National Comprehensive Cancer Network®

NCCN

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Hodgkin's Lymphomas

Version 2.2015

NCCN.org

Continue

Follicular Lymphoma

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2015
Follicular Lymphoma[a] (grade 1-2)

NCCN Guidelines Index
NHL Table of Contents
Discussion

DIAGNOSIS[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]; IRF4/MUM1 for FL grade 3

→ See Workup
(FOLL-2)

---

[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. However, controversy exists regarding management of FL grade 3. Some may treat FL grade 3a as follicular lymphoma and others may treat it as diffuse large B-cell lymphoma (DLBCL). Follicular lymphoma, grade 3 is commonly treated according to the NCCN Diffuse Large B-Cell Lymphoma Guideline (BCEL-1). Any area of DLBCL in a follicular lymphoma of any grade should be diagnosed and treated as a DLBCL.

[b]Germinal center or follicular center cell phenotype 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.

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

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2015
Follicular Lymphoma[a] (grade 1-2)

NCCN Guidelines Index
NHL Table of Contents
Discussion

WORKUP

ESSENTIAL:
- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC, differential, platelets
- LDH
- Beta-2-microglobulin
- Comprehensive metabolic panel
- Hepatitis B testing[g]
- Chest/abdominal/pelvic CT with contrast of diagnostic quality and/or PET-CT scan
- 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
- Uric acid
- Discussion of fertility issues and sperm banking
- SPEP and/or quantitative immunoglobulin levels
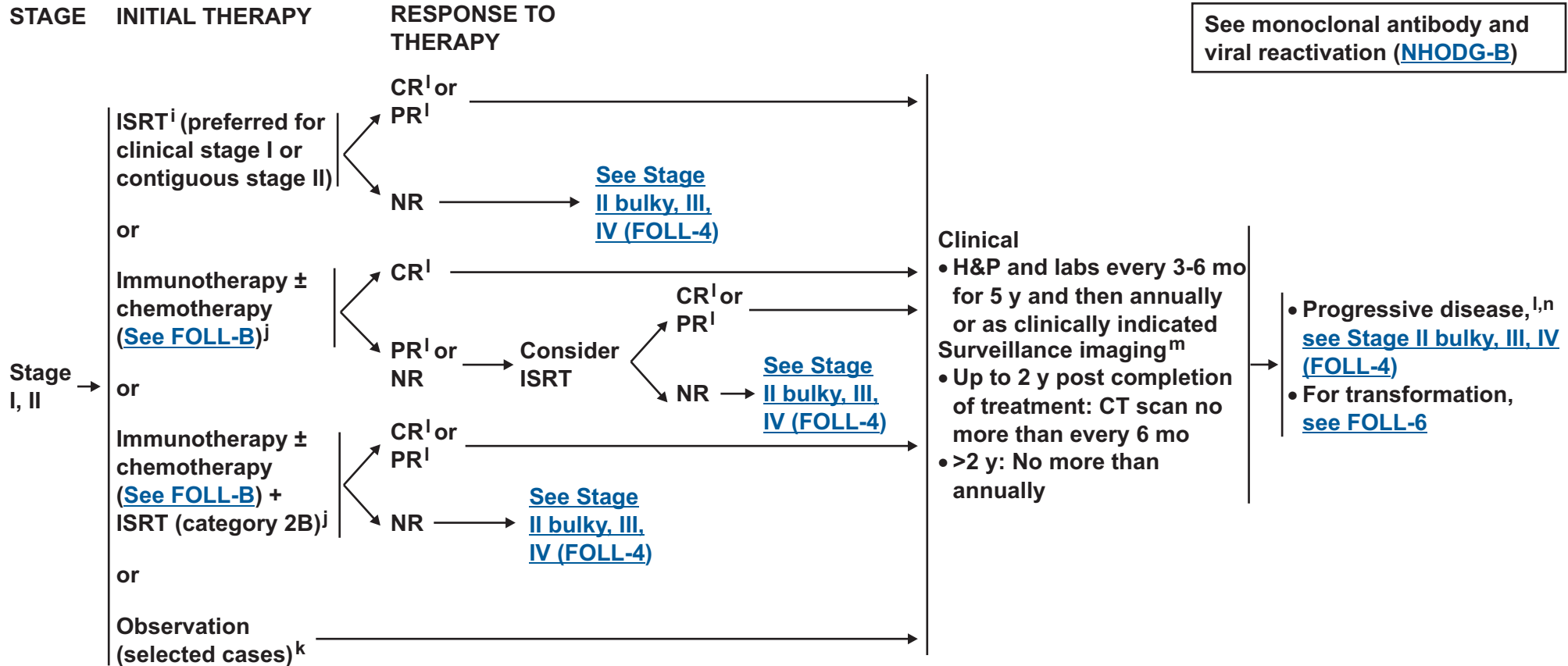- Hepatitis C testing
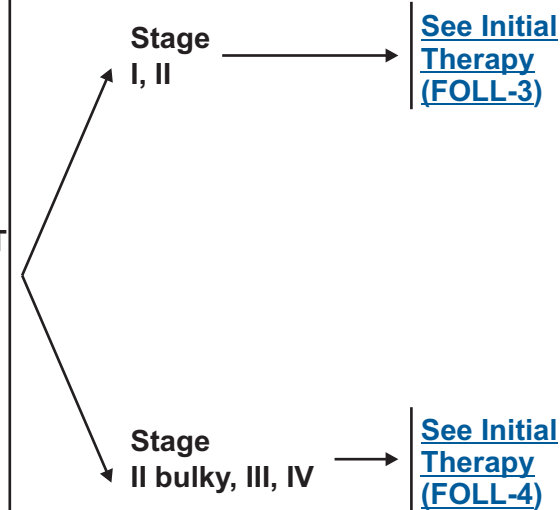
Stage I, II → See Initial Therapy (FOLL-3)

Stage II bulky, III, IV → See Initial Therapy (FOLL-4)

[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. However, controversy exists regarding management of FL grade 3. Some may treat FL grade 3a as follicular lymphoma and others may treat it as DLBCL. Follicular lymphoma, grade 3 is commonly treated according to the NCCN Diffuse Large B-Cell Lymphoma Guideline (BCEL-1). Any area of 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.

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

National Comprehensive Cancer Network®

See monoclonal antibody and viral reactivation (NHODG-B)

STAGE **INITIAL THERAPY** **RESPONSE TO THERAPY**

Stage I, II →

ISRT[i] (preferred for clinical stage I or contiguous stage II)

or

Immunotherapy ± chemotherapy (See FOLL-B)[j]

or

Immunotherapy ± chemotherapy (See FOLL-B) + ISRT (category 2B)[j]

or

Observation (selected cases)[k]

ISRT[i]:
- CR[l] or PR[l] →
- NR → See Stage II bulky, III, IV (FOLL-4)

Immunotherapy ± chemotherapy (See FOLL-B)[j]:
- CR[l] →
- PR[l] or NR → Consider ISRT → CR[l] or PR[l] →
  - NR → See Stage II bulky, III, IV (FOLL-4)

Immunotherapy ± chemotherapy (See FOLL-B) + ISRT (category 2B)[j]:
- CR[l] or PR[l] →
- NR → See Stage II bulky, III, IV (FOLL-4)

Clinical
- H&P and labs every 3-6 mo for 5 y and then annually or as clinically indicated Surveillance imaging[m]
- Up to 2 y post completion of treatment: CT scan no more than every 6 mo
- >2 y: No more than annually

→

- Progressive disease,[l,n] see Stage II bulky, III, IV (FOLL-4)
- For transformation, see FOLL-6

