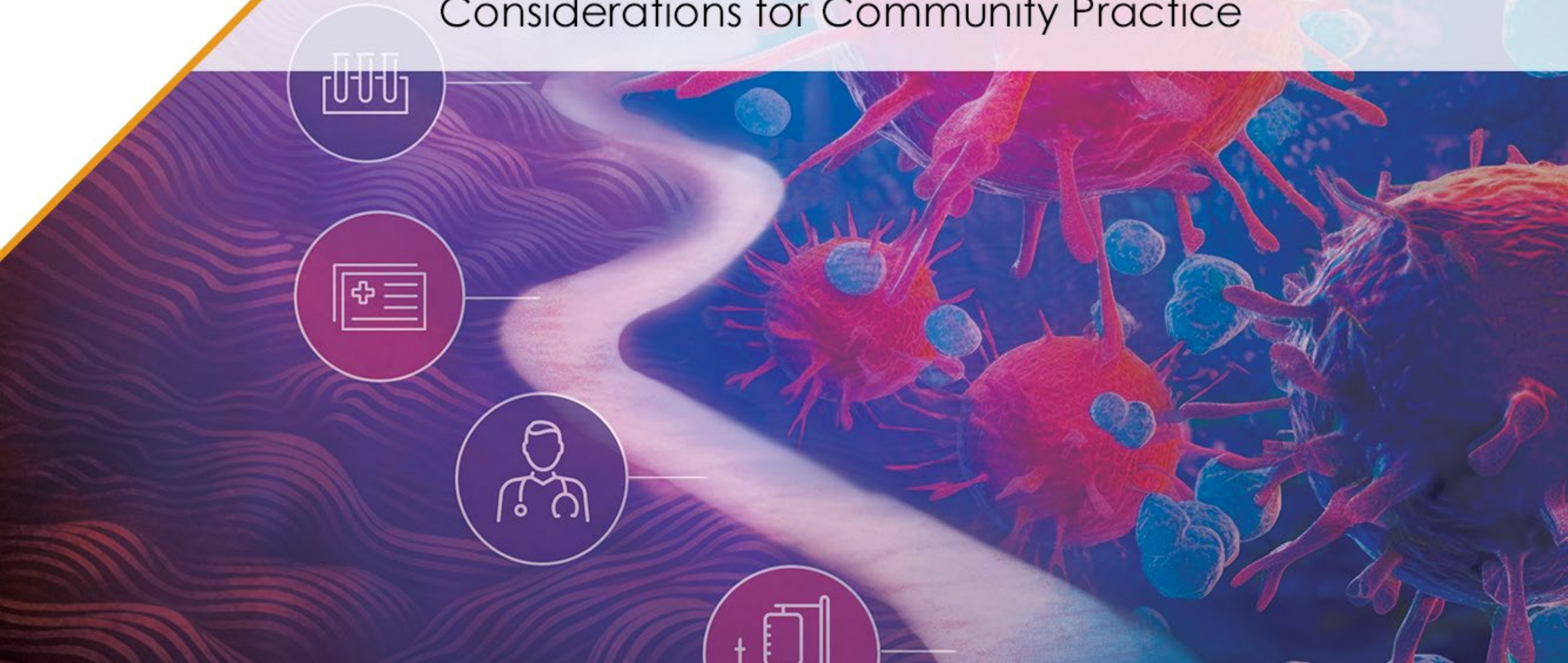
AXIS Medical Education

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

Considerations for Community Practice



DISCLAIMER

This slide deck in its original and unaltered format is for educational purposes and is current as of September 2023. All materials contained herein reflect the views of the faculty, and not those of AXIS Medical Education, the CME provider, or the commercial supporter. Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patients' conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

DISCLOSURE OF UNLABELED USE

This activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. The planners of this activity do not recommend the use of any agent outside of the labeled indications.

The opinions expressed in the activity are those of the faculty and do not necessarily represent the views of the planners. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

USAGE RIGHTS

Learning Objectives

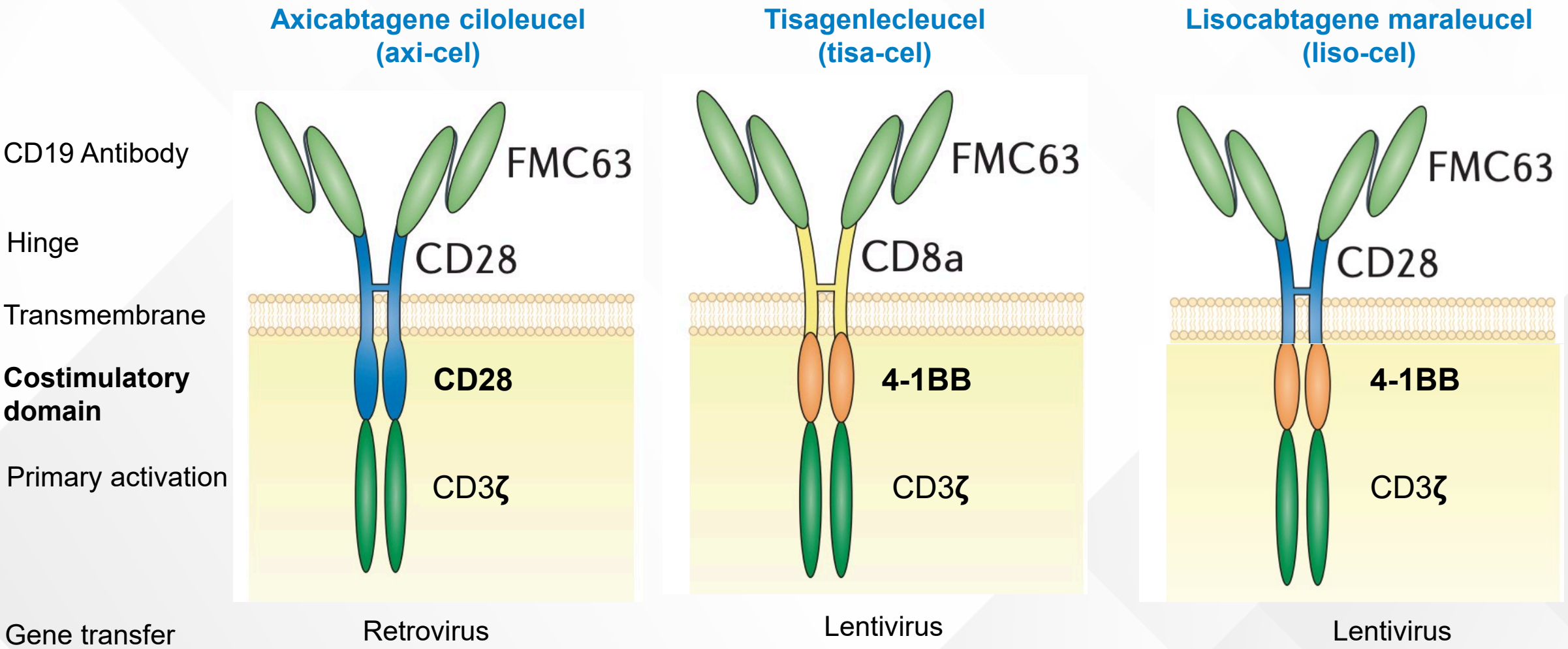
Upon completion of this activity, participants should be better able to:

1. Identify patients with primary refractory disease or early relapse in aggressive NHL who are eligible for CAR T-cell therapy
2. Differentiate similarities and differences among currently available CAR T-cell therapies
3. Apply evidence-based updates into treatment planning for patients eligible for CAR T-cell therapy as second-line treatment
4. Implement expert-recommended practices to mitigate and manage cytokine release syndrome, neurotoxicity, and related CAR T-cell toxicities.
5. Develop collaborative policies and workflows with the multidisciplinary CAR T-cell therapy team to improve access, referrals and outpatient delivery options for patients who are candidates for CAR T-cell therapy

CAR, chimeric antigen receptor.

Understanding CAR T-cell Therapy for NHL: Current Concepts

CD19 Chimeric Antigen Receptor T Cells in the Clinic: LBCL



LBCL, large B-cell lymphoma.

Adapted from van der Stegen SJC, et al. *Nat Rev Drug Discov*. 2015;14(7):499-509.

CD19 CAR T Cells for DLBCL: Pivotal Trial Results After Two or More Lines of Systemic Therapy

	ZUMA-1[1,2]	JULIET[3]	TRANSCEND[4]
Product	**Axi-cel**	**Tisa-cel**	**Liso-cel**
Costimulatory domain	CD28	4-1BB	4-1BB
# pheresed	111	165	344
# treated	101	111	269*
ORR, %	82	52	73
CR, %	54	40	53
6-month ORR, %	41	37	NR
mOS, months	27.1	12	21.1
CRS, %	93	48	42
Grade 3+ CRS, %	13	22*	2
ICANS, %	64	21	30
Grade 3+ ICANS, %	28	12	10

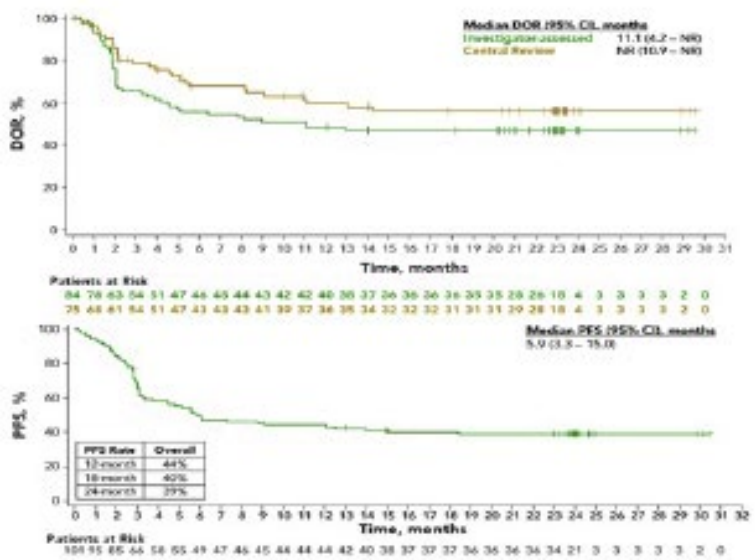
Cross-trial comparisons are for discussion purposes only.

AXIS Medical Education

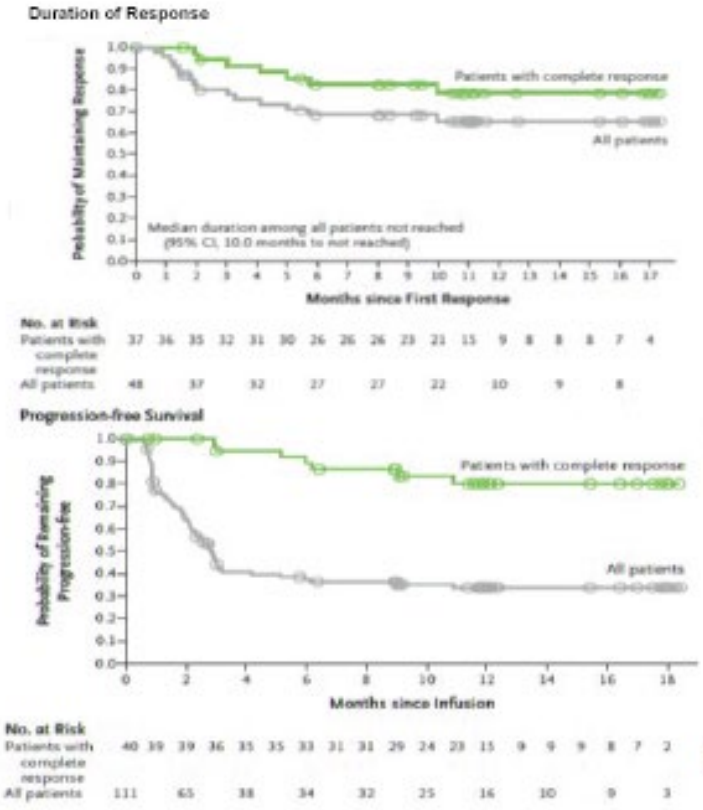
*n = 256 efficacy-evaluable patients.
Axi-cel, axicabtagene ciloleucel; CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; ICANS, immune effector cell-associated neurotoxicity syndrome; Liso-cel, lisocabtagene maraleucel; mOS, median overall survival; NR, not reached; ORR, overall response rate; Tisa-cel, tisagenlecleucel.
1. Neelapu SS, et al. *N Engl J Med*. 2017;377:2531-2544. 2. Locke FL, et al. *Lancet Oncol*. 2019;20:31-42. 3. Schuster SJ, et al. *N Engl J Med*. 2019;380:45-56. 4. Abramson JS, et al. *Lancet*. 2020;396:839-852.

