Tycel J. Phillips, MD

Associate Professor of Medicine

City of Hope Comprehensive Cancer Center

Understanding and Managing Your Patients with Current Immune Effector Therapeutic Options in Lymphomas

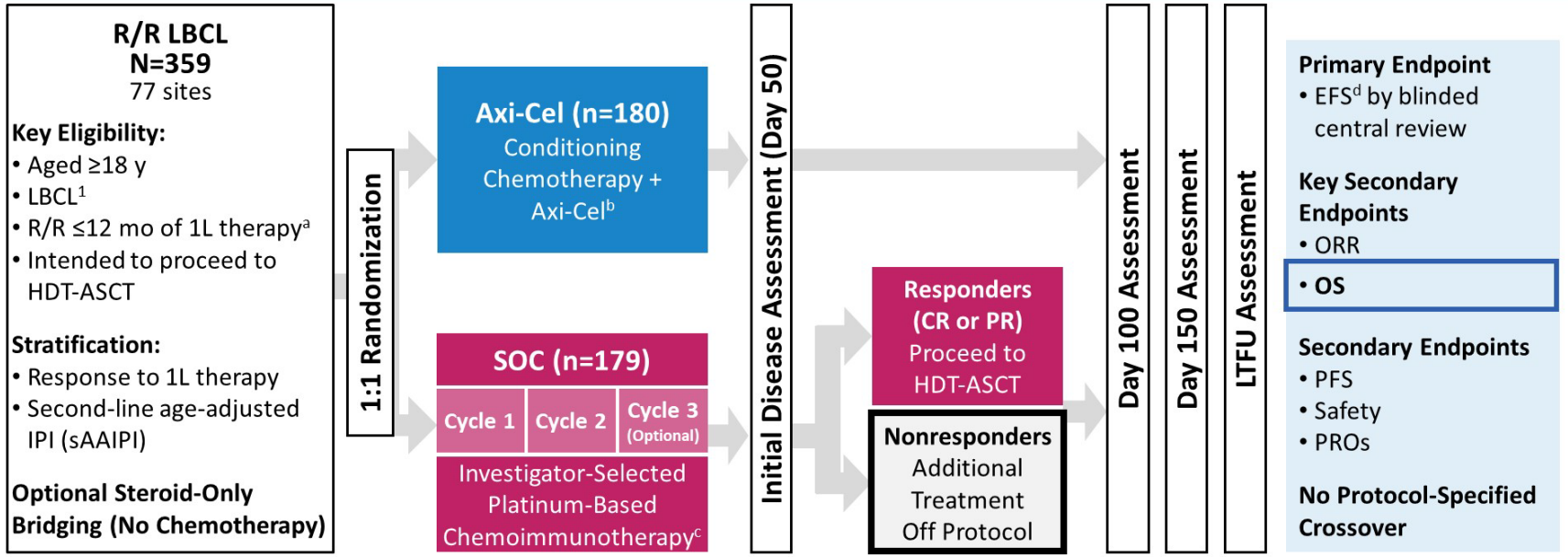
Disclosures

- Research Support
  - Abbvie, Bayer, BMS, Genentech
- Advisory Board
  - Abbvie, ADC Therapeutics, AstraZeneca, Bayer, Beigene, BMS, Genmab, Genentech, Gilead, Eli Lily, Epizyme, Incyte, Pharmacyclics, TG Therapeutics, Seattle Genetics
- Strategic Counsel
  - Epizyme, Genmab
- Scientific Board
  - Genentech, Merck, Genmab

City of Hope™

CAR-T 2L+

ZUMA-7 Study Schema and Endpoints



[a] Refractory disease was defined as no complete response to 1L therapy; relapsed disease was defined as complete response followed by biopsy-proven disease relapse ≤12 months from completion of 1L therapy. [b] Axi-cel patients underwent leukapheresis followed by conditioning chemotherapy with cyclophosphamide (500 mg/m²/day) and fludarabine (30 mg/m²/day) 5, 4, and 3 days before receiving a single axi-cel infusion (target intravenous dose, 2×10^6 CAR T cells/kg). [c] Protocol-defined SOC regimens included R-GDP, R-DHAP, R-ICE, or R-ESHAP. [d] EFS was defined as time from randomization to the earliest date of disease progression per Lugano Classification,[2] commencement of new lymphoma therapy, or death from any cause.

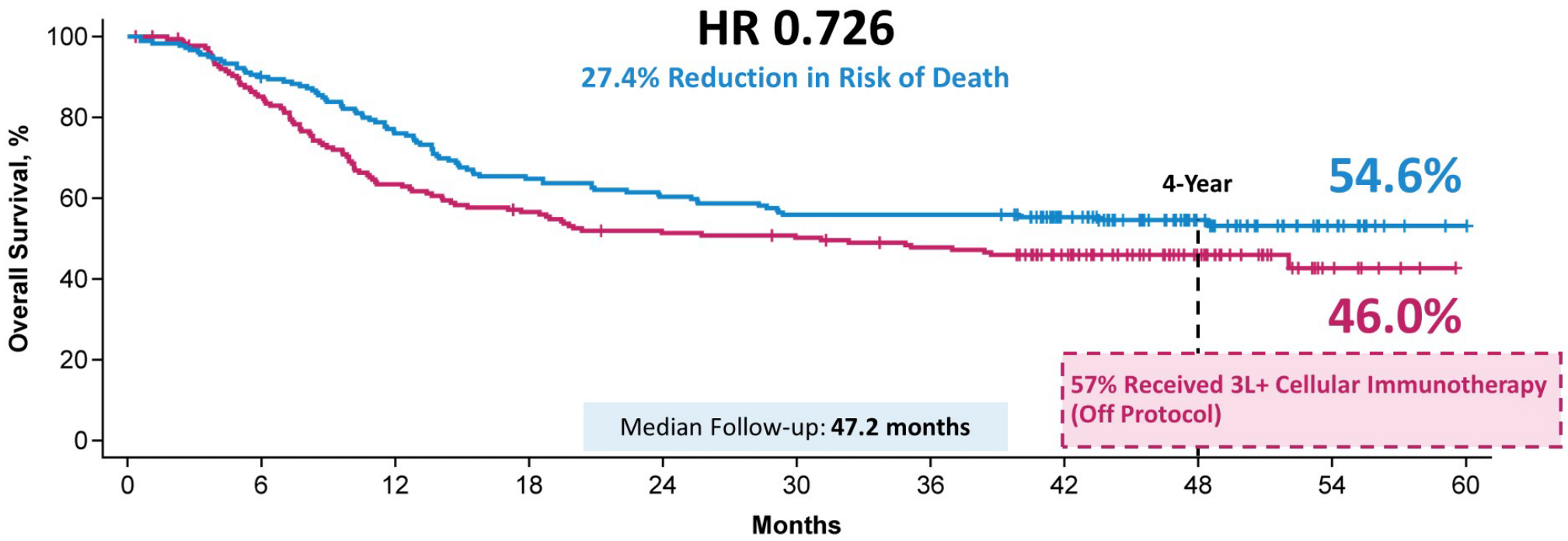
1. Swerdlow SH, et al. *Blood*. 2016;127:2375-2390. 2. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068.

