POST-NEW ORLEANS 2022
Novità dal Meeting della Società Americana di Ematologia

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Milano
Teatro Dal Verme
2-3-4 Febbraio 2023

CAR-T
Linfomi Indolenti

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DICHIARAZIONE

Beatrice Casadei

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(CELGENE–BRISTOL-MYERS SQUIBB, GILEAD SCIENCES, TAKEDA, ABBVIE, JANSSEN, BEIGENE)**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Speakers activity **(NOVARTIS, ROCHE);** Educational activity **(INCYTE)**

CAR T-cell treatment and Indolent Lymphomas at ASH 2022

Follicular lymphoma

- 1 oral presentation: *Dreyling M. et al, abs #608*
- 4 poster presentations: *Neelapu S. et al, abs #4660; Ghione P. et al, abs #2038; Oluwole O. et al, abs #4861; Hasegawa K. et al, abs #1581*

Marginal zone lymphoma:

- 1 poster presentation: *Neelapu S. et al, abs #4660*

Chronic lymphocytic leukemia

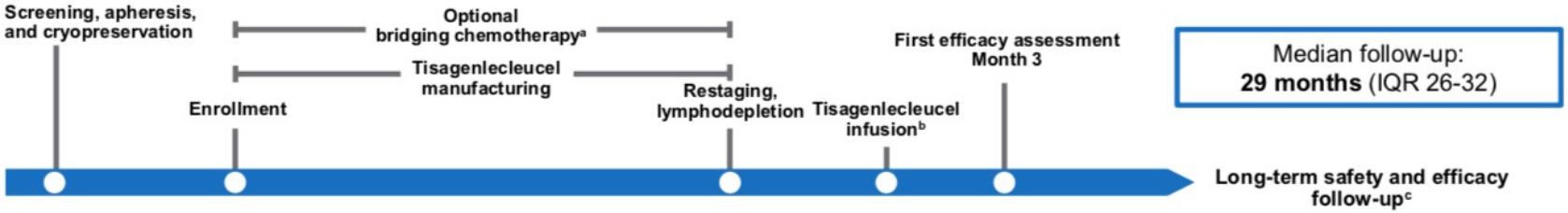
- 2 poster presentations: *Davids M. et al, abs #3319; Zhao Z. et al, abs#4606*

608. Long-Term Clinical Outcomes and Correlative Efficacy Analyses in Patients (Pts) with Relapsed/Refractory Follicular Lymphoma (r/r FL) Treated with Tisagenlecleucel in the Elara Trial. Dreyling M. et al. Oral presentation.

- **Elara trial: a multicenter phase 2 trial of tisagenlecelucel after two or more lines of therapy in adult patients with r/r FL (grade 1, 2 or 3A).**

- **Durability of response, longer-term safety, and exploratory correlative biomarker analyses after a prolonged median follow-up of 29 months**

ELARA: Study Design



Key eligibility criteria	Study treatment	End points
• ≥18 years of age • FL grade 1, 2, or 3A • Relapsed/refractory disease[d] • No evidence of histological transformation/FL3B • No prior anti-CD19 therapy or allogeneic HSCT	Tisagenlecleucel dose range (single IV infusion) was $0.6\text{-}6\times10^8$ CAR-positive viable T cells • Screened n=119 • Enrolled n= 98 • Infused n=97	**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
- 18% (17/97) of patients received tisagenlecleucel in the outpatient setting

CAR, chimeric antigen receptor; CD, cluster of differentiation; CRR, complete response rate; DOR, duration of response; FL, follicular lymphoma; FL3B, FL grade 3B; HSCT, hematopoietic stem cell transplant; IQR, interquartile range; IRC, independent review committee; IV, intravenous; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
[a]Disease was reassessed prior to infusion for all patients requiring bridging therapy. [b]Infusion was conducted on an in- or outpatient basis at investigator discretion. [c]Every 3 months until Month 12, and every 6 months until end of study. [d]Refractory to ≥2nd line of systemic therapy (including an anti-CD20 antibody and alkylating agent) or relapsed within 6 months after ≥2nd line of therapy or after an autologous HSCT.

Dreyling M. et al. abs#608

ELARA: Tisagenlecleucel Induced Consistently High Response in all Patients, including High-Risk Population

Endpoint in Efficacy Analysis Set (IRC Assessment)	% (95% CI) N=94
CRR[a]	68 (58-77)[b]
ORR[c]	86 (78-92)[b]

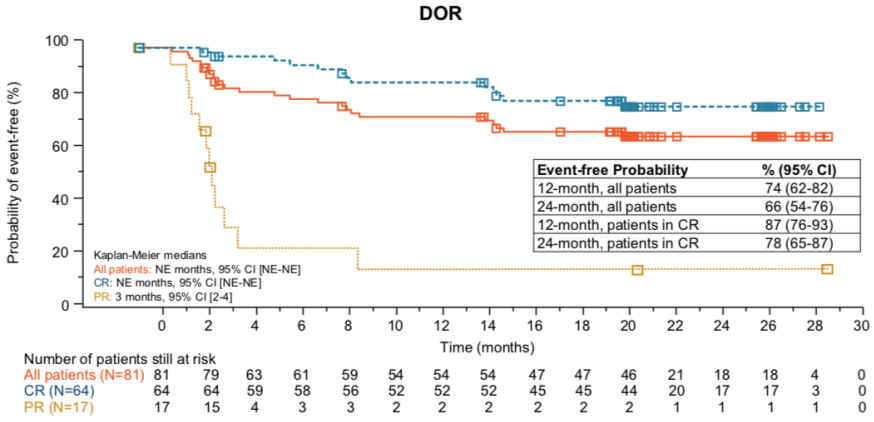
- High ORR (86%) and CRR (68%) is consistent with the primary analysis[1]
- Higher rates of durable responses were observed in most patients in high risk disease subgroups who have poor prognosis with current non CAR T-cell therapy

