Follicular Lymphomas Workshop

Bologna
Royal Hotel Carlton
May 7, 2024

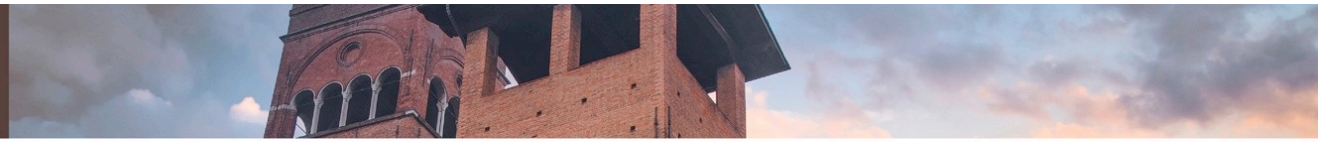
President: *Pier Luigi Zinzani*

Lisocabtagene Maraleucel in Follicular Lymphoma

M. Lia Palomba, MD

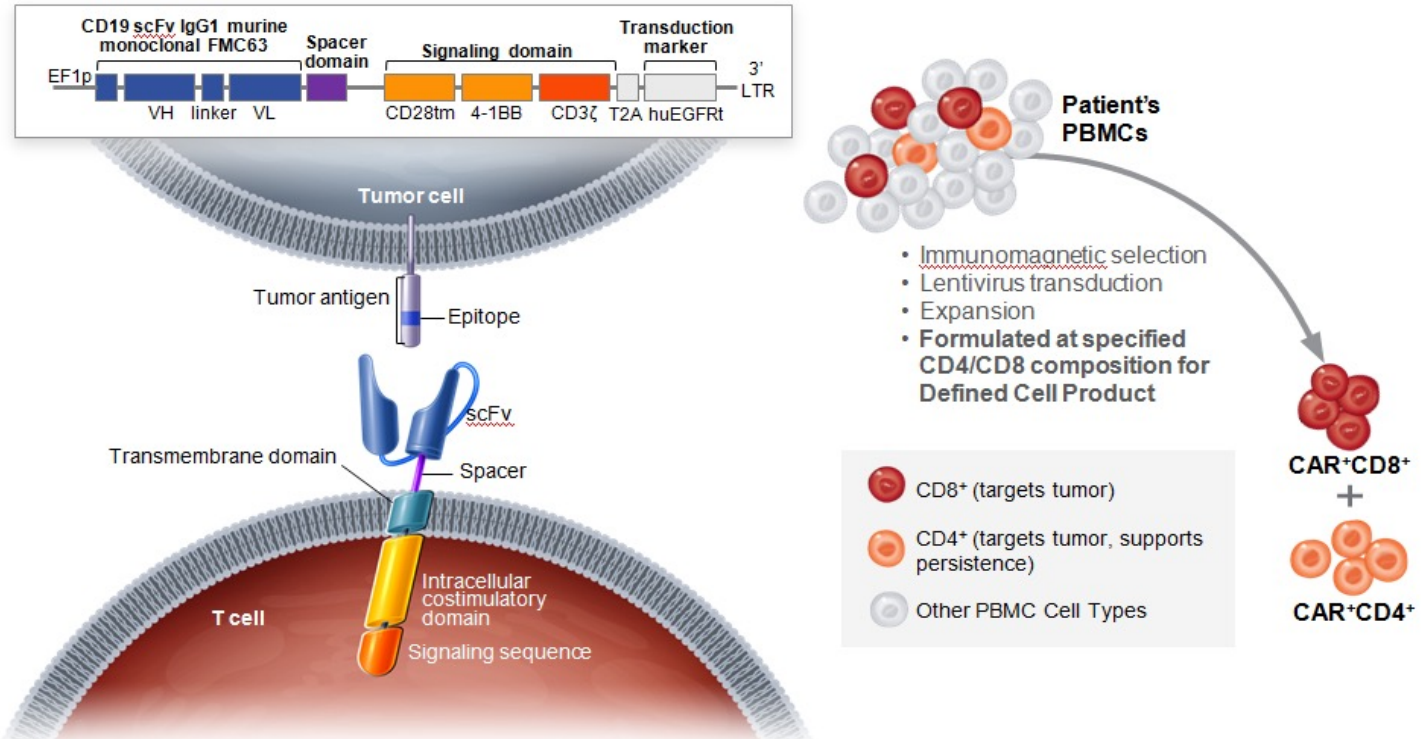
Lymphoma Service and Cellular Therapy Service

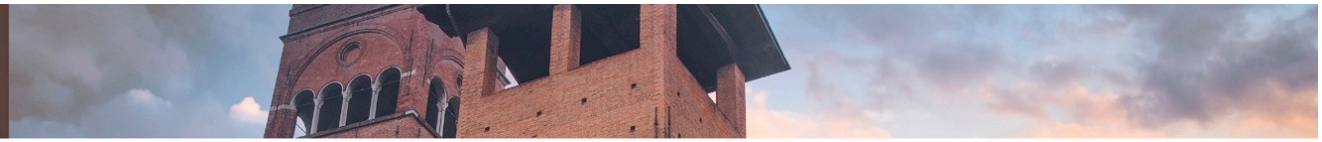
MSKCC, NY



Disclosures of M. Lia Palomba

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Synthekine						X	
Brystol Meyer Squibb						X	
Novartis						X	
Cellectar						X	

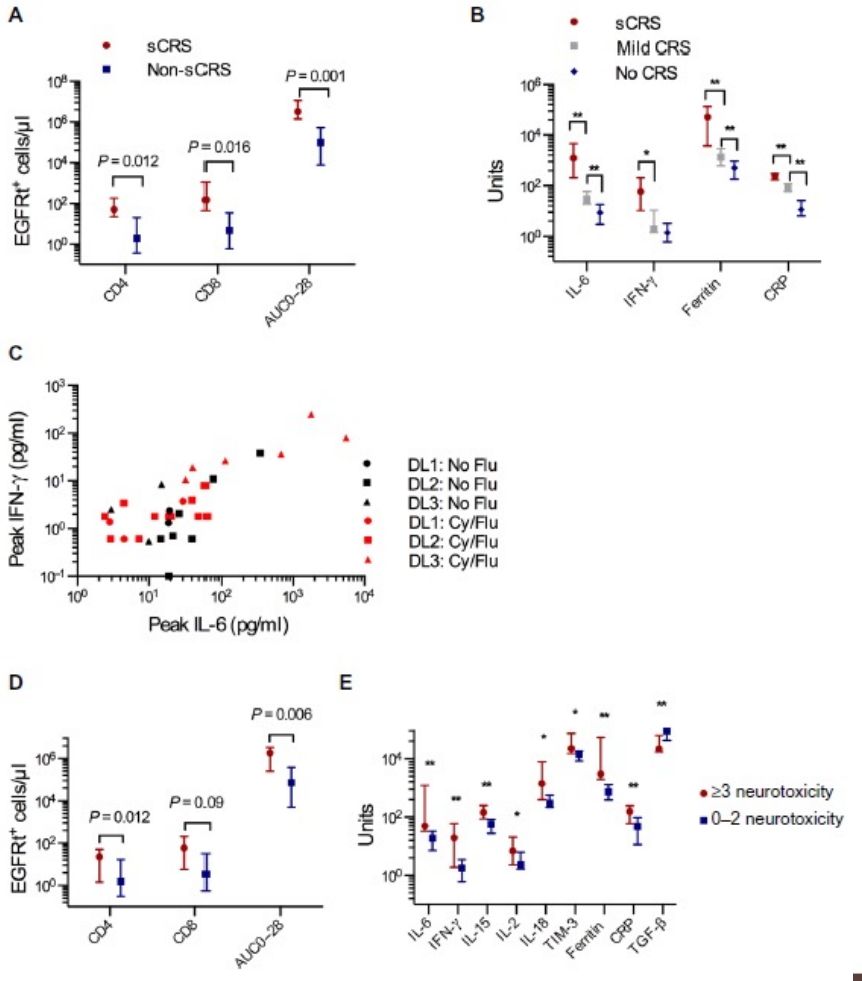

CD19 scFv IgG1 murine monoclonal FMC63
Spacer domain
Signaling domain
Transduction marker
EF1p
VH
linker
VL
CD28tm
4-1BB
CD3ζ
T2A
huEGFRt
3' LTR
Tumor cell
Tumor antigen
Epitope
scFv
Transmembrane domain
Spacer
T cell
Intracellular costimulatory domain
Signaling sequence
Patient's PBMCs
Immunomagnetic selection
Lentivirus transduction
Expansion
Formulated at specified CD4/CD8 composition for Defined Cell Product
CD8+ (targets tumor)
CD4+ (targets tumor, supports persistence)
Other PBMC Cell Types
CAR+CD8+
+
CAR+CD4+