1L, first line; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; EFS, event-free survival; HDT-ASCT, high-dose therapy with autologous stem cell transplantation; IPI, International Prognostic Index; LBCL, large B-cell lymphoma; LTFU, long-term follow-up; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PRO, patient-reported outcome; R/R, relapsed/refractory; SOC, standard of care.

Westin et al ASCO 2023 Late-Breaking Abstract 107 5

DRIVE SCORE 2

Axi-Cel Improved Overall Survival Versus Standard of Care



- 57% (n=102/179) of SOC patients received subsequent cellular immunotherapy (off protocol)
- Despite the increased survival in the SOC arm versus historical studies, axi-cel increased survival over SOC[a,b]

[a] Approximately 30% for early R/R LBCL in ORCHARRD (van Imhoff GW, et al. *J Clin Oncol*. 2017;35:544-551). [b] <40% for those with prior rituximab and early R/R LBCL in CORAL (Gisselbrecht C, et al. *J Clin Oncol*. 2010;28:4184-4190).
3L, third line; axi-cel, axicabtagene ciloleucel; HR, hazard ratio; LBCL, large B-cell lymphoma; R/R, relapsed/refractory; SOC, standard of care.

City of Hope

Key Safety Data At Primary Overall Survival Analysis

AEs of Interest, %	Axi-Cel n=170		SOC n=168	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
CRS	92%	6%	–	–
Neurologic event	61%	21%	20%	1%
Hypogammaglobulinemia	11%	0%	1%	0%
Cytopenia	80%	75%	80%	75%
Infections	45%	16%	32%	12%

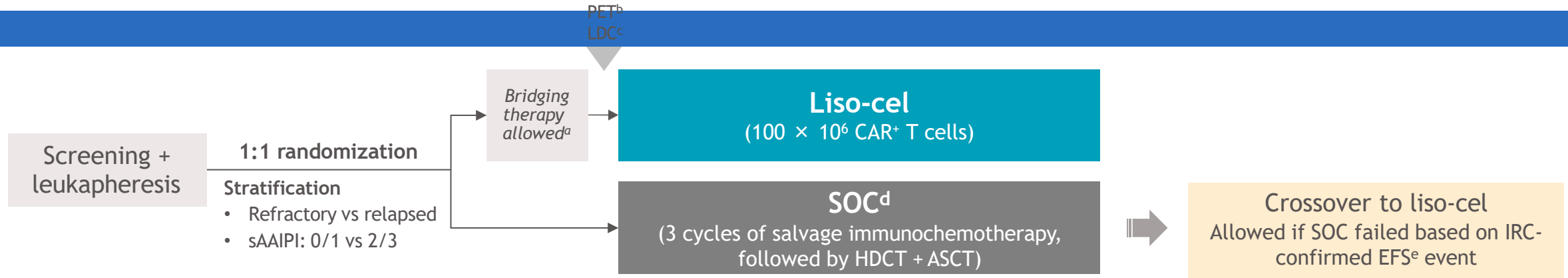
- No changes in cumulative treatment-related serious or fatal AEs occurred since the primary EFS analysis

Reason for Death	Axi-Cel n=170	SOC n=168
Progressive disease, n (%)	51 (30)	71 (42)
Grade 5 AE during protocol-specific reporting period, n (%)	8 (5)[a]	2 (1)[b]
New or secondary malignancy, n (%)	2 (1)[c]	0
Other reason for death,[d] n (%)	13 (8)	18 (11)
Definitive therapy-related mortality,[e] n/N (%)	1/170 (1)[f]	2/64 (3)[g]

Data here are presented for the safety analysis set. Fewer SOC patients remained in the AE reporting period post-progression or start of new lymphoma therapy; thus, cross-arm comparisons of AE rates warrant cautious interpretation. [a] COVID-19 (n=2), sepsis (n=2), hepatitis B reactivation, myocardial infarction, pneumonia, and progressive multifocal leukoencephalopathy (n=1 each). [b] Acute respiratory distress syndrome and cardiac arrest (n=1 each). [c] One patient died of acute myeloid leukemia and one died of lung adenocarcinoma, both deemed unrelated to study treatment per investigator assessment. [d] Includes fatal AEs that occurred outside of the protocol-specified AE reporting window. COVID-19 (n=4), other infection/inflammation (n=3), neurologic organ failure (n=2), respiratory organ failure, cardiac organ failure, progressive disease, and unknown (n=1 each) in the axi-cel arm. Other infection/inflammation (n=7), unknown (n=5), COVID-19 (n=4), respiratory organ failure, and cardiopulmonary/neurologic organ failure (n=1 each) in the SOC arm. [e] Related to axi-cel or high-dose therapy with autologous stem cell transplantation. [f] Hepatitis B reactivation. [g] Cardiac arrest and acute respiratory distress syndrome (n=1 each).
AE, adverse event; axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; EFS, event-free survival; SOC, standard of care.

TRANSFORM: study design

DRIVE SCORE 2



Key patient eligibility criteria

- Age 18—75 years
- Aggressive NHL
  - DLBCL NOS (de novo or transformed from indolent NHL), HGBCL (double/triple hit) with DLBCL histology, FL3B, PMBCL, THRBCL
- Refractory or relapsed ≤ 12 months after 1L treatment containing an anthracycline and a CD20-targeted agent
- ECOG PS ≤ 1
- Eligible for ASCT
- Secondary CNS lymphoma allowed
- LVEF > 40% for inclusion
- No minimum absolute lymphocyte count

Primary endpoint

- EFS[e] (per IRC)

Key secondary endpoints

- CR rate (per IRC), PFS (per IRC), OS

Other secondary endpoints

- Duration of response, ORR (per IRC), PFS on next line of treatment
- Safety, PROs