Baseline Disease Characteristic	All Patients n (%) N=97	CRR % (95% CI)	ORR % (95% CI)
POD24	61 (63)	59 (46-71)	82 (70-91)
High metabolic tumor volume[d]	20 (21)	40 (19-64)	75 (51-91)
Bulky disease[e]	62 (64)	65 (51-76)	86 (74-93)
Double refractory	65 (67)	66 (53-77)	85 (74-92)
High FLIPI (≥3)	57 (59)	61 (48-74)	81 (68-90)

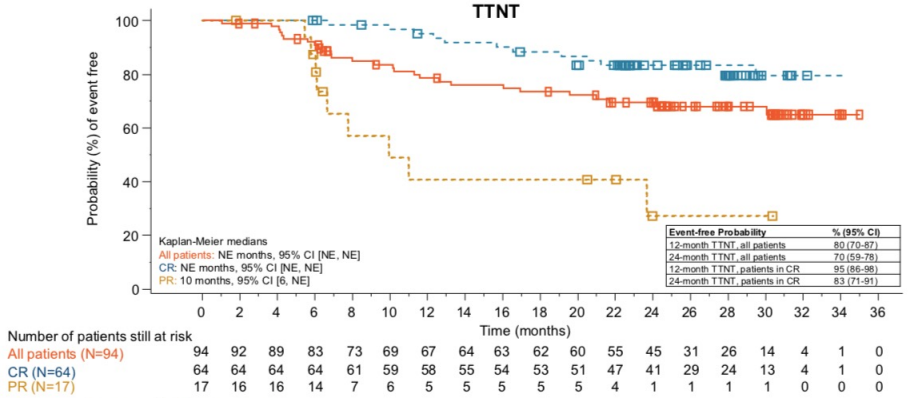
BM, bone marrow; CAR, chimeric antigen receptor; CR, complete response; CRR, CR rate; FLIPI, Follicular Lymphoma International Prognostic Index; IRC, independent review committee; ORR, overall response rate; POD24, progression of disease within 2 years of initial chemotherapy; PR, partial response; TMTV, total metabolic tumor volume.
[a]One patient in CR downgraded to PR due to confirmatory BM biopsy performed out of window. [b]The 95% exact Clopper-Pearson CIs are displayed. As the primary endpoint was met at interim analysis (<0.0001, at 1-sided 0.0025 level to reject the null hypothesis: CRR ≤15%), no formal significance testing was conducted at extended follow-up analysis. [c]ORR is defined as the proportion of patients with a best overall disease response of CR or PR. [d]TMTV >510cm^3. [e]Any nodal or extra nodal tumor mass that is >7 cm in diameter or involvement of at least 3 nodal sites, each with a diameter >3 cm.
1. Fowler NH, et al. *Nat Med.* 2022;28(2):325-332.

Dreyling M. et al. abs#608

ELARA: Median DoR and Median TTNT Were not Reached After a Median Follow-up of 29 Months



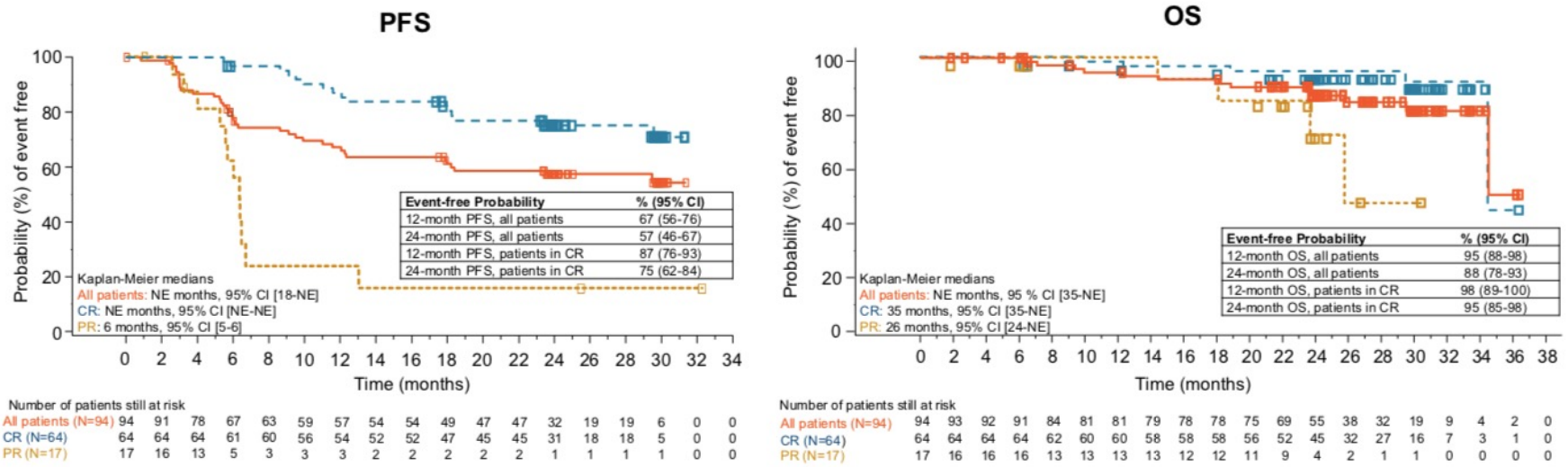
Note: None of the patients received reinfusion of tisagenlecleucel; 1 patient received subsequent antineoplastic treatment while in remission.
CR, complete response; DOR, duration of response; IRC, independent review committee; NE, not estimable; PR, partial response.
Note: DOR is per IRC assessment. Censoring times are shown as squares.



