

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of lymphoma

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ABSTRACT

The recent development and clinical implementation of novel immunotherapies for the treatment of Hodgkin and non-Hodgkin lymphoma have improved patient outcomes across subgroups. The rapid introduction of immunotherapeutic agents into the clinic, however, has presented significant questions regarding optimal treatment scheduling around existing chemotherapy/radiation options, as well as a need for improved understanding of how to properly manage patients and recognize toxicities. To address these challenges, the Society for Immunotherapy of Cancer (SITC) convened a panel of experts in lymphoma to develop a clinical practice guideline for the education of healthcare professionals on various aspects of immunotherapeutic treatment. The panel discussed subjects including treatment scheduling, immune-related adverse events (irAEs), and the integration of immunotherapy and stem cell transplant to form recommendations to guide healthcare professionals treating patients with lymphoma.

BACKGROUND

Lymphoma is a complex group of diverse diseases that can manifest in many forms under the broad subclasses of classical Hodgkin lymphoma (cHL), B cell non-Hodgkin lymphoma (NHL), and T cell NHL, with additional distinction based on the population of lymphoid lineage cells that expand and undergo malignant transformation. Lymphoma affects roughly 870 000 people across the US, with an estimated 85 720 new cases and 20 910 deaths anticipated in 2020 alone.^{1 2} While a number of modalities have improved outcomes for patients with lymphoma including chemotherapies, radiation, stem cell transplantation, targeted therapies, and immunotherapies, there remains a clear and pressing need to identify novel strategies that can overcome treatment-resistant disease and provide curative potential while minimizing adverse events (AEs).

Numerous immunotherapies have demonstrated efficacy for the treatment of lymphoma and, in some cases, exhibited enhanced benefit when compared with traditional treatment modalities. The immunotherapeutic options approved by the US Food and Drug Administration (FDA) for the treatment of patients with lymphoma include monoclonal antibodies (mAbs), immune checkpoint inhibitors (ICIs), antibody-drug conjugates (ADCs), immunomodulatory drugs (IMiDs), and genetically engineered chimeric antigen receptor (CAR) T cells. Due to the novelty and relatively recent clinical introduction of these immunotherapies, however, many questions exist concerning optimal treatment scheduling as well as how best to manage and observe patients treated with novel agents.

Previously, the Society for Immunotherapy of Cancer (SITC) formed an expert panel to generate recommendations for the treatment and management of patients with hematological malignancies, including lymphoma, leukemia, and multiple myeloma, which were published in a 2016 consensus statement.³ More recently, however, treatment options have significantly expanded across individual disease settings. As such, SITC convened a dedicated expert panel to develop recommendations for the use of immunotherapy in the treatment of lymphoma. The expert panel was charged with generating consensus on optimal treatment scheduling and management of unique immune-related adverse events (irAEs) for FDA-approved immunotherapy agents, and on new technologies that may soon enter the clinic, with the goal of creating a well-supported clinical practice guideline (CPG) for the treatment of lymphoma using immunotherapies. These recommendations are not intended



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to supplant sound clinical judgment but to provide clinicians with the most current thinking on how experts integrate immunotherapy into the treatment of patients with lymphoma. Although differences exist in drug approvals, availability, and regulations in some countries, this panel focused solely on drugs approved by the FDA for the treatment of patients in the US. The full series of SITC CPGs can be found via the SITC website.⁴

METHODS

SITC Lymphoma Immunotherapy Guideline Expert Panel

The SITC Lymphoma Immunotherapy Guideline Expert Panel included 12 participants: 9 medical oncologists, 1 pediatric oncologist, 1 nurse practitioner, and 1 patient advocate. All panel members report having experience administering or advocating for cancer immunotherapies including mAbs, ICIs, adoptive cellular therapies, and vaccines. The panel met in person and communicated regularly via email and teleconference, in addition to completing online surveys addressing clinical topics concerning the use of cancer immunotherapy for the treatment of patients with lymphoma, which helped form the basis for the recommendations.

Guideline development process

The Institute of Medicine's (IOM) Standards for Developing Trustworthy Clinical Practice Guidelines were used as a model to develop the recommendations in this manuscript. IOM standards dictate that guideline development is led by a multidisciplinary team using a transparent process where both funding sources and conflicts of interest are readily reported. Recommendations are based on literature evidence, where possible, and clinical experience, where appropriate.⁵ For transparency, a draft of this consensus statement was made publically available for comment after journal submission. All comments were considered for inclusion into the final manuscript. This consensus statement is intended to provide guidance and is not a substitute for the professional judgment of individual treating physicians.

Evidence and consensus ratings

Panel recommendations were derived from evidence within the published literature along with responses to a clinical questionnaire that addressed current practices in the use or recommendation for use of immunotherapy agents. SITC Cancer Immunotherapy Guidelines provide recommendations based on peer-reviewed literature and consensus within the expert panel. Consensus was defined as $\geq 75\%$ agreement among expert panel members.

Conflict of interest policy

As outlined by IOM standards, all financial relationships of expert panel members that might result in actual, potential, or perceived conflicts of interest were individually reported. Disclosures were made prior to the onset of manuscript development and updated on an annual

basis. In addition, panel members were asked to articulate any actual or potential conflicts at all key decision points during guideline development, so that participants would understand all possible influences, biases, and/or the diversity of perspectives on the panel. Although some degree of relationships with outside interests among panel members are to be expected, those with any significant financial connections that may compromise their ability to fairly weigh evidence (either actual or perceived) were not eligible to participate.

Recognizing that guideline panel members are among the leading experts on the subject matter under consideration and guideline recommendations should have the benefit of their expertise, any identified potential conflicts of interests were managed as outlined in SITC's disclosure and conflict of interest resolution policies. As noted in these policies, panel members disclosing a real or perceived potential conflict of interest may be permitted to participate in consideration and decision-making of a matter related to that conflict, but only if deemed appropriate after discussion and agreement by the expert panel.

The financial support for the development of this guideline was provided solely by SITC. No commercial funding was received.

Literature review process

The MEDLINE database was used to search the scientific literature for current therapies related to Hodgkin and NHL and immunotherapy in humans. The literature search was limited to clinical trials, meta-analyses, practice guidelines, and research in humans. The results of the literature search were screened to include only papers with clinically accurate and relevant information and to remove duplicate articles from independent searches. The search was supplemented with additional articles identified by the panel as appropriate and necessary for a comprehensive literature review, resulting in a final bibliography of 241 manuscripts.

GENERAL RECOMMENDATIONS

Participation in a clinical trial may be a consideration for any patient with lymphoma. Supporting this, a systematic review of patient outcomes determined that participation in a clinical trial, on average, does not result in worse health outcomes for patients.⁶ Because participation in clinical trials does not represent an inherent risk to patient health, participation in clinical trials may be recommended as a matter of routine practice, especially in cases where approved treatment options may be limited.

Initial imaging is an important step in staging lymphoma following diagnosis as well as for monitoring response to treatment.^{7,8} Evidence from a systematic review supports a combination of fluoro-2-deoxyglucose positron emission tomography (FDG-PET) and computed tomography (CT) as superior to either modality alone in terms of diagnostic performance.⁹

Patients being treated for lymphoma may be at increased risk of infection as a consequence of immunosuppression, due to either their disease or immunosuppressive or cytotoxic therapies. For example, rituximab or anti-CD19 CAR T cell treatment may lead to hypogammaglobulinemia, and adoptive cell transfer therapies (eg, CAR T cell infusion) frequently necessitate lymphodepletion.^{10–11} Therefore, it is important to monitor patients for the development of both cytopenias and hypogammaglobulinemia during treatment for lymphoma.¹²

A number of therapeutic agents used in the treatment of lymphoma have the potential to cause cardiotoxicity, including some types of immunotherapy, chemotherapy, particularly anthracycline-based regimens, and radiation.^{13–15} For this reason, a thorough baseline workup for cardiovascular function and regular testing of cardiac parameters is important for any patient undergoing lymphoma treatment.¹²

Panel recommendations

- ▶ There was consensus that clinical trials should be strongly considered as a treatment option at each stage of therapy for eligible patients with lymphoma.
- ▶ There was consensus that all patients newly diagnosed with lymphoma should receive initial imaging via FDG-PET-CT.
- ▶ There was consensus that patients should be routinely administered complete blood count (CBC) and serum IgG tests. Infection precautions may be considered in patients with decreased neutrophil and absolute lymphocyte counts from CBC tests, as well as low levels of serum IgG.
- ▶ There was consensus that all patients with newly diagnosed lymphoma should receive assessment of their cardiovascular history and risk factors prior to receiving potentially cardiotoxic therapies (including some forms of radiotherapy, chemotherapy, and immunotherapies). These patients should be examined and routinely monitored through methods such as transthoracic echocardiogram and ECG based on risk assessment.

HODGKIN LYMPHOMA

Available agents and indications

Discussed in the following sections are immunotherapies that have been approved by the FDA for cHL, ordered by history of clinical usage.

Brentuximab vedotin

Brentuximab vedotin (BV) is an anti-CD30 ADC carrying the antimicrotubule agent monomethyl auristatin E as a payload. BV has been investigated as a therapy for patients with cHL and NHL in a number of clinical contexts. For example, in the phase III randomized ECHELON-1 trial (NCT01712490), BV was incorporated into a modification of the doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) chemotherapy regimen, which has been the established standard of care for the first-line treatment of

all stages of cHL for a number of years.^{16–17} In this study, 1334 patients with previously untreated stage III or IV cHL were administered ABVD or BV with doxorubicin, vinblastine, and dacarbazine (A-AVD).¹⁸ Patients who received A-AVD exhibited a significantly higher progression free survival (PFS) rate of 82.1% versus 77.2% for patients who received ABVD (HR 0.77; 95% CI 0.6 to 0.98; $p=0.03$) after a median follow-up of 24.9 months.¹⁹ Patients in the A-AVD group also exhibited higher overall survival (OS) than those in the ABVD group at 24-month follow-up, at 96.6% versus 94.9% (HR 0.72; 95% CI 0.44 to 1.17; $p=0.19$), although this difference was not significant.¹⁹ In April 2018, these data supported FDA approval for the use of BV in combination with doxorubicin, vinblastine, and dacarbazine for the first-line treatment of stage III–IV cHL.²⁰

BV has also been approved for use as a consolidation therapy of cHL. In the AETHERA trial (NCT01100502), BV-naïve patients who had received autologous stem cell transplant (autoSCT) and were considered to be at high risk for relapse were administered BV or placebo.²¹ The median PFS with placebo was 15.8 months, while the median PFS with BV was not reached at 5-year follow-up (HR 0.52; 95% CI 0.38 to 0.72).²² Based on the AETHERA trial, in 2015, the FDA approved BV as consolidation therapy for cHL patients who have received autoSCT and are at high risk of relapse.²⁰