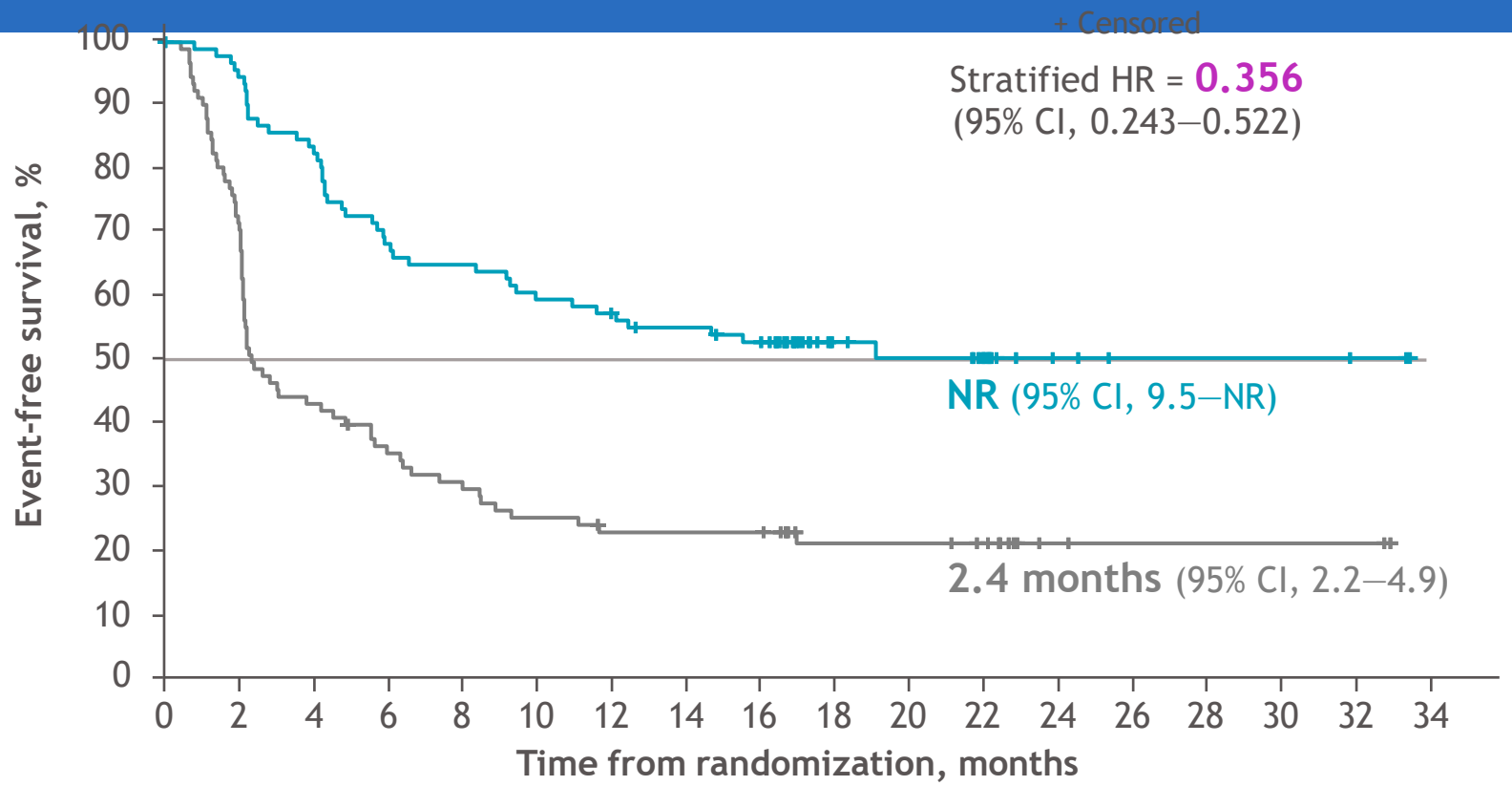
Exploratory endpoints

- Cellular kinetics
- B-cell aplasia

[a]Patients may have received a protocol-defined SOC regimen to stabilize their disease during liso-cel manufacturing; [b]Only for patients who received bridging therapy; [c]Lymphodepletion with fludarabine 30 mg/m^2 and cyclophosphamide 300 mg/m^2 for 3 days; [d]SOC was defined in the protocol as physician's choice of R-DHAP, R-ICE, or R-GDP; [e]EFS was defined as time from randomization to death due to any cause, PD, failure to achieve CR or PR by 9 weeks post-randomization, or start of a new antineoplastic therapy, whichever occurred first.
EFS, event-free survival; FL3B, follicular lymphoma grade 3B; HGBCL, high-grade B-cell lymphoma; IRC, independent review committee; NOS, not otherwise specified; PMBCL, primary mediastinal large B-cell lymphoma; PRO, patient-reported outcome; sAAIPI, secondary age-adjusted International Prognostic Index; THRBCL, T-cell/histiocyte-rich large B-cell lymphoma.

Abramson JS, et al. ASH 2022 [Abstract #655]

TRANSFORM: EFS per IRC (ITT set; primary endpoint)



No. at risk

Liso-cel	92	87	76	62	59	55	52	48	45	24	20	17	5	3	3	3	3	0
SOC	92	66	39	32	27	22	19	19	19	12	12	10	3	2	2	2	2	0

18-month EFS rate	
Liso-cel	**SOC**
52.6%	**20.8%**
(95% CI, 42.3–62.9)	(95% CI, 12.2–29.5)

Median follow-up: 17.5 months

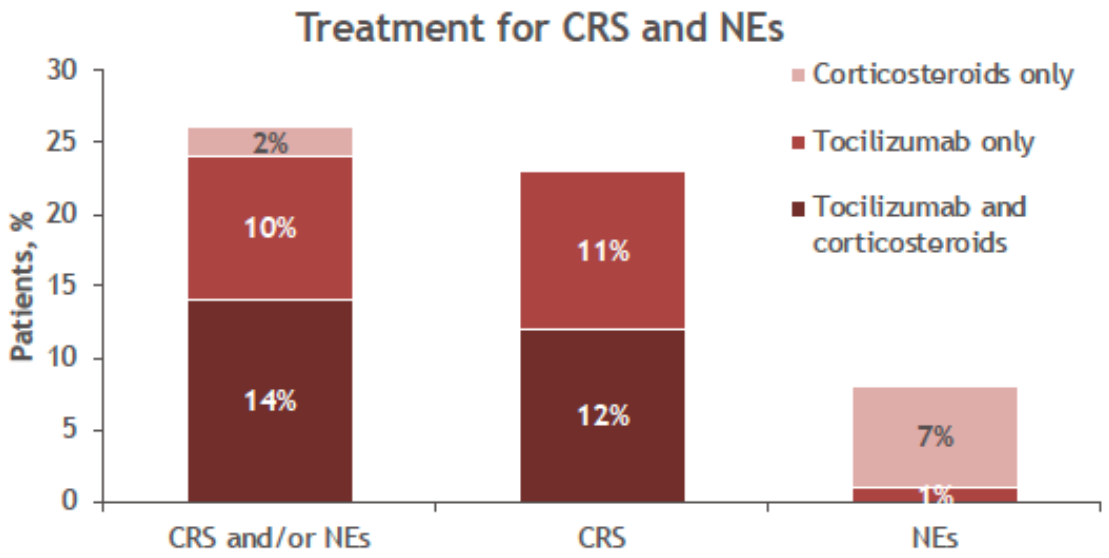
EFS was defined as the time from randomization to death due to any cause, PD, failure to achieve CR or PR by 9 weeks post-randomization, or start of a new antineoplastic therapy due to efficacy concerns, whichever occurred first. This endpoint was not statistically retested for the primary analysis.
NR, not reached.

Abramson JS, et al. ASH 2022 [Abstract #655]

TRANSFORM AEs

TRANSFORM: TEAEs of special interest (safety set)

Patients with CRS and NEs	Liso-cel arm (n = 92)
CRS,[a] n (%)	
Any grade	45 (49)
Grade 1	34 (37)
Grade 2	10 (11)
Grade 3	**1 (1)**
Grade 4/5	**0**
Time to onset, days, median (range)	5.0 (1–63)
Time to resolution, days, median (range)	4.0 (1–16)
NE,[b] n (%)	
Any grade	10 (11)
Grade 1	4 (4)
Grade 2	2 (2)
Grade 3	**4 (4)**
Grade 4/5	**0**
Time to onset, days, median (range)	11.0 (7–17)



- No vasopressors or prophylactic corticosteroids were used

Other adverse events of special interest	Liso-cel arm (n = 92)	SOC arm (n = 91)
Prolonged cytopenia[c]	40 (43)	3 (3)

AEs

- Most notable AE's include CRS and ICANS
  - Managed with antipyretics, anti-IL-6 agents, steroids and other advanced care with higher grade CRS
  - High grade ICANS treatment should include anti-seizure +/- additional medications
  - Other issues of note include HLH, profound/durable cytopenias and infections.