---

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

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

[k]Observation may be appropriate in circumstances where potential toxicity of involved-site RT (ISRT) outweighs potential clinical benefit.
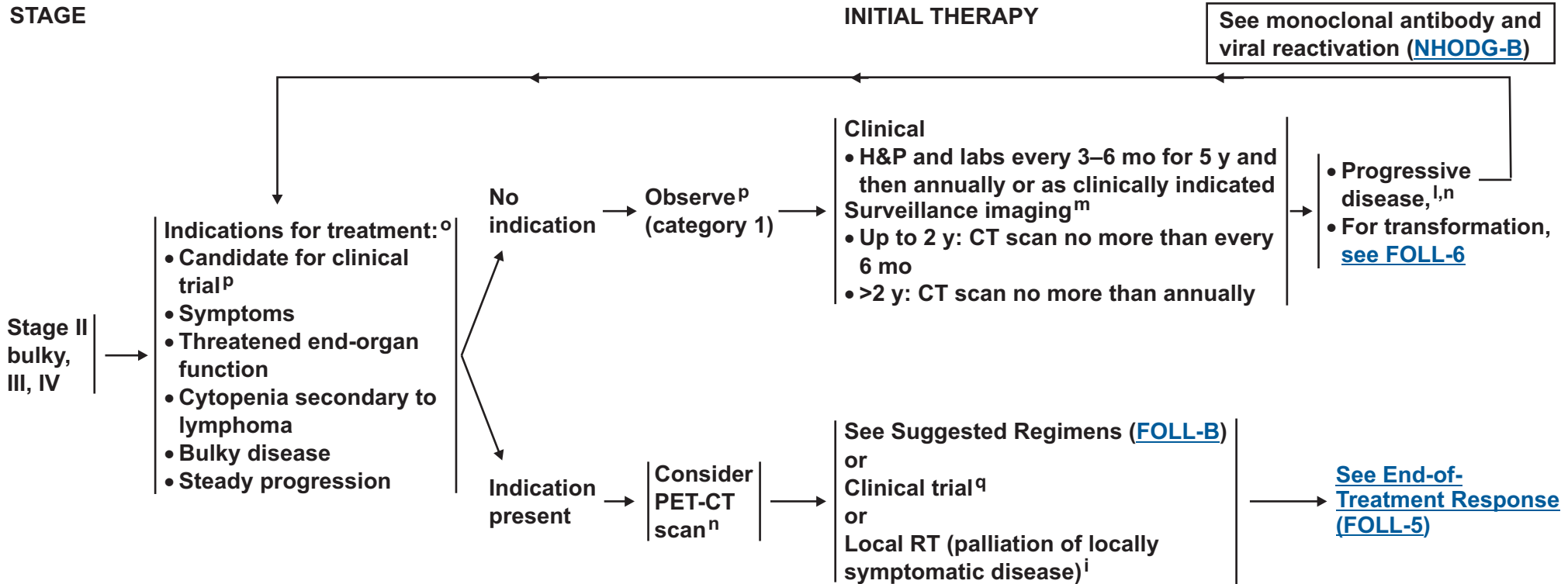
[l]See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).

[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).

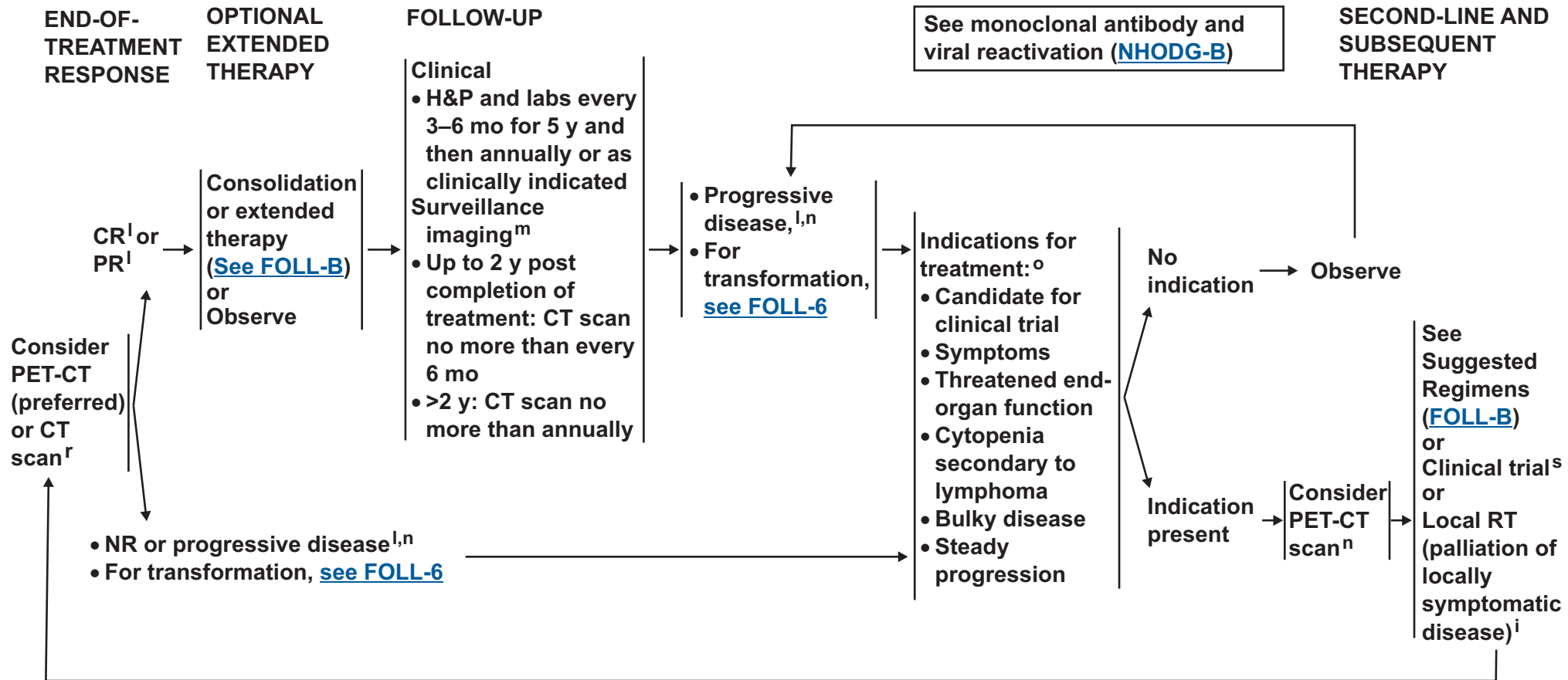| Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. |
| --- |

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2015
Follicular Lymphoma (grade 1-2)

NCCN Guidelines Index
NHL Table of Contents
Discussion

STAGE   **INITIAL THERAPY**

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

Stage II bulky, III, IV →

Indications for treatment:[o]
- **Candidate for clinical trial**[p]
- **Symptoms**
- **Threatened end-organ function**
- **Cytopenia secondary to lymphoma**
- **Bulky disease**
- **Steady progression**

→ **No indication** → **Observe**[p] **(category 1)** →

Clinical
- **H&P and labs every 3–6 mo for 5 y and then annually or as clinically indicated**

Surveillance imaging[m]
- **Up to 2 y: CT scan no more than every 6 mo**
- **>2 y: CT scan no more than annually**

→
- **Progressive disease,**[l,n]
- **For transformation, see FOLL-6**

→ **Indication present** → **Consider PET-CT scan**[n] →

See Suggested Regimens (**FOLL-B**)
or
Clinical trial[q]
or
Local RT (palliation of locally symptomatic disease)[i]

