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MCW 2025 Controversies in Hematologic Malignancies Symposium

Multiple Myeloma Immunotherapies – Targets, Timing, Sequencing, Reusing

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Disclosures

- Research funding: Johnson & Johnson, CRISPR Therapeutics, Novartis
- Consultancies: Johnson & Johnson, Gracell, Abbvie, Regeneron, BMS, Smart Immune, Novartis
- IDMC Membership: Johnson & Johnson
- Intellectual property: Patents and patent applications in field of cellular immunotherapy

Outline

- What we do now and why?
  - CAR T cells: how early?
  - Sequencing of CAR T cells, bispecific antibodies, and targets

- Where are we going?
  - Role for belantamab
  - Fixed-duration bispecific antibody therapy
  - New agents (trispecifics, anito-cel, etc)
  - Ongoing first- and early-line trials

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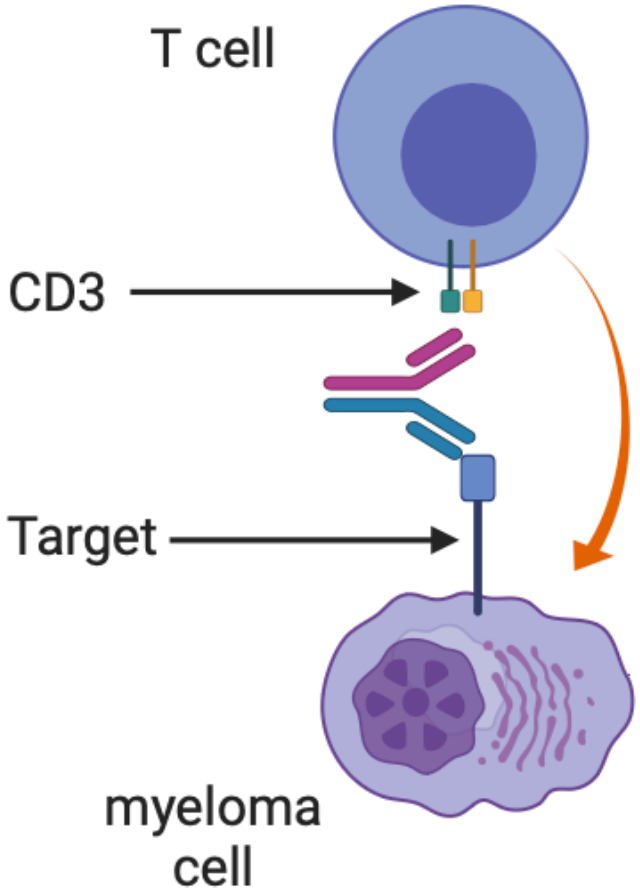
Bispecific Antibody

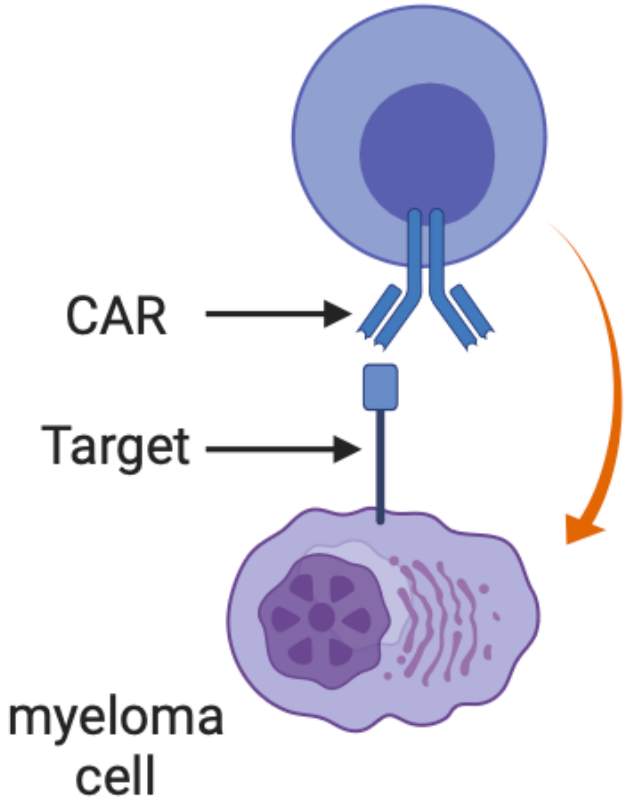
BCMA
Teclistamab*
Elranatamab*
Limvoseltamab
Alnuctamab
ABBV-383

GPRC5D
Talquetamab*
Forimtamig

FCRH5
Cevostamab



CAR T Cell



BCMA
Ide-cel*
Cilta-cel*
PHE-885
BMS-986354
GC012F
ALLO-715
CART-ddBCMA

GPRC5D
BMS-986393
MCARH109

*Therapies with marketing authorization

Image created with BioRender

Phase 1/2 single-arm studies of FDA-approved agents

	Indication	ORR	PFS/DOR	Toxicity

Ide-cel[1]	FDA/NCCN:
	2+ prior lines
		73%
		(67% ITT)
			8.8 m
			10.7 m
				• CRS/neurotoxicity (potentially severe)
				  • ICANS
				  • Others (Parkinsonism, CN palsy)
				• Infections
				• Cytopenias (potentially severe)
				• Misc (enterocolitis, other autoimmune)

