Novel Immunotherapies in Multiple Myeloma

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Disclosures

- **Consultancy:** AbbVie, AstraZeneca, Bristol Myers Squibb, Janssen, Pfizer, Kite/Arcellx

- **Research Funding:** AbbVie, BeiGene, Bristol Myers Squibb, Fate Therapeutics

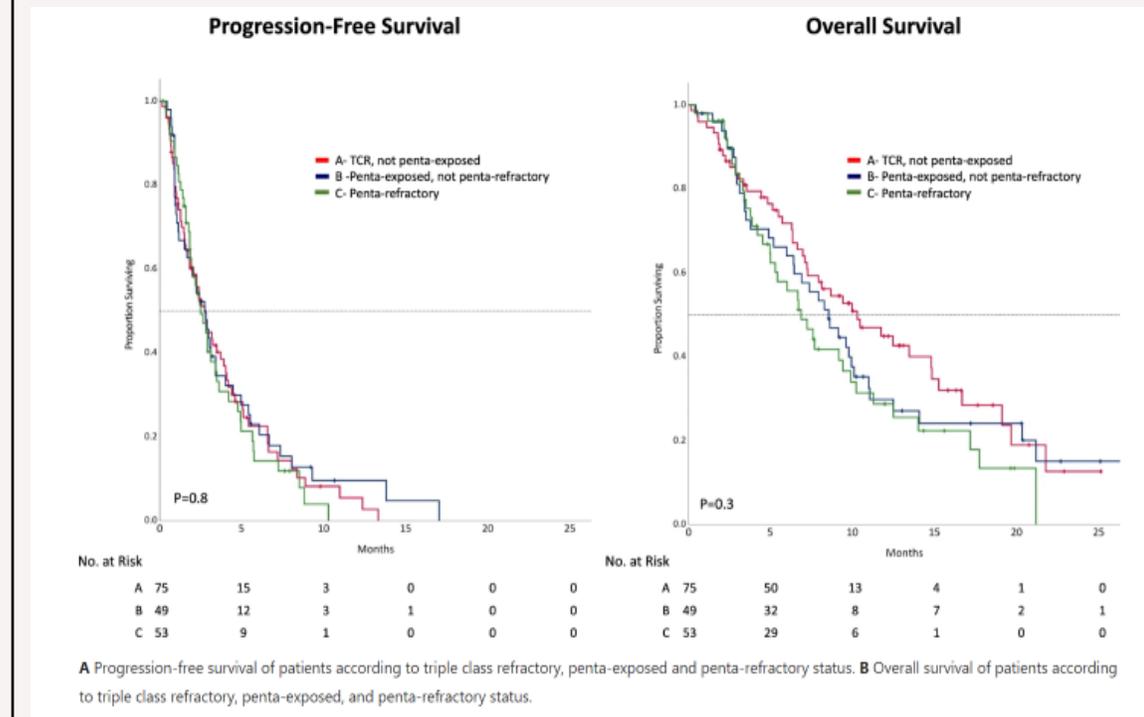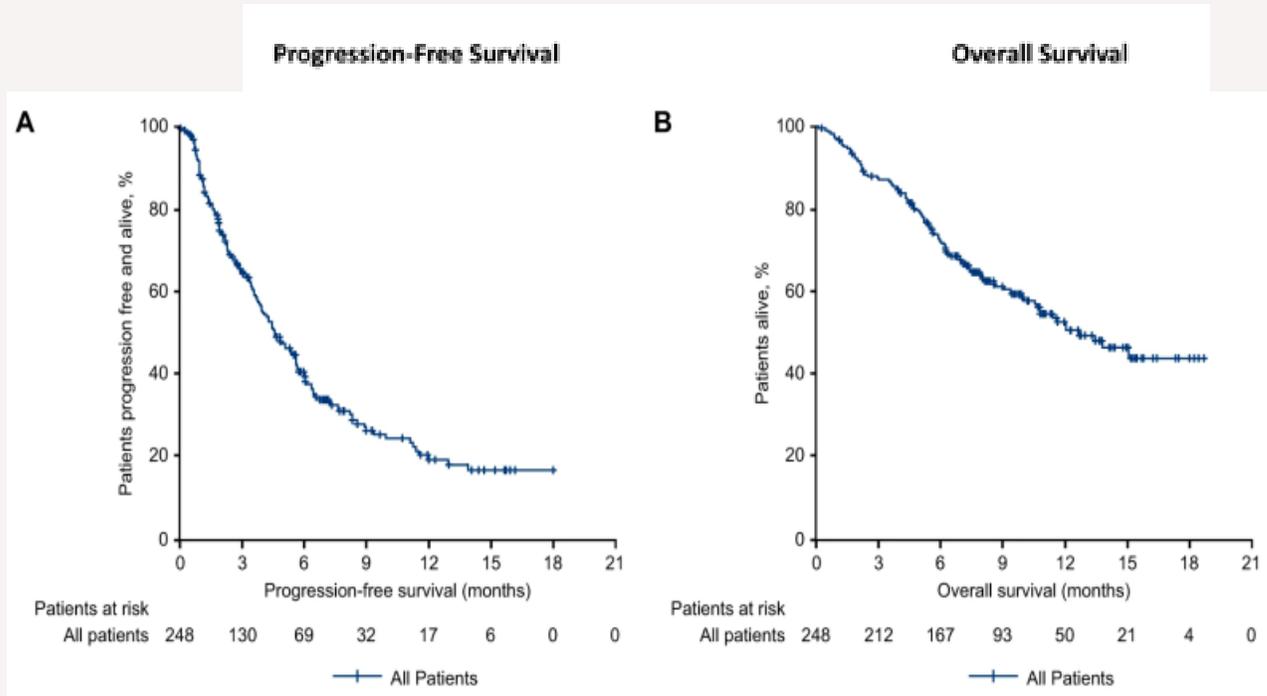- **Honoraria:** Adaptive Biotechnology

Objectives

Mechanistic understanding of immune platforms

Critical interpretation of CAR-T and bispecific data

Clinical integration and sequencing strategies

Future paradigms toward immune control

Triple Class Refractory MM: Therapeutic Challenge

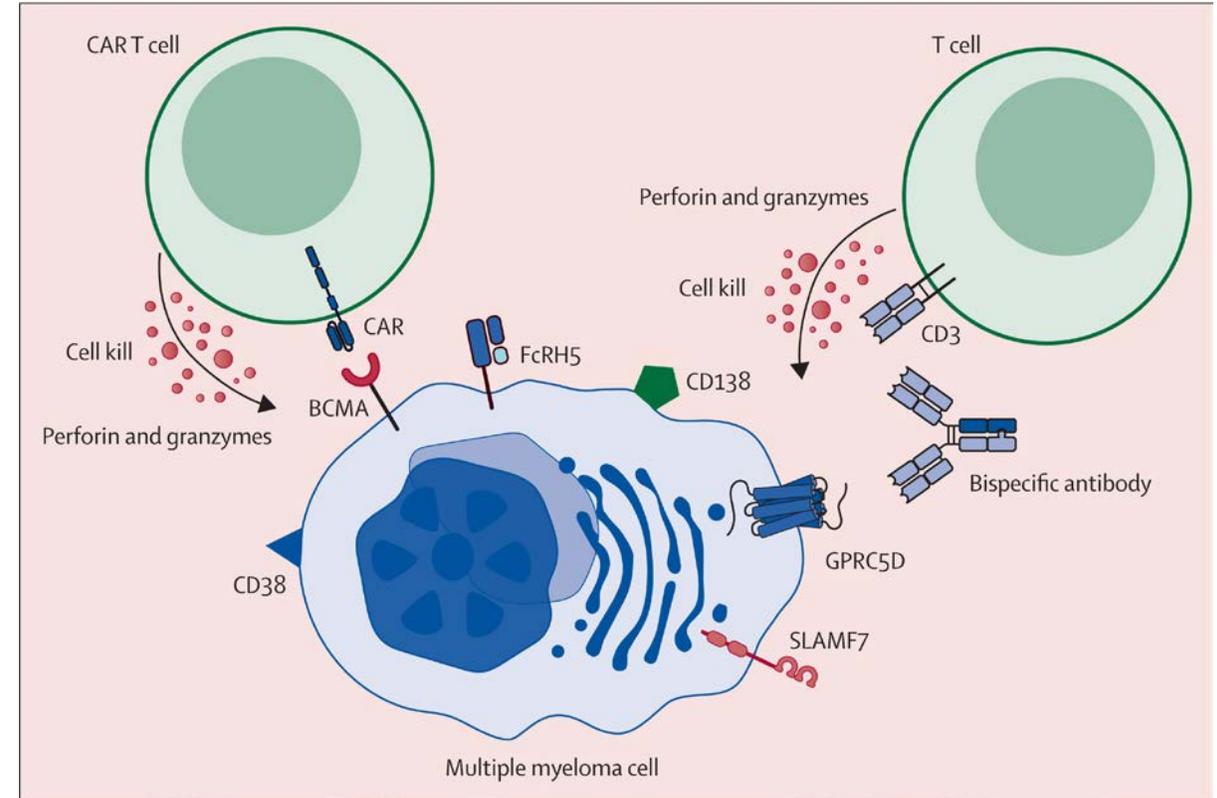Mateos MV et al. Leukemia 2022; Bal S et al. Leukemia 2022

Immunologic Rationale in Myeloma

Profound immune dysregulation drives relapse

T-cell exhaustion and microenvironment suppression

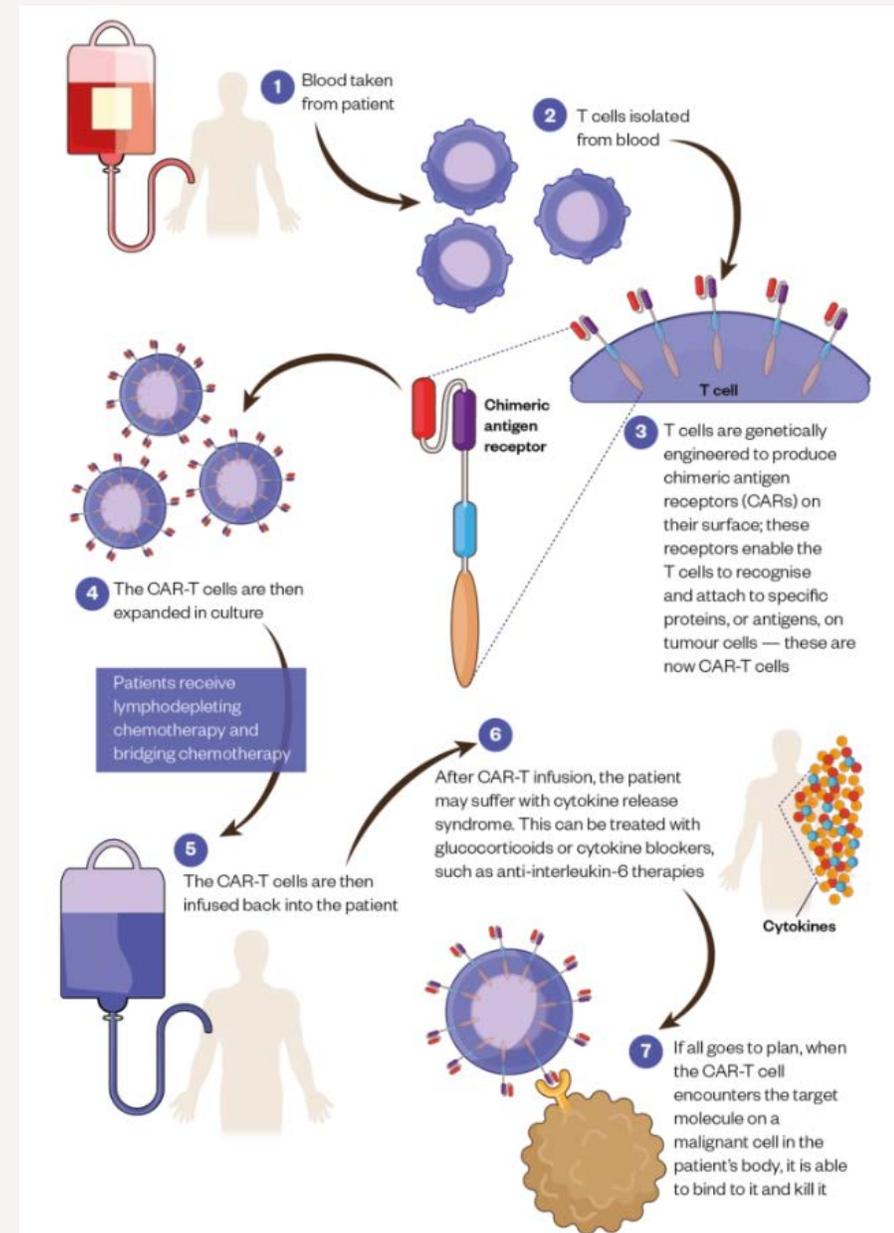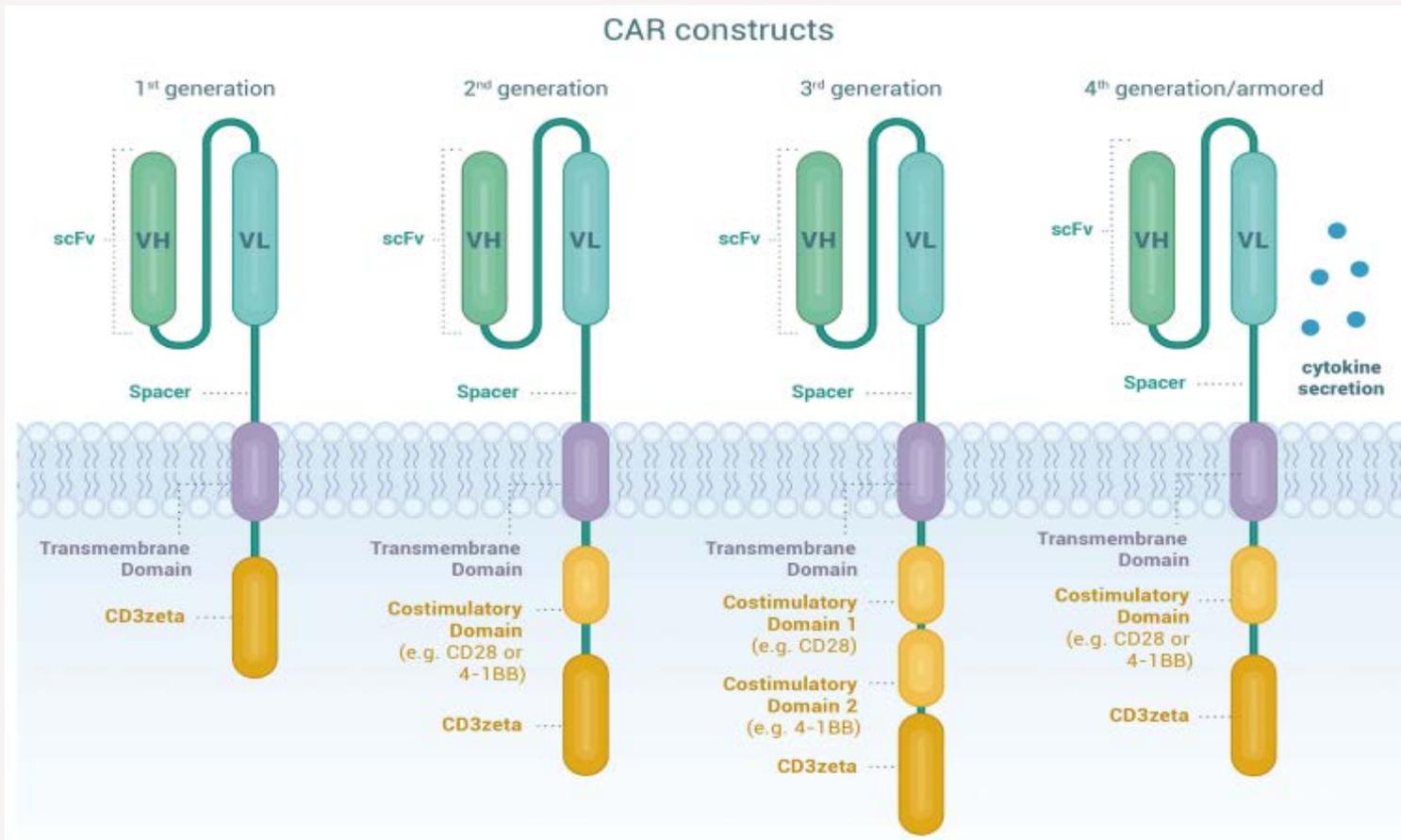Surface antigen density enables immune targeting

Modality of Therapy

- CAR-T
- Bispecific antibodies,
- ADCs,
- CELMoDs/Immune Modulation
- Emerging platforms

Targets in Myeloma
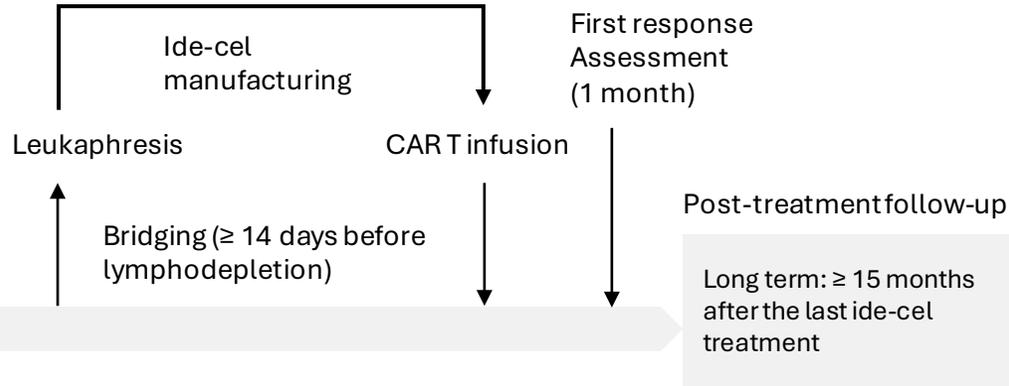
- BCMA
- GPRC5D
- FcRH5
- Emerging targets

Speaker Opinion

Chimeric Antigen Receptor T Cells

Conventional Autologous CAR-T:
Idecabtagene Vicleucel: KarMMa

RMM
- ≥ 3 prior regimens with ≥ 2 consecutive cycles each (or best response of PD)
- Previously exposed to
  - IMiD
  - PI
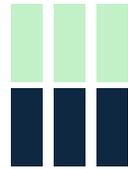 - Anti-CD38 antibody
- Refractory to last therapy per IMWG

Leukaphresis

Ide-cel manufacturing

CAR T infusion

First response Assessment (1 month)

