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Non-Hodgkin's Lymphomas, Version 2.2014

Clinical Practice Guidelines in Oncology

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Overview

Non-Hodgkin's lymphoma (NHL) comprises a heterogeneous group of lymphoproliferative disorders originating in B lymphocytes, T lymphocytes or natural killer (NK) cells. In the United States, B-cell lymphomas represent 80% to 85% of the cases, with 15% to 20% being T-cell lymphomas. NK-cell lymphomas are rare. In 2014, an estimated 70,800 people will be diagnosed with NHL and approximately

Abstract

Non-Hodgkin's lymphomas (NHLs) are a heterogeneous group of lymphoproliferative disorders originating in B lymphocytes, T lymphocytes, or natural killer cells. Follicular lymphoma (FL) is the most common subtype of indolent NHL, accounting for approximately 22% of all newly diagnosed cases of NHL. The incorporation of rituximab to chemotherapy regimens has become a widely accepted standard of care for first-line therapy for patients with FL. Maintenance and consolidation therapy with rituximab and radioimmunotherapy have also been associated with improved progression-free survival in patients experiencing response to first-line therapy. Despite therapeutic advances that have improved outcomes, FL is generally considered a chronic disease characterized by multiple recurrences with current therapies. This manuscript discusses the recommendations outlined in the NCCN Guidelines for the diagnosis and management of patients with FL. (*J Natl Compr Canc Netw* 2014;12:916–946)

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.

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

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. **The full NCCN Guidelines for Non-Hodgkin's Lymphomas Panel are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.**

Disclosures for the NCCN Non-Hodgkin's Lymphomas Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Non-Hodgkin's Lymphomas Panel members can be found on page 946. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

19,020 will die of 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]

The incidence of NHL increased dramatically between 1970 and 1995, but has moderated since the mid-1990s. This increase has been attributed partly to the HIV epidemic and the development of AIDS-related NHL. However, much of the increase has been observed in patients in their sixth and seventh decades, and a large part has paralleled a major decrease in mortality from other causes. The median age of individuals with NHL has increased in the past 2 decades,[2] and therefore may also have significant comorbid conditions, which complicate treatment options.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for NHL were developed as a result of meetings convened by a multidisciplinary panel of NHL experts, with the goal of providing recommendations on the standard diagnostic and treatment approaches based on current evidence. The NCCN Guidelines for NHL focus on the recommendations for diagnostic workup, treatment, and surveillance strategies for the most common subtypes of NHL, and provide a general discussion on the classification systems used in NHL, immunophenotyping, and supportive care considerations for patients with NHL.

This portion of the NCCN Guidelines for NHL discusses the recommendations for the diagnosis and management of patients with follicular lym-

Text cont. on page 928.

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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 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[c,d]
  - IHC panel: CD20, CD3, CD5, CD10, BCL2,[e] BCL6, cyclin D1, CD21, or CD23, or
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Molecular analysis to detect: antigen gene receptor rearrangements; *BCL2* rearrangements[e]
- Cytogenetics or FISH: t(14;18); *BCL6* rearrangements[e]
- IHC panel: Ki-67[f]

*Available online, in these guidelines, at NCCN.org.

[a] Follicular lymphoma, grade 1-2. Follicular lymphoma, 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. Follicular lymphoma, grade 3 is commonly treated according to the NCCN Diffuse Large B-Cell Lymphoma Guideline (BCEL-1*). Any area of diffuse large B-cell lymphoma (DLBCL) in a follicular lymphoma of any grade should be diagnosed and treated as a DLBCL.

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

[c] Typical immunophenotype: CD10+, BCL2+, CD23+/-, CD43-, CD5-, CD20+, cyclin D1, BCL6+. Rare cases of follicular lymphoma may be CD10- or BCL2-.

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

[e] In young patients with localized disease that lack BCL2 rearrangement or t(14;18), consider entity of pediatric follicular lymphoma. Analysis of BCL6 rearrangement may be useful for evaluating the diagnosis of pediatric FL.

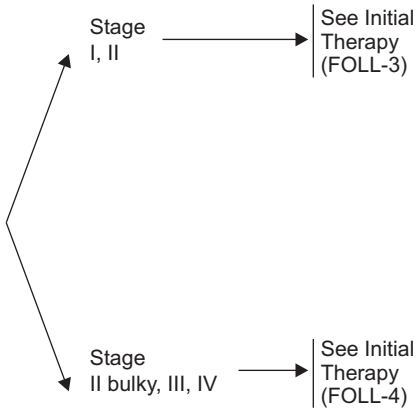
[f] There are reports showing that Ki-67 proliferation fraction of >30 % may be associated with a more aggressive clinical behavior, but there is no evidence that this should guide treatment decisions.

FOLL-1

WORKUP[a]

ESSENTIAL:
- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC, differential, platelets
- LDH
- Beta-2-microglobulin
- Comprehensive metabolic panel
- Hepatitis B testing[g]
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Bone marrow biopsy + aspirate to document clinical stage I-II disease[h]
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

USEFUL IN SELECTED CASES:
- MUGA scan/echocardiogram if anthracycline or anthracenedione-based regimen is indicated
- Neck CT
- PET-CT scan
- Uric acid
- Discussion of fertility issues and sperm banking
- SPEP and/or quantitative immunoglobulin levels
- Hepatitis C testing



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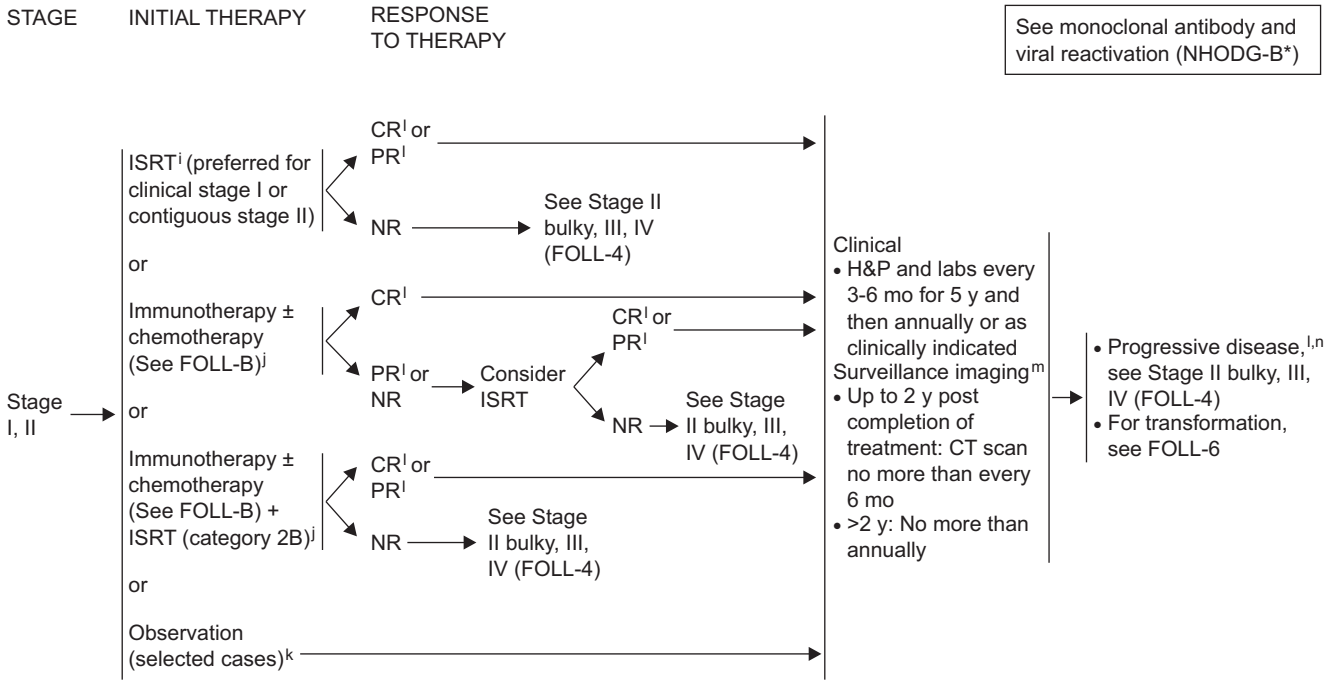
[a]Follicular lymphoma, grade 1-2. Follicular lymphoma, grade 3 is an area of controversy. The distinction between follicular grade 3a and 3b has not been shown to have clinical significance to date. Follicular lymphoma, grade 3 is commonly treated according to the NCCN Diffuse Large B-Cell Lymphoma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