Cilta-cel[2,3]	FDA/NCCN: 1+ prior lines	97% (83% ITT)	34.9 m 33.9 m	
Teclistamab[4,5]	FDA: 4+ prior lines of therapy NCCN: 4+ prior therapies	63%	12.5 m 24 m	• CRS/NT (unlikely severe) • Infection risk (perhaps higher) • Cytopenias (unlikely severe)
Elranatamab[6]		61%	~15 m NR	
Talquetamab[7,8]		~72%	~12m NR	• Oral/taste toxicity (potentially severe) • Skin and nail toxicity

[1]Munshi et al., N Engl J Med 2021; 384:705-716
[2]Berdeja et al., Lancet; 398(10297):314-324
[3]Lin et al., ASCO 2023 abstract 8009
[4]Moreau et al. N Engl J Med 2022; 387:495-505
[5]van de Donk et al., ASCO 2023 abstract 8011
[6]Lesokhin et al., Nat Med, 29:2259–2267 (2023)
[7]Chari et al., NEJM 2022
[8]Schinke et al., ASCO 2023 #8036

Real-world outcomes with cilta-cel

Report from US Myeloma Immunotherapy Consortium

	RWE Cilta-cel (N=236)	CARTITUDE-1 (N=97)[1]
Age, median (range)	64 y (30-84)	61 y (56-68)
Age ≥ 70 years	62 (26%)	-
Race: Black	26 (11%)	17 (18%)
Ethnicity: Hispanic	19 (8%)	6 (6%)
ECOG PS, 0-1	183 (89%)	93 (96%)
High-risk cytogenetics*	81 (39%)	23 (24%)
R-ISS stage III	30 (19%)	ISS-3:14 (14%)
Extramedullary Disease**	60 (26%)	13 (13%)
BM Plasma cells ≥ 50%	35 (18%)	≥ 60%= 21 (22%)
H/o plasma Cell Leukemia	13 (6%)	0
H/o AL amyloidosis	8 (3%)	0

*High-risk cytogenetics: Del 17p, t(14;16), t(4;14)
**EMD included patients with plasmacytomas non-contiguous from bone lesions

	RWE Cilta-cel (N=236)	CARTITUDE-1 (N=97)[1]
Prior Lines of Therapy	6 (2-18)	6 (4-8)
Prior Auto SCT	200 (85%)	87 (90%)
Triple Class Refractory	163 (69%)	85 (88%)
Penta Drug refractory	70 (30%)	41 (42%)
Prior BCMA Therapy	33 (14%)	0%
Bridging Therapy	184 (78%)	73 (75%)
PR (≥ 50%) to Bridging	44 (27%)	15 (21%)
Elevated baseline ferritin > 400 ng/mL	82 (35%)	-
Flu/Cy Lymphodepletion	191 (81%)***	97 (100%)

*** Alternate lymphodepletion, bendamustine: 31(13%), cladribine + cyclophosphamide: 6 (3%); cyclophosphamide alone: 7 (3%), NA:1

Sidana et al., IMS 2024; Blood 2024 (https://doi.org/10.1182/blood.2024025945)

