Cellular Therapies vs Bispecifics for Multiple Myeloma

Kenneth Anderson, MD
Director, Jerome Lipper Multiple Myeloma Center
and LeBow Institute for Myeloma Therapeutics
Dana-Farber Cancer Institute
Kraft Family Professor of Medicine
Harvard Medical School

Disclosures

Advisory Role: Pfizer, Amgen, Astrazeneca, Janssen, Precision Biosciences

Board Membership: C4 Therapeutics, Dynamic Cell Therapies, NextRNA, Window, Mana, Starton

Ownership Interests: C4 Therapeutics, Oncopep, NextRNA, Dynamic Cell Therapies

Cellular Therapies vs Bispecific T Cell Engagers in MM

Both CAR T cells and BiTEs achieve high rates of MRD negative responses in triple/penta refractory MM and have favorable safety profiles, superior to conventional therapy.

Ongoing trials are evaluating CAR T and/or BiTEs and sequencing to treat earlier in the disease course.

Although CARs are now "one and done" and BiTEs are given until progression, trials are evaluating maintenance/combinations. Persistent MRD negativity may inform therapy in future.

Early data suggests responses to CAR T salvage after BiTE therapy, and visa versa.

Current autologous CAR T have logistical challenges versus off the shelf BiTEs. However, novel CART targets (GPRC5D) and constructs (PHE 885, RNA CAR, BAT CAR, allo CAR T, NK CARs) and BiTEs (trispecifics) will improve outcome and availability of both these therapies.

CAR T and BiTEs are likely to be used in combination to restore host anti-MM immunity.

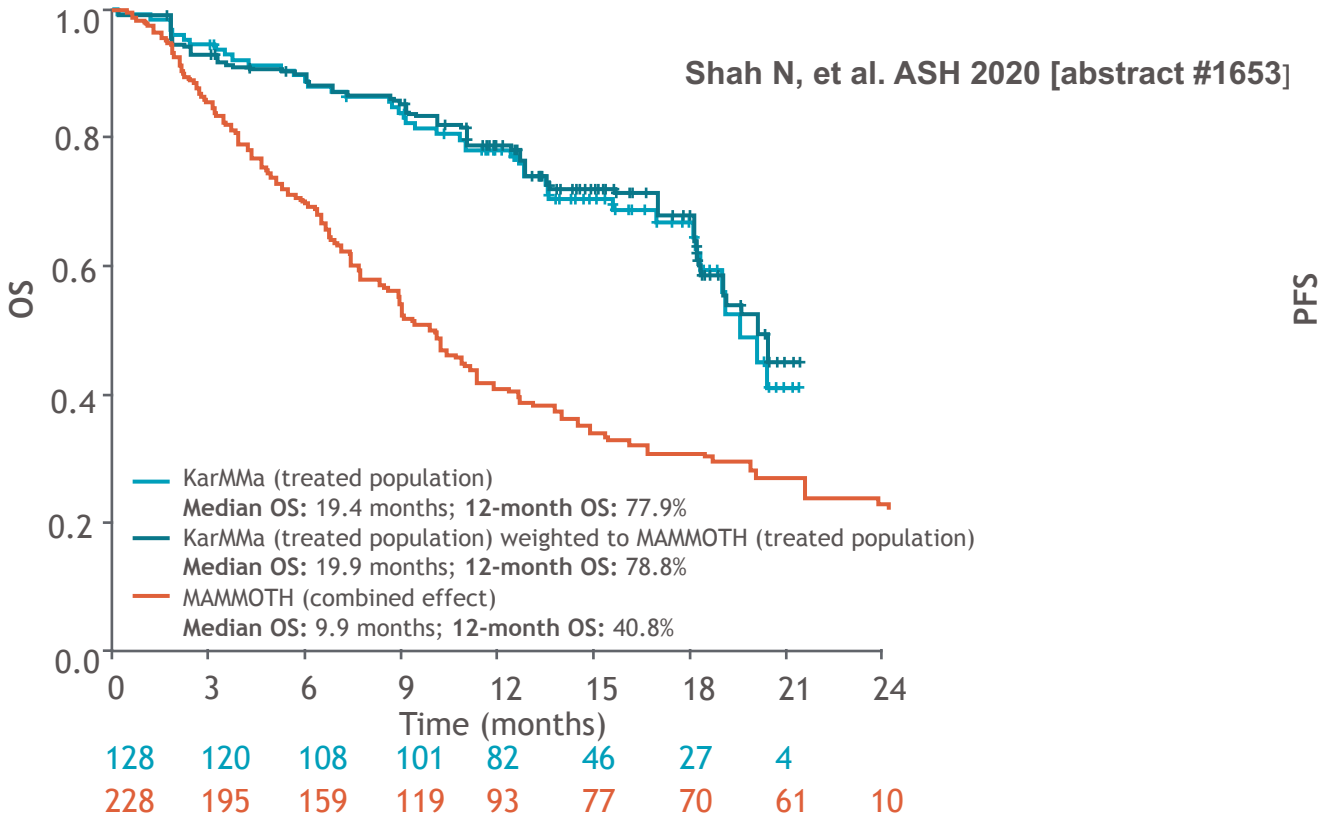
CAR T-Cell Therapy in Multiple Myeloma

	FDA Approved Ide-cel Ph1 N=128	FDA Approved Cilta-cel Ph1b/2 N=97	Orva-cel Ph1b/2 N=62	bb21217 Ph1 N=72	CT053 Ph1b/2 N=20	P-BCMA-101 Ph1/2 N=55	GC012F Ph1 N=16	GPRC5D Ph1 N=18	ALLO-715 Ph1 N=31
CRS, % **All grades** **Grade ≥3**	84% 5%	9% 4%	89% 3%	70% 4%	77% / 83%[a] 0% / 0%	17% 0%	100% 13%	92% 5%	52% 3%
NT, % **All grade** **Grade ≥3**	18% 3%	21% 0.5%	13% 3%	16% 4%	15% / 17%[a] 8% / 0%	4% 4%	0 0	0 0	3% 0
ORR **CR**	73% ≥CR 33% (450: OR 81%, CR 39%)	97.9% ≥sCR 82.5%	92% CR 36%)	75% (≥CR 28%)	94% (≥CR 28%)	44% - 75%[b]	94% (≥CR 56%)	83%	61% in DL3 or DL 4 (n=26)
Median follow-up	13.3 mo	24.0 mo		5.8 mo	6 mo	120-508 days[b]	7.3 mo	13 wks	7.4 mo
Median DOR	10.7 mo (450: 11.3 mo)	21.8-NE mo	Not reported	17.0 mo	Not reported	Not reported	Not reached	Not reached	8.3 mo
Median PFS	8.6 mo 12.2 mo 20.2 CR/sCR	All : NR sCR: NR, 70% at 2 yrs	Not reported	Not reported	Not reported	Not reported	Not reported		Not reported
Median OS	24.8 mo	74% at 2 yrs Median NR	Not reported	Not reported	Not reported	Not reported	Not reported		Not reported

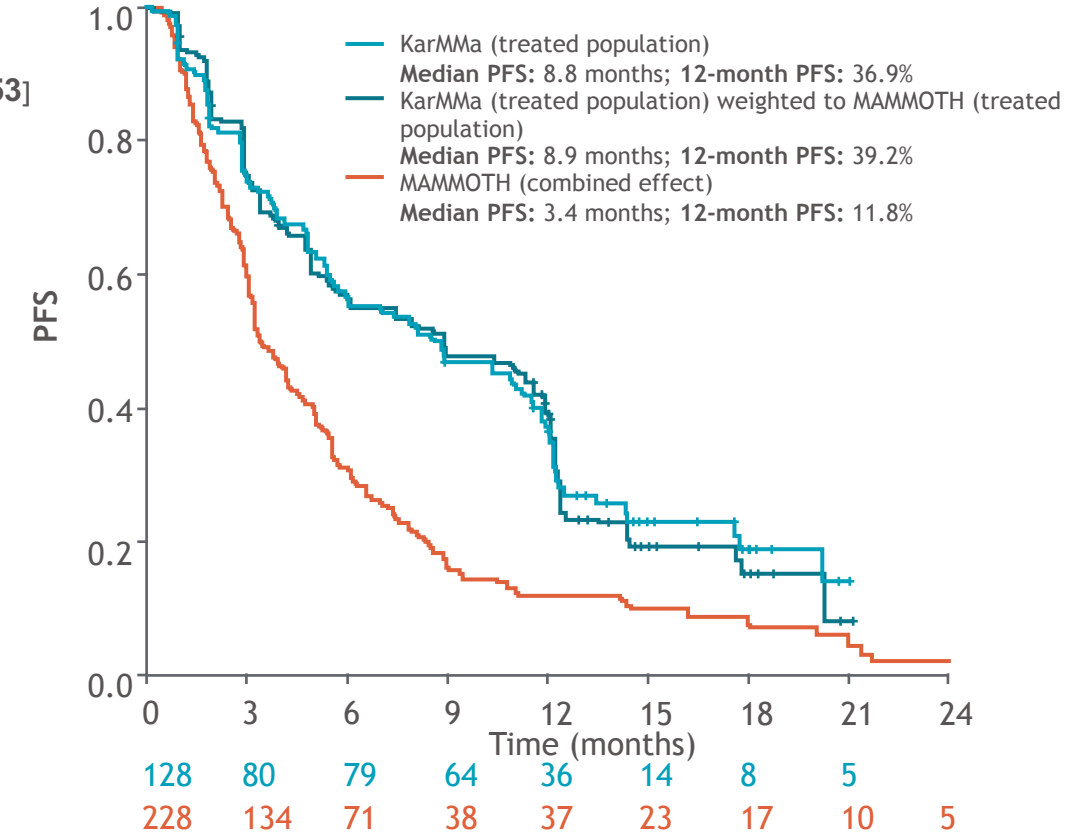
Munshi et al NEJM 2021; 705-16; Berjeda et al Lancet 2021; 398:314-24.; Lin et al; Alsina et al; Kumar et al; Costello et al; Jiang et al; Mailankody et al; Anderson et al; Usmani et al ASH/ASCO 2020,2021; Martin et al; Raje et al; Mailankody et al, ASH 2021

OS and PFS: Ide-Cel Versus Conventional Care

OS: Ide-cel (KarMMa treated population) versus conventional care (MAMMOTH treated population)



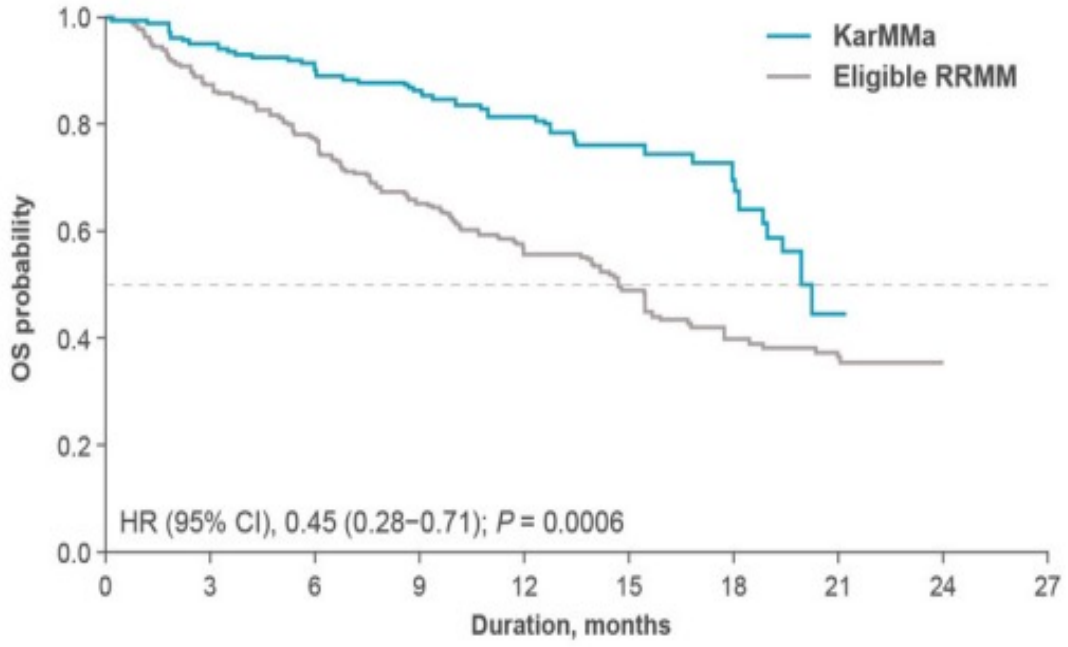
PFS: Ide-cel (KarMMa treated population) versus conventional care (MAMMOTH treated population)



- Median OS and median PFS were significantly longer for the ide-cel-treated population (weight-matched) compared with the conventional care population in MAMMOTH in the base case