→ **See End-of-Treatment Response (FOLL-5)**

---

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

[l]See Lugano 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).
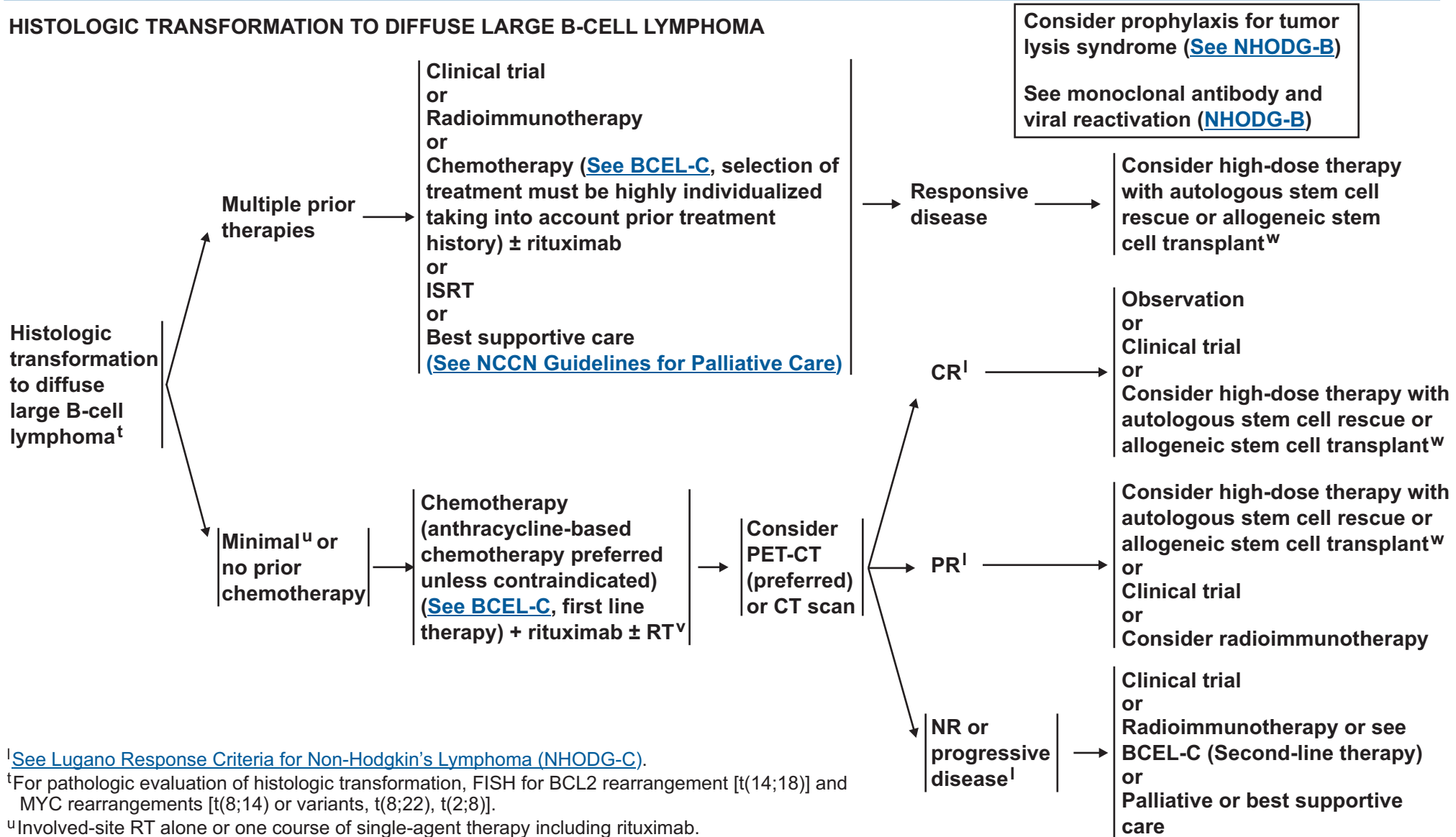
[o]See GELF criteria (FOLL-A).

[p]Consider appropriate clinical trials for patients on observation.

[q]Given incurability with conventional therapy, consider investigational therapy as first line of treatment.

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

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2015
Follicular Lymphoma (grade 1-2)

NCCN Guidelines Index
NHL Table of Contents
Discussion

END-OF-TREATMENT RESPONSE

OPTIONAL EXTENDED THERAPY

FOLLOW-UP

See monoclonal antibody and viral reactivation (NHODG-B)

SECOND-LINE AND SUBSEQUENT THERAPY

CR[l] or PR[l] → Consolidation or extended therapy (See FOLL-B) or Observe

Consider PET-CT (preferred) or CT scan[r]

• NR or progressive disease[l,n]
• For transformation, see FOLL-6

Clinical
• H&P and labs every 3–6 mo for 5 y and then annually or as clinically indicated
Surveillance imaging[m]
• Up to 2 y post completion of treatment: CT scan no more than every 6 mo
• >2 y: CT scan no more than annually

• Progressive disease,[l,n]
• For transformation, see FOLL-6

Indications for treatment:[o]
• Candidate for clinical trial
• Symptoms
• Threatened end-organ function
• Cytopenia secondary to lymphoma
• Bulky disease
• Steady progression

No indication → Observe

Indication present → Consider PET-CT scan[n]

See Suggested Regimens (FOLL-B) or Clinical trial[s] or Local RT (palliation of locally symptomatic disease)[i]

---

[i]See Principles of Radiation Therapy (NHODG-D).
[l]See Lugano 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).
[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.

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

National Comprehensive Cancer Network®

**NCCN Guidelines Version 2.2015
Follicular Lymphoma (grade 1-2)**

NCCN Guidelines Index
NHL Table of Contents
Discussion

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)

Histologic transformation to diffuse large B-cell lymphoma[t]

Multiple prior therapies →

Clinical trial
or
Radioimmunotherapy
or
Chemotherapy (See BCEL-C, selection of treatment must be highly individualized taking into account prior treatment history) ± rituximab
or
ISRT
or
Best supportive care
(See NCCN Guidelines for Palliative Care)

→ Responsive disease → Consider high-dose therapy with autologous stem cell rescue or allogeneic stem cell transplant[w]

Minimal[u] or no prior chemotherapy →

Chemotherapy (anthracycline-based chemotherapy preferred unless contraindicated) (See BCEL-C, first line therapy) + rituximab ± RT[v]

→ Consider PET-CT (preferred) or CT scan →

CR[l] → Observation
or
Clinical trial
or
Consider high-dose therapy with autologous stem cell rescue or allogeneic stem cell transplant[w]

PR[l] → Consider high-dose therapy with autologous stem cell rescue or allogeneic stem cell transplant[w]
or
Clinical trial
or
Consider radioimmunotherapy

NR or progressive disease[l] → Clinical trial
or
Radioimmunotherapy or see BCEL-C (Second-line therapy)
or
Palliative or best supportive care

[l] See Lugano 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.

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

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2015
Follicular Lymphoma (grade 1-2)

NCCN Guidelines Index
NHL Table of Contents
Discussion

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 $<1.0 \times 10^9$/L and/or platelets $<100 \times 10^9$/L)
- Leukemia ($>5.0 \times 10^9$/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

Right Cervical
- Preauricular
- Upper Cervical
- Median or Lower
- Postcervical
- Supraclavicular

Left Cervical
- Preauricular
- Upper Cervical
- Median or Lower
- Postcervical
- Supraclavicular

Mediastinal
- Paratracheal
- Mediastinal
- Hilar

Right Axillary
Left Axillary

Right Epitrochlear
Left Epitrochlear

Para-Aortic
- Para-Aortic
- Common Iliac
- External Iliac

Mesenteric
- Mesenteric
- Splenic Hilar
- Portal
- Celiac

Right Inguinal
- Inguinal
- Femoral

Left Inguinal
- Inguinal
- Femoral

Right Popliteal
Left Popliteal

Legend for labels
Blue = Bilateral
Black = Midline

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

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

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

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

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

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

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

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2015
Follicular Lymphoma (grade 1-2)

NCCN Guidelines Index
NHL Table of Contents
Discussion

SUGGESTED TREATMENT REGIMENS[a,b]
(in preference 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)
- Lenalidomide + rituximab (category 3)

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

First-line Consolidation or Extended Dosing (optional)[f]
- 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
- Radioimmunotherapy (after induction with chemotherapy or chemoimmunotherapy)[d,e,g]

Second-line and Subsequent Therapy
- Chemoimmunotherapy (as listed under first-line therapy)
- Rituximab
- Lenalidomide ± rituximab
- Radioimmunotherapy[d,e] (category 1)
- Idelalisib[i]
- Fludarabine[h] + rituximab
- RFND[h,j] (rituximab, fludarabine, mitoxantrone, dexamethasone)
- See Second-line Therapy for DLBCL (BCEL-C 2 of 4) without regard to transplantability

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

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)

[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] See Special Considerations for Use of B-Cell Receptor Inhibitors (Ibrutinib and Idelalisib) (NHODG-E).
[j] RFND regimen may be associated with stem cell toxicity and secondary malignancies (see Discussion).