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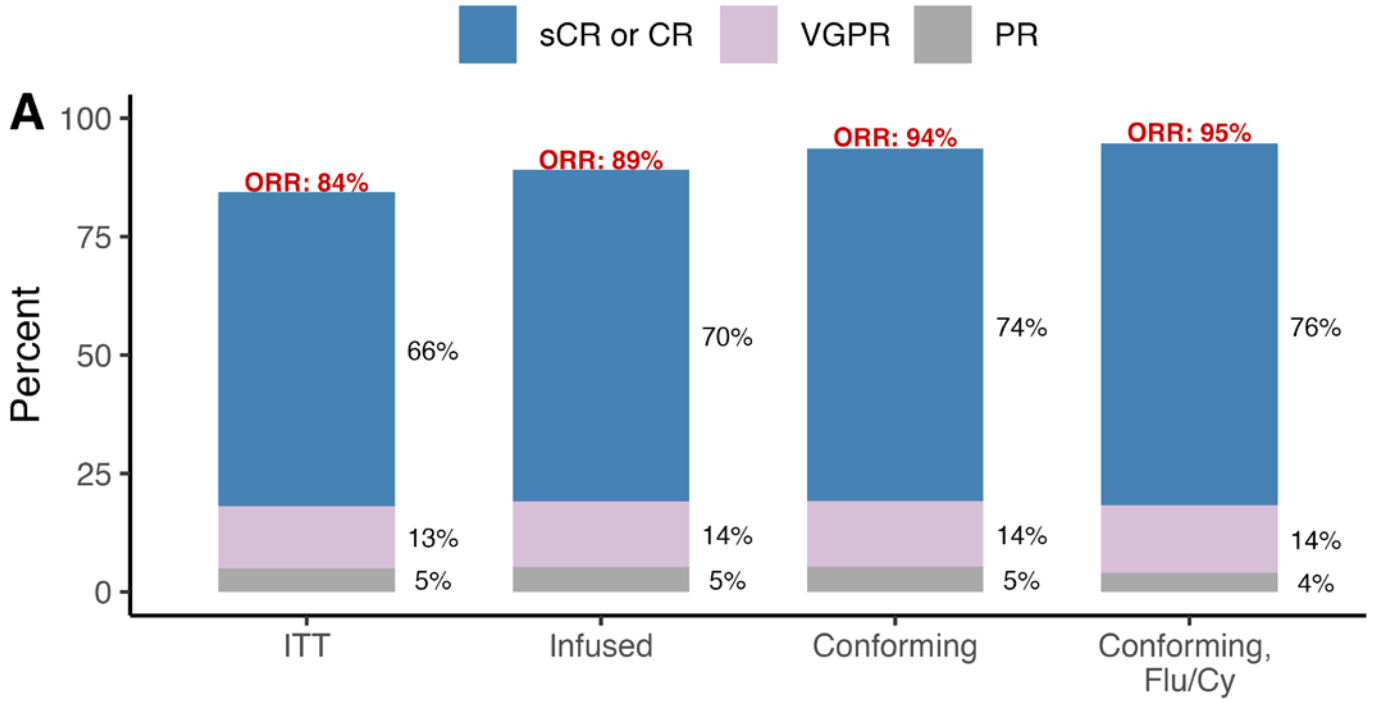
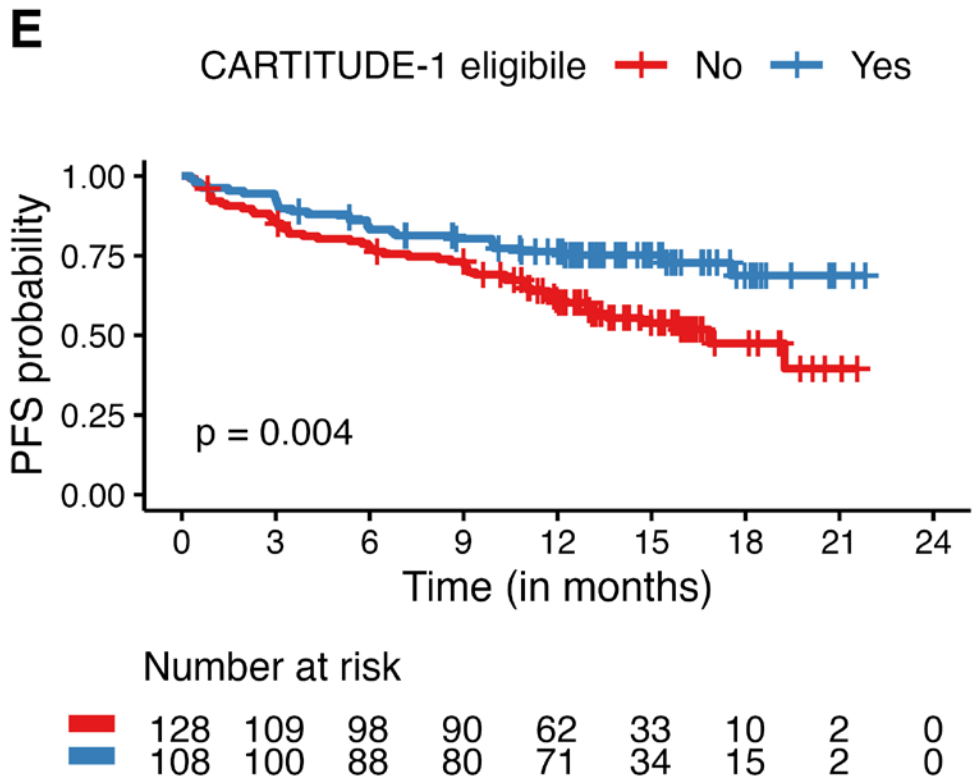
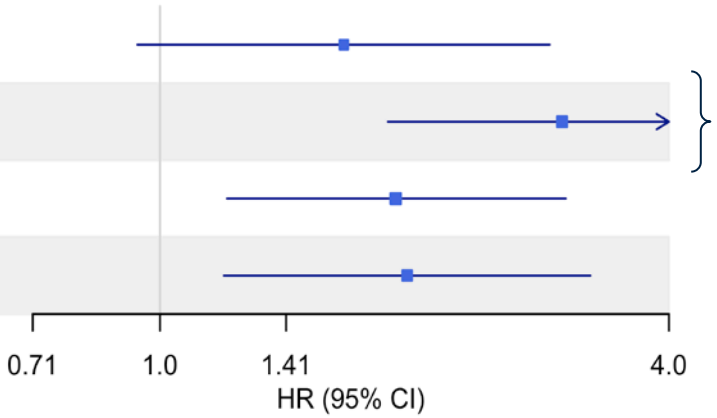




Multivariable analysis for PFS

Variable	HR (95% CI)	P-value
Prior BCMA-TT (Yes vs. No)	1.65 (0.94, 2.89)	0.08
Ferritin (≥ 400 vs. < 400 ng/mL)	2.99 (1.86, 4.80)	<0.001
High-risk cytogenetics (Yes vs. No)	1.90 (1.20, 3.02)	0.006
Extramedullary disease (Yes vs. No)	1.96 (1.19, 3.23)	0.009



ORR 95% vs 78%
High-grade CRS: OR 2.0 (p=0.04)

Sidana et al., IMS 2024; Blood 2024 (https://doi.org/10.1182/blood.2024025945)

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Real-world outcomes with cilta-cel