Cytokine Release Syndrome			ICANS	
Product	Any Grade	Severe	Any Grade	Severe
Axi-cel	93%	13%	64%	28%
Tisa-cel	58%	23%	21%	12%
Liso-cel	37%	1%	25%	15%

City of Hope

AE's (CRS/ICANS) ---Follicular Lymphoma

ZUMA-5

- Cytokine release syndrome occurred in 97 [78%] of 124 with FL.
- Most cases were grade 1 or 2 (89 [72%] of 124 with FL
- Grade 3 or worse cytokine release syndrome occurred in eight [6%] of 124 with FL
- Median time to onset of cytokine release syndrome after infusion was 4 days (IQR 2–6) in patients with FL. Median duration was 6 days (IQR 4–8) in patients with FL
- Neurological events occurred in 70 [56%] of 124 with FL, grade 1 or 2 events occurred in 51 [41%] with FL, grade 3 or 4 events occurred in 19 (15%) with FL.
- No grade 5 neurological events occurred.

ELARA

Table 3 | Overall safety profile

Parameter	Treated patients, $n = 97$
Any AE of special interest within 8 weeks post infusion, *n* (%)	88 (90.7)
AESIs occurring in patients 8 weeks post infusion, regardless of study drug relationship, *n* (%)	
CRS	47 (48.5)
Grade ≥3	0
Neurological events	36 (37.1)
Grade ≥3	3 (3.1)
Headache	23 (23.7)
Grade ≥3	1 (1)
Dizziness	6 (6.2)
Grade ≥3	0
Immune effector-cell-associated neurotoxicity syndrome	4 (4.1)
Grade ≥3	1 (1.0)

City of Hope

Cytokine Release Syndrome/Neurotoxicity

- No Grade 5 CRS occurred

Parameter	N = 68
CRS, n (%)[a]	
Any grade	62 (91)
Grade ≥ 3	10 (15)
Most common any grade symptoms of CRS, n (%)	
Pyrexia	62 (91)
Hypotension	35 (51)
Hypoxia	23 (34)
AE management, n (%)	
Tocilizumab	40 (59)
Corticosteroids	15 (22)
Median time to onset (range), days	2 (1 – 13)
Median duration of events, days	11
Patients with resolved events, n (%)	62/62 (100)

Parameter	N = 68
Neurologic events, n (%)[a]	
Any grade	43 (63)
Grade ≥ 3	21 (31)
Most common any grade symptoms, n (%)	
Tremor	24 (35)
Encephalopathy	21 (31)
Confusional state	14 (21)
AE management, n (%)	
Tocilizumab	18 (26)
Corticosteroids	26 (38)
Median time to onset (range), days	7 (1 – 32)
Median duration of events, days	12
Patients with resolved events, n (%)	37/43 (86)[b]

Wang M et al, KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. N Engl J Med. 2020 Apr 2;382(14):1331-1342. doi: 10.1056/NEJMoa1914347. PMID: 32242358; PMCID: PMC7731441.

Other agents to manage ICANS/CRS

Agent	MOA	Data suggesting benefit
Anakinra	IL-1 receptor antagonist	Preclinical data supporting the role of IL-1 in mediating CRS/ICANS, alongside the impact of IL-1 blockade in treatment of CAR T-cell toxicitie
Emapalumab	IFN-γ–blocking antibody	Preclinical data supporting the role of IFN-γ in mediating CRS/ICANS, alongside the impact of IFN-γ blockade in treatment of CAR T-cell toxicities.[98] Clinical experience is limited
Antithymocyte globulin (ATG)	Direct T-cell targeting	Potential use is based on clinical efficacy of targeting T cells. Data on CRS/ICANS are limited
Alemtuzumab (anti-CD52)	Depletion of T and B cells by binding to CD52 on the cell surface	No published reports on its use for treatment of relapsed/refractory CRS/ICANS
Dasatinib	TKI (BCR-ABL)	Preclinical studies demonstrate the ability of dasatinib to suppress CAR T-cell cytotoxicity, cytokine secretion, and proliferation
Ibrutinib	BTK inhibitor	Based on the role of ibrutinib to inhibit IL-2–induced tyrosine kinases, there is evidence of reduction in cytokine production in a preclinical model of CD19 CAR T cells. Emerging using ibrutinib suggest the potential of reducing CRS severity
Ruxolitinib or alternative JAK1 inhibitors	JAK inhibitor	Preclinical studies demonstrate a role of JAK pathway singling blockade and dose-dependent reduction of multiple cytokines implicated in CRS

- Adapted from Jain et al. Blood 2023 141(20):2340-2442

Late Complications

Bone Marrow Transplantation (2022) 57:1477 – 1488

Table 1. Incidence and characteristics of infectious complications in selected registered studies of patients treated with CD19 chimeric antigen receptor T-cells.

	CD19-positive B cell Non-Hodgkin lymphoma									
	ZUMA-1 (2)	**JULIET (3)**	**TRANSCEND-NHL-001 (4)**	**ZUMA-7 (23)**	**BELINDA (27)**	**TRANSFORM (24)**	**ZUMA-12 (25)**	**ZUMA-2 (5)**	**ZUMA-5 (7)**	**ELARA (26)**
Clinicaltrials.gov Identifier Number	NCT02348216	NCT02445248	NCT02631044	NCT03391466	NCT03570892	NCT03575351	NCT03761056	NCT02601313	NCT03105336	NCT03568461
Patient Population	R/R DLBCL, R/R PMBCL, R/R tFL	R/R DLBCL, R/R HGBL, R/R tFL	R/R DLBCL, R/R tNHL, R/R FL Gr 3, R/R HGBL, R/R PMBCL	R/R DLBCL, R/R PMBCL, R/R tFL	R/R DLBCL, R/R HGBL, R/R tFL	R/R DLBCL, R/R tNHL, R/R FL Gr 3, R/R HGBL, R/R PMBCL	High-risk DLBCL, HGBL	R/R MCL	R/R FL	R/R FL
Number of patients	105	111	269	170 in axi-cel arm	162 in tisa-cel arm	92 in liso-cel arm	40	68	148	97
Median duration of follow-up	15 months	14 months	12.3 months	24.9 months	10 months	6 months	15.9 months	17.5 months	17.5 months	16.6 months
Overall infection										
- Any Grades	38%	34% (<8 wks), 39% (>8 wks)	NR	41%	NR	NR	33%	56%	NR	18.6% (8 wks)
- Grade ≥3	28%	20% (<8 wks), 18% (>8 wks)	12% (5% after day 90)	14%	NR (Grade 5 3.1%)	15%	19%	32% (Grade 5 in 2 pts)	18%	5.2% (8 wks)
Bacterial infection	Any Grades 40%	NR	Grade≥3 10%	NR	NR (3 pts died from bacterial sepsis)	NR	Grade ≥ 3 5%	NR	NR	NR
Viral infection	Any Grades 10%	NR	Grade≥3 1%	NR (1 pt had hepatitis B reactivation, 3 pts had COVID-19 pneumonia (Grade ≥ 3)	NR (2 pts died from COVID-19 pneumonia)	NR	Grade ≥ 3 2%	NR CMV 2% HZV 4% Influenza 4%	NR	NR
Fungal infection	Any Grades 6%	NR	Grade≥3 1%	NR	NR	NR	Grade ≥ 3 1%	NR	NR	NR

R/R relapse/refractory, *DLBCL* diffuse large B cell lymphoma, *PMBCL* primary mediastinal B cell lymphoma, *tFL* transformed follicular lymphoma, *HGBL* high grade B cell lymphoma, *MCL* mantle cell lymphoma, *ALL* acute lymphoblastic leukemia, *NR* not reported, *CMV* cytomegalovirus, *HZV* Herpes Zoster virus, *pt* patient.