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

National Comprehensive Cancer Network®

**NCCN Guidelines Version 2.2015
Follicular Lymphoma (grade 1-2)**

NCCN Guidelines Index
NHL Table of Contents
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.
Flinn IW, van der Jagt R, Kahl BS, et al. Open-label, randomized, noninferiority study of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of advanced indolent NHL or MCL: the BRIGHT study. Blood 2014;123:2944-2952.
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.
Martinelli G, Schmitz SF, Utiger U, et al. Long-term follow-up of patients with follicular lymphoma receiving single-agent rituximab at two different schedules in trial SAKK 35/98. J Clin Oncol 2010;28:4480-4484.
Ardeshna KM, Qian W, Smith P, et al. Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial. The Lancet Oncology 2014;15:424-435.

Lenalidomide + rituximab
Martin P, Jung S-H, Johnson JL, et al. CALGB 50803 (Alliance): A phase II trial of lenalidomide plus rituximab in patients with previously untreated follicular lymphoma [abstract]. J Clin Oncol 2014;32:Abstract 8521.
Fowler N, Davis R, Rawal S, et al. Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: an open-label, phase 2 trial. The Lancet Oncology 2014;15:1311-1318.
Radioimmunotherapy
Scholz CW, Pinto A, Linkesch W, et al. 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)
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.
Chemoimmunotherapy 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. The Lancet 2011;377:42-51.
Salles, G, Seymour JF, Feugier P, et al. Updated 6 year follow-up of the PRIMA study confirms the benefit of 2-year rituximab maintenance in follicular lymphoma patients responding to frontline immunochemotherapy [abstract]. Blood 2013;122:Abstract 509.
Extended dosing with rituximab
Ghielmini M, Schmitz SH, Cogliatti SB, et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule. Blood 2004;103:4416-4423.

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

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2015
Follicular Lymphoma (grade 1-2)

NCCN Guidelines Index
NHL Table of Contents
Discussion

SUGGESTED TREATMENT REGIMENS
References

Second-line and Subsequent Therapy
Fludarabine + rituximab
Czuczman MS, Koryzna A, Mohr A, et al. Rituximab in combination with fludarabine chemotherapy in low-grade of follicular lymphoma. J Clin Oncol 2005;23:694-704.
Idelalisib
Gopal A, Kahl B, De Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med 2014;370:1008-1018.
Lenalidomide ± rituximab
Leonard J, Jung S-H, Johnson JL, et al. CALGB 50401: A randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma [abstract]. J Clin Oncol 2012;30:Abstract 8000.
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.
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.

Follicular Lymphoma

Diagnosis

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

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

The Follicular Lymphoma International Prognostic Index (FLIPI) is a prognostic scoring system based on age, Ann Arbor stage, and number of nodal sites involved, hemoglobin levels and serum LDH levels.[4] The FLIPI was developed based on a large set of retrospective data from patients with FL, and established three distinct prognostic groups with 5-year survival outcomes ranging from 52.5% to 91% (in the pre-rituximab era).[4] In the National LymphoCare study, which analyzed the treatment options and outcomes of 2,728 patients with newly

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

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

The presence of FL-like B-cells in the germinal centers of morphologically reactive lymph nodes (initially called "in situ localization of FL" or "follicular lymphoma in situ"[FLIS]) was first described a decade ago.[9,10] These cases are characterized by the preservation of the lymph node architecture, with the incidental finding of focal strongly

positive staining for BCL2 (restricted to germinal centers) and CD10 in the involved follicles, and the detection of t(14;18) by FISH. [9-12]

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

Pediatric-type Follicular Lymphoma

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

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

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

(with or without RT), and more recently, chemoimmunotherapy with generally favorable outcomes and prognosis.[19,21,23]

Workup

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

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

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

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

Treatment Options for Stage I-II FL

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Radioimmunotherapy (RIT) with the radio-labelled monoclonal antibodies ^{90}Y-ibritumomab tiuxetan[74-78] and ^{131}I-tositumumab[79-82] has been evaluated in patients with newly diagnosed, as well as those with relapsed, refractory or histologically transformed FL. In an international phase II trial, ^{90}Y-ibritumomab when used as a first-line therapy in older patients (age >50 years) with stage III or IV FL (N=59; median age 66 years, range 51–83 years) resulted in an ORR of 87% (CR in 41%, CRu in 15%) at 6 months after therapy.[78] After a median follow-up of approximately 31 months, the median PFS was 26 months and median OS has not been reached. The most common toxicities with first-line ^{90}Y-ibritumomab included grade 3 or 4 thrombocytopenia (48%; grade 4 in 7%) and neutropenia (32%; grade 4 in 17%). No grade 3 or 4 non-hematologic toxicities were reported. Grade 2 infections occurred in 20% and grade 2 GI toxicities in 10% of patients.[78] In a randomized phase III study in patients with relapsed or refractory low-grade, follicular or transformed lymphoma (n=143), ^{90}Y-ibritumomab tiuxetan also produced statistically and clinically significant higher ORR (80% vs. 56%) and CR rate (30% vs. 16%) compared with rituximab alone.[75] At a median follow-up of 44 months, median TTP (15 vs.10 months) and duration of response (17 vs. 11 months) were longer for patients treated with ^{90}Y-ibritumomab compared with rituximab.[76]

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

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

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

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2015
Non-Hodgkin's Lymphomas

NCCN Guidelines Index
NHL Table of Contents
Discussion

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

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

First-line Consolidation with RIT
First-line chemotherapy followed by RIT with ^{90}Y-ibritumomab[89-92] or ^{131}I-tositumumab[93-96] has also been evaluated in several phase II studies.

In the international phase III trial (First-line Indolent Trial; FIT), patients with advanced stage FL responding to first-line induction therapy (n=414) were randomized to receive ^{90}Y-ibritumomab or no further treatment (observation only).[91] After a median follow-up of 7.3 years, the estimated 8-year PFS was 41% with ^{90}Y-ibritumomab tiuxetan consolidation and 22% with observation only, with a median PFS of 4.1 years versus 1.1 years, respectively (*P* <.001).[97] No significant difference in OS was observed between treatment arms. The incidence of secondary malignancies was higher in the consolidation arm compared with the observation arm (13% vs. 7%), but the difference was not statistically significant. MDS/AML occurred more frequently in the consolidation arm (3% vs. <1%), with a significantly increased

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

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

The phase III randomized Intergroup study by the SWOG/CALGB (S0016) evaluated the role of RIT consolidation with ^{131}I-tositumumab (CHOP-RIT) following first-line therapy in patients with advanced stage FL.[7] In this study, 554 patients were randomized to first-line therapy with 6 cycles of R-CHOP or 6 cycles of CHOP followed by consolidation with ^{131}I-tositumumab (CHOP-RIT).[7] After a median follow-up time of 4.9 years, the estimated 2-year PFS (76% vs. 80%) and OS (97% vs. 93%)

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

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

First-line Consolidation with Maintenance Rituximab
Several studies have reported that prolonged administration of rituximab (or rituximab maintenance) significantly improved EFS in chemotherapy-naïve patients responding to initial rituximab induction, although this benefit did not translate to OS advantage.[98-100] In a study that evaluated maintenance rituximab compared with retreatment with rituximab upon progression in patients with chemotherapy-treated indolent lymphomas responsive to rituximab therapy (n=90 randomized), maintenance rituximab significantly improved PFS compared with the retreatment approach (31 months vs. 7 months; *P*=0.007).[101] However, retreatment with rituximab at progression provided the same duration of benefit from rituximab as did maintenance rituximab (31 months vs. 27 months).[101] Therefore, either approach (maintenance or retreatment at progression) appeared to be beneficial for this patient population. The randomized phase III study from ECOG (E1496) demonstrated a PFS benefit with rituximab

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

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

Second-line Consolidation with Maintenance Rituximab
Rituximab maintenance following second-line therapy has also been evaluated in patients with relapsed/refractory disease. Two large randomized trials have demonstrated a PFS advantage with rituximab maintenance over observation for patients treated with chemoimmunotherapy induction.[104-106] In a prospective phase III