CD19 CAR T-Cells Yield Durable Remission in ~40%

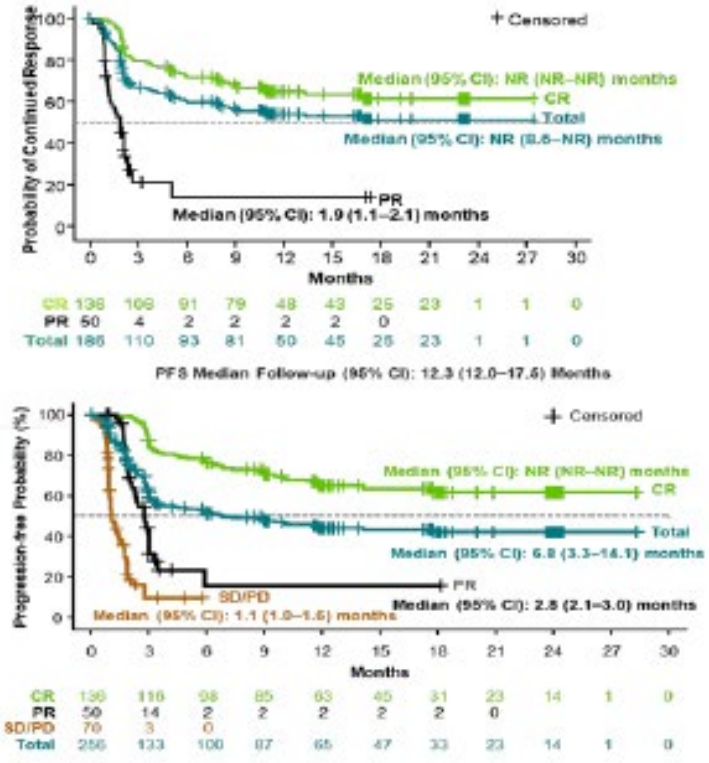
ZUMA-1: axi-cel



JULIET: tisa-cel



TRANSCEND-001: liso-cel



Axi-cel, axicabtagene ciloleucel; DOR, duration of response; Liso-cel, lisocabtagene maraleucel; NR, not reached; PFS, progression-free survival; Tisa-cel, tisagenlecleucel.
Adapted from Locke FL, et al. *Lancet Oncol*. 2019;20:31-42. Schuster SJ, et al. *N Engl J Med*. 2019;380:45-56. Abramson JS, et al. *Lancet*. 2020;396:839-852.

FDA Approvals: Third-Line Therapy

October 2017

axicabtagene ciloleucel

Adult patients with LBCL that is relapsed after 2 or more lines of systemic therapy (including PMBL)

May 2018

tisagenlecleucel

Adult patients with LBCL that is relapsed after 2 or more lines of systemic therapy

February 2021

lisocabtagene maraleucel

Adult patients with LBCL that is relapsed after 2 or more lines of systemic therapy (including PMBL, grade 3B FL)

AXIS Medical Education

FDA, US Food and Drug Administration; FL, follicular lymphoma; LBCL, large B-cell lymphoma; PMBL, primary mediastinal large B-cell lymphoma.
FDA. October 17, 2017. FDA. May 1, 2018. FDA. February 5, 2021.

CD19 CAR T-Cells for DLBCL: Results in the Real-World

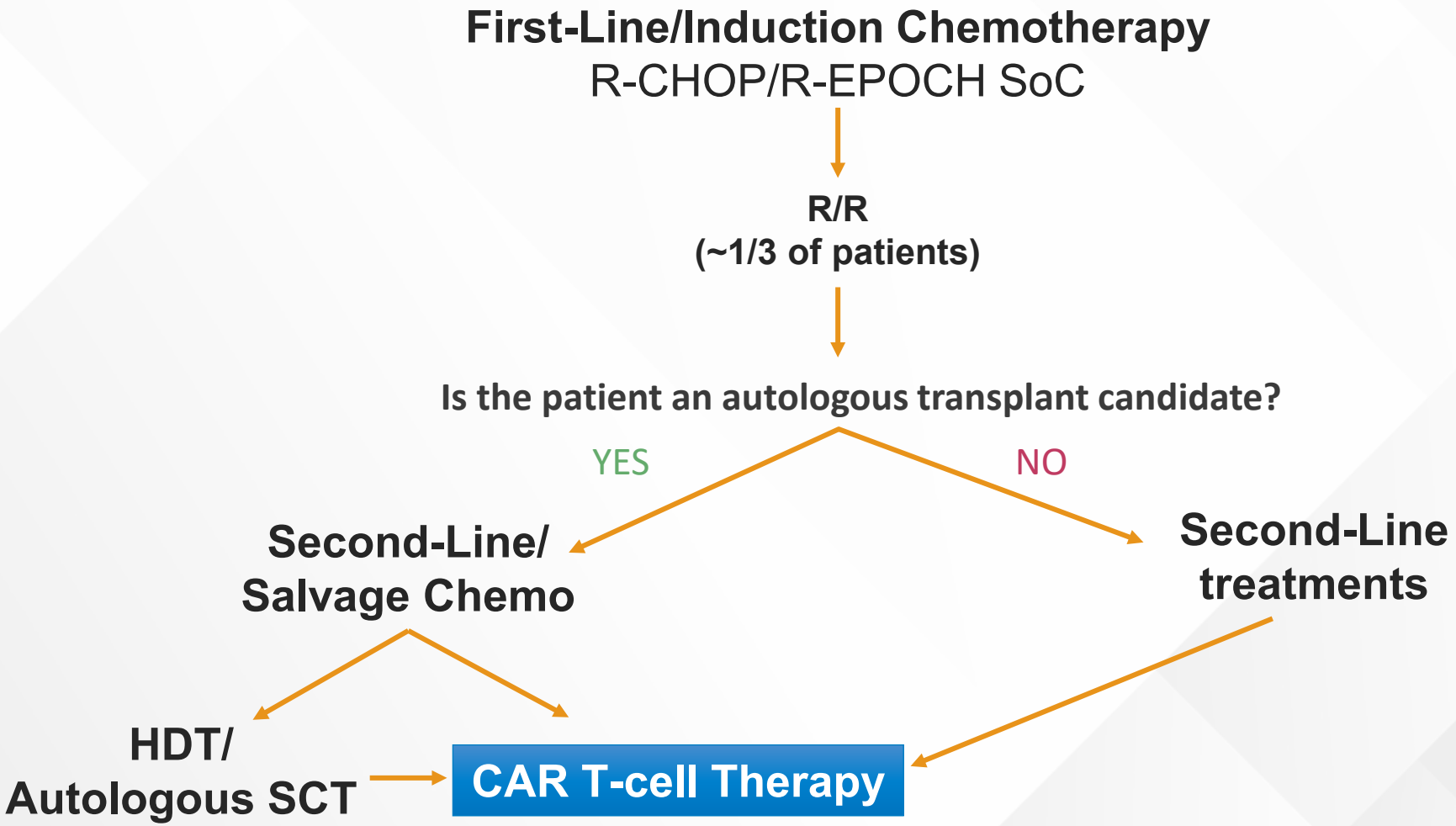
	Jacobson et al, JCO 2020[1]	Nastoupil et al, JCO 2020[2]	Axi-cel CIBMTR[3]	Tisa-cel CIBMTR[4]	CAR T-cell Consortium[5]		UK Experience[6]	
Product	Axi-cel	Axi-cel	Axi-cel	Tisa-cel	Axi-cel	Tisa-cel	Axi-cel	Tisa-cel
# treated	122	275	533	155	158	86	62	29
ORR/CR	70/50	82/64	74/54	62/40	75/53	59/42	21/37	17/29
6m ORR	41	NR	NR	34	~51	~35-40	~35-40	
CRS (%)	93	91	83	45	85	41	NR	
Gr 3+ CRS (%)	16	7	9	5	8	1	11	
NT (%)	70	69	53	18	53	14	NR	
Gr 3+ NT (%)	35	31	17	5	33	0	13	

AXIS Medical Education

Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CIBMTR, Center for International Blood & Marrow Transplant Research; CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; Gr, grade; JCO, Journal of Clinical Oncology; m, month; NR, not reached; NT, neurotoxicity; ORR, overall response rate; Tisa-cel, tisagenlecleucel; UK, United Kingdom.

1. Jacobson CA, et al. *J Clin Oncol.* 2020;38(15 suppl):8008. 2. Nastoupil LJ, et al. *J Clin Oncol.* 2020;38(27):3119-3128. 3. Pasquini MC, et al. *Blood.* 2019;134(suppl 1):764. 4. Pasquini MC, et al. *Blood Adv.* 2020;4(21):5414–5424. 5. Riedell PA, et al. Transplantation and Cellular Therapy Meetings. Abstract 52. 6. Kunhl A, et al. *Blood.* 2019;134(suppl 1):767.

LBCL: Treatment Paradigm 2017-2022



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

Key Patient and Disease Factors in Determining Candidacy for CAR T-Cell Therapy

Factor	Comments
Indications	• Does the patient have a disease and therapy history that meets FDA label? • Does the patient meet the criteria for a clinical trial?
Kinetics of disease progression	• Would the patient be able to go through leukapheresis (without immediate use of steroids/chemotherapy) and remain stable until the T-cell infusion (3-4 weeks)? • Does the patient need alternative therapy prior to CAR T-cell therapy consideration?
Immediate prior therapy	• How would this affect the ability to successfully manufacture CAR T-cells (ie, obtain sufficient numbers of T-cells and expand)?
Concomitant immunosuppressive therapy	• Can this be safely stopped prior to collection?
Active infection	• Higher risk of complications if patient experiences CRS
Non–disease-related comorbidities	• Does the patient have organ function reserve to tolerate toxicities of CAR T-cell therapy, namely CRS and ICANS • Cardiac, pulmonary, renal, bone marrow, CNS

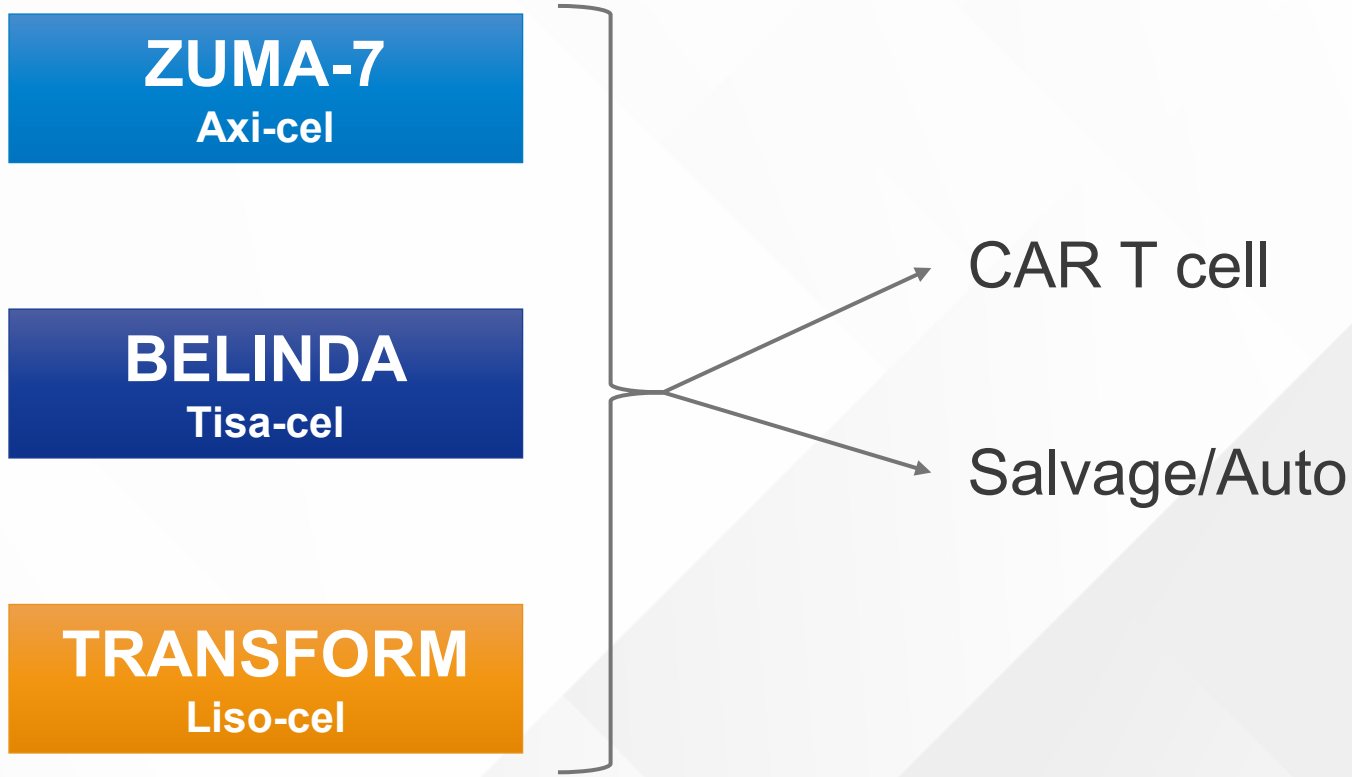
CAR, chimeric antigen receptor; CNS, central nervous system; CRS, cytokine release syndrome; FDA, US Food and Drug Administration; ICANS, immune effector cell-associated neurotoxicity syndrome.