Additionally, BV has been approved for the treatment of relapsed or refractory (R/R) cHL patients who had previously received autoSCT based on a single-arm, phase II study (NCT00848926) where 102 participants who received BV as monotherapy after relapse had a median PFS of 9.3 months (95% CI 7.1 to 12.1).^{23–24} At 3-year follow-up, OS was estimated to be 80% (95% CI 45% to 100%), with an overall response rate (ORR) of 72%.²⁴ These data supported FDA approval in August 2011.²⁰

Nivolumab

The checkpoint inhibitor nivolumab, a mAb that blocks programmed cell death protein 1 (PD-1), has been heavily investigated in solid tumor settings and has also been the subject of therapeutic studies in patients with R/R cHL. The phase II, single-arm CheckMate 205 (NCT02181738) and phase I/II, randomized CheckMate 039 (NCT01592370) studies both examined nivolumab monotherapy in patients with R/R cHL who had previously received autoSCT and, in some cases, both autoSCT and BV consolidation.^{25–26} In a pooled analysis of 243 patients across three cohorts who had disease progression after receiving autoSCT, the ORR for patients treated with nivolumab was 69% (95% CI 63% to 75%), the median duration of response (DOR) was 16.6 months (95% CI 13.2 to 20.3), and the median PFS was 14.7 months (95% CI 11.3 to 18.5). Patients who had previously received both BV and autoSCT (cohort C, $n=100$) had an ORR of 73% (95% CI 63% to 81%), a median DOR of 14.5 months (95% CI 9.5 to 16.6), and a median PFS of 11.9 months (95% CI 11.1 to 18.4).²⁷ On the basis of

data from these two trials, the FDA approved nivolumab monotherapy for the treatment of patients with R/R cHL who have received autoSCT and BV, or who have received three or more prior lines of systemic therapy (including autoSCT) in May 2016.²⁸

A notable phase II trial, NCT02572167, is examining the combination of BV+nivolumab in the second-line treatment of R/R cHL.²⁹ Interim results from this promising study gave an ORR of 83% (95% CI 71.5% to 91.7%) and a complete response (CR) rate of 62% (95% CI 48.2% to 73.9%) and indicate that this regimen is well-tolerated, although this treatment strategy has not received FDA approval and data on secondary endpoints, including DOR and PFS, are still anticipated.³⁰

Pembrolizumab

Another anti-PD-1 checkpoint inhibitor, pembrolizumab, has been evaluated for efficacy in patients with R/R cHL in the non-randomized, phase II KEYNOTE-087 trial (NCT02453594), which enrolled 210 patients with R/R cHL.³¹ The PFS and OS at 6-month follow-up were 72.4% and 99.5%, respectively.³² The observed ORR was 69.0% (95% CI 62.3% to 75.2%).³² Based on these data, the FDA granted accelerated approval in May 2017 to pembrolizumab for the treatment of patients with cHL that is refractory or that has relapsed after three or more lines of prior therapy.³³

Panel recommendations

- ▶ For the first-line therapy of stage I–II (favorable or unfavorable risk) cHL, there was consensus that patients should receive ABVD.
- ▶ For the first-line therapy of stage III–IV cHL, the panel did not reach consensus on a single preferred regimen. Options for treatment include ABVD and A-AVD.
- ▶ For the second-line treatment of cHL, there was consensus that patients should receive salvage chemotherapy or immunotherapy, and should receive autoSCT, if eligible. Treatment options for pre-autoSCT chemotherapy or immunotherapy include

BV+bendamustine, ifosfamide+carboplatin+etoposide (ICE), BV+nivolumab, or BV monotherapy. The panel noted that BV is FDA-approved for consolidation treatment following autoSCT, but that the trial supporting this data only examined patients who were BV-naïve, and that BV consolidation in patients who have previously received BV is still investigational.

- ▶ For the third-line treatment of cHL, the panel did not reach consensus on a single preferred regimen. Options for treatment include salvage chemotherapy or immunotherapy+autoSCT (if transplant-eligible), PD-1 inhibitor therapy, or BV, depending on prior therapies received and patient status.

Therapies in development for cHL

Ongoing phase III trials (at the time of publication) are examining the safety and efficacy of immunotherapies in new clinical contexts for the treatment of cHL (listed in table 1).

NON-HODGKIN LYMPHOMA

NHL may be divided into two major categories, B cell NHL and T cell NHL, each of which is comprised of numerous subtypes. Some immunotherapies are approved for a variety of NHL disease states, whereas others are more limited in indication. B cell NHL disease states discussed in this manuscript include diffuse large B cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), marginal zone lymphoma (MZL), primary mediastinal B cell lymphoma (PMBCL), Burkitt's lymphoma (BL), and post-transplant lymphoproliferative disorder (PTLD). Discussed in the following sections are immunotherapies that have been approved by the FDA in various NHL disease settings, ordered by history of clinical use.

Available agents and indications

Rituximab

Rituximab is a chimeric anti-CD20 anti-CD20 mAb that has been extensively investigated and used for the

Table 1 Immunotherapies in development for the treatment of Hodgkin lymphoma

Trial	Agents investigated	Agent description	Primary outcome for assessment
CheckMate 812 (NCT03138499)	Nivolumab+BV vs BV monotherapy in patients with R/R cHL, not eligible for autoSCT	ICI, ADC	PFS
NCTN S1826 (NCT03907488)	Nivolumab+AVD vs BV+AVD (A-AVD) for first-line treatment of stage III or IV cHL	ICI	PFS
MK-3475–204/KEYNOTE-204 (NCT02684292)	Pembrolizumab vs BV for R/R cHL	ICI	PFS, OS
NCT02572167	BV+nivolumab for R/R cHL	ICI, ADC	Rate of AEs, CR rate

A-AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ADC, antibody-drug conjugate; AEs, adverse events; BV, brentuximab vedotin; cHL, classical Hodgkin lymphoma; CR, complete response; ICI, immune checkpoint inhibitor; mAb, monoclonal antibody; OS, overall survival; PFS, progression-free survival; R/R, relapsed or refractory.

treatment of patients with B cell NHL. In NHL Studies 1, 2, and 3, patients with R/R, low grade or follicular B cell NHL were administered rituximab as a single agent with ORR of 48%, 57%, and 38%, respectively.^{34–36} On the basis of data from these trials, in November 1997, the FDA approved the use of rituximab for the treatment of R/R, low grade or follicular CD20+ B cell NHL.³⁷

Rituximab has also been evaluated for the first-line treatment of FL (in combination with cyclophosphamide, vincristine, prednisone (CVP)). NHL Study 4 randomized patients with previously untreated FL to receive CVP or rituximab+CVP (R-CVP).³⁸ Patients receiving rituximab had a PFS of 2.4 years, compared with 1.4 years without rituximab (HR 0.44; 95% CI 0.29 to 0.65; $p < 0.0001$).³⁸ Rituximab was additionally evaluated as a maintenance therapy for patients achieving response following treatment with rituximab-containing chemoimmunotherapy or chemotherapy alone. In NHL Study 5 (PRIMA, NCT00140582), patients with FL who reached response after initial treatment with rituximab-chemotherapy were randomized to rituximab maintenance or no additional therapy.³⁹ Patients who were administered rituximab as maintenance had a higher PFS than patients who received no additional therapy after a median follow-up of 36 months, at 74.9% versus 57.6%, respectively (HR 0.55; 95% CI 0.44 to 0.68; $p < 0.0001$).⁴⁰ In NHL Study 6 (ECOG 1496), patients with B cell NHL who responded after initial treatment with CVP chemotherapy were randomized to rituximab maintenance or no additional therapy.⁴¹ Rituximab maintenance resulted in a longer median PFS, at 4.3 years versus 1.3 years for patients not administered rituximab (HR 0.4; 95% CI 0.3 to 0.5; $p = 4.4 \times 10^{-10}$).⁴¹ In September 2006, the results of NHL Studies 4, 5, and 6 formed the basis of FDA approval for the administration of rituximab in patients with FL as combination first-line therapy with chemotherapy and as maintenance therapy following response in patients with FL who received rituximab-containing combination chemotherapy.³⁷ These studies also formed the basis of FDA approval for the use of rituximab as a maintenance therapy for patients with low grade, CD20+ B cell NHL following initial CVP chemotherapy.³⁷

Rituximab has been investigated in the treatment of DLBCL, a specific subtype of B cell NHL. During NHL Studies 7 (ECOG-4494, NCT00003150), 8 (GELA LNH-98.5), and 9 (MInT, NCT00064116), patients with previously untreated DLBCL received either cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or rituximab+CHOP (R-CHOP) therapy.^{42–44} In all three trials, R-CHOP provided increased PFS when compared with CHOP. In Study 7, PFS was 53% for R-CHOP and 46% for CHOP at 3-year follow-up (HR 0.78; 95% CI 0.61 to 0.99; $p = 0.04$).⁴⁵ In Study 8, event-free survival (EFS) was 57% for R-CHOP and 38% for CHOP at 2-year follow-up (HR 0.58; 95% CI 0.44 to 0.77; $p < 0.001$).⁴³ In Study 9, EFS was 79% for R-CHOP and 59% for CHOP (log-rank $p < 0.0001$).⁴⁶ On the basis of data from these trials, in February 2006, the FDA approved the use of R-CHOP for

the first-line treatment of DLBCL.³⁷ PMBCL, a subtype of DLBCL, has also been successfully treated with rituximab-chemotherapy combination regimens. A phase II clinical trial (NCT00001337) found that patients ($n = 51$) treated with dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin with rituximab (DA-R-EPOCH) experienced an OS rate of 97% (95% CI 81% to 99%) and EFS rate of 93% (95% CI 81% to 98%) at a median follow-up of 63 months.⁴⁷ A retrospective analysis ($n = 156$) reported an estimated 3-year OS rate of 95.4% (95% CI 91.8% to 99.0%) and EFS rate of 85.9% (95% CI 80.3% to 91.5%).⁴⁸

Rituximab also plays an important role in the treatment of PTLD. In an analysis of the use of rituximab for the treatment of 58 patients who developed B cell PTLD following solid organ or stem cell transplant, CR occurred in 61% of patients. At a median follow-up of 61 months, OS was 46%.⁴⁹ Although the FDA has not issued a specific approval for this purpose, rituximab has become an important component in the treatment of B cell PTLD, alongside other treatments for PTLD, including the withdrawal of immunosuppression, chemotherapeutic regimens, antiviral therapies, and, more recently, histone deacetylase (HDAC) inhibitors (in T cell-related PTLD).^{50–56}