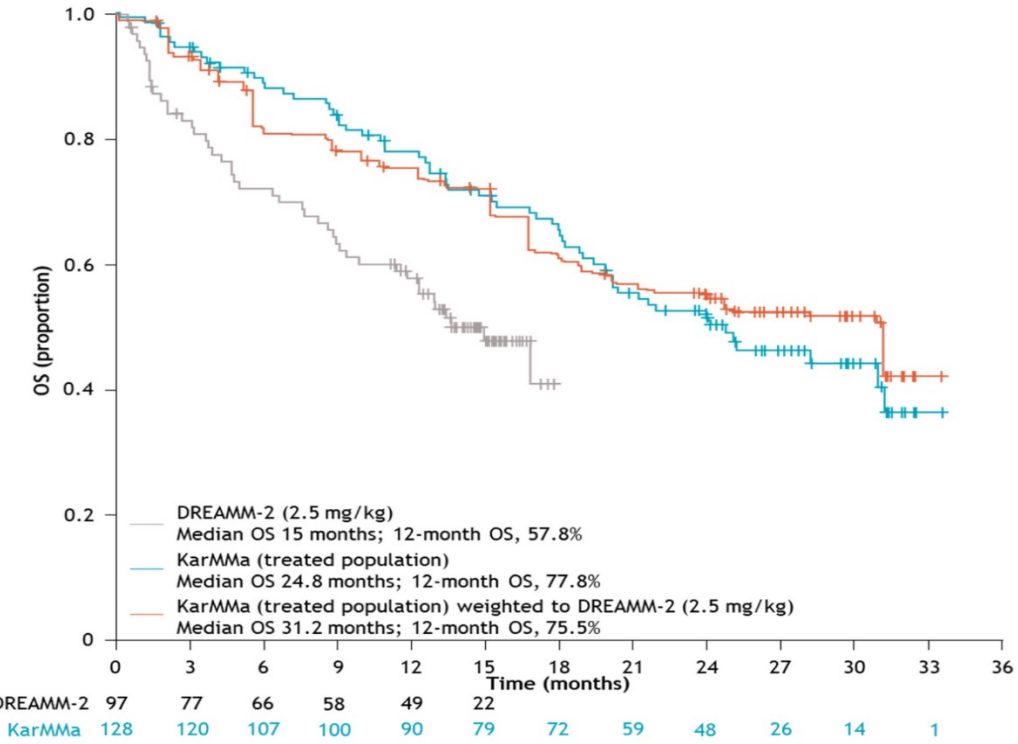
KarMMa-1 (Ide-cel) Comparison with Other Therapies

Ide-cel (KarMMa-1) vs Real World Experience[1]



At risk, N									
KarMMa	128	120	108	101	82	46	27	4	0
Eligible RRMM	190	162	137	111	77	53	36	24	19

Ide-cel (KarMMa-1) vs Belantamab (DREAMM-2)[2]



No. at risk													
DREAMM-2	97	77	66	58	49	22							
KarMMa	128	120	107	100	90	79	72	59	48	26	14	1	

BM, belantamab mafodotin; ide-cel, idecabtagene vicleucel; OS, overall survival.

1.Jagannath S et al. BCJ 2021. 11: 116.
2. Rodriguez-Otero P et al. ASH 2021. Abstr 1978.

Idecel Real World Experience

n=108 pts

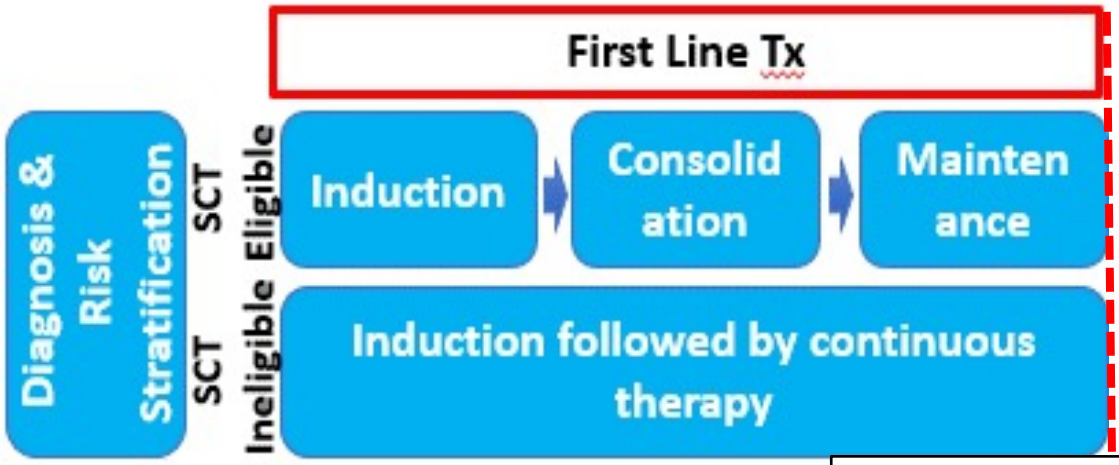
Toxicity similar to KarMMa-1: CRS 82%, grade 3: 4%; ICANS in 15%, grade 3: 5%

Day 30 response (104 pts): PR 83%, VGPR 64%, CR 34%

Conclusion: Safety and 30-day responses in real world setting are compatible with clinial trial KarMMa-1.

Hansen et al ASCO 2022

CAR-T Protocols in Earlier Lines of Therapy



2nd Line | 3rd Line | 4th Line

- Selection Based on Response to Prior Therapy
- Changes between PI & IMiDs classes and or next generation

US FDA Approved LoT

- Idecabtagene vicleucel (Ide-Cel, bb2121, Abecma)
- Ciltacabtagene autoleucel (JNJ68284528, Carvykti)

KarMMa-2: Ide-cel in high-risk MM, early relapse after 1L/ASCT. (NCT03601078)

KarMMa-3: Randomized, controlled study for Ide-cel vs SOC triplet regimens. (NCT03651128)

KarMMa-4: Ide-cel in high risk newly diagnosed MM (NCT04196491)

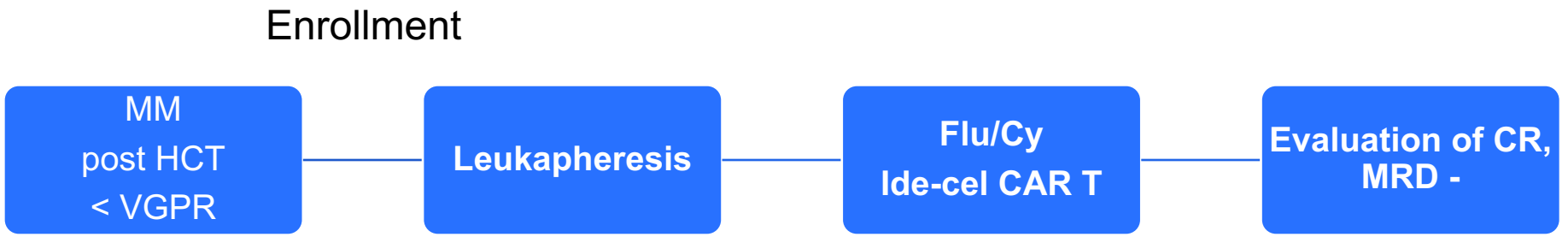
KarMMa-7: Ide-cel with CC-220, BMS-986405 (JSMD194), or other standard triplet regimens. (NCT04855136)

Janssen Oncology

Pharmaceutical Companies of Johnson & Johnson

Courtesy of Yi Lin, M.D.Ph.D.

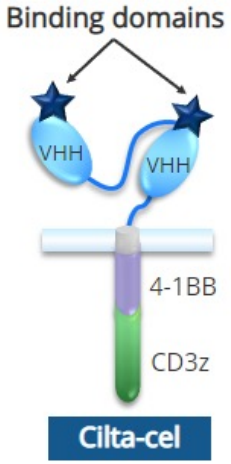
BMT CTN 1902 Study Schema



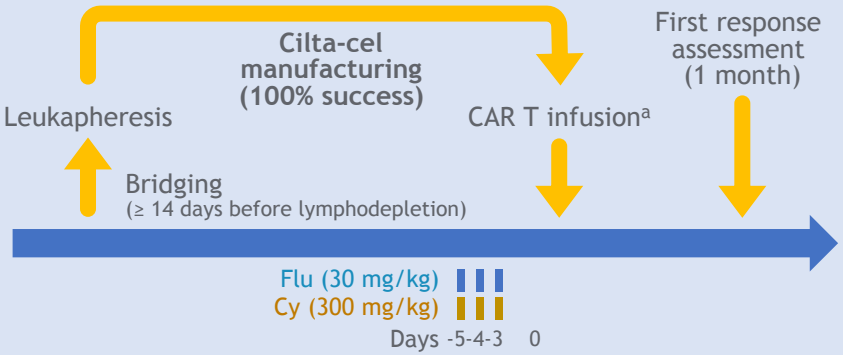
~9 mo post auto HCT
No prior disease Progression

- **Population: Patients with suboptimal response (<VGPR) after an autoHCT and 6 mo of maintenance**
- **Intervention: CAR T cells and continuation of maintenance**
- **Primary endpoint: CR and MRD negative**
  - **Aim to improve 6mo CR from <10% to 30%**

Phase 1b/2 CARTITUDE-1: Cilta-cel in RRMM



- RRMM
- ≥ 3 prior regimens
- Previously exposed to:
  - IMiD® agent
  - Proteasome inhibitor
  - Anti-CD38 Ab
  - Measurable disease
- Progressive MM per IMWG criteria



18 month F/U

Screened N = 113

Leukapheresed N = 113

Bridging N = 73

Cilta-cel infusion N = 97

Median administered dose: 0.71×10^6 ($0.51–0.95 \times 10^6$) CAR+ viable T cells/kg

Endpoints

- Phase 1b: Characterize cilta-cel safety and confirm the recommended phase 2 dose
- Phase 2: Evaluate cilta-cel efficacy

Patient characteristics[2]		
Years since diagnosis, median (range)		5.9 (1.6-18.2)
No. of prior antimyeloma regimens, median (range)		6 (3–18)
Prior autologous SCT, %	1 > 1	89.7 8.2
Any bridging therapies for MM, %		75%
Refractory status, %	Anti-CD38 Ab refractory Triple refractory	99 87.6

Berdeja et al Lancet 2021; 398: 314-24; Martin et al ASH 2021

CARTITUDE-1: BCMA CAR T Cell Phase1b/2 Study

- **Ciltacabtagene autoleucel (cilta-cel; JNJ-68284528) is a chimeric antigen receptor T-cell therapy for the treatment of patients with RRMM[1]**
  - **In the phase 1b/2 CARTITUDE-1 study, early, deep, and durable responses were observed with a single cilta-cel infusion in heavily pretreated patients with RRMM[1]**
    - **At a median follow-up of 12.4 months**
      - **Cilta-cel had a manageable safety profile**
      - **ORR and sCR were 97% and 67%, respectively**
      - **Overall 12-month PFS and OS rates were 77% and 89%, respectively**
      - **Median PFS and duration of response were not reached (95% CI, 16.8–not estimable and 15.9–not estimable, respectively)**
  - **ASH 2021: updated results from the CARTITUDE-1 study with a longer duration of follow-up (median ~2 years)[a]**

Berdeja et al Lancet 2021; 398: 314-24; Martin et al ASH 2021

Cartitude 1 Ciltacel 22 mo median FU

ORR 97%, VGPR 95%, 83% sCR
Two year PFS 60.5%, median PFS and OS not reached
Of 61 evaluable pts, 92% MRD negative
Two year PFS if MRD negative at 6 and 12 months was 91% and 100%
No new safety signals

Usmani et al ASCO 2022, Martin J Clin Oncol 2022

Cartitude 2: Ciltacel in Early Relapse (within one year of ASCT, or within one year in those without ASCT)

n=19 pts
ORR 100%, 90% CR, 95% VGPR
12 mo PFS 90%
84% CRS, ICANs grade 4 1 pt

van de Donk ASCO 2022

Cartitude 2 : Ciltacel for Relapse after 1-3 prior therapies

n=20 pts
ORR 95%, 75% CR/sCR, 85% VGPR
Median DOR not reached
CRS 85%, 10% grade ¾
3 pts ICANS grades 1-2

Agha et al ASCO 2022

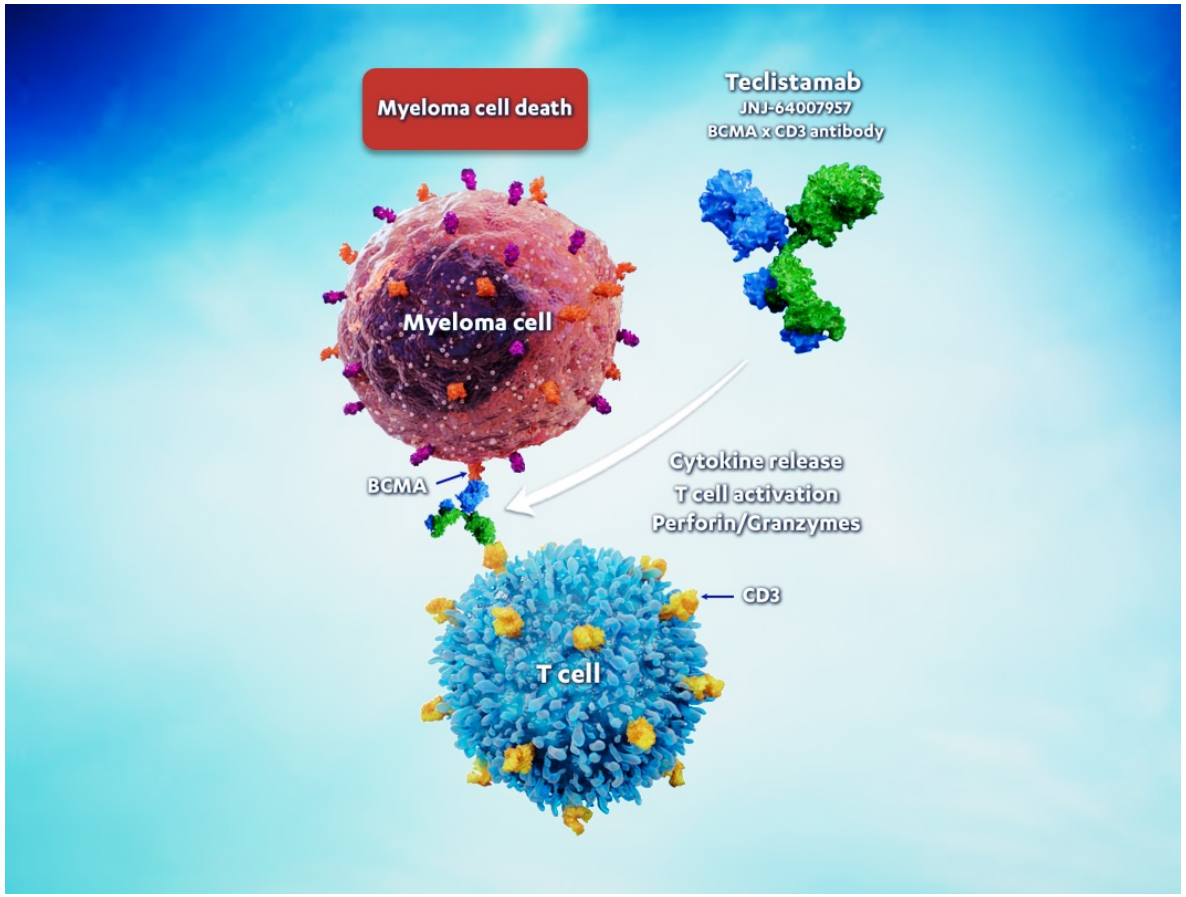
Bispecific T Cell Engagers (Bites) in Multiple Myeloma

