MD Anderson Cancer Center

Allo CAR-T

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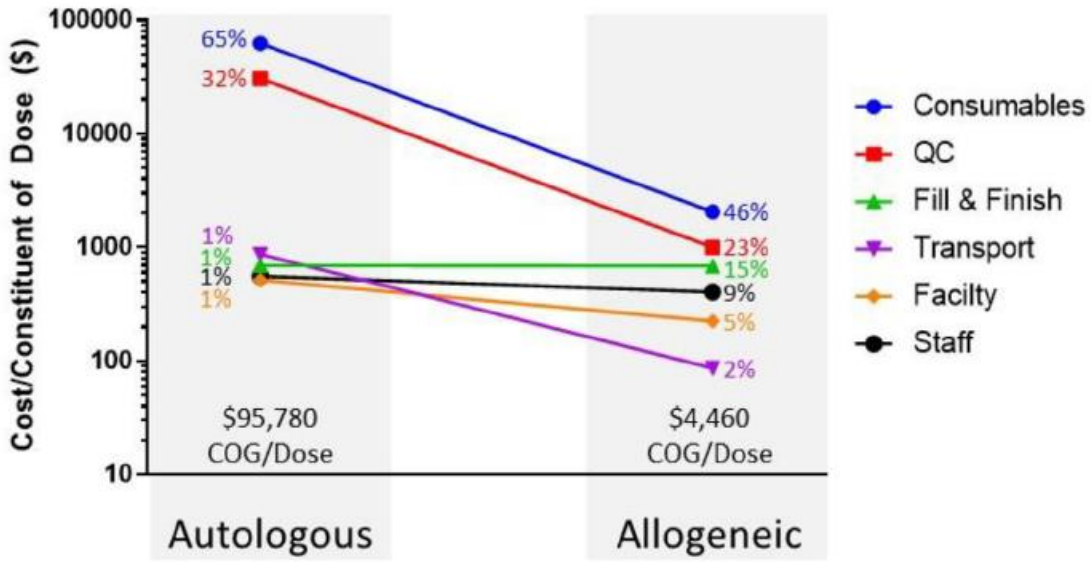
Disclosures

Disclosure	Company name
Research Support	Kite/Gilead, BMS, Allogene, Precision Biosciences, Adicet Bio, Sana Biotechnology, Cargo Therapeutics
Advisory Board / Consultant	Kite/Gilead, Sellas Life Sciences, Athenex, Allogene, Incyte, Adicet Bio, BMS, Bluebird Bio, Fosun Kite, Sana Biotechnology, Caribou, Astellas Pharma, Morphosys, Janssen, Chimagen, ImmunoACT, Orna Therapeutics, Takeda, Synthekine, Carsgen, Appia Bio, GlaxoSmithKline, Galapagos
Honoraria	MJH Life Sciences, PeerView, MD Education
Speaker's Bureau	None
Employment	None
Royalties	None
Stocks / Stock Options	Longbow Immunotherapy
Patents	Related to cell therapy

Rationale for allogeneic CAR T-cell therapy

- Potential to improve efficacy as the T-cell fitness is expected to be better than autologous products
- Consistent product quality
- No wait period as they are off-the-shelf
- Improve access at non-transplant centers
- Potential to lower the cost of CAR T-cell therapy
- Long-term B-cell aplasia and hypogammaglobulinemia less likely
- Long-term risk of insertional mutagenesis less likely

Cost of goods/dose: Auto vs. Allo



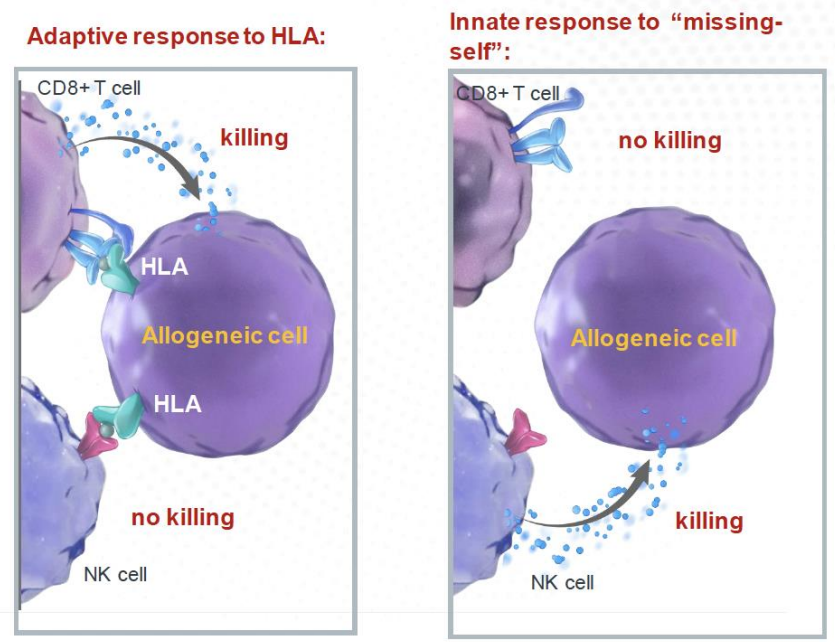
~100 doses/manufacturing run

Harrison et al. *Cytotherapy*, 2019; 21:224-233

Challenges for allogeneic CAR T-cell therapy

- GVHD
  - Mediated by αβ T cells
  - May be overcome by TCR knock-out or by using alternative cell types such as NK cells, NKT, γδ T cells
- Graft rejection
  - Mediated by αβ T cells and NK cells

Graft rejection by T and NK cells



Depil et al. *Nat Rev Drug Discov*, 2020; 19(3) 185-199
Schrepfer et al, 2022 ASH Annual Meeting, Abstract 1690

Allogeneic CAR-T with intensified lymphodepletion

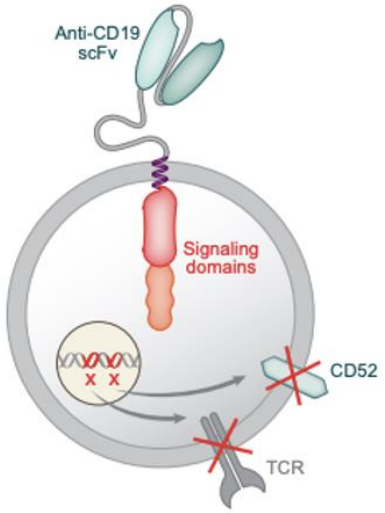
'Brute force approach' for immune evasion: Eliminate host T cells and NK cells for few weeks to allow allo CAR T cells to expand and mediate antitumor effects

Product / Sponsor	Cell type	CAR Target	GVHD prevention	Allorejection strategy	Additional comments
ALLO-501/A Allogene	αβ T cells	CD19	TCR KO (TALEN)	Anti-CD52 Ab + Standard Cy/Flu	CD52 KO
PBCAR0191 Precision Bio	αβ T cells	CD19	TCR KO (ARCUS)	Enhanced Cy/Flu	
CB-010 Caribou Biosciences	αβ T cells	CD19	TCR KO (Cas9 chRNDA)	High-dose Cy/Flu	PD1 KO
ADI-001 Adicet Bio	γδ T cells	CD20	Cell type	Enhanced Cy/Flu	

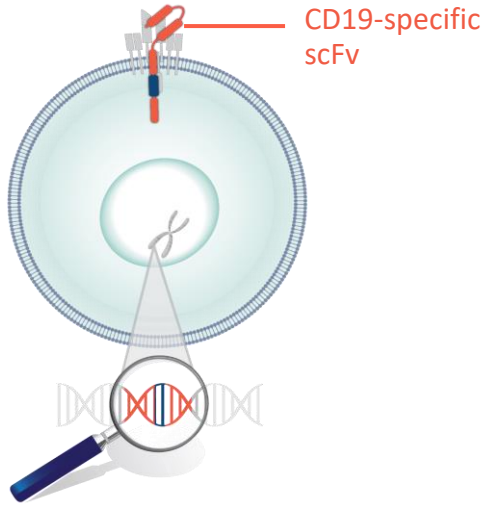
Allogeneic CAR T products in NHL

(GVHD prevention but no built-in immune evasion)

