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Exploring BiSpecifics and CAR-T Therapies

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Orlando, FL
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OBJECTIVES

1. Identify the current indications of CAR T-cell therapy and Bispecifics in B-cell non-Hodgkin lymphomas.
2. Summarize the existing challenges associated with delivery of care with CAR T-cell and bispecific therapies.
3. Discuss therapeutic options to manage relapse post-CAR T-cell therapy.
4. Recognize the future implications for CAR T-cell and bispecific therapies.

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DISCLOSURE

The following relevant financial relationships from the past 24 months have been identified and disclosed for the following faculty of this CE activity:

- **Mohamed A. Kharfan-Dabaja, MD, MBA, FACP**
  - Research/Grant:
    - Mayo Clinic Florida site PI for clinical trial
      - Novartis
      - Bristol Myers Squibb
      - Pharmacyclics
  - Lecture/Honoraria:
    - Kite Pharma

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DISCLOSURE

The following relevant financial relationships within the past 24 months have been identified and disclosed for the reviewers of this CE presentation:

- **Chris Elder, PharmD, BCOP**
  - Advisory board member for which honorarium was received for the following:
    - Boehringer Ingelheim
    - Eiasi
    - Janssen
    - Mirati
    - Novartis
    - Pfizer
    - Pharmacosmos
    - Sanofi

No relevant financial relationships from the past 24 months have been identified and disclosed for other planners of this CE activity:

- **Daisy Doan, PharmD**

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Definition of abbreviations

- BCMA: B-cell maturation antigen
- CAR T-cell: Chimeric antigen receptor T-cell
- CLL: Chronic lymphocytic leukemia
- DLBCL: Diffuse large B-cell lymphoma
- FL: Follicular lymphoma
- MCL: Mantle cell lymphoma
- MZL: Marginal Zone lymphoma
- NRM: Non-relapse mortality
- PFS: Progression-free survival
- OS: Overall survival

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CAR T-Cell Therapy: A Living Therapy

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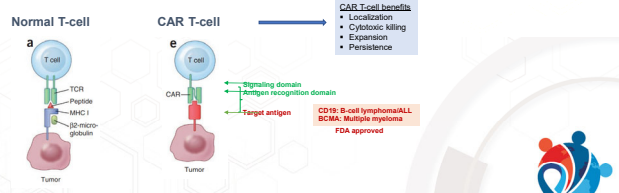
What is CAR T-cell therapy?

- Stands for Chimeric Antigen Receptor T-cell Therapy
- Immunotherapy that uses engineered T lymphocytes to specifically target the intended cancer cell



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Adapted and modified from Klebanoff CA & Rosenberg SP. Nat Biotechnol. 2013; 31(11):999-1008

8

CD19

- Encoded by the 7.41 Kilobase CD19 gene on short arm of chromosome 16
- Expressed in all phases of B-cell development
- It is incorporated in flow cytometry panels to diagnose B-cell malignancies
  - B-cell ALL, B-cell lymphomas (DLBCL, FL, MCL, MZL) and CLL
- Ideal target for immunotherapy

BCMA

- Member of the tumor necrosis factor receptor (TNFR) superfamily
- Expressed preferentially by mature B lymphocytes, with minimal expression in hematopoietic stem cells or nonhematopoietic tissue
- Essential for survival of long-lived bone marrow plasma cells
- Ideal target for immunotherapy

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Kochenderfer JN, et al. Nat Rev Clin Oncol. 2013;10: 267-76
Dogan A, et al. Blood Cancer Journal. 2020; 10: 73

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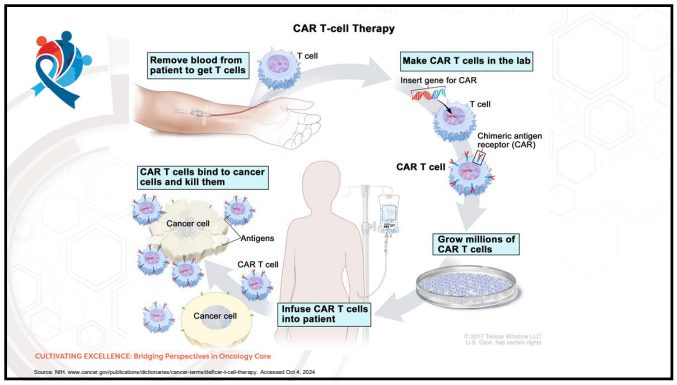

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B-cell lymphoid malignancies: indications by commercially available products 2024 (adults)

	Brexucabtagene autoleucel	Axicabtagene ciloleucel	Tisagenlecleucel	Lisocabtagene maraleucel
3rd line DLBCL	No	Yes	Yes	Yes
Transformed FL	No	Yes	Yes	Yes
PMBCL	No	Yes	No	Yes
2nd line DLBCL	No	Yes	No	Yes
R/R MCL	Yes	No	No	Yes
R/R FL (non-transformed)	No	Yes	Yes	Yes
R/R CLL	No	No	No	Yes
R/R B-cell ALL	Yes	No	Yes	No

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Diffuse Large B-cell Lymphoma

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Before availability of CAR-T

Outcomes of R/R DLBCL after failing 2 prior Rx were dismal

Table 2. Rate of response to chemotherapy after refractory disease

	MDACC (n = 165)	IA/MC (n = 82)	LY.12 (CCTG) (n = 219)	CORAL (LYSARC) (n = 170)	Pooled* (N = 636)
Patients evaluated for response, n†	165	82	106	170	523
Response rate, % (95% CI)	20	26	26	31	26 (21-31)
CR rate	7	8	8	15	7 (3-15)
PR rate	13	18	25	16	18 (13-23)
Response rate by refractory category, % (95% CI)					
Primary refractory					
RR	—	25	27	10	20 (11-34)
CR rate	—	10	1	2	3 (1-11)
Refractory to second-line or later-line therapy					
RR	20	21	20	40	26 (17-39)
CR rate	7	5	20	18	10 (5-20)
Relapse ≤12 mo post-ASCT					
RR	19	35	—	39	34 (24-45)
CR rate	6	10	—	25	15 (6-31)

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Crump M, et al. Blood. 2017; 130 (16): 1800-09

RR, relapsed or refractory; DLBCL, diffuse large B-cell lymphoma; CR, complete remission; RR, response rate; PR, partial response

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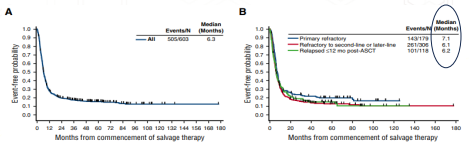
Diffuse large B cell lymphoma: Relapsed or refractory disease



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Crump M, et al. Blood. 2017; 130 (16): 1800-09

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DLBCL: FDA approved agents

	Axicabtagene Ciloleucel	Tisagenlecleucel	Lisocabtagene maraleucel
FDA Approval indication for 3rd line and beyond	**Yes, ZUMA-1**	**Yes, JULIET**	**Yes, TRANSCEND NHL001**
FDA Approval indication for 2nd line and beyond	**Yes, ZUMA-7**	**No**	**Yes, TRANSFORM**
FDA approval for refractory disease to 1st line chemoimmunotherapy or relapse after 1st line chemoimmunotherapy and are **not** eligible for HCT due to comorbidities or age	-	-	**Yes, PILOT**