Evolution of Evidence: Latest Data for CAR T-cell Therapy in Primary Refractory or Early Relapsing Advanced B-Cell NHL

Will CAR T-Cells Be More Effective When Used Earlier and Can It Replace Transplant?

High-Risk DLBCL

- Refractory to first-line treatment
- Relapsed within 12 months of first-line treatment



Auto, autologous; Axi-cel, axicabtagene ciloleucel; Liso-cel, lisocabtagene maraleucel; Tisa-cel, tisagenlecleucel; DLBCL, diffuse large B-cell lymphoma.

Locke FL, et al. *N Engl J Med.* 2022;386(7):640-654. Kamdar M, et al. *Lancet.* 2022;399(10343):2294-2308. Bishop MR, et al. *N Engl J Med.* 2022;386(7):629-639.

ZUMA-7, TRANSFORM, BELINDA Results: Second-Line Treatment

	ZUMA-7[1,2]	TRANSFORM[3,4]	BELINDA[5]
Product	**Axi-cel vs SoC**	**Liso-cel vs SoC**	**Tisa-cel vs SoC**
Costimulatory domain	CD28	4-1BB	4-1BB
ORR (%)	83% vs 50%	87% vs 49%	75% vs 68%
CR (%)	65% vs 32%	74% vs 43%	46% vs 44%
mEFS (months)	10.8 vs 2.3	NR vs 2.4	3.0 vs 3.0
EFS rate (%)	4-year: 39% vs 17%	18-month: 53% vs 21%	---
mPFS (months)	14.7 vs 3.7	NR vs 6.2	---
PFS rate (%)	4-year: 42% vs 24%	18-month: 58% vs 29%	---
mOS (months)	NR vs 31.1	NR vs 29	---
OS rate (%)	4-year: 55% vs 46%	18-month: 73% vs 61%	---

Cross-trial comparisons are for discussion purposes only.

AXIS Medical Education

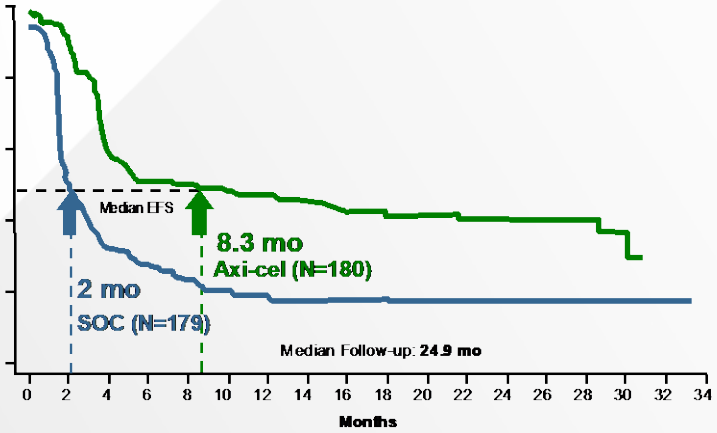
Axi-cel, axicabtagene ciloleucel; CR, complete response; Liso-cel, lisocabtagene maraleucel; mOS, median overall survival; mEFS, median event-free survival; mPFS, median progression-free survival; NR, not reached; ORR, overall response rate; SoC standard of care; Tisa-cel, tisagenlecleucel.

1. Locke et al. *N Engl J Med*. 2022;386(7):640-654. 2. Westin J, et al. *N Engl J Med*. 2023;389:148-157. 3. Kamdar et al. *Lancet*. 2022;399(10343):2294-2308. 4. Abramson et al. *Blood*. 2023;141(14):1675-1684. 5. Bishop et al. *N Engl J Med*. 2022;386(7):629-639.

ZUMA-7, TRANSFORM, BELINDA: EFS

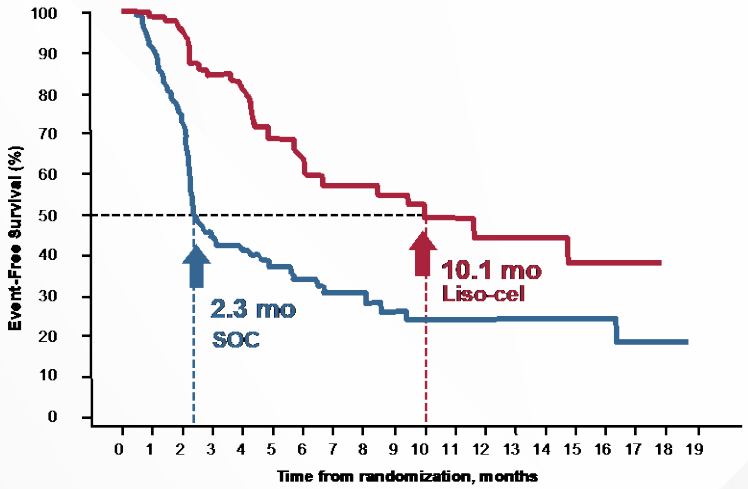
ZUMA-7: axi-cel

HR 0.398 (95% CI, 0.308–0.514); *P* < 0.0001

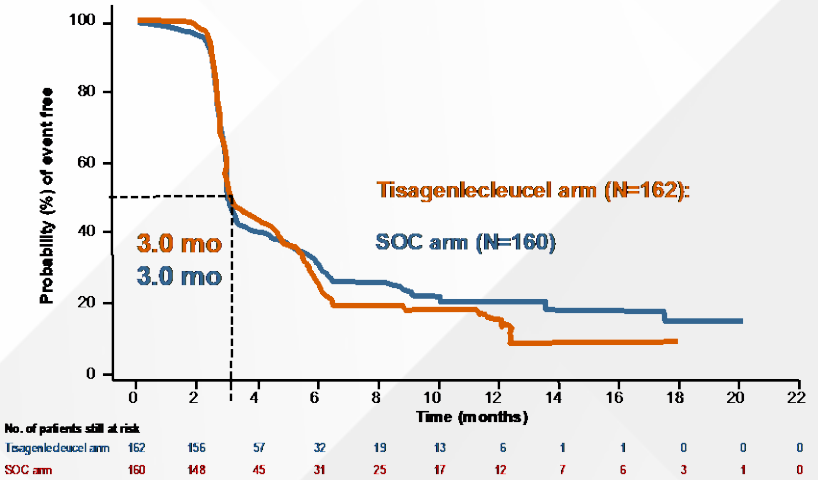


TRANSFORM: liso-cel

HR 0.349 (95% CI, 0.229-0.530); *P* < 0.0001



BELINDA: tisa-cel

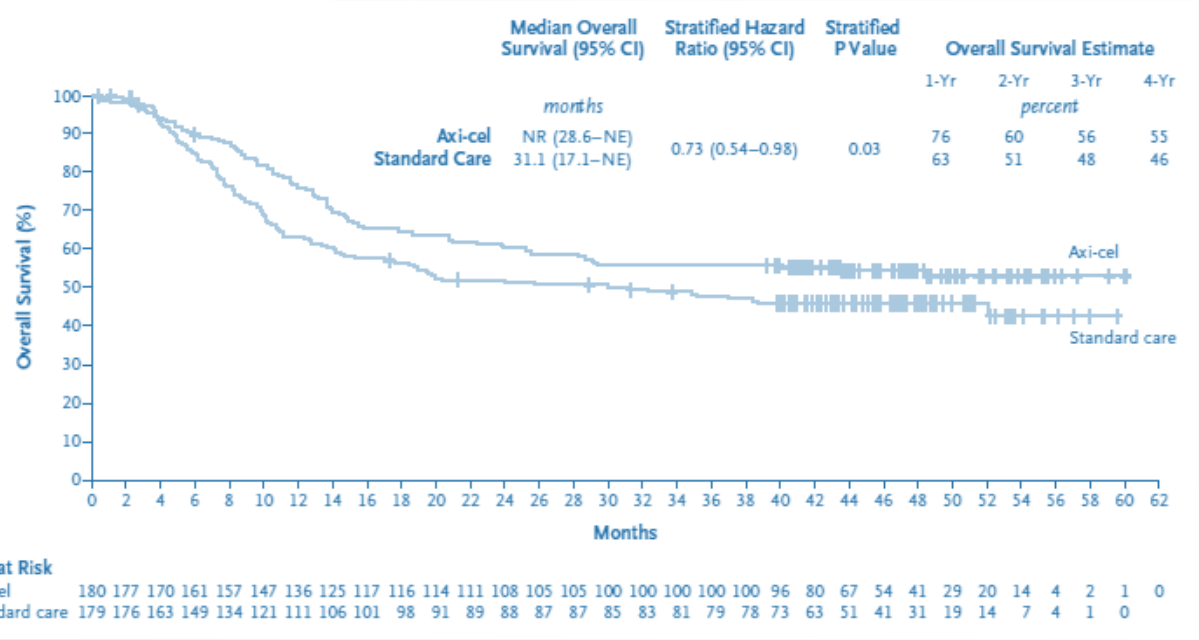


Axi-cel, axicabtagene ciloleucel; EFS, event-free survival; Liso-cel, lisocabtagene maraleucel; SOC standard of care; Tisa-cel, tisagenlecleucel.

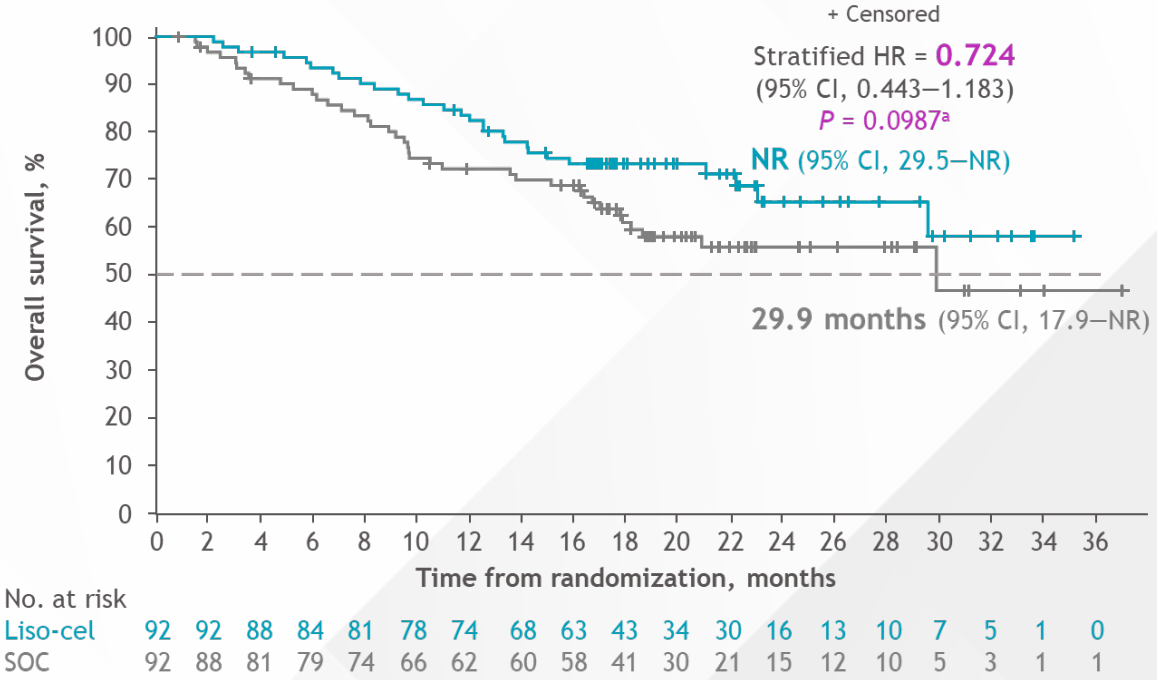
Locke FL, et al. *Blood*. 2021;138:2. Kamdar M, et al *Blood*. 2021;138:91. Bishop MR, et al *Blood*. 2021;138:LBA6.

ZUMA-7, TRANSFORM: OS

ZUMA-7: axi-cel



TRANSFORM: liso-cel



Axi-cel, axicabtagene ciloleucel; HR, hazard ratio; Liso-cel, lisocabtagene maraleucel; OS, overall survival; SOC, standard of care.

Westin J, et al. *N Engl J Med.* 2023;389:148-157. Kamdar M, et al. *Blood.* 2021;138:91.