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

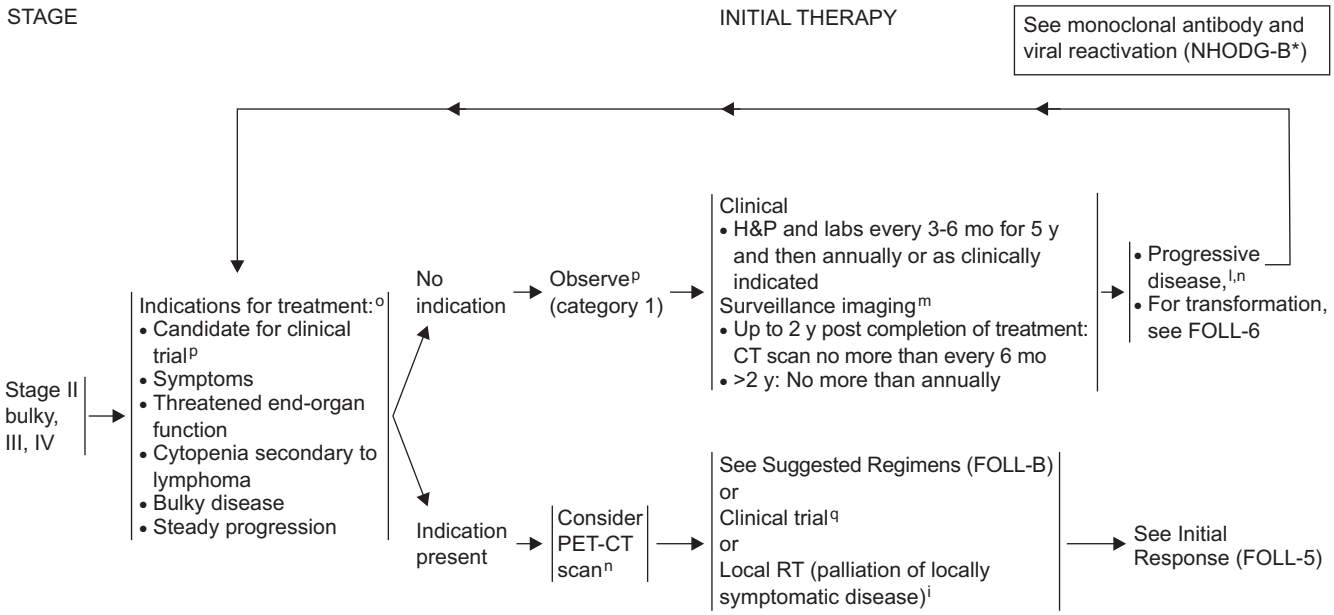
[h]Bilateral or unilateral provided core biopsy is >1.6 cm. If radioimmunotherapy is considered, bilateral cores are recommended and the pathologist should provide the percent of overall cellular elements and the percent of cellular elements involved in the marrow. If observation is initial therapy,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



*Available online, in these guidelines, at NCCN.org.

[i] See Principles of Radiation Therapy (NHODG-D*).
[j] Initiation of chemotherapy or more extended RT can improve FFS (failure-free survival), but has not been shown to improve overall survival. These are options for therapy.
[k] Observation may be appropriate in circumstances where potential toxicity of involved-site RT (ISRT) outweighs potential clinical benefit.
[l] See Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C*).
[m] Imaging should be performed whenever there are clinical indications. For surveillance imaging, see Discussion for consensus imaging recommendations.
[n] Consider possibility of histologic transformation in patients with progressive disease, especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, or there are new B symptoms. If clinical suspicion of transformation, FDG-PET may help identify areas suspicious for transformation. FDG-PET scan demonstrating marked heterogeneity or sites of intense FDG avidity may indicate transformation, and biopsy should be directed biopsy at the most FDG avid area. Functional imaging does not replace biopsy to diagnose transformation. If transformation is histologically confirmed, treat with anthracycline-based therapy. See Management of Transformation (FOLL-6).

FOLL-3



*Available online, in these guidelines, at NCCN.org.

[i] See Principles of Radiation Therapy (NHODG-D*).
[l] See Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C*).
[m] Imaging should be performed whenever there are clinical indications. For surveillance imaging, see Discussion for consensus imaging recommendations.
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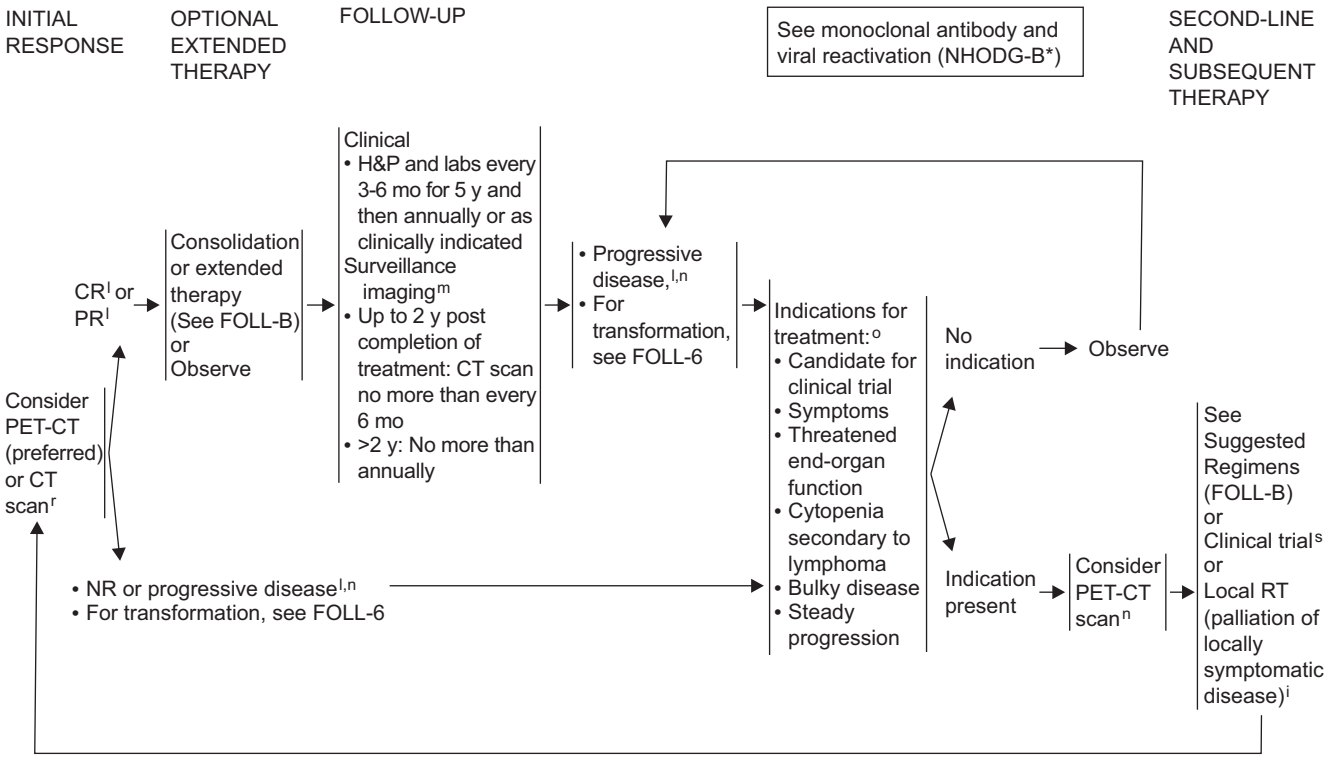
[o] See GELF criteria (FOLL-A).
[p] Consider clinical trials appropriate for patients on observation.
[q] Given incurability with conventional therapy, consider investigational therapy as first line of treatment.



