

Multitargeted and In Vitro CAR T-Cells for Lymphoma

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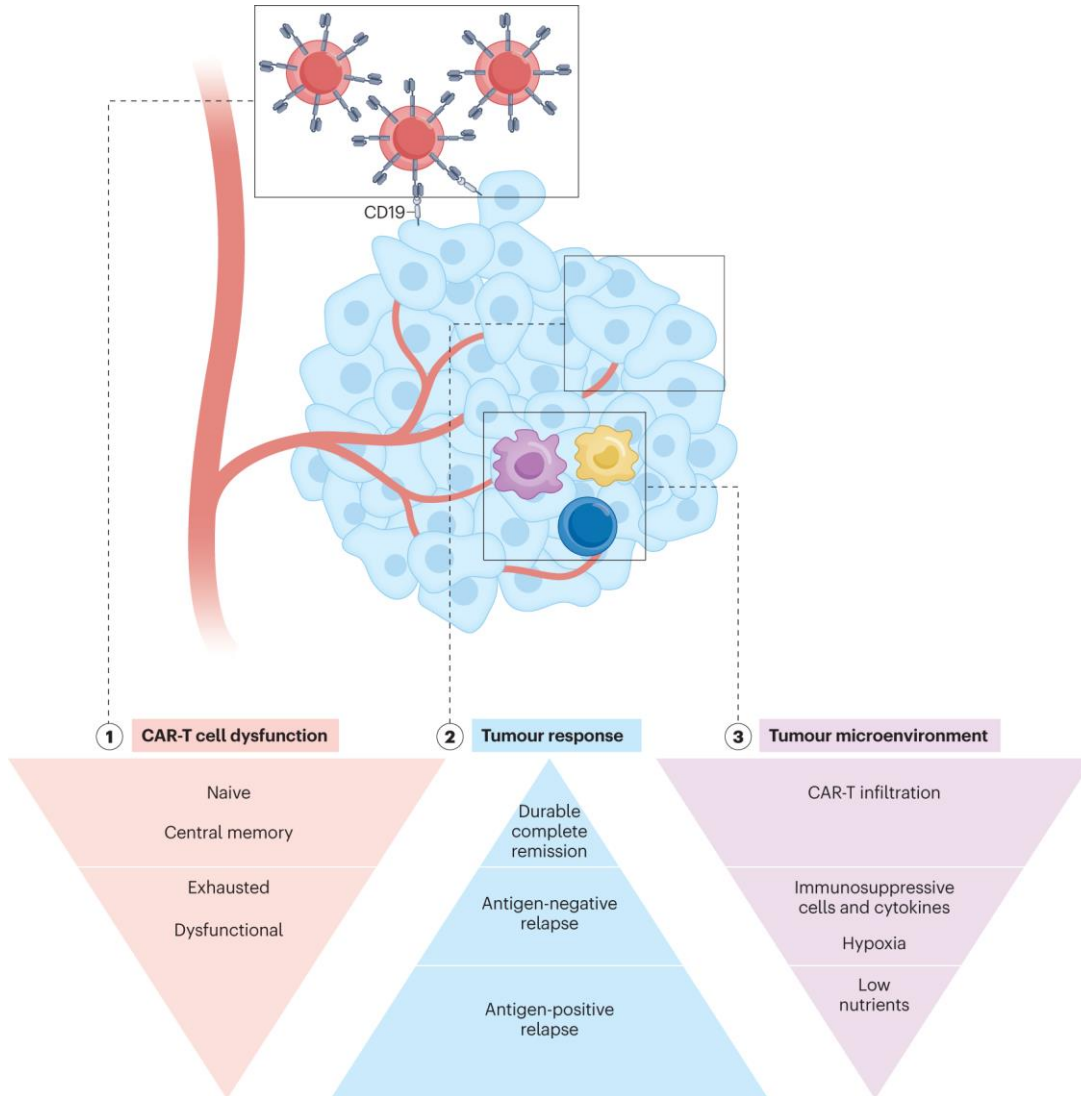
Disclosures for Jeremy Abramson

Consulting for AbbVie, Astra-Zeneca, BMS, Caribou, Foresight Diagnostics, Genentech, Johnson & Johnson, Lilly, Miltenyi Biotec, Novartis, Roche

Research support (to institution) from Allogene, Astra-Zeneca, BMS, Celgene, Collectis, Genentech, Merck, Pfizer, Regeneron, Seagen, Takeda



Overcoming Resistance to CAR T-cell Therapy is an Unmet Need

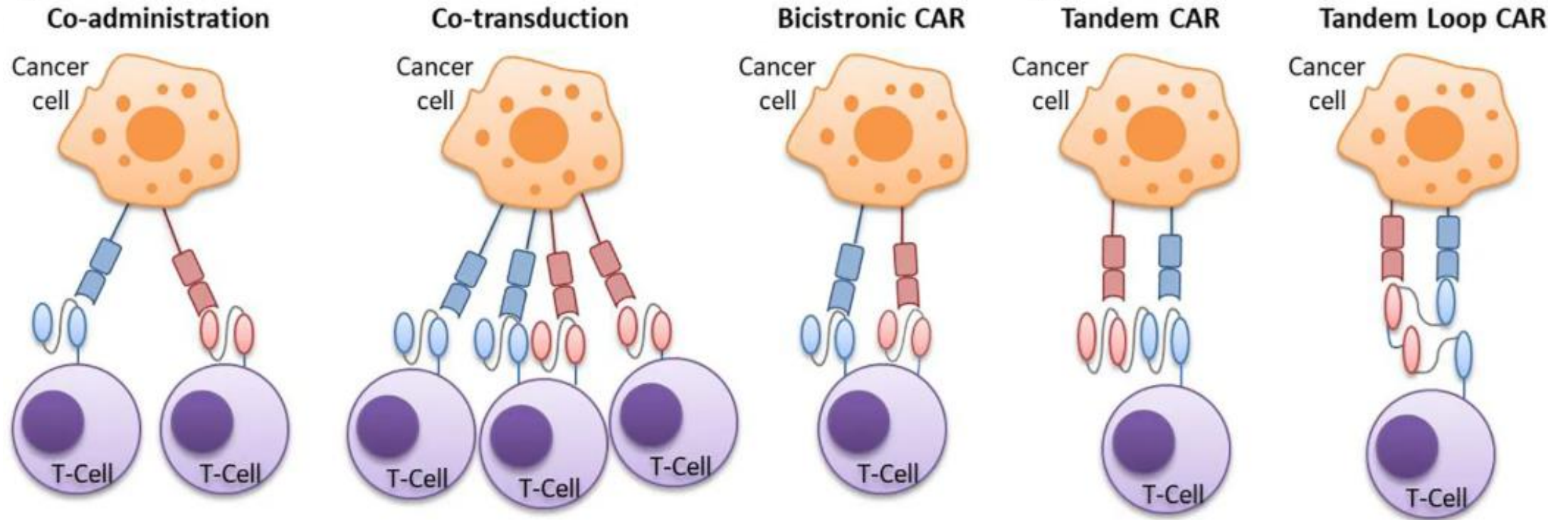


Goals in advancing CAR technology

- Optimize stem memory phenotype
- Speed up manufacturing
- Prevent antigen escape
- Overcome the microenvironment
- Reduce toxicity



Dual-targeting CAR T-cell strategies



Summary of Dual-targeting CAR T-cells in Advanced Development for Lymphoma

Product	Construct	N	ORR	CRR
GLPG5101	Auto CD19/CD20	25	69%	54%
Zamto-cel	Auto CD19/CD20	69	73%	51%
KTE363	Auto CD19/CD20	23	87%	78%
Prizlo-cel	Auto CD19/CD20	44	91%	75%
Ronde-cel	Auto CD19/CD20	37	90%	71%

Kersten et al. Proc ASH 2024; Shah et al. Proc ASH 2024; Dahiya et al. Proc ICML 2025; Patel et al. Proc EHA 2025; Larson, et al Proc ASH 2025.

