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Follow-Up VISIT from PER®



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3 Things You Should Know About Immunotherapy in DLBCL

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LEARNING OBJECTIVES

Upon successful completion of this activity, you should be better prepared to:

- Assess recent pivotal trial data investigating targeted agents in patients with DLBCL across multiple lines of care.
- Select appropriate treatment strategies for patients with relapsed/refractory DLBCL considering efficacy, safety, and patient-specific factors to optimize patient outcomes.
- Discuss mechanisms of treatment resistance/lack of response in patients with DLBCL and how they can affect treatment sequencing in DLBCL.

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Cytotoxic T cells play a vital role in the body's immune defense against tumors. However, their effectiveness can be limited by factors such as the immunosuppressive nature of the tumor microenvironment and the scarcity of T cells that naturally recognize tumor-specific neoantigens. Here are 3 things you should know about immunotherapy in diffuse large B-cell lymphoma (DLBCL).

1 CAR T-cell therapy enhances the immune response to DLBCL.

Chimeric antigen receptor (CAR) T-cell therapy aims to enhance the antitumor capabilities of the adaptive immune system by collecting a patient's T cells and modifying them genetically to express a receptor that specifically targets an antigen expressed on the patient's tumor cells (**Figure 1**).

CD19-targeting CAR T-cell therapy consisting of either axicabtagene ciloleucel (axi-cel) or lisocabtagene maraleucel (liso-cel) is the recommended second-line therapy for patients with DLBCL who are not sensitive to chemotherapy, meaning that their disease is refractory to treatment or that it relapses within the first 12 months of first-line chemotherapy.¹ Liso-cel is also a second-line therapy option for patients who do not intend to proceed to hematopoietic stem cell transplant (HSCT) based on results from the phase 2 PILOT study (NCT03483103).² In this clinical trial, investigators administered liso-cel to 61 patients aged at least 70 years whose disease relapsed after first-line therapy

who met at least 1 prespecified criterion for transplantation not intended. The overall response rate was 80% (95% CI, 68%-89%); a complete response (CR) was noted in 54% of patients. Median event-free survival (EFS) was 7.23 months (95% CI, 3.22-22.60 months). Median overall survival (OS) was not reached (NR) (95% CI, 17.28 months to NR). The most common treatment-emergent adverse events (TEAEs) of grade 3 or 4 were neutropenia (48%), leukopenia (21%), and thrombocytopenia (20%). Cytokine release syndrome (CRS) is an AE of special interest with CAR T-cell therapy; it occurred in 38% of patients in this study, including 1 grade 3 case. Neurological events, including 3 grade 3 cases, also occurred in 31% of patients.

Axi-cel was tested in the open-label, phase 2 ALYCANTE trial (NCT04531046) as second-line therapy in 62 patients aged at least 65 years with relapsed/refractory (R/R) LBCL who are ineligible for HSCT.³ The objective response rate (ORR) was 90%, including 79% of patients who had a CR. Median EFS was 12.3 months (95% CI, 7.2 months to NR). Median progression-free survival (PFS) was 11.8 months (95% CI, 8.4 months to NR). Both median OS and duration of response were not reached. Some 95.2% of patients experienced AEs of grade 3 or greater including neutropenia (66.1%), anemia (38.7%), and thrombocytopenia (38.7%). CRS was reported in 93.5% of patients, including grade 3 or 4 CRS in 8.1% of patients. Immune effector cell-associated neurotoxicity (ICANS) was reported in 51.6% of patients, including grade 3 or 4 ICANS in 14.5% of patients.