HCT, hematopoietic cell transplantation

Neelapu SS, et al. N Engl J Med. 2017; 377:2531-44
Schuster et al. N Engl J Med. 2019; 380: 45-56
Abramson JS, et al. Lancet.2020; 396: 839-52
Locke F, et al. N Engl J Med. 2022; 386: 640-54
Bishop M, et al. N Engl J Med. 2022;386(7):629-639
Kamdar M, et al. Lancet. 2022; 399: 2294-2308
Sehgal A, et al. Lancet. 2022; 23 (8): 1066-77

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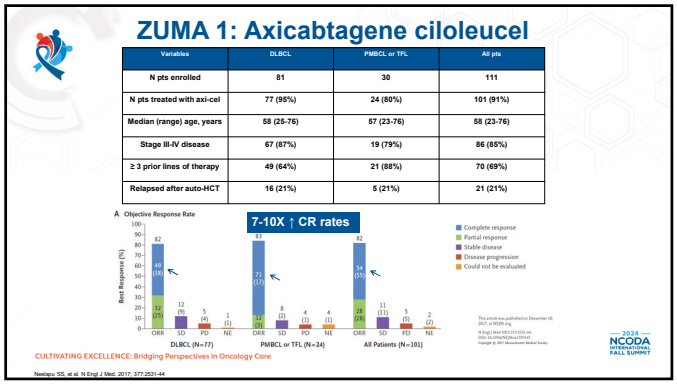
ZUMA 1: Axicabtagene ciloleucel
Variables | DLBCL | PMBCL or TFL | All pts
N pts enrolled | 81 | 30 | 111
N pts treated with axi-cel | 77 (95%) | 24 (80%) | 101 (91%)
Median (range) age, years | 58 (25-76) | 57 (23-76) | 58 (23-76)
Stage III-IV disease | 67 (87%) | 19 (79%) | 86 (85%)
≥ 3 prior lines of therapy | 49 (64%) | 21 (88%) | 70 (69%)
Relapsed after auto-HCT | 16 (21%) | 5 (21%) | 21 (21%)
A Objective Response Rate
7-10X ↑ CR rates
Complete response
Partial response
Stable disease
Disease progression
Could not be evaluated
Best Response (%)
ORR SD PD NE
DLBCL (N=77)
PMBCL or TFL (N=24)
All Patients (N=101)
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Neelapu SS, et al. N Engl J Med. 2017; 377:2531-44

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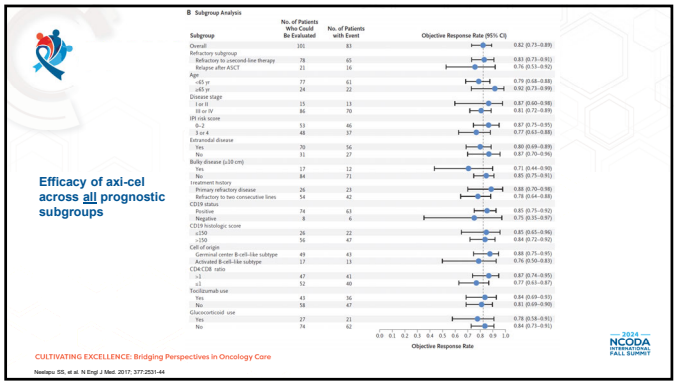
B Subgroup Analysis
No. of Patients Who Could Be Evaluated
No. of Patients with Event
Objective Response Rate (95% CI)
Efficacy of axi-cel across all prognostic subgroups
Objective Response Rate
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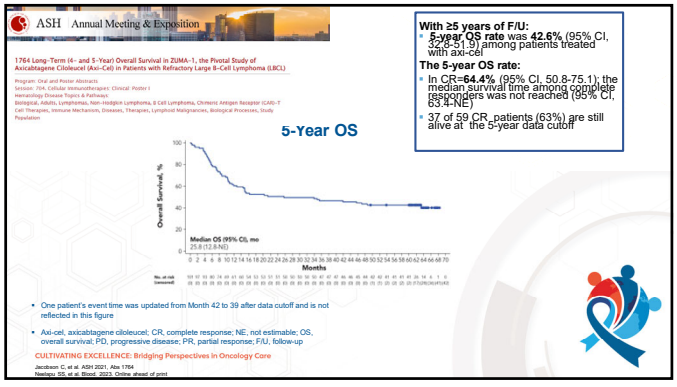
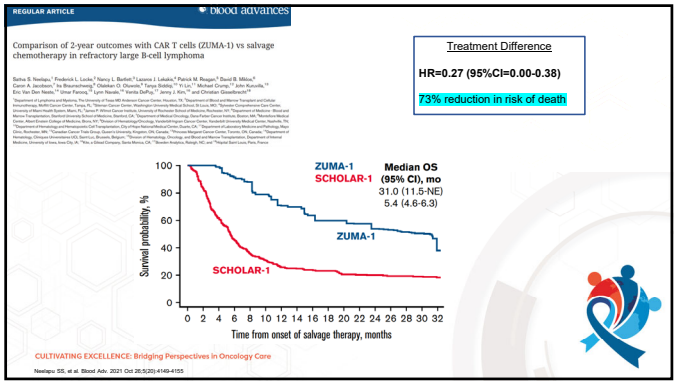
Neelapu SS, et al. N Engl J Med. 2017; 377:2531-44

17


ASH Annual Meeting & Exposition
1764 Long-Term (4- and 5-Year) Overall Survival in ZUMA-1, the Pivotal Study of Axicabtagene Ciloleucel (Axi-Cel) in Patients with Refractory Large B-Cell Lymphoma (LBCL)
5-Year OS
With ≥5 years of F/U:
5-year OS rate was 42.6% (95% CI, 32.6-51.9) among patients treated with axi-cel
The 5-year OS rate:
In CR=64.4% (95% CI, 50.8-75.1); the median survival time among complete responders was not reached (95% CI, 63.4-NE)
37 of 59 CR patients (63%) are still alive at the 5-year data cutoff
Overall Survival, %
Median OS (95% CI), mo
25.8 (12.8-NE)
Months
One patient's event time was updated from Month 42 to 39 after data cutoff and is not reflected in this figure
Axi-cel, axicabtagene ciloleucel; CR, complete response; NE, not estimable; OS, overall survival; PD, progressive disease; PR, partial response; F/U, follow-up
CULTIVATING EXCELLENCE: Bridging Perspectives in Oncology Care
Jacobson C, et al. ASH 2021, Abs 1764
Neelapu SS, et al. Blood. 2023. Online ahead of print

18


REGULAR ARTICLE
blood advances
Comparison of 2-year outcomes with CAR T cells (ZUMA-1) vs salvage chemotherapy in refractory large B-cell lymphoma
Treatment Difference
HR=0.27 (95%CI=0.00-0.38)
73% reduction in risk of death
ZUMA-1
SCHOLAR-1
Median OS (95% CI), mo
31.0 (11.5-NE)
5.4 (4.6-6.3)
Survival probability, %
Time from onset of salvage therapy, months
CULTIVATING EXCELLENCE: Bridging Perspectives in Oncology Care
Neelapu SS, et al. Blood Adv. 2021 Oct 26;5(20):4149-4155

