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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for B-Cell Lymphomas
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for B-Cell Lymphomas

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships:

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B-Cell Lymphomas, Version 5.2021

Featured Updates to the NCCN Guidelines

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ABSTRACT

In the last decade, a better understanding of the molecular pathogenesis of B-cell non-Hodgkin lymphomas has resulted in the development of novel targeted therapies, such as small molecule inhibitors of select kinases in the B-cell receptor pathway, antibody–drug conjugates, and small molecules that target a variety of proteins (eg, CD-19, EZH2, and XPO-1–mediated nuclear export). Anti-CD19 CAR T-cell therapy, first approved for relapsed/refractory (R/R) diffuse large B-cell lymphoma, has also emerged as a novel treatment option for R/R follicular lymphoma and mantle cell lymphoma. These NCCN Guideline Insights highlight the new targeted therapy options included in the NCCN Guidelines for B-Cell Lymphomas for the treatment of R/R disease.

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SUGGESTED TREATMENT REGIMENS^{a,b,c}
 An FDA-approved biosimilar is an appropriate substitute for rituximab.

THIRD-LINE AND SUBSEQUENT THERAPY	
• PI3K inhibitors	
▶ Relapsed/refractory after 2 prior therapies	
◊ Copanlisib ⁿ	
◊ Duvelisib ⁿ	
◊ Idelalisib ⁿ	
▶ Relapsed/refractory after 3 prior therapies	
◊ Umbralisib ⁿ	
• EZH2 inhibitor	
▶ Tazemetostat	
◊ EZH2 mutation positive relapsed/refractory disease after 2 prior therapies	
◊ EZH2 wild type or unknown relapsed/refractory disease in patients who have no satisfactory alternative treatment options	
• Anti CD-19 CAR T-cell Therapy (only after ≥2 lines of systemic therapy)	
▶ Axicabtagene ciloleucel ^o	

THIRD-LINE AND SUBSEQUENT THERAPY FOR ELDERLY OR INFIRM	
• Umbralisib (relapsed/refractory after 3 prior therapies) ⁿ	

HISTOLOGIC TRANSFORMATION TO DLBCL	
• Anti CD-19 CAR T-cell Therapy (only after ≥2 prior chemoimmunotherapy regimens) ^{o,p}	
▶ Axicabtagene ciloleucel	
▶ Lisocabtagene maraleucel	
▶ Tisagenlecleucel	

^a See references for regimens on FOLL-B 4 of 5 and FOLL-B 5 of 5.

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

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

⁹ Selection of patients requires adequate marrow cellularity >15% and <25% involvement of lymphoma in bone marrow, and platelets >100,000. In patients with prior autologous stem cell rescue, referral to a tertiary care center is highly recommended for ibritumomab tiuxetan. If ibritumomab tiuxetan is considered, bilateral cores are recommended and the pathologist should provide the percent of overall cellular elements and the percent of cellular elements involved in the marrow. As of 2010, updates suggest a trend towards an increased risk of MDS with RIT. Cytogenetics/FISH assessment for MDS markers is recommended for patients receiving RIT.

^j Generally, a first-line regimen is not repeated.

^k Prophylaxis for PJP and VZV should be administered; see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

^l In patients intended to receive CAR T-cell therapy, bendamustine should be used with caution unless after leukapheresis prior to CAR T-cell therapy, since it could impact the success of the patient's T-cell collection.

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

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

^o See Guidance for Treatment of Patients with Chimeric Antigen Receptor (CAR) T-Cell Therapy (NHODG-F).

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

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**FOLL-B
3 OF 5**

Overview

B-cell non-Hodgkin lymphomas (NHLs) are a heterogeneous group of lymphoproliferative disorders characterized by a diverse clinical course, ranging from indolent to highly aggressive. Diffuse large B-cell lymphoma (DLBCL; 32%), follicular lymphoma (FL; 17%), marginal zone lymphoma (MZL; 8%), and mantle cell lymphoma (MCL; 4%) constitute the majority of B-cell lymphoma subtypes.^{1,2}

In recent years, a variety of targeted therapies, such as BTK inhibitors, PI3K inhibitors, EZH2 inhibitors, antibody-drug conjugates, anti-CD19 CAR T-cell therapies, and other CD19-directed targeted therapies, have emerged as effective treatment options for relapsed/refractory (R/R) disease in various subtypes of B-cell lymphomas. These NCCN Guideline Insights highlight the new targeted therapy options included in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for B-Cell Lymphomas for the treatment of R/R disease.

Follicular Lymphoma

FL is the most common subtype of B-cell NHL and approximately 90% of patients have a t(14;18) translocation. FL is divided into 3 grades (FL1-2, FL3A, and FL3B).³ FL1-2 is managed according to the treatment recommendations

outlined for FL. FL3B is commonly treated as DLBCL. The management of FL3A is controversial and treatment should be individualized. Frequently, patients with disease relapse or progression of disease (POD) after first-line therapy will benefit from a second period of observation. Systemic therapy options for patients with FL at first relapse with high tumor burden or symptomatic disease include alternate non-cross-resistant anti-CD20 monoclonal antibody (mAb)-based chemoimmunotherapy or a combination of lenalidomide and rituximab.⁴ Rituximab monotherapy may be appropriate for patients with late relapse, particularly if disease burden is low.⁵ However, until recently no FDA-approved treatment options were available specifically for R/R FL in the third-line setting and beyond.⁶

