LEUKEMIA2022

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May 5-6, 2022

AIL President: P. Toro
Coordinators: A.M. Carella, S. Amadori

AIL
ASSOCIAZIONE ITALIANA CONTRO LEUCEMIE LINFOMI E MIELOMA

UNDER THE AUSPICES OF:

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

GITMO

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EXPANDING HORIZONS FOR IMMUNOTHERAPY IN ONCO-HEMATOLOGY

- CAR-T in Indolent NHL

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Disclosures of Alessandro Pulsoni

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
ROCHE					x	x	
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GILEAD					x	x	
BRISTOL MEIER SQUIBB						x	
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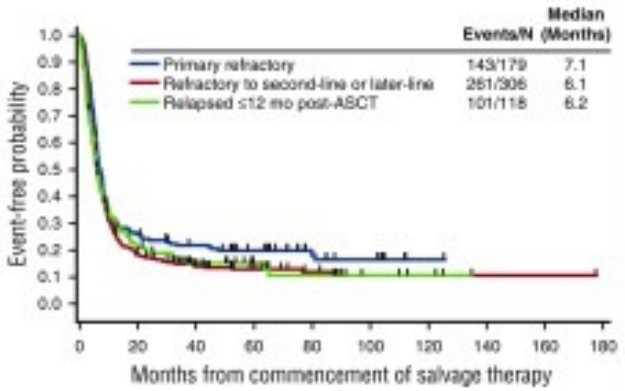
Relapsed / refractory DLBCL:

Unmet clinical need,

- *CAR-T changed the prognosis of relapsed patients*



Indolent NHL:

- *Tendency to multiple recurrences, frequently responsive to the multiple available treatment strategies, with prolonged survival.*

- *Cases with worse prognosis identifiable by clinical and biological markers (POD24, TMTV, metabolic response, MRD..) requires a more effective approach*

CAR-T could play a role in iNHL treatment scenario if:

- *Higher efficacy*
- *Manageable toxicity, compared to the already available and future strategies*

N ENGL J MED 2017

ORIGINAL ARTICLE

Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas

Stephen J. Schuster, M.D., Jakub Svoboda, M.D., Elise A. Chong, M.D., Sunita D. Nasta, M.D., Anthony R. Mato, M.D., Özlem Anak, M.D., Jennifer L. Brogdon, Ph.D., Iulian Pruteanu-Malinici, Ph.D., Vijay Bhoj, M.D., Ph.D., Daniel Landsburg, M.D., Mariusz Wasik, M.D., Bruce L. Levine, Ph.D., Simon F. Lacey, Ph.D., Jan J. Melenhorst, Ph.D., David L. Porter, M.D., and Carl H. June, M.D.

Characteristic	Patients Enrolled (N=38)		Patients Treated (N=28)	
	Follicular Lymphoma (N=15)	Diffuse Large B-Cell Lymphoma (N=23)	Follicular Lymphoma (N=14)	Diffuse Large B-Cell Lymphoma (N=14)
Age — yr				
Median	62	56	59	58
Range	43–72	25–77	43–72	25–77
Female sex — no. (%)	8 (53)	7 (30)	7 (50)	3 (21)
Previous therapies				
Median	5	3	5	3
Range	2–10	1–8	2–10	1–8
Advanced stage disease — no. (%)*	13 (87)	17 (74)	12 (86)	9 (64)
Bone marrow involved — no./total no. (%)	4/15 (27)	4/21 (19)	4/14 (28)	3/14 (21)
Elevated lactate dehydrogenase — no. (%)	10 (67)	16 (70)	9 (64)	8 (57)
ECOG performance-status score†				
Median	0	1	0	1
Range	0–1	0–1	0–1	0–1
Refractory diffuse large B-cell lymphoma — no. (%)‡	—	21 (91)	—	12 (86)
Double refractory follicular lymphoma — no. (%)§	9 (60)	—	8 (57)	—
Previous stem-cell transplantation — no. (%)				
Autologous	3 (20)	9 (39)	3 (21)	7 (50)
Allogeneic	1 (7)	0	1 (7)	0

Complete remission occurred in 6 of 14 patients with diffuse large B-cell lymphoma (**43%**; 95% CI, 18 to 71) and 10 of 14 patients with follicular lymphoma (**71%;** 95% CI, 42 to 92).
Sustained remissions were achieved, and at a median follow-up of 28.6 months, **86%** of patients with diffuse large B-cell lymphoma who had a response (95% CI, 33 to 98) and **89%** of patients with follicular lymphoma who had a response (95% CI, 43 to 98) had maintained the response

Table 2. Adverse Events of Special Interest That May Have Been Related to CTL019 Therapy.*

Adverse Event	Grade					Total Events	Grade 3 or Higher
	1	2	3	4	5		
						number (percent)	
Cytokine release syndrome	0	11	4	1	0	16 (57)	5 (18)
Neurotoxicity	4	4	1	1	1	11 (39)	3 (11)
Encephalopathy	0	0	1	1	1	3 (27)	
Delirium	0	2	0	0	0	2 (18)	
Tremor	2	0	0	0	0	2 (18)	
Cognitive disturbance	1	0	0	0	0	1 (5)	
Confusion	0	1	0	0	0	1 (5)	
Involuntary movements	1	0	0	0	0	1 (5)	
Memory impairment	0	1	0	0	0	1 (5)	

Severe cytokine-release syndrome occurred in 5 patients (18%).
Serious encephalopathy occurred in 3 patients (11%); 2 cases were self-limiting and 1 case was fatal.

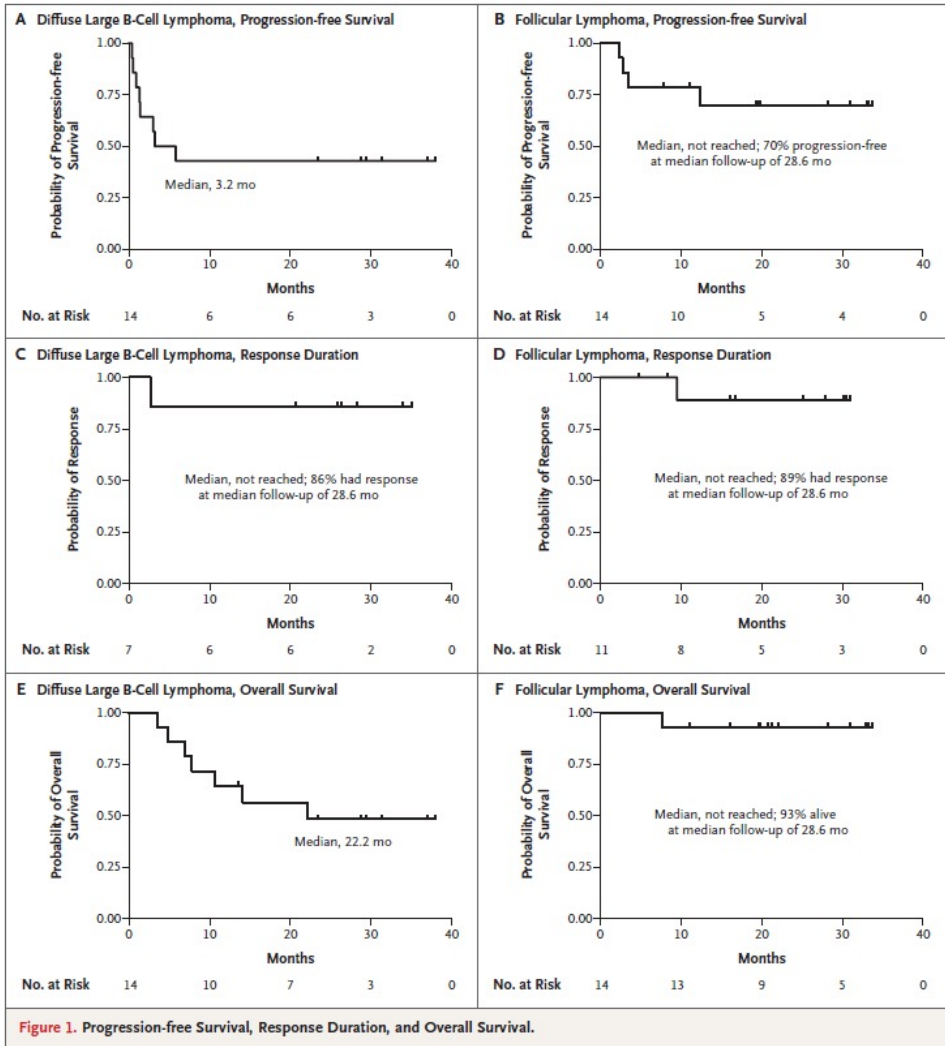


Figure 1. Progression-free Survival, Response Duration, and Overall Survival.