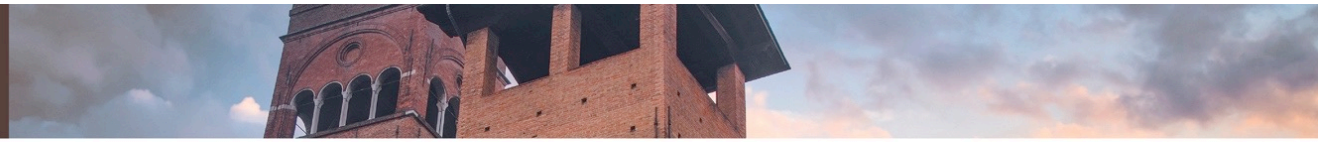
Immunotherapy of non-Hodgkin's lymphoma with a defined ratio of CD8$^+$ and CD4$^+$ CD19-specific chimeric antigen receptor–modified T cells

Cameron J. Turtle,[1,2*] Laïla-Aïcha Hanafi,[1] Carolina Berger,[1,2] Michael Hudecek,[1†] Barbara Pender,[1] Emily Robinson,[1] Reed Hawkins,[1] Colette Chaney,[1] Sindhu Cherian,[3] Xueyan Chen,[3] Lorinda Soma,[3] Brent Wood,[3] Daniel Li,[4] Shelly Heimfeld,[1] Stanley R. Riddell,[1,2‡] David G. Maloney[1,2‡]

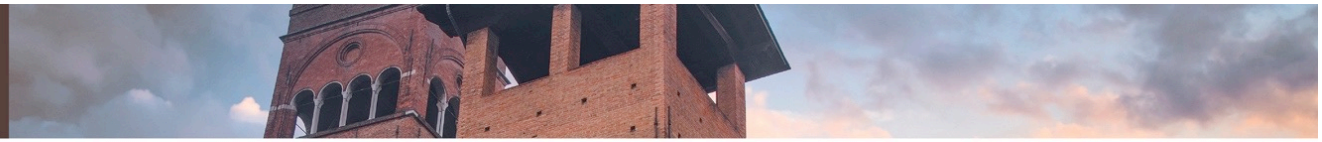
Hypothesized that a 1:1 CD4+/CD8+ ratio would provide a more uniform CAR-T cell product, result in reproducible in vivo activity, and facilitate identification of factors that correlate with efficacy and toxicity



Turtle at Al. Sci Trans Med, 2016



Feature	Tisagenlecleucel	Axicabtagene ciloleucel	Lisocabtagene maraleucel
Construct	FMC-63 murine scFv 41BB costim domain	FMC-63 murine scFv CD28 costim domain	FMC-63 murine scFv 41BB costim domain
Viral transfer	Lentiviral	Gamma retroviral	Lentiviral
Collection	Resting state apheresis, **Cryopreserved** Bulk cells	Resting state apheresis, Fresh only Bulk cells	Resting state apheresis, Fresh only, Selection CD4 and CD8
Manufacture	CD3/CD28 stim	CD3/CD28 stim	**CD4, CD8 selection** CD3/CD28 stimulation
Dose administered	0.6-6.0 x 10^8 CAR-T cells	2 x 10^6/kg Max 200 x 10^6	100 x 10^6 (CD4/CD8) in separate vials (1:1)



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

Screening

Leukapheresis

PET-positive disease reconfirmed

Liso-cel manufacturing

Bridging therapy allowed

Lymphodepletion

FLU 30 mg/m^2 and CY 300 mg/m^2 × 3 days

Day 1

Liso-cel

100 × 10^6 CAR$^+$ T cells (2–7 days after LDC)

Day 29

First disease assessment

Follow-up

On-study: 5 years

Long-term (NCT03435796): up to 15 years after liso-cel infusion

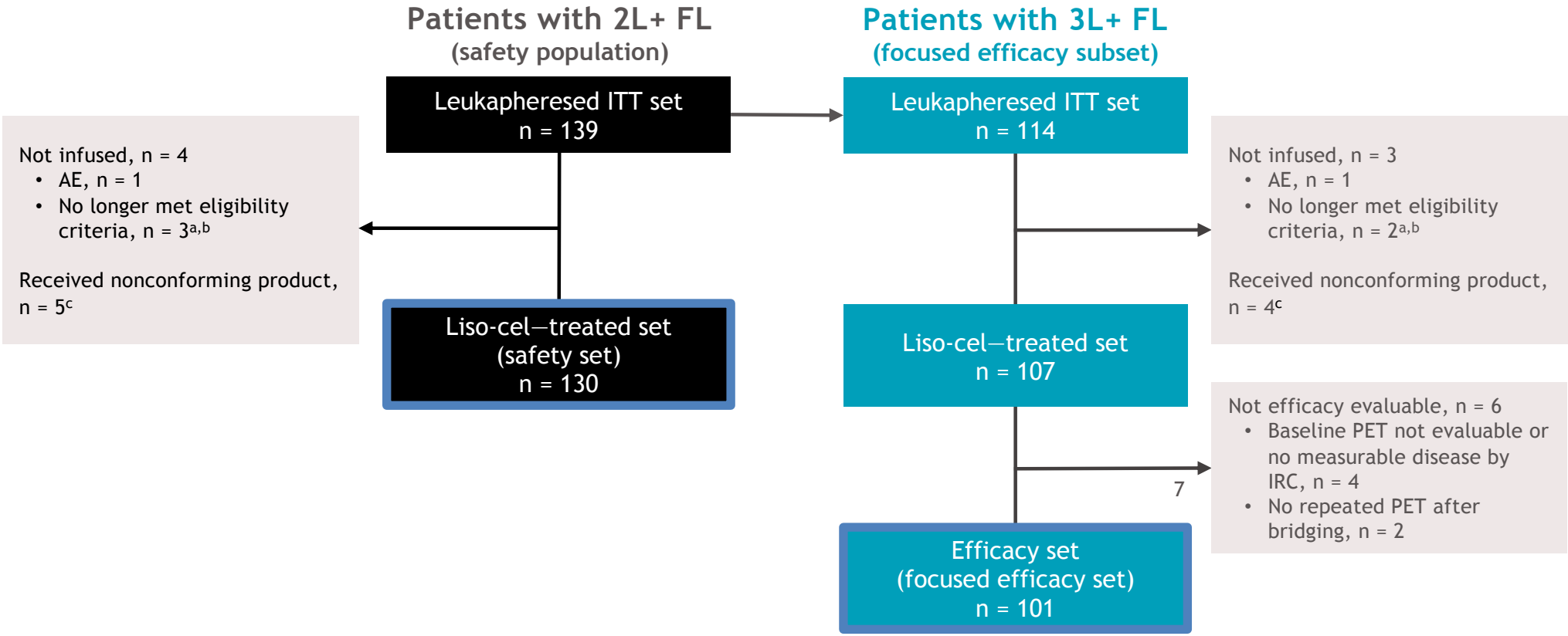
Primary endpoint (efficacy set)

- 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 α = 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%)



[a]History of transformed FL (n = 1); [b]PET-negative at pretreatment assessment (2L+, n = 2; 3L+, n = 1); [c]Nonconforming product was defined as any product wherein one of the CD8 or CD4 cell components did not meet one of the requirements to be considered liso-cel but was considered appropriate for infusion. ITT, intention to treat.