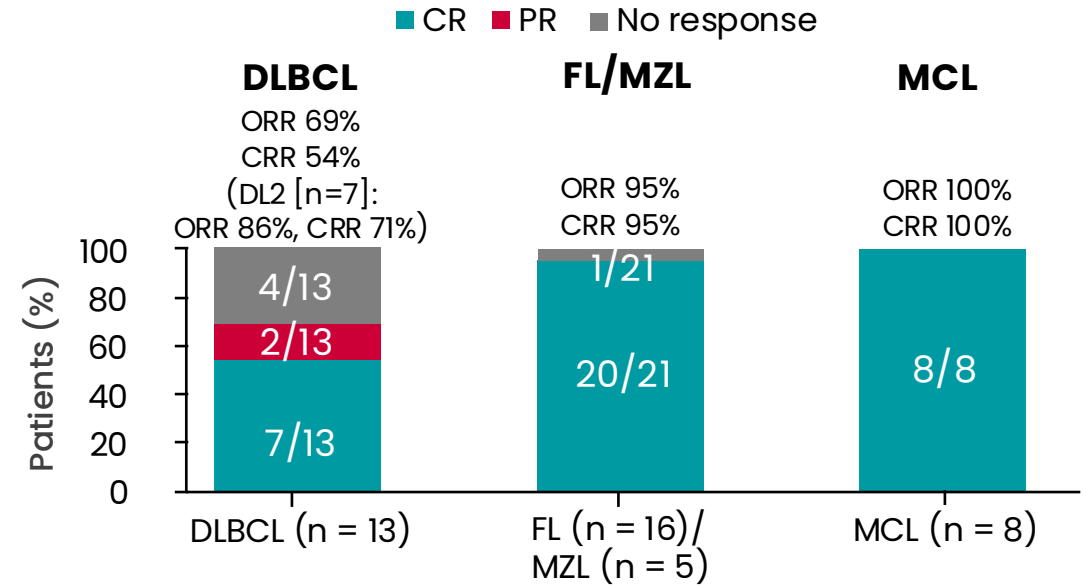


GLPG5101

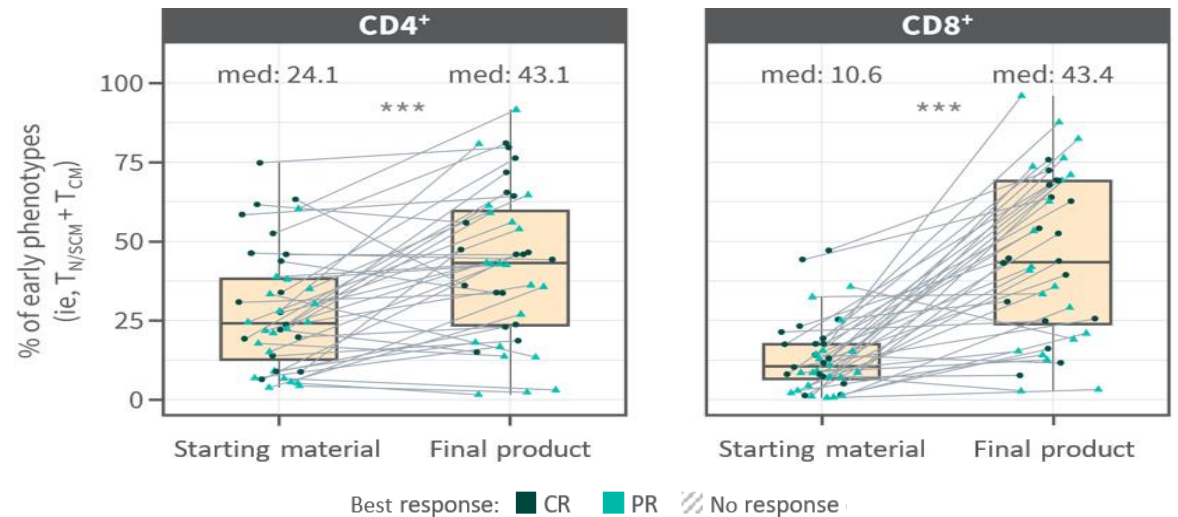
- A fresh stem-like, early memory phenotype anti-CD19/CD20 CAR T-cell therapy with 7-day
- ATALANTA-1: phase I/II trial in patients with R/R B-NHL

Baseline characteristics	Phase I n = 20	Phase II n = 25
Median age, yr (range)	66.5 (25-78)	67 (40-81)
DLBCL, %	65	0
MCL, %	15	30
FL/MZL, %	15/5	64/16
High risk (M/FL) IPI, %	42	56
Median prior therapies (range)	2.5 (1-7)	3 (2-11)

	All patients N = 32
CRS, n (%)	11 (34)
Grade 1	5 (16)
Grade 2	6 (19)
Grade 3	0
ICANS, n (%)	4 (13)
Grade 1	3 (9)
Grade 2	0
Grade 3	1 (3)



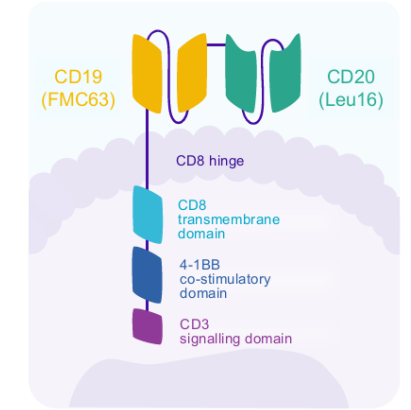
Majority of responses ongoing at median 3.3 mo