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Check for updates

Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial

Nathan Hale Fowler[1,2], Michael Dickinson[3], Martin Dreyling[4], Joaquin Martinez-Lopez[5], Arne Kolstad[6], Jason Butler[7], Monalisa Ghosh[8], Leslie Popplewell[9], Julio C. Chavez[10], Emmanuel Bachy[11], Koji Kato[12], Hideo Harigae[13], Marie José Kersten[14], Charalambos Andreadis[15], Peter A. Riedell[16], P. Joy Ho[17], José Antonio Pérez-Simón[18], Andy I. Chen[19], Loretta J. Nastoupil[1], Bastian von Tresckow[20,21], Andrés José María Ferreri[22], Takanori Teshima[23], Piers E. M. Patten[24,25], Joseph P. McGuirk[26], Andreas L. Petzer[27], Fritz Offner[28], Andreas Viardot[29], Pier Luigi Zinzani[30,31], Ram Malladi[32], Aiesha Zia[33], Rakesh Awasthi[34], Aisha Masood[35], Oezlem Anak[33], Stephen J. Schuster[36,38] and Catherine Thieblemont[37,38]

EMA approved for the treatment of adult patients with R/R FL after 2 or more lines of therapy

Summary of CAR T-Cell Pivotal Studies in DLBCL

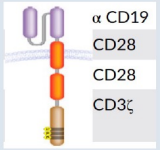
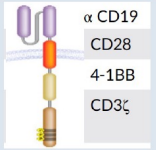
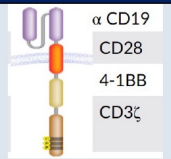
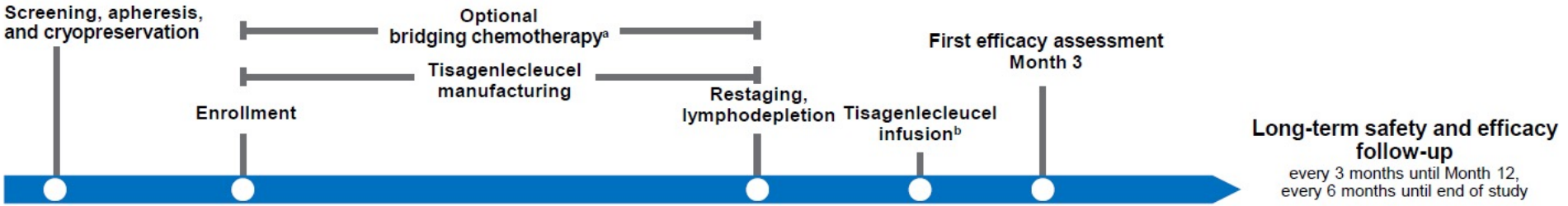
	Axi-cel ZUMA-1 (N = 108 infused)	Tisagenlecleucel JULIET (N = 108 infused)	Liso-cel TRANSCEND (N = 294 infused)
CAR			
Transmembrane domain	α CD19	α CD19	α CD19
Co-stimulatory doman	CD28	CD28	CD28
T-cell activation domain	CD28	4-1BB	4-1BB
	CD3ζ	CD3ζ	CD3ζ
Leukapheresis	Fresh product	Cryopreserved product	Fresh product
Outpatient administration	Not allowed	Allowed	Allowed
Bridging therapy, %	Not allowed	92%	59%
Lymphodepletion chemotherapy	Cy/Flu 500/30 mg/m² × 3d	Cy/Flu 250/25 mg/m² x 3d Bendamustine 90 mg/m² x 2d	Cy/Flu 300/30 mg/m² x 3d

Table 1 | Baseline demographic and disease characteristics of all treated patients

Parameter	Infused patients, *n* = 97
Median age (IQR), years	57.0 (49–64)
≥65 Years, *n* (%)	24 (24.7)
Male, *n* (%)	64 (66.0)
Female, *n* (%)	33 (34)
ECOG PS ≥1 before infusion, *n* (%)	41 (43.3)
Stage at study entry III–IV, *n* (%)	83 (85.6)
Bone marrow involvement at study entry, *n* (%)	37 (38.1)
Bulky disease at baseline, *n* (%)	62 (63.9)
FLIPI high (≥3) at study entry, *n* (%)	58 (59.8)
Median no. of previous therapies (range)	4 (2-13)
>4 lines of therapy, *n* (%)	27 (27.8)
POD24 from first anti-CD20 mAb-containing therapy, *n* (%)	61 (62.9)
Previous antineoplastic therapy, *n* (%)	
Anti-CD20 mAb	97 (100)
Alkylating agents	97 (100)
Anti-CD20 mAb + alkylating agent (same or different regimen)	97 (100)
PI3K inhibitors	20 (20.6)
Lenalidomide	21 (21.6)
Lenalidomide + rituximab	16 (16.5)
Previous therapy to which the disease was refractory,[a] *n* (%)	
Anti-CD20 mAb	84 (86.6)
Alkylating agents	69 (71.1)
Anti-CD20 mAb + alkylating agent combination (same regimen)	61 (62.9)
Anthracyclines	43 (44.3)
Lenalidomide	18 (18.6)
Lenalidomide + anti-CD20 mAb (same regimen)	18 (18.6)
PI3K inhibitors	14 (14.4)
Refractory disease to last line of therapy, *n* (%)	76 (78.4)
Best response SD/PD	54 (55.7)
Relapse within 6 months	22 (22.7)
Previous autologous HSCT, *n* (%)	35 (36.1)
Relapsed ≤12 months after HSCT, n (%)	15 (15.5)
Refractory[a] to at least two regimens, *n* (%)	69 (71.1)
Double refractory,[b] *n* (%)	66 (68.0)

ELARA Study Design



Key eligibility criteria	Study treatment	End points

• ≥18 years of age
• FL grade 1, 2, or 3A
• Relapsed/refractory disease[c]
• No evidence of histological transformation/FL3B
• No prior anti-CD19 therapy or allogeneic HSCT
	• Lymphodepleting chemotherapy options:
	  • Fludarabine (25 mg/m^2 IV daily for 3 days) + cyclophosphamide (250 mg/m^2 IV daily for 3 days)
	  • Bendamustine 90 mg/m^2 IV daily for 2 days
	• Tisagenlecleucel dose range (single IV infusion) was 0.6-6×10^8 CAR-positive viable T cells
		Primary: CRR by IRC
		
		Secondary: ORR, DOR, PFS, OS, safety, cellular kinetics

- Bridging therapy was allowed and was followed by disease re-evaluation before tisagenlecleucel infusion
- Timing of planned analyses

Planned analyses	Minimum follow-up from infusion	Median follow-up
Interim analysis	≈50 patients with ≥6 months follow-up	10 months
Primary analysis	90 patients with ≥6 months follow-up	11 months
Extended follow-up analysis	**90 patients with ≥12 months follow-up**	**17 months**