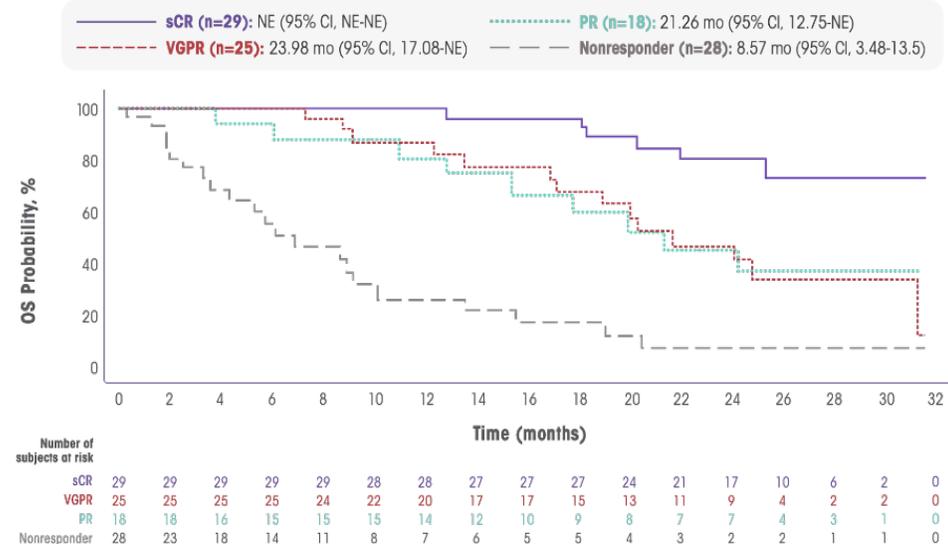Bridging (≥ 14 days before lymphodepletion)

Post-treatment follow-up

Long term: ≥ 15 months after the last ide-cel treatment

Flu (30 mg/m^2)

Cy (300 mg/m^2)

Days -5, -4, -3, 0 and 1

Endpoints
- Primary: ORR
- Secondary: Safety, DOR, CRR, PFS, OS

Survival at 24-month Follow-up Analysis[1,2,4‡]

300-460 x 10^6 CAR-positive T cells (N=100)	mPFS	mPFS with sCR	mOS
ORR‡ (sCR+VGPR+PR) **73%** 95% CI, 63.2-80.8 (n=72)	**11.1** Months (95% CI, 6.08-12.22)	**22.6** Months (95% CI, 14.39-NE) (n=29)	**24.0** Months (95% CI, 18.96-NE)

≥VGPR: 54% (sCR+VGPR) (95% CI, 44.2-63.8) (n=54)

CR§: 33% (95% CI, 20.1-37.9) (n=29)

Munshi et al. NEJM 2021

sCR (n=29): NE (95% CI, NE-NE)
VGPR (n=25): 23.98 mo (95% CI, 17.08-NE)
PR (n=18): 21.26 mo (95% CI, 12.75-NE)
Nonresponder (n=28): 8.57 mo (95% CI, 3.48-13.5)

OS Probability, %

Time (months)

Number of subjects at risk																	
sCR	29	29	29	29	29	28	28	27	27	27	24	21	17	10	6	2	0
VGPR	25	25	25	25	24	22	20	17	17	15	13	11	9	4	2	2	0
PR	18	18	16	15	15	15	14	12	10	9	8	7	7	4	3	1	0
Nonresponder	28	23	18	14	11	8	7	6	5	5	4	3	2	2	1	1	0

Ciltacabtagene Autoleucel: CARTITUDE-1

N=97
ORR: 97.9%

80.4% sCR

94.8% ≥VGPR

80.4%

14.4%

3.1%

Best response: sCR | VGPR | PR

PFS

mPFS: 34.9 months
(95% CI, 25.2–NE)

No. at risk

97 94 85 77 74 67 64 63 60 54 44 25 13 2 1 1 0

Subgroups	30-mo PFS rate
All patients	54.2%
≥CR[a]	66.8%
12-mo sustained MRD negativity[b]	74.9%
12-mo sustained MRD-negative CR[a,b]	78.5%

Responders achieving CR[a]	76	76	75	71	69	63	61	60	57	51	42	25	13	2	1	1	0
Sustained (≥12 mo) MRD negativity[b]	26	26	26	26	26	22	18	11	9	2	1	1	0	0	0	0	0
Sustained (≥12 mo) MRD-negative CR/sCR[a,b]	20	20	20	20	20	17	14	10	9	2	1	1	0	0	0	0	0

Adapted from Lin Y, et al, ASCO 2023 annual meeting presentation.

Berdeja et al. Lancet 2021
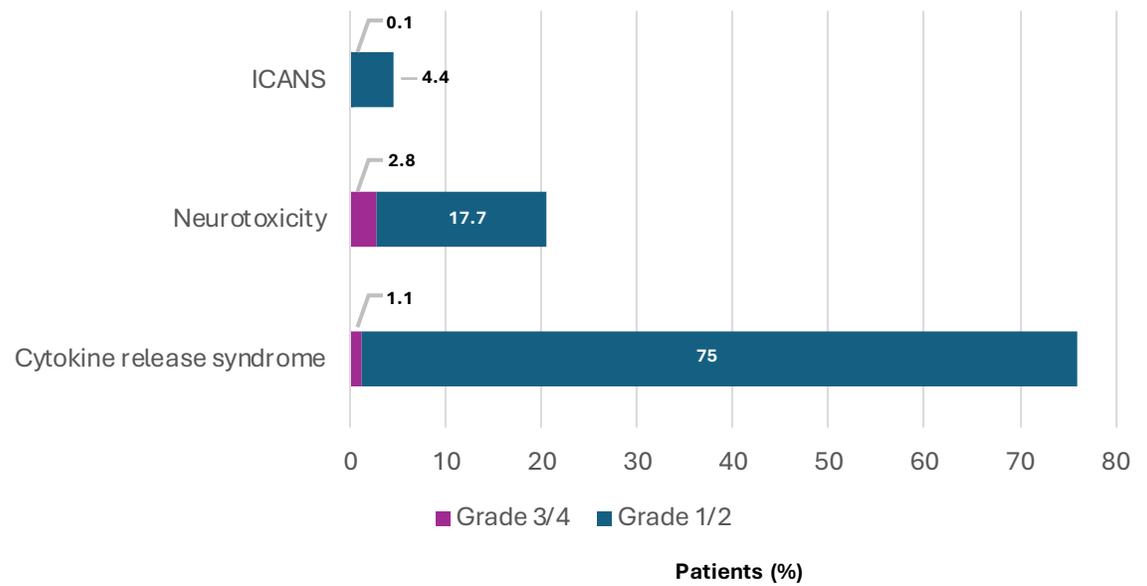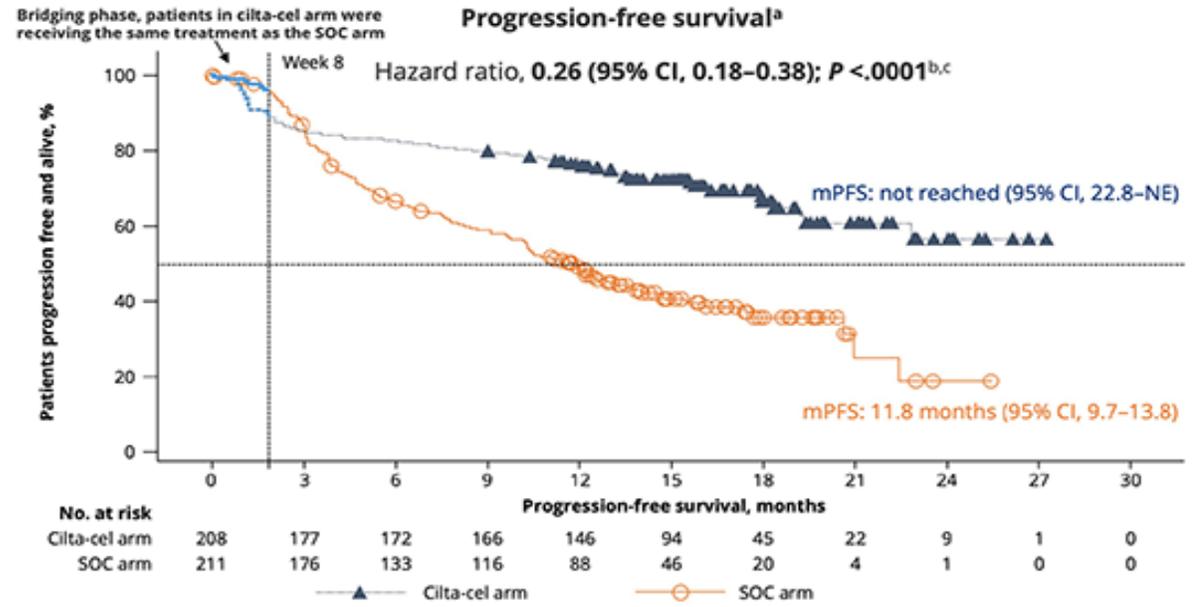Lin Y, et al. Presented at ASCO 2023 annual meeting; June 2-6, 2023. Poster presentation 8009.

Idecabtagene Vicleucel: KarMMa-3

All patients were triple-class exposed

Inclusion criteria:
- **Patients had recieved 2-4 prior regimens,** including an immunomodulatory agent, a PI, and daratumumab
- Patients were refractory to their last regimen
- Clinical Fitness (eg, good performance status and adequate organ function)

Randomized 2:1 (N=386)

ABECMA (n=254)

Leukapheresis[†] → Bridging therapy[‡] (1 cycle; optional) → Lymphodepleting chemotherapy[§] → One-time ABECMA infusion 175 to 529 x 10⁶ CAR-positive T cells

Crossover to ABECMA allowed after confirmed progressive disease (56% rate)[||]

Standard regimens Investigator's choice: DVd, DPd, IRd, EPd, Kd → Continuous treatment until progressive disease (Crossover to ABECMA was allowed after confirmed progressive disease)
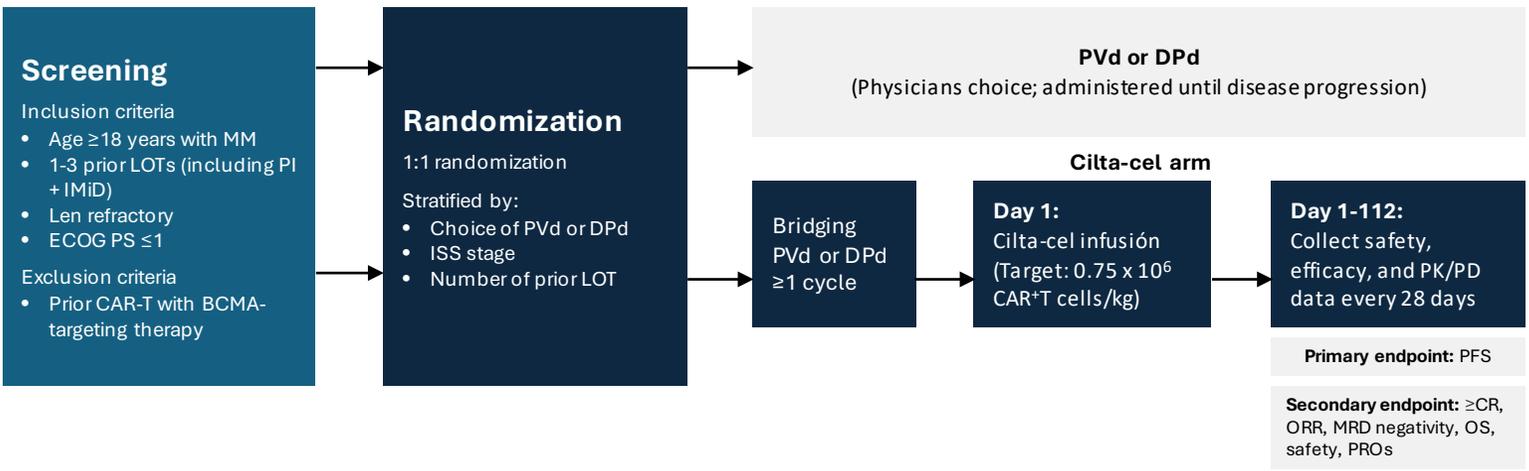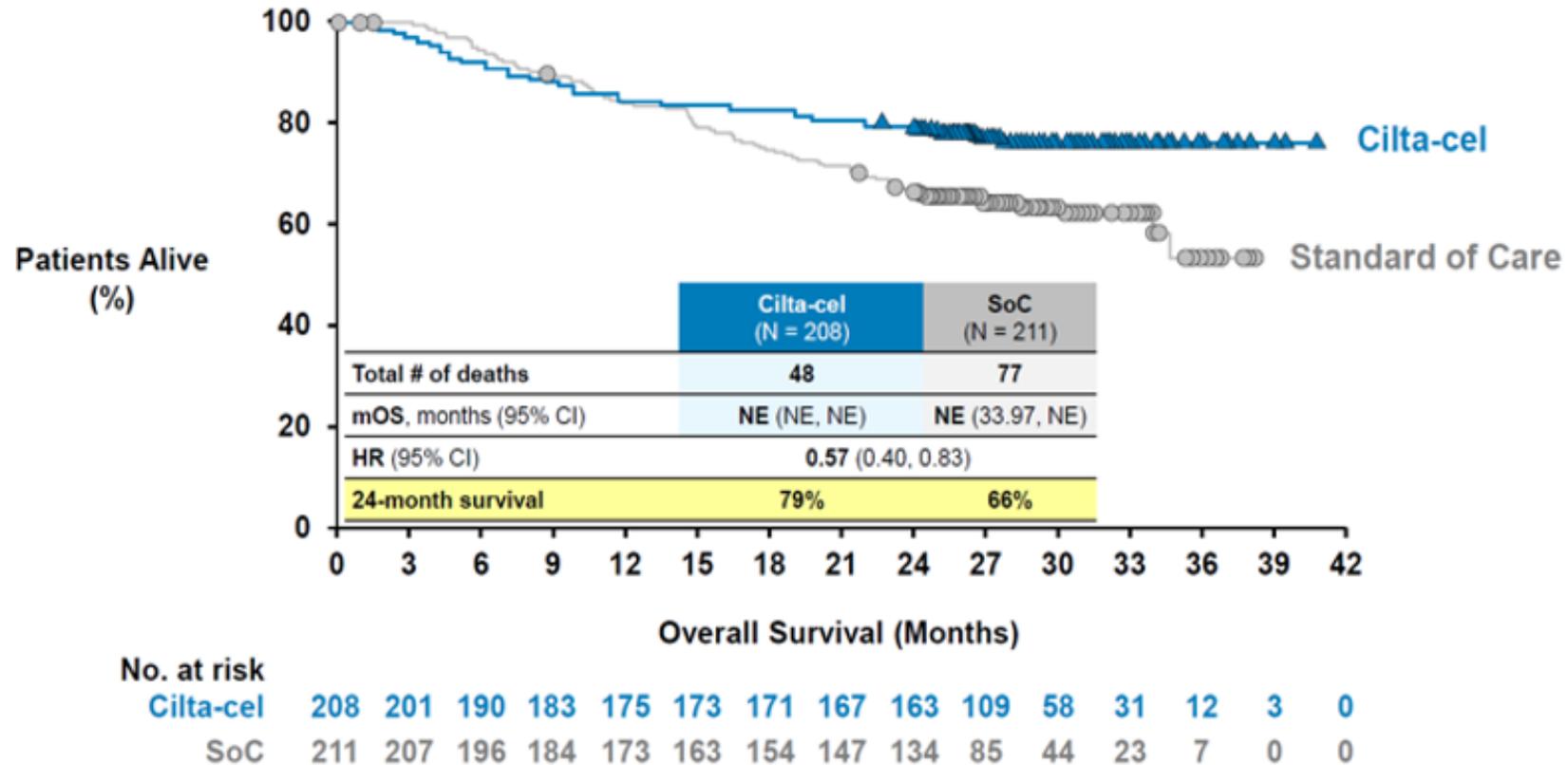
Standard regimens (n=132)

	ORR (sCR+CR+VGPR+PR)	≥VGPR[†] (sCR+CR+VGPR)	≥CR[†]
ABECMA (n=254)	71% (95% Cl, 66-77) (n=181)	61% (n=156)	44% (n=111)
Standard regimens (n=132)	43% (95% Cl, 34-51) (n=56)	83% (n=22)	5% (n=7)

3x
Greater median PFS with ABECMA
Range: 1 to 245 days

PFS, (%) vs Time (months since randomization)

— ABECMA
— Standard regimens
○ Median PFS

Patients at risk:

ABECMA
254 206 177 153 131 111 94 77 54 25 14 7 7 2

Standard regimens
132 76 43 34 31 21 18 12 9 6 5 3 2 1

Rodriguez-Otero et al. NEJM 2023

Ciltacabtagene Autoleucel : CARTITUDE-4

San Miguel et al. NEJM 2023
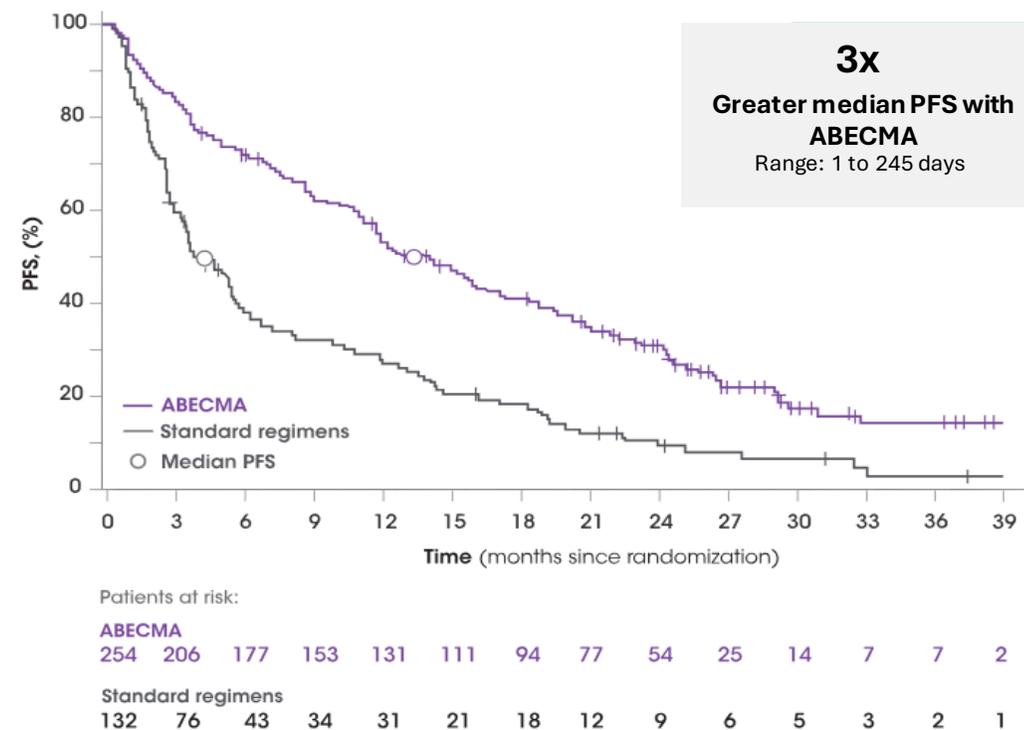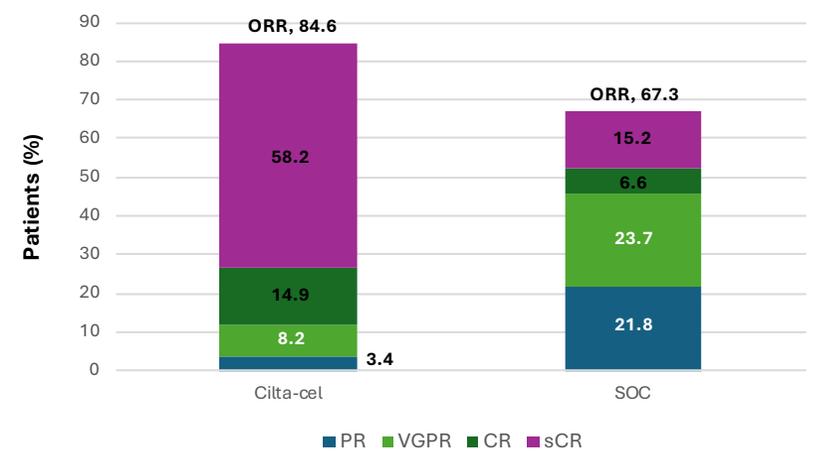
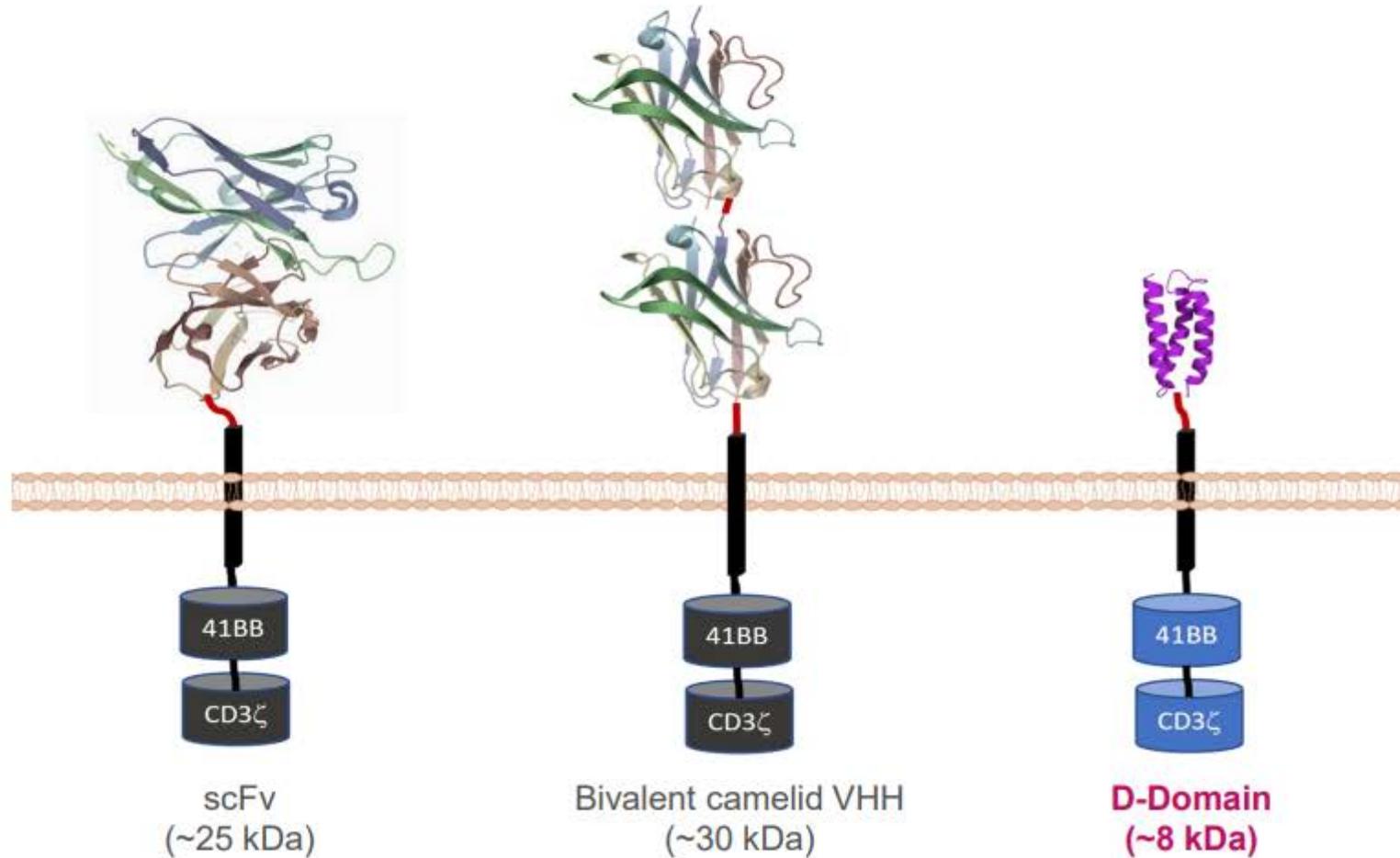# Ciltacabtagene Autoleucel: CARTITUDE-4 Overall Survival

Mateos MV et al. IMS 2024

CARTITUDE 5

CARTITUDE 6
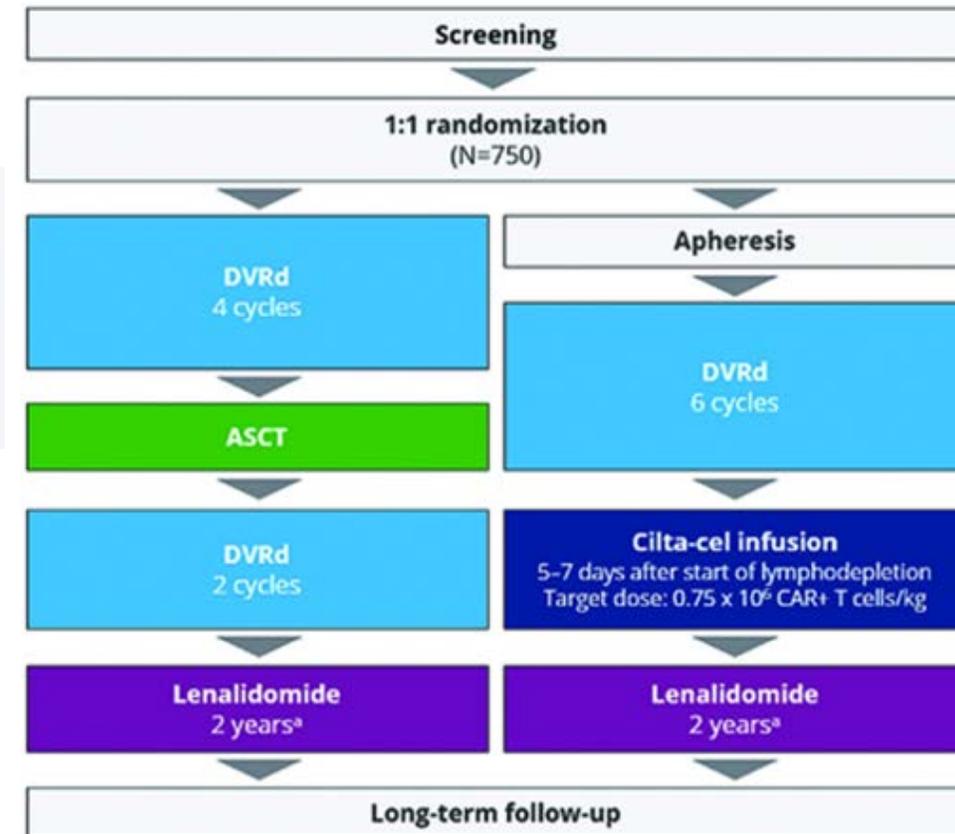
Anitocabtagene Autoleucel

D-Domain Attributes:
Non-Antibody Derived Synthetic Protein[1,2]

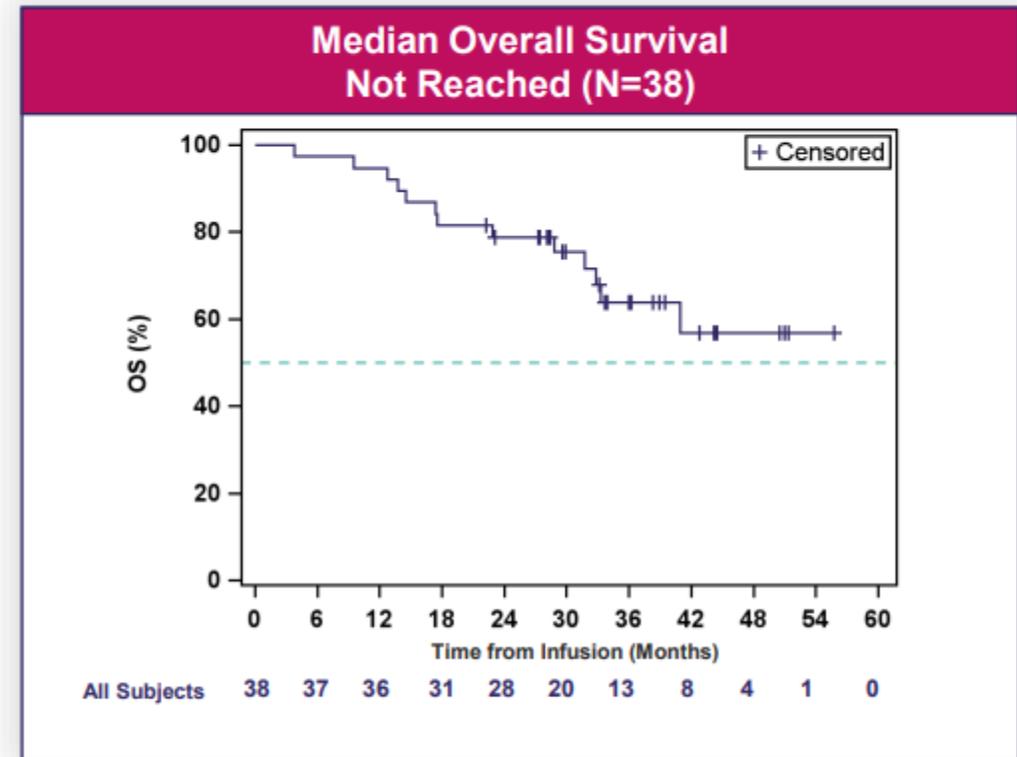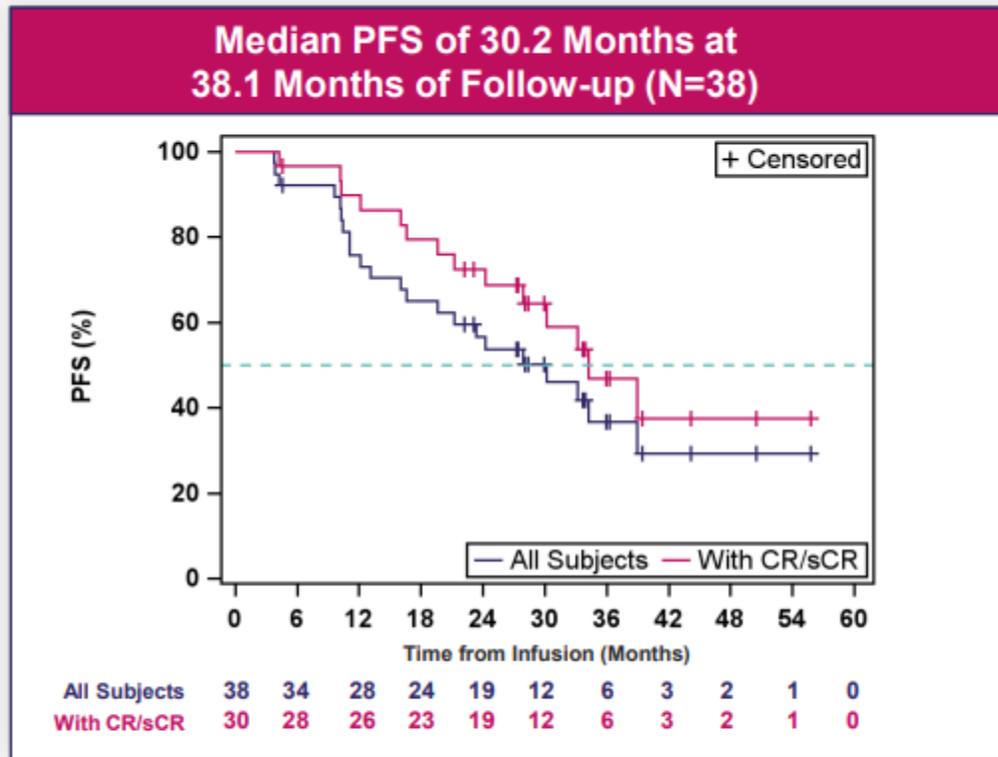|	
Size	Small D-Domain construct facilitates high transduction efficiency and CAR positivity[2-4] resulting in a low total cell dose
Structure & Stability	D-Domain CARs are stable and lack tonic signaling[4,6] due to the rapid folding, lack of disulfide bonds, and hydrophobic core[5,6] of the D-Domain
Binding	The D-Domain binder has a fast off-rate[4] and high CAR surface expression[4]. This combination may allow optimal tumor cell killing without prolonged inflammation

scFv (~25 kDa) · Bivalent camelid VHH (~30 kDa) · D-Domain (~8 kDa)

41BB · CD3ζ

Frigault M, Rosenblatt J, Dhakal B, et al. IMS 2024
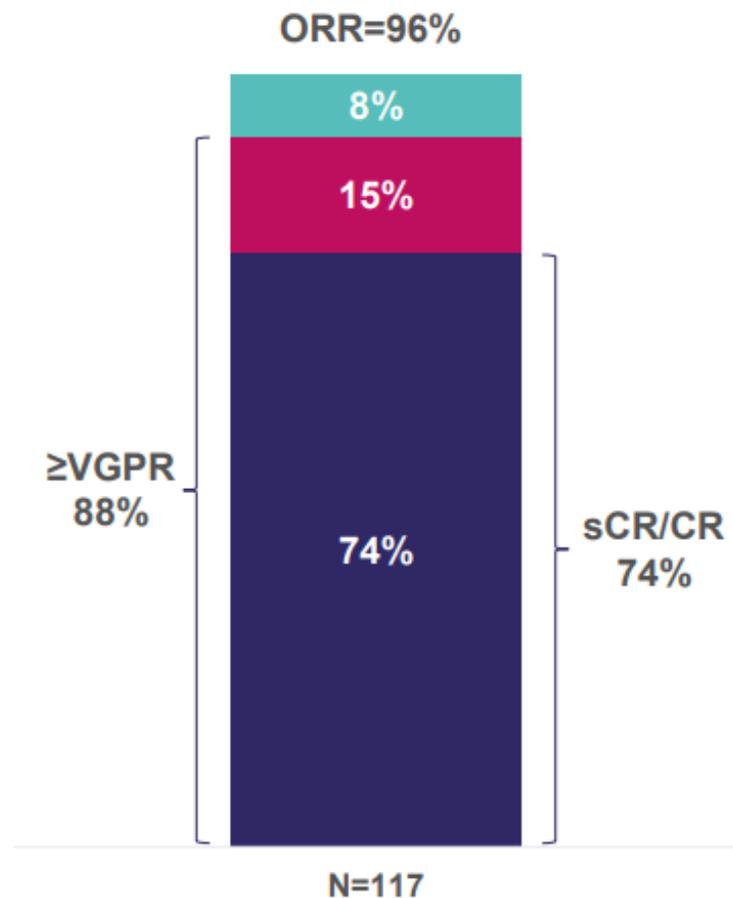
Anitocabtagene Autoleucel: Phase 1 study

With a median follow-up of 38.1 months, anito-cel achieved rapid, high response rates with long-term durable remissions in a refractory, heavily pre-treated 4L+ RRMM population :
- sCR/CR achieved in 79% of patients
- Median PFS of 30.2 months in all patients and 34.3 months in patients with sCR/CR
- Median OS not reached
- Similar efficacy and durable remissions were observed across high-risk subgroups (68% of patients had high-risk features)

The safety profile is predictable and manageable with no delayed or non-ICANS neurotoxicities, including no Parkinsonism, no cranial nerve palsies, and no Guillain-Barré syndrome

Frigault M, Rosenblatt J, Dhakal B, et al. IMS 2024

iMMagine-1: Efficacy

Efficacy Evaluable Patients, N=117

ORR=96%

PR	8%	
VGPR	15%	
sCR/CR	74%	

≥VGPR 88% — sCR/CR 74%

N=117

Best Response: ■ sCR/CR ■ VGPR ■ PR

Median PFS and OS were not reached

N=117	PFS Rate (%) (95% CI)	OS Rate (%) (95% CI)
6-Month	93.1 (86.7, 96.5)	95.7 (90.0, 98.2)
12-Month	82.1 (73.6, 88.1)	94.0 (87.8, 97.1)
18-Month	67.4 (55.4, 76.8)	88.0 (78.8, 93.4)
24-Month	61.7 (48.0, 72.8)	83.0 (70.7, 90.5)

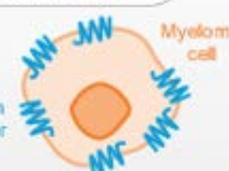Patel et al, American Society of Hematology 2025, Abstract 256

Rapid-Manufacture Autologous CAR-T

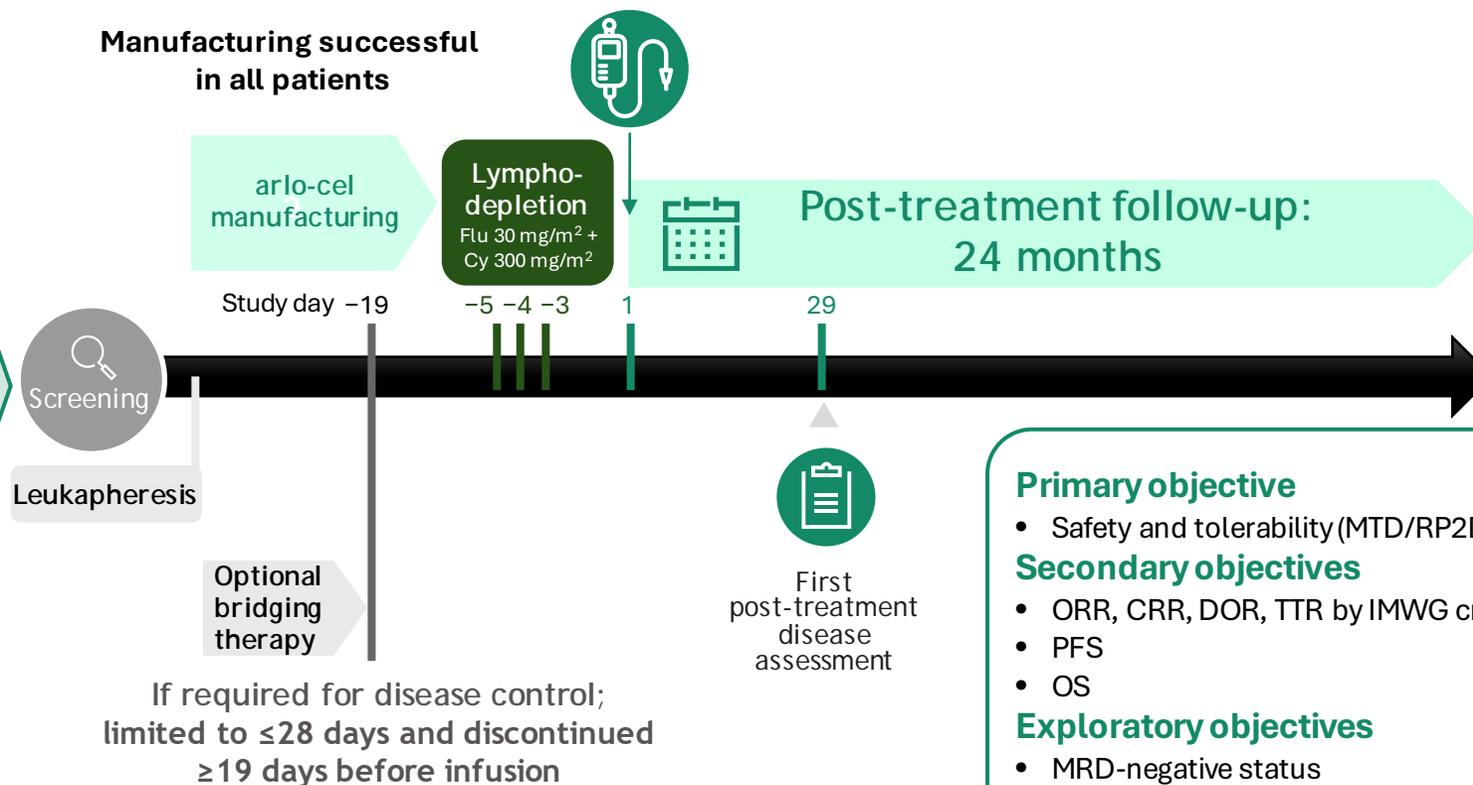| CAR-T Product	Key Study	Patients (N)	Median Prior LOT	ORR	≥CR	Median PFS	Distinguishing Features
BMS-986354	Phase I study	~60	≥3–4	**95%**	46%	12.3 mo	Higher T central memory cells, less differentiated
FasTCAR (GC012F / AZD0120)	FUMANBA-1 Phase I	~40	≥4	**93–100%**	~82–90% sCR	~38 mo	**Rapid manufacturing (≈22–36 hr); dual target BCMA + CD19**
PHE885	Phase I study	~30	≥3	**~93%**	~50%	NR	**Next-day manufacturing (~24 hr) using T-Charge platform**

