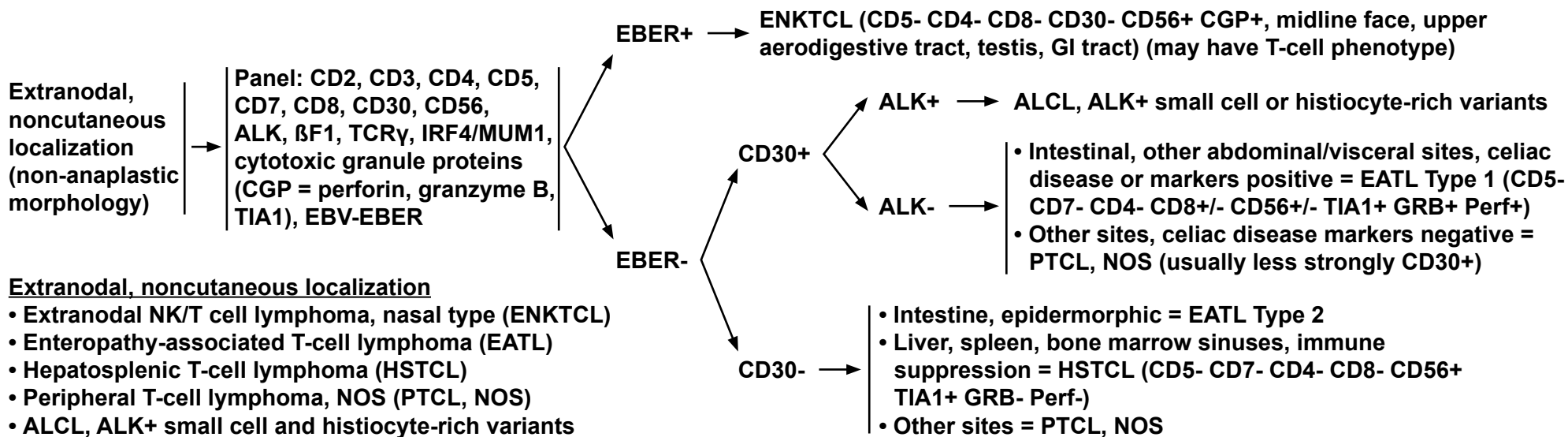
^sAECTCL has distinctive morphology and clinical presentation.

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

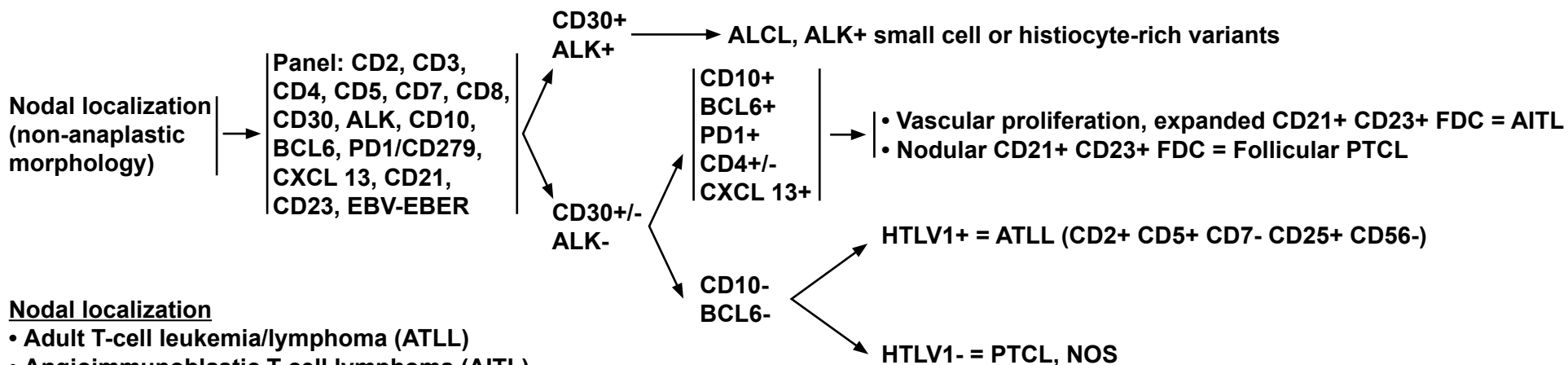
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USE OF IMMUNOPHENOTYPING/GENETIC TESTING IN DIFFERENTIAL DIAGNOSIS OF MATURE B-CELL AND NK/T-CELL NEOPLASMS^a
(TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)



- 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

^aThese 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.

• **High-risk features**

- ▶ Histologies of Burkitt lymphoma and lymphoblastic lymphoma; occasionally patients with DLBCL and CLL
- ▶ Spontaneous TLS
- ▶ Elevated WBC
- ▶ Bone marrow involvement
- ▶ Pre-existing elevated uric acid
- ▶ Ineffectiveness of allopurinol
- ▶ Renal disease or renal involvement by tumor

• **Treatment of TLS:**

- ▶ TLS is best managed if anticipated and treatment is started prior to chemotherapy.
- ▶ Centerpiece of treatment includes
 - ◊ Rigorous hydration
 - ◊ Management of hyperuricemia
 - ◊ Frequent monitoring of electrolytes and aggressive correction is essential
- ▶ First-line and at retreatment for hyperuricemia
 - ◊ Allopurinol beginning 2–3 days prior to chemotherapy and continued for 10–14 days
 - or
 - Rasburicase is indicated for patients with any of the following risk factors:
 - presence of any high-risk feature
 - urgent need to initiate therapy in a high-bulk patient
 - situations where adequate hydration may be difficult or impossible
 - Acute renal failure
 - ◊ One dose of rasburicase is frequently adequate. Doses of 3–6 mg are usually effective.^a Redosing should be individualized.
- ▶ If TLS is untreated, its progression may cause acute kidney failure, cardiac arrhythmias, seizures, loss of muscle control, and death.

^aThere are data to support that fixed-dose rasburicase is very effective in adult patients.

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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.

[Supportive Care](#)
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SUPPORTIVE CARE FOR B-CELL LYMPHOMAS

Monoclonal Antibody Therapy and Viral Reactivation (continued)

Anti-CD52 Antibody Therapy: Alemtuzumab

Cytomegalovirus (CMV) reactivation:

- The current appropriate management is controversial; some NCCN Member Institutions use ganciclovir (oral or IV) preemptively if viremia is present, others only if viral load is rising.
- CMV viremia should be measured by quantitative PCR at least every 2 to 3 weeks.
- Consultation with an infectious disease expert may be necessary. [See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.](#)

Rare Complications of Monoclonal Antibody Therapy

- Rare complications such as mucocutaneous reactions including paraneoplastic pemphigus, Steven-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis can occur. Expert consultation with dermatology is recommended.

Rituximab Rapid Infusion

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

Renal Dysfunction Associated with Methotrexate

- Consider use of glucarpidase if significant renal dysfunction and methotrexate levels are >10 microM beyond 42 to 48 hours. Leucovorin remains a component in the treatment of methotrexate toxicity and should be continued for at least 2 days following glucarpidase administration. However, be aware that leucovorin is a substrate for glucarpidase, and therefore should not be administered within two hours prior to or following glucarpidase.

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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, or 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 indeterminate, 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 or 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 measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5mm x 5mm as the default value. When no longer visible, 0x0 mm For a node >5mm x 5mm, but smaller than normal, use actual measurement for calculation
	Non-measured lesion	Not applicable	Absent/normal, regressed, but no increase
	Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
	New Lesions	None	None
	Bone Marrow	Residual uptake higher than uptake 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 context 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, measurable 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 <1.0 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**

^aScore 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).

^bSee PET Five Point Scale (5-PS).

^cIt 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.

^dFDG-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.

^eFalse-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 \leq mediastinum**
- 3 Uptake $>$ mediastinum but \leq 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^a

- Treatment with photons, electrons, or protons may all be appropriate, depending on clinical circumstances.
- Advanced radiation therapy technologies such as IMRT, breath hold or respiratory gating, image-guided therapy, or proton therapy may offer significant and clinically relevant advantages in specific instances to spare important organs at risk such as the heart (including coronary arteries and valves), lungs, kidneys, spinal cord, esophagus, bone marrow, breasts, stomach, muscle/soft tissue, and salivary glands and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control. Achieving highly conformal dose distributions is especially important for patients who are being treated with curative intent or who have long life expectancies following therapy.
- The demonstration of significant dose-sparing for these organs at risk reflects best clinical practice.
- In mediastinal lymphoma, the use of 4D-CT for simulation and the adoption of strategies to deal with respiratory motion such as inspiration breath-hold techniques, and image guided RT during treatment delivery is also important.
- Since the advantages of these techniques include tightly conformal doses and steep gradients next to normal tissues, target definition and delineation and treatment delivery verification require careful monitoring to avoid the risk of tumor geographic miss and subsequent decrease in tumor control. Image guidance may be required to provide this assurance.
- Randomized studies to test these concepts are unlikely to be done since these techniques are designed to decrease late effects, which take 10+ years to evolve. In light of that, the modalities and techniques that are found to best reduce the doses to the organs at risk (OAR) in a clinically meaningful way without compromising target coverage should be considered.

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^aSee references on [NHODG-D 4 of 4](#).

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**PRINCIPLES OF RADIATION THERAPY^a****Volumes:****• Involved-site radiation therapy (ISRT) for nodal disease**

- ▶ ISRT is recommended as the appropriate field for NHL. Planning for ISRT requires modern CT-based simulation and planning capabilities. Incorporating other modern imaging like PET and MRI often enhances treatment volume determination.
- ▶ ISRT targets the site of the originally involved lymph node(s). The volume encompasses the original suspicious volume prior to chemotherapy or surgery. Yet, it spares adjacent uninvolved organs (like lungs, bone, muscle, or kidney) when lymphadenopathy regresses following chemotherapy.
- ▶ The pre-chemotherapy or pre-biopsy gross tumor volume (GTV) provides the basis for determining the clinical target volume (CTV). Concerns for questionable subclinical disease and uncertainties in original imaging accuracy or localization may lead to expansion of the CTV and are determined individually using clinical judgment.
- ▶ For indolent NHL, often treated with RT alone, larger fields should be considered. For example, the CTV definition for treating follicular lymphoma with radiation therapy alone will be greater than that employed for DLBCL with similar disease distribution being treated with combined modality therapy.
- ▶ Possible movement of the target by respiration as determined by 4D-CT or fluoroscopy (internal target volume- ITV) should also influence the final CTV.
- ▶ The planning treatment volume (PTV) is an additional expansion of the CTV that accounts only for setup variations (see ICRU definitions).
- ▶ The OAR should be outlined for optimizing treatment plan decisions.
- ▶ The treatment plan is designed using conventional, 3-D conformal, or IMRT techniques using clinical treatment planning considerations of coverage and dose reductions for OAR.

• ISRT for extranodal disease

- ▶ Similar principles as for ISRT nodal sites (see above).
- ▶ For most organs and particularly for indolent disease, the whole organ comprises the CTV (eg, stomach, salivary gland, thyroid). For other organs, including orbit, breast, lung, bone, localized skin, and in some cases when RT is consolidation after chemotherapy, partial organ RT may be appropriate.
- ▶ For most NHL subtypes no radiation is required for uninvolved lymph nodes.

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^aSee references on [NHODG-D 4 of 4](#).

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PRINCIPLES OF RADIATION THERAPY^a

General Dose Guidelines:

- **Follicular lymphoma: 24–30 Gy**
- **Marginal zone lymphoma:**
 - ▶ **Gastric: 30 Gy**
 - ▶ **Other extranodal sites: 24–30 Gy**
 - ▶ **Nodal MZL: 24–30 Gy**
- **Early-stage mantle cell lymphoma: 30–36 Gy**
- **Palliation/local control of FL, MZL, MCL: 2 Gy x 2 which may be repeated as needed**

- **DLBCL**
 - ▶ **Consolidation after chemotherapy CR: 30–36 Gy**
 - ▶ **Complimentary after PR: 40–50 Gy**
 - ▶ **RT as primary treatment for refractory or non-candidates for chemotherapy: 40–55 Gy**
 - ▶ **In combination with stem cell transplantation: 20–36 Gy, depending on sites of disease and prior RT exposure**

^aSee references on [NHODG-D 4 of 4](#).

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**PRINCIPLES OF RADIATION THERAPY****REFERENCES**

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**SPECIAL CONSIDERATIONS FOR THE USE OF SMALL-MOLECULE INHIBITORS^{1,2,3}****ACALABRUTINIB**

- **Dosage:** The recommended dose of acalabrutinib is 100 mg PO approximately every 12 hours
- Grade ≥3 bleeding events were observed in 2% of patients on acalabrutinib. The mechanism is not well understood. Acalabrutinib may increase the risk of hemorrhage in patients receiving anti-platelet or anticoagulant therapies. The phase 2 ACE-LY-004 study excluded patients on concomitant warfarin or equivalent vitamin K antagonists. Patients should be monitored for signs of bleeding. Consider the benefit-risk of withholding acalabrutinib for 3-7 days pre-and post-surgery depending on the type of surgery and risk of bleeding.
- Atrial fibrillation and flutter of any grade was reported in 3% of patients and atrial fibrillation grade 3 was reported in 1% of patients. Monitor for atrial fibrillation and flutter and manage as appropriate.

IBRUTINIB

- **Dosage**
 - **MCL:** The recommended dose of ibrutinib is 560 mg PO daily, continuous and should be continued until time of progression.
- **Lymphocytosis**
 - **MCL:** Upon initiation of ibrutinib, transient increase in absolute lymphocyte counts occurred in 33% of patients. The onset of isolated lymphocytosis occurs during the first few weeks of ibrutinib therapy and resolves by a median of 8 weeks.
- Grade >2 bleeding events were observed in 6% of patients on ibrutinib; the mechanism is not well understood. Consider the benefit-risk of ibrutinib in patients requiring anti-platelet or anticoagulant therapies. Clinical trials excluded patients on concurrent warfarin. Ibrutinib should be held 3 days before and after a minor surgical procedure and 7 days before and after a major surgical procedure. Ibrutinib should not be given concomitantly with warfarin.
- New onset atrial fibrillation was reported in 6%–9%, associated with ibrutinib administration.²
 - Consider non-warfarin anticoagulation
 - Monitor carefully
 - Consider switching to alternate therapy
 - Patients with recurrent atrial fibrillation that is not medically controllable should be changed to idelalisib.
- Hypertension associated with ibrutinib has been uncommonly reported as a basis for discontinuation and should be managed 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.

2. Acalabrutinib package insert. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/210259s000lbl.pdf

3. Ibrutinib package insert. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205552s001lbl.pdf.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page [EB-1](#).

All recommendations are category 2A unless otherwise indicated.

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

**SPECIAL CONSIDERATIONS FOR THE USE OF SMALL-MOLECULE INHIBITORS^{1,2,3,4}****IDELALISIB**

- The recommended dose of idelalisib is 150 mg PO twice daily, per prescribing recommendations.
- Fatal and/or serious hepatotoxicity, severe diarrhea or colitis, pneumonitis, and intestinal perforation have been observed in patients treated with idelalisib.
 - ▶ **Hepatotoxicity:** Monitor hepatic function prior to and during treatment. Interrupt (if ALT/AST > 5 x ULN [upper limit of normal] and when resolved may resume at a reduced dose (100 mg PO twice daily).
 - ▶ **Diarrhea or colitis:** Monitor for the development of severe diarrhea or colitis. Interrupt until resolution and then reduce or discontinue idelalisib. Severe diarrhea and colitis can be managed with systemic or nonabsorbable steroids.
 - ▶ **Pneumonitis:** Monitor for pulmonary symptoms and bilateral interstitial infiltrates. Discontinue idelalisib.
 - ▶ **Intestinal perforation:** Discontinue idelalisib if intestinal perforation is suspected.
- **CMV:** Monitor per institutional guidelines or consult with Infectious Disease.

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.
- **Ibrutinib**
 - ▶ Avoid concomitant use of strong and moderate CYP3A inhibitors. Consider alternative agents with less CYP3A inhibition.
 - ◇ For strong CYP3A inhibitors used short-term (eg, antifungals and antibiotics for 7 days or less; eg, ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin), consider interrupting ibrutinib during the duration of inhibitor use. Avoid strong CYP3A inhibitors that are needed chronically.
 - ◇ If a moderate CYP3A inhibitor must be used, reduce ibrutinib dose to 140 mg.
 - ◇ Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of ibrutinib toxicity
- Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, St. John's Wort). Consider alternative agents with less CYP3A induction.
- **Idelalisib**
 - ▶ Avoid concomitant use of strong CYP3A inhibitors or inducers.
 - ▶ Patients taking concomitant strong CYP3A4 inhibitors should be monitored more closely for signs of idelalisib toxicity.

1. Please refer to package insert for full prescribing information and monitoring for adverse reactions, available at www.fda.gov.
2. Acalabrutinib package insert. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/210259s000lbl.pdf
3. Ibrutinib package insert. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205552s001lbl.pdf.
4. Idelalisib package insert. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205858lbl.pdf.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page [EB-1](#).

All recommendations are category 2A unless otherwise indicated.

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



Classification

Table 1

WHO Classification of the Mature B-Cell, T-Cell, and NK-Cell Neoplasms (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's macroglobulinemia
- Monoclonal gammopathy of undetermined significance (MGUS), IgM
- Mu heavy chain disease
- Gamma heavy chain disease
- Alpha heavy chain disease
- Monoclonal gammopathy of undetermined significance (MGUS), IgG/A
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extranasal plasmacytoma
- Monoclonal immunoglobulin deposition diseases
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT type)
- 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 *BCL2* and/or *BCL6* rearrangements
- High-grade B-cell lymphoma, NOS
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

*Provisional entities are listed in italics.

[Continued on next page](#)



Classification

Table 1 continued

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

Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD, Jaffe ES. The 2017 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* 2017;127:2375-2390.



Staging

Lugano Modification of Ann Arbor Staging System* (for primary nodal lymphomas)		
Stage	Involvement	Extranodal (E) status
Limited Stage I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
Stage II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
Stage II bulky**	II as above with “bulky” disease	Not applicable
Advanced Stage III	Nodes on both sides of the diaphragm Nodes above the diaphragm with spleen involvement	Not applicable
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.

Reprinted with permission. © 2014 American Society of Clinical Oncology. All rights reserved. Cheson B, Fisher R, Barrington S, et al. Recommendations for Initial Evaluation, Staging and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma – the Lugano Classification. J Clin Oncol 2014;32:3059-3067.

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated on 05/03/16

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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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 2015, an estimated 71,850 people will be diagnosed with NHL and there will be approximately 19,790 deaths due to the disease; cases of chronic lymphocytic leukemia (CLL) are estimated separately.¹ NHL is the seventh leading site of new cancer cases among men and women, accounting for 4% of new cancer cases and 3% of cancer-related deaths.¹ In a prospectively collected data from the National Cancer Data Base, diffuse large B-cell lymphoma (DLBCL; 32.5%), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL; 18.6%), follicular lymphoma (FL; 17.1%), marginal zone lymphomas (MZL; 8.3%), mantle cell lymphoma (MCL; 4.1%) and peripheral T-cell lymphoma not-otherwise-specified (PTCL-NOS; 1.7%) were the major subtypes of NHL diagnosed in the United States between 1998-2011.²

The incidence of NHL has increased dramatically between 1970 and 1995; the increase has moderated since the mid-90s. This increase has been attributed partly to the human immunodeficiency virus (HIV) epidemic and the development of AIDS-related NHL. However, much of the increase in incidence has been observed in patients in their sixth and seventh decades; a large part of this increase in incidence has paralleled a major decrease in mortality from other causes. The median age of individuals with NHL has risen in the last two decades.³ As a result, patients with NHL may also have significant comorbid conditions, which complicate treatment options.

The National Comprehensive Cancer Network (NCCN®) Guidelines (NCCN Guidelines®) were developed as a result of meetings convened

by a multidisciplinary panel of NHL experts, with the aim to provide recommendations for diagnostic workup, treatment, and surveillance strategies for the most common subtypes of NHL, in addition to a general discussion on the classification systems used in NHL and supportive care considerations.

The most common B-cell Lymphoma subtypes that are covered in these NCCN Guidelines are listed below:

- ◆ Follicular lymphoma (FL)
- ◆ Marginal Zone lymphomas (MZL)
 - Gastric MALT lymphoma
 - Non gastric MALT lymphoma
 - Nodal MZL
 - Splenic MZL
- ◆ Mantle cell lymphoma (MCL)
- ◆ Diffuse large B-cell lymphoma (DLBCL)
- ◆ Burkitt lymphoma (BL)
- ◆ AIDS-related B-cell lymphoma
- ◆ Post-Transplant Lymphoproliferative Disorders
- ◆ Castleman's Disease

Classification

In 1956, Rappaport et al. proposed a lymphoma classification that was based on the pattern of cell growth (nodular or diffuse), and size and shape of the tumor cells.^{4,5} This classification, though widely used in the United States, quickly became outdated with the discovery and the existence of distinct types of lymphocytes (B, T and NK). The Kiel classification became the first and most significant classification that applied this new information to the classification of lymphomas.⁶⁻⁸ According to the Kiel classification, the lymphomas were divided into low-grade and high-grade based on the histological features. This

classification was widely used in Europe. The use of different classification systems in clinical studies made it difficult to compare results from clinical studies. Hence, the International Working Formulation (IWF) for NHLs was developed to standardize the classification of lymphomas.

International Working Formulation Classification

The IWF classified NHL into three major categories as low, intermediate and high grade, based on the morphology and natural history.⁹ This classification divided DLBCL into intermediate and high grade groups. However, these distinctions were not reproducible. Since this classification did not include immunophenotyping, the categories were not reproducible.¹⁰ In addition, after this classification was published many new diseases were described that were not included in the IWF classification.

Revised European American Classification

In 1994, the International Lymphoma Study Group (ILSG) developed the REAL classification, which classified lymphomas based on the cell of origin (B, T, or NK) and included morphology, immunophenotype, genetic and clinical features to define diseases.¹¹ In 1997, the International Lymphoma Classification Project performed a clinical evaluation of the Revised European American Classification (REAL) classification in a cohort of 1,403 cases of NHL.^{12,13} The diagnosis of NHL was confirmed in 1,378 (98.2%) of the cases. This study identified the thirteen most common histological types, comprising about 90% of the cases of NHL in the United States. The findings were as follows: DLBCL, 31%; follicular lymphoma (FL), 22%; small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL), 6%; mantle cell lymphoma (MCL), 6%; peripheral T-cell lymphoma (PTCL), 6%; and mucosa associated lymphoid tissue (MALT) lymphoma, 5%. The

remaining subtypes each occurred in less than 2% of cases. Importantly, in the United States more than 50% of cases of lymphoma are either DLBCL or FL. The study investigators concluded that the REAL classification can be readily applied and identifies clinically distinctive types of NHL.

World Health Organization Classification

In 2001, the World Health Organization (WHO) updated the classification of hematopoietic and lymphoid neoplasms.^{14,15} The 2001 WHO classification applied the principles of REAL classification and represented the first international consensus on classification of hematologic malignancies. The REAL/WHO classification of NHL includes many entities not recognized by the IWF.^{14,15} After consideration of cell of origin (B, T, or NK), the classification subdivides lymphomas into those derived from precursor lymphocytes versus those derived from mature lymphocytes. The classification is further refined based on immunophenotype, genetic, and clinical features. These considerations have aided in defining active treatment for specific subtypes of lymphoma.

In 2008, the International T-cell lymphoma Project evaluated the WHO classification of T-cell lymphoma in a cohort of 1,314 cases of PTCL and natural killer/T-cell lymphomas (NKTCL). The diagnosis of PTCL or NKTCL was confirmed in 1,153 cases (88%). The most common subtypes were PTCL-not otherwise specified (NOS; 25.9%), angioimmunoblastic lymphoma (18.5%), NKTCL (10.4%), adult T-cell leukemia/lymphoma (ATLL; 9.6%), anaplastic large cell lymphoma (ALCL), ALK-positive (6.6%) and ALCL, ALK-negative (5.5%).¹⁶ The findings of this study validated the utility of the WHO classification for defining subtypes of T-cell lymphomas.

The WHO classification was updated again in September 2008 to add new diseases and subtypes that have been recognized in the past decade, and to better define some of the heterogeneous and ambiguous categories based on the recent advances.¹⁷ Genetic features, detected by cytogenetics or fluorescence in-situ hybridization (FISH) are increasingly important in defining specific NHL subtypes. In addition, detection of viruses, particularly Epstein-Barr virus, HHV8 and HTLV1, is often necessary to establish a specific diagnosis.