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[i] See Principles of Radiation Therapy (NHODG-D*).
[l] See Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C*).
[m] Imaging should be performed whenever there are clinical indications. For surveillance imaging, see Discussion for consensus imaging recommendations.
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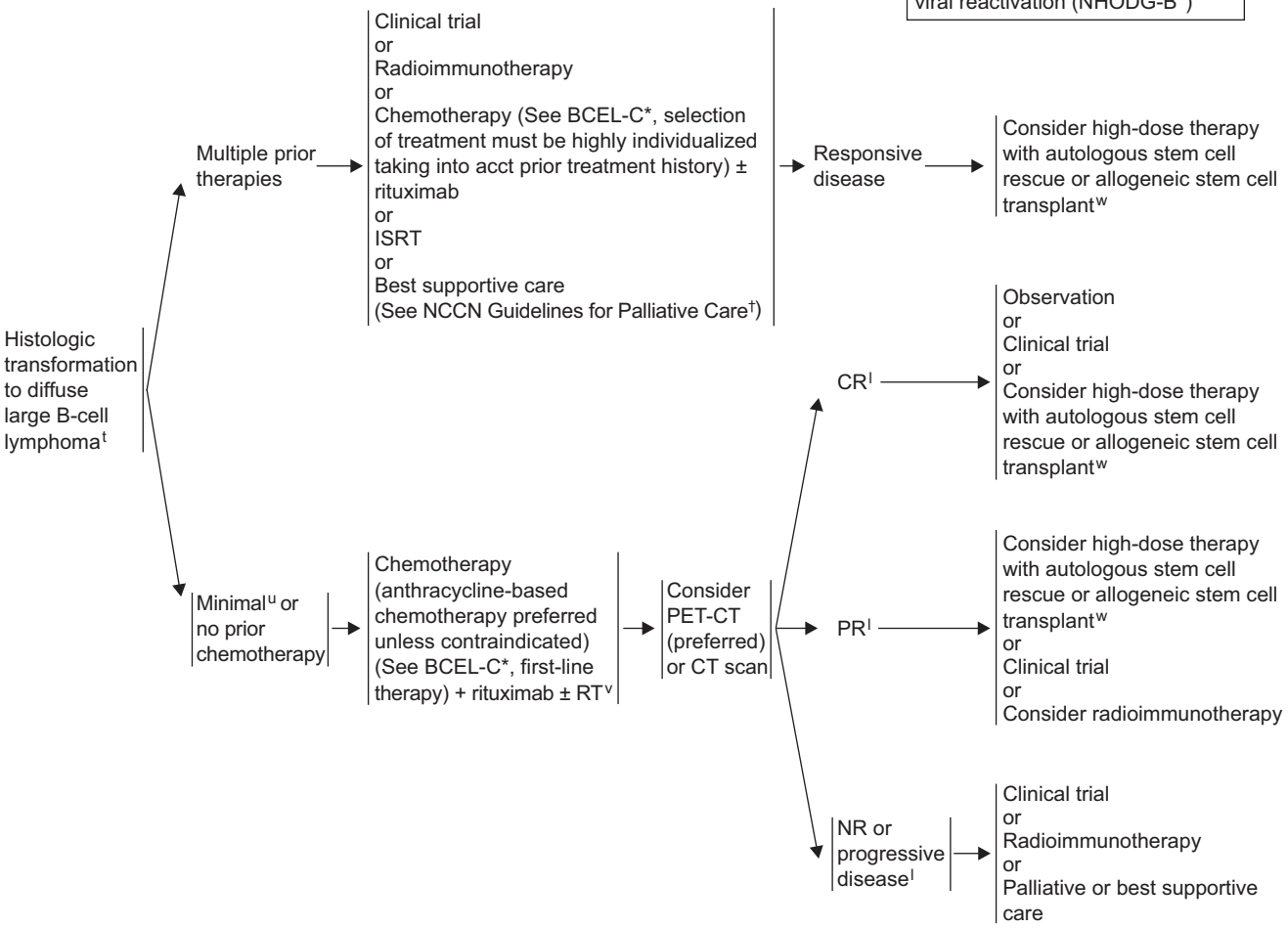
[o] See GELF criteria (FOLL-A).
[r] A PET-positive PR is associated with a shortened PFS (see Discussion); however, additional treatment at this juncture has not been shown to change outcome.
[s] Clinical trials may involve novel agents, regimens, or transplantation.

FOLL-5

HISTOLOGIC TRANSFORMATION TO DIFFUSE LARGE B-CELL LYMPHOMA

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

See monoclonal antibody and viral reactivation (NHODG-B*)



*Available online, in these guidelines, at NCCN.org.
[†]To view the most recent version of these guidelines, visit NCCN.org.

[l]See Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C*).
[t]For pathologic evaluation of histologic transformation, FISH for BCL2 rearrangement [t(14;18)] and MYC rearrangements [t(8;14) or variants, t(8;22), t(2;8)].
[u]Involved-site RT alone or one course of single-agent therapy including rituximab.
[v]If locoregional transformation, consider adding RT.
[w]Strongly recommend this treatment be given in the context of a clinical trial.

GELF CRITERIA[a,b]

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

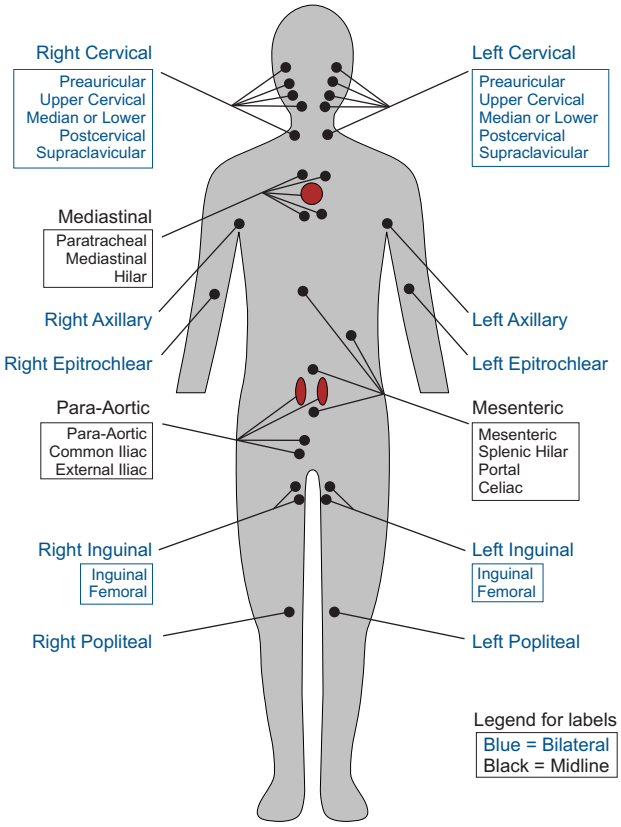
FLIPI - 1 CRITERIA[a,c,d]