GPRC5D

Arlocabtagene Autoleucel in RRMM

Part A and Part B, Cohort A: key eligibility criteria

- **Age ≥ 18 years**
- **RRMM that progressed ≤ 12 months of the most recent regimen per IMWG criteria**[a]
- **Previously exposed to ≥ 3 antimyeloma treatment regimens, including:**
  - a PI
  - IMiD agent
  - Anti-CD38 therapy
  - ASCT (unless ineligible)
- **Prior BCMA-directed therapies allowed, including CAR T cell therapies**
- **ECOG PS 0–1**

Manufacturing successful in all patients

Screening

Leukapheresis

arlo-cel manufacturing

Lympho-depletion
Flu 30 mg/m^2 + Cy 300 mg/m^2

Study day −19 −5 −4 −3 1 29

Post-treatment follow-up: 24 months

Optional bridging therapy

If required for disease control; limited to ≤28 days and discontinued ≥19 days before infusion

First post-treatment disease assessment

Primary objective
- Safety and tolerability (MTD/RP2D)

Secondary objectives
- ORR, CRR, DOR, TTR by IMWG criteria
- PFS
- OS

Exploratory objectives
- MRD-negative status
- Pharmacodynamics

Bal S, et al. ASH 2024 [Abstract #922]

Arlocabtagene Autoleucel: Efficacy

Efficacy-evaluable population[a]

Overall (n = 79): ORR 87%, CRR 53%
- sCR 42
- CR 11
- VGPR 23
- PR 11

150 × 10^6 CAR T cells (n = 23): ORR 91%, CRR 48%
- sCR 35
- CR 13
- VGPR 22
- PR 22

Response: sCR, CR, VGPR, PR

Disease characteristic	n/N	ORR (%) (95% CI)
Triple class-refractory		
Yes	52/60	87 (75–94)
No	17/19	89 (67–99)
Extramedullary disease		
Yes	31/36	86 (71–95)
No	38/43	88 (75–96)
High-risk cytogenetics[b]		
Yes	26/31	84 (66–95)
No	43/48	90 (77–97)
Previous BCMA-targeted therapy		
Yes	30/38	79 (63–90)
No	39/41	95 (84–99)
Yes; refractory	13/16	81 (54–96)

ORR (%)

Bal S, et al. ASH 2024 [Abstract #922]

Arlocabtagene Autoleucel: Efficacy

PFS[a,b]

PFS (%) vs Time since infusion (months)

Legend:
- ○ Prior BCMA-targeted therapy
- △ No prior BCMA-targeted therapy

mPFS (95% CI), month	
Efficacy-evaluable (n = 79)	**18.3 (11.8–21.9)**
Prior BCMA-targeted therapy status[a]	
Yes (n = 38)	19.0 (8.9–NA)
No (n = 41)	18.3 (11.8–23.9)

No. at risk

Prior BCMA-targeted therapy	38	34	29	24	15	11	8	5	2	0
No prior BCMA-targeted therapy	41	39	31	27	20	16	14	7	2	0

OS

OS (%) vs Time since infusion (months)

All treated patients (N = 84)	
mOS (95% CI)	Not reached
OS rate (95% CI)	
12-month	90% (81–95)
18-month	87% (76–93)
21-month	84% (72–91)

No. at risk

	84	81	78	72	59	46	36	26	12	0

Bal S, et al. ASH 2024 [Abstract #922]
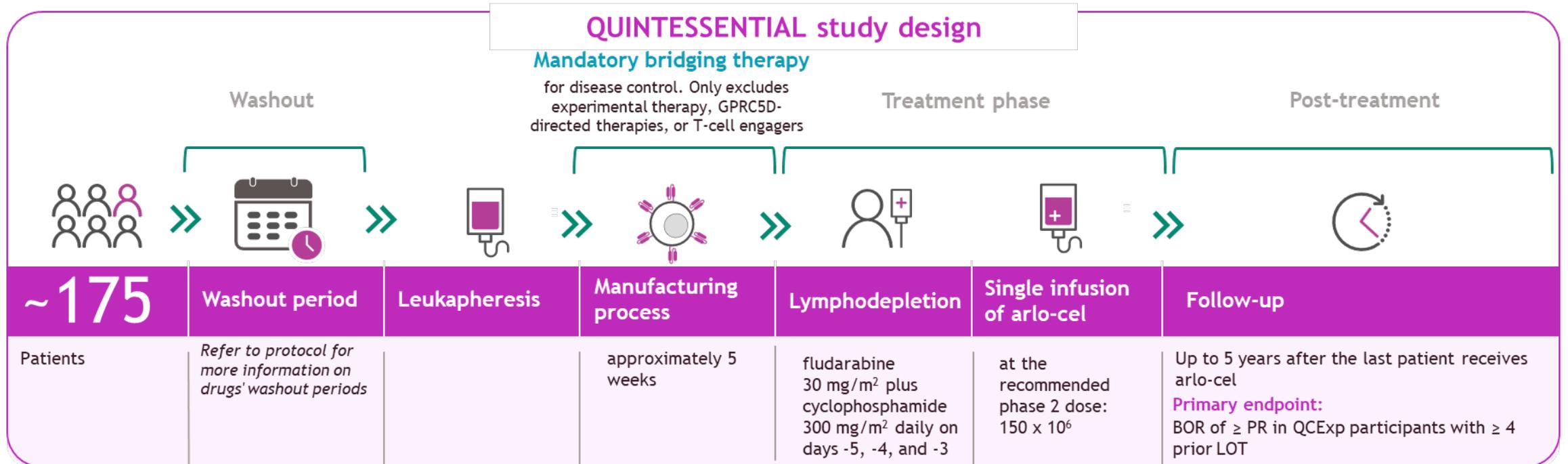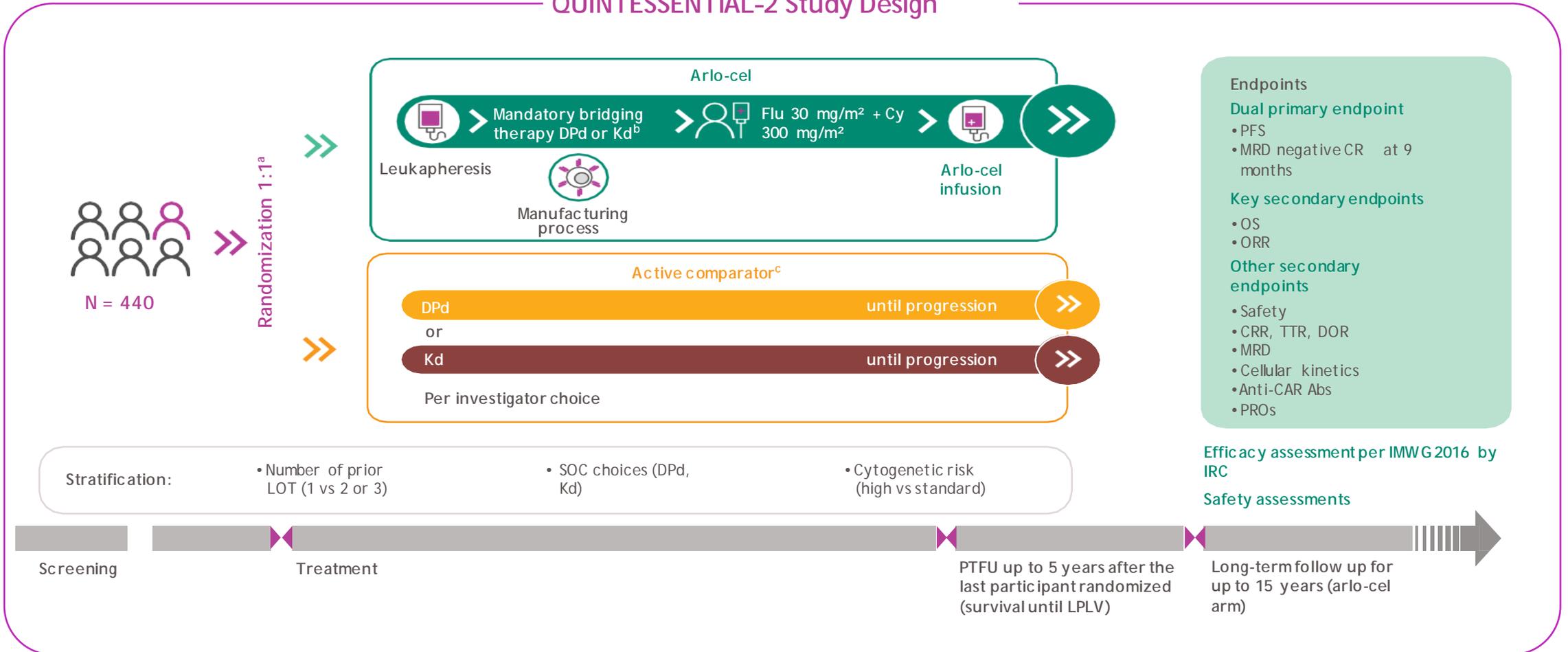
QUINTESSENTIAL

Phase 2, open-label, multicentre study evaluating the efficacy and safety profile of arlo-cel in patients with triple-class exposed RRMM and ≥ 3 prior regimens
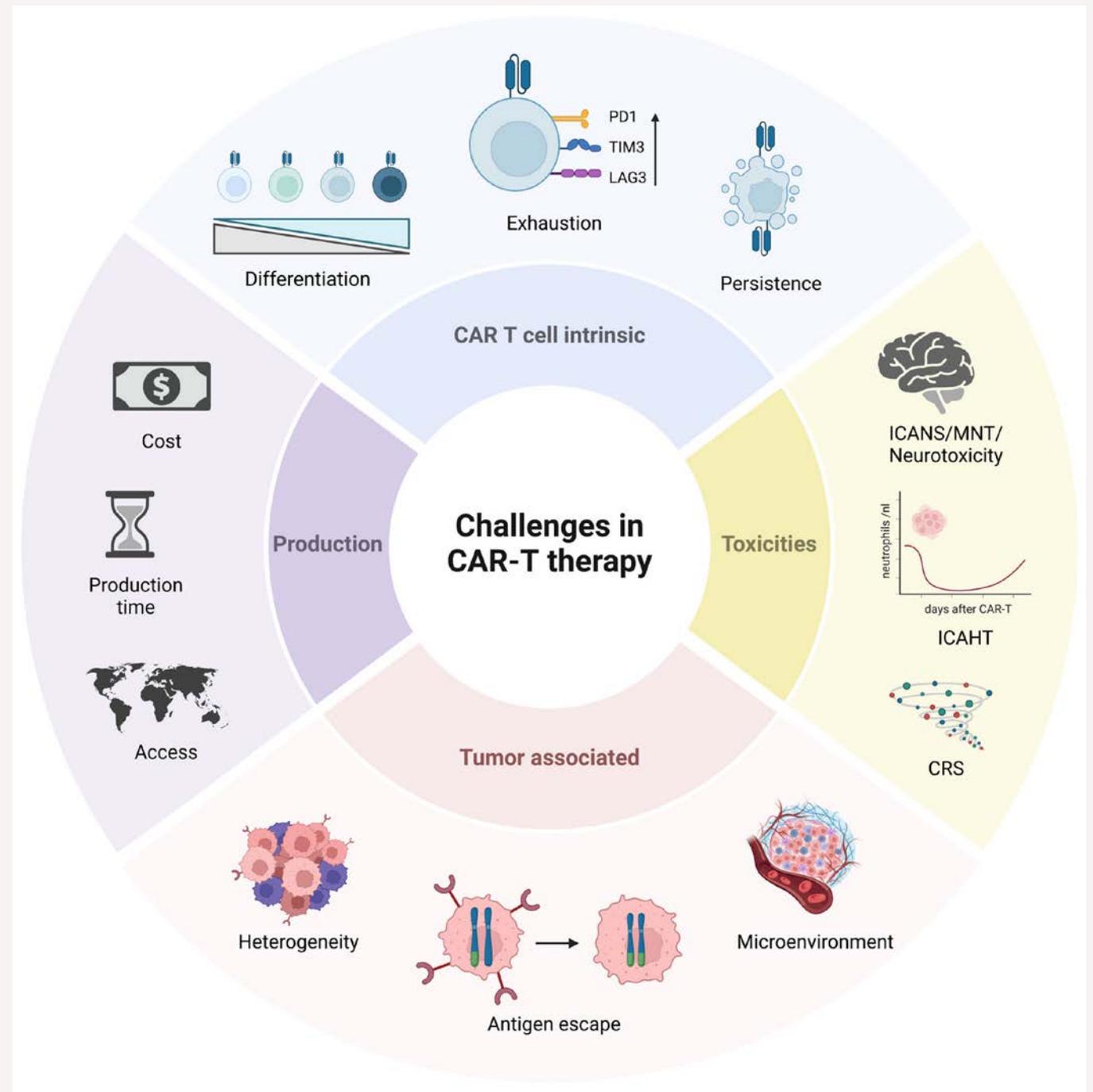

QUINTESSENTIAL study design
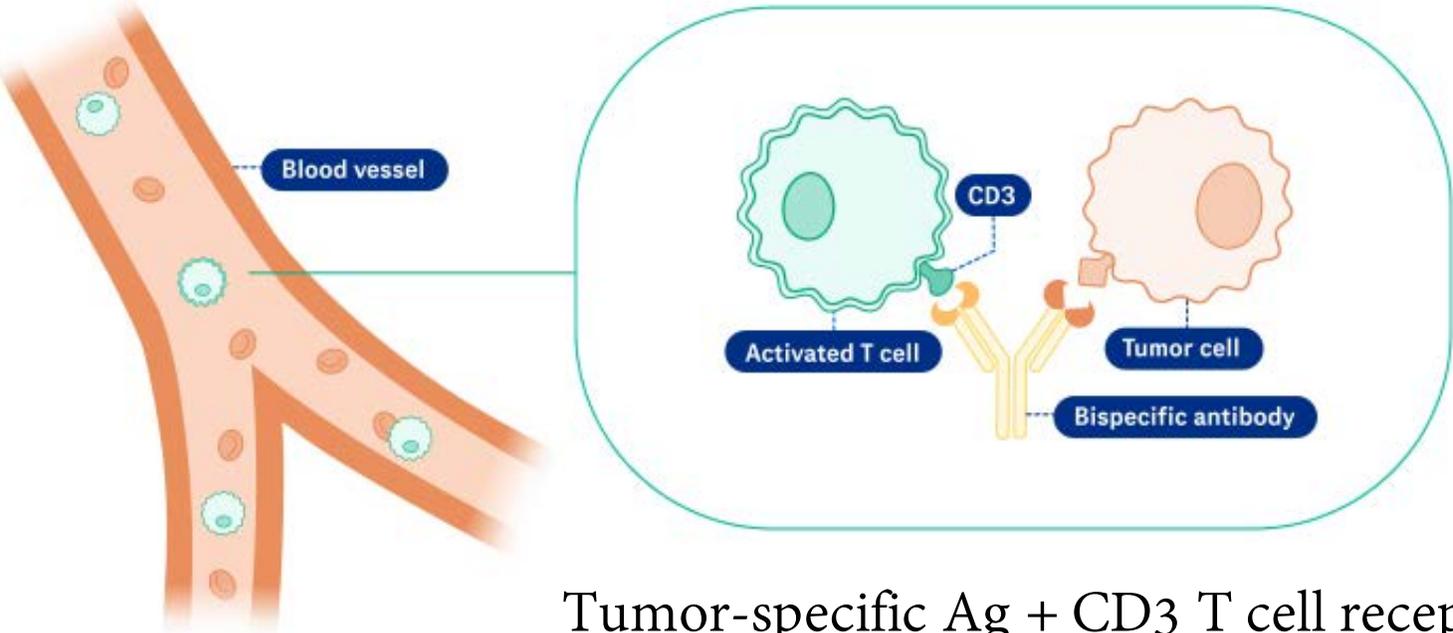
**Mandatory bridging therapy** for disease control. Only excludes experimental therapy, GPRC5D-directed therapies, or T-cell engagers

~175	Washout period	Leukapheresis	Manufacturing process	Lymphodepletion	Single infusion of arlo-cel	Follow-up
Patients	*Refer to protocol for more information on drugs' washout periods*		approximately 5 weeks	fludarabine 30 mg/m² plus cyclophosphamide 300 mg/m² daily on days -5, -4, and -3	at the recommended phase 2 dose: 150 x 10⁶	Up to 5 years after the last patient receives arlo-cel **Primary endpoint:** BOR of ≥ PR in QCExp participants with ≥ 4 prior LOT

Washout — Treatment phase — Post-treatment

Bal S, EHA 2025

QUINTESSENTIAL-2

QUINTESSENTIAL-2 Study Design

N = 440

Randomization 1:1[a]

Arlo-cel

Leukapheresis > Mandatory bridging therapy DPd or Kd[b] > Flu 30 mg/m² + Cy 300 mg/m² > Arlo-cel infusion

Manufacturing process

Active comparator[c]

DPd — until progression

or

Kd — until progression

Per investigator choice

Stratification:
- Number of prior LOT (1 vs 2 or 3)
- SOC choices (DPd, Kd)
- Cytogenetic risk (high vs standard)

Screening — Treatment — PTFU up to 5 years after the last participant randomized (survival until LPLV) — Long-term follow up for up to 15 years (arlo-cel arm)

Endpoints

Dual primary endpoint
- PFS
- MRD negative CR at 9 months

Key secondary endpoints
- OS
- ORR

Other secondary endpoints
- Safety
- CRR, TTR, DOR
- MRD
- Cellular kinetics
- Anti-CAR Abs
- PROs