City of Hope™

Table 1. Early, prolonged and late grade 3-4 cytopenias following CAR T-cell therapy as reported in registry studies and real-world data

	Early (<30 d from infusion)	Prolonged (30-90 d from infusion)	Late (>90 d from infusion)
CD19-directed CAR T-cells, pediatrics			
ELIANA[12]	Neutropenia: 53% Thrombocytopenia: 41%		Neutropenia: 34% Thrombocytopenia: 27%
CD19-directed CAR T-cells, adults			
ZUMA-1[13,14]	Neutropenia: 78% Thrombocytopenia: 38% Anemia: 43%		Neutropenia: 11% Thrombocytopenia: 7% Anemia: 3%
JULIET[15]	Neutropenia: 33% Thrombocytopenia: 28% Anemia: 39%	Neutropenia: 24% Thrombocytopenia: 41%	Grade 3-4 neutropenia: 0% Thrombocytopenia: 38%
TRANSCEND[16]	Neutropenia: 60% Thrombocytopenia: 27% Anemia: 37%		Neutropenia: 7% Thrombocytopenia: 22% Anemia: 2%
ZUMA-2[17]	Neutropenia: 85% Thrombocytopenia: 51% Anemia: 50%		Neutropenia: 16% Thrombocytopenia:16% Anemia: 12%
ZUMA-3[18]	Neutropenia: 27% Thrombocytopenia: 30% Anemia: 49%	Neutropenia: 25% Thrombocytopenia: 18% Anemia: 7%	
ZUMA-5[19]	Neutropenia: 33% Thrombocytopenia: 15% Anemia: 25%		

Locke et al. 2023

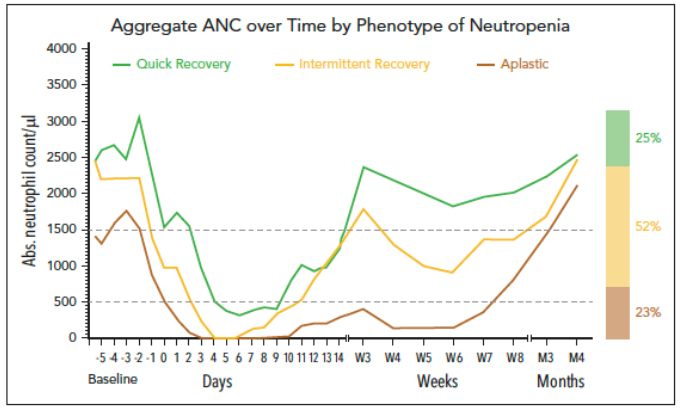


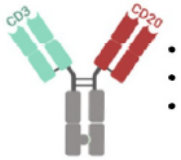
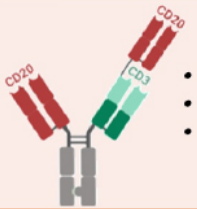
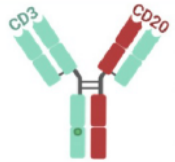
Figure 2. Patterns of neutrophil recovery in lymphoma patients treated with CAR T-cell therapy. Reproduced from Rejeski et al.[27]

City of Hope

So what can you do for these issues???

- Infectious complications
  - Prophylaxis including anti-fungal during the initial period when counts expected to be low.
  - Prolongation of anti-viral therapy during 1st year
  - Monitoring IgG levels and replace for values < 400
- Cytopenias
  - Transfusions prn for thrombocytopenia/anemia
  - GCSF
  - Rare data on stem cell boost (if stem cells are available)

Bispecifics

Bi-Specific Antibody	Targets	Design	Ig Fragment Formats	Ref.
mosunetuzumab	CD20 x CD3		• humanized mouse heterodimeric IgG1-based antibody • monovalent CD20 and monovalent CD3ε binding • modified Fc devoid of FcγR and complement binding	4
glofitamab	$(CD20)_2$ x CD3		• humanized mouse IgG1-based antibody • bivalent CD20 and monovalent CD3ε binding • modified Fc devoid of FcγR and complement binding	5
odronextamab	CD20 x CD3		• fully human IgG4-based heterodimeric antibody • monovalent CD20 and monovalent CD3ε binding • Fc-dependent effector function-minimized antibody with Fc of the anti-CD3ε heavy chain modified to reduce Protein A binding • common κ light chain from anti-CD3ε mAb	6
epcoritamab	CD20 x CD3		• humanized mouse IgG1-based heterodimeric antibody • monovalent CD20 and monovalent CD3 binding • IgG1 Fc modified to minimize Fc-dependent effector functions and to control Fab-arm exchange of mAb half-molecules, resulting in high bispecific product yield	7

Ig, immunoglobulin; scFv, single-chain variable fragment; mAb, monoclonal antibody; Fc, fragment crystallizable; FcγR, Fc gamma receptor

[1]Dufner V, *et al*. Blood Adv (2019) 3:2491; [2]Goebeler ME, *et al*. J Clin Oncol (2016) 34:1104; [3]Viardot *et al*. Blood (2016) 127(11):1410; [4]Schuster SJ, *et al*. ASH 2019, Plenary Abstract 6; [5]Hutchings M, *et al*. ASH 2020, Abstract 403; [6]Bannerji R, *et al*. ASH 2020, Abstract 400; [7]Hutchings M, *et al*. ASH 2020, Abstract 406