Morschhauser F, et al. ICML 2023 [Abstract #LBA4]

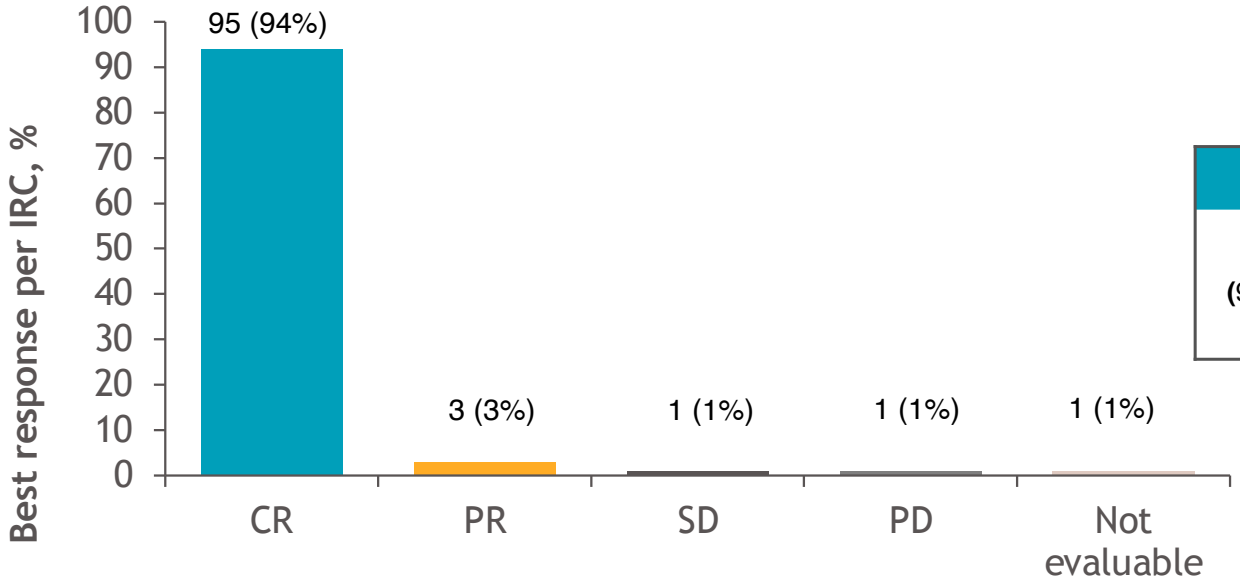
Patients Demographics

Patient demographics and baseline characteristics	Liso-cel—treated set[a]	
	2L+ FL (n = 130)	3L+ FL (n = 107)
Median (range) age, y	60 (23—80)	62 (23—80)
Male, n (%)	83 (64)	66 (62)
FL subtype/grade at screening, n(%)		
Grade 1/2	15 (12) / 83 (64)	9 (8) / 72 (67)
Grade 3A	31 (24)	25 (23)
Unknown	1 (1)	1 (1)
Ann Arbor stage at screening, n (%)		
Stage I/II	2 (2) / 16 (12)	1 (1) / 11 (10)
Stage III/IV	45 (35) / 67 (52)	39 (36) / 56 (52)
FL International Prognostic Index at screening, n (%)		
Low risk (0—1)	23 (18)	12 (11)
Intermediate risk (2)	38 (29)	34 (32)
High risk (3—5)	69 (53)	61 (57)
Lactate dehydrogenase > ULN, n (%)	53 (41)	47 (44)
Met modified GELF criteria at most recent relapse, n (%)	73 (56)	57 (53)
Prior lines of systemic therapy, median (range)	2 (1—10)	3 (2—10)
Prior HSCT,[b] n (%)	33 (25)	33 (31)
Received prior rituximab and lenalidomide, n (%)	23 (18)	23 (21)
Refractory to last systemic therapy,[c] n (%)	86 (66)	72 (67)
Double refractory (anti-CD20 and alkylator), n (%)	80 (62)	69 (64)
POD24,[d] n (%)	73 (56)	58 (54)
Received bridging therapy, n (%)	49 (38)	44 (41)

Morschhauser F, et al. ICML 2023 [Abstract #LBA4]

Primary endpoint: ORR per IRC by best overall response

3L+ FL efficacy set (n = 101)

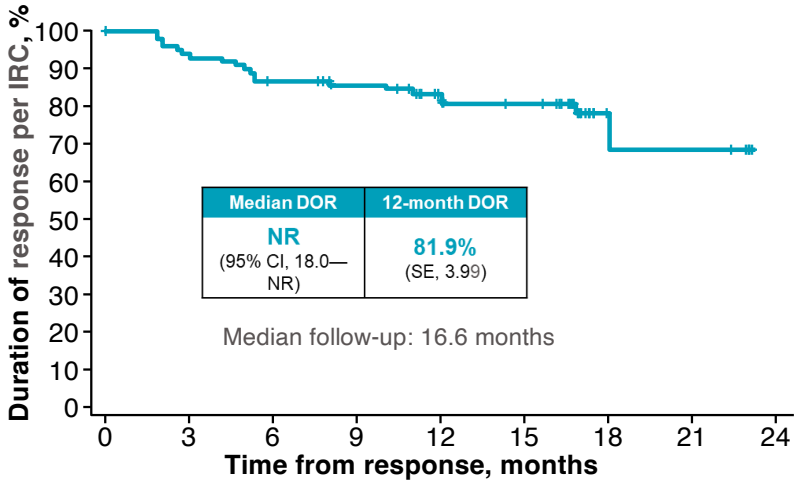


ORR	CR rate
97% (95% CI, 91.6—99.4) $P < 0.0001$[a]	**94%** (95% CI, 87.5—97.8) $P < 0.0001$[a]

- **Primary and key secondary endpoints were met**; all null hypotheses were rejected
- ORR was 97%, with all responders achieving CR except 3
- ORR was consistently high across subgroups

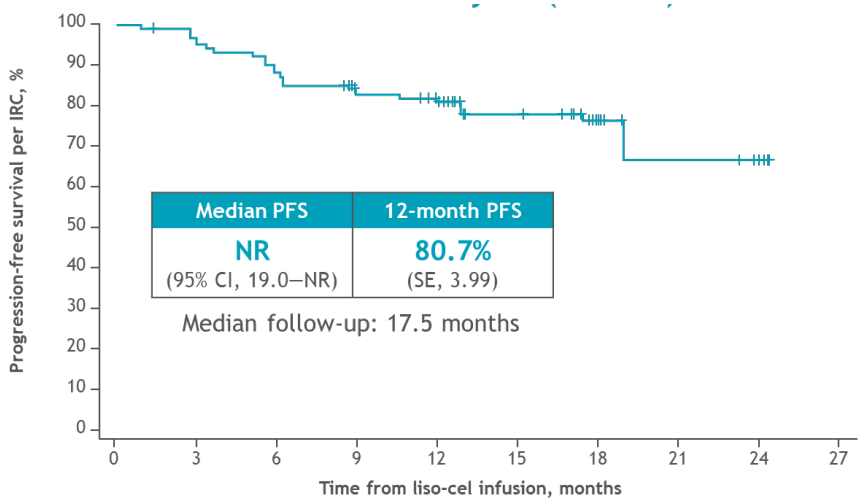
[a]One-sided *P* value (H_0 of ORR ≤ 60%; H_0 of CR rate ≤ 30%).
H_0, null hypothesis; SD, stable disease.

3L+ FL efficacy set (n = 101)



No. at risk (censored)

3L+ FL	98 (0)	91 (1)	83 (1)	77 (5)	62 (12)	49 (12)	8 (40)	7 (0)	0 (7)

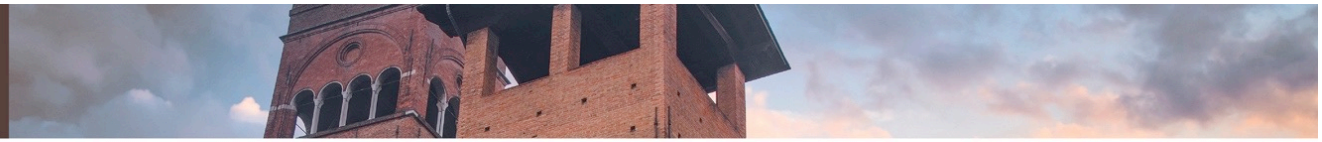


No. at risk (censored)

3L+ FL	101 (0)	96 (1)	89 (0)	78 (6)	72 (3)	50 (20)	19 (30)	7 (11)	2 (5)	0 (2)

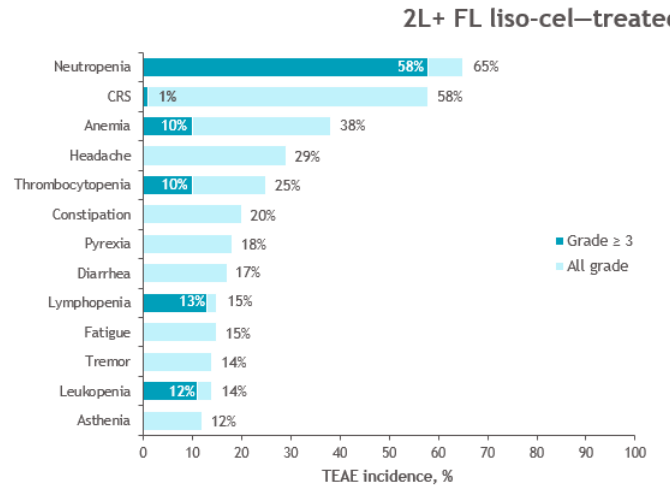
NR, not reached; SE, standard error.

