3rd MEETING ON
T-CELL AND NK-CELL BASED IMMUNOTHERAPIES FOR LYMPHOID MALIGNANCIES

CAR-T for follicular lymphoma

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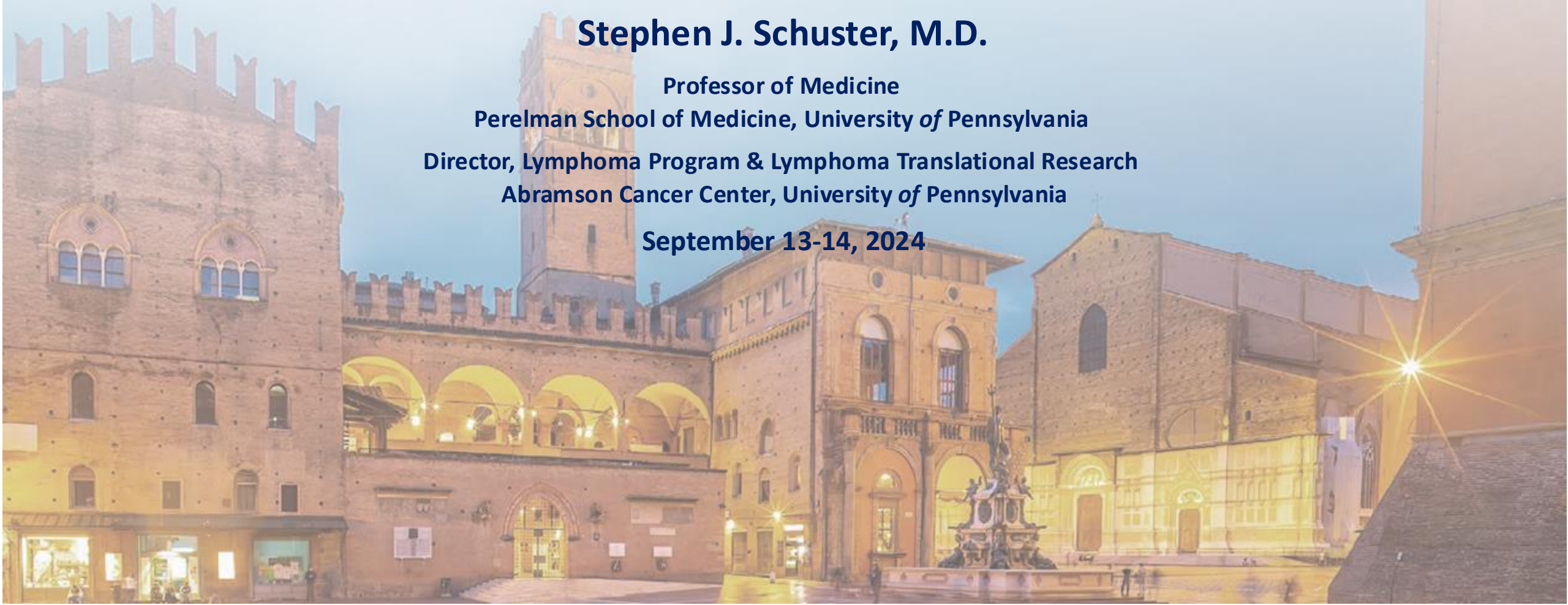

Disclosures for S. J. Schuster

Company	Research support	Employee	Consultant	Stockholder	Speaker's bureau	Advisory board	Other
AbbVie						X	
AstraZeneca						X	
BeiGene						X	
BioNTech			X				
Caribou Biotech			X				Steering committee
Celgene/Juno			X				
Fate Therapeutics							Safety DSMB
Genentech/Roche	X					X	Steering committee
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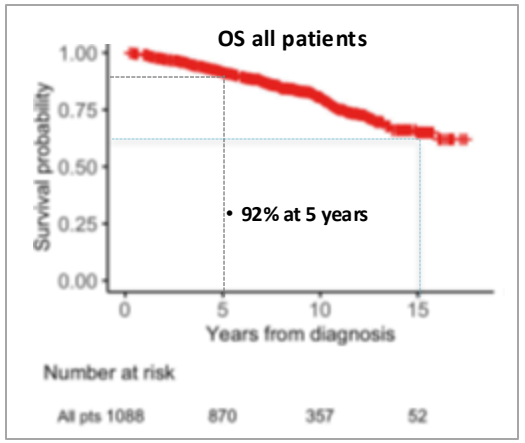
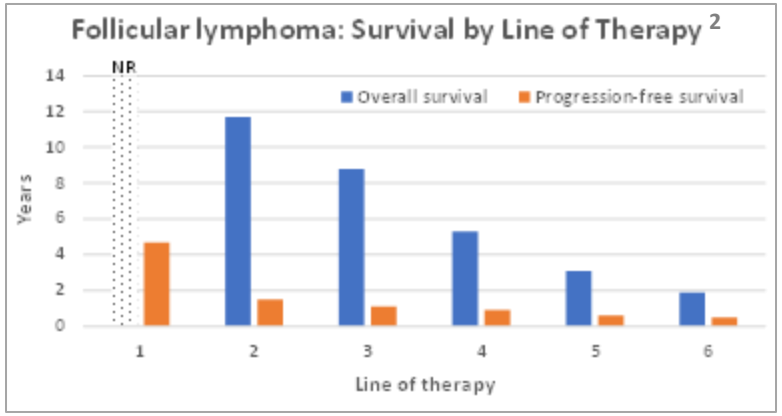
Janssen			X				
Kite Pharmaceuticals						X	
Legend Biotech			X				
Novartis						X	Steering committee
Vittoria Bio			X				Scientific Advisor

