Improving the Road to Remission with CAR T-Cell Therapies in Large B-Cell Lymphoma: Considerations for Community Practice

A PATIENT/CLINICIAN DECISION SUPPORT AID

Key Questions Patients, Caregivers and Clinicians Should Discuss:

- What are your personal goals for treatment/expectations after treatment?
- How does CAR T-therapy work?
- How is CAR T-therapy different from other treatment options?
- Will CAR T-therapy provide a cure or keep cancer from returning?
- What is involved if we decide to move forward with CAR T-therapy?
- How will this impact my daily living?
- What are the side effects that could occur with CAR T-therapy?
- What can we do to help reduce the risk of side effects?
- How involved will my family be during my course of treatment? Will there be an impact on their daily living?
- Will I be able to drive during my treatment?
- How much time will I possibly need to miss from work if we move forward with CAR T-therapy?
- Will we need to arrange a place to stay before, during or after treatment with CAR T?
- Once we review the material on this decision support aid, we will re-discuss this treatment option and any additional questions that may arise. You will have the ability to make the final decision on how we move forward with treatment selection based upon your personal values, preferences, and goals for treatment, okay?
- Can you outline the pros and cons of CAR T over other available therapies?

Evaluating Treatment Options: Key Similarities, Differences, and Efficacy Data of CAR T-Cell Therapies as Second-Line Treatment of LBCL

	Axi-cel	Liso-cel		Tisa-cel
Drug Target/ Costimulatory Domain	CD28	4-1BB		4-1BB
Trial	ZUMA-7	TRANSFORM	PILOT	BELINDA
Patient Population	Primary refractory, early relapsed*	Primary refractory, early relapsed*, PMBCL; upper age limit 75 years	Primary refractory, transplant ineligible	Primary refractory, early relapsed*
Therapy Used to Control Disease While Waiting for CAR T Infusion/ Bridging Therapy	Corticosteroids	Chemotherapy		Chemotherapy
Low-dose chemotherapy	FC	FC		FC or bendamustine
Primary Endpoint: event-free survival (EFS) vs standard of care (SOC)	10.8 months vs 2.3 months	Not reached vs 2.4 months	-	3.0 months vs 3.0 months
Primary Endpoint: overall response rate (ORR)	-	-	80%	-
FDA Approval	Adult patients with LBCL that is refractory to first-line CIT or relapses within 12 months of first-line CIT	Adult patients with LBCL who have refractory disease to first-line CIT or relapse within 12 months of first-line CIT	Adult patients with LBCL who have refractory disease to first-line CIT or relapse after first-line CIT and are not eligible for HSCT due to comorbidities or age	-

*Within 12 months of first-line treatment.

Axi-cel, axicabtagene ciloleucel; Liso-cel, lisocabtagene maraleucel; Tisa-cel, tisagenlecleucel; FC, fludarabine and cyclosphosphamide; CIT, chemoimmunotherapy; HSCT, hematopoietic stem cell transplantation; LBCL, large B-cell lymphoma; FDA, US Food and Drug Administration; PMBCL, primary mediastinal large B-cell lymphoma; ORR, overall response rate.

Weighing Risk vs. Benefits: Safety Profiles for CRS and ICANS

	Axi-cel	Liso-cel		Tisa-cel
Trial	ZUMA-7	TRANSFORM	PILOT	BELINDA
CRS; Grade 3+ CRS, %	92%; 6%	49%; 1%	38%; 2%	61%; 5%
ICANS; Grade 3+ ICANS, %	60%; 21%	11%; 4%	31%; 5%	10%; 2%

Axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; Liso-cel, lisocabtagene maraleucel; Tisa-cel, tisagenlecleucel.

Assessment, Monitoring, and Management Strategies

"Intensive monitoring, accurate grading, and prompt management of toxicities with aggressive supportive care, anti-IL-6 therapy, and/or corticosteroids for severe cases could reduce the morbidity and mortality associated with CAR-T-cell therapy" (Neelapu et al, 2018).