Morschhauser F, et al. ICML 2023 [Abstract #LBA4]



TRA

Most common TEAEs[a] (≥ 10%) in patients with 2L+ FL

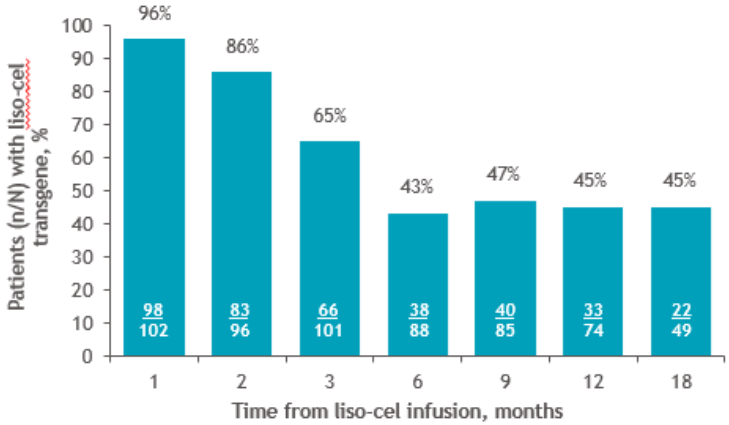


- Most common grade ≥ 3 TEAEs were cytopenias
  - Febrile neutropenia, n = 8 (6%)
- Serious TEAEs were reported in 25% of patients

[a]TEAE period was defined as the time from initiation of liso-cel administration through and including study Day 90.
CRS, cytokine release syndrome; TEAE, treatment-emergent adverse event.

Morschhauser F, et al. ICML 2023 [Abstract #LBA4]

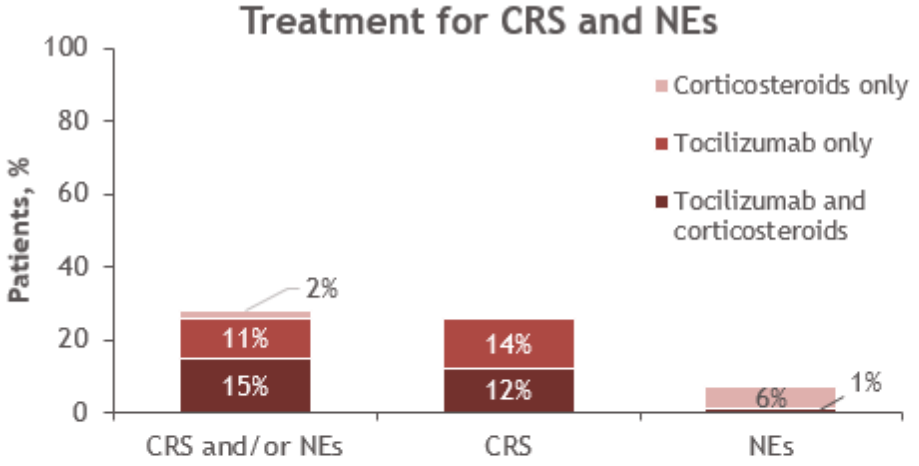
Persistence of liso-cel transgene[c]



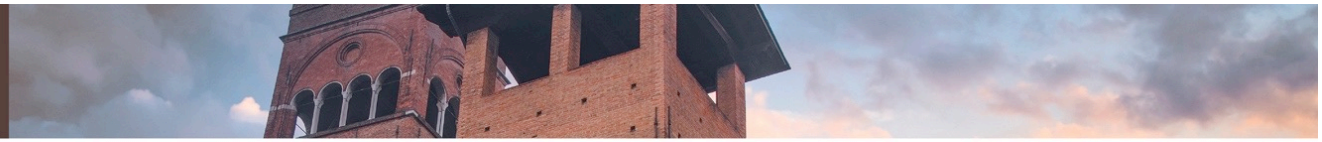
- Persistence of liso-cel was observed up to 18 months after infusion (22 of 49 evaluable patients), with follow-up ongoing

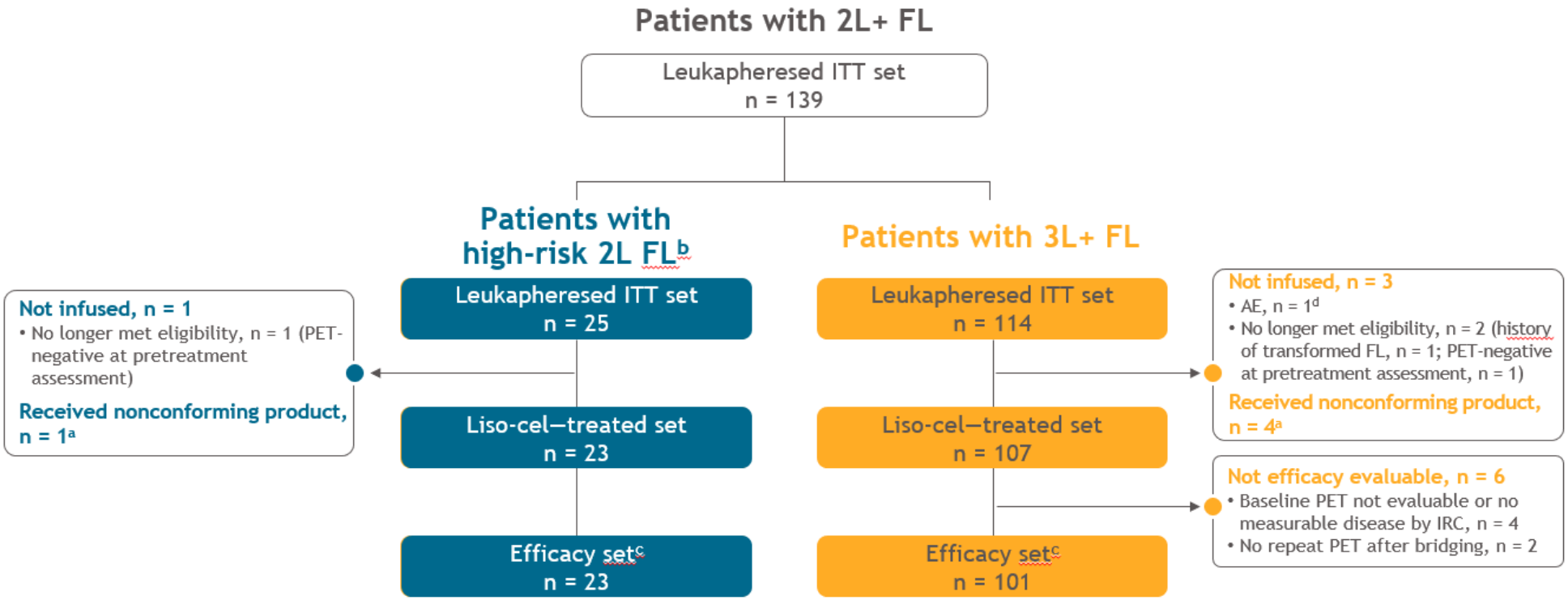
AEs of Special Interest

Patients with CRS and NEs	2L+ FL liso-cel–treated set (n = 130)
CRS,[a] 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)
NE,[b] 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)

