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

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Verona
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CAR-T NEI LINFOMI INDOLENTI

Enrico Derenzini
Istituto Europeo di Oncologia, Milano
Universita' di Milano

Disclosures of Enrico Derenzini

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Takeda	X					X	
Roche					X	X	
Incyte	X				X		
ADC-Therapeutics	X						
Beigene							X
AbbVie					X	X	
Astra Zeneca						X	
Sobi					X	X	
Gilead						X	

BACKGROUND

NEWS FROM ASH 2023: CAR-T IN INDOLENT LYMPHOMA

R/R FOLLICULAR LYMPHOMA

PRODUCT	TARGET	TYPE	CURRENT INDICATION (EMA)	OTHER INDICATIONS
AXICEL	CD19	CAR-T	≥4° LINE	YES (DLBCL, PMBCL)
TISACEL	CD19	CAR-T	≥3° LINE	YES (DLBCL, PMBCL)
LISOCEL	CD19	CAR-T	-	YES (DLBCL, PMBCL)
MOSUNETUZUMAB	CD20xCD3	T-CELL ENGAGER	≥3° LINE	-
RITUXIMAB-LENALIDOMIDE	CD20	mAB + IMiD	≥2° LINE	-
R/O-CHEMO (+/- ASCT)	CD20	R-CHEMO	≥2° LINE	-
IDELALISIB	PI3K	SMALL MOLECULE	≥3° LINE	YES (CLL)

Clinical Outcomes of Patients with Relapsed/Refractory Follicular Lymphoma Treated with Tisagenlecleucel: Phase 2 ELARA 3-Year Follow-up

▪Tisagenlecleucel, a CD19-directed CAR-T cell therapy, is approved in the United States and Europe for adults with r/r FL after ≥2 lines of prior therapy

▪2-year follow-up of the ELARA trial (median follow-up 29 months):

ORR 86%, CRR 68%, durable responses (24-month PFS 57%)

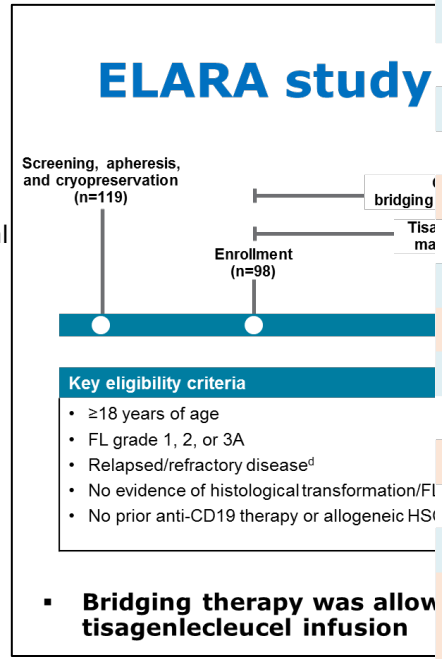
REPORTED DATA:

Longer follow-up (median follow-up of >3 years) :

1-duration of response

2-safety outcomes

3-exploratory analyses



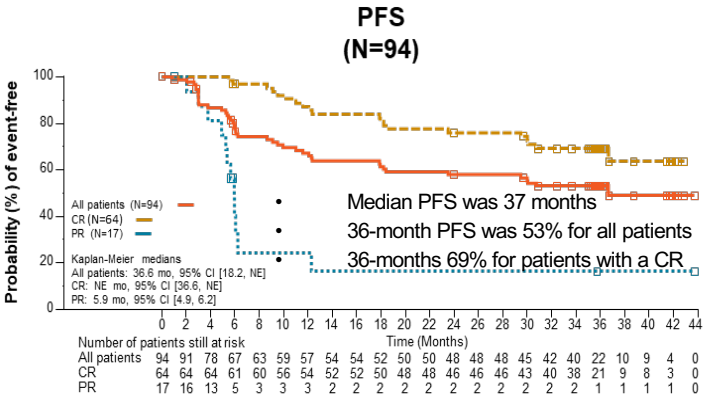
	Infused Set (N=97)
Median age (range), years	57.0 (29-73)
ECOG PS ≥1 prior to infusion, n (%)	42 (43)
Stage at study entry III-IV, n (%)	83 (86)
Bone marrow involvement, n (%)	37 (38)
Bulky disease[a], n (%)	**62 (64)**
FLIPI High at study entry (≥ 3), n (%)	58 (60)
Median no. of prior therapies (range)	4 (2-13)
POD24 from first anti-CD20 mAb 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 mAb + alkylating agent	**66 (68)**
Refractory to PI3K inhibitors	14 (14)
Prior autologous HSCT, n (%)	35 (36)
Comorbidities, n (%)	
Cardiac disorders	**15 (16)**
Diabetes	**10 (10)**
Renal insufficiency	**8 (8)**

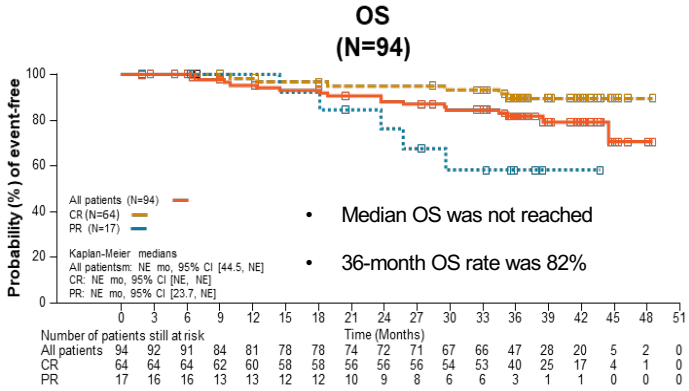
Schuster SJ et al, ASH meeting 2023 Oral Abstract #601