Efficacy assessment per IMWG 2016 by IRC

Safety assessments

Bal S, EHA 2025

Challenges

BISPECIFIC ANTIBODIES

Tumor-specific Ag + CD3 T cell receptor

➔Immunologic Synapse

➔T cell activation + Degranulation

➔Tumor death

Devasia AJ et al. Blood Cancer Journal (2024) 14:158
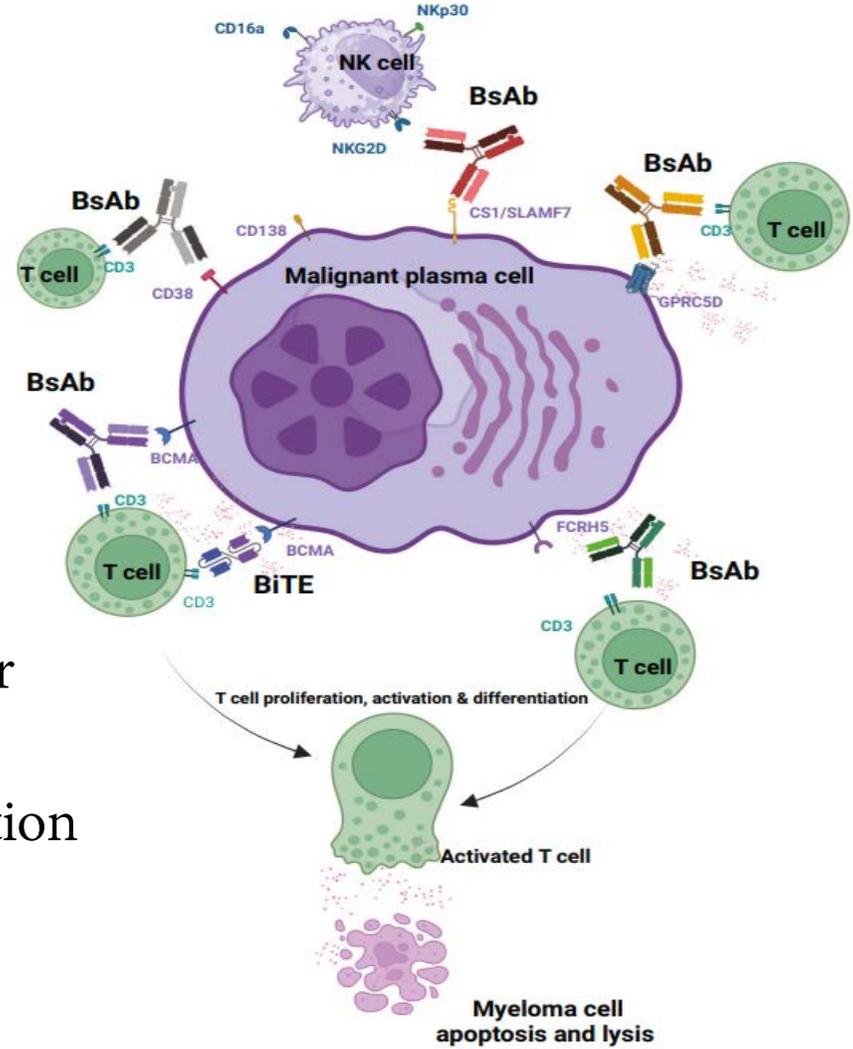
BCMA Targeting BsAb
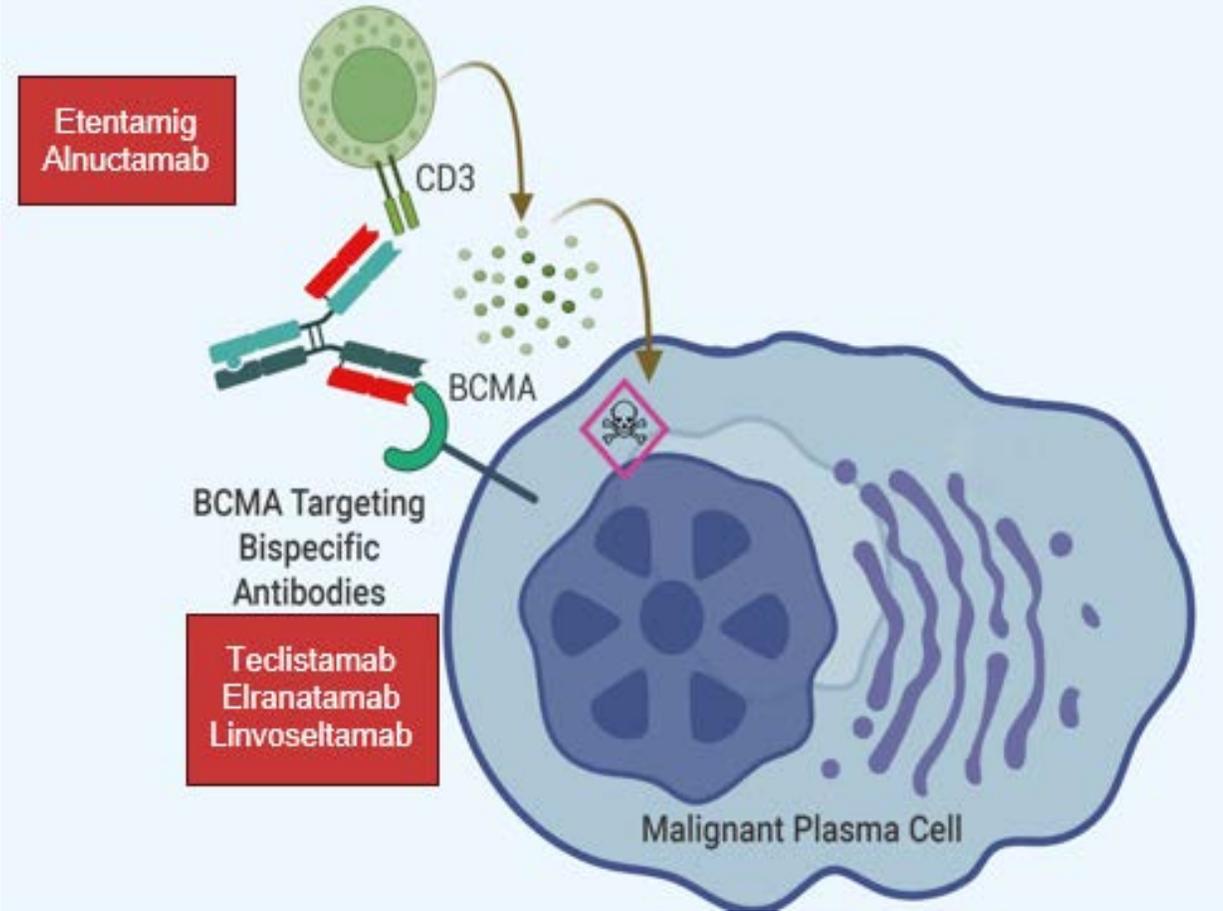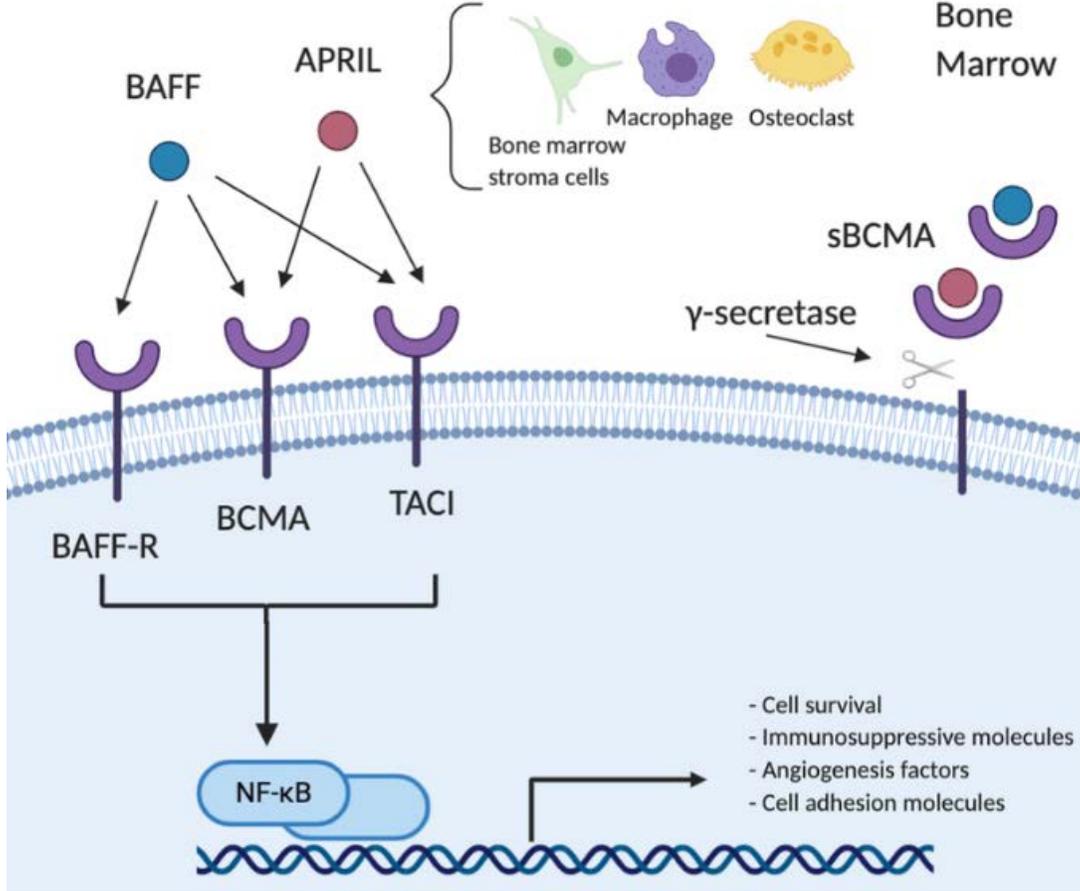
Approved BCMA Bispecific Antibodies: Efficacy

	Teclistamab (MajesTEC-1)	Elranatamab (MagnetisMM-3)	Linvoseltamab (LINKER-MM1, 200 mg)
Median Follow-up	~30.4 months	~28.4 months	~14.3 months
≥VGPR	58.8%	~50–55%	63%
MRD Negativity	26.7% overall; 46% of ≥CR	~90% among evaluable ≥CR	~94% among evaluable ≥CR
Median DoR	24.0 months	Not reached (24mo≈67%)	29.4 months
Median PFS	11.4 months	17.2 months	Not reached
Median OS	22.2 months	24.6 months	~31 months (early estimate)

Moreau et al. NEJM 2022; Lesokhin et al. Nature Medicine 2023; Bumma et al. JCO 2024

Approved BCMA Bispecific Antibodies: Safety

	Teclistamab (MajesTEC-1)	Elranatamab (MagnetisMM-3)	Linvoseltamab (LINKER-MM1)
Any-grade CRS (G≥3 CRS)	72% (~0.6–1%)	57–58% (~0%)	46% (~1%)
Any Infection	~79%	~70%	~70%
Grade ≥3 TEAEs Overall	~94–95%	~88–90%	73.5%
Hypogammaglobulinemia	~74–76%	~70–75%	~60–65%
IVIG Use	~65–70%	~55–60%	~64%

Moreau et al. NEJM 2022; Lesokhin et al. Nature Medicine 2023; Bumma et al. JCO 2024

Teclistamab: Real World Efficacy

	MajecTEC-1	Riedhammer et al. N=123 7/2022-10/2023	Dima et al. N=106 8/2022-8/2023	Mohan et al. N=110 1/2023-8/2023	Perrot et al. N=303 10/2022-9/2023	Tan et al. N=223 5/2022-1/2024
Demographics	mLoT 5 0% prior BCMA Median f/u 30 mos	mLoT 6 37% prior BCMA Median f/u 5.5 mos	mLoT 6 53% prior BCMA Median f/u 3.8 mos	mLoT 6 35% prior BCMA Median f/u 3.5 mos	mLoT 4 14% prior BCMA Median f/u 11.9 mos	mLoT 6 42% prior BCMA Median f/u 14 mos
ORR **CRR** **ORR(Prior BCMA)**	63% 46%	59% (65% BCMA naïve) 22% 55% (Ide-cel 33%, ADC 74%)	66% 29% 59% (57% CART, 50% ADC)	62% (N=98) 20%	69%	66% 25% 55% (CRR 21%)
mPFS **mOS** **mPFS (prior BCMA)**	11 mos 22 mos	8.7 mos NR 1.8 mos	5.4 mos NR (10m estimate 67%)	NR (6m PFS 52%) NR (6m OS 80%)	11.3 mos (DOR 17m) 17 mos	8.8 mos (DOR 17 m) 20 mos
Ineligible for MAJECTEC-1	N/A	39%	83%		46%	76%

Moreau et al. NEJM 2022; Riedhammer C, Leukemia. 2024. Dima D et al. Transplant Cell Ther. 2024; Mohan et al. Blood Cancer J. 2024; Perrot et al. Haematologica. 2024. Tan et al ASH 2024

BCMA BsAb in Earlier Lines: MAJESTEC-3

Costa LJ et al. NEJM 2025

BCMA BsAb in Earlier Lines: MAJESTEC-3

Costa LJ et al. NEJM 2025

BCMA BsAb in NDMM: MAJESTEC-5
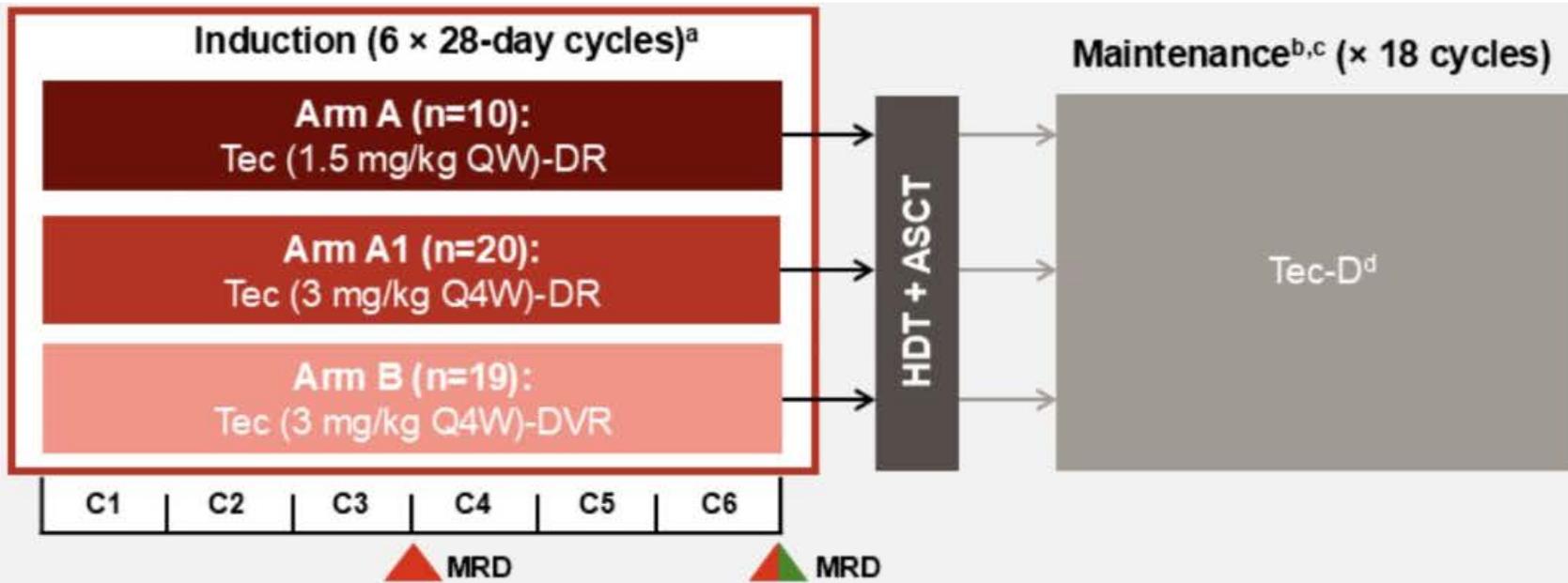
Raab et al. IMS 2025

GPRC5D Targeting BsAb

Talquetamab

anti-CD3

anti-GPRC5D

T cell

Perforin
Granzyme

Forimtamig

Bivalent binding to GPRC5D

Monovalent binding to CD3ε

Silent Fc part, P329G LALA mutation

Miller KC et al. Cancer Management and Research 2025
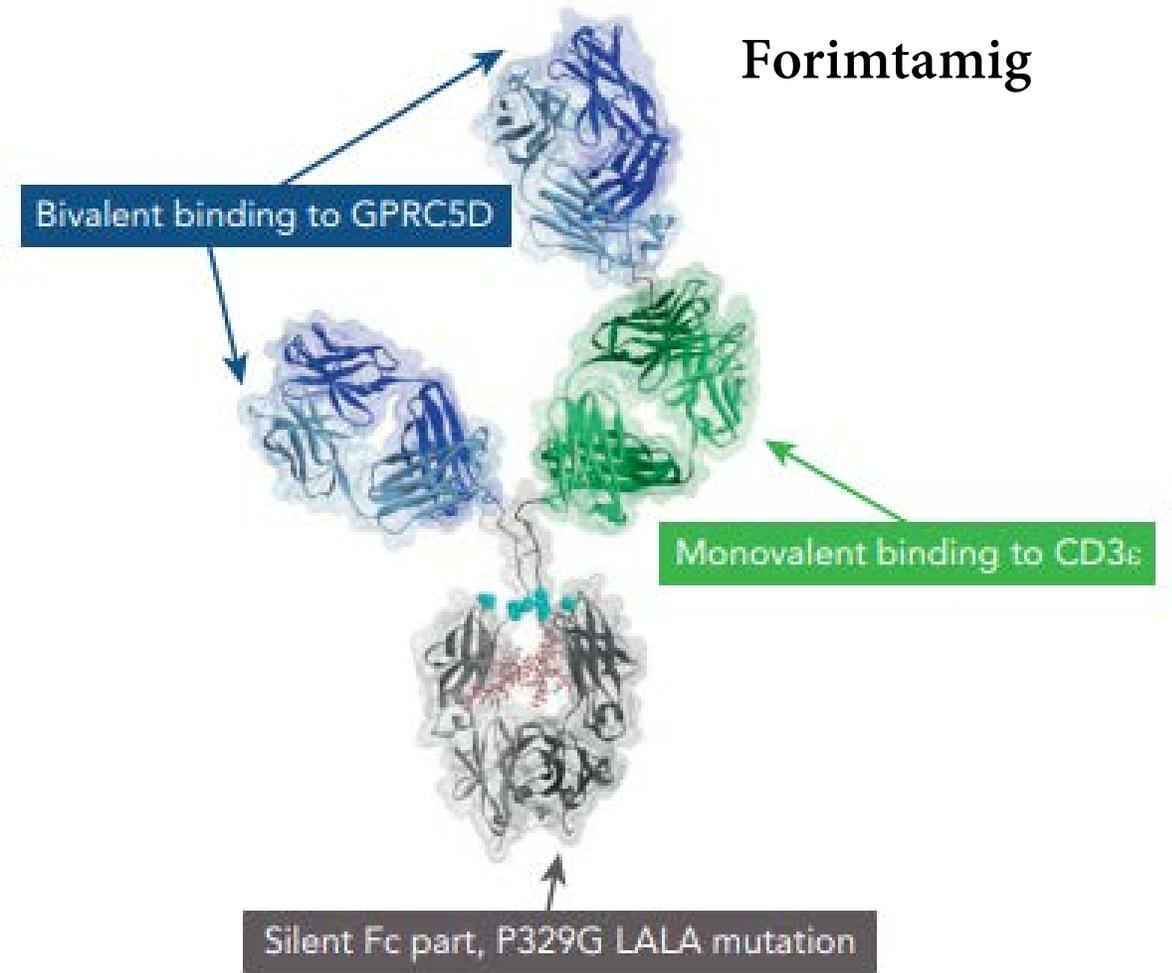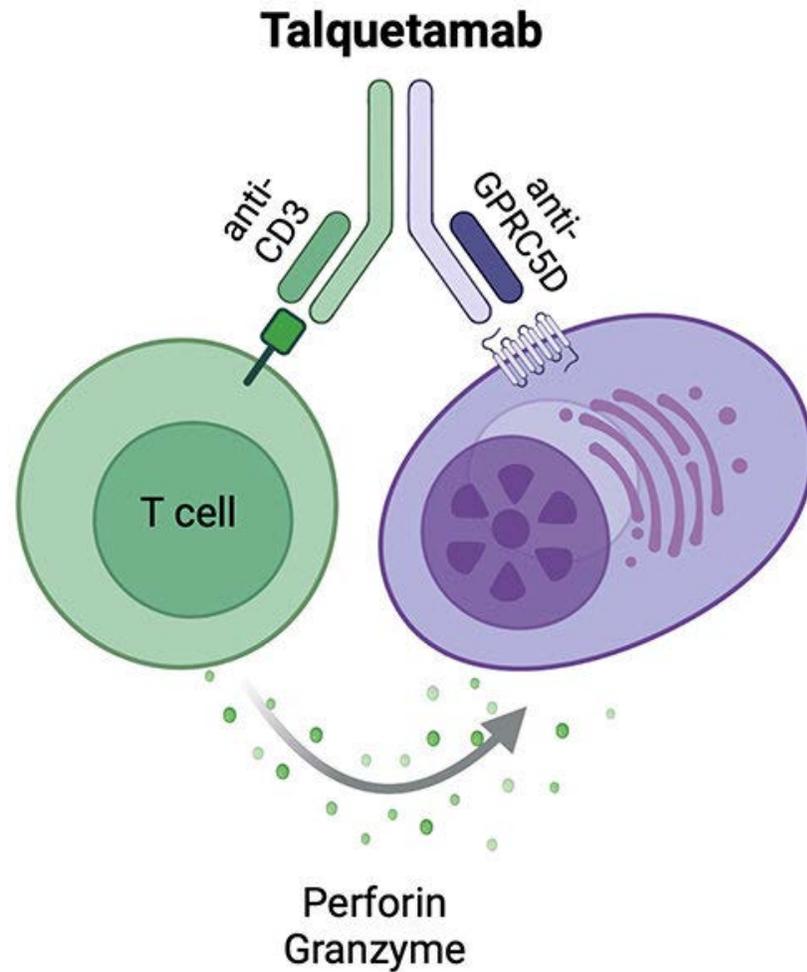
Approved GPRC5D BsAb: Talquetamab

