POST-SAN DIEGO 2023
Novità dal Meeting della Società Americana di Ematologia

Novità dal Meeting della Società Americana di Ematologia

Verona
Palazzo della Gran Guardia
15-16-17 Febbraio 2024

CAR-T nei linfomi aggressivi

MASSIMO MARTINO

Disclosures of MASSIMO MARTINO

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
KITE					x	x	
NOVARTIS					x	x	
BMS					x	x	
JANSENN CILAG					x	x	
MEDAC	x					x	
JAZZ					x		
GSK						x	
SANDOZ	x						
GENTILI					x		
PIERRE FABRE						x	
ABBVIE					x		
INCYTE					x		
MSD						x	
TAKEDA						X	

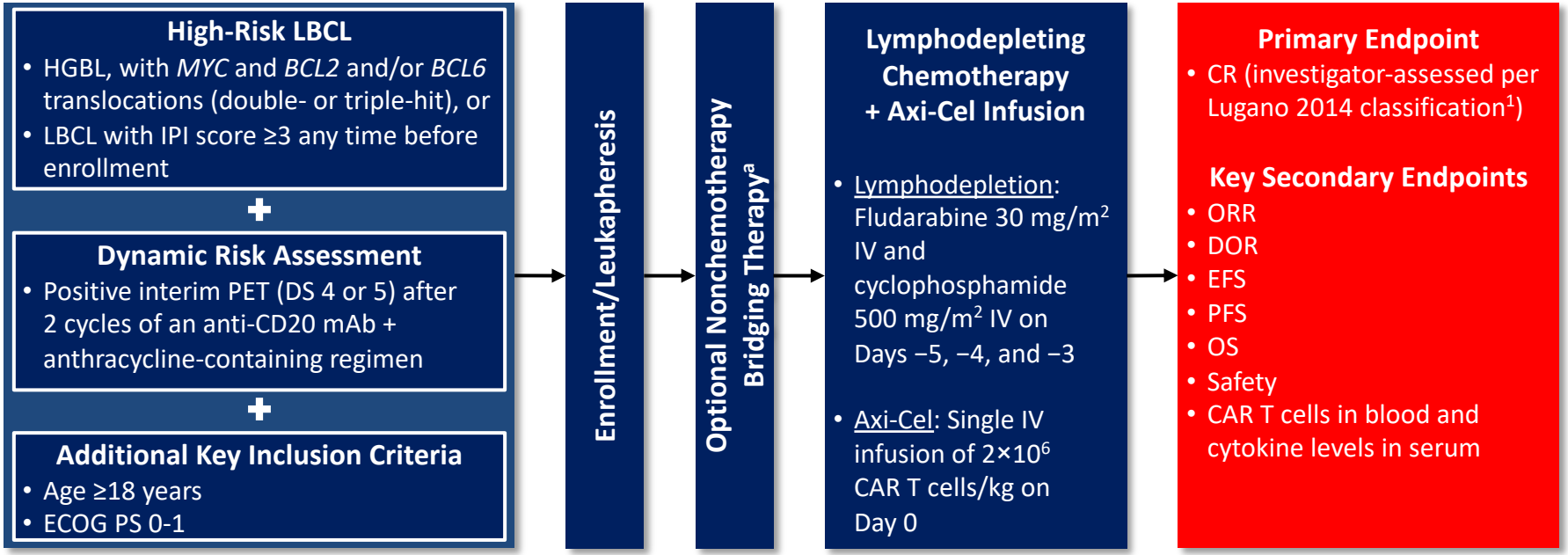
3-Year Analysis of ZUMA-12: A Phase 2 Study of Axicabtagene Ciloleucel as First-Line Therapy in Patients with High-Risk Large B-Cell Lymphoma

Julio C. Chavez, MD[1]; Michael Dickinson, MBBS, D Med Sci, FRACP, FRCPA[2]; Javier Munoz, MD, MS, MBA, FACP[3]; Matthew L. Ulrickson, MD[3]; Catherine Thieblemont, MD, PhD[4]; Olalekan O. Oluwole, MD, MPH, MBBS[5]; Alex F. Herrera, MD[6]; Chaitra S. Ujjani, MD[7]; Yi Lin, MD, PhD[8]; Peter A. Riedell, MD[9]; Natasha Kekre, MD, MPH, FRCPC[10]; Sven de Vos, MD, PhD[11]; Christine Lui, MS[12]; Jacob Wulff, DrPH[12]; Chad M. Williams, PhD[12]; Weixin Peng, MS[12]; Ioana Kloos[12]; Hairong Xu, MD, PhD[12]; and Sattva S. Neelapu, MD[13]

[1]Moffitt Cancer Center, Tampa, FL, USA; [2]Peter MacCallum Cancer Centre, Royal Melbourne Hospital and The University of Melbourne, Melbourne, Victoria, Australia; [3]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [4]Hôpital Saint Louis, Paris, France; [5]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [6]City of Hope National Medical Center, Duarte, CA, USA; [7]Seattle Cancer Care Alliance, Fred Hutchinson Cancer Center, Seattle, WA, USA; [8]Mayo Clinic, Rochester, MN, USA; [9]David and Etta Jonas Center for Cellular Therapy, University of Chicago, Chicago, IL, USA; [10]The Ottawa Hospital, Ottawa, ON, Canada; [11]David Geffen School of Medicine at UCLA, Santa Monica, CA, USA;
[12]Kite, a Gilead Company, Santa Monica, CA, USA; and [13]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

ZUMA-12 Study Design

Phase 2



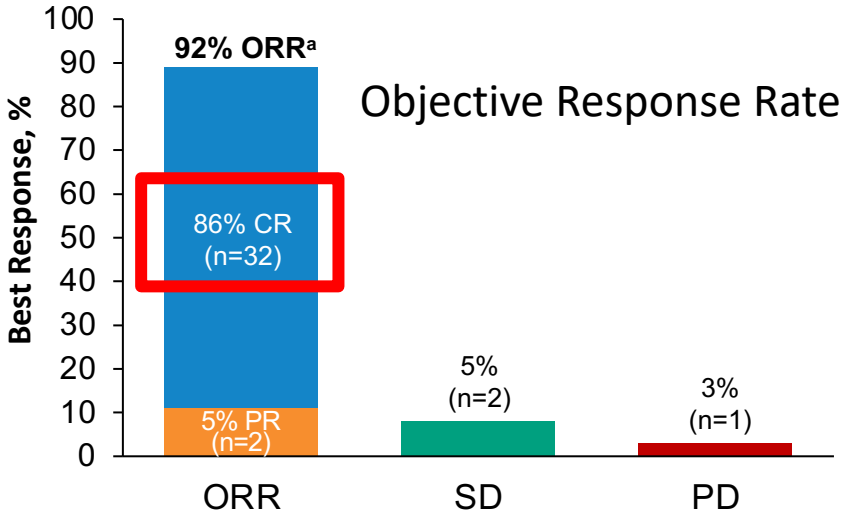
[a] Administered after leukapheresis and completed prior to initiating lymphodepleting chemotherapy. Therapies allowed were corticosteroids, localized radiation, and HDMP+R. PET-CT was required after bridging.

1. Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-3068.

Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; CT, computed tomography; DOR, duration of response; DS, Deauville score; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; HDMP+R, high-dose methylprednisolone plus rituximab; HGBL, high-grade B-cell lymphoma; IPI, International Prognostic Index; IV, intravenous; LBCL, large B-cell lymphoma; mAb, monoclonal antibody; ORR, objective response rate; OS, overall survival; PET, positron-emission tomography; PFS, progression-free survival.

Chavez et al. ASH 2023, Abstract 894

At data cutoff, median follow-up for all patients treated with axi-cel was 40.9 months (range, 29.5-50.2)

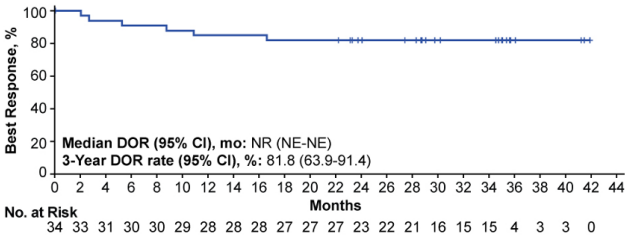


	Efficacy Evaluable n=37
Overall CR rate, % (95% CI)	86 (71-95)
DHL/THL and IPI score ≥3 (n/N)	4/4 100 (40-100)
DHL/THL only (n/N)	5/6 83 (36-100)
IPI score ≥3 only (n/N)	23/27 85 (66-96)
Patients converted from PR/SD to CR, n (%)	9 (24)
PR to CR	8 (22)
SD to CR	1 (3)

- In the efficacy-evaluable population, the CR rate was slightly higher than in the primary analysis[1] due to an additional number of patients converting from PR to CR
- Responses were ongoing in 73% of response-evaluable patients at data cutoff

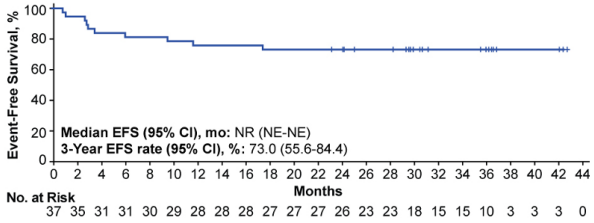
Chavez et al. ASH 2023, Abstract 894

Duration of Response



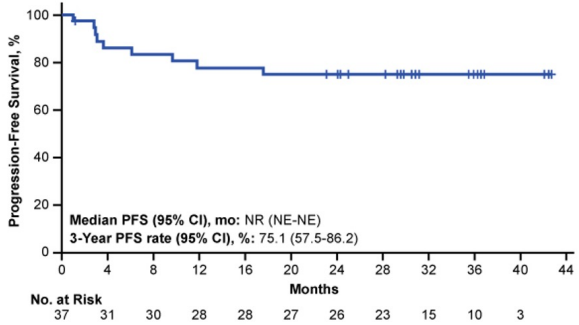
- With extended follow-up since the primary analysis, median DOR was not reached in efficacy-evaluable patients
- Among patients who achieved a CR as best response, the 3-year DOR rate was 84.4% (95% CI, 66.5-93.2)