Zamtocabtagene Autoleucel: DALY 2

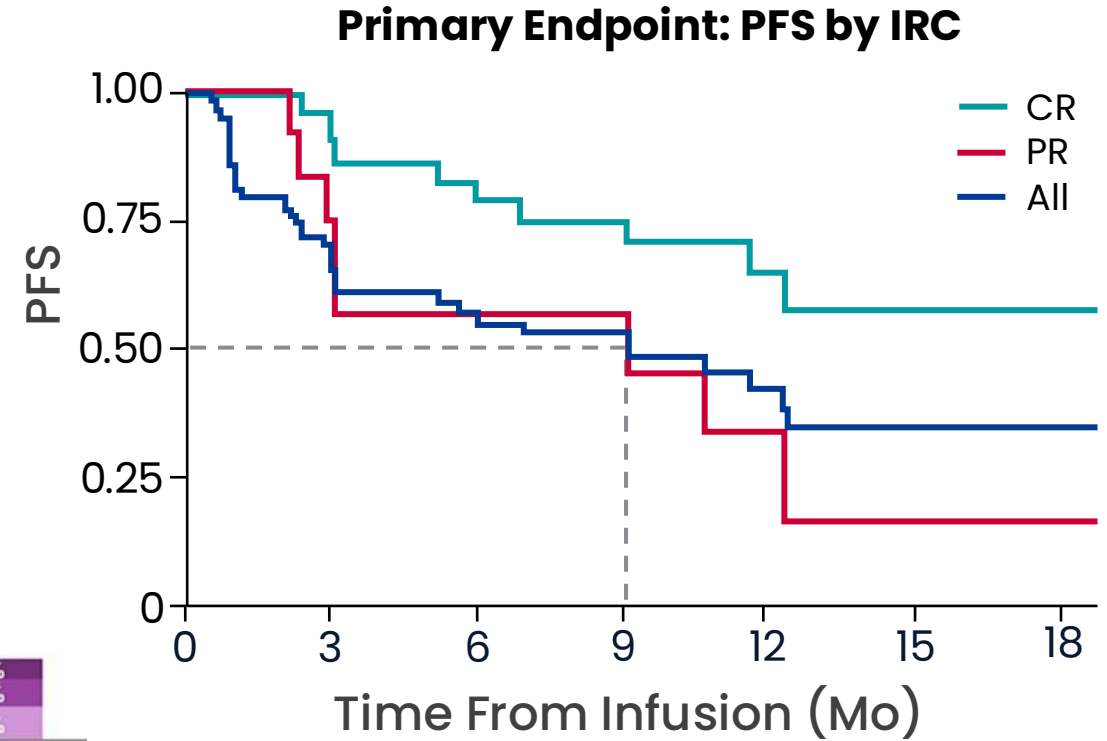
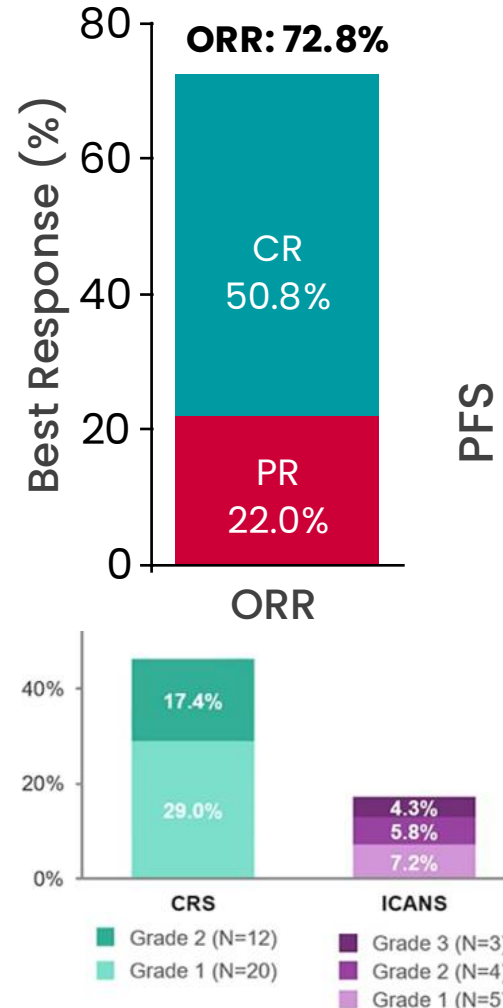
- Anti-CD19/CD20 Fresh CAR T-cell therapy with 14-day vein-to-vein time
- DALY 2: phase II study in patients with R/R DLBCL after ≥ 2 prior lines of treatment

Tandem CD20-CD19 (directed)
CAR-T cell¹ therapy

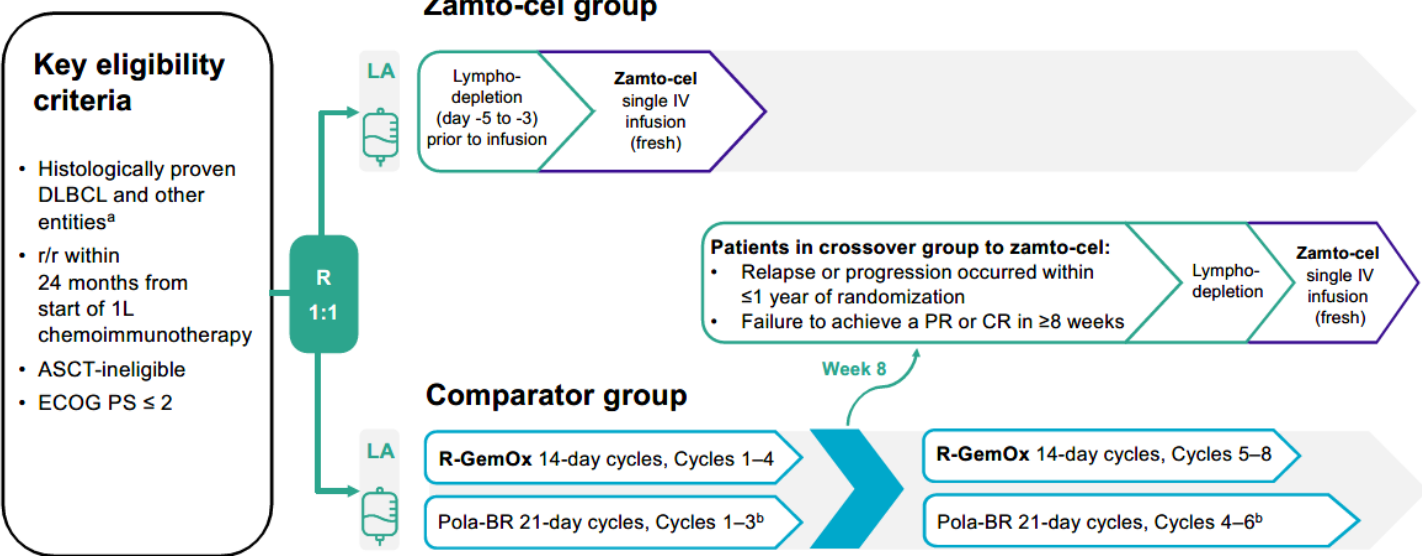


Baseline characteristics	N = 59
Median age, yr (range)	63 (25-85)
Elevated LDH, %	53
IPI 3-5, %	52
2 prior lines of therapy, %	75
≥ 3 prior lines of therapy, %	25
Prior ASCT, %	25

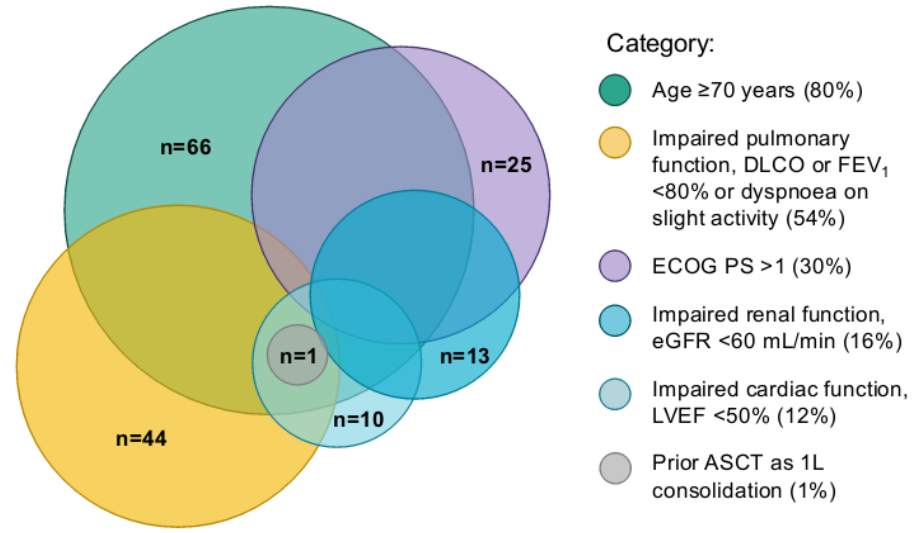
Antigen loss at progression	n = 27
CD19	2
CD20	2
CD19 & CD20	1