Original publication: Fowler NH et al, Nat Med 2022

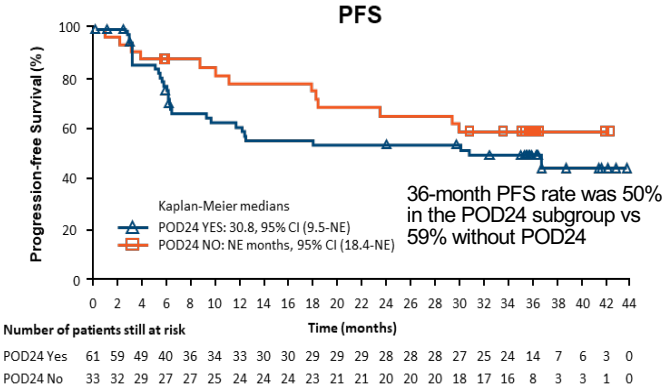
Outcome (PFS & OS)

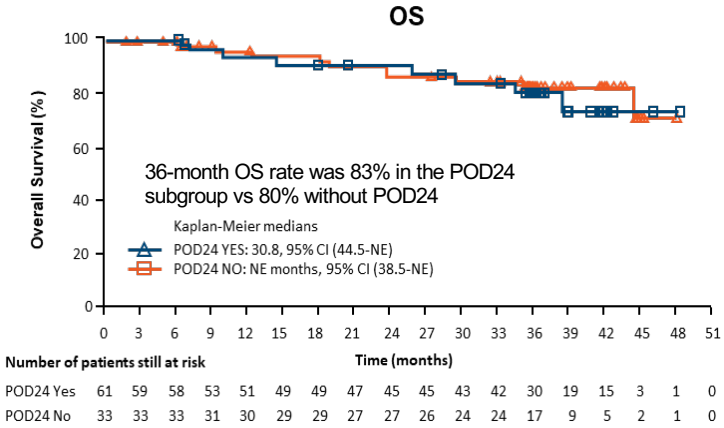
Efficacy evaluable patients=94





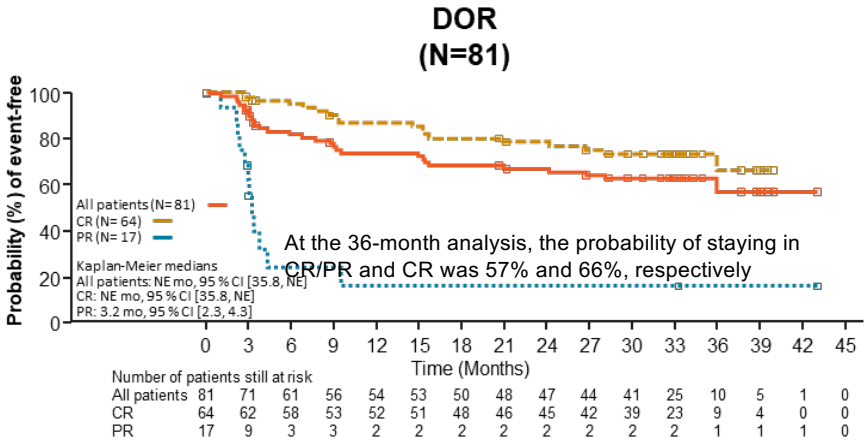
36-month PFS and OS rates with and without POD24



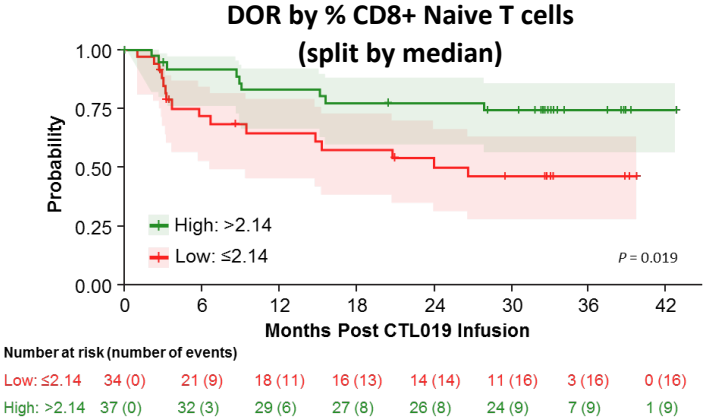


Schuster SJ et al, ASH meeting 2023 Oral Abstract #601

Outcome (DOR & TTNT)



High levels of circulating CD8+ naive T cells at baseline were associated with prolonged PFS and DOR



No new safety signals were reported

AEs occurring any time after tisagenlecleucel infusion Preferred term	Infused Set (N= 97) All grades n (%)	 Grade ≥3 n (%)
Patients with at least one AE	96 (99)	79 (81)
Cytokine release syndrome	48 (50)	1 (1)
Neutropenia	**42 (43)**	**42 (43)**
Anemia	**26 (27)**	**18 (19)**
Diarrhea	25 (26)	3 (3)
Headache	23 (24)	1 (1)
White blood cell count decreased	22 (23)	17 (18)
Nausea	18 (19)	2 (2)
Pyrexia	18 (19)	2 (2)
Thrombocytopenia	18 (19)	11 (11)
Fatigue	17 (18)	3 (3)
Hypogammaglobulinemia	17 (18)	1 (1)
Neutrophil count decreased	17 (18)	17 (18)
Constipation	16 (17)	0

18 patients have died during the study:

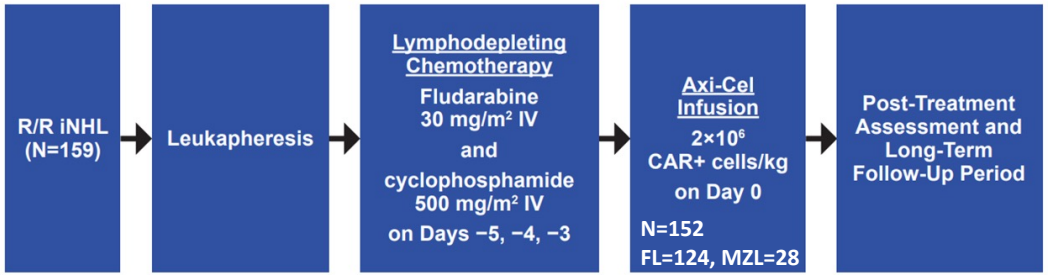
PD n=8

AE n=9 (3 infections, 3 sec neoplasms, 3 other)

Euthanasia n=1

Schuster SJ et al, ASH meeting 2023 Oral Abstract #601

Axicabtagene Ciloleucel in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma: 4-Year Follow-Up From the Phase 2 ZUMA-5 Trial



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 (centrally assessed per Lugano[5])

Key Secondary Endpoints
- CR rate
- DOR, PFS, OS
- AEs
- CAR T-cell and cytokine levels

Median follow-up ≥48 months after infusion

Efficacy outcomes were investigator assessed in all 159 enrolled patients

Safety data were reported for the 152 patients treated with axi-cel

	All PTS
Median Age	61 (53-68)
Stage III-IV	86%
High tumor burden	50%
Median N° prior therapies	3 (2-4)
Prior anti CD20 and alkylating agent	99%
POD24 from anti CD20 + alkylating agent	55%

From Jacobson CA et al, Lancet Oncol 2022

ORR: 92%, CRR 74%

Original publication: Jacobson CA et al, Lancet Oncol 2022

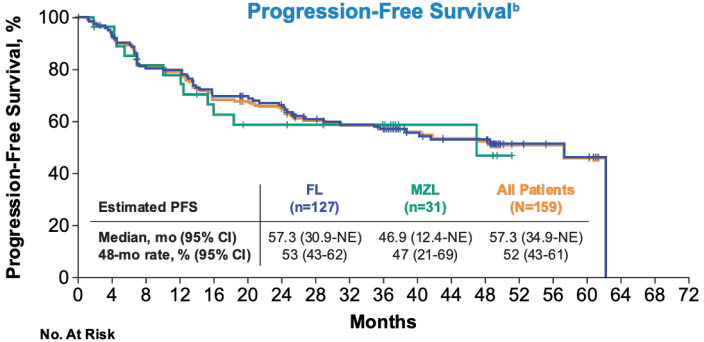
3-y FUP publication: Neelapu SS et al, Blood 2024

Neelapu SS et al, ASH meeting 2023 Poster Abstract #4868

Outcome

- Median follow-up from leukapheresis was 52.5 months (in FL and MZL 53.7 months and 43.8 months respectively)
- The ORR in all patients remained consistent with prior reports (90%), with a 75% complete response (CR) rate

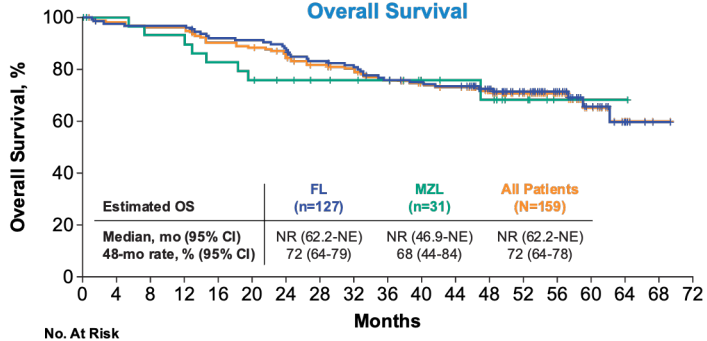
Progression-Free Survival[b]



No. At Risk

FL	127	115	98	96	84	80	75	64	61	57	42	38	38	12	10	9	0
MZL	31	26	22	21	16	14	14	13	12	11	5	5	4	0			
All patients	159	141	120	117	100	94	89	77	73	68	47	43	42	12	10	9	0

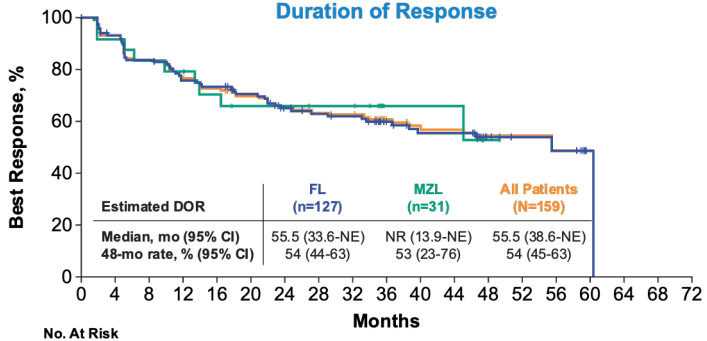
Overall Survival



No. At Risk

FL	127	123	122	122	115	114	110	103	99	92	90	88	69	51	34	17	8	1	0
MZL	31	29	27	27	24	22	20	18	17	16	11	10	9	5	1	1	1	0	
All patients	159	152	149	149	139	136	130	121	116	108	101	98	78	56	35	18	9	1	0

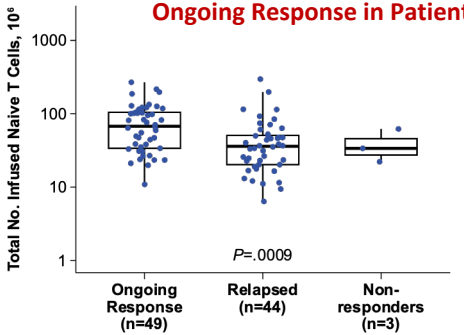
Duration of Response



No. At Risk

FL	119	108	97	87	84	77	65	61	59	44	38	38	13	10	9	1	0
MZL	24	22	20	19	16	14	13	12	12	5	5	5	1	0			
All patients	143	130	117	106	100	91	78	73	71	49	43	43	14	10	9	1	0