ZUMA-7: 2nd- vs 3rd-Line Cell Therapy[1,2]

2nd-Line Axi-cel

- **Median PFS, months:** 14.7 (5.4-NE)
- **Median OS, months:** NR (28.3-NE)
- **ORR, %:** 83 (77-88)
  - **CR, %:** 65 (58-72)

3rd-Line Cellular Immunotherapy in the SOC Arm

- **Median PFS, months:** 6.3 (3.4-16.3)
- **Median OS, months:** 16.3 (8.7-NE)
- **ORR, %:** 57 (45-69)
  - **CR, %:** 34 (23-46)

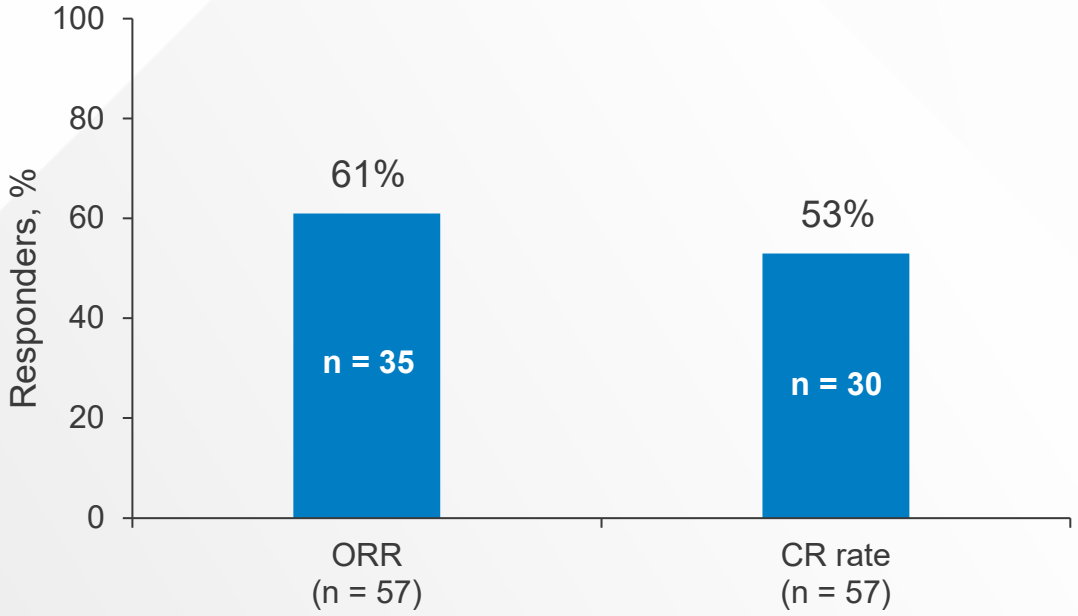
AXIS Medical Education

Axi-cel, axicabtagene ciloleucel; CR, complete response; NE, not evaluable; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SOC, standard of care.

1. Ghobadi A, et al. *Blood*. 2022;140(suppl 1):1595-1597. 2. Locke FL, et al. *New Eng J Med*. 2022;386(7):640-645.

Updated TRANSFORM Results: Cross-over Outcomes[1,2]

- Of 92 patients in the SOC group, 61 (66%) were approved for crossover to receive liso-cel
- 58 received CAR T cells (57 received liso-cel, 1 received nonconforming product)
- Median time from crossover approval to liso-cel infusion was 15 days (range, 8-95)



	Crossover subgroup (n = 57)
Median (range) follow-up, months	12.0 (1.4—28.1)
Median (95% CI) EFS, months	5.9 (3.1—15.1)
Median (95% CI) PFS, months	5.9 (3.2—26.5)
Median (95% CI) OS, months	15.8 (11.8—NR)

All endpoints were evaluated from the time of liso-cel infusion.

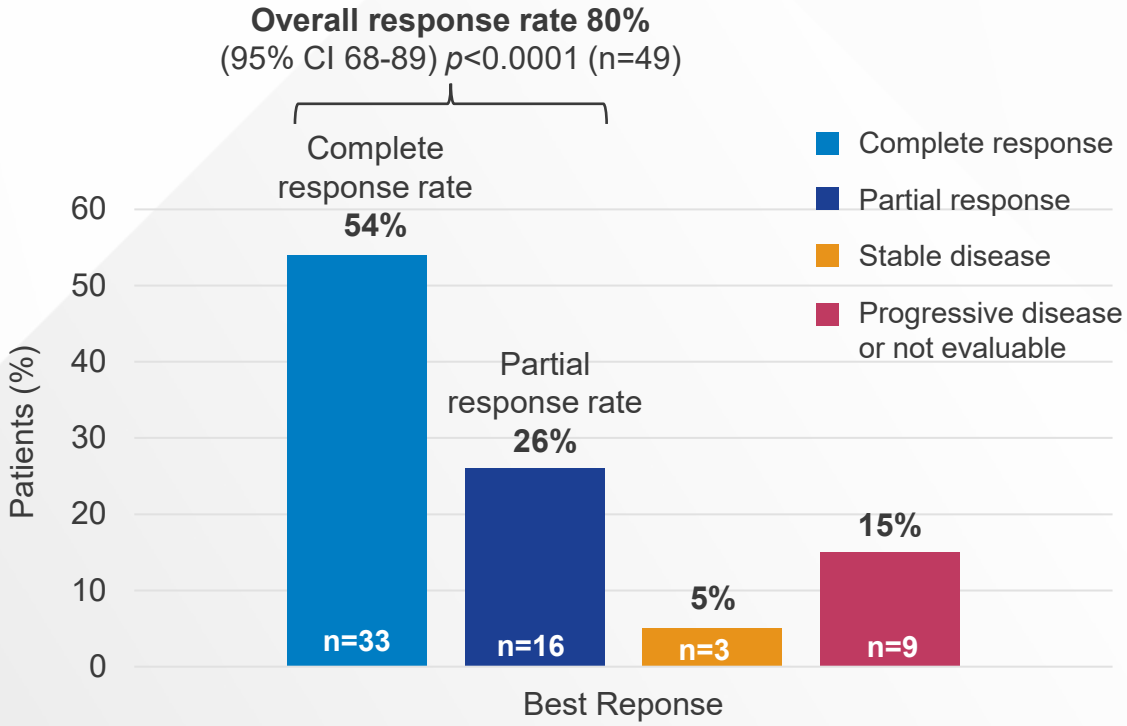
AXIS Medical Education

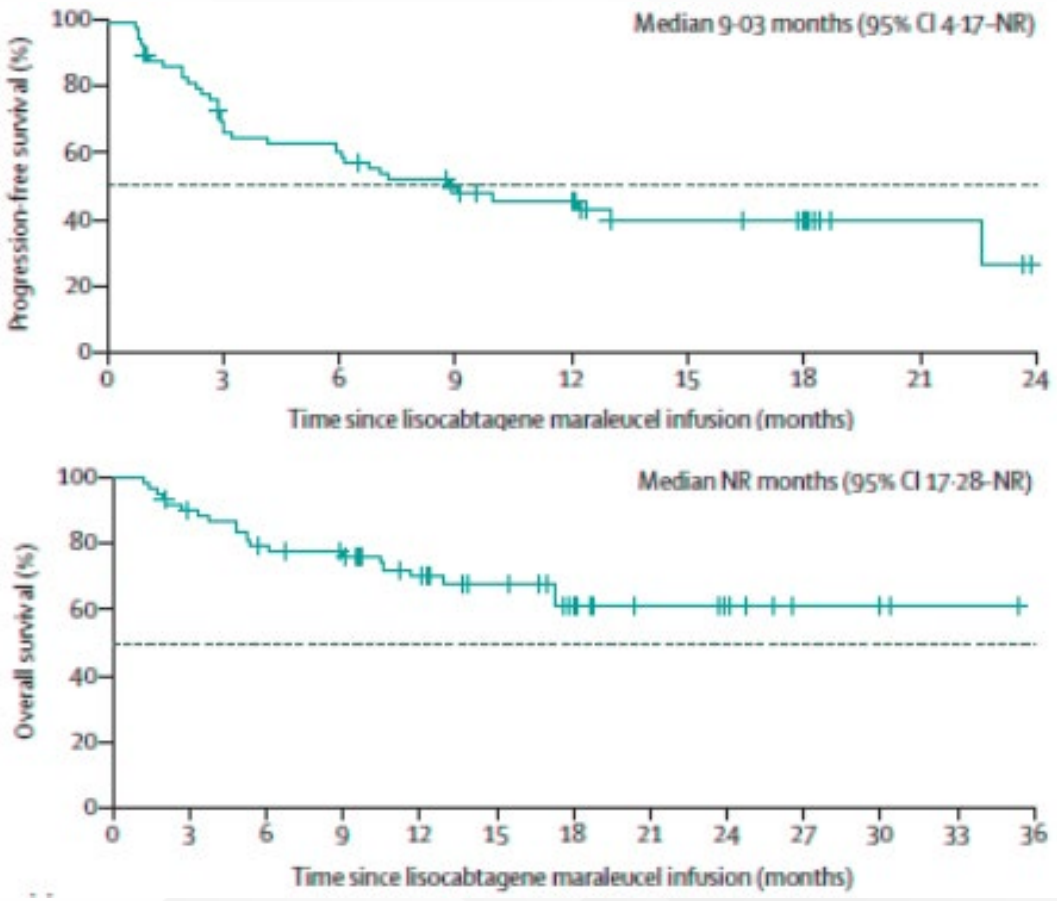
CAR, chimeric antigen receptor; CR, complete response; EFS, event-free survival; liso-cel, lisocabtagene maraleucel; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SOC, standard of care.

1. Abramson JS, et al. *Blood.* 2022;140(suppl 1):1581-1583. 2. Kamdar M, et al. *Lancet.* 2022;399:2294-2308.

PILOT Study: Liso-cel in Second-Line Transplant Ineligible

- CRS any/high grade: 38%/2%
- ICANS any/high grade: 31%/5%





CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; Liso-cel, lisocabtagene maraleucel; NR, not reached.
Adapted from Sehgal A, et al. *Lancet Oncol*. 2022;23:1066-1077.

FDA Approvals: Second-Line Therapy

April 2022

axicabtagene ciloleucel

- Adult patients with LBCL that is refractory to first-line chemoimmunotherapy or relapses within 12 months of first-line chemoimmunotherapy

June 2022

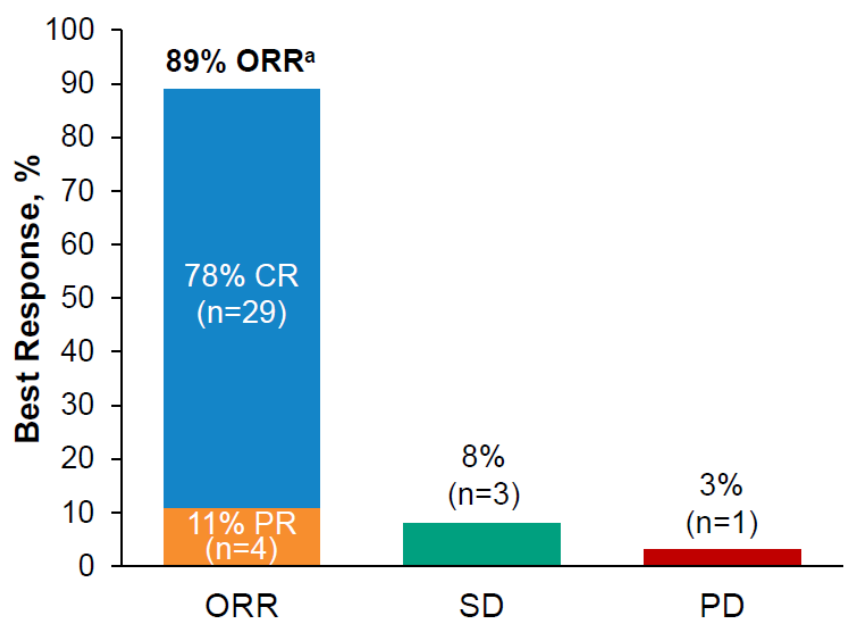
lisocabtagene maraleucel

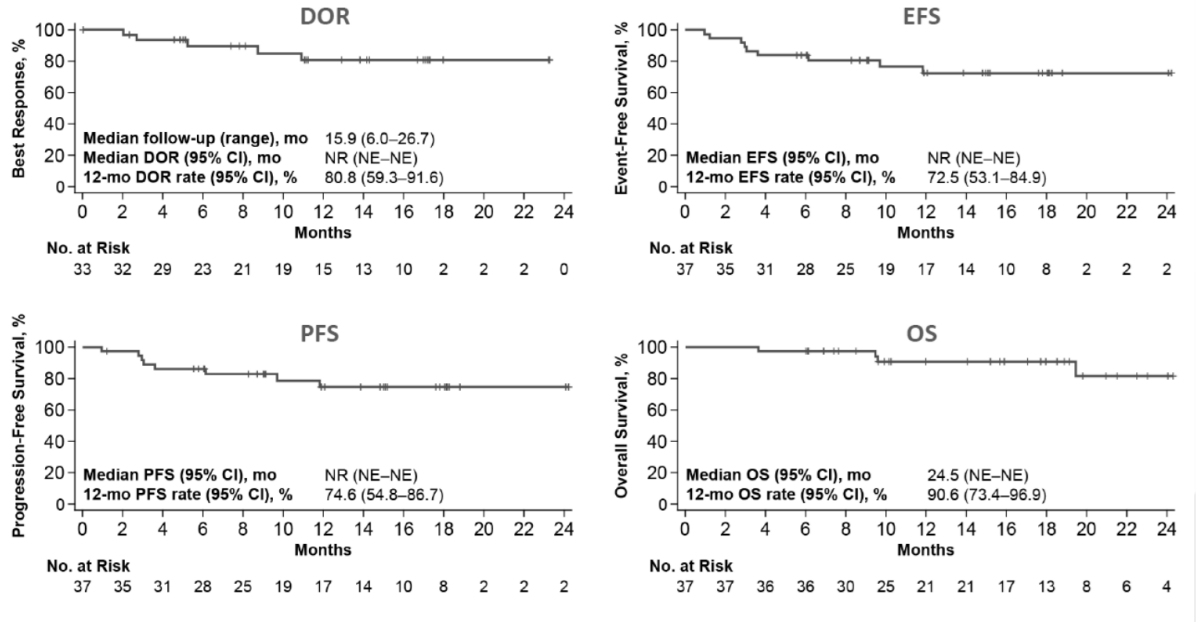
- Adult patients with LBCL who have refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy
- Adult patients with LBCL who have refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for HSCT due to comorbidities or age

