CAR-T therapy for hematologic malignancies and solid tumors

Natalie S. Callander, M.D.

University of Wisconsin Carbone Cancer Center

Disclosures

- I have nothing to disclose
- I will be discussing non-FDA approved indications during my presentation.

1992 Primary T cell engineering

1993 First-generation CARs(CD3ζ-based)

2002 Second-generation CARs (CD28-based)

2003 Demonstration of CD19 as valid CAR target

Second-generation CARs(4-1BB-based)

2007 First IND for CD19 CAR therapy

2010 First case report of CD19 CAR therapy in NHL

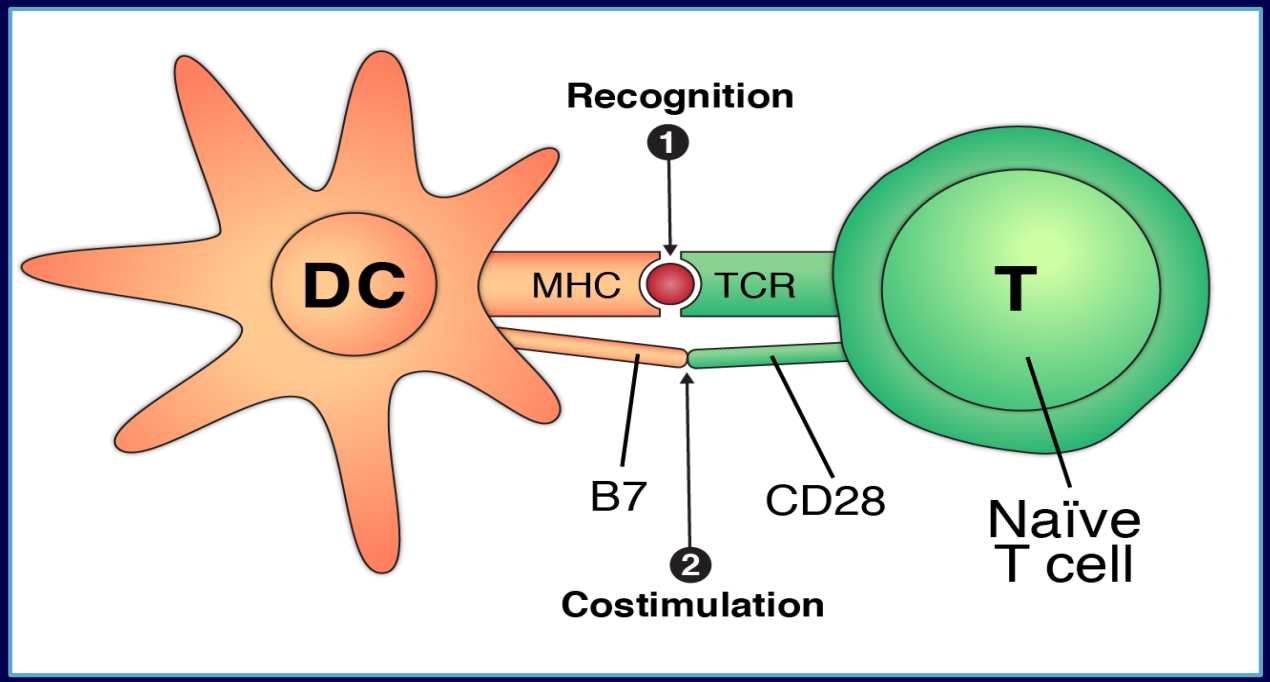
2011 First case report of CD19 CAR therapy in CLL

2013 First case report of CD19 CAR therapy in ALL

2017 FDA approval of CD19 CAR therapy for pediatric for ALL and NHL

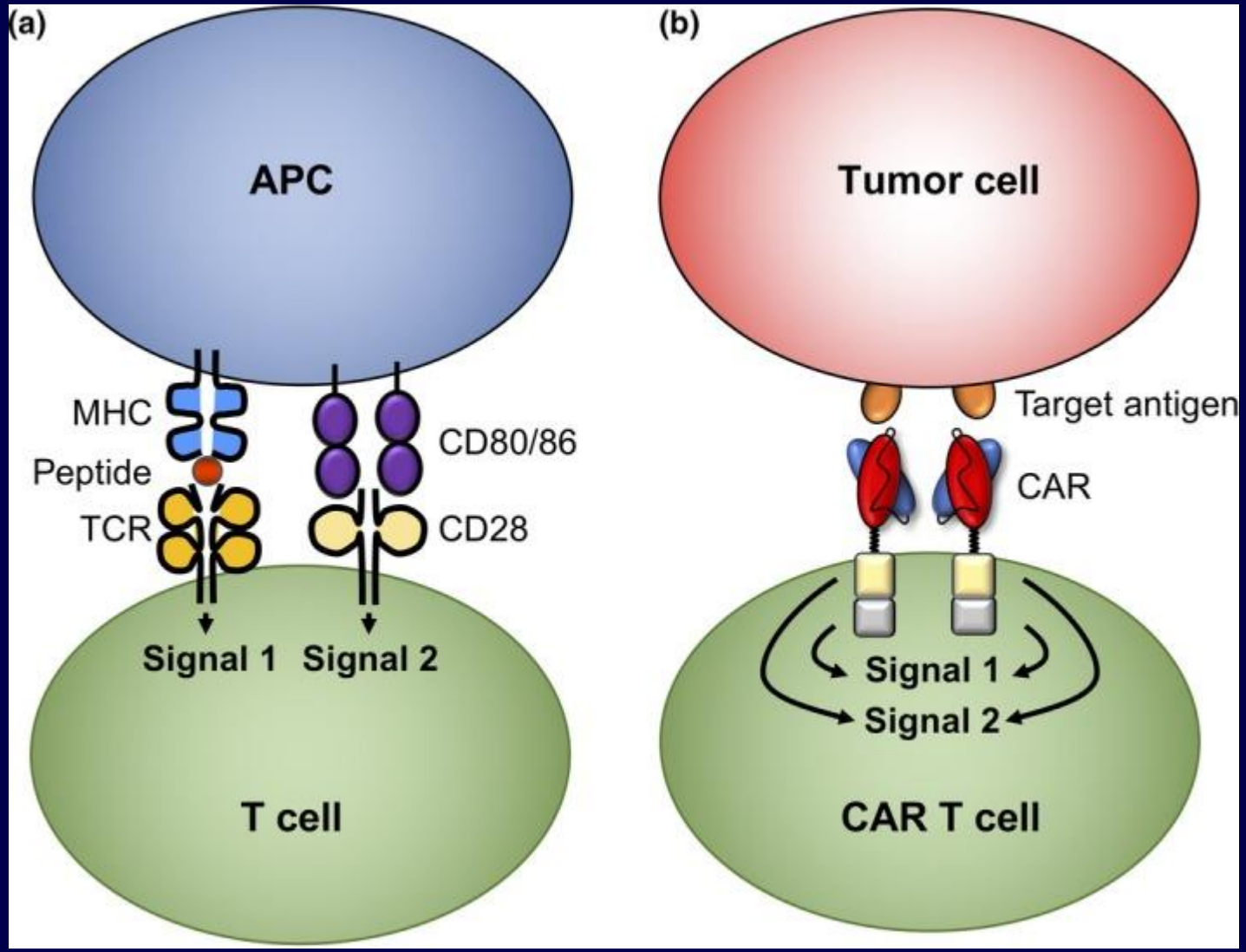
T-Cell Costimulation-necessary for function

- T-cell activation and proliferation requires both signaling through the TCR (signal 1) and signaling through a costimulatory receptor (signal 2) (CD28, 4-1BB, OX-40)
- In the absence of costimulation (signal 2), the T-cell will either become unresponsive (anergic) or undergo activation-induced cell death (AICD/apoptosis)

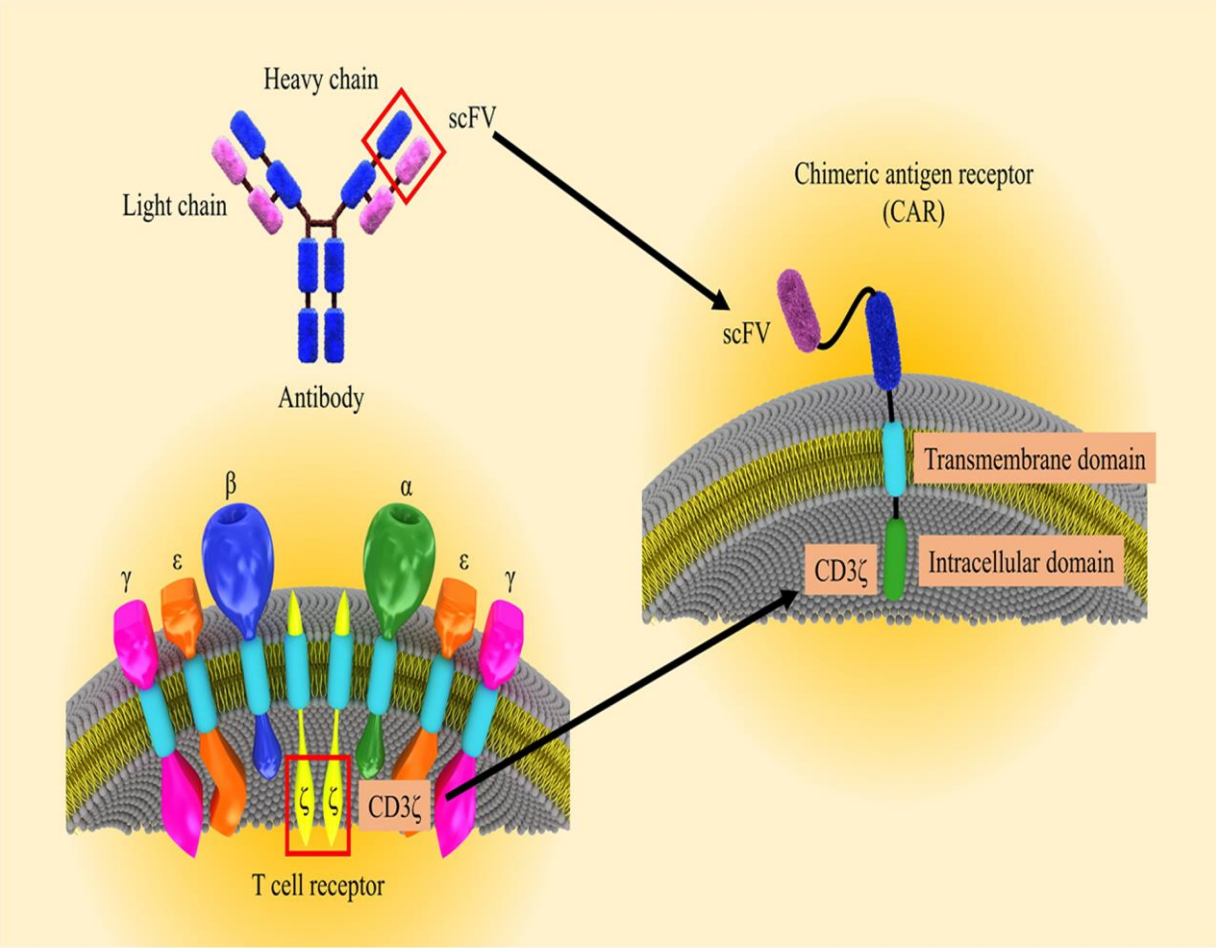


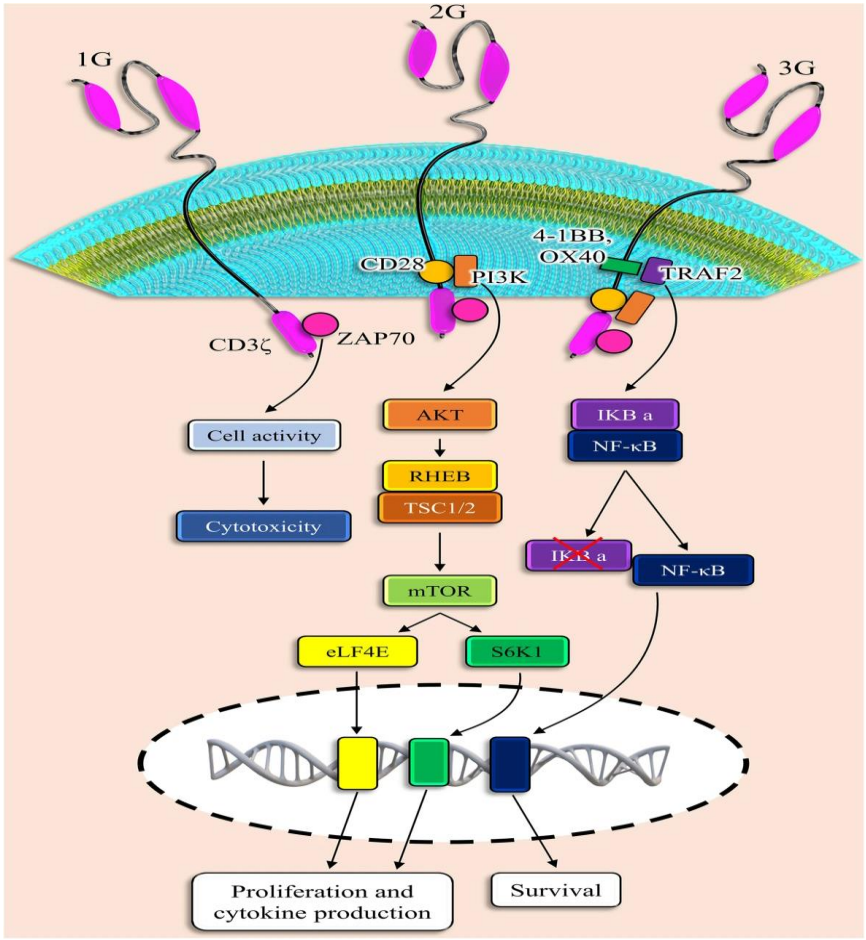
Costimulation eliciting optimal T cell activity, proliferation and survival requires expression of ligands such as CD80 and CD86 on APCs. **(b)** CAR-T cells can undergo potent activation upon exposure to cells expressing the target antigen ***without*** target cell expression of costimulatory receptor ligands

