ER Congressi

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Clinical Result CAR-T for Follicular Lymphoma: What is next?

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4th Meeting on Innovative immunotherapies for Lymphoid Malignancies (Milano, Italy 2026)

Disclosures

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- **Active grants**: Leukemia Lymphoma Society (Blood Cancer United) Scholar in Clinical Research

Agenda

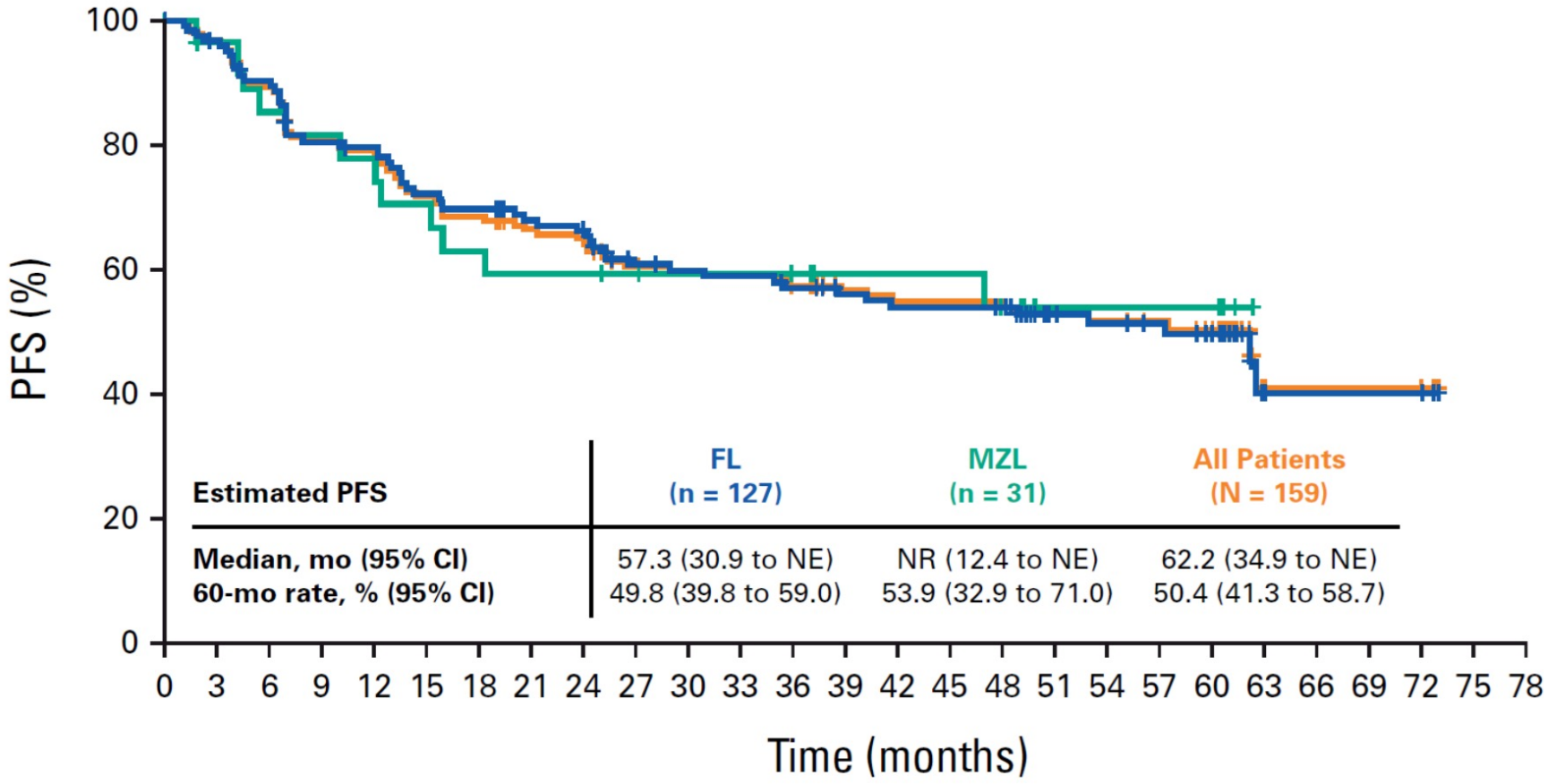
- Clinical results from pivotal clinical trials
- Clinical results from real world experience
- What is next?

Key differences in 3 pivotal trials

	ZUMA-5 (N=159)	ELARA (N=97)	TRANSCEND FL (N=130)
Histology	FL	FL	FL
Product	Axicabtagene ciloleucel	Tisagenlecleucel	Lisocabtagene maraleucel
Developed at	NCI	UPenn	SCH/FHCRC
Sponsor			
Line of therapy	Third +	Third +	**Second+**
Conditioning	Flu-Cy	Flu-Cy or **Benda**	Flu-Cy
ORR	90%	86%	**97%**
CR rate	75%	69%	**94%**
Grade ≥3 CRS	**7%**	0%	1%
Grade ≥3 ICANS	**19%**	3%	2%
Grade ≥3 cytopenia (D30)	**34%**	17%	22%
FDA approval	2021	2022	2024

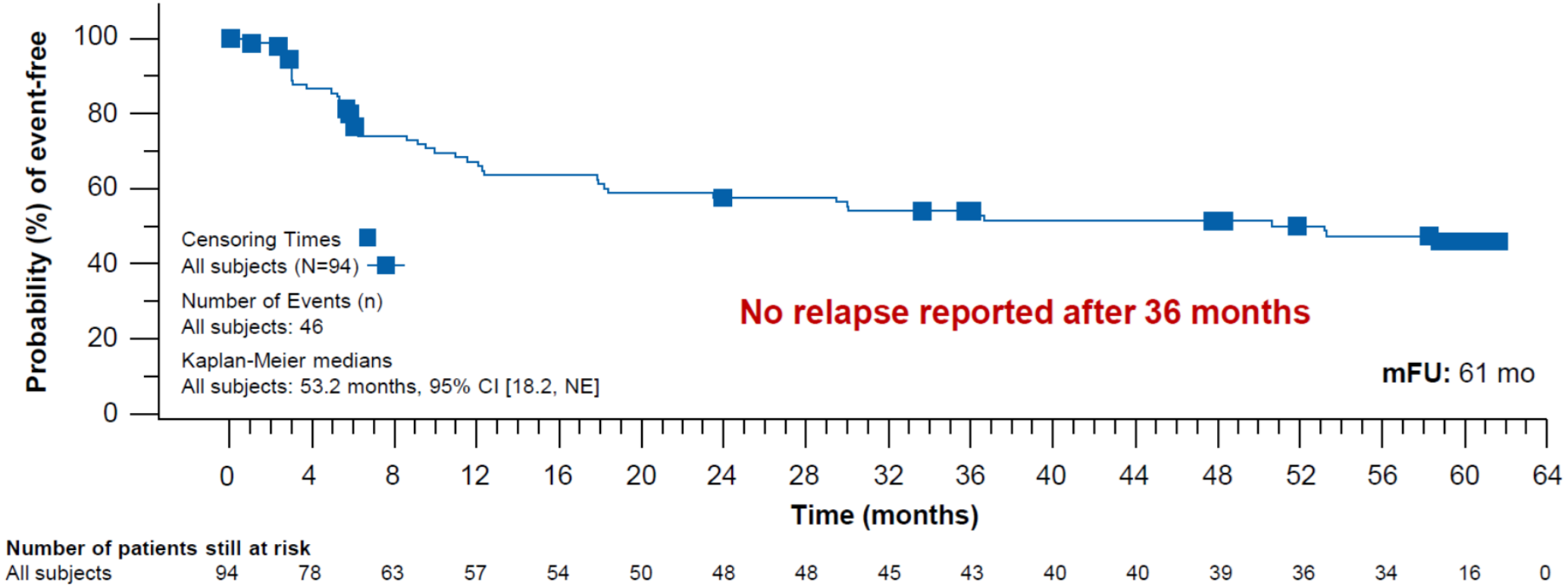
Jacobson CA et al, Lancet Oncol 2022; ***Fowler NH et al***, Nat Med 2022;
Morschhauser F et al, Nat Med 2024