AE, adverse event; NE, not estimable; TTNT, time to next treatment.
Note: TTNT per local assessment. Eighteen patients (19%) experienced prolonged depletion of normal B cells/agammaglobulinemia post infusion and were ongoing in 11 patients at the time of data cutoff or death; none of these AEs were serious or led to fatal infections. Censoring times are shown as squares.

Dreyling M. et al. abs#608

ELARA: Median PFS and OS Were not Reached After a Median Follow-up of 29 Months



BOR, best overall response; CR, complete response; IRC, independent review committee; NE, not estimable; OS, overall survival; PFS, progression-free survival; PR, partial response.
Note: PFS and OS by BOR curves are per IRC assessment. Censoring times are shown as squares.

Dreyling M. et al. abs#608

ELARA: Adverse Events of Special Interest

Selected Adverse Events Anytime Post Infusion	Safety Analysis Set[a] (N=97) All Grade, n (%)	Grade ≥3, n (%)
Number of patients with at least 1 AE	73 (75)	45 (46)
CRS[b,c]	47 (49)	0
Hematological disorders including cytopenias	45 (46)	43 (44)
Neutropenia	23 (24)	23 (24)
Anemia	13 (13)	7 (7)
Thrombocytopenia	6 (6)	5 (5)
Infections	16 (17)	9 (9)
Hypogammaglobulinemia	11 (11)	1 (1)
Serious neurological adverse events	8 (8)	2 (2)
ICANS	4 (4)	1 (1)
Encephalopathy	3 (3)	1 (1)
Dyskinesia	1 (1)	0
Muscular weakness	1 (1)	0
Tremor	1 (1)	0
Deaths >30 days post infusion		13 (13)[d]
Deaths during the long-term follow-up		3 (3)[e]

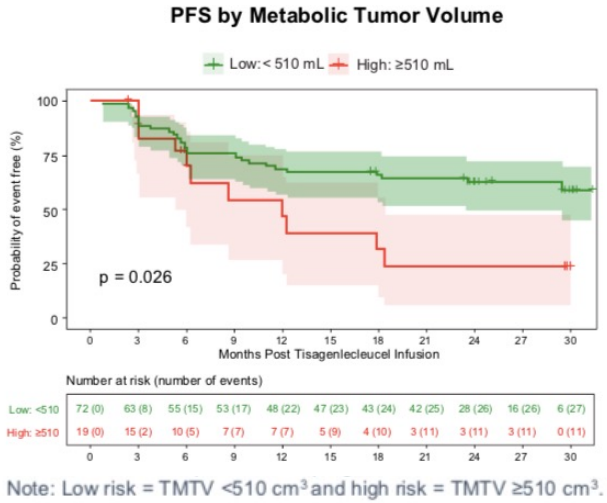
- **No new safety signals** were reported in this long-term analysis
- One patient developed HLH >1 year after receiving tisagenlecleucel[f]
- Rate of all-grade serious neurological events was 8% and 2% were grade ≥3
- The 17 (18%) patients who received tisagenlecleucel in the outpatient setting required no ICU care, and one-third did not require hospitalization for AE management
- Twenty-two patients (23%) received ≥1 new antineoplastic medication after tisagenlecleucel, mostly due to stable disease or progressive disease

Note: Two patients experienced a secondary malignancy during this longer-term follow-up (squamous cell carcinoma and bladder transitional cell carcinoma); neither was considered related to study treatment. Eight patients had SARS-COV-2 infection at the time of data cutoff. Table summarizes selected adverse events anytime post infusion suspected to be related to tisagenlecleucel.
[a]All patients infused with tisagenlecleucel. [b]CRS was graded using Lee scale 2014. [c]Refers to first CRS episode only. [d]Out of total 13 deaths (study indication=7; other=6). [e]3 were new deaths occurred during this longer-term follow-up period (PD, n=1; SAE, n=2, [urothelial bladder carcinoma and post alloSCT complications]). [f]The patient did not have CRS during or immediately preceding HLH. The HLH fatal event occurred on Day 375 and was considered drug-related by the physician.

Dreyling M. et al. abs#608

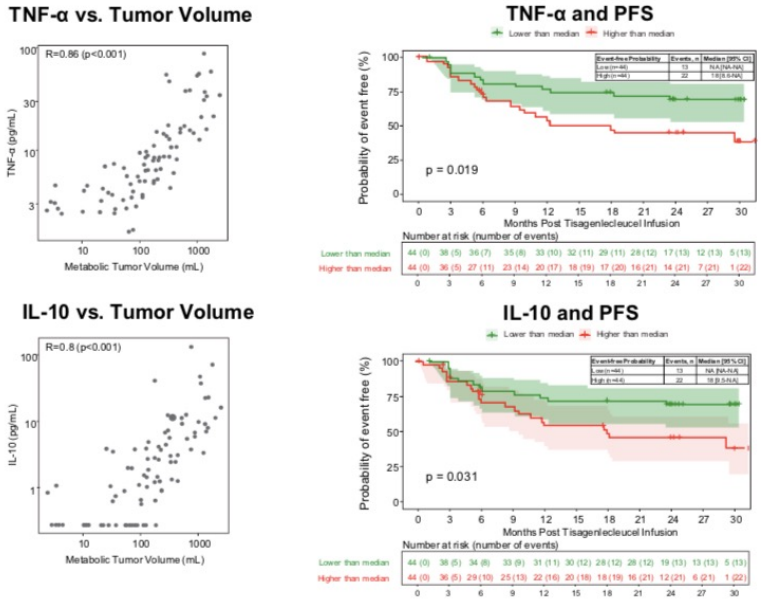
ELARA: Exploratory Correlative Biomarker Analyses

1. Higher baseline metabolic tumor volume is associated with shorter PFS and DoR



Note: Low risk = TMTV <510 cm³ and high risk = TMTV ≥510 cm³.