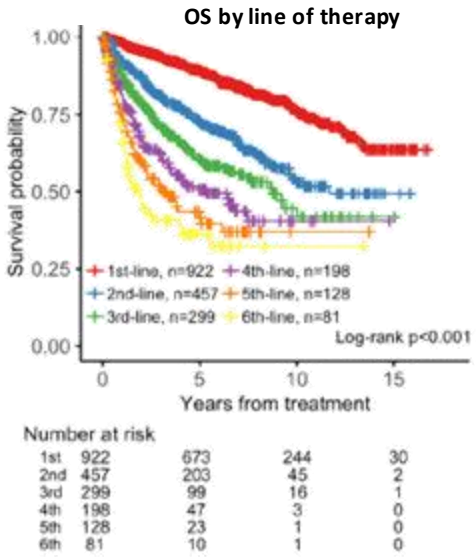
Follicular Lymphoma: Survival by Line of Therapy

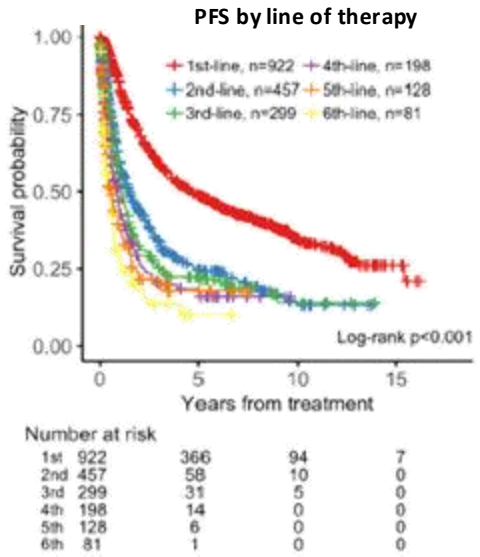
- single institution (MSKCC), retrospective study, **1998-2009**
  - ***post-rituximab/pre-CAR T era***
- N = 1,088 patients with FL, grade 1-3A; 922 patients required treatment
- *survival calculated from time of diagnosis or from time of treatment initiation*

Line of therapy	PFS (*median, years*)	OS (*median, years*)
1	4.7	not reached
2	1.5	11.7
3	1.1	8.8
4	0.9	5.3
5	0.6	3.1
6	0.5	1.9









[1]Batlevi, et al. Blood Cancer J. 2020;10:74.
[2]*adapted from Batlevi, et al.*

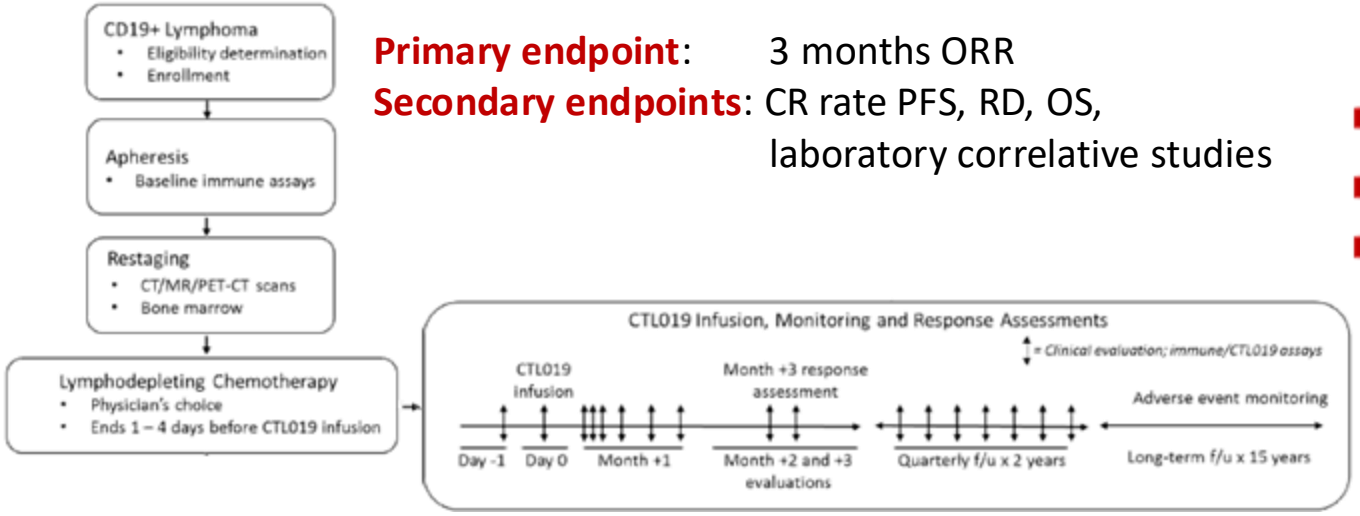
UPenn Pilot Trial UPCC13413: CTL019 in r/r FL *(later tisagenlecleucel)*

"There is no present or future – only the past, happening over and over again"

- **Single center trial at the University of Pennsylvania**
  - 2 cohorts: large B-cell lymphoma and follicular lymphoma
- **CTL019 Construct: anti-CD19 + 4-1BB + CD3ζ**
- **all CTL019 infusions were between 11 March 2014 - 2 August 2016**

Eligibility criteria:

- CD19^{+} refractory/relapsed follicular lymphoma (Grades 1-3a)
- measurable progression of disease less than 2 years after second or later line of immunochemotherapy (excluding single-agent monoclonal antibody therapy)



Primary endpoint: 3 months ORR

Secondary endpoints: CR rate PFS, RD, OS, laboratory correlative studies

Patients Treated (N=38)	Follicular Lymphoma (N=14)
Age – years, median (range)	59 (43-72)
Female sex, no. (%)	7 (50)
Advanced stage, no. (%)	12 (86)
Prior therapies, median (range)	5 (2-10)
ECOG PS, median (range)	0 (0-1)
Bone marrow involvement, no. (%)	4 (29)
Elevated LDH, median (range)	9 (64)
Follicular lymphoma international prognostic index, median (range)	3 (1-5)
POD24 follicular lymphoma, no. (%)	10 (71)
Double refractory follicular lymphoma, no. (%) §	10 (71)
Rituximab refractory follicular lymphoma, no. (%)	14 (100)
Prior autologous stem cell transplant, no. (%)	2 (14)
Prior allogeneic stem cell transplant, no. (%)	1 (7)
Bridging therapy, no. (%)	4 (29)

§ Double-refractory follicular lymphoma is defined as progression of disease within 6 months after receiving the last dose of rituximab and within 6 months after receiving the last dose of an alkylating agent.