POD within ≤24 months of diagnosis (POD24) and failure to achieve event-free survival at 12 months (EFS12) after initial treatment with chemoimmunotherapy have been identified as poor prognostic indicators of overall survival (OS).⁷⁻⁹ Patients with POD24 after first-line therapy should be considered for treatment with lenalidomide-based regimens, novel approaches including clinical trials, or referral for consideration of autologous hematopoietic cell transplant (HCT).¹⁰⁻¹²

SUGGESTED TREATMENT REGIMENS^{a,b,c}

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

SECOND-LINE AND SUBSEQUENT THERAPY
Preferred regimens (in alphabetical order) • Bendamustine + obinutuzumab (not recommended if treated with prior bendamustine) • Bendamustine + rituximab (not recommended if treated with prior bendamustine) (may be considered for both nodal MZL and extranodal [MALT] lymphoma) • CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab • CVP (cyclophosphamide, vincristine, prednisone) + rituximab • Ibrutinib ^{e,f} • Lenalidomide + rituximab (may be considered for both nodal MZL and extranodal [MALT] lymphoma) • Zanubrutinib (relapsed/refractory after at least one prior anti-CD20-mAB-based regimen) ^{e,f} Other recommended regimens (in alphabetical order) • CHOP + obinutuzumab (category 2B) • CVP + obinutuzumab (category 2B) • Ibritumomab tiuxetan ^d (category 2B) • Lenalidomide + obinutuzumab (category 2B) • PI3K inhibitors ▶ Relapsed/refractory after 2 prior therapies ^e ◊ Copanlisib ◊ Duvelisib ◊ Idelalisib ▶ Relapsed/refractory after at least one prior anti-CD20-mAB-based regimen ◊ Umbralisib ^e • Rituximab (if longer duration of remission)

SECOND-LINE AND SUBSEQUENT THERAPY FOR ELDERLY OR INFIRM (if none of the above are expected to be tolerable in the opinion of treating physician)
Preferred regimens (in alphabetical order) • Ibrutinib ^{e,f} • Lenalidomide + rituximab • Rituximab (375 mg/m ² weekly for 4 doses) • Zanubrutinib (relapsed/refractory after at least one prior anti-CD20-mAB-based regimen) ^{e,f} Other recommended regimens (in alphabetical order) • Chlorambucil ± rituximab • Cyclophosphamide ± rituximab • Umbralisib (relapsed/refractory after at least one prior anti-CD20-mAB-based regimen) ^e

^a Consider prophylaxis for tumor lysis syndrome (See NHODG-B 1 of 4). See NHODG-B 2 of 4 for monoclonal antibody therapy and viral reactivation.

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

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

^d Selection of patients requires adequate marrow cellularity >15% and <25% involvement of lymphoma in bone marrow, and platelets >100,000. In patients with prior autologous stem cell rescue, referral to a tertiary care center is highly recommended for ibritumomab tiuxetan. If ibritumomab tiuxetan is considered, bilateral cores are recommended and the pathologist should provide the percent of overall cellular elements and the percent of cellular elements involved in the marrow. As of 2010, updates suggest a trend towards an increased risk of MDS with RIT. Cytogenetics/FISH assessment for MDS markers is recommended for patients receiving RIT.

^e See Special Considerations for the Use of Small-Molecule Inhibitors (NHODG-E).

^f Consider alternate BTKi (acalabrutinib or zanubrutinib) in patients with intolerance or contraindications to ibrutinib.

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MZL-A
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PI3K Inhibitors

Copanlisib (PI3K- α/δ), duvelisib (PI3K- γ/δ), and idelalisib (PI3K- δ) are the FDA-approved PI3K inhibitors for R/R FL after 2 prior therapies. The dual PI3K- δ /CK1- ϵ inhibitor umbralisib was recently FDA-approved for R/R FL after 3 prior therapies.

In phase II studies, copanlisib, duvelisib, and idelalisib have resulted in overall response rates (ORRs) of 59%, 42%, and 56%, respectively (Table 1).¹³⁻¹⁶ Idelalisib and copanlisib have also been shown to be effective for high-risk patients with disease relapse ≤ 2 years after first-line therapy. Infections, diarrhea, colitis, hepatotoxicity, and transient cytopenias are common treatment-emergent adverse events (TEAEs), and the various PI3K inhibitors exhibit differences in their toxicity profiles (Table 2), depending on the PI3K isoform inhibition. For example, copanlisib is also associated with hyperglycemia and hypertension but a lower incidence of diarrhea.

In a multicenter phase IIb study (UNITY-NHL) of 208 patients with R/R indolent NHL (MZL, n=69; FL, n=117; small lymphocytic lymphoma, n=22) with a median follow-up of 27.5 months, umbralisib resulted in an overall response rate of 45% (5% complete response [CR] and 40% partial response [PR]) among patients with

FL.¹⁷ All patients had received ≥ 2 prior lines of therapy including anti-CD20 mAb and an alkylating agent. The median progression-free survival (PFS) was 11 months and the estimated 2-year PFS rate was 18%.