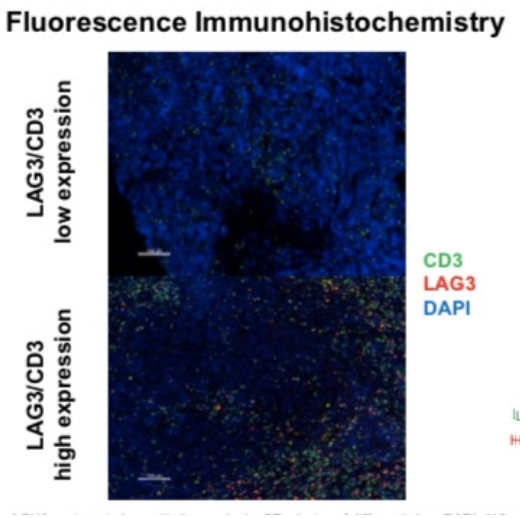
2. Lower pre-LD serum TNF-a and IL-10 levels correlated with tumor volume and prolonged PFS

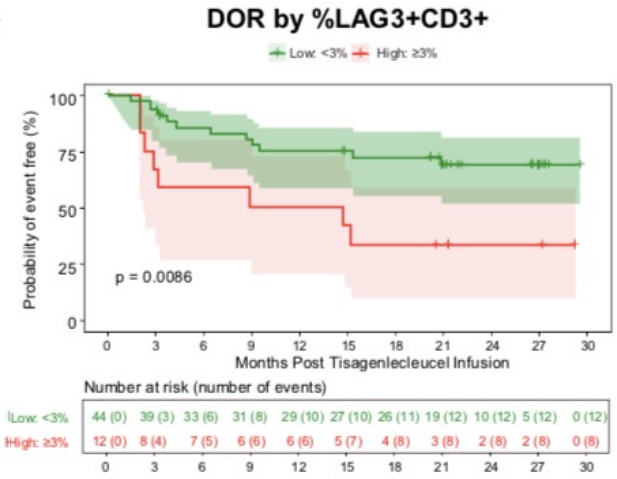


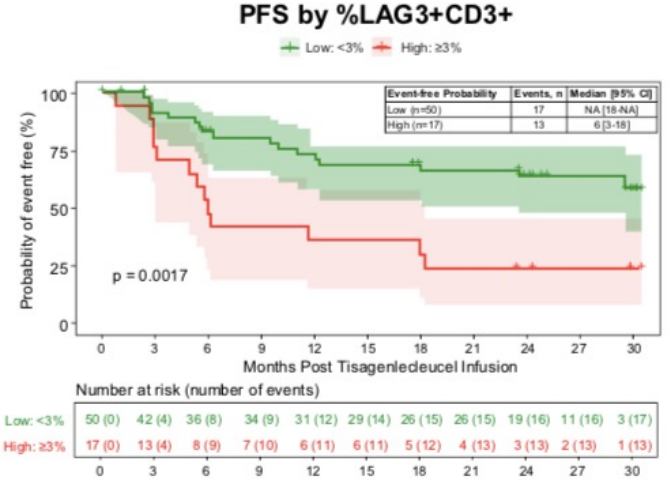
Dreyling M. et al. abs#608

ELARA: Exploratory Correlative Biomarker Analyses

3. Lower tumor-infiltrated LAG3+ exhausted T-cell (< 3% of total T-cells), representing a favorable TME, is associated with longer DOR and PFS







Dreyling M. et al. abs#608

ELARA: Conclusions

- Tisagenlecleucel induced **high rates of durable responses** in all patients including those with **high-risk disease characteristics** such as POD24 and high baseline tumor burden;
- **Median DOR, PFS, and OS** were **not reached** in the ELARA trial after >2 years of follow-up;
- Tisagenlecleucel was found to be **well-tolerated** and feasible for **out-patient administration**;
- Exploratory biomarker analyses suggest that a favorable TME and decreased inflammatory status were associated with improved clinical outcomes;
- Extended follow-up of >2years from the ELARA trial continues to demonstrate **durable efficacy** and a **favorable safety profile** following tisagenlecleucel in patients with r/r FL

Dreyling M. et al. abs#608

4660. 3-Year Follow-up Analysis of ZUMA-5: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) in Patients with Relapsed/Refractory (R/R) Indolent Non-Hodgkin Lymphoma (iNHL). Neelapu S. et al. Poster presentation.