Report from US Myeloma Immunotherapy Consortium

	Real-world N=236	CARTITUDE-1 [1-2] N=97
CRS - Any grade Grade ≥ 3	177 (75%) 12 (5%)	95% 4%
Median time to onset of CRS	7 days (0-14)	
ICANS – Any grade Grade ≥ 3	32 (14%) 9 (4%)	17% 2%
Delayed neurotoxicity Parkinsonism Cranial nerve palsy Others	24 (10%) 5 (2%) 11 (5%) 8	12 (12%) 5 (5%) 1 (1%) 6 (6%)
IEC-HS/HLH	5 (2%)	~1%
Severe infections	49 (21%)	20%

Other delayed NT: Diplopia in 4, posterior reversible encephalopathy syndrome (PRES) in 2, dysautonomia in 1 patient, and polyneuropathy in 1 patient

	Real-world N=236
Non-relapse mortality (NRM)	**23 (10%)**
• Infections • CRS • CRS and infection • Delayed neurotoxicity • IEC-HS • ICANS • SPM	12 3 1 3 2 1 1
SPMs	**20 (8.5%)**
Excl. non-melanoma skin cancer	13 (5.5%)
Myeloid neoplasm/acute leukemia	3 (1.3%)
T cell lymphoma	1

Sidana et al., IMS 2024; Blood 2024 (https://doi.org/10.1182/blood.2024025945)

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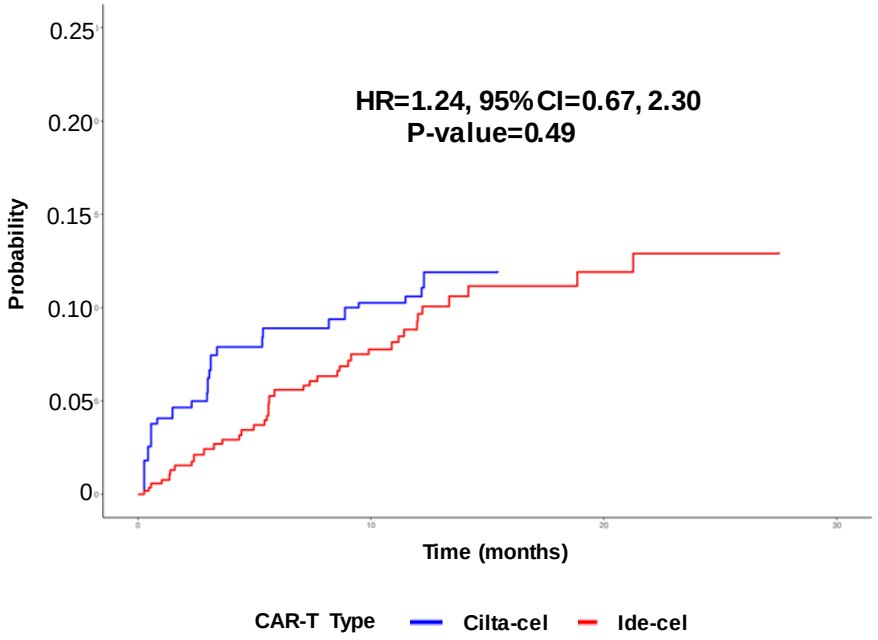
Ide-cel vs cilta-cel real-world comparison
(propensity-score matching from US Myeloma Immunotherapy Consortium)

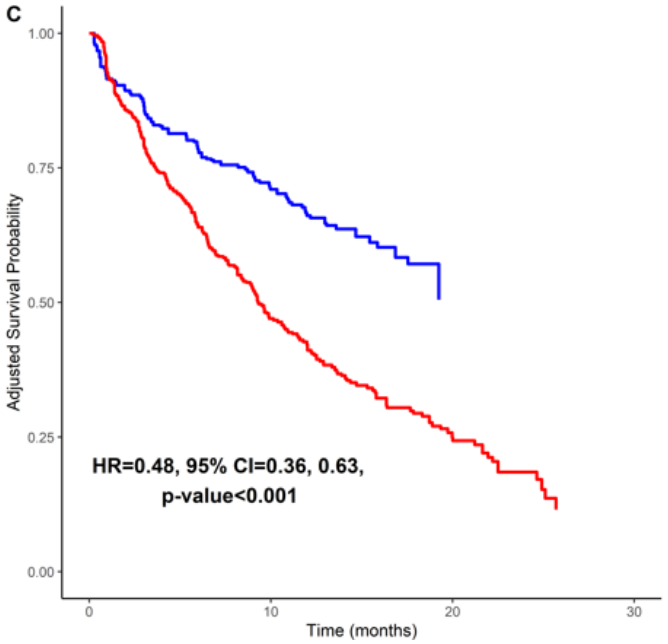
Hansen et al. ASH 2024 [Abstract #936]

Ide-cel vs cilta-cel real-world comparison
(propensity-score matching from US Myeloma Immunotherapy Consortium)