ZUMA-5: 5-year follow-up



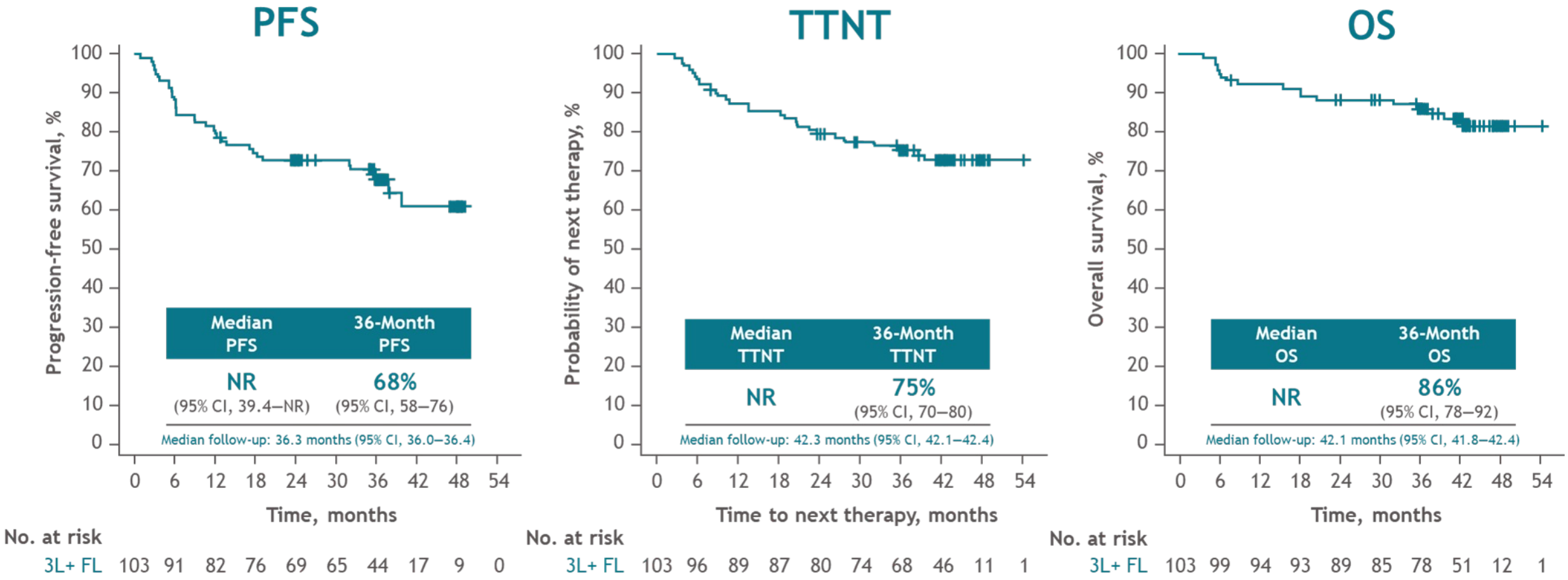
Neelapu SS et al, JCO 2025

ELARA: 5-year follow-up



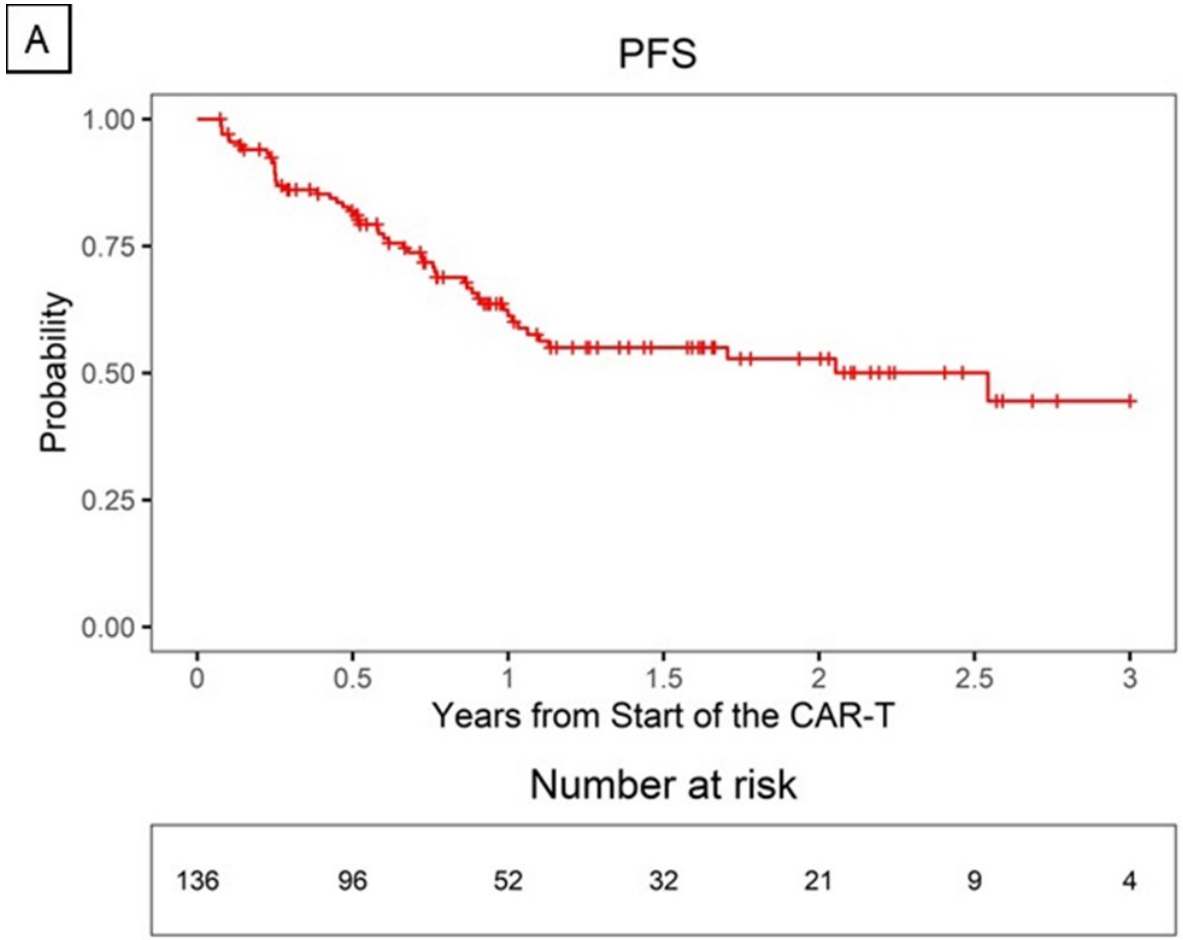
Schuster S et al, ASH 2025

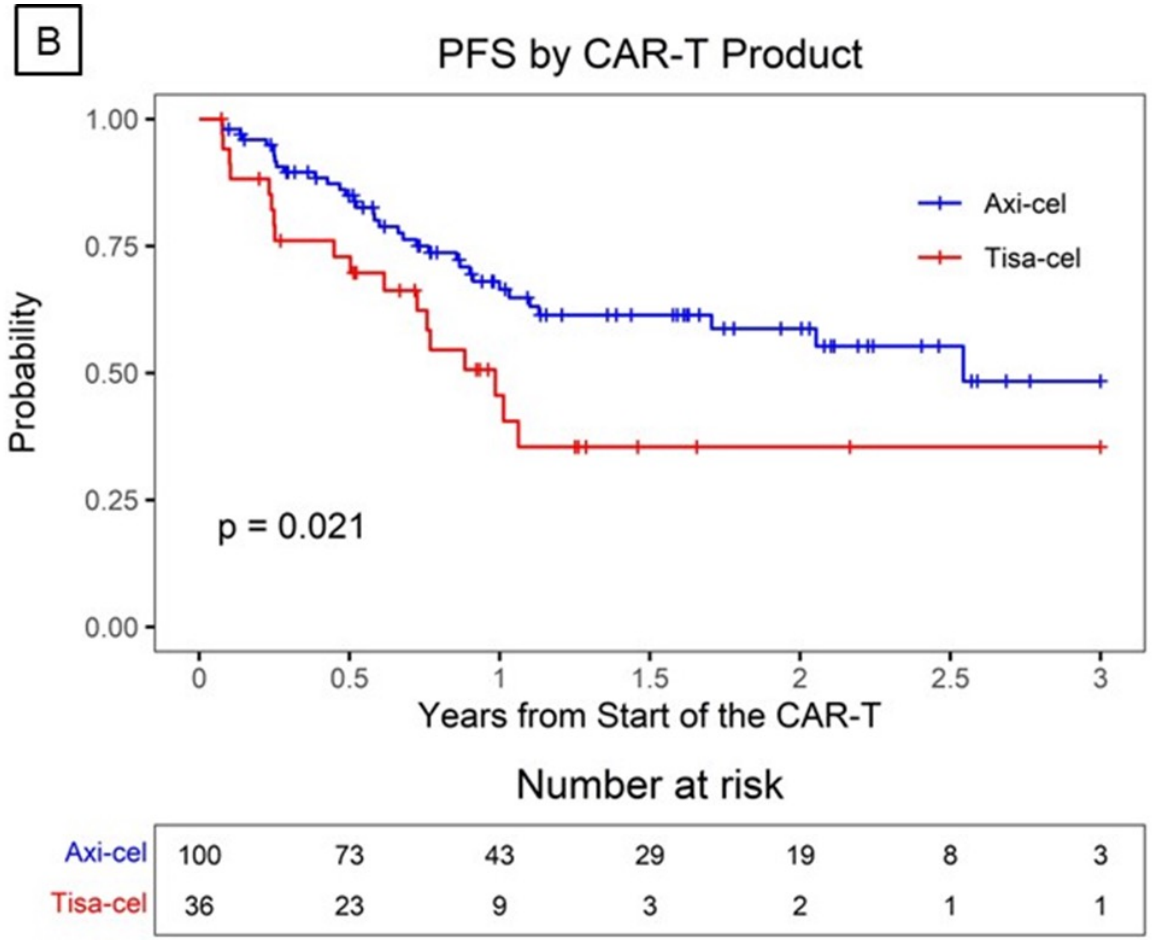
TRANSCEND-FL: 3-year follow-up



Ahmed S et al, ASH 2025

Real world data are limited



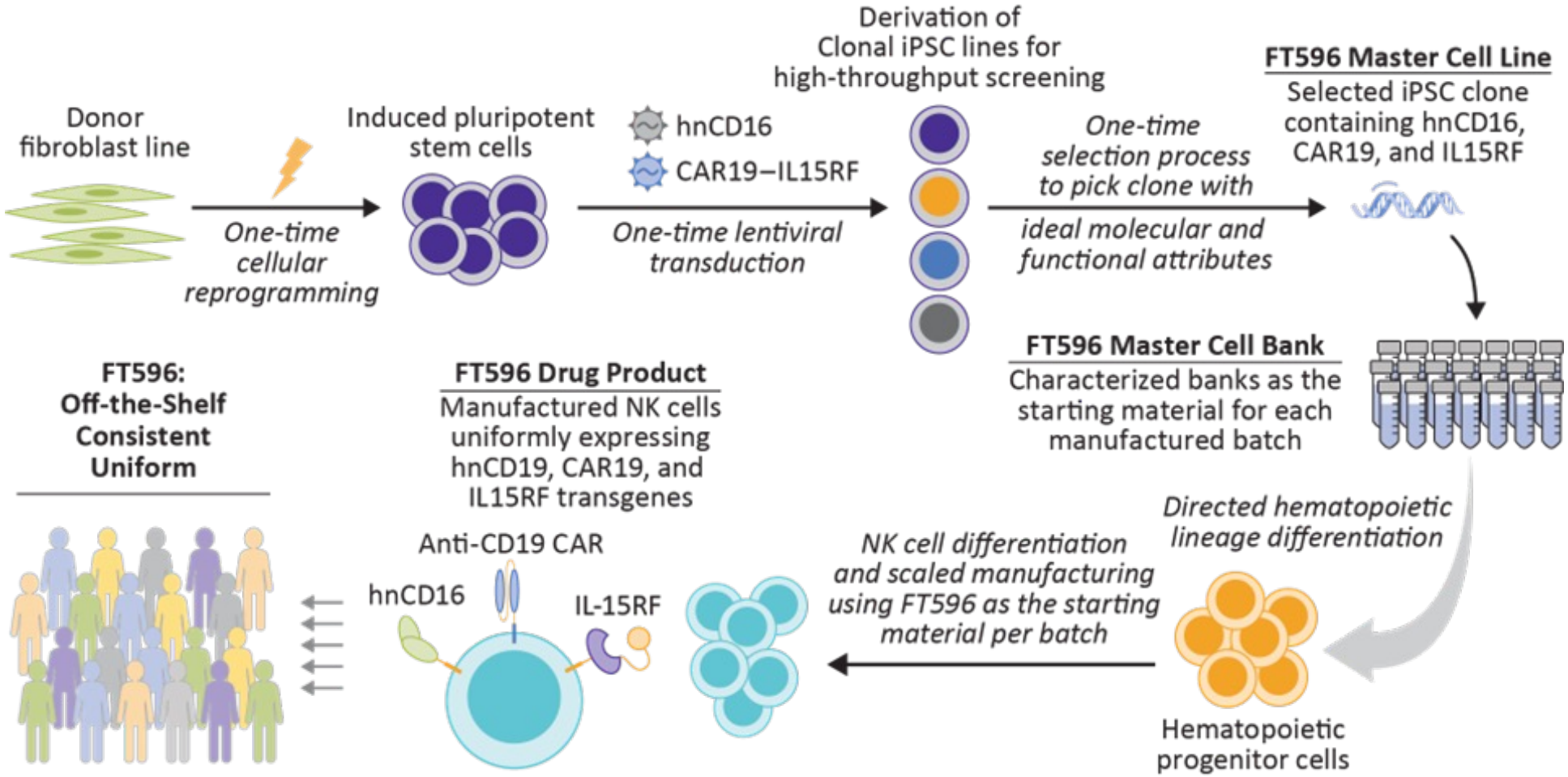


***Sharp J, Strati P et al**, Blood Adv 2026*

What is next?

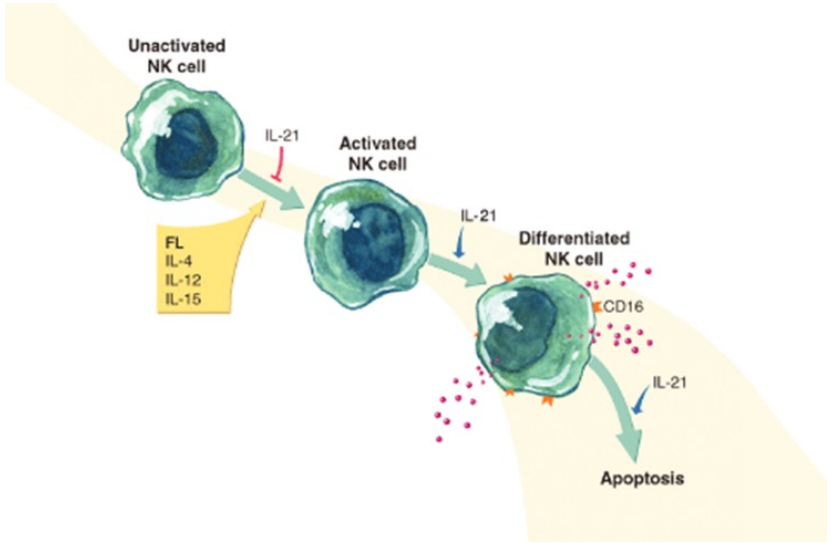
- Multiple targets (early for FL; may matter more for DLBCL)
- Allogeneic products (no impact of prior bendamustine)
- Products not requiring LDC (chemo-free approach in elderly)
- Non-T-cell-based products (less toxicity)

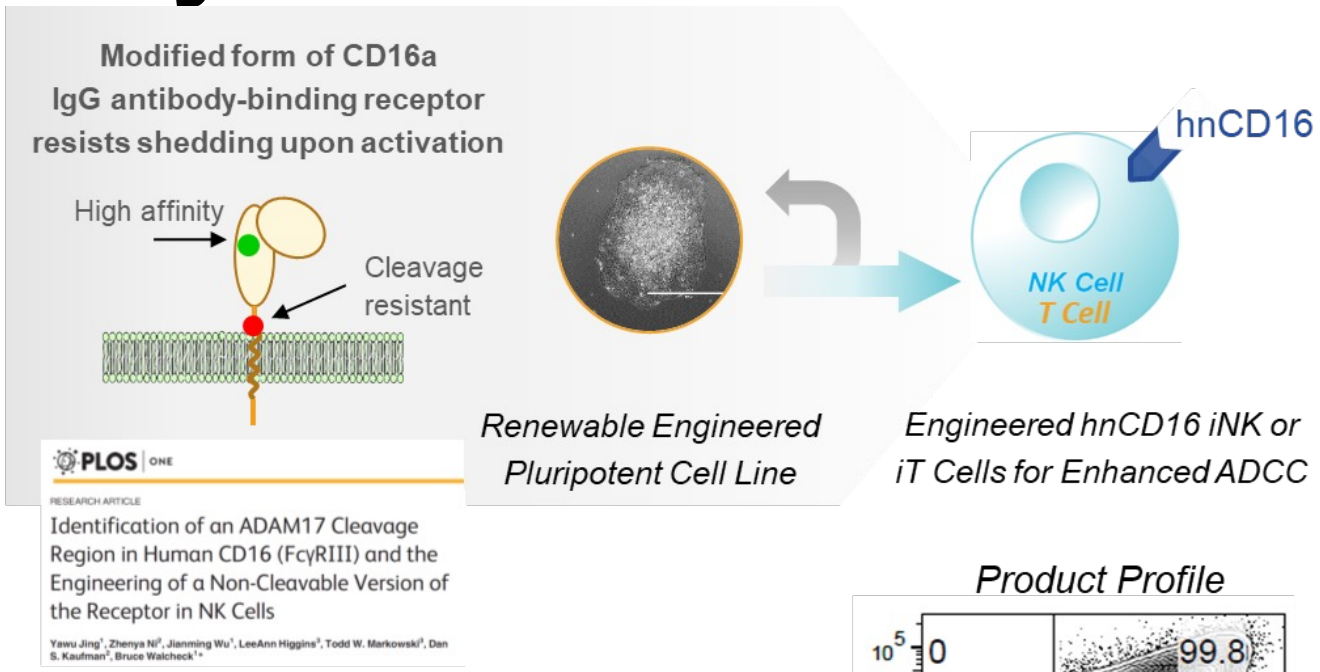
Induced pluripotent stem cells-derived NK cells (iPSC-NK)