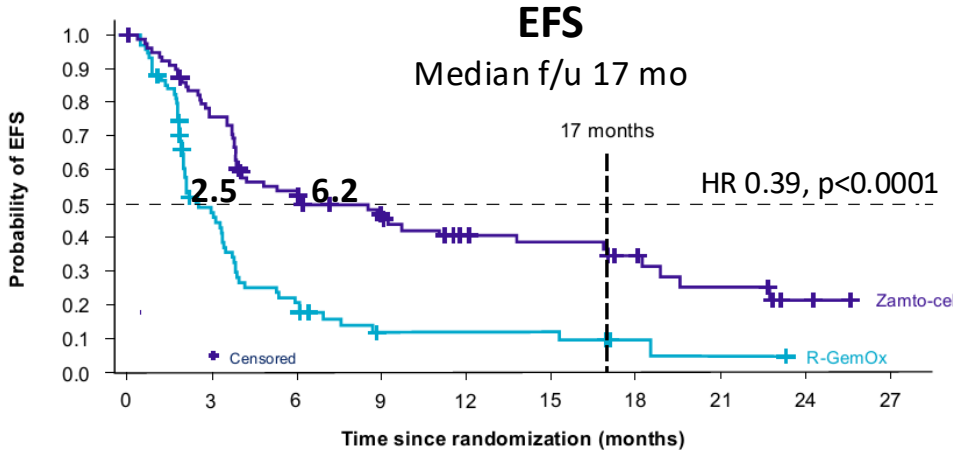
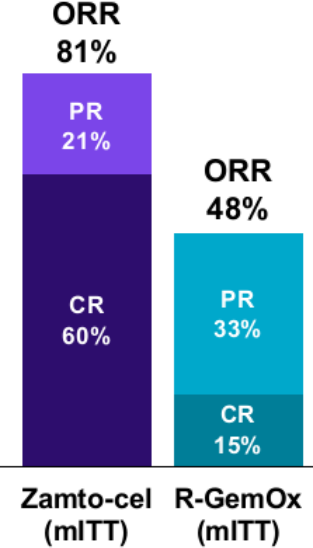
Zamtocabtagene Autoleucel: DALY 2-EU study in 2nd line LBCL



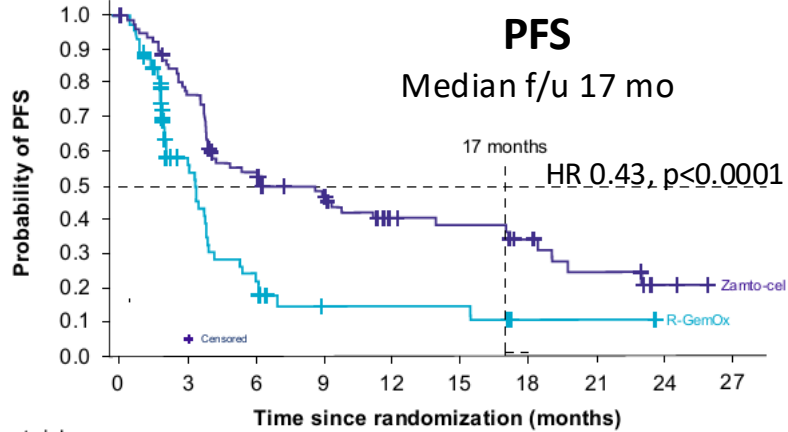
Baseline characteristics	Zamto-cel N = 82	R-GemOx N=78
Median age, yr (range)	75 (19-87)	74 (55-86)
Elevated LDH, %	45	60
IPI 3-5, %	57	58
Refractory	24	23



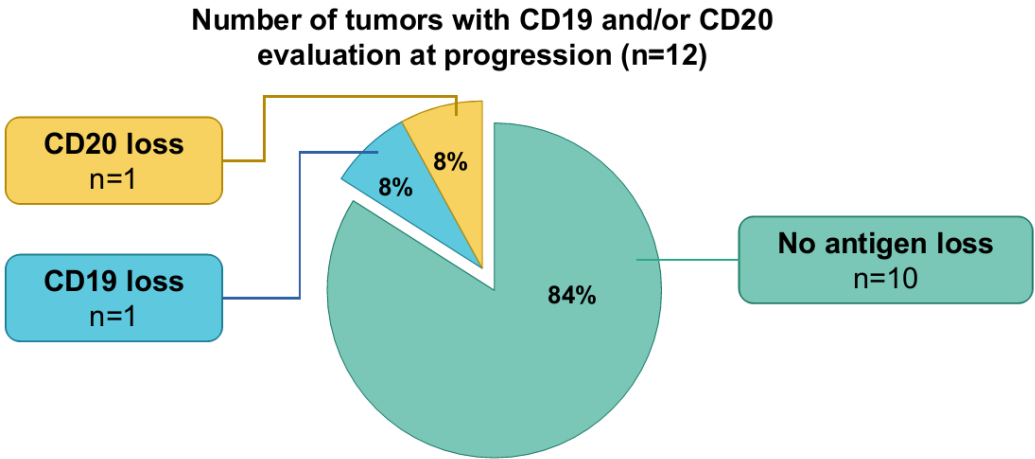
DALY 2-EU: Results



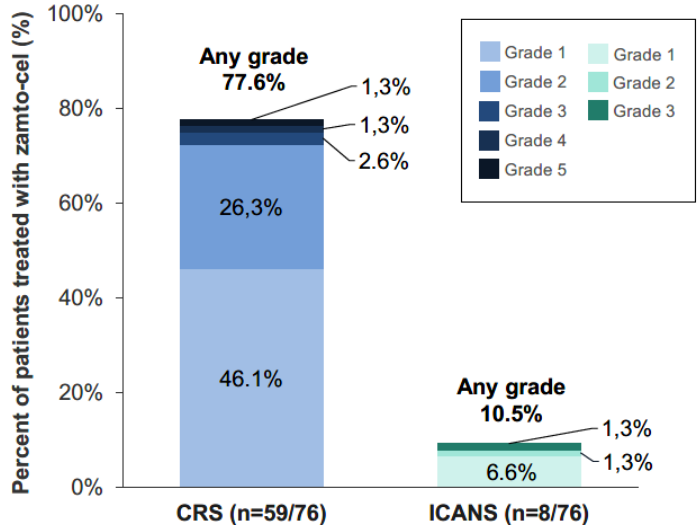
Number at risk, n	0	3	6	9	12	15	18	21	24	27
Zamto-cel	82	59	41	31	21	19	12	8	2	0
R-GemOx	78	32	14	5	5	5	2	1	0	0



Number at risk, n	0	3	6	9	12	15	18	21	24	27
Zamto-cel	82	59	41	31	21	19	12	8	2	0
R-GemOx	78	27	11	4	4	4	1	1	0	0