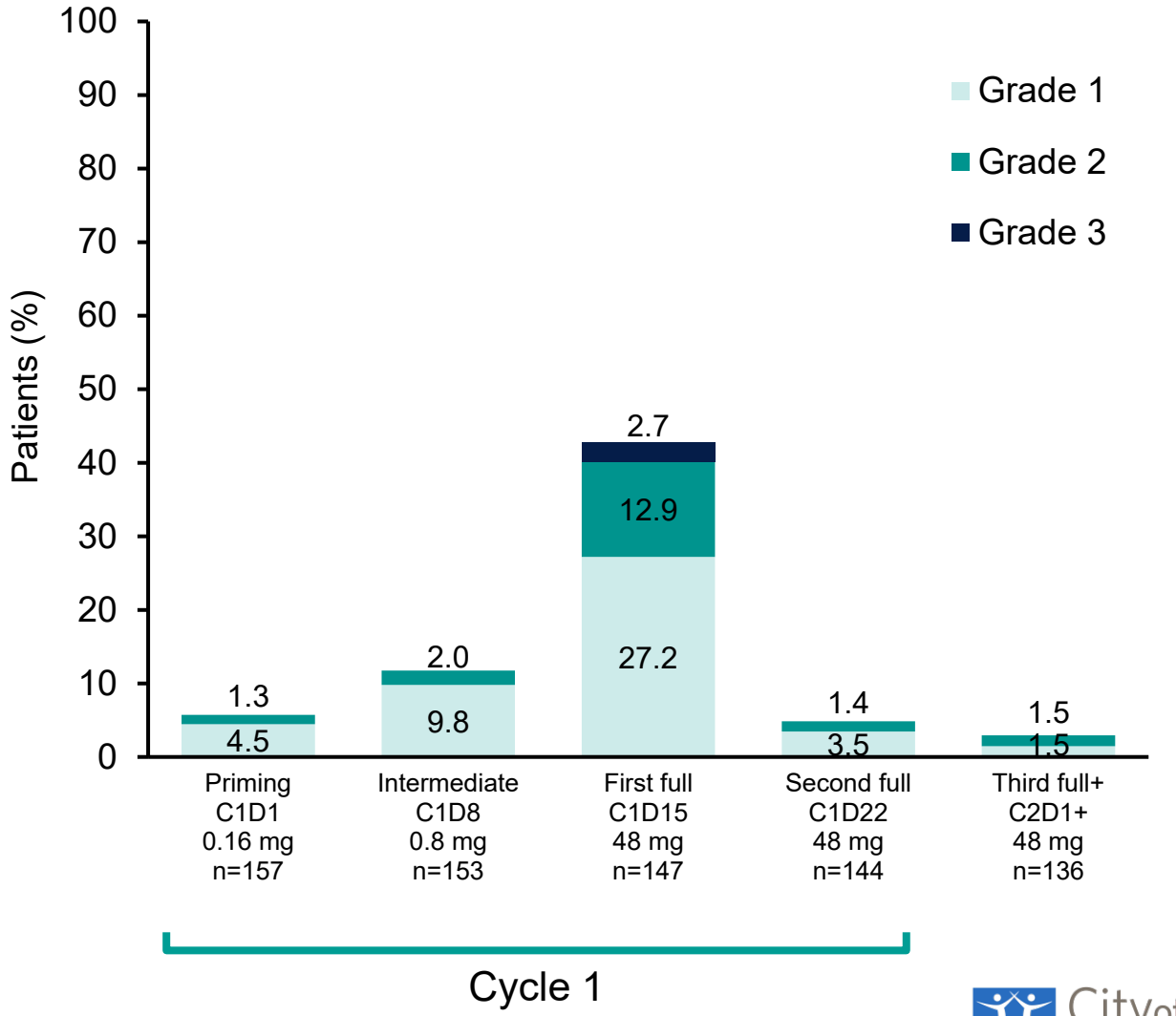
City of Hope™

SC Administration and Step-up Dosing May Mitigate CRS (LBCL)

	LBCL N=157
CRS events, n (%)[a]	78 (49.7)
Grade 1	**50 (31.8)**
Grade 2	24 (15.3)
Grade 3	4 (2.5)
Median time to onset from first full dose, d	**0.8 (20 h)**
CRS resolution, n (%)	77 (98.7)
Median time to resolution from first full dose, d	**2 (48 h)**
Treated with tocilizumab, n (%)	22 (14.0)
Treated with corticosteroids, n (%)	16 (10.2)
Leading to treatment discontinuation, n (%)	**1 (0.6)**

[a]Graded by Lee et al. 2019 criteria.

CRS Events by Dosing Period



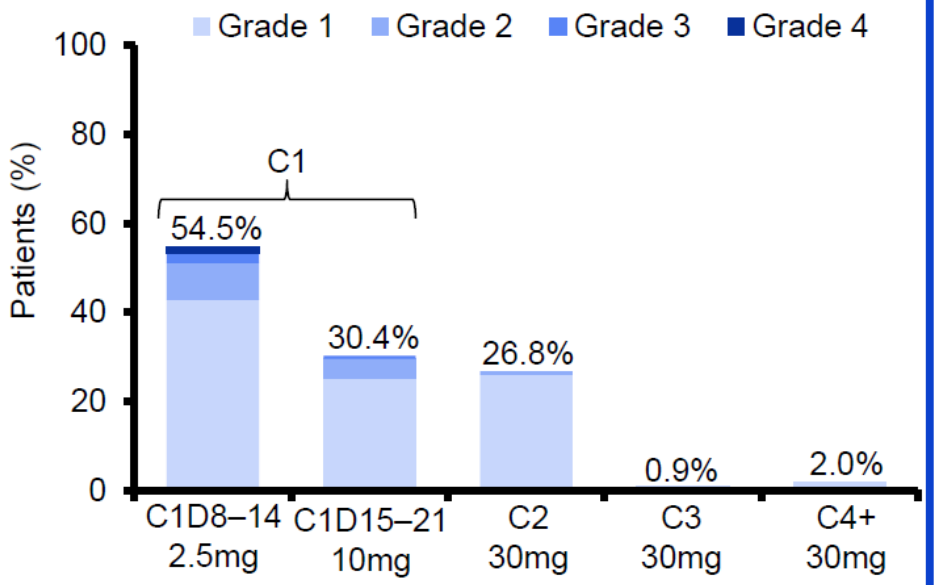
City of Hope

CRS (LBCL)

Cytokine release syndrome

n (%)	N=154
CRS (any grade)*	97 (63.0)
Grade 1 (fever)	73 (47.4)
Grade 2	18 (11.7)
Grade 3	4 (2.6)
Grade 4	2 (1.3)
Median time to CRS onset from C1D8 dose, hours (range)	13.6 (6.2–51.8)
Corticosteroids for CRS management	27/97 (27.8)
Tocilizumab for CRS management	31/97 (32.0)

CRS by cycle and grade†



CRS was mostly low grade, time of onset was predictable, and most events occurred during C1

City of Hope

Mosunetuzumab Safety (FL)

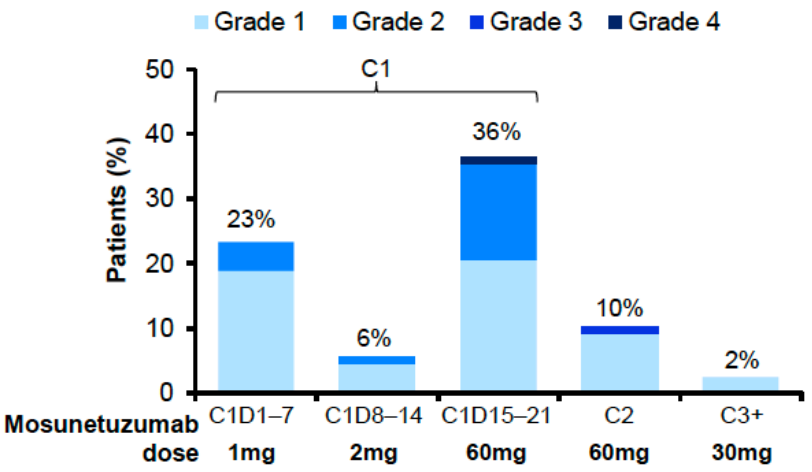
Safety profile

Adverse events (AEs)	N=90
AE	100%
Mosunetuzumab related	92%
Grade 3/4 AE	70%
Mosunetuzumab related	51%
Serious AE	47%
Mosunetuzumab related	33%
Grade 5 (fatal) AE	2%*
Mosunetuzumab related	0
AE leading to treatment discontinuation	4%†
Mosunetuzumab related	2%