- **Zuma-5 trial: a multicenter, single arm, phase 2 trial of axi-cel in adult patients with r/r iNHL (FL and MZL).**
- **In the 2-year analysis of Zuma-5 the ORR in patients with FL and MZL were 94% (CR: 79%) and 83% (CR: 65%) respectively[1].**
- **Presentation of clinical and pharmacological outcome after > 3 years median follow-up**

[1]Jacobson A.C. et al, *Lancet Oncol* 2022; 23: 91–103

ZUMA-5 TRIAL

Enrolled/Leukapheresed
N = 153
(127 FL, 25 MZL, 1 DLBCL)

- **Patients not treated (n = 5)**
  - **DLBCL via pretreatment biopsy (n = 1)[a]**
  - **Ineligible (n = 3)[b]**
  - **Death (n = 1)[c]**

Conditioning Chemotherapy
n = 148
(124 FL, 24 MZL)

Received Axi-Cel
n = 148
(124 FL, 24 MZL)

- **Efficacy analysis (n = 109)**
  - **Patients with FL who had ≥ 18 months follow-up (n = 86)**
  - **Patients with MZL who had ≥ 4 weeks follow-up (n = 23)**
- **Safety analysis (n = 148)**
  - **All treated patients**

Key Eligibility Criteria

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

Conditioning Regimen

- Fludarabine 30 mg/m^2 IV and cyclophosphamide 500 mg/m^2 IV on Days −5, −4, −3

Axi-Cel: 2 × 10^6 CAR+ cells/kg

Primary Endpoint

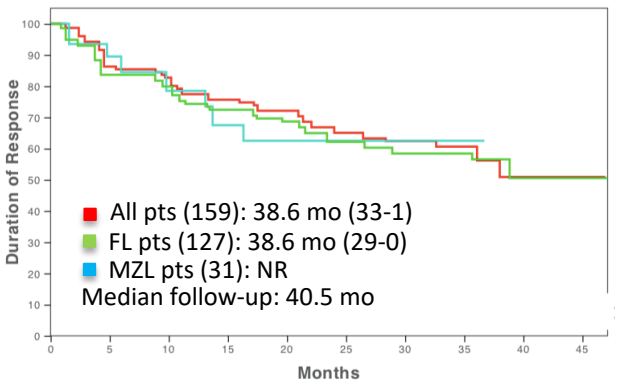
- ORR (IRRC-assessed per the Lugano classification[1])

Key Secondary Endpoints

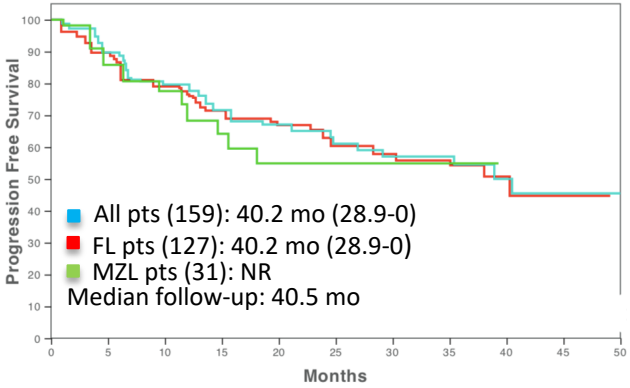
- CR rate (IRRC-assessed)
- Investigator-assessed ORR[1]
- DOR, PFS, OS
- AEs
- CAR T cell and cytokine levels