Number and Percent Naive T Cells in CAR Product by Ongoing Response in Patients With FL



	Ongoing Response (n=49)	Relapsed (n=44)	Non-responders (n=3)
Median no. cells, 10^6	67.6	36.0	33.8

Patients with FL and ongoing response at 48 months had a higher proportion of naive (CCR7+CD45RA+) T cells in axi-cel product

Neelapu SS et al, ASH meeting 2023 Poster Abstract #4868

Deaths After Axi-Cel Infusion by Year

n (%)	All Patients N=152	Year 1	Year 2	Year 3	Year 4	Year >4
Patients who died	**45 (30)**	**10 (7)**	**15 (10)**	**11 (7)**	**6 (4)**	**3 (2)**
Primary cause of death						
Progressive disease	14 (9)	5 (3)	5 (3)	2 (1)	1 (1)	1 (1)
Adverse event	8 (5)	3 (2)	3 (2)	1 (1)	1 (1)	0
New malignancy	6 (4)	1 (1)	2 (1)	1 (1)	2 (1)	0
Other	17 (11)	1 (1)	5 (3)	7 (5)	2 (1)	2 (1)

- After the 3-year data cutoff date, 1 patient with FL had a serious event of Grade 3 myelodysplastic syndrome, considered related to axi-cel per investigator[4]
- In total, 30% of treated patients with iNHL have died as of the data cutoff date
- Deaths occurring after the 3-year data cutoff date included
  - Progressive disease in 2 patients with FL (progressive disease reported on Days 479 and 610 post-leukapheresis)
  - New malignancy in 1 patient with MZL (acute myeloid leukemia)
  - Other in 4 patients with FL (2 cardiac events, 1 acute respiratory distress syndrome/methicillin-resistant *Staphylococcus aureus*, 1 unknown)

Neelapu SS et al, ASH meeting 2023 Poster Abstract #4868

Real-Word Experience of CAR T-Cells in Patients with Relapsed/Refractory Follicular Lymphoma: A Descart Registry Analysis from the Lysa

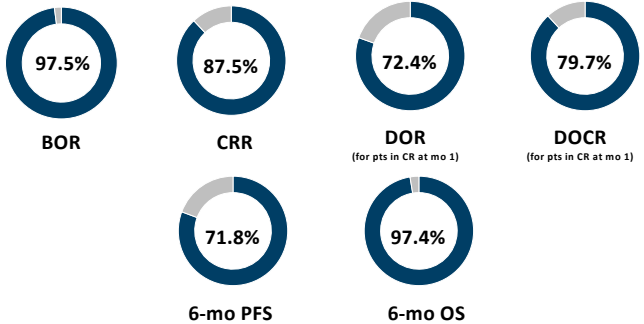
- Multicenter DESCAR-T registry reporting real-world outcomes in pts with r/r FL who received ≥2L for tisa-cel (n=62) and ≥3L for axi-cel (n=8) as a part of the French early access program label between Dec 2021 and Jan 2023 (N=70 with ≥1 mo FU; data cutoff: March, 2023)

Baseline Characteristics

Pts infused:	87
Median age, years	62
Median prior LOTs, n (range)	3 (2-9)
Prior auto-SCT, %	44.3
FLIPI Score 3-5, %	49.5
Bulky disease (>5cm), %	22
LDH > N, %	52.2%
POD24 post 1st frontline IC, %	62.8
Bridging therapy, %	58.6
Median time from order or leukapheresis to infusion, days	48 / 41

Efficacy

❖ mFU: 7.3 mo (from product order), and 5.4 mo (from CAR infusion)



- 21.4% of pts progressed (median time from infusion to first relapse: 3 mo
- One patient died from lymphoma progression

Safety

CRS

Any grade:	74.3%
Grade ≥3:	1.4%
Grade 5:	None

ICANS

Any grade:	27.1%
Grade ≥ 3:	4.3%
Grade 5:	None

- Persisting grade 3-4 hematologic toxicities at 1 mo and 3 mo were: neutropenia (50% and 12.3%), thrombocytopenia (18.6% and 0%), and anemia (8.6% and 0%)

- **DESCAR-T registry data confirms the promising response rates and safety of CAR-T therapy in patients with r/r FL after ≥2 lines of therapy**
  - **Longer follow-up is necessary to evaluate the long-term disease control**

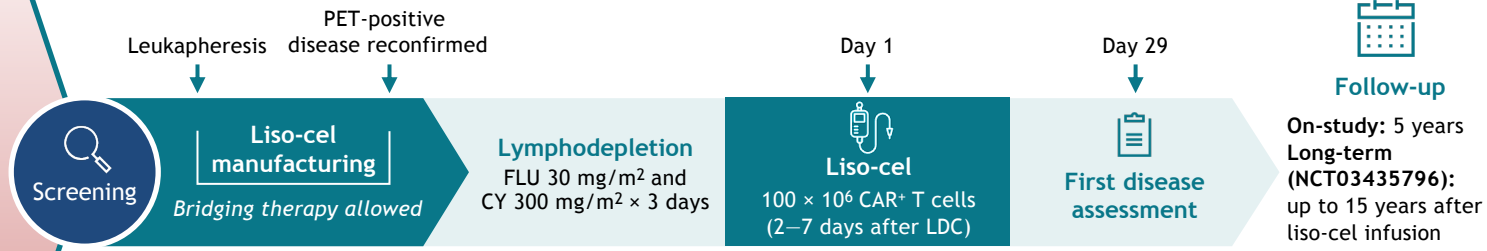
BOR, best overall response rate; CAR, chimeric antigen receptor; CR, complete response; CRR, complete response rate; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; FL, follicular lymphoma; LDH, lactate dehydrogenase; mo, month; OS, overall survival; PFS, progression-free survival; pts, patients; r/r, relapsed/refractory.