Event-Free Survival

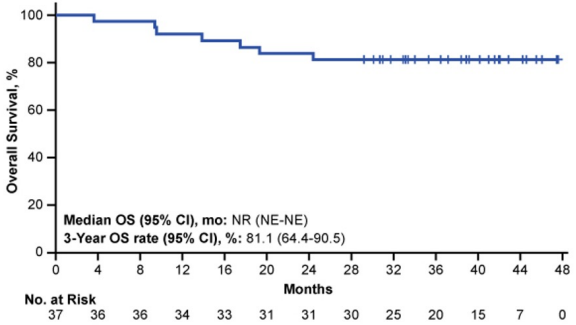


- Median EFS was not reached in efficacy-evaluable patients; the 3-year EFS rate was 73% (95% CI, 55.6-84.4) and a plateau in the curve emerged by Month 18
- Among patients who achieved a CR as best response, the 3-year EFS rate was 84.4% (95% CI, 66.5-93.2)

Progression-Free Survival



Overall Survival



- Medians for PFS and OS were not reached in efficacy-evaluable patients
- Among patients who achieved a CR as best response, the 3-year PFS and OS rates were 84.4% (95% CI, 66.5-93.2) and 90.6% (95% CI, 73.6-96.9), respectively

Chavez et al. ASH 2023, Abstract 894

Adverse Events and Deaths

New TEAEs After Primary Analysis, n (%)	All Treated (N=40)
Any TEAE[a]	5 (13)
Grade ≥3	3 (8)
Serious TEAEs	3 (8)
Any infection/infestation	4 (10)
Grade ≥3	2 (5)
COVID-related infections	3 (8)
Device related infection	1 (3)
Sinusitis	1 (3)

- In total, there were 8 deaths in ZUMA-12
  - 5 were due to PD (1 occurring after the primary analysis data cutoff)[1]
  - 1 COVID-19 (Day 350; Grade 5 and unrelated to axi-cel)
  - **1 esophageal adenocarcinoma (Day 535, occurring after the primary analysis data cutoff; Grade 5 and unrelated to axi-cel)[1]**
  - 1 septic shock (Day 287; unrelated to axi-cel)

- No new cases of CRS or neurologic events of any grade occurred since the prior data cut and all cases previously reported[1] were resolved by data cutoff
- Since the primary analysis,[1] prolonged cytopenia[b] of any grade occurred in only 1 patient and was resolved by data cutoff

[a] AEs were graded per CTCAE version 5.0. Neurologic events were identified based on modified Topp et al 2015.[2] CRS events were graded according to a modification of the criteria of Lee and colleagues.[3]

[b] Present on Day ≥30 post-infusion.

1. Neelapu SS, et al. *Nat Med*. 2022;28:735-742. 2. Topp CW, et al. *Psychother Psychosom*. 2015;84:167-176. 3. Lee DW, et al. *Blood*. 2014;124:188-195.

AE, adverse event; axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; PD, progressive disease; TEAE, treatment-emergent adverse event.

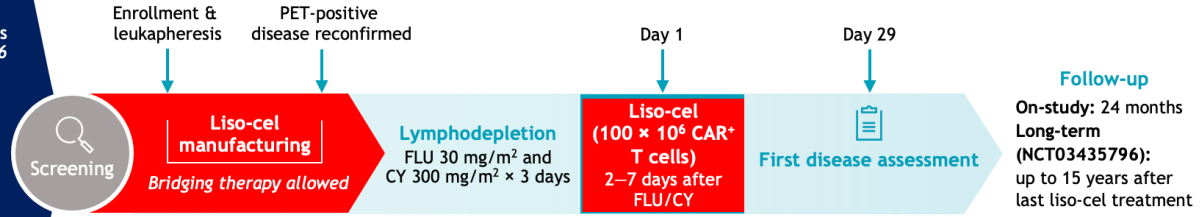
Chavez et al. ASH 2023, Abstract 894

Lisocabtagene maraleucel as second-line therapy for relapsed or refractory large B-cell lymphoma in patients not intended for hematopoietic stem cell transplant: final analysis of the phase 2 PILOT study

PILOT study design

Key eligibility criteria

- Age ≥ 18 years
- LBCL: DLBCL NOS (de novo; transformed from FL), high-grade B-cell lymphoma (HGBCL) with rearrangements in *MYC* and *BCL2* and/or *BCL6* (double/triple hit), or FL3B
- One prior line of therapy containing an anthracycline and a CD20-targeted agent
- Not intended for HSCT by investigator and met ≥ 1 of the following TNI criteria:
  - Age ≥ 70 years
  - ECOG PS of 2
  - DLCO ≤ 60%
  - LVEF < 50%
  - CrCl < 60 mL/min
  - AST/ALT > 2 × ULN
- Patients with secondary CNS lymphoma were allowed



Primary endpoint

- ORR by independent review committee (IRC) per Lugano 2014 criteria[1]

Key secondary endpoints

- CR rate by IRC, duration of response (DOR), DOR for patients whose best overall response (BOR) was CR, PFS, event-free survival (EFS),[a] OS, and AEs and laboratory abnormalities

Sehgal et al. *Abstract number 105*

Baseline demographics and disease characteristics

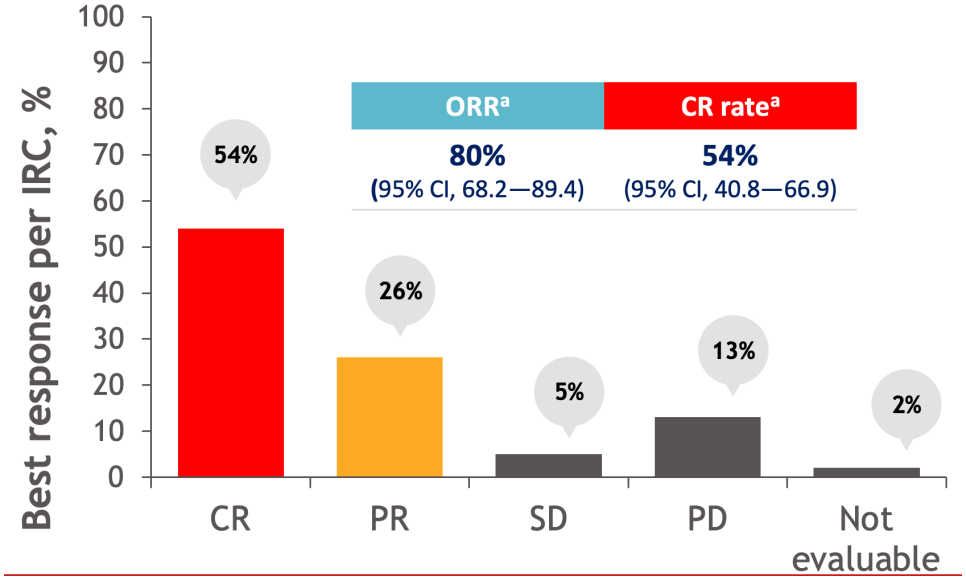
	Liso-cel—treated analysis set (n = 61)
Age, y	
Median (range)	74 (53—84)
≥ 65 to < 75, n (%)	27 (44)
≥ 75, n (%)	28 (46)
Histology, n (%)	
DLBCL NOS	33 (54)
Transformed FL	9 (15)
HGBCL	18 (30)
FL3B	1 (2)
Relapsed or refractory, n (%)	
Relapsed total / ≤ 12 mo / > 12 mo	28 (46) / 13 (21) / 15 (25)
Refractory[a]	33 (54)
Received bridging therapy,[b] n (%)	32 (52)

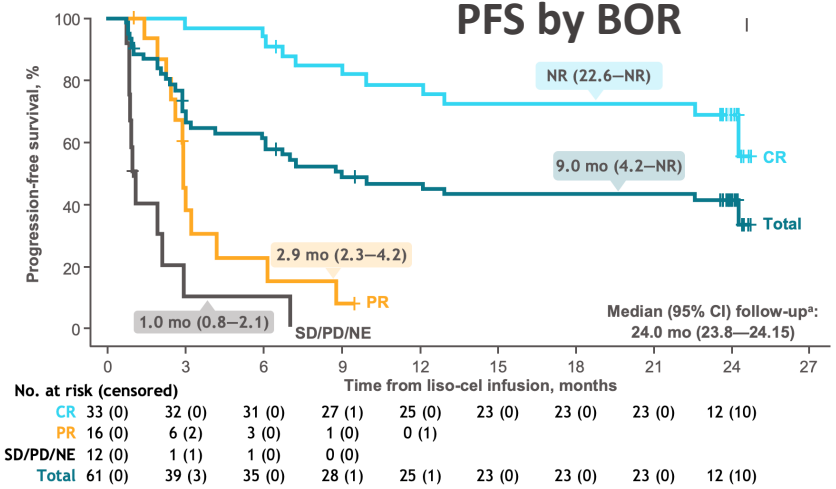
Transplant not intended characteristics

	Liso-cel—treated analysis set (n = 61)
Age, y ≥ 70, n (%)	48 (79)
Screening ECOG PS of 2, n (%)	16 (26)
CrCl < 60 mL/min, n (%)	15 (25)
DLCO ≤ 60%,[a] n (%)	4 (7)
LVEF < 50%, n (%)	1 (2)
AST/ALT > 2 × ULN, n (%)	0