The CAR-T cell switch is permanently on "ON"



CAR-T structure: theoretically any surface protein can be targeted





Marofi F Stem Cell Res Ther 202 12:811

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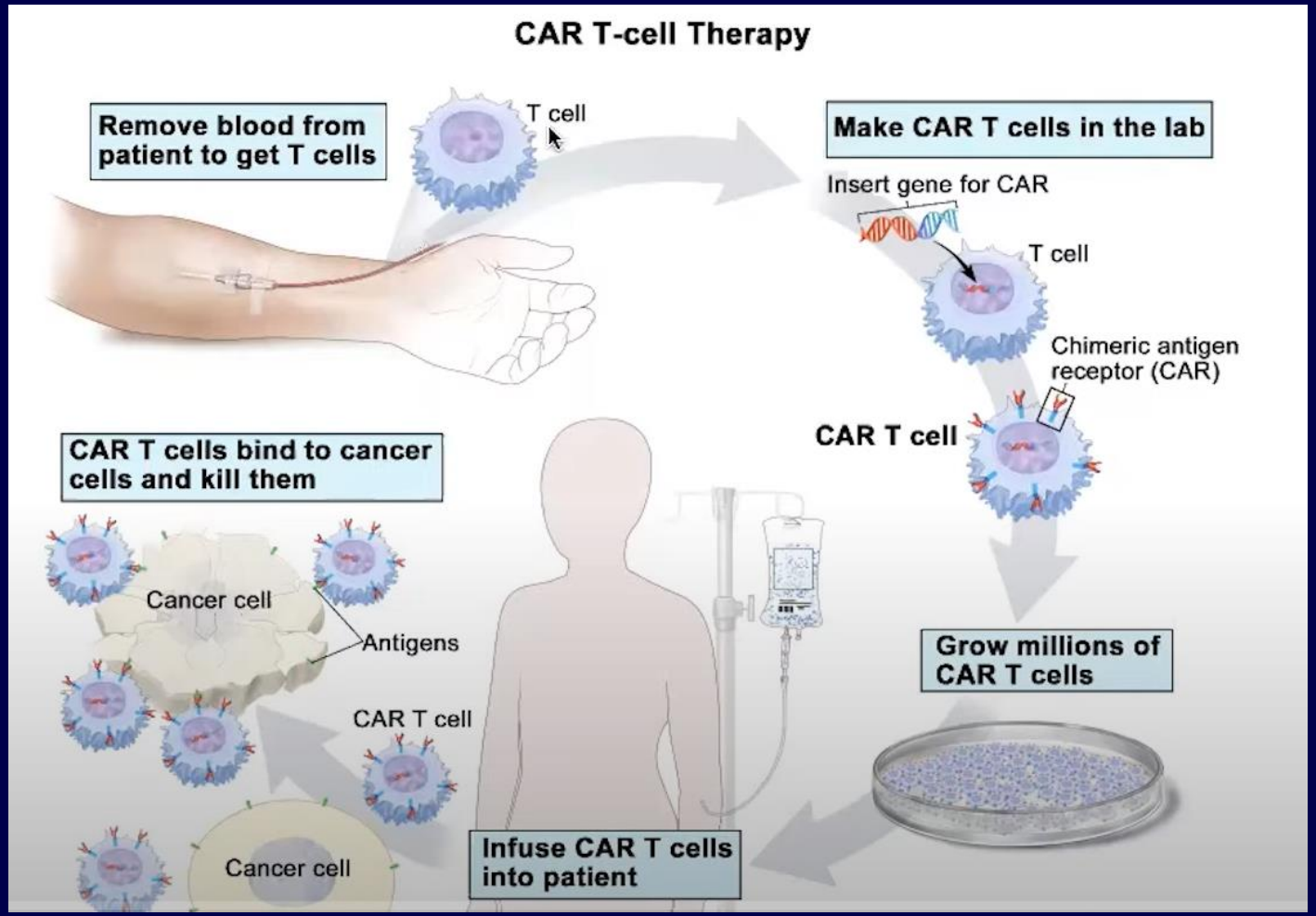
Tumor antigen that is present on all, or most, of the cancer cells and is necessary for that cancer cell's survival

Tumor antigen that is not present on normal healthy cells such that immune attack on those normal healthy cells would lead to unacceptable toxicity

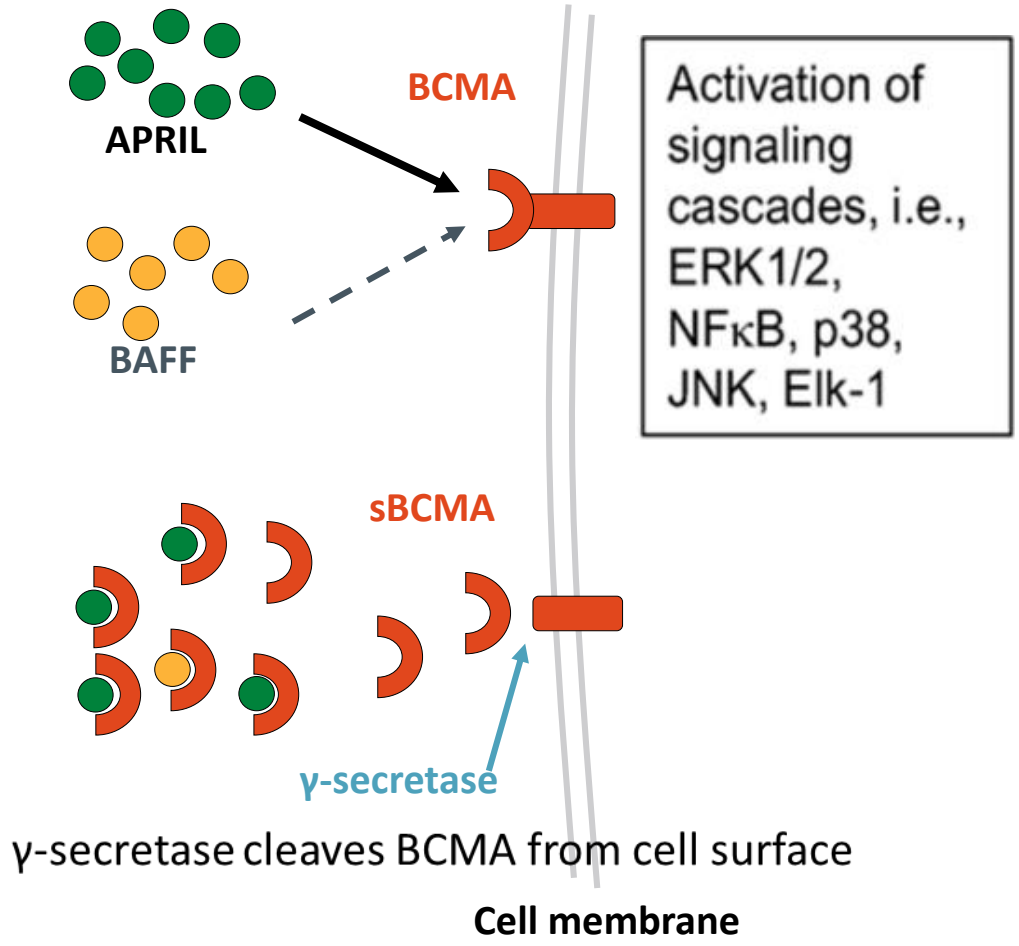
A Good CAR T-cell Candidate



FDA-Approved CAR T-Cell Therapies

Generic Name	Brand Name	Target Antigen	Targeted Disease	Patient Population
Tisagenlecleucel	Kymriah	CD19	B-cell acute lymphoblastic leukemia (ALL)	Children and young adults with refractory or relapsed B-cell ALL
			B-cell non-Hodgkin lymphoma (NHL)	Adults with relapsed or refractory B-cell NHL
Axicabtagene ciloleucel	Yescarta	CD19	B-cell non-Hodgkin lymphoma (NHL)	Adults with relapsed or refractory B-cell NHL
			Follicular lymphoma	Adults with relapsed or refractory follicular lymphoma
Brexucabtagene autoleucel	Tecartus	CD19	Mantle cell lymphoma (MCL)	Adults with relapsed or refractory MCL
			B-cell acute lymphoblastic leukemia (ALL)	Adults with refractory or relapsed B-cell ALL
Lisocabtagene maraleucel	Breyanzi	CD19	B-cell non-Hodgkin lymphoma (NHL)	Adults with relapsed or refractory B-cell NHL
Idecabtagene vicleucel	Abecma	BCMA	Multiple myeloma	Adults with relapsed or refractory multiple myeloma
Ciltacabtagene autoleucel	Carvykti	BCMA	Multiple myeloma	Adults with relapsed or refractory multiple myeloma

BCMA as a Target in Myeloma Treatment



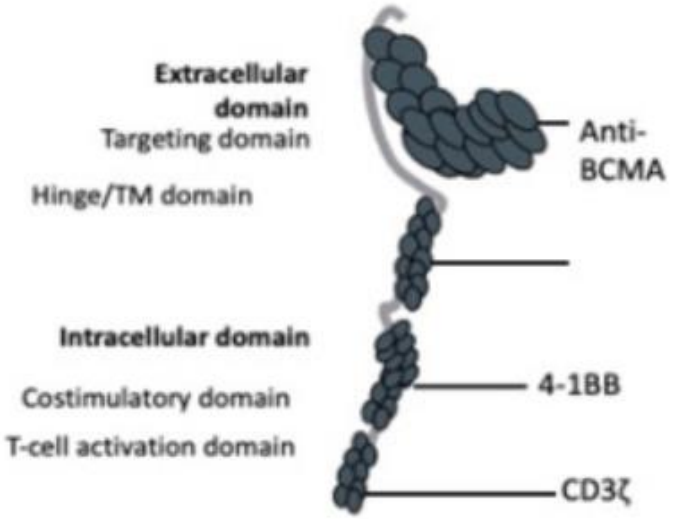
- BCMA: Antigen expressed specifically on plasma and myeloma cells
- Higher expression on myeloma cells than normal PCs
- Not expressed in other tissues
- In plasma cells, supports survival of long-lived PCs, antibody production, class switch of immunoglobulin
- Promotes myeloma cell growth, chemotherapy resistance, immunosuppression in bone marrow microenvironment
- Expression of BCMA increases with progression from MGUS to advanced myeloma
- Increased sBCMA level associated with poorer outcome

Cho. Front Immunol. 2018;9:1821.

2022: two approved BCMA Directed CAR Ts

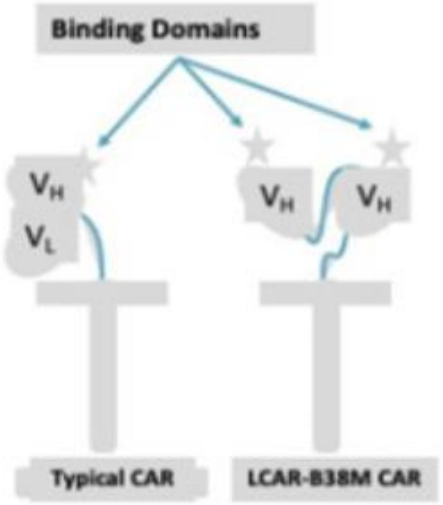
Idecabtagene Vicleucel

- Autologous T-cells transduced with a lentiviral vector encoding CAR specific for BCMA
- Targeting domain: Anti-BCMA
- Costimulatory domain: 4-1BB
- T-cell activation domain: CD3 ζ



Ciltacabtagene Autoleucel

- Lentiviral vector-based + 4-1BB costimulatory domain;
- BCMA-catching domain targets 2 different epitopes simultaneously



Martino M Cancers 2021 13:2639

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KarMMa Update: Duration of Response: Best DOR in Patients who Achieve CR

Outcome	Ide-cel 150 x 10^6 (n = 4)	Ide-cel 300 x 10^6 (n = 70)	Ide-cel 450 x 10^6 (n = 54)	All Ide-cel Patients (n = 128)
Median DoR, mo	--	9.9	11.3	10.9 (9.0-11.4)
Median DoR by no. of prior therapy lines, mo (95% CI) ▪ 3 ▪ ≥4	--	--	--	 8.0 (3.3-11.4) 10.9 (9.2-13.5)
Median DoR by best response, mo (95% CI) ▪ CR/sCR ▪ VGPR ▪ PR	--	--	--	 21.5 (12.5-NE) 10.4 (5.1-12.2) 4.5 (2.9-6.7)
24-month event-free DoR by no. of prior therapy lines, % ▪ 3 ▪ ≥4	--	--	--	 18.2 21.3

Anderson. ASCO 2021. Abstr 8016.

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KarMMa Update: Survival

Outcome	3 Prior Therapy Lines (n = 15)	≥4 Prior Therapy Lines (n = 113)	All Ide-cel Patients (n = 128)
Median PFS, mo (95% CI)	8.6 (2.9-12.1)	8.9 (5.4-11.6)	8.6 (5.6-11.6)
Median OS, mo (95% CI)	22.0 (10.0-NE)	25.2 (19.9-NE)	24.8 (19.9-31.2)
OS, % ▪ 12 mo ▪ 18 mo ▪ 24 mo	--	--	 78 65 51

- Median PFS at 300 x 10^6 CAR T-cells was 5.8 mo vs 12.2 mo with 450 x 10^6 CAR T-cells
- Median OS in subgroups at high risk of progression (age ≥65 yr, extramedullary disease, triple refractory) was ≥20 mo
- Median OS in subgroup with R-ISS stage III disease was 8.8 mo

Anderson. ASCO 2021. Abstr 8016.