2008 WHO Classification of Mature B-cell Lymphomas

Follicular Lymphoma

In FL, pathological grading according to the number of centroblasts is considered to be a clinical predictor of outcome. In the 2001 WHO classification, three grades were recommended: FL1, FL2, and FL3; FL3 could be optionally stratified into 3A (centrocytes still present) or 3B (sheets of centroblasts). However, clinical outcomes for patients with FL1 and FL2 do not differ and this classification was deemed unreliable. Therefore, in the updated 2008 WHO classification, these grades are grouped under a single grade (FL1-2). Hans et al reported that there was no difference in survival outcomes between patients with Grade 3A and 3B FL, whereas patients with FL3 with more than 50% diffuse component have an inferior survival similar to the survival of those with DLBCL.¹⁸ FL3B with cytogenetic abnormalities of BCL6 (at 3q27) are thought to be genetically more akin to germinal center type DLBCL than FL1-3A, and is associated with a more aggressive clinical course. Patients with FL3B with BCL2 translocation appear to have a clinical course similar to patients with FL1-3A.¹⁹ Since FL3B is rare, the clinical behavior of FL3 in most studies is based mainly on FL3A cases. The 2008 WHO classification mandates stratifying FL3 into either 3A or 3B. FL is thus still divided into three grades (FL1-2, FL3A and FL3B) based on the number of centroblasts. Any diffuse areas in FL should be given

a separate diagnosis of DLBCL, if it meets the criteria for FL3A or 3B. Pediatric-type FL, primary intestinal FL, other extranodal FLs and follicular lymphoma “in situ” (FLIS) are the other variants that are included under FL.

Pediatric-type follicular lymphoma: Pediatric-type FL is considered a rare variant of FL in the 2008 WHO classification and is generally characterized by lack of *BCL2* rearrangement and t(14,18), which constitute the genetic hallmark of conventional FL seen in adults.²⁰⁻²⁴ Pediatric-type FL has a better prognosis than adult FL and is often cured with minimal therapy.

Primary intestinal follicular lymphoma: FL of the gastrointestinal tract is a recently described entity, which is common in the small intestine with the vast majority of cases occurring in the duodenum. The morphology, immunophenotype, and genetic features are similar to those of nodal FL. However, most patients have clinically indolent and localized disease. Survival appears to be excellent even without treatment.

Other extranodal follicular lymphoma: In many of the other extranodal sites, the morphology, immunophenotype, and genetic features are similar to those of nodal FL. Patients usually have localized disease and systemic relapses are rare.

Follicular Lymphoma “in situ”: FLIS is characterized by the preservation of the lymph node architecture, with the incidental finding of focal strongly positive staining for BCL2 (restricted to germinal centers) and CD10 in the involved follicles, and the detection of t(14;18) by FISH.^{21,25-27} FLIS has been reported in patients with prior FL or concurrent FL (at other sites), as well as in individuals with no known history of FL.^{21,25,26} The occurrence of FLIS in the general population appears to be rare.

Primary Cutaneous Follicle Center Lymphoma (PC-FCL)

This is a new category in the 2008 classification and is defined as a tumor of neoplastic follicle center cells, including centrocytes and variable numbers of centroblasts, with a follicular, follicular and diffuse or a diffuse growth pattern. PC-FCL is the most common B-cell lymphoma of the skin and it is classified as a distinct entity in the EORTC classification of cutaneous lymphomas.²⁸ Gene expression profiling studies have also provided evidence in support of this classification.²⁹ PC-FCL presents as a solitary or localized skin lesion on the scalp, forehead or the trunk. It is characterized by an indolent course and rarely disseminates to extracutaneous sites. PC-FCL is consistently BCL6-positive, may be CD10-positive in cases with a follicular growth pattern. BCL2 is often either negative or dim (predominantly seen in cases with a follicular growth pattern). PC-FCL has an excellent prognosis with a 5-year survival rate of 95%.^{28,30} PC-FCL must be distinguished from primary cutaneous DLBCL, leg type, which is not always possible histologically, and can be identified by expression of IRF4/MUM1, is strongly BCL2+ and has a more unfavorable prognosis.^{31,32}

Diffuse Large B-cell Lymphomas

Some of the new categories of DLBCL are defined by extranodal primary sites and the association with viruses such as EBV or HHV8. Two borderline categories have also been included to incorporate cases in which it is not possible to distinguish between adult Burkitt lymphoma (BL) and DLBCL, and primary mediastinal large B-cell lymphoma (PMBL) and nodular sclerosis classical Hodgkin lymphoma (NSCHL). The ALK-positive DLBCL, plasmablastic lymphoma and primary effusion lymphoma are considered as distinct entities. The 2008 classification also has new category of large B-cell lymphoma arising in HHV8-associated multicentric Castleman's disease.

DLBCL, Not Otherwise Specified (NOS)

The 2008 classification has included DLBCL, NOS as a new category to include germinal center B-cell (GCB) subtype, activated B-cell (ABC) subtype as well as other DLBCL cases that do not belong to any of the four specific subtypes (T-cell/histiocyte rich large B-cell lymphoma, primary CNS DLBCL, primary cutaneous DLBCL (“leg type”) or EBV+ DLBCL of the elderly).

Gene expression profiling (GEP) has been used to identify distinct subtypes of DLBCL: GCB subtype, ABC subtype, PMBL, and type 3 which includes cases that cannot be classified as GCB, ABC, or PMBL subtypes.³³ GEP is not yet recommended for routine clinical use. Immunostaining algorithms have been developed to differentiate between GCB and ABC subtypes using a combination of CD10, BCL6, IRF4/MUM1, GCET1, FOXP1, and LMO2.³⁴⁻³⁶ GCB subtype is associated with an improved outcome compared to non-GCB subtype.³⁶⁻³⁸ However, at the present time, the upfront standard of care remains the same for both GCB and non-GCB subtypes.

B-cell Lymphoma, Intermediate between BL and DLBCL

BL is characterized by t(8;14), which results in the juxtaposition of *MYC* gene from chromosome 8 with the immunoglobulin heavy chain variable (*IGHV*) region on chromosome 14 and variant translocations involving *MYC* and the immunoglobulin light chain genes.³⁹ Nevertheless, *MYC* translocations also occur in DLBCL. GEP studies have confirmed that the distinction between BL and DLBCL is not reliably reproducible with the use of the current criteria of morphology, immunophenotype, and genetic abnormalities.^{40,41} Mature aggressive B-cell lymphomas without a molecular BL signatures (non-mBL) with *MYC* rearrangements⁴¹ as well as those with both t(8;14) and t(14;18) translocations are associated with a poor prognosis.⁴²

This provisional category replaces the “Atypical Burkitt Lymphoma” that was included in the 2001 WHO classification. The new category includes lymphomas with features of both DLBCL and BL, but for biological and clinical reasons should not be diagnosed as DLBCL or BL. Lymphomas in this provisional category include those that are morphologically intermediate between BL and DLBCL with immunophenotype suggestive of BL (CD10-positive, BCL6-positive, BCL2-negative and IRF4/MUM1-negative or weakly positive), lymphomas that are morphologically similar to BL but are strongly BCL2-positive and those with *MYC* rearrangement in addition to *BCL2* and/or *BCL6* rearrangements by FISH or standard cytogenetics (“double hit”) and complex karyotypes.

B-cell Lymphoma Intermediate between PMBL and NSCHL

PMBL has been recognized as a subtype of DLBCL based on its distinctive clinical and morphological features. NSCHL is the most common form of HL. Both tumors occur in the mediastinum and affect adolescents and young adults. GEP studies strongly support a relationship between PMBL and CHL. About a third of the genes that were more highly expressed in PMBL were also characteristically expressed in CHL cells.⁴³ Traverse-Glehen, et al., reported borderline cases with biologic and morphologic features of both CHL and B-cell NHL, known as “mediastinal gray zone lymphomas”.⁴⁴

This provisional category includes lymphomas with overlapping features between CHL and DLBCL, especially PBML. Those cases that morphologically resemble NSCHL have a strong expression of CD20 and other B-cell associated markers. Those cases that resemble PBML may have dim or no expression of CD20, strong expression of CD30 and CD15. These lymphomas have a more aggressive course and poorer outcome than either CHL or PBML.

Primary Cutaneous DLBCL, Leg Type (PC-DLBCL)

PC-DLBCL, leg type, is an unusual form of DLBCL composed of large transformed B cells most commonly arising on the leg (85-90%) although it can arise at other sites (10-15%).³⁰ These tumors arise from post-germinal center B-cell with expression of CD20, IRF4/MUM1, FOXP1, and BCL2; many cases express BCL6 and lack expression of CD10.^{30,45,46} These tumors can disseminate to non-cutaneous sites, including the CNS. Studies have reported the development of extracutaneous relapse in 17-47% of patients with PC-DLBCL.^{30,47,48} In a study in patients with PC-DLBCL (N=60), CNS was the most common site of visceral progression, occurring in 27% of patients with extracutaneous relapse (or in 12% of all patients on this study).⁴⁷ The high frequency of extracutaneous relapse in PC-DLBCL results in a poorer prognosis than the other cutaneous B-cell lymphomas, especially when the presentation involves multiple cutaneous lesions.⁴⁷

Role of PET Scans

Response Assessment

The International Working Group (IWG) published the guidelines for response criteria for lymphoma in 1999.⁴⁹ These response criteria are based on the reduction in the size of the enlarged lymph node as measured by CT scan and the extent of bone marrow involvement that is determined by bone marrow aspirate and biopsy.⁴⁹ These guidelines were revised in 2007 by the International Harmonization Project to incorporate IHC, flow cytometry and 18-fluorodeoxyglucose (FDG)-positron emission tomography (PET) scans in the definition of response for lymphoma.⁵⁰ In the revised guidelines, the response category of complete response uncertain (CRu) was essentially eliminated because residual masses were defined as a partial response (PR) or a complete response (CR) based on the result of a PET scan.

The response is categorized as CR, PR, stable disease (SD) and relapsed disease or progressive disease (PD).

In 2014, revised response criteria, known as the Lugano criteria, were introduced for staging and response assessment using PET-CT scans.^{51,52} PET-CT is recommended for initial staging of all FDG-avid lymphomas. The use of 5-point scale (5-PS) is recommended for the interpretation and reporting of PET-CT scans. The 5-PS is based on the visual assessment of FDG uptake in the involved sites relative to that of the mediastinum and the liver.⁵³⁻⁵⁵ A score of 1 denotes no abnormal FDG-avidity, while a score of 2 represents uptake less than the mediastinum. A score of 3 denotes uptake greater than the mediastinum but less than the liver, while scores of 4 and 5 denote uptake greater than the liver, and greater than the liver with new sites of disease, respectively. Different clinical trials have considered scores of either 1-2 or 1-3 to be PET-negative, while scores of 4-5 are universally considered PET-positive. A score of 4 on an interim or end of treatment restaging scan may be consistent with a partial response if the FDG-avidity has declined from initial staging, while a score of 5 denotes progressive disease.

However, the application of PET-CT to response assessment is limited to histologies where there is reliable FDG uptake in active tumor and the revised response criteria have thus far only been validated for DLBCL and Hodgkin lymphoma. The application of the revised response criteria to other histologies requires validation and the original IWG guidelines should be used. Of note, the Lugano response criteria may not be applicable for several of the tumor subtypes included in the NCCN Guidelines. Tumor specific response criteria are included in the guidelines for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), hairy cell leukemia (HCL), mycosis

fungoides/Sezary syndrome (MF/SS), adult T-cell leukemia/lymphoma (ATLL), and T-cell-prolymphocytic leukemia (T-PLL).

Staging

PET-CT scans are now employed for initial staging, restaging and end of treatment response assessment in the majority of patients with NHL.⁵⁶ In a meta-analysis study, PET showed a high positivity and specificity when used for the staging and restaging of patients with lymphoma.⁵⁷ PET is nearly universally positive at diagnosis in Hodgkin lymphoma, DLBCL, and follicular lymphoma,⁵⁸ about 90% in T-cell lymphoma⁵⁹ and nodal MZL but less sensitive for extra-nodal MZL.⁶⁰ However, a number of benign conditions including sarcoid, infection, and inflammation can result in false-positive PET scans, complicating the interpretation. Lesions smaller than 1 cm are not reliably visualized with PET scans. Although PET scans may detect additional disease sites at diagnosis, the clinical stage is modified only in 15-20% of patients and a change in treatment in only 8% of patients. PET scans are now virtually always performed as combined PET-CT scans.

PET-CT has distinct advantages in both staging and restaging compared to full-dose diagnostic CT or PET alone.^{61,62} In a retrospective study, PET-CT performed with low-dose non-enhanced CT was found to be more sensitive and specific than the routine contrast-enhanced CT in the evaluation of lymph node and organ involvement in patients with Hodgkin disease or high-grade NHL.⁶² Preliminary results of another recent prospective study (47 patients; patients who had undergone prior diagnostic CT were excluded) showed a good correlation between low-dose unenhanced PET-CT and full-dose enhanced PET-CT in the evaluation of lymph nodes and extranodal disease in lymphomas.⁶¹ PET-CT is particularly important for staging before consideration of RT and baseline PET-CT will aid in

the interpretation of post-treatment response evaluation based on the 5-PS as described above.⁵²

PET-CT is recommended for initial staging of FDG-avid lymphomas. PET should be done with contrast-enhanced diagnostic CT. Staging imaging with CT is recommended for lymphomas that are minimally FDG-avid (CLL/SLL, marginal zone lymphomas, HCL, cutaneous B-cell lymphomas, MF/SS, CD30+ cutaneous lymphomas and T-cell large granular lymphocytic leukemia), except in selected circumstances. FDG-avid lymphomas should have response assessed by PET-CT using the 5-PS. False-positive PET scans may be observed related to infectious or inflammatory conditions. Biopsy of affected sites remains the gold standard for confirming new or persistent disease at end of therapy.

Principles of Radiation Therapy

Radiation therapy (RT) can be delivered with photons, electrons or protons, depending upon clinical circumstances. Advanced RT techniques emphasize tightly conformal doses and steep gradients next to normal tissues. Therefore, target definition and delineation and treatment delivery verification require careful monitoring to avoid the risk of missing geographic location of the tumor and subsequent decrease in tumor control. Image guidance may be required to facilitate target definition. Preliminary results from single-institution studies have shown that significant dose reduction to organs at risk (OAR; eg, lungs, heart, breasts, kidneys, spinal cord, esophagus, carotid artery, bone marrow, stomach, muscle, soft tissue and salivary glands) can be achieved with advanced RT planning and delivery techniques such as 4D-CT simulation, intensity-modulated RT (IMRT), image-guided RT, respiratory gating or deep inspiration breath hold.⁶³⁻⁶⁶ These techniques offer significant and clinically relevant advantages in specific instances

to spare OAR and decrease the risk for normal tissue damage and late effects without compromising the primary goal of local tumor control.⁶⁷⁻⁷⁰ In mediastinal lymphoma, the use of 4D-CT simulation and the adoption of strategies to deal with respiratory motion such as inspiration breath-hold techniques, and image guided RT during treatment delivery is also important.

Randomized prospective studies to test these concepts are unlikely to be done since these techniques are designed to decrease late effects, which usually develop ≥ 10 years after completion of treatment. Therefore, the guidelines recommend that RT delivery techniques that are found to best reduce the doses to the OAR in a clinically meaningful manner without compromising target coverage should be considered.

Involved-site RT (ISRT) is intended to limit radiation exposure to adjacent uninvolved organs (such as lungs, bone, muscle, or kidney) when lymphadenopathy regresses following chemotherapy, thus minimizing the potential long term complications. Extended-field RT (EFRT) and involved-field RT (IFRT) techniques have now been replaced by ISRT, in an effort to restrict the size of the RT fields to smaller volumes.^{71,72} ISRT targets the initially involved nodal and extra-nodal sites detectable at presentation.^{71,72} Larger RT fields should be considered for limited stage indolent NHL, often treated with RT alone.⁷¹

Treatment planning for ISRT requires the use of CT-based simulation. The incorporation of additional imaging techniques such as PET and MRI often enhances the treatment planning. The OAR should be outlined for optimizing treatment plan decisions. The treatment plan is designed using conventional, 3D conformal, or IMRT techniques using clinical treatment planning considerations of coverage and dose reductions for OAR.⁷¹

The principles of ISRT are similar for both nodal and extranodal disease. The gross tumor volume (GTV) defined by radiological imaging prior to biopsy, chemotherapy or surgery provides the basis for determining the clinical target volume (CTV).⁷³ Possible movement of the target by respiration as determined by 4D-CT or fluoroscopy should also influence the final CTV. The presence of suspected subclinical disease and uncertainties in original imaging accuracy or localization may lead to the expansion of the CTV. The planning treatment volume (PTV) is an additional expansion of the CTV that accounts only for setup variations.

In the case of extranodal disease, particularly for indolent lymphoma, in most cases, the whole organ comprises the CTV (eg, stomach, salivary gland, and thyroid). For other organs, including orbit, breast, lung, bone, localized skin, and in some cases when RT is consolidation after chemotherapy, partial organ RT may be appropriate. No radiation is required for uninvolved lymph nodes for most NHL subtypes.

The general dose guidelines for individual subtypes of NHL are outlined in the “Principles of RT” section of the guidelines.

Diagnosis

In all cases of NHL, the most important first step is an accurate pathologic diagnosis. The basic pathological evaluation is the same in each Guidelines (by tumor subtype), although some further evaluation may be useful in certain circumstances to clarify a particular diagnosis; these are outlined in the pathological evaluation of the individual Guidelines.

An incisional or excisional lymph node biopsy is recommended to establish the diagnosis of NHL. Core needle biopsy is discouraged unless the clinical situation dictates that this is the only safe means of

obtaining diagnostic tissue. Fine needle aspiration (FNA) biopsy is widely used in the diagnosis of malignant neoplasms, but its role in the diagnosis of lymphoma is still controversial.^{74,75} Since the revised REAL/WHO classification is based on both morphology and immunophenotyping, FNA alone is not acceptable as a reliable diagnostic tool for NHL. However, its use in combination with ancillary techniques may provide precise diagnosis thereby obviating the need for a more invasive biopsy in highly selected circumstances. Recent studies have shown that the diagnostic accuracy of FNA improves significantly when it is used in combination with IHC and flow cytometry.⁷⁶⁻⁷⁸

In the NCCN Guidelines, FNA alone is not suitable for an initial diagnosis of NHL, though it may be sufficient to establish relapse. However, in certain circumstances, when a lymph node is not easily accessible, a combination of core biopsy and FNA in conjunction with appropriate ancillary techniques [PCR for *IGHV* and/or T-cell receptor (*TCR*) gene rearrangements; FISH for major translocations; immunophenotypic analysis] may be sufficient for diagnosis. This is particularly true for the diagnosis of CLL. In other entities presenting in leukemic phase, such as FL or MCL, a biopsy is still preferred to clarify histological subtype.

Immunophenotypic analysis is essential for the differentiation of various subtypes of NHL to establish the proper diagnosis. It can be performed by flow cytometry and/or IHC; the choice depends on the antigens as well as the expertise and resources available to the hematopathologist. In some cases flow cytometry and IHC are complementary diagnostic tools.⁷⁹ Cytogenetic or molecular genetic analysis may be necessary under certain circumstances to identify the specific chromosomal translocations that are characteristic of some NHL subtypes or to establish clonality.

After the publication of the 2008 WHO Classification, the NHL Guidelines panel developed a series of algorithms for the use of immunophenotyping in the diagnosis of mature lymphoid neoplasms. These algorithms were developed to provide guidance for surgical pathologists as well as an aid to the clinician in the interpretation of pathology reports and they should be used in conjunction with clinical and pathological correlation. See *Immunophenotyping/Genetic Testing* in the guidelines.

Workup

Essential workup procedures include a complete physical exam with particular attention to node bearing areas and the size of liver and spleen, symptoms present, performance status, laboratory studies including CBC, serum lactate dehydrogenase (LDH), hepatitis B virus testing (see below), comprehensive metabolic panel, and CT chest/abdominal/pelvic with oral and intravenous contrast (unless co-existent renal insufficiency). MUGA scan or echocardiograms are recommended when anthracyclines and anthracenedione containing regimens are used. Due the risk of hepatitis B reactivation, the panel has included hepatitis B testing (hepatitis B surface antigen and hepatitis B core antibody) as part of essential workup prior to initiation of treatment in all patients who will receive anti CD20 monoclonal antibody-based regimens. Furthermore, hepatitis B reactivation has been reported with chemotherapy alone and testing should be considered in anyone with a risk factor (e.g. blood transfusion, IV drug abuse) or if from a region with a non-negligible prevalence of hepatitis B infection (see *“Hepatitis B Reactivation”* in the Supportive Care section below). Hepatitis C testing is needed in high-risk patients and patients with splenic marginal zone lymphoma.

Optional procedures (depending on specific lymphoma type) include beta-2-microglobulin, CT or PET-CT scans, endoscopic ultrasound (gastric MALT lymphoma), head CT or brain MRI and lumbar puncture to analyze cerebrospinal fluid (MCL and DLBCL). Discussion of fertility issues and sperm banking should be addressed in the appropriate circumstances.⁸⁰

Bone marrow biopsy with or without aspirate is essential in all cases where treatment is considered; however, there are circumstances where it may be deferred. Bone marrow biopsy is usually included in the workup for all patients with NHL with the exception of SLL/CLL when there is a clonal lymphocytosis identified by flow cytometry. Bone marrow involvement occurs in 39% of low-grade, 36% of intermediate grade and 18% of high-grade lymphomas. Bone marrow involvement was associated with significantly shorter survivals in patients with intermediate or high-grade lymphomas.⁸¹ In a retrospective analysis, the incidence of bone marrow involvement and the parameters predicting bone marrow involvement were analyzed in 192 patients with stage I and II in DLBCL.⁸² Overall incidence of BM involvement was 3.6%. The authors concluded that bone marrow biopsy may be safely omitted in selected patients with early stage DLBCL.⁸² In cutaneous B-cell lymphomas, bone marrow biopsy is essential for PC-DLBCL, leg type, since this is an aggressive lymphoma that will probably require systemic treatment, whereas the role of bone marrow biopsy in the PC-FCL and PC-MZL subtypes is less clear. Recent studies have indicated that bone marrow biopsy is an essential component of staging in patients with PC-FCL first presenting in the skin, whereas it appears to have limited value in patients with MZL presenting in the skin, and may be considered only in selected cases.^{83,84}

In the NCCN Guidelines, bone marrow biopsy with or without aspirate is included as part of essential workup for all lymphomas. However, in patients with low bulk indolent disease with radiographic clinical stage III disease, an initial staging bone marrow evaluation can be deferred if observation is recommended as it will not change the clinical recommendations. However, in the evaluation of potentially early stage indolent lymphoma (stage I or II), bone marrow biopsy is essential; some panel members advocate bilateral core biopsies in this situation.⁸⁵ Bilateral cores are recommended if radioimmunotherapy is considered.

Supportive Care

Supportive care remains an important component of managing patients with NHL, particularly during active therapy. Supportive care measures for NHL may include (but are not limited to) management of infectious complications, management of tumor lysis syndrome, and use of myeloid growth factors or blood product transfusions. These measures may help to maximize the benefit of NHL therapy for patients by enhancing tolerability, reducing treatment-related toxicities, and ensuring timely delivery of planned treatment courses. Patients with hematologic malignancies are at increased risk for infectious complications due to profound immunosuppression stemming from myelosuppressive therapy and/or the underlying malignancy. For example, reactivation of latent viruses may occur in the setting of significant immunosuppression in patients with NHL.