CRS summary

CRS by ASTCT criteria[1]	N=90
CRS (any grade)	44%
Grade 1	26%
Grade 2	17%
Grade 3	1%
Grade 4	1%
Median time to CRS onset, hours (range)	
C1D1	5.2 (1.2–24)
C1D15	27 (0.1–391)
Median CRS duration, days (range)	3 (1–29)
Corticosteroids for CRS management	11%
Tocilizumab for CRS management	8%
Events resolved	100%

CRS by cycle and grade



CRS was predominantly low grade and during Cycle 1
All CRS events resolved; no new events were reported with 10 months of additional follow-up

City of Hope

C1 Optimization Reduced Risk and Severity of CRS

	Pivotal Cohort N=128	C1 Optimization Cohort[a] N=50
CRS, n (%)[b]	85 (66)	24 (48)
Grade 1	51 (40)	20 (40)
Grade 2	32 (25)	4 (8)
Grade 3	2 (2)	0
Treated with tocilizumab, n/n (%)	31/85 (36)	6/24 (25)
Leading to epcoritamab discontinuation, n (%)	**0**	**0**
CRS resolution, n/n (%)	**85/85 (100)**	**24/24 (100)**
Median time to resolution, d (range)	2 (1–54)	3 (1–14)

- Patient baseline characteristics were consistent between cohorts
- C1 optimization substantially reduced rate and severity of CRS
- In both cohorts, CRS was mostly confined to C1
- Similar response rates were observed in the C1 optimization cohort
- There were no cases of ICANS in the C1 optimization cohort; 8 cases were observed in the pivotal cohort (all grade 1–2 and resolved; none led to discontinuation)

[a]Data cutoff: September 21, 2023. Median follow-up: 3.8 mo (range, 1.9–8.7). [b]Graded by Lee et al 2019 criteria.[1] **1.** Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-38.

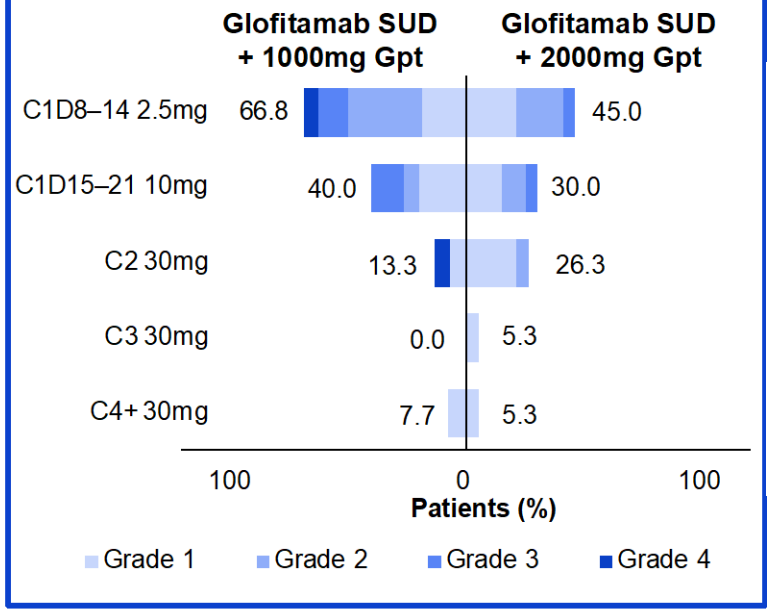
➤ Linton et al. ASH 2023

Cytokine Release Syndrome

Cytokine release syndrome*

n (%) of patients with ≥1 AE unless stated	Glofitamab SUD + 1000mg Gpt (n=16)	Glofitamab SUD + 2000mg Gpt (n=21)	All patients (N=37)
Any CRS	14 (87.5)	14 (66.7)	28 (75.7)
Grade 1	4 (25.0)	7 (33.0)	11 (29.7)
Grade 2	6 (37.5)	5 (23.8)	11 (29.7)
Grade 3	2 (12.5)	2 (9.5)	4 (10.8)
Grade 4	2 (12.5)	0 (0.0)	2 (5.4)
Serious AE of CRS (any grade)	10 (62.5)	5 (23.8)	15 (40.5)
Median time to CRS onset, hours (range)	7.55 (4.4–14.0)	9.77 (5.0–20.8)	9.31 (4.4–20.8)
Tocilizumab for CRS management	11 (68.8)	6 (28.6)	17 (45.9)
Corticosteroid for CRS management	8 (50.0)	6 (28.6)	14 (37.8)

CRS by cycle, grade and regimen



CRS with Glofitamab in DLBCL

n (%)	N=154
CRS (any grade)*	97 (63.0)
Grade 1 (fever)	73 (47.4)
Grade 2	18 (11.7)
Grade 3	4 (2.6)
Grade 4	2 (1.3)
Median time to CRS onset from C1D8 dose, hours (range)	13.6 (6.2–51.8)
Corticosteroids for CRS management	27/97 (27.8)
Tocilizumab for CRS management	31/97 (32.0)

Higher Gpt (2000mg) was associated with a lower rate of CRS, with no Grade 4 events reported in this group

*By American Society for Transplantation and Cellular Therapy (ASTCT) criteria.[1]

1. Lee et al. Biol Blood Marrow Transplant 2019.

City of Hope

Study design: Phase II dose expansion

Study design: Phase II dose expansion

Key inclusion criteria

- R/R MCL
- ECOG PS 0–2
- ≥2 prior therapies (including an anti-CD20 antibody, anthracycline or bendamustine therapy, and BTKi)

Objectives

- Primary: efficacy of mosun-pola (best ORR[1] by IRC)
- Secondary: efficacy by INV, durability of response, and safety

Mosun-pola fixed duration administration (NCT03671018)

Mosun

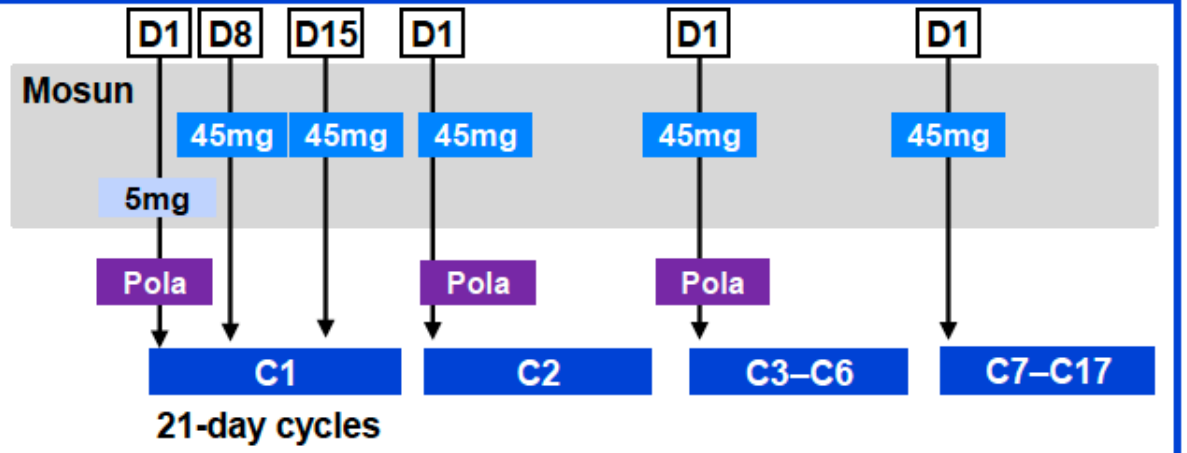
- SC administered in 21-day cycles with step-up dosing in Cycle (C) 1; total of 17 cycles