FIGURE 1. Overview of CAR T-Cell Therapy

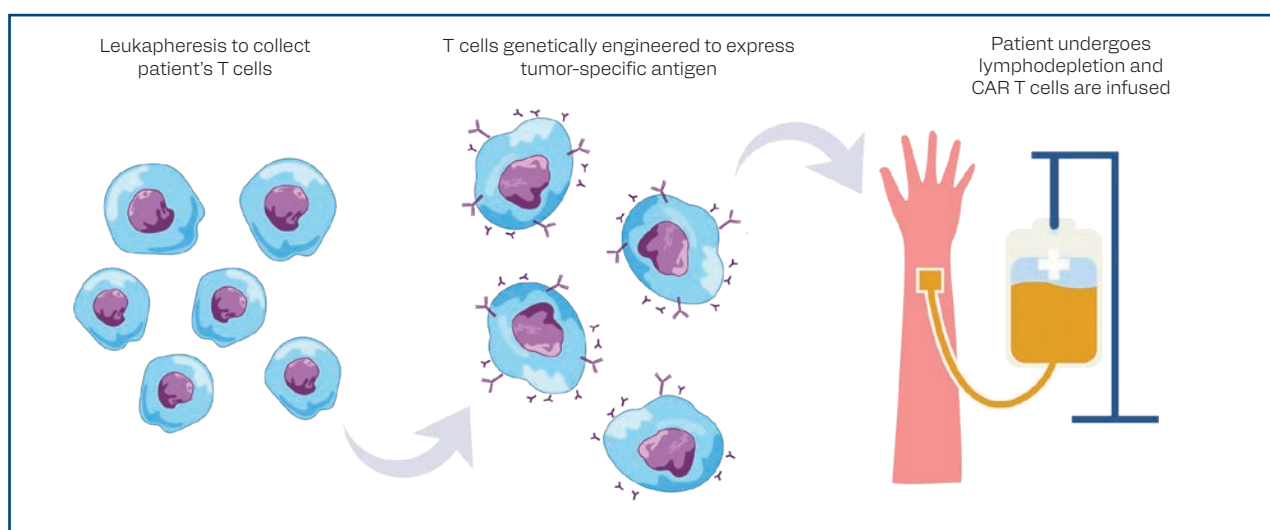
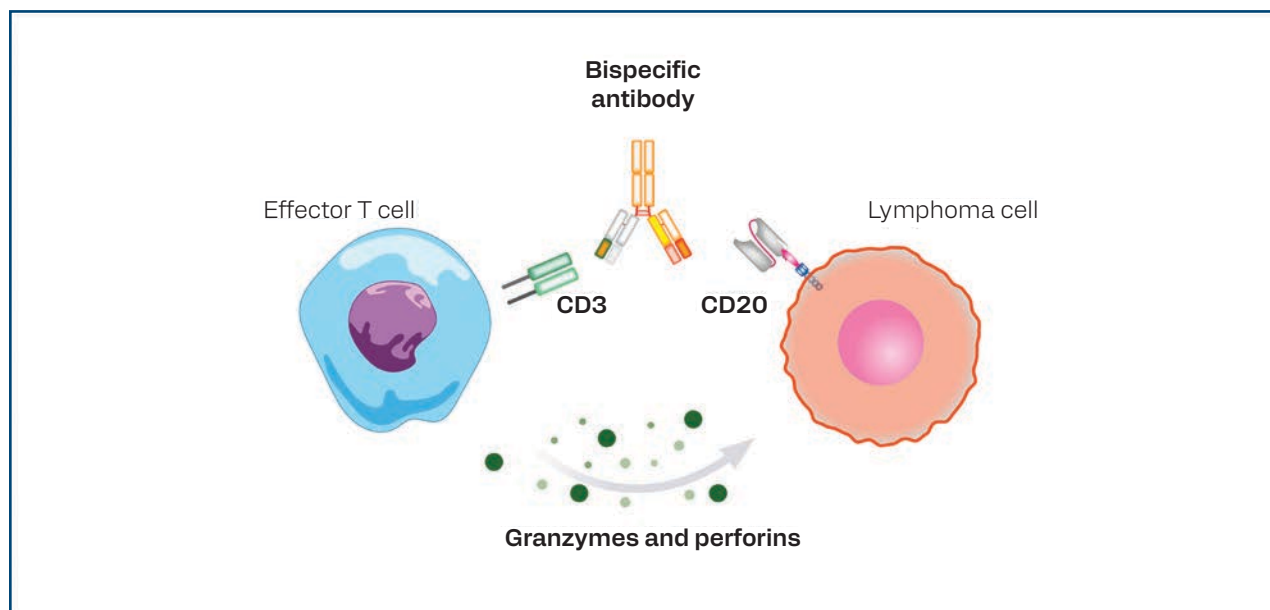


FIGURE 2. CD3xCD20 Bispecific Antibodies



2 Bispecific antibodies provide an off-the-shelf immune enhancement option in the R/R disease setting.

For patients whose disease progressed during or after at least 2 lines of systemic treatment, which can include HSCT or CAR T-cell therapy, use of the CD3xCD20 bispecific antibodies (BsAbs) epcoritamab or glofitamab can be an option (Figure 2).¹