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

Hematopoietic Stem Cell Transplantation (HSCT) After Induction

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

Imaging Studies for FL

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

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

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

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

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

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

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

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2015
Non-Hodgkin's Lymphomas

NCCN Guidelines Index
NHL Table of Contents
Discussion

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

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

NCCN Recommendations for Treatment of Stage I-II Disease

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

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

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

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

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

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2015
Non-Hodgkin's Lymphomas

NCCN Guidelines Index
NHL Table of Contents
Discussion

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

First-line Therapy

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

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

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

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

First-line Consolidation or Extended Dosing

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

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

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

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

Second-line Therapy for Relapsed or Progressive Disease

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

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

Second-line Consolidation or Extended Dosing

For patients in remission after second-line therapy, optional maintenance therapy with rituximab (one dose every 12 weeks for 2 years) can be recommended (category 1). However, the NCCN Guidelines panel recognizes that the efficacy of maintenance rituximab in the second-line setting would likely be impacted by a patient's response to first-line maintenance with rituximab. If a patient progressed during or within 6 months of first-line maintenance with rituximab, the clinical benefit of maintenance in the second-line setting is likely very minimal. HDT/ASCR is an appropriate consolidative therapy for patients with second or third remission. Allogeneic HSCT may also be considered for highly selected patients. For patients receiving consolidation therapy, clinical follow-up with a complete physical exam and laboratory assessment should be performed every 3 to 6 months for the first 5 years, and then annually (or as clinically indicated) thereafter. Surveillance imaging with CT scans can be performed no more than every 6 months up to the first 2 years following completion of treatment, and then no more than annually (or as clinically indicated) thereafter.

Histological Transformation to DLBCL

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

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

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

References

1. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 1997;89:3909-3918. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9166827.

2. Koster A, Tromp HA, Raemaekers JM, et al. The prognostic significance of the intra-follicular tumor cell proliferative rate in follicular lymphoma. Haematologica 2007;92:184-190. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17296567.

3. Wang SA, Wang L, Hochberg EP, et al. Low histologic grade follicular lymphoma with high proliferation index: morphologic and clinical features. Am J Surg Pathol 2005;29:1490-1496. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16224216.

4. Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood 2004;104:1258-1265. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15126323.

5. Friedberg JW, Taylor MD, Cerhan JR, et al. Follicular lymphoma in the United States: first report of the national LymphoCare study. J Clin Oncol 2009;27:1202-1208. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19204203.

6. Federico M, Bellei M, Marcheselli L, et al. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. J Clin Oncol 2009;27:4555-4562. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19652063.

7. Press OW, Unger JM, Rimsza LM, et al. Phase III randomized intergroup trial of CHOP plus rituximab compared with CHOP chemotherapy plus (131)iodine-tositumomab for previously untreated follicular non-Hodgkin lymphoma: SWOG S0016. J Clin Oncol 2013;31:314-320. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23233710.

8. Press OW, Unger JM, Rimsza LM, et al. A comparative analysis of prognostic factor models for follicular lymphoma based on a phase III trial of CHOP-rituximab versus CHOP + 131iodine--tositumomab. Clin Cancer Res 2013;19:6624-6632. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24130072.

9. Cong P, Raffeld M, Teruya-Feldstein J, et al. In situ localization of follicular lymphoma: description and analysis by laser capture microdissection. Blood 2002;99:3376-3382. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11964306.

10. Harris NL, Swerdlow SH, Jaffe ES, et al. Follicular lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:220-226.

11. Sotomayor EA, Shah IM, Sanger WG, Mark HF. In situ follicular lymphoma with a 14;18 translocation diagnosed by a multimodal approach. Exp Mol Pathol 2007;83:254-258. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17482162.

12. Carbone A, Gloghini A, Santoro A. In situ follicular lymphoma: pathologic characteristics and diagnostic features. Hematol Oncol 2012;30:1-7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21560142.

13. Henopp T, Quintanilla-Martinez L, Fend F, Adam P. Prevalence of follicular lymphoma in situ in consecutively analysed reactive lymph nodes. Histopathology 2011;59:139-142. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21771030.

14. Jegalian AG, Eberle FC, Pack SD, et al. Follicular lymphoma in situ: clinical implications and comparisons with partial involvement by follicular lymphoma. Blood 2011;118:2976-2984. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21768298.

15. Pillai RK, Surti U, Swerdlow SH. Follicular lymphoma-like B-cells of uncertain significance (in situ follicular lymphoma) may infrequently

progress, but precedes follicular lymphoma, is associated with other overt lymphomas and mimics follicular lymphoma in flow cytometric studies. Haematologica 2013;98:1571-1580. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23831923.

16. Bonzheim I, Salaverria I, Haake A, et al. A unique case of follicular lymphoma provides insights to the clonal evolution from follicular lymphoma in situ to manifest follicular lymphoma. Blood 2011;118:3442-3444. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21940830.

17. Frizzera G, Murphy SB. Follicular (nodular) lymphoma in childhood: a rare clinical-pathological entity. Report of eight cases from four cancer centers. Cancer 1979;44:2218-2235. Available at: http://www.ncbi.nlm.nih.gov/pubmed/389411.

18. Ribeiro RC, Pui CH, Murphy SB, et al. Childhood malignant non-Hodgkin lymphomas of uncommon histology. Leukemia 1992;6:761-765. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1640726.

19. Lorsbach RB, Shay-Seymore D, Moore J, et al. Clinicopathologic analysis of follicular lymphoma occurring in children. Blood 2002;99:1959-1964. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11877266.

20. Oschlies I, Salaverria I, Mahn F, et al. Pediatric follicular lymphoma--a clinico-pathological study of a population-based series of patients treated within the Non-Hodgkin's Lymphoma--Berlin-Frankfurt-Munster (NHL-BFM) multicenter trials. Haematologica 2010;95:253-259. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19679882.

21. Louissaint A, Jr., Ackerman AM, Dias-Santagata D, et al. Pediatric-type nodal follicular lymphoma: an indolent clonal proliferation in children and adults with high proliferation index and no BCL2 rearrangement. Blood 2012;120:2395-2404. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22855608.

22. Liu Q, Salaverria I, Pittaluga S, et al. Follicular lymphomas in children and young adults: a comparison of the pediatric variant with usual follicular lymphoma. Am J Surg Pathol 2013;37:333-343. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23108024.

23. Kumar R, Galardy PJ, Dogan A, et al. Rituximab in combination with multiagent chemotherapy for pediatric follicular lymphoma. Pediatr Blood Cancer 2011;57:317-320. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21462303.

24. Bain BJ. Bone marrow trephine biopsy. J Clin Pathol 2001;54:737-742. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11577117.

25. Bishop PW, McNally K, Harris M. Audit of bone marrow trephines. J Clin Pathol 1992;45:1105-1108. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1479037.

26. Schoder H, Noy A, Gonen M, et al. Intensity of 18fluorodeoxyglucose uptake in positron emission tomography distinguishes between indolent and aggressive non-Hodgkin's lymphoma. J Clin Oncol 2005;23:4643-4651. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15837966.

27. Campbell BA, Voss N, Woods R, et al. Long-term outcomes for patients with limited stage follicular lymphoma: involved regional radiotherapy versus involved node radiotherapy. Cancer 2010;116:3797-3806. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20564082.

28. Guadagnolo BA, Li S, Neuberg D, et al. Long-term outcome and mortality trends in early-stage, Grade 1-2 follicular lymphoma treated with radiation therapy. Int J Radiat Oncol Biol Phys 2006;64:928-934. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16243446.

29. Mac Manus MP, Hoppe RT. Is radiotherapy curative for stage I and II low-grade follicular lymphoma? Results of a long-term follow-up study of patients treated at Stanford University. J Clin Oncol 1996;14:1282-1290. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8648385.

30. Wilder RB, Jones D, Tucker SL, et al. Long-term results with radiotherapy for Stage I-II follicular lymphomas. Int J Radiat Oncol Biol Phys 2001;51:1219-1227. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11728680.