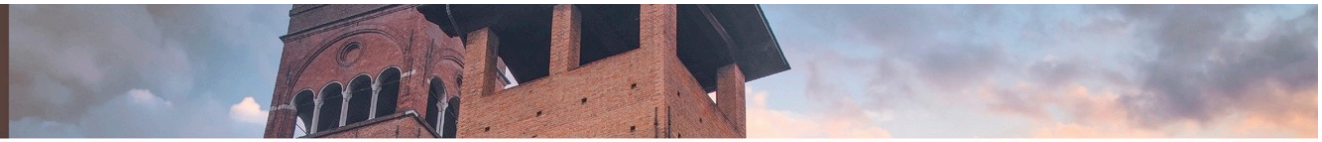


Other AESIs, n (%)	2L+ FL liso-cel–treated set (n = 130)
Prolonged cytopenia (grade ≥3 at Day 29)[c]	29 (22)
Recovery to grade ≤ 2 neutropenia at Day 90[d], n/N (%)	18/20 (90)
Recovery to grade ≤ 2 anemia at Day 90[d], n/N (%)	5/6 (83)
Recovery to grade ≤ 2 thrombocytopenia at Day 90[d], n/N (%)	11/19 (58)
Grade ≥ 3 infection[e]	7 (5)
MAS	1 (1)
Tumor lysis syndrome	0
Hypogammaglobulinemia[f]	6 (5)
SPM (2 AML, 1 rectal cancer, 1 colon adenocarcinoma)[f]	4 (3)



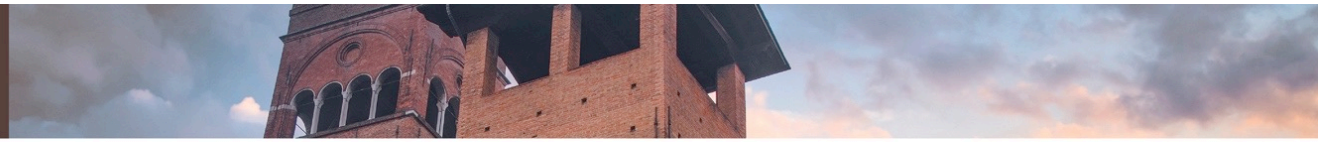


[a]Nonconforming product was defined as any product wherein one of the CD8 or CD4 cell components did not meet one of the requirements to be considered liso-cel but was considered appropriate for infusion; [b]The high-risk 2L FL cohort included patients with POD24 from diagnosis and/or mGELF; [c]Liso-cel-treated patients with PET-CT positive disease per IRC prior to infusion; [d]Acute respiratory failure (enterovirus/rhinovirus pneumonia).

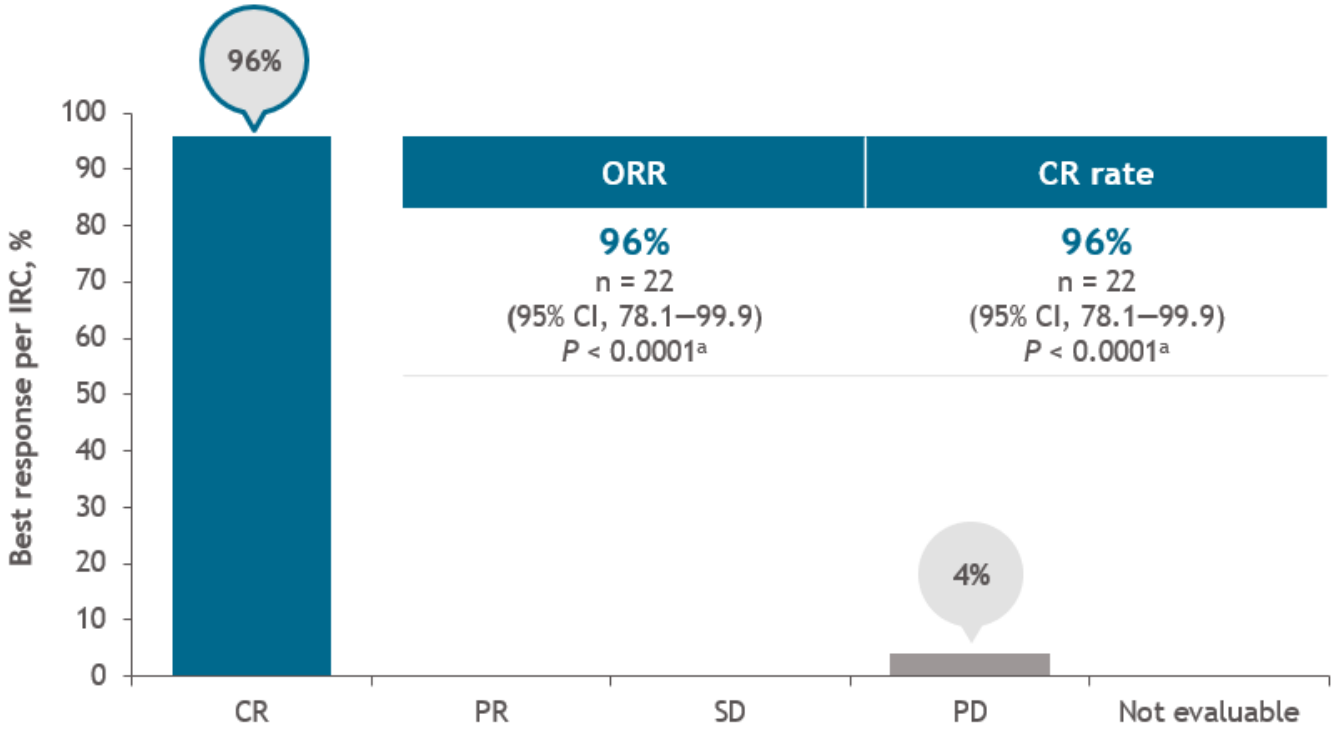


Patient demographics and baseline characteristics

	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 FL efficacy set (n = 23)



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

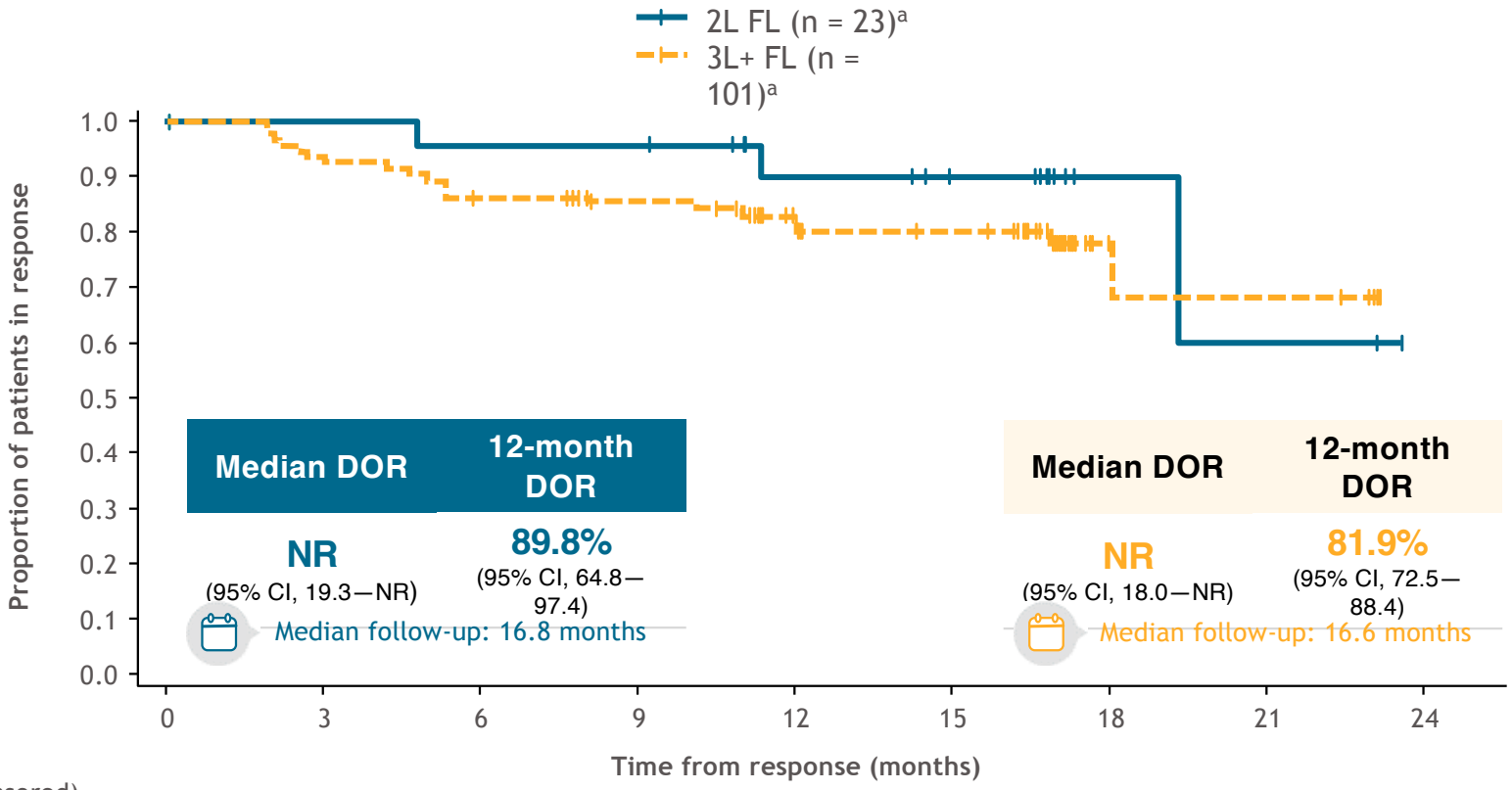
Primary and key secondary endpoints were met
All null hypotheses were rejected