Viral Reactivation and Infections

Hepatitis B Virus Reactivation

Hepatitis B virus (HBV) reactivation has been reported in patients treated with chemotherapy with or without immunotherapy agents.⁸⁶ HBV carriers with lymphoid malignancies have a high risk of HBV

reactivation and disease,⁸⁷ especially those treated with anti-CD20 monoclonal antibodies (e.g., rituximab, ofatumumab).⁸⁶ Cases of liver failure and death associated with HBV reactivation have occurred in patients receiving rituximab-containing regimens.⁸⁶

Testing for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) can determine the HBV status of an individual. Because of the widespread use of the hepatitis B vaccine, hepatitis B surface antibody (HBsAb) positivity is of limited value; however, in rare cases, HBsAb levels can help to guide therapy. Patients with malignancies who are positive for either HBsAg or HBcAb are at risk for HBV reactivation with cytotoxic chemotherapy; approximately 20% to 50% of patients with HBsAg positivity and 3% to 45% with HBcAb positivity develop HBV reactivation.⁸⁸⁻⁹⁷ False-negative HBsAg results may occur in chronic liver disease; therefore, patients with a history of hepatitis in need of chemotherapy should be assessed by viral load measurement.⁹⁸ HBsAb positivity is generally equated with protective immunity, although reactivated HBV disease may occur in the setting of significant immunosuppression in HBcAb-positive individuals.^{95,99} In patients with B-cell lymphoid malignancies treated with rituximab-containing regimens, HBV reactivation was observed in patients with HBcAb positivity (with or without HBsAb positivity), even among those who were HBsAg negative prior to initiation of treatment.^{90,96,97} A recent meta-analysis and evaluation of the FDA safety reports concerning HBV reactivation in patients with lymphoproliferative disorders reported that HBcAb positivity was correlated with increased incidence of rituximab-associated HBV reactivation.⁸⁹ Vaccination against HBV should be strongly considered in HBV-naïve patients (i.e., negative for HBsAg, HBsAb, and HBcAb).^{95,100}

Recommended strategies for the management of HBV reactivation in patients with hematologic malignancies undergoing immunosuppressive therapy include upfront antiviral prophylaxis or pre-emptive therapy. Prophylactic approaches involve treating patients who are HBsAg-positive or HBcAb-positive with prophylactic antiviral therapy, regardless of viral load or presence of clinical manifestations of HBV reactivation. The alternative strategy of pre-emptive therapy involves close surveillance with a highly sensitive quantitative assay for HBV, combined with antiviral therapy upon a rising HBV DNA load.⁹⁵ Antiviral prophylaxis with lamivudine has been shown to reduce the risks for HBV reactivation in HBsAg-positive patients with hematologic malignancies treated with immunosuppressive cytotoxic agents.^{87,101-104} A small randomized study in HBsAg-positive patients with lymphoma (N=30) showed that antiviral prophylaxis with lamivudine was superior to deferred pre-emptive therapy (i.e., antivirals given at the time of serological evidence of HBV reactivation based on viral DNA in serum samples).¹⁰¹ HBV reactivation occurred in 53% of patients in the deferred therapy arm compared with none in the prophylaxis arm. In a meta-analysis of clinical trials evaluating the benefit of lamivudine prophylaxis in HBsAg-positive lymphoma patients treated with immunosuppressive regimens, prophylaxis resulted in significant reductions in HBV reactivation (risk ratio=0.21; 95% CI, 0.13–0.35) and a trend for reduced HBV-related deaths (risk ratio=0.68; 95% CI, 0.19–2.49) compared with no prophylaxis.¹⁰⁴

Recent studies have shown entecavir to be more effective than lamivudine in preventing rituximab-associated HBV reactivation.¹⁰⁵⁻¹⁰⁷

The results of a randomized controlled trial showed that entecavir prophylaxis (before initiation of chemotherapy to 3 months after completion of chemotherapy) was more effective in preventing HBV-reactivation than the control (initiation of entecavir therapy at the

time of HBV reactivation and HBsAg reverse seroconversion after chemotherapy).¹⁰⁵ The cumulative HBV reactivation rates at months 6, 12, and 18 after chemotherapy were 8%, 11.2%, and 25.9%, respectively, in the control group, and 0%, 0%, and 4.3% in the entecavir prophylaxis ($P = .019$). In another prospective study that compared the efficacy of antiviral prophylaxis with entecavir (n= 61) and lamivudine (n= 60) in HBsAg-positive patients with newly diagnosed DLBCL treated with R-CHOP chemoimmunotherapy, entecavir was associated with significantly lower rates of HBV reactivation (6.6% vs 30.0%, $P = .001$), HBV-related hepatitis (0% vs 13.3%, $P = .003$) and disruption of chemotherapy (1.6% vs 18.3%, $P = .002$).¹⁰⁷

Although prophylaxis with lamivudine has been evaluated in the setting of immunosuppressive anti-tumor therapy (as mentioned above), the optimal antiviral strategy remains unclear. Concerns over the development of resistance to lamivudine exist.¹⁰⁸⁻¹¹² Adefovir combined with lamivudine has been evaluated in patients with lamivudine-resistant HBV infections.¹¹³ Tenofovir has demonstrated superior antiviral efficacy compared with adefovir in randomized double-blind phase III studies in patients with chronic HBV infection, and may be the preferred agent in this setting, however, limited data are available regarding its use in patients with cancer.¹¹⁴ Entecavir and telbivudine have also been evaluated in randomized open-label studies with adefovir as the comparator in patients with chronic HBV infection, and both agents have shown improved antiviral activity compared with adefovir.^{115,116}

The panel recommends HBsAg and HBcAb testing for all patients planned for treatment with anti-CD20 monoclonal antibody-containing regimens. In individuals who test positive for HBsAg and/or HBcAb, baseline quantitative PCR for HBV DNA should be obtained to determine viral load. However, a negative baseline PCR does not preclude the possibility of reactivation. Patients receiving intravenous

immunoglobulin (IVIG) may be HBcAb positive as a consequence of IVIG therapy, although HBV viral load monitoring is recommended.¹¹⁷

Prophylactic antiviral therapy with entecavir is recommended for patients who are HBsAg positive and undergoing anti-lymphoma therapy. Lamivudine prophylaxis should be avoided due to the risks for the development of resistance. For patients who are HBsAg negative but HBcAb positive, antiviral prophylaxis with entecavir is also the preferred approach; however, if these patients concurrently have high levels of HBsAb, they may be monitored with serial measurements of HBV viral load and treated with pre-emptive antivirals upon increasing viral load. During the treatment period, viral load should be monitored monthly with PCR and then every 3 months after completion of treatment. If viral load is consistently undetectable, prophylaxis with antivirals should be continued. If viral load fails to drop or a previously undetectable PCR becomes positive, consultation with a hepatologist and discontinuation of anti-CD20 antibody therapy is recommended.

As mentioned above, several antiviral agents are available for prophylactic measures. The optimal choice will be driven by institutional standards or recommendation from hepatology or infectious disease consultant. The appropriate duration of prophylaxis remains undefined, but the panel recommended that surveillance and antiviral prophylaxis should be continued for up to 12 months after the completion of oncologic treatment.⁹⁵

Hepatitis C Virus-associated B-cell NHL

Case-control studies have demonstrated a strong association between seropositivity for hepatitis C virus (HCV) and development of NHL, particularly for B-cell lymphomas.¹¹⁸⁻¹²⁶ In large population-based or multicenter case-control studies, prevalence of HCV seropositivity was consistently increased among patients with B-cell histologies, including

DLBCL and marginal zone lymphomas.^{120,121,124,126} A retrospective study in patients with HCV infection (N=3209) showed that the cumulative incidence of developing malignant lymphomas was significantly higher among patients with persistent HCV infection compared with those who had sustained virologic response (SVR) to interferon-containing therapy (15-year incidence rate 2.6% vs. 0%; $P=0.016$).¹²⁷ Based on multivariate analysis, persistent HCV infection remained a significant independent factor associated with development of malignant lymphomas. This study suggested that achievement of SVR with interferon-based therapy may reduce the incidence of malignant lymphoma in patients with HCV infection.¹²⁷ Several published reports suggested that treatment with antivirals (typically, interferon with or without ribavirin) led to regression of NHLs in HCV-positive patients, which provide additional evidence for the involvement of HCV infection in the pathogenesis of lymphoproliferative diseases.¹²⁸⁻¹³⁴ In a retrospective study in patients with NHL (N=343; indolent and aggressive histologies) who achieved a CR after chemotherapy, the subgroup of HCV-positive patients treated with antivirals (interferon and ribavirin; n=25) had significantly longer disease-free survival compared with HCV-positive patients who did not receive antiviral therapy (n=44); the probability of relapse-free survival at 5-year follow up was 76% and 55%, respectively.¹³³ In addition, none of the patients with a SVR to antivirals (n=0 of 8) relapsed compared with 29% who did not respond to antivirals (n=5 of 17).

In a multicenter retrospective study from a large series of HCV-positive patients with indolent NHL, antiviral therapy (interferon or pegylated interferon, with or without ribavirin), resulted in HCV-RNA clearance was achieved in 80% of patients who received first-line antivirals (n=100) and in 67% of those who received antivirals as second-line therapy after failure of initial treatment (n=34).¹³⁴ Patients in this analysis did not require immediate treatment for their lymphoma. The ORR for

patients treated with antiviral in the first-line setting was 77% (44% CR and 33% PR) and the ORR for patients treated with antiviral in the second-line setting was 85% (56% CR and 29% PR). In the group of patients who received antivirals in first line, hematologic response was significantly associated with achievement of HCV-RNA clearance. Thus, in HCV-positive patients with indolent NHL not requiring immediate anti-tumor therapy with chemoimmunotherapy regimens, initial treatment with interferon (with or without ribavirin) appeared to induce lymphoma regression in a high proportion of patients. In HCV-positive patients with NHL who achieve a remission with anti-tumor therapy, subsequent treatment with antivirals may be associated with lower risk of disease relapse.

The optimal management of HCV-positive patients with NHL remains to be defined. Patients with indolent NHL and HCV seropositivity may benefit from antiviral treatment as initial therapy, as demonstrated in several reports.^{128,130,132,134,135} In patients with aggressive NHL, an earlier analysis of pooled data from GELA clinical studies (prior to the rituximab era) suggested that HCV seropositivity in patients with DLBCL was associated with significantly decreased survival outcomes, due, in part, to severe hepatotoxicity among those with HCV infection.¹³⁶ Subsequent studies in the rituximab era showed that HCV seropositivity was not predictive of outcomes in terms of PFS or OS in patients with DLBCL.^{137,138} However, the incidence of hepatotoxicity with chemoimmunotherapy was higher among HCV-positive patients, confirming the observation made from the GELA studies.

The treatment of chronic HCV infection has improved with the advent of newer antiviral agents, especially those that target carriers of HCV genotype 1. Direct acting antiviral agents (DAA) administered in combination with standard antivirals (pegylated interferon and ribavirin) have shown significantly higher rates of SVR compared with standard

therapy alone in chronic carriers of HCV genotype 1.¹³⁹⁻¹⁴² Telaprevir and boceprevir are DAAs that were recently approved by the FDA for the treatment (in combination with pegylated interferon and ribavirin) of patients with HCV genotype 1 infection. The updated guidelines for the management of HCV infection from the American Association for the Study of Liver Diseases (AASLD) recommended that DAAs be incorporated into standard antiviral therapy for patients infected with HCV genotype 1.¹⁴³

The panel recommends initial antiviral therapy in asymptomatic patients with HCV-positive low-grade B-cell NHL. For those with HCV genotype 1, triple antiviral therapy with inclusion of DAAs should be considered as per AASLD guidelines. Patients with HCV-positive aggressive B-cell NHL should initially be treated with appropriate chemoimmunotherapy regimens according to the NCCN Guidelines for NHL. Liver function and serum HCV RNA levels should be closely monitored during and after chemoimmunotherapy for development of hepatotoxicity. Antiviral therapy should then be considered in patients who achieve a CR after completion of chemoimmunotherapy.

Cytomegalovirus Reactivation

Cytomegalovirus (CMV) reactivation may occur among patients with lymphoproliferative malignancies receiving alemtuzumab therapy, and occurs most frequently between 3 to 6 weeks after initiation of therapy when T-cell counts reach a nadir. CMV reactivation is a well-documented infectious complication in patients receiving treatment with alemtuzumab, occurring in up to 25% of treated patients. Current management practices for prevention of CMV reactivation include the use of prophylactic ganciclovir (oral or IV) if CMV viremia is present prior to alemtuzumab therapy, or pre-emptive use of these drugs when the viral load is found to be increasing during therapy.

Patients with hematologic malignancies treated with alemtuzumab-containing regimens should be closely monitored and managed for potential development of CMV reactivation. To this end, periodic monitoring for the presence of CMV antigens using quantitative polymerase chain reaction (PCR) assays is an effective management approach. The panel recommends routine surveillance for CMV viremia (every 2–3 weeks) during the treatment course with alemtuzumab and for 2 months following completion of alemtuzumab treatment.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a rare but serious and usually fatal CNS infection caused by reactivation of the latent JC polyoma virus. Cases of PML generally occur in severely immunocompromised individuals, as in the case of patients with AIDS. Patients with hematologic malignancies who have profound immunosuppression (due to the underlying disease and/or immunosuppressive therapies) are also at risk of developing PML. In a report of 57 cases from the Research on Adverse Drug Events and Reports project, 52 patients with lymphoproliferative disorders developed PML after treatment with rituximab and other treatments which included hematopoietic stem cell transplantation or chemotherapy with purine analogs or alkylating agents.¹⁴⁴ Median time from last rituximab dose to PML diagnosis was 5.5 months. Median time to death after PML diagnosis was 2 months. The case fatality rate was 90%.¹⁴⁴ The use of rituximab may be associated with an increased risk of PML in immunocompromised patients with lymphoproliferative malignancies.¹⁴⁵ PML has been reported with rituximab treatment (usually in combination with chemotherapy regimens) in patients with CLL/SLL or other types of NHL. Patients with low CD4+ T-cells prior to or during anti-tumor treatment with rituximab-containing regimens may be particularly susceptible to PML.^{144,146,147} Patients with NHL receiving treatment with another

anti-CD20 monoclonal antibody ofatumumab,¹⁴⁸ or the anti-CD30 antibody-drug conjugate brentuximab vedotin, may also be at potential risk for PML.¹⁴⁹⁻¹⁵¹

Development of PML is clinically suspected based on neurological signs and symptoms that may include confusion, motor weakness or poor motor coordination, visual changes, and/or speech changes.¹⁴⁴ PML is usually diagnosed with PCR of cerebrospinal fluid (CSF) or in some cases, by analysis of brain biopsy material. There is no effective treatment for PML. Patients should be carefully monitored for the development of any neurological symptoms. There is currently no consensus on pretreatment evaluations that can be undertaken to predict for the subsequent development of PML.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is a potentially serious complication of anticancer therapy characterized by metabolic and electrolyte abnormalities caused by the abrupt release of intracellular contents into the peripheral blood resulting from cellular disintegration induced by anticancer therapy. It is usually observed within 12 to 72 hours after start of chemotherapy.¹⁵² Untreated TLS can induce profound metabolic changes resulting in cardiac arrhythmias, seizures, loss of muscle control, acute renal failure, and even death.

Cairo and Bishop have classified TLS into laboratory TLS and clinical TLS. Laboratory TLS is defined as a 25% increase in the levels of serum uric acid, potassium, or phosphorus or a 25% decrease in calcium levels.¹⁵³ Clinical TLS refers to laboratory TLS with clinical toxicity that requires intervention. Clinical complications may include renal insufficiency, cardiac arrhythmia, or seizures. The four primary electrolyte abnormalities of TLS are hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia. Symptoms associated with

TLS may include nausea and vomiting, diarrhea, seizures, shortness of breath, or cardiac arrhythmias. The risk factors for TLS include bone marrow involvement, bulky tumors that are chemosensitive, rapidly proliferative or aggressive hematologic malignancies, an elevated leukocyte count or pretreatment LDH, pre-existing elevated uric acid, renal disease or renal involvement of tumor. Patients diagnosed with lymphoblastic lymphoma or Burkitt lymphoma are at a higher risk of developing TLS. Occasionally, patients with bulky presentation of DLBCL and patients with CLL and high white blood cell count may experience TLS at a moderately high frequency.

TLS is best managed if anticipated and when treatment is started prior to chemotherapy. The cornerstone of TLS management is hydration and the management of hyperuricemia. Allopurinol (xanthine oxidase inhibitor) and rasburicase (recombinant urate oxidase) are highly effective for the management of hyperuricemia. Allopurinol is a xanthine analog and a competitive inhibitor of xanthine oxidase, thereby blocking conversion of purine metabolites to uric acid. Allopurinol will decrease the formation of uric acid production and has been shown to reduce the incidence of uric-acid uropathy.¹⁵⁴ Since the drug inhibits new uric acid formation rather than reduce existing uric acid, it can take several days for elevated levels of uric acid to normalize after the initiation of treatment, which may delay the start of chemotherapy. Furthermore, allopurinol may lead to the accumulation of xanthine crystals in renal tubules leading to acute obstructive uropathy. Allopurinol will also reduce clearance of 6-mercaptopurine and high-dose methotrexate. Rasburicase is a recombinant urate oxidase, which catalyzes the oxidation of uric acid to a highly soluble non-toxic metabolite that is readily excreted. It has been shown to be safe and highly effective in the prevention and treatment of chemotherapy-induced hyperuricemia in both children and adults with hematologic malignancies.¹⁵⁵ In an international compassionate use

trial in patients at risk for TLS during chemotherapy (N=280 enrolled), rasburicase (0.20 mg/kg/day IV for 1–7 days) resulted in uric acid response in all evaluable patients (n=219; adults, n=97).¹⁵⁵ Among the subgroup of adults with hyperuricemia (n=27), mean uric acid levels decreased from pretreatment levels of 14.2 mg/dL to 0.5 mg/dL 24 to 48 hours after administration of last dose of rasburicase. Among adult patients at risk for TLS (but without baseline hyperuricemia; n=70), mean uric acid levels decreased from 4.8 mg/dL to 0.4 mg/dL.¹⁵⁵ The GRAAL1 trial evaluated the efficacy and safety of rasburicase (0.20 mg/kg/day IV for 3–7 days, started on day 0 or day 1 of chemotherapy) for the prevention and treatment of hyperuricemia in adult patients with aggressive NHL during induction chemotherapy (N=100).¹⁵⁶ Prior to chemotherapy, 66% of patients had elevated lactate dehydrogenase (LDH) levels and 11% had elevated uric acid levels (>7.56 mg/dL). Uric acid levels were normalized and maintained within normal ranges during chemotherapy in all patients. Uric acid levels decreased within 4 hours after the first injection of rasburicase. In addition, serum creatinine levels and other metabolites were also controlled with the administration of rasburicase.¹⁵⁶

A prospective, multicenter randomized phase III trial compared the efficacy and safety of rasburicase and allopurinol in adult patients with hematological malignancies at high or potential risk for TLS (N=275).¹⁵⁷ Patients were randomized to receive treatment with rasburicase alone (0.20 mg/kg/day IV for days 1–5; n=92), rasburicase combined with allopurinol (rasburicase 0.20 mg/kg/day IV for days 1–3; allopurinol 300 mg/day PO for days 3–5; n=92) or allopurinol alone (300 mg/day PO for days 1–5; n=91). The rate of uric acid response (defined as plasma uric acid levels ≤7.5 mg/dL for all measurements from days 3–5) was 87% for rasburicase, 78% for rasburicase combined with allopurinol and 66% for allopurinol.¹⁵⁷ The incidence of clinical TLS was similar across treatment arms, occurring in 3%, 3%

and 4% of patients, respectively. The incidence of laboratory TLS was 21%, 27%, and 41%, respectively, with significantly lower incidence observed in the rasburicase arm compared with allopurinol ($P=.003$). The response rate with rasburicase was superior to allopurinol in the overall study population (87% vs. 66%, as above; $P=.001$) as well as in patients with high risk TLS (89% vs. 68%; $P=.001$) and in patients with baseline hyperuricemia (90% vs. 53%; $P=.015$). The median time to control for serum uric acid in hyperuricemic patients was 4 hours for rasburicase, 4 hours for rasburicase combined with allopurinol and 27 hours for allopurinol.¹⁵⁷ Potential hypersensitivity to study regimen was reported in 4% of patients in the rasburicase arm and 1% in the combination arm; no anaphylaxis or grade 4 hypersensitivity reactions were reported in this trial.¹⁵⁷ However, rasburicase can induce anaphylactic reactions. Other adverse reactions include methemoglobinemia and severe hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. A single fixed dose of rasburicase (6 mg)^{158,159} or a single weight-based dose of rasburicase (0.05–0.15 mg/kg)^{160,161} has been shown to be effective in the management of uric acid levels in adult patients with hyperuricemia or with high-risk factors for TLS. A recent phase II randomized trial compared the efficacy of rasburicase administered as a single dose (0.15 mg/kg, followed by additional days of dosing as needed) versus rasburicase (0.15 mg/kg/day) given for 5 days in adult patients at high risk or potential risk for TLS (N=80 treated).¹⁶² The median pretreatment uric acid level was 8.5 mg/dL for high-risk patients (n=40) and 5.6 mg/dL for potential risk patients (n=40). Nearly all treated patients (99%) showed normalization of uric acid levels within 4 hours after the first dose of rasburicase; levels of uric acid were undetectable (<0.7 mg/dL) in 84% of patients.¹⁶² In the single-dose rasburicase arm, 85% of patients had sustained uric acid response compared with 98% of patients in the 5-day rasburicase

arm. Among high-risk patients within the single-dose arm, 6 patients received a second dose of rasburicase to achieve uric acid response.¹⁶²

Allopurinol should be administered prior to the initiation of chemotherapy. Rasburicase is indicated in cases where the uric acid level remains elevated despite treatment with allopurinol or in patients with renal insufficiency. Electrolytes and renal function should be monitored every 6 to 8 hours with appropriate interventions for hyperkalemia and hyperphosphatemia. Careful clinical monitoring will help to preempt complications, and in many cases, admission to ICU may be appropriate. Cardiac monitoring or serial ECG may be beneficial to identify early electrolyte-related cardiac abnormalities. Dialysis may be necessary in cases of anuric acute renal failure.

The NCCN Guidelines recommend allopurinol or rasburicase as first-line and at retreatment of hyperuricemia. Allopurinol be started 2–3 days prior to chemotherapy and continued for 10–14 days. Rasburicase is recommended for patients with any of the following risk factors: presence of any high risk feature (i.e., Burkitt lymphoma or lymphoblastic lymphomas; spontaneous TLS; elevated WBC count; elevated uric acid levels; bone marrow involvement; renal disease or renal involvement by tumor); bulky disease requiring immediate therapy; patients in whom adequate hydration is not possible; allopurinol is ineffective; or acute renal failure. A single dose is adequate in most cases; repeat dosing should be given on an individual basis.

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Discussion
update in
progress

This discussion is being updated to correspond with the newly updated algorithm. Last updated 10/28/2014.

Follicular Lymphoma

Diagnosis

FL is the most common subtype of indolent NHL, and accounts for about 22% of all newly diagnosed cases of NHL.¹ About 90% of the cases have a t(14;18) translocation, which juxtaposes *BCL2* with the *IgH* locus resulting in the deregulated expression of *BCL2*.

Immunophenotyping using IHC and/or flow cytometry for cell surface marker analysis is required to establish a diagnosis. FL has a characteristic immunophenotype, which includes CD20+, CD10+, *BCL2*+, CD23+/-, CD43-, CD5-, CCND1- and *BCL6*+. Occasional cases of FL may be CD10- or *BCL2*-. The diagnosis is easily established on histological grounds, but immunophenotyping is encouraged to distinguish FL from a nodular MCL or SLL. Low-grade FL with a high proliferation index (as determined by Ki-67 immunostaining) has been shown to be associated with an aggressive clinical behavior. There is no evidence, however, that high Ki-67 should guide the selection of therapy.^{2,3} Molecular genetic analysis to detect *BCL2* rearrangement, cytogenetics or FISH to identify t(14;18), and immunohistochemistry for Ki-67 may be useful under certain circumstances. In patients with *BCL2*-negative localized disease, the diagnosis of pediatric-type FL may be considered.

The Follicular Lymphoma International Prognostic Index (FLIPI) is a prognostic scoring system based on age, Ann Arbor stage, and number of nodal sites involved, hemoglobin levels and serum LDH levels.⁴ The FLIPI was developed based on a large set of retrospective data from patients with FL, and established three distinct prognostic groups with 5-year survival outcomes ranging from 52.5% to 91% (in the

pre-rituximab era).⁴ In the National LymphoCare study, which analyzed the treatment options and outcomes of 2,728 patients with newly diagnosed FL, FLIPI was able to categorize patients into three distinct prognostic groups.⁵ In a more recent study conducted by the International Follicular Lymphoma Prognostic Factor Project, a prognostic model (FLIPI-2) was developed based on prospective collection of data from patients with newly diagnosed FL treated in the era of rituximab-containing chemoimmunotherapy regimens.⁶ The final prognostic model included age, hemoglobin levels, longest diameter of largest involved lymph node, beta-2 microglobulin levels, and bone marrow involvement. FLIPI-2 was highly predictive of treatment outcomes, and separated patients into three distinct risk groups with 3-year progression-free survival (PFS) rates ranging from 51% to 91%, and OS rates ranging from 82% to 99%; the FLIPI-2 also defined distinct risk groups among the subgroup of patients treated with rituximab-containing regimens, with a PFS rate ranging from 57% to 89%.⁶ Thus, FLIPI-2 may be useful for assessing prognosis in patients receiving active therapy with rituximab-based treatments. Both the FLIPI-1 and FLIPI-2 predict for prognosis, but these index scores have not yet been established as a means of selecting treatment options. Most recently, a simpler prognostic index incorporating only the baseline serum beta 2-microglobulin and LDH levels has been devised, which appears to be as predictive of outcomes as the FLIPI-1 and FLIPI-2 indices, and is easier to apply.^{7,8}

In-situ Involvement of Follicular Lymphoma-like Cells of Unknown Significance (Follicular Lymphoma “in situ”)

The presence of FL-like B-cells in the germinal centers of morphologically reactive lymph nodes (initially called “in situ localization of FL” or “follicular lymphoma in situ”[FLIS]) was first described a decade ago.^{9,10} These cases are characterized by the preservation of

the lymph node architecture, with the incidental finding of focal strongly positive staining for BCL2 (restricted to germinal centers) and CD10 in the involved follicles, and the detection of t(14;18) by FISH.⁹⁻¹²

Cases of FLIS have been reported in patients with prior FL or concurrent FL (at other sites), as well as in individuals with no known history of FL.⁹⁻¹¹ The occurrence of FLIS in the general population appears to be rare. Based on data from a consecutive series of unselected surgical samples of reactive lymph nodes from patients (N=132; 1294 samples), the prevalence of FLIS was 2.3%.¹³ Development of (or progression to) overt lymphoma in patients found to have FLIS has been reported, although this appears to be uncommon (5–6%).^{14,15} The significance or potential for malignancy of FLIS in patients without known FL remains unclear. These cases may potentially represent the tissue counterpart of circulating B-cells with t(14;18), or may represent a very early lesion with t(14;18) but without other genetic abnormalities that lead to overt lymphoma.^{10,14,16} The WHO classification recommends that a diagnosis of FL not be made in such cases, but that the report should suggest evaluation for the presence of FL elsewhere, and possibly close follow-up.