Ghobadi A, et al, Strati P. Lancet 2024

CD16 expression is crucial for the anti-tumoral activity of NK cells

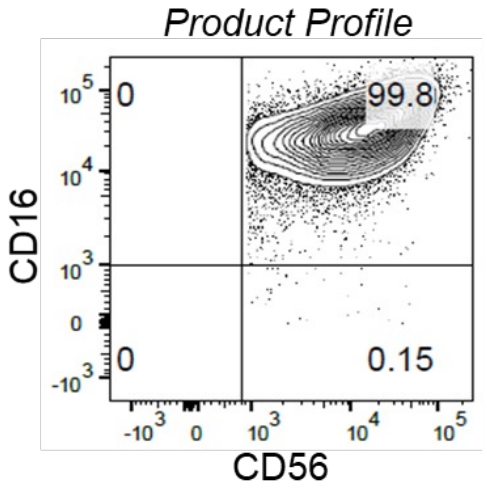




Antibody-dependent cytotoxicity

Direct cytotoxicity

Product Profile



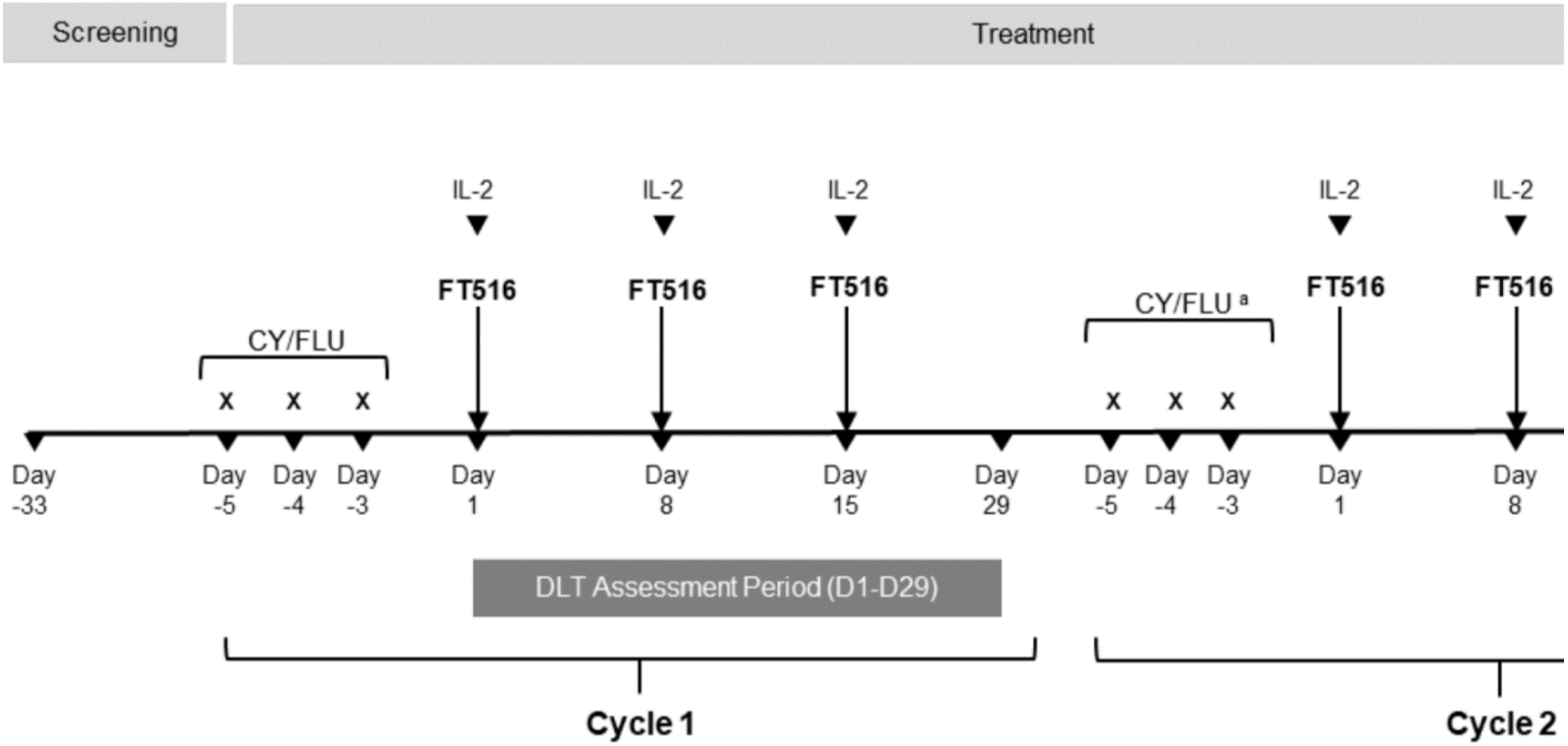
***Zhu H et al**, Blood 2020*

THE LANCET
Haematology

Off-the-shelf induced pluripotent stem-cell-derived natural killer-cell therapy in relapsed or refractory B-cell lymphoma: a multicentre, open-label, phase 1 study

Paolo Strati, Januario Castro, Aaron Goodman, Veronika Bachanova, Manali Kamdar, Farrukh T Awan, Scott R Solomon, Lilly Wong, Carol Wong, Deepa Patel, Cara Bickers, Wei Zhao, Zahid Bashir, Bahram Valamehr, Rebecca L Elstrom, Krish Patel

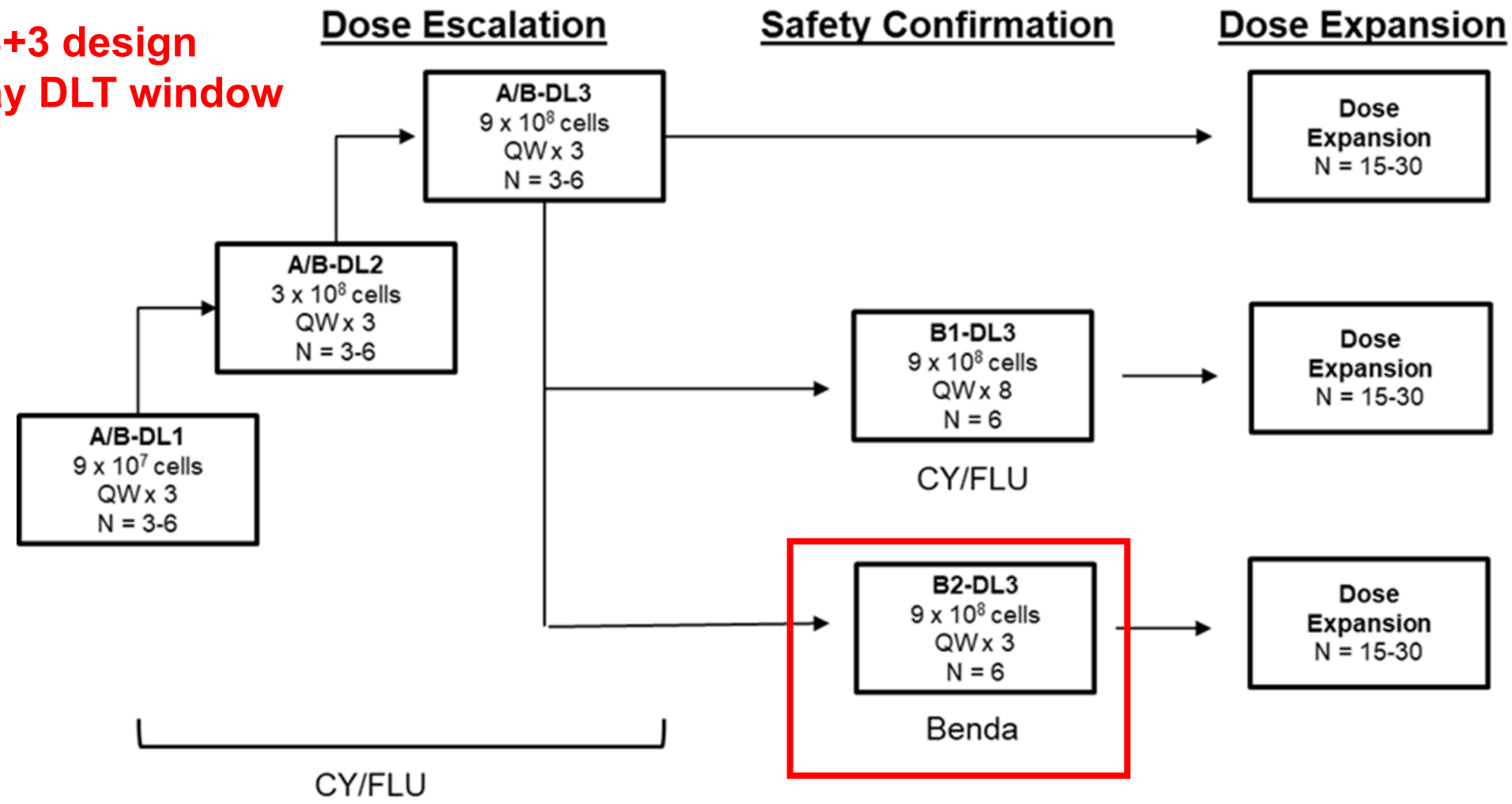
Treatment schema



Phase I first in human (NCT04023071)
No hospitalization required

Dose levels and statistical design

3+3 design
30-day DLT window



Baseline characteristics

October 2019 to November 2022
35 pts had 2 cycles

Characteristic	FT516 plus rituximab N=47	FT516 plus Obinutuzumab N=8	Total N=55
Age (years)	65 (27, 84)	62.5 (43, 77)	65 (27, 84)
≥65, n (%)	25 (53·2)	4 (50)	29 (52·7)
Male, n (%)	28 (66·7)	4 (50)	32 (58·2)
NHL histology, n (%)			
DLBCL (de novo)	25 (53·2)	0	25 (45·5)
tFL/FL G3B	4 (8·5)	1 (12·5)	5 (9·1)
HGBCL (DH/TH)	5 (10·6)	0	5 (9·1)
Gray zone lymphoma	1 (1·8)	0	1 (1·8)
Richter transformation	1 (2·1)	0	1 (1·8)
FL low grade	3 (6·4)	7 (87·5)	10 (18·2)
MZL	2 (4·3)	0	2 (3·6)
Mantle cell lymphoma	4 (8·5)	0	4 (7·3)
TCRHLBCL	1 (2·1)	0	1 (1·8)
Burkitt lymphoma	1 (2·1)	0	1 (1·8)

Characteristic	FT516 plus rituximab N=47	FT516 plus Obinutuzumab N=8	Total N=55
Prior therapies			
Prior no. of therapies	3 (1, 10)	2 (1, 3)	3 (1, 10)
Prior no. anti-CD20 therapies	2 (1, 6)	2 (1, 3)	2 (1, 6)
Refractory patients	20 (42·6)	0	20 (36·4)
Prior CD19 CAR T	20 (42·6)	1 (12·5)	21 (38·2)
Prior autologous HSCT	6 (12·8)	1 (12·5)	7 (12·7)

Treatment-emergent adverse event

	Any Grade N= 55 n (%)	Grade ≥3 N=55 n (%)
Neutropenia	46 (83·6)	46 (83·6)
Fatigue	37 (67·3)	1 (1·8)
Nausea	34 (61·8)	0
Thrombocytopenia	32 (58·2)	20 (36·4)
Anaemia	26 (47·3)	15 (27·3)
Diarrhoea	24 (43·6)	0
Headache	24 (43·6)	0
Pyrexia	22 (40)	0
Decreased appetite	20 (36·4)	2 (3·6)
Dizziness	18 (32·7)	1 (1·8)
Chills	17 (30·9)	0
Cough	16 (29·1)	0
Constipation	15 (27·3)	1 (1·8)
Dyspnoea	14 (25·5)	2 (3·6)
Hypokalaemia	13 (23·6)	0
Leukopenia	12 (21·8)	11 (20·0)
Oedema peripheral	11 (20·0)	0

CTCAE V5 and ASTCT grading system

	Total N= 55 n (%)	
	Any grade	Grade ≥3
Cytokine release syndrome	1 (1.8)	0
ICANS	0	0
Graft-versus-host disease	0	0
Infection	31 (56)	19 (35)

22% D30 G3-4 cytopenia

No DLT; RP2D: 9 X 10^8 cells/dose, 3 doses per cycles

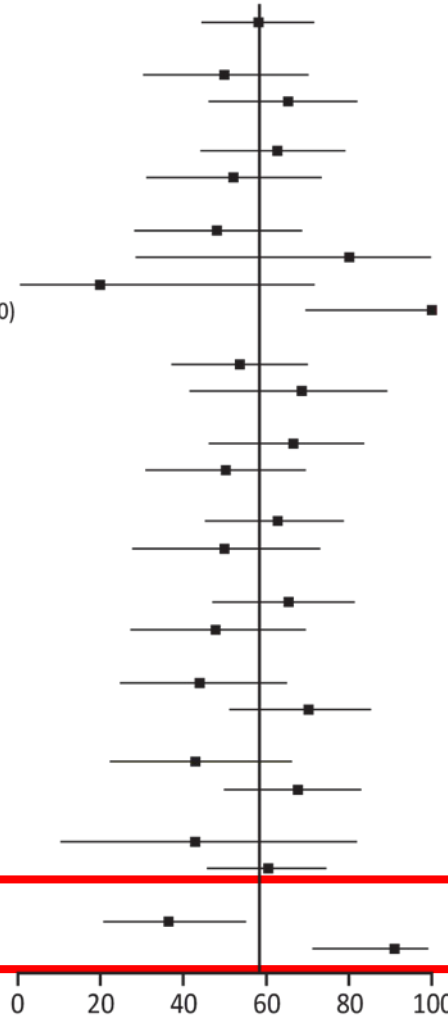
Response to treatment

Best overall response rate	Aggressive CAR-T naïve N=18 n (%)	Aggressive Post CAR-T N=19 n (%)	Aggressive Total N=37 n (%)	Indolent N=12 n (%)	MCL N = 4 n (%)	Total N=55 n (%)
Overall Response rate	10 (56)	8 (42)	18 (49)	12 (100)	2 (50)	32 (58)
Complete Response	6 (33)	5 (26)	11 (30)	11 (92)	2 (50)	24 (44)
Partial Response	4 (22)	3 (16)	7 (19)	1(8)	0	8 (15)
Stable Disease	0	1 (5)	1 (3)	0	1 (25)	2 (4)
Progressive Disease	7 (39)	10 (53)	17 (46)	0	1 (25)	20 (36)
NE	1 (6)	0	1 (3)	0	0	1 (2)