	Tesclistamab Ph1 N=149	AMG-701 Ph1 N=85	REGN5458 Ph1 N=49	PF-3135 Ph1 N=30	Talquetamab Ph1 N=157	Cevostamab Ph1 N=53
Target	**BCMA-CD3**	**BCMA-CD3**	**BCMA-CD3**	**BCMA-CD3**	**GPRC5D-CD3**	**FcRH5-CD3**
Dosing Schedule	Q2W→QW IV or SC IV: 0.3-19.2 µg/kg SC: 80-3000 µg/kg	QW IV (0.005-18 mg)	QW→Q2W IV (3-96mg)	QW SC (80-1000µg/kg)	QW or Q2W IV: 0.5-180 µg/kg SC: 5-800 µg/kg	Q3W IV (0.05-160mg)
CRS, % **Any grade** **Grade ≥3**	 55% 0	 65% 9%	 39% 0	 73% 0%	 54% 3%	 76% 2%
NT, % **Any grade** **Grade ≥3**	 5% 1%	Not reported	 12% 0	Not reported	 6% 2%	Not reported
ORR	At RP2D (1500 µg/kg SC): 73% (≥CR, 23%)	26% (≥CR, 10%)	39% (≥CR, 16%)	80%	At RP2D (405 µg/kg SC): 69% (≥CR, 15%)	In ≥20 mg cohorts: 53% (≥CR, 18%)
Median follow-up	At RP2D: 3.9 mo	6.5 mo	2.6 mo	Not reported	≥60 µg/kg: 7.4 mo ≥405 µg/kg: 3.7 mo	8.1 mo
Median DOR	Not reached	Not reached	6.0 mo	Not reported	Not reached	8 patients ≥6 mo
Median OS	Not reached	Not reported	Not reported	Not reported	Non reported	Not reported

Garfall et al; Harrison et al; Madduri et al Chari et al; Cohen et al ASH 2020

Teclistamab: A Novel BCMA × CD3 T-Cell Bispecific Antibody

- Teclistamab (JNJ-64007957) is an off-the-shelf, T-cell redirecting, bispecific antibody binds to CD3 on T cells and BCMA on plasma cells to mediate T-cell lysis of BCMA-expressing MM cells
- RP2D teclistamab monotherapy: 1.5 mg/kg subcutaneous (SC) QW with step-up doses of 0.06 and 0.3 mg/kg[3]
- **ASH 2021: pivotal phase 1/2 data from the 1.5 mg/kg dose of MajesTEC-1 shows 62% ORR with deepening responses over time**



Moreau et al ASH 2021, NEJM 2022; Usmani et al. Lancet 2021; 398: 665-74.

Teclistamab (9 month followup)

ORR 64%, > CR 30%
Median DOR not reached , 12 mo DOR 66%
Infections 63%, 35% grade ¾
CRS 72% 0.6% grade 3 grade ½ ICANS

Nooka et al ASCO 2022

Prior Exposure to BCMA (9.9 month followup)

38 pts, 25 evaluable for efficacy
Prior ADC 64%, prior CAR T 44%, both 2%
ORR 38% in ADC exposed and 45% in CAR T exposed pts
Infections 42%, 26% grade ¾
CRS 63%, 1 pt ICANS
Safety similar to BCMA non exposed pts

Touzeau et al ASCO 2022

Teclistamab versus Real World Clinical Practice

LocoMMotion 248 pts control group

Teclistamab vs real world: ORR (RR 2.31, p<0.0001; VGPR (RR 5.54, p<0.0001); CR rate (RR 91.5, p<0.0001); DOR (HR 0.17, p<0.0001); PFS (HR0.47, p<0001); and OS (HR 0.69, p=0.08).

Van de Donk, ASCO 2022

Flatiron Health multiple myeloma control group

Teclistamab vs real world: PFS (HR 0.43, p<0.0001); TTNT (HR 0.42, p <0.0001); OS (HR 0.73, P=0.13)

Krishnan et al ASCO 2022

CASTOR, POLLUX, EQUULEUS and APOLLO trials control group

Teclistamab vs real world: ORR (OR 4.58, p<0.001); > CR (OR 12.62, p<0.0001); > VGPR (OR 11.64, p<0.0001); PFS (HR 0.62, p= 0.0024); TTNT (HR 0.38, p<0.0001); and OS (HR 0.47, p<0.0001)

Mateos et al ASCO 2022

Teclistamab with Daratumumab

Pts treated with CD38 Ab within 90 d were excluded

n=46 patients

ORR 78%, VGPR 73%, median DOR not reached
CRS 61% Infections 63%, grade 3/4 28%

Upregulation of CD38+/CD8+ T cells and proinflammatory cytokines support synergy of combination.

Otero et al ASCO 2022

Anti-Myeloma Therapy for Relapse MM Post Idecel

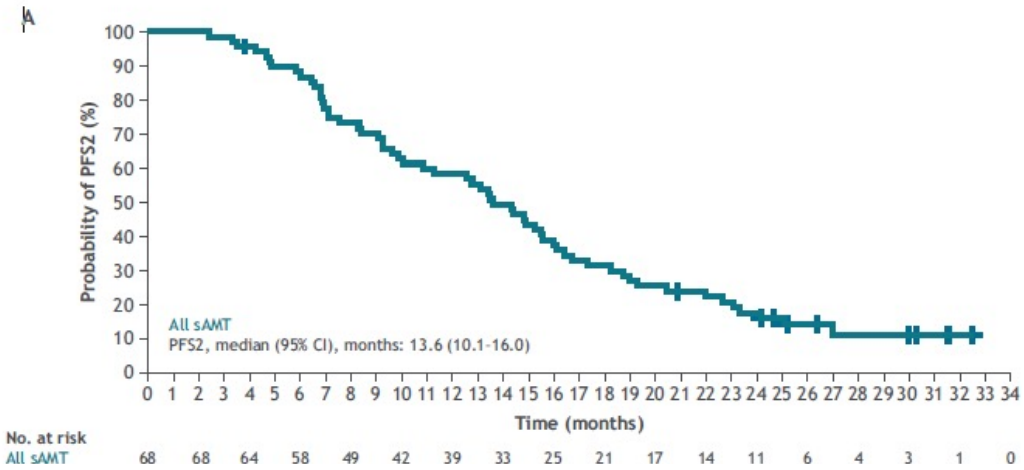
sAMT classes and agents (≥ 20%), n (%)	Patients who received sAMT, including anti-BCMA sAMT (n = 68)
Corticosteroids	58 (85.3)
Dexamethasone	56 (82.4)
PIs	47 (69.1)
Carfilzomib	32 (47.1)
Bortezomib	23 (33.8)
Alkylating agents	31 (45.6)
Cyclophosphamide	24 (35.3)
Immunomodulatory agents	31 (45.6)
Pomalidomide	22 (32.4)
Monoclonal antibodies[a]	30 (44.1)
Other	26 (38.2)
Venetoclax	14 (20.6)
Not coded[b]	21 (30.9)
Platinum (all cisplatin)	14 (20.6)

- Anti-BCMA agents used: Belantamab mafodotin (n = 10) and inducible T-cell co-stimulator teclistamab (n = 1)
- Among all patients who received sAMT, 23 (33.8%) received Repeat-ide-cel as first sAMT