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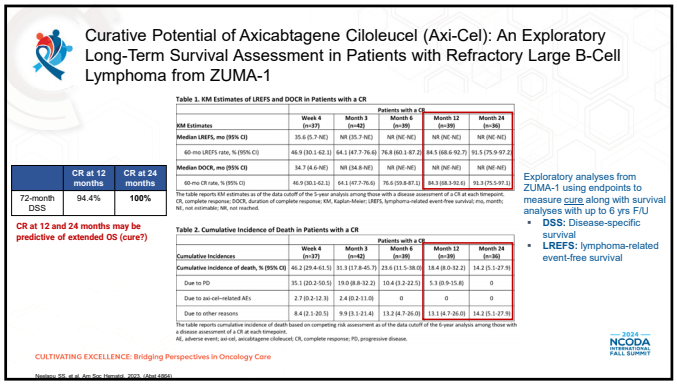
Curative Potential of Axicabtagene Ciloleucel (Axi-Cel): An Exploratory Long-Term Survival Assessment in Patients with Refractory Large B-Cell Lymphoma from ZUMA-1
Table 1. KM Estimates of LREFS and DOCR in Patients with a CR
Table 2. Cumulative Incidence of Death in Patients with a CR
CR at 12 months
CR at 24 months
72-month DSS
94.4%
100%
CR at 12 and 24 months may be predictive of extended OS (cure?)
Exploratory analyses from ZUMA-1 using endpoints to measure cure along with survival analyses with up to 6 yrs F/U
DSS: Disease-specific survival
LREFS: lymphoma-related event-free survival
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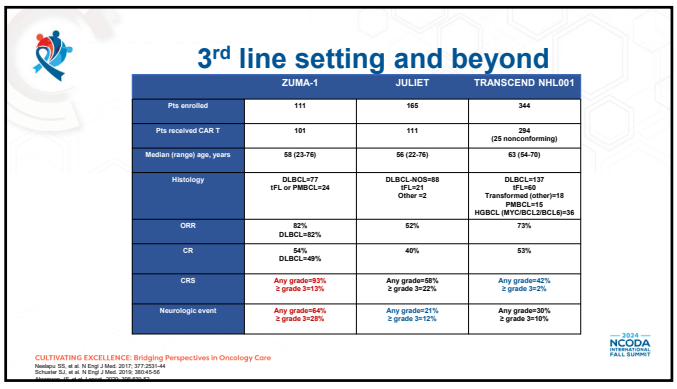
3rd line setting and beyond
ZUMA-1
JULIET
TRANSCEND NHL001
Pts enrolled
Pts received CAR T
Median (range) age, years
Histology
ORR
CR
CRS
Neurologic event
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Hypoalbuminemia

Serum albumin retains independent prognostic significance in diffuse large B-cell lymphoma in the post-rituximab era

OS and Albumin

log rank p-value < 0.001

Albumin
<3.7
>=3.7

Impact of hypoalbuminemia on the prognosis of relapsed/refractory B-cell lymphoma treated with axicabtagene ciloleucel

N=81 patients

CAR T-cell therapy overcomes the adverse prognosis of hypoalbuminemia

PFS

P=0.01

OS

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Datia S, et al. Ann Hematol. 2014; 93: 1305-12
Melody M, et al. Eur J Haematol. 2021; 107: 46-53

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Five Year Outcomes of Patients with Large B-Cell Lymphoma Treated with Standard-of-Care Axicabtagene Ciloleucel: Results from the US Lymphoma CAR-T Cell Consortium

42% would not have met eligibility criteria for ZUMA-1

- 17 US academic centers
- 297 pts underwent leukapheresis with intent to manufacture axi-cel
- 275 infused, OS and PFS calculated from infusion date
- Median F/U of 58 months, median OS was 34.9 months and median PFS was 8.7 months
- 5-year OS **40.3%** (95% CI 34.2 - 46.4%)
- 5-year PFS and **28.5%** (95% CI 23 - 34.2%)
- MVA for ↓ OS: Male, LDH > ULN, ECOG of 2-4, elevated bilirubin > 1.5 mg/dL
- MVA for ↓ PFS: Male, LDH > ULN, ECOG of 2-4, elevated bilirubin > 1.5 mg/dL, ≥3 prior Rxs

Real World Data

- 5-year cum relapse risk= 55.2%
- 5-year risk NRM=16.2%

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Spiegel JY, et al. Am Soc Hematol. 2023 (Abs 1032)

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Moving CAR T-cell therapy to 2nd line

- **3 randomized studies**:
  - **ZUMA-7:** Axi-cel vs. SOC (Axi-cel better)
  - **TRANSFORM:** Liso-cel vs. SOC (Liso-cel better)
  - **BELINDA:** Tisagenlecleucel vs. SOC (no difference)

SOC: standard of care

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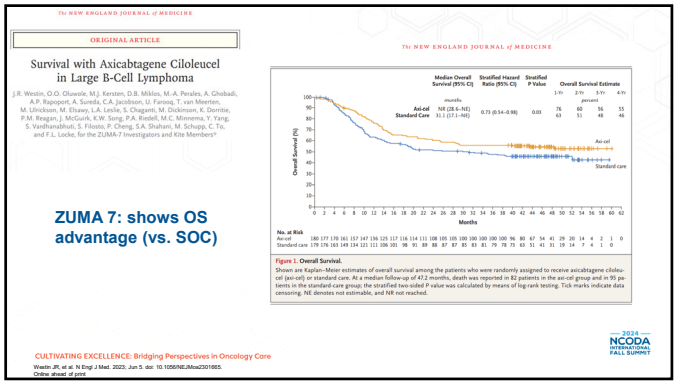
Locke F, et al. N Engl J Med. 2022; 386: 640-54
Kamdar M, et al. Lancet. 2022; 399: 2294-2308
Bishop M, et al. N Engl J Med. 2022;390:701-714