Ysebaert L …. Bachy E, ASH meeting 2023 Oral Abstract #296

TRANSCEND FL: phase 2, open-label, multicenter, multicohort study

Key FL eligibility criteria

- Age ≥ 18 years
- R/R FL
  - 4L+ cohort
  - 3L cohort
  - 2L cohort (POD24 and/or mGELF)[a]
- FL histologically confirmed ≤ 6 months before screening with PET-positive and measurable disease
- Received combination of anti-CD20 antibody and alkylator
- ECOG PS ≤ 1
- Adequate organ function



Primary endpoint (efficacy set)

- ORR (BOR of CR or PR) per IRC by PET/CT per Lugano 2014 criteria[1]

Secondary endpoints

- CR rate, DOR, DOR if BOR is CR, and PFS per IRC by PET/CT per Lugano 2014,[1] and OS
- Safety, cellular kinetics, HRQOL; B-cell aplasia (exploratory)

- Study endpoints of ORR and CR rate were tested hierarchically with null hypotheses in the following order at 1-sided $\alpha = 0.025$ significance:
  - Sequence 1: 3L+ FL (ORR ≤ 60%), 4L+ FL (ORR ≤ 50%), 3L+ FL (CR rate ≤ 30%), and 4L+ FL (CR rate ≤ 20%); sequence 2: 2L FL (ORR ≤ 50%) and 2L FL (CR rate ≤ 19%)

ClinicalTrials.gov identifier: NCT04245839.

[a]POD24 was defined as progression within 24 months of diagnosis after treatment with an anti-CD20 antibody and an alkylating agent within the first 6 months of initial FL diagnosis. Patients who did not meet criteria of POD24 had to meet at least 1 criterion of the mGELF criteria (symptoms attributable to FL; threatened end-organ function, or cytopenia secondary to lymphoma or bulky disease [single mass > 7 cm, or 3 or more masses > 3 cm]; splenomegaly; or steady progression over at least 6 months).

Patient demographics and baseline characteristics

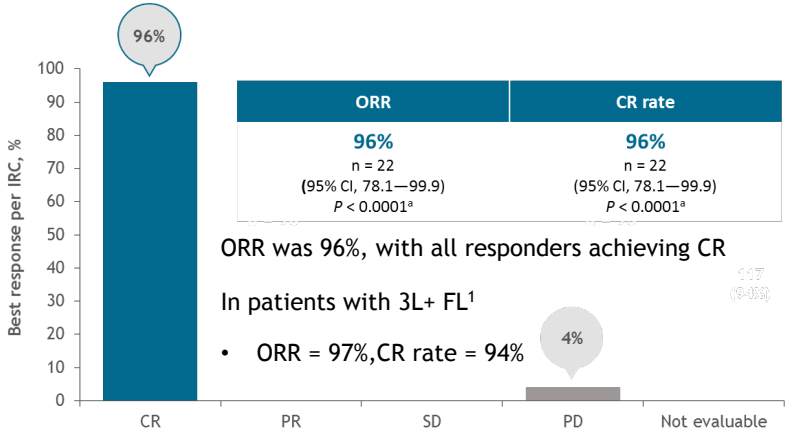
	2L FL (n = 23)	3L+ FL (n = 107)
Median (range) age, y	53 (34–69)	62 (23–80)
Male, n (%)	17 (74)	66 (62)
FL grade 1 or 2 / 3a at screening,[a] n (%)	17 (74) / 6 (26)	81 (76) / 25 (23)
Ann Arbor stage at screening, n (%)		
Stage I/II	6 (26)	12 (11)
Stage III/IV	17 (74)	95 (89)
FL International Prognostic Index at screening, n (%)		
Low risk (0–1) / intermediate risk (2)	11 (48) / 4 (17)	12 (11) / 34 (32)
High risk (3–5)	8 (35)	61 (57)
LDH > ULN before lymphodepletion, n (%)	6 (26)	47 (44)
Met mGELF criteria at most recent relapse, n (%)	16 (70)	57 (53)
Symptoms attributable to FL	6 (26)	13 (12)
Threatened end-organ function/cytopenia secondary to lymphoma/bulky disease	7 (30)	24 (22)
Splenomegaly	0	4 (4)
Steady progression over at least 6 months	3 (13)	16 (15)
Median (range) prior lines of systemic therapy	1 (1–1)	3 (2–10)
Prior HSCT, n (%)	0	33 (31)
Received prior rituximab and lenalidomide, n (%)	0	23 (21)
Refractory to last systemic therapy,[b] n (%)	15 (65)	72 (67)
Double refractory (anti-CD20 and alkylator),[c] n (%)	11 (48)	69 (64)
POD24 from initial immunochemotherapy, n (%)	15 (65)	58 (54)
POD24 from diagnosis, n (%)	12 (52)	46 (43)
Received bridging therapy, n (%)	5 (22)	44 (41)

2L, second line; 3L+, third line or later; FL, follicular lymphoma; HSCT, hematopoietic stem cell transplantation; LDH, lactate dehydrogenase; mGELF, modified Groupe d'Etude des Lymphomes Folliculaires; POD24, progression of disease within 24 months; ULN, upper limit of normal.