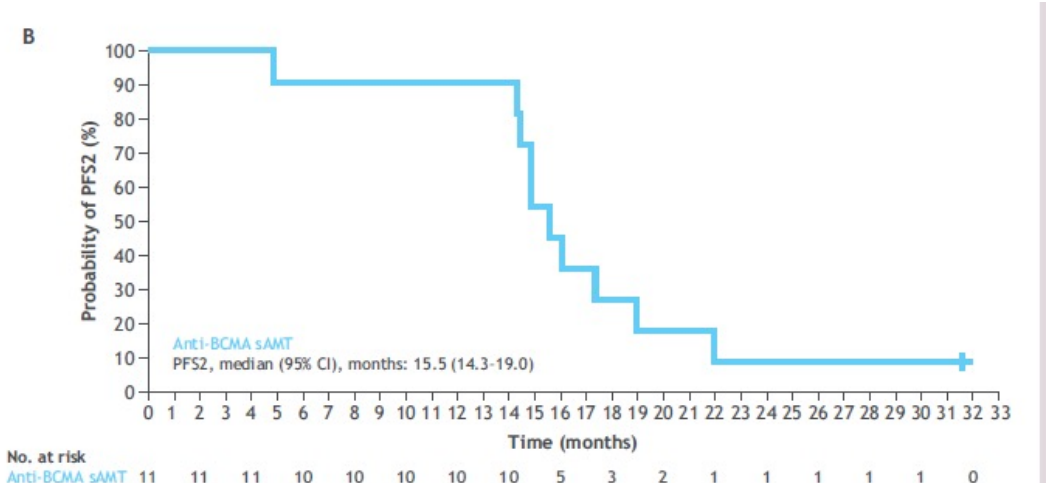
Otero et al ASH 2021

Outcome of Patients Who Relapsed After ide-cel and Receive sAMT

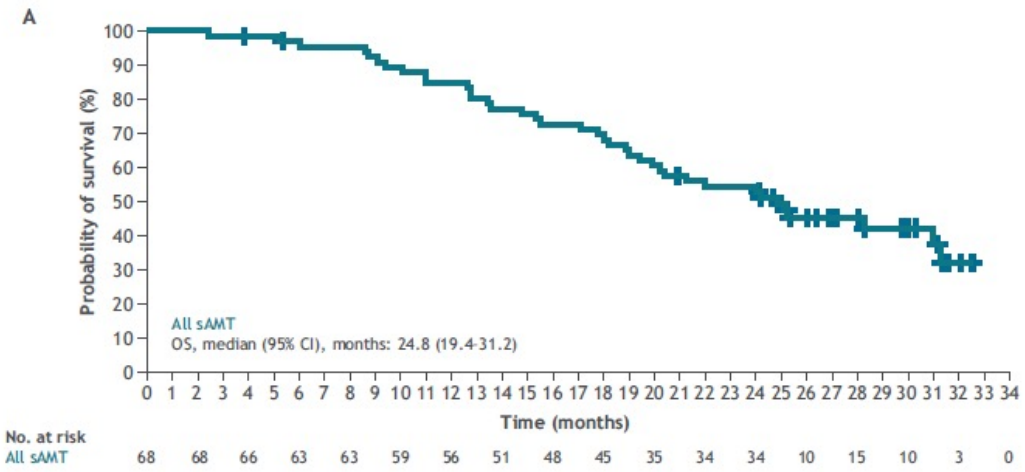
PFS in all patients who received sAMT



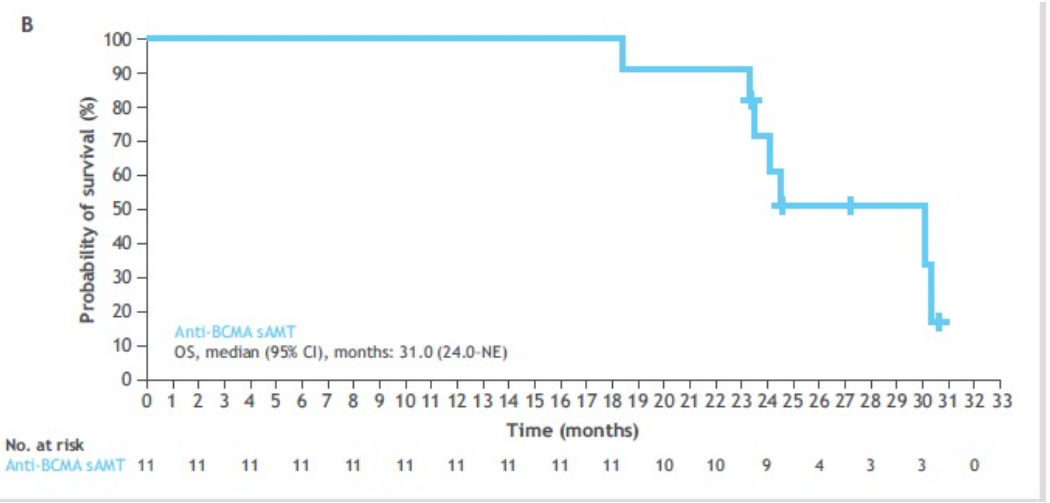
PFS following anti-BCMA sAMT



OS in all patients who received sAMT

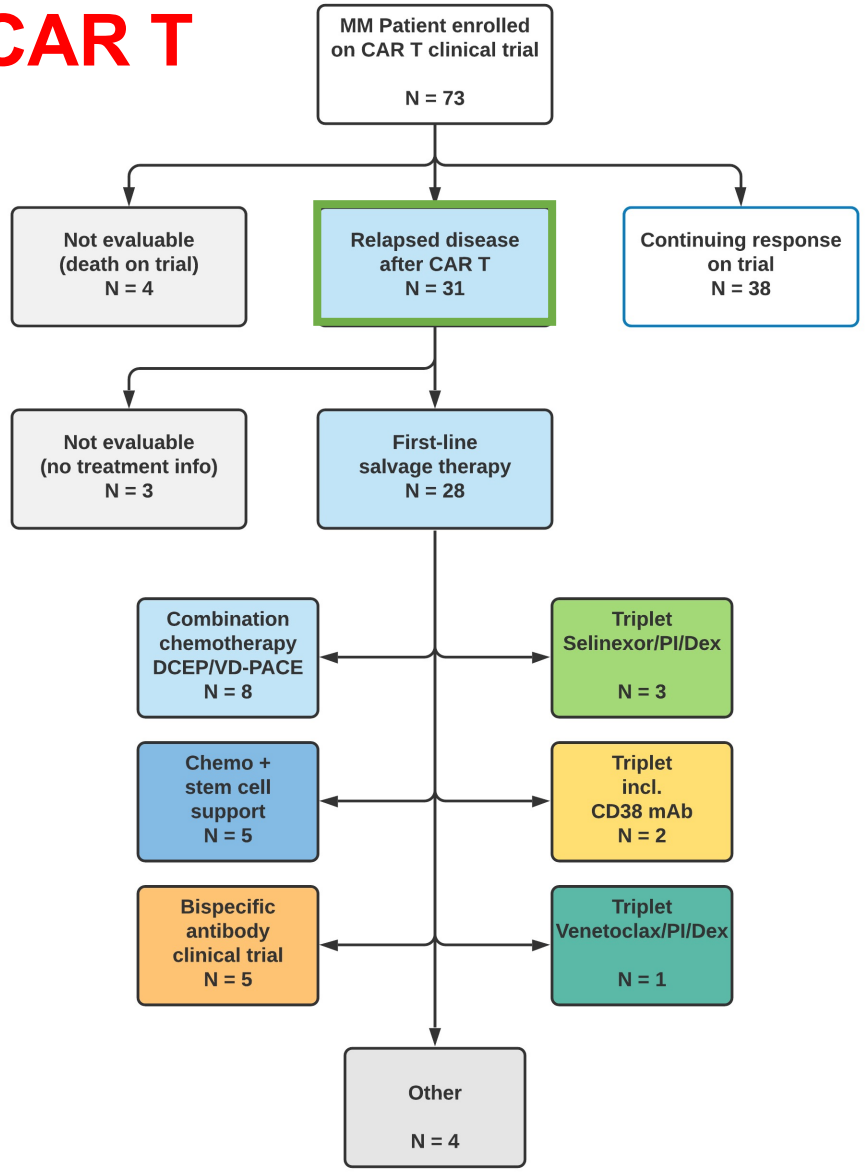


OS following anti-BCMA sAMT



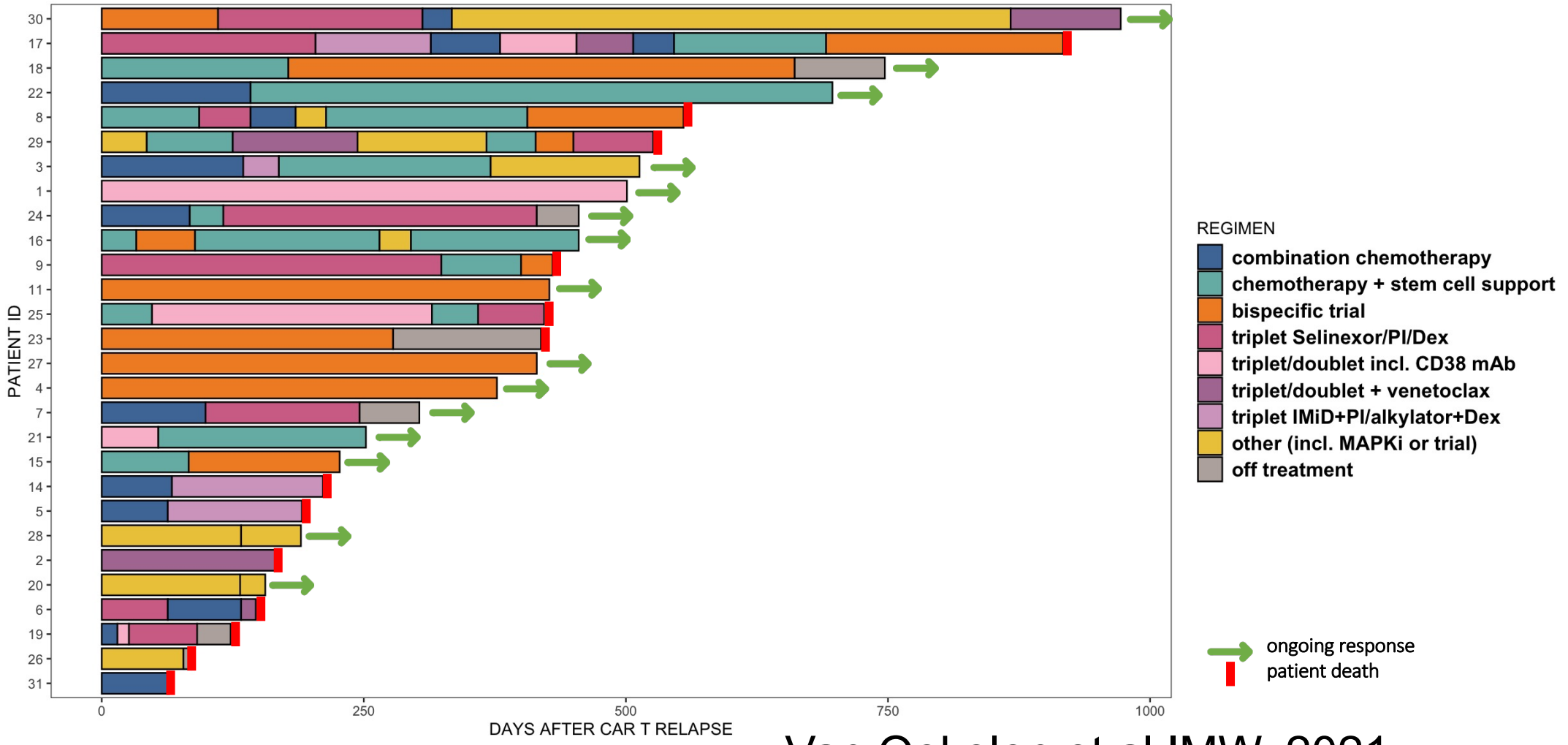
Outcome After Relapse on BCMA-Targeted CAR T (3 CAR T Products)

- 28 patients received salvage therapy
- Median time from relapse to subsequent treatment: 30 days (range 0-201)
- Median of 2 additional treatment lines (range 0-8)
- **Most common <u>initial</u> treatment:**
  - DCEP±V or VD(T)-PACE: 8/28 (29%)
  - Chemo → stem cell support: 5/28 (18%)
  - Bispecific antibody: 5/28 (18%)
  - Selinexor + doublet: 3/28 (11%)
  - CD38 mAb + doublet: 2/28 (7%)
  - Venetoclax + doublet 1/28 (4%)
  - Other 4/28 (14%)



Van Oekelen et al IMW, 2021

Post-CAR T Salvage Treatments & Duration of Response



Van Oekelen et al IMW, 2021

Durable Responses After Relapse on BCMA-Targeted CAR T

- 33 occurrences of **responses > 120 days (range 128-555 days)** at various treatment lines post-relapse

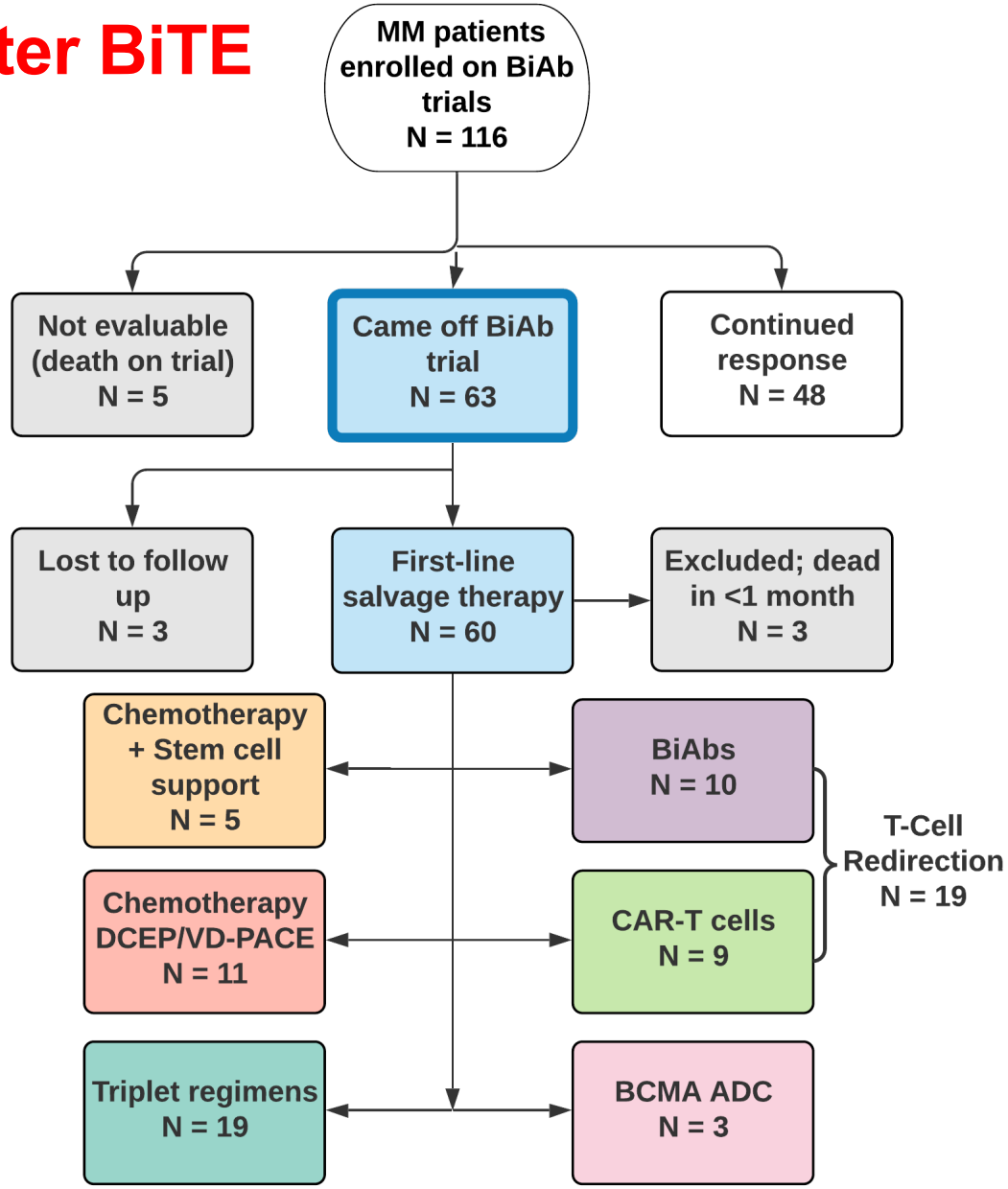
- **Durable response treatment regimens:**
  - Chemo + stem cell support N = 8
  - **Bispecific antibodies** (incl. BCMA-targeted) N = 8
  - Selinexor + doublet N = 5
  - MAPK inhibition ± other N = 3