24


The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
Survival with Axicabtagene Ciloleucel in Large B-Cell Lymphoma
ZUMA 7: shows OS advantage (vs. SOC)
The NEW ENGLAND JOURNAL of MEDICINE
Median Overall Survival (95% CI)
Stratified Hazard Ratio (95% CI)
Stratified P Value
Overall Survival Estimate
Axi-cel
Standard Care
Overall Survival (%)
Months
No. at Risk
Figure 1. Overall Survival.
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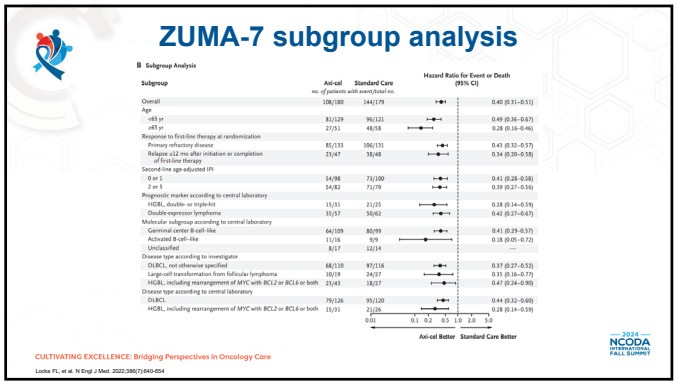
ZUMA-7 subgroup analysis
B Subgroup Analysis
Subgroup
Axi-cel
Standard Care
Hazard Ratio for Event or Death (95% CI)
Overall
Age
Response to first-line therapy at randomization
Second-line age-adjusted IPI
Prognostic marker according to central laboratory
Molecular subgroup according to central laboratory
Disease type according to investigator
Disease type according to central laboratory
Axi-cel Better
Standard Care Better
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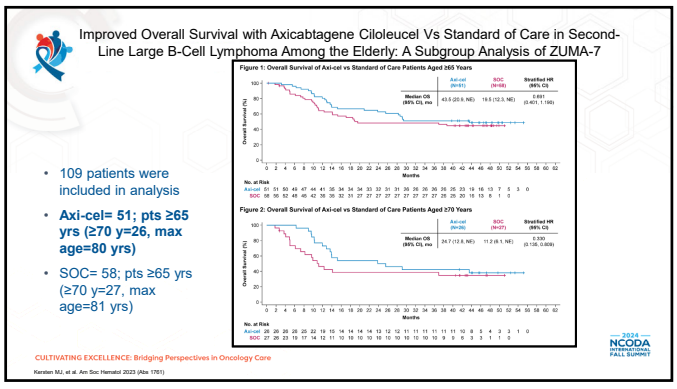
Improved Overall Survival with Axicabtagene Ciloleucel Vs Standard of Care in Second-Line Large B-Cell Lymphoma Among the Elderly: A Subgroup Analysis of ZUMA-7
109 patients were included in analysis
Axi-cel= 51; pts ≥65 yrs (≥70 y=26, max age=80 yrs)
SOC= 58; pts ≥65 yrs (≥70 y=27, max age=81 yrs)
Figure 1: Overall Survival of Axi-cel vs Standard of Care Patients Aged ≥65 Years
Figure 2: Overall Survival of Axi-cel vs Standard of Care Patients Aged ≥70 Years
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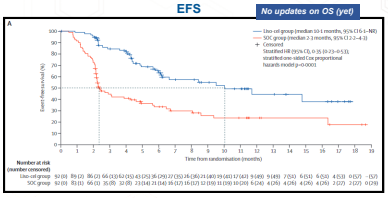
Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial

EFS

No updates on OS (yet)



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EFS, event-free survival

Kamdar M, et al. *Lancet* 2022; 399: 2294–308

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QUESTION 1

Mr. J.M. is a 65 y/o old man who was diagnosed with stage IV diffuse large B cell lymphoma. He received front-line treatment with chemoimmunotherapy and achieved a complete remission. Unfortunately, his disease relapsed within 9 months. Which of the following treatment options are **correct**?

a. He can be treated with axicabtagene ciloleucel based on results of ZUMA-7 showing superior EFS compared to standard of care

b. He can be treated with lisocabtagene maraleucel based on results of TRANSFORM showing superior EFS compared to standard of care

c. He can be treated with tisagenlecleucel based on results of BELINDA showing superior EFS compared to standard of care

d. A and B

e. All of the above

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Mantle Cell Lymphoma

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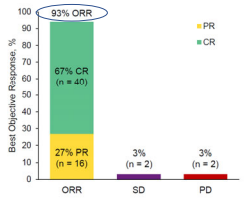
ZUMA-2: ORR

ORR by IRRC Assessment Was 93% (95% CI, 84 – 98) and CR Rate Was 67% (95% CI, 53 – 78)



	Efficacy-Evaluable N = 60
Median follow-up (range), mo	12.3 (7.0 – 32.3)
Patients with ≥ 24 mo follow-up, n (%)	28 (47)
Median time to response (range), mo	
Initial response	1.0 (0.8 – 3.1)
CR	3.0 (0.9 – 9.3)
Patients converted from PR/SD to CR, n (%)	24 (40)
PR to CR	21 (35)
SD to CR	3 (5)

Investigator-assessed ORR in N = 60 was 88% (CR rate 70%), with 95% and 90% concordance between IRRC- and investigator-assessed ORR and CR rate, respectively. IRRC-assessed ORR in ITT (N = 74) was 85% (CR Rate 59%).
CR, complete response; IRRC, Independent Radiology Review Committee; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

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Wang M, et al. ASH 2019. Abs 754.
Wang M, et al. NEJM. 2020; 382:1331.

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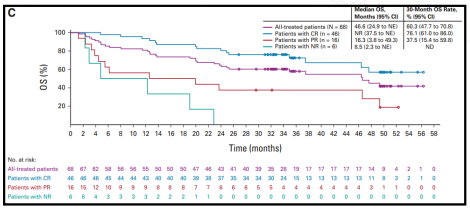
Mantle cell lymphoma: ZUMA-2 study 3-year update (OS)



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OS, overall survival; CR, complete response; PR, partial response; NR, no response
Wang M, et al. J Clin Oncol. 2022;41(3):555-567.

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Lisocabtagene Maraleucel in Relapsed/Refractory Mantle Cell Lymphoma: Primary Analysis of the Mantle Cell Lymphoma Cohort From TRANSCEND NHL 001, a Phase I Multicenter Seamless Design Study

Liso-cel treated set (N=88)	
Median (range) age, years	68.5 (36-86)
White race, n (%)	77 (87.5%)
***TP53* mutation, n (%)**	20 (23%)
Blastoid morphology, n (%)	27 (31%)
Complex karyotype, n (%)	26 (30%)
Median (range) prior Rx	3 (1-11)
Previous BTKi, n (%)	83 (94%)
Previous venetoclax, n (%)	23 (26%)
Previous HCT, n (%)	Auto=26 (30%) Allo=6 (7%)
Disease status	Relapsed=27 (31%) Refractory=61 (69%)

Median F/U= 16.1 (0.4-60.5) months

ORR= 83.1%
CR= **72.3%**

Median DOR= 15.7 months

CRS (any grade)= 61%; **Grade 3-4=1%**

Neuro events (any grade)= 31%
Grade 3-4= 9%

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Wang M, et al. J Clin Oncol. 2024; 42(10): 1146-1157

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Follicular Lymphoma

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Follicular Lymphoma: ZUMA-5

Axicabtagene Ciloleucel (Axi-Cel) in Patients with Relapsed/Refractory Indolent Non-Hodgkin Lymphoma: 4-Year Follow-up from the Phase 2 ZUMA-5 Trial

Program: Oral and Poster Abstracts
Session: 705. Cellular Immunotherapies: Late Phase and Commercially Available Therapies: Poster III
Hematology Disease Topics & Pathways:
Research, clinical trials, Biological therapies, adult, Lymphomas, non-Hodgkin lymphoma, Clinical Research, Chimeric Antigen Receptor (CAR) T Cell Therapies, Diseases, indolent lymphoma, Therapies, Lymphoid Malignancies, Study Population, Human
Monday, December 11, 2023, 6:00 PM-8:00 PM

Neelapu SS, et al. Am Soc Hematol. 2023 (Abs 4668)