ORR was 96%, with all responders achieving CR

In patients with 3L+ FL[1]

- ORR = 97%
- CR rate = 94%

Duration of response per IRC in efficacy set



No. at risk (censored)

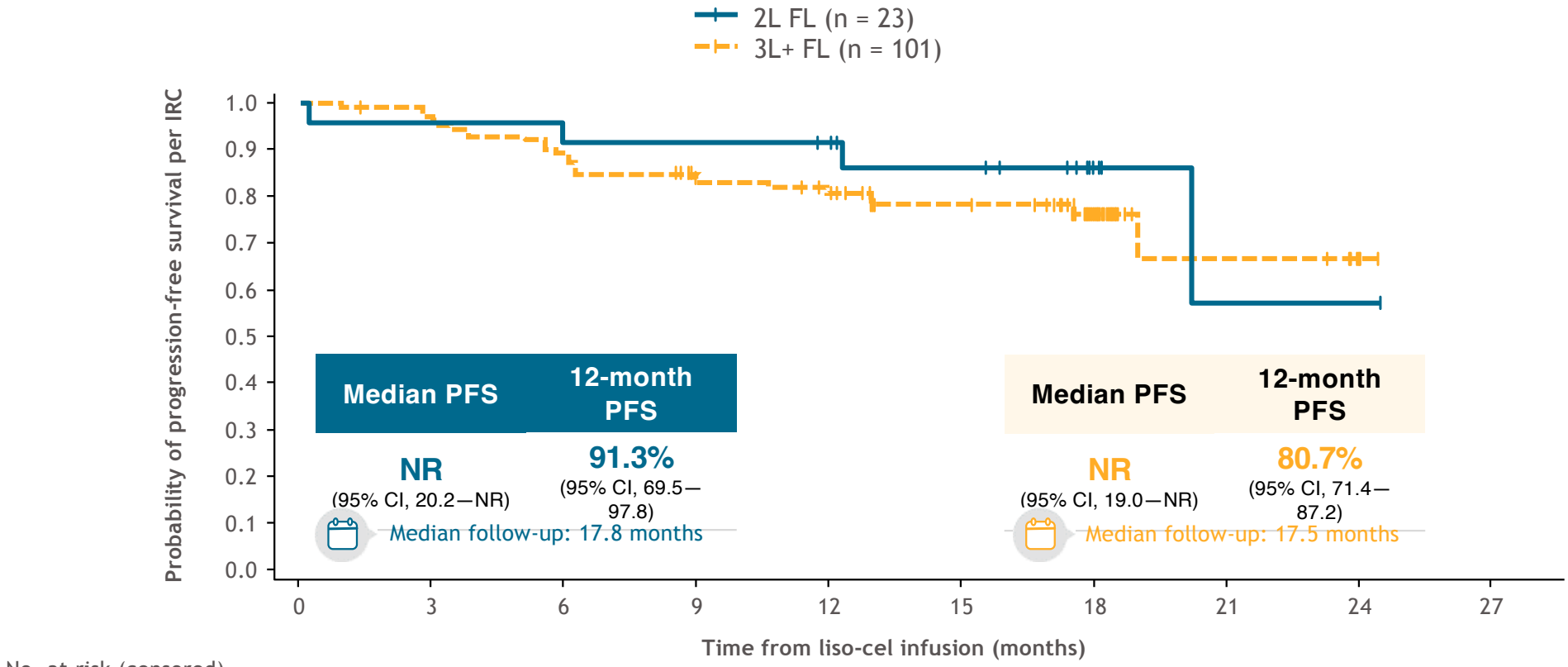
2L FL	22 (0)	22 (0)	21 (0)	21 (0)	16 (4)	13 (3)	3 (10)	2 (0)	0 (2)
3L+ FL	98 (0)	91 (1)	83 (1)	77 (5)	62 (12)	49 (12)	8 (40)	7 (0)	0 (7)

[a]Twenty-two of the 23 patients with 2L FL were responders; 98 of the 101 patients with 3L+ FL were responders.

NR, not reached

Morschhauser F, et al. ASH 2023 [Presentation #602]

Progression-free survival per IRC in efficacy set

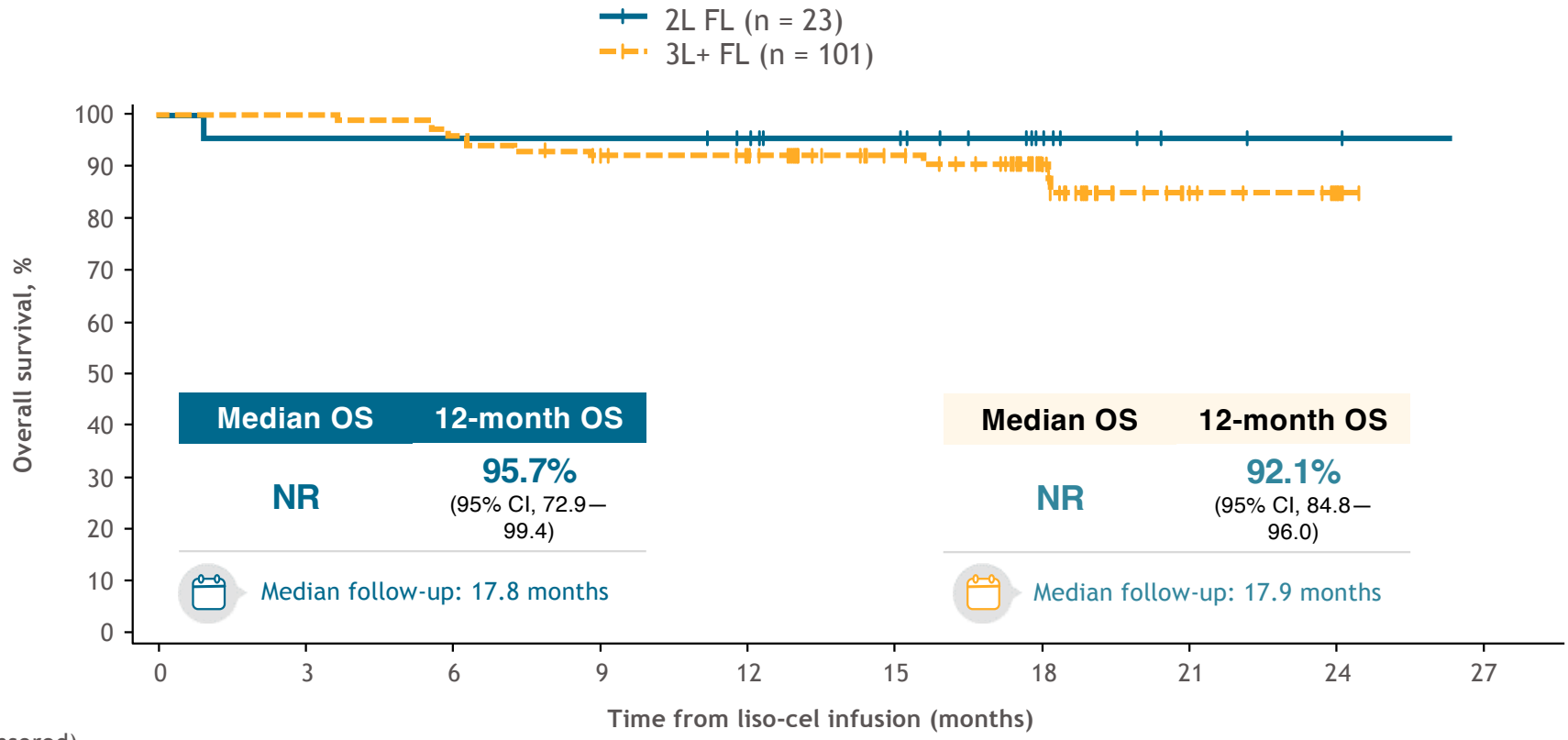


No. at risk (censored)