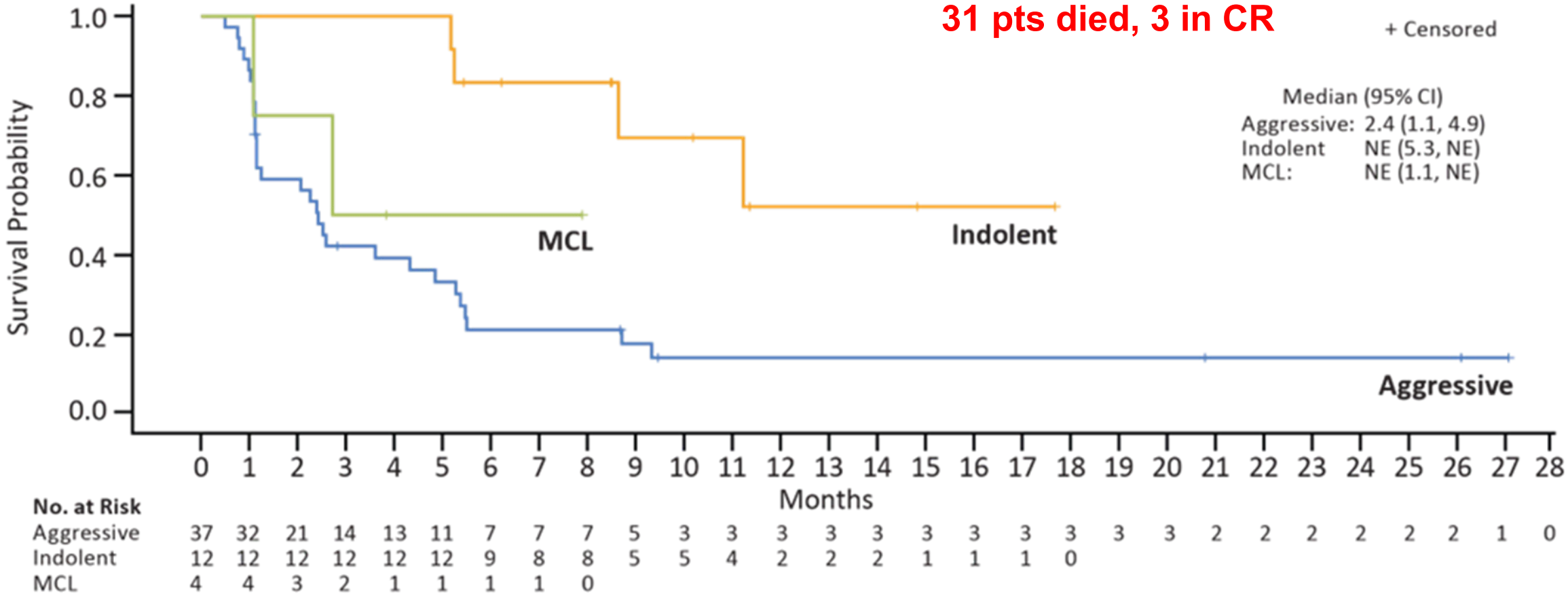
Lugano 2014; 9 pts improved to CR after 2nd cycle

Response to treatment

Subgroups	Response/Subjects	ORR (95% CI)*
All subjects	32 / 55	58.2 (44.1, 71.3)
Age		
<65	13 / 26	50.0 (29.9, 70.1)
≥65	19 / 29	54.1 (45.7, 82.1)
Sex		
Male	20 / 32	62.5 (43.7, 78.9)
Female	12 / 23	52.2 (30.6, 73.2)
NHL histology		
DLBCL (de novo)	12 / 25	48.0 (28.7, 68.7)
Transformed iNHL/Gr3B FL	4 / 5	80.0 (28.4, 99.5)
HGBCL	1 / 5	20.0 (0.5, 71.6)
Follicular lymphoma (low grade)	10 / 10	100.0 (69.2, 100.0)
Stage IV at study entry		
Yes	21 / 39	53.8 (37.2, 69.9)
No	11 / 16	68.8 (41.3, 89.0)
Baseline target lesion SPD (cm^2)		
<21.48	18 / 27	55.9 (37.9, 72.8)
≥21.48	14 / 28	52.9 (35.1, 70.2)
Prior no. of therapies		
1-3	22 / 35	62.9 (44.9, 78.5)
4+	10 / 20	54.3 (27.2, 72.8)
Prior no. anti-CD20 regimens		
1-2	21 / 32	65.6 (46.8, 81.4)
3+	11 / 23	47.8 (26.8, 69.4)
Refractory subjects		
Yes	11 / 25	44.0 (24.4, 65.1)
No	21 / 30	70.0 (50.6, 85.3)
Prior CD19 CAR T-cell therapy		
Yes	9 / 21	51.9 (31.9, 71.3)
No	23 / 34	67.6 (49.5, 82.6)
Prior HSCT		
Yes	83 / 7	42.9 (9.9, 81.6)
No	29 / 48	60.4 (45.3, 74.2)
Baseline LDH>ULN		
Yes	12 / 33	36.4 (20.4, 54.9)
No	20 / 22	90.9 (70.8, 98.9)

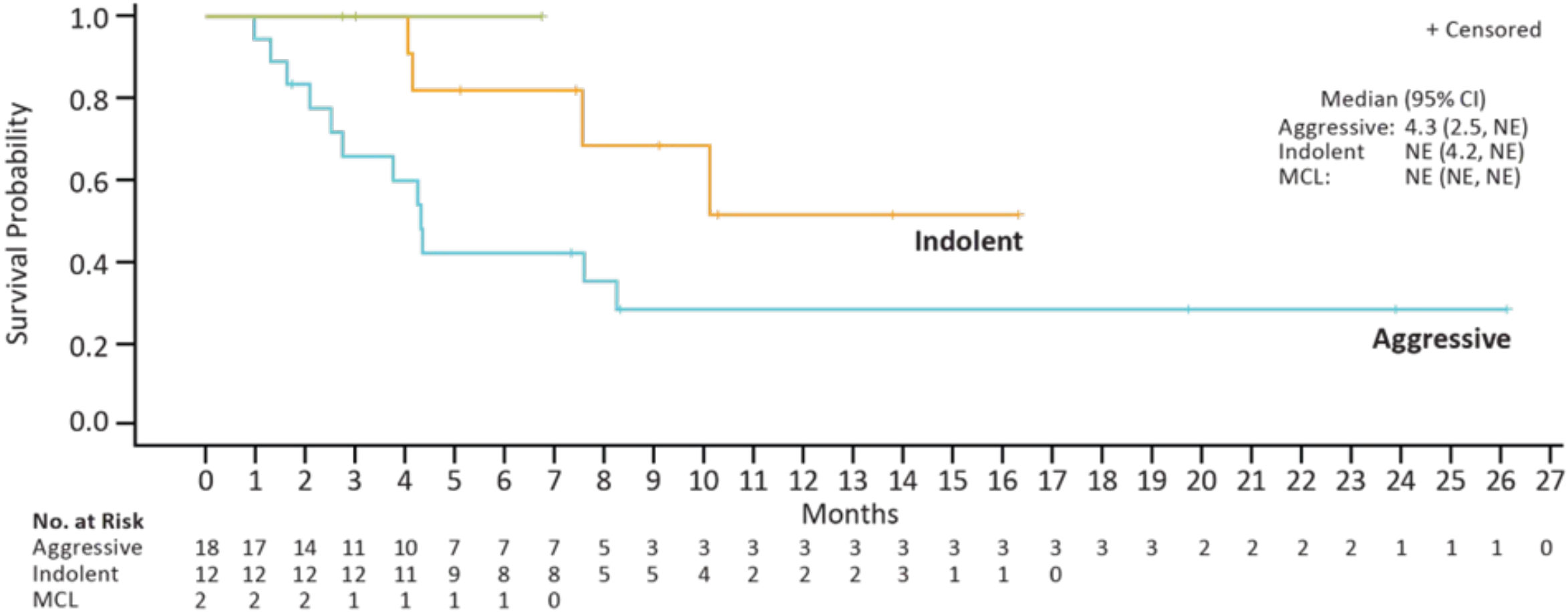


Progression-free survival

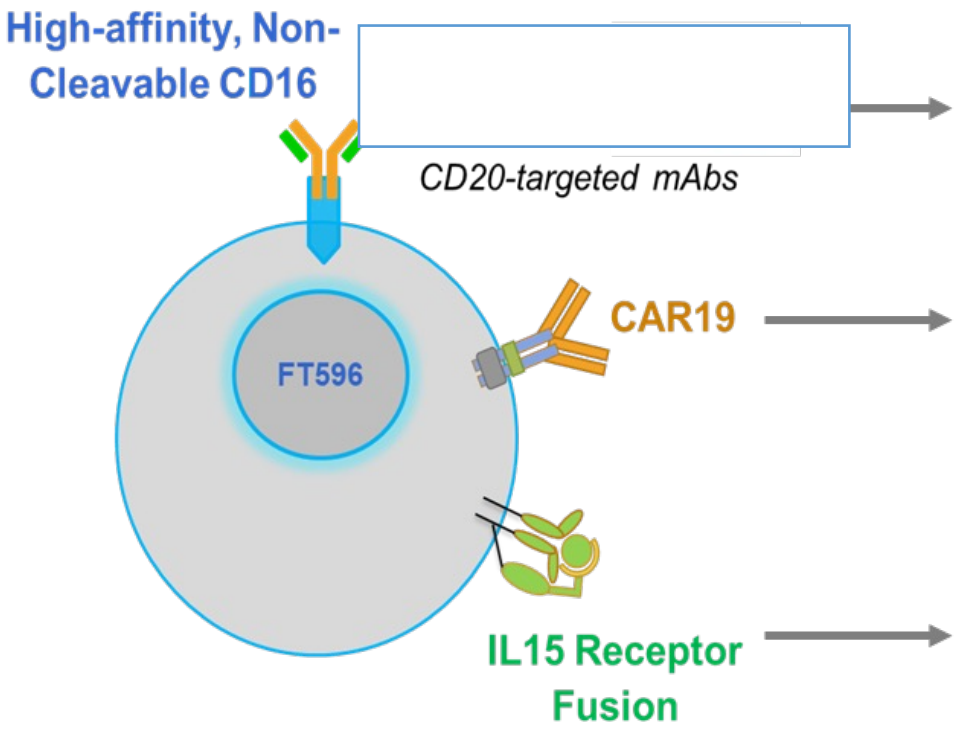


Duration of response

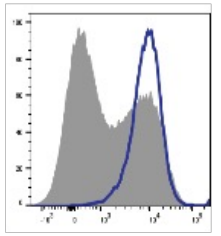
No patient received consolidative SCT



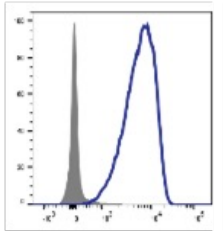
Next generation: FT596 (NK-CAR)



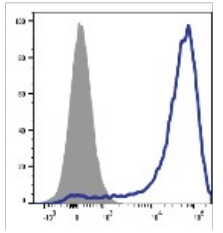
hnCD16: High-affinity 158V, non-cleavable CD16 Fc receptor that has been modified to augment antibody-dependent cellular cytotoxicity by preventing CD16 down-regulation and enhancing CD16 binding to tumor-targeting antibodies



CAR19: Chimeric antigen receptor optimized for NK cell biology, which contains a NKG2D transmembrane domain, a 2B4 co-stimulatory domain and a CD3-zeta signaling domain, that targets B-cell antigen CD19



IL-15RF: Interleukin-15 receptor fusion, a potent cytokine complex that promotes survival, proliferation and trans-activation of NK cells and CD8 T cells



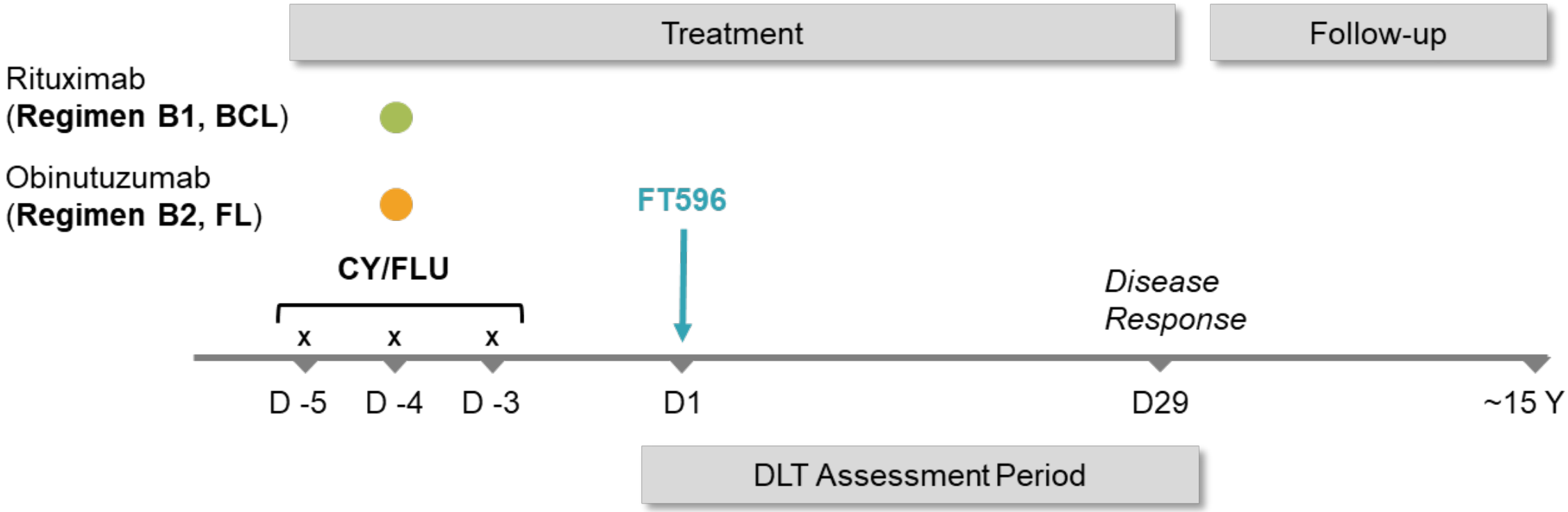
Goodridge JP et al. ASH 2019

THE LANCET

Induced pluripotent stem-cell-derived CD19-directed chimeric antigen receptor natural killer cells in B-cell lymphoma: a phase 1, first-in-human trial