Slide credit: clinicaloptions.com

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Characteristics associated with better responses to ide-cel

Table 1. Baseline characteristics of patients with CR/sCR and non-CR/sCR

Characteristic	CR/sCR (n = 42)	Non-CR/sCR (n = 86)
Age, median (range), years	59.5 (38–78)	61.0 (33–77)
Female, n (%)	19 (45.2)	33 (38.4)
ECOG performance status, n (%)		
0	18 (42.9)	39 (45.3)
1	24 (57.1)	44 (51.2)
2	0	3 (3.5)
Revised ISS Stage III (derived), n (%)	2 (4.8)	19 (22.1)
High risk cytogenetics,[a] n (%)	15 (35.7)	30 (34.9)
Number of prior regimens, median (range)	6 (3–13)	6 (3–16)
Triple refractory, n (%)	35 (83.3)	73 (84.9)
Heavy chain disease, n (%)	27 (64.3)	77 (89.5)
IgG	14 (33.3)	65 (75.6)
Bone marrow biopsy CD138+ plasma cells, median (range), %	(n = 40) 35 (0–95)	(n = 82) 60.0 (0–100)
β-2-microglobulin, median (range), mg/L	3.1 (1.3–23.0)	4.1 (1.6–32.0)

[a]Includes del (17p), t(4:14), and t(14;16).

Shah N ASH 2021 Abstract # 1739

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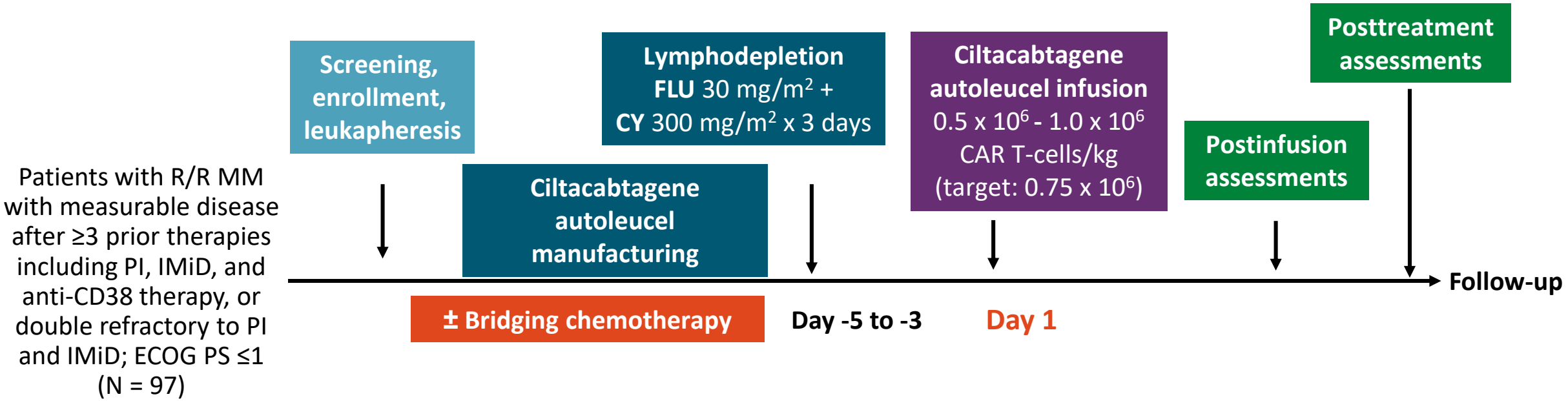
CARTITUDE-1 Update: Study Design

- Single-arm, open-label phase Ib/II trial conducted in the United States



- **Primary endpoints:** safety and dose (phase I), ORR (phase II)
- **Secondary endpoints**: PFS, OS, MRD negativity at 10^{-5}

Lin. ASCO 2023. Abstr 8009.

CARTITUDE-1 Update: Efficacy Summary

Efficacy Outcome	Patients (N = 97)
ORR, % (95% CI)*	97.9 (92.7-99.7)
▪ sCR	82.5 (73.4-89.4)
Median DoR, mo (95% CI)	33.9 (25.5-NE)
Median PFS, mo (95% CI)	34.9 (25.2-NE)
Median OS	NR
▪ 3-yr OS, %	62.9

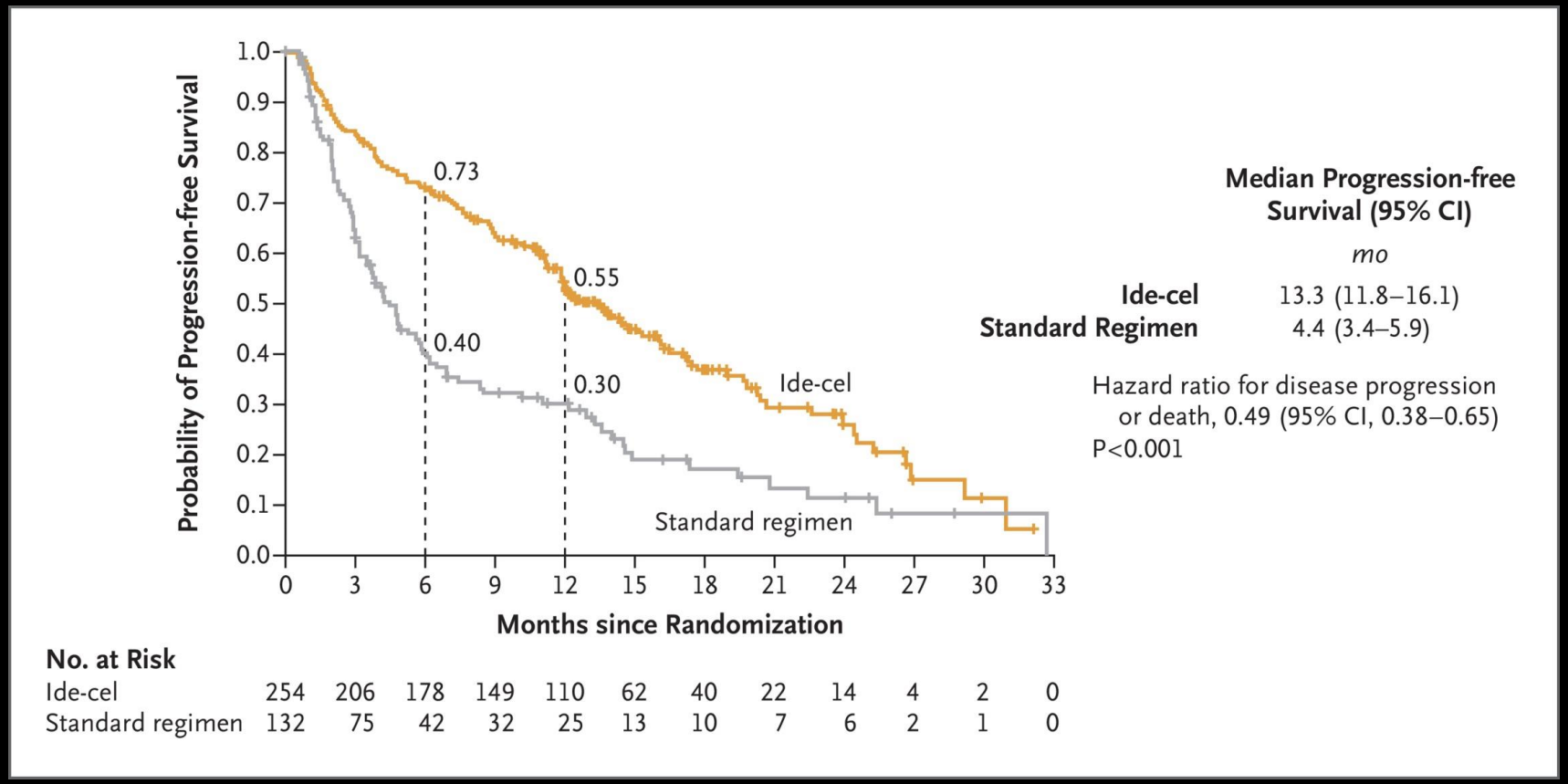
*Previously reported; assessed by IRC.

- MRD negativity ≥12 mo in 26/49 evaluable patients
  - 20/26 had sustained MRD negative ≥ CR
- 18 patients remained MRD negative with ≥ CR 24-mo post infusion

Lin. ASCO 2023. Abstr 8009.

KARMMA 3: Progression-free Survival (Intention-to-Treat Population

RRMM in patients with 2-4 lines of therapy

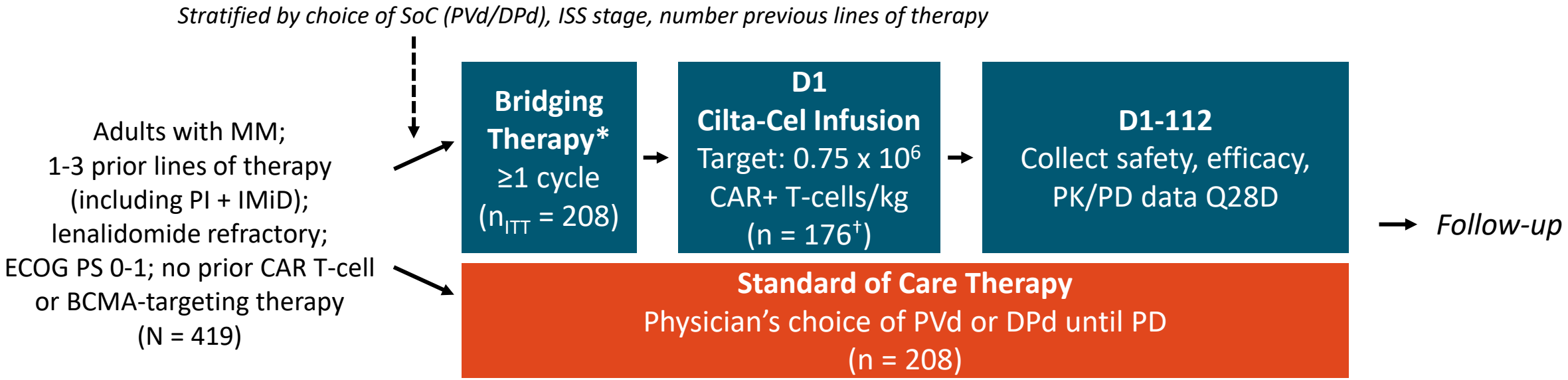


Rodriguez-Otero P et al. N Engl J Med2023;388:1002-1014

The NEW ENGLAND JOURNAL of MEDICINE

CARTITUDE-4: Study Design

- Randomized, open-label phase III trial

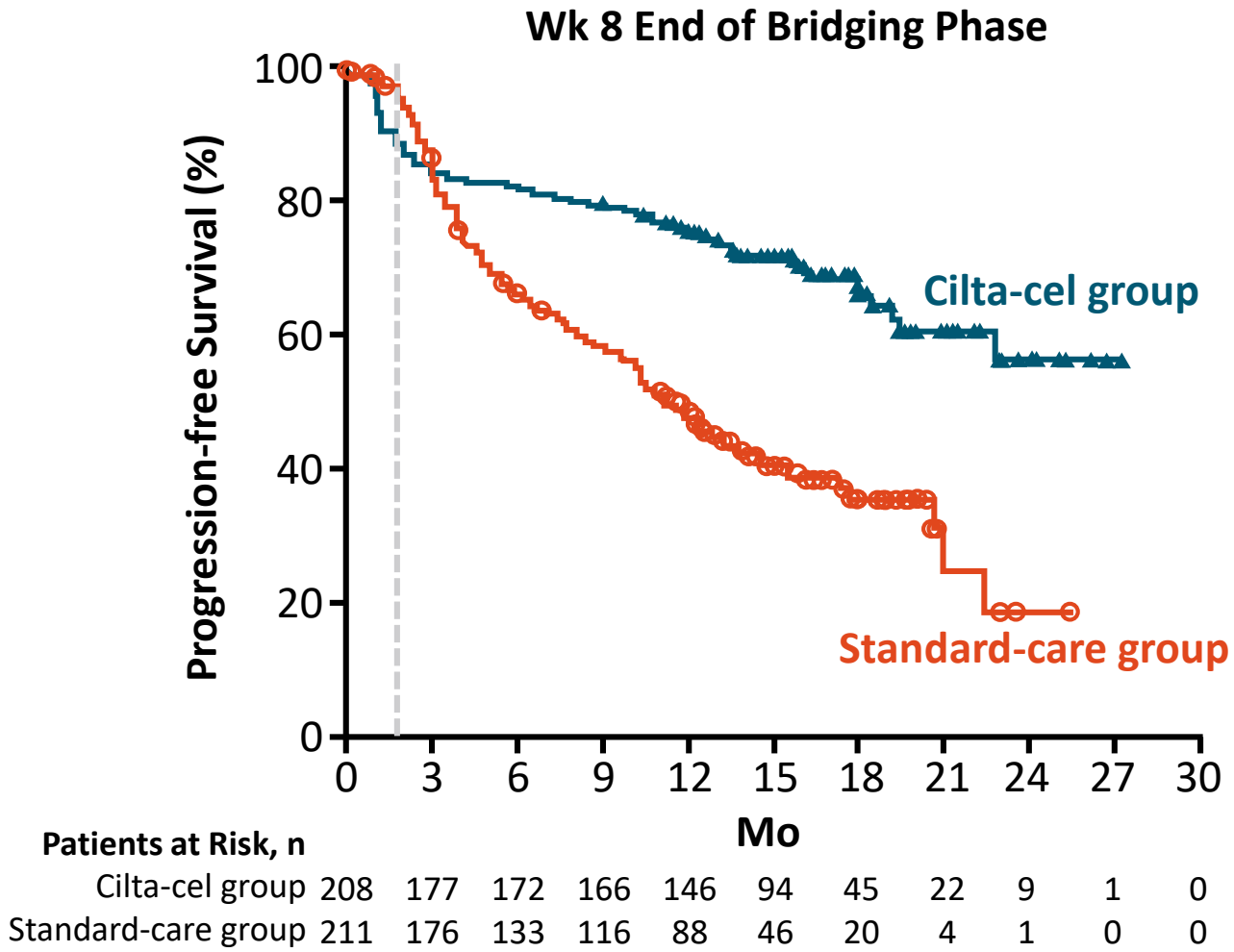


*Physician's choice of PVd or DPd. †As-treated population (n = 176): 32 patients did not receive cilta-cel as part of study due to PD (n = 30) or death (n = 2) during bridging therapy/lymphodepletion.