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

Risk group according to FLIPI chart

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

Nodal Areas



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

[a] This provides useful prognostic information that may be used to guide therapeutic decisions.
[b] Solal-Celigny P, Lepage E, Brousse N, et al. Doxorubicin containing regimen with or without interferon alfa 2b for advanced follicular lymphomas: final analysis of survival and toxicity in the Groupe d'Etude des Lymphomes Folliculaire 86 trial. J Clin Oncol 1998;16:2332-2338.
[c] This research was originally published in Blood. Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood 2004;104:1258-1265. (c) the American Society of Hematology.
[d] FLIPI-2 (Federico M, Bellei M, Marcheselli L, et al. J Clin Oncol 2009;27:4555-4562) predicts for outcomes after active therapy, see Discussion.
[e] The map is used to determine the number of nodal sites in FLIPI-1 criteria and is different than the conventional Ann Arbor site map.

FOLL-A

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

First-Line Therapy[c]
- Bendamustine + rituximab (category 1)
- RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)
- RCVP (rituximab, cyclophosphamide, vincristine, prednisone) (category 1)
- Rituximab (375 mg/m^2 weekly for 4 doses)

First-Line Therapy for Elderly or Infirm (if none of the above are expected to be tolerable in the opinion of treating physician)
- Radioimmunotherapy[d,e]
- Rituximab (preferred) (375 mg/m^2 weekly for 4 doses)
- Single-agent alkylators (eg, chlorambucil or cyclophosphamide) ± rituximab

First-Line Consolidation or Extended Dosing (optional)[f]
- Radioimmunotherapy (after induction with chemotherapy or chemoimmunotherapy)[d,e,g] (category 1)
- Rituximab maintenance 375 mg/m^2 one dose every 8 wks for 12 doses for patients initially presenting with high tumor burden (category 1)
- If initially treated with single-agent rituximab, consolidation with rituximab 375 mg/m^2 one dose every 8 weeks for 4 doses

Second-Line and Subsequent Therapy
- Chemoimmunotherapy (as listed under first-line therapy)
- FCMR[h] (fludarabine, cyclophosphamide, mitoxantrone, rituximab) (category 1)
- Fludarabine[h] + rituximab
- Lenalidomide ± rituximab
- Radioimmunotherapy[d,e] (category 1)
- Rituximab
- RFND[h,i] (rituximab, fludarabine, mitoxantrone, dexamethasone)
- See Second-Line Therapy for DLBCL (BCEL-C 1 of 3*) without regard to transplantability

Second-Line Consolidation or Extended Dosing
- High-dose therapy with autologous stem cell rescue
- Allogeneic stem cell transplant for highly selected patients
- Rituximab maintenance 375 mg/m^2 one dose every 12 wks for 2 years (category 1) (optional)

For patients with locally bulky or locally symptomatic disease, consider ISRT 4-30 Gy ± additional systemic therapy.

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

See monoclonal antibody and viral reactivation (NHODG-B*)

*Available online, in these guidelines, at NCCN.org.

[a] See references for regimens FOLL-B 2 of 3 and FOLL-B 3 of 3.
[b] The choice of initial therapy requires consideration of many factors, including age, comorbidities, and future treatment possibilities (eg, HDT with SCR). Therefore, treatment selection is highly individualized.
[c] In combination chemotherapy, addition of rituximab has consistently increased overall response rate, response duration, and progression-free survival. In addition, some studies have demonstrated an overall survival benefit.
[d] Selection of patients requires adequate marrow cellularity >15% and <25% involvement of lymphoma in bone marrow, and platelets >100,000. In patients with prior autologous stem cell rescue, referral to a tertiary care center is highly recommended for radioimmunotherapy.
[e] 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. Cytogenetics ± FISH for known MDS markers. As of 2010, updates suggest a trend towards an increased risk of MDS with RIT treatment.
[f] First-line consolidation with radioimmunotherapy or extended dosing of rituximab after bendamustine + rituximab has not been studied.
[g] The full impact of an induction regimen containing rituximab on RIT consolidation is unknown.
[h] Fludarabine-containing regimens negatively impact stem cell mobilization for transplant.
[i] RFND regimen may be associated with stem cell toxicity and secondary malignancies (see Discussion).

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.

Cyclophosphamide

Peterson BA, Petroni GR, Frizzera G, et al. Prolonged single-agent versus combination chemotherapy in indolent follicular lymphomas: a study of the cancer and leukemia group B. J Clin Oncol 2003;21:5-15.

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.

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.

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.

Radioimmunotherapy

Kaminski MS, Tuck M, Estes J, et al. 131I-tositumomab therapy as initial treatment for follicular lymphoma. N Engl J Med 2005;352:441-449.

Kaminski MS, Tuck M, Estes J, et al. Tositumomab and iodine I-131 tositumomab for previously untreated, advanced-stage, follicular lymphoma: Median 10 year follow-up results. Blood 2009;114:3759.

Scholz CW, Pinto A, Linkesch W, et al. 90Yttrium ibritumomab tiuxetan as first line treatment for follicular lymphoma. First results from an international phase II clinical trial [abstract]. Blood 2010;116:Abstract 593.

First-Line Consolidation or Extended Dosing

Radioimmunotherapy (after induction with chemotherapy or chemoimmunotherapy)

Press OW, Unger JM, Braziel RM, et al. Phase II trial of CHOP chemotherapy followed by tositumomab/iodine I-131 tositumomab for previously untreated follicular non-Hodgkin's lymphoma: five-year follow-up of Southwest Oncology Group Protocol S9911. J Clin Oncol 2006;24:4143-4149.

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.

Hagenbeek A, Radford J, Van Hoof A, et al. 90Y-Ibritumomab tiuxetan (Zevalin®) consolidation of first remission in advanced-stage follicular non-hodgkin's lymphoma: updated results after a median follow-up of 66.2 months from the international, randomized, phase III First-Line Indolent Trial (FIT) in 414 patients [abstract]. Blood 2010;116:Abstract 594.

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

Chemotherapy followed by rituximab

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

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.

FOLL-B
2 of 3

SUGGESTED TREATMENT REGIMENS
References

Second-Line and Subsequent Therapy

FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab)

Forstpointner R, Dreyling M, Repp R, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared to FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas - results of a prospective randomized study of the German low grade lymphoma study group (GLSG). Blood 2004;104:3064-3071.

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.

Lenalidomide ± rituximab

Leonard J, Jung SH, Johnson JL, et al. CALGB 50401: a randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma [abstract]. J Clin Oncol 2012;30:Abstract 8000.

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 ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol 2002;20:2453-2463.

Kaminski MS, Zelenetz AD, Press OW, et al. Pivotal study of iodine I 131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. J Clin Oncol 2001;19:3918-3928.

Fisher RI, Kaminski MS, Wahl RL, et al. Tositumomab and iodine-131 tositumomab produces durable complete remissions in a subset of heavily pretreated patients with low-grade and transformed non-Hodgkin's lymphomas. J Clin Oncol 2005;23:7565-7573.

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.