	0.4 mg/kg Weekly (n=143)	0.8 mg/kg Q2W (n=154)	Prior TCR* (n=78)
Overall Response Rate (ORR)	74% (95% CI 66–81)	69% (62–77)	67% (55–77)
≥VGPR	59%	59%	55%
Median Time to Response	1.2 mo	1.3 mo	1.2 mo
Median Duration of Response	9.5 mo	16.9 mo	12-mo DoR: 56%
Median PFS	7.5 mo	11.2 mo	7.7 mo
12-mo Overall Survival	76%	77%	74%

Chari et al. Lancet Haem 2025

Approved GPRC5D BsAb: Talquetamab

	0.4 mg/kg Weekly	0.8 mg/kg Q2W	Prior TCR
Cytokine Release Syndrome (CRS)	79%	75%	73%
Taste Changes (Dysgeusia)	72%	71%	76%
Infections	59%	68%	76%
Neutropenia	31%	21%	47%

Chari et al. Lancet Haem 2025

Talquetamab: Ongoing trials

RedirecTT-1

Talq + Tec

MonumenTAL -6

Talq + Pom
Talq + Tec
Epd/PVd

MonumenTAL -3

Talq + Dara
Talq + Pom + Dara
DPd

MajesTEC - 7

Talq + Rev + Dara
Tec + Rev + Dara
DRd
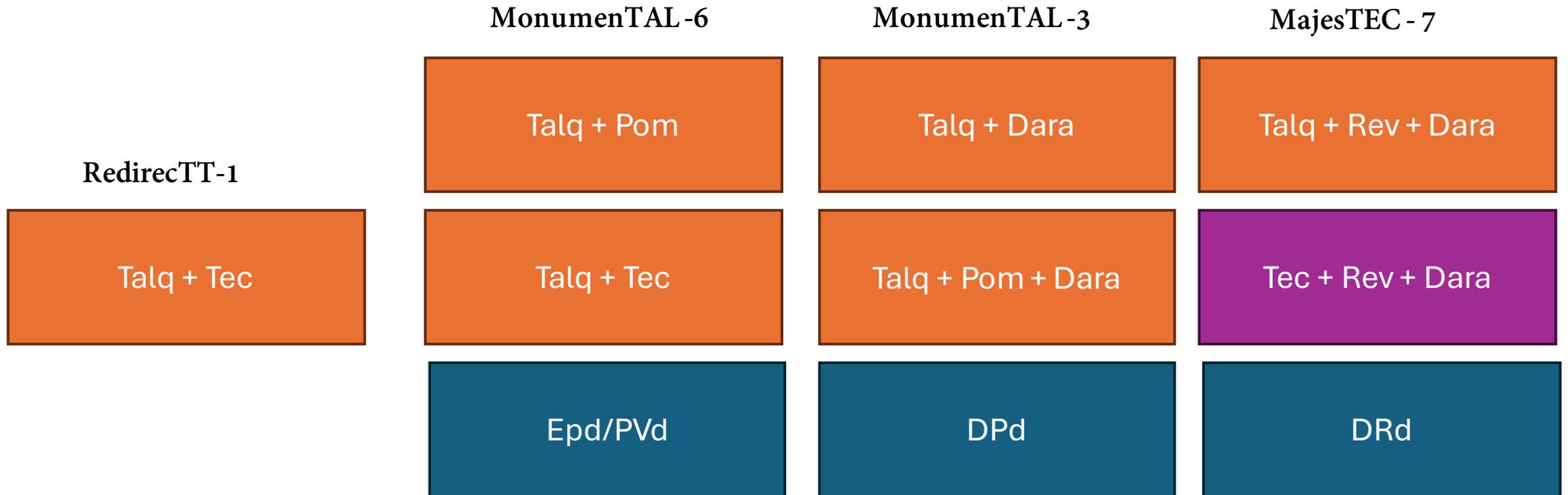
FCHR5 Targeting BsAb: Cevostamab
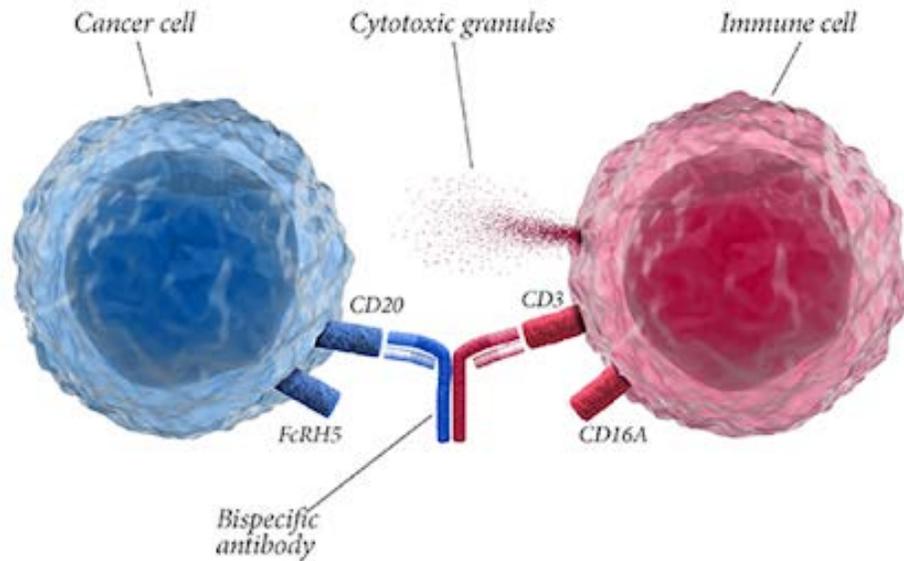
Median Prior Lines of Therapy	~6
Triple-Class Refractory	~70–80%
Overall Response Rate (ORR)	~54–56%
≥VGPR	~32–36%
Complete Response (CR/sCR)	~10–15%
Median Time to Response	~1 month
Median Duration of Response	~11–12 months
Median PFS	~8–9 months
Cytokine Release Syndrome (CRS)	~70–75% (G3 1-2%)
Neutropenia	~30–35%
Anemia	~25–30%
Thrombocytopenia	~20–25%
Fatigue	~30%

Miller KC et al. Cancer Management and Research 2025; Richter et al. ASH 2024

Myeloma Targets: Toxicity Heat Map

Toxicity Heat Map by Target (Relative Intensity)

Speaker Opinion
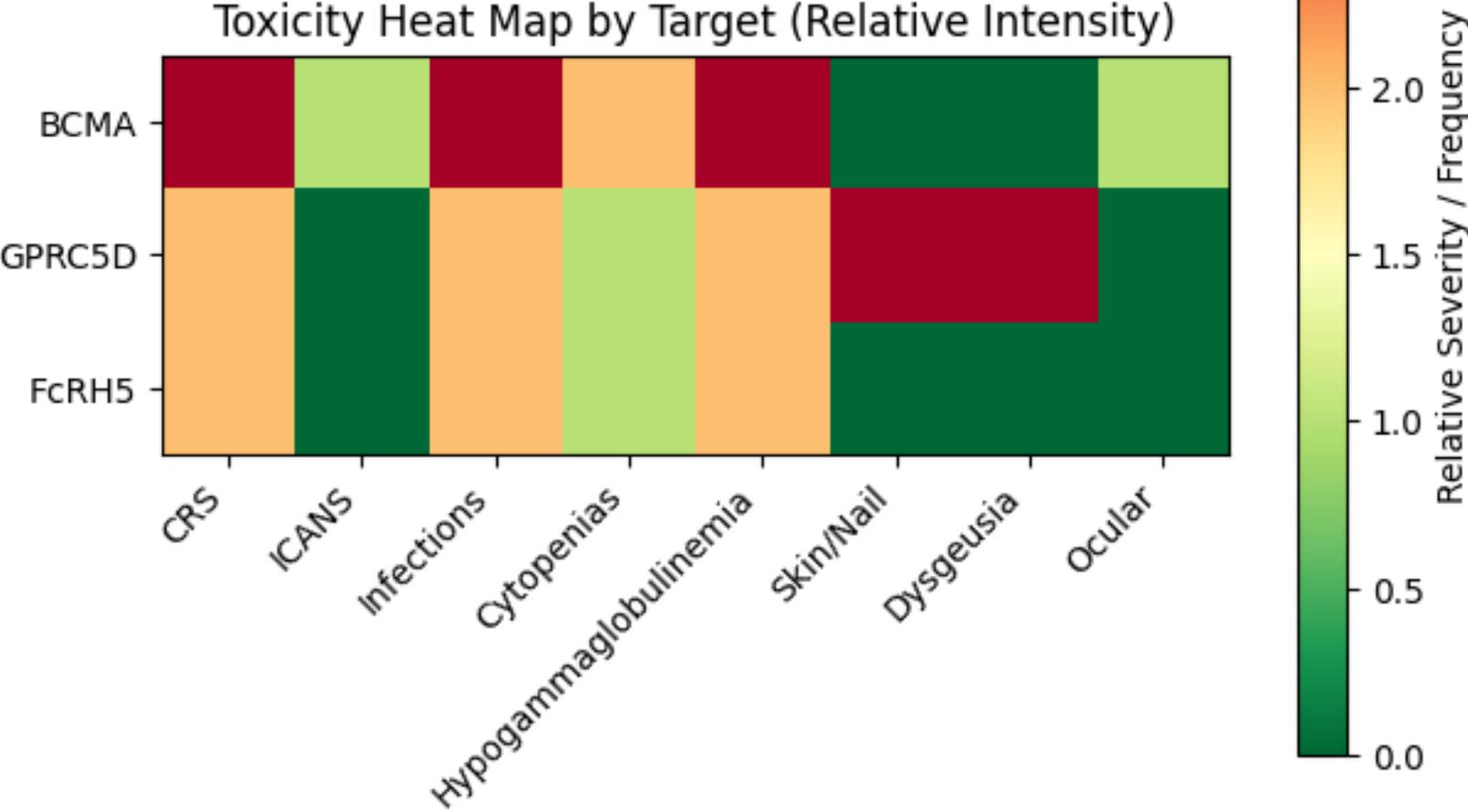
Antibody Drug Conjugates: Belantamab Mafodotin

BCMA Overexpression on Tumor Cells

B-cell maturation antigen

BCMA

Multiple Myeloma Cell

Binding Phase

Antibody-drug conjugate (ADC)

Belantamab Mafodotin

ADC's toxin payload release

Direct cytotoxic effect

Belantamab Mafodotin

Multiple Myeloma Cell

Cytotoxic agent delivered inside the myeloma cell

Tumor cell apoptosis

Cytotoxic Effects

Immune cell activation by Belantamab-bound BCMA

Lonial S Clin Cancer Res 2021
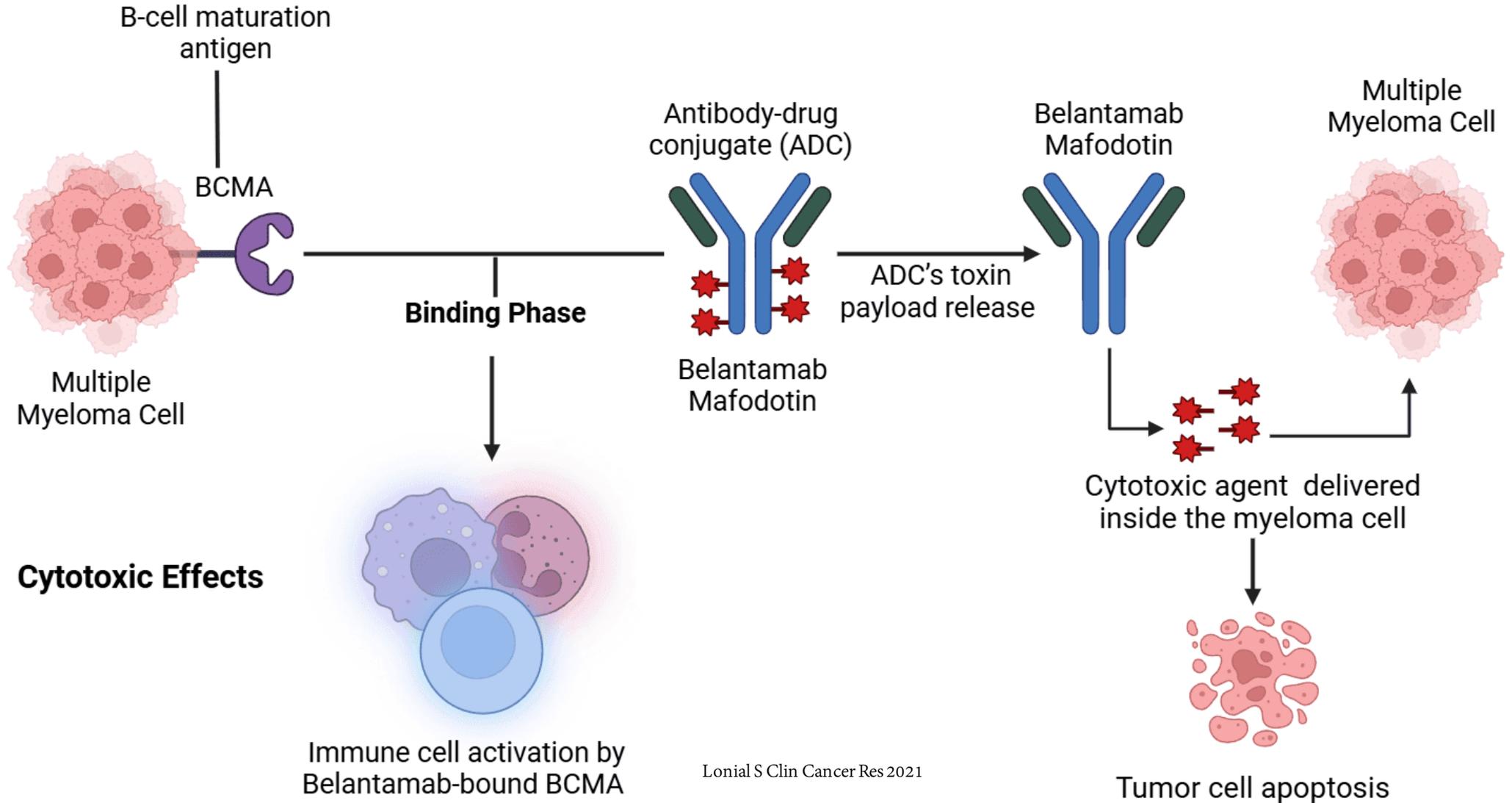
Belantamab Mafodotin: Clinical Trials

	DREAMM-1	DREAMM-2	DREAMM-3	DREAMM-7	DREAMM-8	DREAMM-9
Phase	Phase 1	Phase 2	Phase 3	Phase 3	Phase 3	Phase 3
Population	Heavily pretreated RRMM	≥3 prior lines, triple-class refractory	≥3rd line relapse	≥1 prior line RRMM	Len-exposed RRMM	**Newly diagnosed transplant-ineligible MM**
N	35	196	Large randomized	494	302	~445
Intervention	Belamaf 3.4 mg/kg	Belamaf 2.5 vs 3.4 mg/kg	Belamaf vs Pd	**BVd vs DVd**	**BPd vs PVd**	**Belantamab + VRd vs VRd**
ORR	60%	31–34%	—	—	77%	Data pending
CR/≥CR	—	—	—	—	40%	Data pending
Median PFS	12 mo	~11.2 mo	11.2 vs 7.0 mo	**36.6 vs 13.4 mo**	12m 71% vs. 51% HR 0.52	Primary endpoint: PFS
Other efficacy	DoR 14.3 mo	—	PFS endpoint not met	OS 84% vs 73% (18 mo)	≥CR 40% vs 16%	Study ongoing