SAFETY

- **Median follow-up was 17 months** (range, 10-26 months)
- 17 patients (18%) were treated in the outpatient setting

Adverse Events of Special Interest within 8 Weeks[a]	Patients (N=97)	
	All Grades n (%)	Grade ≥3 n (%)
All adverse events	94 (96.9)	69 (71.1)
CRS[b,c]	47 (48.5)	0
All nervous system disorders[d]	36 (37.1)	3 (3.1)
ICANS	4 (4.1)	1 (1.0)
Infections	18 (18.6)	5 (5.2)
Tumor lysis syndrome	1 (1.0)	1 (1.0)
Hypogammaglobulinemia	9 (9.3)	0
Hematologic disorders including cytopenias		
Neutropenia[e,f]	32 (33.0)	31 (32.0)
Anemia[e]	24 (24.7)	13 (13.4)
Thrombocytopenia[e]	16 (16.5)	9 (9.3)

CRS

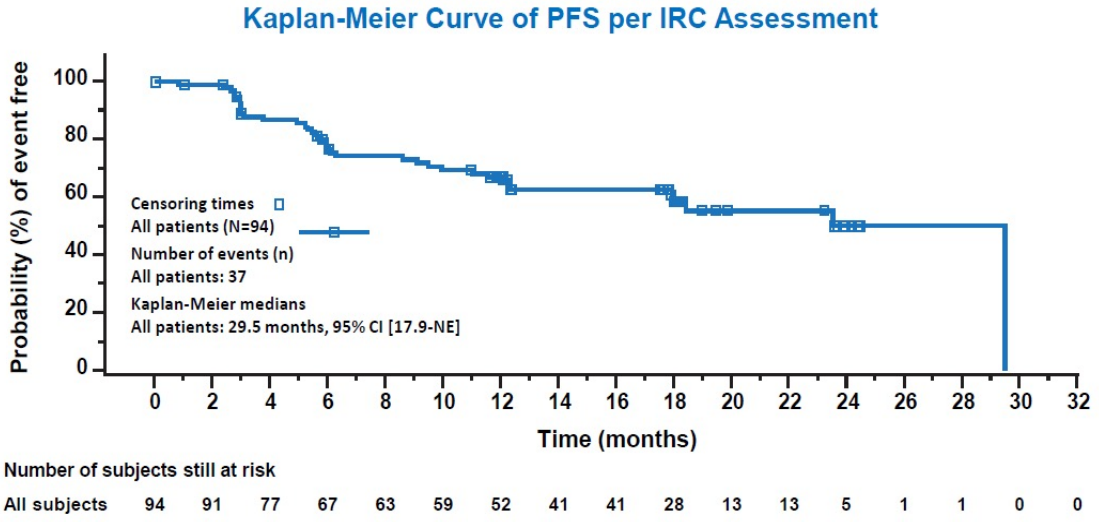
Events Within 8 Weeks of Infusion,[a] %	All Patients (N=97)
Patients with CRS (Lee scale)[1]	48.5
Maximum CRS grade	
Grade 1	27.8
Grade 2	20.6
Grade 3/4	0
Median onset of CRS, days	4.0
Min-Max	1-14
Median duration of CRS, days	4.0
Min-Max	1-24

CRS management

Events Within 8 Weeks of Infusion, n (%)	Patients with CRS (n=47)
Concurrent infections	7 (14.9)
Admitted to ICU	4 (8.5)
Median duration of ICU stay, days	4
Tocilizumab	16 (34.0)
Corticosteroids	3 (6.4)
Hypotension that required IV fluids and/or vasopressors	19 (40.4)
One vasopressor administered	3 (6.4)
High-dose vasopressors	0
Hypoxia observed	9 (19.1)
Low-flow oxygen supplementation	9 (19.1)

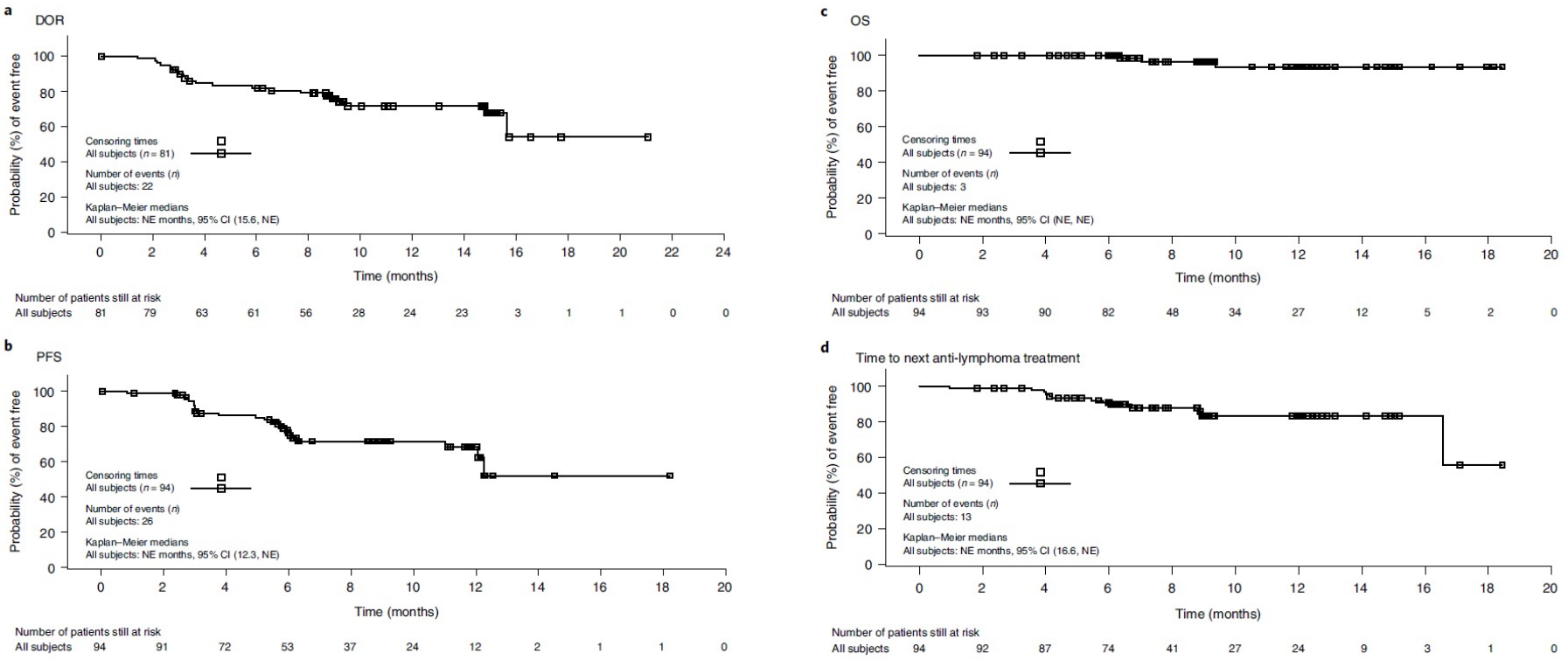
Efficacy Results of Extended Follow-up Analysis

Endpoint	% (95% CI)
ORR[a]	**86.2** (77.5-92.4)
CRR[a]	**69.1** (58.8-78.3)
12-mo PFS	**67.0** (56.0-75.8)
9-mo DOR	**76.0** (64.6-84.2)