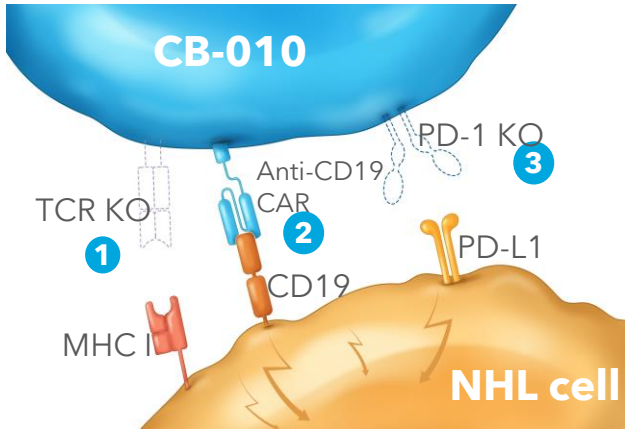
ALLO-501A (Cema-cel)



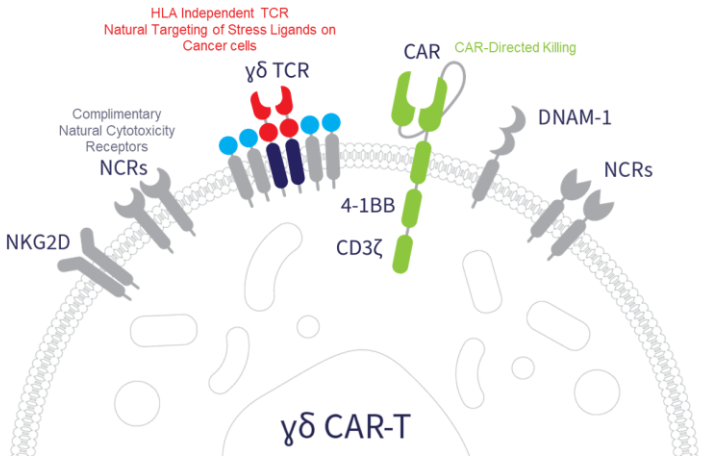
PBCAR0191



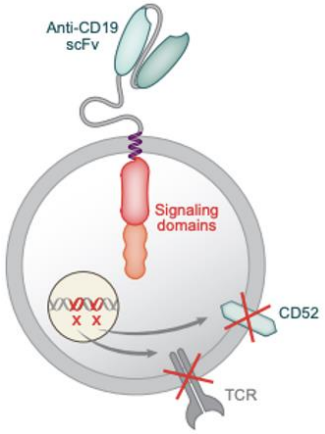
CB-010



ADI-001



ALPHA 1&2 Studies: Patient disposition



Safety Analysis Population (N=87)[a]

Received ALLO-647 by study:
- ALPHA (n=49)
- ALPHA2 (n=38)

Received ALLO-647 in LD
- 39 mg (n=11)
- 60 mg (n=39)
- 90 mg (n=37)

R/R LBCL (n=61)[b]

CAR T Cell–Naive Pts Who Received ALLO-501 Manufactured With the Phase 2 Selected Process (n=33)[c]

R/R FL (n=26)

Locke et al. Neelapu, ASH 2023 Abstract 2095

ALPHA 1&2 Studies: Baseline characteristics

Characteristic	All (N=87)	LBCL		FL (n=26)
		All LBCL (n=61)	CAR T Cell–Naive Pts Who Received ALLO-501/501A Manufactured With the Phase 2 Selected Process (n=33)	
Median age, years (range)	64 (31-77)	64 (31-76)	66 (31-76)	64 (34-77)
Stage IV disease, n (%)	51 (59)	40 (66)	19 (58)	11 (42)
ECOG PS 1, n (%)	61 (70)	48 (79)	26 (79)	13 (50)
Baseline LDH >ULN, n (%)	54 (62)	44 (72)	22 (67)	10 (38)
IPI score 3-5, n (%)	43 (49)	35 (57)	19 (58)	8 (31)
Germinal center subtype, n (%)	42 (48)	38 (62)	18 (55)	4 (15)
Double or triple hit, n (%)	23 (26)	20 (33)	10 (30)	3 (12)
Median number of prior regimens, n (range)	3 (2-12)	3 (2-9)	3 (2-8)	4 (2-12)
Prior autologous transplant, n (%)	6 (7)	6 (10)	3 (9)	0
Extranodal disease, n (%)	48 (55)	36 (59)	19 (58)	12 (46)

Locke et al. Neelapu, ASH 2023 Abstract 2095

ALPHA 1&2 Studies: Safety

TEAEs, n (%)	All (N=87)		LBCL				FL (n=26)	
			All LBCL (n=61)		CAR T Cell–Naive Pts Who Received ALLO-501/501A Manufactured With the Phase 2 Selected Process (n=33)			
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
CRS	21 (24)	1 (1)	17 (28)	1 (2)	8 (24)	0	4 (15)	0
ICANS	1 (1)	0	1 (2)	0	0	0	0	0
Neurotoxicity	24 (28)	3 (3)	19 (31)	3 (5)	13 (39)	2 (6)	5 (19)	0
GvHD	0	0	0	0	0	0	0	0
IRR	48 (55)	5 (6)	31 (51)	4 (7)	16 (48)	3 (9)	17 (65)	1 (4)
Infections	50 (57)	18 (21)	34 (56)	13 (21)	19 (58)	5 (15)	16 (62)	5 (19)

Locke et al. Neelapu, ASH 2023 Abstract 2095

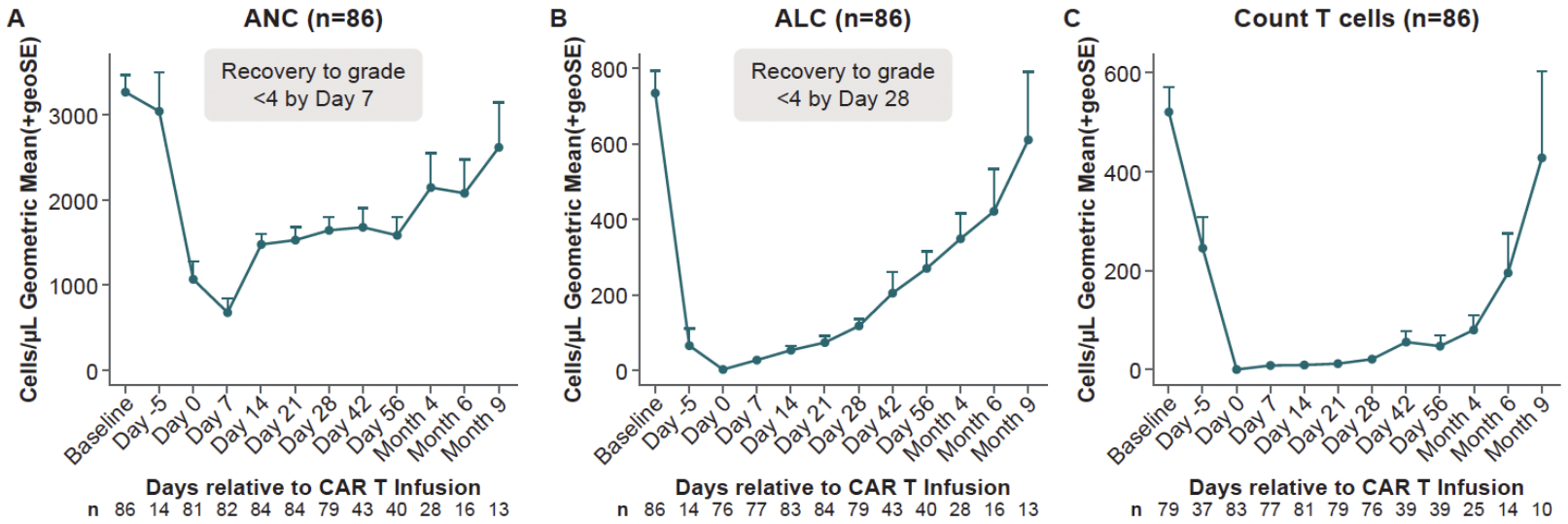
ALPHA 1&2 Studies: Infections (>5% Any grade)

TEAEs, n (%)	All (N=87)		LBCL				FL (n=26)	
			All LBCL (n=61)		CAR T Cell–Naive Pts Who Received ALLO-501/501A Manufactured With the Phase 2 Selected Process (n=33)			
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Viral infections	34 (39)	12 (14)	22 (36)	9 (15)	13 (39)	4 (12)	12 (46)	3 (12)[a]
CMV	22 (25)	8 (9)	16 (26)	7 (11)	10 (30)	4 (12)	6 (23)	1 (4)
COVID-19	5 (6)	1 (1)	2 (3)	1 (2)	2 (6)	1 (3)	3 (12)	0
Other infections	25 (29)	12 (14)[b]	16 (26)	8 (13)	8 (24)	5 (15)	9 (35)	4 (15)[b]
Pneumonia	8 (9)	6 (7)[b]	4 (7)	4 (7)	4 (12)	3 (9)	4 (15)	3 (12)[b]
Sepsis	5 (6)	5 (6)	4 (7)	3 (5)	2 (6)	2 (6)	1 (4)	1 (4)
Bacterial infections	10 (11)	4 (5)	9 (15)	4 (7)	3 (9)	2 (6)	1 (4)	0
Fungal infections	7 (8)	2 (2)	5 (8)	1 (2)	2 (6)	0	2 (8)	1 (4)