In the MCL setting, rituximab has been used in combination with the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib. A phase II study of 50 patients with R/R MCL (NCT01880567) reported favorable safety profiles with 88% (95% CI 75.7% to 95.5%) of patients achieving an objective response at a median follow-up of 16.5 months.^{57–58} Rituximab has also been incorporated into first-line regimens with chemotherapy for MCL. In a study of 638 patients treated with a variety of chemotherapy regimens, 2-year OS was 63% and 52%, respectively, for patients treated with rituximab+chemotherapy versus chemotherapy alone ($p < 0.001$).⁵⁹ Another chemoimmunotherapy regimen involving rituximab has also been examined for the first-line treatment of MCL: bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP). During the clinical trial NCT00722137, 487 patients randomly received either R-CHOP or VR-CAP. Patients treated with VR-CAP experienced higher median PFS of 24.7 months (95% CI 19.8 to 31.8) versus 14.4 months (95% CI 12.0 to 16.9; HR=0.63; 95% CI 0.50 to 0.79; $p < 0.001$).⁶⁰ Rituximab has also been used as a maintenance therapy in patients who have received autoSCT for MCL. During a clinical trial (NCT00921414) including 257 patients who received either maintenance rituximab or observation following autoSCT, the 4-year PFS rate was 83% (95% CI 73% to 88%) versus 64% (95% CI 55% to 73%) for rituximab versus observation, respectively (HR 0.40; 95% CI 0.23 to 0.68; $p < 0.001$). The OS at 4 years was also significantly higher for patients treated with rituximab, at 89% (95% CI 81% to 94%) compared with 80% (95% CI 72% to 88%; HR 0.50; 95% CI 0.26 to 0.99; $p = 0.04$).⁶¹

Two rituximab biosimilars (rituximab-abbs and rituximab-pvvr) are also currently approved by the FDA.^{62 63} Biosimilars can potentially increase patient access to important immunotherapies, and are typically approved following comparative studies that demonstrate no significant clinical difference from the reference agent.^{64 65} An alternative formulation of rituximab, containing hyaluronidase, is also available for subcutaneous administration after a patient has received at least one dose of intravenous rituximab.⁶⁶

Obinutuzumab

Obinutuzumab, another anti-CD20 mAb, which is humanized and binds to a different epitope of CD20, is used in the treatment of FL as an alternative to rituximab. During the GADOLIN trial (NCT01059630), patients with R/R indolent B cell NHL that had been previously treated with a rituximab-containing regimen were administered obinutuzumab+bendamustine or standard of care bendamustine.^{67 68} The majority of these patients had follicular B cell NHL.⁶⁹ Patients receiving obinutuzumab during treatment also received it as maintenance therapy.⁶⁷ At the time of follow-up (median 21.9 months for obinutuzumab+bendamustine, 20.3 months for bendamustine), median PFS was not reached for obinutuzumab+bendamustine, and was 13.8 months for bendamustine alone (HR 0.49; 95% CI 0.35 to 0.68; log-rank $p < 0.0001$).⁶⁹ Based on the results of this trial, in February 2016, the FDA approved the use of obinutuzumab in combination with bendamustine (with obinutuzumab maintenance) for the treatment of R/R FL in patients who have previously received a rituximab-containing regimen.⁷⁰

In the GALLIUM trial (NCT01332968), obinutuzumab was investigated for the first-line treatment of FL in comparison to rituximab. Patients received a chemotherapy regimen (CHOP, CVP, or bendamustine) in combination with obinutuzumab or rituximab.⁷¹ At 3 years maintenance with the assigned antibody, patients who received obinutuzumab exhibited a higher estimated rate of PFS, at 80.0% versus 73.3% (HR 0.66; 95% CI 0.51 to 0.85; $p = 0.001$).⁷² The FDA approved the use of obinutuzumab in combination with chemotherapy (followed by obinutuzumab maintenance) for the first-line treatment of bulky stage II, stage III, and stage IV FL in November 2017.⁷⁰ Notably, however, the GALLIUM trial results did not demonstrate statistically significant differences in OS at 3 years for obinutuzumab compared with rituximab (94.0% vs 92.1%; HR 0.75; 95% CI 0.49 to 1.17; $p = 0.21$), despite reported benefits for PFS.⁷² Obinutuzumab was also investigated as a first-line therapy for DLBCL, in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (G-CHOP), in the GOYA trial (NCT01287741).⁷³ However, when compared with standard of care R-CHOP, G-CHOP did not significantly improve PFS.⁷⁴

Ibritumomab tiuxetan

Ibritumomab tiuxetan (IT) is an anti-CD20 antibody, conjugated to the radioisotope ⁹⁰Y. IT was evaluated for the treatment of patients with R/R, low grade or follicular B cell NHL in three clinical trials, IDEC 106-04, IDEC 106-05, and IDEC 106-06.⁷⁵ In the single-arm IDEC 106-05, the ORR for patients with R/R B cell NHL was 89% (95% CI 70% to 97%).⁷⁶ In IDEC 106-04, IT was compared with rituximab in the treatment of R/R B cell NHL. The ORR was significantly higher in patients receiving IT, at 83% versus 55% ($p < 0.001$).⁷⁷ In IDEC 106-06, IT was used as a therapy for patients with R/R B cell NHL who had previously received rituximab. The ORR in this study was 74%.⁷⁸ These data were the basis for FDA approval of the treatment of R/R low-grade or follicular B cell NHL with IT in February 2002.⁷⁹

IT has also been approved as a consolidation therapy for FL. In the trial NCT00185393, patients achieving partial response (PR) or CR following first-line chemotherapy were administered either IT or no consolidation therapy.⁸⁰ The median PFS was significantly higher in the IT arm, at 36.5 months versus 13.3 months in the control arm (HR 0.47; 95% CI 0.36 to 0.61; $p < 0.0001$).⁸¹ Based on the results of this trial, in September 2009, the FDA approved the use of IT as consolidation for patients with FL who achieve PR or CR following chemotherapy.⁷⁹ Tositumomab, another anti-CD20 antibody conjugated to ¹³¹I, received FDA approval for the treatment of R/R FL in June 2003; however, tositumomab is no longer manufactured or sold.⁸²

Brentuximab vedotin

In addition to approvals in the cHL setting, BV has also been investigated and approved for the treatment of some subsets of T cell lymphomas (TCL). In the single-arm study NCT00866047, BV was evaluated as a therapy for R/R systemic anaplastic large cell lymphoma (sALCL), a type of peripheral TCL.⁸³ At 5-year follow-up, the median PFS was 20 months, the OS rate was 60% (95% CI 47% to 73%), and the ORR was 86% (95% CI 74.6% to 93.9%).⁸⁴ In August 2011, the FDA approved the use of BV for the treatment of R/R sALCL after the failure of at least one multi-agent chemotherapy regimen.²⁰

In the ECHELON-2 trial (NCT01777152), patients with CD30+, peripheral T cell lymphoma (PTCL) received CHOP chemotherapy or BV with cyclophosphamide, doxorubicin, prednisone (A+CHP) as first-line therapy.⁸⁵ Treatment with A+CHP was associated with significantly increased median PFS of 48.2 months versus 20.8 months (HR 0.71; 95% CI 0.53 to 0.94; log-rank $p = 0.011$).⁸⁶ These data were the basis of FDA approval of BV in combination with CHP for the first-line treatment of CD30+ PTCL, including sALCL, angioimmunoblastic TCL, and PTCL otherwise not specified, in November 2018.²⁰

BV has also been approved for the treatment of two subtypes of cutaneous TCL, mycosis fungoides (MF) and primary cutaneous anaplastic large cell lymphoma (pcALCL). The ALCANZA trial (NCT01578499)

compared BV to chemotherapy with methotrexate or bexarotene in patients with R/R MF or pcALCL.⁸⁷ The ORR in patients receiving BV was significantly higher, at 67% compared with 20% ($p < 0.0001$).⁸⁶ Median PFS was also higher with BV treatment, at 16.7 months versus 3.5 months (HR 0.27; 95% CI 0.169 to 0.430; $p < 0.0001$).⁸⁶ In November 2017, the FDA approved the use of BV for the treatment of R/R CD30+ MF and pcALCL.²⁰

In addition to TCL, BV has been examined as a therapy for CD30+ B cell lymphomas (although the FDA has not approved BV for this purpose). A phase II trial (NCT01421667) examined BV monotherapy for patients with R/R DLBCL ($n = 48$). All responding patients had quantifiable CD30 expression, although the level of CD30 expression did not correlate with response. The ORR was 44% (95% CI 27.8% to 60.4%), and median PFS was 4 months.⁸⁸ A small number of patients ($n = 9$) have been treated with BV for CD30+ PTL. A systematic review that pooled outcomes from BV-treated patients with CD30+ PTL ($n = 9$) across clinical trials and case studies found that results were mostly positive, with 56% ($n = 5$) of patients experiencing complete remission.⁸⁹

Polatuzumab vedotin-piiq

Polatuzumab vedotin-piiq is an ADC targeted to CD79b. Study GO29365 (NCT02257567) compared polatuzumab vedotin-piiq with bendamustine+rituximab (BR) to BR alone in patients with R/R DLBCL or FL.⁹⁰ In patients with DLBCL, those treated with polatuzumab vedotin-piiq exhibited significantly higher median PFS, at 9.5 months versus 3.7 months (HR 0.37; 95% CI 0.21 to 0.66; $p < 0.001$).⁹¹ The ORR was also significantly increased, at 45.0% versus 17.5%.⁹¹ The FDA approved the use of polatuzumab vedotin-piiq in combination with BR for the treatment of R/R DLBCL after at least two prior therapies in June 2019.⁹²

Mogamulizumab-kpkc

Mogamulizumab-kpkc is an mAb targeted to CC chemokine receptor 4 (CCR4). Mogamulizumab has been evaluated for the treatment of two types of cutaneous TCL: MF and Sézary syndrome (SS). During the MAVORIC trial (NCT01728805), patients with R/R cutaneous TCL received mogamulizumab or vorinostat.⁹³ The median PFS was 7.7 months for mogamulizumab and 3.1 months for vorinostat (HR 0.53; 95% CI 0.41 to 0.69; log-rank $p < 0.0001$), and ORR for each group was 23% and 4%, respectively ($p < 0.00001$).⁹⁴ Based on this trial, in August 2018 the FDA approved mogamulizumab for the treatment of R/R MF or SS after at least one prior systemic therapy.⁹⁵

Pembrolizumab

Pembrolizumab has been approved for the treatment of R/R PMBCL in patients who have received two or more prior lines of therapy, based on the KEYNOTE-170 trial (NCT02576990), which observed an ORR of 45% (95% CI 32% to 60%), median PFS of 5.5 months (95% CI 2.8 months to 12.1 months), and OS at 1-year follow-up

estimated at 58%.^{96 97} The trial formed the basis for FDA approval in June 2018.³³

Lenalidomide

Lenalidomide, an IMiD, has been investigated and approved for a few subtypes of NHL, namely MCL, FL, and MZL. In the single-arm EMERGE trial (NCT00737529), patients with R/R MCL were administered lenalidomide.⁹⁸ The ORR of this treatment was 30%, and the median PFS was 4.0 months (95% CI 3.7 to 7.2).⁹⁹ On the basis of data from this trial, the FDA approved lenalidomide for the treatment of patients with R/R MCL who had received two or more prior therapies (one of which was bortezomib) in June 2013.¹⁰⁰