AXIS Medical Education

FDA, US Food and Drug Administration; HSCT, hematopoietic stem cell transplantation; LBCL, large B-cell lymphoma.
FDA. April 1, 2022. FDA. June 24, 2022.

CAR T cells in Frontline: ZUMA-12





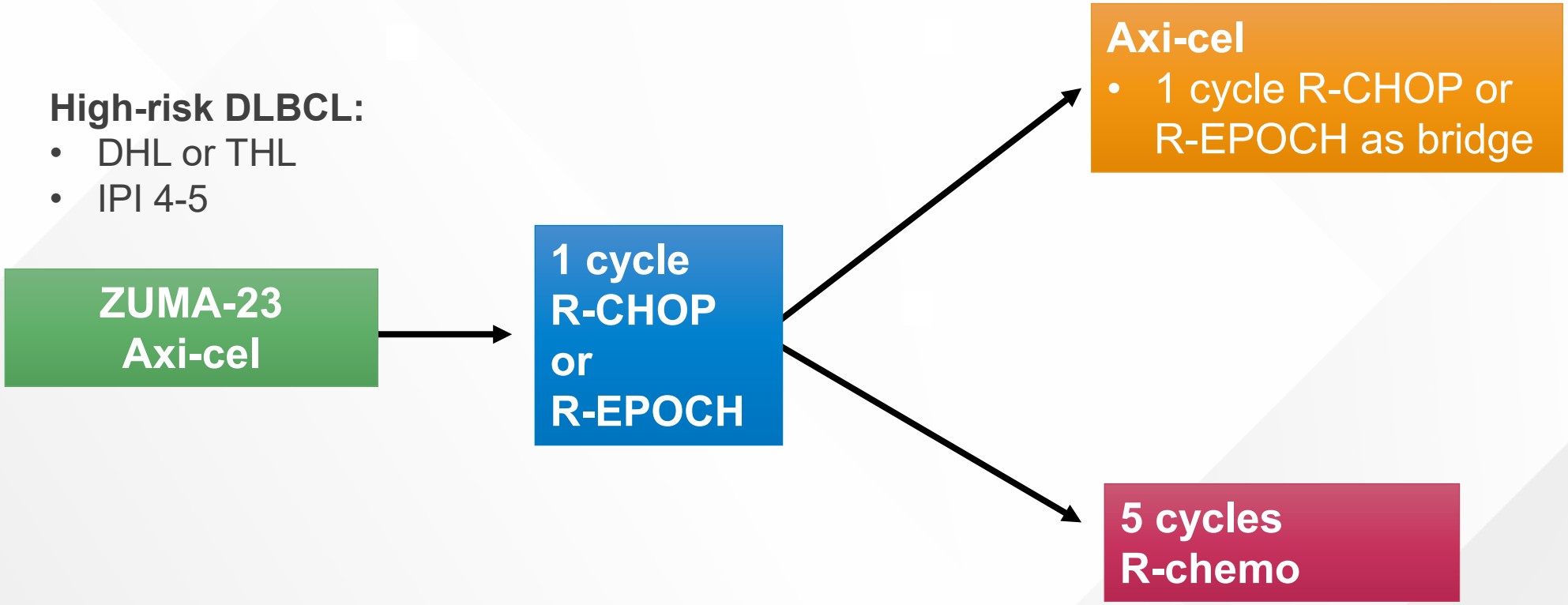
Parameter, Median (Range)	ZUMA-12 (N=40)	ZUMA-1 Cohort 1 (N=77)
Total no. of T cells infused x10^6	304 (165–603)	295 (149–760)
Total no. of CAR T cells infused x10^6	165 (95-200)	160 (96-200)
Total no. of CCR7+CD45RA+ T cells infused x10^6	105 (33-254)	40 (2-215)
CCR7+CD45RA+ T cells, %	35 (7–80)	14 (1–76)
Doubling time, days	1.6 (1.3-3.4)	1.5 (1.0–3.8)
IFN-γ, pg/mL	4013 (529–14,700)	5826 (858–17,800)

AXIS Medical Education

CAR, chimeric antigen receptor; CR, complete response; DOR, duration of response; EFS, event-free survival; IFN, Interferon; NE, not evaluable; NR, not reached; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
Adapted from Neelapu SS, et al. *Nature Medicine.* 2022;28:735-742.

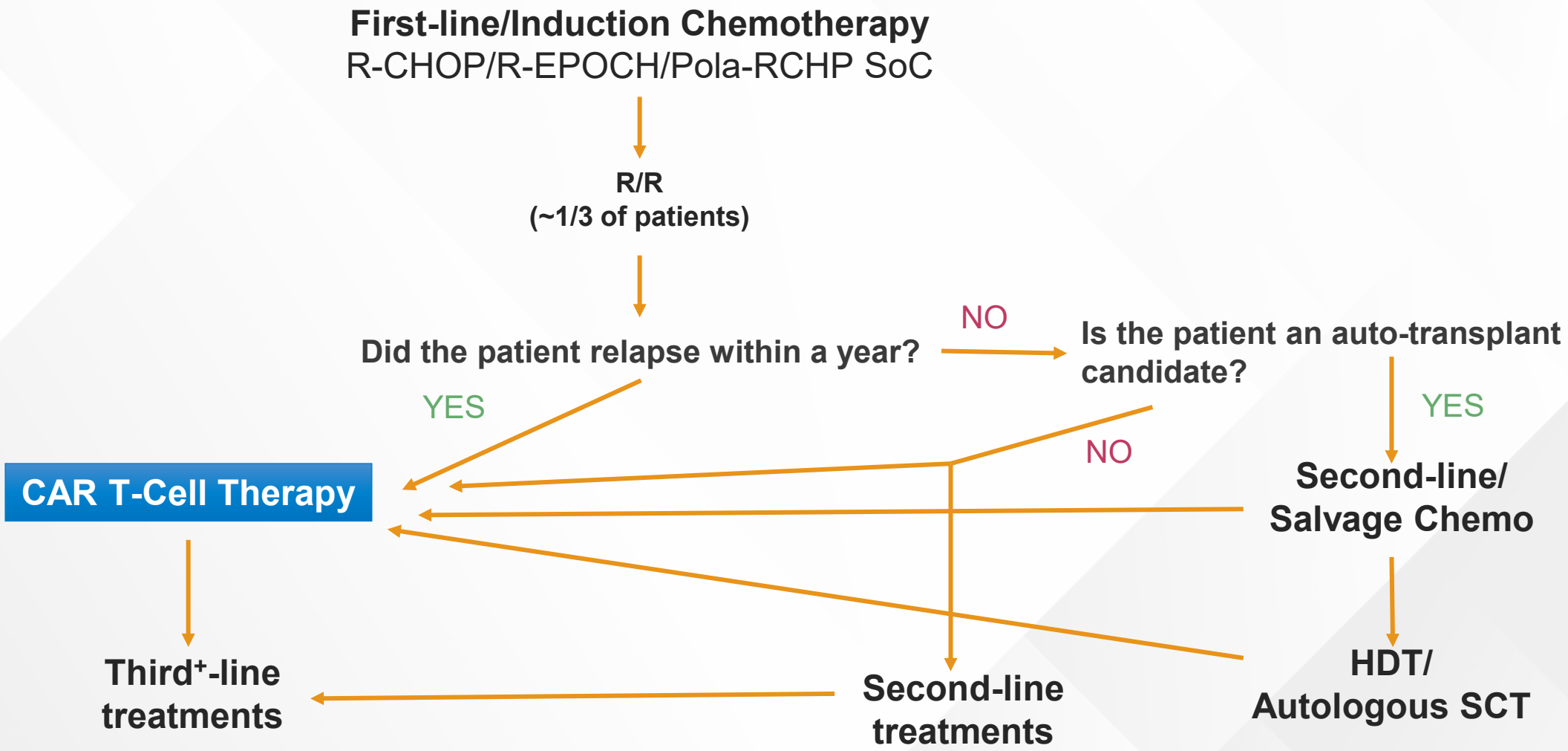
CAR T cells in Frontline: ZUMA-23

High-risk DLBCL:
- DHL or THL
- IPI 4-5



Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CHOP, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone; DHL, double-hit lymphoma; DLBCL, diffuse large B-cell lymphoma; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, hydroxydaunorubicin; IPI, International Prognostic Index; R, rituximab; THL, triple-hit lymphoma.
NCT05605899; Westin et al. *Journal of Clinical Oncology* 41, no. 16_suppl (June 01, 2023) TPS7578-TPS7578.

LBCL: Treatment Paradigm 2023



Courtesy of Caron Jacobson, MD.

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.

Screening and Referral Recommendations:
How Has the 2nd-Line Approval Changed Clinical Practice?

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 chemoimmunotherapy

Optimal referral practices change with 2L approval

- 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

3rd-line CAR:

Refer at the time of first relapse

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

AXIS Medical Education

Courtesy of Caron Jacobson, MD.

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.

Bridging:
How Has the 2nd-Line Approval Changed Clinical Practice?

Bridging and managing patients

- 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

Preferred Bridging 3L CAR:

- Steroids alone
- Radiation
- Polatuzumab with or without R (prefer to avoid bendamustine*)

Preferred Bridging 2L CAR, Primary Refractory:

- Steroids alone
- Radiation
- Traditional salvage chemotherapy (RICE, RDHAC)

Preferred Bridging 2L CAR, Later Relapse:

- Steroids alone
- Radiation
- Polatuzumab with or without R (prefer to avoid bendamustine*)

AXIS Medical Education

Courtesy of Caron Jacobson, MD.
*Defer bendamustine use in bridging until after apheresis.
AR, chimeric antigen receptor; R, rituximab; RDHAC, rituximab, dexamethasone, cytarabine, carboplatin; RICE, rituximab, ifosfamide, carboplatin, etoposide.

Approach to Unanswered Questions:
How Has the 2nd-Line Approval Changed Clinical Practice?