Locke et al. Neelapu, ASH 2023 Abstract 2095

ALPHA 1&2 Studies: Prolonged cytopenias (Grade ≥3)

Time	All (N=87)	LBCL		FL (n=26)
		All LBCL (n=61)	CAR T Cell–Naive Pts Who Received ALLO-501/501A Manufactured With the Phase 2 Selected Process (n=33)	
Day 28, n (%)	25 (29)	20 (33)	11 (33)	5 (19)
Day 56, n (%)	17 (20)	14 (23)	7 (21)	3 (12)
Day 121 (Month 4), n (%)	13 (15)	11 (18)	6 (18)	2 (8)

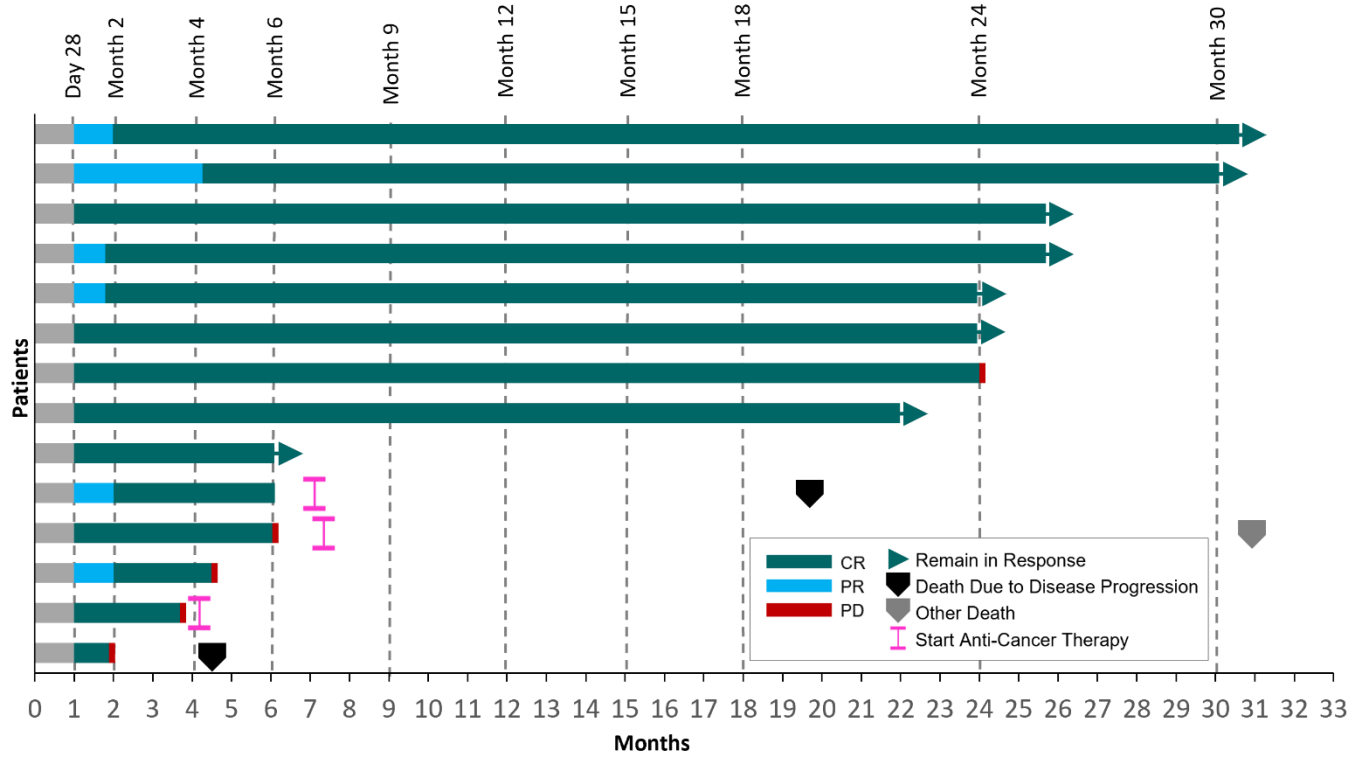


Locke et al. Neelapu, ASH 2023 Abstract 2095

ALPHA 1&2 Studies: Efficacy

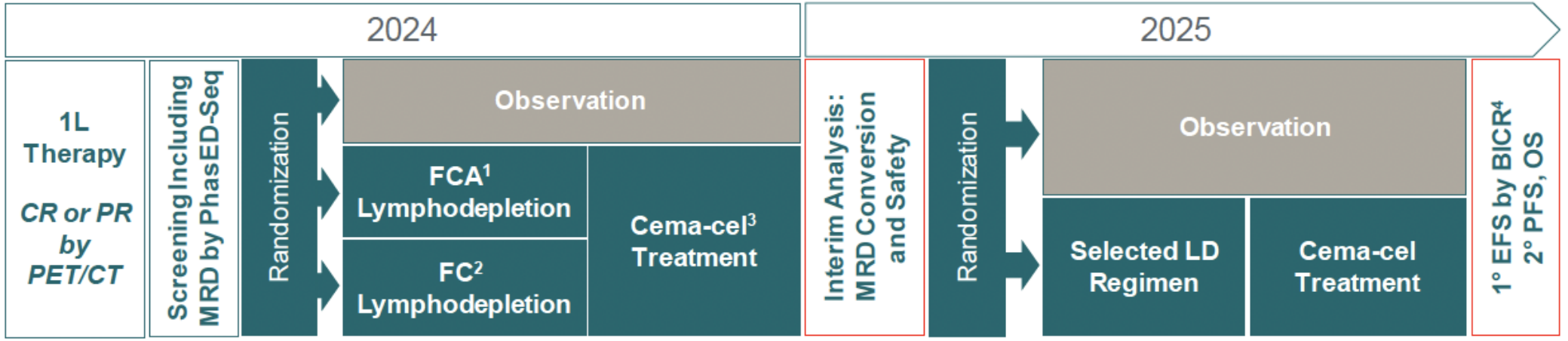
CAR naïve LBCL

	All (N=33)	Phase 2 Regimen (N=12)
ORR, n (%)	19 (58)	8 (67)
CRR, n (%)	14 (42)	7 (58)
6 months CRR*, n (%)	10 (30)	5 (42)



Locke et al. Neelapu, ASH 2023 Abstract 2095

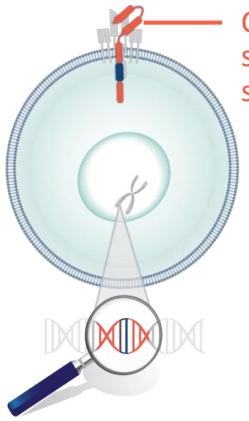
ALPHA 3: Phase 3 study in first line LBCL



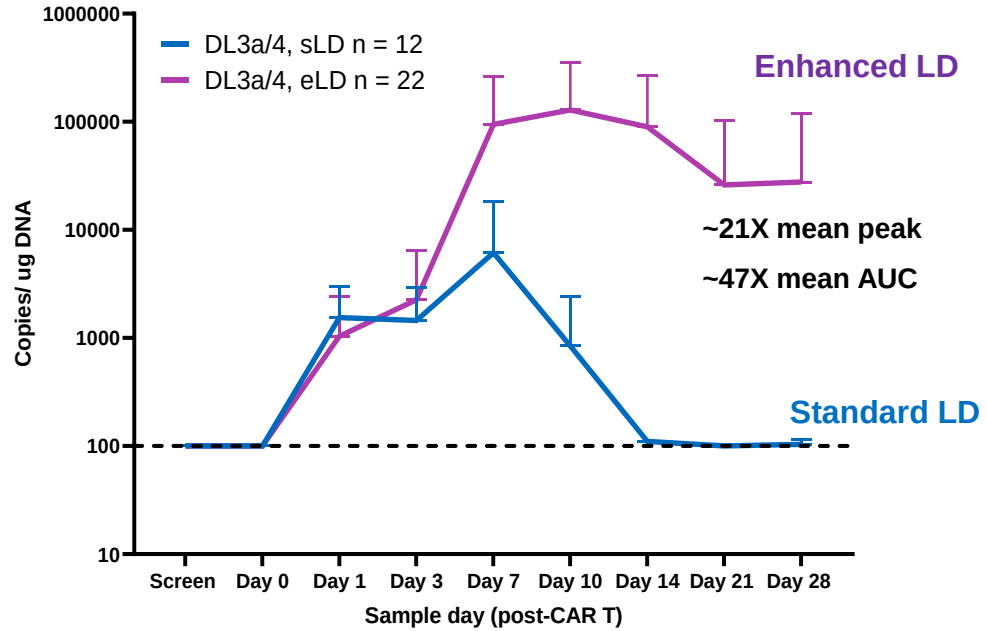
ALPHA3 Startup Underway, Enrollment Projected to Commence Mid-2024