- **Primary endpoint:** PFS
- **Secondary endpoints:** ≥ CR, ORR, MRD negativity, OS, safety, PROs
- Current analysis after 15.9 mo median follow-up (range: 0.1-27 mo)

Dhakal. ASCO 2023. Abstr LBA106. San-Miguel. NEJM. 2023;[Epub].

CARTITUDE-4: Progression-Free Survival (ITT Population)

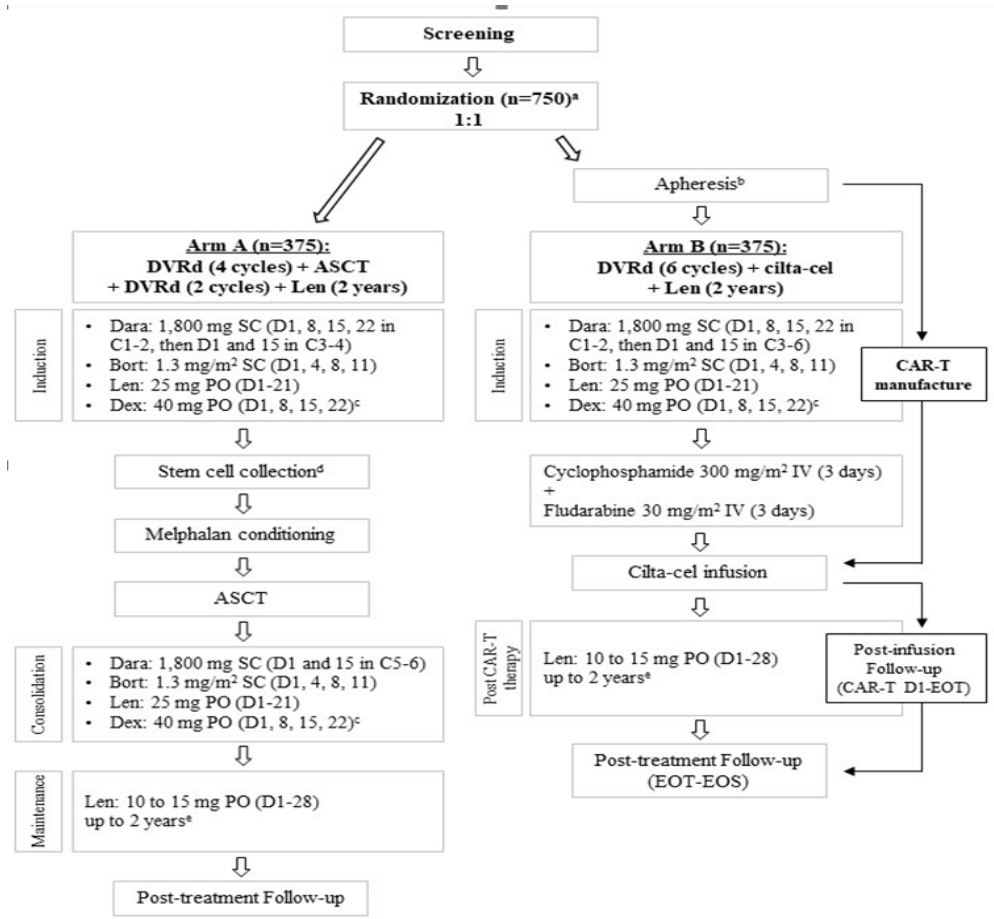


	Cilta-Cel (n = 208)	SoC (n = 211)
mPFS, mo (95% CI)	NR (22.8-NE)	11.8 (9.7-13.8)
	HR: 0.26 (95% CI: 0.18-0.38; *P* <.0001)	
12-mo PFS, %	76	49

San-Miguel. NEJM. 2023;[Epub].

Slide credit: clinicaloptions.com

A Phase 3 Randomized Study Comparing Daratumumab, Bortezomib, Lenalidomide and Dexamethasone (DVRd) followed by Ciltacabtagene Autoleucel versus Daratumumab, Bortezomib, Lenalidomide and Dexamethasone (DVRd) followed by Autologous Stem Cell Transplant (ASCT) in Participants with Newly Diagnosed Multiple Myeloma who are Transplant Eligible: EMN 28/CARTITUDE 6



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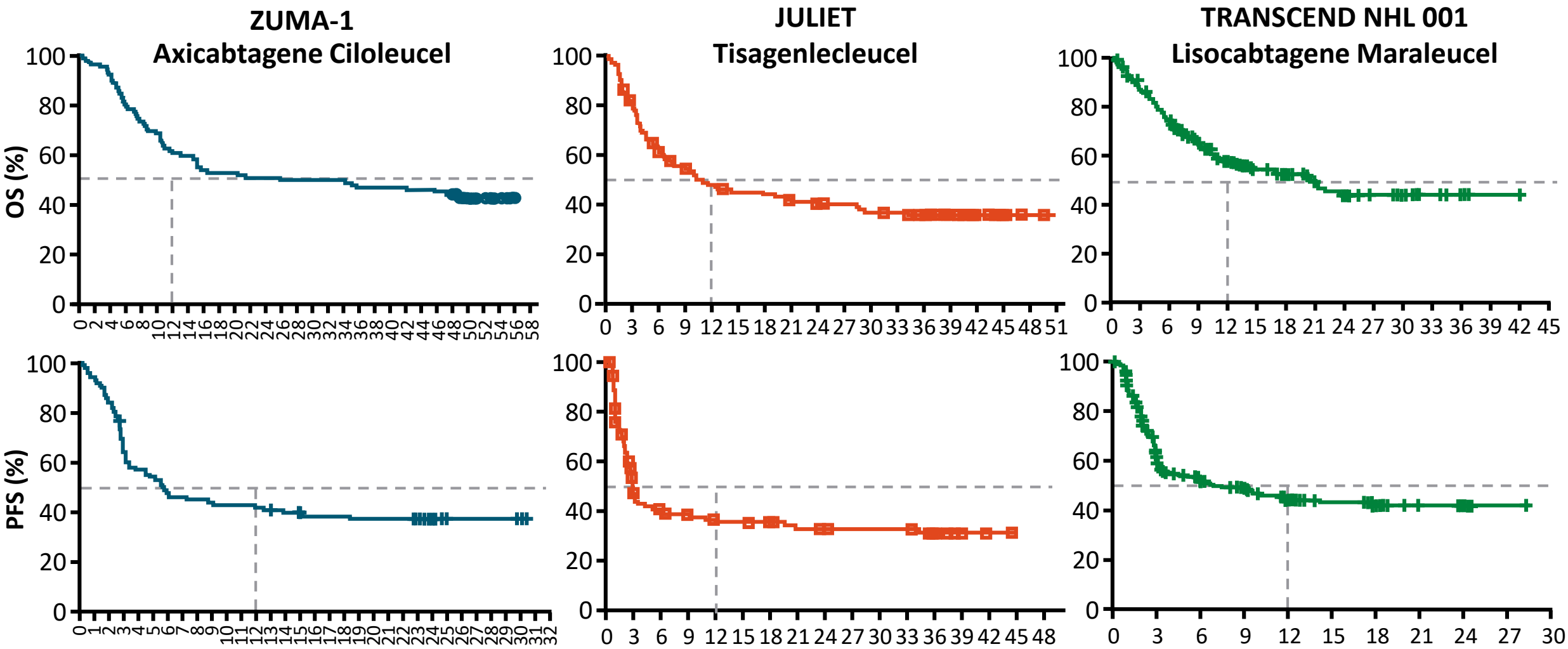
Survival With Anti-CD19 CAR T-Cell Therapy in DLBCL: appears to be actual cure rate



Locke. Lancet Oncol. 2019;20:31. Jacobson. ASH 2020. Abstr 1187. Jaeger. ASH 2020. Abstr 1194. Abramson. Lancet. 2020;396:839.

Slide credit: clinicaloptions.com

TRANSFORM Subgroup Analyses: Liso-Cel vs SOC in Primary Refractory or Early Relapsed LBCL

- Liso-cel as 2L treatment demonstrated clinical benefit vs SOC in primary refractory and early-relapsed LBCL (median FU: 17.5 mo)

Primary Refractory

Parameter	Liso-Cell (n = 67)	SoC (n = 70)
EFS per IRC		
▪ Median, mo (95% CI)	12.0 (6.0-NR)	2.2 (2.1-2.7)
▪ 12-mo EFS, % (95% CI)	50 (37.9-62.1)	18.3 (9.0-27.5)
▪ 18-mo EFS, % (95% CI)	45.4 (33.4-57.4)	16.0 (6.9-25.1)
PFS per IRC		
▪ Median, mo (95% CI)	19.2 (6.6-NR)	4.9 (2.3-7.5)
▪ 12-mo PFS, % (95% CI)	55.9 (43.7-68.2)	28.7 (15.7-41.7)
▪ 18-mo PFS, % (95% CI)	50.9 (38.5-63.3)	25.1 (11.9-38.2)
OS		
▪ Median, mo (95% CI)	29.5 (22.2-NR)	20.9 (15.1-NR)
▪ 12-mo EFS, % (95% CI)	80.4 (70.8-89.9)	67.3 (56.0-78.5)
▪ 18-mo EFS, % (95% CI)	68.0 (56.7-79.3)	55.8 (43.6-67.9)

- ORR (95% CI): 85% (74.3%-92.6%) vs 39% (27.2%-51.0%)
- CRS: 49% (grade ≥3, 1%)
- Neurotoxicity: 12% (grade ≥3, 4%)

Early Relapse

Parameter	Liso-Cel (n = 25)	SoC (n = 22)
EFS per IRC		
▪ Median, mo (95% CI)	NR (15.6-NR)	8.3 (2.9-NR)
▪ 12-mo EFS, % (95% CI)	76.0 (59.3-92.7)	36.4 (16.3-56.5)
▪ 18-mo EFS, % (95% CI)	71.8 (54.0-89.5)	36.4 (16.3-56.5)
PFS per IRC		
▪ Median, mo (95% CI)	NR (NR-NR)	9.0 (6.0-NR)
▪ 12-mo PFS, % (95% CI)	82.8 (67.4-98.1)	40.2 (18.7-61.7)
▪ 18-mo PFS, % (95% CI)	78.2 (61.2-95.1)	40.2 (18.7-61.7)
OS		
▪ Median, mo (95% CI)	NR (NR-NR)	NR (17.9-NR)
▪ 12-mo EFS, % (95% CI)	91.7 (80.6-100.0)	86.4 (72.0-100.0)
▪ 18-mo EFS, % (95% CI)	87.3 (73.9-100.0)	75.2 (56.1-94.3)

- ORR (95% CI): 92% (74%-99%) vs 82% (59.7%-94.8%)
- CRS: 48% (grade ≥3, 0%)
- Neurotoxicity: 8% (grade ≥3, 4%)

Nastoupil. ASCO 2023; Abstr 7526.