Rates of CRS and ICANS in patients treated with zamto-cel

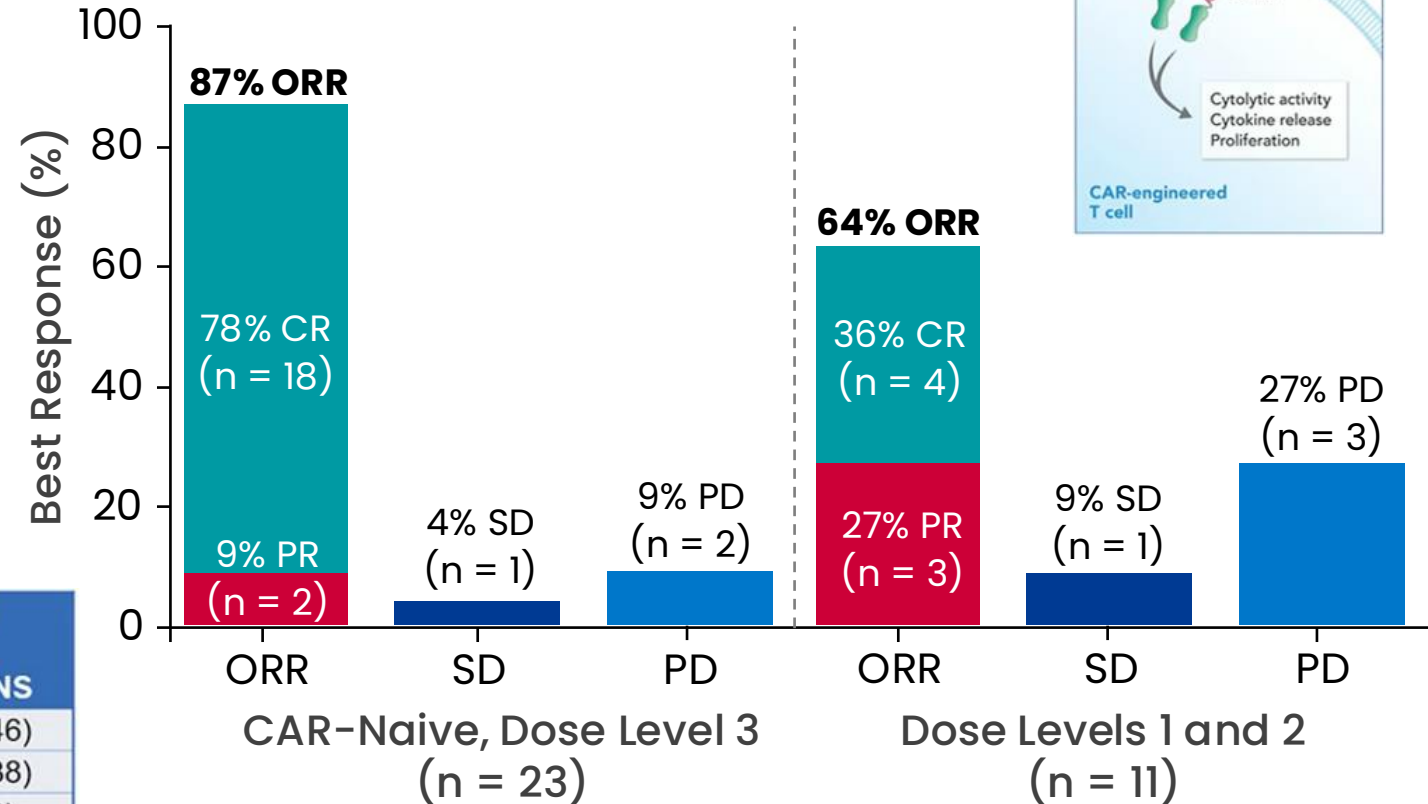


KITE-363

- A bicistronic, lentiviral-encoded, autologous anti-CD19/CD20 CAR t-cell therapy
- Phase I trial in patients with R/R BCL

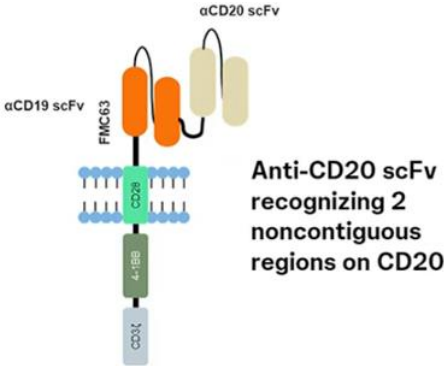
Baseline characteristics	N = 37
Median age, yr (range)	62 (25-83)
IPI 3-4, %	44
1 prior line of therapy (primary refractory), %	46
≥2 prior lines of therapy, %	54
Prior anti-CD19 CAR, %	19

Parameter	Dose Levels 1 & 2 (N=11)		Dose Level 3 (N=26)	
	CRS	ICANS	CRS	ICANS
Any grade, n (%)^a	7 (64)	1 (9)	24 (92)	12 (46)
Grade 1/2	7 (64)	0	23 (88)	10 (38)
Grade 3	0	1 (9)	1 (4)	2 (8)
Grade 4	0	0	0	0
Grade 5	0	0	0	0

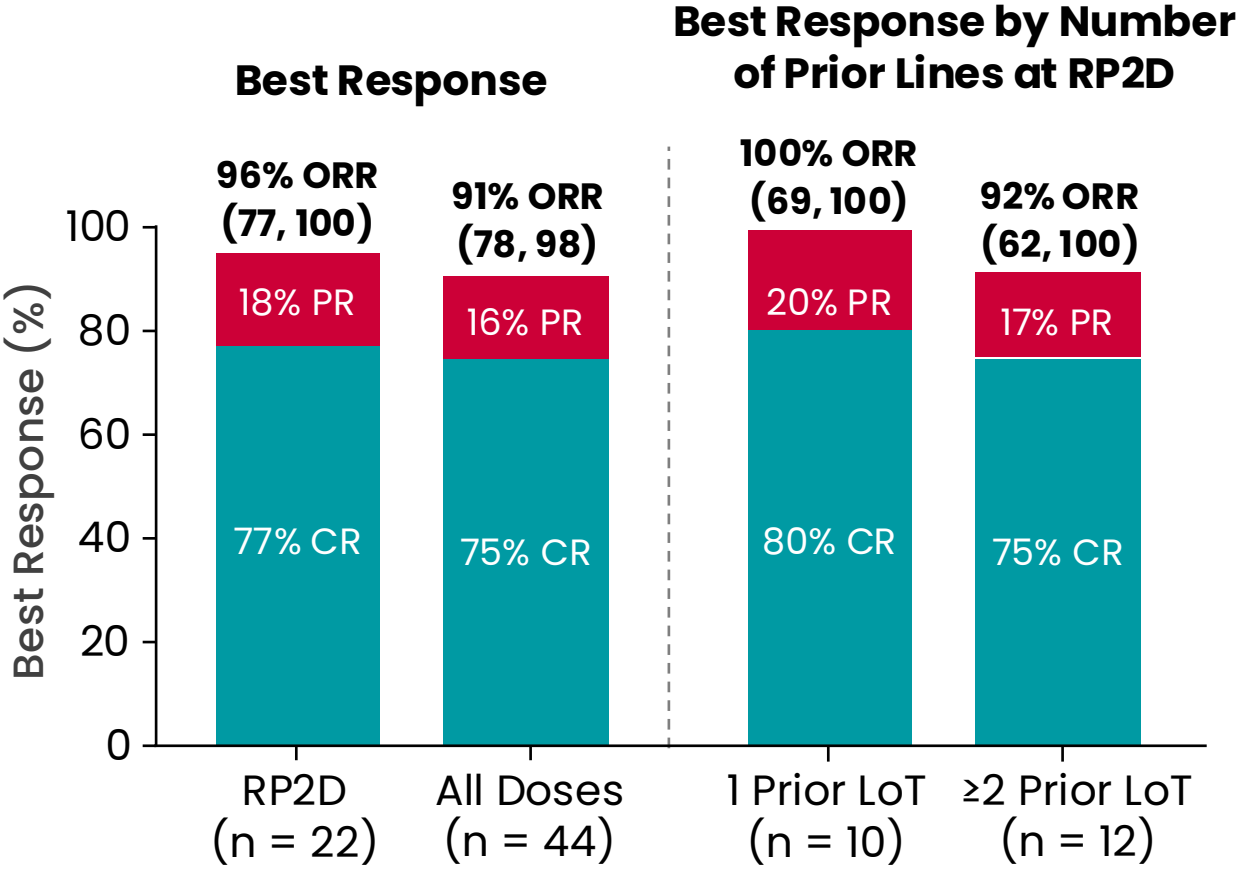
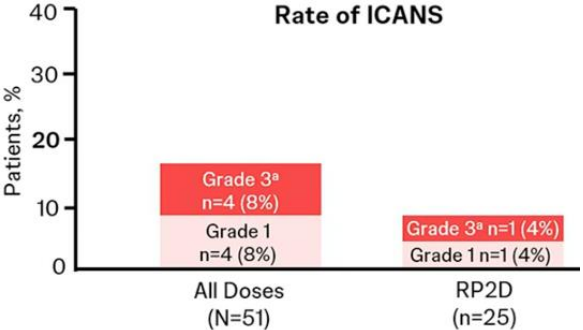
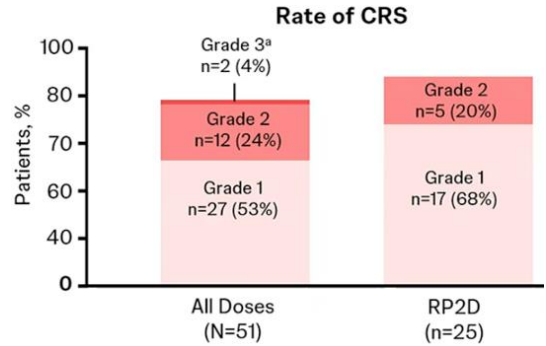