Van Oekelen et al IMW, 2021

Initials Salvage Therapy for MM Relapse after BiTE

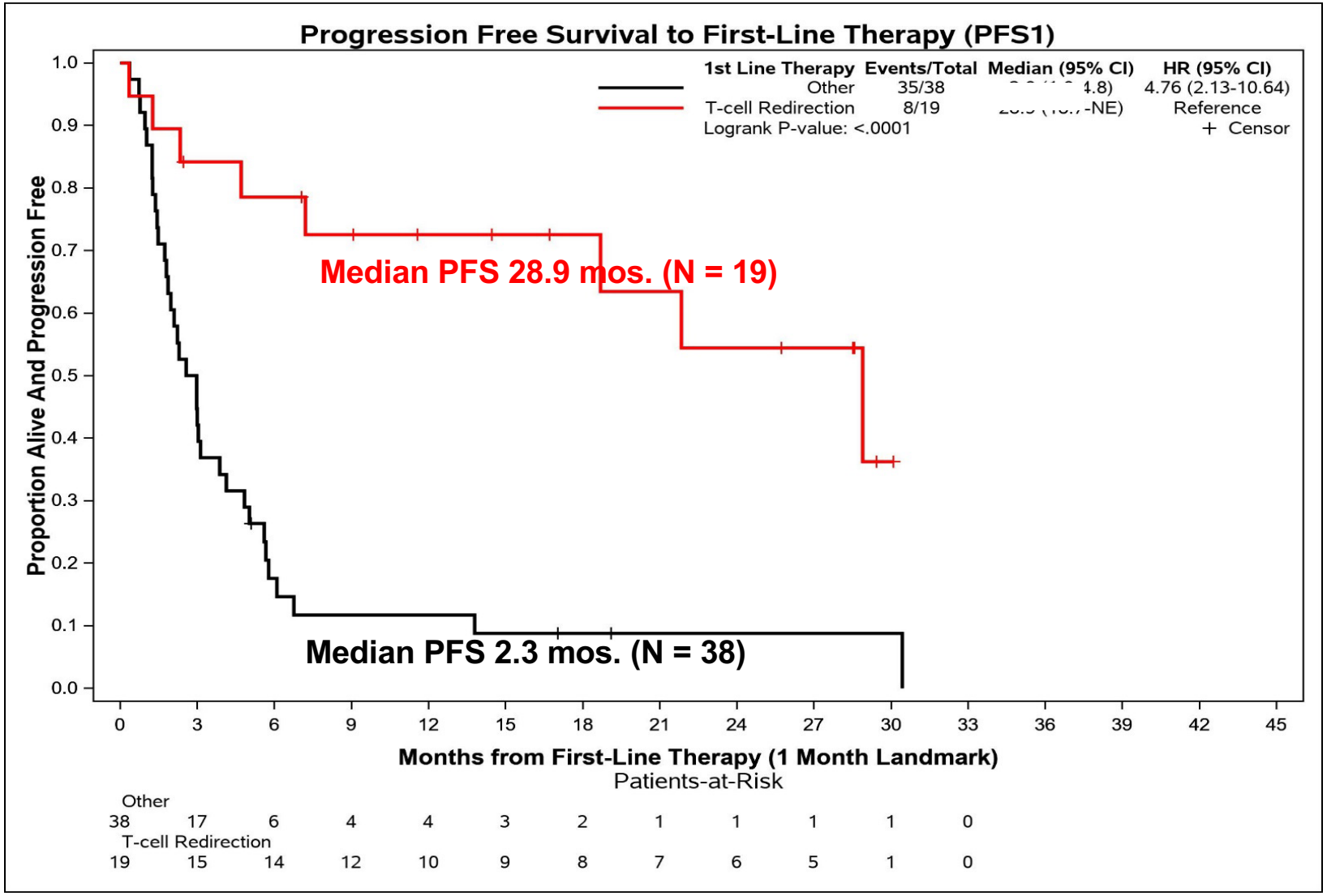
- 60 patients received salvage therapy
- 3 patients excluded due to death in <1 month
- Median of 2 lines after BiAb trial (range: 1-9)
- Followed up for a median of **28.5 mos.** **(range 1.7 – 44)**

- Initial salvage therapy:
  - **T-cell redirection:** **19/57** **(33%)**
  - Triplet regimens: 19/57 (33%)
    - Anti-CD38, Selinexor, or Venetoclax-based combinations
  - DCEP+/-V or VD(T)-PACE: 11/57 (19%)
  - Chemo + Stem cell support: 5/57 (9%)
  - BCMA ADC: 3/57 (5%)



Mouhieddine et al ASH 2021

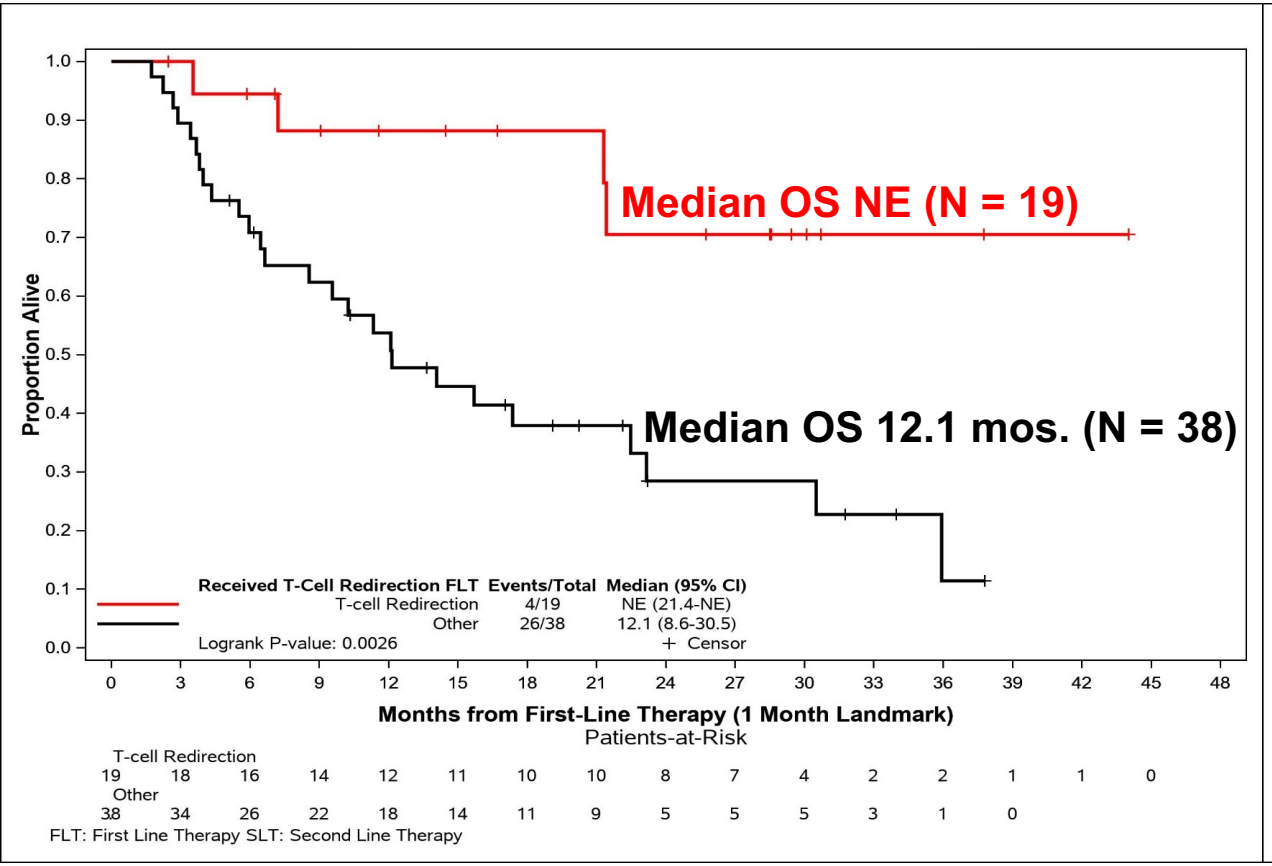
PFS of Patients Receiving T-cell Redirecting vs. Non-Redirecting Therapy of Relapsed MM After BiTE Therapy



Mouhieddine et al ASH 2021

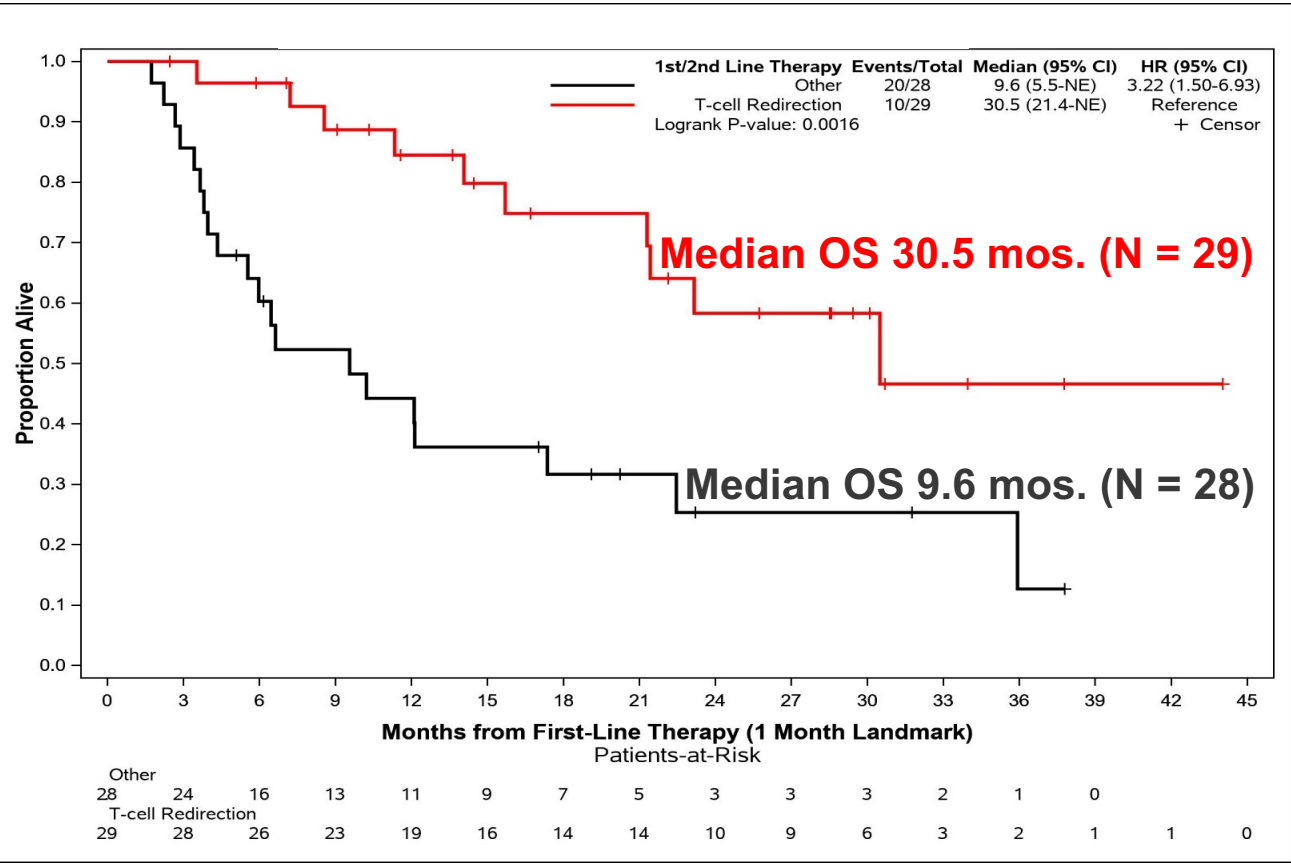
OS of Patients with Relapsed MM After BiTE Who Received T-cell Redirecting vs. Non-Redirecting Therapy as First or Second Salvage