Text cont. from page 917.

phoma (FL). The most recent and complete version of these guidelines is available at NCCN.org.

Follicular Lymphoma

Diagnosis

FL is the most common subtype of indolent NHL, accounting for approximately 22% of all newly diagnosed cases of NHL.[3] Approximately 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 immunohistochemistry (IHC) and/or flow cytometry for cell surface marker analysis is required to establish a diagnosis. FL has a characteristic immunophenotype, which includes CD20+, CD10+, BCL2+, CD23+/-, CD43, CD5-, CCND1-, and BCL6+. Occasional cases of FL may be CD10- or BCL2-. The diagnosis is easily established on histologic grounds, but immunophenotyping is encouraged to distinguish FL from a nodular mantle cell lymphoma (MCL) or small lymphocytic lymphoma (SLL). 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. No evidence suggests, however, that high Ki-67 should guide the selection of therapy.[4,5] Molecular genetic analysis to detect *BCL2* rearrangement, cytogenetics or fluorescence in situ hybridization (FISH) to identify t(14;18), and IHC 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, number of nodal sites involved, hemoglobin levels, and serum LDH levels.[6] The FLIPI was developed based on a large set of retrospective data from patients with FL, and established 3 distinct prognostic groups with 5-year survival outcomes ranging from 52.5% to 91.0% (in the pre-rituximab era).[6] In the National LymphoCare study, which analyzed the treatment options and outcomes of 2728 patients with newly diagnosed FL, FLIPI was able to categorize patients into 3 distinct prognostic groups.[7] 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.[8] The final prognostic model included age, hemoglobin levels, longest diameter of largest involved lymph node, β_2-microglobulin levels, and bone marrow involvement. FLIPI-2 was highly predictive of treatment outcomes, and separated patients into 3 distinct risk groups with 3-year progression-free survival (PFS) rates ranging from 51% to 91%, and overall survival (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%.[8] 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 β_2-microglobulin and lactate dehydrogenase (LDH) levels has been devised, which seems to be as predictive of outcomes as the FLIPI-1 and FLIPI-2 indices, and is easier to apply.[9,10]

In Situ Involvement of FL-Like Cells of Unknown Significance (FL "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.[11,12] 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.[11–14]

Cases of FLIS have been reported in patients with prior FL or concurrent FL (at other sites), and in individuals with no known history of FL.[11,12,14] The occurrence of FLIS in the general population seems 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%.[15] Development of (or progression to) overt lymphoma in patients found to have FLIS has been reported, although this seems to be uncommon (5%–6%).[16,17] 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.[12,16,18] The WHO classification recommends that a diagnosis of FL not be made in these cases, but that the report should suggest evaluation for the presence of FL elsewhere, and possibly close follow-up.

Pediatric-Type FL

Pediatric-type FL is considered a rare variant of FL in the 2008 WHO classification,[12] and has been reported to comprise less than 2% of childhood NHLs.[19–22] In published studies, the median age at diagnosis of pediatric FL was approximately 11 years, and most cases were stage I or II at diagnosis with a predilection for localized nodal involvement in the head and neck region.[20–24] 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.[21,23,24] 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 most cases.[20,21,23,24]

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.[12,20,21,23,24] Rearrangement of *BCL6* is also typically absent in pediatric FL.[21,24] 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 previously.[21,23,24] Pediatric FL without *BCL2* rearrangements tend to be associated with localized disease and have an indolent course and favorable prognosis, with only rare instances of disease progression or relapse.[20,21,23,24] In a recent analysis of FL cases in younger patients (age <40 years; n=27), a highly indolent pediatric-type FL was identified based on the lack of *BCL2* rearrangement concurrent with a high proliferation index (defined as ki-67 ≥30%).[24] 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%) 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 experienced progression or relapse after a median follow-up time of 61 months.[24] 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 radiation therapy [RT]), excision only (with or without RT), and, more recently, chemoimmunotherapy, with generally favorable outcomes and prognosis.[20,24,25]

Workup

The diagnostic workup for FL is similar to that 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 a CBC with differential and a comprehensive metabolic panel, in addition to measurements of serum LDH levels and serum β_2-microglobulin. Hepatitis B virus (HBV) testing is recommended because of 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.

Most patients with FL will present with disseminated disease. The approach to therapy differs dramatically among patients with localized and those with disseminated disease. Bone marrow biopsy with aspirate is essential for documenting clinical stage I–II disease. An adequate trephine biopsy (specimen ≥1.6 cm)[26,27] should be obtained for the initial staging evaluation, along with bone marrow aspiration. If radioimmunotherapy (RIT) is considered, bilateral core biopsy is recommended; in these 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.

Most NCCN Member Institutions routinely use chest, abdominal, and pelvic CT as part of the diagnostic evaluation. CT scan of the neck may also help define the extent of local disease. In patients presenting with what seems to be localized disease, a

PET scan may be helpful in identifying occult sites of disease or if concern exists about histologic transformation.[28] PET does not replace histologic confirmation of the diagnosis; however, if sites are present 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 multigated acquisition 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 diffuse large B-Cell lymphoma (DLBCL).

Involved-site RT (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.[29–32] In patients with stage I or II low-grade FL initially treated with involved- or extended-field RT, the median OS was approximately 14 years; 15-year OS rate was 40%, and the 15-year relapse-free survival (RFS) or PFS was also approximately 40%.[31,32] 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 involved-field RT (IFRT; 49% vs 40%, respectively).[32] Long-term outcomes from another study of RT in patients with early-stage grade 1 to 2 FL (with or without chemotherapy) reported a median OS of 19 years and a 15-year OS rate of 62%.[30] In this study, most patients (74%) had stage I disease and 24% had received chemotherapy with RT, which may have resulted in the higher OS rate compared with the aforementioned studies. In a recent study of patients with limited-stage FL (grade 1–3A) treated with IFRT or reduced IFRT (RT of involved nodes only), the 10-year PFS and OS rates were 49% and 66%, respectively.[29] 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 patients who were treated with RT.[33]

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 (cyclophosphamide, doxorubicin, vincristine, prednisone, and bleomycin) to RT resulted in 5-year failure-free survival (FFS) and OS rates of 74% and 89%, respectively.[34] The combination treatment seemed to improve FFS but did not affect OS in patients with early-stage disease.[34] 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 RFS or OS in the subgroup of patients with early-stage low-grade NHL.[35]

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).[36] First-line management strategies included observation only (ie, "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 before 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 (hazard ratios [HRs] of 0.36 and 0.11, respectively).[36] PFS outcomes did not differ for 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.[36] 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 6 different first-line treatment options: observation, chemotherapy alone, RT alone, RT combined with chemotherapy, rituximab monotherapy, or rituximab combined with chemotherapy (chemoimmunotherapy).[37] 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 underwent active therapy, the complete response (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.[37] The 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).[37]

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 show a survival advantage with immediate treatment versus a watchful waiting approach in patients with advanced-stage, low-tumor-burden (or asymptomatic) FL.[38–40] These studies used chemotherapy regimens for the immediate treatment arm, because the studies were conducted before 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).[41] The primary end point 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 end point chosen for this trial, however, is rather controversial considering that one arm of the trial involved initiation of early therapy; a more justifiable end point for this study could have been time to initiation of second therapy. Moreover, no differences in OS were observed between the study arms.[41] 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 (according to GELF criteria) were treated with standard doses of rituximab, of which patients experiencing response were then randomized to receive immediate maintenance with rituximab (n=140) or retreatment with rituximab on progression (n=134).[42] The primary end point 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, the median TTF was similar in the maintenance and retreatment arms (3.9 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 watchful waiting approaches in a similar population.[42] 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 watchful waiting approach (n=107).[43] All of these patients 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. To assess whether an initial watchful waiting 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).[43] 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, disease relapse, or death from any cause. In the watchful waiting cohort, initiation of first-line therapy was not considered an event for FFTF. The 4-year FFTF was 79% in the watchful waiting 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).[43] The investigators concluded that watchful waiting remained a valid strategy, even in the rituximab era, for the management of patients with prognostically favorable low-tumor-burden FL,

Collectively, findings from these 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 Groupe d'Etudes des Lymphomes Folliculaires [GELF] criteria).