- All LBCL potentially eligible: no upfront risk assessment (e.g., IPI score, double-hit, HGBCL)
- Approximately 110 patients in observation and treatment arms
  - All patients treated with "Selected LD Regimen" during LD selection will count toward pivotal sample
  - Continuous enrollment planned, no pause in enrollment for LD regimen selection
- Expected median time to EFS in observation arm ~8 months

PBCAR0191: Safety, efficacy, and cellular kinetics in r/r LBCL

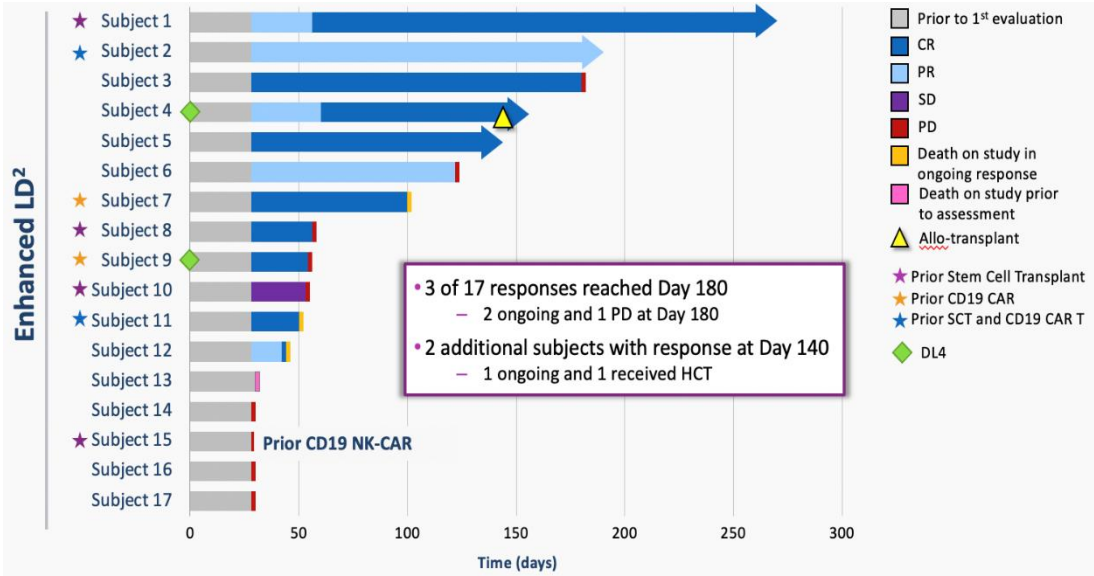


PBCAR0191 (CD19 αβ CAR)



PBCAR0191 (CD19 αβ CAR)

ORR/CR rate % = 69/56



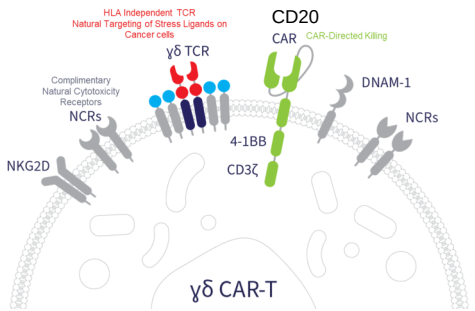
- No GvHD, Grade ≥3 NE or CRS
- Higher rate of grade ≥3 infections with enhanced LD

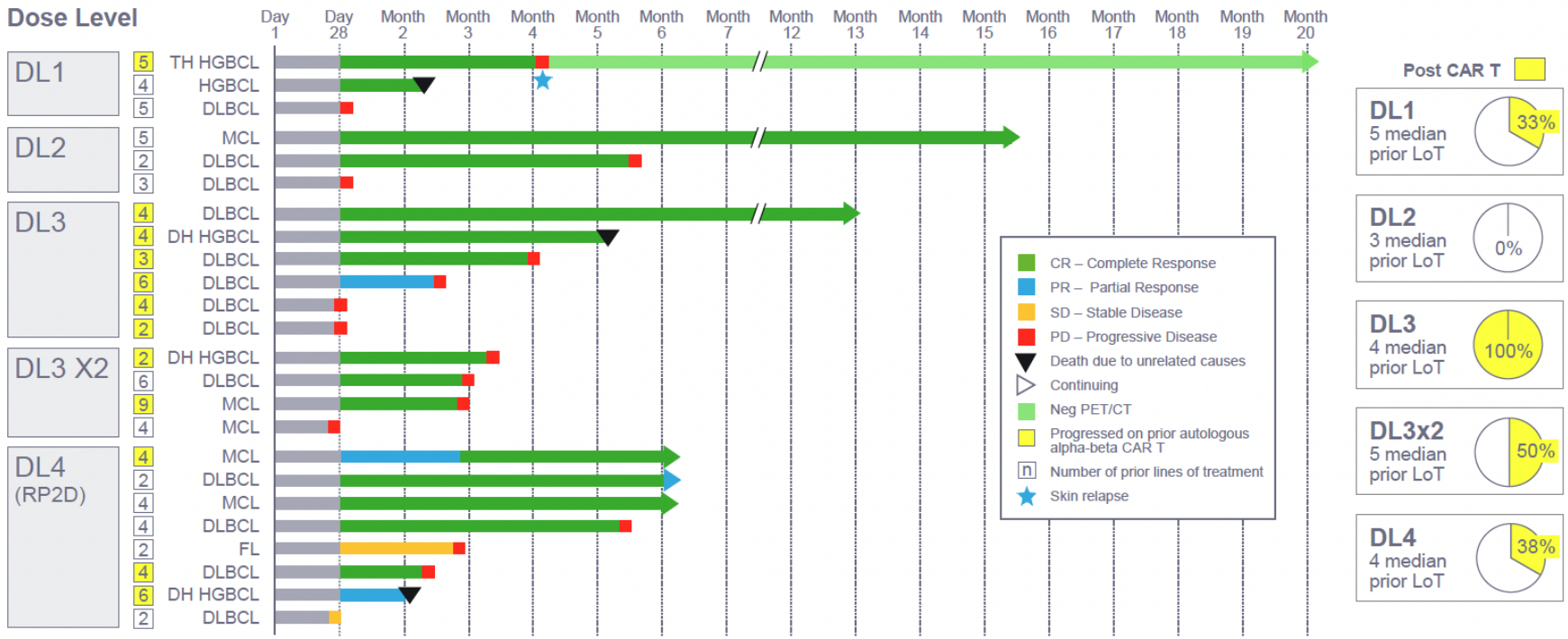
Shah et al. 2021 ASH Annual Meeting, Abstract 302

ADI-001: Safety and efficacy

N = 24
ORR = 71%; CR rate = 63%
6-month CR rate – 33% at DL4

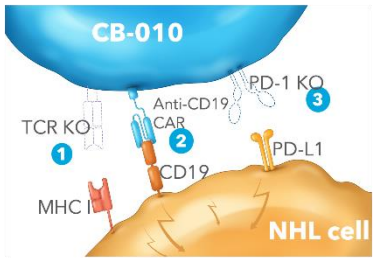
- **Grade ≥3 CRS = 4%**
- **Grade ≥3 ICANS = 4%**
- **No GVHD**