Schuster SJ, et al. N Engl J Med. 2017;377(26):2545-2554.
Chong, EA, et al. N Engl J Med. 2021;384:673-674.

Clinicaltrials.gov Identifier: NCT02030834

UPenn Pilot Trial UPCC13413: CTL019 in r/r FL *(later tisagenlecleucel)*

- *Median follow-up 60.7 months*

Efficacy in relapsed/refractory follicular lymphoma

Best ORR: 79% (11/14)

CR rate: 71% (10/14)

5-year PFS: 43% (95% CI, 18-66)

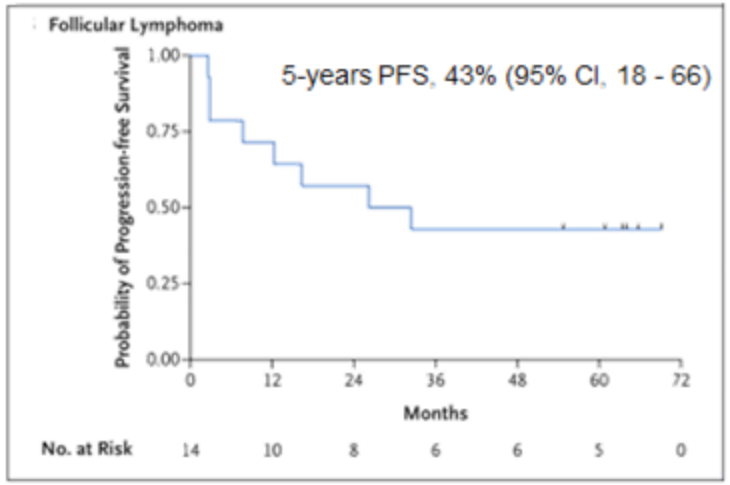
5-year response rate: 60% (95% CI, 25-83)

Adverse Events of Special Interest That May Have Been Related to CTL019 Therapy * : All Patients infused

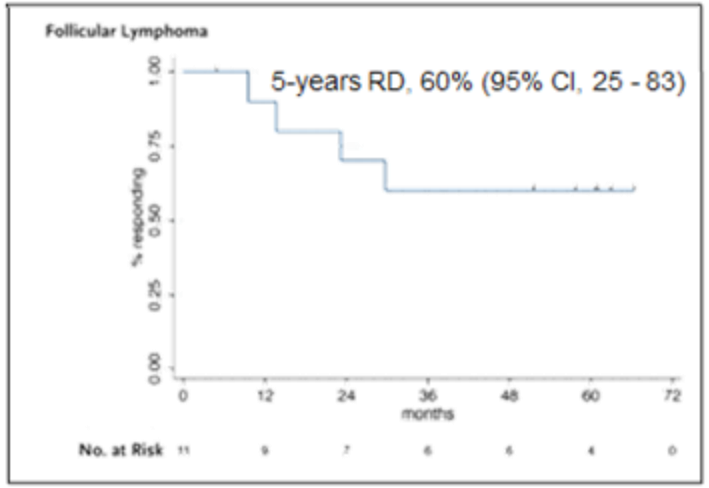
Adverse Event	Grade					Total Events	Grade 3 or Higher
	1	2	3	4	5	*number (percent)*	
Cytokine release syndrome	0	11	4	1	0	16 (57)	5 (18)
Neurotoxicity	4	4	1	1	1	11 (39)	3 (11)
Encephalopathy	0	0	1	1	1	3 (27)	
Delirium	0	2	0	0	0	2 (18)	
Tremor	2	0	0	0	0	2 (18)	
Cognitive disturbance	1	0	0	0	0	1 (5)	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

*Cytokine-release syndrome was graded with the use of the Penn scale:
Porter DL, et al. Sci Transl Med 2015;7:303ra139.

Progression-free Survival



Response Duration



Chong, Ruella and Schuster N Engl J Med 2021;384:673-674.

The NEW ENGLAND JOURNAL of MEDICINE

ELARA (*tisagenlecleucel*): Study Schema

- **Tisagenlecleucel, an anti-CD19 4-1BB/TCRζ CAR-T, in relapsed or refractory follicular lymphoma as ≥ 3rd line of therapy**

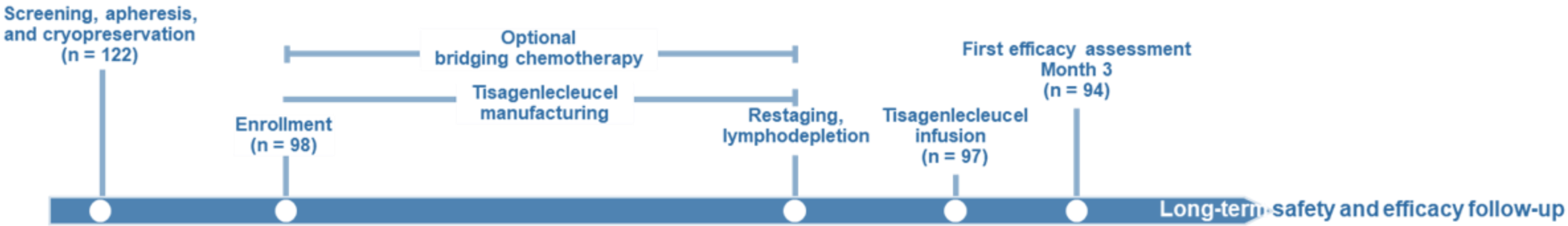
Study Design

- **Single arm, multi-center phase II study to determine the efficacy and safety of tisagenlecleucel in adult patients with relapsed or refractory follicular lymphoma after two or more treatment lines, or who relapsed after ASCT**
- **Primary objective: Complete remission rate**

Key Inclusion Criteria

- **≥18 years of age**
- **FL grade 1, 2, or 3A**
- **Relapsed/refractory disease***
- **No evidence of histological transformation/FL3B**
- **No prior anti-CD19 therapy**
- **No prior allogeneic SCT**

*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 ASCT.