In the single-arm, pivotal EPCORE NHL-1 trial (NCT03625037), 157 patients with R/R LBCL, including 139 patients with DLBCL, were given epcoritamab as a third- or later-line therapy.⁴ At a median follow-up of 20 months (range, 0.3-28.2 months), the ORR in patients with DLBCL was 61.9%, including CR in 39.6%. The median duration of CR was 20.8 months. CR was achieved at a median of 2.7 months from the start of treatment; however, 8 patients converted from a partial response to a CR after 36 weeks or more of follow-up. Median OS was 18.5 months (95% CI, 11.7 months to NR). TEAEs occurring in more than 20% of patients were CRS (51%), neutropenia (24%), pyrexia (24%), fatigue (23%), nausea (22%), and diarrhea (21%). In patients who experienced CRS, 94% of the events were grade 1 or 2 with the remainder being grade 3. All cases of CRS occurred after the first full dose of epcoritamab. ICANS occurred in 10 patients; 9 patients experience grade 1 or 2 events, 1 patient had a grade 5 event with confounding factors. Two fatal TEAEs (COVID-19 and ICANS) were attributed to

epcoritamab therapy.

Glofitamab is another CD3xCD20 BsAb approved for use as a third-line or later treatment for patients with R/R DLBCL based on the results of a pivotal phase 2 trial (NCT03075696).⁵ Of 154 patients with R/R LBCL who had received at least 2 prior therapies, investigator-assessed ORR was 59%, including CR in 38%. The median duration of CR was 24.1 months (95% CI, 19.8 months to not estimated). The 18-month OS rate was 41% (95% CI, 32.1%-49.3%). CRS was reported in 64% of patients; these included grade 1 (48%), grade 2 (12%), grade 3 (3%), and grade 4 (1%) events. The most common grade 3 or 4 AE was neutropenia (27%).⁶ No treatment-emergent deaths were attributed to glofitamab.

3 Antibody-drug conjugates and other targeted therapies offer increased options in downstream therapy.

In addition to CAR T-cell therapy and bispecific antibodies, the DLBCL armamentarium includes a variety of treatments beyond chemotherapy for patients who have progressed on first-line therapy (Table).¹ Brentuximab vedotin recently joined the list of second-line options after its use demonstrated improved ORR, CR, OS, and PFS when combined with lenalidomide and rituximab vs lenalidomide and rituximab alone in the ECHELON-3 trial (NCT04404283).⁷ ■

TABLE. Selected Treatments in the Second Line or Greater¹

THERAPY	MECHANISM OF ACTION	INDICATION
Polatuzumab vedotin	Antibody-drug conjugate	Bridging therapy during CAR T or second line for patients who have no intention to proceed to transplant
Tafasitamab (combined with lenalidomide)	Anti-CD19 monoclonal antibody	Second line for patients who have no intention to proceed to transplant
Brentuximab vedotin	Antibody-drug conjugate	Second line for patients with CD30+ who have no intention to proceed to transplant
Loncastuximab tesirine	Antibody-drug conjugate	Third line and beyond
Selinexor	Inhibitor of nuclear export	Third line and beyond including patients with prior transplant or CAR T

CAR T, chimeric antigen receptor T-cell therapy.

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- 1 Relapse that occurs how long after chemoimmunotherapy is considered to be **chemosensitive**?
 - A. At least 3 months
 - B. At least 6 months
 - C. At least 9 months
 - D. At least 12 months

- 2 A 65-year-old male has been diagnosed with nongerminal center DLBCL with high CD20 expression. He has refractory disease following treatment with R-CHOP and is not a candidate for high-dose chemotherapy followed by autologous stem cell transplantation (ASCT), nor is he a candidate for CAR T-cell therapy. Which of the following is an appropriate treatment for this patient at this time?
 - A. R-CHOP
 - B. Bendamustine plus rituximab
 - C. Tafasitamab plus lenalidomide
 - D. R-ICE (rituximab, ifosfamide, carboplatin, etoposide)

- 3 In the randomized, phase 3 ECHELON-3 trial, addition of brentuximab vedotin to lenalidomide-rituximab led to which of the following compared with placebo-lenalidomide-rituximab?
 - A. Significantly improved OS
 - B. Significantly worse OS
 - C. No significant difference in OS