Pediatric-type Follicular Lymphoma

Pediatric-type FL is considered a rare variant of FL in the 2008 WHO classification,¹⁰ and has been reported to comprise less than 2% of childhood NHLs.¹⁷⁻²⁰ In published studies, the median age at diagnosis of pediatric FL was approximately 11 years, and the large majority of cases were stage I or II at diagnosis with a predilection for localized nodal involvement in the head and neck region.¹⁸⁻²² Histologically, pediatric FL cases tend to be associated with large expansive follicles with a “starry sky” pattern, high histologic grade (grade 3), and a high proliferation index.²⁰⁻²² Expression of BCL-2 protein may be observed in

approximately 40% to 50% of cases, and expression of Bcl-6 protein can be seen in the majority of cases.¹⁹⁻²²

Importantly, the pediatric variant of FL is generally characterized by lack of *BCL2* rearrangement and t(14,18), which constitute the genetic hallmark of conventional FL cases seen in adults.^{10,19-22} Rearrangement of *BCL6* is also typically absent in pediatric-type FL.^{20,21} Expression of BCL-2 protein (by IHC) has been reported in approximately half of the cases of FL without *BCL2* rearrangement or t(14,18), as mentioned above.²⁰⁻²² Pediatric FL without *BCL2* rearrangements tend to be associated with localized disease with an indolent course and favorable prognosis, with only rare instances of disease progression or relapse.¹⁹⁻²² In a recent analysis of FL cases in younger patients (age <40 years; n=27), a highly indolent pediatric-type FL was identified based on the lack of *BCL2* rearrangement concurrent with a high proliferation index (defined as ki-67 \geq 30%).²¹ These cases without *BCL2* rearrangement but with high proliferation index (n=21) were all stage I disease and none showed disease progression or relapse. In contrast, the remaining cases (n=6) with *BCL2* rearrangement and/or low proliferation index (defined as ki-67 <30%) all patients had stage III or IV disease, and 83% of these patients experienced disease progression or recurrence. Cases of indolent pediatric-type FL were also found among a separate cohort of adult patients; similar to the finding from the younger cohort of patients, adult patients without *BCL2* rearrangement but with high proliferation index (n=13) all had stage I disease, and none had progressed or relapsed after a median follow-up time of 61 months.²¹ This study showed that pediatric-type FL characterized by lack of *BCL2* rearrangement, early-stage disease, and an indolent disease course can be diagnosed in adults. Cases of pediatric-type FL have primarily been managed with chemotherapy (with or without RT), excision only (with or without RT), and more

recently, chemoimmunotherapy with generally favorable outcomes and prognosis.^{19,21,23}

Workup

The diagnostic workup for FL is similar to the workup for other lymphomas. The initial workup for newly diagnosed patients should include a thorough physical examination with attention to node-bearing areas, and evaluation of performance status and constitutional symptoms. Laboratory assessments should include CBC with differential and a comprehensive metabolic panel, in addition to measurements of serum lactate dehydrogenase (LDH) levels and serum beta-2 microglobulin. HBV testing is recommended due to increased risks of viral reactivation when chemoimmunotherapy regimens are being considered for treatment. Measurement of uric acid and hepatitis C testing may be useful for certain cases.

The majority of patients with FL will present with disseminated disease. The approach to therapy differs dramatically between patients with localized and those with disseminated disease. Bone marrow biopsy with aspirate is essential for documenting clinical stage I-II disease. Adequate trephine biopsy (specimen ≥ 1.6 cm)^{24,25} should be obtained for initial staging evaluation, along with bone marrow aspiration. If radioimmunotherapy is considered, bilateral core biopsy is recommended; in such instances, the pathologist should provide the percent of overall cellular elements and the percent of cellular elements involved in the marrow. Bone marrow biopsy can be deferred if observation is the initial option.

The majority of the NCCN Member Institutions routinely employ chest, abdominal and pelvic CT as part of the diagnostic evaluation. CT scan of the neck may also assist in defining the extent of local disease. In patients presenting with what appears to be localized disease, a PET

scan may be helpful in identifying occult sites of disease or if there is concern about histologic transformation.²⁶ PET does not replace histologic confirmation of the diagnosis; however, if there are sites with discordant high FDG-avidity, these represent the most likely sites of transformation. For patients being considered for treatment regimens containing anthracyclines or anthracenediones, a MUGA scan or echocardiogram should be obtained.

Treatment Options for Stage I-II FL

The NCCN Guidelines for FL apply to patients with grade FL1-2. Cases of FL3A and FL3B are commonly treated according to treatment recommendations for DLBCL.

Involved-site radiotherapy (ISRT) remains the current standard of care for patients with early-stage FL. Results from studies with long-term follow up showed favorable outcomes with RT in these patients.²⁷⁻³⁰ In patients with stage I or II low-grade FL initially treated with involved- or extended-field RT, the median overall survival (OS) was about 14 years; 15-year OS rate was 40% and the 15-year relapse-free survival (RFS) or progression-free survival (PFS) was also about 40%.^{29,30} In both of these studies, 41% of patients had stage I disease. The 15-year PFS outcomes were influenced by factors such as disease stage (66% for stage I vs. 26% for stage II disease) and maximal tumor size (49% for tumors < 3 cm vs. 29% for ≥ 3 cm). The OS rate was not significantly different between extended-field RT compared with IFRT (49% vs. 40%, respectively).³⁰ Long-term outcomes from another study of RT in patients with early-stage grade 1-2 FL (with or without chemotherapy) reported a median OS of 19 years and a 15-year OS rate of 62%.²⁸ In this study, the majority of patients (74%) had stage I disease and 24% had received chemotherapy with RT, which may have resulted in the higher OS rate reported compared with the aforementioned studies. In a

recent study of patients with limited stage FL (grade 1 to 3A) treated with IFRT or reduced IFRT (RT of involved nodes only), the 10-year PFS and OS rates were 49% and 66%, respectively.²⁷ The reduction in radiation field size did not impact PFS or OS outcomes. Observation alone has been evaluated in patients with early-stage FL for whom toxicities related to IFRT were a concern. In a retrospective analysis of patients with stage I-II disease, carefully selected patients (requirement of large abdominal radiation field, advanced age, concern for xerostomia or patient refusal) who did not receive immediate treatment had comparable outcomes to those who were treated with RT.³¹

Sequential combination treatment with RT and chemotherapy has also been evaluated in patients with early-stage FL. In a prospective study of 44 patients with stage I-II low-grade NHL, the addition of cyclophosphamide, vincristine, prednisone, and bleomycin (COP-bleomycin) or CHOP-bleomycin to RT resulted in a 5-year failure-free survival (FFS) rate and OS rate of 74% and 89%, respectively.³² The combination treatment appeared to improve failure-free survival but did not impact OS in patients with early-stage disease.³² In a small prospective randomized study of RT alone compared with RT with adjuvant CHOP in patients with stage I low- or intermediate-grade NHL (n=44), the addition of adjuvant CHOP to RT did not improve relapse-free survival (RFS) or OS in the subgroup of patients with early-stage low-grade NHL.³³

In a prospective analysis based on data from the National LymphoCare study registry, outcomes with different first-line management approaches were evaluated in the subgroup of patients (rigorously staged with bone marrow biopsy and complete imaging studies) with stage I FL (n=206).³⁴ First-line management strategies included observation only (i.e., “watch and wait”) in 17%, RT only in 27%, rituximab monotherapy in 12%, rituximab combined with chemotherapy

(chemoimmunotherapy) in 28%, and combined modality with RT (typically involved chemoimmunotherapy prior to RT) in 13%. With a median follow up of 57 months, the median PFS with RT alone was 72 months; median PFS had not been reached with the other management approaches. After adjusting for tumor grade, LDH level and presence of B symptoms, treatment with chemoimmunotherapy or combined modality with RT improved PFS compared with RT alone (HRs of 0.36 and 0.11 respectively).³⁴ PFS outcomes did not differ between RT alone, observation alone and rituximab monotherapy. With the current follow up time, no differences in OS outcomes were observed between the various management approaches.³⁴ The study investigators suggested that the ‘standard’ approach of treating early-stage symptomatic FL with RT alone may be challenged in the current era of diverse therapeutic strategies.

A recent multicenter retrospective analysis evaluated outcomes in 145 patients with stage I or II FL who were managed with six different first-line treatment options (observation (i.e., “watchful waiting”), chemotherapy alone, RT alone, RT combined with chemotherapy, rituximab monotherapy and rituximab combined with chemotherapy (chemoimmunotherapy)).³⁵ The median age was 55 years; 58% had stage I disease and 42% had stage II disease. Bulky disease was present in 15% of patients. For patients who received active therapy, the CR rates were 57% for single-agent rituximab, 69% for chemotherapy alone, 75% for chemoimmunotherapy, 81% for RT alone and 95% for RT combined with chemotherapy.³⁵ PFS rate at 7.5 years was highest with chemoimmunotherapy (60%) compared with other management options (19% with RT alone, 23% with chemotherapy alone, 26% with RT combined with chemotherapy and 26% for observation only; $P = .00135$). However, no significant differences were observed in OS at 7.5 years across the different approaches (66% with

RT alone, 74% with chemotherapy alone, 67% with RT combined with chemotherapy, 72% with observation only, and 74% with chemoimmunotherapy).³⁵

Treatment Options for Stage II (bulky) and Stage III-IV

Despite therapeutic advances that have improved outcomes, FL is generally considered a chronic disease characterized by multiple recurrences with current therapies. Several prospective randomized trials have failed to demonstrate a survival advantage with immediate treatment versus a “watch and wait” approach in patients with advanced stage, low tumor burden (or asymptomatic) FL.³⁶⁻³⁸ These studies used chemotherapy regimens for the immediate treatment arm, as the studies were conducted prior to the standard incorporation of rituximab in FL therapy.

A randomized phase III intergroup trial evaluated the role of immediate treatment with rituximab (with or without additional rituximab maintenance) versus watchful waiting in patients with advanced stage, asymptomatic FL (n=462).³⁹ The primary endpoint of this trial was time to initiation of new therapy from randomization. Results from an interim analysis of this trial showed that immediate treatment with rituximab resulted in significantly longer median time to initiation of new therapy compared with observation alone (not reached at 4 years vs. 33 months; $P < .001$); median PFS was also significantly longer with rituximab compared with observation (not reached vs. approximately 24 months; $P < .001$). The endpoint chosen for this trial, however, is rather controversial considering that one arm of the trial involved initiation of early therapy; a more justifiable endpoint for this study could have been “time to initiation of second therapy”. Moreover, no differences in OS were observed between the study arms.³⁹ Further follow up is needed to

evaluate whether immediate treatment with rituximab has an impact on time to second-line therapy.

In a more recent randomized phase III trial conducted by ECOG (E4402 study; RESORT), patients with low tumor burden FL (by GELF criteria) were treated with standard doses of rituximab, of which responding patients were then randomized to receive immediate maintenance with rituximab (n=140) or retreatment with rituximab upon progression (n=134).⁴⁰ The primary endpoint of this trial was time to treatment failure (TTF). Results from a planned interim analysis showed that at a median follow up of 3.8 years, median TTF was similar between the maintenance arm and retreatment arm (3.9 years vs. 3.6 years). Time to initiation of cytotoxic therapy was longer with maintenance rituximab compared with retreatment (95% vs. 86% remained free of cytotoxic therapy at 3 years), but both approaches delayed the initiation of cytotoxic therapy compared with historical “watch and wait” approaches in a similar population.⁴⁰ Evaluation of OS outcomes will require further follow up.

In a recent analysis based on data from the F2-study registry of the International Follicular Lymphoma Prognostic Factor Project, outcomes were evaluated in a cohort of patients with low-tumor burden FL who were initially managed by a “watch and wait” approach (n=107).⁴¹ All of the patients in this cohort were asymptomatic, and 84% had stage III or IV disease. With a median follow up of 64 months, the median time observed without treatment was 55 months. Fifty-four patients (50%) required therapy, and among these patients, 71% received first-line treatment with rituximab-containing regimens. Multivariate analysis showed that involvement of more than 4 nodal areas was a significant independent predictor of shorter time to initiation of treatment. In order to assess whether an initial “watch and wait” approach would have negative effects on treatment efficacy during subsequent treatment,



outcomes in this cohort were compared with those of patients from the F2-study registry who had low-tumor burden, asymptomatic FL, but were initially treated with rituximab-containing regimens (n=242).⁴¹ The endpoint for the comparison was freedom from treatment failure (FFTF), which was defined as the time from diagnosis to one of the following events: progression during treatment, initiation of salvage therapy, relapse, or death from any cause. In the “watch and wait” cohort, initiation of first-line therapy was not considered an event for FFTF. The 4-year FFTF was 79% in the “watch and wait” cohort compared with 69% in the cohort initially treated with rituximab-containing regimens; the difference was not significant after adjusting for differences in baseline disease factors between the cohorts. In addition, the 5-year OS was similar (87% vs. 88%, respectively).⁴¹ The investigators concluded that “watch and wait” remained a valid strategy even in the rituximab era, for the management of patients with prognostically favorable, low-tumor burden FL,

Collectively, findings from the above studies suggest that outside of clinical trials, observation is still the standard practice for patients with advanced stage low tumor burden FL. In the clinical practice setting, treatment should only be initiated when a patient presents with indications for treatment (based on GELF criteria).

Rituximab has demonstrated single-agent activity in previously untreated patients, as well in those with relapsed or refractory disease.⁴²⁻⁴⁴ The addition of rituximab to combination chemotherapy regimens has consistently been associated with increased ORR, response duration and PFS outcomes.⁴⁵⁻⁴⁹ In addition, some studies have demonstrated OS benefit with the addition of rituximab; a recent meta-analysis has confirmed the benefit in OS despite what is still limited follow up for FL.⁵⁰

Long-term follow-up data from a multicenter phase II trial demonstrated the safety and efficacy of rituximab combined with CHOP chemotherapy (R-CHOP) in patients with relapsed or newly diagnosed indolent NHL.⁴⁶ The ORR rate was 100% with 87% of patients achieving a CR or CRu. The median time to progression and the duration of response was 82 months and 83.5 months respectively. The superiority of R-CHOP to CHOP as first-line therapy was established in a prospective randomized phase III study conducted by the German Low-Grade Lymphoma Study Group (GLSG) in previously untreated patients with advanced-stage FL (N=428). R-CHOP was associated with a 60% reduction in the relative risk for treatment failure, significantly prolonged time to treatment failure, higher ORR (but no difference in CR rate) and prolonged duration of remission.⁴⁷ OS analysis was complicated by a second randomization (for patients age <60 years), which included high-dose therapy followed by autologous stem cell rescue (HDT/ASCR). Outcomes were not significantly different with and without rituximab, in patients who received consolidation with HDT/ASCR. However, in patients who received interferon maintenance (who did not undergo HDT/ASCR), duration of remission was significantly improved with R-CHOP followed by interferon compared with CHOP/interferon (median not reached vs. 26 months). In addition, among the subgroup of older patients (age ≥60 years) who received interferon maintenance (as these patients were not eligible for HDT/ASCR), R-CHOP/interferon was associated with significantly improved 4-year PFS rate (62% vs. 28%) and OS rate (90% vs. 81%) compared with CHOP/interferon.⁵¹

In a randomized phase III study, addition of rituximab to CVP chemotherapy (R-CVP; n=162) compared with CVP (n=159) significantly improved outcome in patients with previously untreated FL, with no significant increase in toxicity.⁴⁸ At a median follow-up of

53 months, R-CVP was associated with improved ORR (81% vs. 57%), CR/CRu rate (41% vs. 10%), median time to progression (34 months vs. 15 months) and 4-year OS rate (83% vs. 77%).⁴⁹

The addition of rituximab to fludarabine or fludarabine-based combination has also been evaluated in various clinical studies.⁵²⁻⁵⁵ In a phase II study, rituximab combined with fludarabine (FR) was evaluated in patients with previously untreated or relapsed low-grade or follicular NHL (n=40; 68% previously untreated).⁵² The ORR was 90% with 80% of patients achieving a CR. With a median follow-up time of 44 months, the median response duration, time to progression and OS had not been reached. The probability of OS at 50 months was estimated to be 80%. No significant differences in response or OS outcomes were noted between previously untreated and relapsed patients.⁵² In a prospective randomized phase III trial (n=147; 128 evaluable patients), the combination of rituximab and FCM (fludarabine, cyclophosphamide, mitoxantrone; R-FCM) was associated with superior outcomes compared with FCM in patients with relapsed or refractory FL and MCL.⁵³ R-FCM resulted in significantly higher ORR (79% vs. 58%; $P=0.01$), higher CR rates (33% vs. 13%; $P=.005$), improved median PFS (16 months vs. 10 months; $P=.038$) and improved median OS (not reached at 3 years vs. 24 months; $P=0.003$) compared with FCM alone. In addition, among the subgroup of patients with FL (n=65), R-FCM was associated with significantly improved median PFS (not reached at 3 years vs. 21 months; $P=.014$); median OS (not reached in either treatment arm) was not significantly different.⁵³ In a randomized trial from the MD Anderson Cancer Center (MDACC), concurrent administration of rituximab with FND regimen (fludarabine, mitoxantrone and dexamethasone; R-FND) resulted in a significantly higher 3-year FFS rate (84% vs. 59% for sequential arm) in the subset of patients with FL.⁵⁴ In a subsequent report from the MDACC that

included an analysis of this study (concurrent or sequential inclusion of rituximab with FND) in patients with FL (n=151), the median FFS and OS had not been reached at a median follow up of 3.3 years; the 5-year FFS rate and OS rate with the regimen was 60% and 95%, respectively.⁵⁶ The combination of rituximab with fludarabine and mitoxantrone (R-FM) was evaluated in a phase II trial in patients with relapsed/refractory FL with high tumor burden (based on GELF criteria; n=50).⁵⁷ None of the patients were previously treated with rituximab, fludarabine or mitoxantrone. The ORR with this regimen was 84% (CR/CRu in 68%). The 3-year PFS rate and OS rate was 47% and 66%, respectively.⁵⁷

The incorporation of rituximab to chemotherapy regimens has become a widely accepted standard of care for first-line therapy for patients with FL. However, no head-to-head randomized studies have shown superiority of one chemoimmunotherapy regimen over another with regards to OS outcomes. A report from the prospective, multicenter observational National LymphoCare Study based on the data collected from a large population of previously untreated patients with FL in the U.S. (n=2,738) showed that rituximab-containing chemoimmunotherapy was used in 52% of patients.⁵ Among these patients, the most commonly employed regimens included R-CHOP (55%), R-CVP (23%) and rituximab with fludarabine-based regimens (R-Flu; 15.5%). In a recent analysis of patients treated with these rituximab-containing regimens in the National LymphoCare Study, 2-year PFS rates were similar between patients treated with R-CHOP, R-CVP or R-Flu (78% vs. 72% vs. 76%).⁵⁸ The 2-year OS rate showed significant differences, however (94% vs. 88% vs. 91%, respectively), with OS benefits observed for R-CHOP compared with R-CVP; this benefit with R-CHOP was more apparent in the subgroup of patients with poor-risk FLIPI scores.⁵⁸

The phase III randomized trial of the Italian Lymphoma group (FOLL-05 Trial) evaluated the efficacy of three chemoimmunotherapy regimens (R-CVP, R-CHOP and R-FM) as first-line therapy in patients with advanced stage FL (n=534).⁵⁹ The primary endpoint of this study was time to treatment failure (TTF). The 3-year TTF rate was 46% for patients randomized to R-CVP, 62% for R-CHOP ($P=.003$ versus R-CVP) and 59% with R-FM ($P=0.006$ versus R-CVP), after a median follow up of 34 months. The 3-year PFS was 52%, 68%, and 63%, respectively ($P=.011$). No significant differences were observed between treatment arms for ORR or CR rates. The 3-year OS rate was 95% for all patients in this study.⁵⁹ Grade 3 or 4 neutropenia was more common in the R-FM arm, occurring in 64% of patients, compared with 28% with R-CVP and 50% with R-CHOP. The incidence of secondary malignancies was also more common with R-FM (8%) than with R-CVP (2%) or R-CHOP (3%).⁵⁹ Although these studies suggest a potential advantage of R-CHOP over R-CVP, both regimens are considered standard first-line therapies, and the selection of the optimal therapy would mainly depend on individual patient factors.