Figure 1. Progression-Free Survival

Estimated PFS	FL (n=127)	NDL (n=31)	All Patients (N=158)
Median (95% CI), mo	57.3 (30.9-NE)	40.8 (12.4-NE)	57.3 (34.9-NE)
48-mo rate, % (95% CI)	53 (43-62)	47 (21-69)	52 (43-61)

- Updated outcomes from ZUMA-5 after ≥4 years median follow-up
- 159 pts enrolled (127 FL; 31 MZL) and 152 treated with axi-cel (124 FL; 28 MZL)
- **Median F/U 52.5 months** (range, 20.3-69.4; FL: 53.7, MZL: 43.8)
- Median progression-free survival= 57.3 months (95%CI=34.9-NE)
  - **4-year PFS=52%**
- **Median overall survival (OS)= Not reached**
  - **4-year OS=72%**

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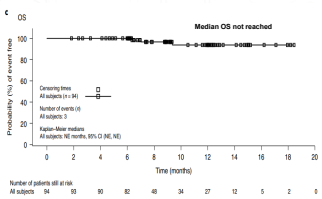
Tisagenlecleucel in Adult Relapsed or Refractory Follicular Lymphoma: The Phase 2 ELARA Trial

N=97
Median prior therapies of 4 (2-13)
FLIPI high >3=59.8%
Median F/U 9.9 months



Events, n (%)	Infused patients N=97
CRS	47 (48.5)
Grade 1 or 2	47 (48.5)
Grade ≥3	0
In patients with CRS (n=47)	
Tocilizumab use during CRS	16 (34.0)
1 dose	8 (17.0)
2 doses	5 (10.6)
3 doses	3 (6.4)
Corticosteroids	3 (6.4)
Median time to onset, days (IQR)	4.0 (2–7)
Admitted to ICU, n (%)	4 (8.5)
Median total duration of ICU stay during CRS, days (range)	4.0 (2.5–5)
Patients with resolved events, n (%)	47 (100)

Events, n (%)	Treated patients N=97 All Grades	Grade ≥3
Number of patients with at least one event	36 (37.1)	3 (3.1)
Headache	23 (23.7)	1 (1.0)
Dizziness	6 (6.2)	0
Encephalopathy	2 (2.1)	0
Immune effector cell-associated neurotoxicity syndrome	4 (4.1)	1 (1.0)
Paraesthesia	2 (2.1)	0
Tremor	2 (2.1)	0
Dyskinesia	1 (1.0)	0
Dysgeusia	1 (1.0)	0
Migraine	1 (1.0)	0
Peripheral sensory neuropathy	1 (1.0)	0
Syncope	1 (1.0)	1 (1.0)

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Fowler NH, Nat Med. 2021, Dec 17. doi: 10.1038/s41591-021-01622-0. Online ahead of print

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Tisagenlecleucel in Adult Relapsed or Refractory Follicular Lymphoma: The Phase 2 ELARA Trial

Table 2 | Best overall response in the EAS and per-protocol population*

Parameter	Per-protocol set, *n* = 85		EAS, *n* = 94	
	Local assessment	IRC assessment	Local assessment	IRC assessment
Best overall response, *n* (%)				
CR	64 (75.3); 95% CI, 64.7–84.0	62 (72.9); 95% CI, 62.2–82.0	68 (72.3); 95% CI, 62.2–81.1	65 (69.1); 95% CI, 58.5–78.3
PR	14 (16.5)	12 (14.1)	17 (18.1)	16 (17.0)
SD	2 (2.4)	3 (3.5)	3 (3.2)	3 (3.2)
PD	5 (5.9)	8 (9.4)	6 (6.4)	9 (9.6)
UNK				1 (1.1)
Overall response rate (CR + PR), *n* (%)	78 (91.8); 95% CI, 83.8–96.6	74 (87.1); 95% CI, 78.0–93.4	85 (90.4); 95% CI, 82.6–95.5	81 (86.2); 95% CI, 77.5–92.4

*The per-protocol set is a subset of patients in the primary analysis efficacy set with no major protocol deviations. UNK, unknown.

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Fowler NH. Nat Med. 2021, Dec 17. doi: 10.1038/s41591-021-01622-0. Online ahead of print.

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TRANSCEND FL: Phase 2 Study Results of Lisocabtagene Maraleucel (Liso-Cel) in Patients (Pts) with Released/Refractory (R/R) Follicular Lymphoma (FL)

- R/R FL: 3L+ and 2L pts with progression within 24 months (POD24) of Dx and/or modified Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria
- Liso-cel (100 x10^6 CAR+ T cells) after LD chemotherapy
- 1^{ry} endpoint ORR per IRC by PET/CT
- N of patients who underwent leukapheresis=139
  - N infused= 130
  - N evaluable for efficacy=124
  - Median age= 62 (23-80) years
  - High-risk FLIPI=57%
  - Median (range) prior lines of therapy= 3 (2–10)

- Median F/U=18.9 (0.3-28.2) months
- Evaluable 3L+ pts=101
- **ORR= 97%**
- **CR=94.1%**

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Morschhauser F, et al. ICML 2023 (pp 977-980).

FDA. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-lisocabtagene-maraleucel-follicular-lymphoma. Accessed 7, October 2024.

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Chronic Lymphocytic Leukemia

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CAR T-cell in CLL vs. other low grade lymphoid malignancies

	CLL (TRANSCEND CLL004)[1] (N=23)	Follicular lymphoma (ZUMA 5)[2] (N=124)	Follicular lymphoma (ELARA)[3] (N=85)*
CAR T-cell product	Lisocabtagene Maraleucel	Axicabtagene Ciloleucel	Tisagenlecleucel
Study type	Phase 1	Phase 2	Phase 2
ORR	82%	94%	87.1%
CR	45%	79%	72.9%
PR	36%	15%	14.1%

*per protocol

1. Siddiqi T, et al. Blood. 2022; 139(12):1794–1806
2. Jacobson CA, et al. Lancet Oncol. 2022 Jan;23(1):91–103

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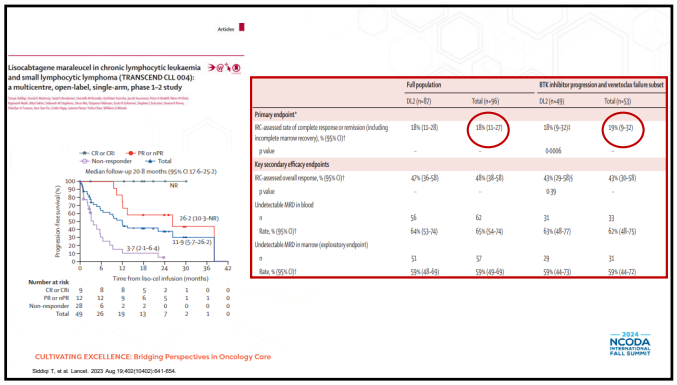

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Bispecifics in B-cell Lymphomas