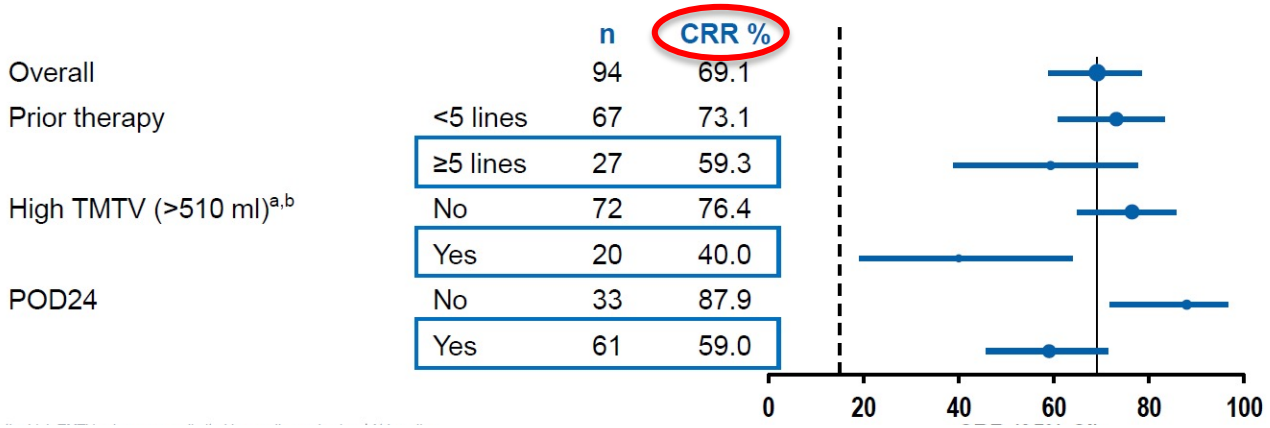
- **Median PFS was 29.5 months** (95% CI, 17.9-NE)

- **Among patients who achieved CR, 12- month PFS was 85.5% (95% CI, 74-92) and estimated DOR rate at 9 months was 86.5% (95% CI, 75-93)**



Kaplan–Meier curves for patients with r/r FL who received tisagenlecleucel infusion. **a**, DOR, **b**, PFS, **c**, OS and **d**, time to next anti-lymphoma treatment.

ELARA: *high-risk subgroups*



Disease Characteristic	Descriptive Analysis		Multivariate Analysis
	High-Risk 12-Month PFS (%)	Low-Risk 12-Month PFS (%)	Hazard Ratio (95% CI)
POD24	60.8	77.9	2.3 (1.0-5.3)
TMTV[a]	54.5	68.5	2.5 (1.3-5.6)

Although POD24 and high TMTV (>510 ml) were associated with less favorable PFS in the multivariate analysis of high-risk factors, ***efficacy in these high-risk subgroups was still superior to the current non CAR-T standards of care***

Conclusions

Overall patient population

- At a median follow-up of 17 months in patients with r/r FL and ≥2 prior lines of therapy, tisagenlecleucel demonstrated
  - High ORR (86.2%) and CRR (69.1%)
  - Durable responses and promising 12-month PFS (67.0%)
- Safety data are consistent with the established favorable tisagenlecleucel safety profile

High-risk subgroups

- Tisagenlecleucel induced high rates of durable responses among patients with high-risk disease
- In multivariate analyses, POD24 and TMTV appeared to impact PFS vs the low-risk group, but is still superior to the current non-CAR-T cell therapy standards of care for patients with r/r FL[1-11]
  - POD24: 12-month PFS 60.8%
  - High TMTV: 12-month PFS 54.5%
- Further exploration of the prognostic value of high TMTV in the CAR-T cell therapy setting is warranted

Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial

Caron A Jacobson, Julio C Chavez, Alison R Sehgal, Basem M William, Javier Munoz, Gilles Salles, Pashna N Munshi, Carla Casulo, David G Maloney, Sven de Vos, Ran Reshef, Lori A Leslie, Ibrahim Yakoub-Agha, Olalekan O Oluwole, Henry Chi Hang Fung, Joseph Rosenblatt, John M Rossi, Lovely Goyal, Vicki Plaks, Yin Yang, Remus Vezan, Mauro P Avanzi, Sattva S Neelapu

***Lancet Oncol* 2022; 23: 91–103**

Summary of CAR T-Cell Pivotal Studies in DLBCL

	Axi-cel ZUMA-1 (N = 108 infused)	Tisagenlecleucel JULIET (N = 108 infused)	Liso-cel TRANSCEND (N = 294 infused)
CAR	α CD19	α CD19	α CD19
Transmembrane domain	CD28	CD28	CD28
Co-stimulatory doman	CD28	4-1BB	4-1BB
T-cell activation domain	CD3ζ	CD3ζ	CD3ζ
Leukapheresis	Fresh product	Cryopreserved product	Fresh product
Outpatient administration	Not allowed	Allowed	Allowed
Bridging therapy, %	Not allowed	92%	59%
Lymphodepletion chemotherapy	Cy/Flu 500/30 mg/m² × 3d	Cy/Flu 250/25 mg/m² x 3d Bendamustine 90 mg/m² x 2d	Cy/Flu 300/30 mg/m² x 3d

R/R iNHL (N=157) → **Leukapheresis** → **Conditioning Chemotherapy**
Fludarabine 30 mg/m² IV
cyclophosphamide 500 mg/m² IV
on Days −5, −4, −3 → **Axi-Cel Infusion**
2×10⁶ CAR+ cells/kg
on Day 0 → **Post-treatment assessment and long-term follow-up periods**

Key ZUMA-5 Eligibility Criteria

- R/R FL (Grades 1–3a) or MZL (nodal or extranodal)[a]
- ≥2 Prior lines of therapy that must have included an anti-CD20 mAb combined with an alkylating agent[b]

Primary Endpoint

- ORR (IRRC-assessed per the Lugano classification[1])

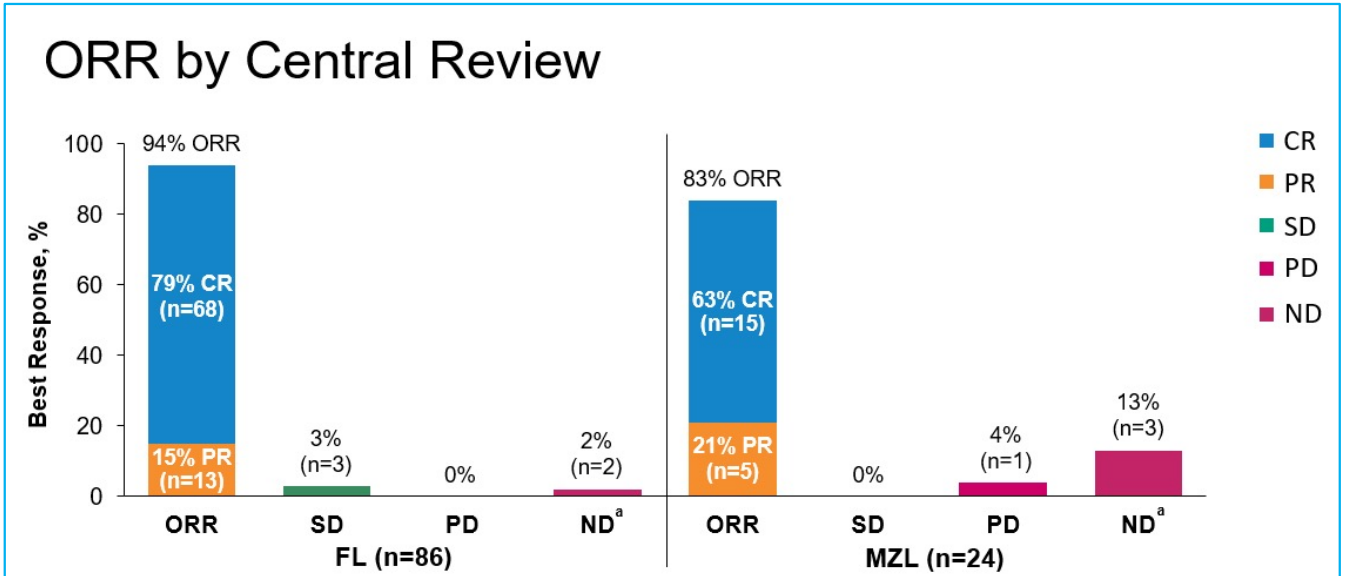
Key Secondary Endpoints

- CR rate (IRRC-assessed)
- Investigator-assessed ORR[a]
- DOR, PFS, OS
- AEs
- CAR T-cell and cytokine levels