In addition to being used as a monotherapy in the treatment of MCL, lenalidomide is commonly administered in combination with rituximab for the treatment of FL and MZL. In the AUGMENT trial (NCT01938001), patients with MZL or FL (grade 1–3a) were administered lenalidomide+rituximab or rituximab+placebo.¹⁰¹ Patients receiving lenalidomide+rituximab exhibited significantly increased median PFS, at 39.4 months versus 14.1 months (HR 0.46; 95% CI 0.34 to 0.62; $p < 0.0001$). The ORR was also significantly increased in the lenalidomide arm, at 78% versus 53% ($p < 0.0001$).¹⁰²

In the MAGNIFY trial (NCT01996865), patients with R/R FL (grade 1–3b or transformed), MZL, or MCL were administered lenalidomide+rituximab, with either rituximab or lenalidomide+rituximab (R2) administered as maintenance therapy afterward.¹⁰³ While a comparison between the rituximab and R2 arms has not yet been published, the ORR in patients with MZL was 65%, and the ORR in patients with FL was 74% for patients treated with R2 maintenance.¹⁰⁴ Based on data from MAGNIFY and AUGMENT, in May 2019 the FDA approved the use of lenalidomide+rituximab for the treatment of R/R FL and MZL.¹⁰⁰ Lenalidomide was also tested as part of a first-line therapy regimen for FL (grade 1–3a) in combination with rituximab as part of the RELEVANCE trial (NCT01476787 and NCT01650701).^{105 106} In comparison between the R2 regimen and a selection of rituximab-containing chemoimmunotherapy regimens, rates of ORR, PFS, and OS were similar and did not show a clear advantage for either treatment arm. However, the safety profiles of the two treatment arms were different, with R2 resulting in a higher rate of grade ≥ 3 cutaneous reactions and rituximab+chemotherapy resulting in a higher rate of grade ≥ 3 neutropenia and febrile neutropenia.¹⁰⁷

Lenalidomide has also been investigated as a treatment for DLBCL. Lenalidomide has resulted in similar efficacy to investigator's choice therapies, as in the phase II/III DLC-001 trial (NCT01197560).¹⁰⁸ While lenalidomide did not demonstrate a clear OS advantage over other therapies as a single agent, it is sometimes used clinically in the treatment of DLBCL as an alternative with a different toxicity profile.

Axicabtagene ciloleucel

At the time of manuscript preparation, three CAR T cell therapies have been approved by the FDA for the treatment of patients with lymphoma. All target cells expressing CD19, but differ in the costimulatory and hinge domains used in the CAR constructs. The single-arm ZUMA-1 trial (NCT02348216) of axicabtagene ciloleucel reported an ORR of 83%, a median PFS of 5.9 months (95% CI 3.3 to 15.0), and a DOR of 11.1 months (95% CI 4.2 to not estimable) in patients with large B cell lymphomas. At a median follow-up of 27.1 months, 39% of patients exhibited ongoing remission and median OS was not reached.^{109 110} Based on this study, in October 2017, the FDA granted approval to axicabtagene ciloleucel for the treatment of R/R large B cell lymphomas (including DLBCL, PMBCL, high-grade B cell lymphoma, and transformed FL) after two or more prior lines of systemic therapy.¹¹¹

Tisagenlecleucel

Another CD19-targeting CAR T cell therapy, tisagenlecleucel, is also approved for the treatment of R/R large B cell lymphomas. In the single-arm, phase II JULIET trial (NCT02445248) for R/R DLBCL and transformed FL, tisagenlecleucel therapy resulted in an ORR of 52% (95% CI 41% to 62%). At the data cut-off, the median DOR had not yet been reached, the median OS was 12 months (95% CI 7 to not reached), and the median PFS had not been reached.¹¹² In May 2018, the FDA approved the use of tisagenlecleucel for the treatment of R/R large B cell lymphomas after two or more prior lines of systemic therapy.¹¹³

Brexucabtagene autoleucel

In July 2020, the FDA approved brexucabtagene autoleucel (formerly KTE-X19), an anti-CD19 CAR T cell therapy, for the treatment of R/R MCL.¹¹⁴ This approval was based on the phase II, open-label ZUMA-2 trial (NCT02601313).¹¹⁵ In this trial, 60 patients in the primary efficacy analysis with R/R MCL received brexucabtagene autoleucel, and exhibited an ORR of 93% (95% CI 84% to 98%) and a CR rate of 67% (95% CI 53% to 78%). At 12 months, the estimated OS and PFS were 83% and 61%, respectively.¹¹⁶

Tafasitamab-cxix

During the L-MIND trial (NCT02399085), a phase II, open-label trial, 80 patients received tafasitamab-cxix (an anti-CD19 mAb) with lenalidomide for the treatment of R/R DLBCL.¹¹⁷ The ORR among these patients was 60% (95% CI 48% to 71%), the median DOR was 21.7 months (95% CI 21.7 to not reached), the median PFS was 12.1 months (95% CI 5.7 to not reached), and the median OS was not reached at a median follow-up of 19.6 months.¹¹⁸ On the basis of data from L-MIND, the FDA approved tafasitamab-cxix+lenalidomide for the treatment of R/R DLBCL in patients who are not eligible for autoSCT.¹¹⁹

Epstein-Barr virus-directed T lymphocytes

It is hypothesized that PTLD is often linked to Epstein-Barr virus (EBV) infection or reactivation, and BV represents a potential treatment option for the resulting CD30+ PTLD (as discussed earlier). A recent case study demonstrated the successful combination of BV and EBV-directed allogeneic T lymphocytes to treat CD30+, EBV-associated PTLD, achieving a lasting CR.¹²⁰ While EBV-directed T lymphocytes have seen clinical use in the treatment of PTLD, no FDA approvals exist for these cellular therapies at the time of publication.

Panel recommendations

Diffuse large B cell lymphoma

- ▶ There was consensus that the first-line regimen for newly diagnosed DLBCL in adult patients should be R-CHOP.
- ▶ For pediatric patients with newly diagnosed DLBCL, there was consensus that first-line treatment should consist of rituximab with French-American-British (FAB) backbone chemotherapy.
- ▶ For the second-line therapy of DLBCL, there was consensus that transplant-eligible patients should receive a chemoimmunotherapy regimen that includes rituximab (such as rituximab+ICE (R-ICE) or rituximab+dexamethasone+cytarabine+cisplatin (R-DHAP)), followed by autoSCT consolidation if CR is achieved.
- ▶ In transplant-eligible patients who receive salvage therapy and exhibit PR, the panel did not reach consensus on a preferred consolidation regimen. Options include anti-CD19 CAR T cell therapy or autoSCT.
- ▶ For second-line therapy of DLBCL in patients who are transplant-ineligible, the panel did not reach consensus on a salvage chemotherapy or immunotherapy regimen. Treatment options include lenalidomide, lenalidomide+tafasitamab-cxix, polatuzumab vedotin-piiq+BR or an appropriate salvage chemoimmunotherapy regimen (including R-GemOx or R-GDP).
- ▶ There was consensus that the third-line treatment for DLBCL in fit patients should be anti-CD19 CAR T cell therapy (axicabtagene ciloleucel or tisagenlecleucel).
- ▶ There was consensus that patients who are ineligible for third-line anti-CD19 CAR T cell therapy should instead receive polatuzumab vedotin-piiq+BR.

Mantle cell lymphoma

- ▶ The panel did not reach consensus on first-line treatment for patients with MCL who are eligible for transplant. Options include chemoimmunotherapy with autoSCT or chemoimmunotherapy alone. The standard of care for first-line MCL treatment includes an anti-CD20 mAb as part of the chemoimmunotherapy regimen.
- ▶ Patients who receive autoSCT for MCL should also receive rituximab maintenance.

- ▶ For transplant-ineligible patients with MCL, there was consensus that first-line treatment should consist of an appropriate chemoimmunotherapy regimen with rituximab as maintenance therapy.
- ▶ The panel did not reach consensus on second-line or later lines of treatment for patients with MCL. Treatment options include brexucabtagene autoleucel, proteasome inhibitors, BTK inhibitors, BTK inhibitors+rituximab, or lenalidomide+rituximab.

Follicular lymphoma

- ▶ The panel did not reach consensus on a preferred treatment for patients with low tumor burden FL (once treatment is indicated). Treatment options include rituximab monotherapy, lenalidomide+rituximab, or chemoimmunotherapy (eg, R-CHOP or BR).
- ▶ In patients with high tumor burden FL, there was consensus that first-line treatment should consist of an appropriate chemoimmunotherapy regimen (eg, R-CHOP or BR).
- ▶ There was consensus that second-line (or later) treatment regimens for patients with FL will vary, and should be decided on a case-by-case basis using factors that include prior therapies, time of relapse, tumor bulk, age, and comorbidity status. Ibritumomab tiuxetan may be used in this context, if deemed appropriate.
- ▶ There was consensus that when anti-CD20 antibody therapy is indicated, rituximab should be used over obinutuzumab when possible, since obinutuzumab has not demonstrated an OS benefit in comparison to rituximab.
- ▶ In patients who have been treated with rituximab, if relapse occurs less than 6 months after the last dose of rituximab, there was consensus that obinutuzumab should be used (if anti-CD20 antibody therapy is indicated). If relapse occurs more than 6 months after the last dose of rituximab, there was consensus that rituximab should be administered again (if anti-CD20 antibody therapy is indicated).

Marginal zone lymphoma

- ▶ There was consensus that first-line treatment of advanced stage, low tumor burden MZL should consist of rituximab monotherapy.
- ▶ There was consensus that first-line treatment of advanced stage, high tumor burden MZL should consist of an appropriate chemoimmunotherapy regimen.
- ▶ There was consensus that second-line (or later) treatment regimens for patients with MZL will vary, and should be decided on a case-by-case basis using factors that include prior therapies, time of relapse, tumor bulk, age, and comorbidity status.

Primary mediastinal B cell lymphoma

- ▶ There was consensus that first-line treatment of PMBCL should consist of DA-R-EPOCH.

- ▶ There was consensus that second-line treatment of PMBCL should be identical to the recommendations listed for DLBCL (see earlier).
- ▶ The panel did not reach consensus on a specific treatment regimen for the third-line treatment of PMBCL. Treatment options include axicabtagene ciloleucel, BV+pembrolizumab, or appropriate salvage chemotherapy regimens.