Sequencing Framework

CAR-T earlier for eligible patients

Target switching after relapse

Clinical trials preferred
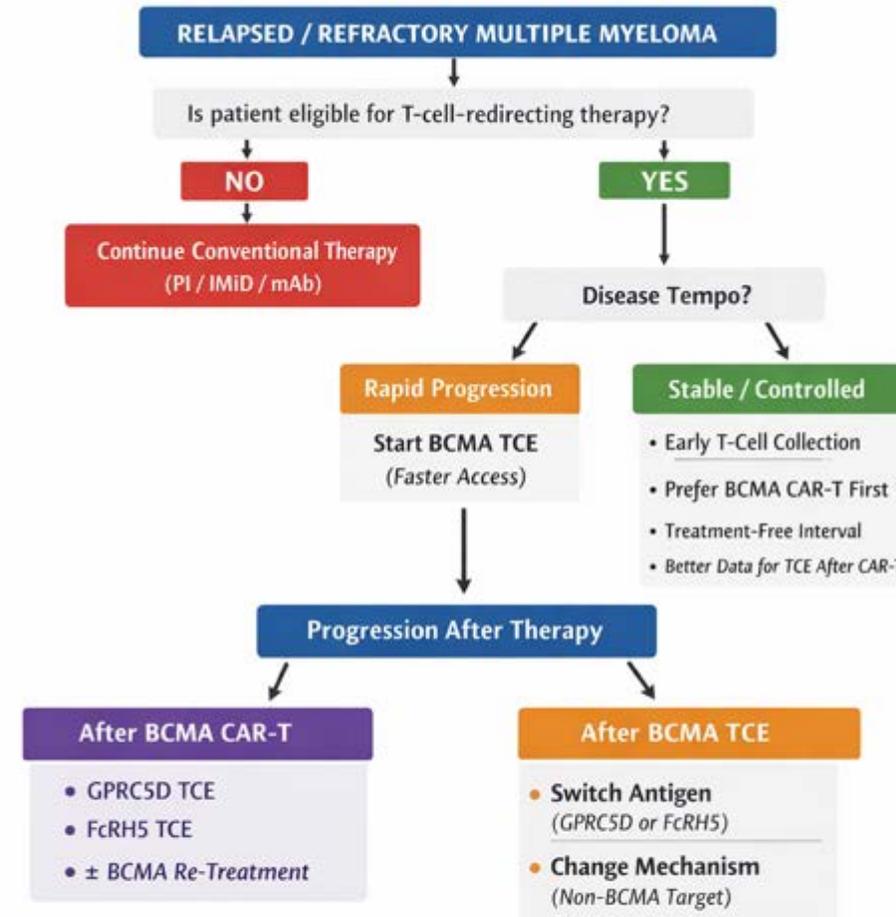
Costa LJ et al. Leukemia 2025

Insights into Relapse

Tumor: Loss of antigen

- TNFRSF17 monoallelic copy loss ~ 4%-6% of patients
- Biallelic loss or monoallelic + extracellular domain mutation in ~ 40% upon progression on TCE
- Less frequent (< 10%) post-CAR T cell therapy
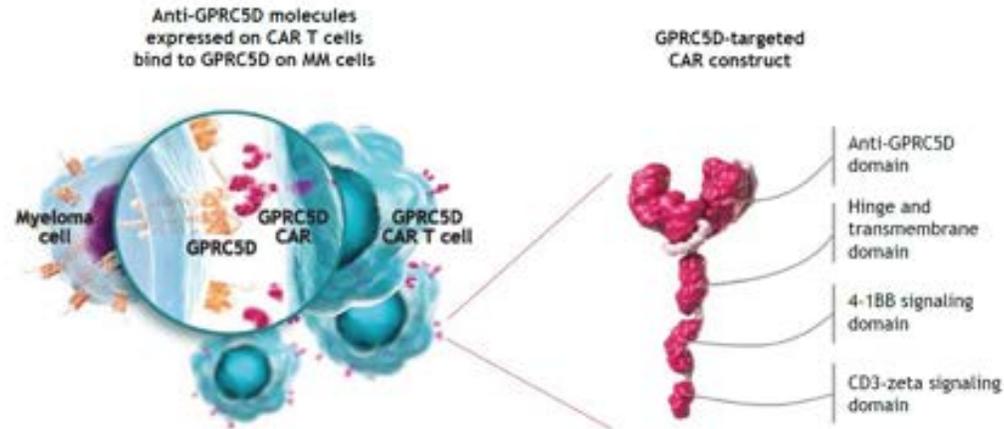
T cells: Exhaustion/dysfunction

- Disease burden and MM progression impacts T-cell function

Tumor microenvironment

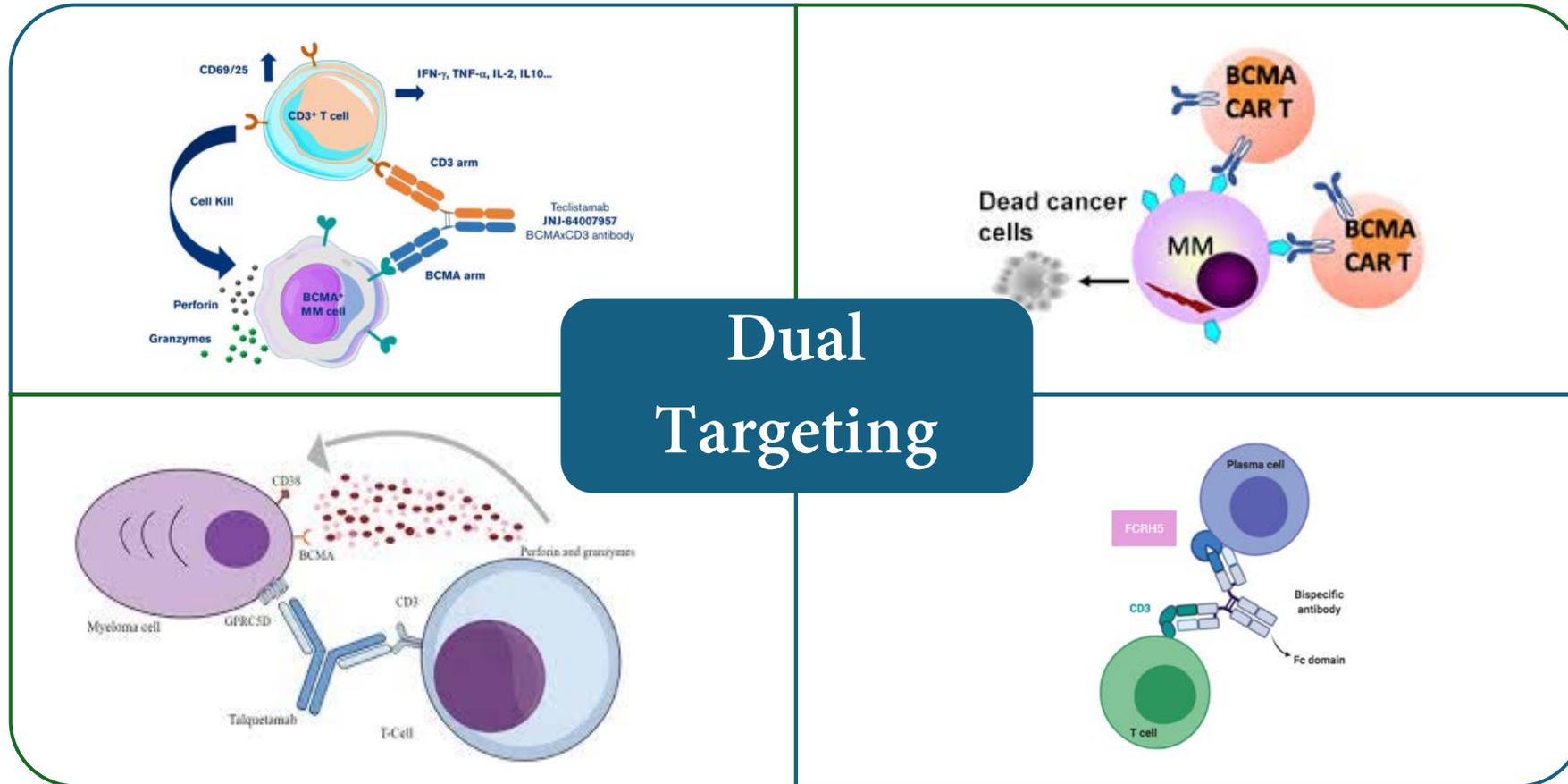- The BMME plays a key role in resistance to drugs that regulate the anti-multiple myeloma immune response
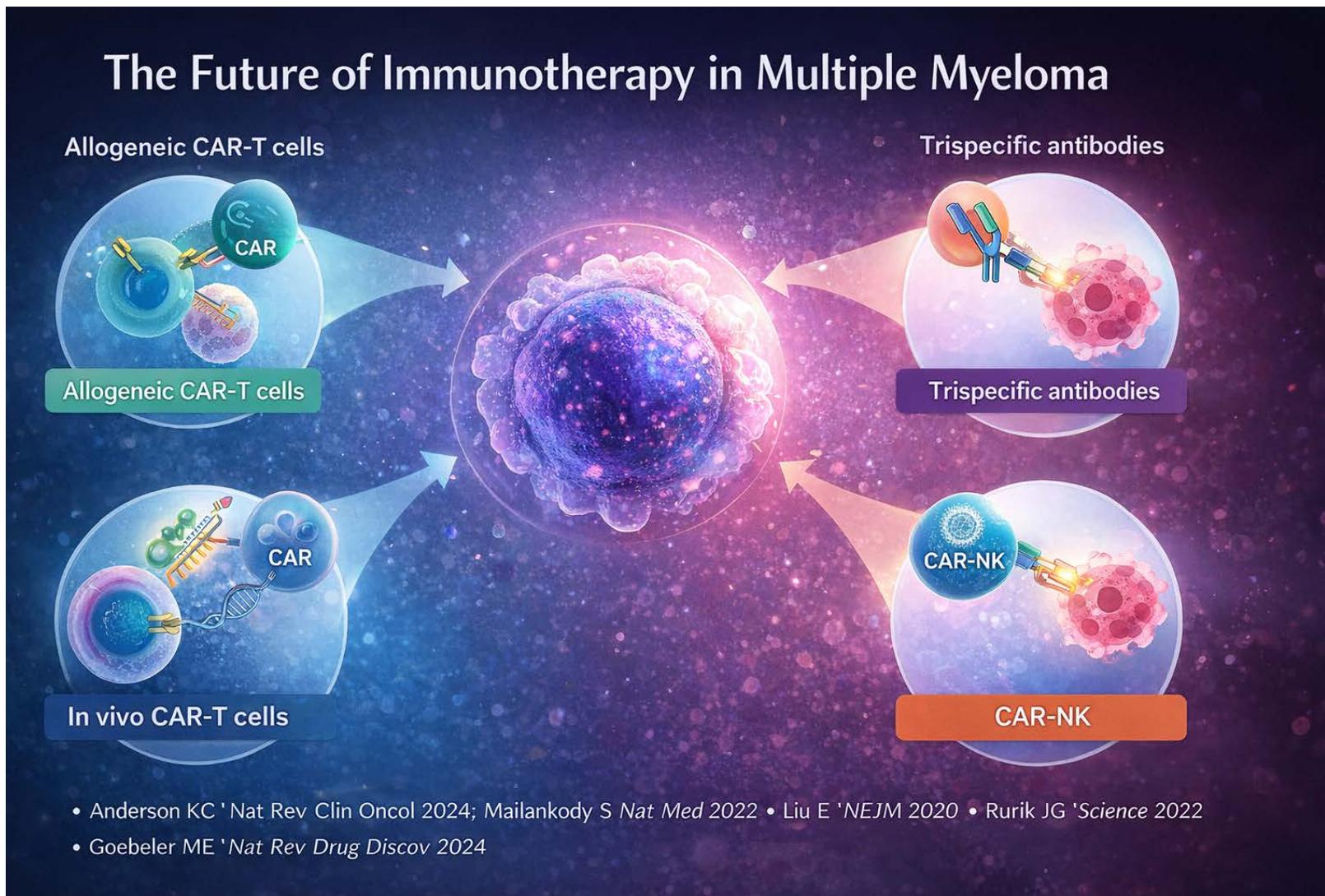
Lee, H et al. Nat Med 2023; Zhou X, et al. Haematologica 2023; Lee H, et Al. Blood 2024;Midha S, et al. Nat Rev Clin Onc 2023;Friedrich MJ et al. Cancer Cell 2023; Wu P, et al. Front Cell Dev Biol 2021;Neumeister P, et al. Int J Mol Sci 2022

Combating T-Cell Exhaustion

Bal S et al. ASH 2025

Combating Antigen Loss

Dual Targeting

Emerging Platforms

The Future of Immunotherapy in Multiple Myeloma

Allogeneic CAR-T cells

CAR

Allogeneic CAR-T cells

In vivo CAR-T cells

CAR

Trispecific antibodies

Trispecific antibodies

CAR-NK

CAR-NK

- Anderson KC 'Nat Rev Clin Oncol 2024; Mailankody S *Nat Med 2022* • Liu E '*NEJM 2020* • Rurik JG '*Science* 2022
- Goebeler ME '*Nat Rev Drug Discov 2024*
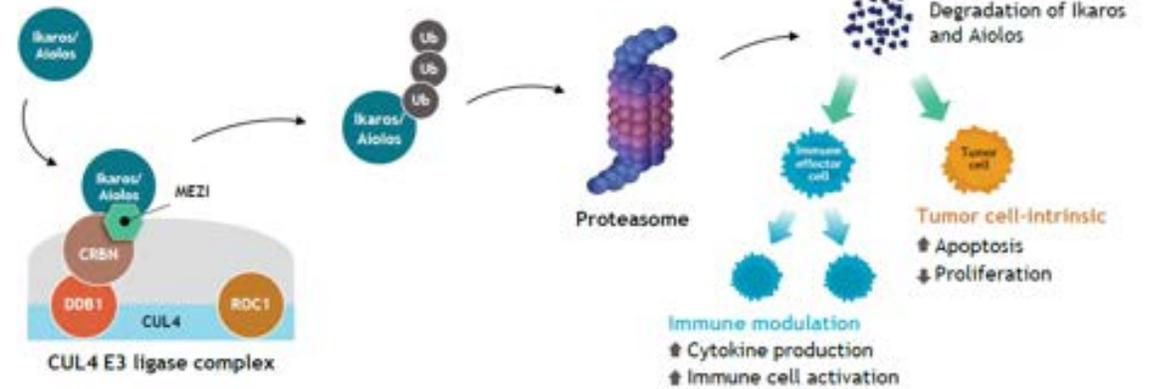
Dual Antigen Targeting

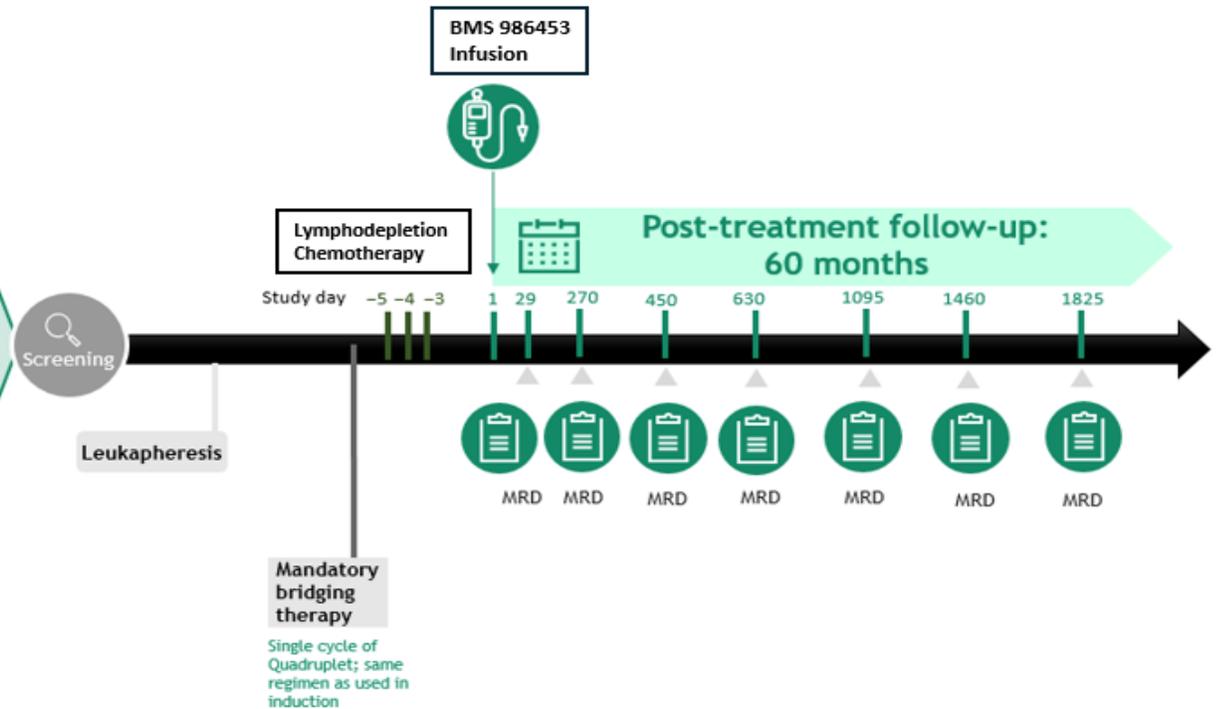| Feature	BCMA + CD19 CAR-T	BCMA + GPRC5D CAR-T
Example platform	GC012F (FasT CAR)	Bicistronic / tandem dual CAR
Targets	BCMA + CD19	BCMA + GPRC5D
Biological rationale	Target plasma cells and precursor clones	Prevent BCMA antigen escape
Manufacturing	Rapid FasT platform (~1–2 days)	Conventional CAR-T manufacturing
Typical population studied	Relapsed myeloma and high-risk NDMM	Relapsed/refractory myeloma
ORR	~93–100%	~80–100% (early cohorts)
MRD negativity	Very high (~38–100%)	Early signals of deep responses
CRS	Mostly grade 1–2	Mostly grade 1–2
ICANS	Rare	Rare
Key concept	Eliminates myeloma progenitors	Eliminates BCMA-negative relapse clones