[1]Jacobson A.C. et al, *Lancet Oncol* 2022; 23: 91–103

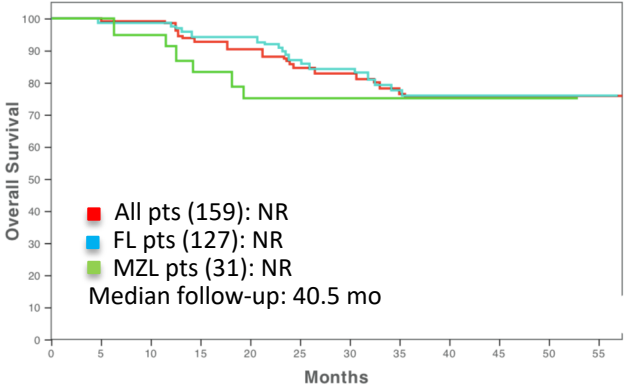
median DoR



median PFS

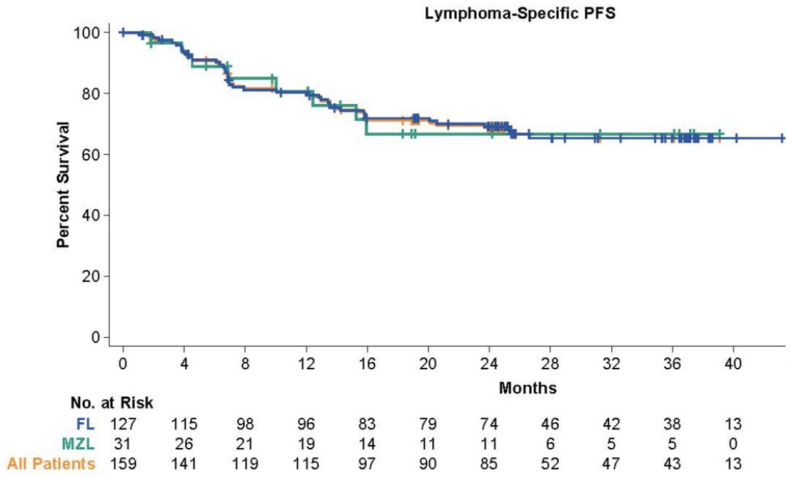


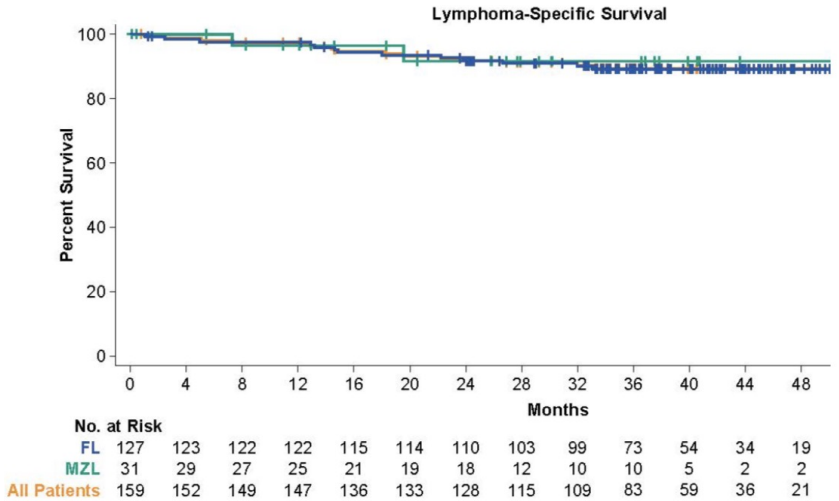
median OS



- ORR and CRR were similiar to the 2-year analysis (Jacobson A.C. et al, *Lancet Oncol* 2022; 23: 91–103);
- Estimated 36-month PFS was largely consistent in all patients with iNHL, regardless of other high-risk characteristics;
- Median PFS among FL with POD24 (n=70) was consistent with that of all enrolled patients (median 40.2 mo).
- Peak CAR T-cell levels were higher in pts with ongoing responses at 36 months (53.9 cells/µL) than in those who relapsed (29.6 cells/µL) or non-responders (22.2 cells/µL).
- Pre-infusion immunosuppressive Treg-related biomarkers (TNF-alfa, CCL-17, CCL-22, IL-16) and tumor burden were associated with relapse in patients with FL.

Neelapu S. et al. abs#4660



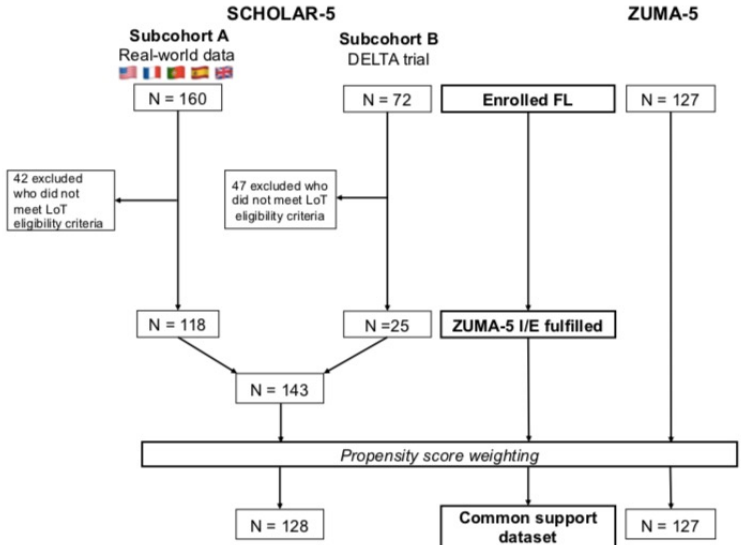


- Late progression or death due to lymphoma or study treatment were uncommon and no new safety signals arose since the 2-year analysis.
- At data cut-off, 15 deaths were lymphoma specific: 11 due to complications of underlying lymphoma and 3 due to AEs related to study treatment (1 covid-19 pneumonia, 1 multi organ failure in the context of CRS, and 1 PML)

Neelapu S. et al. abs#4660

2038. A 3-Year Follow-up Comparison of Clinical Outcomes from Zuma-5 (Axicabtagene Ciloleucel) and the International SCHOLAR-5 External Control Cohort in Relapsed/Refractory Follicular Lymphoma (R/R FL). Ghione P. et al. Poster presentation.

- **Previously, ZUMA-5 24-month data were compared to SCHOLAR-5 using a propensity score methods, and a clinically significant benefits in ORR and survival outcomes were shown in patients treated with axi-cel[1]**
- **Here is reported an updated comparative analysis at 36-month.**



Median follow-up time for ZUMA-5 and SCHOLAR-5 were 36.8 and 26.2 months, respectively.

[1]Ghione P, et al, Blood 2022; 140 (8): 851–860

Table 2. Comparison of response outcomes

		SCHOLAR-5 (n=128)	ZUMA-5 (n=127)	Odds ratio (95% CI)	P value
≥3rd LoT	ORR, n (%)	69 (54%)	119 (93.7%)	12.66 (5.24, 30.57)	<.001
	CR, n (%)	45 (34.9%)	100 (78.7%)	6.9 (3.62, 13.18)	<.001
≥4th LoT	ORR, n (%)	31 (41.6%)	70 (93.3%)	19.63 (6.57, 58.64)	<.001
	CR, n (%)	16 (21.8%)	58 (77.3%)†	12.21 (5.22, 28.55)	<.001