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…
    - But in reality, it is logistically and financially challenging to switch to auto-transplant given prior insurance authorization
    - Sticking with CAR may be clinically the right thing to do anyway given the survival benefits

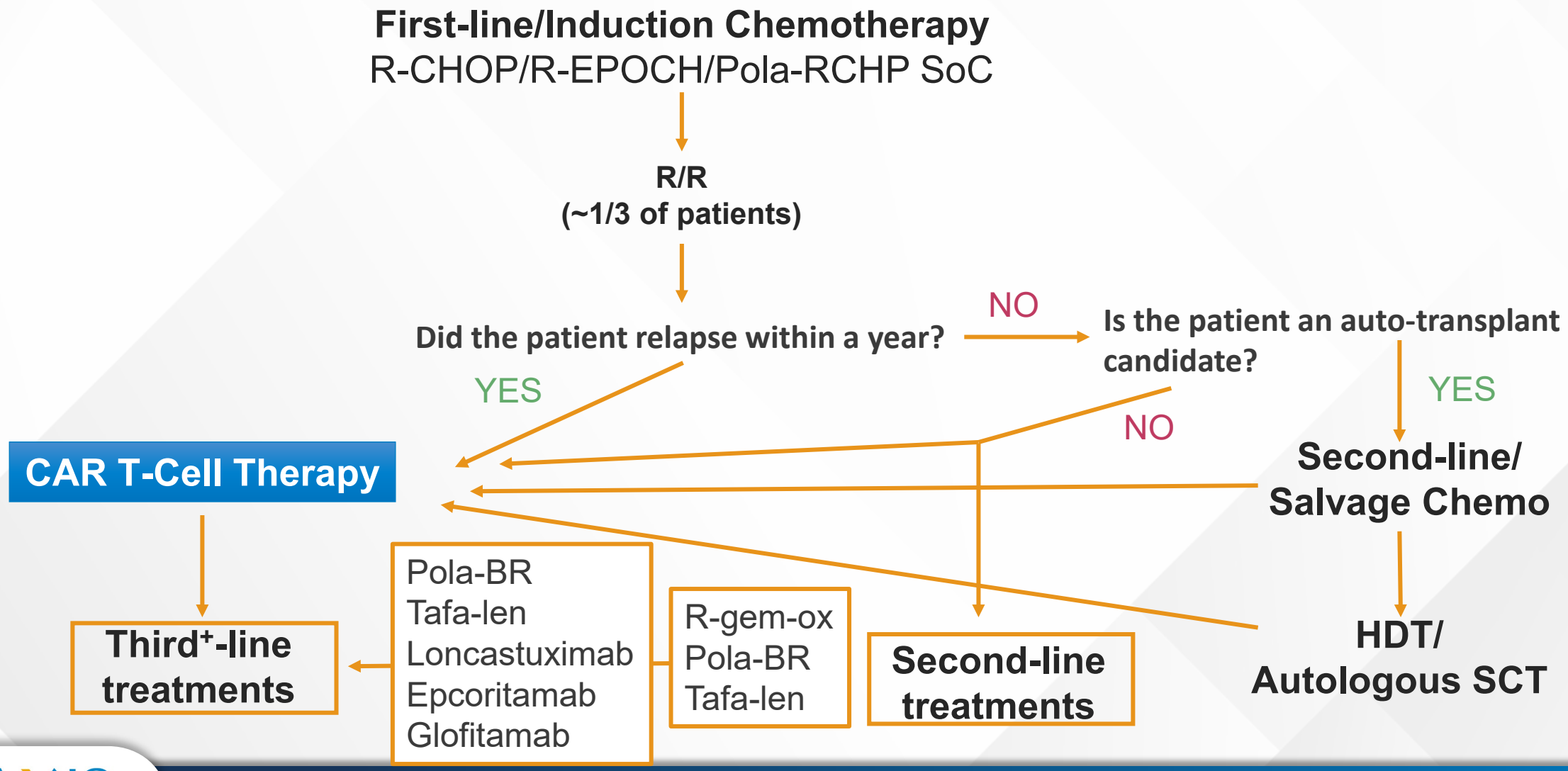
What about salvage/auto after 2nd-line CAR?

- On ZUMA-7, this was feasible and for patients who got to auto-transplant, outcomes were promising
- May be impossible for 25-30% of patients with prolonged cytopenias

AXIS Medical Education

Courtesy of Caron Jacobson, MD.
auto, autologous; CAR, chimeric antigen receptor.

LBCL: Treatment Paradigm 2023



Courtesy of Caron Jacobson, MD.

BR, bendamustine, rituximab; CAR, chimeric antigen receptor; CHOP, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, hydroxydaunorubicin; gem, gemcitabine; HDT, high-dose therapy; LBCL, large B-cell lymphoma; len, lenalidomide; ox, oxaliplatin; Pola, polatuzumab vedotin; R, rituximab; RCHP, rituximab, cyclophosphamide, doxorubicin, prednisone; R/R, relapsed/refractory; SCT, stem cell transplantation; SoC, standard of care; tafa, tafasitamab.

How to Sequence Newer 2nd- and 3rd-Line Therapies

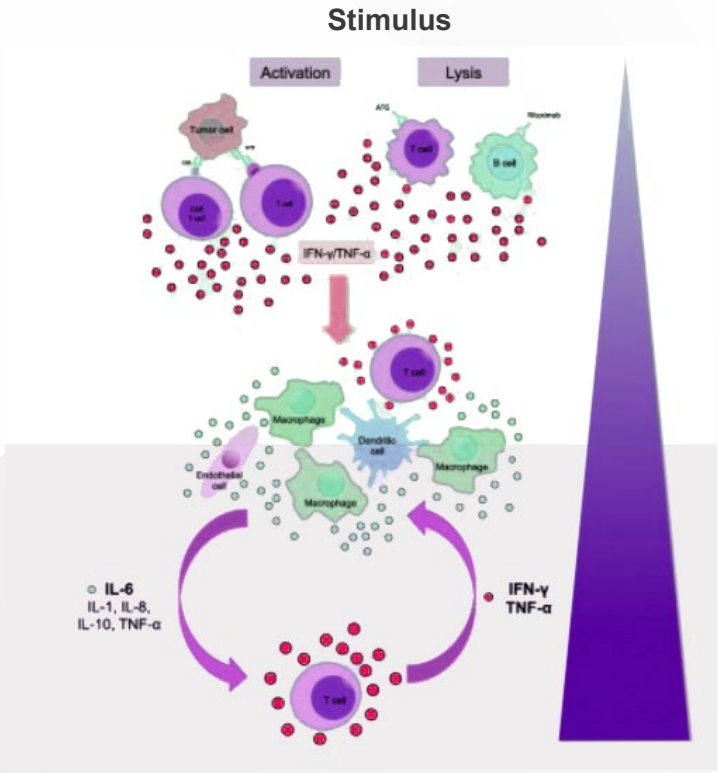
- Hypothetical concern of targeting CD19 ahead of CD19 CAR T-cells, so best to avoid if CD19 CAR T-cells are planned
  - Tafasitimab: receptor occupancy issue, wash-out of at least 6-12 weeks is ideal
  - Loncastuximab: less of a concern but still best to reserve for CD19+ relapses AFTER CAR or for CAR ineligible
    - > Loncastuximab after CAR has been shown to be safe and effective
- Hypothetical concern of T-cell exhaustion due to bispecific antibody engagement if bispecifics used prior to CAR T-cells
  - Try to avoid bispecifics ahead of CAR T-cells until proven effective
  - CAR T-cells before bispecific known to be safe and effective from trials
  - If cannot avoid, try to have a 12+ week wash out

CAR, chimeric antigen receptor.

CAR T-Cell Toxicities: Mitigation and Management via Interprofessional Teams

CAR T-Cell Toxicities: The Yin to Their Yang

Cytokine Release Syndrome (CRS)



CRS Grading

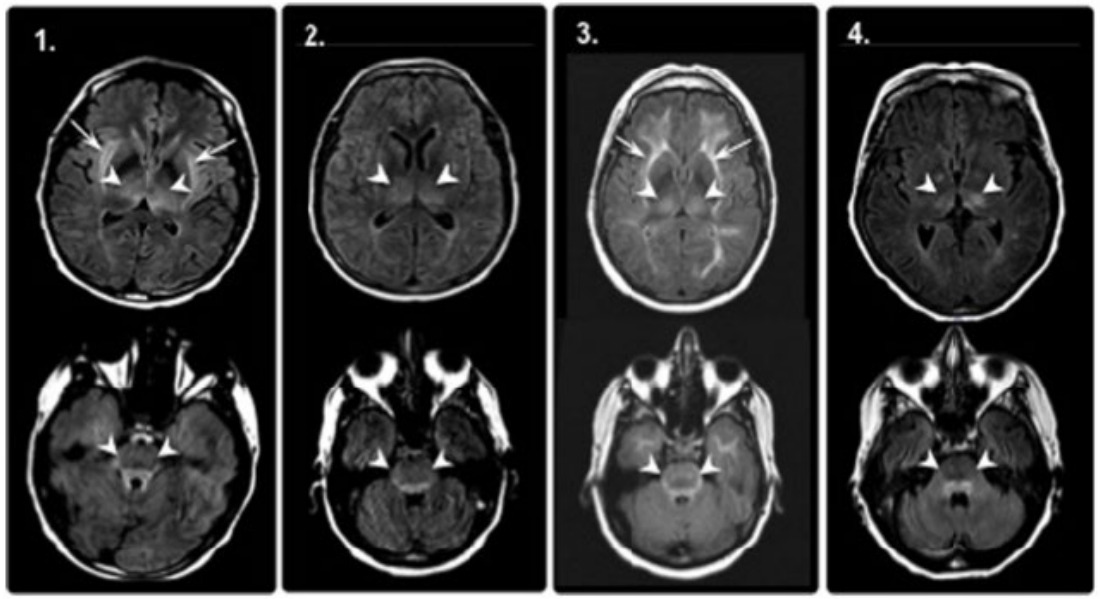
Grade 1
- Fever
- Constitutional symptoms

Grade 2
- Hypotension responding to fluids/low dose vasopressors
- Grade 2 organ toxicities

Grade 3
- Shock requiring high dose/multiple vasopressors
- Hypoxia requiring ≥ 40% FiO2
- Grade 3 organ toxicities, grade 4 transaminases

Grade 4
- Mechanical ventilation
- Grade 4 organ toxicities (excl. transaminases)

Neurotoxicity/ICANS



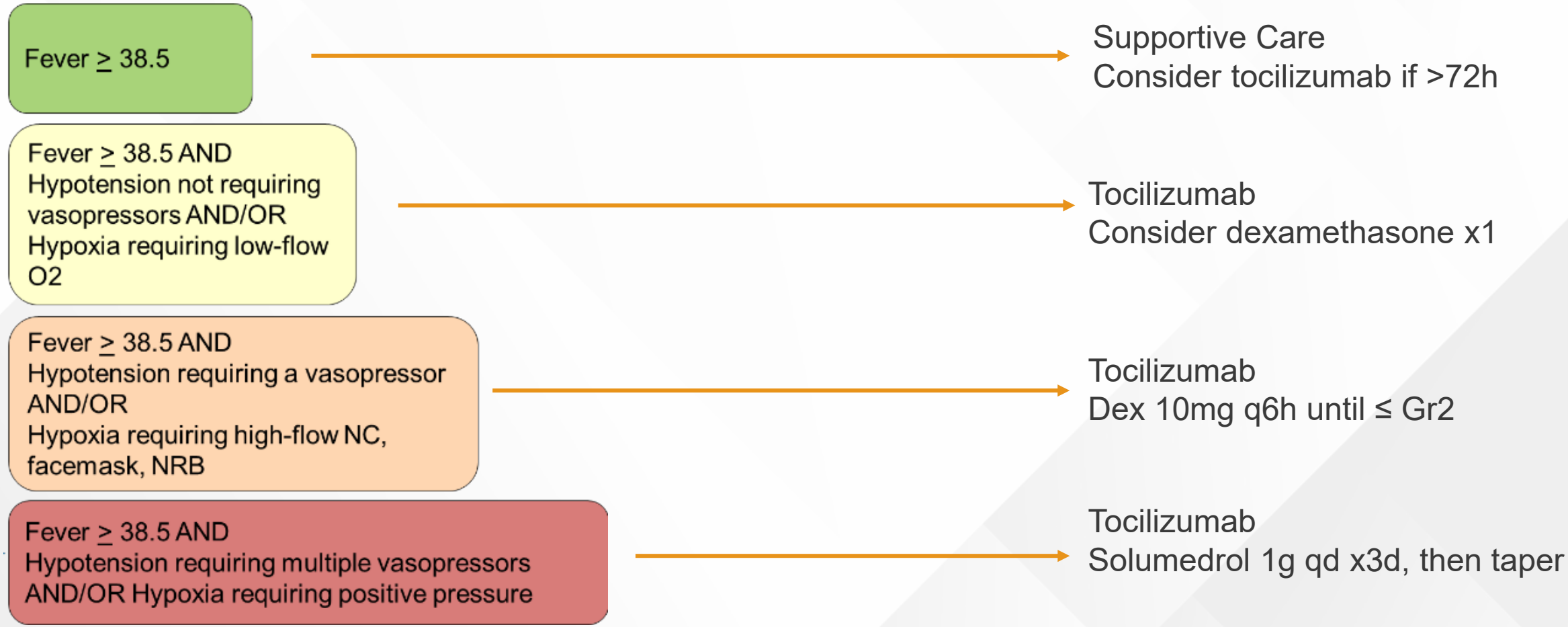
CAR, chimeric antigen receptor; FiO2, fraction of inspired oxygen; ICANS, immune effector cell-associated neurotoxicity syndrome; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.
Adapted from Shimabukuro-Vornhagen A, et al. *J Immunother Cancer*. 2018;6:56.