CAR T-Cells vs SoC in High-Risk DLBCL: Results

ZUMA-7

Parameter	Axi-Cel (n = 180)	SoC (n = 179)
Median EFS, mo	8.3	2.0
	HR: 0.398; *P* <.0001	
24-mo EFS, %	41	16
ORR, %	83	50
	P <.001	
CR, %	65	32
Median OS*, mo	NR	31.0
	HR: 0.726; *P* = .0168	
48-mo OS, %	54.6	46.0
Grade ≥3 CRS, %	6	N/A
Grade ≥3 ICANS, %	21	1
Tocilizumab, %	65	N/A

*Median FU: 47.2 mo

- Bridging therapy: 36%
- SoC: 36% received autoSCT; 57% received subsequent CAR T-cell tx
- ABC: 7%; double/triple hit: 16%

BELINDA

Parameter	Tisa-Cel (n = 162)	SoC (n = 160)
Median EFS, mo	3	3
	HR: 1.07; *P* = .61	
ORR (12 wk), %	46.3	42.5
CR (12 wk) %	28.4	27.5
Grade ≥3 CRS, %	5.2	N/A
Grade ≥3 ICANS, %	1.9	N/A

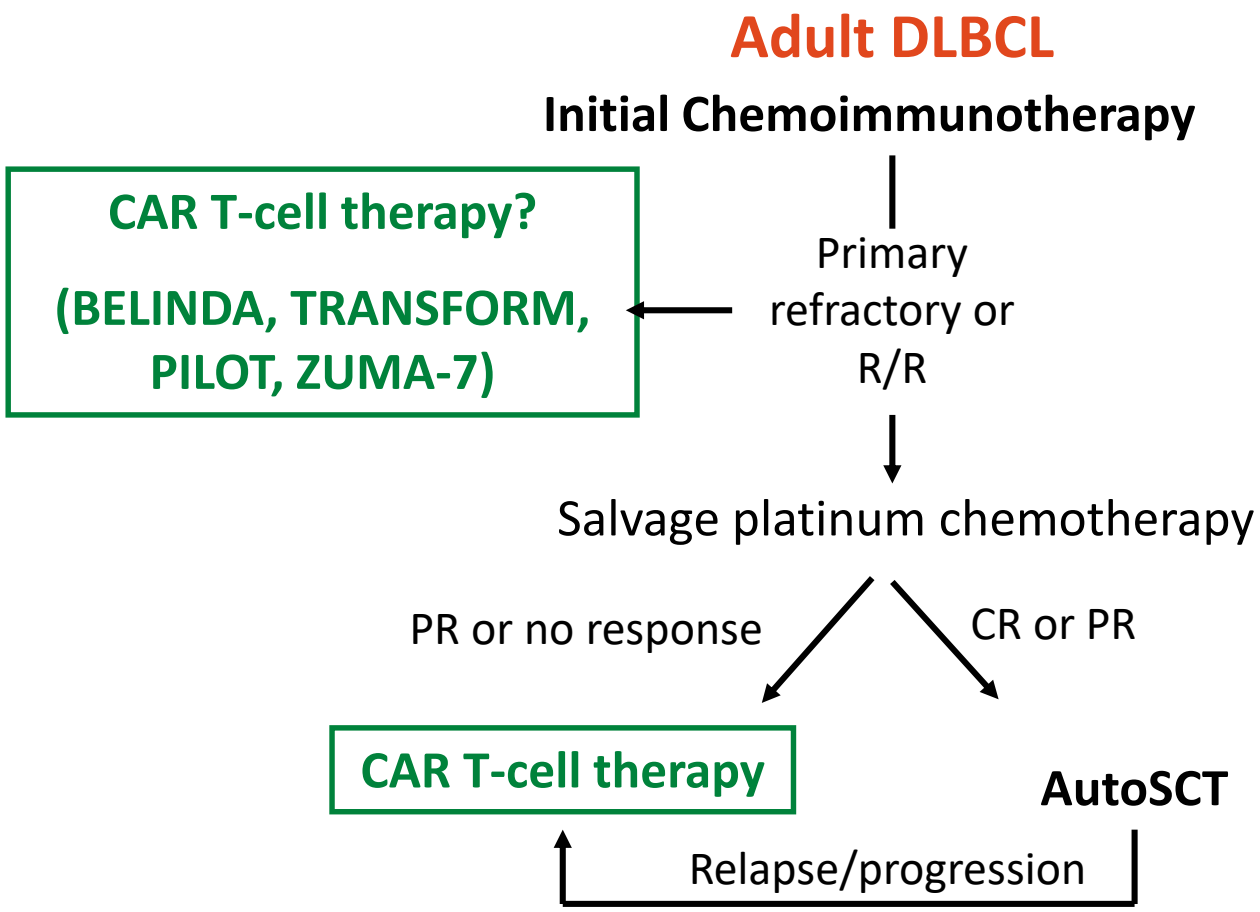
- Bridging therapy: 83.3% (35.8%, 1 cycle; 47.5%, ≥2 cycles)
- SoC: 50.6% received autoSCT
- ABC: 29% (32% tisa-cel); double/triple hit: 16%

Locke. NEJM. 2022; 386:640. Westin. ASCO 2023; Abstr LBA107. Westin. NEJM.2023[Epub]; Abstr LBA107. Bishop. NEJM. 2021;386:629.

ZUMA7, TRANSFORM, BELINDA RESULTS

	ZUMA-7 [1]	TRANSFORM [2]	BELINDA [3]
Product	**Axi-cel vs SOC**	**Liso-cel vs SOC**	**Tisa-cel vs SOC**
ORR (%)	83% vs 50%	86% vs 48%	75% vs 68%
CR (%)	65% vs 32%	66% vs 39%	46% vs 44%
mEFS	8.3 vs 2.0 mos	10.1 vs 2.3 mos	3.0 vs 3.0 mos
EFS rate	2-year: 40.5% vs 16.3%	12-month: 44.5% vs 23.7%	---
mPFS	14.7 vs 3.7 mos	14.8 vs 5.7 mos	---
PFS rate	2-year: 46% vs 27%	12-month: 52.3% vs 33.9%	---
mOS	NR vs 35.1 mos	NR vs 16.4 mos	---
OS rate	---	12-month: 79.1% vs 64.2%	---

Fitting CAR T-Cell Therapy Into Current Treatment Paradigms in DLBCL



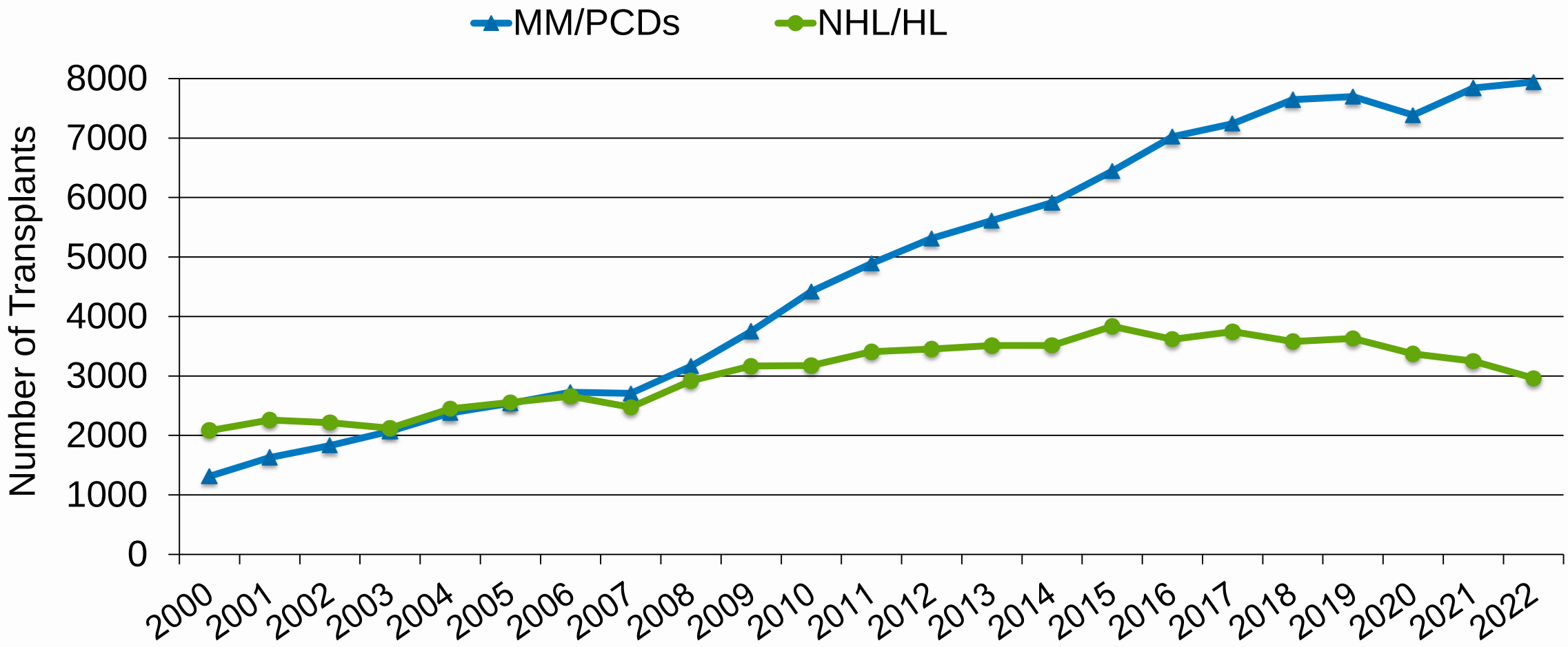
Key items to consider:

- Refer patients early to CAR T-cell center
- Avoid therapies that cause severe T-cell lymphopenia
- Unknown impact of prior CD19-directed therapies
- Stop novel agents (eg, ibrutinib, lenalidomide) prior to infusion
- Bridging therapy needed? What if CR obtained from bridging?
- Lower disease burden = lower toxicity
- CNS involvement?
- Flu/Cy vs bendamustine?
- Always rule out active infection
- Check HIV status

Jain. Biol Blood Marrow Transplant. 2019;25:2305.

Slide credit: clinicaloptions.com

Number of Autologous HCTs in the US by Selected Disease: clear decline in number of auto transplants for NHL due to CAR-T



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Abbreviations – MM: Multiple myeloma; PCDs: Plasma cell disorders; NHL: Non-Hodgkin lymphoma; HL: Hodgkin lymphoma

- Current price tag for product only-$350-500,000
- Only transplant centers currently able to offer therapy
- Access limited
- Toxicity considerations
- Sequencing of CAR-T therapy versus less expensive alternatives

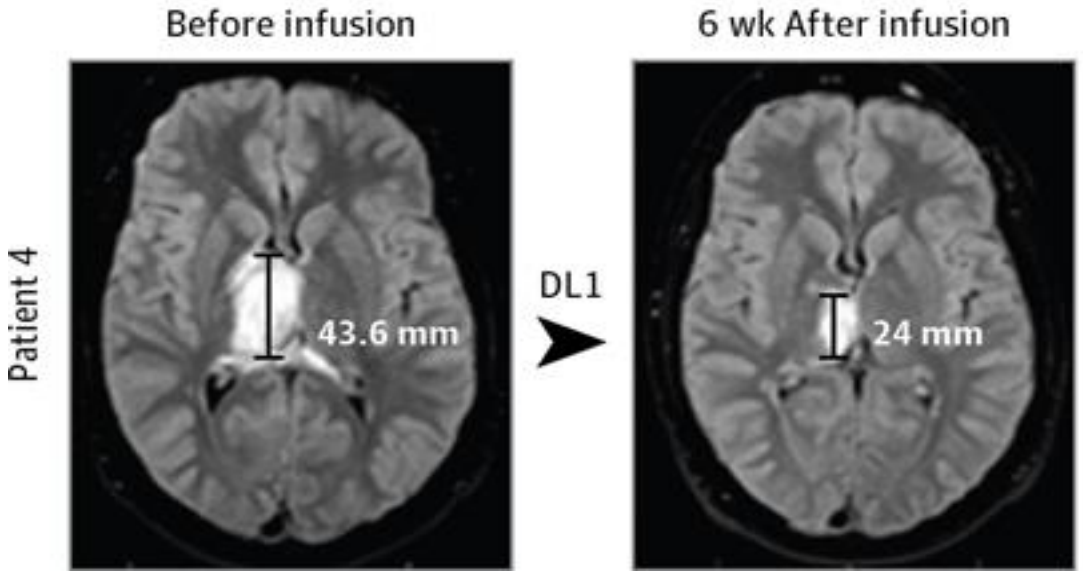
TABLE 2 | A summary of solid tumor antigens being targeted using CAR T cell therapy.

Antigen	Type of cancer	Endomains	Gene transfer method	Reference
CD171	Recurrent/refractory neuroblastoma	CD3ζ	Electroporation	(37)
EGFRvIII	Glioma	CD28+CD3ζ, 4-1BB	Gamma-retrovirus	(38)
Epidermal growth factor receptor	Gastric cancer	–	Gamma-retrovirus	(39)
Carbonic anhydrase IX	Metastatic renal cell carcinoma	FcRγ	Gamma-retrovirus	(40)
α-folate receptor	Ovarian	FcRγ	Gamma-retrovirus	(41)
HER2	Sarcoma	CD28-CD3ζ	Gamma-retrovirus	(42)
HER2	Glioblastoma	CD28-CD3ζ	pigyBac	(43)
HER2	Osteosarcoma	CD28-CD3ζ	SFG retroviral	(44)
αHER2/CD3	Gastric cancer	CD28-CD3ζ	Gamma-retrovirus	(45)
Carcinoembryonic antigen	Liver metastases	CD28-CD3ζ	Gamma-retrovirus	(46)
IL13Rα2	Glioblastoma	CD3ζ	Electroporation	(47)
IL13Rα2	Glioblastoma	4-1BB, CD3ζ	Lentivirus	NEJM
HER2	Metastatic colon cancer	4-1BB, CD28, CD3ζ	Gamma-retrovirus	(48)
GD2	Neuroblastoma	CD3ζ	Gamma-retrovirus	(49)
GD2	Neuroblastoma	CD28, CD3ζ, OX40	SFG retroviral	(50)
ErbB2 + MUC1	Breast cancer	CD28, CD3ζ	SFG retroviral	(51)
Vascular endothelial growth factor receptor 2 + gp100 + TRP-1 + or TRP-2	Melanoma	–	Gamma-retrovirus	(24)
FAP	Colon and ovarian cancer	CD8α, CD3ζ, 4-1BB	Gamma-retrovirus	(17)
HER2 + CD19	Medulloblastoma	CD28 + CD3ζ	SFG retroviral	(23)
Mesothelin (MSLN)	Malignant Pleural Mesothelioma	CD3ζ and 4-1BB	Lentiviral	(22)
NKG2D	Breast cancer	CD28 + CD3ζ	Gamma-retrovirus	(21)
MSLN	Pancreatic cancer	CD3ζ and 4-1BB	Gamma-retrovirus	(8)
MSLN	Malignant pleural mesothelioma	CD3ζ and 4-1BB	Gamma-retrovirus	(8)