2L FL	23 (0)	22 (0)	21 (0)	21 (0)	20 (1)	16 (3)	5 (11)	2 (2)	2 (0)	0 (2)
3L+ FL	101 (0)	96 (1)	89 (0)	78 (6)	72 (3)	50 (20)	19 (30)	7 (11)	2 (5)	0 (2)

Morschhauser F, et al. ASH 2023 [Presentation #602]

Overall survival in efficacy set



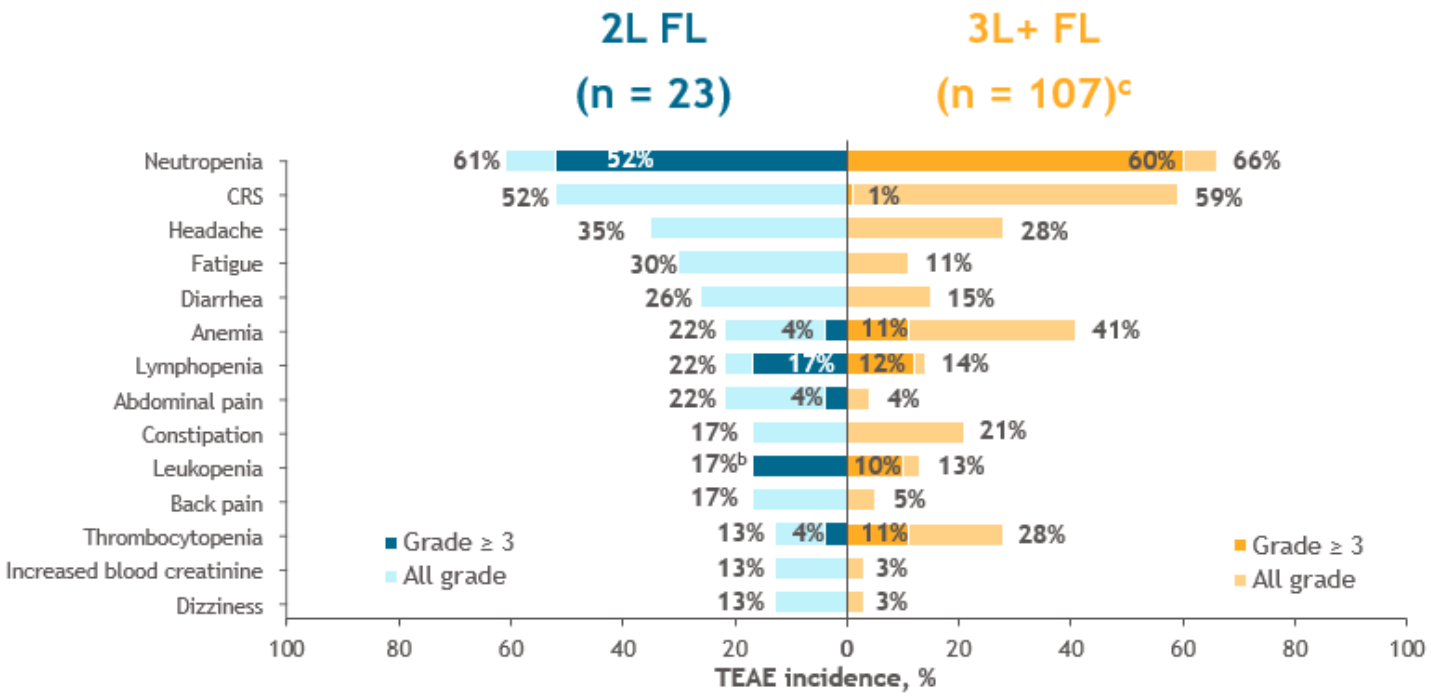
No. at risk (censored)

2L FL	23 (0)	22 (0)	22 (0)	22 (0)	20 (2)	17 (3)	8 (9)	3 (5)	2 (1)	0 (2)
3L+ FL	101 (0)	101 (0)	97 (0)	90 (3)	86 (4)	63 (23)	38 (24)	11 (25)	3 (8)	0 (3)

[a]A total of 39% of patients in the efficacy set were censored from the OS analysis at data cutoff.

Morschhauser F, et al. ASH 2023 [Presentation #602]

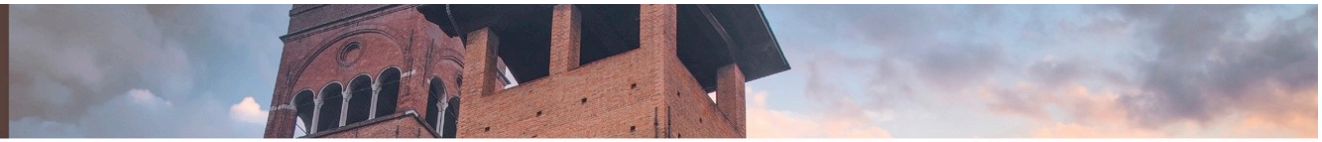
TEAEs (≥ 10%) in liso-cel—treated set



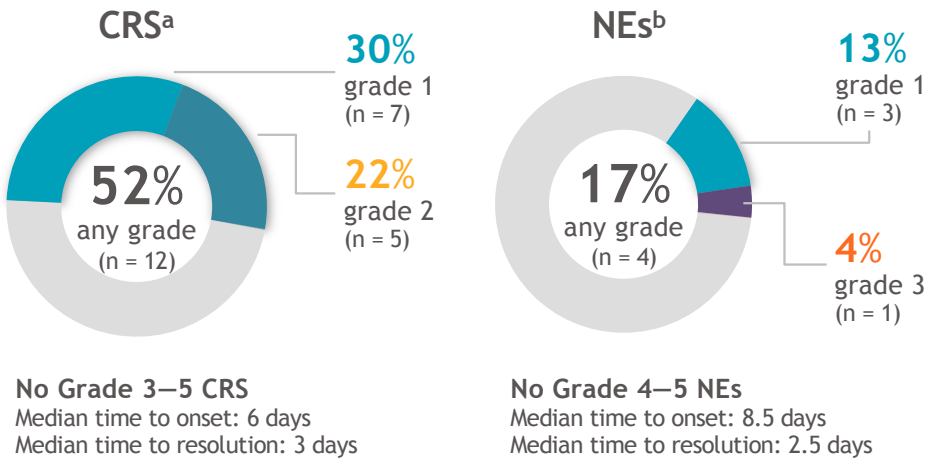
TEAEs in 2L vs 3L+ FL

- 61% vs 78% with grade ≥ 3 TEAEs
- 17% vs 26% with serious TEAEs
- Most common grade ≥ 3 TEAE was neutropenia (52% vs 60%)
  - 1 (4%) vs 5 (5%) with febrile neutropenia
- There was no grade ≥ 3 CRS in 2L FL

[a]TEAE period was defined as the time from initiation of liso-cel administration through and including study Day 90; [b]All cases of leukopenia in 2L FL were grade ≥ 3; [c]Only TEAEs that occurred in ≥ 10% of patients with 2L FL are shown for 3L+ FL.
CRS, cytokine release syndrome; TEAE, treatment-emergent adverse event.