Rates and Kinetics of CRS and ICANS

	ZUMA-1[1]	JULIET[2]	TRANSCEND CORE[3]	ZUMA-7[4]	TRANSFORM[5]	BELINDA[6]
Product	**Axi-cel**	**Tisa-cel**	**Liso-cel**	**Axi-cel**	**Liso-cel**	**Tisa-cel**
# treated	101	111	269	170	92	155
CRS, %	93	58	42	92	49	61
Gr 3+ CRS, %	13	22	2	6	1	5
Medan Onset (d)	2	3	5	3	5	4
ICANS, %	64	21	30	60	11	10
Gr 3+ ICANS, %	28	12	10	21	4	2
Median Onset (d)	5	6	9	7	11	5

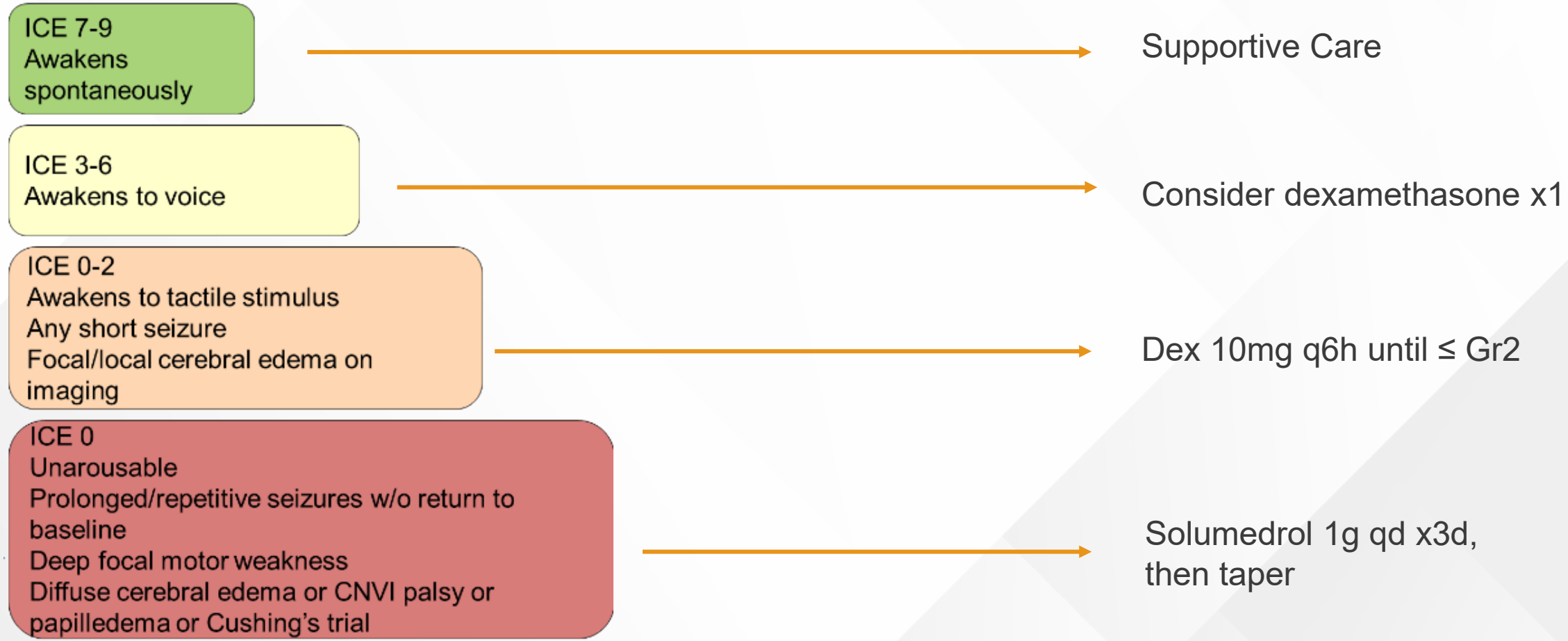
1. Neelapu SS, et al. *N Engl J Med.* 2017;377:2531-2544. 2. Schuster SJ, et al. *N Engl J Med.* 2019;380:45-56.
5. Kamdar M, et al. *Lancet.* 2022;399(10343):2294-2308. 6. Bishop MR, et al. *N Engl J Med.* 2022;386(7):629-639.
Axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; Liso-cel, lisocabtagene maraleucel; Tisa-cel, tisagenlecleucel.

Cytokine Release Syndrome (CRS)*



*Potential use of prophylactic dexamethasone 10mg daily on d0,1,2 of axi-cel with decreased rates of Grade 3+ CRS and ICANS and equivalent efficacy outcomes.
See Risk Evaluation and Mitigation Strategy (REMS).
Dex, dexamethasone; NC, nasal cannula; NRB, non-rebreather mask; q, every; d, day; h, hour; Gr, Grade.
Neelapu et al. *Nat Rev Clin Oncol*. 2018;15(1):47-62. Lee et al. *Biol Blood Marrow Transplant*. 2019;25:625-638.

Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)*



*Potential use of prophylactic dexamethasone 10mg daily on d0,1,2 of axi-cel with decreased rates of Grade 3+ CRS and ICANS and equivalent efficacy outcomes.
See Risk Evaluation and Mitigation Strategy (REMS).
CNVI, cranial nerve VI; Dex, dexamethasone; ICE, immune effector cell-associated encephalopathy; q, every; d, day; h, hour; Gr, Grade.
Neelapu et al. *Nat Rev Clin Oncol*. 2018;15(1):47-62. Lee et al. *Biol Blood Marrow Transplant*. 2019;25:625-638.

CAR T-Cells Long-Term Toxicities

B-cell aplasia/ hypogammaglobulinemia

- ~40-50% B-NHL pts s/p CD19 CARs will NOT have IgG recovery by 24 months
- Immunoglobulin levels should be monitored following therapy

Cytopenias

- Grade ≥ 3 cytopenias unresolved by Day 30 post treatment occur in 25-30% of patients
- Median time to recovery 6m
- Blood counts should be monitored

Infections

- Occurred in 35-50% of patients treated with approved agents in pivotal trials
- Median time to infection is 1m for bacterial infections, and 2-3m for viral and fungal infections

AXIS Medical Education

B-NHL, B-cell non-Hodgkin lymphoma; CAR, chimeric antigen receptor; IgG, immunoglobulin G.

Short-Term Monitoring: Days to Weeks From Infusion

Outpatient

- 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

Inpatient

- 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
- Patients are monitored for ongoing cytopenias, hydration status; first response assessment at **4 weeks**

Caregiver present 24h a day for whatever portion of the 4 weeks post-CAR-T is spent out of the hospital

CAR, chimeric antigen receptor; CRS, cytokine release syndrome; NT, neurotoxicity.

Long-Term Monitoring: Weeks to Months from Infusion

- 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
- Antibiotic (herpes and PJP) prophylaxis
  - Variable practices – we continue for at least 6 months at which time we measure the CD4 count and only discontinue when >200
- Vaccination
  - Influenza – yearly
  - Post-transplant vaccines – resume 12 months after CAR T-cell therapy?
  - COVID vaccination – 3 months from CAR T-cell therapy (unknown)
- Upon relapse patients should be biopsied whenever possible to help determine next treatment

AXIS Medical Education

CAR, chimeric antigen receptor; COVID, Coronavirus disease; G-CSF, granulocyte colony stimulating factor; IgG, immunoglobulin G; IVIG, intravenous immunoglobulin; PJP, Pneumocystis jirovecii pneumonia.

Future Real World Factors Determining Success of Delivering Outpatient CAR T-Cell Therapy

Patient Volume
How Has the 2nd-Line Approval Changed Clinical Practice?

Assumption:

- Overall volume would not change after an initial influx because most of the patients eligible for 2nd-line therapy would eventually fail SoC and then need CAR T cells in the 3rd-line

Reality:

- Approvals in 2nd-line led to an increase in referrals for CAR T cells overall and more patients are getting to CAR because of earlier referral

Result:

- Volume is up, taxing apheresis and inpatient hospital capacity

Solutions:

- Establishing and expanding an outpatient CAR program
- Expanding apheresis capacity
- Creating flexibility inpatient by training a second inpatient team to absorb some CAR patients

CAR, chimeric antigen receptor, SoC, standard of care.

Developing an Outpatient CAR T-Cell Therapy Program

- Expanding CAR T-cell therapies in lymphoma and myeloma are taxing the system
- Outpatient CAR T-cell therapy may address issues with inpatient capacity

Outpatient CAR T-cell programs can follow two different models:

Select low-risk patients and products:

- Patients/caregivers taught how to monitor vitals and mental status and log results
- Seen once/day with labs
- Phone check in once/evening
- Wearable devices could help but not absolutely necessary

Offer all patients and products outpatient:

- Requires increased infrastructure (ie, centralized housing with potential remote nursing services)
- Wearable devices become more important

CAR, chimeric antigen receptor.

Developing an Outpatient CAR T-Cell Therapy Program

How do you manage outpatient toxicities that arise?

Admit all Grade 1 CRS:

- Necessary if patients need to pass through ED and cannot be directly admitted
- Necessary if ability to give outpatient TOCI/DEX limited/impossible
- Necessary for certain medically and socially at-risk patients

Manage Grade 1 CRS outpatient, admit for Grade 2+:

- Possible if TOCI/DEX are readily available to outpatients and outpatient hours are conducive
- Reliant on a reserved “crash bed” for direct inpatient admission and a clinical team able to meet the patient upon presentation to the hospital

AXIS Medical Education

CAR, chimeric antigen receptor; CRS, cytokine release syndrome; DEX, dexamethasone; ED, emergency department; TOCI, tocilizumab.

Collaborating with the Multidisciplinary CAR T-Cell Therapy Team

CAR T-Cell Patient Journey

Patient identification (meets FDA label)

- LBCL 2+ or 3+L
- MCL 2+L
- FL 3+L
- No age cut-off
- No requirement for CD19+
- CAR centers will have variable eligibility criteria so best to refer and let them decide
- Patients can be CAR candidates who are not auto-transplant candidates
- The earlier the referral the better!

Referral to CAR T-cell specialist

- Eligibility evaluation
- Insurance authorization
- Consent and education

T-cell collection

LD chemotherapy and T-cell infusion

- LD chemo mostly outpatient (i.e Flu/Cy x 3 days)
- CAR infusion can be inpatient or outpatient
- Post-CAR monitoring involves daily labs, close vital sign monitoring, and exams for at least 7 days to assess for CRS/NT

Close monitoring +/- bridging therapy

- Is the patient experiencing significant symptoms or at risk for organ function impairment?
- Bridging could include steroids, palliative RT, chemotherapy, and/or newer targeted agents

Acute post-CAR monitoring

- Patients remain within 2 hours of CAR center for 4 weeks after CAR T-cell infusion
- Monitor for late CRS/NT and/or ongoing cytopenias
- First response assessment often at 4-week mark

Long-term post-CAR monitoring

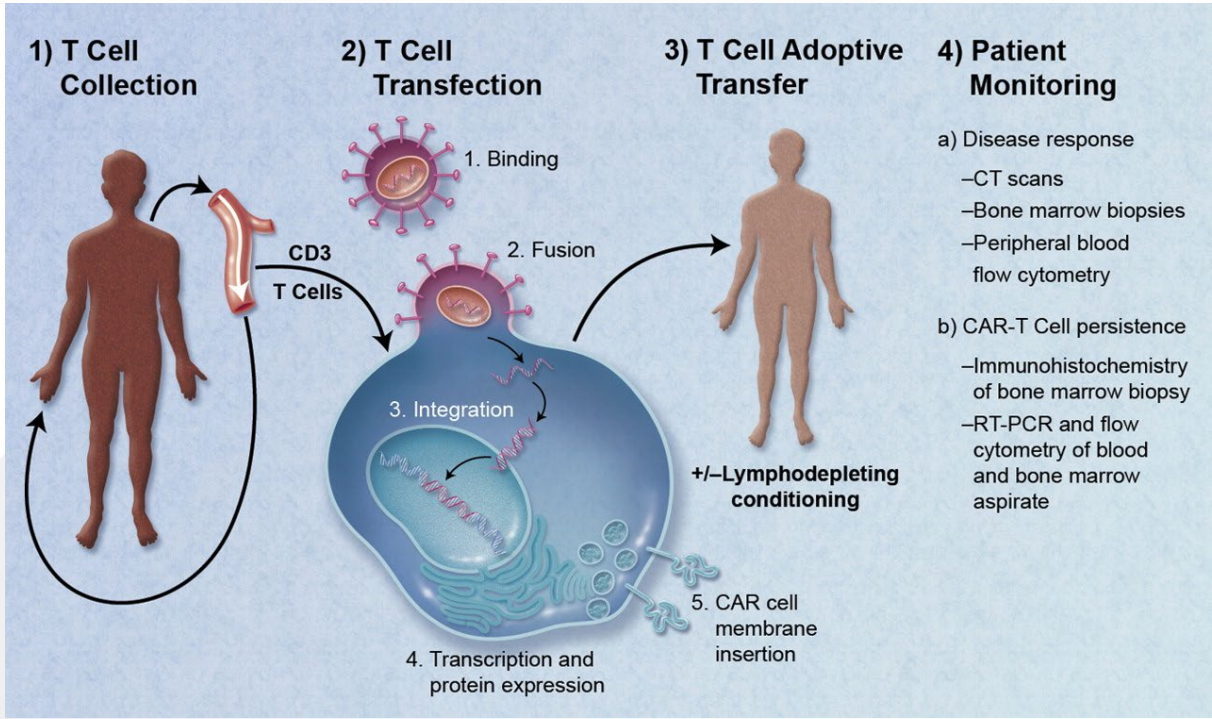
AXIS Medical Education

Auto, autologous; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; FDA, U.S. Food and Drug Administration; FL, follicular lymphoma; Flu/Cy, fludarabine/cyclophosphamide; LBCL, large B-cell lymphoma; LD, low-dose; MCL, mantle cell lymphoma; NT, neurotoxicity; RT, radiation therapy.