Efficacy analyses **are reported in the 110 efficacy-eligible patients (86 with FL; 24 with MZL)[a]**

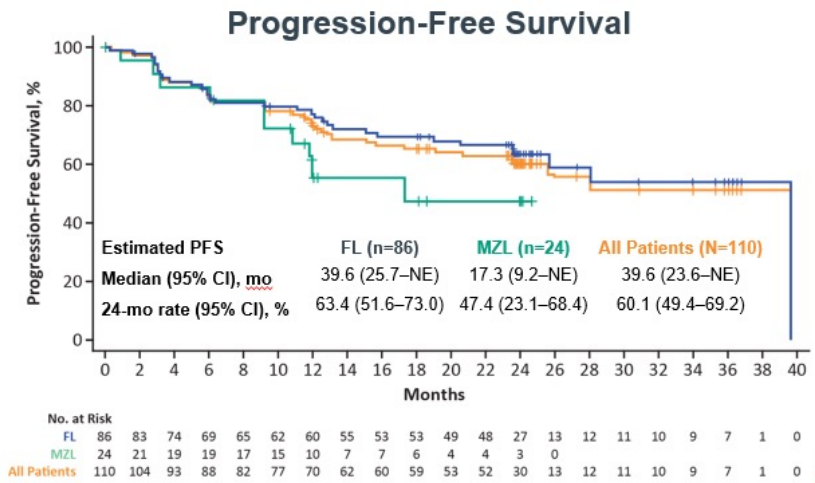
- **The median follow-up for patients with FL was 30.9 months (range, 24.7–44.3)**
- **The median follow-up for patients with MZL was 23.8 months (range, 7.4–39.4)**

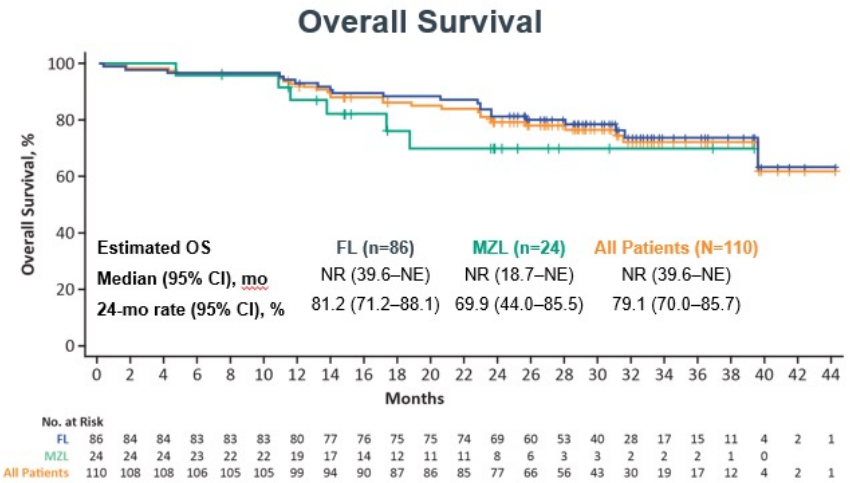
Safety data **are reported for all 149 patients treated with axi-cel (124 with FL; 25 with MZL)**



- Among efficacy-eligible patients with iNHL (n=110), the ORR was 92% (95% CI, 85–96), with a 75% CR rate
- Among all treated patients with iNHL (n=149), the ORR was 92% (95% CI, 86–96), with a 77% CR rate

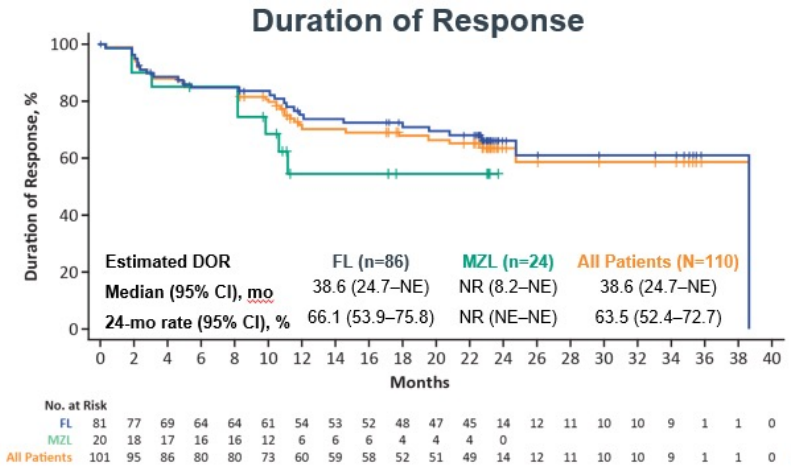
PFS and OS

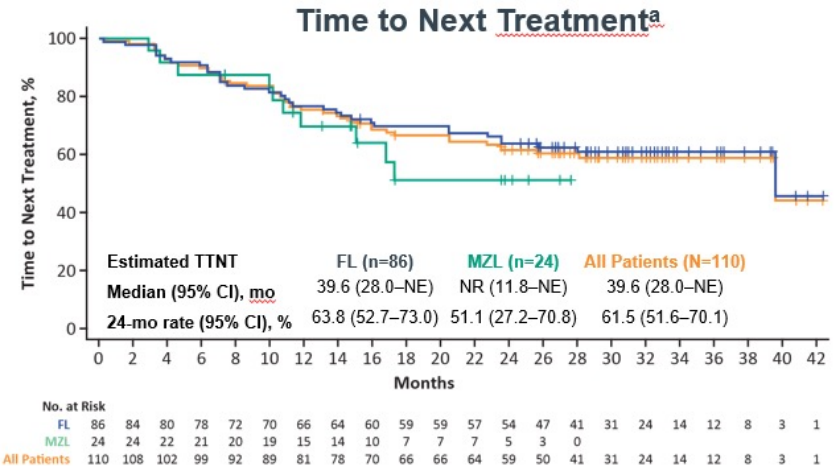




- Median OS was not yet reached in efficacy-eligible patients with FL or MZL
- Among patients with FL, 3 deaths occurred after Month 24[a]; no disease progression events occurred after Month 24

DOR and TTNT





- At data cutoff, 57% of efficacy-eligible patients with FL (49 of 86) and 50% of patients with MZL (12 of 24) had ongoing responses
  - Of patients who achieved a CR, 68% of patients with FL (46 of 68) and 73% of patients with MZL (11 of 15) had ongoing responses

High risk subgroups

Efficacy Outcomes In Patients With FL by POD24 Status

Parameter (95% CI)	Follicular Lymphoma (n=78)[a]	
	With POD24 (n=49)	Without POD24 (n=29)
Median DOR, months	38.6 (14.5–NE)	NR (24.7–NE)
24-month rate, %	61.1 (44.3–74.3)	72.4 (50.2–85.9)
Median PFS, months	39.6 (13.1–NE)	NR (25.7–NE)
24-month rate, %	57.3 (41.2–70.4)	73.0 (51.1–86.2)
Median OS, months	NR (39.6–NE)	NR (NE–NE)
24-month rate, %	77.6 (63.1–86.9)	85.9 (66.7–94.5)