Median follow-up:
40.6 months (range, 34.2-49.7)

CR, complete response; FL, follicular lymphoma; ASCT, autologous stem cell transplant

ClinialTrials.gov NCT03568461
Schuster, et al. ASH 2023: Abstract #601 (oral presentation)

ELARA: Patient Characteristics and Outcomes

Patient Characteristics[2]	Infused set (N=97)[2]
Median age (range), years	57.0 (29-73)
ECOG PS ≥1 prior to infusion, n (%)	42 (43)
Stage at study entry III-IV, n (%)	83 (86)
Bone marrow involvement, n (%)	37 (38)
Bulky disease[a], n (%)	**62 (64)**
FLIPI high at study entry (≥3), n (%)	58 (60)
Median no. of prior therapies (range)	4 (2-13)
POD24[b] from first anti-CD20 moAb containing therapy, n (%)	**61 (63)**
Refractory disease to last line of therapy, n (%)	76 (78)
Refractory to ≥2 regimens, n (%)	69 (71)
Double refractory: anti-CD20 moAb + alkylating agent	**66 (68)**
Refractory to PI3K inhibitors	14 (14)
Prior autologous ASCT, n (%)	35 (36)
Comorbidities, n (%)	
Cardiac disorders	**15 (16)**
Diabetes	**10 (10)**
Renal insufficiency	**8 (8)**

[a]Bulky disease defined as 1 lesions >7 cm or 3 lesions >3 cm
[b]POD24, progression of disease within 2 years of frontline systemic therapy

Primary efficacy assessments[1]	Efficacy set (n = 97)
Follow-up, median	29 months (IQR, 22-38)
ORR	86% (95% CI, 78-92)
CR rate	68% (95% CI, 58-77)
median PFS	*not reached*
24-month PFS	54% (95% CI 46-67)
Duration of response	*not reached*
24-month PFS for CR	66% (95% CI, 54-76)

Table 3 | Overall safety profile

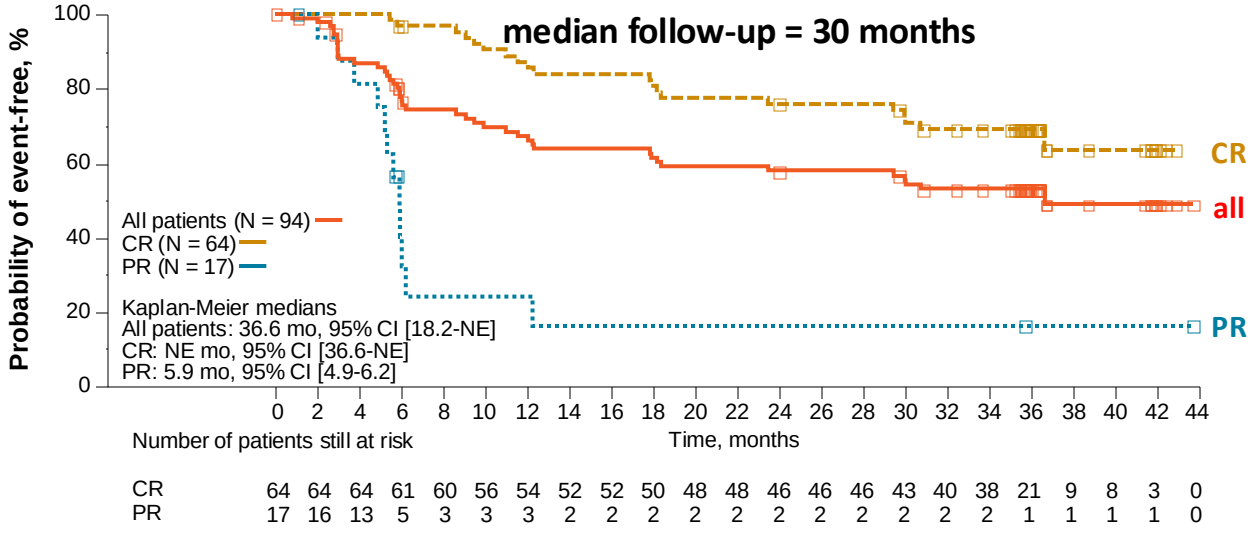
Parameter	Treated patients, $n = 97$
CRS	47 (48.5)
Grade ≥3	0
Immune effector-cell-associated neurotoxicity syndrome	4 (4.1)
Grade ≥3	1 (1.0)

[1]Dreyling, et al. Blood. 2024;143(17):1713-1725.
[2]Schuster, et al. ASH 2023: Abstract #601 (oral presentation)

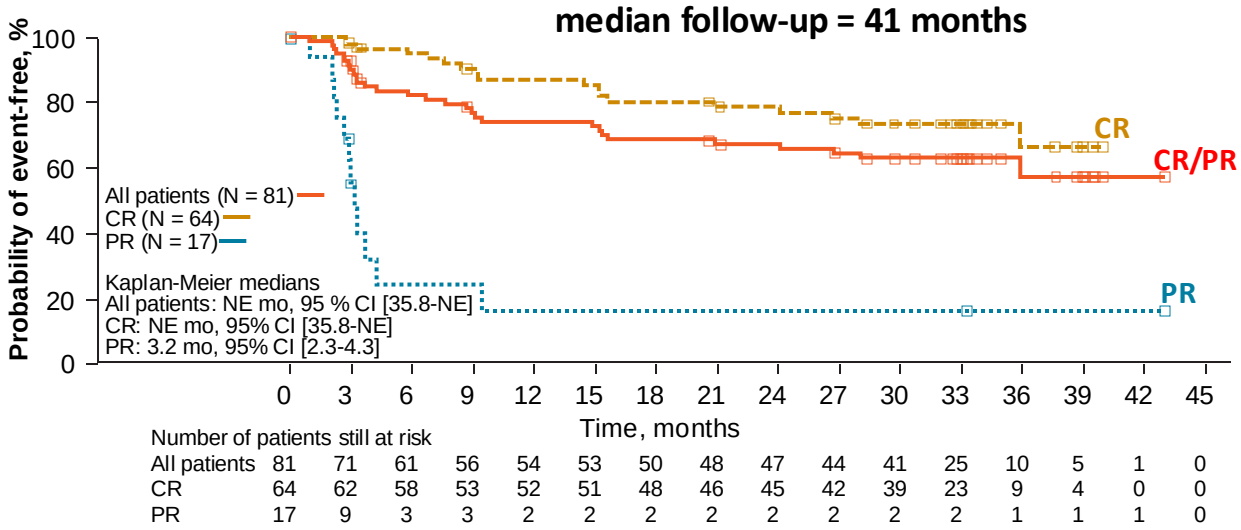
blood Regular Article

ELARA: 36-month Progression-free and Overall Survival

Progression-free survival
(N = 94)