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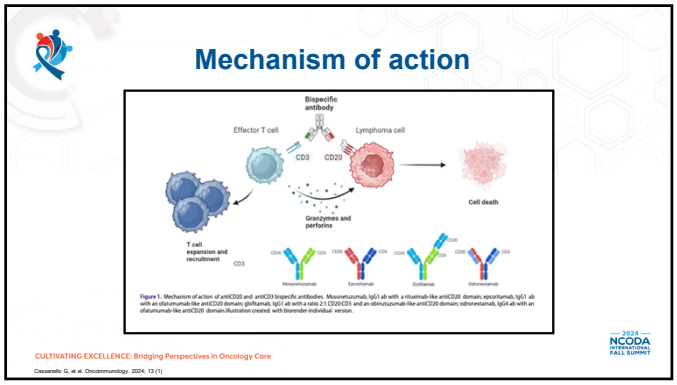
Mechanism of action
Bispecific antibody
Effector T cell
Lymphoma cell
CD3
CD20
Cell death
Granzymes and perforins
T cell expansion and recruitment
CD3
Mosunetuzumab
Epcoritamab
Glofitamab
Odronextamab
Figure 1. Mechanism of action of anti-CD20 and anti-CD3 bispecific antibodies. Mosunetuzumab, IgG1 ab with a rituximab-like anti-CD20 domain; epcoritamab, IgG1 ab with an ofatumumab-like anti-CD20 domain; glofitamab, IgG1 ab with a ratio 2:1 CD20:CD3 and an obinutuzumab-like anti-CD20 domain; odronextamab, IgG4 ab with an ofatumumab-like anti-CD20 domain.Illustration created with biorender-individual version.
CULTIVATING EXCELLENCE: Bridging Perspectives in Oncology Care
Cassanello G, et al. Oncoimmunology. 2024; 13 (1)
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NCODA
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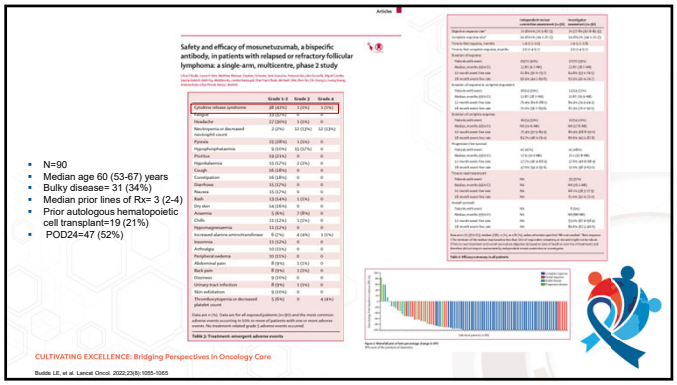
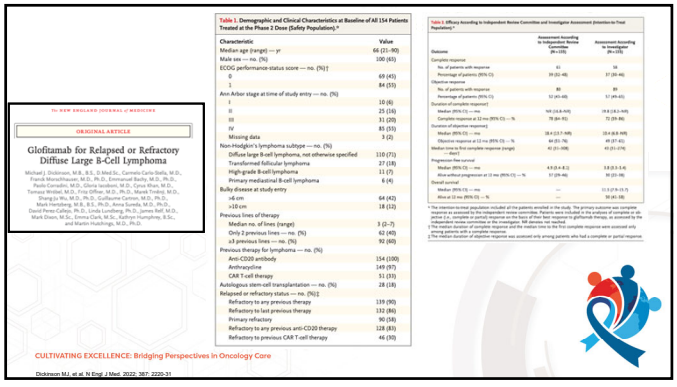
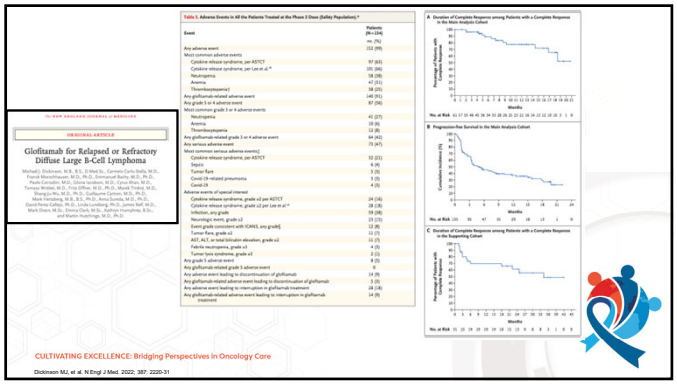

Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study
N=90
Median age 60 (53-67) years
Bulky disease= 31 (34%)
Median prior lines of Rx= 3 (2-4)
Prior autologous hematopoietic cell transplant=19 (21%)
POD24=47 (52%)
CULTIVATING EXCELLENCE: Bridging Perspectives in Oncology Care
Budde LE, et al. Lancet Oncol. 2022;23(8):1055-1065

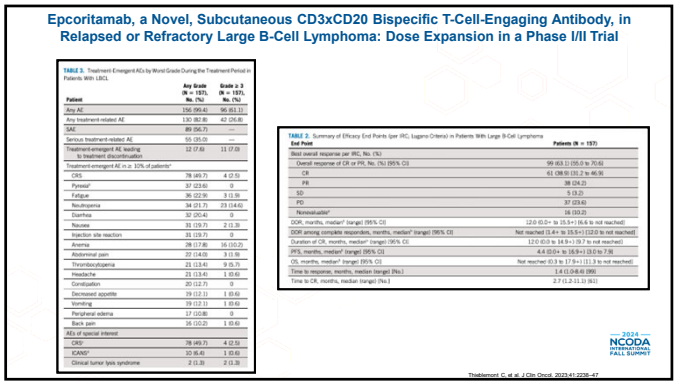
44


ORIGINAL ARTICLE
Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma
Table 1. Demographic and Clinical Characteristics at Baseline of All 154 Patients Treated at the Phase 2 Dose (Safety Population).
CULTIVATING EXCELLENCE: Bridging Perspectives in Oncology Care
Dickinson MJ, et al. N Engl J Med. 2022; 387: 2220-31

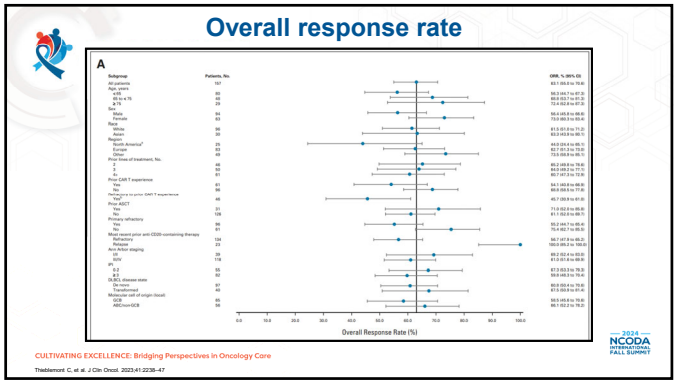
45


ORIGINAL ARTICLE
Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma
CULTIVATING EXCELLENCE: Bridging Perspectives in Oncology Care
Dickinson MJ, et al. N Engl J Med. 2022; 387: 2220-31

46


Epcoritamab, a Novel, Subcutaneous CD3xCD20 Bispecific T-Cell-Engaging Antibody, in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial
Thieblemont C, et al. J Clin Oncol. 2023;41:2238–47

47


Overall response rate
Overall Response Rate (%)
CULTIVATING EXCELLENCE: Bridging Perspectives in Oncology Care
Thieblemont C, et al. J Clin Oncol. 2023;41:2238–47