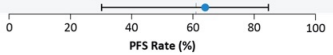
- Patients with FL who had POD24 benefitted from axi-cel, with estimated medians and 24-month rates of DOR and PFS consistent with all efficacy-eligible patients
  - Medians of DOR and PFS among patients without POD24 were not yet reached at data cutoff

PFS Rate at 24 Months in Key FL Subgroups

		No. of Patients	No. of Patients At Risk	PFS Rate (95% CI)
Overall		86	27	63 (52–73)
Age, years	<65	55	17	65 (50–76)
	≥65	31	10	61 (41–77)
Sex	Male	48	13	59 (43–72)
	Female	38	14	69 (51–82)
ECOG performance status	0	51	17	67 (52–79)
	1	35	10	56 (36–72)
High tumor burden (GELF criteria)	Yes	42	10	55 (37–69)
	No	44	17	71 (55–83)
Relapse/refractory subgroup	Relapsed	23	8	73 (49–87)
	Refractory	63	19	60 (46–72)
Number of prior lines of therapy	2	26	11	73 (51–86)
	3	20	3	45 (22–66)
	≥4	40	13	66 (48–79)
Prior stem cell transplantation	Yes	21	7	85 (61–95)
	No	65	20	56 (42–68)
Prior lenalidomide	Yes	27	6	58 (36–75)
	No	59	21	66 (51–77)
Prior PI3K inhibitor	Yes	28	9	56 (35–73)
	No	58	18	67 (53–78)
Prior BTK inhibitor	Yes	6	2	50 (11–80)
	No	80	25	64 (52–74)

PFS Rate at 12 Months in Key MZL Subgroups

		No. of Patients	No. of Patients At Risk	PFS Rate (95% CI)
Overall		24	10	61 (37–79)
Age, years	<65	11	3	63 (22–87)
	≥65	13	7	58 (27–80)
Sex	Male	11	3	49 (17–75)
	Female	13	7	73 (37–90)
ECOG performance status	0	14	7	74 (39–91)
	1	10	3	47 (15–74)
High tumor burden (GELF criteria)	Yes	10	4	53 (17–79)
	No	14	6	67 (34–86)
Relapse/refractory subgroup	Relapsed	6	2	50 (6–85)
	Refractory	18	8	66 (39–83)
Number of prior lines of therapy	2	8	3	71 (26–92)
	3	7	5	83 (27–98)
	≥4	9	2	38 (9–67)
Prior stem cell transplantation	Yes	3	1	50 (1–91)
	No	21	9	64 (38–81)
Prior lenalidomide	Yes	8	4	75 (32–93)
	No	16	6	55 (26–77)
Prior PI3K inhibitor	Yes	9	4	63 (23–86)
	No	15	6	61 (29–82)
Prior BTK inhibitor	Yes	12	4	61 (27–84)
	No	12	6	64 (30–85)



the PFS rate at 12 months appeared to be consistent among key subgroups, including prior treatment with a BTK inhibitor

Safety

Most common Grade ≥3 AEs were neutropenia (33%) and anemia (25%)

Grade ≥3 cytokine CRS and NEs occurred in **7%** of patients (6% FL; 8% MZL) and **19%** of patients (15% FL; 36% MZL), respectively

Most CRS cases (120 of 121) and NEs (82 of 87) of any grade resolved by data cutoff[a]

Nearly half of NEs (49%) resolved ≤2 weeks after onset; most NEs (76%) resolved ≤8 weeks after onset

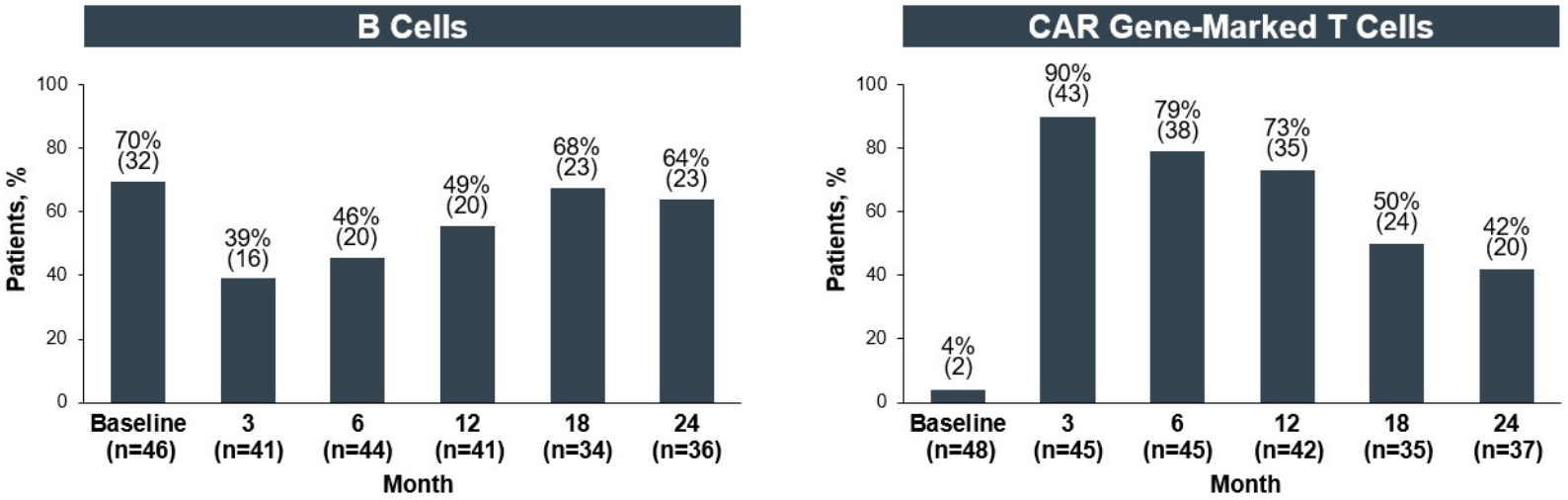
Grade ≥3 cytopenias present ≥30 days post-infusion were reported in 34% of patients (33% FL; 36% MZL), most commonly neutropenia in 29% of patients (27% FL; 36% MZL)

Late toxicity

AE, n (%)	Follicular Lymphoma (N=124)		Marginal Zone Lymphoma (N=25)		All Patients (N=149)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any AE	27 (22)	14 (11)	11 (44)	6 (24)	38 (26)	20 (13)
Serious AE	11 (9)	11 (9)	4 (16)	4 (16)	15 (10)	15 (10)
Cytopenia	8 (6)	4 (3)	3 (12)	3 (12)	11 (7)	7 (5)
Infection	18 (15)	7 (6)	7 (28)	4 (16)	25 (17)	11 (7)
CRS	0 (0)	0 (0)	2 (8)	0 (0)	2 (1)	0 (0)
Neurologic event	0 (0)	0 (0)	2 (8)	0 (0)	2 (1)	0 (0)
Hypogammaglobulinemia	2 (2)	0 (0)	2 (8)	0 (0)	4 (3)	0 (0)
Tumor lysis syndrome	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

- Grade 5 AEs occurred in 6 patients after the data cutoff of the primary analysis[b]
  - Grade 5 infectious AEs occurred in 5 patients: 1 COVID-19 (FL, Day 717, unrelated), 1 COVID-19 pneumonia (FL, Day 780, related to axi-cel), 1 PML[c] (FL, Day 697, related to axi-cel and CC) and 2 sepsis (FL, Day 1204; MZL, Day 139; both unrelated)
  - Acute bilineal leukemia occurred in 1 patient (FL, Day 623, CC related)

Detectable B Cells and CAR T Cells Over Time in Patients With FL and Ongoing Responses at 24 Months