Table 3. Comparison of time to event outcomes

		36 months % (95% CI)		Median months (95% CI)		Hazard ratio (95% CI)	p value
		SCHOLAR-5	ZUMA-5	SCHOLAR-5	ZUMA-5		
≥3rd LoT	OS	64.2 (52.1-76.3)	75.5 (66.9-82.2)	NR* (38.4-NE)	NR (NE-NE)	0.56 (0.33-0.95)	.03
	PFS	6.5 (0.0-17.0)	54.4 (44.2-63.5)	12.97 (7.75-15.47)	40.21 (28.94-NE)	0.27 (0.18-0.41)	<.001
	TTNT	45.7 (33.1, 58.4)	59.5 (50.2-67.6)	26.61 (12.65-NE)	NE (37.85-NE)	0.60 (0.39 – 0.93)	.02
≥4th LoT	OS	49.7 (34.8-64.5)	73.8 (62.0-82.4)	32.23* (12.53-NE)	NR (NE-NE)	0.36 (0.20-0.64)	<.001
	PFS	NE†	52.0 (38.7-63.8)	4.75 (2.22-12.97)	40.21 (24.18-NE)	0.18 (0.11-0.30)	<.001
	TTNT	42.3 (27.4-57.2)	56.2 (44.1-66.7)	16.44 (5.97-NE)	NR (26.61-NE)	0.55 (0.33-0.93)	.02

Figure 2. Time to event curves, ≥3rd LoT

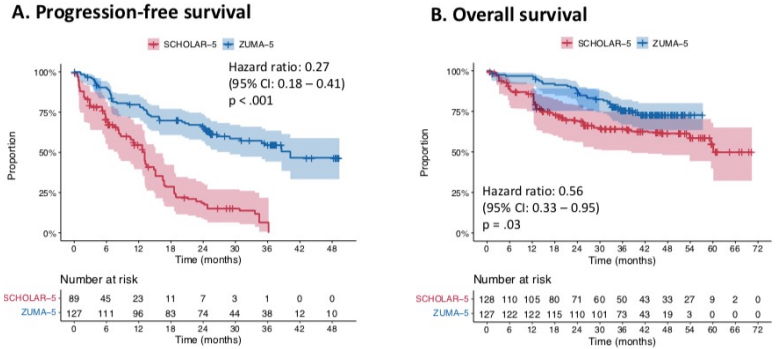
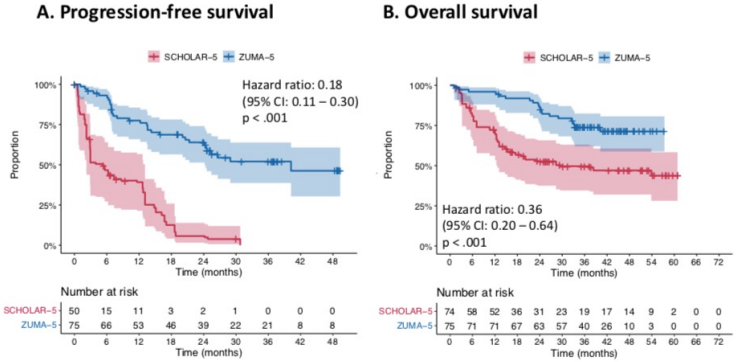


Figure 3. Time to event curves, ≥4th LoT



Ghione P. et al. abs#2038

Conclusions:

- After a median follow-up of 36.8 months, axi-cel continues to demonstrate a substantial and statistically significant improvement in meaningful clinical endpoints compared to currently available therapies for r/r FL patients.

- These findings suggest that axi-cel addresses an important unmet medical need for r/r FL patients, and that the observed treatment effects are significant for at least three years post-treatment.

3319. ZUMA-8: A Phase 1 Study of KTE-X19, an Anti-CD19 Chimeric Antigen Receptor (CAR) T-Cell Therapy, in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia. Davids S.M. et al. Poster presentation.

- **Brexucabtagene autoleucel (brexu-cel; KTE-X19) is a CD19-directed genetically modified autologous CAR T-cell therapy approved for relapsed/refractory (R/R) mantle cell lymphoma and R/R B-cell precursor acute lymphoblastic leukemia patients;**

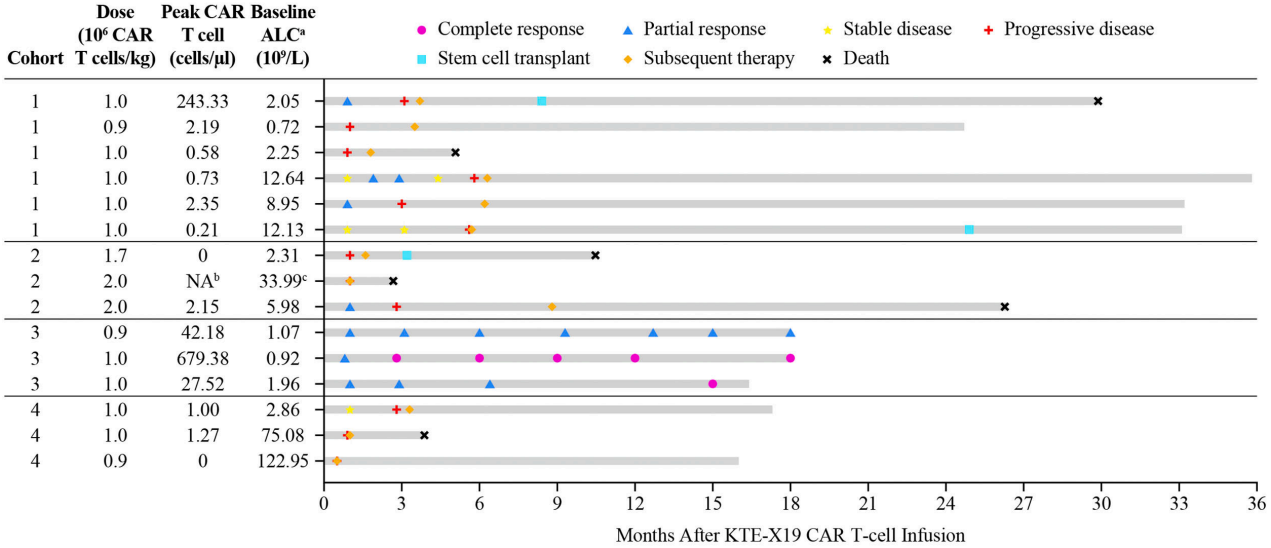
- **The multicohort, multicenter Phase 1 ZUMA-8 (NCT03624036) trial is the first to evaluate the safety and tolerability of KTE-X19 in patients with R/R CLL.**