Sehgal et al. *Abstract number 105*

Liso-cel—treated efficacy analysis set (n = 61)





	Total (n = 61)	CR (n = 33)
12-mo rate (95% CI)[b]	46.6% (33.4—58.8)	78.4% (59.9—89.1)
18-mo rate (95% CI)[b]	42.9% (29.9—55.2)	72.1% (53.2—84.4)

Abstract number 105

Adverse events of special interest in the TE and post-TE periods

	TE period (n = 61)	Post-TE period (n = 57)
CRS,[a] n (%)		
Any grade	23 (38)	0
Grade 1/2	22 (36)	0
Grade 3/4	1 (2)	0
Grade 5	0	0
NEs,[b] n (%)		
Any grade	19 (31)	0
Grade 1/2	16 (26)	0
Grade 3/4	3 (5)	0
Grade 5	0	0
Prolonged cytopenia at Day 29,[c] n (%)	52 (85)	N/A
Grade ≥ 3 infections, n (%)	4 (7)	1 (2)
Hypogammaglobulinemia, n (%)	5 (8)	1 (2)
Second primary malignancy, n (%)	**0**	**2 (4)**

treatment-emergent (TE) period (≤ 90 days after liso-cel administration)

- Bacteremia and sepsis (n = 1)
- Squamous cell carcinoma of skin and malignant external ear neoplasm (n = 1)
- Myelodysplastic syndrome (n = 1)

Abstract number 105

Multicenter, real-world study in patients with relapsed or refractory large B-cell lymphoma who received lisocabtagene maraleucel in the United States

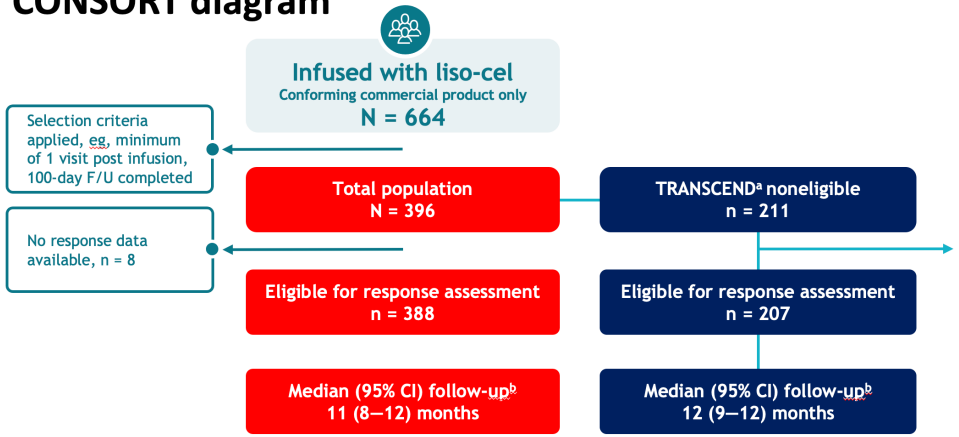
Jennifer L. Crombie,[1] Loretta J. Nastoupil,[2] Charalambos Andreadis,[3] Iris Isufi,[4] Bradley Hunter,[5] Allison Winter,[6] Brian Hess,[7] Stefan K. Barta,[8] Michael J. Frigault,[9] M. Lia Palomba,[10] Natalie Grover,[11] Michael D. Jain,[12] Tamara K. Moyo,[13] Sagar S. Patel,[14] Priyanka A. Pophali,[15] David Bernasconi,[16] Charimar Santiago Parrilla,[17] Amani Kitali,[18] Fei Fei Liu,[18] Mecide Gharibo,[18] Marcelo C. Pasquini[17]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA, USA; [4]Yale University School of Medicine, New Haven, CT, USA; [5]Intermountain LDS Hospital, Salt Lake City, UT, USA; [6]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA; [7]Medical University of South Carolina, Charleston, SC, USA; [8]Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA, USA; [9]Massachusetts General Hospital, Boston, MA, USA; [10]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [11]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [12]Moffitt Cancer Center, Tampa, FL, USA; [13]Atrium Health, Levine Cancer Institute, Charlotte, NC, USA; [14]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [15]University of Wisconsin, Carbone Cancer Center, Madison, WI, USA; [16]Celgene, a Bristol Myers Squibb Company, Boudry, Switzerland; [17]Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, WI, USA; [18]Bristol Myers Squibb, Princeton, NJ, USA

- Liso-cel is an autologous, CD19-directed, 4-1BB CAR T cell product composed of $CD8^+$ and $CD4^+$ CAR^+ T cells
- Approved in the United States for the treatment of adults with R/R LBCL after ≥ 1 lines of systemic therapy
- Report real-world clinical effectiveness and safety of commercial liso-cel in patients with R/R LBCL based on a postmarketing study using data collected at the Center for International Blood and Marrow Transplant Research (CIBMTR)

Abstract number 104

CONSORT diagram



Of the total patient population, 211 (53%) were not eligible for TRANSCEND NHL 001 because of:

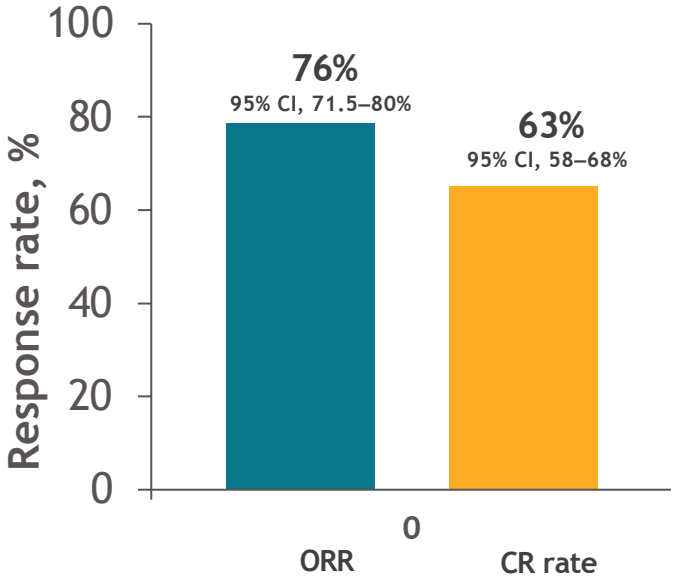
- Severity of comorbidities
- ECOG performance status

Abstract number 104

Baseline demographics and disease characteristics

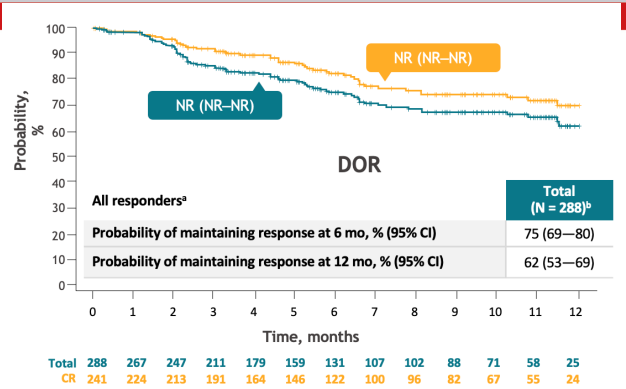
	Total (N = 396)
Male, n (%)	247 (62)
Median (range) age, y	70 (23–91)
< 65, n (%)	129 (33)
≥ 65, n (%)	267 (67)
≥ 75, n (%)	117 (30)
Histology, n (%)	
DLBCL	332 (84)
DLBCL not otherwise specified	323 (82)
Transformed from CLL (Richter transformation)	26 (7)
Transformed from other lymphoma histology	83 (21)
Primary mediastinal B-cell lymphoma	2 (1)
Follicular lymphoma grade 3B	3 (1)
High-grade B-cell lymphoma (HGBCL)	42 (11)
HGBCL with *c-MYC* and either *BCL2* and/or *BCL6* translocation at infusion	35 (9)
Other	12 (3)
ECOG PS of 0–1 / 2 / 3–4, n (%)	332 (84) / 24 (6) / 2 (1)
Comorbidities, n (%)	301 (76)
Active CNS involvement, n (%)	21 (5)
IPI score (before liso-cel infusion), n (%)	
0–2	259 (65)
3–5	137 (35)
Median (range) prior lines of therapy and HSCT	3 (1–12)
Received ≥ 2 lines of prior systemic therapy, n (%)	343 (87)
HSCT, n (%)	
Autologous	56 (14)
Allogeneic	4 (1)
Received bridging therapy for disease control, n (%)	134 (34)
Received standard LDC (FLU/CY), n (%)	354 (89)
Median (IQR) time from leukapheresis to liso-cel infusion, d	37 (34–42)

Eligible for response assessment (n = 388)

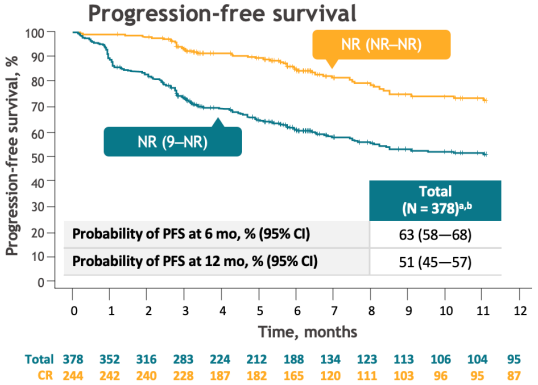


Median (range) time to initial response, mo, 1 (0—10)