Duration of response[a]
(N = 81)



- **At 30 months' median follow-up, median PFS:**
  - for all patients: 37 months
  - for patients with CR: not reached
  - For patients with PR: 6 months
- **36-month PFS rates: 53% for all patients; 69% for patients with a CR**
- **54% of responders had ongoing responses at data cutoff**
- **36-month post-infusion probabilities of maintaining CR/PR and CR were 63% and 73%, respectively**
- **36-month OS rate was 82%**

BOR, best overall response; CR, complete response; ; DOR, duration of response; PR, partial response, NE, not estimated; OS, overall survival; PFS, progression-free survival

[a]Defined as the time from the date of first documented disease response (CR or PR) to the date of first documented progression or death due to FL.

Schuster, et al. ASH 2023: Abstract #601 (oral presentation)

UPenn Pilot and ELARA Trials: Similar Results

	UPenn [1,3]	ELARA [2,4]
Disease state	FL, grades 1-3A	FL, grades 1-3A
Number of patients infused, n	14	97
Follow-up, median	60.7 months	30 months
Efficacy evaluable, n	n = 14	n = 94
CR rate	71% [best response]	68% [best response]
Duration of response	60% @ 60-months	63% @ 36-months
Safety evaluable	n = 38 (also includes LBCL AEs)	n = 97
CRS	18% grade ≥3*	0 grade ≥3
Neurotoxicity	11% grade ≥3	3% grade ≥3

CR, complete remission; DLBCL, diffuse large B-cell lymphoma; tFL, transformed follicular lymphoma; FL, follicular lymphoma

* Penn Scale

1. Schuster SJ, et al. N Engl J Med. 2017;377(26):2545-2554.
2. Fowler, et al. Nature Medicine 2022;28::325–332.
3. Chong, EA, et al. N Engl J Med. 2021;384:673-674.
4. Schuster, et al. ASH 2023: Abstract #601.

ZUMA-5 (*axicabtagene ciloleucel*): Study Schema

- **Axicabtagene ciloleucel, an anti-CD19 CD28/TCRζ CAR-T, in relapsed or refractory *indolent* non-Hodgkin lymphomas**

Study Design

- Multicenter phase 2, single-arm, pivotal study of axi-cel in r/r FL and r/r MZL
- Primary objective: ORR per IRC by Lugano 2014 criteria
- Secondary objectives CR rate, DOR, PFS, OS, safety, cytokine and CAR-T cell levels

Key Inclusion Criteria

- Age ≥ 18 years
- ECOG PS ≤ 1
- relapsed/refractory FL (grade 1-3a) and MZL
- received ≥ 2 prior systemic lines of therapy that included an anti-CD20 antibody + an alkylator
- Post-progression biopsy required to exclude large cell transformation or other histology
- At least 1 measurable lesion per Lugano Response Criteria

Enrolled
r/r FL, n=127
MZL, n= 31

→ **Leukapheresis**

→ **Conditioning Chemotherapy**
Fludarabine 30 mg/m^2 IV and cyclophosphamide 500 mg/m^2 IV on Days −5, −4, −3

→ **Axi-Cel Infusion**
2 × 10^6 CAR+ cells/kg on Day 0

→ **Post-treatment**
assessment and long-term follow-up

FL, follicular lymphoma; MZL, marginal zone lymphoma; ORR, overall response rate; IRC, independent review committee; CR, complete response; DOR, duration of response; PFS, progression-free survival; OS, overall survival; FL, follicular lymphoma; ASCT, autologous stem cell transplant

Neelapu, et al. Blood 2024;143(6):496-506.
Clinicaltrials.gov NCT03105336

ZUMA-5: Patient Characteristics and Outcomes

Characteristic	FL (n = 127)
Age, median (range), y	60 (34-79)
≥65 y, n (%)	40 (31)
Male sex, n (%)	75 (59)
FL histological category, n (%)	
Grade 1	34 (27)
Grade 2	63 (50)
Grade 3a	30 (24)
MZL histological category, n (%)	
Nodal	—
Extranodal	—
ECOG PS of 1, n (%)	48 (38)
Stage III-IV disease, n (%)	109 (86)
High-risk FLIPI (≥3), n (%)	56 (44)
High tumor bulk (GELF criteria), n (%)	65 (51)
SPD, median (range), mm^2	2604.15 (289.2-34 675.0)
TMTV, median (range), mL	438.50 (11.21-5 576.58)
Number of prior therapies, median (range)	3 (1-10)
R/R subgroup, n (%)	
Refractory to last prior therapy	87 (69)
Double refractory to prior anti-CD20 mAb and alkylating agent	56 (44)
POD24 from initiating first anti-CD20 mAb–containing therapy§	70 (56)
Lymphoma present in bone marrow, n (%)	35 (28)
Received bridging therapy, n (%)	4 (3)

• Efficacy

	FL (n = 127)
ORR, n (%)	119 (94)
CR	100 (79)
PR	19 (15)
SD, n (%)	2 (2)
PD, n (%)	2 (2)
Not done, n (%)	4 (3)
DOR, median (95% CI), mo	38.6 (29.0-NE)
Estimate at 36 mo (95% CI), %	57 (47-66)
Duration of CR, median (95% CI), mo	NR (35.4-NE)
Estimate at 36 mo (95% CI), %	62 (48-72)
Duration of PR, median (95% CI), mo	4.9 (2.2-8.2)
Estimate at 36 mo (95% CI), %	NR (NE-NE)