Umbralisib at a dose of 800 mg once daily has a relatively favorable toxicity profile among PI3K inhibitors and was also associated with a lower incidence of treatment discontinuations related to TEAEs. Grade ≥ 3 TEAEs, including neutropenia, diarrhea, and increased levels of alanine transaminase and aspartate aminotransferase, were reported in 12%, 10%, 6.7%, and 7.2% of the patients, respectively (Table 2). In comparison with the other 3 available PI3K inhibitors, umbralisib had a better toxicity profile and was also associated with a lower incidence of treatment discontinuations due to TEAEs. In the UNITY-NHL trial, discontinuations related to TEAEs occurred in 15% of patients compared with 21%, 31%, and 28% discontinuation rates reported with copanlisib, duvelisib, and idelalisib, respectively.

Copanlisib, duvelisib, and idelalisib are included as options for R/R FL after ≥ 2 prior therapies in fit patients (FOLL-B, 3 of 5, opposite page). Umbralisib is included as an option for R/R FL after ≥ 3 prior therapies in fit as well as elderly or infirm patients (FOLL-B, 3 of 5, opposite page).

SUGGESTED TREATMENT REGIMENS^{a,b}
 An FDA-approved biosimilar is an appropriate substitute for rituximab.

SECOND-LINE AND SUBSEQUENT THERAPY
Preferred regimens (in alphabetical order) • BTK inhibitors ^{f,g} ▶ Acalabrutinib ^h ▶ Ibrutinib ± rituximab ▶ Zanubrutinib • Lenalidomide + rituximab Useful in Certain Circumstances (in alphabetical order) • Bendamustine + rituximab (if not previously given) • Bendamustine + rituximab + cytarabine (RBAC500) (if not previously given) • Bortezomib ± rituximab • DHAP (dexamethasone, cisplatin, cytarabine) + rituximab • DHAX (dexamethasone, cytarabine, oxaliplatin) + rituximab • GemOx (gemcitabine, oxaliplatin) + rituximab • Ibrutinib, lenalidomide, rituximab (category 2B) • Ibrutinib ⁱ + venetoclax (category 2B) • Venetoclax ^f ± rituximab

SECOND-LINE CONSOLIDATION
• Allogeneic hematopoietic cell transplant (nonmyeloablative or myeloablative)
THIRD-LINE THERAPY
• Brexucabtagene autoleucel ⁱ (only given after chemoimmunotherapy and BTK inhibitor)

^a Consider prophylaxis for tumor lysis syndrome (See NHODG-B 1 of 4). See NHODG-B 2 of 4 for monoclonal antibody therapy and viral reactivation.

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

^d In patients intended to receive HDT/ASCR, bendamustine should be used with caution as there are conflicting data regarding ability to collect peripheral progenitor cell collection.

^f See Special Considerations for Use of Small-Molecule Inhibitors (NHODG-E).

^g Acalabrutinib and zanubrutinib have not been shown to be effective for ibrutinib-refractory mantle cell lymphoma with BTK C481S mutations. Patients with ibrutinib intolerance have been successfully treated with acalabrutinib or zanubrutinib without recurrence of symptoms.

^h The phase 2 ACE-LY-004 study excluded patients treated with Bruton's tyrosine kinase (BTK) or BCL-2 inhibitor and concomitant warfarin or equivalent vitamin K antagonists.

ⁱ See Guidance for Treatment of Patients with Chimeric Antigen Receptor (CAR) T-Cell Therapy (NHODG-F).

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MANT-A
2 OF 4

Tazemetostat

Tazemetostat, an EZH2 inhibitor, is FDA-approved for *EZH2* mutation-positive R/R FL after ≥2 prior systemic therapies, and for those with R/R FL who have no satisfactory alternative treatment options.

In a phase II trial of 99 patients with R/R FL (45 patients with *EZH2*-mutated [*EZH2*mut] FL; 54 patients with wild-type *EZH2* (*EZH2*wt) after ≥2 systemic therapies, including PI3K inhibitor or an immunomodulatory drug, tazemetostat resulted in an ORR of 69% (13% CR; 56% PR; 29% stable disease) in the *EZH2*mut cohort (median follow-up was 22 months) and 35% (4% CR; 31% PR; 33% stable disease) in the *EZH2*wt cohort.¹⁸ With a median follow-up of 36 months, the median PFS was 14 months and 11 months for *EZH2*mut and *EZH2*wt cohorts, respectively. The median OS was not reached in either cohort. The ORR was higher for patients with *EZH2*mut FL than those with *EZH2*wt FL in all subgroups: POD24 (63% vs 25%), double-refractory disease (no objective response to rituximab-based regimen and relapse within 6 months or refractory to alkylating agent-based chemotherapy; 78% vs 27%), and refractory to rituximab (no objective response to rituximab-based regimens or progressive disease within 6 months of completion

of rituximab-based therapy; 59% vs 31%). Notably, this study was not designed to compare the outcomes based on the *EZH2* mutation status.

Tazemetostat had a favorable toxicity profile, with thrombocytopenia (3%), neutropenia (3%), and anemia (2%) being the most common grade ≥3 adverse events and serious TEAEs reported in only 4% of patients.

Tazemetostat is included as an option for third-line and subsequent therapy for patients with *EZH2*mut R/R FL (FOLL-B, 3 of 5, page 1220). Testing for *EZH2* mutation status is feasible using paraffin-embedded tissue, and should be performed by an approved sequencing assay. Tazemetostat is also recommended as an option for R/R FL (*EZH2*wt or unknown) in patients who have no satisfactory alternative treatment options (FOLL-B, 3 of 5, page 1220).