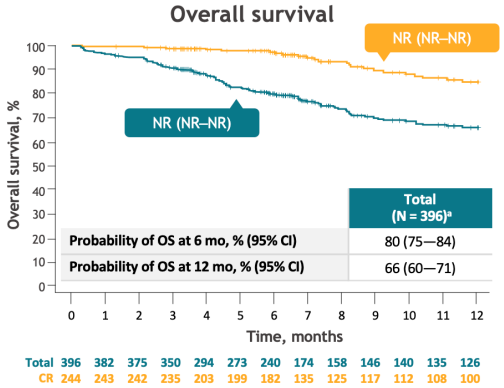
Abstract number 104



All responders[a]	Total (N = 288)[b]
Probability of maintaining response at 6 mo, % (95% CI)	75 (69—80)
Probability of maintaining response at 12 mo, % (95% CI)	62 (53—69)



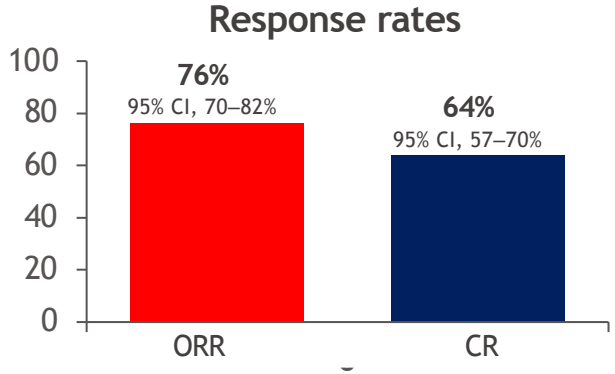
	Total (N = 378)[a,b]
Probability of PFS at 6 mo, % (95% CI)	63 (58—68)
Probability of PFS at 12 mo, % (95% CI)	51 (45—57)

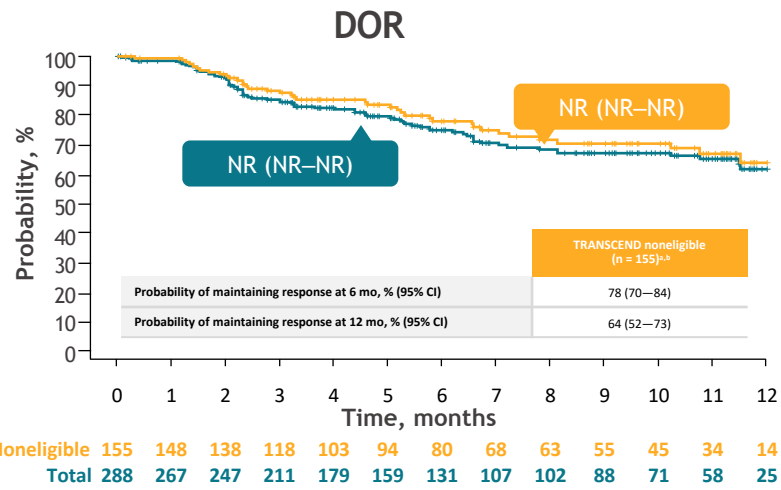


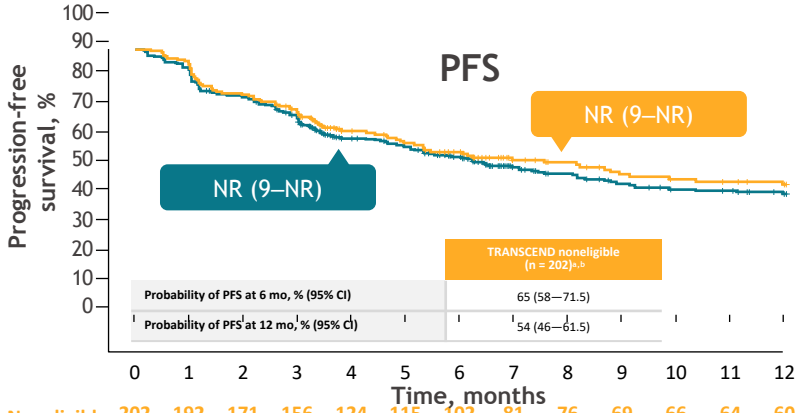
	Total (N = 396)[a]
Probability of OS at 6 mo, % (95% CI)	80 (75—84)
Probability of OS at 12 mo, % (95% CI)	66 (60—71)

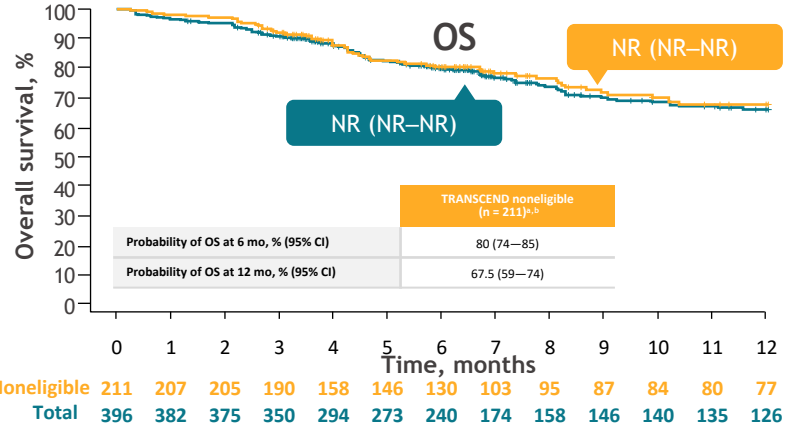
Efficacy in TRANSCEND noneligible population

Abstract number 104



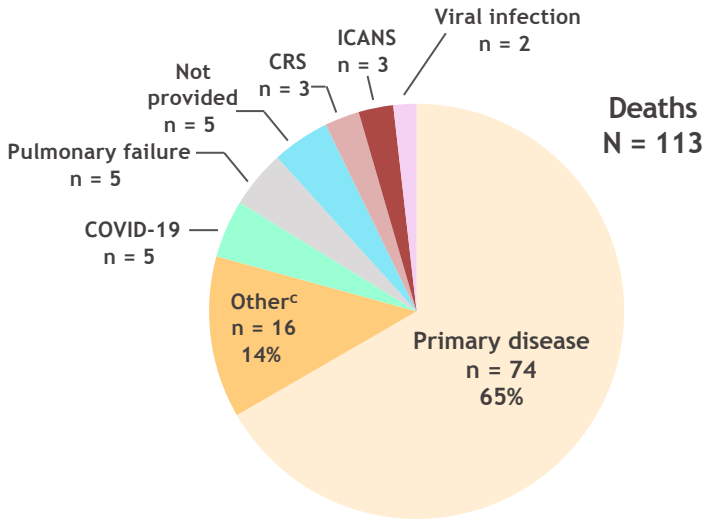






Adverse events of special interest and deaths

Adverse event of special interest	Total (N = 396)
Clinically significant infections,[a] n (%)	162 (41)
Viral	113 (29)
Bacterial	77 (19)
Other	24 (6)
Fungal	8 (2)
Parasitic	1 (< 1)
Prolonged cytopenia,[b] n (%)	49 (12)
Hypogammaglobulinemia, n (%)	219 (55)
Median (range) time to onset, d	34 (1–716)
Median (range) time to resolution, d	148.5 (11–373)
Tumor lysis syndrome, n (%)	2 (< 1)
Grade 3 or 4	2 (< 1)
Grade 3 or 4 organ toxicity, n (%)	20 (5)
Second primary malignancy, n (%)	13 (3)
Squamous cell skin malignancy	5 (1)
Myelodysplasia	3 (1)
Basal cell skin malignancy	2 (< 1)
Gastrointestinal malignancy	2 (< 1)
Melanoma	1 (< 1)
Myeloproliferative neoplasm	1 (< 1)



Safety was consistent between the two age subgroups of < 65 and ≥ 65 years, and between the TRANSCEND noneligible subgroup and the Total patient population

[a]Defined as any infection requiring treatment; [b]Defined as grade 4 thrombocytopenia and/or neutropenia persistent at 30 days after infusion; [c]Acute respiratory distress syndrome, acute respiratory failure with hypoxia, cardiac failure, cardiopulmonary arrest, CNS failure, gastrointestinal hemorrhage, idiopathic pneumonia syndrome, metabolic encephalopathy, obstructive shock, prior malignancy, pulmonary embolism, respiratory failure, septic shock, suicide, and unknown (n = 1 each).

CNS, central nervous system; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome.