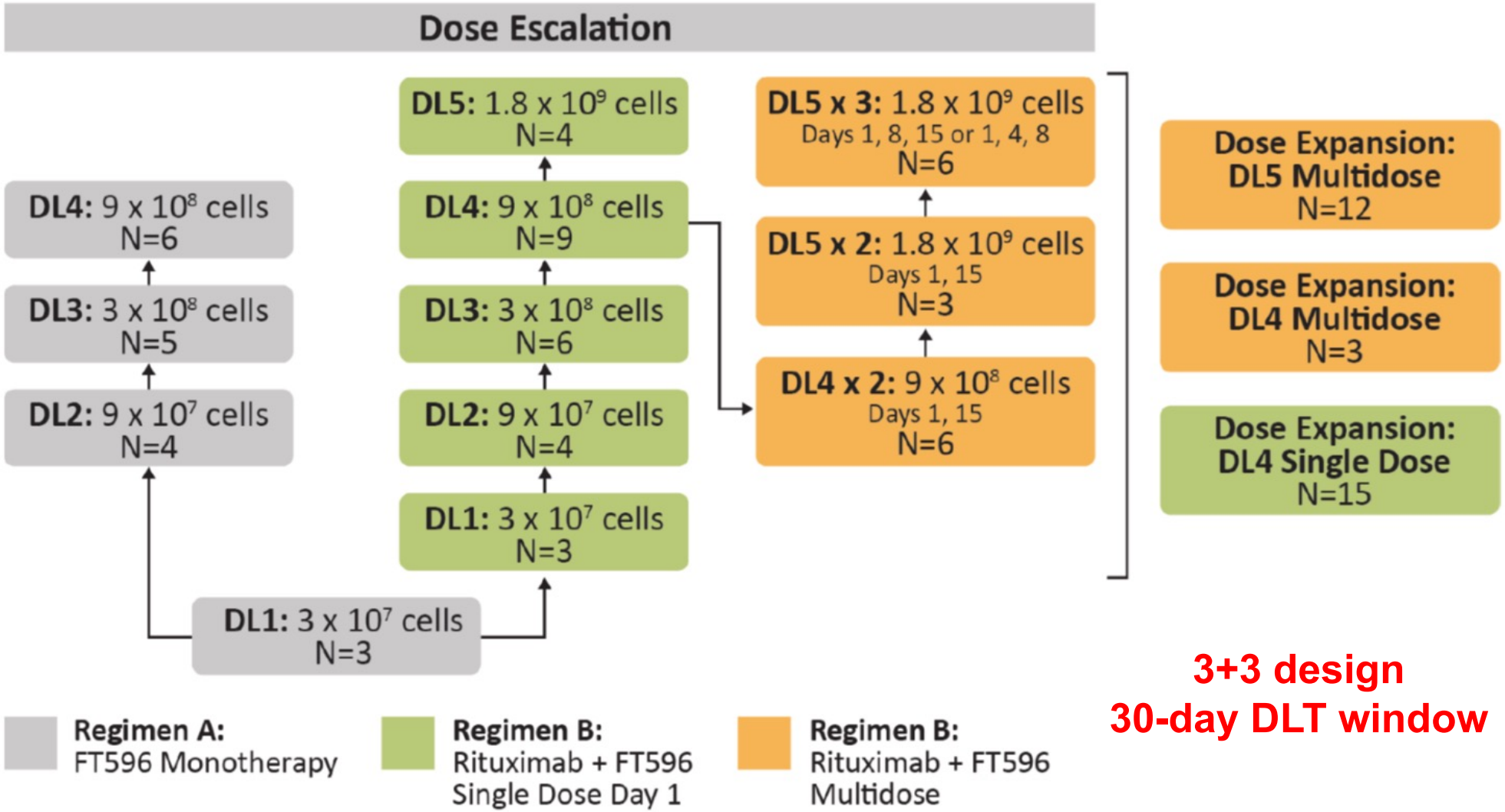
Armin Ghobadi, Veronika Bachanova, Krish Patel, Jae H Park, Ian Flinn, Peter A Riedell, Carlos Bachier, Catherine S Diefenbach, Carol Wong, Cara Bickers, Lilly Wong, Deepa Patel, Jode Goodridge, Matthew Denholt, Bahram Valamehr, Rebecca L Elstrom, Paolo Strati

Treatment schema



Phase I first in human (NCT04245722)
No hospitalization required

Dose levels and statistical design

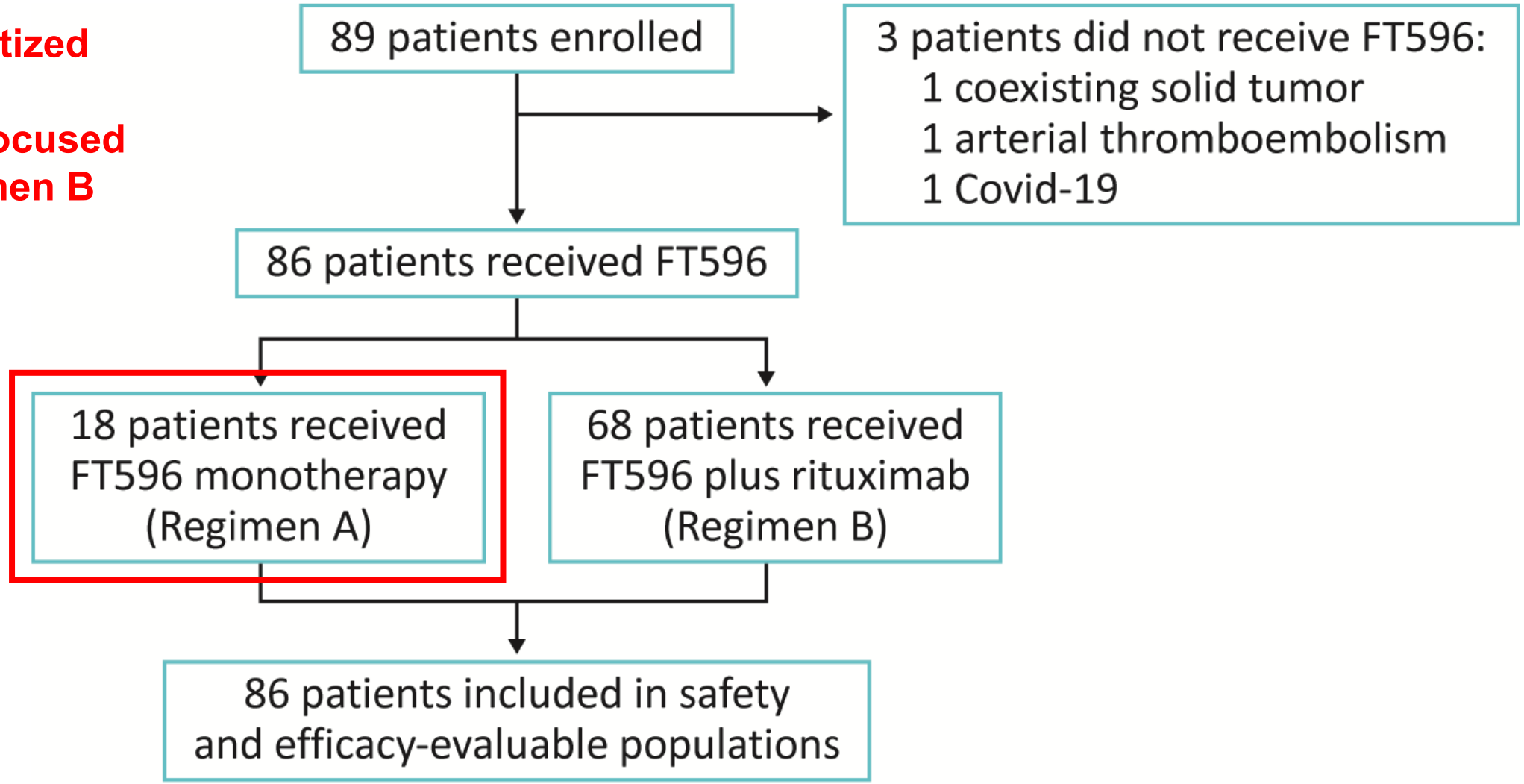


3+3 design
30-day DLT window

Treatment disposition

Deprioritized

Efficacy focused on regimen B



Baseline characteristics

March 2020 to January 2023
39 pts had 2 cycles

Characteristic	Regimen A N=18	Regimen B N=68	Total N=86
Age (years)	63·5 (43, 78)	66 (24, 85)	65·5 (24, 85)
≥65, n (%)	9 (50)	37 (55·4)	46 (53·5)
Male, n (%)	12 (66·7)	52 (76·5)	64 (74·4)
NHL histology, n (%)			
DLBCL (de novo)	5 (27·8)	21 (30·9)	26 (30·2)
tFL/FL G3B	0	7 (10·3)	7 (8·1)
HGBCL (DH/TH)	2 (11·1)	3 (4·4)	5 (5·8)
Gray zone lymphoma	0	1 (1·5)	1 (1·2)
Richter transformation	2 (11·1)	10 (14·7)	12 (14)
FL low grade	3 (16·7)	13 (19·1)	16 (18·6)
Other indolent lymphoma[b]	4 (22·2)	3 (4·4)	7 (8·1)
Mantle cell lymphoma	2 (11)	10 (14·7)	12 (14)

Characteristic	Regimen A N=18	Regimen B N=68	Total N=86
Prior therapies			
Prior no. of therapies	4 (1, 8)	4 (1, 11)	4 (1, 11)
Prior no. anti-CD20 regimens	3 (1, 6)	2 (1, 6)	2 (1, 6)
Refractory patients, n (%)	12 (66·7)	29 (42·6)	41 (47·7)
Prior CD19 CART	6 (33·3)	27 (39·7)	33 (38·4)
Prior HSCT, n (%)	4 (22·2)	11 (16·2)	15 (17·4)

Treatment-emergent adverse event

	Regimen A N=18 n (%)		Regimen B N=68 n (%)	
	Any	G ≥3	Any	G ≥3
Neutropenia*	15 (83)	14 (78)	60 (88)	60 (88)
Anemia	11 (16)	7 (39)	40 (59)	30 (44)
Thrombocytopenia*	12 (67)	7 (39)	39 (57)	33 (49)
Nausea	10 (56)	0	36 (53)	0
Fatigue	7 (39)	0	30 (44)	1 (1)
Decreased appetite	4 (22)	0	17 (25)	1 (1)
Diarrhea	5 (28)	0	16 (24)	1 (1)
Constipation	5 (28)	0	15 (22)	0
Hypophosphatemia	3 (17)	0	17 (25)	0
Leukopenia*	9 (50)	9 (50)	10 (15)	9 (13)
Pyrexia	6 (33)	0	11 (16)	0
Dizziness	4 (22)	0	11 (16)	0
Peripheral edema	5 (28)	0	10 (15)	0
Febrile neutropenia	5 (28)	5 (28)	5 (7)	5 (7)
Lymphopenia*	6 (33)	6 (33)	3 (4)	3 (4)

	Regimen A N=18 n (%)			Regimen B N=68 n (%)		
	G1	G2	G≥3	G1	G2	G≥3
CRS	1 (6)	0	0	7 (10)	3 (4)	0
ICANS	0	0	0	0	0	0
GVHD	0	0	0	0	0	0

CTCAE V5 and ASTCT grading system

24% G3-4 D30 cytopenia

1 DLT (thrombocytopenia); RP2D: 1.8 X 10^9 cells/dose, 3 doses per cycles

Response to treatment

Regimen B only

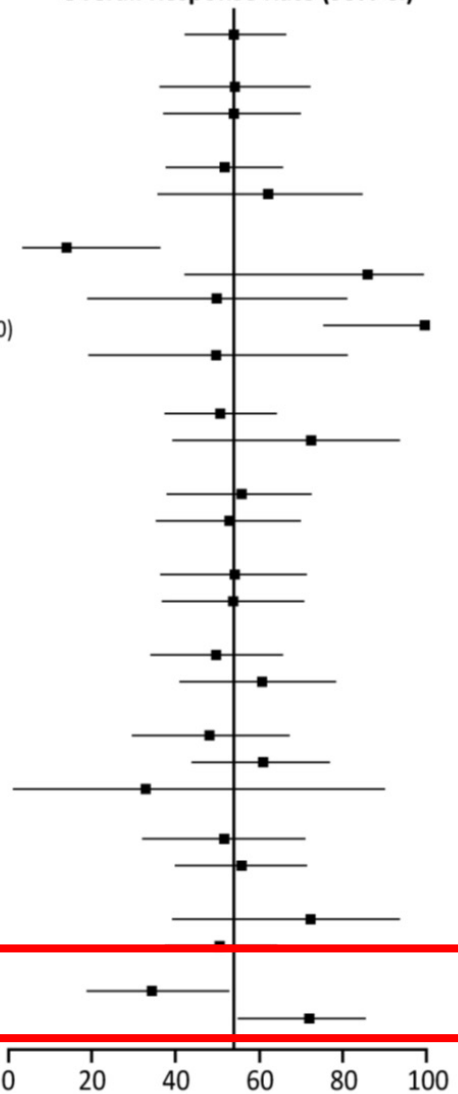
Best Overall Response	Large B-Cell Lymphoma				Follicular Lymphoma N=13 n (%)	Other (RT, MCL, MZL, SLL) N=23 n (%)	Total N=68 n (%)
	Total N=32 n (%)	de novo DLBCL N=21 n (%)	Other LBCL* N=11 n (%)	Prior CAR T N=20 n (%)			
Objective response rate	12 (38)	3 (14)	9 (82)	9 (45)	13 (100)	12 (52)	37 (54)
Complete response	8 (25)	1 (5)	7 (64)	6 (30)	11 (85)	6 (26)	25 (37)
Partial response	4 (13)	2 (10)	2 (18)	3 (15)	2 (15)	6 (26)	12 (17)
Stable disease	6 (19)	5 (24)	1 (9)	2 (10)	0	2 (9)	8 (12)
Progressive disease	14 (44)	13 (62)	1 (9)	9 (45)	0	5 (22)	23 (34)