Burkitt's lymphoma

- ▶ There was consensus that first-line treatment of BL in children, adolescents, and young adults should consist of a rituximab-containing chemoimmunotherapy regimen, either rituximab+FAB chemotherapy backbone or rituximab+Berlin-Frankfurt-Münster (BFM) chemotherapy backbone.
- ▶ There was consensus that second-line treatment of BL in children, adolescents, and young adults should consist of a rituximab-containing chemoimmunotherapy regimen (eg, R-ICE or rituximab, cytarabine, etoposide (R-CYVE)).
- ▶ There was consensus that children, adolescents, and young adults who achieve PR or CR should receive stem cell transplantation as consolidation therapy (if eligible). In the event of prior bone marrow involvement, allogeneic stem cell transplant (alloSCT) is indicated, whereas autoSCT is recommended in all other cases.
- ▶ There was consensus that first-line treatment of BL in adults should consist of a rituximab-containing chemoimmunotherapy backbone. Options include rituximab+Lymphome Malins de Burkitt (R-LMB), rituximab+cyclophosphamide+doxorubicin+methotrexate / ifosfamide+etoposide+cytarabine (R-CO-DOXM/IVAC), DA-R-EPOCH, rituximab+ German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia Protocol (R-GMALL), and rituximab+cyclophosphamide+vincristine+doxorubicin+dexamethasone alternating with rituximab+methotrexate+cytarabine (R-HyperCVAD).
- ▶ There was consensus that second-line treatment of BL in adults should consist of rituximab-containing chemoimmunotherapy regimens similar to those recommended for the first-line treatment of BL, with consolidation being identical to recommendations for consolidation in patients with DLBCL.

T cell lymphoma

- ▶ The panel did not reach consensus on a single recommended regimen for the first-line treatment of CD30+ PTCL. Treatment options include BV with cyclophosphamide+doxorubicin+prednisone (CHP), chemotherapy alone, or chemotherapy+autoSCT (if eligible).
- ▶ There was consensus that first-line treatment for CD30-negative PTCL should consist of an appropriate chemotherapy regimen+autoSCT.

- ▶ The panel did not reach consensus on a single recommended regimen for second-line treatment of PTCL in patients eligible for stem cell transplant. Treatment options include chemotherapy+autoSCT, chemotherapy+alloSCT, or HDAC inhibitors.
- ▶ There was consensus that second-line treatment for CD30+ PTCL in patients ineligible for stem cell transplant should consist of BV, up to 16 total doses.
- ▶ There was consensus that second-line treatment for CD30-negative PTCL should consist of HDAC inhibitors.
- ▶ Patients with anaplastic large cell lymphoma that is anaplastic lymphoma kinase-positive (ALK+) should not receive autoSCT.
- ▶ The panel did not reach consensus on a single recommended regimen for the first-line treatment of cutaneous TCL. Treatment options include BV, HDAC inhibitors, and an appropriate chemotherapy regimen.
- ▶ The panel did not reach consensus on a single recommended regimen for the second-line treatment of cutaneous TCL. Treatment options include HDAC inhibitors, an appropriate chemotherapy regimen (such as pralatrexate), and BV.

Post-transplant lymphoproliferative disorder

- ▶ The panel did not reach consensus on a preferred regimen for the treatment of B cell PTL. Treatment options include the withdrawal of immunosuppression, rituximab, appropriate chemoimmunotherapy regimens, and antiviral agents.
- ▶ The panel did not reach consensus on a preferred regimen for the treatment of T cell PTL. Treatment options include the withdrawal of immunosuppression, appropriate chemotherapy regimens, HDAC inhibitors, and antiviral agents.

Immunotherapies in development for NHL

A number of late-stage clinical trials are currently in progress for NHL (listed in [table 2](#)). Notably, new CAR T cell therapies including lisocabtagene maraleucel (a CAR T cell therapy targeted to CD19, being examined for the treatment of R/R B cell NHL) are currently in development.

CHRONIC LYMPHOCYTIC LEUKEMIA

FDA-approved immunotherapies for the treatment of chronic lymphocytic leukemia (CLL) are discussed in this section, ordered by history of clinical use.

Available agents and indications

Rituximab

Rituximab has been approved for the treatment of CLL in both first-line and R/R settings, in combination with fludarabine and cyclophosphamide (FC). In the phase III CLL-8 study (NCT00281918), patients received either rituximab+FC or FC for previously untreated CLL.¹²¹

Patients receiving rituximab+FC in this study exhibited significantly higher PFS at 5-year follow-up, 56.8 months compared with 32.9 months (HR 0.59; 95% CI 0.50 to 0.69; $p < 0.001$). The ORR with rituximab+FC was also significantly higher, at 90% versus 80% ($p < 0.001$).¹²² In the REACH trial (NCT00090051), patients with R/R CLL received rituximab+FC or FC alone.¹²³ Patients treated with rituximab+FC had significantly higher median PFS of 27.0 months versus 21.9 months (HR 0.76; 95% CI 0.60 to 0.96; $p = 0.0218$).¹²⁴ The ORR was also significantly higher in rituximab-treated patients (61% vs 49%; $p = 0.0048$).¹²⁴ Based on these results, in February 2010, the FDA approved the use of rituximab in combination with FC to treat CLL, with no restrictions related to prior therapy.³⁷

Another combination regimen including the BTK inhibitor ibrutinib with rituximab for the first-line treatment of CLL was approved by the FDA in April, 2020.¹²⁵ During the phase III E1912 trial (NCT02048813), patients received first-line ibrutinib+rituximab or rituximab+fludarabine+cyclophosphamide.¹²⁶ The median PFS was not reached for either group, but the percentage of progression-free patients was higher for those treated with ibrutinib at 3 years (89.4% vs 72.9%; HR 0.35; 95% CI 0.22 to 0.58; $p < 0.001$). OS was also significantly higher at 3 years for patients treated with ibrutinib (98.8% vs 91.5%; HR 0.17; 95% CI 0.05 to 0.54; $p < 0.001$).¹²⁷

Obinutuzumab

Obinutuzumab has been evaluated in the first-line setting for CLL. In CLL11 (NCT01010061), patients received obinutuzumab+chlorambucil, rituximab+chlorambucil, or chlorambucil alone.¹²⁸ Compared with chlorambucil alone, obinutuzumab+chlorambucil treatment was associated with a significantly longer median PFS of 31.1 months versus 11.1 months (HR 0.21; 95% CI 0.16 to 0.28; $p < 0.0001$) after median follow-up of 62.5 months. At a median follow-up of 59.4 months, patients treated with obinutuzumab+chlorambucil also exhibited a clear advantage in median PFS over patients treated with rituximab+chlorambucil, at 28.9 months versus 15.7 months (HR 0.49; 95% CI 0.41 to 0.58; $p < 0.0001$).¹²⁹ On the basis of data from CLL11, the FDA approved the use of obinutuzumab+chlorambucil for the first-line treatment of CLL in November 2013.⁷⁰

Ofatumumab

Ofatumumab, an anti-CD20 mAb, has been approved for the treatment of CLL as a first-line, maintenance, or salvage therapy. In the COMPLEMENT 1 trial (NCT00748189), patients with untreated CLL received chlorambucil with or without ofatumumab.¹³⁰ Treatment with ofatumumab+chlorambucil resulted in a significantly higher median PFS of 22.4 months versus 13.1 months (HR 0.57; 95% CI 0.45 to 0.72; $p < 0.0001$), which led to FDA approval of ofatumumab+chlorambucil for the first-line treatment of CLL in April 2017.^{131 132}

Table 2 Immunotherapies in development for the treatment of non-Hodgkin lymphoma

Trial	Agents investigated	Agent description	Primary outcome for assessment
POLARGO (NCT04182204)	Polatuzumab vedotin-piiq+R-GemOx vs R-GemOx for R/R DLBCL	ADC	Rate of adverse events, OS
POLARIX (NCT03274492)	Polatuzumab vedotin-piiq+R-CHP vs R-CHOP for first-line DLBCL	ADC	PFS
BELINDA (NCT03570892)	Chemotherapy+tsagenlecleucel vs Chemotherapy+autoSCT for R/R B cell NHL	CAR T cell	EFS
TRANSCEND-NHL-001 (NCT02631044)	Lisocabtagene maraleucel	CAR T cell	Treatment-related adverse events, dose-limiting toxicities, ORR
TRANSFORM (NCT03575351)	SOC (R-DHAP, R-ICE, or R-GDP; followed by HDCT (BEAM) and stem cell transplant) vs JCAR017 (lisocabtagene maraleucel) for R/R B cell NHL	CAR T cell	EFS
ZUMA-5 (NCT03105336)	Axicabtagene ciloleucel+cyclophosphamide+fludarabine for R/R indolent NHL	CAR T cell	ORR
ZUMA-7 (NCT03391466)	Axicabtagene ciloleucel vs SOC for R/R DLBCL	CAR T cell	EFS
NIVEAU (NCT03366272)	Nivolumab+R-GemOx vs R-GemOx for R/R B cell NHL	ICI	PFS
NCT03016000	Thalidomide maintenance for DLBCL	IMiD	Relapse-free survival
ROBUST (NCT02285062)	Lenalidomide+R-CHOP vs placebo+R-CHOP for first-line DLBCL	IMiD	PFS
B-MIND (NCT02763319)	BR vs MOR208 (tafasitamab-cxix)+bendamustine for R/R DLBCL	mAb	PFS
NCT01974440	Ibrutinib+BR or R-CHOP vs placebo+BR or R-CHOP for R/R indolent NHL	mAb and BTKi	PFS
NCT04002297	Zanubrutinib+rituximab vs BR for first-line MCL	mAb and BTKi	PFS
NCT04212013	Ibrutinib+rituximab vs Ibrutinib+placebo	mAb and BTKi	CR rate
CHRONOS-3 (NCT02367040)	Copanlisib+rituximab vs placebo for R/R B cell NHL	mAb and PI3Ki	PFS
CHRONOS-4 (NCT02626455)	Copanlisib+rituximab-chemotherapy vs placebo+rituximab-chemotherapy for R/R indolent NHL	mAb and PI3Ki	Rate of dose-limiting toxicities/AEs, PFS
UNITY-NHL (NCT02793583)	TGR-1202+ublituximab vs TGR-1202 vs TGR-1202+ublituximab+bendamustine for R/R NHL	mAb and PI3Ki	ORR
NCT02320292	Rituximab+IT vs rituximab for first-line FL	Radioimmunotherapy	CR rate

ADC, antibody-drug conjugate; AEs, adverse events; AutoSCT, autologous stem cell transplant; BR, bendamustine, rituximab; BTKi, Bruton's tyrosine kinase inhibitor; CAR, chimeric antigen receptor; CR, complete response; DA-R-EPOCH, dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; DLBCL, diffuse large B cell lymphoma; EFS, event-free survival; FL, follicular lymphoma; ICI, immune checkpoint inhibitor; IMiD, immunomodulatory drug; mAb, monoclonal antibody; MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI3Ki, phosphoinositide 3-kinase inhibitor; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CHP, rituximab, cyclophosphamide, doxorubicin, prednisone; R-GemOx, rituximab, gemcitabine, oxaliplatin; R/R, relapsed or refractory; SOC, standard of care.