Abstract number 104

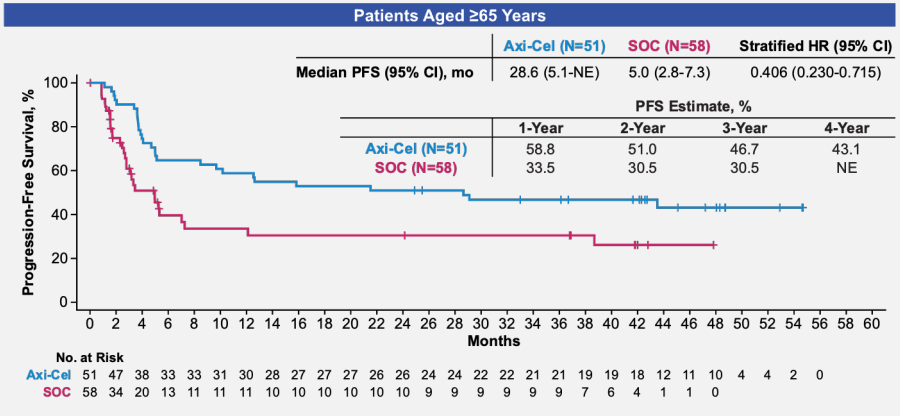
Improved Overall Survival With Axicabtagene Ciloleucel vs Standard of Care in Second-Line Large B-Cell Lymphoma Among the Elderly: A Subgroup Analysis of ZUMA-7

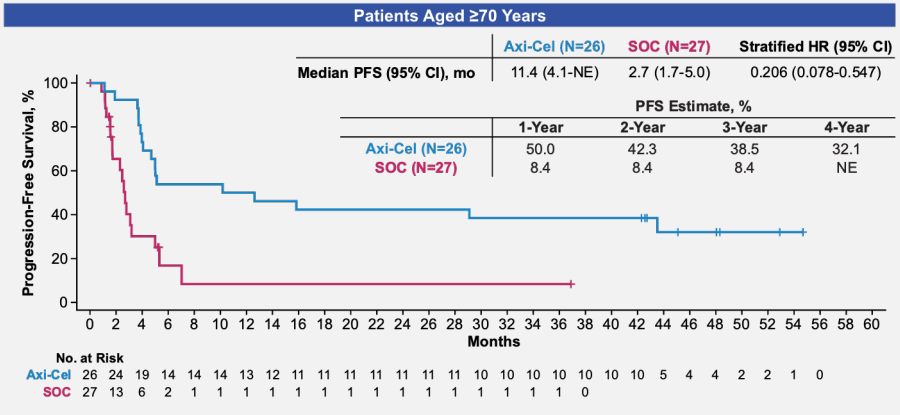
Kersten et al. ASH 2023, Abstract 1761

- In ZUMA-7 (NCT03391466), the first randomized, global, multicenter, Phase 3 study of axi-cel versus standard of care (SOC) as second-line treatment in patients with early R/R LBCL, axi-cel showed significantly improved event-free survival (EFS) compared with second-line SOC (hazard ratio [HR], 0.398, *P*<.0001; median 8.3 versus 2.0 months, respectively; 24-month EFS rate: 41% versus 16%, respectively; 24.9-month median follow-up)[1]
  - Similar findings were observed among patients aged ≥65 years, whereby axi-cel was safely administered and resulted in improved EFS, response rates, and quality of life compared with SOC[2]
- At a median follow-up of 47.2 months, results from the ZUMA-7 primary overall survival (OS) analysis demonstrated superior OS in the intention-to-treat (ITT) population (HR, 0.726; 95% CI, 0.540-0.977; one-sided *P*=.0168)[3]

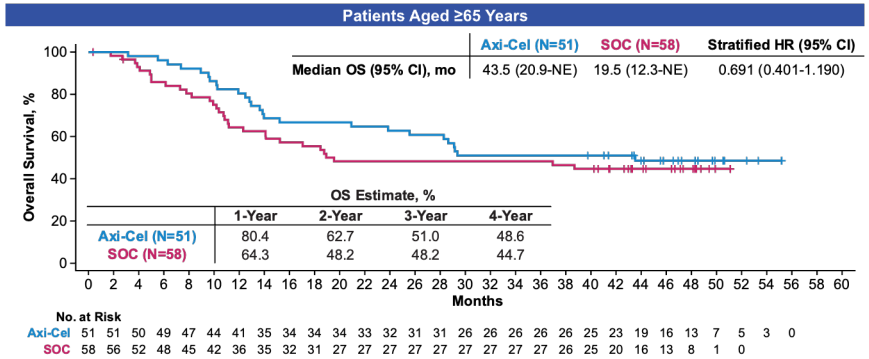
1. Locke FL, et al. *N Engl J Med.* 2022;386:640-654. 2. Westin JR, et al. *Clin Cancer Res.* 2023;29:1894-1905. 3. Westin JR, et al. *N Engl J Med.* 2023;389:148-157.

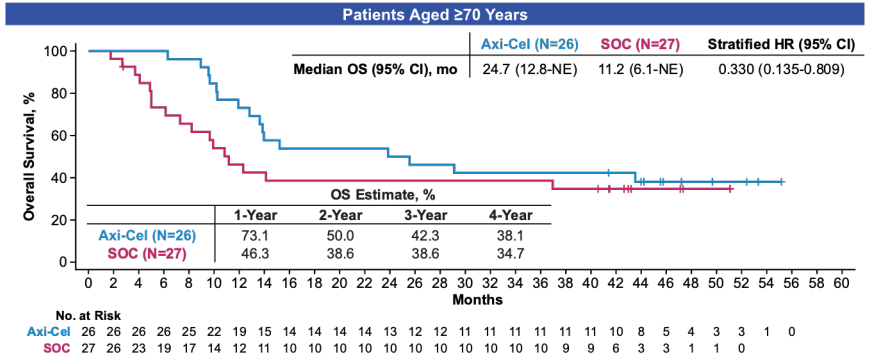
PFS of Axi-Cel Versus SOC in Patients Aged ≥65 Years and ≥70 Years





OS of Axi-Cel Versus SOC in Patients Aged ≥65 Years and ≥70 Years





Kersten et al. ASH 2023, Abstract 1761

Key Safety Data Among Elderly Patients Since Start of Treatment

	Axi-Cel, ≥65 Years N=49		SOC, ≥65 Years N=55	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
AEs of Interest, n (%)				
CRS	48 (98)	4 (8)	-	-
Neurologic event	33 (67)	13 (27)	14 (25)	1 (2)
Hypogammaglobulinemia	10 (20)	0 (0)	1 (2)	0 (0)
Cytopenia	41 (84)	41 (84)	45 (82)	42 (76)
Infections	30 (61)	14 (29)	21 (38)	9 (16)
Reason for Death, n (%)	25 (51)		29 (53)	
Progressive disease	20 (41)		20 (36)	
Grade 5 AE during protocol-specific reporting period	2 (4)[a]		1 (2)[b]	
New or secondary malignancy	***1 (2%)*** *acute myeloid leukemia*		***0 (0)***	
Other reason for death	2 (4)		8 (15)	
Definitive therapy–related mortality	0 (0)		1 (2)	

Kersten et al. ASH 2023, Abstract 1761

Pre- and post-treatment immune contexture correlates with long term response in large B cell lymphoma patients treated with Axicabtagene ciloleucel (axi-cel)

Mattie et al. ASH 2023, Abstract 226

Tumor immune contexture analysis

- The association between immune cell subset density and probability to **relapse** was evaluated in a subset of ZUMA-1 patients.

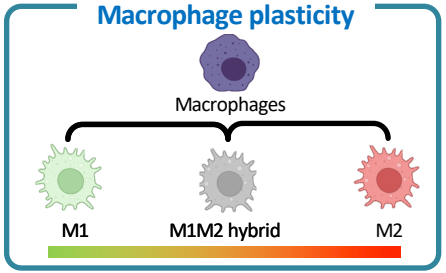
SAMPLING

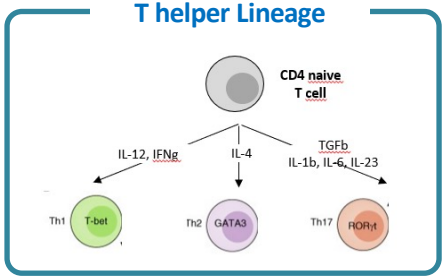
26 patients treated
- 11 relapsed (6 CR/5 PR)
- 15 durable response (15 CR)

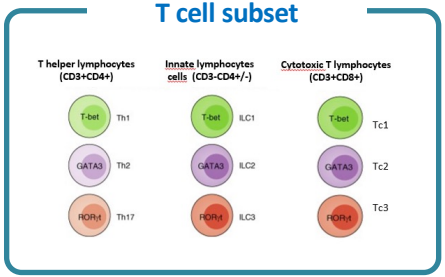
32 tumor biopsies
- 15 at baseline (13 CR/2 PR)
- 17 post-infusion (13 CR/4 PR)

MULTIOMICS ANALYSIS

- Brightplex® T cell infiltration
  CD3 CD8 FOXP3 TIM3 PD1 LAG3 TOX
- Brightplex® regulatory T cell subtyping
  CD3 CD8 GATA3 TBET RORg BCL6 FOXP3
- Brightplex® T cell activation/exhaustion
  CD3 CD8 TIM3 LAG3 PD1 GZMB KI67
- Brightplex® Macrophage
  CD68 CD64 CD163 CD204 CD206 PDL1
- Brightplex® MDSC
  CD3 CD11B CD68 CD14 CD15 LOX1 S100A9
- \+ Transcriptomic analysis, nCounter® PanCancer panel