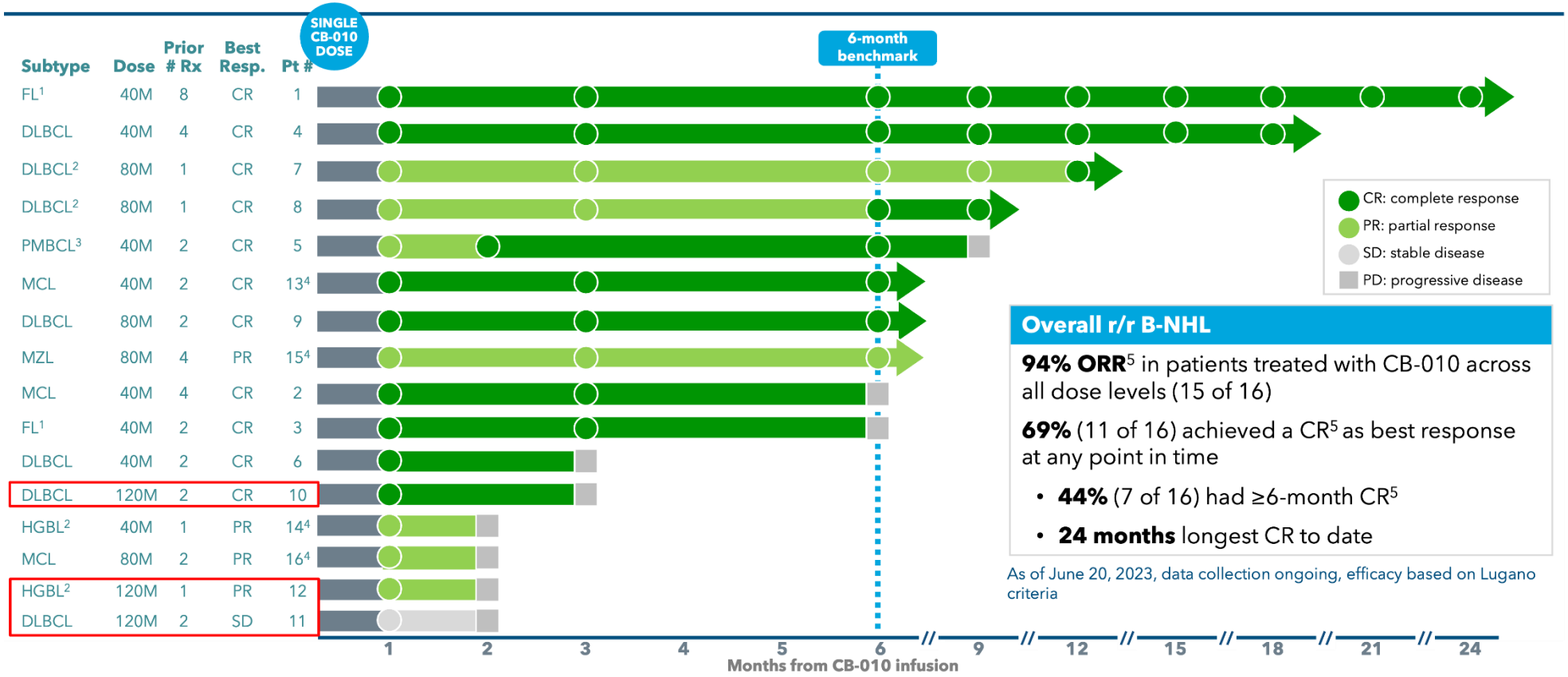


Neelapu et al, ASH 2022 ASH, Abstract 2018
Moreno et al, ASH 2023, Abstract 3478

CB-010: Efficacy



Subtype	Dose	Prior # Rx	Best Resp.	Pt #
FL[1]	40M	8	CR	1
DLBCL	40M	4	CR	4
DLBCL[2]	80M	1	CR	7
DLBCL[2]	80M	1	CR	8
PMBCL[3]	40M	2	CR	5
MCL	40M	2	CR	13[4]
DLBCL	80M	2	CR	9
MZL	80M	4	PR	15[4]
MCL	40M	4	CR	2
FL[1]	40M	2	CR	3
DLBCL	40M	2	CR	6
DLBCL	120M	2	CR	10
HGBL[2]	40M	1	PR	14[4]
MCL	80M	2	PR	16[4]
HGBL[2]	120M	1	PR	12
DLBCL	120M	2	SD	11



Overall r/r B-NHL

94% ORR[5] in patients treated with CB-010 across all dose levels (15 of 16)

69% (11 of 16) achieved a CR[5] as best response at any point in time

- **44%** (7 of 16) had ≥6-month CR[5]
- **24 months** longest CR to date

As of June 20, 2023, data collection ongoing, efficacy based on Lugano criteria

Nastoupil et al. EHA, 2023
Corporate update, July 2023

Allogeneic CAR-T with hypoimmune strategy

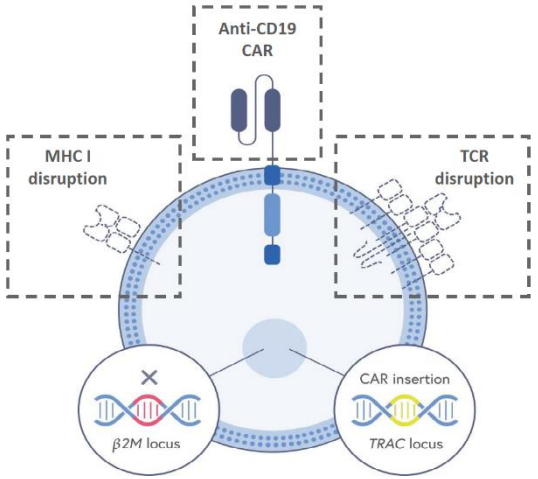
'Refined approach' for immune evasion: Make the allo CAR T cells invisible to host T and/or NK cells to allow their expansion and mediate antitumor effects

Product / Sponsor	Cell type	CAR Target	GVHD prevention	Allorejection strategy	Additional comments
CTX110 CRISPR Therapeutics	αβ T cells	CD19	TCR KO	B2M KO	Standard Cy/Flu
CTX130 CRISPR Therapeutics	αβ T cells	CD70	TCR KO	B2M KO	Standard Cy/Flu CD70 KO
KUR-502 Athenex	iNKT cells	CD19	Cell type	B2M & CD74 down regulation	Standard Cy/Flu IL-15 transgene
CNTY-101 Century Therapeutics	iPSC CAR NK	CD19	Cell type	B2M KO, CIITA KO, & HLA-E overexpression	Standard Cy/Flu IL-15 transgene
SC291 Sana Biotechnology	αβ T cells	CD19	TCR KO	B2M KO, CIITA KO, & CD47 overexpression	Standard Cy/Flu

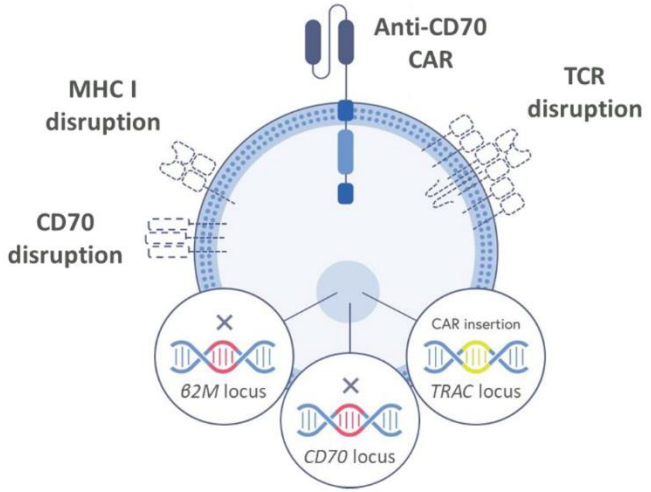
Allogeneic CAR T products in NHL

(GVHD prevention with built-in immune evasion)