	Median age (range), years	Median no. prior regimens (range)	Prior CAR T-cell therapy (%)	Baseline elevated LDH (%)	Primary refractory (%)
DLBCL N=21	64 (24-80)	4 (1-8)	13 (62)	13 (62)	15 (71)
Other large B-cell lymphoma N=11	62 (36-85)	4 (2-8)	7 (64)	6 (55)	6 (55)

Lugano 2014; 5 pts improved to CR after 2nd cycle

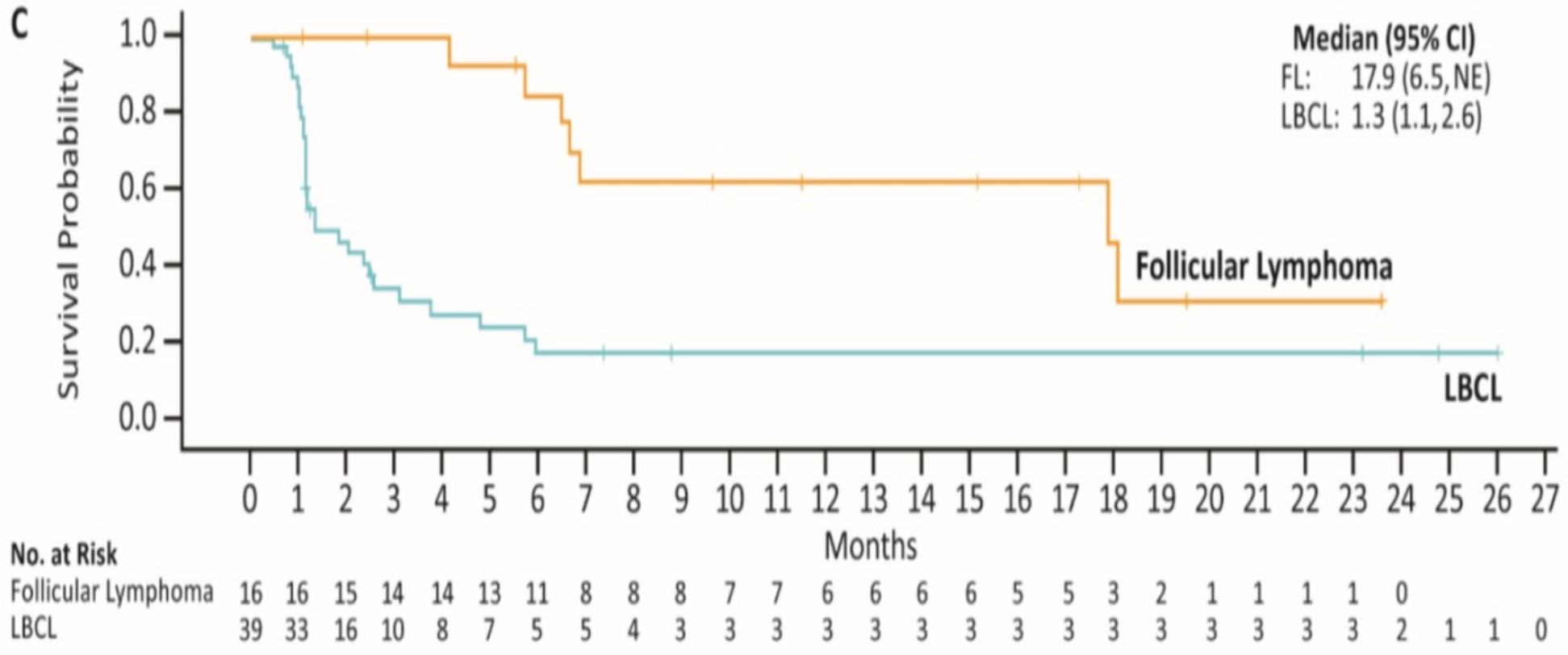
Response to treatment

Subgroups	Response/Subjects	ORR (95% CI)*
All subjects	37 / 68	54.4 (41.9, 66.5)
Age		
<65	17 / 31	54.8 (36.0, 72.7)
≥65	20 / 37	54.1 (36.9, 70.5)
Sex		
Male	27 / 52	51.9 (37.6, 66.0)
Female	10 / 16	62.5 (35.4, 84.8)
NHL histology		
DLBCL (de novo)	3 / 21	14.3 (3.0, 36.3)
Transformed iNHL/Gr3B FL	6 / 7	85.7 (42.1, 99.6)
Richter transformation	5 / 10	50.0 (18.7, 81.3)
Follicular lymphoma (low grade)	13 / 13	100.0 (75.3, 100.0)
Mantle cell lymphoma	5 / 10	50.0 (18.7, 81.3)
Stage IV at study entry		
Yes	29 / 57	50.9 (37.3, 64.4)
No	8 / 11	72.7 (39.0, 94.0)
Baseline target lesion SPD (cm^2)		
<20.75	19 / 34	55.9 (37.9, 72.8)
≥20.75	18 / 34	52.9 (35.1, 70.2)
Prior no. of therapies		
1-3	18 / 33	54.5 (36.4, 71.9)
4+	19 / 35	54.3 (36.6, 71.2)
Prior no. anti-CD20 regimens		
1-2	20 / 40	50.0 (33.8, 66.2)
3+	17 / 28	60.7 (40.6, 78.5)
Refractory subjects		
Yes	14 / 29	48.3 (29.4, 67.5)
No	22 / 36	61.1 (43.5, 76.9)
Unknown	1 / 3	33.3 (0.8, 90.6)
Prior CD19 CAR T-cell therapy		
Yes	14 / 27	51.9 (31.9, 71.3)
No	23 / 41	56.1 (39.7, 71.5)
Prior HSCT		
Yes	8 / 11	72.7 (39.0, 94.0)
No	29 / 57	50.9 (37.3, 64.4)
Baseline LDH>ULN		
Yes	11 / 32	34.4 (18.6, 53.2)
No	26 / 36	72.2 (54.8, 85.8)



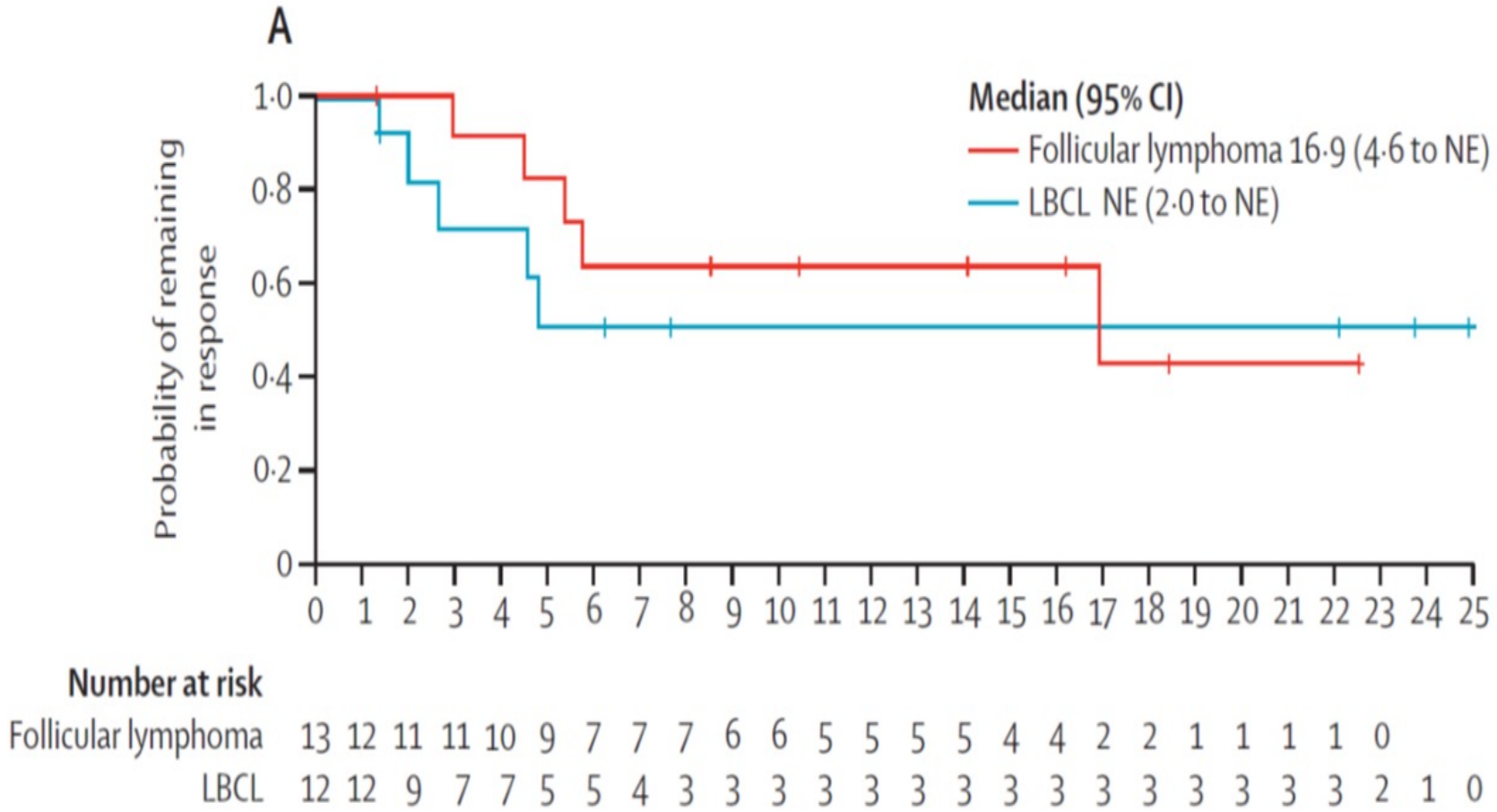
Progression-free survival

43 pts died, 2 in CR

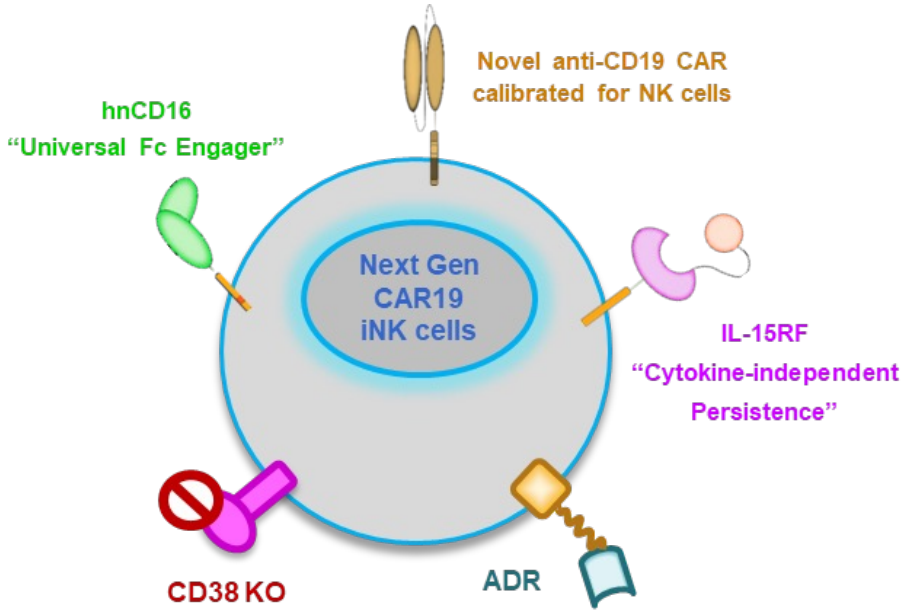


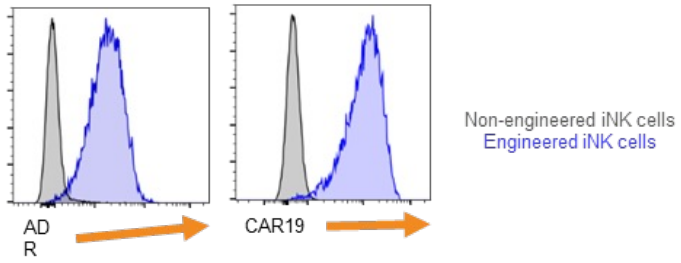
Duration of response

2 patients received consolidative SCT



Future directions: FT-522





hnCD16: High-affinity 158V, non-cleavable CD16 Fc receptor to maximize ADCC

IL-15RF: Interleukin-15 receptor fusion to elicit cytokine autonomy and increase persistence

CD38 KO: resistance to anti-CD38 mAb-mediated fratricide opens new opportunities in targeting and conditioning; enhanced NK cell metabolic fitness and persistence.