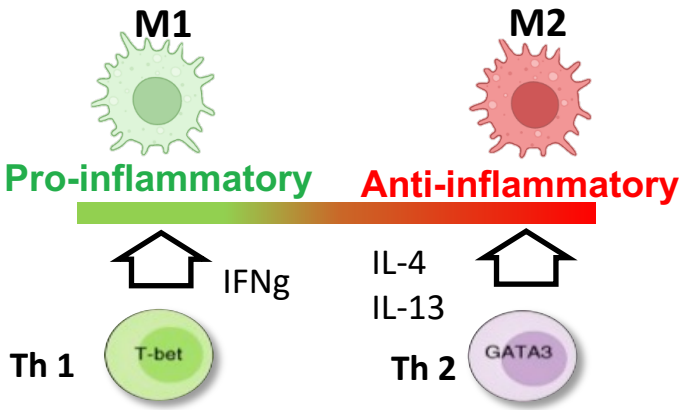




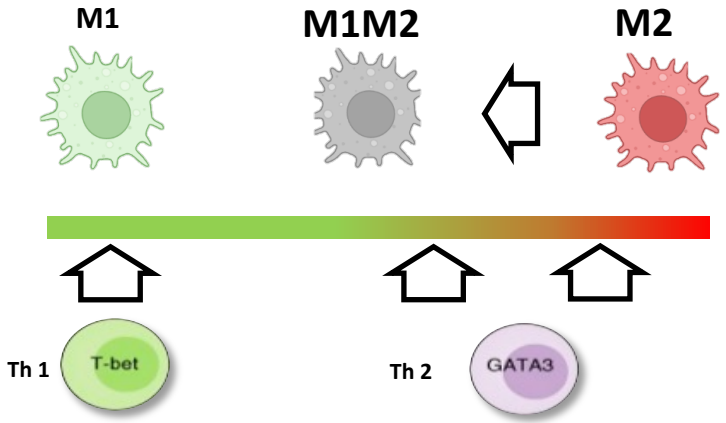
Mattie et al. ASH 2023, Abstract 226

Axicel impact on Tumor Immune Contexture in DLBCL

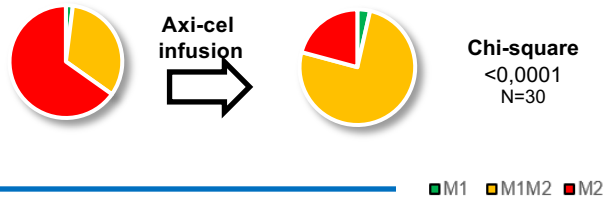
Th2 mediates M2 Polarization



Axi-cel promotes M2 to M1M2 polarization



Axi-cel infusion impacts macrophage plasticity



After Axi-cel infusion

- Switch from M2 protumoral macrophages to hybrid M1M2 macrophages phenotype ($p<0.0001$)
- Global increase of T lymphocyte subset cell density (Especially in Ongoing Responder: TC1/TC2 $p=0.023$)

→ **Axi-cel drastically impacts the tumor immune contexture correlated with ongoing response**

Mattie et al. ASH 2023, Abstract 226

Summary

Results

- Low proinflammatory M1 macrophage density seen at baseline and post-infusion
- In relapsed patients, a higher proportion of protumoral M2 macrophage was observed at baseline (p<0.0001)

After axi-cel infusion

- Post-infusion, a significant shift in M2 to M1M2 macrophage proportions (M1, M1M2, M2) (p<0,0001) was observed.
- Ongoing response was associated with a significant increase of cell densities:
  - ✓ CD4 and CD8 naïve T cells
  - ✓ T helper Th2
  - ✓ Cytotoxic T lymphocyte TC2 and TC1+TC2

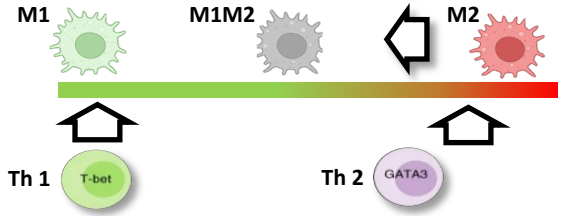
Conclusion

- Warrants validation to determine if baseline proportion of protumor M2 macrophage predicts axi-cel relapse.
- Axi-cel treatment significantly impacts densities of specific T cell subpopulations and macrophage proportions

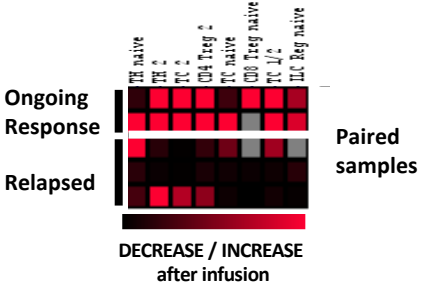
→ Leading to a drastic change of the tumor immune contexture correlated with ongoing response.

M2 macrophage proportion at baseline could predict axi-cel relapse

Axi-cel promotes M2 to M1M2 polarization



T lymphocyte change after infusion correlates with OR



Mattie et al. ASH 2023, Abstract 226

781 Autologous Transplant (auto-HCT) Is Associated with Improved Clinical Outcomes Compared to CAR-T Therapy in Patients (pts) with Large B-Cell Lymphoma (LBCL) Achieving a Complete Remission

Program: Oral and Poster Abstracts
Type: Oral
Session: 731. Autologous Transplantation: Clinical and Epidemiological: Role of Autologous Stem Cell Transplantation in Multiple Myeloma and Lymphomas: A Therapeutic Approach

Monday, December 11, 2023: 10:30 AM

Mazyar Shadman, MD, MPH[1,2], *Kwang Wooahn, PhD*[3*], *Manmeet Kaur*[4*], *Mohamed A. Kharfan-Dabaja, MD, MBA*[5], *Alex F. Herrera, MD*[6], *Craig S Sauter, MD*[7] *and Mehdi Hamadani, MD*[8]

Pts who are intended to receive CAR-T, commonly require interim therapy before leukapheresis, where in a small fraction may achieve a complete remission (CR). Having chemosensitive disease, these pts can be considered for auto-HCT. Also, there are reports indicating the efficacy of CAR-T therapy in CR pts (Strati et al., Haematologica, 2023; Wudhikarn et al., Blood Adv, 2022)

Shadman S, et al. Abstract #781. Presented at the 65th ASH

LBCL who were in a CR

Pts aged 18-75 years with DLBCL or primary mediastinal lymphoma who received CAR-T (between 2018-2021) or auto-HCT (between 2015-2021) while in a CR by PET or CT endpoints.

No. Patients in CR	360
CAR-T	79
Tisa-Cel	53%
Axi-Cel	46%
Liso-Cell	1%
Auto-HCT	**281**

Table-1: Selected baseline characteristics

	CAR-T	auto-HCT	P-value
Age, years	64	59	0.14
Extra-nodal disease	58%	63%	0.37
Refractory disease to first-line	29%	20%	0.22
Prior lines of therapy, n	3	2	**<0.01**
Early treatment failure (within 12 months)	72%	58%	**0.02**
Elevated LDH before treatment	37%	31%	**0.04**
high-grade B-cell lymphoma with MYC and BCL2 or BCL6 rearrangement	14%	27%	**0.03**

Shadman S, et al. Abstract #781. Presented at the 65th ASH

Univariate analysis

	CAR-T	Auto-HCT	
2-years RR	48%	27.8%	p < 0.001
2-year PFS	47.8%	66.2%	p < 0.001
2-year OS	65.6%	78.9%	P=0.037
2-year TRM	4.1%	5.9%	P=0.673
Patients with early (12 months) treatment failure			
No. Patients	57	163	
2-years RR	45.9%	22.8%	P<0.001
2-year PFS	48.3%	70.9%	P<0.001
No differences in 2 year OS or TRM			

Progression-Free Survival

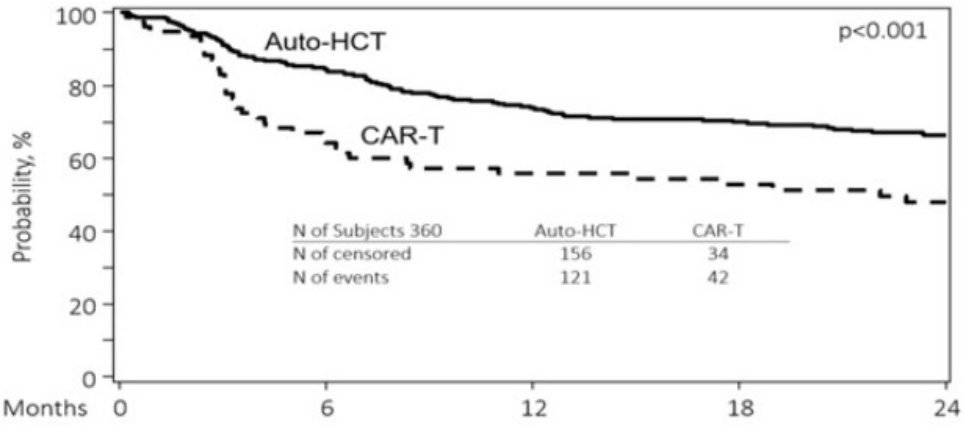


Figure-1: PFS in pts with LBCL who received auto-HCT vs. CAR-T while in CR

Multivariate analysis

CAR-T was associated with higher risk of relapse (HR 2.18; p < 0.0001) and an inferior PFS (HR 1.83; p=0.0011) compared to auto-HCT. There was no difference in the risk of TRM (HR 0.59; p=0.36) or OS (HR 1.44; p=0.12).