Rituximab has demonstrated single-agent activity in previously untreated patients, and in those with relapsed or refractory disease.[44–46] The addition of rituximab to combination chemotherapy regimens has consistently been associated with improved overall response rate (ORR), response duration, and PFS outcomes.[47–51] In addition, some studies have shown an OS benefit with the addition of rituximab; a recent meta-analysis confirmed this benefit despite what is still limited follow-up for FL.[52]

Long-term follow-up data from a multicenter phase II trial showed the safety and efficacy of rituximab combined with CHOP chemotherapy (R-CHOP) in patients with relapsed or newly diagnosed indolent NHL.[48] The ORR was 100%, with 87% of patients achieving a CR or unconfirmed CR (uCR). The median time to progression and the duration of response were 82.0 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 a prolonged duration of remission.[49] OS analysis was complicated by a second randomization (for patients aged <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 (because these patients were not eligible for HDT/ASCR), R-CHOP/interferon was associated with significantly improved 4-year PFS (62% vs 28%) and OS rates (90% vs 81%) compared with CHOP/interferon.[53]

In a randomized phase III study, the addition of rituximab to the cyclophosphamide, vincristine, and prednisone chemotherapy regimen (R-CVP; n=162) compared with CVP (n=159) significantly improved outcome in patients with previously untreated FL, with no significant increase in toxicity.[50] At a median follow-up of 53 months, R-CVP was associated with improved ORR (81% vs 57%), CR/uCR rate (41% vs 10%), median time to progression (34 vs 15 months), and 4-year OS rate (83% vs 77%).[51]

The addition of rituximab to fludarabine (FR) or fludarabine-based combination has also been evaluated in various clinical studies.[54–57] In a phase II study, FR was evaluated in patients with previously untreated or relapsed low-grade or follicular NHL (n=40; 68% previously untreated).[54] The ORR was 90%, with 80% of patients experiencing 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 patients and those who experienced a relapse after treatment.[54] 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.[55] R-FCM resulted in significantly higher ORRs (79% vs 58%; *P*=.01), higher CR rates (33% vs 13%; *P*=.005), improved median PFS (16 vs 10 months; *P*=.038), and improved median OS (not reached at 3 years vs 24 months; *P*=.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.[55] In a randomized trial from the MD Anderson Cancer Center (MDACC), concurrent administration of rituximab and FND (fludarabine, mitoxantrone and dexamethasone; R-FND) resulted in a significantly higher 3-year FFS rate compared with sequential adminstration (84% vs 59%) in the subset of patients with FL.[56] In a subsequent report from 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 and OS rates with the regimen were 60% and 95%, respectively.[58] 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).[59] None of the patients were previously treated with rituximab, fludarabine, or mitoxantrone. The ORR with this regimen was 84% (CR/uCR in 68%). The 3-year PFS and OS rates were 47% and 66%, respectively.[59]

The incorporation of rituximab in chemotherapy regimens has become a widely accepted standard of care in first-line therapy for patients with FL. However, no head-to-head randomized studies have shown superiority of one chemoimmunotherapy regimen over another regarding 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 United States (n=2738) showed that rituximab-containing chemoimmunotherapy was used in 52% of patients.[7] Among these patients, the most commonly used regimens included R-CHOP (55%), R-CVP (23%), and rituximab with fludarabine-based regimens (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 among patients treated with R-CHOP, R-CVP, or rituximab with fludarabine-based regimens (78% vs 72% vs 76%, respectively).[60] 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.[60]

The phase III randomized trial of the Italian Lymphoma group (FOLL-05 Trial) evaluated the efficacy of 3 chemoimmunotherapy regimens (R-CVP, R-CHOP, and R-FM) as first-line therapy in patients with advanced-stage FL (n=534).[61] The primary end point of this study was TTF. The 3-year TTF rate was 46% for patients randomized to R-CVP, 62% for R-CHOP (*P*=.003 vs R-CVP), and 59% with R-FM (*P*=.006 vs R-CVP) after a median follow-up of 34 months. The 3-year PFS rates were 52%, 68%, and 63%, respectively (*P*=.011). No significant differences were observed between treatment arms for ORR or CR rate. The 3-year OS rate was 95% for all patients in this study.[61] 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%).[61] 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 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 these regimens.[62–64] 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.[47,62–64]

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 because of 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 and heavily pretreated relapsed or refractory indolent or mantle cell histologies or transformed NHL.[65–70] A multicenter, randomized, open-label phase III study conducted by the German Study Group for Indolent Lymphomas (StiL) compared rituximab combined with bendamustine (BR) versus R-CHOP as first-line treatment in patients with advanced follicular, indolent, and mantle cell lymphomas (n=514).[71] The primary end point of this study was PFS, which was significantly longer with BR compared with R-CHOP (median PFS, 69.5 vs 31.0 months; HR, 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).[71] With a median follow-up of 45 months, no significant difference in OS was observed between treatment arms, and the 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 incidences of grade 3 or 4 neutropenia (29% vs 69%) or infection (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 (9%) with R-CHOP.[71]

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).[72] Among evaluable patients (N=419), the CR rate (assessed by an independent review committee) with BR was not inferior to that with 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.[72] 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).[69] The median duration of response and PFS were 21 and 23 months, respectively. Outcomes were similar for patients with indolent or mantle cell histologies.[69]

Bendamustine combined with rituximab and the proteasome inhibitor bortezomib (BVR) has been evaluated in 2 recent phase II studies in patients with relapsed and/or refractory FL.[65,66] 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%).[66] 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 caused by sepsis.[66] 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%).[65] 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.[65]

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/uCR in 7%).[73] 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.[73] 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).[74] 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 event-free survival was significantly longer with the combination (2.0 vs 1.2 years; *P*=.0063). Approximately 19% of patients in each arm discontinued therapy because of 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%).[74] 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).[75] Among the subgroup of patients with FL (n=46), the ORR was 98% (CR/uCE in 87%) and the 2-year PFS was 89%. In patients with FL who had a positive PET scan before therapy (n=45), 93% experienced a 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%).[75]

RIT with the radiolabelled monoclonal antibodies ^{90}Y-ibritumomab tiuxetan[76–80] and ^{131}I-tositumumab[81–84] has been evaluated in patients with newly diagnosed and those with relapsed, refractory, or histologically transformed FL. In an international phase II trial, ^{90}Y-ibritumomab, when used as a first-line therapy in older patients (age >50 years) with stage III or IV FL (N=59; median age, 66 years; range, 51–83 years), resulted in an ORR of 87% (CR in 41%, uCR in 15%) at 6 months after therapy.[80] After a median follow-up of approximately 31 months, the median PFS was 26 months and the median OS has not been reached. The most common toxicities with first-line ^{90}Y-ibritumomab included grade 3 or 4 thrombocytopenia (48%; grade 4 in 7%) and neutropenia (32%; grade 4 in 17%). No grade 3 or 4 nonhematologic toxicities were reported. Grade 2 infections occurred in 20% and grade 2 gastrointestinal toxicities in 10% of patients.[80] In a randomized phase III study in patients with relapsed or refractory low-grade follicular or transformed lymphoma (n=143), ^{90}Y-ibritumomab tiuxetan also produced a statistically and clinically significant higher ORR (80% vs 56%) and CR rate (30% vs 16%) compared with rituximab alone.[77] At a median follow-up of 44 months, median time to progression (15 vs 10 months) and duration of response (17 vs 11 months) were longer for patients treated with ^{90}Y-ibritumomab compared with rituximab.[78]