CAR T-Cell Therapy

Axicabtagene ciloleucel was FDA-approved for the treatment of R/R FL following ≥2 lines of systemic therapy based on the results of the ZUMA-5 trial.

ZUMA-5 was a phase II trial evaluating the efficacy of axicabtagene ciloleucel in 146 patients with R/R indolent lymphoma (FL, n=124; MZL, n=22) after ≥2 prior lines of

SUGGESTED TREATMENT REGIMENS^{a,b}
 An FDA-approved biosimilar is an appropriate substitute for rituximab.

SECOND-LINE AND SUBSEQUENT THERAPY^{d,i,j} (intention to proceed to transplant)	SECOND-LINE AND SUBSEQUENT THERAPY^{d,i,j} (non-candidates for transplant)
Preferred regimens (in alphabetical order) <ul style="list-style-type: none"> • DHAP (dexamethasone, cisplatin, cytarabine) ± rituximab • DHAX (dexamethasone, cytarabine, oxaliplatin) ± rituximab • GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab • ICE (ifosfamide, carboplatin, etoposide) ± rituximab Other recommended regimens (in alphabetical order) <ul style="list-style-type: none"> • ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± rituximab • GemOx (gemcitabine, oxaliplatin) ± rituximab • MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± rituximab 	Preferred regimens (in alphabetical order) <ul style="list-style-type: none"> • GemOx ± rituximab • Polatuzumab vedotin ± bendamustine ± rituximab^{k,l} Other recommended regimens (in alphabetical order) <ul style="list-style-type: none"> • CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) ± rituximab - PO and IV • CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± rituximab • DA-EPOCH ± rituximab • GDP ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab • Gemcitabine, vinorelbine ± rituximab (category 3) • Rituximab • Tafasitamab^m + lenalidomide Useful in certain circumstances <ul style="list-style-type: none"> • Brentuximab vedotin for CD30+ disease • Bendamustine^k ± rituximab (category 2B) • Ibrutinibⁿ (non-GCB DLBCL) • Lenalidomide ± rituximab (non-GCB DLBCL)

^a Consider prophylaxis for tumor lysis syndrome (See NHODG-B 1 of 4). See NHODG-B 2 of 4 for monoclonal antibody therapy and viral reactivation.

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

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

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

^j Rituximab should be included in second-line therapy if there is relapse after a reasonable remission (>6 mo); however, rituximab should often be omitted in patients with primary refractory disease.

^k In patients intended to receive CAR T-cell therapy, bendamustine should be used with caution unless after leukapheresis prior to CAR T-cell therapy, since it could impact the success of the patient's T-cell collection.

^l Bendamustine, rituximab, and polatuzumab vedotin-piiq is indicated for the treatment of adult patients with relapsed or refractory DLBCL or HGBL with translocations of MYC and BCL2 and/or BCL6.

^m It is unclear if tafasitamab or loncastuximab tesirine or if any other CD-19 directed therapy would have a negative impact on the efficacy of subsequent anti-CD19 CAR T-cell therapy.

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

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systemic therapy.¹⁹ Treatment with axicabtagene ciloleucel resulted in an ORR of 92% (76% CR) among the 104 patients with indolent lymphoma evaluable for efficacy. The ORR was 94% (80% CR) among the 84 patients with FL (median age was 61 years [range, 34–79 years]; 38% of patients had an ECOG performance status of 1; 86% of patients had stage III/IV disease).¹⁹ With a median follow-up of 18 months, the median PFS and OS were not reached for all patients on study. The estimated 12-month PFS and OS were 74% and 93%, respectively. In an updated analysis that stratified patients with FL based on the presence or absence of POD24, treatment with axicabtagene ciloleucel resulted in similar ORR in the 2 cohorts (92%) with a CR rate of 75% in patients with POD24 and 86% in patients without POD24.²⁰ With a median follow-up of 23 months, the median PFS and OS were not reached in both groups. The estimated 18-month PFS rates were 55% and 84% for patients with and without POD24, respectively. The corresponding OS rates were 85% and 94%, respectively.

Neutropenia and anemia were the most common grade ≥3 adverse events, reported in 33% and 23% of patients, respectively. Grade ≥3 cytokine release syndrome (CRS) and neurologic events were reported in 6% and 15% of patients, respectively. Notably, 3 deaths occurred

in the study, with 1 due to CRS related to treatment with axicabtagene ciloleucel and the other 2 due to aortic dissection and coccidiomycosis infection unrelated to treatment with axicabtagene ciloleucel.

Axicabtagene ciloleucel is included as an option for third-line and subsequent therapy for R/R FL in fit patients (FOLL-B, 3 of 5, page 1220).

Marginal Zone Lymphomas

MZLs originate in the marginal zone of lymphoid follicles found in the mucosa-associated lymphoid tissues (MALT), spleen, and lymph nodes. Extranodal MZLs of MALT (MALT lymphomas), nodal MZL (NMZL), and splenic MZL (SMZL) are the 3 distinct subtypes of MZLs. MZLs represent a clinical challenge in that the heterogeneity and relative rarity of individual subtypes has largely precluded the use of conventional treatment approach across all subtypes. Alternate non-cross-resistant chemotherapy regimens, rituximab monotherapy, and ibritumomab tiuxetan are included as options for R/R disease in patients with indications for treatment. In recent years, improved understanding of the complex pathobiology of MZLs has resulted in the development of novel treatment options for R/R disease.