Morschhauser F et al, ASH meeting 2023 Oral Abstract #602

Outcome & Safety

2L FL efficacy set (n = 23)

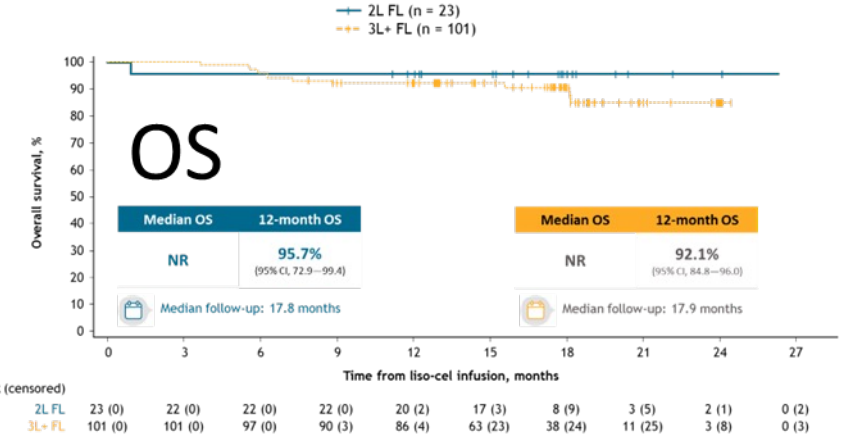


ORR	CR rate
96% n = 22 (95% CI, 78.1—99.9) *P* < 0.0001[a]	96% n = 22 (95% CI, 78.1—99.9) *P* < 0.0001[a]

ORR was 96%, with all responders achieving CR

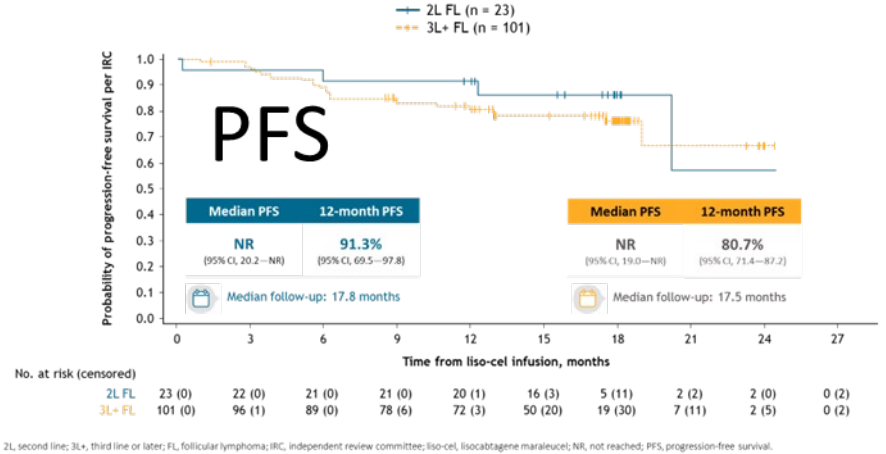
In patients with 3L+ FL[1]

- ORR = 97%,CR rate = 94%



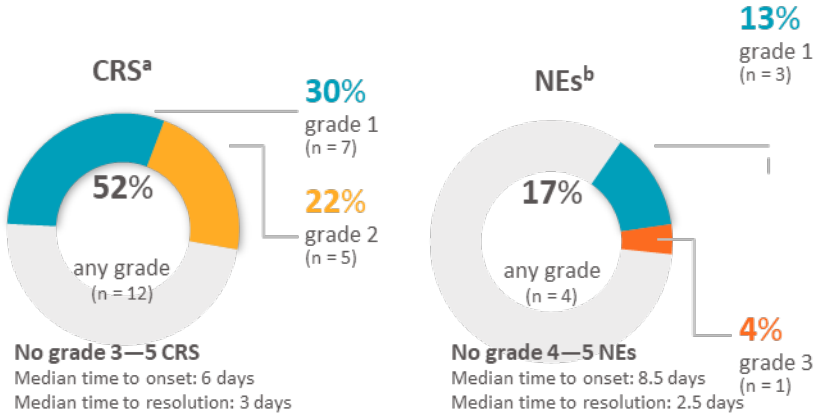
[a]A total of 90% of patients in the efficacy set were censored from the OS analysis at data cutoff.

2L, second line; 3L+, third line or later; FL, follicular lymphoma; liso-cel, lisocabtagene maraleucel; NR, not reached; OS, overall survival.



2L, second line; 3L+, third line or later; FL, follicular lymphoma; IRC, independent review committee; liso-cel, lisocabtagene maraleucel; NR, not reached; PFS, progression-free survival.

2L FL (n = 23)