Pola

- 1.8mg/kg IV on Day [D],1 of C1–6

No mandatory hospitalization

All patients received corticosteroid premedication prior to each dose in C1*



*From C2 and beyond, premedication was optional for patients who did not experience CRS in the previous cycle; corticosteroid premedication consisted of 20mg of dexamethasone or 80mg of methylprednisolone, either IV or orally.

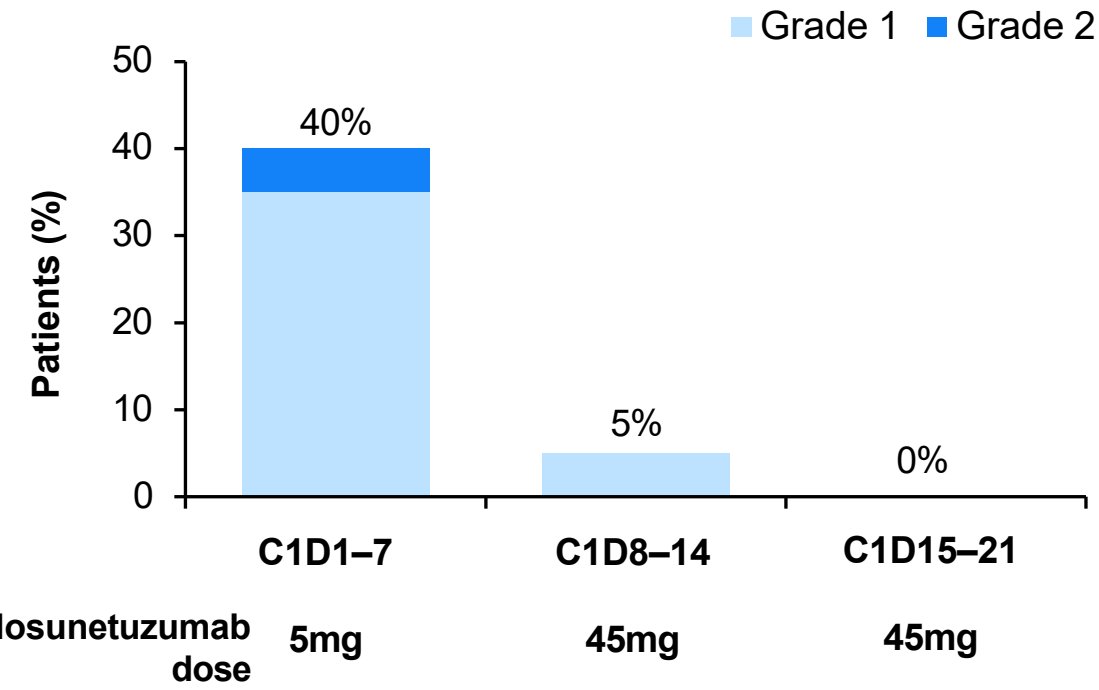
1. Cheson BD, et al. J Clin Oncol 2014;32:3059–68.

*From C
premedication consisted of 20mg of dexamethasone or 80mg of methylprednisolone, either IV or orally.
1. Cheson BD, et al. J Clin Oncol 2014;32:3059–68.

CRS summary

CRS by ASTCT criteria[1]	N=20
Any grade, n (%)	9 (45)
Grade 1	8 (40)
Grade 2*	1 (5)
Grade 3+	0
Median time to first CRS onset relative to last dose, days (range)	1 (0–2)
Median CRS duration, days (range)	3 (1–9)
CRS management, n (%)	
Corticosteroids	1 (5)
Tocilizumab	1 (5)
Low-flow oxygen	1 (5)

CRS by cycle and grade



All CRS events were low grade and resolved within C1

Clinical cut-off date: July 6, 2023. *This patient experienced Grade 2 fever, confusion, and hypoxia on D3; management included tocilizumab, low-flow oxygen, acetaminophen, and broad-spectrum antibiotics.
ASTCT, American Society for Transplantation and Cellular Therapy

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

City of Hope

Late Complications

- Infections are a risk with bispecifics but not to the degree or severity as compared to CAR-T. During SUD prophylaxis is recommended as well as during concurrent steroid use.
  - Thereafter no overt need for prophy (PJP) but consideration for continuation of HSV prophy can be given due to B cell depletion and hypogammaglobulinemia.
  - Most common infections overall are viral and likely could be avoided with careful monitoring and replacement of IgG

Integration into the community

- Major issues remain CRS during SUD
  - Companies have looked at methods to reduce incidence for FL and LBCL but overall most events are grade 1……so doesn't require hospitalization or use of toci.
  - Issue remains in identifying which patients will and won't experience CRS as well as labels suggesting hospitalization during SUD
  - Good news is for both epco and glofit outpatient studies are ongoing
    - Hopefully will remove this wording from label
  - For smalled community settings the first step is being comfortable with giving drugs and having mechanisms in place to manage rare complication
  - Alternative is partnering with larger center for SUD then resuming care for remainder……unicorn to get late complications.

City of Hope™

Conclusions

- CAR-T approved in both 2L+ (primary refractory) and 3L+ DLBCL
  - Provides another curative option for patients
  - Recent data indicates that in 2L setting CAR-T has an OS benefit
- FL with two agents approved for R/R patients
  - Responses durable but cure unlikely to be proved in near future
- MCL more difficult space given increased AE and no hint that treatment is curative.
  - Liso-cel with potential to provide response with improved AE profile as compared to brexu-cel

City of Hope™

Lymphoma Center at COH

- Steve Rosen MD
- Larry Kwak MD PhD
- Jasmine Zain MD
- Alex Herrera MD
- Tanya Siddiqi MD
- Matt Mei MD
- Elizabeth Budde MD, PhD
- Lili Wang PhD
- Vu Ngo PhD
- Joo Song MD

- Geoff Shouse MD
- James Godfrey MD
- John Baird MD
- Swetha Kambhampati MD
- Niloufer Khan MD
- Avy Kallam MD
- Lu Chen PhD
- Alexey Danilov MD, PhD
- Leslie Popplewell MD
- CRNs and CRCs

LEUKEMIA & LYMPHOMA SOCIETY®

CURE ACCELERATOR®
funding from
CuresWithinReach

SWOG
Leading cancer research. Together.

City of Hope.

Questions

City of Hope™