48

Challenges Associated with Delivery of Care with CAR T-Cell and Bispecific Therapies

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Challenges associated with Rx delivery

CAR T-Cell Therapy

- Cost (approx. $ 450,000)
  - Parts without labor
- Complex logistics
  - Limited number of centers
- Manufacturing takes time
  - 14-28 days
- Short-term toxicities
  - CRS, neurotoxicity
- Long-term toxicities
  - Pancytopenia, 2nd malignancies

Bispecifics

- Cost (albeit apparently less costly)
  - Epcoritamab 9 cycles=$120,000
    - But usually prescribed until disease progression
- No data on 2nd line setting
- Transitioning pts from the inpatient to outpatient setting
- Management of side effects in the community setting
  - CRS, neurotoxicity

Choi G, et al. Int J Environ Res Public Health. 2022; 19: 12366
Patnis KC, et al. Blood Adv. 2023; 7: 801-10

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QUESTION 2

Which of the following statements in **incorrect**:

a. Axicabtagene ciloleucel is approved in the second line setting in patients with diffuse large B-cell lymphoma
b. Epcoritamab is a bispecific therapy approved in the second line setting in patients with diffuse large B-cell lymphoma
c. T-cell cancers have been reported after CAR T-cell therapy
d. Bispecifics are off-the shelf, providing an advantage for faster administration

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Short-Term Toxicities

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Cytokine Release Syndrome (CRS)


ImmunoTargets and Therapy

REVIEW

Cytokine Release Syndrome: Current Perspectives

- Potentially serious complication of CAR-T therapy
- Knowledge about exact mechanism continues to evolve
- Cytokine mediated inflammatory response:
  - *In vivo* CAR-T activation and expansion
  - Also, from immune cells (macrophages) that respond to CAR-T activation
- Symptoms: Mild (pyrexia) → severe (hemodynamic compromise and organ failure)
- Median time to onset 2-3 days
- Rare: Hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS)

CULTIVATING EXCELLENCE: Bridging Perspectives in Oncology Care

Murthy H, et al. Immunotargets Ther. 2019; 8: 43-52

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ASTCT consensus grading (CRS)

Always rule out a possible infectious cause of the fever
Blood and urine cultures, chest X-ray, examine sites of IV lines

Table 2
ASTCT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[a]	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or[c]		
Hypoxia	None	Requiring low-flow nasal cannula[c] or blow-by	Requiring high-flow nasal cannula[c], facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.
[a] Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
[b] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.
[c] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

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Lee DW, et al. Biol Blood Marrow Transplant. 2019; 25: 625-38

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Neurotoxicity

- Generally, manifests as a toxic encephalopathy
  - Confusion, disorientation, difficulty finding words, etc.
  - In more severe cases, seizures, elevated intracranial pressure, cerebral edema
- May last few hours to several days
- It is generally reversible, although deaths have been reported
- Biphasic presentation
  - Phase 1: Days 0-5, may have concurrent CRS
  - Phase 2: After day +5, by then CRS has generally subsided
    - Onset can be later with certain CAR T-cells

ASTCT Consensus Grading (ICE score*)

ICE
• **Orientation:** orientation to year, month, city, hospital: 4 points
• **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points
• **Following commands:** ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point
• **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point
• **Attention:** ability to count backwards from 100 by 10: 1 point

**ICE: Immune Effector Cell-Associated Encephalopathy score*

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Lee DW, et al. Biol Blood Marrow Transplant. 2019; 25: 625-38

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ASTCT consensus Grading (ICANS*)

Table 6
ASTCT ICANS Consensus Grading for Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[a]	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness[b]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings[c]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[d]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.
N/A indicates not applicable.
[a] A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.
[b] Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).
[c] Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.
[d] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

**ICANS: Immune effector cell-associated neurotoxicity syndrome*

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Lee DW, et al. Biol Blood Marrow Transplant. 2019; 25: 625-38

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Future Implications with CAR T-Cell Therapy Failure and Bispecific Use after Long-Term Toxicity Exposure

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Long-term toxicities

Cytopenia (CAR-to-penia)

- Duration of cytopenias post CAR T-cell therapy is variable, ranging from 14 to 180 days, sometimes longer
- Significant percentage experience persistent cytopenias lasting >30 days

→ **Infections**
→ **Transfusion dependence**
→ **Prolonged hospitalization**
→ **Increased medical costs**

CULTIVATING EXCELLENCE: Bridging Perspectives in Oncology Care

Zhu F et al. Cell Transplant. 2020 Jan-Dec;29:963689720919434

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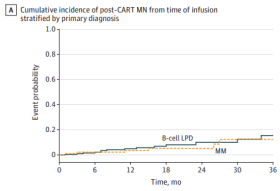
Features and Factors Associated with Myeloid Neoplasms after Chimeric Antigen Receptor T-Cell Therapy

Incidence of myeloid neoplasm is comparable between LPD and MM

- **At 1-year=4%**
- **At 2-year=6%**
- **At 3-year=9%**



CULTIVATING EXCELLENCE: Bridging Perspectives in Oncology Care

Gurney M, et al. JAMA Oncol. 2024;10(4):532-535

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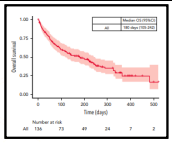
CAR T-cell therapy failure

- Dismal prognosis in general
  - Median overall survival after failing axicabtagene ciloleucel approximately 6 months

TO THE EDITOR:

Outcomes of patients with large B-cell lymphoma progressing after axicabtagene ciloleucel therapy



CULTIVATING EXCELLENCE: Bridging Perspectives in Oncology Care

Spiegel JY, et al. Blood. 2021; 137 (13): 1832-35

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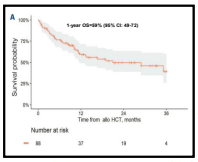
Allogeneic Transplant following CAR T-cell Therapy for Large B-cell Lymphoma

- N=88
- Median age 54 (19-72) years
- 18 US centers



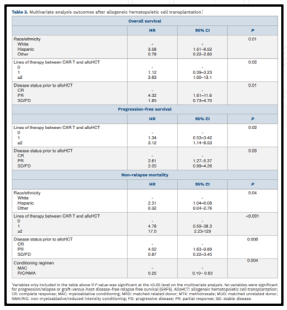


Table 3. Multivariate analysis outcomes after allogeneic hematopoietic cell transplantation.