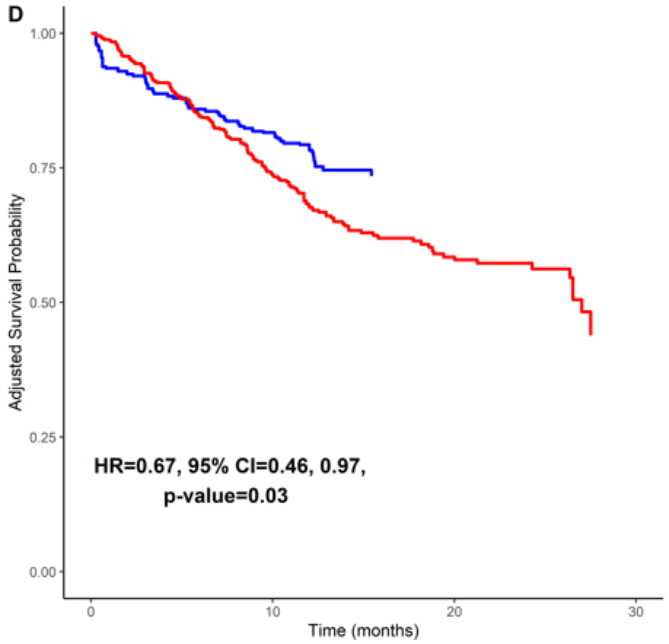
Non-relapse mortality



Progression-free Survival



Overall Survival



Hansen et al. ASH 2024 [Abstract #936]

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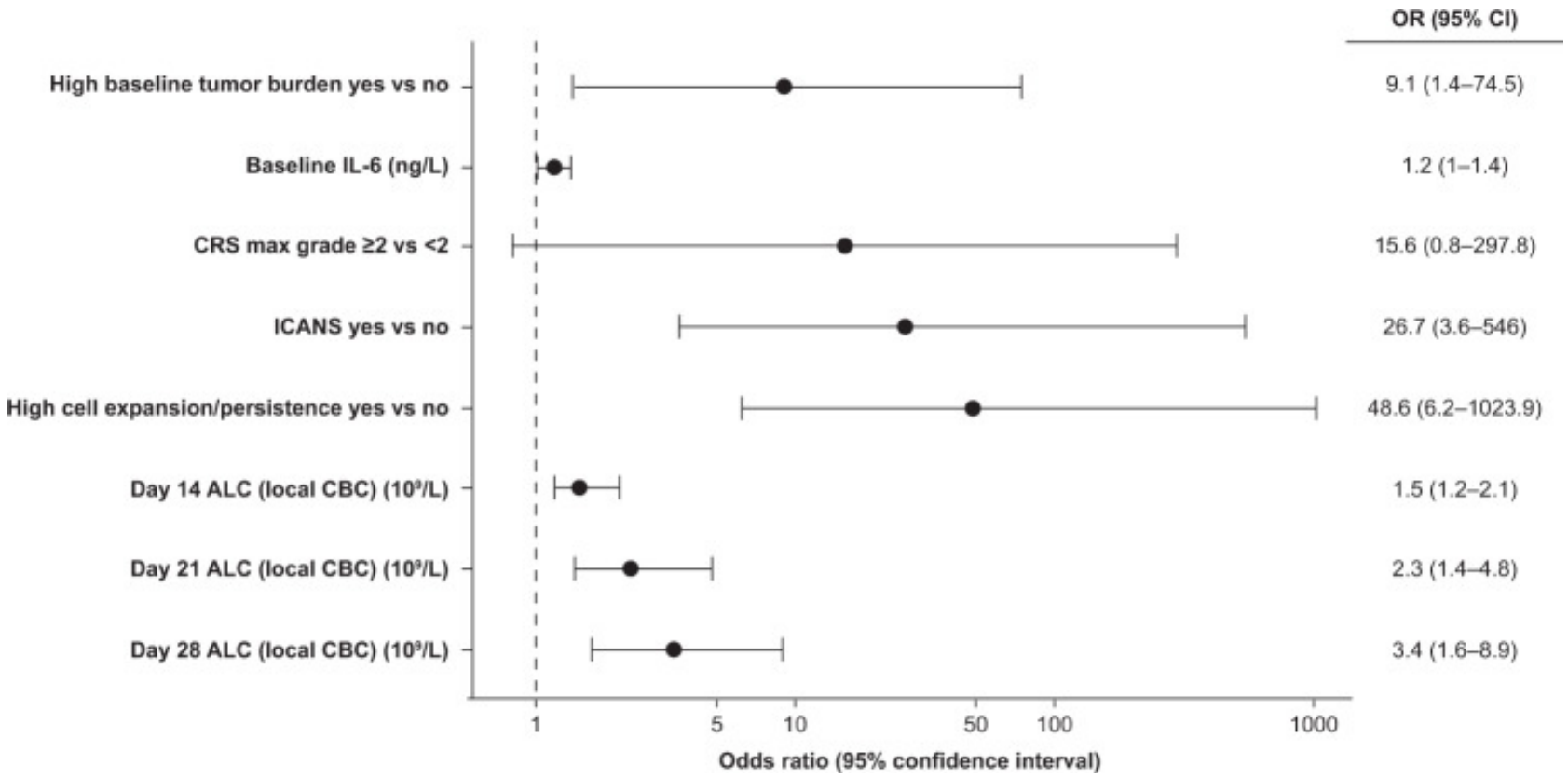
Tumor burden and severe CAR T cell toxicity

Risk of movement/neurocognitive toxicity after cilta-cel



Cohen AD, Blood Cancer J. 2022 Feb; 12(2): 32

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Rationale for earlier line CAR T cell therapy