• Safety

Table S7. Common Adverse Events, Cytokine Release Syndrome, and Neurologic Events

	Follicular Lymphoma (n=124)	
	Any Grade	Grade ≥3
Any adverse event, n (%)*	123 (99)	105 (85)
CRS, n (%)*,†	97 (78)	8 (6)
Pyrexia	94 (97)	6 (6)
Hypotension	39 (40)	3 (3)
Chills	25 (26)	0
Hypoxia	23 (24)	6 (6)
Sinus tachycardia	25 (26)	2 (2)
Headache	19 (20)	0
Neurologic events, n (%)*	70 (56)	19 (15)
Tremor	36 (29)	1 (1)
Confusional state	28 (23)	6 (5)
Encephalopathy	24 (19)	10 (8)

* Included are any adverse events of any grade occurring in ≥20% of patients, and CRS and neurologic events of any grade occurring in ≥15% of patients

† Percentages in the CRS rows were calculated out the 121 patients who experienced CRS

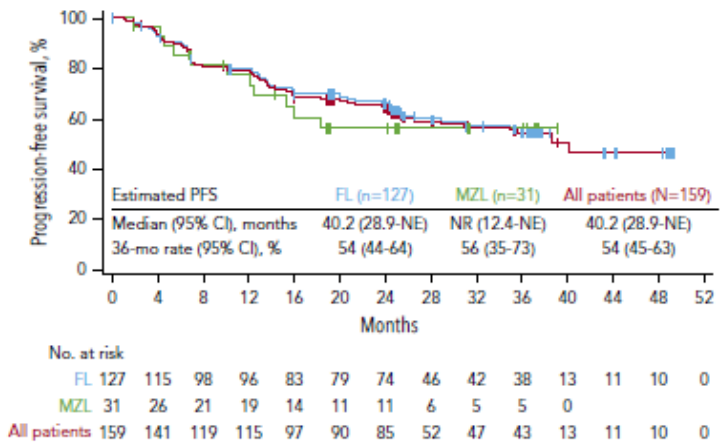
FL, follicular lymphoma; MZL, marginal zone lymphoma; ORR, overall response rate; IRC, independent review committee; CR, complete response; DOR, duration of response; PFS, progression-free survival; OS, overall survival; FL, follicular lymphoma; ASCT, autologous stem celltransplant

[1]Neelapu, et al. Blood 2024;143(6):496-506.
[2]Jacobson, et al. Lancet Oncol. 2022; 23:91–103.
Clinicaltrials.gov NCT03105336

ZUMA-5: Survival and Time to Next Treatment

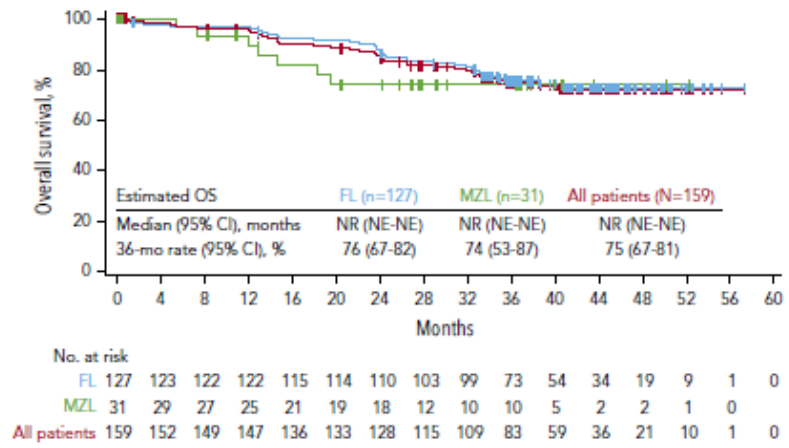
Estimated PFS	FL (n=127)
Median (95% CI), months	40.2 (28.9-NE)
36-mo rate (95% CI), %	54 (44-64)

A



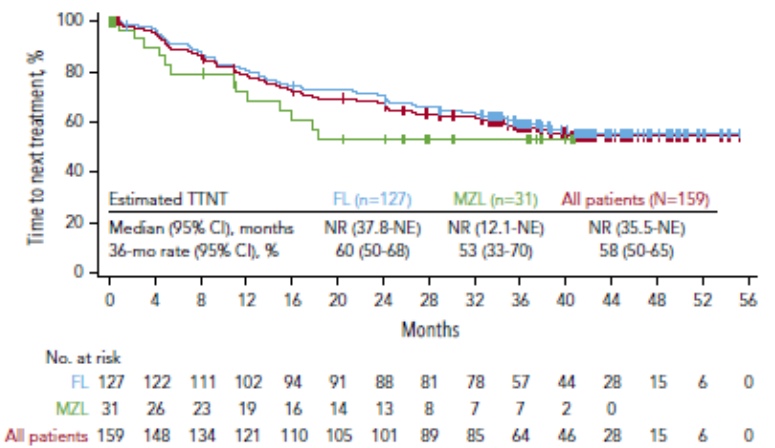
Estimated OS	FL (n=127)
Median (95% CI), months	NR (NE-NE)
36-mo rate (95% CI), %	76 (67-82)

B



Estimated TTNT	FL (n=127)
Median (95% CI), months	NR (37.8-NE)
36-mo rate (95% CI), %	60 (50-68)

C



FL, follicular lymphoma; MZL, marginal zone lymphoma; PFS, progression-free survival; OS, overall survival; TTNT, time to next treatment; mo, month; NE, not estimable; NR, not reached