SUGGESTED TREATMENT REGIMENS^a**CONSOLIDATION AFTER ALTERNATE SECOND-LINE THERAPY**

- Allogeneic hematopoietic cell transplant (nonmyeloablative or myeloablative) for CR/PR following alternative second-line therapy

THIRD-LINE AND SUBSEQUENT THERAPY

- Anti-CD19 CAR T-cell therapy (only after ≥2 prior chemoimmunotherapy regimens)^p
 - ▶ Axicabtagene ciloleucel
 - ▶ Lisocabtagene maraleucel
 - ▶ Tisagenlecleucel^q
- Loncastuximab tesirine^{m,r} (only after ≥2 lines of systemic therapy)
- Selinexor (only after at least two lines of systemic therapy; including patients with disease progression after transplant or CAR T-cell therapy)^o

^a Consider prophylaxis for tumor lysis syndrome (See NHODG-B 1 of 4). See NHODG-B 2 of 4 for monoclonal antibody therapy and viral reactivation.

^m It is unclear if tafasitamab or loncastuximab tesirine or if any other CD-19 directed therapy would have a negative impact on the efficacy of subsequent anti-CD19 CAR T-cell therapy.

^o Selinexor is FDA approved only for DLBCL and transformed DLBCL arising from FL.

^p See Guidance for Treatment of Patients with Chimeric Antigen Receptor (CAR) T-Cell Therapy (NHODG-F).

^q Tisagenlecleucel is not FDA-approved for relapsed/refractory primary mediastinal large B-cell lymphoma.

^r Loncastuximab tesirine is FDA approved for relapsed or refractory DLBCL, high-grade B-cell lymphoma (HGBL) with translocation of MYC and BCL2 and/or BCL6 (double-/triple-hit lymphoma), and HGBL, NOS, as well as DLBCL arising from FL and MZL.

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BTK Inhibitors

Ibrutinib and zanubrutinib are the 2 FDA-approved BTK inhibitors for the treatment of R/R MZL.^{21,22}

In a multicenter phase II study of 60 patients with R/R MZL (after prior therapy with an anti-CD20-mAb–based regimen), ibrutinib resulted in an ORR of 48% (50% for extranodal MZL, 54% for splenic MZL, and 41% for nodal MZL).²¹ After a median follow-up of 19 months, the median PFS was 14 months. The median PFS by subtype was 14 months for extranodal MZL, 19 months for SMZL, and 8 months for NMZL. The median OS has not been reached and the 18-month estimated OS rate was 81%. Infections (19%), anemia (14%), pneumonia (8%), and fatigue (6%) were the most common grade ≥3 adverse events. Bleeding events (all were grades 1–2) were reported in 59% of patients, and major bleeding (grade 5) occurred only in 2% of patients.

Zanubrutinib was recently FDA-approved for the treatment of R/R MZL after at least one prior anti-CD20-mAb–based regimen, based on the results of the MAGNOLIA trial. The phase II multicenter MAGNOLIA trial included 68 patients with R/R MZL after ≥1 line of therapy (including ≥1 anti-CD20-mAb–based regimen).²² At a median follow-up of 16 months, zanubrutinib resulted in

an ORR of 68% (as assessed by independent review committee; 26% CR) among the 65 patients evaluable for efficacy. The median PFS was not reached and the PFS rate was 83% at both 12 and 15 months. Responses were observed in all subtypes with an ORR of 64% (40% CR), 76% (20% CR), 67% (8% CR), and 50% (25% CR) in extranodal, nodal, splenic, and indeterminate subtypes, respectively. Infections (46%), diarrhea (22%), neutropenia (13%), thrombocytopenia (13%), atrial fibrillation/flutter (3%), and hypertension (3%) were the most common all-grade adverse events. Bleeding events were reported in 37% of patients, but there were no events of major hemorrhages. Grade ≥3 neutropenia and infections were reported in 10% and 16% of patients, respectively.

Ibrutinib and zanubrutinib are included as options for preferred regimens for second-line and subsequent therapy in fit as well as elderly or infirm patients with R/R MZL (MZL-A, 2 of 4, page 1221). Zanubrutinib may be considered as an option for patients with R/R MZL with contraindications or intolerance to ibrutinib.^{23,24}

PI3K Inhibitors

Umbralisib is the only PI3K inhibitor that is FDA-approved for MZL. In the UNITY-NHL trial described

Table 1. PI3K Inhibitors in R/R FL and MZL: Efficacy Data From Phase II Trials

PI3K Inhibitor/Trial	Patients, n	ORR	Median Follow-Up	Median PFS	Median OS
Copanlisib (phase II study; CHRONOS-1) ¹³	FL (n=104)	59%	24 mo	12.5 mo (median follow-up 14 mo; estimated 2-y PFS rate: 34%)	43 mo (median follow-up: 32 mo; estimated 2-y OS rate: 69%)
	MZL (n=23)	78%			
Duvelisib (phase II study; DYNAMO) ¹⁴	FL (n=83)	42%	32 mo	9.5 mo (estimated 6-mo PFS rate: 62%)	29 mo (estimated 1-y OS rate: 77%)
	MZL (n=18)	39%			
Idelalisib (phase II study; 101-09) ¹⁶	FL (n=72)	56%	34 mo	11 mo	61 mo
	MZL (n=15)	47%		7 mo	Not reached
Umbralisib (phase IIb study; UNITY-NHL) ¹⁷	FL (n=117)	45%	27.5 mo	11 mo (estimated 2-y PFS rate: 18%)	Not reported
	MZL (n=69)	49%	28 mo	Not reached (estimated 2-y PFS rate: 51%)	Not reported