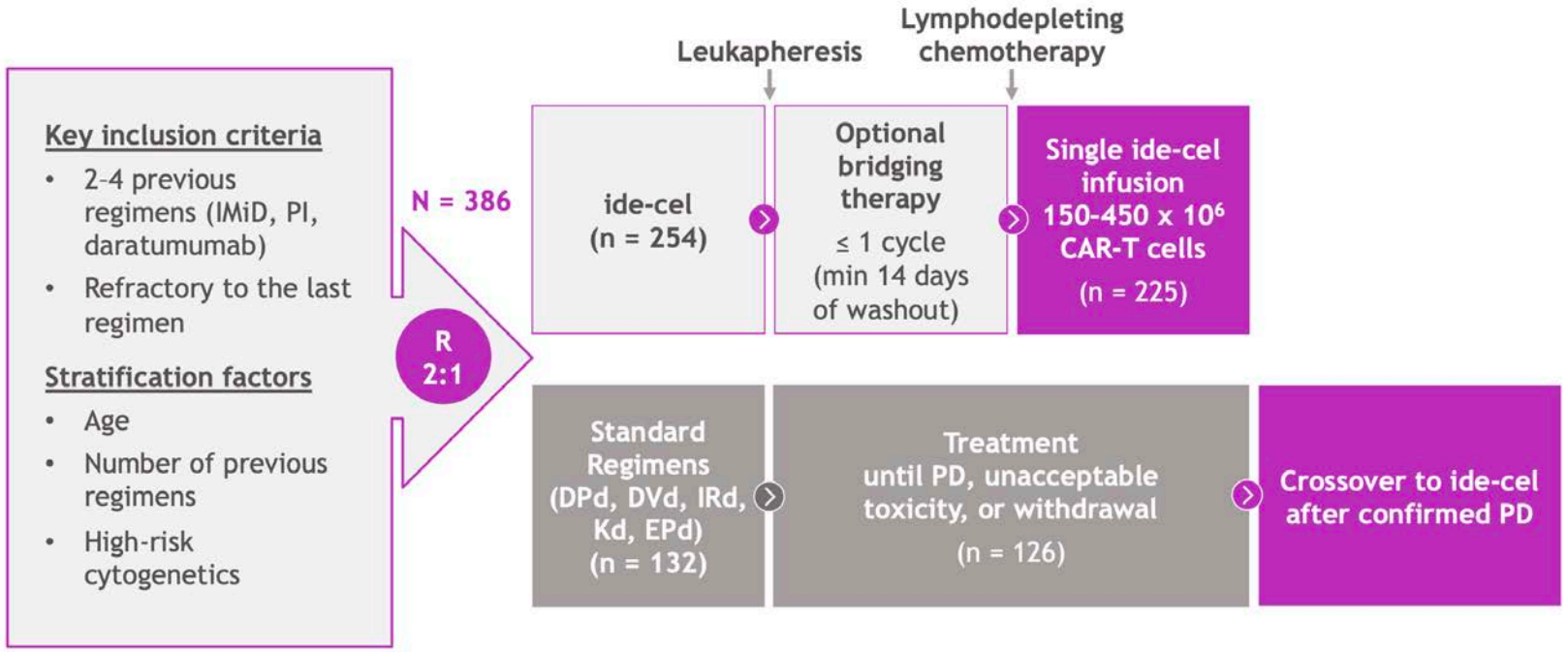
- Improved efficacy?
  - Healthier T cells → better responses (maybe even cure?)

- Improved safety?
  - Lower disease burden
  - Better bridging options

- RCTs of CAR T cells in early-line MM therapy
  - Do CAR T cells confer net benefit?
  - What toxicities are attributable to CAR T cells?
  - What is the optimal timing?
    - Do CAR T cells work better when used earlier?
    - Where is the best risk/benefit balance?