31. Advani R, Rosenberg S, Horning S. Stage I and II follicular non-Hodgkin's lymphoma: long-term follow-up of no initial therapy. J Clin Oncol 2004;22:1454-1459. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15024027.

32. McLaughlin P, Fuller L, Redman J, et al. Stage I-II low-grade lymphomas: a prospective trial of combination chemotherapy and radiotherapy. Ann Oncol 1991;2 Suppl 2:137-140. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1710918.

33. Yahalom J, Varsos G, Fuks Z, et al. Adjuvant cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy after radiation therapy in stage I low-grade and intermediate-grade non-Hodgkin lymphoma. Results of a prospective randomized study. Cancer 1993;71:2342-2350. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8453557.

34. Friedberg JW, Byrtek M, Link BK, et al. Effectiveness of first-line management strategies for stage I follicular lymphoma: analysis of the National LymphoCare Study. J Clin Oncol 2012;30:3368-3375. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22915662.

35. Michallet AS, Lebras LL, Bauwens DD, et al. Early stage follicular lymphoma: what is the clinical impact of the first-line treatment strategy? J Hematol Oncol 2013;6:45. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23816219.

36. Young RC, Longo DL, Glatstein E, et al. The treatment of indolent lymphomas: watchful waiting v aggressive combined modality treatment. Semin Hematol 1988;25:11-16. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2456618.

37. Brice P, Bastion Y, Lepage E, et al. Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 1997;15:1110-1117. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9060552.

38. Ardeshna KM, Smith P, Norton A, et al. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. Lancet 2003;362:516-522. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12932382.

39. Ardeshna K, Qian W, Smith P, et al. An Intergroup randomized trial of rituximab versus a watch and wait strategy in patients with stage II, III, IV, asymptomatic, non-bulky follicular lymphoma (grades 1, 2 and 3a). A preliminary analysis [abstract] Blood 2010;116:Abstact 6. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/6.

40. Kahl BS, Hong F, Williams ME, et al. Results of Eastern Cooperative Oncology Group Protocol E4402 (RESORT): A Randomized Phase III Study Comparing Two Different Rituximab Dosing Strategies for Low Tumor Burden Follicular Lymphoma [abstract]. Blood 2011;118:Abstract LBA-6. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/118/21/LBA-6.

41. Solal-Celigny P, Bellei M, Marcheselli L, et al. Watchful waiting in low-tumor burden follicular lymphoma in the rituximab era: results of an F2-study database. J Clin Oncol 2012;30:3848-3853. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23008294.

42. Colombat P, Salles G, Brousse N, et al. Rituximab (anti-CD20 monoclonal antibody) as single first-line therapy for patients with follicular lymphoma with a low tumor burden: clinical and molecular evaluation. Blood 2001;97:101-106. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11133748.

43. Witzig TE, Vukov AM, Habermann TM, et al. Rituximab therapy for patients with newly diagnosed, advanced-stage, follicular grade I non-Hodgkin's lymphoma: a phase II trial in the North Central Cancer Treatment Group. J Clin Oncol 2005;23:1103-1108. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15657404.

44. McLaughlin P, Grillo-Lopez AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol 1998;16:2825-2833. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9704735.

45. Czuczman MS, Grillo-Lopez AJ, White CA, et al. Treatment of patients with low-grade B-cell lymphoma with the combination of chimeric anti-CD20 monoclonal antibody and CHOP chemotherapy. J Clin Oncol 1999;17:268-276. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10458242.

46. Czuczman MS, Weaver R, Alkuzweny B, et al. Prolonged clinical and molecular remission in patients with low-grade or follicular non-Hodgkin's lymphoma treated with rituximab plus CHOP chemotherapy: 9-year follow-up. J Clin Oncol 2004;22:4711-4716. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15483015.

47. Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2005;106:3725-3732. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16123223.

48. Marcus R, Imrie K, Belch A, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood 2005;105:1417-1423. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15494430.

49. Marcus R, Imrie K, Solal-Celigny P, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J Clin Oncol 2008;26:4579-4586. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18662969.

50. Schulz H, Bohlius JF, Trelle S, et al. Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis. J Natl Cancer Inst 2007;99:706-714. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17470738.

51. Buske C, Kneba M, Lengfelder E, et al. Front - line combined immuno-chemotherapy (R-CHOP) significantly improves the time to treatment failure and overall survival in elderly patients with advanced stage follicular lymphoma - results of a prospective randomized trial of the german low grade lymphoma study group (GLSG) [abstract] Blood 2006;108:Abstract 482. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/108/11/482.

52. Czuczman MS, Koryzna A, Mohr A, et al. Rituximab in combination with fludarabine chemotherapy in low-grade or follicular lymphoma. J Clin Oncol 2005;23:694-704. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15681517.

53. Forstpointner R, Dreyling M, Repp R, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2004;104:3064-3071. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15284112.

54. McLaughlin P, Hagemeister FB, Rodriguez MA, et al. Safety of fludarabine, mitoxantrone, and dexamethasone combined with rituximab in the treatment of stage IV indolent lymphoma. Semin Oncol

2000;27:37-41. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/11225999.

55. Zinzani PL, Pulsoni A, Perrotti A, et al. Fludarabine plus mitoxantrone with and without rituximab versus CHOP with and without rituximab as front-line treatment for patients with follicular lymphoma. J Clin Oncol 2004;22:2654-2661. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15159414.

56. Liu Q, Fayad L, Cabanillas F, et al. Improvement of overall and failure-free survival in stage IV follicular lymphoma: 25 years of treatment experience at The University of Texas M.D. Anderson Cancer Center. J Clin Oncol 2006;24:1582-1589. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16575009.

57. Morschhauser F, Mounier N, Sebban C, et al. Efficacy and safety of the combination of rituximab, fludarabine, and mitoxantrone for rituximab-naive, recurrent/refractory follicular non-Hodgkin lymphoma with high tumor burden: a multicenter phase 2 trial by the Groupe d'Etude des Lymphomes de l'Adulte (GELA) and Groupe Ouest Est des Leucemies et Autres Maladies du Sang (GOELAMS). Cancer 2010;116:4299-4308. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20549824.

58. Nastoupil L, Sinha R, Byrtek M, et al. A Comparison of the Effectiveness of First-Line Chemoimmunotherapy Regimens for Follicular Lymphoma (FL) Used in the United States [abstract]. Blood 2011;118:Abstract 97. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/118/21/97.

59. Federico M, Luminari S, Dondi A, et al. R-CVP Versus R-CHOP Versus R-FM for the Initial Treatment of Patients With Advanced-Stage Follicular Lymphoma: Results of the FOLL05 Trial Conducted by the Fondazione Italiana Linfomi. J Clin Oncol 2013;31:1506-1513. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23530110.

60. Kalaycio M, Rybicki L, Pohlman B, et al. Risk factors before autologous stem-cell transplantation for lymphoma predict for secondary myelodysplasia and acute myelogenous leukemia. J Clin Oncol 2006;24:3604-3610. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16877727.

61. Ketterer N, Salles G, Moullet I, et al. Factors associated with successful mobilization of peripheral blood progenitor cells in 200 patients with lymphoid malignancies. Br J Haematol 1998;103:235-242. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9792315.

62. Micallef IN, Apostolidis J, Rohatiner AZ, et al. Factors which predict unsuccessful mobilisation of peripheral blood progenitor cells following G-CSF alone in patients with non-Hodgkin's lymphoma. Hematol J 2000;1:367-373. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11920216.

63. Fowler N, Kahl BS, Lee P, et al. Bortezomib, Bendamustine, and Rituximab in Patients With Relapsed or Refractory Follicular Lymphoma: The Phase II VERTICAL Study. J Clin Oncol 2011;29:3389-3395. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21810687.

64. Friedberg JW, Vose JM, Kelly JL, et al. The combination of bendamustine, bortezomib, and rituximab for patients with relapsed/refractory indolent and mantle cell non-Hodgkin lymphoma. Blood 2011;117:2807-2812. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21239695.