Ofatumumab also demonstrated clinical benefit as a maintenance therapy in the phase IV PROLONG trial (NCT00802737), which enrolled patients with prior response to ofatumumab.¹³³ Patients who received ofatumumab maintenance exhibited longer PFS, with a median of 30.4 months versus 14.8 months (HR 0.55; 95% CI 0.42 to 0.72; $p < 0.0001$).¹³⁴ In January 2016, the FDA approved the use of ofatumumab as maintenance therapy for patients with CLL in CR or PR following at least two lines of therapy.¹³²

In the setting of R/R CLL, ofatumumab has been the subject of multiple trials. During COMPLEMENT 2 (NCT00824265), patients with R/R CLL were administered FC with or without ofatumumab; patients treated in the ofatumumab arm had significantly longer median PFS, at 28.9 months versus 18.8 months (HR 0.67; 95% CI 0.51 to 0.88; $p = 0.0032$).^{135 136} The ORR was also significantly higher in the ofatumumab treatment arm—84% versus 68% ($p = 0.0003$).¹³⁶ In August 2016, the FDA approved ofatumumab+FC for the treatment of relapsed CLL.¹³² During the single-arm NCT00349349 trial, patients with R/R CLL who had previously received fludarabine and alemtuzumab were treated with ofatumumab monotherapy.¹³⁷ The ORR was 58% (99% CI 40% to 74%) with median PFS of 5.7 months (95% CI 4.5 to 8.0).¹³⁸ Based on NCT00349349, the FDA approved ofatumumab for the treatment of R/R CLL in patients who have previously been treated with fludarabine and alemtuzumab in October 2009.¹³²

Alemtuzumab

Alemtuzumab, an anti-CD52 mAb, has been approved for the treatment of B cell CLL as a monotherapy. In the phase III CAM307 trial (NCT00046683), alemtuzumab

was compared with chlorambucil as first-line therapy for CLL.¹³⁹ Patients receiving alemtuzumab exhibited prolonged PFS, at a median of 14.6 months versus 11.7 months (HR 0.58; 95% CI 0.43 to 0.77; log-rank $p = 0.0001$).¹⁴⁰ Based on the results of CAM307, the FDA approved the use of alemtuzumab for the first-line treatment of CLL in September 2007, expanding the existing indication to include all B cell CLL.¹⁴¹

Alemtuzumab also demonstrated safety and efficacy in the treatment of R/R CLL during three single-arm studies with reported ORRs of 42% (95% CI 23% to 61%), 33%, and 31%.^{142–144} Based on an analysis of these studies, in May 2001 the FDA approved the use of alemtuzumab for the treatment of R/R CLL.¹⁴¹

Panel recommendations

- ▶ The panel did not reach consensus on preferred regimens for the first-line or second-line treatment of CLL. Options include targeted therapy (if eligible) and chemoimmunotherapy regimens, which may include rituximab, obinutuzumab, ofatumumab, and alemtuzumab.

Immunotherapies in development for CLL

Late-stage clinical trials evaluating novel agents and new combinations of immunotherapies for the treatment of CLL are listed in [table 3](#).

INTEGRATION OF HEMATOPOIETIC STEM CELL TRANSPLANT AND IMMUNOTHERAPIES

Stem cell transplant has been and remains a mainstay treatment option with curative potential for patients with lymphoma.^{145–147} Indeed, one can consider alloSCT

Table 3 Immunotherapies in development for the treatment of chronic lymphocytic leukemia

Trial	Agents investigated	Agent description	Primary outcome for assessment
ZUMA-8 (NCT03624036)	brexucabtagene autoleucel for R/R CLL	CAR T cell	Rate of dose-limiting toxicity, ORR
TRANSCEND-CLL-004 (NCT03331198)	JCAR017 (lisocabtagene maraleucel) vs JCAR017+ibrutinib for R/R CLL	CAR T cell and BTKi	Recommended dose, rate of AEs, rate of laboratory abnormalities, CR rate
NCT00774345	Lenalidomide vs placebo for maintenance of CLL	IMiD	OS, PFS
GAIA (NCT02950051)	Rituximab-FC+venetoclax vs obinutuzumab+venetoclax vs obinutuzumab+venetoclax+ibrutinib for first-line CLL	mAb	MRD negativity rate, PFS
GENUINE (NCT02301156)	Ublituximab+ibrutinib vs ibrutinib	mAb	ORR, PFS
UNITY-CLL (NCT02612311)	Ublituximab+TGR-1202 vs obinutuzumab+chlorambucil vs ublituximab vs TGR-1202 for first-line and R/R CLL	mAb	PFS

AEs, adverse events; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CR, complete remission; FC, fludarabine, cyclophosphamide; IMiD, immunomodulatory drug; mAb, monoclonal antibody; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed or refractory.

one of the oldest and most successful forms of immunotherapy for lymphoma with the ability to generate a graft-versus-lymphoma effect. The introduction of novel immunotherapies, however, has given rise to a number of questions concerning optimal scheduling with and around stem cell transplant. There are many questions to consider, including whether to schedule immunotherapy pre-transplant or post-transplant, and whether immunotherapy may alter transplant efficacy, which have yet to be conclusively resolved in the clinic. Specifically, ICIs are a source of concern, since these therapies have the potential to induce lasting changes in the host immune system, which could conceivably increase the risk of complications following transplantation (eg, graft vs host disease (GVHD)). There is also a theoretical concern that using CAR T cells collected from patients after alloSCT, when they are likely to be of donor origin, could induce GVHD.

Modality-specific considerations

Immune checkpoint inhibitors

Both nivolumab and pembrolizumab, which are currently approved for the treatment of select lymphomas, are typically administered in contexts where patients have already undergone autoSCT. In this setting, ICIs have exhibited promising response rates and tolerable levels of toxicity.^{27 148} In contrast, little data currently exists regarding the administration of ICIs prior to autoSCT for patients with lymphoma.

AlloSCT, when used in conjunction with ICI therapy, appears to carry some risk of AEs, including GVHD. In a retrospective analysis of 31 cHL patients receiving nivolumab or pembrolizumab following alloSCT, ORR was 77% (95% CI 58% to 90%), but 55% (n=17) of patients developed GVHD (19% acute (n=6), 23% chronic (n=7), and 13% acute/chronic overlap (n=4)).¹⁴⁹ Similarly, a retrospective analysis of 107 patients from seven studies who received ICIs prior to alloSCT exhibited an ORR of 68%, but 56% of patients developed acute GVHD and 29% developed chronic GVHD. 60% of patient deaths reported were GVHD-related.¹⁵⁰ Another analysis of patients who received anti-PD-(L)1 inhibitors prior to alloSCT demonstrated that patients were at higher risk of acute GVHD if time to transplant was short, and that prophylactic cyclophosphamide improved patient outcomes while reducing the risk of chronic GVHD.¹⁵¹ Generally, the use of ICIs in conjunction with alloSCT may result in improved response rates, but caution must be exercised due to the high likelihood of GVHD. Future studies may also identify ways to integrate these two therapeutic methods while minimizing the risk of GVHD.

CAR T cell therapies

Concerning CAR T cell therapies, confirmatory clinical trials resulting in approval of tisagenlecleucel and axicabtagene ciloleucel included patients who had received prior autologous stem cell transplant, and reported consistent

efficacy across subgroups.^{112 152} There is ongoing debate in the field of lymphoma treatment as to the potential for CAR T cell therapy to be used in conjunction with, or to replace, traditional autoSCT.^{153 154}

Little data exists regarding the use of CAR T cell therapy in conjunction with alloSCT for the treatment of lymphoma. In patients with a different hematological malignancy, B cell acute lymphoblastic leukemia, anti-CD19 CAR T cell therapies have been successfully used as a bridge therapy to enable subsequent alloSCT, with promising rates of CR and no reported incidence of GVHD.^{155 156} This result may serve as a blueprint for future research in the use of alloSCT after CAR T cell therapies.

Panel recommendations

- ▶ There was consensus that ICI and CAR T cell therapy are both acceptable after a patient has received autoSCT. The panel did not reach consensus on the subject of whether ICIs or CAR T cell therapy should be administered prior to autoSCT.
- ▶ There was consensus that CAR T cell therapy is safe and could be considered following alloSCT, if the patient does not have active GVHD or require immunosuppression. Caution should also be exercised for patients with a history of severe GVHD.
- ▶ The panel did not reach consensus on the subject of whether ICIs should be considered contraindicated before or after alloSCT.

RECOGNITION AND MANAGEMENT OF IRAES

Management of AEs that may arise during administration of immunotherapies is an important and ongoing area of research. Additionally, the administration of CAR T cell therapies carries the risk of cytokine release syndrome (CRS) and/or neurotoxicities, both of which can be fatal if not properly identified and managed. Potentially life-threatening toxicities are noted through a 'black box warning' on FDA labeling information. A summary of black box warnings for immunotherapies discussed in this document can be found in [table 4](#).

CRS and CNS events

CRS and CNS events are of primary concern during CAR T cell therapy, although they have also been reported after treatment with other forms of immunotherapy, such as nivolumab and rituximab.^{157–160} One hallmark of CRS is profoundly increased interleukin (IL)-6 serum concentration, and treatment with the IL-6 receptor antagonist tocilizumab has been demonstrated to be effective in mitigating this AE.¹⁶¹ Indeed, tocilizumab was approved by the FDA to manage CRS concurrently with the initial approval of tisagenlecleucel.¹⁶² Corticosteroids are also frequently used together with tocilizumab to manage CRS, as well as alone, in refractory cases.^{155 163} Importantly, tocilizumab does not alleviate ICANS. Currently, corticosteroids are commonly administered for ICANS,

Table 4 Food and Drug Administration black box warnings for lymphoma immunotherapies

Therapy	Warning due to
Alemtuzumab	<ul style="list-style-type: none"> ▶ Autoimmune conditions (immune thrombocytopenia, anti-glomerular basement membrane disease) ▶ Severe infusion reactions ▶ Anaphylaxis ▶ Cancer (thyroid, melanoma, lymphoproliferative disorders) ▶ Infections
Axicabtagene ciloleucel	<ul style="list-style-type: none"> ▶ CRS ▶ ICANS ▶ Do not administer to patients with active infection or inflammatory disorders
Brexucabtagene autoleucel	<ul style="list-style-type: none"> ▶ CRS ▶ ICANS ▶ Do not administer to patients with active infection or inflammatory disorders
Brentuximab vedotin	<ul style="list-style-type: none"> ▶ PML
Ibritumomab tiuxetan	<ul style="list-style-type: none"> ▶ Severe infusion reactions ▶ Severe cytopenia ▶ Severe cutaneous/mucocutaneous reactions ▶ Do not administer if patient exhibits altered biodistribution
Lenalidomide	<ul style="list-style-type: none"> ▶ Embryo-fetal toxicity (pregnancy must be excluded prior to treatment) ▶ Significant neutropenia, thrombocytopenia
Obinutuzumab	<ul style="list-style-type: none"> ▶ Hepatitis B virus reactivation ▶ PML
Rituximab (and biosimilars)	<ul style="list-style-type: none"> ▶ Severe infusion reactions ▶ TLS ▶ Severe mucocutaneous reactions ▶ PML ▶ Hepatitis B virus reactivation
Tisagenlecleucel	<ul style="list-style-type: none"> ▶ CRS ▶ ICANS ▶ Do not administer to patients with active infection or inflammatory disorders