Who is Eligible for CAR T-Cell Therapy?

- Eligibility is expanding with time given improved toxicity mitigation and increased experience
  - Early referral remains the most important risk factor to maximize efficacy and minimize toxicity related to tumor volume
- There are many disease and patient features associated with poor response and toxicity and efforts should be made to minimize these
  - Early referral
  - Improved bridging and sequencing choices
- At the present time, there are no risk scores or stratification that should rule-out CAR T-cell therapy for any patient
  - No current alternative therapy that is better than CAR T-cell for highest-risk patients
  - High-risk patients represent an unmet need for whom we need better cellular therapies

CAR T-Cell Therapy Built-in Delays



- Insurance authorization: **2-4 weeks**
- Pheresis and line placement availability: **1-2 weeks** (but can be booked ahead of insurance authorization)
- Sponsor manufacturing slot availability: **immediate – 6 weeks** depending on sponsor
- Manufacturing time: **17-30 days**

CT, computed tomography; RT-PCR, reverse transcription-polymerase chain reaction.

Jacobson CA, et al. *Blood*. 2011;118(18):4761-4762.

CAR T-Cell Patient Identification: Early ID and Referral Matters!

- Long-term remission is associated with fitter patients, with lower tumor burden and fitter T cells, so early referral can optimize outcomes for a multitude of reasons
- Toxicity risk is also minimized in patients with lower pretreatment tumor burden and lower levels of inflammation
- Patients with borderline organ function and comorbid conditions may do less well but they still do better than expected with other available therapies
  - Non-autologous transplant patients may still be good CAR T-cell candidates
- ID and refer patients early and let the treating center evaluate eligibility to ensure optimal outcomes

CAR, chimeric antigen receptor.

Screening and Referral Recommendations:
How Has the 2nd-Line Approval Changed Clinical Practice?

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 chemoimmunotherapy

Optimal referral practices change with 2L approval

- 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

3rd-line CAR:

Refer at the time of first relapse

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

AXIS Medical Education

Courtesy of Caron Jacobson, MD.

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.

Bridging Therapy for CAR T-Cell Therapy in Lymphoma

Indications

- Rapidly growing lymphoma
- Bulky disease
- Symptomatic patient (pain)
- Major organ involvement or obstruction
- Expected delay in CAR T-cell production

Regimens

- Steroids (eg, dexamethasone)
- Polatuzumab ± rituximab
- Radiation therapy
- Rituximab ± chemotherapy
- Ibrutinib, lenalidomide

Regimen Selection

- Prior therapies
- Regimen-related toxicities
- Site(s) of disease
- Comorbidities
- Blood counts
- Simplicity of administration

CAR, chimeric antigen receptor.

Bridging Therapy: Lessons Learned

- Bridging with standard myelosuppressive chemoimmunotherapy may affect prognosis negatively
  - Failure to effectively debulk chemoresistant patients
  - Myelosuppressive effects of chemotherapy may increase treatment-related mortality
- Bridging with non-myelosuppressive therapies is therefore preferable
  - Theoretical immunologic advantages of radiotherapy when feasible
  - DLBCL: Newer agents like polatuzumab have theoretically improved safety to efficacy profile
  - Avoidance of lymphodepleting and myelosuppressive therapies and therapies that target CD19 or exhaust T cells immediately before CAR T-cells therapy
  - Steroids can be given up to 1 week before pheresis and up to the day before LD chemotherapy
  - Low dose steroids (prednisone 5-10mg daily or decadron 2mg daily) have been continued through pheresis, LD chemo, and CAR infusion when they cannot be discontinued w/o ill effect

CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; LD, low-dose.

Bridging:
How Has the 2nd-Line Approval Changed Clinical Practice?

Bridging and managing patients

- 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

Preferred Bridging 3L CAR:

- Steroids alone
- Radiation
- Polatuzumab with or without R (prefer to avoid bendamustine*)

Preferred Bridging 2L CAR, Primary Refractory:

- Steroids alone
- Radiation
- Traditional salvage chemotherapy (RICE, RDHAC)

Preferred Bridging 2L CAR, Later Relapse:

- Steroids alone
- Radiation
- Polatuzumab with or without R (prefer to avoid bendamustine*)

AXIS Medical Education

Courtesy of Caron Jacobson, MD.
*Defer bendamustine use in bridging until after apheresis.
CAR, chimeric antigen receptor; R, rituximab; RDHAC, rituximab, dexamethasone, cytarabine, carboplatin; RICE, rituximab, ifosfamide, carboplatin, etoposide.

Determining Who Can Get CAR T-Cells Outpatient

Outpatient CAR T-cell programs can follow two different models and patient selection depends on them:

Select low-risk patients and products:

- Patients must have a reliable and willing caregiver
- Patients must have means to pay for travel/housing/food
- Patients/caregivers taught how to monitor vitals and mental status and log results
- Wearable devices could help but not absolutely necessary

Offer all patients and products outpatient:

- Requires increased infrastructure (ie, centralized housing with potential remote nursing services)
- Requires means to reimburse or prorate patients for travel, lodging, food
- Requires means to monitor the patient 24h/d, 7d/wk
- Wearable devices become more important

CAR T-Cells Long-Term Toxicities

B-cell aplasia/ hypogammaglobulinemia

- ~40-50% B-NHL pts s/p CD19 CARs will NOT have IgG recovery by 24 months
- Immunoglobulin levels should be monitored following therapy

Cytopenias

- Grade ≥ 3 cytopenias unresolved by Day 30 post treatment occur in 25-30% of patients
- Median time to recovery 6m
- Blood counts should be monitored

Infections

- Occurred in 35-50% of patients treated with approved agents in pivotal trials
- Median time to infection is 1m for bacterial infections, and 2-3m for viral and fungal infections

B-NHL, B-cell non-Hodgkin lymphoma; CAR, chimeric antigen receptor; IgG, immunoglobulin G.

CAR T-Cell Referral to and From the Community: Lessons Learned

- Refer all eligible patients as early as possible – ideally one line of therapy BEFORE it is indicated
  - Regardless of age or comorbidities: let the treating center decide
  - Know your CAR T-cell MDs for easier and direct referral
  - Education, screening, insurance authorization are all managed by the CAR T-cell treatment center
- Patient may require bridging and often prefer this to be done locally
  - Vital that the CAR T-cell center be forthcoming and specific with dates of collection and treatment for timing of bridging, recommendations for bridging, and monitoring for response and progression
  - Vital that the referring center communicate any new status changes with the patient with the CAR T-cell center in real-time

CAR, chimeric antigen receptor.

CAR T-Cell Referral to and From the Community: Lessons Learned (continued)

- Patient will remain at CAR T-cell center for 4-5 weeks from LD chemotherapy through 1m following CAR T-cell infusion
  - This is when CRS and ICANS happen and are monitored and managed
- Upon referral back to community:
  - CAR T-cell center MUST update local practice about CAR T-cell course and disease response assessment; ongoing toxicities and how to monitor and manage them; recommendations for long-term screening and surveillance
  - Community practices should update CAR T-cell center on persistence/resolution of ongoing toxicities, new toxicities, results of disease response surveillance assessments

CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; LD, low-dose.

Practical Application
Case Study

Case Study: Patient Presentation and History

- GS is a 68-year-old woman who presented with low back pain
  - Scans showed a 6x9cm retroperitoneal lymph node mass
  - A biopsy showed DLBCL with *MYC* and *BCL2* overexpression but no *MYC* translocation
  - PET showed nodal disease in the chest and abdomen/pelvis as well as in the bones, liver, and kidneys
  - LDH was elevated at 560
  - PMH: HTN and hypothyroidism

DLBCL, diffuse large B-cell lymphoma; HTN, hypertension; LDH, lactate dehydrogenase; PET, positron emission tomography; PMH, past medical history.

Case Study:
What is the Best Frontline Treatment for GS?

a) RCHOP x6 cycles
b) Pola-RCHP x6 cycles
c) REPOCH x6 cycles
d) CD19 CAR T cells
e) Unsure

AXIS Medical Education

CAR, chimeric antigen receptor; CHOP, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, hydroxydaunorubicin; Pola, polatuzumab vedotin; R, rituximab.

Case Study: What is the Best Second-Line Treatment?

- GS was not interested in participating in a clinical trial and therefore received 6 cycles of Pola-RCHP
- PET after 3 cycles showed a very good partial response
- PET after 6 cycles showed progressive disease compared to her mid-treatment PET

- What is the best treatment option now?
  a) CD19 CAR T-cells with tisagenlecleucel
  b) CD19 CAR T-cells with lisocabtagene maraleucel
  c) Loncastuximab
  d) RICE chemotherapy and if responsive, autologous stem cell transplant
  e) Unsure

AXIS Medical Education

CAR, chimeric antigen receptor; PET, positron emission tomography; REPOCH, rituximab, cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone; RICE, rituximab, ifosfamide, carboplatin, etoposide.

Case Study: What is the Best Second-Line Treatment?

- What if GS had a complete response to treatment after 6 cycles of Pola-RCHP and stayed in remission for 18 months?
- What is the best treatment for her next?
  a) CD19 CAR T-cells with axicabtagene ciloleucel
  b) CD19 CAR T-cells with tisagenlecleucel
  c) CD19 CAR T-cells with lisocabtagene maraleucel
  d) Loncastuximab
  e) RICE chemotherapy and if responsive, autologous stem cell transplant

CAR, chimeric antigen receptor; REPOCH, rituximab, cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone; RICE, rituximab, ifosfamide, carboplatin, etoposide.

Case Study: What is the Best Second-Line Treatment?

- What if GS had a complete response to treatment after 6 cycles of Pola-RCHP and stayed in remission for 18 months, but was 78 years old instead of 68?

- What is the best follow-up treatment in that case?
  a) CD19 CAR T-cells with axicabtagene ciloleucel
  b) CD19 CAR T-cells with tisagenlecleucel
  c) CD19 CAR T-cells with lisocabtagene maraleucel
  d) RICE chemotherapy and if responsive, autologous stem cell transplant
  e) Unsure

CAR, chimeric antigen receptor; REPOCH, rituximab, cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone; RICE, rituximab, ifosfamide, carboplatin, etoposide.

Case Study: What is the Best Third-Line Treatment?

- GS had CD19 CAR T-cell treatment for primary refractory disease with axicabtagene ciloleucel
- She had a complete response at 1m but by 6m she had relapsed disease
- Biopsy shows that the disease is CD19+

- All of the following are appropriate next treatments **except:**
  a) CD19 CAR T-cell retreatment with axicabtagene ciloleucel
  b) Epcoritamab
  c) Loncastuximab
  d) Polatuzumab-bendamustine-rituximab
  e) Tafasitimab-Lenalidomide

CAR, chimeric antigen receptor.

Key Takeaways

- Relapsed LBCL is still curable!
- Late-relapsing, transplant-eligible patients should get salvage chemo and ASCT (if chemosensitive)
- Early relapsing or transplant ineligible patients should get CAR T cells
- Third-line patients should get CAR T cells
- Patients who relapse after CAR T cells or patients who are transplant- and/or CAR-ineligible have increasing options for palliation or bridging to alloSCT
- Ongoing studies moving all of these therapies into earlier (and even frontline) settings will turn the sequencing of therapies for LBCL on its head
- The FDA has approved axi-cel and liso-cel as second-line treatment of LBCL

ASCT, autologous stem cell transplant; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; LBCL, large B-cell lymphoma; FDA, Food and Drug Administration; liso-cel, lisocabtagene maraleucel; R, rituximab; SCT, stem cell transplantation.

AXIS Medical Education

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

Considerations for Community Practice