First Salvage Therapy

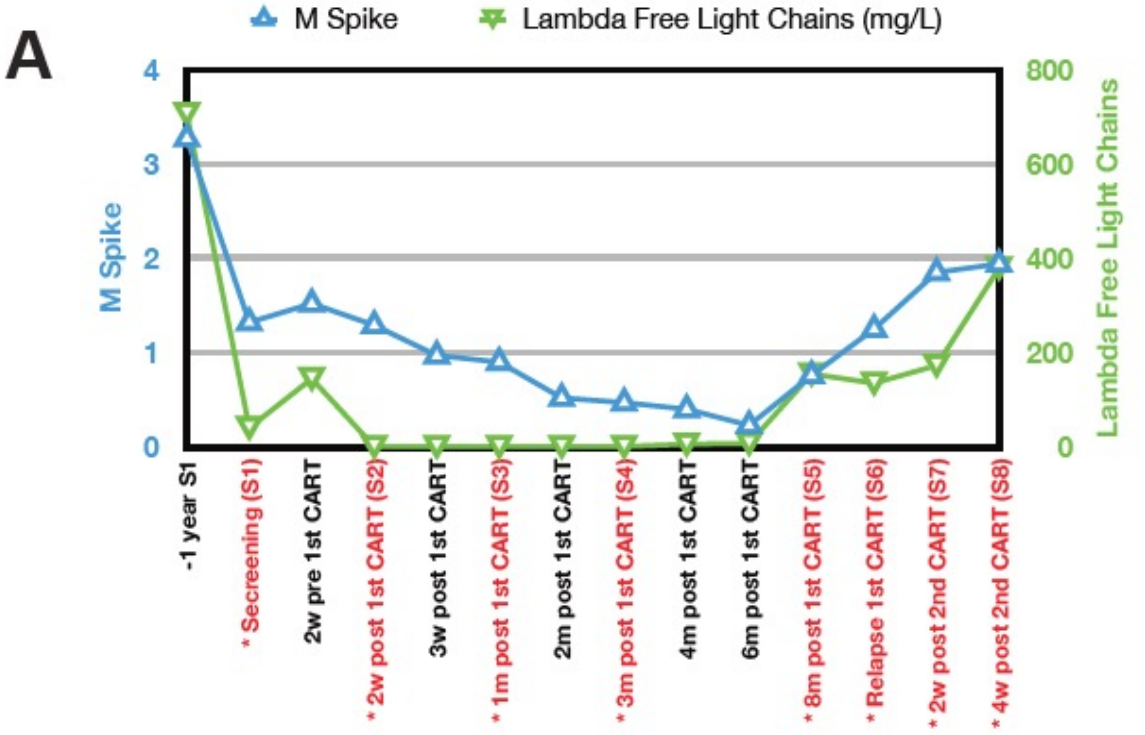


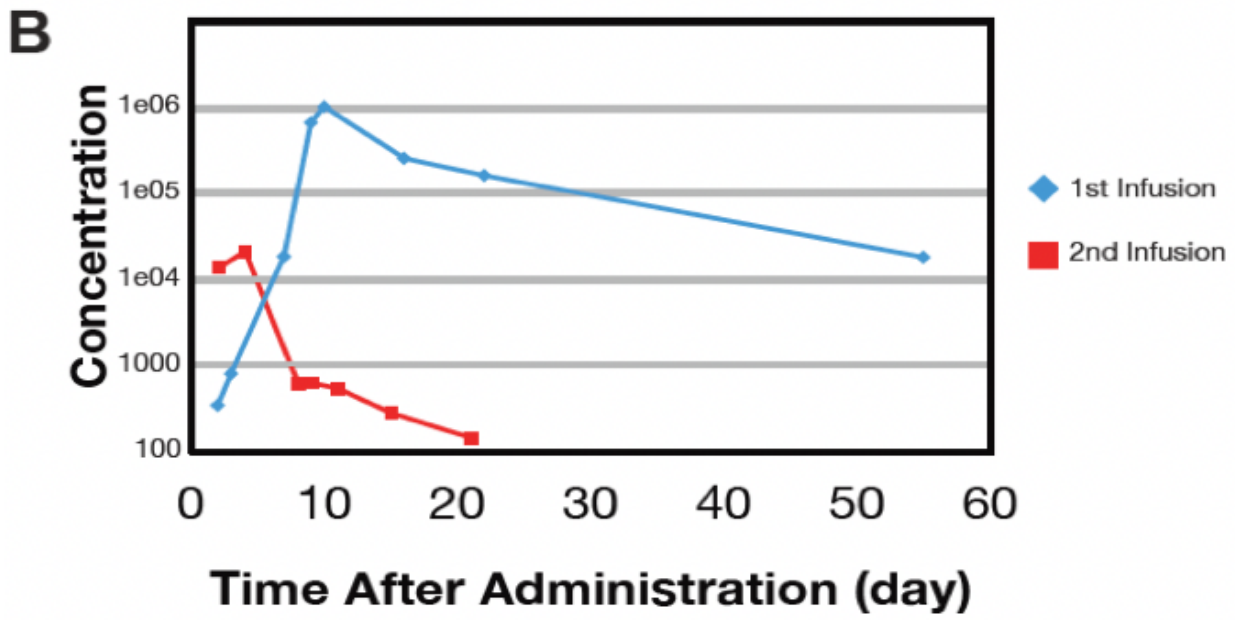
FLT: First Line Therapy SLT: Second Line Therapy

Second Salvage Therapy



Biallelic BCMA Loss Confers Resistance to BCMA CAR T Cells



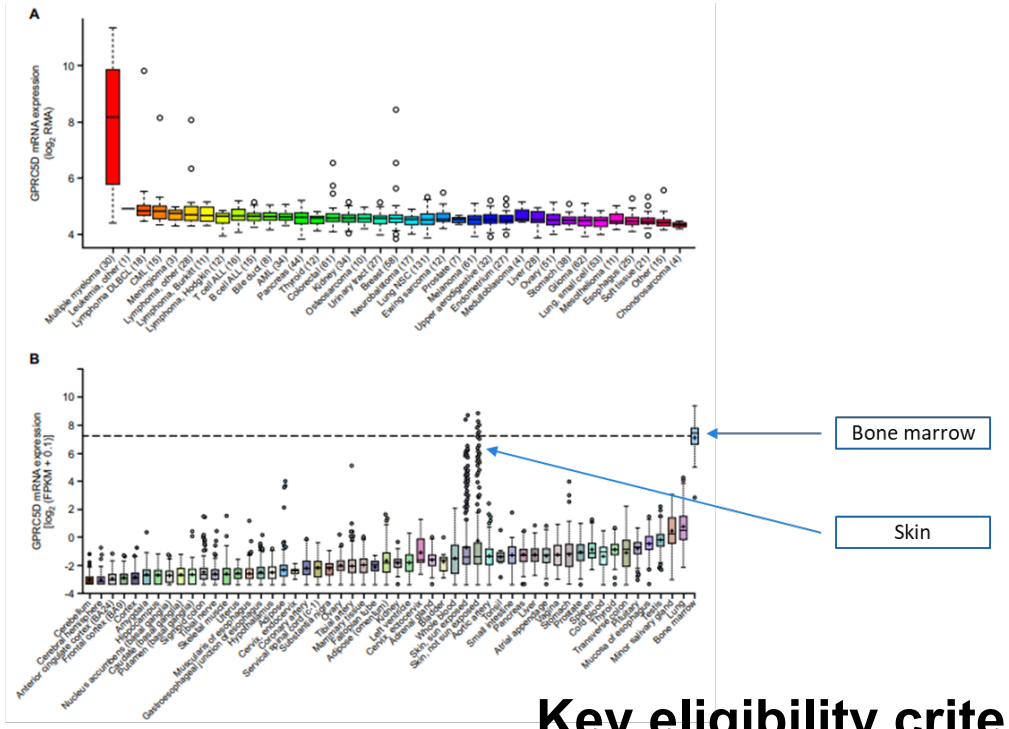


BCMA on 16p: should we be screening patients before BCMA therapy?

Dual targeting to avoid resistance: GPRC5D, CD19, FcHR5, CD38, CD138, SLAMF-7

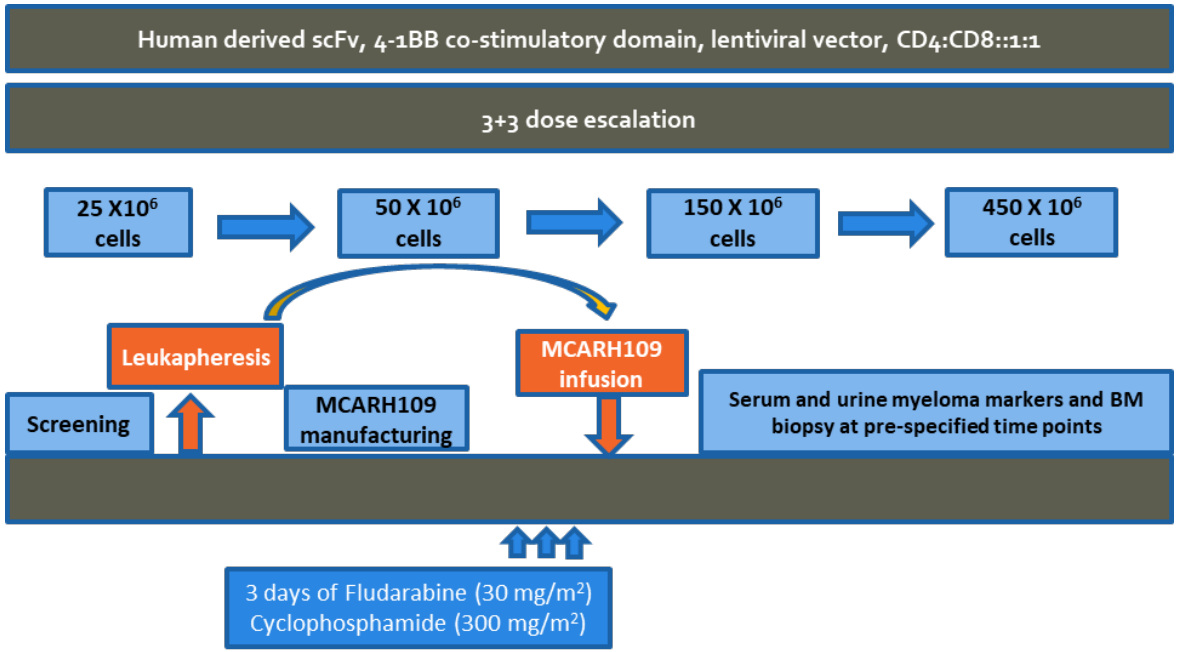
Samur et al Nat Comm 2021; 12: 868

Phase I First-in-Class Trial of MCARH109, a G Protein Coupled Receptor Class C Group 5 Member D (GPRC5D) Targeted CAR T Cell Therapy in Relapsed or Refractory Multiple Myeloma



Smith EL. et al. Science Translational Medicine 2019

Study Design



Key eligibility criteria:

- 3 or more lines of therapy; Prior PI, ImiD, CD38 antibody-based therapy
- Prior BCMA and CART allowed; Non-secretory myeloma allowed

Mailankody et al ASH 2021

GPRC5D Targeted CAR T Cell Therapy in RR Multiple Myeloma (N=16)

Response	25 X10^6 CAR+ T cells (n=3)	50 X10^6 CAR+ T cells (n=3)	150 X10^6 CAR+ T cells (n=5)	450 X10^6 CAR+ T cells (n=5)	Total (N=16)
PR or better, n (%)	1 (33)	3 (100)	2 (40)	5 (100)	11 (69)
VGPR or better, n (%)	1 (33)	2 (67)	0 (0)	4 (80)	7 (44)
CR or better (%)	0 (0)	1 (33)	0 (0)	3 (60)	4 (25)
MRD negativity, n (%)	2 (67)	2 (67)	2 (40)	2 (50)	8 (50)

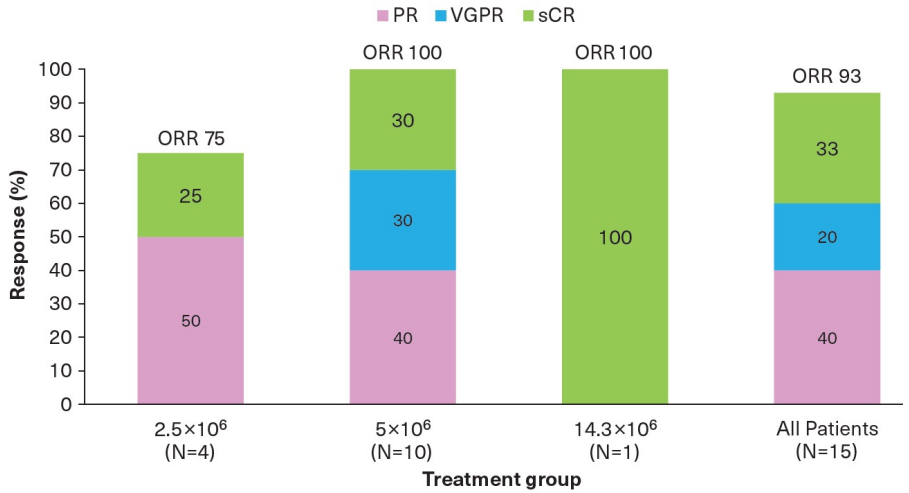
Response	Prior BCMA therapy (n=10)	Prior CAR T therapy (n=8)
Partial Response or better, n (%)	8 (80)	6 (75)
Complete Response or better	3 (30)	3 (38)
BM MRD negativity*, n (%)	5 (50)	2 (25)

Mailankody et al ASH 2021

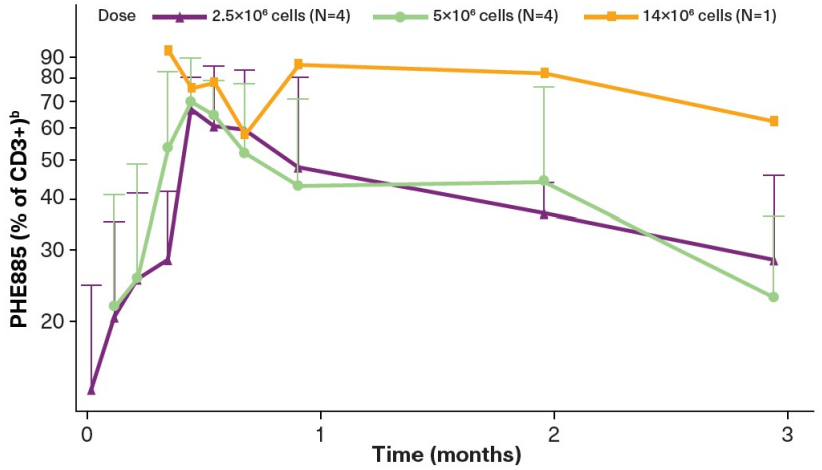
Phase I Study of PHE885, a Fully Human BCMA-Directed CAR-T Cell Therapy for Relapsed/Refractory Multiple Myeloma Manufactured in <2 Days Using the T-Charge™ Platform

- **Anti-BCMA CAR-T cells PHE885 is manufactured using the T-Charge™ platform, which reduces ex vivo culture time to about 24 hours and takes <2 days to manufacture the final product, thereby relying entirely on in vivo expansion after CAR-T cell infusion**

Figure 2. Summary of Tumor Response by ORR[a]