Prizloncabtogene Autoleucel (JNJ-90014496)

- Bispecific anti-CD19/CD20 CAR using a single lentiviral vector
- Phase Ib study in R/R LBCL

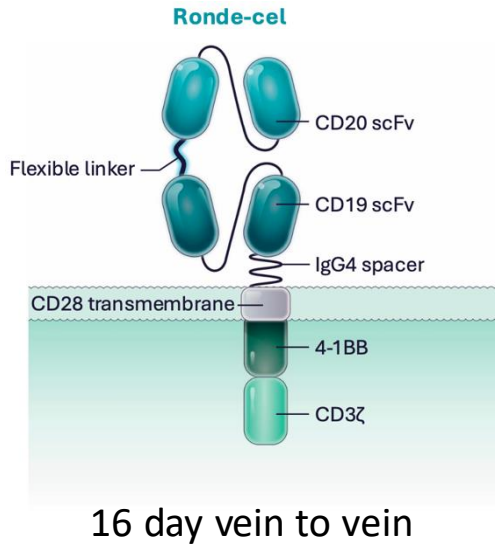


Baseline characteristics	All (N = 51)	RP2D (n = 25)
Median age, yr (range)	72 (39–87)	72 (40–87)
Primary refractory, %	57	56
Elevated LDH, %	35	36
Median prior lines of therapy (range)	1 (1–3)	1 (1–3)



Rondecabtagene Autoleucel (LYL314)

Dual-Targeting CD19/CD20 CAR T Cells Enriched for Stem-Like Phenotype (CD62L+)



Baseline characteristics	3L+ N=45	2L n=24
Median age, yr (range)	64 (21–87)	65 (26–85)
Primary refractory, %	49	92
Elevated LDH, %	44	42
DLBCL/HGBCL/tFL, %	51/18/18	63/25/8
Double hit, %	16	29

Best Overall Response (3L+ LBCL)	N = 29
Overall Responses, n (%)	27 (93%)
Complete Responses, n (%)	22 (76%)
Partial Response, n (%)	5 (17%)

Best Overall Response (3L+ HGBCL)	N = 8
Overall Responses, n (%)	7 (88%)
Complete Responses, n (%)	4 (50%)
Partial Response, n (%)	3 (38%)

	Prophylaxis N = 25	All N = 69
CRS	13 (52%)	42 (61%)
Grade 1	10 (40%)	22 (32%)
Grade 2	3 (12%)	20 (29%)
Grade ≥ 3	0 (0%)	0 (0%)
Median time to onset, days (range)	6 (3 - 18)	5 (1 - 18)
Median time to resolution, days (range)	2 (1 - 21)	3 (1 - 21)

	Prophylaxis N = 25	All N = 69
ICANS	3 (12%)	16 (23%)
Grade 1	2 (8%)	6 (9%)
Grade 2	0 (0%)	2 (3%)
Grade ≥ 3	1 (4%)	8 (12%)
Median time to onset, days (range)	7 (4 - 14)	7 (2 - 14)
Median time to resolution, days (range)	4 (1 - 9)	4 (1 - 10)



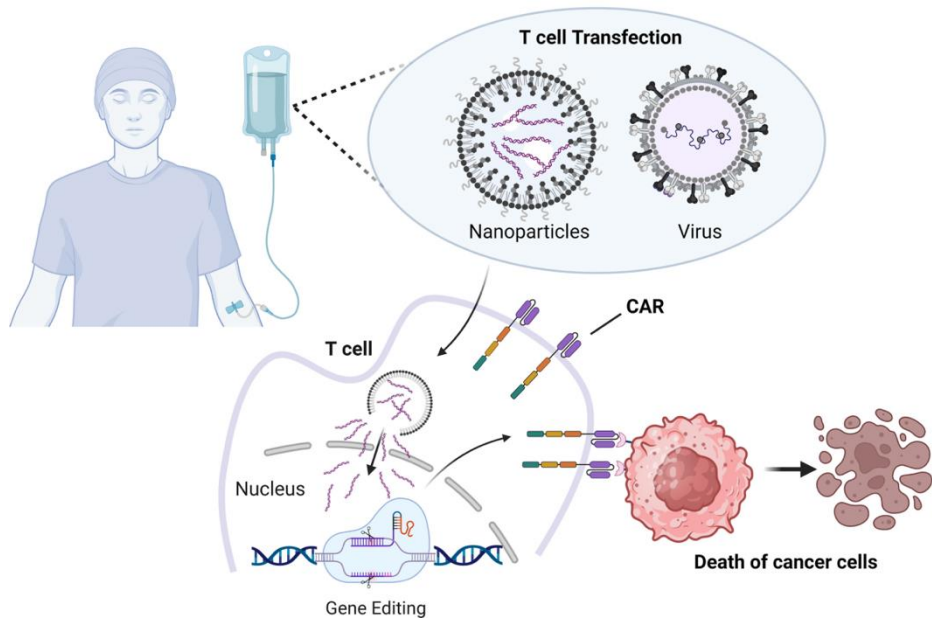
Unanswered questions for dual targeted CAR T-cells

- Are they better than mono-targeted autologous CAR T-cells?
- Is the dual targeting the secret to their success, or is it the manufacturing?
- Do they prevent antigen loss or work better in the setting of antigen loss?