Neelapu, et al. Blood 2024;143(6):496-506.
Clinicaltrials.gov NCT03105336

Transcend-FL (*lisocabtagene maraleucel*): Study Schema

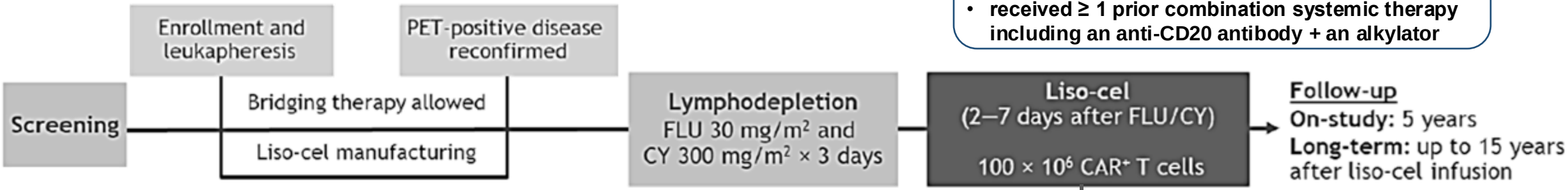
- **Lisocabtagene maraleucel, an anti-CD19 4-1BB/TCRζ CAR-T, in relapsed or refractory *indolent* non-Hodgkin lymphomas**

Study Design

- **Global, phase 2, single-arm, multicohort, pivotal study of liso-cel in pts with r/r indolent NHL, including FL**
- **Primary objective: ORR per IRC by Lugano 2014 criteria**
- **Secondary objectives CR rate, DOR, PFS, OS, safety, pharmacokinetics**

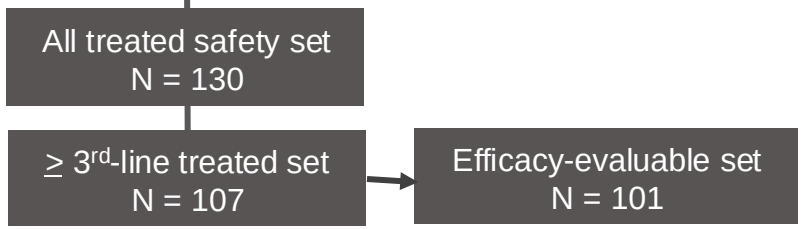
Key Inclusion Criteria

- **Age ≥ 18 years**
- **ECOG PS ≤ 1**
- **FL histology confirmed ≤ 6 months of screening**
- **r/r follicular lymphoma, 3 cohorts:**
  - **≥ 4th-line**
  - **3rd-line**
  - **2nd-line with POD24 +/- modified GELF criteria**
- **received ≥ 1 prior combination systemic therapy including an anti-CD20 antibody + an alkylator**



Data as of January 27, 2023

- **r/r FL cohort: 1) efficacy in ≥ 3rd-line**
  2) safety in all liso-cel–treated FL patients



NHL, non-Hodgkin lymphoma; FL, follicular lymphoma; ORR, overall response rate; IRC, independent review committee; CR, complete response; DOR, duration of response; PFS, progression-free survival; OS, overall survival; FL, follicular lymphoma; ASCT, autologous stem cell transplant

Morschhauser et al., ICML 2023
ClinialTrials.gov NCT04245839

Transcend-FL: Patient Characteristics and Outcomes

Efficacy-evaluable set, r/r FL n = 101

- **Follow-up, median: 17.5 months**
- **OOR: 97%**
- **CR rate: 94%**
- **median PFS: not reached**
- **12-month PFS rate: 80.7%**

Patient characteristics, FL ≥ 3rd-line therapy	N = 107
Age, median (range)	62 years (23–80)
Median prior lines of therapy (range)	3 (2–10)
Ann Arbor stage III/IV	89%
high-risk FLIPI	57%
POD24	43%
GELF criteria for treatment met	53%
double refractory to anti-CD20 + alkylator	64%

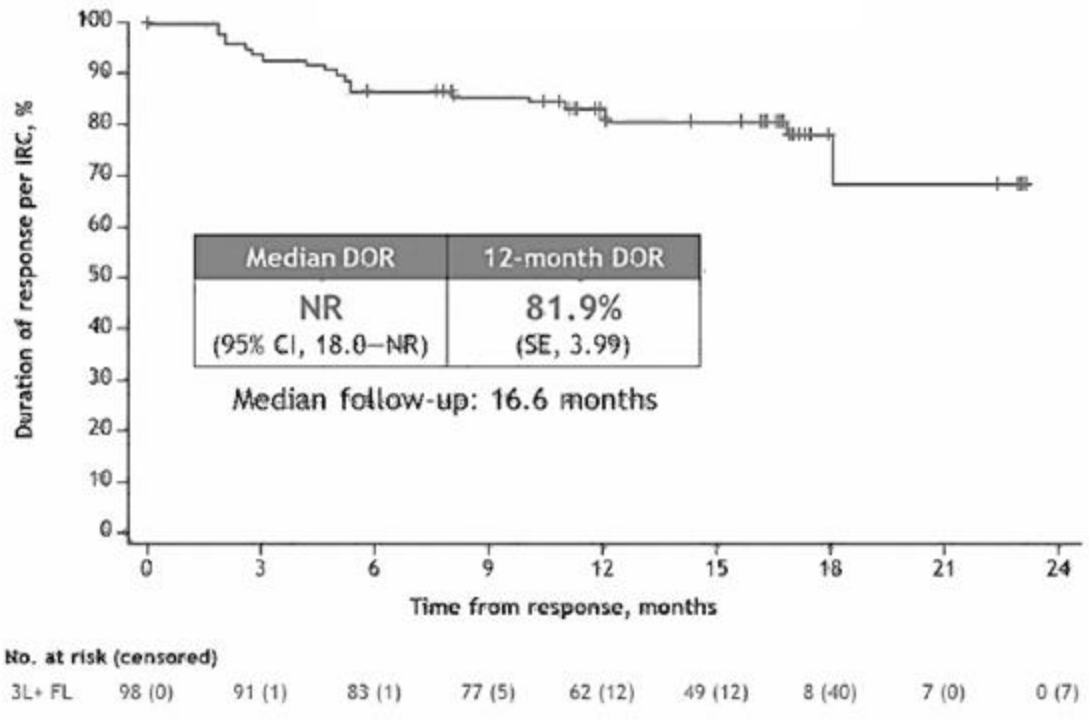
POD24, progression of disease within 2 years of frontline systemic therapy