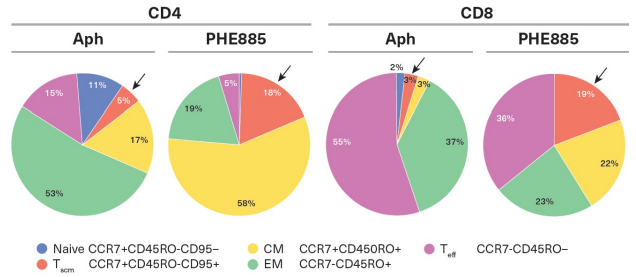


Cellular Kinetics of PHE885 by Flow Cytometry



T-Charge™ Process Preserves T-Cell Stemness in Final Product

Figure 6. PHE885 Product Stemness

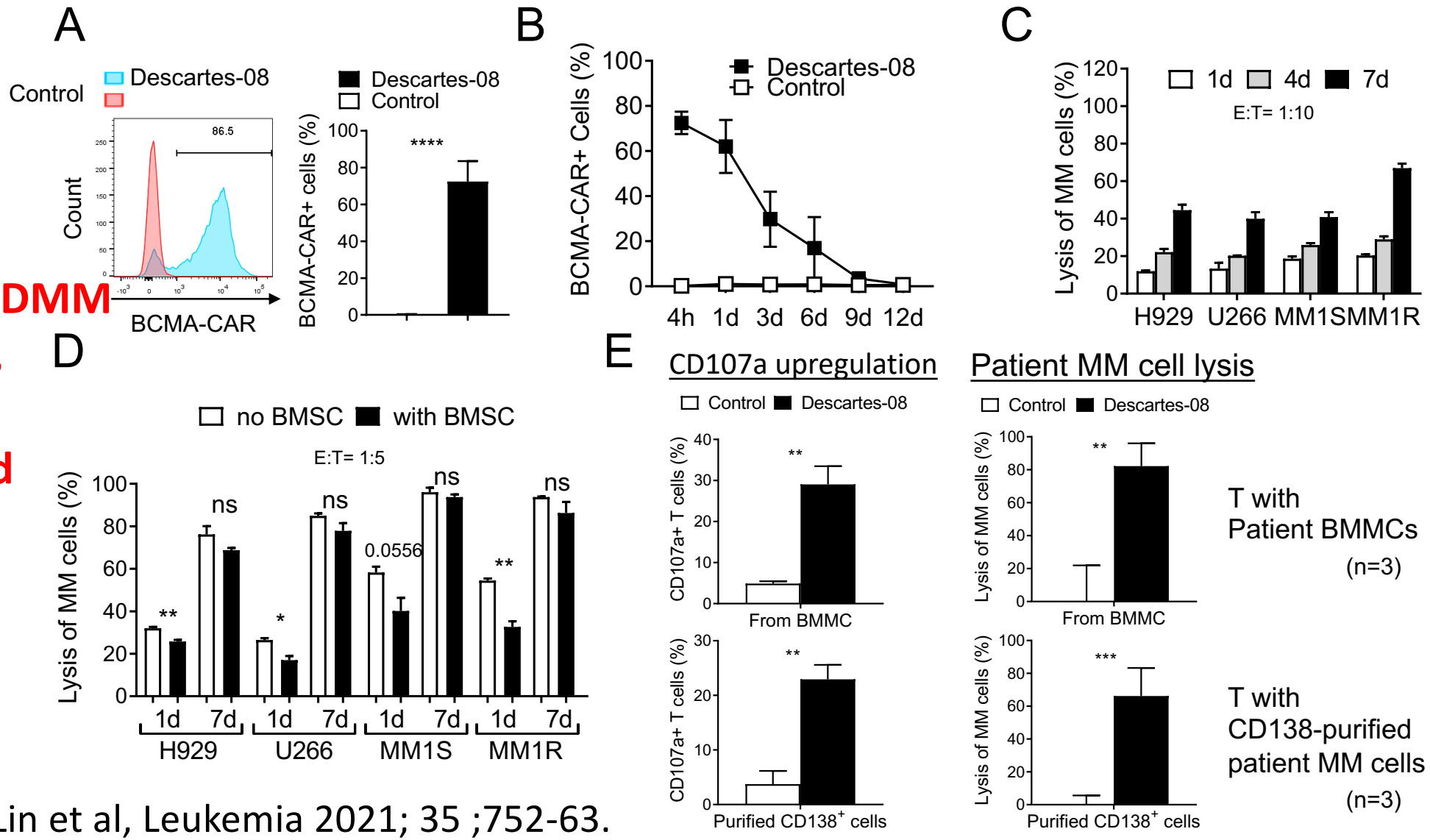


- **A Shift Toward Naive/Tscm Phenotype Is Observed in Patients Following PHE885 Treatment**
- **A shift to Tscm/Tnaive population in both CD4 and CD8 T cells in the >VGPR group but not PD group**

Sperling et al ASH 2021, EHA 2022.

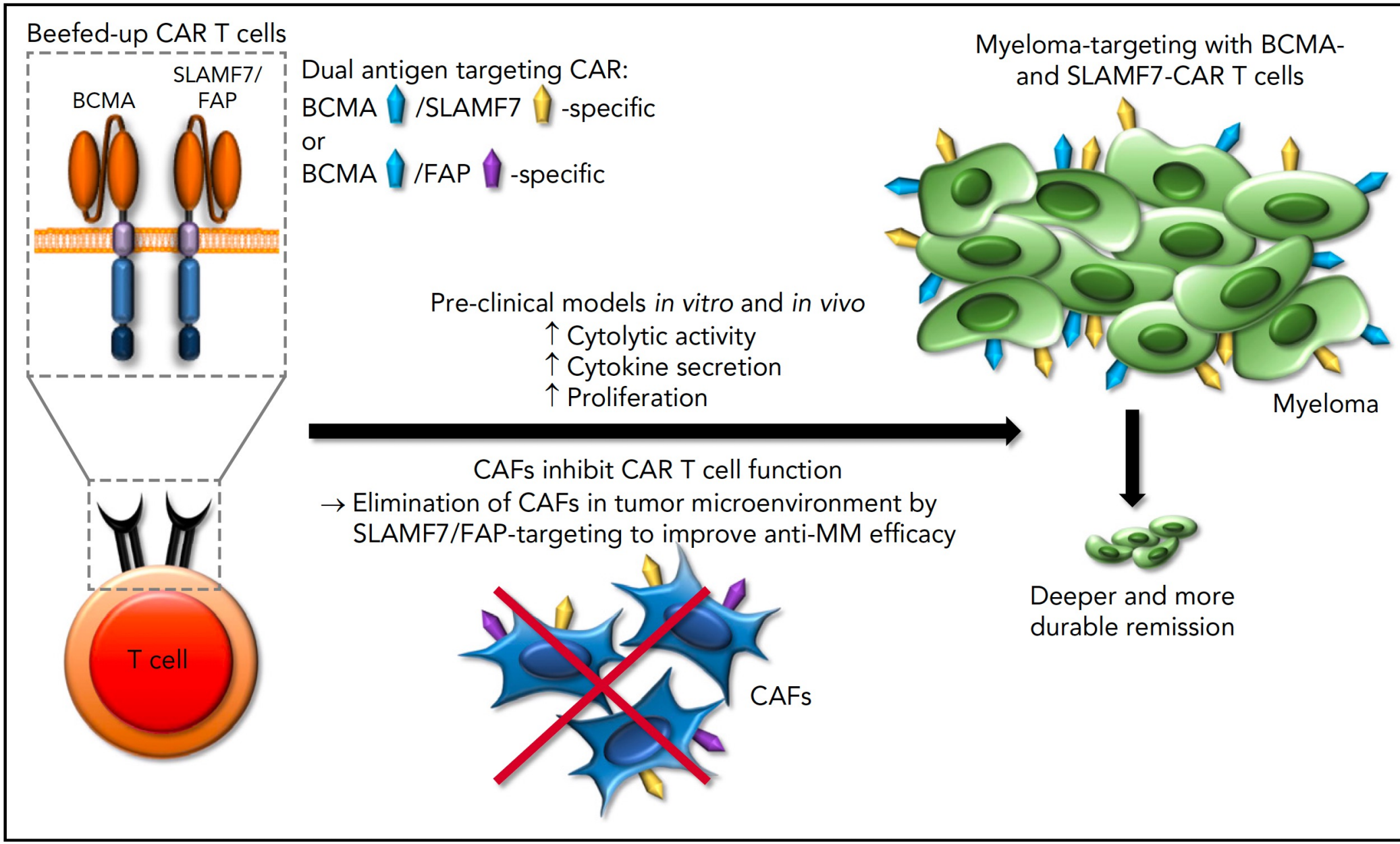
Transiently Active Anti-BCMA mRNA-Electroporated CD8+ CAR T-Cells (Descartes-08) for MM

Trial in NDMM
Ongoing,
No CRS,
Repeated
Doses



Lin et al, Leukemia 2021; 35 ;752-63.

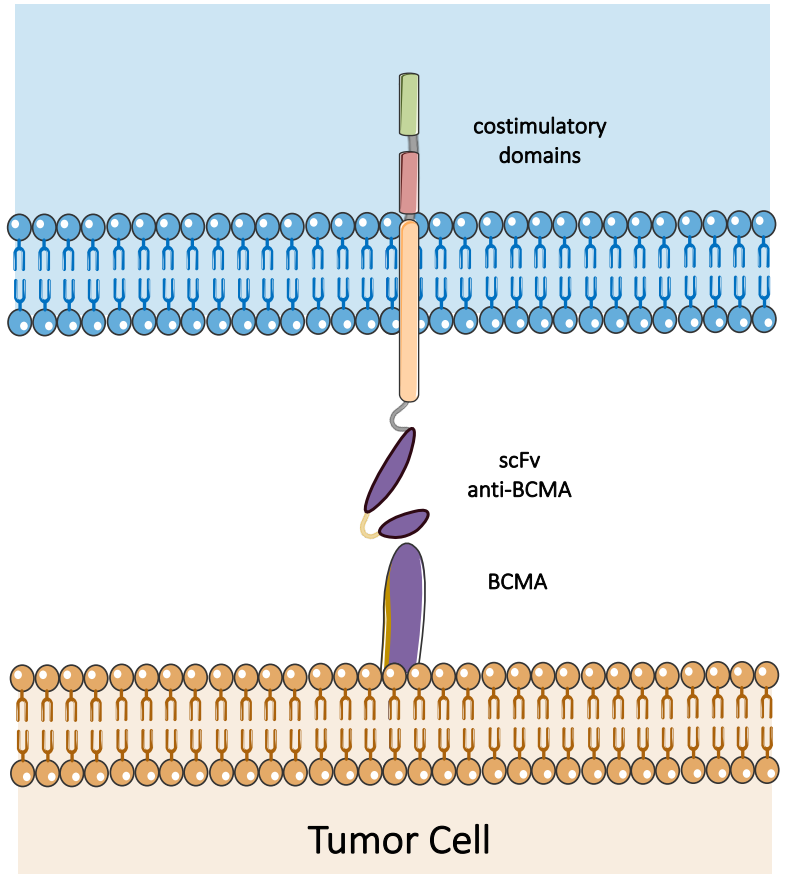
Dual CAR T Cells Targeting Myeloma and the Microenvironment



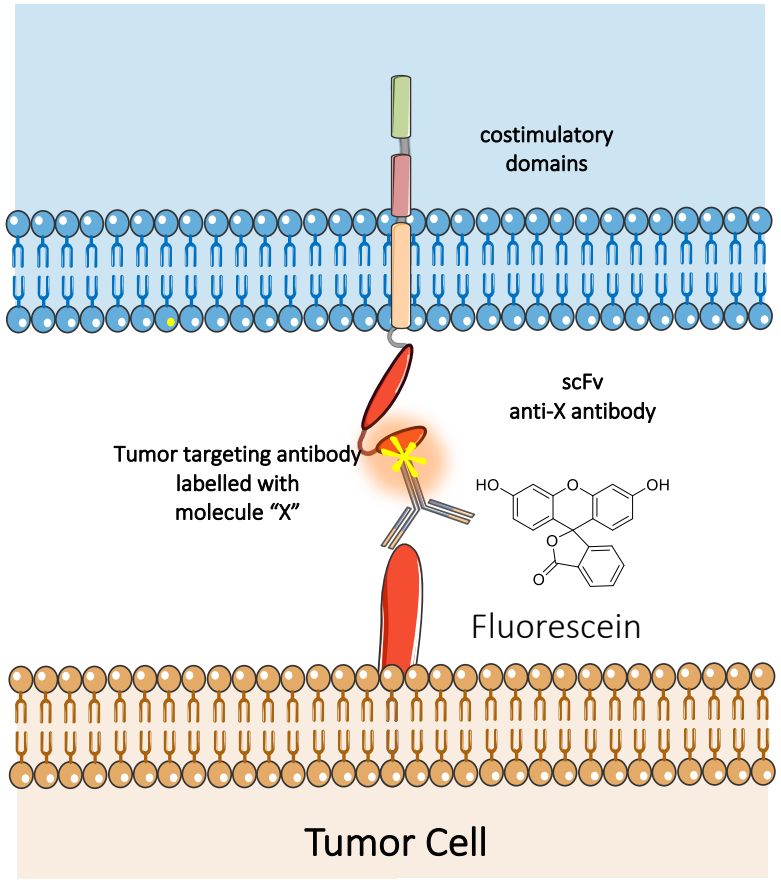
Sakemura et al Blood 2022; 139: 3708-21; Hudecek and Einsele. Blood 2022; 139: 3671-2.