Randomized trials versus anti-CD19 products ongoing and planned (Prizlo-cel, Rondecel, KTE363)!

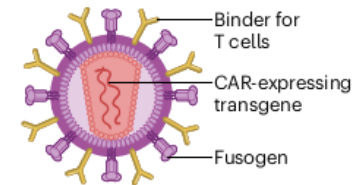


In Vivo CAR T-cells

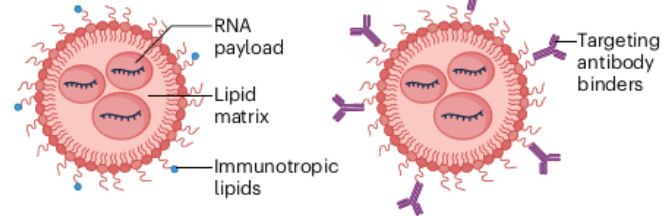


Engineered vector

a Viral vector

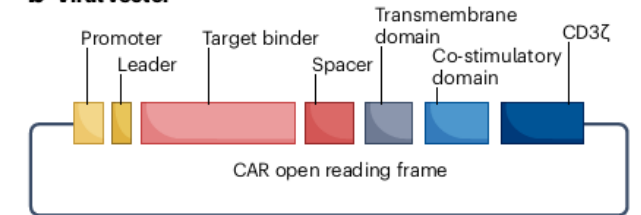


c LNP-RNA

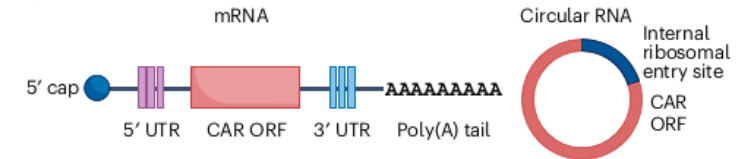


Payload

b Viral vector

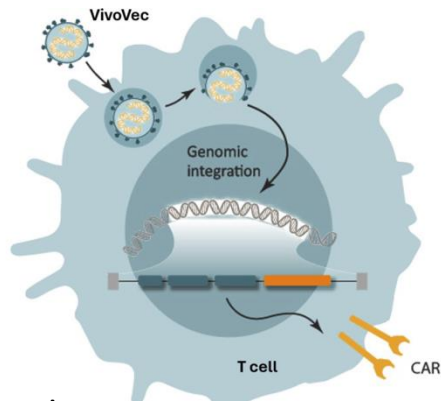


d LNP-RNA

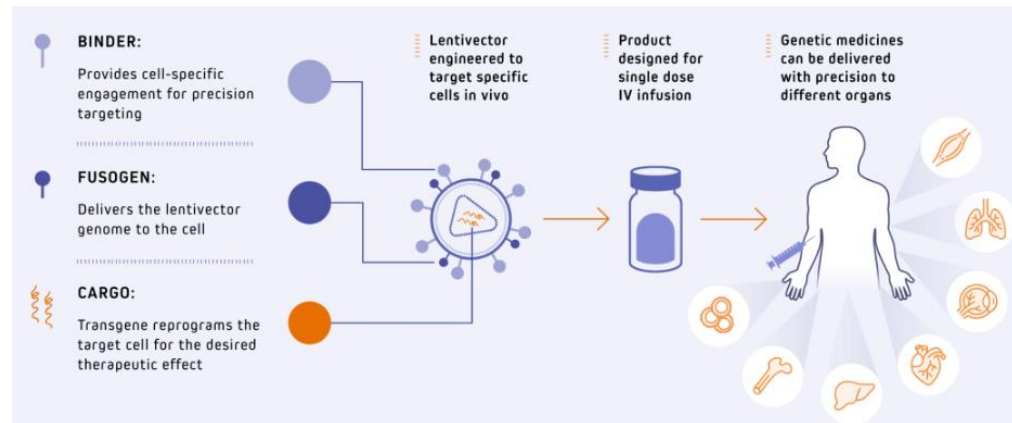


In Vivo CARs in Development for Lymphoma

Product	Company	Platform	Construct	Target	
UB-VV111	Umoja	Lentivirus	CD3-scFv LV	CD19	Phase 1, fast track
UB-VV300/310	Umoja	Lentivirus	CD3-scFv LV	CD20	Preclinical
UB-VV400/410	Umoja	Lentivirus	CD3-scFv LV	CD22	Phase 1
INT2104	Interius/Kite	Lentivirus	CD7-scFv LV	CD20	Phase 1
GCAR	EXUMA	Lentivirus	CD3-LV	CD19	Preclinical
ORN-101/145	Orna	LNP	Pan immune cells	CD19 circRNA	Preclinical
JCXH-213	Immorna	LNP	mRNA	CD19	Phase 1



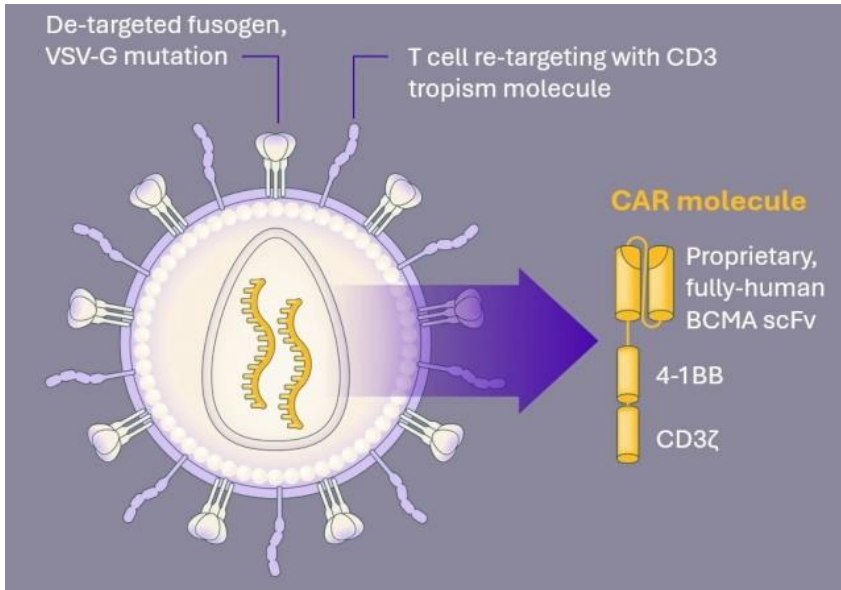
Umoja



Interius



Proof of Principle: KLN-1010 in Multiple Myeloma



Patient population

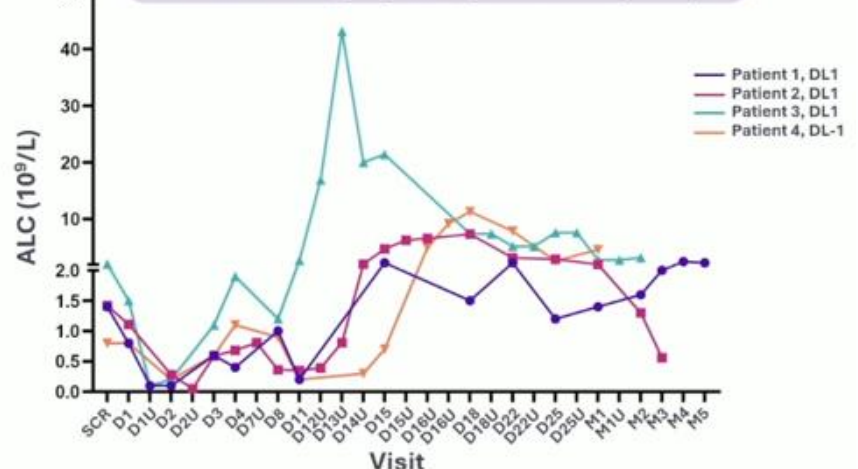
- RRMM after ≥3 lines of therapy; prior PI, IMiD, CD38 mAb
- ECOG Performance Status of 0, 1
- Adequate bone marrow and end organ function