65. Friedberg JW, Cohen P, Chen L, et al. Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin's lymphoma: results from a phase II multicenter, single-agent study. J Clin Oncol 2008;26:204-210. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18182663.

66. Kahl BS, Bartlett NL, Leonard JP, et al. Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma: results from a multicenter study. Cancer 2010;116:106-114. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19890959.

67. Robinson KS, Williams ME, van der Jagt RH, et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma. J Clin Oncol 2008;26:4473-4479. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18626004.

68. Rummel MJ, Kaiser U, Balser C, et al. Bendamustine plus rituximab versus fludarabine plus rituximab in patients with relapsed follicular, indolent and mantle cell lymphomas - final results of the randomized phase III study NHL 2-2003 on behalf of the StiL (Study Group Indolent Lymphomas, Germany) [abstract]. Blood 2010;116:Abstract 856. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/856.

69. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet 2013;381:1203-1210. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23433739.

70. Flinn IW, Van der Jagt RH, Kahl BS, et al. An Open-Label, Randomized Study of Bendamustine and Rituximab (BR) Compared with Rituximab, Cyclophosphamide, Vincristine, and Prednisone (R-CVP) or Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) in First-Line Treatment of Patients with Advanced Indolent Non-Hodgkin's Lymphoma (NHL) or Mantle Cell Lymphoma (MCL): The Bright Study [abstract]. Blood 2012;120:Abstract 902. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/120/21/902.

71. Witzig TE, Wiernik PH, Moore T, et al. Lenalidomide oral monotherapy produces durable responses in relapsed or refractory indolent non-Hodgkin's Lymphoma. J Clin Oncol 2009;27:5404-5409. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19805688.

72. Leonard J, Jung S-H, Johnson JL, et al. CALGB 50401: A randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma [abstract]. J Clin Oncol 2012;30:Abstract 8000. Available at: http://meeting.ascopubs.org/cgi/content/abstract/30/15_suppl/8000.

73. Fowler NH, Neelapu SS, Hagemeister FB, et al. Lenalidomide and Rituximab for Untreated Indolent Lymphoma: Final Results of a Phase II Study [abstract]. Blood 2012;120:Abstract 901. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/120/21/901.

74. Witzig TE, Flinn IW, Gordon LI, et al. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. J Clin Oncol 2002;20:3262-3269. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12149300.

75. Witzig TE, Gordon LI, Cabanillas F, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol 2002;20:2453-2463. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12011122.

76. Gordon LI, Witzig T, Molina A, et al. Yttrium 90-labeled ibritumomab tiuxetan radioimmunotherapy produces high response rates and durable remissions in patients with previously treated B-cell lymphoma. Clin Lymphoma 2004;5:98-101. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15453924.

77. Scholz CW, Pinto A, Linkesch W, et al. 90Yttrium ibritumomab tiuxetan as first line treatment for follicular lymphoma. first results from an international phase II clinical trial [abstract]. Blood 2010;116:Abstract 593. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/593.

78. Scholz CW, Pinto A, Linkesch W, et al. (90)Yttrium-ibritumomab-tiuxetan as first-line treatment for follicular lymphoma: 30 months of follow-up data from an international multicenter phase II clinical trial. J Clin Oncol 2013;31:308-313. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23233718.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2015
Non-Hodgkin's Lymphomas

NCCN Guidelines Index
NHL Table of Contents
Discussion

79. Kaminski MS, Tuck M, Estes J, et al. 131I-tositumomab therapy as initial treatment for follicular lymphoma. N Engl J Med 2005;352:441-449. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15689582.

80. Vose JM, Wahl RL, Saleh M, et al. Multicenter phase II study of iodine-131 tositumomab for chemotherapy-relapsed/refractory low-grade and transformed low-grade B-cell non-Hodgkin's lymphomas. J Clin Oncol 2000;18:1316-1323. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10715303.

81. Kaminski MS, Zelenetz AD, Press OW, et al. Pivotal study of iodine I 131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. J Clin Oncol 2001;19:3918-3328. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11579112.

82. Horning SJ, Younes A, Jain V, et al. Efficacy and safety of tositumomab and iodine-131 tositumomab (Bexxar) in B-cell lymphoma, progressive after rituximab. J Clin Oncol 2005;23:712-719. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15613695.

83. Kaminski MS, Tuck M, Estes J, et al. Tositumomab and iodine I-131 tositumomab for previously untreated, advanced-stage, follicular lymphoma: median 10 year follow-up results [abstract]. Blood 2009;114:Abstract 3759. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/114/22/3759.

84. Kaminski MS, Zelenetz AD, Press OW, et al. Tositumomab and I 131 Tositumomab achieves complete remissions lasting > 10 years in patients with chemotherapy-refractory low-grade and transformed B-cell lymphomas [abstract]. Blood 2010;116:Abstract 3960. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/3960.

85. Pauls SD, Lafarge ST, Landego I, et al. The phosphoinositide 3-kinase signaling pathway in normal and malignant B cells: activation mechanisms, regulation and impact on cellular functions. Front Immunol 2012;3:224. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22908014.

86. Lannutti BJ, Meadows SA, Herman SE, et al. CAL-101, a p110delta selective phosphatidylinositol-3-kinase inhibitor for the treatment of B-cell malignancies, inhibits PI3K signaling and cellular viability. Blood 2011;117:591-594. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20959606.

87. Gopal AK, Kahl BS, de Vos S, et al. PI3Kdelta inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med 2014;370:1008-1018. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24450858.

88. Full prescribing information for idelalisib. 2014 Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206545lbl.pdf.

89. Hainsworth JD, Spigel DR, Markus TM, et al. Rituximab plus short-duration chemotherapy followed by Yttrium-90 Ibritumomab tiuxetan as first-line treatment for patients with follicular non-Hodgkin lymphoma: a phase II trial of the Sarah Cannon Oncology Research Consortium. Clin Lymphoma Myeloma 2009;9:223-228. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19525191.

90. Jacobs SA, Swerdlow SH, Kant J, et al. Phase II trial of short-course CHOP-R followed by 90Y-ibritumomab tiuxetan and extended rituximab in previously untreated follicular lymphoma. Clin Cancer Res 2008;14:7088-7094. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18981007.

91. Morschhauser F, Radford J, Van Hoof A, et al. Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma. J Clin Oncol 2008;26:5156-5164. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18854568.

92. Zinzani PL, Tani M, Pulsoni A, et al. Fludarabine and mitoxantrone followed by yttrium-90 ibritumomab tiuxetan in previously untreated patients with follicular non-Hodgkin lymphoma trial: a phase II non-

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2015
Non-Hodgkin's Lymphomas

NCCN Guidelines Index
NHL Table of Contents
Discussion

randomised trial (FLUMIZ). Lancet Oncol 2008;9:352-358. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18342572.

93. Leonard JP, Coleman M, Kostakoglu L, et al. Abbreviated chemotherapy with fludarabine followed by tositumomab and iodine I 131 tositumomab for untreated follicular lymphoma. J Clin Oncol 2005;23:5696-5704. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16110029.

94. Press OW, Unger JM, Braziel RM, et al. Phase II trial of CHOP chemotherapy followed by tositumomab/iodine I-131 tositumomab for previously untreated follicular non-Hodgkin's lymphoma: five-year follow-up of Southwest Oncology Group Protocol S9911. J Clin Oncol 2006;24:4143-4149. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16896003.

95. Press OW, Unger JM, Braziel RM, et al. A phase 2 trial of CHOP chemotherapy followed by tositumomab/iodine I 131 tositumomab for previously untreated follicular non-Hodgkin lymphoma: Southwest Oncology Group Protocol S9911. Blood 2003;102:1606-1612. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12738671.

96. Link BK, Martin P, Kaminski MS, et al. Cyclophosphamide, vincristine, and prednisone followed by tositumomab and iodine-131-tositumomab in patients with untreated low-grade follicular lymphoma: eight-year follow-up of a multicenter phase II study. J Clin Oncol 2010;28:3035-3041. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20458031.