2L FL (n = 23)



No Grade 3–5 CRS
Median time to onset: 6 days
Median time to resolution: 3 days

No Grade 4–5 NEs
Median time to onset: 8.5 days
Median time to resolution: 2.5 days

CRS in 2L vs 3L+ FL

- 52% vs 59% with any-grade CRS
- Grade 1–2 CRS only vs 1% grade 3 CRS (all others grade 1–2)
- Median time to onset of 6 days in both cohorts
- Median time to resolution of 3 vs 4 days

NEs in 2L vs 3L+ FL

- 17% vs 15% with any-grade NEs
- No grade 4–5 NEs in either cohort
  - 4% vs 2% with grade 3 NEs
- Median time to onset of 8.5 days in both cohorts
- Median time to resolution of 2.5 vs 4.5 days

13% vs 31% received tocilizumab and/or corticosteroids to manage CRS/NEs

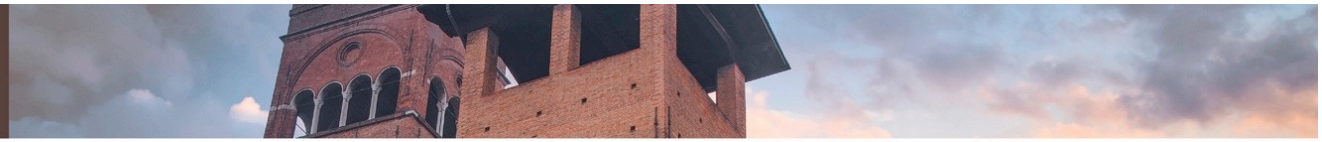
[a]Graded according to ASTCT criteria; [b]Defined as investigator-identified neurological AEs related to liso-cel and graded per the NCI CTCAE, version 5.0; NE, neurological event.
Morschhauser F, et al. ASH 2023 [Presentation #602]

Other AESI in liso-cel–treated set

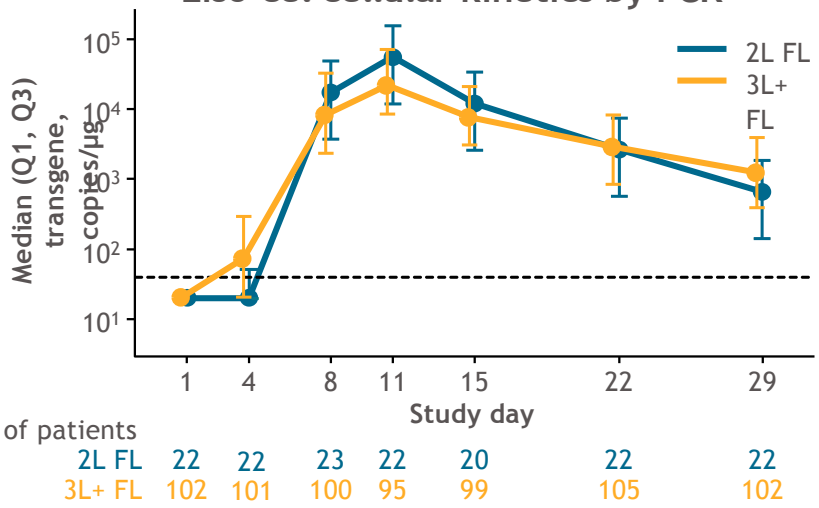
AESI, n (%)	2L FL (n = 23)	3L+ FL (n = 107)
Prolonged cytopenia[a] (grade ≥ 3 at Day 29)	3 (13)	26 (24)
Recovery to grade ≤ 2 neutropenia at Day 90[b], n/N (%)	2/2 (100)	16/18 (89)
Recovery to grade ≤ 2 anemia at Day 90[b], n/N (%)	NA[b]	5/6 (83)
Recovery to grade ≤ 2 thrombocytopenia at Day 90[b], n/N (%)	1/1 (100)	10/18 (56)
Grade ≥ 3 infection	0	7 (7)
Grade 5 TEAE of MAS/HLH	1 (4)	0
Tumor lysis syndrome	0	0
Hypogammaglobulinemia[c]	1 (4)	4 (4)
Second primary malignancy[c]	1 (4)[d]	3 (3)[e]

[a]Grade ≥ 3 laboratory abnormalities of neutropenia, anemia, or thrombocytopenia on Day 29; [b]Recovery data are presented for patients with prolonged cytopenia who had laboratory results after Day 29. No patients with 2L FL had grade ≥ 3 anemia at Day 29. [c]Could occur within or beyond the 90-day treatment-emergent period; [d]Colon adenocarcinoma; [e]Acute myeloid leukemia, rectal cancer, and squamous cell carcinoma of the skin. AESI, adverse events of special interest; MAS/HLH, macrophage activation syndrome/hemophagocytic lymphohistiocytosis.

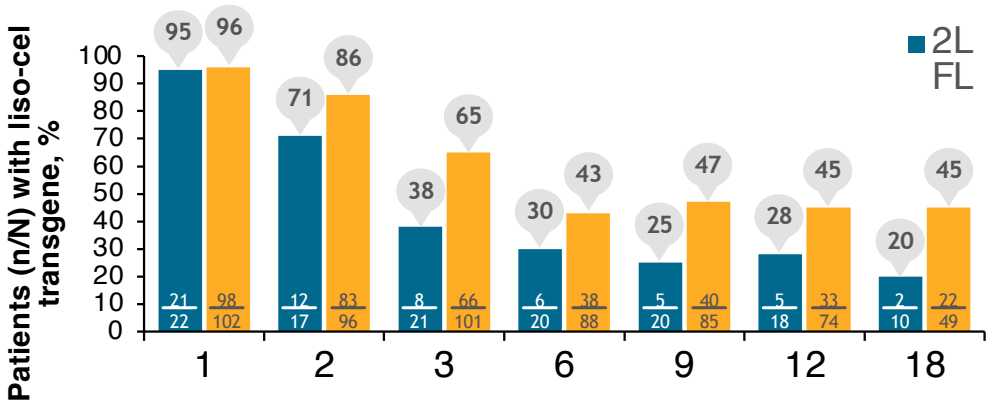
Morschhauser F, et al. ASH 2023 [Presentation #602]



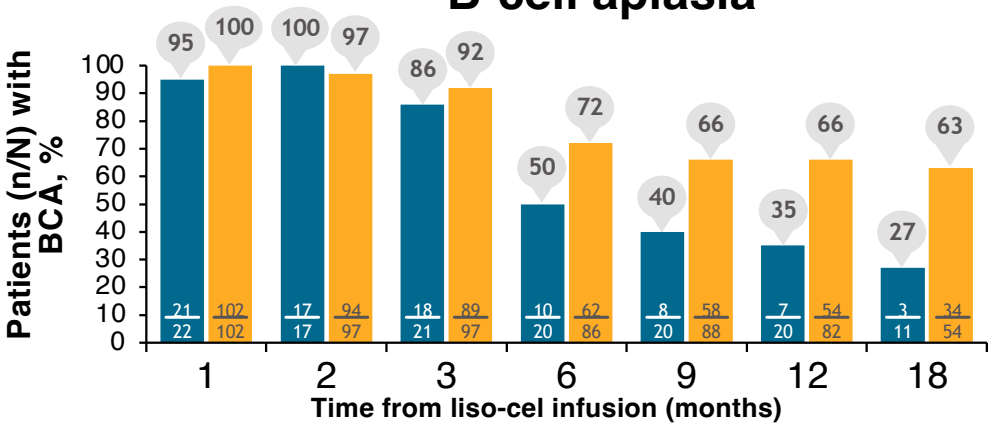
Liso-cel cellular kinetics by PCR[a,b]



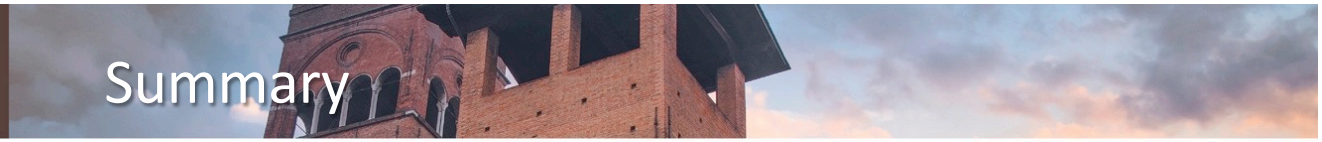
Persistence of liso-cel transgene



B-cell aplasia



Morschhauser F, et al. ASH 2023 [Presentation #602]



Summary

- Liso-cel demonstrated high response rate and a good safety profile in patients with 2L and 3L R/R FL, with no grade ≥ 3 CRS or infections and low rates of NEs and prolonged cytopenia
- Liso-cel will likely be FDA-approved for the above indications in the US this month, adding another IEC to the available options for pts with R/R FL
- FDA-required specifications to meet liso-cel definition were loosened last week, which will likely result in decreased proportion of out of spec products and faster turn around for patients

Morschhauser F, et al. ASH 2023 [Presentation #602]