RCTs of ide-cel and cilta-cel in early lines of therapy

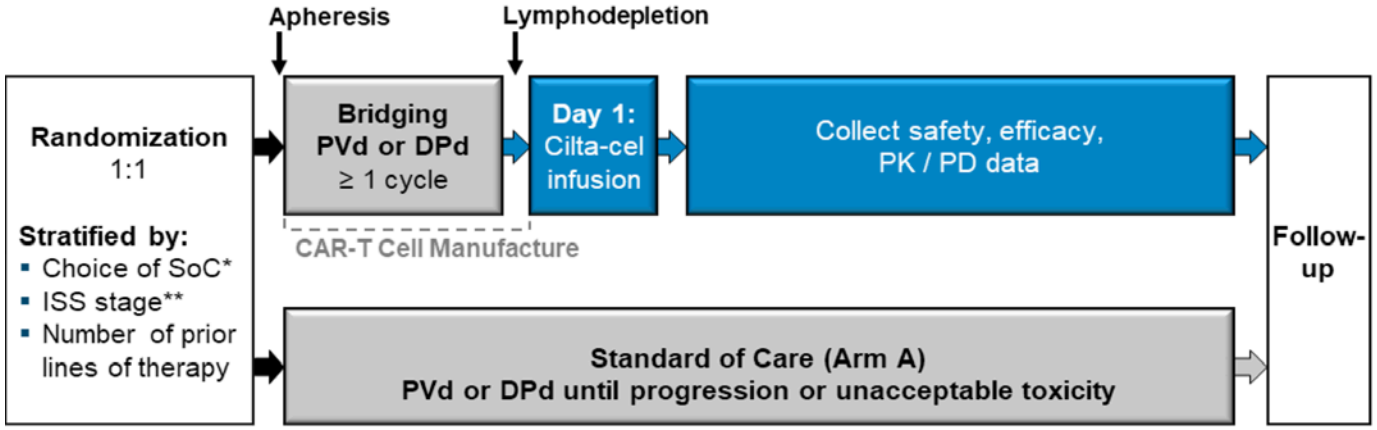
KarMMa 3



CARTITUDE-4

1-3 prior lines of therapy

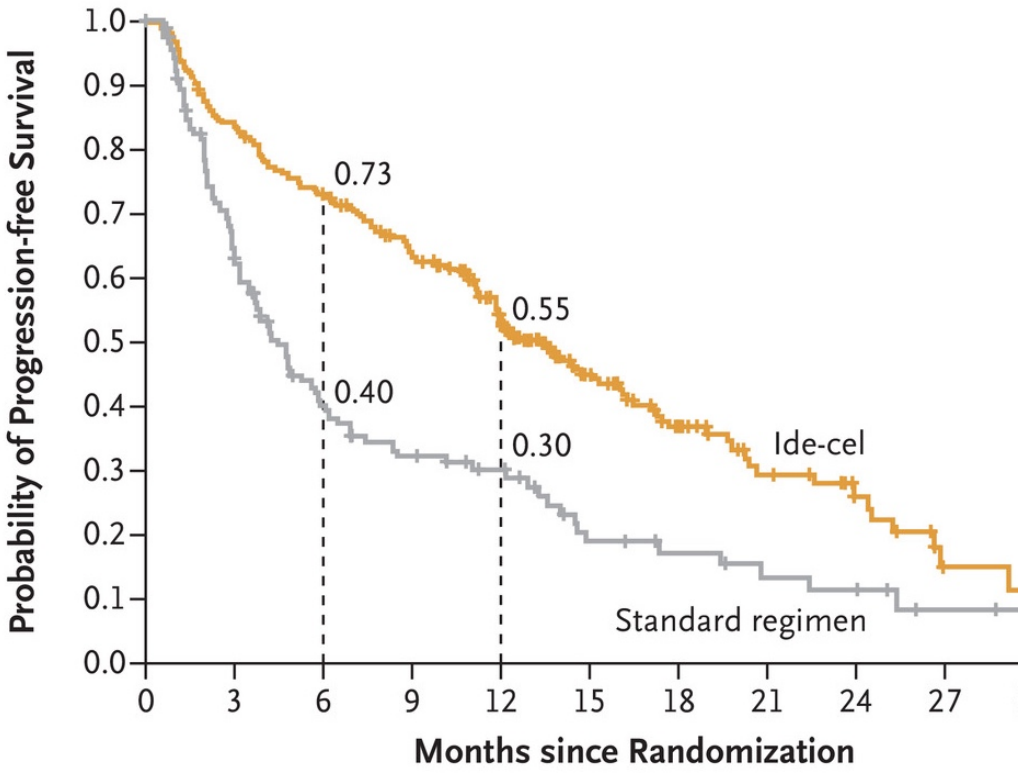
Lenalidomide-refractory



Net benefit of CAR T cells vs SOC in intermediate line of therapy

KARMMA-3: ide-cel vs SOC

Median 3 prior lines



CARTITUDE-4: cilta-cel vs SOC

Median 2 prior lines

Rodriguez-Otero et al., N Engl J Med 2023; 388:1002-1014
Dhakal et al., ASCO 2023 LBA-106 & NEJM DOI: 10.1056/NEJMoa2303379
Mateos et al., IMS 2024