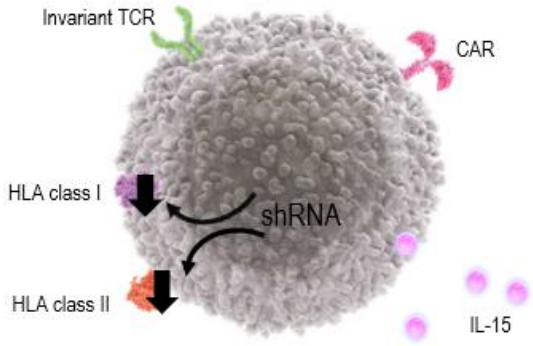
CTX110



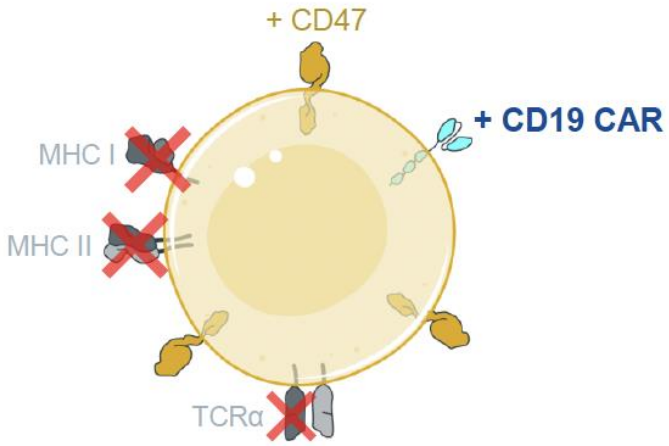
CTX130



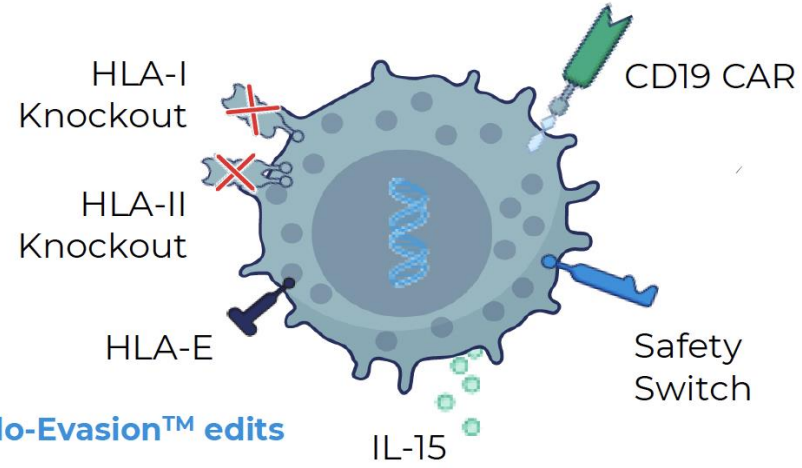
KUR-502



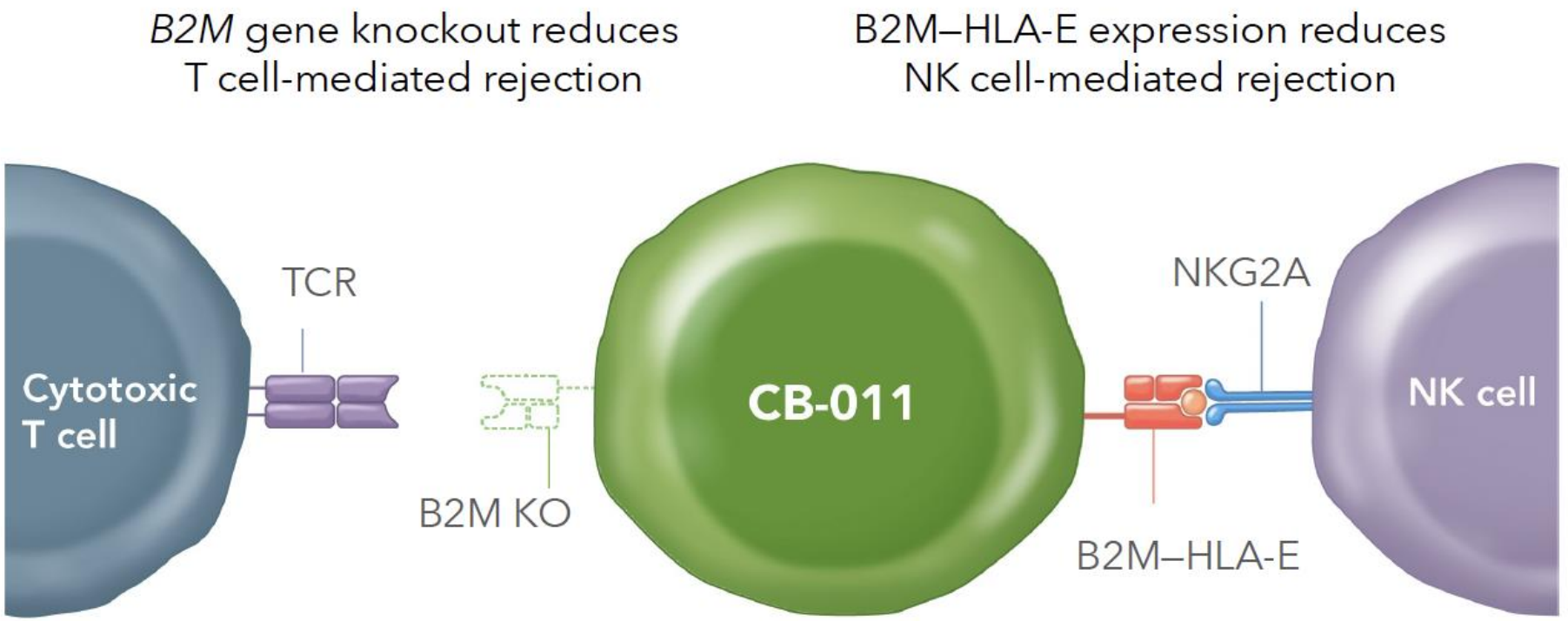
SC291



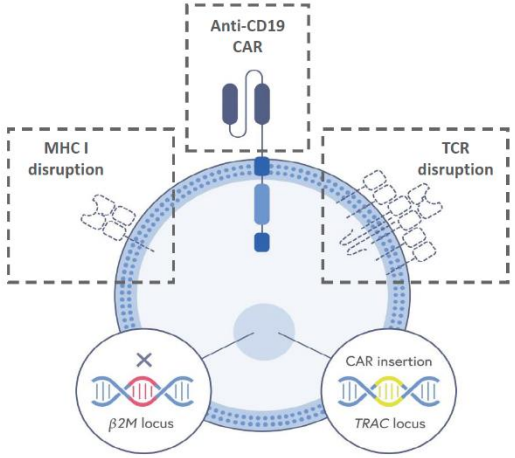
CNTY-101



Immune evasion of host T and NK cells

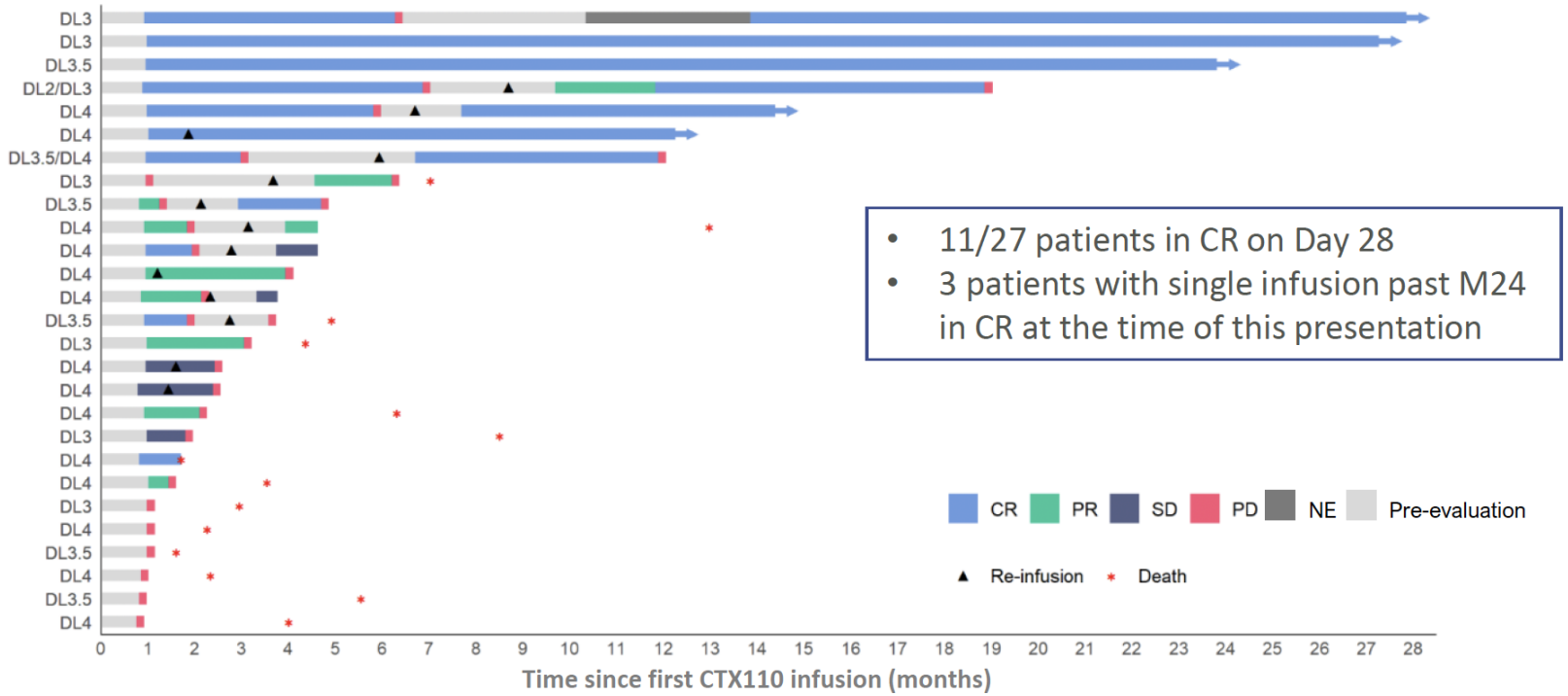


CTX110: Safety and efficacy in LBCL



- **No grade ≥3 CRS**
- **Grade ≥3 ICANS = 6%**
- **No GVHD**

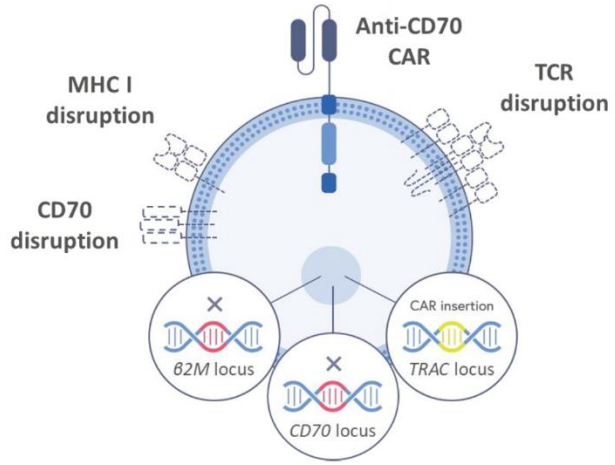
Cell dose (CAR+ T cells)	DL1-DL2 30-100x10^6 N=6[2]	DL3 300x10^6 N=6	DL3.5 450x10^6 N=6	DL4 600x10^6 N=14	≥1 Infusion at DL≥3 N=27