Fludarabine-based chemoimmunotherapy regimens may not be an ideal treatment option in the front-line setting because of the stem cell toxicity and increased risks for secondary malignancies associated with such regimens.⁶⁰⁻⁶² This may be of particular concern for younger patients with FL who may be candidates for autologous stem cell transplantation in the future. Prior exposure to fludarabine has been associated with poorer mobilization of peripheral blood stem cells in patients with lymphoma.^{45,60-62}

Bendamustine, an alkylating agent with a purine-like benzimidazole ring component, has been shown to have low or incomplete cross-resistance with other alkylating agents due to its unique cytotoxic properties. Bendamustine (as a single agent or in

combination with rituximab) has shown promising results with acceptable toxicity in patients with newly diagnosed as well as heavily pretreated relapsed or refractory indolent or mantle cell histologies or transformed NHL.⁶³⁻⁶⁸ A multicenter randomized open-label phase III study conducted by the StiL (Study Group Indolent Lymphomas) compared rituximab combined with bendamustine (BR) with R-CHOP as first-line treatment in patients with advanced follicular, indolent, and mantle cell lymphomas (n=514).⁶⁹ The primary endpoint of this study was PFS, which was significantly longer with BR compared with R-CHOP (median 69.5 months vs. 31 months; hazard ratio=0.58, 95% CI 0.44–0.74; $P<.0001$). Median PFS was significantly longer with BR in the subgroup of patients with FL (n=279; not reached vs. 41 months; $P=.0072$). The ORR was similar between treatment arms (93% with BR; 91% with R-CHOP), although the CR rate was significantly higher in the BR arm (40% vs. 30%; $P=.021$).⁶⁹ With a median follow up of 45 months, no significant difference in OS was observed between treatment arms, and median OS has not been reached in either arm. The BR regimen was associated with a lower incidence of serious adverse events compared with R-CHOP (19% vs. 29%). In addition, BR was associated with less frequent grade 3 or 4 neutropenia (29% vs. 69%) or infections (any grade; 37% vs. 50%). Erythema (16% vs. 9%) and allergic skin reactions (15% vs. 6%) were more common with BR compared with R-CHOP. The incidence of secondary malignancies was similar, with 20 cases (8%) in the BR arm and 23 cases (9%) with R-CHOP.⁶⁹

Another ongoing multicenter randomized open-label phase III study is evaluating the efficacy and safety of the BR regimen compared with R-CHOP/R-CVP in patients with previously untreated indolent NHL or mantle cell lymphoma (BRIGHT Study).⁷⁰ Among evaluable patients (N=419), the CR rate (assessed by an independent review committee) with BR was not inferior to R-CHOP/R-CVP (31% vs. 25%). The CR

rate in the subgroup of patients with indolent NHL was 27% and 23%, respectively. BR was associated with less grade 3 or 4 neutropenia (by laboratory assessment: 44% vs. 70%) but more infusion-related reactions (6% vs. 4%) compared with R-CHOP/R-CVP. Fatal adverse events occurred in 6 patients (3%) in the BR arm and 1 patient (<1%) in the R-CHOP/R-CVP arm.⁷⁰ In a phase II multicenter study, BR resulted in an ORR of 92% (CR in 41%) in patients with relapsed or refractory indolent and mantle cell lymphomas (N=67).⁶⁷ The median duration of response and PFS were 21 months and 23 months, respectively. Outcomes were similar for patients with indolent or mantle cell histologies.⁶⁷

Bendamustine combined with rituximab and the proteasome inhibitor bortezomib (BVR) has been evaluated in two recent phase II studies in patients with relapsed and/or refractory FL.^{63,64} In a study of 30 patients with relapsed/refractory indolent or mantle cell lymphoma (16 patients had FL; high-risk FLIPI, 56%; median 4 prior therapies), BVR regimen was associated with an ORR of 83% (CR in 52%).⁶⁴ The ORR was 93% among the subgroup of patients with FL and 75% for the subgroup with rituximab-refractory disease (n=10). The 2-year PFS rate was 47% and the median PFS for all patients was approximately 22 months. Serious adverse events were reported in 8 patients, which included 1 death due to sepsis.⁶⁴ In another study (VERTICAL) that evaluated a different BVR combination regimen in patients with relapsed/refractory FL (n=73; high-risk FLIPI, 38%; median 2 prior therapies), the ORR (among n=60 evaluable) was 88% (CR in 53%).⁶³ The median duration of response was 12 months. Among the subgroup of patients refractory to prior rituximab (n=20 evaluable), the ORR was 95%. The median PFS for all patients on the study was 15 months. Serious adverse events were reported in 34% of patients; the most common grade 3 or 4 adverse events were

myelotoxicities, fatigue, peripheral neuropathy, and gastrointestinal symptoms.⁶³

The immunomodulating agent lenalidomide (a thalidomide analog indicated for the treatment of multiple myeloma and myelodysplastic syndromes), with or without rituximab, has also been evaluated in the treatment of both patients with previously untreated and relapsed/refractory indolent NHL. In a phase II trial of patients with relapsed/refractory indolent NHL (n=43; median 3 prior therapies), single-agent lenalidomide induced an ORR of 23% (CR /CRu in 7%).⁷¹ Among the subgroup of patients with FL (n=22), the ORR was 27%. The median duration of response was longer than 16.5 months, and has not been reached. Median PFS for all patients was 4.4 months.⁷¹ An ongoing randomized phase II trial is assessing the activity of lenalidomide alone compared with lenalidomide in combination with rituximab (CALGB 50401 study) in patients with recurrent FL (N=94; n=89 evaluable).⁷² The ORR with lenalidomide alone was 49% (CR in 13%) and with the combination regimen was 75% (CR in 32%). With a median follow up of 1.5 years, median EFS was significantly longer with the combination (2 years vs. 1.2 years; *P*=.0063). Approximately 19% of patients in each arm discontinued therapy due to adverse events. Grade 3 or 4 adverse events were reported in a similar proportion of patients in the monotherapy and combination arms (49% vs. 52%; grade 4 in 9% in each arm). The most common grade 3 or 4 toxicities included neutropenia (16% vs. 19%), fatigue (9% vs. 14%), and thrombosis (16% vs. 4%).⁷² The combination of lenalidomide and rituximab was also evaluated in a phase II study in patients with previously untreated indolent NHL (N=110; n=103 evaluable).⁷³ Among the subgroup of patients with FL (n=46), the ORR was 98% (CR/CRu in 87%) and the 2-year PFS was 89%. In patients with FL who had a positive PET scan prior to therapy (n=45), 93% achieved PET-negative response after treatment. Grade 3 or greater

neutropenia was common, and occurred in 40% of patients overall. Thrombosis was reported in 3 patients (3%).⁷³

Radioimmunotherapy (RIT) with the radio-labelled monoclonal antibodies ⁹⁰Y-ibritumomab tiuxetan⁷⁴⁻⁷⁸ and ¹³¹I-tositumumab⁷⁹⁻⁸² has been evaluated in patients with newly diagnosed, as well as those with relapsed, refractory or histologically transformed FL. In an international phase II trial, ⁹⁰Y-ibritumomab when used as a first-line therapy in older patients (age >50 years) with stage III or IV FL (N=59; median age 66 years, range 51–83 years) resulted in an ORR of 87% (CR in 41%, CRu in 15%) at 6 months after therapy.⁷⁸ After a median follow-up of approximately 31 months, the median PFS was 26 months and median OS has not been reached. The most common toxicities with first-line ⁹⁰Y-ibritumomab included grade 3 or 4 thrombocytopenia (48%; grade 4 in 7%) and neutropenia (32%; grade 4 in 17%). No grade 3 or 4 non-hematologic toxicities were reported. Grade 2 infections occurred in 20% and grade 2 GI toxicities in 10% of patients.⁷⁸ In a randomized phase III study in patients with relapsed or refractory low-grade, follicular or transformed lymphoma (n=143), ⁹⁰Y-ibritumomab tiuxetan also produced statistically and clinically significant higher ORR (80% vs. 56%) and CR rate (30% vs. 16%) compared with rituximab alone.⁷⁵ At a median follow-up of 44 months, median TTP (15 vs. 10 months) and duration of response (17 vs. 11 months) were longer for patients treated with ⁹⁰Y-ibritumomab compared with rituximab.⁷⁶

Initial treatment with a single one-week course of ¹³¹I-tositumomab induced prolonged clinical and molecular remissions in patients with advanced FL (N=76).⁷⁹ After a median follow-up of 10 years, the median duration of response was 6 years. For the 57 patients with a CR, median PFS was almost 11 years.⁸³ Ten-year PFS and OS rates were approximately 40% and 82%, respectively. Secondary

malignancies were reported in 11 patients (14%) during this long-term follow-up period, and 1 patient (1%) developed MDS about 8 years after therapy.⁸³ A single course of ¹³¹I-tositumumab was significantly more efficacious than the last qualifying chemotherapy in extensively pretreated patients with refractory, low-grade, or transformed NHL (n=60).⁸¹ The final results of the study demonstrated that ¹³¹I-tositumumab resulted in long-term durable CRs. Among the 12 patients who achieved a CR, the median duration of response was nearly 10 years; among the 5 patients who continued in CR (lasting ≥10 years), none had received prior rituximab therapy.⁸⁴

Phosphatidylinositol 3-kinase (PI3K) plays a central role in the normal B-cell development and function.⁸⁵ PI3Kδ signaling pathways are frequently hyperactive in B-cell neoplasms. Idelalisib, the isoform-selective oral inhibitor of PI3K-delta, has demonstrated promising clinical activity in phase I studies in patients with indolent NHL.⁸⁶ The safety and efficacy of idelalisib in patients with relapsed indolent NHL was evaluated in a phase II multicenter single arm study.⁸⁷ In this study, 122 patients with indolent NHL (72 patients with FL, 28 patients with SLL and 15 patients with MZL) that had not responded to previous treatment with rituximab and an alkylating agent were treated with idelalisib (150 mg oral, BID) until disease progression or patient withdrawal from the study.⁸⁷ Majority of the patients (89%) had stage III or IV disease. Among patients with FL, 79% of patients were of intermediate-risk or high-risk, based on FLIPI scores and 17% of patients had FL grade 3a. The primary end point of the study was the ORR. The median duration of treatment with idelalisib was 6.6 months. Idelalisib resulted in tumor reductions in 90% of the patients, with an ORR of 57% (6% CR and 50% PR). Response rates were similar across all subtypes of indolent NHL. The median duration of response, median PFS and OS were 12.5 months, 11.0 months and 20.3 months, respectively. At 48 weeks, 47% of the

patients remained progression-free. The median follow-up was 9.7 months. The most common adverse events of grade 3 or higher were neutropenia (27%), elevations in aminotransferase levels (13%), diarrhea (13%), and pneumonia (7%). Fatal and/or serious hepatotoxicity, severe diarrhea or colitis, pneumonitis, and intestinal perforation have been observed in patients treated with idelalisib.⁸⁸ See “*Special Considerations for the use of BCR Inhibitors*” in the guidelines for monitoring and management of adverse reactions associated with idelalisib.

Based on the results of this study, idelalisib (150 mg oral, BID) was recently approved by the FDA for the treatment of relapsed FL that has not responded to at least two prior systemic therapies. The NCCN Guidelines have included idelalisib as an option for second-line therapy for patients with relapsed or refractory FL.

First-line Consolidation with RIT

First-line chemotherapy followed by RIT with ⁹⁰Y-ibritumomab⁸⁹⁻⁹² or ¹³¹I-tositumomab⁹³⁻⁹⁶ has also been evaluated in several phase II studies.

In the international phase III trial (First-line Indolent Trial; FIT), patients with advanced stage FL responding to first-line induction therapy (n=414) were randomized to receive ⁹⁰Y-ibritumomab or no further treatment (observation only).⁹¹ After a median follow-up of 7.3 years, the estimated 8-year PFS was 41% with ⁹⁰Y-ibritumomab tiuxetan consolidation and 22% with observation only, with a median PFS of 4.1 years versus 1.1 years, respectively ($P < .001$).⁹⁷ No significant difference in OS was observed between treatment arms. The incidence of secondary malignancies was higher in the consolidation arm compared with the observation arm (13% vs. 7%), but the difference was not statistically significant. MDS/AML occurred more frequently in

the consolidation arm (3% vs. <1%), with a significantly increased actuarial 8-year incidence rate (4.2% vs. 0.6%; $P < .042$). The median time from randomization to second malignancies was 58 months. The FIT study included only a small number of patients (14%) who received rituximab in combination with chemotherapy as induction.^{91,97} Among these patients, the estimated 8-year PFS rate was 56% with ⁹⁰Y-ibritumomab consolidation and 45% with observation alone; the median PFS was greater than 7.9 years and 4.9 years, respectively. The difference in PFS outcomes was not significant in this subgroup; however, the trial was not statistically powered to detect differences in subgroups based on induction therapies.⁹⁷ Since only a small proportion of patients enrolled in the FIT trial received rituximab-containing induction therapy, the effects of RIT consolidation following rituximab-containing regimens cannot be fully evaluated.

In the Southwest Oncology Group (SWOG S9911) trial, CHOP followed by ¹³¹I-tositumomab resulted in an ORR of 91%, including a 69% CR rate in patients with previously untreated, advanced FL (n=90).⁹⁵ After a median follow-up of 5 years, the estimated 5-year PFS rate and OS rate was 67% and 87%, respectively.⁹⁴ In a historical comparison, these results were more favorable than those reported for CHOP alone. In a multicenter phase II study, CVP chemotherapy followed by ¹³¹I-tositumomab resulted in an ORR of 100% with a 93% CR rate in untreated patients with FL (n=30). The 5-year PFS rate and OS rate was 56% and 83%, respectively.⁹⁶

The phase III randomized Intergroup study by the SWOG/CALGB (S0016) evaluated the role of RIT consolidation with ¹³¹I-tositumomab (CHOP-RIT) following first-line therapy in patients with advanced stage FL.⁷ In this study, 554 patients were randomized to first-line therapy with 6 cycles of R-CHOP or 6 cycles of CHOP followed by consolidation with ¹³¹I-tositumomab (CHOP-RIT).⁷ After a median follow-up time of 4.9

years, the estimated 2-year PFS (76% vs. 80%) and OS (97% vs. 93%) rates were not significantly different between R-CHOP and CHOP-RIT. Median time to progression has not yet been reached for either study arm. Both the ORR (84% in each arm) and CR rates (40% vs. 45%, respectively) were also similar between treatment arms. CHOP-RIT was associated with a higher incidence of grade 3 or 4 thrombocytopenia (18% vs. 2%) but fewer febrile neutropenia (10% vs. 16%) compared with R-CHOP. The incidences of secondary malignancies (9% vs. 8%) and AML/MDS (1% vs. 3%) were not different between R-CHOP and CHOP-RIT.⁷

An ongoing trial (SWOG study S0801) is evaluating whether R-CHOP with RIT consolidation and with maintenance rituximab will provide improved efficacy outcomes. Data from this trial are awaited to assess the role of RIT consolidation in patients with FL treated with rituximab-containing induction.

First-line Consolidation with Maintenance Rituximab

Several studies have reported that prolonged administration of rituximab (or rituximab maintenance) significantly improved EFS in chemotherapy-naïve patients responding to initial rituximab induction, although this benefit did not translate to OS advantage.⁹⁸⁻¹⁰⁰ In a study that evaluated maintenance rituximab compared with retreatment with rituximab upon progression in patients with chemotherapy-treated indolent lymphomas responsive to rituximab therapy (n=90 randomized), maintenance rituximab significantly improved PFS compared with the retreatment approach (31 months vs. 7 months; $P=0.007$).¹⁰¹ However, retreatment with rituximab at progression provided the same duration of benefit from rituximab as did maintenance rituximab (31 months vs. 27 months).¹⁰¹ Therefore, either approach (maintenance or retreatment at progression) appeared to be beneficial for this patient population. The randomized phase III study

from ECOG (E1496) demonstrated a PFS benefit with rituximab maintenance in patients with advanced indolent lymphoma responding to first-line chemotherapy with CVP (n=311; FL, n=282).¹⁰² The 3-year PFS rate was 68% for maintenance rituximab compared with 33% for observation for all patients with advanced indolent lymphoma with response or stable disease after CVP chemotherapy. For the subgroup of patients with FL, the corresponding PFS rates were 64% and 33%, respectively; the 3-year OS rate was not significantly different in patients with FL (91% vs. 86%, respectively).¹⁰²

The phase III randomized PRIMA trial prospectively evaluated the role of rituximab maintenance in patients responding to first-line chemotherapy in combination with rituximab.¹⁰³ In this study, patients with FL responding to first-line chemoimmunotherapy (R-CVP, R-CHOP or R-FCM) were randomized to observation only or rituximab maintenance for 2 years (n=1018). After a median follow-up of 36 months, the 3-year PFS rate was 75% in the rituximab maintenance arm and 58% in the observation arm ($P=.0001$). Two years after randomization, 71.5% of patients in the rituximab maintenance arm were in CR/CRu compared with 52% in the observation group.¹⁰³ However, no significant difference was observed in OS between the two groups. Based on multivariate analysis, induction therapy with R-CHOP or R-FCM was one of the independent factors associated with improved PFS, suggesting that R-CVP induction was not as beneficial in this study. Longer follow up is needed to evaluate the effect of rituximab maintenance on OS.

Second-line Consolidation with Maintenance Rituximab

Rituximab maintenance following second-line therapy has also been evaluated in patients with relapsed/refractory disease. Two large randomized trials have demonstrated a PFS advantage with rituximab maintenance over observation for patients treated with

chemoimmunotherapy induction.¹⁰⁴⁻¹⁰⁶ In a prospective phase III randomized study by the GLSG, rituximab maintenance after second-line treatment with R-FCM significantly prolonged duration of response in the subgroup of patients with recurring or refractory FL (n=81); median PFS with rituximab maintenance was not reached compared with 26 months in the observation arm ($P=.035$).¹⁰⁴ In a phase III randomized Intergroup trial (EORTC 20981) in patients with relapsed or resistant FL (n=334), responding to CHOP or R-CHOP induction therapy, maintenance rituximab significantly improved median PFS (3.7 years vs. 1.3 years; $P<.001$) compared with observation alone.^{105,106} This PFS benefit was observed regardless of the induction therapy employed (CHOP or R-CHOP). With a median follow-up of 6 years, the 5-year OS rate was not significantly different between study arms (74% vs. 64%, respectively).¹⁰⁶

Hematopoietic Stem Cell Transplantation (HSCT) After Induction

HDT/ASCR has been shown to prolong OS and PFS in patients with relapsed or refractory disease.¹⁰⁷⁻¹⁰⁹ The GELA recently conducted a retrospective analysis of patients treated with chemotherapy alone in the first-line setting and found that EFS and survival after relapse were superior for patients treated with rituximab-containing regimens compared to chemotherapy only-based HDT/ASCR in relapsed or refractory FL.¹¹⁰ The combination of rituximab-based second-line therapy followed by HDT/ASCR resulted in favorable survival rates after relapse, which was 90% at 5 years. Allogeneic HSCT is associated with high treatment-related mortality (TRM) rates (about 30-40% for myeloablative and 25% for nonmyeloablative allogeneic HSCT).^{111,112} In a recent report from IBMTR, both myeloablative and nonmyeloablative HSCT resulted in similar TRM rates; however, nonmyeloablative allogeneic HSCT was associated with an increased risk of disease progression.¹¹³

Imaging Studies for FL

Imaging studies using CT or PET-CT scans are important components of diagnostic workup, interim restaging, and post-treatment assessments in patients with lymphomas. For patients with FL, CT scans of the chest, abdominal and pelvic regions are considered essential for diagnostic workup. The use of PET-CT is considered optional or useful in selected patients with FL during workup or for post-treatment assessment. Although PET-CT is now considered a standard part of post-treatment response evaluation in patients with aggressive NHLs or Hodgkin lymphoma, its role in patients with indolent lymphomas is less certain.

Several studies have reported on the potential usefulness of PET imaging in patients with indolent lymphomas, and documented the ability of this modality to detect lesions with high sensitivity (94–98%) and specificity (88–100%).¹¹⁴⁻¹¹⁷ Studies have also suggested that PET/CT scans may be more accurate than CT scans alone in detecting disease.^{116,118,119} In addition, post-treatment PET/CT scans have demonstrated prognostic utility in patients with indolent lymphomas. Several studies have shown that PET status (i.e., PET-positivity or PET-negativity at the end of induction therapy) was associated with PFS outcomes. In these studies, PET-negativity was associated with a longer PFS compared to PET-positivity.^{114,119,120} In a retrospective study in patients with FL treated with R-CHOP, PET/CT imaging was found to be more accurate than CT imaging in detecting both nodal and extranodal lesions at staging and in assessing response to treatment.¹²⁰ Post-treatment PET/CT-negativity was associated with more favorable PFS outcomes; median PFS was 48 months among PET/CT-negative cases compared with 17 months for positive cases ($P<.001$).¹²⁰ An exploratory retrospective analysis of the prognostic value of post-induction PET/CT scans was conducted based on data obtained

from the PRIMA trial of patients with FL. In this trial, patients with previously untreated FL treated with rituximab-containing chemoimmunotherapy were randomized to rituximab maintenance (for 2 years) or observation only.¹⁰³ Among patients with a post-induction PET/CT scan (n=122), those with a positive PET/CT scan had a significantly inferior PFS rate compared with those who were PET negative (33% vs. 71% at 42 months; $P < .001$).¹²¹ The median PFS was 20.5 months and not reached, respectively. Among the patients randomized to observation (n=57), PET/CT status remained significantly predictive of PFS outcomes. In this group, the 42-months PFS rate was 29% for PET/CT-positive patients compared with 68% in PET/CT-negative cases; median PFS was 30 months and 52 months, respectively.¹⁰³ Among the patients randomized to rituximab maintenance (n=47), PET/CT positivity was associated with inferior (but not statistically significant) PFS outcomes compared with PET/CT-negative cases (56% vs. 77% at 41 months); median PFS has not yet been reached in either the PET/CT-positive or PET/CT-negative subgroups. Moreover, PET/CT status was also associated with OS outcomes in this exploratory analysis. Patients who were PET/CT-positive after induction therapy had significantly inferior OS compared with PET/CT-negative patients (78.5% vs. 96.5% at 42 months; $P = .001$).¹⁰³

In a recent prospective study, the prognostic value of PET imaging was evaluated in patients with high-tumor burden FL treated with first-line therapy with 6 cycles of R-CHOP (n=121; no maintenance rituximab administered).¹²² PET scans were performed after 4 cycles of R-CHOP (interim PET) and at the end of treatment (final PET), and all scans were centrally reviewed. A positive PET was defined as Deauville score 4 or higher. Among patients with an interim PET scan (n=111), 76% had a PET-negative response. Among patients with a final PET (n=106),

78% had a PET-negative response.¹²² At the end of treatment, nearly all patients (98%) who achieved a CR based on IWC also achieved a PET-negative response. Interim PET was associated with significantly higher 2-year PFS (86% for PET negative vs. 61% for positive; $P = 0.0046$) but no significant difference in terms of OS. Final PET-negativity was associated with both significantly higher 2-year PFS (87% vs. 51%; $P < .001$) and higher OS (100% vs. 88%; $P = 0.013$).¹²² These studies suggest that post-treatment imaging studies may have a role as a predictive factor for survival outcomes in patients with FL. Further prospective studies are warranted to determine whether interim and/or end-of-treatment PET scans have a role in guiding post-induction therapeutic interventions.

PET scans may be useful in detecting transformation in patients with indolent NHL. Standard FDG uptake values (SUV) on PET have been reported to be higher among transformed than non-transformed cases of indolent lymphomas.¹¹⁶ High SUVs on PET imaging should raise the suspicion of transformation to aggressive lymphoma, and can be used to direct the optimal site of biopsy for histological confirmation.¹²³

Little data exist on the potential role of follow-up surveillance imaging for detection of relapse in patients with indolent NHL. In an early retrospective study, patients with stage I to stage III FL with a CR after induction were evaluated with clinical, laboratory and imaging studies during routine follow up (n=257).¹²⁴ Patients underwent CT scans of the abdomen and/or pelvis during follow-up visits. Follow up was typically performed every 3 to 6 months for the first 5 years of treatment, and then annually thereafter. The median follow-up time was 80 months (range, 13–209 months). Relapse was detected in 78 patients, with the majority of relapses (77%) occurring within the first 5 years of treatment.¹²⁴ Eleven of the relapses were detected with abdominal and/or pelvic CT scans alone. Thus, in this analysis, 4% of patients with

an initial CR had recurrence determined by routine surveillance with CT scans.¹²⁴ A more recent prospective study evaluated the role of surveillance PET scans in patients with lymphomas (Hodgkin lymphoma and NHL) with a CR after induction.¹²⁵ PET scans were performed every 6 months for the first 2 years after completion of induction, then annually thereafter. In the cohort of patients with indolent NHL (n=78), follow-up PET scans detected true relapses in 10% of patients (8 of 78) at 6 months, 12% (8 of 68) at 12 months, 9% (5 of 56) at 18 months, 9% (4 of 47) at 24 months, 8% (3 of 40) at 36 months and 6% (2 of 34) at 48 months.¹²⁵ Among 13 patients who were PET-positive without a corresponding abnormality on CT scan, relapse was documented in 8 of these patients by biopsy. Of the 47 patients with PET-positive relapses, 38 patients were detected on CT and 30 patients were detected clinically at the same time as the PET. It is unclear whether this earlier detection of relapse in a proportion of patients translates to improved outcomes.

In the absence of evidence demonstrating improved survival outcomes with early PET detection of relapse, PET scans are not recommended for routine surveillance in patients who have achieved a CR after treatment.

NCCN Recommendations for Treatment of Stage I-II Disease

Involved-site radiotherapy (ISRT; 24–30 Gy, with an additional 6 Gy in selected patients with bulky disease) is the preferred treatment option for patients with stage I or contiguous stage II disease. In selected cases where toxicity of ISRT outweighs the potential clinical benefit, observation may be appropriate. Alternate treatment options include immunotherapy with or without chemotherapy with or without RT. Because chemotherapy added to RT was not shown to provide

relapse-free survival benefit, chemotherapy plus RT is included in the NCCN Guidelines with a category 2B recommendation.

For patients with a PR following initial immunotherapy with or without chemotherapy (but without RT), additional treatment with ISRT should be considered. Otherwise, for patients with a clinical PR (following ISRT) or CR, clinical follow-up with a complete physical exam and laboratory assessment should be performed every 3 to 6 months for the first 5 years, and then annually (or as clinically indicated) thereafter. Surveillance imaging with CT scans can be performed no more than every 6 months up to the first 2 years following completion of treatment, and then no more than annually (or as clinically indicated) thereafter. Patients with no response to initial therapy should be managed in the same manner as patients with advanced disease, as described below.

NCCN Recommendations for Treatment of Stage II (bulky) and Stage III-IV Disease

As previously mentioned, treatment for patients with advanced-stage FL in the clinical practice setting should only be initiated when indicated by the GELF criteria. The modified criteria used to determine treatment initiation include: symptoms attributable to FL (not limited to B-symptoms); threatened end-organ function; cytopenia secondary to lymphoma; bulky disease (single mass >7 cm or 3 or more masses >3 cm), splenomegaly; and steady progression over at least 6 months. Treatment decisions should also consider the patient's preference; however, patients opting for immediate treatment in the absence of a clinical indication should be referred to an appropriate clinical trial. The selection of treatment should be highly individualized according to the patient's age, extent of disease, presence of comorbid conditions, and the goals of therapy. When choosing an initial therapy, care should be given to avoid excessively myelotoxic regimens in patients who may subsequently be candidates for HDT/ASCR. Chemoimmunotherapy

regimens (containing rituximab) frequently used in the management of FL may be associated with risks for reactivation of HBV, which can lead to hepatitis and hepatic failure. Therefore, prior to initiation of therapy, HBV testing (including HBsAg and HBcAb testing) should be performed for all patients; viral load should be monitored routinely for patients with positive test results. In addition, the use of empiric antiviral therapy or upfront prophylaxis should be incorporated into the treatment plan.