Endpoints

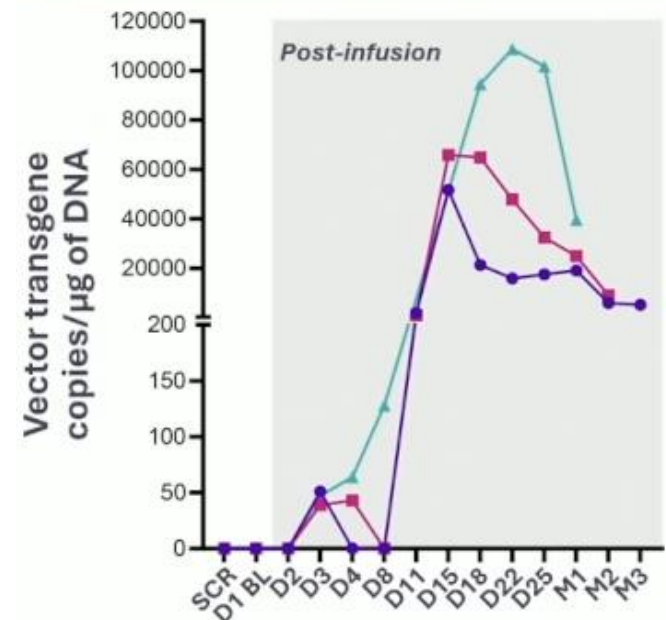
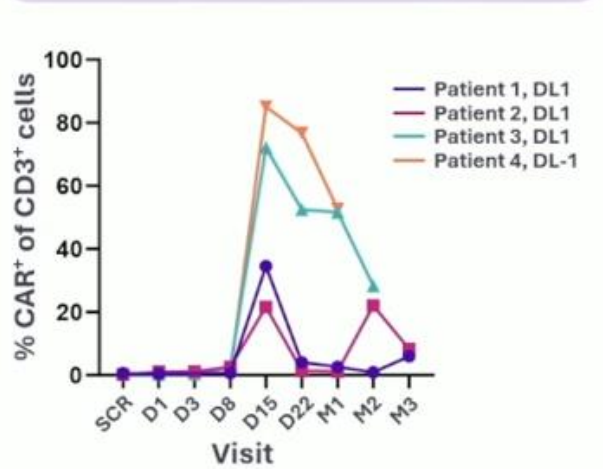
- **Primary:** Safety & tolerability, RP2D
- **Secondary:**
 - CAR T-cell expansion and persistence
 - ORR (IMWG criteria), MRD, DOR, PFS

Whole blood

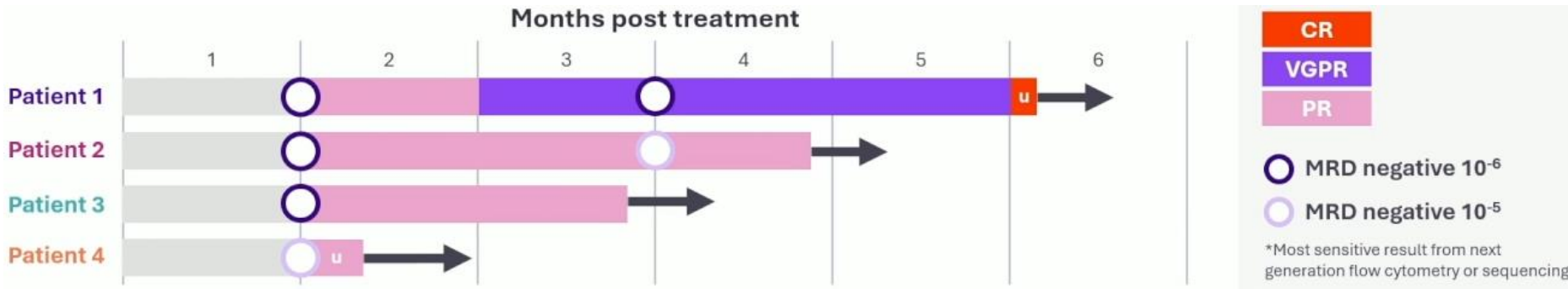
Absolute lymphocyte count (ALC)



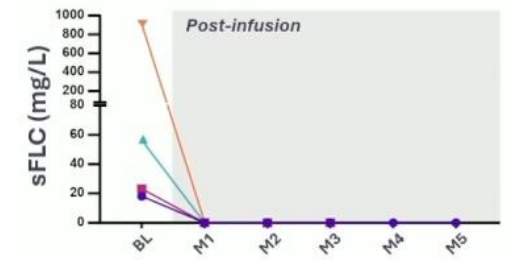
% CAR⁺ of CD3⁺ cells in blood



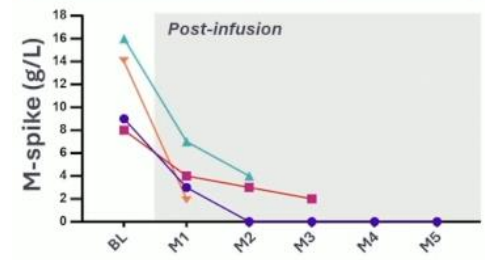
KLN-1010 induces deep responses in Multiple Myeloma



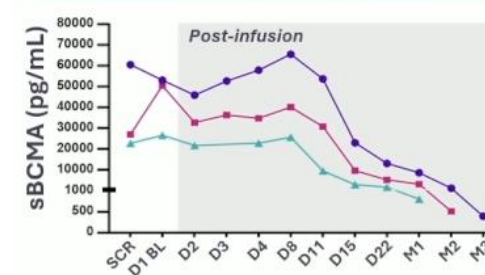
Involved sFLC



M-spike levels



Soluble BCMA



CRS (patient population, N=4)		
Onset, study day (range)		
Median onset	10 (10-12)	
Duration, days (range)		
Median duration	5.5 (2-8)	
Event, n	Grade 1-2	Grade ≥3
Dose level 1	2	0
Dose level -1	1	0
Supportive care, n		
Dexamethasone	3	
Tocilizumab	3	

ICANS, delayed neurotoxicity (patient population, N=4)		
Event, n	Grade 1-2	Grade ≥3
ICANS	0	0
Delayed neurotoxicity (parkinsonism, cranial nerve palsy, peripheral neuropathy)	0	0



Conclusions

- Multiple Dual Targeted CAR T-cells showing early promise in small studies
- Benefit likely due to optimized manufacturing as well as target antigens
- Randomized trials ongoing and planned in 2nd line LBCL (Prizlo-cel, Ronde-cel, KTE363)
- In vitro CARs are exciting but very early and hold unique opportunities and challenges
- Early proof of principle suggests in vivo CAR may overcome many liabilities of current autologous products



Thank you for your attention!



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