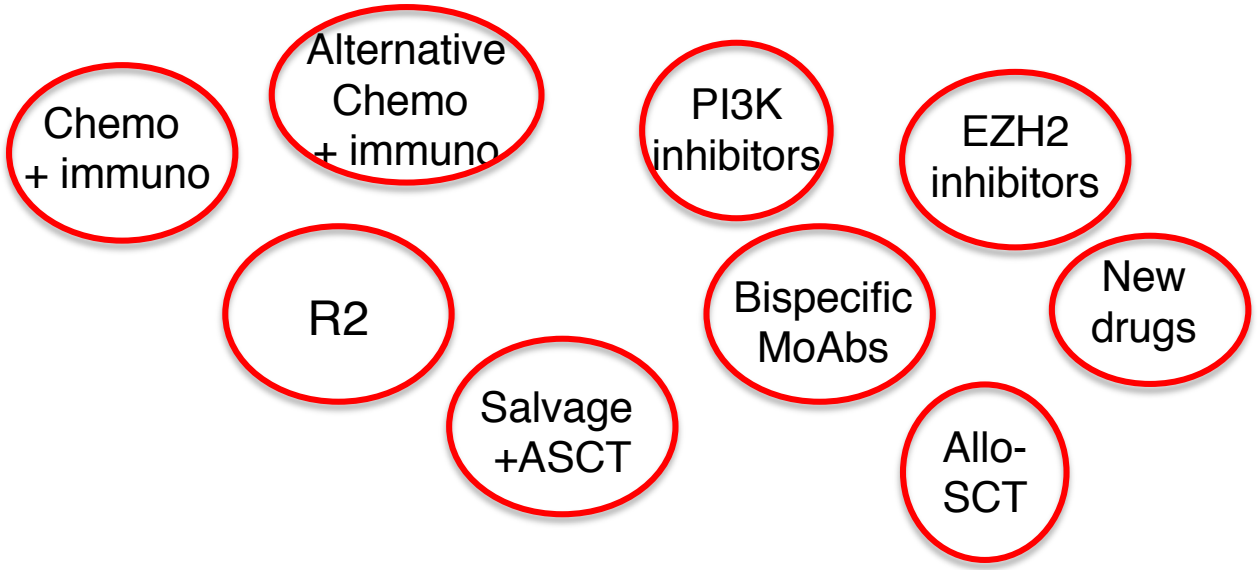


- The majority of patients with FL and an ongoing response had detectable B cells by Month 18; by Month 24, less than half had low levels of detectable CAR gene-marked cells
  - The levels of CAR gene-marked T cells were inversely correlated with that of B cells at each timepoint post-infusion

Authors' Conclusions

- With long-term follow-up in ZUMA-5, axi-cel demonstrated substantial and continued benefit in patients with R/R iNHL
  - In FL, high response rates translated to durability after 31 months median follow-up
    - Median DOR was 38.6 months, and 57% of efficacy-eligible patients were in ongoing response at data cutoff
    - Median PFS was nearly 40 months, and median OS was not yet reached
  - In MZL, efficacy outcomes appeared to improve with longer follow-up (median, 24 months)
    - Median DOR and OS not yet reached; median PFS was 17.3 months
    - 50% of patients were in ongoing response at data cutoff
- Axi-cel maintained a manageable safety profile in iNHL, with no new safety signals
- Results of the long-term pharmacokinetic analysis suggest that functional CAR T-cell persistence may not be required for long-term remissions in patients with FL, consistent with prior findings in aggressive lymphomas[1]
- Axi-cel is a highly effective therapeutic approach for patients with R/R iNHL

Considering these results, in terms of efficacy, duration of response and toxicity,
Where to fit CAR-T in the treatment program of iNHL?

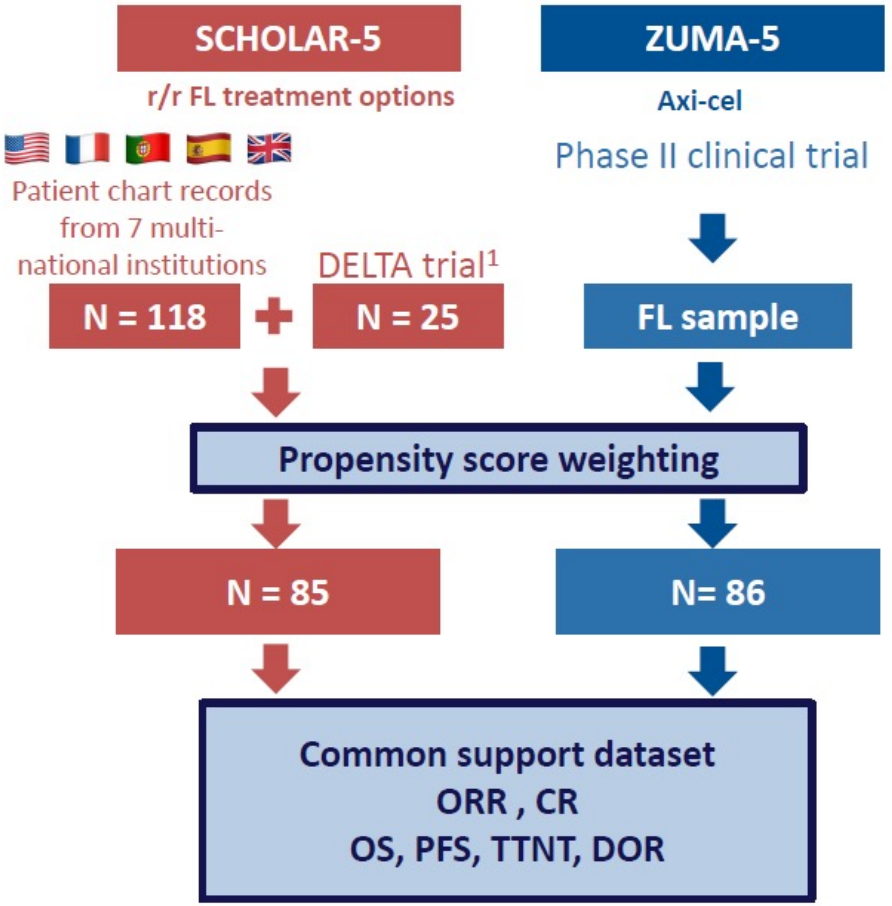


Should CAR-T be confined to the third or subsequent treatment line?

A Comparison of Clinical Outcomes from Updated ZUMA-5 (Axicabtagene Ciloleucel) and the International SCHOLAR-5 External Control Cohort in Relapsed/Refractory Follicular Lymphoma

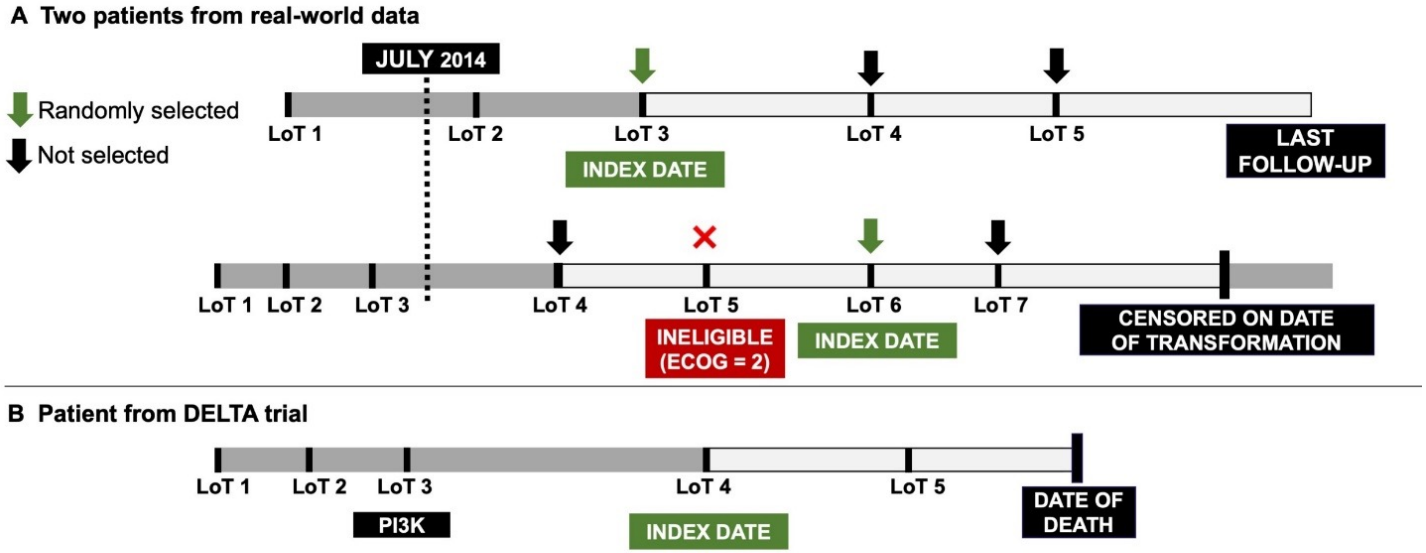
Palomba M Lia, et al.
Abstract #3543 - ASH 2021