First-line Therapy

In the absence of an appropriate clinical trial, patients with indications for treatment should be treated with systemic therapy. In selected cases such as the elderly frail patient who would not tolerate chemotherapy, ISRT (4 Gy) may be used for local palliation. Asymptomatic patients, especially those older than 70 years of age, should be observed.³⁸

Based on the reported data, rituximab in combination with bendamustine, CHOP or CVP chemotherapy for first-line therapy in patients with advanced FL are all category 1 recommendations. In the absence of a randomized trial showing superior OS with R-CHOP versus R-CVP, either of these regimens can be considered appropriate in the first-line setting. The BR regimen has been shown to have less toxicity and a superior PFS compared to R-CHOP in a randomized phase III study; however, the OS outcomes were not significantly different. Furthermore, we have limited data on the risk of secondary MDS/AML after bendamustine. Data from a limited subset of patients suggests that peripheral blood stem cells can be collected after both BR and R-CHOP; additional data are needed to confirm this finding. Other suggested regimens include rituximab either as a single agent or in combination with fludarabine-based chemotherapy. As discussed earlier, the use of fludarabine-containing regimens may not

be ideal in the first-line setting for younger, physically fit patients (who may be candidates for future HDT/HSCR) because of the stem cell toxicity and risks for secondary malignancies. Thus, the use of regimens such as R-FND in the first-line setting is included as a category 2B recommendation. RIT is included as a category 3 option due to the absence of additional data from randomized studies. ISRT (4–30 Gy) with or without systemic therapy can be considered for palliation in patients with locally bulky or symptomatic disease if they are unable to tolerate systemic therapy.

Single-agent rituximab is the preferred first-line therapy for elderly or infirm patients. Single-agent cyclophosphamide had equivalent OS and CR rates compared to cyclophosphamide-based combination chemotherapy.¹²⁶ The NCCN Guidelines have also included RIT, alkylating agent-based chemotherapy (cyclophosphamide or chlorambucil) with or without rituximab, as alternative options for elderly or infirm patients.

First-line Consolidation or Extended Dosing

Patients with CR or PR to first-line therapy can either be observed or can be treated with optional consolidation or extended therapy. Based on the results of the PRIMA study,¹⁰³ maintenance therapy with rituximab (one dose every 8 weeks) up to 2 years is recommended (category 1) for patients responding to first-line chemoimmunotherapy. Based on the results of the FIT trial,^{91,97} RIT is recommended (category 1) for patients who received first-line chemotherapy.

As of February 2014,¹³¹ -tositumumab has been discontinued and will no longer be available for the treatment of patients with FL.

For patients receiving consolidation therapy, clinical follow-up with a complete physical exam and laboratory assessment should be performed every 3 to 6 months for the first 5 years, and then annually

(or as clinically indicated) thereafter. Surveillance imaging with CT scans can be performed no more than every 6 months up to the first 2 years following completion of treatment, and then no more than annually (or as clinically indicated) thereafter.

Second-line Therapy for Relapsed or Progressive Disease

Frequently, patients will benefit from a second period of observation after progressing from first-line therapy. Thus, treatment for relapsed or progressive disease is based on the modified GELF criteria as in first-line therapy. Progressive disease should be histologically documented to exclude transformation, especially in the presence of raising LDH levels, disproportional growth in one area, development of extranodal disease or development of new constitutional symptoms. Areas of high SUV, especially in values in excess of 13.1, should raise suspicion for the presence of transformation. However, a positive PET/CT scan does not replace a biopsy; rather, results of the PET/CT scan should be used to direct a biopsy to enhance the diagnostic yield from the biopsy. For patients requiring second-line therapy or treatment for disease unresponsive to first-line regimens, the options include chemoimmunotherapy regimens used for first-line treatment, BVR (bendamustine, bortezomib, rituximab), fludarabine combined with rituximab, FCM-R regimen (category 1) or RIT (category 1) or any of the second-line regimens used for patients with DLBCL. Based on the recent FDA approval, idelalisib is also included as an option for second-line therapy.

As of February 2014, ¹³¹¹-tositumumab has been discontinued and will no longer be available for the treatment of patients with FL.

Second-line Consolidation or Extended Dosing

For patients in remission after second-line therapy, optional maintenance therapy with rituximab (one dose every 12 weeks for 2

years) can be recommended (category 1). However, the NCCN Guidelines panel recognizes that the efficacy of maintenance rituximab in the second-line setting would likely be impacted by a patient's response to first-line maintenance with rituximab. If a patient progressed during or within 6 months of first-line maintenance with rituximab, the clinical benefit of maintenance in the second-line setting is likely very minimal. HDT/ASCR is an appropriate consolidative therapy for patients with second or third remission. Allogeneic HSCT may also be considered for highly selected patients. For patients receiving consolidation therapy, clinical follow-up with a complete physical exam and laboratory assessment should be performed every 3 to 6 months for the first 5 years, and then annually (or as clinically indicated) thereafter. Surveillance imaging with CT scans can be performed no more than every 6 months up to the first 2 years following completion of treatment, and then no more than annually (or as clinically indicated) thereafter.

Histological Transformation to DLBCL

In patients with FL, histological transformation to DLBCL is generally associated with a poor clinical outcome. Histological transformation to DLBCL occurs at an annual rate of approximately 3% for 15 years and the risk of transformation falls after that time, for reasons that remain unclear.¹²⁷ In a multivariate analysis, advanced stage disease at diagnosis was the only predictor of future transformation. The median OS after transformation has been reported to be less than 2 years.¹²⁷ However, patients with limited disease with no previous exposure to chemotherapy may have the favorable outcomes similar to *de novo* DLBCL.¹²⁸ The 5-year OS rate for patients with limited extent transformation was 66% compared with 19% for those with advanced disease ($P<0.0001$).¹²⁷



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B-cell Lymphomas

In cases where the patient has had multiple prior therapies, the prognosis is much poorer and enrollment in an appropriate clinical trial is the preferred option. In the absence of a suitable clinical trial, treatment options include RIT, chemotherapy with or without rituximab, ISRT or best supportive care. HDT/ASCR or allogeneic HSCT can be considered as consolidation therapy for patients in remission after initial treatment. In a multicenter cohort study (172 patients) conducted by the Canadian blood and bone marrow transplant group, HDT/ASCR was associated with better outcomes than rituximab-based chemotherapy alone for patients aggressive histological transformation.¹²⁹ The 5-year OS after transformation was 65%, 61% and 46% respectively for patients treated with HDT/ASCR, rituximab-containing chemotherapy and allogeneic SCT. The corresponding 5-year PFS rates after transformation were 55%, 40% and 46% respectively.

If the patient has had minimal (ISRT alone or one course of single-agent therapy including rituximab) or no prior chemotherapy, anthracycline-based chemotherapy with rituximab, with or without RT is included as a treatment option. Enrollment in clinical trial is recommended for all patients following initial therapy. Patients responding to initial treatment (with a PR or CR) could also be considered for consolidation therapy with HDT/ASCR or allogeneic HSCT. Alternatively, patients with CR to initial therapy may be observed and RIT may be considered for those with PR. Patients with no response or progressive disease following initial therapy should be treated with RIT, palliative therapy or best supportive care.

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This discussion is being updated to correspond with the newly updated algorithm. Last updated on 05/03/16

Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphomas (DLBCL) are the most common lymphoid neoplasms in adults, accounting for approximately 32.5% of NHLs diagnosed annually.¹ DLBCL NOS, follicular lymphoma (grade 3 only), DLBCL coexistent with a low-grade lymphoma of any kind (e.g., follicular lymphoma, gastric MALT or non-gastric MALT lymphoma), intravascular large B-cell lymphoma, DLBCL associated with chronic inflammation, ALK-positive DLBCL, EBV-positive DLBCL in older patients and T-cell/histiocyte rich large B-cell lymphoma are also managed according to the DLBCL guidelines.

Gene expression profiling (GEP) has revealed significant heterogeneity within DLBCL.² However, incorporation of this information into treatment algorithms awaits further investigation. Immunohistochemical markers such as CD10, BCL6, and IRF4/MUM1 have been reported to recapitulate the GEP in classifying DLBCL into 2 different subtypes: germinal center B-cell (GCB) subtype (CD10+, or BCL6+, IRF4/MUM1-) and non-GCB subtype (CD10-, IRF4/MUM1+ or BCL6-, IRF4/MUM1-).³ See “Use of Immunophenotyping/Genetic Testing in the Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A, Page 6)” in the guidelines. Immunohistochemical algorithms including GCET1, FOXP1, and LMO2 in addition to CD10, BCL6 and IRF4/MUM1 have also been proposed.^{4,5} MYC gene rearrangements have been reported in 5-8% of patients with DLBCL, and often correlate with GCB phenotype.⁶⁻⁸ GCB subtype is associated with an improved outcome compared to non-GCB subtype in patients treated with R-CHOP. Ongoing randomized clinical trials are exploring whether the addition of novel targeted agents to R-CHOP will selectively improve the outcome

in patients with non-GCB DLBCL.^{9,10} Presently, the upfront standard of care remains the same for both GCB and non-GCB subtypes.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for Non-Hodgkin’s Lymphomas an electronic search of the PubMed database was performed to obtain key literature in “Diffuse large B-cell lymphoma” published between June 2014 and October 2015 using the following search terms: diffuse large B-cell lymphoma, aggressive B-cell lymphoma, primary mediastinal B- cell lymphoma, double-hit lymphoma, gray zone lymphoma. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.¹¹

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 108 citations and their potential relevance was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel’s review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN [webpage](#).

Diagnosis

Adequate immunophenotyping is required to establish the diagnosis and to determine GCB versus non-GCB origin. The typical immunophenotype is CD20+, CD45+, and CD3-. The recommended immunophenotyping panel includes CD20, CD3, CD5, CD10, CD45, BCL2, BCL6, Ki-67, IRF4/MUM1 and MYC. Patients with GCB-like immunophenotype along with the expression of MYC and either BCL2 or BCL6 by IHC should undergo FISH or karyotype testing for the detection of *MYC*, *BCL2*, and *BCL6* gene rearrangements. Additional markers such as CD138, CD30, cyclin D1, ALK1, SOX11, EBV and HHV-8 may be useful under certain circumstances to establish the subtype. SOX11 positivity may be useful in differentiating rare cases of cyclin D1-negative pleomorphic or blastoid MCL from CD5-positive DLBCL.^{12,13}

Workup

The initial workup for newly diagnosed patients with DLBCL should include a thorough physical examination with attention to node-bearing areas, and evaluation of performance status (PS) and constitutional symptoms. Laboratory assessments should include standard blood work including CBC with differential, a comprehensive metabolic panel, and measurements of serum lactate dehydrogenase (LDH). Patients with high tumor burden and elevated LDH should be assessed for spontaneous tumor lysis syndrome (TLS), including measurements of uric acid, potassium, phosphorous, calcium, and renal function. HBV testing (surface antigen, surface antibody, and core antibody) is recommended especially if rituximab-based treatment regimens are being considered due to increased risks of viral reactivation,¹⁴ though viral reactivation has also been described after chemotherapy alone without rituximab. HIV testing and serum beta-2-microglobulin levels would be useful in selected patients.

PET-CT scans have a more clear-cut role in selected patients with DLBCL than in other lymphoid neoplasms. PET scans are particularly informative in the initial staging where upstaging resulting in altered therapy occurs about 9% of the time, and for response assessment after treatment because they can distinguish residual fibrotic masses from masses containing viable tumor.¹⁵ PET-CT scan ± chest/abdominal/pelvic CT with contrast of diagnostic quality is recommended for initial workup. As PET scans have now been incorporated into the response criteria, a baseline PET scan is necessary for optimal interpretation of post-treatment PET scans. PET-CT has also been reported to be accurate and complementary to bone marrow biopsy for the detection of bone marrow involvement in patients with newly diagnosed DLBCL.^{16,17} Bone marrow biopsy may not be needed if there is clearly positive marrow uptake by PET-CT. Bone marrow biopsy may also be omitted in the absence of any skeletal uptake on the staging PET/CT scan, unless finding another lymphoma subtype (discordant low-grade lymphoma) would be considered important for treatment decisions.

The staging workup is designed to identify all sites of known disease and determine prognosis with known clinical risk factors. International Prognostic Index (IPI) identifies specific groups of patients who are more or less likely to be cured with standard therapy.^{18,19} IPI scores are based on patient's age, stage of disease, serum LDH level, PS, and the number of extranodal sites. In patients who are 60 years or younger, the prognostic factors include tumor stage, PS, and serum LDH level. Zhou et al reported an enhanced IPI (NCCN-IPI) to stratify patients with newly diagnosed DLBCL into 4 different risk groups (low, low-intermediate, high-intermediate, and high) based on their clinical features (age, LDH, sites of involvement, Ann Arbor stage, ECOG PS).²⁰ This analysis included 1650 patients identified in NCCN database that were diagnosed with DLBCL between 2000 and 2010 and treated with

rituximab-based therapy. The NCCN-IPI discriminated patients in the low- and high-risk subgroups better (5-year OS rate 96% vs 33%) than the IPI (5 year OS rate 90% vs 54%). The NCCN-IPI was also validated using an independent cohort of 1138 patients from the British Columbia Cancer Agency. While the IPI, revised IPI (R-IPI), and NCCN-IPI predict clinical outcome with high accuracy, R-IPI and NCCN-IPI could also identify a specific subgroup of patients with very good prognosis (3-year progression-free survival [PFS] and overall survival [OS] of 100%).²¹

Elevated LDH, ≥ 2 extranodal sites and involvement of specific sites (the testes, paranasal sinus and bone marrow) are associated with increased risk for developing central nervous system (CNS) relapse.²²⁻²⁴ The German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL) recently proposed a prognostic model to predict the risk of CNS relapse incorporating the 5 clinical factors (age > 60 years, LDH > normal, stage III or IV, ECOG PS >1, and involvement of the kidney or adrenal gland) and this model was validated in an independent cohort of 1597 patients by Savage et al.^{25,26} This prognostic model separated patients into three risk categories based on the rate of developing CNS disease at 2 years: low-risk (0 or 1 risk factor; rate of CNS disease $\leq 1\%$), intermediate-risk (2 or 3 factors; rate of CNS disease 2–10%) and high-risk group (4 or 5 factors; rate of CNS disease at 17.0%). In both datasets, involvement of the kidney or adrenal gland was highly associated with CNS relapse. Lumbar puncture should be considered in patients with 4-6 risk factors identified in the DSHNHL prognostic model, the presence of ≥ 2 extranodal sites plus elevated LDH, involvement of testes, HIV-associated lymphoma, or double hit lymphoma. The diagnostic yield is improved if flow cytometric analysis of cerebrospinal fluid is undertaken.

Treatment

Treatment options for DLBCL differ between patients with localized (Ann Arbor stage I-II) and advanced (Ann Arbor stage III-IV) disease. Prognosis is extremely favorable for patients with no adverse risk factors (elevated LDH, stage II bulky disease, older than 60 years or ECOG PS ≥ 2). Patients with advanced disease should be enrolled in clinical trials, whenever possible.

Stage I-II

In the SWOG 8736 study, 3 cycles of CHOP followed by involved field radiation therapy (IFRT) produced significantly better progression-free survival (PFS; 5-year estimated PFS: 77% vs. 64% for CHOP alone) and OS (82% vs. 72% for CHOP alone) than 8 cycles of CHOP alone in patients with localized aggressive NHL;²⁷ however, this difference disappeared with further follow-up. The benefit of CHOP (3 cycles) followed by IFRT (5-year OS of 95%) in patients with limited-stage DLBCL (60 years or younger with no adverse risk factors) was also confirmed in a series from the British Columbia Cancer Agency.²⁸ Another randomized trial (ECOG 1484 study) showed that the addition of RT to CHOP (8 cycles) prolonged disease-free survival (DFS) in patients with limited stage DLBCL who had achieved complete remission (CR) to CHOP alone (6-year DFS was 73% for IFRT and 56% for observation).²⁹ In the a GELA study (LNH 93-4), however, the addition of RT to 4 cycles of CHOP did not provide any advantage over 4 cycles of CHOP alone for the treatment of older patients with low-risk localized aggressive lymphoma. The estimated 5-year event-free survival (EFS) was not different between the two groups (61% and 64%, respectively) and the 5-year estimated OS rates were 68% and 72%, respectively.³⁰ However, in this study, administration of RT was markedly delayed and 12% of patients on the RT arm did not receive RT.

The efficacy of the addition of rituximab to CHOP (R-CHOP) and IFRT has also been reported in patients with limited stage DLBCL. In the SWOG 0014 study that evaluated 3 cycles of R-CHOP followed by IFRT in patients with at least one adverse factor (non-bulky stage II disease, age > 60 years, ECOG PS 2, or elevated serum LDH) as defined by the stage-modified IPI (N=60), the 4-year PFS rate was 88%, after a median follow-up of 5 years; the corresponding 4-year OS rate was 92%.³¹ In historical comparison, these results were favorable relative to the survival rates for patients treated without rituximab (4-year PFS and OS were 78% and 88%, respectively). A phase III trial (MabThera International Trial [MInT]) compared 6 cycles of CHOP-like chemotherapy to 6 cycles of CHOP-like chemotherapy plus rituximab.^{32,33} All patients were younger than 60 years of age and had 0-1 IPI risk factors. Three quarters of patients had limited stage disease, and RT was included for all extranodal sites of disease or any site >7.5 cm. The trial found a benefit to rituximab-based chemotherapy with a 6-year OS rate of 90.1% versus 80% ($P = .0004$). The 6-year EFS rate (74.3% vs. 55.8%; $P < .0001$) and PFS rate (80.2% vs. 63.9%; $P < .0001$) were also significantly higher for patients assigned to chemotherapy plus rituximab compared to chemotherapy alone.³³

Abbreviated course R-CHOP with RT is also associated with reduced short-term toxicity compared to 6-8 cycles of R-CHOP alone. A SEER-Medicare database analysis of a large cohort of older patients with stage I-II DLBCL confirmed that 3 cycles of R-CHOP with RT and 6-8 cycles of R-CHOP alone have similar OS; however, 3 cycles of R-CHOP with RT was associated with significantly lower risk of second-line therapy and lower incidences of neutropenia including those requiring hospitalization.³⁴ The study suggested better upfront disease control and less toxicity with abbreviated RCHOP with RT.

In the two GELA studies, intensified chemotherapy [ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone) followed by consolidation with methotrexate, etoposide, ifosfamide and cytarabine] with or without rituximab was found to be superior to CHOP with or without rituximab (3 cycles) plus RT in patients with low-risk early-stage disease.^{35,36} However, this regimen was also associated with significant toxicity and includes vindesine, which is not available in the United States.

Stage III-IV

R-CHOP-21 chemotherapy is the standard treatment for patients with advanced stage DLBCL based on the results of the GELA study (LNH98-5) that demonstrated the addition of rituximab to CHOP-21 improved PFS and OS in older patients with advanced DLBCL. In this study, older patients (age 60–80 years; N=399) were randomized to receive 8 cycles of R-CHOP or CHOP.³⁷⁻³⁹ Long-term follow-up of this study showed that PFS (36.5% vs. 20%), DFS (64% vs. 43%), and OS (43.5% vs. 28%) rates were significantly in favor of R-CHOP at a median follow-up of 10 years.⁴⁰ These findings have been confirmed in three additional randomized trials including the MInT (6 cycles of R-CHOP or CHOP) which extended the findings to young patients with 0 or 1 risk factors according to the IPI.^{32,33} The Dutch HOVON and Nordic Lymphoma Group study (8 cycles of R-CHOP-14 or CHOP-14) and the ECOG/CALGB study confirmed the findings in patients older than 60 years.^{41,42} The ECOG/CALGB 9703 study also showed that maintenance rituximab in first CR offered no clinical benefit to patients who received R-CHOP as their induction therapy.⁴²

The DSHNHL studies demonstrated that 6 cycles of dose dense CHOP (CHOP-14) as first-line therapy was superior to 6 cycles of CHOP-21, prior to the introduction of rituximab.⁴³⁻⁴⁵ In the RICOVER 60-trial, older patients (age 61–80 years) were randomized to receive

6 or 8 cycles CHOP-14 with or without 8 cycles of rituximab.^{46,47} RT was administered to sites of initial bulky disease with or without extranodal involvement. The addition of rituximab to 6 or 8 cycles of CHOP-14 (R-CHOP-14) significantly improved clinical outcomes compared with CHOP-14 alone. With a median observation time of 82 months, EFS was significantly improved after R-CHOP-14 ($P < .001$) compared with CHOP-14. OS rate was also significantly improved in patients treated with R-CHOP-14. No difference in clinical benefit but increased toxicity was seen in patients treated with 8 cycles compared with 6 cycles of therapy.⁴⁷ The investigators concluded that 6 cycles of R-CHOP-14 in combination with 8 doses of rituximab should be the preferred regimen in this patient population.

The role of IFRT following CR (evaluated by CT criteria) to initial bulky sites ≥ 7.5 cm or extranodal involvement was evaluated in the RICOVER-noRTh trial (an amendment to the RICOVER-60 trial).⁴⁸ In this study, 164 patients with stage III-IV disease were treated with 6 cycles of R-CHOP-14 (best arm of the RICOVER-60 trial) but RT to bulky sites or extranodal involvement was omitted. The 3-year PFS and OS rates were significantly inferior, compared to the corresponding survival rates in patients from the RICOVER-60 trial treated with same chemoimmunotherapy with RT to bulky sites.⁴⁸ The study was therefore discontinued. Similarly, subgroup analyses of the MInT and RICOVER-60 trial showed that patients with skeletal involvement significantly benefitted from RT to sites of skeletal involvement.⁴⁹ Although retrospective subgroup analyses may be subjected selection biases, the benefit of RT held up on multivariate analysis in both studies and may be considered.

Two randomized trials have compared R-CHOP-21 with dose-dense R-CHOP-14.^{50,51} A large phase III randomized trial involving 1080 patients with newly diagnosed DLBCL found no significant difference

in either PFS or OS at a median follow up of 46 months.⁵⁰ The 2-year OS rate was 82.7% in the R-CHOP-14 arm and 80.8% in the R-CHOP-21 arm ($P = .3763$). The corresponding 2-year PFS rates were 75.4% and 74.8%, respectively ($P = .5907$). Toxicity was similar, except for a lower rate of grade 3 or 4 neutropenia in the R-CHOP-14 arm (31% vs. 60%), reflecting the fact that all patients in the R-CHOP-14 arm received primary growth factor prophylaxis with G-CSF whereas no primary prophylaxis was given with R-CHOP-21.⁵⁰ Notably, there was no difference in outcome between GCB-like and non-GCB-like DLBCL by IHC in this large prospective study. The phase III LNH03-6B GELA study compared 8 cycles of R-CHOP-14 with R-CHOP-21 in 602 older patients (age 60–80 years) with untreated DLBCL. After a median follow-up of 56 months, no significant differences between R-CHOP-14 and R-CHOP-21 were observed in terms of 3-year EFS (56% vs. 60%; $P = .7614$), PFS (60% vs. 62%) or OS rates (69% vs 72%).⁵¹ Grade 3 or 4 neutropenia were observed more frequently in the R-CHOP-14 arm (74% compared to 64% in the R-CHOP 21 arm) despite a higher proportion of patients having received G-CSF (90%) compared with patients in the R-CHOP-21 arm (66%).

The results of the dense-R-CHOEP trial showed that doubling the number of rituximab (375 mg/m^2) infusions (from 6 to 12) administered with 8 x CHOEP-14 did not result in a significant improvement of EFS and OS in aalPI2 patients with DLBCL.⁵² After a median follow-up of 24 months, the 2-year EFS and OS rates were 69% and 82% respectively. The corresponding survival rates in patients treated with 8 x CHOEP-14 with 6 infusions of rituximab in the R-MegaCHOEP study were 71% and 85% respectively.⁵³ The lack of improvement in survival rates could be attributed to more aggressive chemotherapy (CHOP vs. CHOEP), different timing of rituximab infusions and

differences in the pharmacokinetic profile of younger and older patients. There was an improvement in EFS and OS rates in patients with aIPI 3; however, it was not statistically significant because this group had only 11 patients.

Collectively, these studies suggest that R-CHOP-21 remains the standard treatment regimen for patients with newly diagnosed DLBCL with no improvement in outcome observed for dose-dense therapy in the rituximab era.