Median follow-up:
CAR-T - 24.7 months (range 3.3-49.4)
Auto-HCT - 49.7 months (range 3.0-95.4)

Shadman S, et al. Abstract #781. Presented at the 65th ASH

228 Efficacy of Chimeric Antigen Receptor T-Cell Therapy Is Not Impaired By Previous Bispecific Antibody Treatment in Patients with Large B-Cell Lymphoma

Program: Oral and Poster Abstracts
Type: Oral
Session: 705. Cellular Immunotherapies: Late Phase and Commercially Available Therapies: Translational Data and Prognostic Factors
Hematology Disease Topics & Pathways:
Research, Biological therapies, Lymphomas, Bispecific Antibody Therapy, Clinical Research, B Cell lymphoma, Chimeric Antigen Receptor (CAR)-T Cell Therapies, Diseases, real-world evidence, aggressive lymphoma, Therapies, therapy sequence, Lymphoid Malignancies

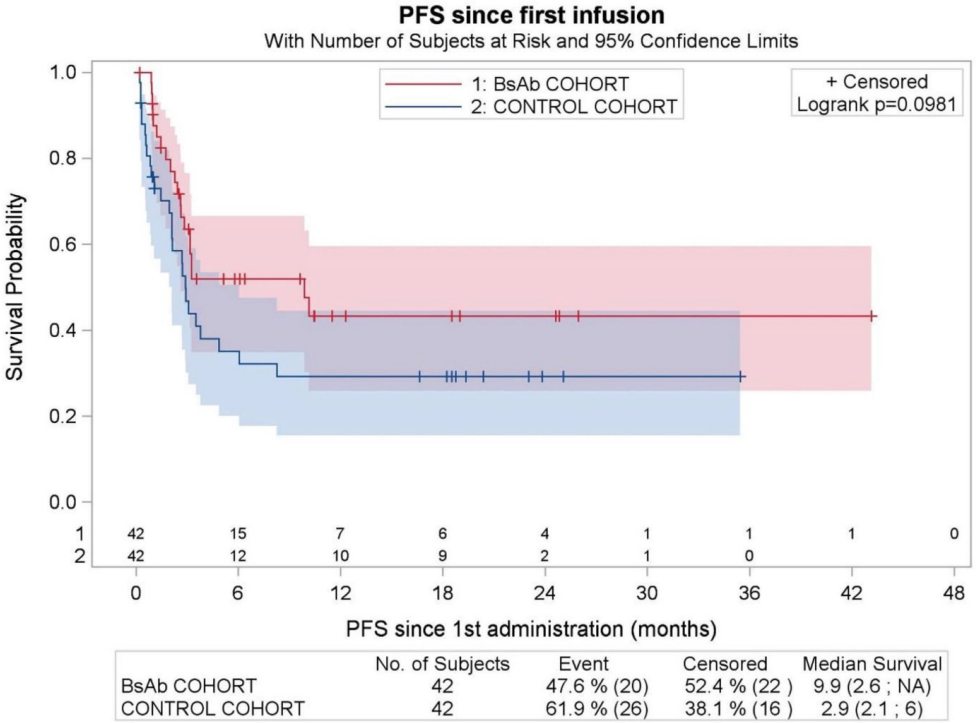
Saturday, December 9, 2023: 3:15 PM

Gloria Iacoboni, MD[1*], *Gilles Crochet, MD*[2*], *Audrey Couturier, MD*[3*], *Emmanuel Bachy, MD, PhD*[4*], *Josu Iraola*[1*], *Thomas Gastinne, MD*[5*], *Charles Herbaux, MD, PhD*[6*], *Tom Fradon*[7*], *Mi Kwon*[8], *Romain Gounot*[9*], *Nuria Martinez-Cibrian, MD*[10*], *Cristina Castilla-Llorente, MD*[11*], *Manuel Guerreiro, MD*[12*], *Clementine Sarkozy*[13*], *Jose Aspa-Cilleruelo*[1*], *Vincent Camus, MD*[14*], *Stephanie Guidez*[15*], *Adrien Chauchet*[16*], *Eric Deconinck*[16], *Krimo Bouabdallah, MD*[17*], *Pere Barba, MD*[1], *Roch Houot, MD, PhD*[3*] *and Franck Morschhauser*[18]

Introduction: Potential T-cell exhaustion after bispecific antibody (BsAb) treatment remains an open question, raising the theoretical concern that prior BsAb exposure could affect subsequent chimeric antigen receptor (CAR) T-cell efficacy. Clinical data on CAR T-cell outcomes after prior BsAb treatment in the setting of large B-cell lymphoma (LBCL) are scarce and highly awaited to better define treatment sequencing in relapsed/refractory (R/R) patients.

Methods: We conducted a retrospective, international study including R/R LBCL patients treated with CD19-targeted CAR T-cells at 15 centers between July 2018 and January 2023 who had been exposed to BsAbs prior to apheresis. Then, we identified a control cohort from patients included in the DESCAR-T Registry (n=764). We carried out a 1:1 propensity score matching (PSM) to achieve balance between cohorts; 13 baseline covariates were included in the PSM. We compared response rates, survival outcomes and toxicity after CAR T-cell therapy, according to previous BsAb exposure.

Variables	BsAb cohort n=42	Control cohort n=42	SMD
Patient and lymphoma characteristics			
Male gender, n (%)	29 (69)	31 (74)	-0.085
Age, median years (range)	63 (31-82)	67 (21-78)	0.061
Histology, n (%)			
- DLBCL/HGBL	35 (83)	31 (74)	0.196
- PMBL/Transformed	7 (17)	11 (26)	
> 2 prior lines, n (%)	36 (86)	36 (86)	0
Previous SCT, n (%)	8 (19)	7 (17)	-0.05
Bulky disease, n (%)	15 (36)	19 (45)	0.16
CRP > 3mg/dL, n (%)	16 (38)	12 (29)	-0.164
LDH > 2xULN, n (%)***	12 (29)	16 (38)	0.168
ECOG >1, n (%)***	4 (10)	3 (7)	-0.069
CAR-T related characteristics			
Axi-cel, n (%)	22 (52)	20 (48)	-0.078
Months between last prior treatment and CAR-T infusion, median (IQR)	2.7 (2.3-3.8)	2.5 (2.0-3.5)	0.201
Response to bridging, n (%)			
- Responder	8 (19)	5 (12)	-0.159
- Non responder	26 (62)	22 (52)	
- No bridge	5 (12)	11 (26)	
- Not evaluated	3 (7)	4 (10)	
Year of CAR-T infusion ≥2020, n (%)	29 (69)	29 (69)	0



Iacoboni G ASH 2023, Abstract 228

2113 Seven-Day Vein-to-Vein Point-of-Care Manufactured CD19 CAR T Cells (GLPG5101) in Relapsed/Refractory NHL: Results from the Phase 1 Atalanta-1 Trial

Program: Oral and Poster Abstracts
Session: 704. Cellular Immunotherapies: Early Phase and Investigational Therapies: Poster I
Hematology Disease Topics & Pathways:
clinical trials, Research, Biological therapies, Lymphomas, non-Hodgkin lymphoma, Clinical Research, B Cell lymphoma, Chimeric Antigen Receptor (CAR)-T Cell Therapies, Diseases, Therapies, Immunotherapy, Lymphoid Malignancies, Adverse Events

Saturday, December 9, 2023, 5:30 PM-7:30 PM

Marie José Kersten, MD, PhD[1], *Kirsten Saevels*[2*], *Yves Beguin*[3*], *Joost S.P Vermaat, MD, PhD, MSc*[4], *Nadia Verbruggen*[5*], *Maike Spoon*[6*], *Marte C. Liefaard*[6*], *Margot Pont*[6*], *Anna D.D. van Muyden*[6*], *Maria T. Kuipers*[1*] *and Sébastien Anguille*[2*]

[1]*Cancer Center Amsterdam, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, Netherlands*
[2]*Antwerp University Hospital, Antwerp, Belgium*
[3]*Centre Hospitalier Universitaire de Liège, Liège, Belgium*
[4]*Leiden University Medical Center, Leiden, Netherlands*
[5]*Galapagos NV, Mechelen, Belgium*
[6]*CellPoint BV, a Galapagos company, Oegstgeest, Netherlands*

Chimeric antigen receptor (CAR) T-cell therapies improve survival for patients (pts) with relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL). Recent studies highlighted the importance of shortening time from leukapheresis to infusion to improve clinical outcomes (Chen et al., 2022; Locke et al., 2022). A novel decentralized and automated point-of-care (PoC) manufacturing model was developed to administer fresh autologous CAR-T treatments within 7 days of apheresis. This avoids the need for cryopreservation and complex logistics, and potentially makes CAR-T therapy accessible for pts with rapidly progressive disease. Here we provide an update on the Phase (Ph) 1 Atalanta-1 trial of PoC manufactured GLPG5101 in pts with R/R NHL.

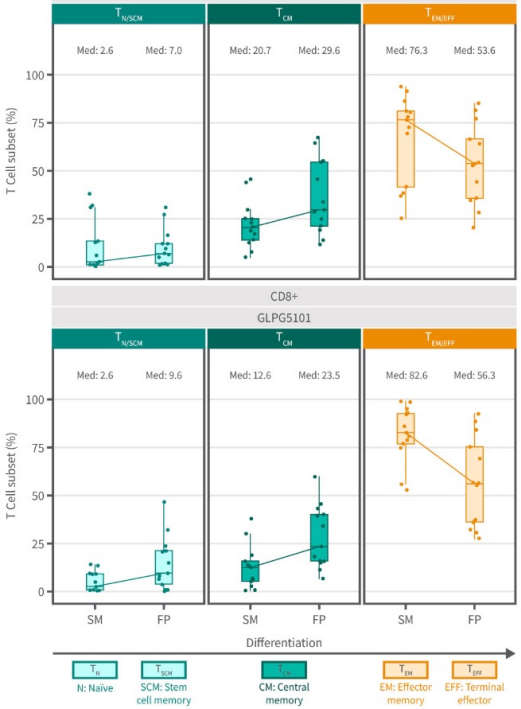
Methods

Atalanta-1 (CTIS: 2022-502661-23-00) is a Ph1/2, multicenter trial of PoC-manufactured GLPG5101 in pts with R/R diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), marginal zone lymphoma (MZL) or mantle cell lymphoma (MCL). GLPG5101 is an anti-CD19/4-1BB CAR-T therapy, administered as a fresh product after fludarabine/cyclophosphamide lymphodepleting chemotherapy. Primary Ph1 objectives are safety and establishment of a recommended Ph2 dose. The primary Ph2 objective is efficacy (objective response rate [ORR]). Secondary objectives include feasibility of PoC manufacturing, safety, additional efficacy endpoints, and pharmacokinetics.