- The international SCHOLAR-5 cohort data were extracted for r/r FL patients who initiated a third or higher line of therapy (LoT) on or after July 2014



Methods: LoT Selection for Real-World Data

- For the real-world data, lines that were eligible for inclusion in the analysis were entered into a random selection. A single LoT for each patient was included in the analysis set
- The SCHOLAR-5 and ZUMA-5 cohorts were balanced (SMD <0.1) for patient characteristics through propensity scoring on prespecified prognostic factors and standardized mortality ratio weighting[1]
- ORR and CR were compared using odds ratio. OS, PFS and NTFS were evaluated using Kaplan-Meier analysis
- Subgroup analyses were conducted on patients who initiated ≥4th LoT



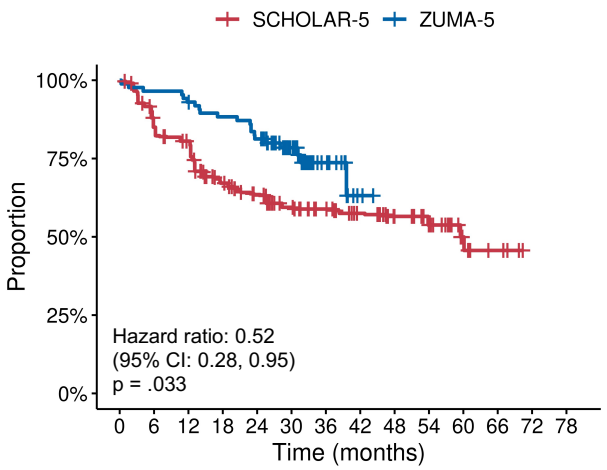
- 143 patients were identified in SCHOLAR-5, reducing to a weighted sum of 85 after applying propensity score weights, versus 86 patients in ZUMA-5
- Median follow-up time for ZUMA-5 and SCHOLAR-5 were 29.4 and 26.2 months respectively

		SCHOLAR-5 before weighting (n = 143)	ZUMA-5 (n = 86)	SCHOLAR-5 after weighting (n = 85)	SMD (p-value)
Median age (range), years		64 (36 – 89)	62 (34 – 79)	61 (36 – 89)	0.036 (.85)
Male, n (%)		81 (56.6%)	48 (55.8%)	53 (61.9%)	0.123 (.46)
POD24, n (%)		51 (35.7%)	49 (57.0%)	47 (55.9%)	0.022 (.90)
Prior lines of therapy, median (range)		2 (2-8)	3 (2-9)	3 (2-8)	0.047 (.81)
Refractory to prior line, n (%)		87 (60.6%)	63 (73.3%)	65 (76.6%)	0.077 (.61)
Prior SCT, n (%)		31 (21.7%)	21 (24.4%)	24 (28.0%)	0.080 (.64)
Size of largest nodal mass (cm)*		4.16 (2.75 – 6.50)	4.35 (3.27 – 6.43)	4.02 (2.90 – 6.25)	0.094 (.59)
Time since last therapy (months)*		6.76 (1.16 – 22.66)	3.53 (1.77 – 9.01)	2.30 (0.69-7.99)	0.056 (.67)
Time since diagnosis (months)*		84.79 (52.99 – 130.47)	59.86 (35.10– 96.62)	64.55 (40.96 – 115.79)	0.100 (.52)
ECOG, n (%):	0	39 (33.1%)	51 (59.3%)	21 (29.0%)	0.640 (.002)
	1	79 (66.9%)	35 (40.7%)	51 (71.0%)	

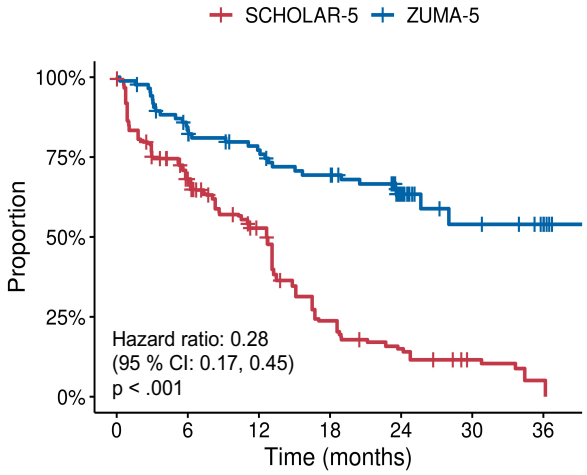
- Variables that were successfully balanced (SMD <0.1) included POD24, number of prior LoT, relapsed vs refractory, prior stem cell transplant, size of largest nodal mass, response to prior LoT, time since last therapy and age

		SCHOLAR-5	ZUMA-5	Odds ratio	P value
Primary analysis: ≥ 3rd LoT	ORR	42/85 (**49.9%**)	81/86 (**94.2%**)	16.2 (5.6, 46.9)	< .001
	CR	25/85 (**29.9%**)*	68/86 (**79.1%**)**	8.85 (4.3, 18.25)	< .001
Sub-group analysis: ≥ 4th LoT	ORR	24/59 (**40.3%**)	57/60 (**95%**)	28.14 (7.38, 107.33)	< .001
	CR	12/59 (**20.6%**)*	48/60 (**80%**)	15.42 (5.82, 40.83)	< .001

A. Overall Survival



B. Progression Free Survival



ZUMA-5:
median OS not reached
median PFS 39.6 m

SCHOLAR-5:
median OS 59,8 m
median PFS 12,7 m

With the limits of a retrospective analisys:

- **Analysis of real-world outcomes shows poor clinical outcomes that worsen with increasing LoT**
- **Axi-cel demonstrated a clinically and statistically significant improvement in ORR and CR, as well as PFS and OS**
- **CAR-T address an important unmet medical need for r/r FL patients**

CAR-T in iNHL ***conclusive remarks***:

iNHL: long survival, easy to re induce after multiple lines, multiple effective approaches.. CAR-t perceived as less important than in aggressive NHL, but:

- Data swow higher efficacy over standard of care
- Side effects manageable

High risk iNHL (POD24): Unmet clinical need, in wich CAR-t can play an important role. ASCT still employed in this setting, the experience in DLCL shows a possible higher efficacy of CAR-T.

Today, in a policy of conservative treatment of iNHL, CAR-T represent a relevant step forward in R/R disease.

Tomorrow, if we move to the objective of iNHL eradication in a subset of young patients, could be reasonable to test CAR-T or new immunotherapy strategies even in the context of first line, as attempted in aggressive NHL (ZUMA12)