Multiple randomized trials (RICOVER 60, NHL-B2, MInT, and the MegaCHOEP trials) have demonstrated superior outcomes in women relative to men, particularly in older adults with older women benefiting more from the addition of rituximab than men.⁵⁴ This could be explained by a slower clearance rate of rituximab in older women. Based on these data, a prospective non-randomized trial evaluated R-CHOP with rituximab dose of 500 mg/m² in men over the age of 60 with DLBCL and demonstrated that the serum levels and OS rates improved compared to historical data in older men treated with rituximab dose of 375mg/m², and similar to older women treated with rituximab dose of 375 mg/m².⁵⁵ Based on these data, a rituximab dose of 500 mg/m² may be considered in older men (under the age of 80 years) treated with R-CHOP. A randomized clinical trial is ongoing.

Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) plus rituximab (DA-EPOCH-R) has shown significant activity in patients with untreated DLBCL.^{56,57} In a multicenter phase II CALGB study, DA-EPOCH-R (6–8 cycles) was evaluated in patients with previously untreated DLBCL (n=69; 48 patients with DLBCL).⁵⁶ IPI score was high-intermediate risk in 19% and high risk in 21% of patients. After a median follow up of 62 months, the 5-year TTP was 81% and OS was 84% in all patients. The 5-year TTP

rates among patients with low/low-intermediate, high-intermediate, and high risk IPI were 87%, 92%, and 54%, respectively ($P=.0085$); the 5-year OS in these subgroups were 95%, 92%, and 43%, respectively ($P<.001$).⁵⁶ The TTP rate was significantly higher in the subgroup with GCB phenotype compared with non-GCB phenotype (100% vs. 67%; $P=.008$); the GC phenotype was also associated with a higher 5-year OS rate (94% vs. 68%; $P=.04$). High tumor proliferation index (Ki-67 $\geq 60\%$) was associated with significantly decreased TTP and OS only for the subgroup with non-GCB phenotype. Febrile neutropenia occurred in 36% (grade 4 in 7%) and no significant grade 4 non-hematologic toxicities were observed. The most common grade 3 non-hematologic toxicities included neuropathies (25%), fatigue (16%), and arrhythmia (6%).⁵⁶ In another multi-institutional study that assessed the safety and efficacy of DA-EPOCH-R in patients with untreated large B-cell lymphomas and poor prognosis (IPI > 1; n = 81; DLBCL, n = 68; primary mediastinal DLBCL, n = 6) and follicular lymphoma grade 3b, n = 7), DA-EPOCH-R produced a CR rate of 80.2%.⁵⁷ After a median follow-up time of 64 months, 10-year EFS and OS rates were 47.8% and 63.6%, respectively.⁵⁷

An ongoing phase III randomized study (CALGB 50303) is evaluating DA-EPOCH-R compared with R-CHOP in untreated patients with DLBCL. Pending results of that study, there is insufficient evidence to recommend DA-EPOCH-R as standard initial therapy for patients with newly diagnosed DLBCL except in highly selected circumstances such as poor left-ventricular function, B-cell lymphoma unclassifiable with intermediate features between DLBCL and Burkitt lymphoma, double-hit lymphomas, and primary mediastinal B-cell lymphoma (PMBL).

Patients older than 80 years have not been represented in prospective clinical trials of R-CHOP and are usually not appropriate candidates for full-dose therapy. To address this, the GELA study group

conducted a multicenter single-arm prospective phase II study evaluating the safety and efficacy of a decreased dose of CHOP with a conventional dose of rituximab (R-mini-CHOP) in 149 patients older than 80 years with DLBCL.⁵⁸ After a median follow-up of 20 months, the median OS and PFS were 29 months and 21 months respectively. The 2-year OS and PFS rates were 59% and 47% respectively. An update with extended follow-up reports the 4-year PFS and OS rates to be 41% and 49%, respectively.⁵⁹ Grade ≥ 3 neutropenia was the most frequent hematological toxicity observed in 59 patients. The guidelines have included R-miniCHOP as a treatment option for patients older than 80 years.

Role of HDT/ASCR

In the randomized GELA LNH87-2 study, patients with DLBCL in first CR after induction therapy received consolidation therapy with either sequential chemotherapy or HDT/ASCR.⁶⁰ Although no difference in outcome was prospectively observed in this trial, a retrospective subset analysis of patients with aIPI high/intermediate- or high-risk disease ($n=236$), found that HDT/ASCR resulted in significantly improved outcomes compared with sequential chemotherapy with regards to both 8-year disease-free survival rate (55% vs. 39%; $P=0.02$) and 8-year OS rate (64% vs. 49%; $P=0.04$) in the high-intermediate/high-risk subset.⁶⁰ This study was performed prior to rituximab-based induction chemoimmunotherapy.

In the SWOG 9704 trial, 253 patients with high-intermediate/high IPI were randomized to receive 3 cycles of R-CHOP or HDT/ASCR, following initial remission with 5 cycles of CHOP or R-CHOP induction.⁶¹ The 2-year PFS rate was significantly higher with HDT/ASCR compared with chemoimmunotherapy alone (69% vs. 55%; $P=0.005$); the 2-year OS rates were not significantly different (74% vs. 71%, respectively; $P=.30$). In an exploratory subset analysis, HDT/ASCR was associated with

an OS benefit for high-risk patients. In this subgroup, the 2-year OS rates were 82% and 63% respectively, for patients treated with HDT/ASCR and chemoimmunotherapy. Notably, in this study a third of the patients did not receive rituximab as part of their induction regimen.

The role of upfront HDT/ASCR has also been evaluated in prospective studies.^{53,62,63} In the French GOELAMS 075 study, patients aged ≤ 60 years with DLBCL ($N=286$ evaluable) were randomized to receive 8 cycles of R-CHOP-14 or HDT with rituximab (R-HDT) followed by ASCR.⁶² The 3-year PFS rate and OS rates were 76% and 83%, respectively, with no significant differences between treatment arms.⁶² In a randomized trial of the German High-Grade NHL Study Group, patients aged ≤ 60 years with aggressive lymphomas ($N=262$ evaluable) were treated with 8 cycles of CHOEP-14 (cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone) combined with 6 doses of rituximab (R-CHOEP-14) or 4 cycles of MegaCHOEP combined with 6 doses of rituximab and followed by ASCR (R-MegaCHOEP).⁵³ No significant differences were observed between the R-CHOEP-14 and R-MegaCHOEP arms for PFS (3-year rate: 74% vs. 70%, respectively) or OS outcomes (3-year rate: 85% vs. 77%, respectively). Among patients with high/intermediate aIPI (score of 2), EFS (75.5% vs. 63.5%; $P=.0509$) and OS rates (91% vs. 77.1%; $P=.01$) were significantly better with R-CHOEP-14 compared with R-MegaCHOEP.⁵³

In the randomized DLCL04 trial of the Italian Lymphoma Foundation, patients aged ≤ 65 years with DLBCL, 399 patients were randomized to receive rituximab-containing first-line regimens (8 cycles of R-CHOP-14 or 6 cycles of R-MegaCHOP-14) with or without HDT/ASCR.⁶³ The 3-year PFS rate was significantly higher in the HDT/ASCR groups compared with the non-HDT/ASCR groups (70% vs. 59%; $P=.010$), but the 3-year OS rate was not significantly different between the two

groups (81% and 78% respectively; $P = .556$). In addition, no significant differences were observed in the 3-year PFS rates between the two rituximab-based first-line regimens.

The above studies, overall, found no benefit to upfront HDT/ASCR as compared with first-line rituximab-based chemoimmunotherapy, except in high-risk IPI patients, but this remains controversial since this finding emerged only on a retrospective subset analysis involving a small number of patients. Presently, first-line consolidation with HDT/ASCR is recommended only in selected high risk patients (category 2B), or in the context of a clinical trial.

NCCN Recommendations

R-CHOP (3 cycles) with ISRT or R-CHOP (6 cycles) with or without ISRT is recommended for patients with non-bulky (<7.5 cm) stage I or II disease.^{31,33} Patients with bulky disease (≥ 7.5 cm) may be treated more effectively with R-CHOP (6 cycles) with or without locoregional RT (category 1).³³ Regarding the addition RT, it is important to consider the results from the RICOVER-noRTh trial that showed a significant advantage to adding RT to initial bulky sites ≥ 7.5 cm.⁴⁸ R-mini-CHOP may be substituted for patients over the age of 80 to improve chemotherapy tolerability^{58,59} and ISRT alone is recommended for patients who are not candidates for any chemotherapy. See "Principles of Radiation Therapy" in the guidelines for the ISRT dose recommendations.

R-CHOP-21 for a total of 6 cycles (category 1) is recommended for patients with stage III-IV disease.^{33,41,42} In selected patients, RT to bulky sites may be beneficial (category 2B). In patients with bulky disease or impaired renal function, initial therapy should include monitoring and prophylaxis for TLS. R-CHOP-21 for a total of 6 cycles is the preferred regimen due to reduced toxicities. Other comparable

anthracycline-based regimens may also be used. Suggested alternate regimens include DA-EPOCH-R (category 2B)^{56,57} or dose-dense R-CHOP-14 (category 3).^{50,51} Participation in clinical trials is recommended, if available.

Inclusion of any anthracycline or anthracenedione in patients with impaired cardiac function should include more frequent cardiac monitoring. The following regimens are used at NCCN Member Institutions for the first-line treatment of DLBCL in very frail patients or those with poor left ventricular function, based on limited published data.

- R-miniCHOP (for frail patients over 80 years of age)^{58,59}
- RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine)
- RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone)⁶⁴⁻⁶⁶
- DA-EPOCH-R^{56,57}
- RCEOP (rituximab, cyclophosphamide, etoposide, vincristine, and prednisone)⁶⁷
- RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, and prednisolone)⁶⁸

For concurrent presentation of CNS disease with parenchymal involvement, systemic methotrexate (≥ 3 g/m²) should be incorporated as part of the treatment plan. Intrathecal methotrexate/cytarabine and/or 3 to 3.5 g/m² systemic methotrexate should be incorporated as part of the treatment plan for concurrent presentation of CNS disease with leptomeningeal involvement. Ommaya reservoir placement should be considered in patients with leptomeningeal disease. When administering high dose methotrexate, patients must be pretreated with hydration and alkalinization of the urine, and then receive leucovorin

rescue beginning 24 hours after the initiation of methotrexate infusion. Renal and hepatic function must be monitored. Adequate recovery of blood counts should be confirmed prior to initiating the next cycle of R-CHOP.

Patients with risk factors for CNS involvement (age > 60 years, elevated LDH, stage III or IV, ECOG PS > 1, extranodal sites >1, kidney or adrenal gland involvement) should be considered for CNS prophylaxis.²²⁻²⁶ The method by which prophylaxis should be given is controversial. Intrathecal methotrexate given at least once per systemic treatment cycle has been used for many years. More recent retrospective studies have suggested that high-dose IV methotrexate-based prophylaxis may be associated with a lower incidence of CNS relapses.⁶⁹⁻⁷² Systemic methotrexate with leucovorin rescue has been safely incorporated into R-CHOP-21, with methotrexate administered on day 15 of the 21-day R-CHOP cycle.⁶⁹ However, other reports suggest that CNS prophylaxis is insufficient to prevent CNS relapse.^{73,74} The NCCN Guidelines currently recommend CNS prophylaxis with 4 to 8 doses of intrathecal methotrexate and/or cytarabine, or 3-3.5 g/m² of systemic methotrexate.

Response Assessment

Interim restaging is performed to identify patients whose disease has not responded to or has progressed on induction therapy. A negative PET scan after 2 to 4 cycles of induction therapy has been associated with favorable outcomes in several studies.⁷⁵⁻⁷⁸ In patients with aggressive lymphoma (N=90) treated with first-line anthracycline-based induction chemoimmunotherapy with rituximab (41% of patients), those with a negative PET scan (n=54) after 2 cycles of induction therapy had significantly higher 2-year EFS rate (82% vs. 43%; $P < .001$) and OS rate (90% vs. 61%; $P = .006$) compared with those with a positive PET scan (n=36).⁷⁷ In another study, among patients with aggressive

lymphoma (N=103) treated with first-line CHOP or CHOP-like regimens (with rituximab in 49% of cases), the 5-year EFS rates were significantly higher for those with a negative PET scan (n=77) compared to patients with a positive PET scan (n=22) following 4 cycles of induction therapy (80% vs. 36%; $P < .0001$).⁷⁸

However, interim PET scans can produce false positive results and some patients treated with chemoimmunotherapy have a favorable long-term outcome despite a positive interim PET scan. In a prospective study that evaluated the significance of interim PET scans in patients with DLBCL (after 4 cycles of accelerated R-CHOP), only 5 of 37 patients with a positive interim PET scan had a biopsy demonstrating persistent disease; PFS outcome in patients who were interim PET-positive, biopsy-negative was identical to that in patients with a negative interim PET scan.⁷⁹ A retrospective analysis of 88 newly diagnosed patients with DLBCL treated with 6-8 cycles of R-CHOP also reported only a minor difference in the 2-year PFS rates between patients with a positive interim PET scan and a negative interim PET scan; the 2 year PFS rates were 72% and 85% respectively ($P = .0475$).⁸⁰ Conversely, the end-of-treatment PET scan was highly predictive of PFS; the 2-year PFS rate was 64% for patients with a final positive PET scan compared to 83% for those with a final negative PET scan ($P < .001$).

More recent reports have also confirmed the limited prognostic value of interim PET scans in patients with DLBCL treated with R-CHOP.⁸¹⁻⁸⁴ In a prospective study that evaluated the predictive value of interim PET scans after 2 cycles of R-CHOP in 138 evaluable patients, the 2-year EFS rate was significantly shorter for patients with a positive interim PET-scan compared to those with a negative interim PET scan (48% vs. 74%; $P = .004$); however, the 2-year OS was not significantly different between the two groups (88% vs. 91%; $P = .46$).⁸³

Therefore, interim PET imaging is not recommended to be used to guide changes in therapy. If treatment modifications are considered based on interim PET scan results, a repeat biopsy of residual masses should be strongly considered to confirm PET-positivity prior to additional therapy. If the biopsy is negative, the planned course of treatment as recommended for PET-negative guidelines should be completed. Patients should undergo evaluation prior to receiving RT, including all positive studies. If RT is not planned, interim restaging after 3–4 cycles of R-CHOP is appropriate to confirm response. End of treatment restaging is performed upon completion of treatment. The optimal time to end of treatment restaging is not known. However, the panel recommends waiting for 6-8 weeks after completion of therapy before repeating PET scans.

Response assessment by PET-CT should be done according to the 5-point scale (5-PS).^{16,85} The 5-PS is based on the visual assessment of FDG uptake in the involved sites relative to that of the mediastinum and the liver.⁸⁶⁻⁸⁸ A score of 1 denotes no abnormal FDG-avidity, while a score of 2 represents uptake less than the mediastinum. A score of 3 denotes uptake greater than the mediastinum but less than the liver, while scores of 4 and 5 denote uptake greater than the liver, and greater than the liver with new sites of disease, respectively. Different clinical trials have considered scores of either 1-2 or 1-3 to be PET-negative, while scores of 4-5 are universally considered PET-positive. A score of 4 on an interim or end of treatment restaging scan may be consistent with a partial response if the FDG-avidity has declined from initial staging, while a score of 5 denotes progressive disease.

Follow-up

Considerable debate remains with the routine use of imaging for surveillance in patients who achieve a CR after induction therapy.

Although positive scans can help to identify patients with early asymptomatic disease relapse, false positive cases remain common and problematic, and may lead to unnecessary radiation exposure for patients as well as increased healthcare costs. In a study that evaluated the use of surveillance CT scans (at 3 and 12 months after completion of chemotherapy) in patients with DLBCL who achieved a CR with induction chemotherapy (N=117), 35 patients relapsed, and only 6% of these relapses were detected by follow-up CT scan in asymptomatic patients; 86% of cases of relapse were associated with development of new symptoms or signs of relapse.⁸⁹ The investigators therefore concluded that routine surveillance with CT scans had limited value in the detection of early relapse in patients with a CR following induction therapy. In a retrospective study evaluating the use of surveillance imaging in patients with relapsed aggressive lymphoma who had a CR to initial chemotherapy (N=108), 20% of relapses were detected by imaging in asymptomatic patients.⁹⁰ In the remaining 80% of cases, relapse was identified by clinical signs and/or symptoms. Moreover, the cases of relapse detected by imaging were more likely to represent a population of patients with low-risk disease based on age-adjusted IPI at the time of relapse.⁹⁰ Thus, routine imaging during remission may help to identify patients with more limited disease at the time of relapse, but has not been shown to improve ultimate outcome.

In a prospective study that evaluated the role of PET scans (at 6, 12, 18, and 24 months after completion of induction therapy) in patients with a CR after induction therapy for lymphomas, surveillance using PET scans was found to be useful for detecting early relapse.⁹¹ Among the cohort of patients with aggressive lymphomas in this study (n=183), follow-up PET scans detected true relapses in 10% of patients at 6 months, 5% at 12 months, and 11% at 18 months; the rate of false-positive scans was low, at 1% (including cohorts of patients with

indolent and aggressive NHL).⁹¹ Inconclusive PET scans were obtained in 4% of patients (8 out of 183), 6 of those had confirmed relapse based on biopsy evaluation. In a retrospective study that evaluated the use of follow-up PET/CT scan in patients with DLBCL who achieved a CR after induction therapy (N=75), follow-up PET/CT scan detected relapse in 27 patients, of which 23 patients had confirmed relapse based on biopsy evaluation; thus, the positive predictive value of PET/CT scan for detecting relapse was 0.85.⁹² In this study, patient age (>60 years) and the presence of clinical signs of relapse were significant predictors of disease relapse.

Data from more recent retrospective studies also suggest that routine surveillance with PET or CT scans is of limited utility in the detection of relapse in majority of patients with DLBCL.⁹³⁻⁹⁵ A study comparing the performance of surveillance PET scans in patients with DLBCL treated with CHOP alone versus R-CHOP, found higher false positive results in patients treated with R-CHOP (77% vs. 26%; $P < .001$).⁹³ Another study reported a positive predictive value of 56% for surveillance PET-CT scans in patients IPI score <3 compared with 80% for patients with IPI score ≥ 3 , suggesting that surveillance PET-CT has a very limited role in the majority of patients in CR after primary therapy.⁹⁴ Another multi-institutional retrospective study evaluated the utility of surveillance scans in two independent prospectively enrolled cohorts of patients with DLBCL treated with anthracycline-based chemoimmunotherapy.⁹⁵ In one cohort (n = 680; 552 patients entered post-treatment observation), post treatment surveillance scans detected DLBCL relapse prior to clinical manifestations only in 1.6% of patients (9 out of 552 patients) during a planned follow-up visit. In another cohort (n = 261; 222 patients entered post-treatment observation), surveillance imaging detected asymptomatic relapse only in 1.8% of patients (4 out of 222 patients). A population-based study of patients from the Danish and Swedish

lymphoma registries also showed that imaging-based surveillance strategy had no impact on survival for patients DLBCL in first complete remission.⁹⁶

A multi-institutional retrospective study evaluated the EFS at 24 months (EFS24) in two independent prospectively enrolled cohorts of 767 patients with DLBCL treated with anthracycline-based chemoimmunotherapy.⁹⁷ Patients who achieved EFS24 had an OS equivalent to that of the age-matched and sex-matched general population ($P = .25$). This was also confirmed in another data set that included 820 patients from a GELA LNH2003B program and the hospital-based registry in France ($P = .71$). These data indicate that EFS24 should be useful for developing strategies for post-therapy surveillance, patient counseling, and as an end point in clinical studies for patients with DLBCL.

In the absence of evidence demonstrating an improved outcome favoring routine surveillance imaging for the detection of relapse, the NCCN Guidelines do not recommend the use of PET or CT for routine surveillance for patients with stage I-II disease who have achieved a CR to initial therapy. For patients with stage III-IV disease who achieve remission to initial therapy, the NCCN Guidelines recommend CT scans no more than once every 6 months for up to 2 years after completion of treatment, with no ongoing routine surveillance imaging after that time, unless it is clinically indicated. When surveillance imaging is performed, CT scan is preferred over PET/CT for the majority of patients. PET/CT may be preferable for patients with primarily osseous presentations, with the caveat that bone remodeling may also be FDG-avid, so a biopsy is recommended for PET positive sites prior to instituting second line therapy.

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

When the treatment plan involves RT, restaging should be done after completion of first-line chemoimmunotherapy prior to initiation of RT as the dose of RT will be influenced by the result (see “Principles of RT” in the Guidelines). If interim restaging demonstrates CR (PET-negative), the planned course of treatment with same dose of RT is completed. If the interim restaging demonstrates a PR (PET-positive), treatment with a higher dose of RT (see Guidelines section on “Principles of RT”) is appropriate. It is appropriate to enroll patients with an interim PR on a clinical trial. At the present time, there is no data to suggest that a PR with persistent PET positivity after 3 cycles should prompt a change in treatment. If the PET scan is positive after 6 cycles of RCHOP, the patient can proceed to second-line therapy followed by HDT/ASCR with or without RT. Patients with primary refractory or progressive disease are managed as refractory or relapsed disease. After end of treatment restaging, follow-up at regular intervals (every 3–6 months for 5 years and then annually or as clinically indicated thereafter) is recommended for patients with CR. In these patients, follow-up CT scans are recommended only if clinically indicated. Patients with PR and those with no response to treatment or progressive disease are treated as described for relapsed or refractory disease. Palliative RT is recommended for selected patients who are not candidates for chemoimmunotherapy.

Interim and End of Treatment Response Evaluation for Stage III-IV

If interim staging (after 2–4 cycles of R-CHOP-21) demonstrates a CR and PR, the planned course of R-CHOP to a total of 6 cycles is completed. End of treatment restaging is performed upon completion of treatment. After end of treatment restaging, observation is preferred for patients with CR. RT to initially bulky disease (category 2B) or first-line consolidation with HDT/ASCR can be considered in selected high-risk patients (category 2B).^{60,61} Patients in CR are followed up at regular

intervals (every 3–6 months for 5 years and then annually or as clinically indicated thereafter). In these patients, follow-up imaging CT scans should be performed no more than every 6 months for 2 years after completion of therapy, and then only as clinically indicated thereafter. Patients with PR (after completion of initial therapy) and those with no response to treatment or progressive disease are treated as described below for relapsed or refractory disease. Palliative RT is recommended for selected patients who are not candidates for chemoimmunotherapy.

Relapsed or Refractory Disease

The role of HDT/ASCR in patients with relapsed or refractory disease was demonstrated in an international randomized phase III trial (PARMA study).⁹⁸ In this study, patients with DLBCL responding to induction DHAP (dexamethasone, cisplatin and cytarabine) chemotherapy after first or second relapse (N=109) were randomized to receive additional DHAP chemotherapy plus RT or RT plus HDT/ASCR. The 5-year EFS rate was significantly higher among the transplant group compared with the non-transplant group (46% vs. 12%; $P=.001$), as was the 5-year OS (53% vs. 32%; $P=.038$).⁹⁸ This study was performed prior to the availability of rituximab. A recent retrospective analysis based on data from the EBMT registry evaluated the role of HDT/ASCR in patients achieving a second CR after salvage therapy (N=470).⁹⁹ In this analysis, 25% of patients had received rituximab-based therapy prior to ASCR. The 5-year DFS and OS was 48% and 63% after ASCR for all patients. The median DFS after ASCR was 51 months, which was significantly longer than the duration of first CR (11 months; $P<.001$). The longer DFS with ASCR compared with first CR was also significant in the subgroup of patients previously treated with rituximab (median not reached vs. 10 months;

$P < .001$) and the subgroup who relapsed within 1 year of first-line therapy (median 47 months vs. 6 months; $P < .001$).⁹⁹

The efficacy of second-line therapy is predicted by the second-line age-adjusted IPI.^{100,101} Furthermore, pre-transplantation PET scans have been identified as predictive factors following HDT/ASCR.^{102,103} PET positivity before transplant and chemoresistance are associated with a poor outcome.^{104,105} The results of studies from the GEL-TAMO group and ABMTR suggested that HDT/ASCR should be considered for patients who do not achieve a CR but who are still sensitive to chemotherapy.¹⁰⁶⁻¹⁰⁸

Rituximab as a single agent is modestly active in patients with relapsed or refractory DLBCL and is reserved for the frail older patient.¹⁰⁹

Several chemotherapy regimens (with or without rituximab) such as DHAP (dexamethasone, cisplatin and cytarabine), ESHAP (etoposide, methylprednisolone, cytarabine and cisplatin), ICE (ifosfamide, carboplatin and etoposide), MINE (mesna, ifosfamide, mitoxantrone and etoposide), EPOCH and CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) have been evaluated in patients with relapsed or refractory DLBCL.¹¹⁰⁻¹¹⁸ In an outpatient setting, rituximab in combination with ICE (R-ICE) produced an ORR of 71% (25% CR) and an estimated 1-year EFS rate and OS rate of 60% and 72%, respectively, in patients with refractory B-cell lymphoma (N=28).¹¹⁴ In a phase II study, R-ICE regimen produced a CR rate of 53% in patients with relapsed or refractory DLBCL (N=34), which was significantly better than historical controls treated with ICE alone (27%).¹¹⁵

An international randomized intergroup study (CORAL study; N=477) evaluated second-line therapy of relapsed or refractory DLBCL with R-ICE versus R-DHAP, followed by ASCR in all chemosensitive patients.^{119,120} No significant difference in outcome was found between

treatment arms. The overall response rates were 63% after R-ICE and 64% after R-DHAP. The 4-year EFS rate was 26% with R-ICE compared with 34% with R-DHAP ($P = .2$) and the 4-year OS rate was 43% and 51%, respectively ($P = .3$).¹²⁰ Notably, patients relapsing less than 1 year after initial R-CHOP therapy had a particularly poor outcome with 3-year PFS of 23%. Moreover, the subgroup of patients with *MYC* gene rearrangement (with or without concurrent in *BCL2* and/or *BCL6* gene rearrangements) had poor outcomes regardless of treatment arm.¹²¹ The 4-year PFS was 18% among patients with *MYC* gene rearrangements compared with 42% in those without ($P = .032$); 4-year OS was 29% and 62%, respectively ($P = .011$). Among patients with *MYC* gene rearrangements, the 4-year PFS was 17% with R-DHAP and 19% with R-ICE; OS was 26% and 31%, respectively.¹²¹ Novel approaches are needed for these poor-risk patients. Interestingly, a subgroup analysis from the CORAL study (Bio-CORAL) showed that for patients with a GCB phenotype (based on Hans algorithm), R-DHAP resulted in improved PFS (3-year PFS 52% vs. 31% with R-ICE).¹²² This difference was not observed among patients with non-GCB phenotype (3-year PFS 32% with R-DHAP vs. 27% with R-ICE).¹²² R-DHAP and R-ICE are acceptable options for patients with relapsed or refractory DLBCL.