	Assessment/Monitoring	Management
Cytokine Release Syndrome (CRS)	Assessment of vital signs at least every 4 hours, and daily review of organ systems, physical exam, CBC with differential, complete metabolic profile, coagulation profiles, and measurement of serum CRP and ferritin levels. • Fever (≥38 ºC) • Hypotension (systolic BP <90 mmHg) • Hypoxia (needing oxygen for SaO_2 >90%) • Evidence of organ toxicity (cardiac, respiratory, GI, hepatic, renal, dermatologic, coagulopathy)	CRS grade should be determined at least twice daily, and at any time when a change in the patient's status is observed. Depending on Grade, options include: • Supportive care • IV fluids • Tocilizumab or siltuximab ± corticosteroids • Vasopressors • Supplemental oxygen • Transfer to ICU and obtain EKG (Grade ≥3) • Dexamethasone (Grade ≥3) • Methylprednisolone (Grade 4) • Mechanical ventilation (Grade 4)
Immune effector cell associated neurotoxicity syndrome (ICANS)	• CARTOX-10 • Seizures • Increased ICP • Motor weakness	Depending on Grade, options include: • Supportive care • Neurology consultation • Anti-IL-6 therapy (tocilizumab or siltuximab; Grade ≥1) • Corticosteroids (Grade ≥2) • ICU transfer (Grade ≥3) • Methylprednisolone (Grade 4) • Mechanical ventilation (Grade 4)
B-cell aplasia/ hypogamma-globulinemia	Immunoglobulin levels should be monitored following therapy	Replete with IVIG for IgG levels <400 in all patients versus only in patients with recurrent infections, at the discretion of the treating oncologist.
Cytopenias	Monitor blood counts	Transfuse as indicated. G-CSF may be indicated for an ANC <500. TPO-mimetics may be indicated for severe persistent thrombocytopenia. If cytopenias persist after 6 months, recommend bone marrow biopsy.

Patient Role/Considerations

Patients and caregivers play an important role in the early identification of side effects.	It is important for your own health and safety to alert your healthcare team if you experience any signs of side effects so they can help you remain comfortable and potentially avoid them from getting worse.	If you feel lightheaded, experience shortness of breath, or have a fever, contact your healthcare professional right away.	If you feel muscle weakness or experience increased fatigue, contact your healthcare team.	If you experience confusion, word finding issues, focal weakness, and/or tremor, contact your healthcare team.

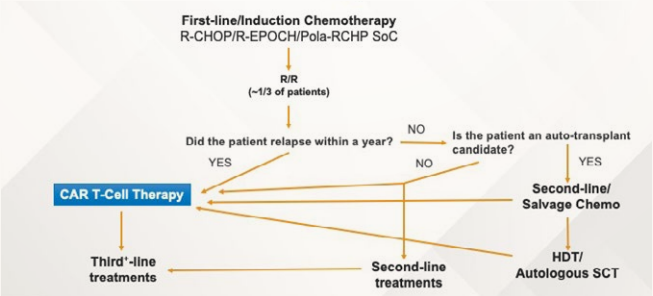
BP, blood pressure; CBC, complete blood count; ICANS, immune effector cell associated neurotoxicity syndrome; GI, gastrointestinal: IV, intravenous; EKG, echocardiogram; ICP, intracranial pressure; CARTOX-10, CAR-T-cell-therapy-associated toxicity 10-point neurological assessment.

Short- and Long-Term Monitoring Considerations

Short-Term Patient Impact: Days to Weeks From Infusion		Long-Term Patient Impact: Weeks to Months from Infusion
Outpatient	**Inpatient**	
• Patient housed near treating center for **4 weeks** • Patient instructed on how to take vital signs and monitor for neurologic toxicity and given tools (eg, thermometers) for assessing and recording these data • Patient scheduled to return to the treating center daily for at least **7 days** for labs and review of vital signs/labs • Patient admitted at the onset of fever and/or confusion until resolution of CRS and/or NT	• Patient is admitted for up to **7 days** or until the resolution of CRS and/or NT • After discharge, patients remain within **2 hours of the treating center for up to 4 weeks** – **Abstain from driving for up to 8 weeks** following CAR T-cell infusion due to a low risk of recurrent CRS and/or NT • Monitor for late CRS/NT and/or ongoing cytopenias • **First response assessment at 4 weeks**	Patients should be monitored for: • Prolonged cytopenias – transfusions as indicated; G-CSF as needed • B-cell aplasia (IgG levels) – replete with IVIG for levels <400 • Infection • Relapse • Secondary malignancies

CAR, chimeric antigen receptor; CRS, cytokine release syndrome; NT, neurotoxicity; G-CSF, granulocyte colony stimulating factor; IgG, immunoglobulin G; IVIG, intravenous immunoglobulin; PJP, Pneumocystis jirovecii.