Results

As of May 2, 2023, 14 pts were enrolled in the Ph1 study at dose level (DL) 1 (50×10^6 CAR+ T cells, n=7) or DL2 (110×10^6 CAR+ T cells, n=7); no screen failures occurred. Pts were diagnosed with R/R MCL (n=3), DLBCL (n=7), FL (n=3), or MZL (n=1). Median age was 65 years (range 50–77), 11/14 pts were male. Median prior lines of therapy was 4 (range 1–8). GLPG5101 was manufactured for all pts and administered as a fresh infusion; 13 pts were infused within 7 days of leukapheresis, 1 within 8 days. Three pts received DL1 instead of the intended DL2 due to a lower CAR+ T-cell yield during manufacturing. GLPG5101 showed a preserved early memory phenotype for both CD4+ and CD8+ CAR T cells in the final product, compared to apheresis starting material (**Figure**).

Figure. GLPG5101 preserves an early memory phenotype of CD4+ and CD8+ CAR T cells in the final product.



Exploratory flow cytometry analysis of T cell subsets in the apheresis starting material (SM) and final product (FP), showing box plots with first quartile (Q1), median (Q2) and third quartile (Q3), whiskers as well as all the individual datapoints. The whiskers extend from Q1 [Q3] to the smallest [largest] datapoint which is still within Q1 - 1.5 interquartile range (IQR) [Q3 + 1.5 IQR]. Data beyond the end of the whiskers are considered "outlying" points. GLPG5101 preserves naïve/stem cell memory T cells and central memory T cells in the FP compared to the SM. Phenotype percentages of CD4 or CD8 (gated on CAR+ T cells for FP) for paired patient samples (n=13): naïve/stem cell memory=CD45RO-CD197+, central memory=CD45RO+CD197+, effector memory/terminal effector=CD45RO-/+CD197-. Med: median.

Table. TEAEs of all grades occurring in ≥3 patients[a] and Grade 5 TEAEs occurring in all patients.

TEAE	Total (N=14) n (%)	Grade 1/2 n	Grade 3 n	Grade 4 n	Grade 5 n
Hematological					
Neutropenia/Neutrophil count decreased	12 (85.7)	0	4	8	0
Anemia	9 (64.3)	3	6	0	0
Thrombocytopenia/platelet count decreased	8 (57.1)	3	2	3	0
Leukopenia/White blood cell count decreased	6 (42.9)	0	3	3	0
Lymphopenia	5 (35.7)	0	0	5	0
Other					
Cytokine release syndrome	7 (50.0)	6	1	0	0
Hypotension	7 (50.0)	6	1	0	0
Pyrexia	7 (50.0)	5	2	0	0
ICANS	6 (42.9)	6	0	0	0
C-reactive protein increased	4 (28.6)	4	0	0	0
Dizziness	4 (28.6)	4	0	0	0
Dyspnea	4 (28.6)	3	0	1	0
Chills	3 (21.4)	3	0	0	0
Diarrhea	3 (21.4)	3	0	0	0
Fatigue	3 (21.4)	3	0	0	0
Sinus tachycardia	3 (21.4)	3	0	0	0
Intra-abdominal hemorrhage	1 (7.1)	0	0	0	1
Sepsis	1 (7.1)	0	0	0	1

Adverse events were coded using MedDRA version 25.0 preferred terms.
[a]Listed in order of decreasing incidence per category.
ICANS, immune effector cell-associated neurotoxicity syndrome; TEAE, treatment-emergent adverse event.

1025 C-CAR039, a Novel Anti-CD20/CD19 Bi-Specific CAR T-Cell Therapy Shows Deep and Durable Clinical Benefits in Patients with Relapsed or Refractory (r/r) B-Cell Non-Hodgkin Lymphoma (B-NHL) in Long Term Follow up

Program: Oral and Poster Abstracts
Type: Oral
Session: 704. Cellular Immunotherapies: Early Phase and Investigational Therapies: CAR-T Cell Therapies for Multiple Myeloma and B Cell Lymphomas
Hematology Disease Topics & Pathways:
Research, clinical trials, Biological therapies, Lymphomas, Clinical Research, B Cell lymphoma, Chimeric Antigen Receptor (CAR)-T Cell Therapies, Diseases, Therapies, Lymphoid Malignancies

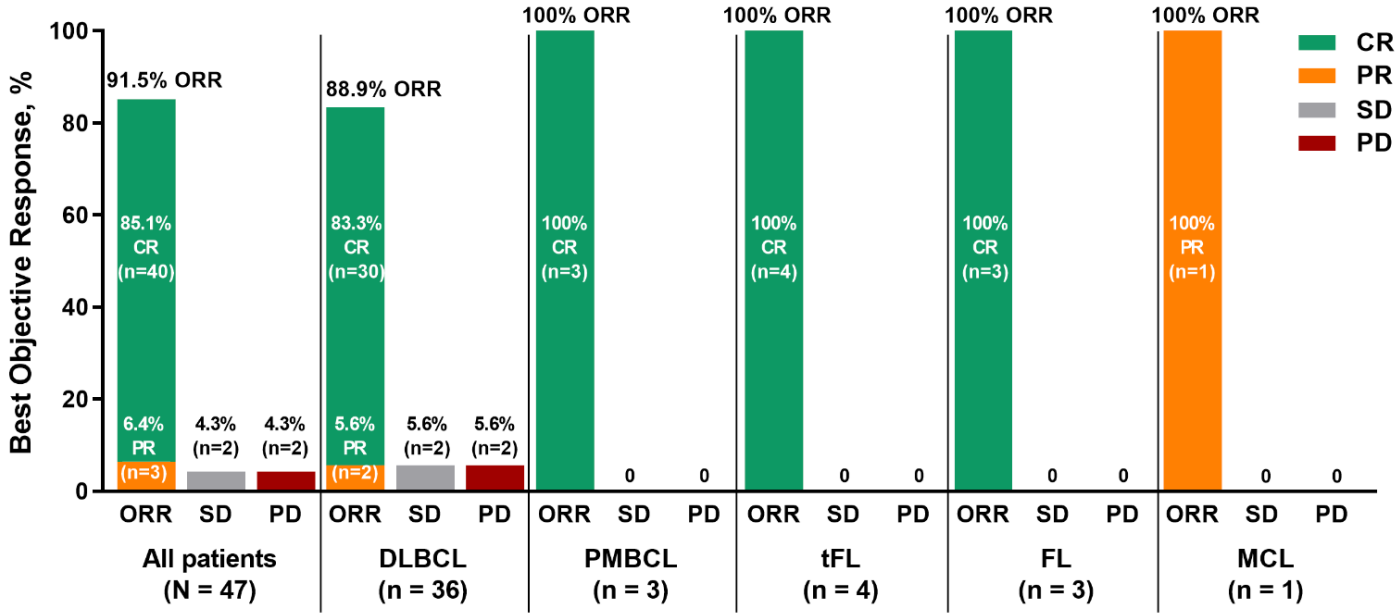
Monday, December 11, 2023: 5:30 PM

Ping Li[1], Wen-Juan Yu[2*], Lili Zhou[1*], Min Yang, MD[3*], Shiguang Ye[4*], Judy Zhu, MD[5*], Jiaqi Huang, MD, PhD[5*], Yan Zhang, MD[6*], Lanfang Li[7*], Jing Zhao, MD[7*], Kevin Zhu, BS[8*], Jing Li, MD[5*], Chengxiao Zheng, MD[5*], Liping Lan, MS[5*], Hui Wan, MD, PhD[5*], Yihong Yao, PhD[9], Huilai Zhang, MD[7*], Daobin Zhou, MD[6*], Jie Jin[10] and* ***Aibin Liang, MD, PhD[1*]***

Methods:

This is an open-label, dose escalation and expansion investigator-initiated trial (IIT) of C-CAR039. This trial was conducted at 4 sites to determine the safety and efficacy of C-CAR039 in pts with r/r B-NHL. Pts with r/r diffuse large B cell lymphoma (DLBCL), primary mediastinal large B cell lymphoma (PMBCL), follicular lymphoma (FL) or mantle cell lymphoma (MCL) were enrolled and received a single C-CAR039 infusion at a dose of 1.0-5.0x10^6 CAR-T cells/kg after a 3-day conditioning chemotherapy. The primary objective was to assess the safety and tolerability. CRS and ICANS were graded according to ASTCT 2019 criteria. The secondary objectives were to evaluate C-CAR039 efficacy and pharmacokinetics. Response was assessed per Lugano 2014 criteria.

At a longer median follow-up of 23.9 months, C-CAR039 demonstrated a favorable safety profile with deep and durable response in pts with r/r B-NHL, especially in LBCL pts.



GITMO

XVIII Congresso della Società GITMO

RIUNIONE NAZIONALE GITMO

NAPOLI, Hotel Royal Continental
13 - 14 Maggio 2024

DA VITA NASCE VITA: PROMUOVERE LA DONAZIONE DI CELLULE STAMINALI EMOPOIETICHE IN ITALIA