Initial treatment with a single 1-week course of ^{131}I-tositumomab induced prolonged clinical and molecular remissions in patients with advanced FL (N=76).[81] 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.[85] 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 myelodysplastic syndromes (MDS) approximately 8 years after therapy.[85] A single course of ^{131}I-tositumumab was significantly more efficacious than the last qualifying chemotherapy in extensively pretreated patients with refractory, low-grade, or transformed NHL (n=60).[83] The final results of the study showed that ^{131}I-tositumumab resulted in long-term durable CRs. Among the 12 patients who experienced 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.[86]

First-Line Consolidation With RIT: First-line chemotherapy followed by RIT with ^{90}Y-ibritumomab[87–90] or ^{131}I-tositumumab[91–94] has also been evaluated in several phase II studies.

In the international phase III trial (First-Line Indolent Trial; FIT), patients with advanced-stage FL responding to first-line induction therapy (n=414) were randomized to receive ^{90}Y-ibritumomab or no further treatment (observation only).[89] After a median follow-up of 7.3 years, the estimated 8-year PFS was 41% with ^{90}Y-ibritumomab tiuxetan consolidation and 22% with observation only, with a median PFS of 4.1 versus 1.1 years, respectively (*P*<.001).[95] 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/acute myeloid leukemia (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.[89,95] Among these patients, the estimated 8-year PFS rate was 56% with ^{90}Y-ibritumomab consolidation and 45% with observation alone; the median PFS was greater than 7.9 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.[95] Because only a small proportion of patients enrolled in the FIT trial received rituximab-containing induction therapy, the effects of RIT consolidation after rituximab-containing regimens cannot be fully evaluated.

In the Southwest Oncology Group (SWOG S9911) trial, CHOP followed by ^{131}I-tositumomab resulted in an ORR of 91%, including a 69% CR rate in patients with previously untreated, advanced FL (n=90).[93] After a median follow-up of 5 years, the estimated 5-year PFS and OS rates were 67% and 87%, respectively.[92] In a historical comparison, these results were more favorable than those reported for CHOP alone. In a multicenter phase II study, CVP chemotherapy followed by ^{131}I-tositumomab resulted in an ORR of 100% with a 93% CR rate in untreated patients with FL (n=30). The 5-year PFS and OS rates were 56% and 83%, respectively.[94]

The phase III randomized Intergroup study by the SWOG/CALGB (S0016) evaluated the role of RIT consolidation with ^{131}I-tositumumab (CHOP-RIT) after first-line therapy in patients with advanced-stage FL.[9] In this study, 554 patients were randomized to first-line therapy with 6 cycles of R-CHOP or 6 cycles of CHOP followed by consolidation with ^{131}I-tositumumab (CHOP-RIT).[9] After a median follow-up time of 4.9 years, the estimated rates of 2-year PFS (76% vs 80%) and OS (97% vs 93%) 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 rate (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 less incidence of febrile neutropenia (10% vs 16%) compared with R-CHOP. The incidences of secondary malignancies (9% vs 8%) and MDS/AML (1% vs 3%) were not different between R-CHOP and CHOP-RIT.[9]

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 event-free survival in chemotherapy-naïve patients experiencing a response to initial rituximab induction, although this benefit did not translate to an OS advantage.[96–98] In a study that evaluated maintenance rituximab compared with rituximab retreatment on 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 vs 7 months; *P*=.007).[99] However, retreatment with rituximab at progression provided the same duration of benefit from rituximab as did maintenance rituximab (31 vs 27 months).[99] Therefore, either approach (maintenance or retreatment at progression) seemed to be beneficial for this patient population. The randomized phase III study from ECOG (E1496) showed a PFS benefit with rituximab maintenance in patients with advanced indolent lymphoma responding to first-line chemotherapy with CVP (n=311; FL: n=282).[100] The 3-year PFS rate was 68% for maintenance rituximab compared with 33% for observation in 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).[100]

The phase III randomized PRIMA trial prospectively evaluated the role of rituximab maintenance in patients responding to first-line chemotherapy in combination with rituximab.[101] 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/uCR compared with 52% in the observation group.[101] However, no significant difference was observed in OS between the 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 after second-line therapy has also been evaluated in patients with relapsed/refractory disease. Two large randomized trials have shown a PFS advantage with rituximab maintenance over observation for patients treated with chemoimmunotherapy induction.[102–104] 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).[102] 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 vs 1.3 years; P<.001) compared with observation alone.[103,104] 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 rates were not significantly different between study arms (74% vs 64%, respectively).[104]

Hematopoietic Stem Cell Transplantation After Induction: HDT/ASCR has been shown to prolong OS and PFS in patients with relapsed or refractory disease.[105–107] The GELA recently conducted a retrospective analysis of patients treated with chemotherapy alone in the first-line setting and found that event-free survival and survival after relapse were superior for patients treated with rituximab-containing regimens compared with chemotherapy only–based HDT/ASCR for relapsed or refractory FL.[108] The combination of rituximab-based second-line therapy followed by HDT/ASCR resulted in a favorable survival rate after relapse, which was 90% at 5 years. Allogeneic HSCT is associated with high treatment-related mortality rates (≈30%–40% for myeloablative and 25% for nonmyeloablative allogeneic HSCT).[109,110] In a recent report from the International Bone Marrow Transplant Registry, both myeloablative and nonmyeloablative HSCT resulted in similar treatment-related mortality rates; however, nonmyeloablative allogeneic HSCT was associated with an increased risk of disease progression.[111]

Imaging Studies for FL

Imaging studies using CT or PET/CT scans are important components of diagnostic workup, interim restaging, and posttreatment 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 posttreatment assessment. Although PET/CT is now considered a standard part of posttreatment 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%).[112–115] Studies have also suggested that PET/CT scans may be more accurate than CT scans alone in detecting disease.[114,116,117] In addition, posttreatment PET/CT scans have shown prognostic utility in patients with indolent lymphomas. Several studies have shown that PET status (ie, 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.[112,117,118] 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.[118] Posttreatment 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).[118] 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-con-

taining chemoimmunotherapy were randomized to rituximab maintenance (for 2 years) or observation only.[101] Among patients with a postinduction PET/CT scan (n=122), those with a positive PET/CT scan had a significantly inferior PFS rate compared with those who had a negative PET scan (33% vs 71% at 42 months; $P<.001$)[119]; 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-month PFS rate was 29% for PET/CT-positive patients compared with 68% in PET/CT-negative cases; the median PFS was 30 and 52 months, respectively.[101] 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; $P=.001$).[101]

In a recent prospective study, the prognostic value of PET imaging was evaluated in patients with high-tumor-burden FL treated using first-line therapy with 6 cycles of R-CHOP (n=121; no maintenance rituximab administered).[120] 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 who had an interim PET scan (n=111), 76% had a PET-negative response. Among patients who had a final PET (n=106), 78% had a PET-negative response.[120] At the end of treatment, nearly all patients (98%) who experienced a CR based on International Workshop Criteria also had a PET-negative response. Interim PET was associated with significantly higher 2-year PFS rate (86% for PET negative vs 61% for positive; $P=.0046$) but no significant difference in terms of OS. Final PET negativity was associated with both a significantly higher 2-year PFS rate (87% vs 51%; $P<.001$) and a higher OS rate (100% vs 88%; $P=.013$).[120] These studies suggest that posttreatment 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 postinduction therapeutic interventions.