Overall Response Rate (ORR), n (%)	1 (0.16)	4 (66.7)	4 (66.7)	9 (64.3)	18 (66.7)
CR	1 (0.16)	2 (33.3)	4 (66.7)	4 (28.6)	11 (40.7)
PR	0	2 (33.3)	0	5 (35.7)	7 (25.9)

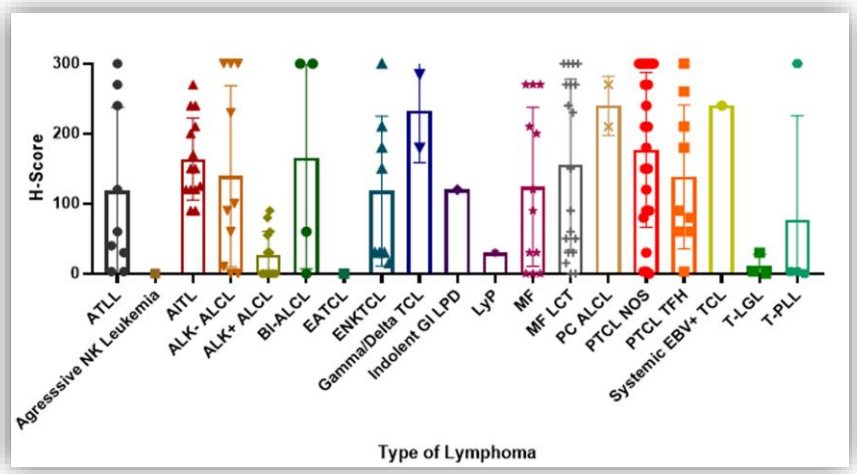


- 11/27 patients in CR on Day 28
- 3 patients with single infusion past M24 in CR at the time of this presentation

McGuirk et al. EBMT 2023

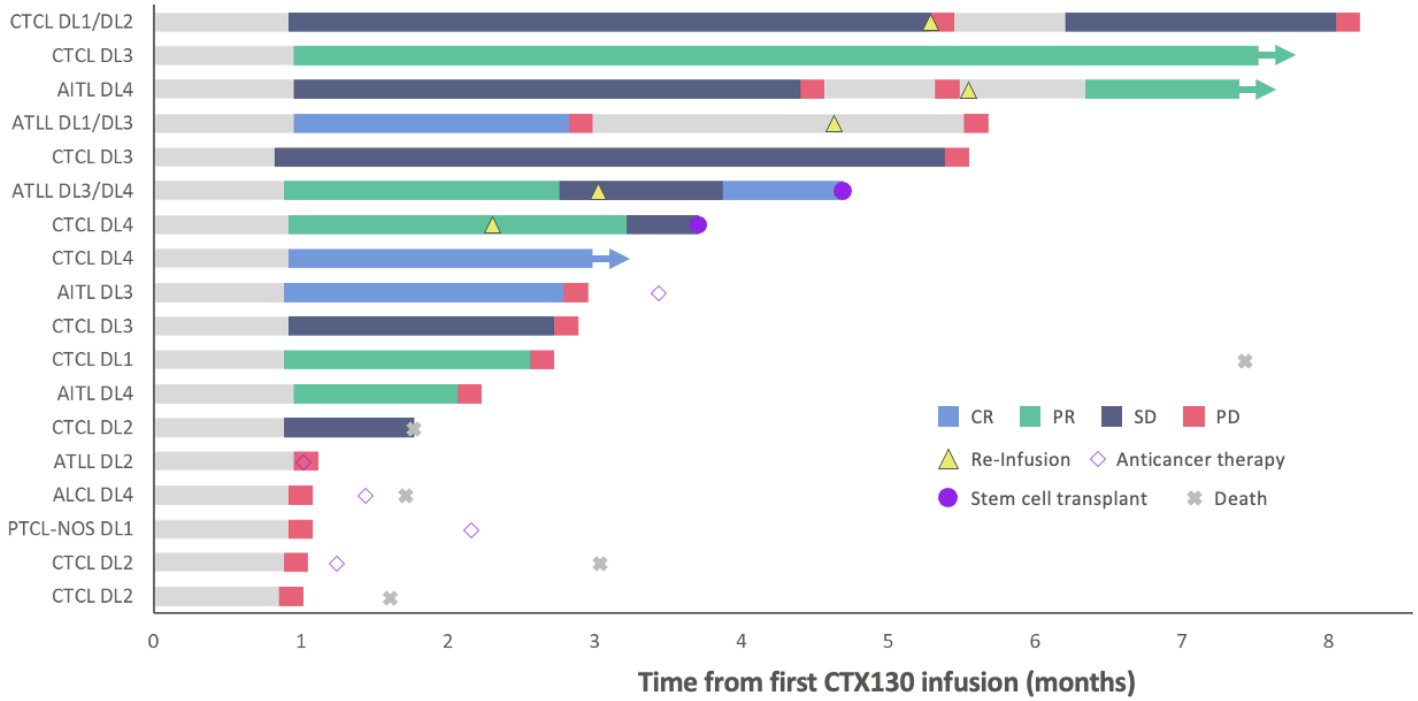
CTX130: Safety and efficacy in T cell lymphomas





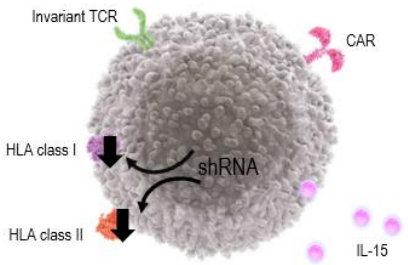
- No grade ≥3 CRS
- No grade ≥3 ICANS
- No GVHD