Safety	2L+ FL liso-cel–treated set (n = 130)
Cytokine release syndrome (CRS)	
CRS, n (%)	
Any grade	75 (58)
Grade 1	55 (42)
Grade 2	19 (15)
Grade 3	**1 (1)**
Grade 4/5	**0**
Median (range) time to onset, days	6 (1–17)
Median (range) time to resolution, days	3 (1–10)
Neurologic Events (NE)	
NE, n (%)	
Any grade	20 (15)
Grade 1	15 (12)
Grade 2	2 (2)
Grade 3	**3 (2)**
Grade 4/5	**0**
Median (range) time to onset, days	8.5 (4–16)
Median (range) time to resolution, days	3.5 (1–17)

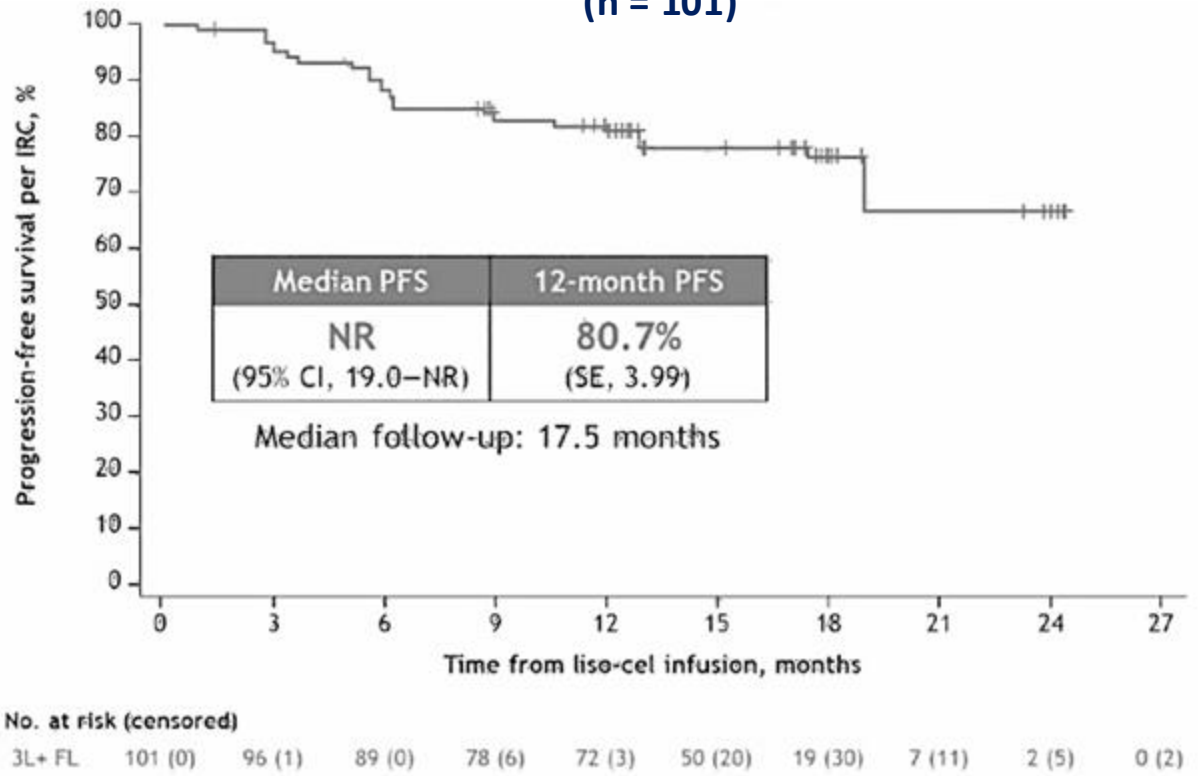
Morschhauser et al., ICML 2023
ClinialTrials.gov NCT04245839

Transcend-FL: Response Duration and Progression-free Survival

Response Duration, ≥ 3rd-line therapy (n = 101)



Progression-free Survival, ≥ 3rd-line therapy (n = 101)



Morschhauser et al., ICML 2023
ClinialTrials.gov NCT04245839

CAR-T for r/r Follicular Lymphoma ≥ 3rd-line Therapy: Summary

Product	Tisagenlecleucel	Axicabtagene ciloleucel	Lisocabtagene maraleucel
Trial	**ELARA[1]**	**ZUMA-5[2]**	**TRANSCEND-FL[3]**
Design	Phase II	Phase II	Phase II
Patients, N	N = 94	N = 127	N = 101
Median prior therapies	4	3	3
Median follow-up, months	30 mo	42 mo	18 mo
ORR	86%	94%	97%
CRR	69%	79%	94%
median PFS	37 mo	40 mo	NR @ 18 mo
12-month (mo) PFS rate	67%	79%	81%
36-month PFS rate	53%	54%	--
Any grade CRS/NT	48%/37%	78%/56%	58%/15%
Grade ≥ 3 CRS	0%	7%	1%
Grade ≥ 3 NT	3%	15%	2%

r/r, relapsed/refractory; FL, follicular lymphoma; ORR, overall response rate; CRR, complete response rate; PFS, progression free survival; NR, not reached; mo, months; CRS, cytokine release syndrome; NT, neurotoxicity

[1]Schuster, et al. ASH 2023; Abstract #601 (oral)
[2]Neelapu, et al. Blood 2024;143(6):496-506.
[3]Morschhauser, et al. ICML 2023

CAR-T for ≥ 3rd-line Therapy of Follicular Lymphoma: Conclusions

Conclusions

- Patients with r/r FL have a high rates of durable responses more than 3 years after CAR-T cell infusion with median DOR for patients with CR, and OS and TTNT for all patients not reached
  - PFS is superior compared with other available therapies in this patient population
- CAR-T cell-related toxicities can be significant but are generally manageable
- CAR T-cell safety and efficacy in the real-world setting and in trial-ineligible and older populations approximate the results of registrational trials (data not discussed)

FL, follicular lymphoma; DOR, duration of response; CR, complete response; OS, overall survival; TTNT, time to next treatment; PFS, progression free survival

3rd MEETING ON
T-CELL AND NK-CELL BASED IMMUNOTHERAPIES FOR LYMPHOID MALIGNANCIES

CAR-T for follicular lymphoma and real-world data

Stephen J. Schuster, M.D.

Grazie molto / Many Thanks!