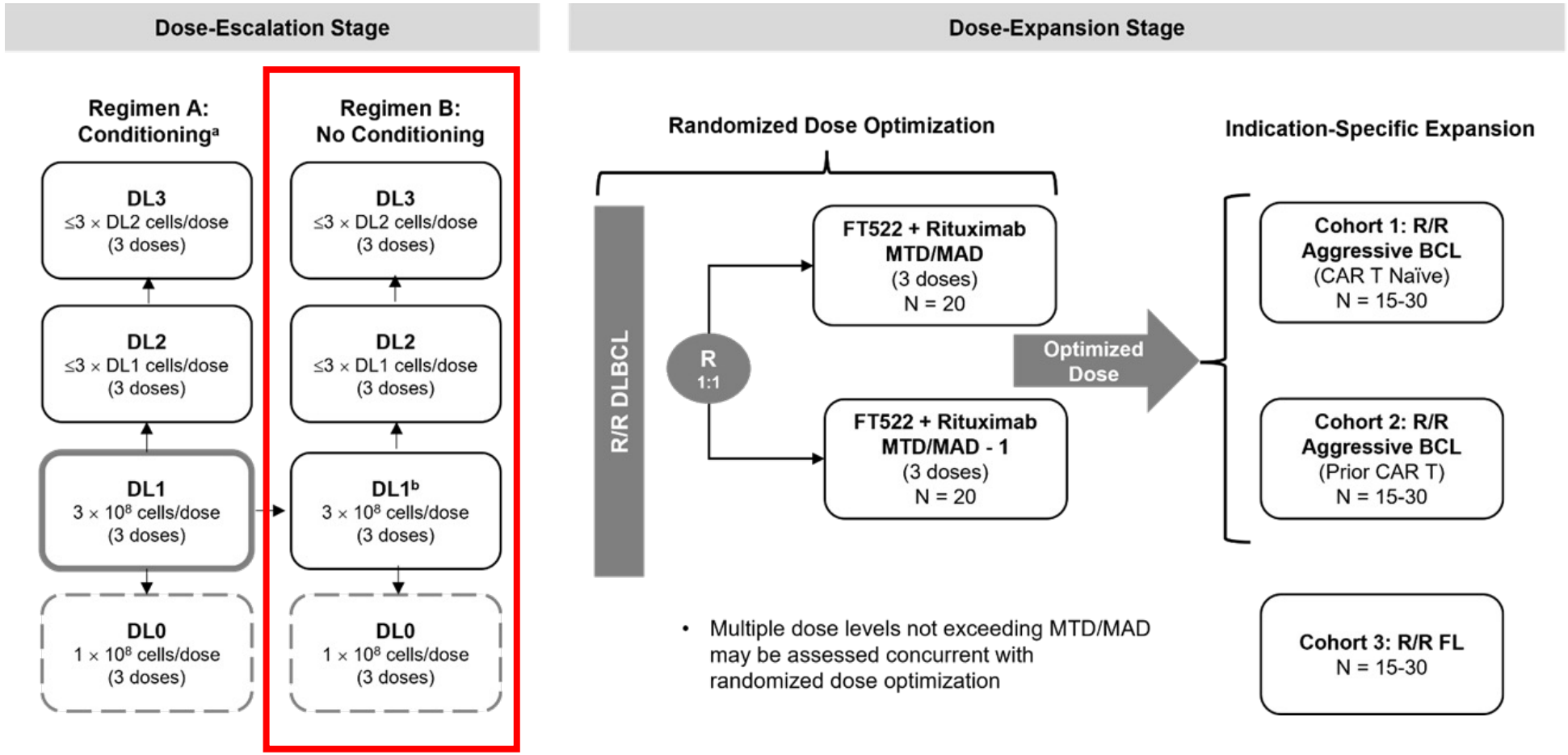
CAR-19: Optimized CAR activity against CD19

ADR: CAR activity 41BB; unique opportunity for temporal potentiation and reduced dependency on lympho-conditioning **Alloimmune Defense Receptor (targeting 4-1BB)**

RMAT for FT516 withdrawn

Bachanova V et al. ASH 2024

Future directions: FT-522



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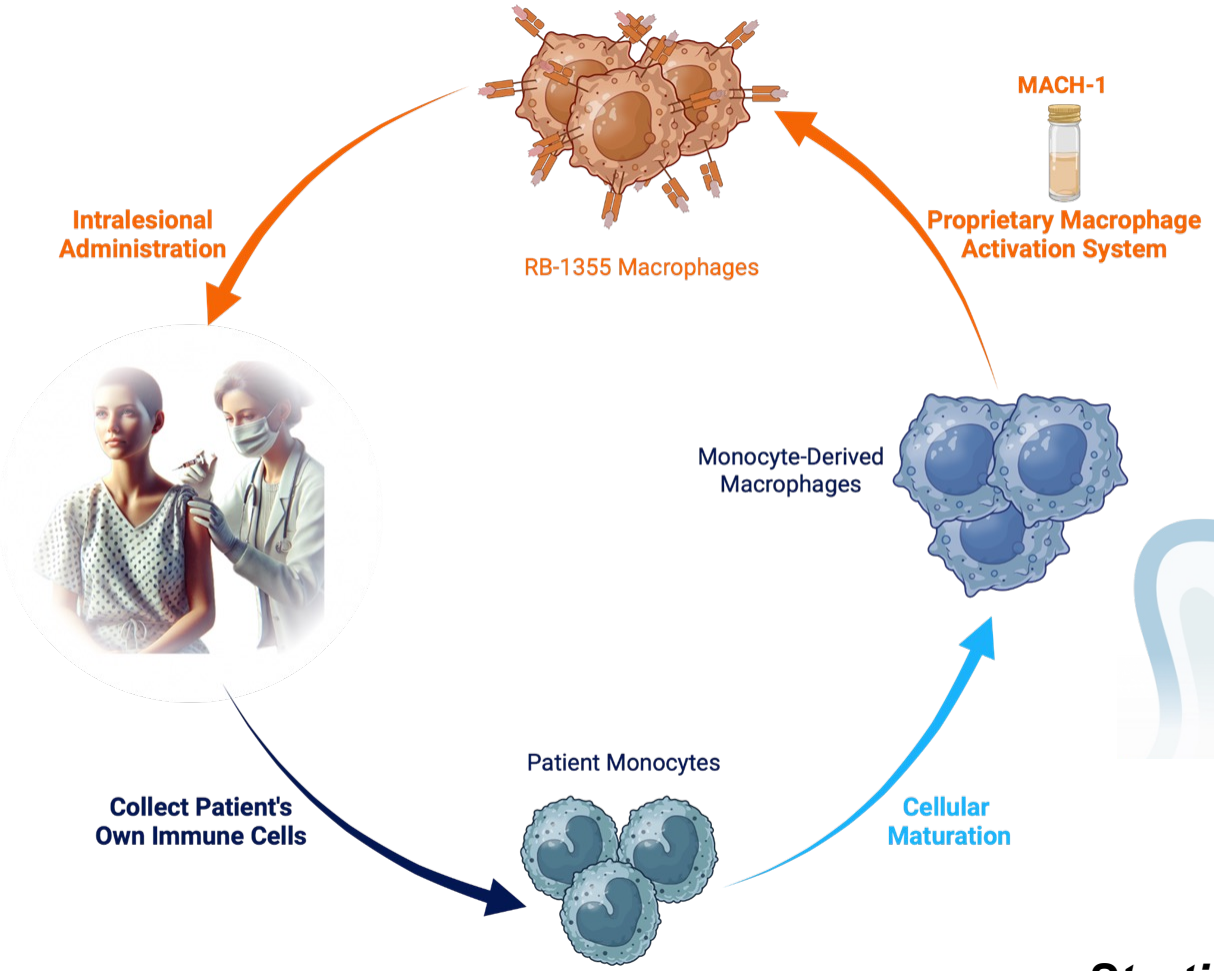
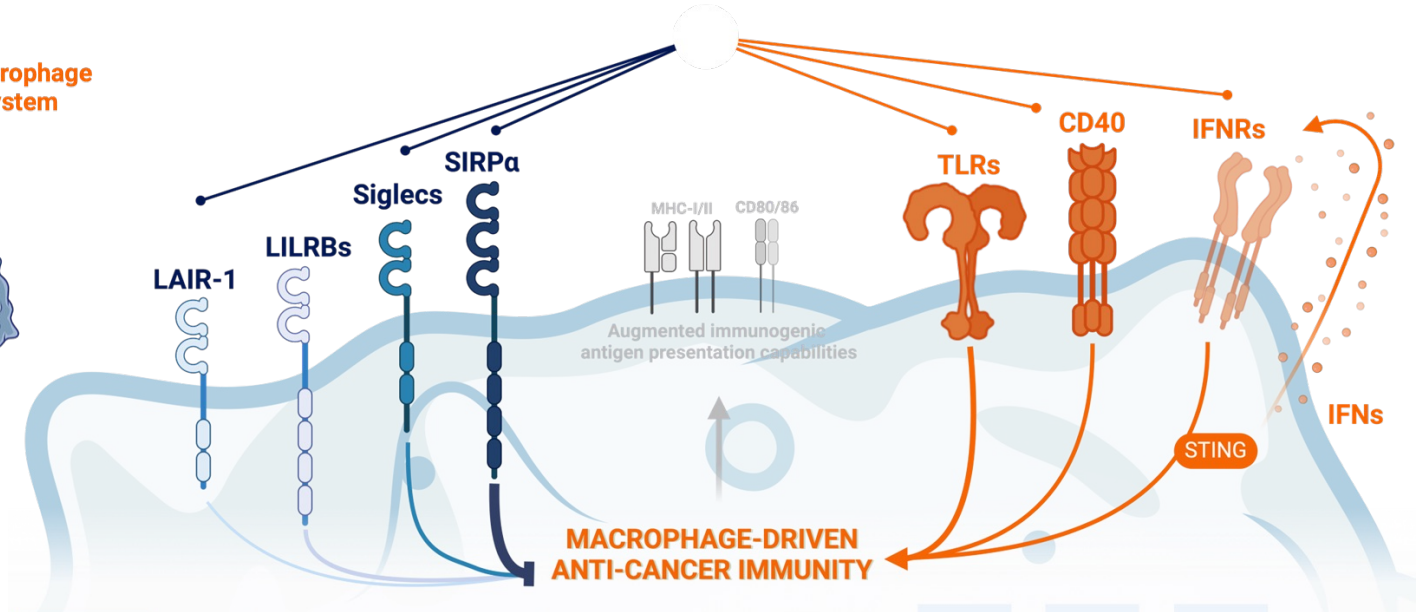
Autologous macrophages: RB-1355





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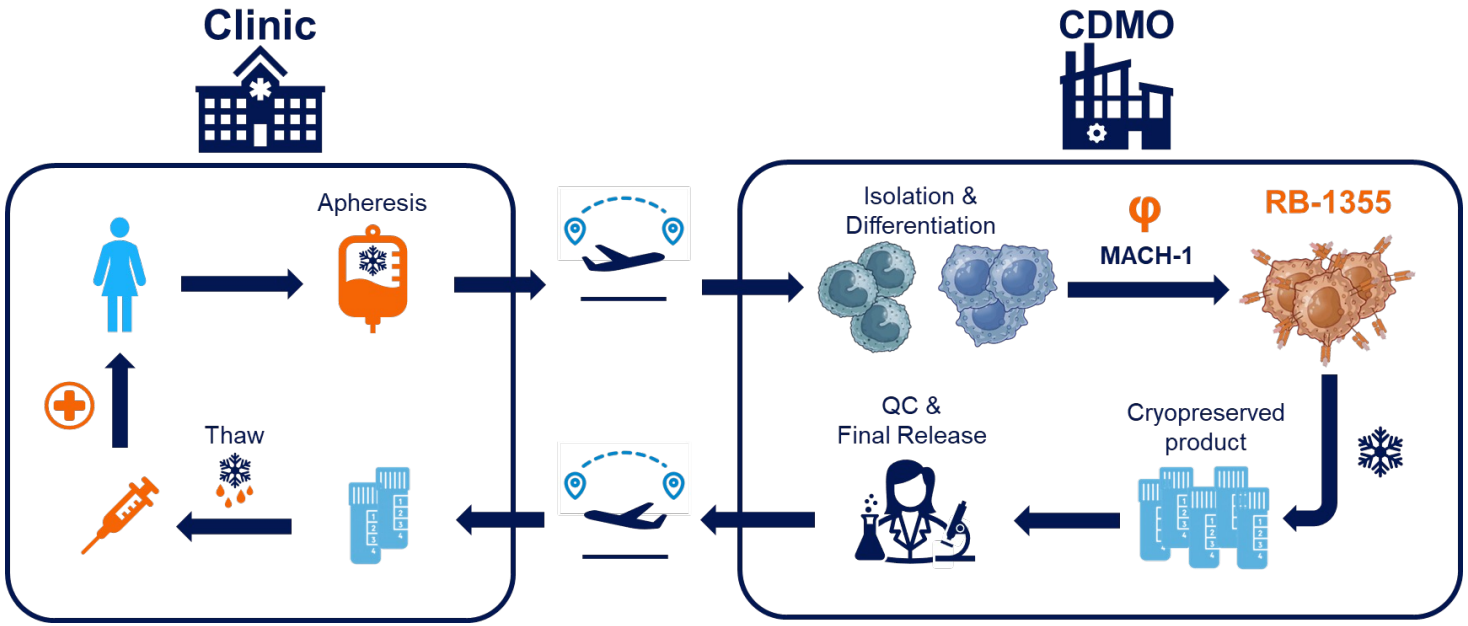
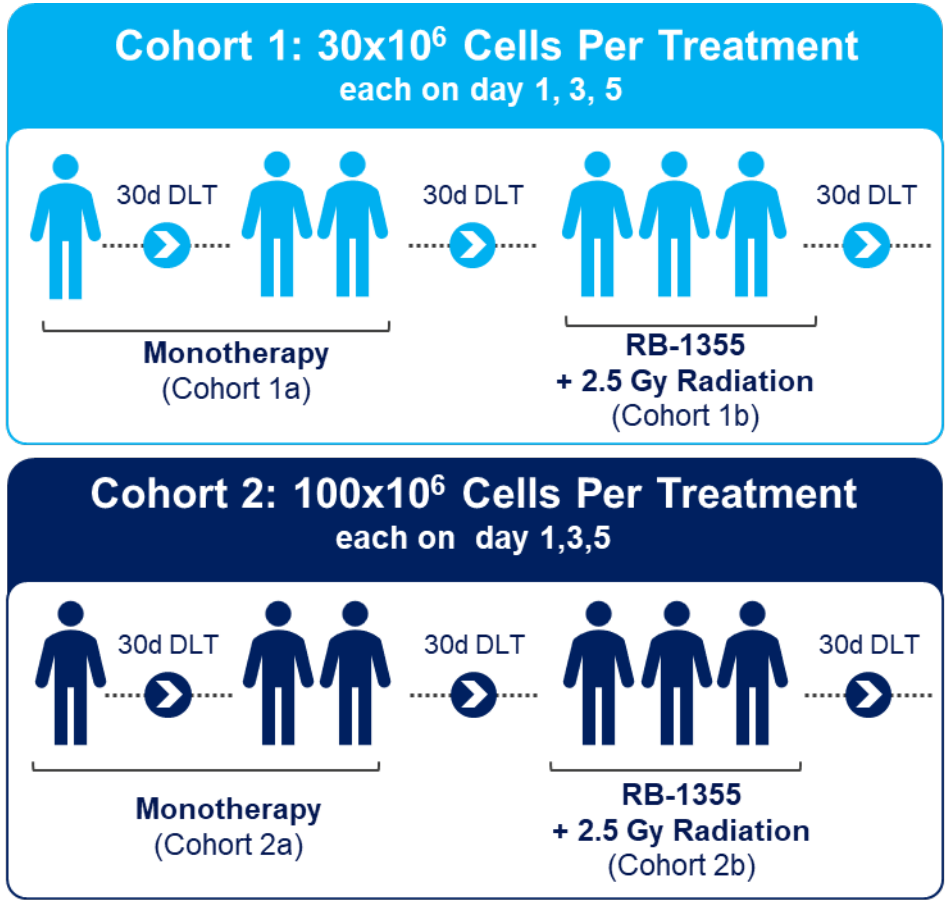
Treatment schema