Abbreviations: FL, follicular lymphoma; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory.

earlier that included 69 patients with relapsed/refractory indolent MZL after ≥ 1 prior line of therapy with anti-CD20 mAb based regimen, umbralisib resulted in an ORR of 49% (16% CR; 33% PR).¹⁷ The ORRs were comparable across all subtypes (45% for both MALT lymphoma and splenic MZL; 60% for nodal MZL). With a median follow-up of 28 months, median PFS was not reached and

the estimated 2-year PFS rate was 51%. Umbralisib was also associated with better toxicity profile than the other 3 available PI3K inhibitors (Table 2) and it was associated with a low incidence of discontinuations related to TEAEs (as described earlier).

Umbralisib is included as an option for second-line and subsequent therapy in fit as well as elderly or infirm

Table 2. PI3K Inhibitors in R/R FL and MZL: Safety Data From Phase II Trials

Treatment-Related Adverse Events	Copanlisib ¹³		Duvelisib ¹⁴		Idelalisib ¹⁵		Umbralisib ¹⁷	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Nonhematologic toxicities								
Hyperglycemia	49%	39%	—	—	—	—	—	—
Hypertension	30%	23%	—	—	—	—	—	—
Diarrhea	34%	6%	49%	15%	43%	13%	59%	10%
Nausea	23%	<1%	30%	2%	30%	2%	39%	<1%
Vomiting	13%	0%	19%	4%	15%	2%	24%	<1%
Fatigue	25%	2%	28%	5%	30%	2%	31%	3%
Cough	17%	0%	27%	0%	29%	0%	21%	0%
Pyrexia	25%	4%	25%	0%	28%	2%	12%	0%
Upper respiratory infection	13%	1%	—	—	14%	0%	14%	0%
Pneumonia	13%	9%	8%	5%	19%	11%	7%	—
Hematologic toxicities								
Neutropenia	25%	9%	29%	25%	56%	27%	16%	12%
Anemia	14%	4%	26%	15%	28%	2%	—	—
Thrombocytopenia	13%	5%	19%	12%	26%	6%	—	—
Laboratory abnormalities								
Increased alanine transaminase	3%	<1%	14%	5%	47%	13%	20%	7%
Increased aspartate aminotransferase	1%	0%	10%	3%	35%	8%	19%	7%
Increased alkaline phosphatase	—	—	—	—	22%	0%	—	—
Increased blood creatinine	—	—	—	—	—	—	14%	<1%

Abbreviations: FL, follicular lymphoma; MZL, marginal zone lymphoma; R/R, relapsed/refractory.

patients with R/R MZL after at least one prior anti-CD20-mAb-based regimen (MZL-A, 2 of 4, page 1221).

Other PI3K inhibitors (copanlisib, duvelisib, and idelalisib) have demonstrated activity in R/R MZL resulting in ORRs of 78%, 39%, and 47%, respectively (Table 1) and are included as options for third-line therapy in fit patients with R/R MZL after 2 prior therapies (MZL-A, 2 of 4, page 1221).^{14,16,25} However, these are not FDA-approved for the treatment of R/R MZL.

Mantle Cell Lymphoma

MCL is characterized by the reciprocal chromosomal translocation t(11;14) and is thought to possess the unfavorable characteristics of both indolent and aggressive B-cell NHL subtypes owing to the incurability of disease with conventional chemoimmunotherapy and a typically more aggressive disease course compared with indolent lymphomas.²⁶ Aggressive induction with a cytarabine-based chemoimmunotherapy followed by consolidation with autologous HCT and rituximab maintenance is recommended for fit younger patients with MCL who are eligible for transplant. Rituximab maintenance after autologous HCT is associated with survival benefit in patients who achieve a CR or a very good PR ($\geq 75\%$ disease reduction) after induction chemoimmunotherapy.^{27–29} The presence of *TP53* mutation, however, is associated with poor prognosis in younger patients (inferior responses to both induction chemotherapy and high-dose chemotherapy followed by HCT), and patients with *TP53* mutation should be considered for clinical trials investigating novel agents.³⁰ Rituximab maintenance following less aggressive induction chemoimmunotherapy (eg, R-CHOP or modified R-HyperCVAD) is recommended for patients not eligible for transplant.^{31,32} Data from a prospective, randomized phase II trial suggest that there is no benefit to rituximab maintenance after induction therapy with the bendamustine-based regimen,³³ whereas rituximab maintenance following bortezomib-based regimens has not been evaluated in clinical trials.