The CORAL study was also designed to evaluate the role of rituximab maintenance (every 2 months for 1 year) following ASCR. Among the patients randomized post-ASCR to rituximab maintenance or observation (n=242), the 4-year EFS after ASCR was similar between randomized groups: 52% with rituximab versus 53% with observation.¹²⁰ The proportion of patients with progression or relapse was similar between randomized groups. In addition, the 4-year OS was not statistically different (61% and 65%, respectively). Serious adverse events were more frequent in the rituximab maintenance arm. Given

that this study showed no benefit with rituximab maintenance compared with observation post-ASCR, maintenance therapy cannot be recommended in this setting.¹²⁰

Gemcitabine-based chemotherapy regimens such as GDP (gemcitabine, dexamethasone, cisplatin) and GemOx (gemcitabine and oxaliplatin),¹²³⁻¹²⁸ bendamustine and rituximab (BR)¹²⁹⁻¹³² and lenalidomide (with or without rituximab)¹³³⁻¹³⁷ have also been evaluated in patients with relapsed or refractory DLBCL.

GemOx in combination with rituximab (R-GemOx) was evaluated in patients with relapsed or refractory DLBCL who are not eligible for transplant.^{124,126,127} In a pilot study of 46 patients with relapsed or refractory B-cell lymphoma, the majority of whom (72%) had DLBCL, R-GemOx resulted in an ORR of 83% and half of the patients achieved a CR.¹²⁴ The 2-year EFS and OS rates in this study were 43% and 66%, respectively. In a subsequent multicenter phase II study that included 49 patients with relapsed or refractory DLBCL, R-GemOx resulted in an ORR of 61% (44% CR and 17% PR).¹²⁷ The 5-year PFS and OS rates were 12.8% and 13.9%, respectively.

In a small dose-escalation study of patients with relapsed/refractory aggressive NHL (N=9; DLBCL, n=5), BR regimen resulted in PR in 1 patient (90 mg/m² dose of bendamustine; n=3) while the same combination with 120 mg/m² dose of bendamustine (n=6) resulted in CR in 5 patients and a PR in 1 patient.¹³⁰ In a recent phase II study of the BR regimen (bendamustine dose 120 mg/m²) in patients with relapsed/refractory DLBCL (N=59; median age 67 years), the ORR was 63% with a CR in 37% of patients.¹³¹ Patients had received 1 to 3 prior therapies, and were not considered suitable for (or have undergone) ASCR. Nearly all patients (97%) had received prior therapy with rituximab-based regimens.¹³¹ The median PFS was approximately 7

months. The most common grade 3 or 4 toxicities were neutropenia (76%) and thrombocytopenia (22%).¹³¹ In older patients with relapsed/refractory DLBCL (59 patients; median age 74 years; 48 evaluable patients), the BR regimen (with bendamustine dose 120 mg/m²) resulted in an ORR of 45.8% (15.3% CR; 30.5% PR).¹³² The median duration of response and median PFS were 17.3 months and 3.6 months, respectively. Myelosuppression was the most common grade 3 or 4 toxicity.

Lenalidomide monotherapy has been shown to induce an ORR of 28% in patients with relapsed or refractory DLBCL.^{133,134} Data from retrospective analysis suggest that the response rates are higher in patients with non-GCB DLBCL versus GCB-DLBCL (ORR: 52.9% vs. 8.7%; *P* = .006; CR rate: 23.5% versus 4.3%).¹³⁵ In a multicenter randomized study, 102 patients with relapsed/refractory DLBCL (≥2 prior therapies or ineligible for stem cell transplantation; GCB-DLBCL, n=48; non-GCB DLBCL, n=54) were randomized to lenalidomide monotherapy or single-agent investigator's choice.¹³⁸ Lenalidomide resulted in improved ORR, PFS and OS in patients with non-GCB subtype compared to those with GCB subtype. In another phase II trial, 45 patients with relapsed or refractory DLBCL (n=32), transformed large cell lymphoma (n=9) or follicular lymphoma grade 3 (n=4), lenalidomide in combination with rituximab induced ORR in 33% of patients.¹³⁶ The median response duration, PFS and OS were 10.2 months, 3.7 months and 10.7 months, respectively.¹³⁶ Myelosuppression was the most common grade 3 or 4 toxicity.

Brentuximab vedotin, a CD30-directed antibody-drug conjugate, has demonstrated activity in patients with relapsed or refractory CD30-positive lymphomas. A phase 2, open-label study evaluated the efficacy of brentuximab vedotin in relapsed or refractory CD30-positive NHL.¹³⁹ In a planned subset analysis that included 49 patients with

DLBCL, the ORR was 44% (17% CR) with a median duration of 16.6 months. Although there was no statistical correlation between the response and the level of CD30 expression, all patients with responding disease had quantifiable CD30 by IHC.

Brentuximab vedotin (for CD30-positive DLBCL), lenalidomide ± rituximab (for non-GCB-DLBCL) and bendamustine ± rituximab are included as options for patients with relapsed or refractory DLBCL who are not candidates for HDT/ASCR.

NCCN Recommendations

All patients with relapsed or refractory DLBCL should be considered for enrollment in available clinical trials. HDT/ASCR is the treatment of choice for patients with relapsed or refractory DLBCL that is chemosensitive at relapse. Patients who are candidates for HDT/ASCR should be treated with second-line chemotherapy, with or without rituximab (depending on whether the patient is deemed to be refractory to prior rituximab regimens). Suggested regimens (with or without rituximab) include the following:

- DHAP (dexamethasone, cisplatin, cytarabine)
- ESHAP (methylprednisolone, etoposide, cytarabine, cisplatin)
- GDP (gemcitabine, dexamethasone, cisplatin)
- ICE (ifosfamide, carboplatin and etoposide)
- MINE (mitoxantrone, ifosfamide, mesna, etoposide)

Patients with CR or PR to second-line therapy should be considered for further consolidation with HDT/ASCR (category 1 for patients with CR) with or without RT.^{98,99} ISRT before HDT/ASCR has been shown to result in good local disease control and improved outcome.¹⁴⁰ Additional RT can be given to limited sites with prior positive disease before or

after ASCR. Pertinent clinical trials, including the option of allogeneic stem cell transplantation, may also be considered.

Patients who are not eligible for HDT/ASCR should be treated in the context of a clinical trial. Alternatively, in the absence of suitable clinical trials, patients can also be treated single agent rituximab or the following chemotherapy regimens (with or without rituximab).

- Bendamustine
- Brentuximab vedotin for CD30+ disease (category 2B)
- CEPP
- CEOP (cyclophosphamide, etoposide, vincristine, prednisone)
- DA-EPOCH
- GDP
- Gemcitabine, dexamethasone, carboplatin
- GemOx
- Lenalidomide (non-GCB DLBCL)

Patients with disease relapse following HDT/ASCR should be treated in the context of a clinical trial or treatment should be individualized. However, those with progressive disease after three successive regimens are unlikely to derive additional benefit from currently available chemotherapy regimens, except for patients who have experienced a long disease-free interval.

Primary Mediastinal Large B-cell Lymphoma

PMBL is a distinct subtype of NHL that can be histologically indistinguishable from DLBCL that tends to occur in young adults with a median age of 35 years with a slight female predominance.^{141,142} PMBL arises from thymic B-cells with initial local regional spread to supraclavicular, cervical, hilar nodes and into the mediastinum and

lung.¹⁴¹ Widespread extranodal disease is uncommon at initial diagnosis, present in approximately one quarter of patients, but can be more common at recurrence.¹⁴² Clinical symptoms related to rapid growth of a mediastinal mass include superior vena cava (SVC) syndrome, pericardial and pleural effusions.

GEP has indicated that PMBL is distinct from DLBCL; the pattern of gene expression in PMBL is more similar to classical Hodgkin lymphoma (CHL).^{143,144} PMBL expresses B-cell antigens and lacks surface immunoglobulins. PMBL is CD19+, CD20+, CD22+, CD21-, IRF4/MUM1+ and CD23+ with a variable expression of BCL2 and BCL6. CD30 is weakly and heterogeneously expressed in more than 80% of cases and CD15 is occasionally present.¹⁴² CD10 positivity is seen in 8-32% cases. PMBL is also characterized by a low expression of HLA I or II molecules. There have been rare cases of mediastinal gray zone lymphomas with combined features of PMBL and CHL. Cytogenetic abnormalities that are common in PMBL include gains in chromosome 9p24 (involving the *JAK2* in 50–75% of patients) and chromosome 2p15 (involving the *c-REL*, encoding a member of the NF- κ B family of transcription factors) and loss in chromosomes 1p, 3p, 13q, 15q, and 17p.¹⁴² Age-adjusted IPI is of limited value in determining the prognosis of PMBL at diagnosis.^{141,145,146} In a retrospective analysis of 141 patients from MSKCC, ≥ 2 extranodal sites and the type of initial therapy were predictors of outcome for EFS, whereas only the initial therapy was a predictor for OS.¹⁴⁵

In retrospective analyses, intensive chemotherapy regimens have appeared more effective than CHOP¹⁴⁶⁻¹⁴⁸ and the addition of IFRT has been associated with improved PFS; however, these studies were conducted in the pre-rituximab era.^{149,150} The results of subsequent retrospective studies suggest that although the addition of rituximab to MACOP-B (methotrexate, leucovorin, doxorubicin, cyclophosphamide,

vincristine, prednisone and bleomycin) or VACOP-B (etoposide, leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin) did not appear to result in significant differences in clinical outcomes, its addition to CHOP improves outcome in patients with PMBL.¹⁵¹⁻¹⁵⁵ In an analysis of the subgroup of patients with PMBL (N=87) from the randomized MInT study, which evaluated CHOP-like regimens with or without rituximab, the addition of rituximab significantly improved the CR rate (80% vs. 54% without rituximab; $P=.015$) and 3-year EFS rate (78% vs. 52%; $P=.012$), but not the OS rate (89% vs. 78%; $P=.158$).¹⁵² The MInT study, however, only included young low-risk patients with IPI scores 0-1. In a recent follow-up report with a median observation time of 62 months in patients with PMBL, the increase in EFS with rituximab remained significant at 5 years (79% vs. 47%; $P=.011$).¹⁵⁴ The 5-year PFS was also significantly increased in the rituximab arm (90% vs. 60%; $P=.006$); 5-year OS was not significantly different (90% vs. 78%), but was similar to OS outcomes in patients with DLBCL in this study (92% with rituximab vs. 81% without; $P<.001$).¹⁵⁴ In a retrospective analysis of 95 consecutive patients treated with chemotherapy (VACOP-B or CHOP) with and without rituximab, the 5-year PFS and OS rates were 79% and 97% for patients treated with rituximab-based chemotherapy compared with 58% and 88%, respectively for those treated with chemotherapy alone. The 5-year PFS rates in patients treated with R-VACOP-B, R-CHOP, VACOP-B, and CHOP were 83%, 69%, 62%, and 20%, respectively.¹⁵⁵ Sequential dose dense R-CHOP followed by ICE consolidation (without RT) was also highly effective in patients with PMBL, with similar outcomes to the above analysis with R-chemotherapy from the MInT study.¹⁵⁶ At a median follow up for surviving patients at 3 years, the OS and PFS rates were 88% and 78%, respectively.¹⁵⁶ A retrospective analysis of 63 patients with PMBL treated with R-CHOP found a 21% rate of primary induction failure, with adverse predictors of outcome being advanced

stage and high-risk IPI scores, suggesting that R-CHOP may not be the optimal chemotherapy backbone in PMBL, particularly for high-risk patients.¹⁵⁷

DA-EPOCH-R has also been evaluated in small cohorts of patients with PMBL.^{158,159} A small prospective NCI study of the DA-EPOCH-R without RT demonstrated an encouraging 91% EFS at a median follow-up of 4 years. In a subsequent prospective phase II study from the NCI, DA-EPOCH-R (6–8 cycles) and filgrastim, without RT, was evaluated in 51 patients with previously untreated PMBL.¹⁵⁸ Stage IV disease was present in 29% of patients. After treatment with DA-EPOCH-R, 2 patients showed persistent focal disease and 1 patient had disease progression; 2 of these patients required mediastinal RT while 1 patient was observed after excision biopsy. At a median follow up of 63 months, EFS and OS rates were 93% and 97%, respectively. Grade 4 neutropenia and thrombocytopenia occurred in 50% and 6% of treatment cycles, respectively. Hospitalization for febrile neutropenia occurred in 13% of cycles.¹⁵⁸ This study showed that DA-EPOCH-R is a highly effective regimen in patients with PMBL and obviates the need for RT in the large majority of patients. A single institution retrospective analysis also showed that R-CHOP/R-VACOP-B with RT and DA-EPOCH-R without RT result in excellent outcomes in patients with stage I-II PMBL.¹⁵⁹

The role of consolidation RT remains unclear. A few studies have evaluated the utility of PET scans (based on the 5-PS) to identify patients at high-risk of progression who could be considered for RT after completion of chemotherapy.^{160,161} However, these findings need to be confirmed in larger prospective randomized trials.

In the absence of randomized trials, optimal first-line treatment for patients with PMBL is more controversial than other subtypes of NHL.

However, based on the available data, the following regimens are included as options for first-line therapy.

- R-CHOP (6 cycles) ± RT
- DA-EPOCH-R (6 cycles)¹⁵⁸ + RT only for persistent PET-positive local disease
- R-CHOP (4 cycles) followed by ICE (3 cycles)¹⁵⁶ with or without RT (category 2B)

Post-treatment PET-CT is considered essential; if PET-CT is negative at the end of treatment and initial disease was non-bulky, patients may be observed. Residual mediastinal masses are common. For patients initially treated with R-CHOP, consolidation with RT should be considered, particularly if increased FDG-activity persists in the primary tumor. For patients who are PET-CT negative after more intensive therapies (e.g., DA-EPOCH-R), observation may be appropriate. If PET-CT is positive, biopsy is recommended before additional treatment is contemplated.

Grey Zone Lymphoma

Grey zone lymphomas, a provisional diagnostic category included in the 2008 WHO classification, refer to a group of lymphomas with features intermediate between DLBCL and classical Hodgkin lymphoma (cHL).^{154,162-165} Other synonyms include large B-cell lymphoma with Hodgkin features or Hodgkin-like anaplastic large cell lymphoma. The morphology of grey zone lymphomas is characterized by sheet-like growth of pleomorphic cells in a diffusely fibrous stroma; cells are typically larger and more pleomorphic than those in PMBL, and may sometimes resemble lacunar or Hodgkin-like cells.¹⁶⁴ Necrosis without neutrophilic infiltration is frequently present.^{154,162,164} Patients with grey zone lymphomas may present with mediastinal or non-mediastinal disease. Mediastinal grey zone lymphomas are more commonly seen in

young adult males between the ages of 20 to 40 years and are characterized by the presence of a large anterior mediastinal mass with or without supraclavicular lymph node involvement.^{162,163,165}

Non-mediastinal gray zone lymphomas occur in older patients, have a higher incidence of bone marrow involvement, more than one extranodal disease, advanced stage disease and high-risk IPI score than mediastinal grey zone lymphomas.¹⁶⁶ In a retrospective multicenter analysis of 112 patients with grey zone lymphomas, mediastinal presentations were found in 43% of patients, while 57% presented with non-mediastinal grey zone lymphomas.¹⁶⁶

The immunophenotype is atypical, often showing transitional features between PMBL and CHL. In general, CD45 is often positive, and CD15, CD20, CD30, and CD79a are also frequently positive. CD10 and ALK are usually negative. B-cell transcription factors such as PAX5, BOB.1, and OCT-2 are often positive.^{162,164,167} BCL6 is variably expressed. EBV is more often negative.^{162,163} If the morphology more closely resembles PMBL, absence of CD20, or CD15 positivity, would be suggestive of grey zone lymphoma. If the morphology more closely resembles cHL, strong CD20 expression (and/or other B-cell markers) and absence of CD15 would be suggestive of grey zone lymphoma.¹⁶² A study that evaluated epigenetic changes based on DNA methylation analysis of microdissected tumor cells from patients with mediastinal grey zone lymphomas, PMBL, cHL, and DLBCL showed distinct methylation signatures (hypomethylated and hypermethylated sites) of CpG targets between PMBL and cHL.¹⁶⁸ The methylation profiles of patients with grey zone lymphoma were intermediate to those of PMBL and cHL, but distinct from patients with DLBCL. Among 235 CpG targets that were identified as being differentially methylated between the lymphomas, 22 targets could be used to readily distinguish between PMBL and CHL cHL, with grey zone lymphomas showing an overlap of both signatures.

The investigators concluded that the unique epigenetic signature of mediastinal grey zone lymphomas provide validation of its classification as a separate disease entity in the 2008 WHO classification.¹⁶⁸

The treatment of patients with grey zone lymphomas poses a challenge, as these lymphomas appear to be associated with a worse prognosis compared with PMBL or cHL.^{164,167,169} In a prospective study that evaluated 6 to 8 cycles of DA-EPOCH-R in a small group of patients with mediastinal grey zone lymphoma (n=24), the EFS and OS were 62% and 74%, respectively, at the median follow-up of 59 months.¹⁷⁰ With a median follow-up of 5 years, the EFS (62% vs 93%; $P = .0005$) and OS (74% vs 97%; $P = .0012$), were significantly lower for patients with mediastinal grey zone lymphoma compared to patients with PMBL (n = 51) enrolled in the same study. In a multicenter retrospective analysis of gray zone lymphoma (that did not have central pathology review), patients treated with CHOP-like regimens with or without rituximab had superior outcomes compared to subjects treated with ABVD, with 2 year PFS rates of 52% and 22%, respectively.¹⁶⁶

Patients with grey zone lymphomas are best managed in cancer centers with experience in treating this type of lymphoma, preferably in the context of clinical trials where appropriate. No standard of care or consensus exists for the management of patients with grey zone lymphomas, although patients are typically treated with multiagent chemotherapy regimens used for patients with DLBCL. The addition of rituximab is generally suggested for tumors expressing CD20. In the absence of suitable clinical trials, R-CHOP-21 or DA-EPOCH-R should be considered. Given the apparent inferior outcomes among gray zone lymphomas treated with traditional chemotherapy regimens, consolidative RT should be strongly considered for patients with limited stage disease amenable to RT.

Double-hit lymphomas

DLBCL or high-grade B-cell lymphoma unclassifiable (intermediate between DLBCL and BL) with *MYC* gene rearrangement in addition to *BCL2* and/or *BCL6* gene rearrangements by FISH or standard cytogenetics are known as double-hit lymphomas (DHL).

Immunohistochemical staining can also identify DLBCL with dual expression of both *MYC* and *BCL2* proteins, known as double-expressing DLBCL (DEL).^{171,172} These patients have an inferior prognosis compared to those with DLBCL as a whole, but not to the same magnitude as patients with true DHL on the basis of gene rearrangements. FISH for *MYC*, *BCL2*, and *BCL6* gene rearrangements is recommended for those with expression of *MYC* and either *BCL2* or *BCL6* by IHC, and a GCB-like immunophenotype. Nearly all DHL are GCB-DLBCL and are characterized by highly aggressive clinical behavior and overlapping pathologic features with DLBCL, Burkitt lymphoma (BL) and B-cell lymphoblastic lymphoma/leukemia (B-LBL).¹⁷³ DHL have been observed in 2% to 11% of newly diagnosed patients with DLBCL.

DHL are highly aggressive with very poor clinical outcomes, even with rituximab-based chemoimmunotherapy or intensive therapy with stem cell transplantation.^{171,172,174,175} In a series of 193 patients with DLBCL uniformly treated with standard R-CHOP, the median OS (13 months vs. 95 months) and PFS (6 months vs. 95 months), 3-year PFS rate (46% vs. 65%; $P=.012$) and 3-year OS rate (46% vs. 75%; $P=.002$) were significantly lower in patients with DHL compared with those without DHL.¹⁷¹ In another study with a longer follow-up, 5-year PFS and OS were 18% and 27%, respectively, in patients with double-hit DLBCL treated with R-CHOP.¹⁷² These studies have also shown that high expressions of both *MYC* and *BCL2* protein levels (assessed by IHC but not *MYC* or *BCL2* expression alone) were associated with

significantly inferior outcomes after treatment with R-CHOP.^{171,172} In the multivariate analysis that included IPI score and cell of origin, concurrent *MYC/BCL2* expression remained a significant independent predictor of poorer PFS and OS after R-CHOP.^{171,172}

Data from retrospective studies suggest that more intensive chemotherapy regimens may result in better outcomes.¹⁷⁶⁻¹⁷⁸ In a multicenter retrospective analysis of 106 patients (77% of patients had DHL characterized by *MYC* and *BCL2* gene rearrangements), treatment with intensive regimens such as DA-EPOCH-R, R-HyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone) or R-CODOX-M/IVAC (rituximab, cyclophosphamide, doxorubicin, vincristine, methotrexate/ifosfamide, etoposide, high dose cytarabine) resulted in superior complete remissions and PFS compared to R-CHOP.¹⁷⁶ A recent meta-analysis compared survival outcomes in patients with DHL treated with more aggressive regimens including R-HyperCVAD, R-CODOX-M/IVAC or R-EPOCH versus standard-dose regimens (R-CHOP) in the first-line setting.¹⁷⁹ The median PFS for the R-CHOP, DA-EPOCH-R and other dose intensive regimens was 12.1, 22.2, and 18.9 months, respectively. DA-EPOCH-R significantly reduced the risk of progression compared with R-CHOP; however, OS was not significantly different across treatment approaches.

DA-EPOCH-R is being evaluated in a prospective phase II study of 52 patients with newly diagnosed with DLBCL or B-cell lymphoma unclassifiable with features intermediate between DLBCL and BL).¹⁸⁰ All patients had a *MYC* gene rearrangement. *BCL2* gene rearrangement and *BCL2* overexpression were identified in 45% and 56% of patients respectively. Preliminary reports from this study showed that PFS and OS were 79% and 77% respectively for all patients, at a median follow-up of 14 months. PFS was 87% and 64% in cases that were FISH positive (double-hit) and IHC positive for *BCL2* respectively.¹⁸⁰



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Additional prospective studies are needed to evaluate the efficacy of DA-EPOCH-R as well as other regimens and stem cell transplantation strategies in patients with DHL. Alternative treatment strategies are needed to improve outcomes in this poor-risk patient population.

The standard of care for the treatment of patients with DHL with concurrent *MYC* and *BCL2* gene rearrangements nor for DEL has not been established. R-CHOP is associated with inferior outcomes.

DA-EPOCH-R, R-HyperCVAD (alternating with high-dose methotrexate and cytarabine) or R-CODOX-M/R-IVAC are used in NCCN Member Institutions for the treatment of DHL. HDT/ASCR is also done at some NCCN Member Institutions; however its role is not established.

Currently, no data supports the use of one regimen over another in the setting of DEL, and clinical trials are needed.

Discussion
update in
progress

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