1 week for final product
No LDC used



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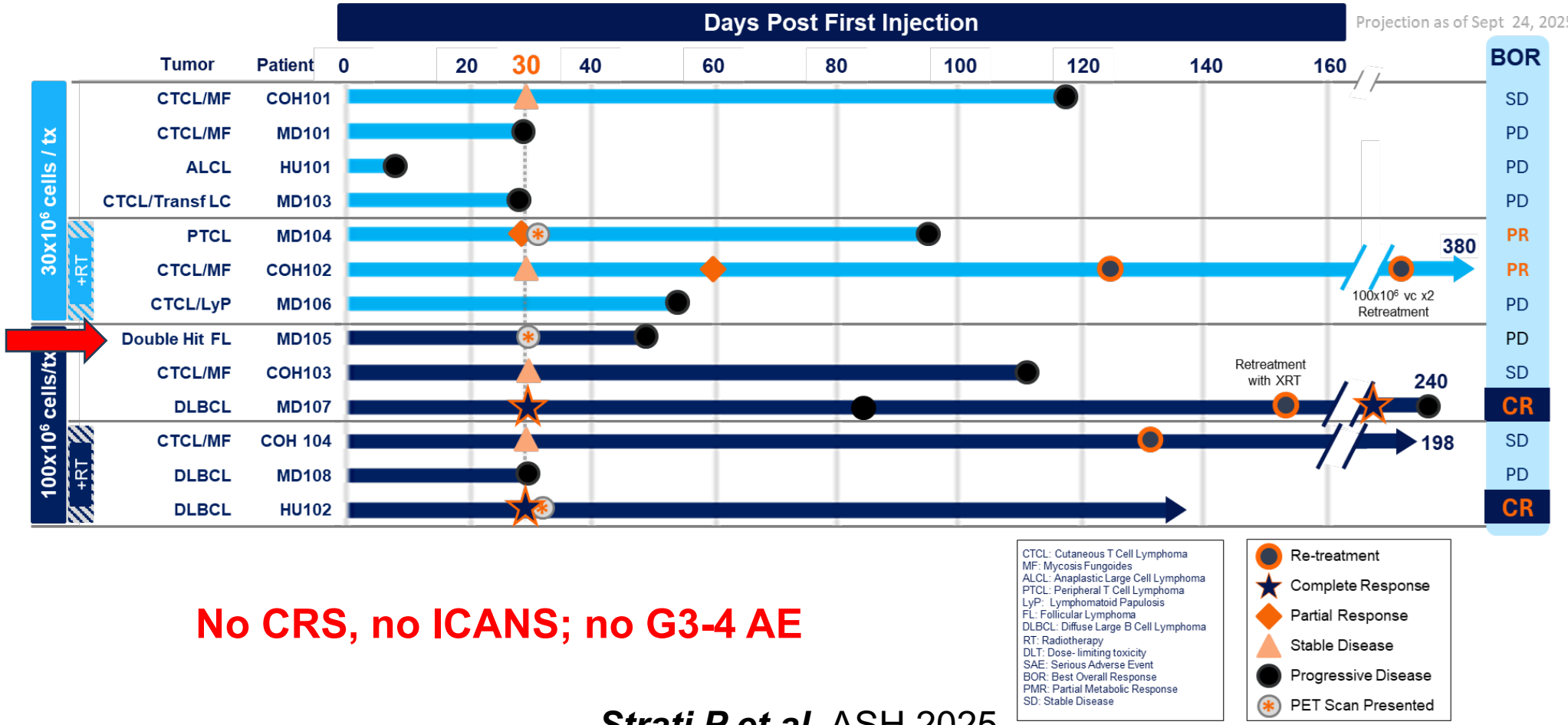
Safety and efficacy data



No CRS, no ICANS; no G3-4 AE

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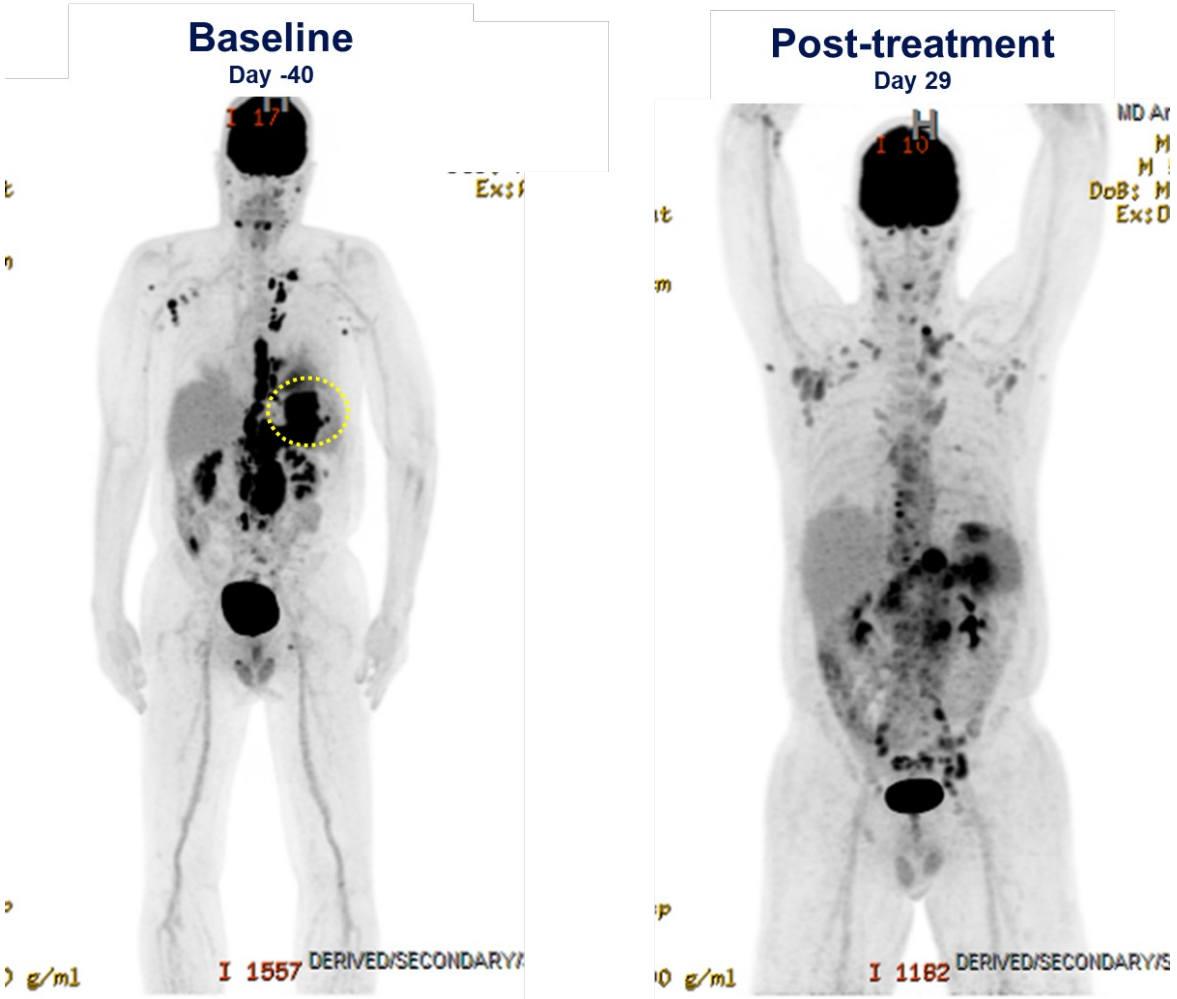
Efficacy in double hit FL case



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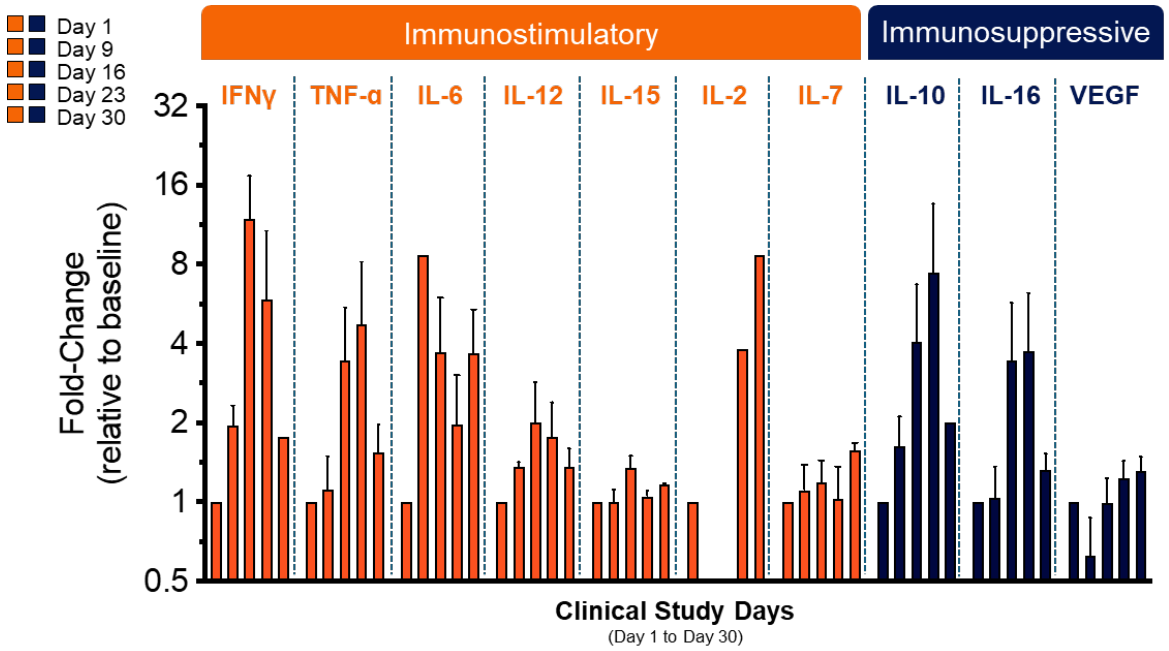
Triggering of systemic immune activation



Detected in Blood

Before Tx | Post-Treatment

Circulating T cells

Clone #	CDR3 (TCRB)	Cluster	T Cell Type	Day 01	Day 09	Day 16	Day 23	Day 30
Clone 1	CASSPAGGLKFNEQFF	5	Cytotoxic CD8 T cells		■			
Clone 2	CATWTGDSNQPQHF	5	Cytotoxic CD8 T cells		■		■	■
Clone 3	CASSEGQDTDTQYF	6	Memory CD8 T cells				■	■
Clone 4	CSGTKTRPGGTNTGELFF	15	Regulatory CD4 T cells					■
Clone 5	CAISESRQSESPLHF	5	Cytotoxic CD8 T cells		■			
Clone 6	CAISESRQSESPLHF	11	Memory CD8 T cells		■			
Clone 7	CAISESRQSESPLHF	5	Cytotoxic CD8 T cells	■	■	■	■	■
Clone 8	CASSLGHFNYGYTF	5	Cytotoxic CD8 T cells		■		■	
Clone 9	CASSQGQGTEAFF	5	Cytotoxic CD8 T cells		■			
Clone 10	CASSPSGTGVPSGANVLTF	5	Cytotoxic CD8 T cells			■		

Circulating B cells

Clone #	CDR3 (IGL)	Cluster	B Cell Type	Day 01	Day 09	Day 16	Day 23	Day 30
Clone 1	CAAWDDSLSGFYVF	3	Naïve B cells		■			■
Clone 2	CCSYAGSSTLVF	0, 2, 3, 17	Naïve/Activated B cells	■	■	■	■	■
Clone 3	CGTWDSSLSAVVF	0, 2, 3, 12,17	Naïve/ABC-FGR/Activated B cells	■	■	■	■	■
Clone 4	CGTWDSSLSAWVF	0, 3	Naïve B cells		■		■	■
Clone 5	CLLYYGGAWVF	0, 2, 3, 18	Naïve/Activated Memory B cells	■	■	■		■
Clone 6	CMIWHSSAWVF	0, 2, 3	Naïve B cells	■	■	■	■	■
Clone 7	CNSRDSSGNHLVF	0, 3, 12,17	Naïve/ABC-FGR/Activated B cells	■	■	■	■	■
Clone 8	CQAWDSSIVVF	3, 17	Naïve/Activated B cells		■		■	
Clone 9	CQAWDSSTVVF	0, 2, 3, 12,17	Naïve/ABC-FGR/Activated B cells	■	■	■	■	■
Clone 10	CQSYDSSLSGSKVF	2, 3	Naïve B cells		■			■
Clone 11	CQSYDSSLSGSVF	0, 2, 3, 12	Naïve B cells/ABC-FGR	■	■	■	■	■
Clone 12	CSSYTSSSTWVF	0, 2, 3	Naïve B cells	■	■	■	■	■

Detected in treated tumor

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Summary

- Multiple autologous anti-CD19 CART are available for FL
- While axi-cel is clearly more toxic, no clear difference in efficacy across products is currently evident
- Real world data of CART in FL are limited
- Development of non-T-cell based allogeneic products and/or products not requiring LDC is next in FL

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