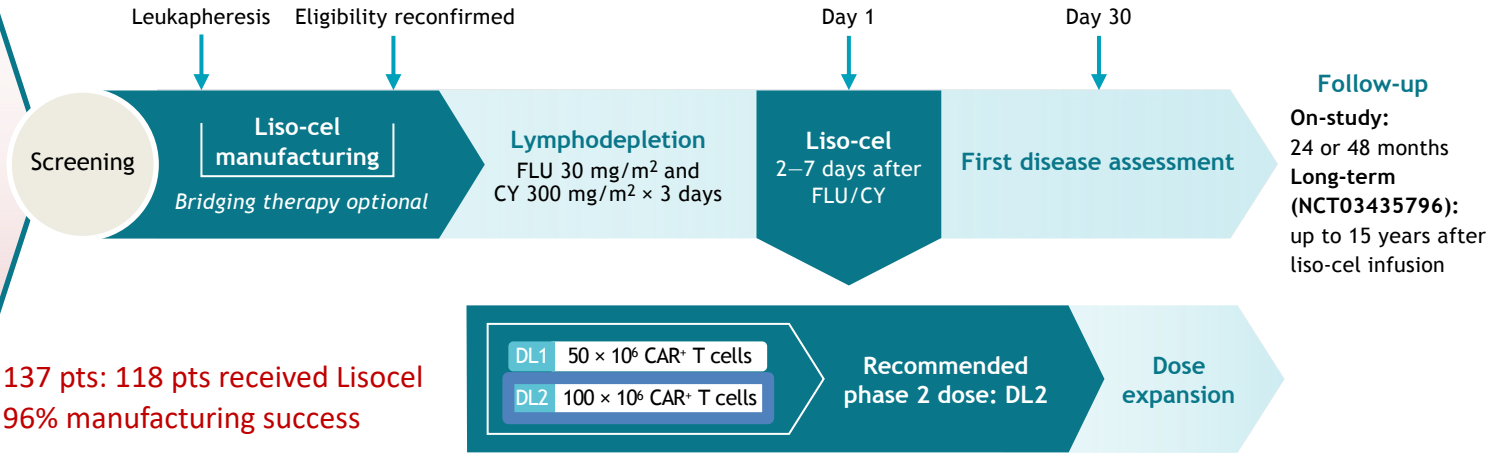
Morschhauser F et al, ASH meeting 2023 Oral Abstract #602

Lisocabtagene maraleucel in relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma: 24-month median follow-up of TRANSCEND CLL 004

Key eligibility criteria

- Age ≥ 18 years
- R/R CLL/SLL
- Previously failed or ineligible for BTKi
- Failure of ≥ 2 (high risk) or ≥ 3 (standard risk) lines of prior therapy
- ECOG PS ≤ 1
- Adequate bone marrow, organ, and cardiac function
- No Richter transformation nor active CNS involvement by malignancy

TRANSCEND CLL 004: phase 1/2, open-label, multicenter study



137 pts: 118 pts received Lisocel
96% manufacturing success

Primary endpoint (PEAS at DL2)
CR/CRi rate per iwCLL 2018 by IRC assessment

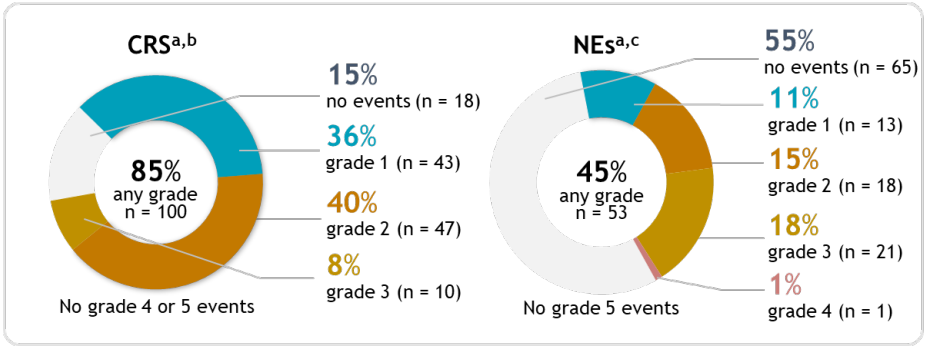
Key secondary endpoints (PEAS at DL2)
ORR, uMRD rate in blood

Post hoc analyses
Median time to next treatment

Siddiqi T et al, ASH meeting 2023 Oral Abstract #330

First data published in: Siddiqi T et al, Blood 2022
Siddiqi et al, Lancet 2023

Safety: full study population (n = 118)



Other AESIs, n (%)

- Prolonged cytopenias[d]: 64 (54%)
- Grade ≥ 3 infections[e]: 21 (18%)
- Hypogammaglobulinemia: 18 (15%)

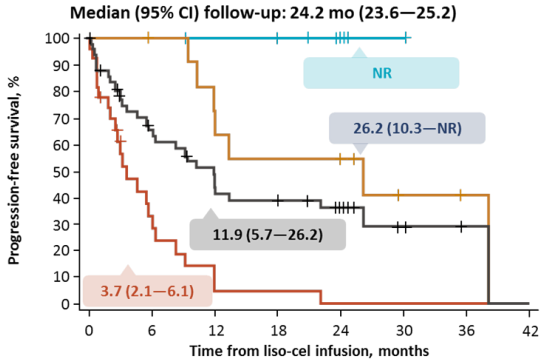
Deaths due to TEAEs, n = 5 (4%)

- 1 (1%) considered related to liso-cel by investigators (MAS)

Efficacy: DL2 (n = 88)

	Full study population at DL2 (n = 88)	BTKi progression/venetoclax failure subset at DL2 (n = 50)
Primary endpoint: IRC-assessed CR/CRi rate per iwCLL 2018, n (%) [95% CI]	17 (19) [12—29]	10 (20) [10—34]
Key secondary endpoints		
IRC-assessed ORR, n (%) [95% CI]	42 (48) [37—59]	22 (44) [30—59]
uMRD rate in blood, n (%) [95% CI]	58 (66) [55—76]	32 (64) [49—77]
Exploratory endpoint: uMRD rate in marrow, n (%) [95% CI]	53 (60) [49—71]	30 (60) [45—74]

BTKi progression/venetoclax failure subset at DL2 (n = 50)



No. at risk								
CR/CRi	10	10	9	9	5	1	0	0
PR/nPR	12	11	8	6	5	2	1	0
Nonresponder	28	7	2	1	0	0	0	0
Total	50	28	19	16	10	3	1	0

Siddiqi T et al, ASH meeting 2023 Oral Abstract #330

Phase 1 CAR-T in iNHL

Efficacy and Safety of a Third Generation CD20 CAR-T (MB-106) for Treatment of Relapsed/Refractory Indolent B-cell Non-Hodgkin Lymphoma: Phase-1 Results from a Multicenter Trial