97. Morschhauser F, Radford J, Van Hoof A, et al. 90Yttrium-Ibritumomab Tiuxetan Consolidation of First Remission in Advanced-Stage Follicular Non-Hodgkin Lymphoma: Updated Results After a Median Follow-Up of 7.3 Years From the International, Randomized, Phase III First-Line Indolent Trial. J Clin Oncol 2013;31:1977-1983. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23547079.

98. Ghielmini M, Schmitz SH, Cogliatti SB, et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases

event-free survival and response duration compared with the standard weekly x 4 schedule. Blood 2004;103:4416-4423. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14976046.

99. Martinelli G, Hsu Schmitz SF, Utiger U, et al. Long-term follow-up of patients with follicular lymphoma receiving single-agent rituximab at two different schedules in trial SAKK 35/98. J Clin Oncol 2010;28:4480-4484. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20697092.

100. Taverna CJ, Bassi S, Hitz F, et al. Rituximab maintenance treatment for a maximum of 5 years in follicular lymphoma: safety analysis of the randomized phase III trial SAKK 35/03. Blood 2010;116:1802. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/1802.

101. Hainsworth JD, Litchy S, Shaffer DW, et al. Maximizing therapeutic benefit of rituximab: maintenance therapy versus re-treatment at progression in patients with indolent non-Hodgkin's lymphoma--a randomized phase II trial of the Minnie Pearl Cancer Research Network. J Clin Oncol 2005;23:1088-1095. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15657401.

102. Hochster H, Weller E, Gascoyne RD, et al. Maintenance rituximab after cyclophosphamide, vincristine, and prednisone prolongs progression-free survival in advanced indolent lymphoma: results of the randomized phase III ECOG1496 Study. J Clin Oncol 2009;27:1607-1614. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19255334.

103. Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. Lancet 2011;377:42-51. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21176949.

104. Forstpointner R, Unterhalt M, Dreyling M, et al. Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients

with recurring and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG). Blood 2006;108:4003-4008. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16946304.

105. van Oers MHJ, Klasa R, Marcus RE, et al. Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: results of a prospective randomized phase 3 intergroup trial. Blood 2006;108:3295-3301. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16873669.

106. van Oers MHJ, Van Glabbeke M, Giurgea L, et al. Rituximab maintenance treatment of relapsed/resistant follicular non-Hodgkin's lymphoma: long-term outcome of the EORTC 20981 phase III randomized intergroup study. J Clin Oncol 2010;28:2853-2858. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20439641.

107. Freedman AS, Neuberg D, Mauch P, et al. Long-term follow-up of autologous bone marrow transplantation in patients with relapsed follicular lymphoma. Blood 1999;94:3325-3333. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10552941.

108. Rohatiner AZS, Nadler L, Davies AJ, et al. Myeloablative therapy with autologous bone marrow transplantation for follicular lymphoma at the time of second or subsequent remission: long-term follow-up. J Clin Oncol 2007;25:2554-2559. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17515573.

109. Schouten HC, Qian W, Kvaloy S, et al. High-dose therapy improves progression-free survival and survival in relapsed follicular non-Hodgkin's lymphoma: results from the randomized European CUP trial. J Clin Oncol 2003;21:3918-3927. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14517188.

110. Sebban C, Brice P, Delarue R, et al. Impact of rituximab and/or high-dose therapy with autotransplant at time of relapse in patients with

follicular lymphoma: a GELA study. J Clin Oncol 2008;26:3614-3620. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18559872.

111. Peniket AJ, Ruiz de Elvira MC, Taghipour G, et al. An EBMT registry matched study of allogeneic stem cell transplants for lymphoma: allogeneic transplantation is associated with a lower relapse rate but a higher procedure-related mortality rate than autologous transplantation. Bone Marrow Transplant 2003;31:667-678. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12692607.

112. van Besien K, Loberiza FR, Bajorunaite R, et al. Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. Blood 2003;102:3521-3529. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12893748.

113. Hari P, Carreras J, Zhang M-J, et al. Allogeneic transplants in follicular lymphoma: higher risk of disease progression after reduced-intensity compared to myeloablative conditioning. Biol Blood Marrow Transplant 2008;14:236-245. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18215784.

114. Bishu S, Quigley JM, Bishu SR, et al. Predictive value and diagnostic accuracy of F-18-fluoro-deoxy-glucose positron emission tomography treated grade 1 and 2 follicular lymphoma. Leuk Lymphoma 2007;48:1548-1555. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17701586.

115. Blum RH, Seymour JF, Wirth A, et al. Frequent impact of [18F]fluorodeoxyglucose positron emission tomography on the staging and management of patients with indolent non-Hodgkin's lymphoma. Clin Lymphoma 2003;4:43-49. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12837154.

116. Karam M, Novak L, Cyriac J, et al. Role of fluorine-18 fluoro-deoxyglucose positron emission tomography scan in the evaluation and follow-up of patients with low-grade lymphomas. Cancer 2006;107:175-183. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16721817.

117. Wohrer S, Jaeger U, Kletter K, et al. 18F-fluoro-deoxy-glucose positron emission tomography (18F-FDG-PET) visualizes follicular lymphoma irrespective of grading. Ann Oncol 2006;17:780-784. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16497824.

118. Janikova A, Bolcak K, Pavlik T, et al. Value of [18F]fluorodeoxyglucose positron emission tomography in the management of follicular lymphoma: the end of a dilemma? Clin Lymphoma Myeloma 2008;8:287-293. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18854283.

119. Zinzani PL, Musuraca G, Alinari L, et al. Predictive role of positron emission tomography in the outcome of patients with follicular lymphoma. Clin Lymphoma Myeloma 2007;7:291-295. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17324337.

120. Le Dortz L, De Guibert S, Bayat S, et al. Diagnostic and prognostic impact of 18F-FDG PET/CT in follicular lymphoma. Eur J Nucl Med Mol Imaging 2010;37:2307-2314. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20717826.

121. Trotman J, Fournier M, Lamy T, et al. Positron emission tomography-computed tomography (PET-CT) after induction therapy is highly predictive of patient outcome in follicular lymphoma: analysis of PET-CT in a subset of PRIMA trial participants. J Clin Oncol 2011;29:3194-3200. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21747087.

122. Dupuis J, Berriolo-Riedinger A, Julian A, et al. Impact of [18F]Fluorodeoxyglucose Positron Emission Tomography Response Evaluation in Patients With High-Tumor Burden Follicular Lymphoma Treated With Immunochemotherapy: A Prospective Study From the Groupe d'Etudes des Lymphomes de l'Adulte and GOELAMS. J Clin Oncol 2012;30:4317-4322. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23109699.

123. Noy A, Schoder H, Gonen M, et al. The majority of transformed lymphomas have high standardized uptake values (SUVs) on positron emission tomography (PET) scanning similar to diffuse large B-cell lymphoma (DLBCL). Ann Oncol 2009;20:508-512. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19139176.

124. Oh YK, Ha CS, Samuels BI, et al. Stages I-III follicular lymphoma: role of CT of the abdomen and pelvis in follow-up studies. Radiology 1999;210:483-486. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10207433.

125. Zinzani PL, Stefoni V, Tani M, et al. Role of [18F]fluorodeoxyglucose positron emission tomography scan in the follow-up of lymphoma. J Clin Oncol 2009;27:1781-1787. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19273712.

126. Peterson BA, Petroni GR, Frizzera G, et al. Prolonged single-agent versus combination chemotherapy in indolent follicular lymphomas: a study of the cancer and leukemia group B. J Clin Oncol 2003;21:5-15. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12506163.

127. Al-Tourah AJ, Gill KK, Chhanabhai M, et al. Population-based analysis of incidence and outcome of transformed non-Hodgkin's lymphoma. J Clin Oncol 2008;26:5165-5169. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18838711.

128. Yuen AR, Kamel OW, Halpern J, Horning SJ. Long-term survival after histologic transformation of low-grade follicular lymphoma. J Clin Oncol 1995;13:1726-1733. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7602362.

129. Villa D, Crump M, Panzarella T, et al. Autologous and allogeneic stem-cell transplantation for transformed follicular lymphoma: a report of the Canadian blood and marrow transplant group. J Clin Oncol 2013;31:1164-1171. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23401459.