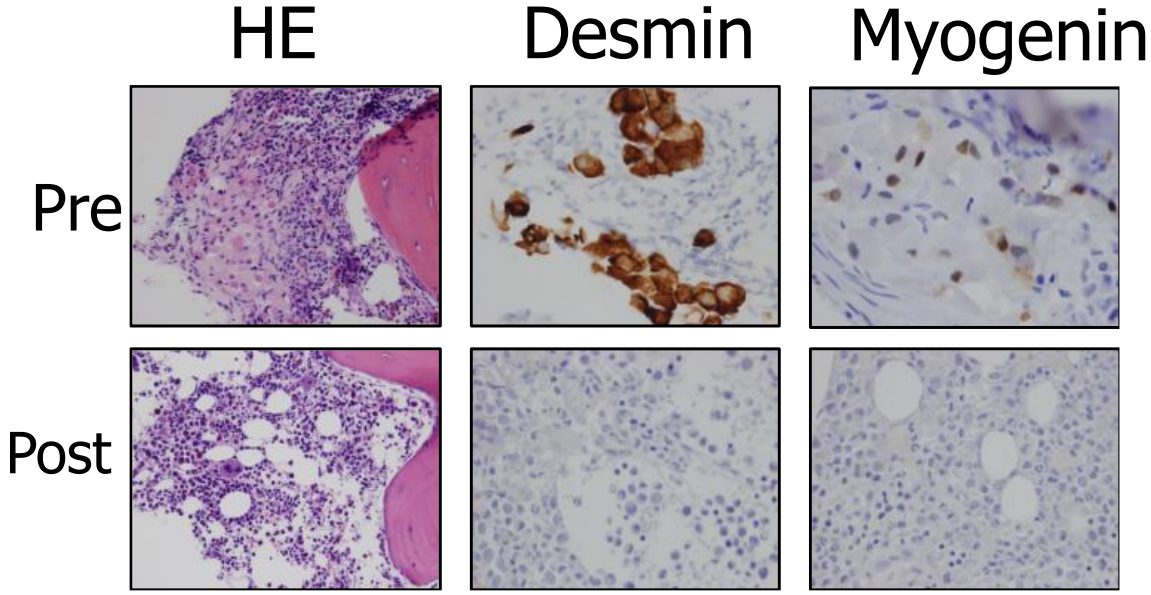
Mirzaei H. 2017 Front. Immunol. 8:1850.

CARs in Solid Tumors: Early Responses generated great enthusiasm

Her2Neu CARTs in glioblastoma



Recurrent/refractory Rhabdomyosarcoma: CR post HER2-CART



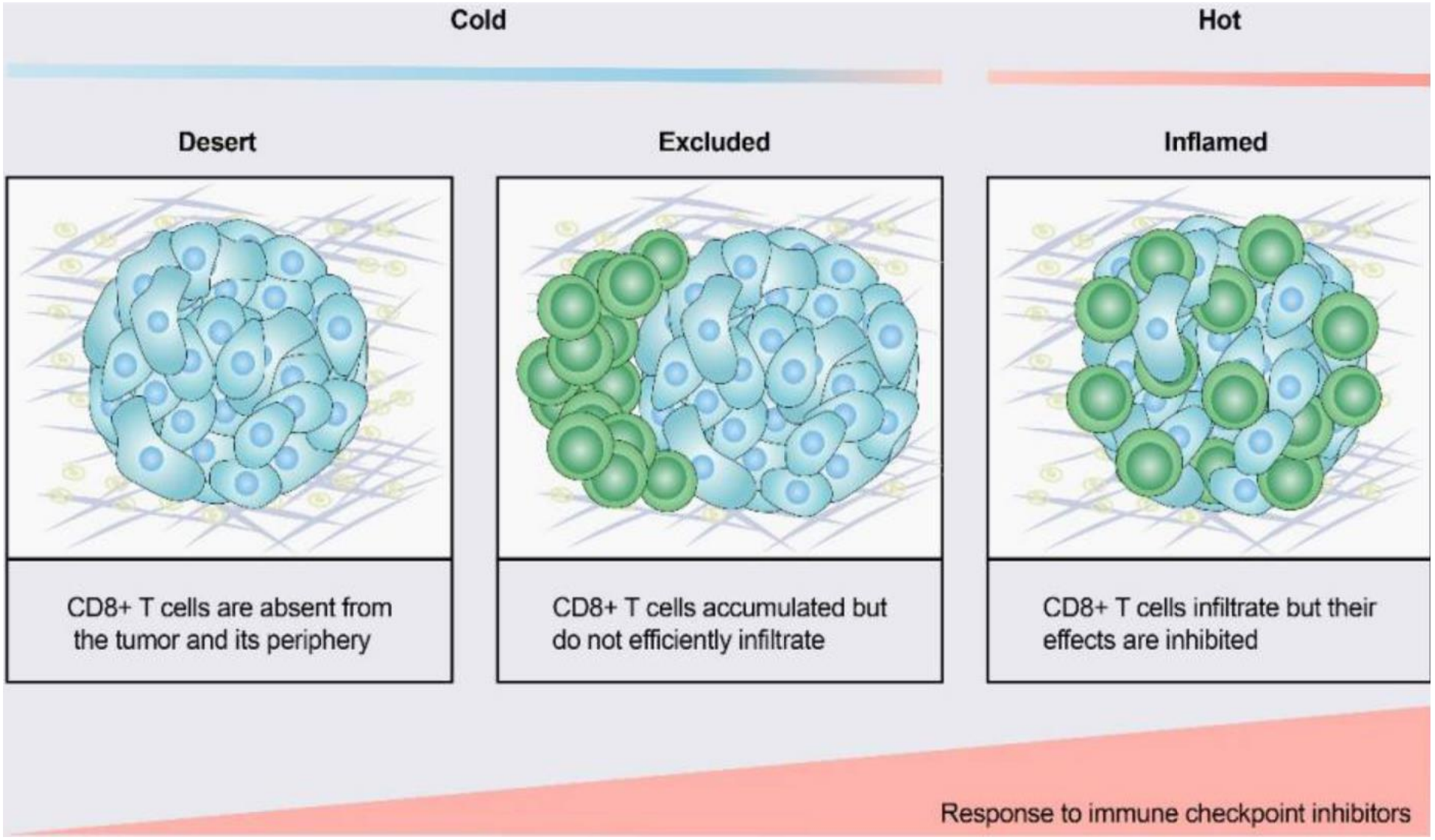
Malcolm Brenner, Stephen Gottschalk,
Nabil Ahmed, Meena Hegde

Published Cellular Therapies for Pediatric Solid Tumors (2006-2020)

Antigen	Diagnosis	Outcome	Center
	no lymphodepleting chemotherapy		
CD171	Neuroblastoma	**1/6 PR**	Seattle
GD2	Neuroblastoma	**3/11 CR**	Baylor
HER2	Sarcoma	4/17 SD	Baylor
HER2	High grade glioma	3/17 SD	Baylor
	post lymphodepleting chemotherapy		
EGFRvIII	High grade glioma	17/18 NR, 1/18 NE	
GD2	Diffuse intrinsic pontine glioma	3/4 “clinical improvement”, ongoing	Stanford
GD2 (CAR NKT)	Neuroblastoma	1/3 CR	Baylor
HER2	Sarcoma	**2/13 CR**; 4/13 SD	Baylor
GD2	Neuroblastoma	3/12 regression short of PR	GOSH
	locoregional delivery		
IL13Rα2	High grade glioma	1/3 tumor necrosis	City of Hope
HER2	Refractory CNS tumors	3/3 “inflammation”	Seattle

adapted from Gottschalk et al, Molecular Therapy, 2020

Same features that distinguish response to IO agents likely applicable in CAR-T



Liu Y. Theranostics. 2021; 11(11): 5365–5386

Challenges to treat solid tumors with CAR T cells

- Limited number of promising/safe target antigens
- Limited trafficking to tumor site due to poor vascularization, hypoxia, stroma inhibitory microenvironment
- Lack of elaboration of essential molecules
  - Appears IFN γ may be critical for solid organ CAR-T function[1]
- Limited persistence of transformed cells
- Severe off target toxicity due to lack of tumor Ag specificity
- Microenvironment-related factors
  - Presence of inhibitory signals (i.e. metabolites, TGF-β, adenosine, checkpoints)
  - Lack of supportive signals (IL-7, -15, -21; nutrients, costimulation)

Larson R et al Nature 2022 604:563

Claudin 6 as a CAR-T target in solid tumors

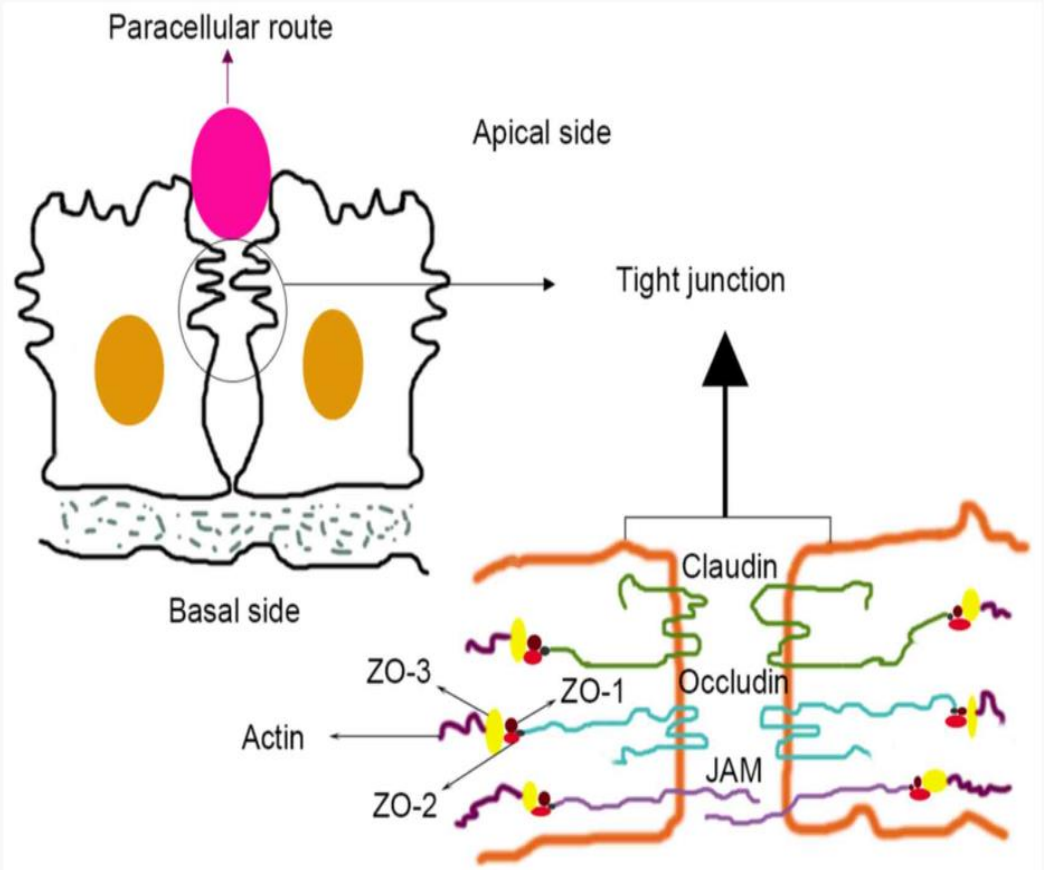
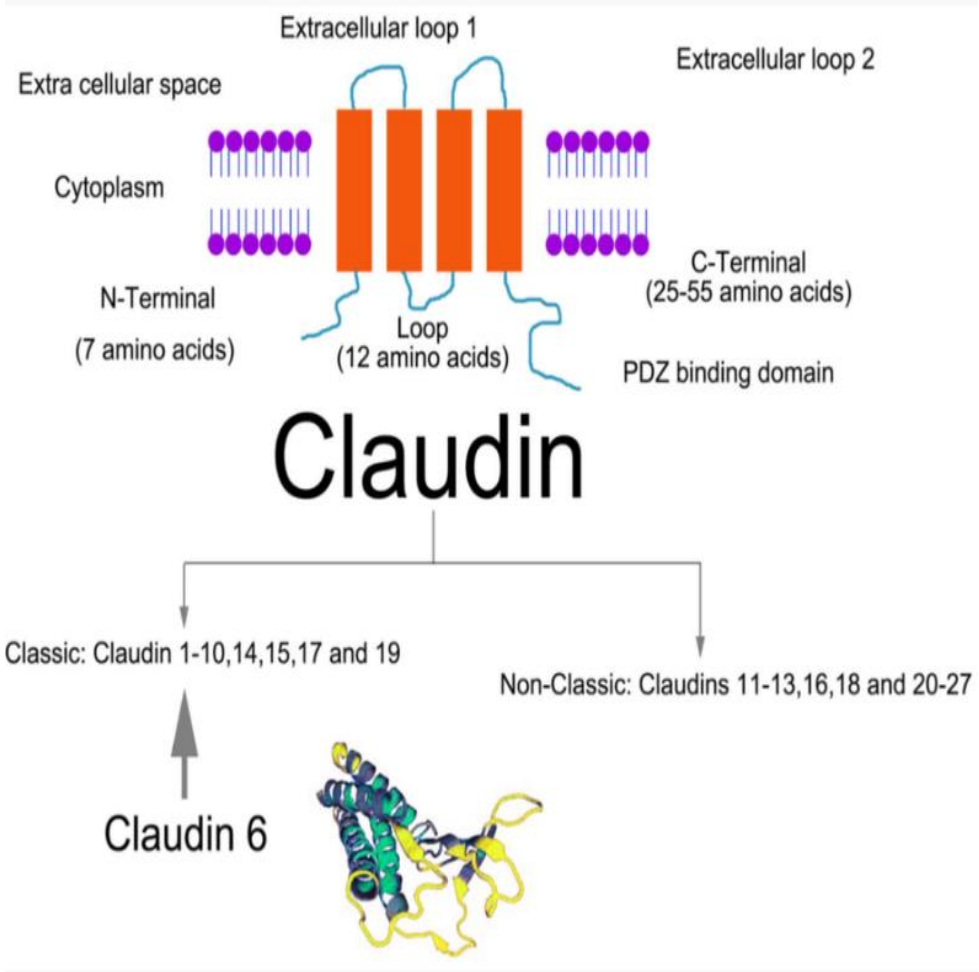
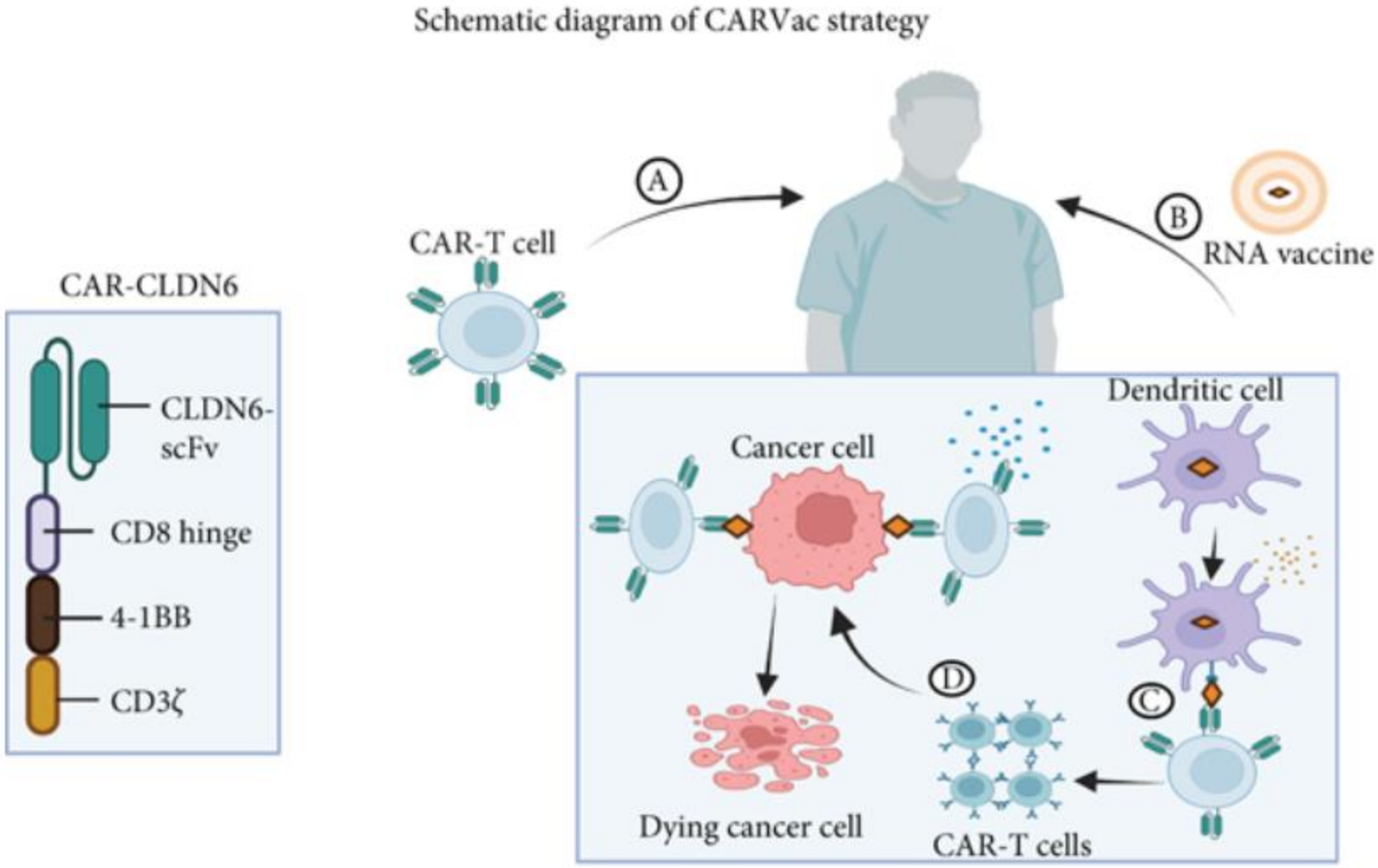