CNS, central nervous system; CRS, cytokine release syndrome; PML, progressive multifocal leukoencephalopathy; TLS, tumor lysis syndrome.

and how to best manage neurological toxicities remains an active and important area of study.^{164–166}

Infusion reactions

Infusion reactions with immunotherapies include both typical hypersensitivity (allergic, immune-mediated) and non-allergic reactions.^{167 168} Despite some similarities in

symptoms, infusion reactions should not be confused with tumor-lysis syndrome (TLS), which is a distinct AE resulting from the widespread lysis of tumor cells following administration of therapy (whereas infusion reactions represent a response to the therapy itself). Allergic reactions are relatively uncommon, but are potentially serious and can lead to anaphylaxis.^{169–172} Infusion reactions, by contrast, are common when mAbs are administered to patients or following autoSCT/alloSCT, and are typically short-lived. While the majority of infusion reactions are mild, a small percentage are severe and can be fatal.^{173 174}

In the case of mAbs, infusion reactions are most common on first infusion, with frequency decreasing during subsequent infusions.^{170 175} Of the therapies discussed in this guideline, rituximab carries the greatest risk of infusion reactions, with 77% of patients developing a reaction on first infusion.³⁷ In the case of CAR T cell infusion, one analysis estimated that infusion reactions occurred in 12.6% of patients who received ex vivo manipulated T cells (including CAR T cells), and were typically mild.¹⁷⁶ More detailed guidance on the management of infusion reactions may be found in published guidelines.¹⁷⁷

Tumor-lysis syndrome

TLS, occurring due to a sudden and massive release of metabolites after widespread lysis of tumor cells, is also a potential side effect of immunotherapies, and the risk of TLS is especially high in patients with hematological malignancies and high disease burdens.¹⁷⁸ A systematic review of TLS in patients with hematological malignancies determined that the incidence of TLS after treatment with immunotherapy ranged from no recorded TLS cases (ofatumumab) to as much as 10% (CAR T cell therapies).¹⁷⁹ TLS can be managed through a combination of prophylactic methods such as hydration and hypouricemic agents like allopurinol, and reactive methods like dialysis.¹⁸⁰

Immune-related adverse events

In addition to the toxicities listed earlier, a number of irAEs, collectively termed irAEs, are associated with ICIs. These irAEs frequently resemble autoimmune reactions, and can manifest with a wide variety of symptoms affecting several distinct organ systems.^{181 182} The most commonly diagnosed irAEs include rash, pruritus, fatigue, diarrhea/colitis, endocrinopathies, hepatic toxicities, and pneumonitis.¹⁸¹ Treatment of irAEs commonly involves temporary withdrawal of therapy (in the case of ICIs) and management of symptoms with corticosteroids.¹⁸³ Severe (\geq grade 3) irAEs may necessitate permanent cessation of the immunotherapy and/or additional immunosuppressive agents.¹⁸³ In contrast to toxicities arising from conventional cancer treatment modalities, toxicity from immunotherapy can occur after a significant delay, sometimes arising months, or years, after a treatment regimen has been discontinued.¹⁸⁴ Based on currently available data, there is no direct evidence that patients with lymphoma being treated with immunotherapies are any more or

less likely to experience AEs compared with patients with solid tumors being treated with the same agents.

More detailed discussion of ICI-associated irAEs, which have a very wide range of clinical manifestations, is beyond the scope of this manuscript. Guidance on the management of toxicity and irAEs in patients treated with ICIs may be found in SITC's Guide to Managing Immunotherapy Toxicity, or in other published guidelines.^{182 183 185 186}

PATIENT CONSIDERATIONS FOR IMMUNOTHERAPY IN THE TREATMENT OF LYMPHOMA

To ensure both safety and efficacy, patient characteristics including age, history of viral infection, and immune system function must be considered when determining whether a patient with lymphoma should be a candidate for immunotherapy. For example, lymphoma can arise in both pediatric and elderly patient populations, presenting questions of tolerability and fitness. Research suggests that HIV, hepatitis C virus (HCV), and EBV viral infections can give rise to lymphoma, so the possibility of viral reactivation after immunotherapy is another risk, especially in the case of treatment regimens that result in the elimination of patient B cells.^{187–189} Additionally, immune system function and lymphocyte count must be considered prior to a decision to proceed with CAR T cell therapy or other therapies that rely on the collection of autologous T cells.

Patients with viral infections

No unique exclusion criteria exist for the treatment of patients with lymphoma with FDA-approved immunotherapies compared with approvals granted in other disease settings. The field of oncology in general, however, does often consider specific circumstances where immunotherapy administration may worsen a pre-existing condition. In particular, any form of adoptive cell therapy, including CAR T cell therapies, autoSCT, and alloSCT, may be contraindicated by the presence of active bacterial or viral infections. Concerns have also been noted regarding the possibility that CAR T cell therapies could impair host humoral immunity through the removal of healthy B cells and subsequent loss of, for example, antibody titers to common vaccines. An analysis of 39 adults with durable remission of B cell malignancies following anti-CD19 CAR T cell therapy noted that, while total IgG was reduced, measles-specific IgG remained similar to pre-CAR T cell infusion levels. Further, patients were evaluated to determine the number of viruses and viral epitopes to which there was a detectable antibody response. Pre- and post-CAR T cell therapy, the median numbers of viruses (10 vs 10) and the median numbers of viral epitopes (144 vs 139) were similar, suggesting that humoral immunity was not strongly affected by CAR T cell treatment.¹⁹⁰ Detailed guidelines on best practices in this area are outside the scope of this manuscript, but have been published by other societies.¹⁹¹

Patients with HIV have historically been excluded from receiving immunotherapies due to limited information concerning potential effects on a patient's weakened immune system. Of importance, HIV is a risk factor for the development of NHL, so the incidence of lymphoma in patients with HIV is increased compared with other disease settings.¹⁸⁸ Recent data investigating checkpoint inhibitor safety in HIV+ patients with cancer enrolled in the CITN-12 trial—including three patients with lymphoma—showed that the overall irAE profile resembled what was seen in clinical trials limited to HIV-negative patients.^{192 193} Additional studies of patients with HIV include the prospective DURVAST trial (NCT03094286), which included 20 patients with solid tumors and HIV treated with durvalumab, and a meta-analysis of 73 patients with HIV and advanced cancer treated with ICIs. In both of these studies, rates of AEs were similar to those seen in the general population, and no significant effects on CD4+ T cell counts or HIV load were detected.^{194 195} Similarly, two retrospective studies of 23 and 16 patients with HIV and a variety of cancer types found that treatment with anti-PD-1 ICIs was well-tolerated, with no significant effect on CD4+ T cell counts or HIV load, and that anti-PD-1 ICIs appeared to be efficacious despite the potential for patients with HIV+ to be immunocompromised.^{196 197} Additional trials specifically examining the efficacy and safety of ICIs in HIV+ patients with lymphoma are ongoing, and include AMC 095 (NCT02408861), which is recruiting patients with HIV-associated cHL or solid tumors.¹⁹⁸ As with ICIs, patients with HIV have been commonly excluded from CAR T cell therapy trials. However, a small case series showed that axicabtagene ciloleucel treatment can induce responses in HIV+ DLBCL patients without causing significant toxicity.^{199 200}

Rituximab has also been the subject of extensive study for the treatment of HIV+ patients with lymphoma. A pooled analysis of AIDS-Malignancy Consortium trials of R-CHOP and R-EPOCH for HIV-associated NHL found that patients (n=150) with CD4+ T cell counts ≥ 50 cells/ μ L exhibited typical rates of treatment-related mortality (6% for R-CHOP and 5% for R-EPOCH).²⁰¹ Another study of 52 patients with HIV-associated NHL found that R-CHOP was efficacious (CR rate 77%) and did not result in large numbers of infections or AIDS-related events, although CD4+ T cell counts of < 100 cells/ μ L were associated with treatment failure.²⁰²

Reactivation of hepatitis has been reported in patients treated with immunogenic mAbs including rituximab and BV, among others. In one example, 26.3% of HCV+ patients with NHL treated with EPOCH-R experienced viral reactivation, compared with 2.1% in uninfected patients.²⁰³ However, antiviral prophylaxis may be effective in the prevention of hepatitis reactivation during ICI therapy. During the CheckMate 040 and the KEYNOTE-224 trials, which included HBV+ and HCV+ patients with hepatocellular carcinoma, anti-HBV prophylaxis was required and no viral flares were detected.^{204 205}

Members of the herpesvirus family may also reactivate in patients who are latently infected. For example, a retrospective study of 46 NHL patients (all of whom were seropositive for cytomegalovirus (CMV)) observed that patients who were treated with rituximab following autoSCT were significantly more likely to experience CMV reactivation than patients who were not (17.6% vs 0%, respectively).²⁰⁶ Treatment with alemtuzumab may also increase the risk of CMV reactivation. A multi-hospital study of 102 patient outcomes determined that the risk of CMV reactivation following treatment with alemtuzumab was 38.9% (although this was not directly compared with patients not receiving alemtuzumab).²⁰⁷

Another notable virus that carries a risk of reactivation during immunotherapy is polyoma virus JC, or JC virus. JC virus exists in a latent state in brain tissue in a significant portion of the population, and viral reactivation may lead to progressive multifocal leukoencephalopathy (PML), a serious and potentially fatal disease.^{208 209} Due to the risk of this severe complication, a number of immunotherapies, including BV, rituximab, and obinutuzumab, have received black box warnings from the FDA (table 4) for JC virus reactivation. Fortunately, the development of PML appears to be a rare occurrence. A retrospective analysis following rituximab treatment in NHL patients found five cases of PML in 821 patients, or 0.6% of patients.²¹⁰ In comparison, patients with hematological malignancies as a whole develop PML at an estimated rate of 0.07%.²¹¹

Patients with bacterial infections

The presence of active bacterial infection is typically considered a contraindication to adoptive cell therapies due to potential exacerbation of infection with immunosuppressive conditioning regimens. In at least one case study, a death following CAR T cell therapy for the treatment of CLL was attributed to a cryptic infection leading to fatal sepsis, although the patient's blood cultures were negative prior to infusion.²¹²

Patients of advanced age

The median age for diagnosis of NHL is 67, and higher patient age is associated with poorer prognosis.^{213–215} A number of clinical trials have yielded data for patients of advanced age (≥ 65 years), and have demonstrated that efficacy is not compromised for most forms of immunotherapy. In a subgroup analysis of cHL patient trials, ORRs following nivolumab treatment were similar between patients less than 65 years of age and older patients, but the patients greater than 65 years of age exhibited a higher rate of grade 3 or grade 4 irAEs (37.5% in <65 , 42.9% in ≥ 65).²¹⁶ A trial treating cHL patients with pembrolizumab also demonstrated similar rates of response between the younger than 65 and older than 65 cohorts.³² CAR T cell therapy exhibits similar response rates across age groups, with NHL patients over 65 in the ZUMA-1 clinical trial experiencing comparable outcomes to other patient groups.^{152 217} Despite these promising results, elderly patients are underrepresented in clinical trials of

ICI therapies, and a number of trials that have included elderly patients did not analyze age-based subgroups.²¹⁸ Further research in this area is warranted, especially considering the high number of elderly patients with lymphoma.