BTK inhibitors (acalabrutinib, ibrutinib, or zanubrutinib; all 3 are FDA-approved for the treatment of R/R MCL),^{34–38} lenalidomide + rituximab,³⁹ bortezomib $\pm$ rituximab,^{40,41} and bendamustine-based regimens (bendamustine + rituximab or RBAC [rituximab/bendamustine/cytarabine])^{42,43} are appropriate options for R/R MCL. Results from clinical studies also suggest that the use of ibrutinib-based combination regimens (ibrutinib + rituximab, ibrutinib + venetoclax, ibrutinib + lenalidomide + rituximab) may be better than ibrutinib monotherapy.^{44–46}

Early treatment failure after first-line therapy (disease relapse and initiation of second-line therapy within 12 months after up-front autologous HCT) and POD24 are associated with a poor prognosis. Additionally,

patients with POD after ≥ 2 lines of therapy are considered a high-risk group with a shortened median time to subsequent relapse.^{47–49} In the MANTLE-FIRST study that evaluated the clinical outcomes of patients with R/R MCL following cytarabine-based induction chemoimmunotherapy, ibrutinib was particularly effective for refractory disease to induction chemoimmunotherapy or early POD, and bendamustine-based regimens had similar efficacy to ibrutinib for late POD.⁵⁰ However, longer follow-up is needed to confirm these findings from this retrospective study. Limited data from retrospective studies suggest that venetoclax monotherapy and the RBAC regimen result in favorable response rates in patients with R/R MCL after BTK inhibitor therapy.^{43,51–53} However, the optimal second-line therapy for management of R/R MCL after BTK inhibitor therapy has not been established in prospective studies.^{48,54,55}

Allogeneic HCT is a potentially curative option for eligible patients with R/R disease that is in remission following second-line therapy.⁵⁶ However, with the recent approval of CAR T-cell therapy for R/R MCL, in most NCCN Member Institutions allogeneic HCT has been deferred to disease relapse following multiple prior therapies (including disease relapse following CAR T-cell therapy). Data on the outcomes of allogeneic HCT following CAR T-cell therapy are not yet available.

CAR T-Cell Therapy

Brexucabtagene autoleucel was recently FDA-approved for the treatment of R/R MCL after chemoimmunotherapy and BTK inhibitor therapy based on the results of the ZUMA-2 trial.⁵⁷

ZUMA-2 included 74 patients with R/R MCL who had been treated with up to 5 prior lines of therapy, including anthracycline-based or bendamustine-based chemotherapy, anti-CD20 mAb, and BTK inhibitor. Brexucabtagene autoleucel resulted in an ORR of 85% (59% CR).⁵⁷ The ORRs were consistently higher among patients with poor prognostic features, including pleomorphic or blastoid morphology, *TP53* mutation, or Ki-67 index $\geq 50\%$. With a median follow-up of 12 months, the estimated 12-month PFS and OS rates were 61% and 83%, respectively.

Grade ≥ 3 cytopenias and infections were the most common adverse events, reported in 94% and 32% of patients, respectively. Grade ≥ 3 CRS and neurologic events occurred in 15% and 31% of patients, respectively.

Brexucabtagene autoleucel is included as an option for third-line therapy for fit patients with R/R MCL after prior treatment with chemoimmunotherapy and BTK inhibitor (MANT-A, 2 of 4, page 1222).

Diffuse Large B-Cell Lymphoma

DLBCL is the most common subtype of mature B-cell NHL. Gene expression profiling has identified distinct subtypes within DLBCL based on cell of origin: germinal center B-cell (GCB) subtype and activated B-cell (ABC) subtype.^{3,58} GCB DLBCL is associated with an improved outcome compared with ABC DLBCL in patients treated with conventional chemoimmunotherapy with R-CHOP. Currently, the up-front treatment approach remains the same for both GCB and ABC subtypes. Chemoimmunotherapy followed by high-dose therapy with autologous stem cell rescue (HDT/ASCR) is the appropriate treatment for R/R DLBCL that is chemotherapy-sensitive at relapse, in patients who are candidates for transplant, and outcomes differ based on the response to initial therapy, timing of relapse, and opportunity to undergo HDT/ASCR.⁵⁹ Optimal management for patients who are not candidates for transplant has not been established, and therefore enrollment in a clinical trial is preferred for these patients. Gemcitabine and oxaliplatin ($\pm$ rituximab)⁶⁰ and polatuzumab vedotin (monotherapy or in combination with bendamustine $\pm$ rituximab)^{61,62} are appropriate chemoimmunotherapy treatment options for R/R disease in patients who are not candidates for transplant. Other appropriate nonchemotherapy options for transplant-ineligible patients include lenalidomide ($\pm$ rituximab)^{63,64} and ibrutinib⁶⁵ (particularly for patients with non-GCB DLBCL) or tafasitamab (anti-CD19 mAb).⁶⁶ Brentuximab vedotin can be considered as an option for patients with CD30-positive DLBCL.⁶⁷

The prognosis, however, remains poor for patients with refractory disease after ≥ 2 second-line therapy regimens.^{68,69} Anti-CD19 CAR T-cell therapy has emerged as an effective treatment option for this group of patients. Axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel are the 3 anti-CD19 CAR T-cell therapies that are FDA-approved for R/R DLBCL (after ≥ 2 prior systemic therapy regimens, regardless of eligibility for transplant).^{70–72} More recently, tafasitamab (anti-CD19 mAb) + lenalidomide, loncastuximab tesirine (anti-CD19 antibody–drug conjugate), polatuzumab vedotin (anti-CD79B antibody–drug conjugate) in combination with bendamustine and rituximab, and selinexor (selective small molecule inhibitor of XPO1-mediated nuclear export) have been FDA-approved for R/R DLBCL.^{61,62,66,73,74} Recent clinical trial data support the use of tafasitamab + lenalidomide as the preferred treatment option for transplant-ineligible patients with R/R DLBCL.