Figure 1. - Structural diagram of tight connection. Upper panel represents the location diagram of the TJ. The lower panel is the schematic diagram of the main components of TJs. Pink oval, paracellular route. TJ, tight junction. JAM, junctional adhesion molecule; ZO-1, Zona Occludens 1.



Du et al. https://doi.org/10.3892/mmr.2021.12316

Combination of CAR-T and mRNA based vaccine to boost activity



Ansah, et al https://doi.org/10.1155/2023/8030440

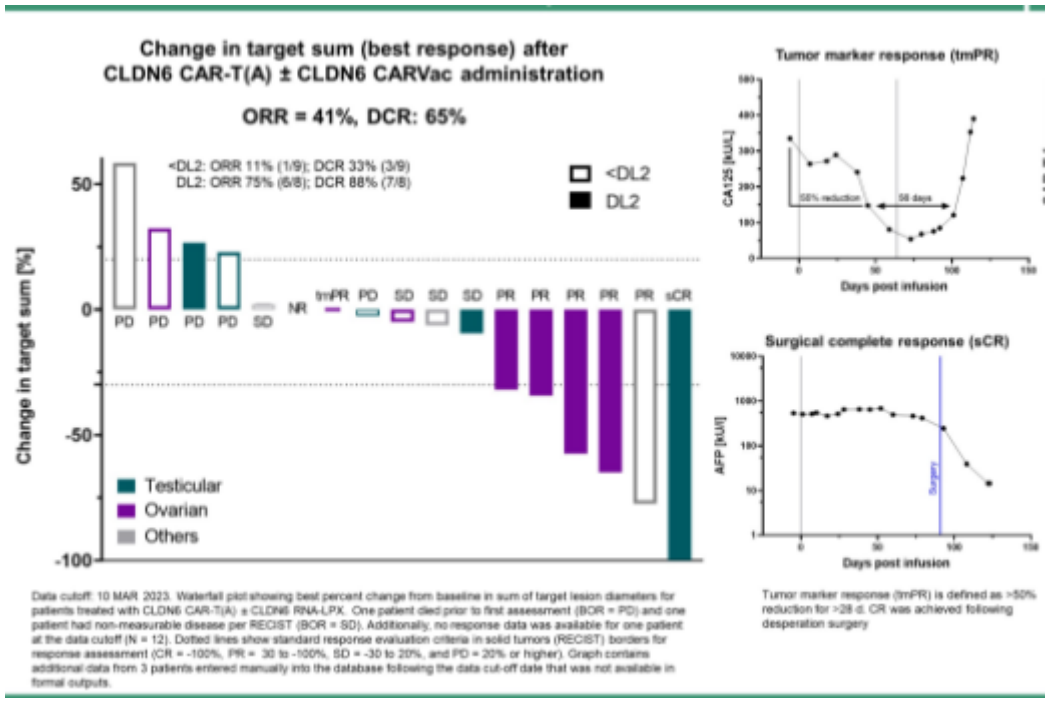
CLDN6 CAR-T cell therapy of R/R solid tumors ± a CLDN6-encoding mRNA vaccine: Dose escalation data from the BNT211-01 phase 1 trial using an automated product

Patient demographics

Characteristic	Cohort					
	DL0, Part 1 (N=2)	DL1, Part 1 (N=4)	DL2, Part 1 (N=6)	DL1, Part 2 (N=3)	DL2, Part 2 (N=4)	Total (N=19)
Median age, years (range)	55.5 (50-61)	54.5 (36-62)	44.5 (30-69)	48.0 (42-65)	44.0 (37-52)	50.0 (30-69)
Gender (male/female), n	1/1	3/1	2/4	2/1	3/1	11/8
Cancer type, n						
Lung	0	0	0	1	0	1
Testicular	1	0	1	1	3	6
Ovarian	1	1	4	1	1	8
Other [2]	0	3	1	0	0	4
Median (range) CLDN6+ cells [1], %	82.5 (80-85)	97.5 (80-100)	92.5 (90-100)	100.0 (95-100)	82.5 (70-100)	95.0 (70-100)
Median (range) prior treatment lines	3.0 (2-4)	4.0 (3-7)	4.0 (2-5)	3.0 (2-9)	4.0 (3-5)	4 (2-9)

Data cutoff: 10 MAR 2023. [1] Displaying an intermediate (2+) or strong (3+) membrane staining intensity as determined using a semi-quantitative immunohistochemistry assay; [2] Includes adenocarcinoma, extragonadal germ cell tumor, desmoplastic small round cell tumor (DSRCT), and esophageal carcinoma (one patient each).

Efficacy



Data cutoff: 10 MAR 2023. Waterfall plot showing best percent change from baseline in sum of target lesion diameters for patients treated with CLDN6 CAR-T(A) ± CLDN6 RNA-LPX. One patient died prior to first assessment (BOR = PD) and one patient had non-measurable disease per RECIST (BOR = SD). Additionally, no response data was available for one patient at the data cutoff (N = 12). Dotted lines show standard response evaluation criteria in solid tumors (RECIST) borders for response assessment (CR = -100%, PR = -30 to -100%, SD = -30 to 20%, and PD = 20% or higher). Graph contains additional data from 3 patients entered manually into the database following the data cut-off date that was not available in formal outputs.

Tumor marker response (tmPR) is defined as >50% reduction for >28 d. CR was achieved following desperation surgery

Mackensen et al ASCO 2023 #2518

Unique Considerations in Solid Tumor CAR-T vs use in hematologic malignancies

- Administration
  - Cell doses are very different. **Lymphodepleting chemo intensity often higher**
  - More often **multiple infusions** - with and without repeat LD chemo…..duration of hospitalization?
  - More often given with **supportive cytokines** – e.g., IL-2, IL-15
  - **Intratumoral** injection, intraperitoneal installation, introduction to **CNS** (?Ommaya)
  -hepatic artery injection

- Combination Therapy:
  - **Checkpoint inhibition or Ipilimumab** anti-CTLA-4 agent
  - Often part of SOC prior to treatment, may be part of protocol or may go on therapy AFTER progression on protocol
  - Unknown impact on efficacy and toxicity (e.g., Zuma 6, but what can we extrapolate?)

- Totally different expectations for **response criteria** – reevaluate cost/benefit ratio

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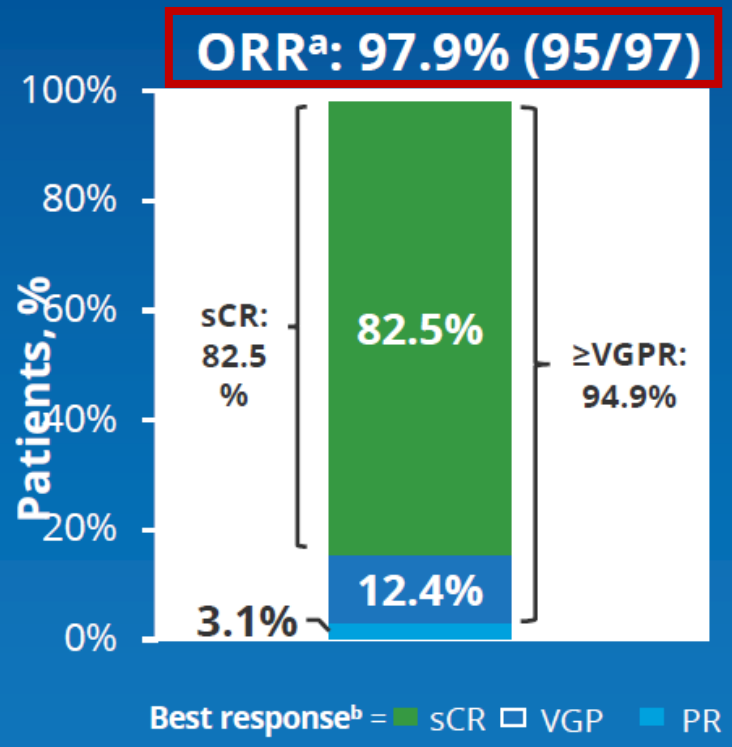
CARTITUDE-1: Efficacy Response

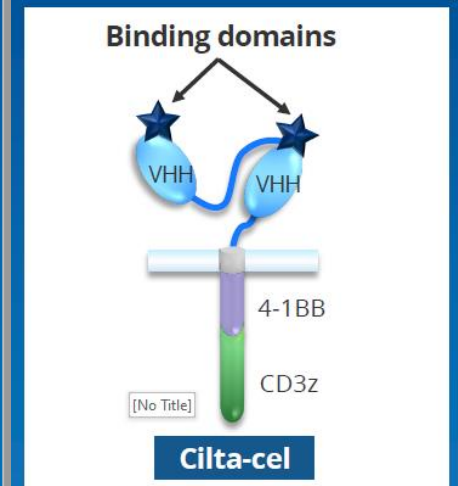


Responses deepened over time from the 1-year follow-up

Best response at any time	Median–1 year follow-up	Median–2 years follow-up
sCR, %	67	83

- Median time to first response was 1 month (range, 0.9–10.7)
- Median time to best response was 2.6 months (range, 0.9–17.8)
- Median time to CR or better was 2.9 months (range, 0.9–17.8)
- Median duration of response was not estimable (21.8 months–NE)

[a]ORR assessed by independent review committee; [b]No patient had CR or stable d sease as best response.
CR, complete response; NE, not estimable; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response



Early results in cellular therapy trials for solid tumors: stable disease rather than CR

	Cohort Size	Mean # Prior Therapies	Objective Response Rate (ORR)	Disease Control Rate (DCR)	Median Duration of Response (DOR)
Melanoma	66	3.3	36.4%	80.3%	Not reached as of 18.7 months of follow-up
Cervical Cancer	24	2.4	44%	85%	Not reached as of 7.4 months of follow-up
Non-Small Cell Lung Cancer	12	n/a	25%	n/a	Not reached

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Source: https://ir.iovance.com/static-files/dd026048-1c0a-42ff-bf4d-bec7f9acbd98

Different Starting Material and Manufacturing

- Acquisition of Raw Materials
  - More **tumor tissue** –for sequencing or TILs => **Surgeons, OR staff, Pathology**

- Manufacturing
  - Starting patient marrow reserve and starting cell numbers may be different
  - Often **extended manufacturing times**
    - Prior **Heme CAR expectations 16 days to 3 weeks.** Myeloma stretching to months
    - Tumor/normal tissue sequencing, protein synthesis, T-cell expansion, QC can take up to **5-6 months.**

  Solid tumor patients may not be able to wait that time **and clinical changes** very challenging

- **General Bandwidth Issues –** Apheresis, OR, screening…..inpatient?!