Patients with pre-existing autoimmune disorders

Patients with autoimmune diseases have not been included in most clinical trials of ICIs. Because the irAEs associated with ICI therapy resemble some autoimmune disorders, and because ICIs function by interfering with the mechanisms that prevent autoimmunity, it was believed that these patients would be at increased risk for irAEs and for flare-ups of existing autoimmune disorders. However, the potential use of ICIs in these patients is important to study due to the efficacy of ICIs in cancer treatment. This is especially relevant to the treatment of lymphomas, since some autoimmune disorders (including Sjögren syndrome, systemic lupus erythematosus, and hemolytic anemia) are associated with an elevated risk of NHL.²¹⁹

A retrospective study of 30 melanoma patients with autoimmune diseases who received ipilimumab (an anti-CTLA-4 ICI) showed that 27% of patients had an exacerbation of their existing autoimmune disease, while 33% of patients experienced conventional grade 3–5 irAEs.²²⁰ Another study of 56 patients with non-small cell lung cancer and an existing autoimmune disease found that 23% of patients experienced exacerbation of existing autoimmunity and 38% of patients developed an irAE (26% of irAEs were grade 3 or grade 4) following treatment with PD-1 inhibitor treatment.²²¹ These results indicate that while ICIs may cause exacerbations of existing autoimmune conditions, patients treated with anti-PD-(L)1-axis ICIs do not appear to develop new irAEs more frequently than patients without autoimmune diseases. The possibility of a flare-up should be weighed based on the autoimmune disease that is present as some autoimmune disorders are more dangerous than others when active. It is important to note that because the aforementioned data on patients with autoimmune disorders was gathered from studies of patient with solid tumors, patients with lymphoma and existing autoimmune disorders may respond differently.

Patients who have received solid organ transplant

Historically, patients who have previously received solid organ transplants have been excluded from trials involving immunotherapies, owing to concerns that enhanced immune activation could lead to increased rates of transplant rejection or graft loss. However, since the clinical introduction of ICIs, a number of patients with solid organ transplants have undergone ICI therapy. In a retrospective study of 39 patients fitting these criteria, 41% experienced allograft rejection following initiation of ICI therapy. Within the group of patients experiencing rejection, 13 patients (81%) progressed to graft loss.²²² Given this result, it is clear that further research is needed on the safety and efficacy of cancer immunotherapy in

solid organ transplant recipients, and that caution should be exercised in the use of immunotherapy within this group of patients.

Panel recommendations

- ▶ There was consensus that patients with an existing autoimmune disorder that requires immunosuppressive therapy should not receive ICIs.
- ▶ The panel did not reach consensus on the subject of whether patients with active bacterial infections should receive ICI therapy. There was consensus that patients with active bacterial infections should not receive CAR T therapy, autoSCT, or alloSCT.
- ▶ The panel did not reach consensus on the subject of whether patients with active viral infections should receive ICI therapy or autoSCT. There was consensus that patients with active viral infections should not receive CAR T therapy or alloSCT.
- ▶ Patients with HIV and lymphoma should be considered for immunotherapy, provided that their HIV infection is well controlled.
- ▶ Patients should be evaluated for HBV and HCV prior to initiating immunotherapy. If patients are positive for HBV or HCV, immunotherapy may be considered provided that an appropriate antiviral is initiated.
- ▶ There was consensus that patients with active inflammatory disorders should not receive CAR T cell therapy.
- ▶ There was consensus that elderly patients should be considered for immunotherapy and for stem cell transplant.

PATIENT SUPPORT AND QUALITY OF LIFE ISSUES

Immunotherapies can be complex in terms of their administration and monitoring requirements, and often require extensive education for both providers and patients to ensure optimal outcomes. As AEs that arise during immunotherapeutic treatment have unique underlying mechanisms compared with AEs that arise during treatment with chemotherapy and/or radiotherapy, it is imperative that patients can effectively communicate with healthcare providers concerning the treatments they have received or are currently receiving as well as the symptoms they may be experiencing. Additionally, many patients receive immunotherapies only in advanced disease settings after being heavily treated previously, which brings forth a number of quality of life (QOL) considerations.

Immunotherapy encompasses multiple complex treatment modalities that require education for healthcare providers to ensure optimal patient management. Education is especially important for management of AEs that may arise during treatment with an immunotherapy, as these toxicities are predicated on different underlying biological mechanisms compared with similar events that arise during treatment with other modalities.¹⁸³ To assist in this regard, many programs currently advocate for increased patient outcome reporting to assess toxicities as well as value.²²³

As immunotherapies for lymphoma are numerous, diverse, and approved for specific settings only, confusion on the part of both patients and healthcare professionals can exist regarding appropriate treatment scheduling. In general, many patients with cancer are unaware of the opportunities for treatment with immunotherapy for their given disease. According to patient attendee survey data presented by Cancer Support Community at the 2017 SITC Annual Meeting and Pre-Conference Programs, 47.2% of respondents were not confident in immunotherapy being appropriate for treatment of their disease, and only 33% of respondents had discussed immunotherapy as an option with their physician.²²⁴

A patient's health-related quality of life (HRQOL) is an important consideration during the administration of any therapy. There has been a general trend in the modern era towards improvement in assessing HRQOL through patient self-reporting both during clinical trials and during standard treatment.^{225 226} A number of tools have been developed to assess patient-reported outcomes of toxicity and HRQOL, including the patient-reported outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE),²²⁷ the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30),²²⁸ and the MD Anderson Symptom inventory (MDASI).²²⁹ In studies of patients with lymphoma receiving immunotherapies, immunotherapies appear to compare favorably to other therapies. HRQOL data from the phase III MAVORIC trial on patients with cutaneous TCL showed that mogamulizumab compared favorably to chemotherapy at all stages of treatment.²³⁰ Additionally, HRQOL for patients receiving CAR T cell therapy was not significantly different from HRQOL in patients receiving autoSCT or alloSCT in a study of 45 patients with hematological malignancies.²³¹

CAR T cell therapies hold unique considerations for patient QOL beyond typical concerns about AEs and financial toxicity. Due to the nature of CAR T cell therapy as populations of living cells within the body and the possibility of severe AEs such as CRS and ICANS, the approved products are all sold under a risk evaluation and mitigation strategy (REMS) that mandates patients remain within 2 hours of the treatment facility where CAR T cell therapy was administered for at least 4 weeks after CAR T cell infusion.^{232 233} These REMS for each product also mandate monitoring requirements: once daily for 1 week post-infusion for axicabtagene ciloleucel and brexucabtagene autoleucel, and two to three times in the week post-infusion for tisagenlecleucel.^{111 113} Furthermore, patients treated with CAR T cells must carry a wallet card at all times to ensure correct triage and specialist care in an emergency.^{232 233} However, though many patients had symptoms of fatigue and some may have prolonged cytopenias and hypogammaglobulinemia, the majority of toxicities occur in the first 2–3 weeks after infusion. This is quite favorable compared with the often prolonged courses of typical chemotherapy regimens, or the very

long convalescence period required for most patients after alloSCT. CAR T cell therapies do hold a significant risk of financial toxicity, however, given their high cost and considerable requirements for patient monitoring.²³⁴

The financial burden that patients with cancer bear has increased dramatically in recent times, partially due to the introduction of novel, high-cost therapies. In many cases, recently introduced therapies (such as CAR T cell therapies) present difficulties in obtaining adequate reimbursement from health insurance or programs such as Medicare and Medicaid.^{235 236} Financial toxicity can, in turn, reduce the quality of care that patients can afford and reduce patient QOL.^{237–239} CAR T cell therapies are expensive, in the range of \$373 000 for lymphoma treatment, not including post-treatment care and management of toxicities. With difficulties in obtaining payer support from insurers or Medicaid, the cost of CAR T cell therapies may represent an insurmountable obstacle for a number of patients who would otherwise be well-suited to the therapy.^{240 241}

Considerations of the value of immunotherapy is beyond the scope of this manuscript, but as CAR T cell therapies have provided durable responses in patients with lymphoma, a limited discussion concerning the introduction of ‘off-label’ CAR T cell therapy into earlier lines of treatment may be warranted. Current FDA approvals limit axicabtagene ciloleucel and tisagenlecleucel to third-line or later treatment options in patients with select NHLs.^{232 233} There are seemingly no biological limitations, however, preventing the introduction of CAR T cell therapies into earlier lines of treatment, other than the limitation of potentially fatal AEs compared with those observed via induction chemotherapy, which is effective in a significant number of patients with lymphoma.

Panel recommendations

- ▶ There was consensus that patient reporting on toxicity and QOL issues should be emphasized for patients receiving immunotherapy, and that these patients should receive educational tools regarding immunotherapy and these potential issues.
- ▶ There was consensus that financial burden influences the availability and scheduling of immunotherapy treatments. Insurance coverage was noted as a major financial barrier.
- ▶ There was consensus that the extended time needed for cell therapy manufacturing and high financial burden are likely to impair clinical trials of cell-based therapies, such as CAR T cell therapy.

CONCLUSION

The rapid introduction and clinical implementation of new immunotherapies has revolutionized oncology and led to tremendous improvements in outcomes specifically for patients with lymphoma, especially in the advanced setting. Multiple novel immunotherapeutic strategies have been approved or are in development for the treatment of patients with Hodgkin and NHLs, as well as CLL,

including mAbs, ICIs, ADCs, and CAR T cell therapies. Further innovations will likely bring about even greater improvements for patient outcomes. The treatment recommendations within this manuscript represent the consensus of the SITC Lymphoma Immunotherapy Guideline expert panel based on the evidence available at the time of publication. As the field continues to move forward, the expert panel will evaluate the potential need for updates to recommendations in this CPG.

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