Tafasitamab + Lenalidomide

In a multicenter, single-arm phase II trial (L-MIND) of 156 patients with R/R DLBCL after at least one prior systemic therapy (but no more than 3 lines of prior therapy) and ineligible for transplant, the combination of

tafasitamab + lenalidomide (12 cycles followed by tafasitamab monotherapy for patients with stable disease given until POD) resulted in an ORR of 60% (43% CR; 18% PR).⁶⁶ At a median follow-up of 17 months, the median PFS was 12 months. The estimated 12- and 18-month PFS rates were 50% and 46%, respectively. At a median follow-up of 20 months, the median OS was not reached. The estimated 12- and 18-month OS rates were 64% and 38%, respectively. Tafasitamab + lenalidomide also resulted in promising response rates in patients with GCB-DLBCL, suggesting activity for this combination that was irrespective of the cell of origin, in contrast to previous data of lenalidomide monotherapy for the treatment of relapsed/refractory DLBCL.⁶⁴ However, a more definitive interpretation was not possible, because 27% of patients had undetermined cell of origin or the gene-expression profiling results were unevaluable in 60% of patients. Notably, patients with DLBCL refractory to first-line treatment were excluded from this study.

Neutropenia (48%), thrombocytopenia (17%), and febrile neutropenia (12%) were the most common grade ≥ 3 hematologic toxicities. Most nonhematologic adverse events were grade 1–2, with diarrhea (32%) and rash (27%) being the most common. The incidence and severity of treatment-related adverse events decreased upon discontinuation of lenalidomide after 12 cycles as per study protocol.

Tafasitamab in combination with lenalidomide is included as an option for second-line subsequent therapy for R/R DLBCL in patients who are not candidates for transplant (BCEL-C, 2 of 5, page 1223).

Loncastuximab Tesirine

In a multicenter, single-arm, phase II trial (LOTIS-2) of 145 patients with R/R DLBCL after ≥ 2 multiagent systemic therapy regimens (including high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements and primary mediastinal B-cell lymphoma), loncastuximab tesirine resulted in an ORR of 48% (24% CR; 24% PR).⁷³ The median PFS, OS, and relapse-free survival were 5, 10, and 13 months, respectively. A subgroup of patients (10%) achieved an ORR of 47% (40% CR) to subsequent CD19-directed CAR T-cell therapy, and the results of another small study also showed that CD19 antigen loss after loncastuximab tesirine is not common.⁷⁵ These findings suggest that the use of loncastuximab tesirine does not preclude subsequent responses to CD19-directed CAR T-cell therapy. However, these preliminary results need to be confirmed in a larger cohort of patients, and at this time it is unclear whether loncastuximab tesirine or any other CD19-directed therapy (eg, tafasitamab) would have a negative impact on the efficacy of subsequent anti-CD19 CAR T-cell therapy.

Neutropenia (26%) and thrombocytopenia (18%) were the most common grade ≥ 3 hematologic toxicities. Most nonhematologic adverse events were grade 1–2, with fatigue (26%), nausea (23%), cough (21%), and peripheral edema (19%) being the most common. Elevated levels of gamma-glutamyl transferase (24%), alkaline phosphatase (19%), aspartate aminotransferase (15%), and alanine aminotransferase (13%) were the most common grade 1–2 biochemical treatment-emergent adverse events, with elevated gamma-glutamyl transferase being the most common treatment-related adverse event leading to treatment discontinuation in 10% of patients.

Loncastuximab tesirine is included as an option for third-line subsequent therapy for R/R DLBCL, regardless of eligibility for transplant (BCEL-C, 2 of 5, page 1223).

Selinexor

In a multicenter, phase IIb study (SADAL) of heavily pretreated R/R DLBCL (2–5 lines of previous therapies and POD after autologous HCT or were not candidates for autologous HCT), selinexor resulted in an ORR of 29% (12% CR; 17% PR).⁷⁴ In this study, 267 patients were randomly assigned, with 175 assigned to the 60-mg group and 92 assigned to the 100-mg group, which was discontinued due to the improved therapeutic window observed with 60 mg in a prespecified interim analysis (which included highly selected patients with refractory DLBCL who had to be off-treatment for at least 3 months since the end of their last therapy). The primary analysis included 127 of 175 the patients assigned to the 60-mg

group. The median follow-up was 11 months. The median OS for all patients was 9 months (median OS not reached in patients with PR or better, and 18 months in patients with stable disease). In a subgroup analysis, selinexor resulted in an ORR of 34% (14% CR) in GCB-DLBCL compared with an ORR of 21% (10% CR) in the non-GCB DLBCL.

Thrombocytopenia (46%), neutropenia (25%), anemia (22%), fatigue (11%), hyponatremia (8%), and nausea (6%) were the most common grade 3–4 adverse events.

Selinexor is included as a third-line and subsequent therapy option for R/R DLBCL after ≥ 2 lines of systemic therapy, including in patients with POD after transplant or CAR T-cell therapy (BCEL-C, 2 of 5, page 1223).

Summary

The advent of novel targeted therapies represents a major paradigm shift in the management of patients with R/R B-cell lymphomas. Accurate diagnosis of the B-cell lymphoma subtype, appropriate patient selection, and effective management of unique spectrum of adverse events associated with targeted therapies should be an integral part of the management of patients with R/R disease. Referral of appropriate patients for participation in well-designed prospective clinical trials should be considered to facilitate the development novel chemotherapy-free treatment options.

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