	Cohort 1 (low dose) n=6	Cohort 2 (high dose) n=3	Cohort 3 (low tumor burden) n=3	Cohort 4 (post ibrutinib) n=3	Overall N=15
Median follow-up duration, months (range)	35.8 (33.6–40.4)	30.3 (29.9–30.6)	18.2 (18.2–18.4)	17.05 (15.5–17.9)	30.3 (15.5–40.4)
Baseline Characteristics					
Median age, years (range)	60.5 (53–68)	61.0 (52–63)	69.0 (56–79)	67.0 (53–70)	63.0 (52–79)
Male, n (%)	3 (50)	2 (67)	3 (100)	2 (67)	10 (67)
ECOG PS 1, n (%)	4 (67)	1 (33)	1 (33)	2 (67)	8 (53)
>3 prior therapy lines, n (%)	6 (100)	3 (100)	1 (33)	2 (67)	12 (80)
17p deletion, n (%)	1 (17)	1 (33)	0	2 (67)	4 (27)
Complex karyotype, n (%)[a]	3 (50)	3 (100)	1 (33)	0	7 (47)
Median tumor burden, mm^2 (range)	7,026.0 (464.0–26,688.3)	7,458.1 (2,140.4–9,715.0)	625.0 (614.0–2,472.0)	1,434.0 (786.0–2,308.5)	2,308.50 (464.0–26,688.3)
Median CLL lymphocytes in bone marrow aspirate, % (range)[b]	75.0 (0.1–93.5)	86.4 (16.0–97.0)	30.0 (5.0–40.0)	91.0 (33.0–96.0)	75.0 (0.1–97.0)
AE Summary					
Grade ≥3 AE, n (%)					
Any	6 (100)	3 (100)	3 (100)	3 (100)	15 (100)
Treatment related	4 (67)	2 (67)	2 (67)	1 (33)	9 (60)
CRS					
Any	5 (83)	2 (67)	3 (100)	2 (67)	12 (80)
Grade ≥3	0	0	1 (33)	0	1 (7)
NE					
Any	6 (100)	1 (33)	3 (100)	1 (33)	11 (73)
Grade ≥3	2 (33)	0	1 (33)	0	3 (20)

[a]Complex karyotype status defined as ≥3 clonal chromosomal abnormalities; status was unknown for 1 patient in Cohort 4.
[b]Based on local assessment.
AE, adverse event; CLL, chronic lymphocytic leukemia; CRS, cytokine release syndrome; ECOG PS, Eastern Cooperative Oncology Group performance status; NE, neurologic event.
Data cutoff date: May 2, 2022.

- 15 patients with R/R CLL after at least 2 prior lines of therapy (including BTKi) were enrolled.
- Optional BT (targeted therapy, anti-CD20 mAb, high-dose steroids) before LD was allowed (13/15 pts had BT).
- At data cut-off the median follow-up duration was 30.3 months.
- **Primary endpoint**: incidence of DLTs (1 pts in cohort 3).
- **Secondary endpoints**: incidence of AEs, objective response rate per investigator review according to the International Workshop CLL 2018 criteria, and CAR T-cell expansion.

Figure: Patient-level Peak CAR T-cell Expansion, Baseline ALC, Objective Response, and Survival Over Time.



- Objective response: 7/15 pts; CR: 2/15 (all in the cohort 3).
- CAR T-cell expansion occurred in 4/15 pts overall and in 3/3 pts with a low tumor burden (cohort 3).
- Peak CAR T-cell expansion and objective responses in heavily pretreated patients with low tumor burden appeared to be improved compared to other cohorts

CONCLUSIONI

FOLLICULAR LYMPHOMA

- Long term follow-up of both II generation, CD-19 directed CAR T-cells (tisa-cel and axi-cel) continues to demonstrate **durable efficacy** and a **favorable safety profile** in patients with r/r FL, regardless disease characteristics.

- In both ELARA and ZUMA-5 trials, exploratory biomarker analyses suggest that a favorable TME, a low tumor burden and a decreased inflammatory status are associated with improved clinical outcomes.

- In a matched comparison analysis between ZUMA-5 FL patients and a SCHOLAR-5 external control cohort, axi-cel demonstrates a statistically significant improvement compared to currently available therapies, addressing an important unmet medical need for r/r FL patients.

MARGINAL ZONE LYMPHOMA

- After 2 year of follow-up in ZUMA-5, axi-cel demonstrates continued durable responses in patients with R/R iNHL, with improved survival observed in patients with MZL, regardless to disease characteristics.

CHRONIC LYMPHOCYTIC LEUKEMIA

- In ZUMA-8 trial, brexu-cel seems to have a better outcome and an higher peak of expansion in R/R CLL with low tumor burden (cohort 3, ≤1% malignant cells in peripheral blood or absolute lymphocyte count <5,000 cells/µL) in comparison to other cohorts.

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GRAZIE PER L'ATTENZIONE