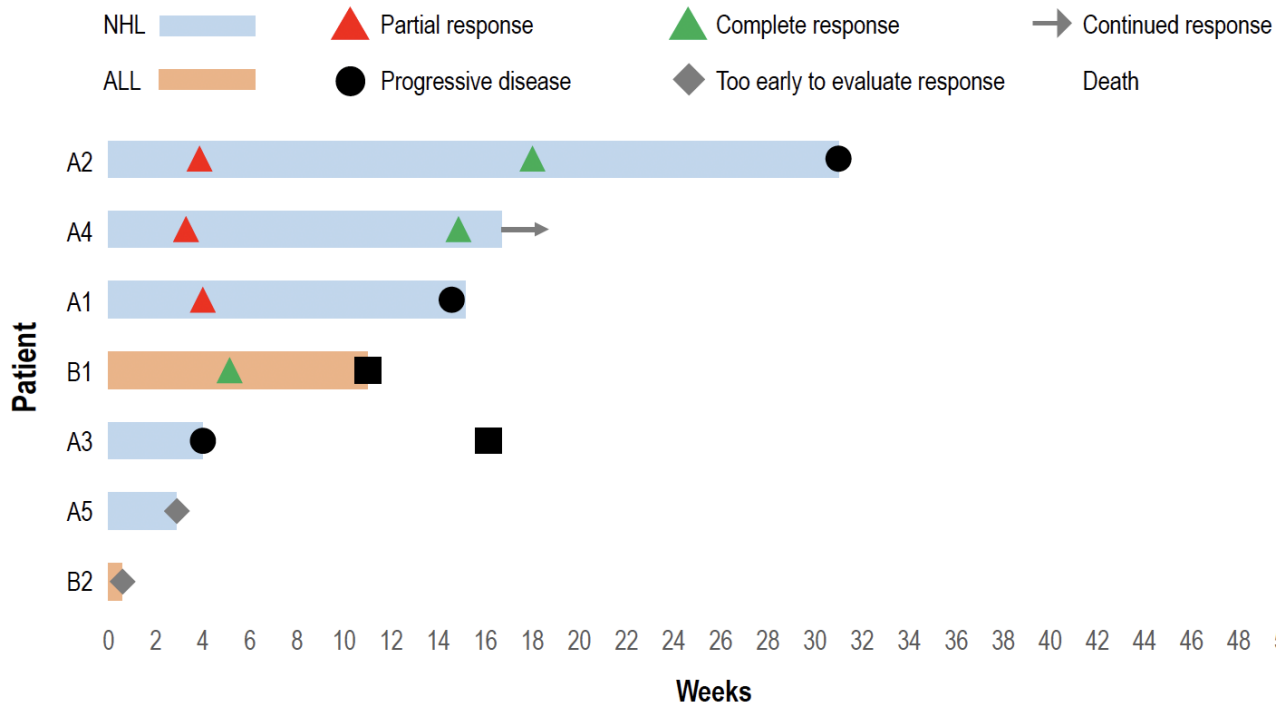
N = 18 (10 ≥DL3)
ORR ≥DL3 = 70%
CR rate ≥DL3 = 30%



Slide courtesy: Swami Iyer
Iyer et al, EHA 2022

KUR-502 (iNKT): Safety and efficacy

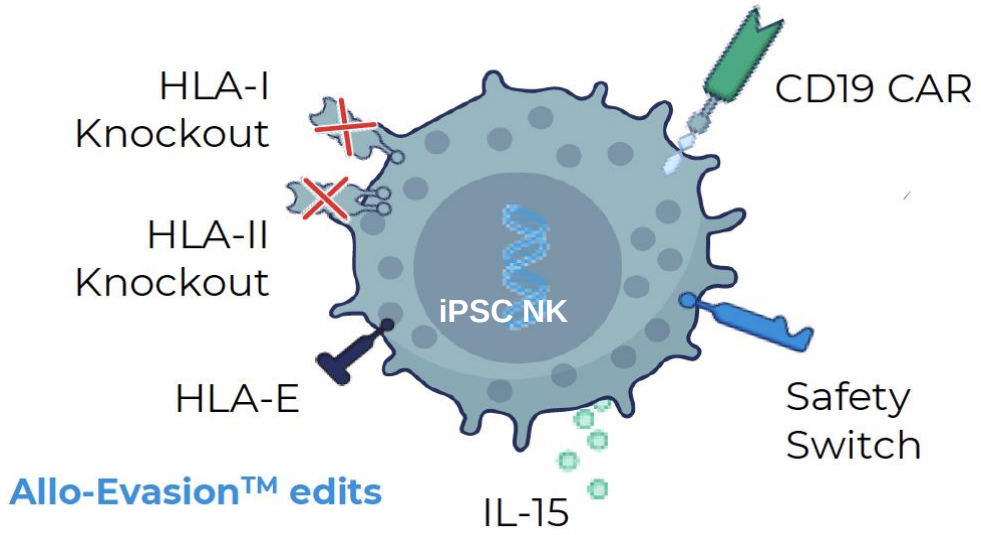




- **1 Grade 1 CRS**
- **No ICANS**
- **No GVHD**

Ramos et al, ASH 2021

CNTY-101: Safety and efficacy



N = 7 (DL1 and DL2)

5 LBCL, 1 FL, 1 MZL

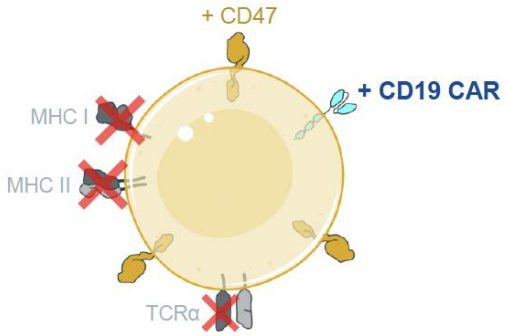
ORR = 3 (42%)

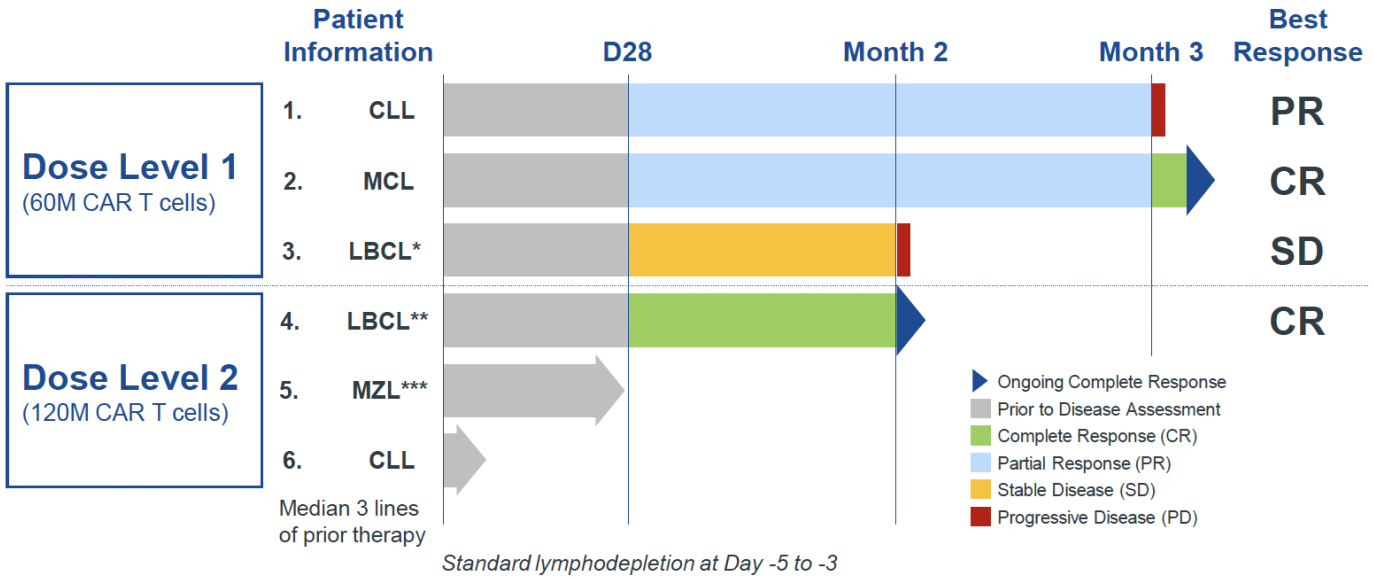
CR rate = 2 (29%)

No major toxicities

Patel et al. Neelapu, ASH 2023 Abstract 1654
Century Therapeutics Corporate presentation, Jan 2024

SC291: Safety and efficacy





Safety

- No dose limiting toxicities
- No SC291-related SAEs
- No CRS or ICANS
- No Grade 3 or higher infections

Neelapu et al, ASH 2023
Sana Biotechnology Corporate presentation, Jan 2024

Allogeneic CAR T-cell therapy: Summary

- CRS and ICANS similar to autologous CAR T
- GVHD can be prevented by TCR KO or using alternative cell types such as NK, NKT, or γδ T cells
- Response rates in LBCL with allogeneic CAR T is comparable to autologous CAR T regardless of the cell type (αβ, γδ, NK, iNKT)
- But durability of responses is suboptimal
- Persistence for 1 month is likely not sufficient to maintain durability of responses
- More effective approaches to prevent immune rejection that are needed to improve *in vivo* expansion and persistence of allogeneic CAR products and durability

Thank you for your attention!

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