	HR	95% CI	P
Overall survival			
Race/ethnicity			0.01
White			
Hispanic	0.58	1.51–6.02	
Other	0.76	0.33–2.66	
Lines of therapy between CAR T and alloHCT			0.02
0	-	-	
1	1.12	0.39–3.23	
≥2	2.83	1.05–19.1	
Disease status prior to alloHCT			0.01
CR	-	-	
PR	4.32	1.81–11.6	
SD/PD	1.85	0.73–4.70	
Progression-free survival			
	HR	95% CI	P
Lines of therapy between CAR T and alloHCT			0.02
0	-	-	
1	1.34	0.53–3.42	
≥2	2.12	1.14–8.02	
Disease status prior to alloHCT			0.03
CR	-	-	
PR	2.81	1.27–6.37	
SD/PD	2.05	0.99–4.26	
Non-relapse mortality			
	HR	95% CI	P
Race/ethnicity			0.04
White			
Hispanic	2.51	1.04–6.08	
Other	0.32	0.04–2.76	
Lines of therapy between CAR T and alloHCT			<0.001
0	-	-	
1	4.78	0.58–38.3	
≥2	17.0	2.25–128	
Disease status prior to alloHCT			0.006
CR	-	-	
PR	4.62	1.63–9.69	
SD/PD	0.87	0.23–3.45	
Conditioning regimen			0.004
MAC			
RIC/NMA	0.25	0.10–0.63	

Variables only included in the table above if P value was significant at the <0.05 level on the multivariate analysis. No variables were significant for progression/relapse or graft-versus-host disease-free-relapse-free survival (GRFS). alloHCT, allogeneic hematopoietic cell transplantation; CR, complete response; MAC, myeloablative conditioning; MFD, myeloid-related donor; MTX, methotrexate; MUD, matched unrelated donor; NMA/RIC, non myeloablative/reduced intensity conditioning; PD, progressive disease; PR, partial response; SD, stable disease.

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Zurko J, et al. Haematologica. 2023; 108: 98-109

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What about bispecifics (CD3*CD20) in the setting of post CAR T-cell failure

	Epcoritamab[1]	Glofitamab[2]
n CAR T failed/**N** total	61/157 (38.9%)	51/155 (31%)
ORR	54.1%	Not reported
CR	34.4%	35%
Median DOR	9.7 months	Not reported

CULTIVATING EXCELLENCE: Bridging Perspectives in Oncology Care

Thieblemont C, et al. J Clin Oncol. 2023;41:2238–47

Dickinson MJ, et al. N Engl J Med. 2022; 387: 2220-31

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Secondary Cancers after Chimeric Antigen Receptor T-Cell Therapy

As of 12-31-2023, the FDA had become aware of 22 cases of T-cell cancers that occurred after CAR-T product treatment. Such cancers include: **T-cell lymphoma, T-cell LGL, PTCL, and CTCL**

Among 14 cases with data, cancers manifested within 2 years after CAR T cells (range, 1 to 19 months), with roughly half occurring within the 1st year

Some are still under investigation. In 3 cases for which genetic sequencing was performed, the CAR transgene was detected in the malignant clone

With > 27,000 doses of the 6 approved products having been administered in the USA, the overall rate of T-cell cancers is low (22/27,000= 0.081%)

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Verdun N, et al. N Engl J Med. 2024;390(7):584-586

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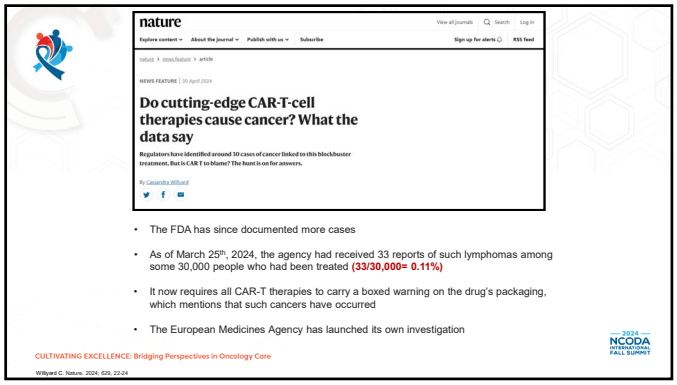

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CAR T-cell therapy vs. Bispecifics (DLBCL)

	CAR T-cell	Bispecifics	Winner
Indications	**2nd line, 3+ line**	3+ line	CAR T
Pre-treatment requirements	Complex (leukapheresis, LD)	**Simpler (off-the-shelf)**	Bispecifics
Rx. frequency	**Single infusion**	Multiple (months)	CAR T
Administration	Specialized centers	**Community setting possible**	Bispecifics
Lymphodepletion	Needed	**Not needed**	Bispecifics
CNS efficacy	**Present, but limited**	?	CAR T
IP vs. OP	Mostly IP (but doable OP)	**OP**	Bispecifics
Toxicities	+++	**+**	Bispecifics
Cost	+++	**++ (for up to 9 months)**	Bispecifics
Follow-up	**Longer (5+ yrs)**	Short	CAR T

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QUESTION 3

Which of the following statements is **incorrect**?

a. The incidence of neurotoxicity is higher with bispecifics compared to CAR T-cell

b. The incidence of neurotoxicity is lower with bispecifics compared to CAR T-cell

c. Bispecifics are off-the–shelf products whereas CAR T-cell require long-term manufacturing time of 14-28 days

d. Bispecifics are more feasible for administration in the community setting

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SUMMARY

- **CAR T-cell** revolutionized Rx of DLBCL, MCL, and FL. **Here to stay**!
- In relapsed/refractory DLBCL
  - CR at 12 and 24 months→ suggest durable response **(?cure)**
- In primary refractory DLBCL or early relapse (<12 months)
  - Axi-cel better than SOC (↑EFS, ↑OS)
  - Liso-cel better than SOC (↑EFS)
- Brexu-cel and liso-cel approved in R/R mantle cell lymphoma
- Axi-cel, tisagenlecleucel and liso-cel in R/R follicular lymphoma
- Efficacy reproducible in the "real world" setting
- Long-term toxicities of CAR T-cell are challenging
  - CAR-to-penia
  - Hypogammaglobulinemia
  - Therapy-related myeloid neoplasms (9% at 3 year)
    - CHIPs* prior to CAR T-cell vs. after CAR T-cell?
- T-cell lymphoma(s) derived from CAR T product (CAR transgene)
  - Real phenomenon
  - Incidence very low= **0.081-0.11%**

CHIP: Clonal hematopoiesis of indeterminate potential

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SUMMARY

- **Bispecifics** represent an important addition to treatment algorithm of DLBCL and follicular lymphoma
  - Efficacy of bispecifics in post-CAR T-cell failure→ bridging to allogeneic HCT
  - More feasible in the community setting
  - Appears to have a more "friendly" toxicity profile (vs. CAR T-cell)
  - Long-term toxicities lacking
  - No reported cases of T-cell cancers

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QUESTION & ANSWERS

Exploring BiSpecifics and CAR-T Therapies

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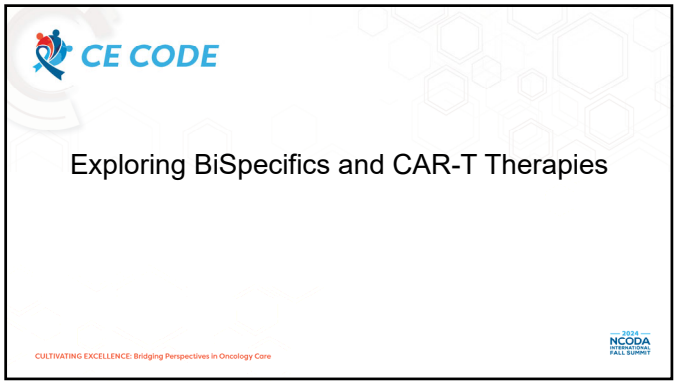
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