Baseline Patient Characteristics

Number of patients enrolled	9*
Age, median (range)	56 (39-79)
Sex, male (%)	7 (78%)
Histology • Follicular lymphoma (FL) • Waldenström macroglobulinemia (WM) • Hairy cell leukemia – variant (HCL-v)	 5 3 1
Prior lines of therapy, median (range)	4 (1-9)

Safety *[Combined results for DL1 (N=4) and DL2 (N=5)]*

CRS & ICANS

	Grade 1	Grade 2	Grade 3	Grade 4
CRS	5 (56%)	0	0	0
ICANS	0	0	0	0

Grade ≥3 Adverse Events (First 28 Days), Regardless of Causality

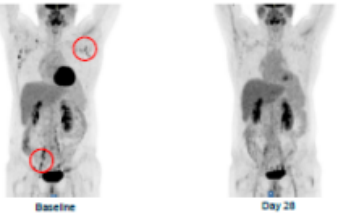
	Grade 3	Grade 4
Neutrophil count decreased	1	5
Febrile Neutropenia	0	0
Anemia	1	0
Appendicitis	1	0
Worsening Pain (Extremity Knees)	1	0
Blood bilirubin increased*	0	1

Complete Response in Follicular Lymphoma Patient with Prior CD19 CAR-T (Liso-cel) - Representative PET-CT

Best Response:
CR (Day 28) by PET-CT & bone marrow

Patient's first CR despite 6 prior therapies

Safety:
CRS: None
ICANS: None



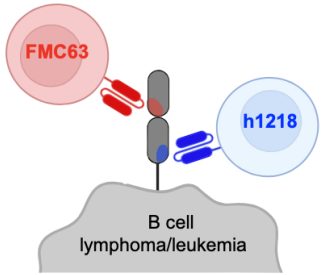
Shadman M et al, ASH meeting 2023 Poster Abstract #2102

A First-in-Human Phase I Study of AT101, a Novel Anti-CD19 Chimeric Antigen Receptor T Cell Product Targeting a Membrane-Proximal Domain of CD19 in Adults with Relapsed or Refractory B Cell Non-Hodgkin Lymphoma

Hypothesis:

anti-CD19 scFv that engages an alternative CD19 membrane-proximal epitope independent of FMC63 with low avidity could:

1. ***mitigate CD19 epitope loss;***
2. ***enhance CART functions***

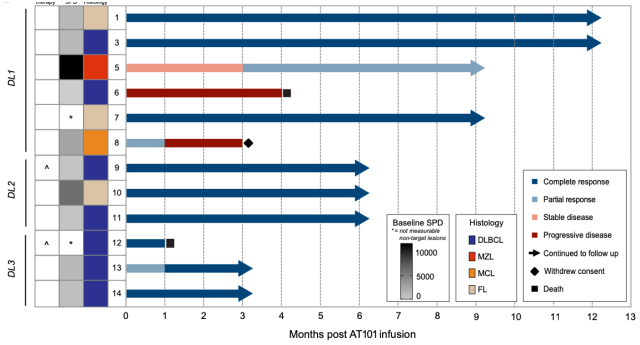


- Overcome epitope loss: mutation and epitope masking
- Enhance CAR-T function due to low avidity and reduced activation-induced cell death

CR in 8/12 pts (66.6%)
ORR in 83.3% at day 28

In DL2 and DL3: CR rate was 100.0%.

Of the 8 pts in CR none has relapsed (median follow-up 6.0 months).



Zhang Y et al, ASH meeting 2023 Poster Abstract #2096

CONCLUSIONS

CAR-T cell therapy is changing the natural history of FL (and potentially of MZL), reshaping treatment algorithms

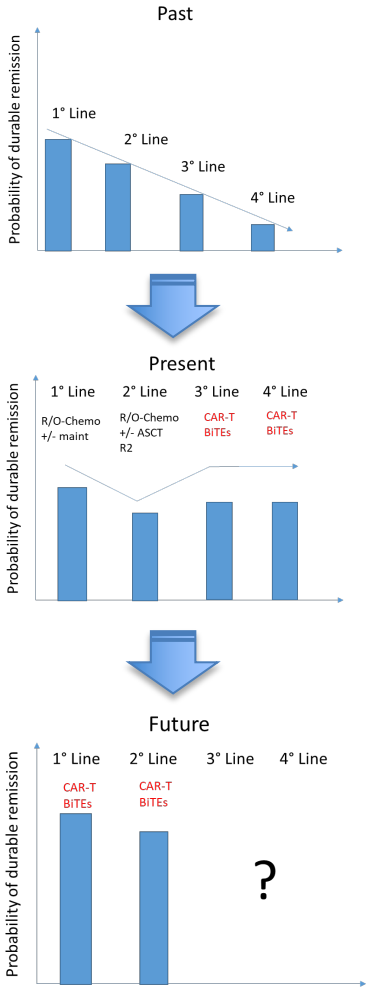
High rates of durable complete remission confirmed with Tisacel and Axicel in heavily pretreated FL patients, (efficacy confirmed in real world studies)

Reliable biomarkers are emerging to monitor and predict CAR-T cell activity and expansion in FL and MZL (es. Naive T-cells at baseline and in CAR products)

Second-line Lisocel activity in high-risk FL is very promising
(longer follow-up and perhaps larger sample size to determine long term and differential efficacy in POD24)

CAR-T cell therapy (Lisocel) in double refractory r/r CLL/SLL determines CR in a sizeable fraction of patients.
Possibly increased CRS and NE incidence (similar to other CAR-T CLL studies).

As novel immunotherapies (CAR-T and BiTEs) move to earlier lines, predictive biomarkers are urgently needed to define target populations, which is crucial for the sustainability of these treatments



GRAZIE PER L’ATTENZIONE