PET scans may be useful in detecting transformation in patients with indolent NHL. Standard FDG uptake values (SUVs) on PET have been reported to be higher among transformed versus nontransformed cases of indolent lymphomas.[114] 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 histologic confirmation.[121]

Few data exist on the potential role of follow-up surveillance imaging for detecting relapse in patients with indolent NHL. In an early retrospective study, patients with stage I–III FL with a CR after induction were evaluated with clinical, laboratory, and imaging studies during routine follow-up (n=257).[122] 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 most relapses (77%) occurring within the first 5 years of treatment.[122] 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.[122] 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.[123] PET scans were performed every 6 months for the first 2 years after completion of induction, and 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.[123] Among 13 patients who were PET-positive without a corresponding abnormality on CT scan, relapse was documented in 8 based on biopsy results. Of the 47 patients with PET-positive relapses, 38 were detected on CT and 30 were detected clinically at the same time as the PET. Whether this earlier detection of relapse in a proportion of patients translates to improved outcomes is unclear.

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

NCCN Recommendations for Treatment of Stage I–II Disease

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

For patients experiencing a partial response after initial immunotherapy with or without chemotherapy (but without RT), additional treatment with ISRT should be considered. Otherwise, for patients with a clinical partial response (after ISRT) or CR, clinical follow-up with a complete physical examination 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 after 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 those with advanced disease, as described later.

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

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, before initiation of therapy, HBV testing (including hepatitis B surface antigen [HBsAg] and hepatitis B core antibody [HBcAb] testing) should be performed for all patients, and 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, should be observed.[40]

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 with R-CHOP in a randomized phase III study; however, the OS outcomes were not significantly different. Furthermore, limited data exist on the risk of secondary MDS/AML after bendamustine. Data from a limited subset of patients suggest 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. 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 because of 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 with cyclophosphamide-based combination chemotherapy.[124] These guidelines also include RIT and 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 experiencing a CR or partial response to first-line therapy can either be observed or be treated with optional consolidation or extended therapy. Based on the results of the PRIMA study,[101] maintenance therapy with rituximab (one dose every 8 weeks) up to 2 years is recommended (category 1) for patients experiencing a response to first-line chemoimmunotherapy. Based on the results of the FIT trial,[89,95] RIT is recommended (category 1) for patients who received first-line chemotherapy. As of February 2014, ^{131}I-tositumumab has been discontinued and will no longer be available for the treatment of patients with FL.

For patients receiving consolidation therapy, clinical follow-up with a complete physical examination 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 after 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 experiencing disease progression on 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, the FCM-R regimen (category 1), RIT (category 1), or any of the second-line regimens used for patients with DLBCL.

Second-Line Consolidation or Extended Dosing: For patients experiencing 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 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 experienced progression 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 experienceing a 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 examination 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 after completion of treatment, and then no more than annually (or as clinically indicated) thereafter.

Histologic Transformation to DLBCL

In patients with FL, histologic transformation to DLBCL is generally associated with a poor clinical outcome. Histologic transformation to DLBCL occurs at an annual rate of approximately 3% for 15 years; the risk of transformation decreases after that time for reasons that remain unclear.[125] 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.[125] However, patients with limited disease and no previous exposure to chemotherapy may have the favorable outcomes similar to de novo DLBCL.[126] The 5-year OS rate for patients with limited extent transformation was 66% compared with 19% for those with advanced disease ($P<.0001$).[125]

In patients who have undergong 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 experiencing remission after initial treatment. In a multicenter cohort study (172 patients) conducted by the Canadian Blood and Marrow Transplant Group, HDT/ASCR was associated with better outcomes than rituximab-based chemotherapy alone for patients aggressive histologic transformation.[127] The 5-year OS rates after transformation were 65%, 61%, and 46%, respectively, for patients treated with HDT/ASCR, rituximab-containing chemotherapy, and allogeneic stem cell transplant. The corresponding 5-year PFS rates after transformation were 55%, 40%, and 46%, respectively.

If the patient has had minimal chemotherapy (ISRT alone or 1 course of single-agent therapy including rituximab) or none prior, anthracycline-based chemotherapy with rituximab, with or without RT, is included as a treatment option. Enrollment in clinical trial is recommended for all patients after initial therapy. Patients experiencing response to initial treatment (with a partial response or CR) could also be considered for consolidation therapy with HDT/ASCR or allogeneic HSCT. Alternatively, patients experiencing a CR to initial therapy may be observed, and RIT may be considered for those with a partial response. Patients with no response or progressive disease after initial therapy should be treated with RIT, palliative therapy, or best supportive care.

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Individual Disclosure for the NCCN Non-Hodgkin's Lymphomas Panel

Panel Member	Clinical Research Support/Data Safety Monitoring Board	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
Jeremy S. Abramson, MD	Celgene Corporation; Millennium Pharmaceuticals, Inc.; Novartis Pharmaceuticals Corporation; Onyx Pharmaceuticals, Inc.; Constellation, Inc.; and Seattle Genetics, Inc.	Genentech, Inc.; Jannsen Pharmaceutica Products, LP; Millennium Pharmaceuticals, Inc.; Seattle Genetics, Inc.; and Spectrum Pharmaceuticals	None	None	5/23/14
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C. Babis Andreadis, MD, MSCE	GlaxoSmithKline	Millennium Pharmaceuticals, Inc.; Spectrum Pharmaceuticals, Inc.; and Pharmacyclics, Inc.	Roche Laboratories, Inc.	None	5/28/14
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Naresh Bellam, MD, MPH	None	Celgene Corporation	None	None	7/16/13
John C. Byrd, MD	None	None	None	None	3/26/13
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Richard I. Fisher, MD	None	Johnson & Johnson; Coherus BioSciences, Inc.; and Gilead Sciences, Inc.	None	None	5/5/14
Martha J. Glenn, MD	Amgen Inc.; Institutional DSMC; and sanofi-aventis U.S.	None	None	None	6/2/14
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Nancy Lee Harris, MD	Pharmacyclics, Inc.	None	None	None	5/19/14
Richard T. Hoppe, MD	None	Clarient Diagnostic Services, Inc.	None	None	5/19/14
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Christopher R. Kelsey, MD	Varian Medical Systems, Inc.	None	None	None	6/2/14
Youn H. Kim, MD	Merck & Co., Inc.; Millennium Pharmaceuticals, Inc.; Allos Therapeutics, Inc.; Ceptaris Therapeutics, Inc.; Kyowa Hakko Kirin Co., Ltd.; and Seattle Genetics, Inc.	Celgene Corporation; and Medicis	None	Eisai Inc.; and Millennium Pharmaceuticals, Inc.	3/10/13
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Pierluigi Porcu, MD	None	None	None	None	3/4/13
Oliver Press, MD, PhD	Genentech, Inc.; and Roche Laboratories, Inc.	Algeta; and BIND Therapeutics, Inc.	Emergent BioSolutions Inc.	None	4/7/14
Rachel Rabinovitch, MD	RTOG Data Safety and Monitoring Board	None	None	Accuray Incorporated	4/22/14
Nishitha Reddy, MD	Celgene Corporation	Celgene Corporation	None	None	11/21/13
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The NCCN Guidelines staff have no conflicts to disclose.