BAT-CAR: Binary Activated T Cell with Chimeric Antigen Receptor

Traditional (Direct) CAR-T cell



Indirect CAR-T cell



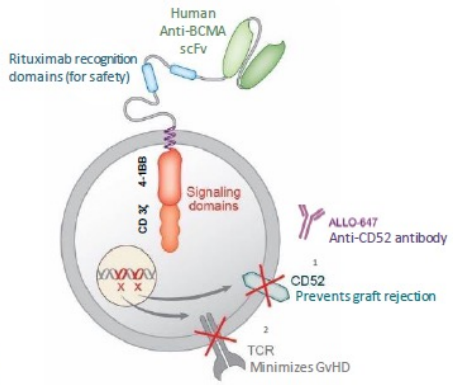
Titratability to improve therapeutic window

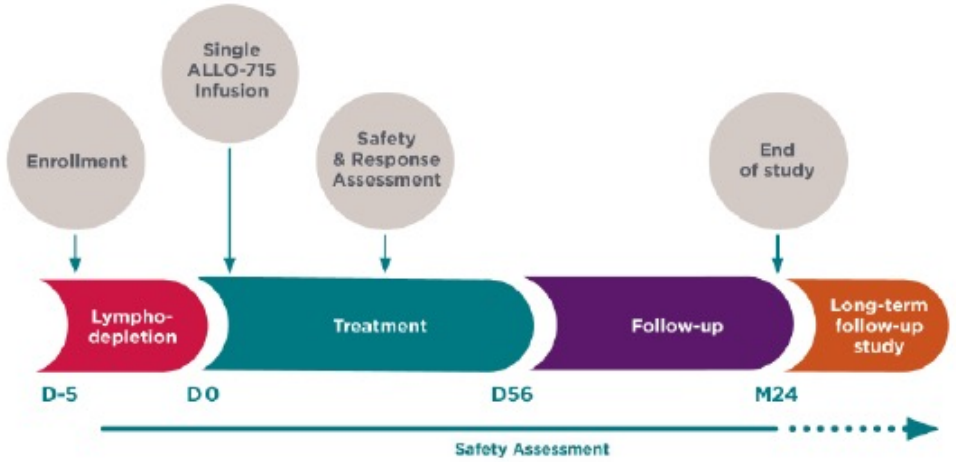
Multiplexability to expand use of existing targets

Redundancy to prevent antigen escape

Alberto Nobili, PhD and Carl Novina, MD PhD.

Phase 1 Data Validates the Feasibility of Allogeneic Anti-BCMA ALLO-715 Therapy for Relapsed/Refractory Multiple Myeloma





ALLO-715 Dose Escalation: 40, 160, 320, 480 x 10^6 CAR+ T cells	
Lymphodepletion Regimens (FCA, CA†)**	**Doses**
Fludarabine	30 mg/m²/day x 3 days
Cyclophosphamide	300 mg/m²/day x 3 days
ALLO-647	13 to 30 mg x 3 days

Cell Dose & LD Regimen	DL3 (320M CAR+ T Cells)*				DL4 (480M CAR+ T Cells)	
	FCA39 N=11	FCA60 N=10	FCA90 N=3	FCA ALL N=24	FCA39 N=3	FCA60 N=3
ORR†, n (%) (95% CI)	7 (64) (31, 89)	8 (80) (44, 98)	2 (67) (9, 99)	17 (71) (49, 87)	1 (33) (0.8, 91)	2 (67) (9, 99)
VGPR+ Rate, n (%)	5 (46)	5 (50)	1 (33)	11 (46)	0	2 (67)
CR/sCR Rate, n (%)	3 (27)	3 (30)	0	6 (25)	0	0
mDOR, months (95% CI)	8.3 (3.4, 11.3)	NE (5.6, NE)	3.1 (2.4, 3.1)	8.3 (3.4, 11.3)	1.4 (NE, NE)	NE (1.5, NE)

TEAE of Interest* (N=43)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	All Grades
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Cytokine Release Syndrome	13 (30)	10 (23)	1 (2)	0	0	24 (56)
Neurotoxicity†	4 (9)	2 (5)	0	0	0	6 (14)
Graft-versus-Host Disease	0	0	0	0	0	0
Infection‡	3 (7)	10 (23)	7 (16)	0	3 (7)	23 (54)
Infusion Reaction to ALLO-647	7 (16)	5 (12)	0	0	0	12 (28)

11 (46%) were VGPR+, of those 6 (25%) were CR/sCR

Mailankody et al ASH 2021

Advantages of NK Cells over T-Cells for CAR Therapy

CAR-T

- Autologous Product
  - Production time
  - Cost
  - 1 patient, 1 product
  - Autologous immune cells in cancer patients can be dysfunctional
- If allogeneic: GVHD Risk
- Toxicity: cytokine release syndrome; neurotoxicity (50% need ICU care)
- Currently available only at select institutions around the country
- CAR-mediated killing

CAR-NK

- Allogeneic Product
  - “Off the shelf”
  - Potential low cost
  - 1 cord, > 100 doses
  - Functionally active
- Low/absent GVHD
- Low toxicity -> increased availability
- CAR + NK Receptor mediated

Talquetamab GPRC5D Bispecific T cell Engager

405ug/kg and 800ug/kg cohorts

ORR 70% and 64%; VGPR 57% and 52%

Infections: 47% and 34%, grade ¾ 7% and 9%

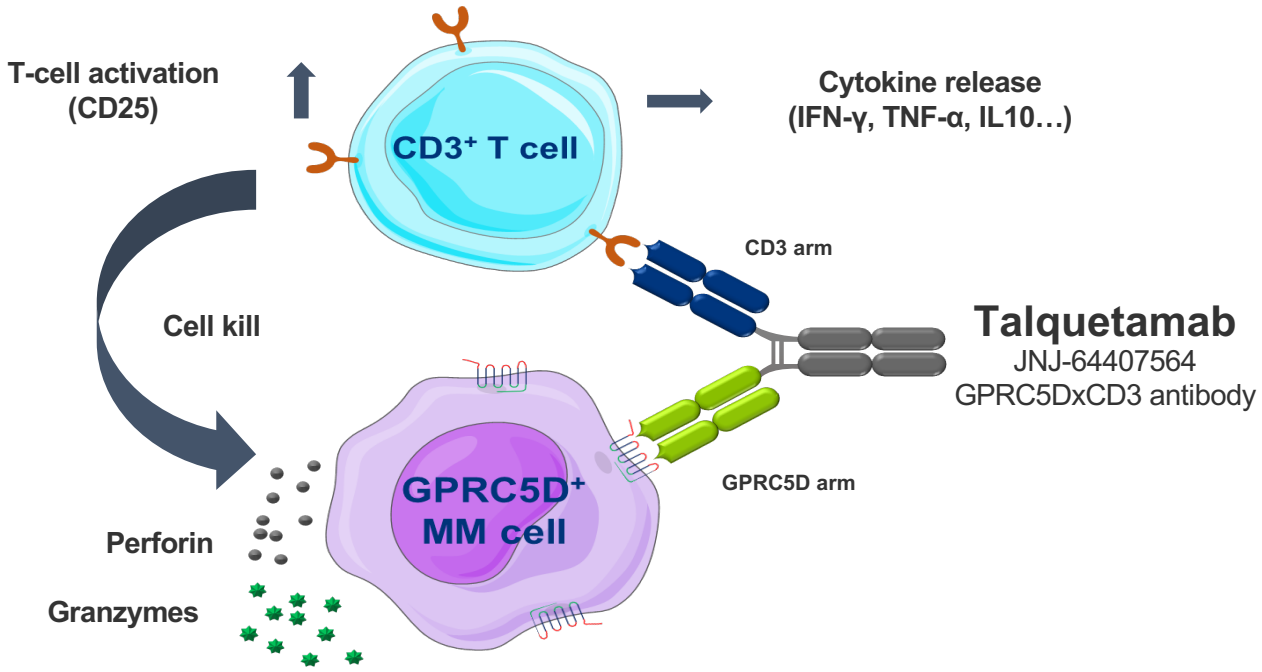
CRS 77% and 80%, grade 3: 3% and 0%

Skin and nails: 83% and 75%

Dysgeusia 63% and 57%

Minnema et al ASCO 2022

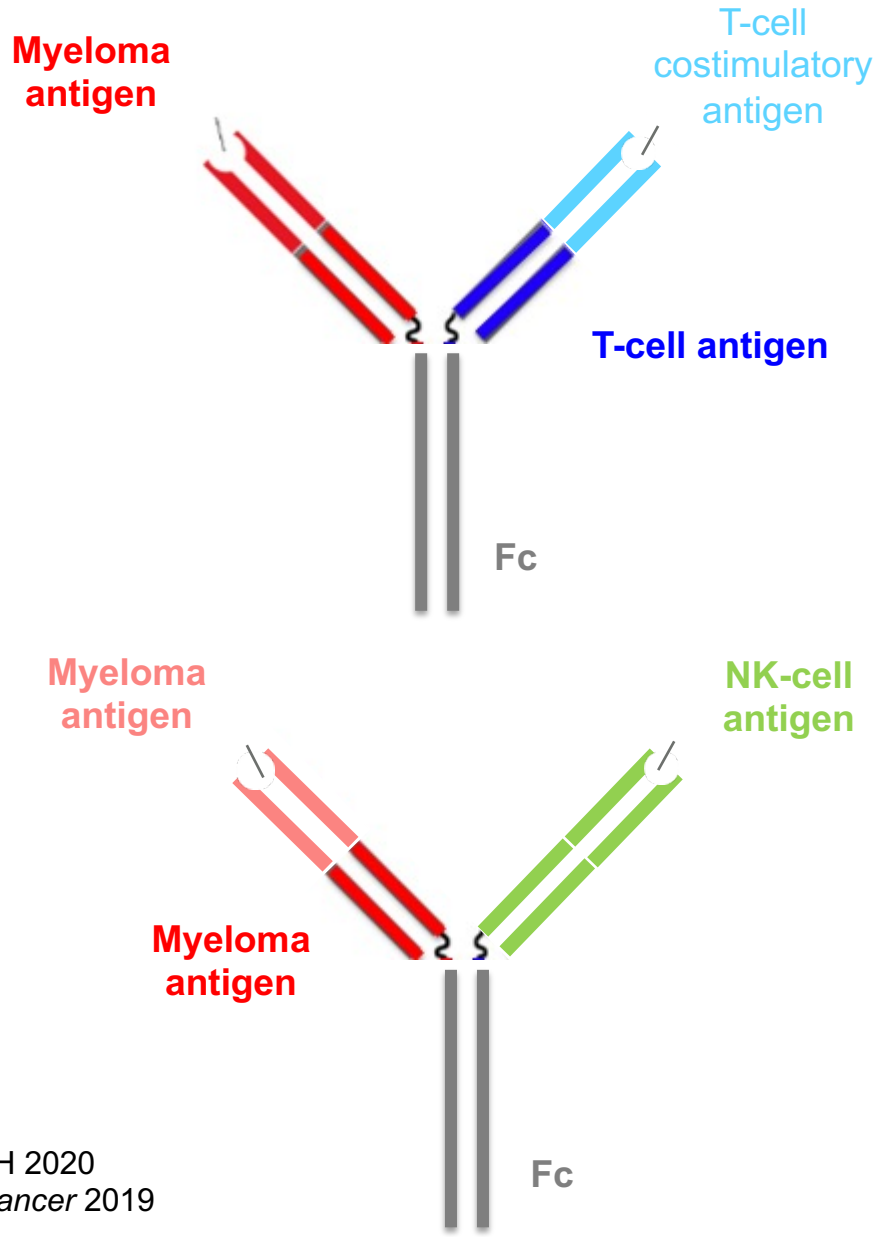
Talquetamab GPRC5D BiTE and Daratumumab



- **Talquetamab, binds to GPRC5D and CD3, well tolerated in heavily pretreated patients with RRMM, with at efficacy and safety 800 µg/kg SC Q2W or 405 µg/kg SC QW dosing**
- **QW or Q2W doses of talquetamab: 60-70% ORR in triple-class and penta-refractory patients (30% prior BCMA therapy) Responses were durable and deepened over time**
- **The combination of talquetamab + daratumumab appears tolerable, with ORR (77–85%) in these heavily pretreated patients/ Responses were observed in both CD38–exposed and –refractory patients**

Krishnan et al, Chari et al ASH 2021

Trispecific Antibodies



- Still in pre-clinical stages of development
- **With bispecifics, absence of T cell co-stimulation may increase likelihood of anergy and suboptimal anti-tumor response**
- A **trispecific T cell engager** targeting CD38, CD3, and CD28 (co-stimulatory protein on T-cells)
  - very potent killing of CD38+ MM cell lines, 3- to 4-log higher than daratumumab
  - suppressed MM growth in mice and promoted proliferation of memory and effector T-cells and downregulation of regulatory T-cells in primates
- **Trispecific NK cell engagers** also being developed targeting CD16A on NK cell as well as BCMA and CD200 on MM cells

Lancman, et al. ASH 2020
Wu, et al. *Nature Cancer* 2019

Future Directions

Combination PI, IMiD, Dex, CD38MoAb will achieve high rates MRD negativity in NDMM, including high risk MM

CARs and BiTEs will then be used to induce long term MRD negative responses associated with memory anti-MM immunity.

Long term disease-free survival and potential cure of MM will be achieved with combination targeted and immune therapies to both achieve MRD negativity and restore host memory anti-MM immunity.

These patients will then be free of disease and off all therapy..

“Cure is Growing Old and Dying from Something Else”

Francesca Thompson, MD
1986

1980-2000	Stem cell transplantation
2000-2020	Novel Agents
2020-present	Immune Agents