Yan et al. *JCO* 2023; Lee et al. *Nat Med* 2023

Dual Targeting in NDMM

This is a single center, open-label, Phase 1b study of BMS-986453, a dual targeting CAR-T cell product targeting BCMA and GPRC5D, in participants with NDMM (NCT07333261)
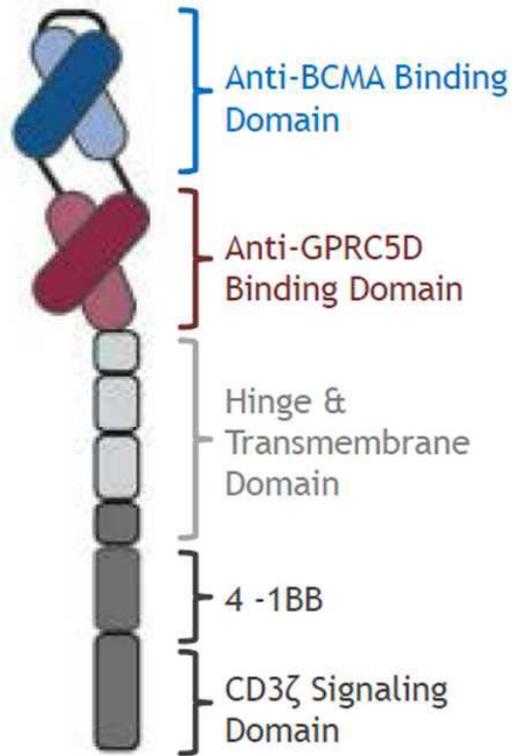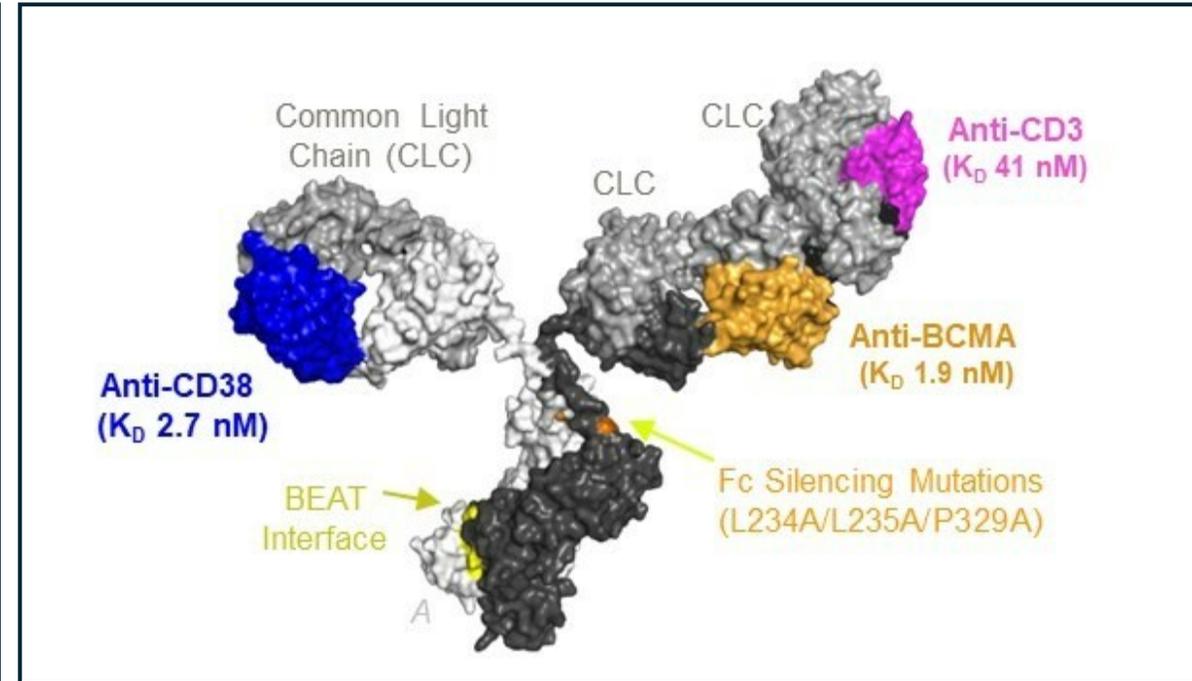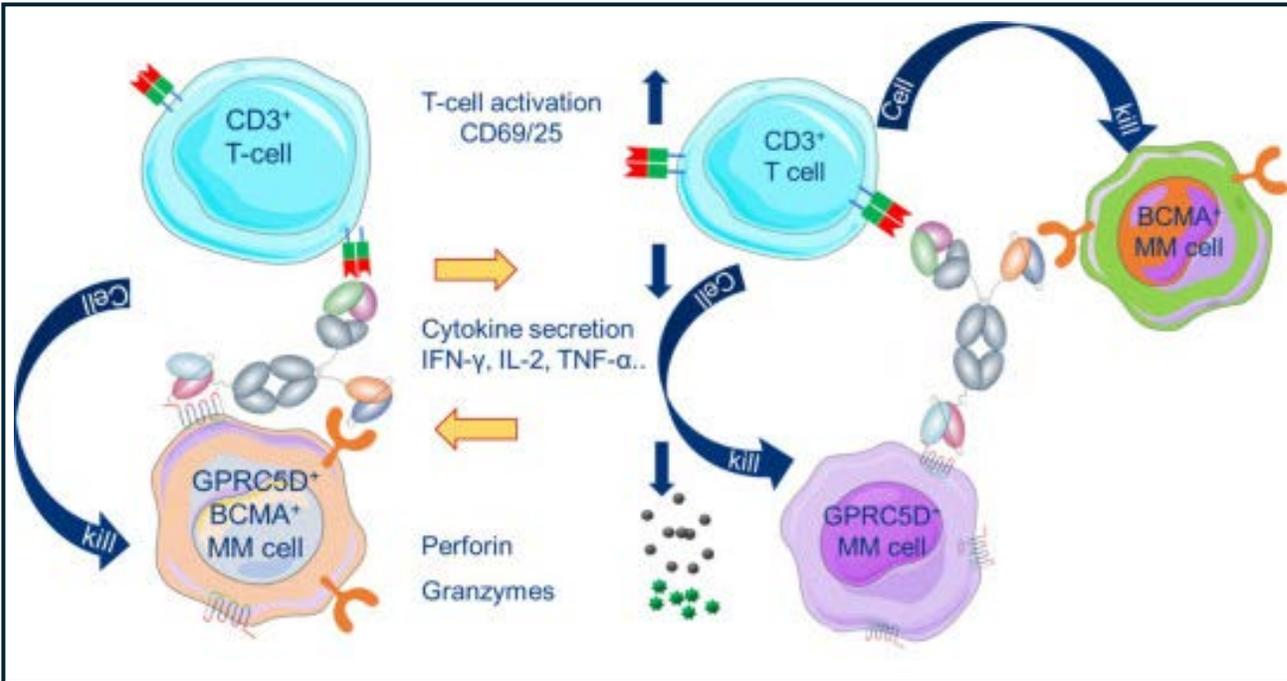
Trispecific Antibodies

JNJ-79635322	ISB 2001

Pillarisetti R, et al. Blood 2023

Ichnos Glenmark Innovation

Allogeneic CAR-T cells

Lv Z, et al. Front. Immunol. 2023
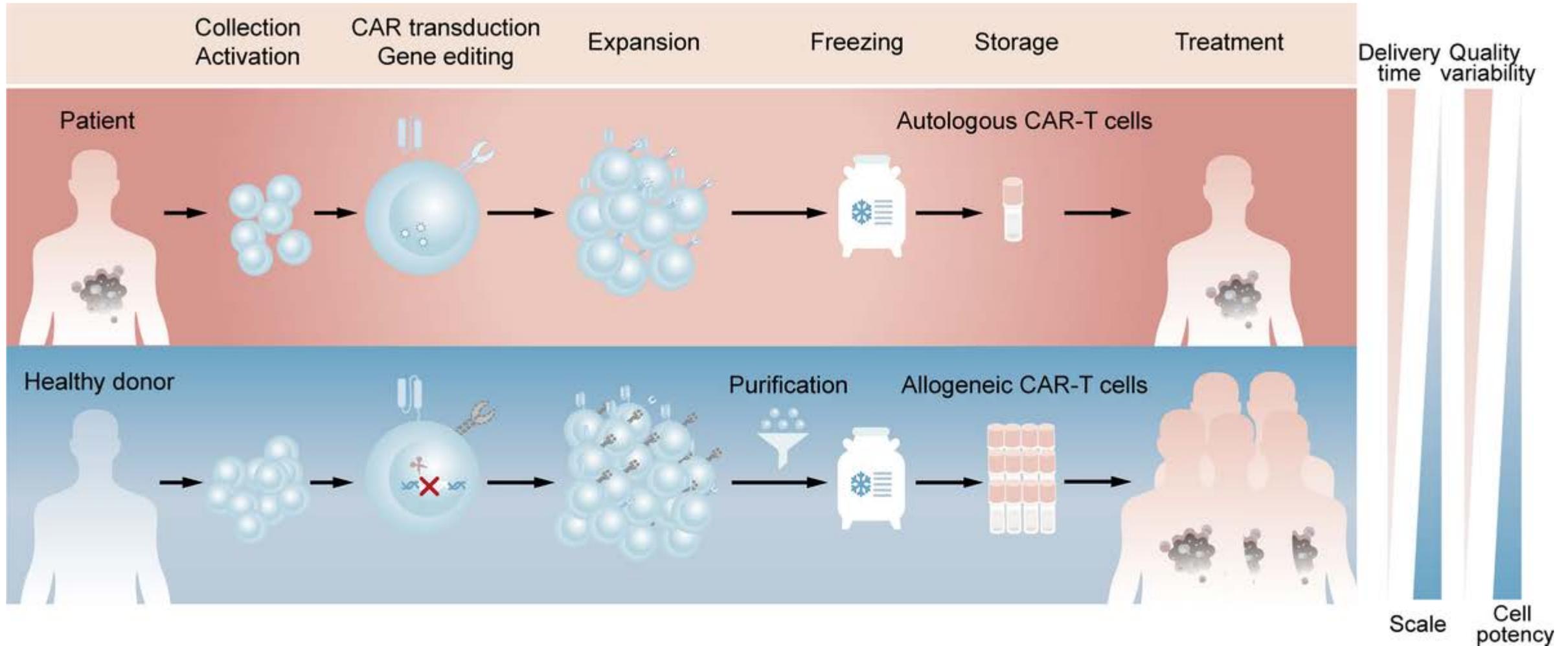
In Vivo Platforms in Development

Bot, A. et al. Nat Rev Drug Discov 2026; Blakemore R, 2026
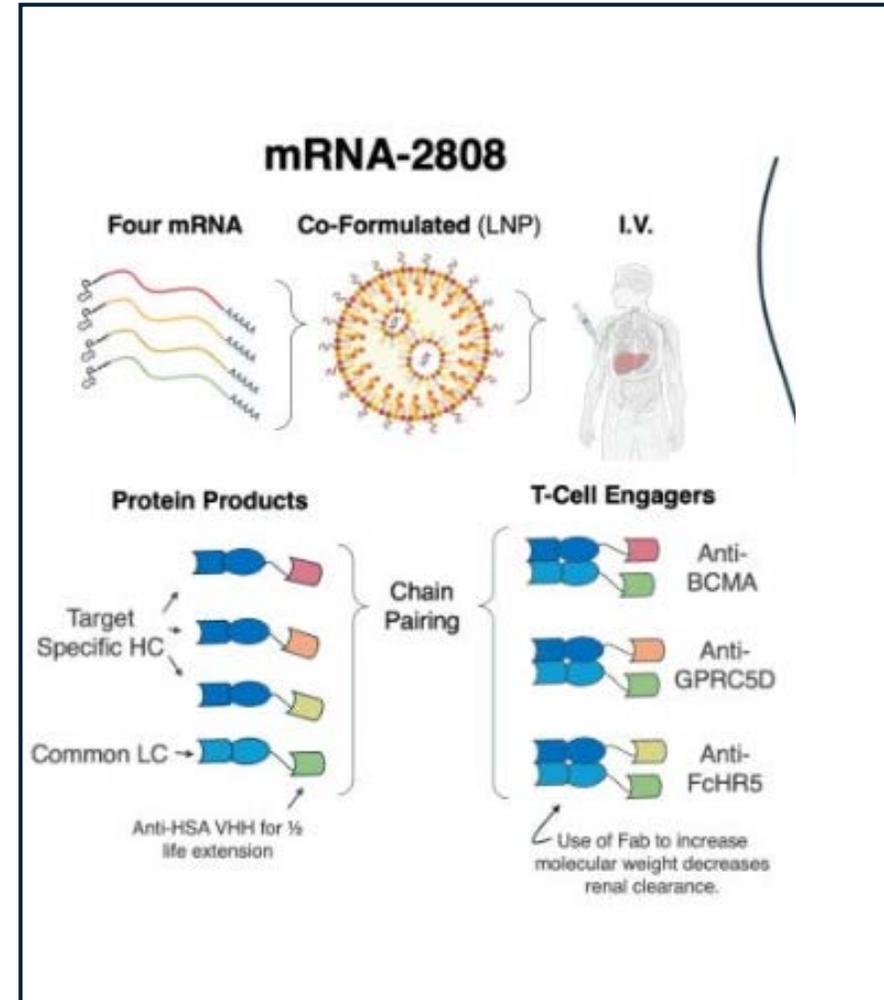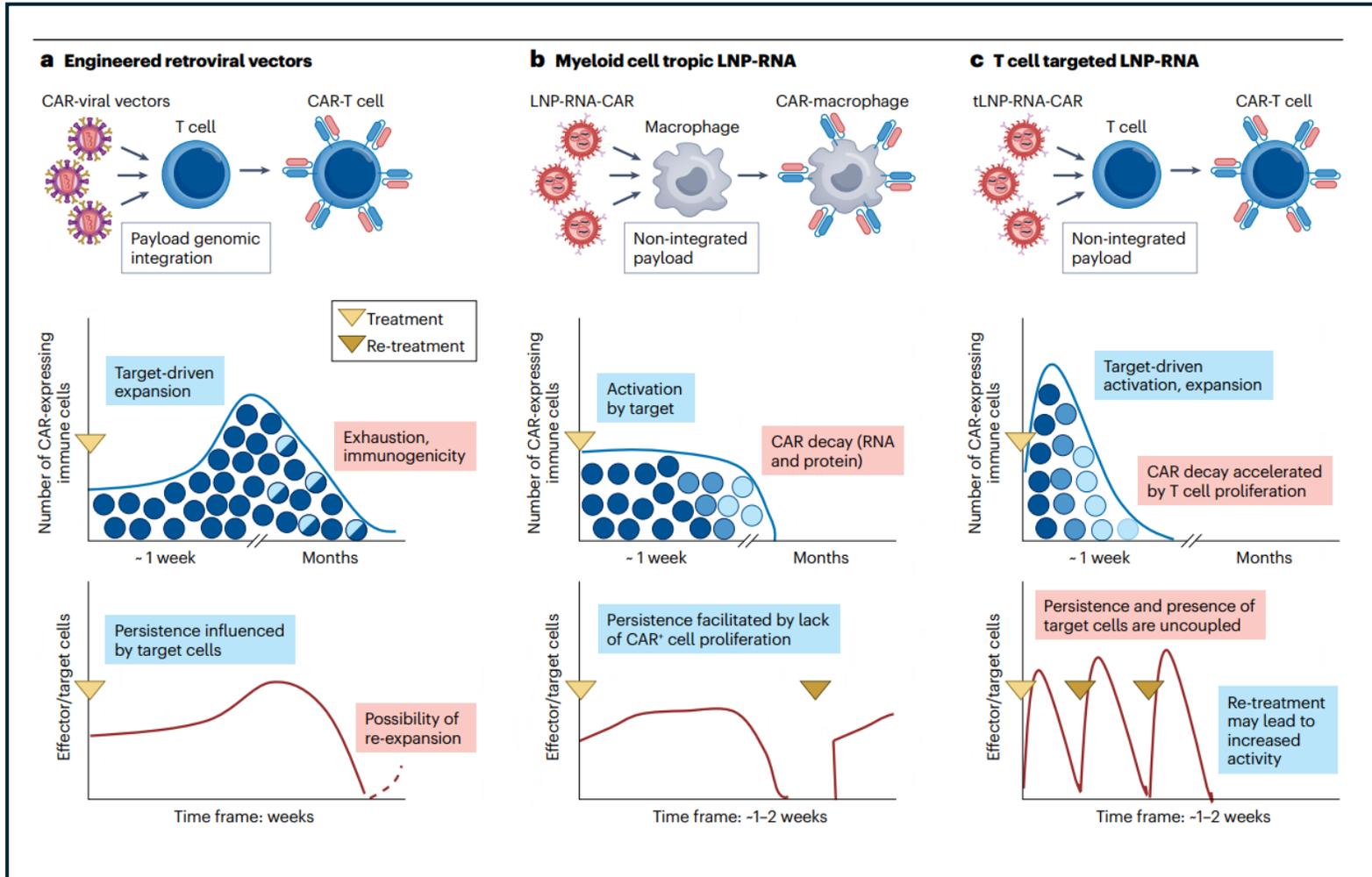
Phase 1 inMMyCAR trial

Traditional CAR-T workflow:
1. Leukapheresis
2. Ex-vivo genetic engineering
3. Manufacturing (3–5 weeks)
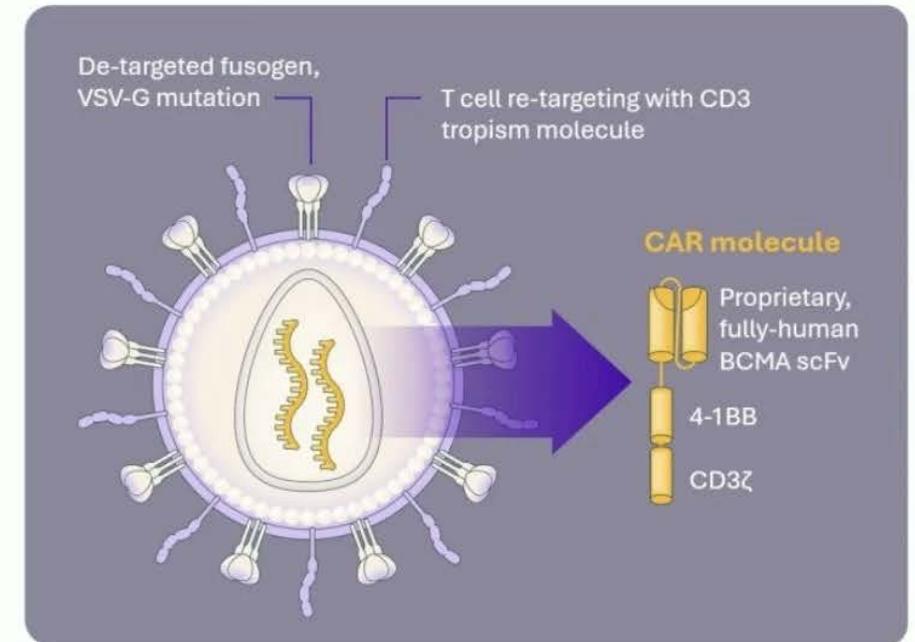4. Lymphodepletion
5. Infusion

KLN-1010 approach:
1. Single infusion of vector
2. T cells engineered inside patient
3. CAR-T cells expand in vivo

Potential advantages:
- No manufacturing delay
- No apheresis
- No lymphodepleting chemotherapy
- Off-the-shelf accessibility
- Scalable, accessible

KLN-1010: a modified LVV generating anti-BCMA CAR-T cells *in vivo*

- **Envelope-modified, replication-incompetent, self-inactivating lentiviral vector**

- **De-targeted VSV-G fusogen** avoids delivery to LDL-expressing cells while maintaining high transduction efficiency

- **Precise re-targeting to T cells** with a CD3 scFv; avoids liver uptake and drug sinks

- Anti-BCMA CAR was **selected based on high levels of activity to BCMA-positive tumors**

De-targeted fusogen, VSV-G mutation

T cell re-targeting with CD3 tropism molecule

CAR molecule
- Proprietary, fully-human BCMA scFv
- 4-1BB
- CD3ζ

BCMA, anti-B-cell maturation antigen; CAR, chimeric antigen receptor; CD3, cluster of differentiation 3; CD3ζ, cluster of differentiation 3 zeta chain; LDL, low-density lipoprotein; LVV, lentiviral vector; scFv, single-chain variable fragment; VSV-G, vesicular stomatitis virus glycoprotein.
Wood JT et al. Toward treatment with gene-modified B cells engineered *in vivo* using iGPS particles (abstract #1281). Poster presented at: ASGCT 28th Annual Meeting; May 13-17, 2025.

kelonia   inMMyCAR

Harrison S, Ho PJ, Lim SL, et al. ASH 2025 LBA-1

Future Paradigm: Toward Immune Control

FIXED-DURATION IMMUNE THERAPY

MRD-GUIDED TREATMENT

COMBINATION IMMUNE APPROACHES

Speaker Opinion

Summary

Immunotherapy has transformed the treatment landscape, producing unprecedented response rates in relapsed myeloma; complementary platforms

❖ CAR-T therapy achieves deep MRD-negative remissions with durable disease control with single infusion

❖ Bispecific antibodies provide highly active, off-the-shelf T-cell redirecting therapy

❖ Antibody-drug conjugates expand BCMA-directed treatment options, particularly in combination regimens

Opportunities

❖ Earlier use of CAR-T and bispecific antibodies

❖ Target diversification (BCMA, GPRC5D, FcRH5)

❖ Dual-target and next-generation cellular therapies

❖ Optimizing sequencing and managing immune-related toxicities

Acknowledgement

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