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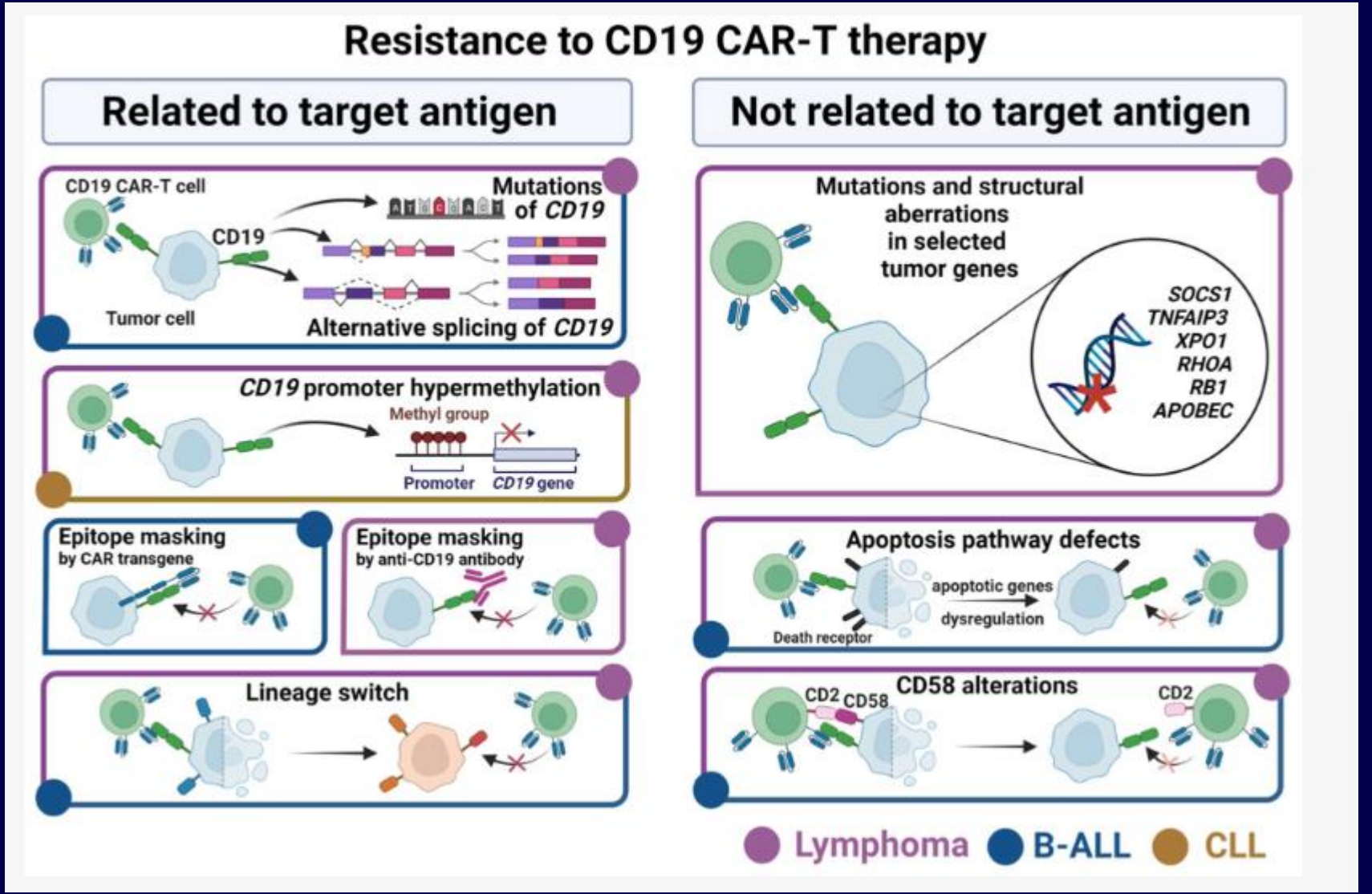


Marhelava 2022 11:1804

“tan” CAR to overcome target loss/resistance

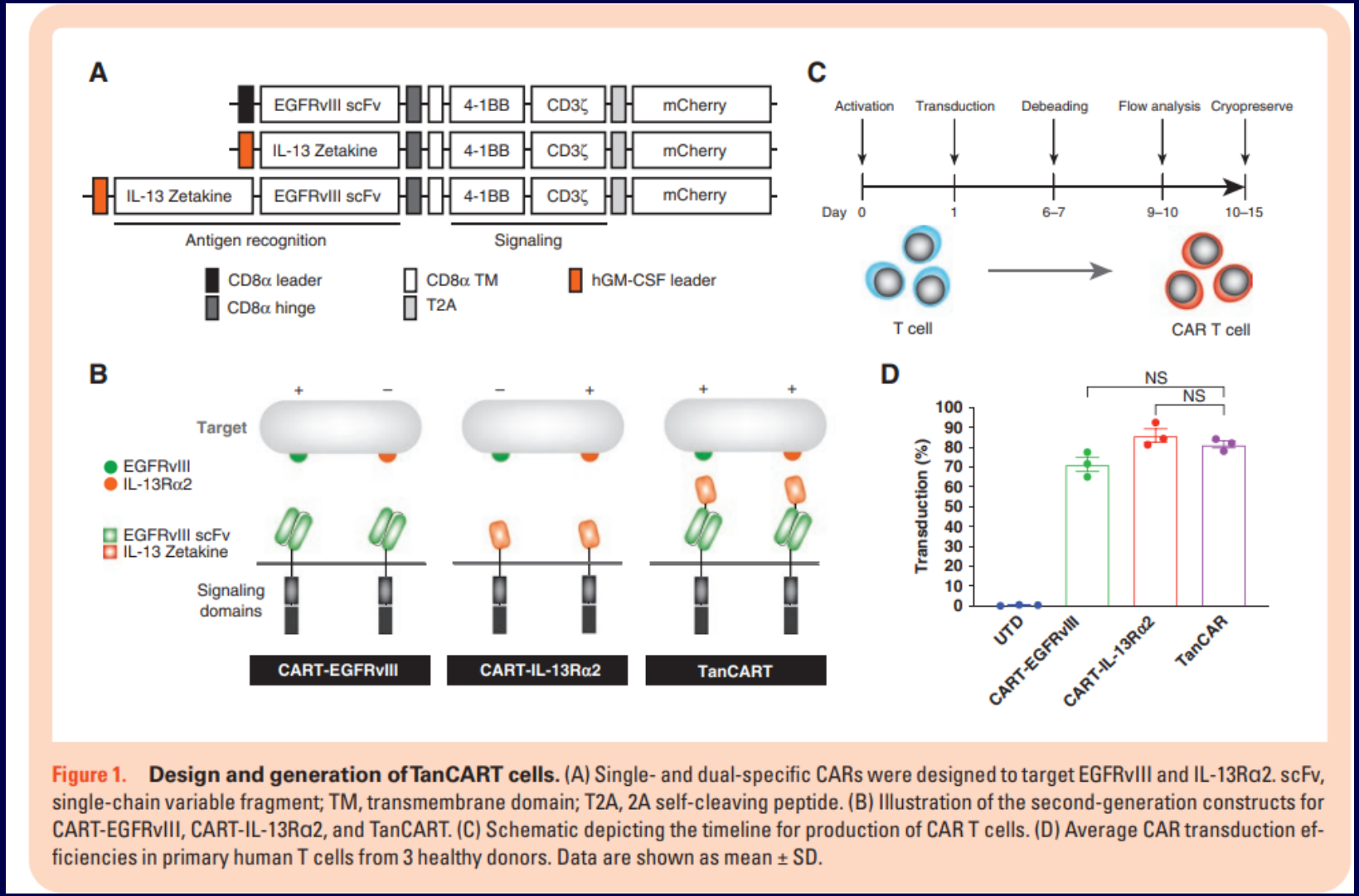
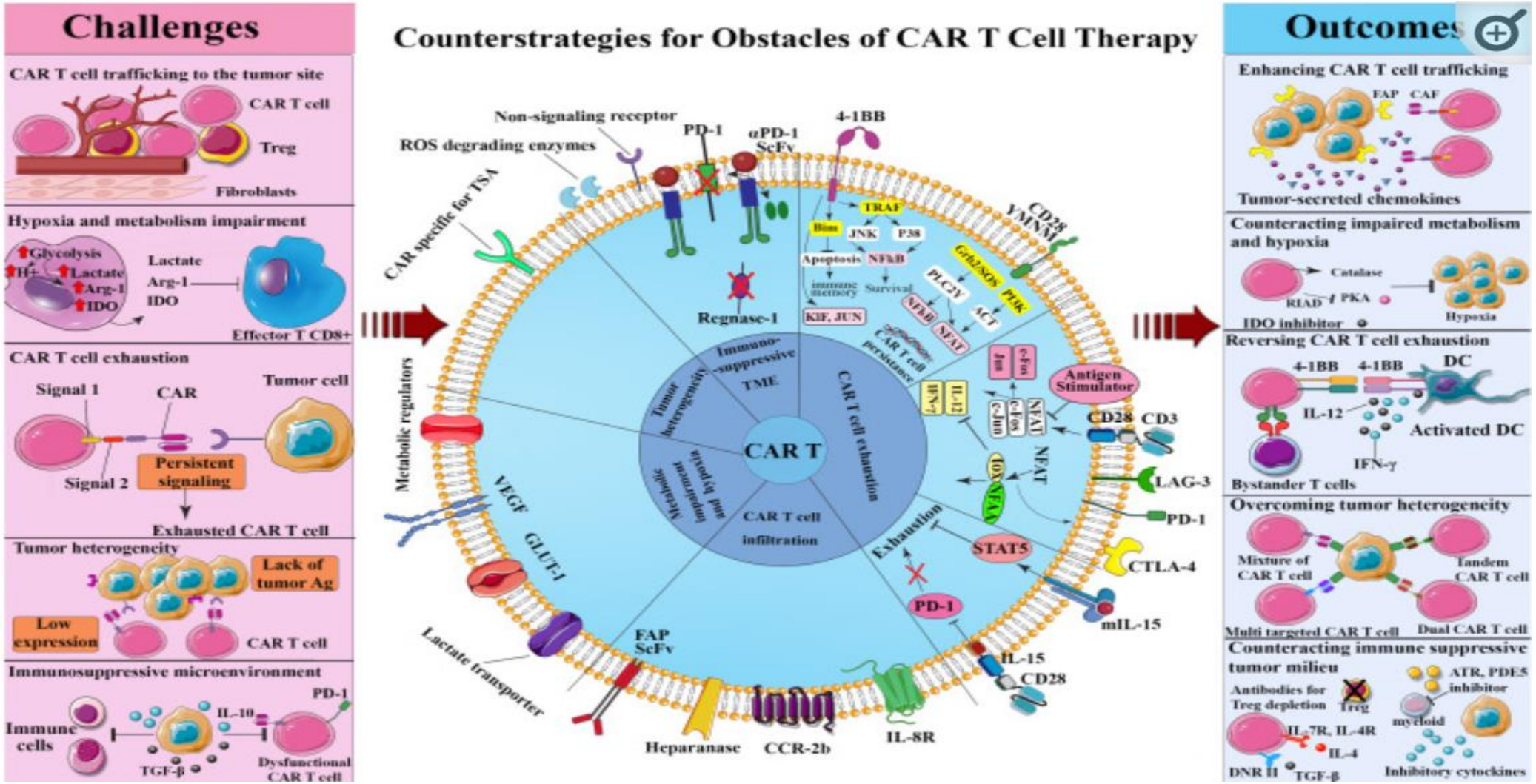


Figure 1. Design and generation of TanCART cells. (A) Single- and dual-specific CARs were designed to target EGFRvIII and IL-13Rα2. scFv, single-chain variable fragment; TM, transmembrane domain; T2A, 2A self-cleaving peptide. (B) Illustration of the second-generation constructs for CART-EGFRvIII, CART-IL-13Rα2, and TanCART. (C) Schematic depicting the timeline for production of CAR T cells. (D) Average CAR transduction efficiencies in primary human T cells from 3 healthy donors. Data are shown as mean ± SD.

Schmidts A. NeuroOncol 2022 5:1

Possible Strategies to overcome CAR-T resistance



Sorkhabi A Front Immuno 2023 14: 1113882

Conclusions:

- CAR-T therapy has become a mainstay of therapy in treating ALL, NHL and multiple myeloma
- Use will continue to expand to earlier lines of therapy

- Use of CAR-T to treat solid tumors is still investigational but innovations such as 4th generation CAR-T, dual CAR-T, CAR-NK and CAR-M, as well as combination therapy coming