LBCL: Treatment Paradigm 2023



CHOP, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, hydroxydaunorubicin; HDT, high-dose therapy; LBCL, large B-cell lymphoma; Pola, polatuzumab vedotin; R, rituximab; RCHP, rituximab, cyclophosphamide, doxorubicin, prednisone; R/R, relapsed/refractory; SCT, stem cell transplantation; SoC, standard of care.

How Has the Second-Line Approval of CAR T-Cell Therapies Changed Clinical Practice and Patient Considerations?

Screening

Screening patients in first remission

- Pre-approval: No routine surveillance screening, waited for clinical relapse
- Post-approval: Perform on surveillance PET or CT scan just prior to 12 months from the completion of frontline CIT

Referral

Optimal referral practices change with second-line approval

- Refer all eligible patients as early as possible – ideally one line of therapy **BEFORE** it is indicated
- CAR T-cell therapy is always easiest and quickest if the patient is known to the CAR T-cell treatment center
- Advocate for referring patients one line of therapy **BEFORE** CAR T cells are needed
- 2nd-line CAR:
  - Refer high-risk patients (HGBL, DHL/THL, IPI 4-5 LBCL) at or around diagnosis (especially pertinent now that randomized trials in frontline are open)
  - Refer any patient without complete response mid treatment
  - For all others, need to refer at time of relapse
    - Provide availability to consult regarding "bridging" strategies before and after apheresis in real-time
- 3rd-line CAR: Refer at the time of first relapse

Therapy Used to Control Disease While Waiting for CAR T Infusion/Bridging

- Patients are largely primary refractory and have rapidly progressive and large volume disease
- Patients are largely unknown to CAR T-cell treatment centers, so therapy is delayed beyond just insurance approval and manufacturing time, but also now includes time to initial consult
- Bridging now needs to be started **BEFORE** apheresis as well as **DURING** manufacturing
- What if someone responds to bridging therapy?
  - If primary refractory or relapsing <6 months: would take to CAR no matter what
  - If relapsing 6-12 months: could consider switching to consolidating auto-transplant, or continue with CAR given the survival benefits

CAR, chimeric antigen receptor; CT, computed tomography; DHL, double-hit lymphoma; HGBL, high grade B-cell lymphoma; IPI, International Prognostic Index; LBCL, large B-cell lymphoma; PET, positron emission tomography; THL, triple-hit lymphoma.

References

Abramson JS, Solomon SR, Arnason J, et al. Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study. *Blood*. 2023;141(14):1675-1684.

Bishop MR, Dickinson M, Purtill D, et al. Second-Line Tisagenlecleucel or Standard Care in Aggressive B-Cell Lymphoma. *N Engl J Med*. 2022;386(7):629-639.

Kamdar M, Solomon SR, Arnason JE, et al. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial. *Lancet*. 2022;399(10343):2294-2308.

Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. *N Engl J Med*. 2022;386(7):640-654.

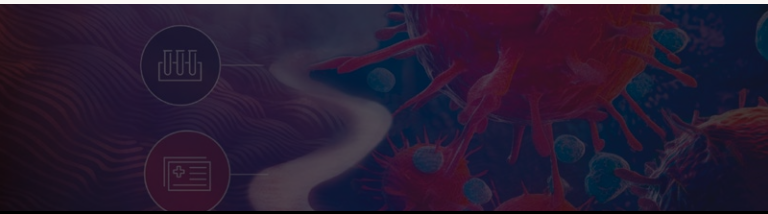
Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nat Rev Clin Oncol*. 2018;15(1):47-62.

Sehgal A, Hoda D, Riedell PA, et al. Lisocabtagene maraleucel as second-line therapy in adults with relapsed or refractory large B-cell lymphoma who were not intended for haematopoietic stem cell transplantation (PILOT): an open-label, phase 2 study. *Lancet Oncol*. 2022;23:1066-1077.

U.S. Food and Drug Administration (FDA). FDA approves axicabtagene ciloleucel for second-line treatment of large B-cell lymphoma. April 1, 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-axicabtagene-ciloleucel-second-line-treatment-large-b-cell-lymphoma

U.S. Food and Drug Administration (FDA). FDA approves lisocabtagene maraleucel for second-line treatment of large B-cell lymphoma. June 24, 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lisocabtagene-maraleucel-second-line-treatment-large-b-cell-lymphoma

Westin J, Oluwole OO, Kersten MJ, et al. Survival with Axicabtagene Ciloleucel in Large B-Cell Lymphoma. *N Engl J Med*. 2023;389(2):148-157.



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This resource is supported by an educational grant from Bristol-Myers Squibb Company.