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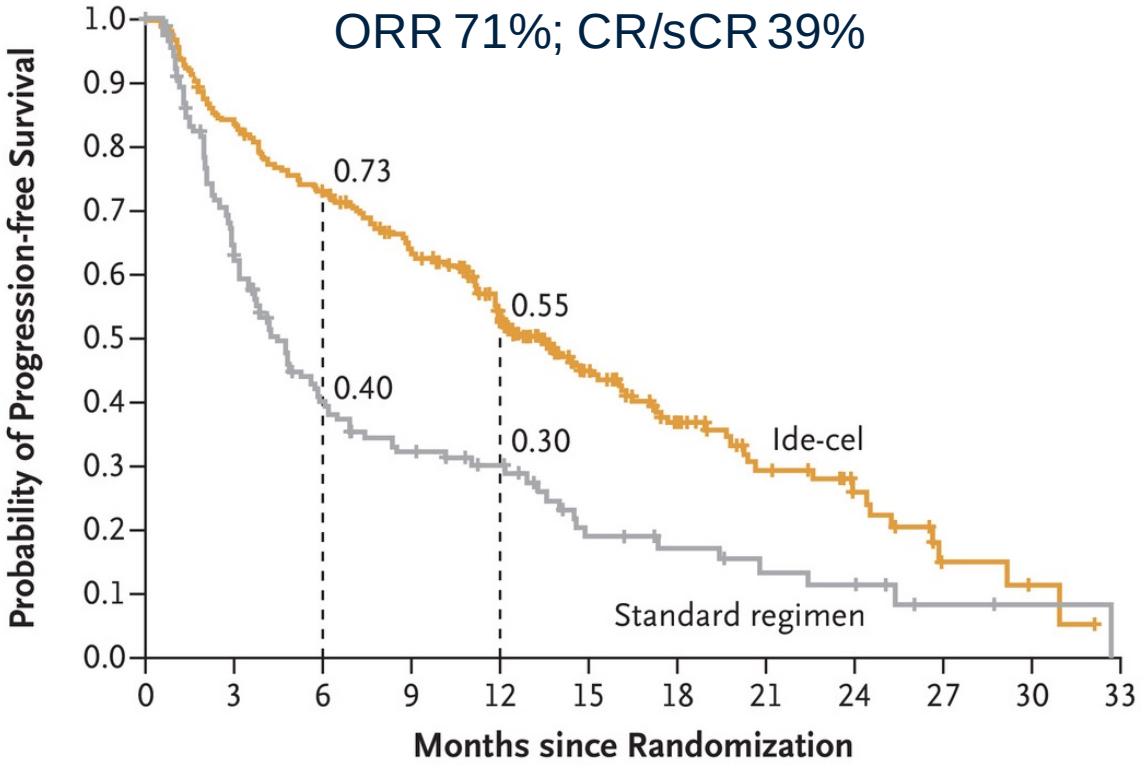
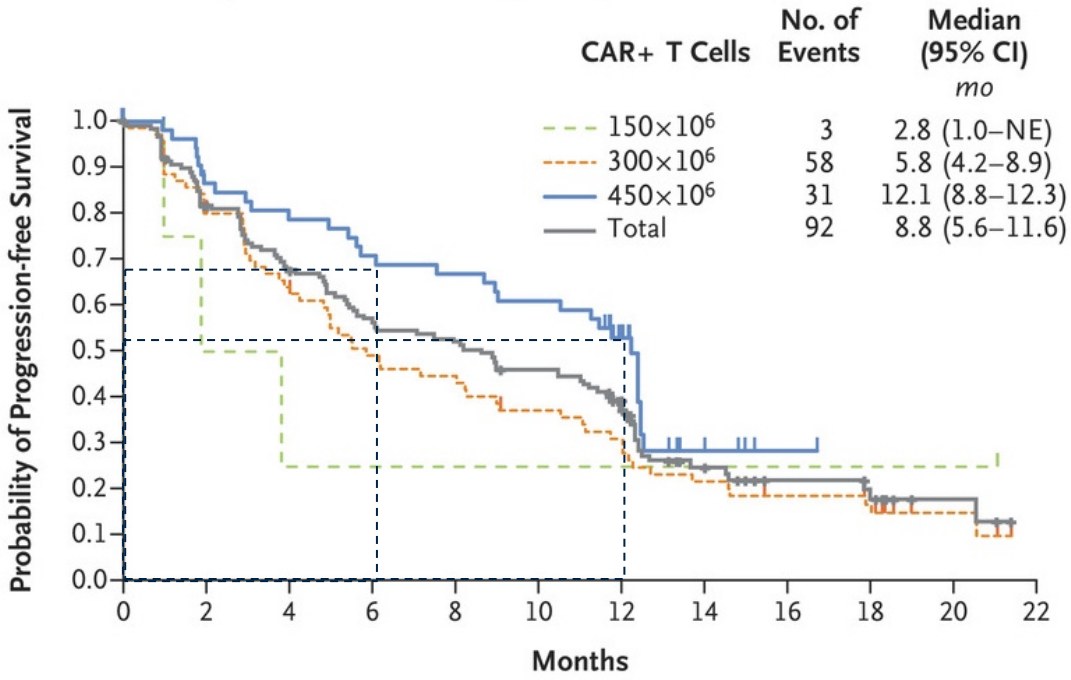
Are CAR T cells more effective in early-line setting?

Ide-cel in intermediate-line vs late-line setting: similar ORR and PFS

KarMMa-3
ORR 71%; CR/sCR 39%



KarMMa-1
ORR 81%; CR/sCR 39%



Munshi et al., N Engl J Med 2021; 384:705-716
Rodriguez-Otero et al., N Engl J Med 2023; 388:1002-1014

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Are CAR T cells more effective in early-line setting?

Cilta-cel in 1-3 prior lines

Median 2 prior lines (range 1-3)
14% triple-class refractory
2% penta-drug refractory

Median 6 prior lines (range 3-18)
88% triple-class refractory
42% penta-drug refractory

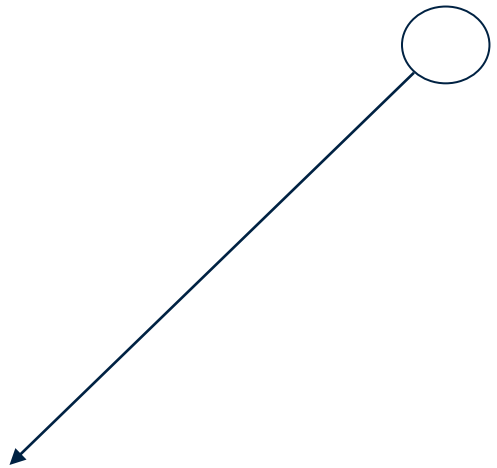
Cilta-cel vs SOC safety

CART-specific AEs	Conforming Cilta-cel As-treated Patients* (N = 188) Any Grade	Grade 3 – 4	Median Time to Onset (days)	Median Duration (days)	Resolved (%)
CRS	78%	3%	8	3	99%
ICANS	7%	0.5%	9	2	93%
Cranial nerve palsy	9%	1%	21	77	88%
Peripheral neuropathy	7%	0.5%	51	168	57%
MNT (Parkinsonism)	1%	0	60	265	Ongoing at Clinical Cut-off

No fatal CRS or neurotoxicity

Dhakal et al., ASCO 2023 LBA-106 & NEJM DOI: 10.1056/NEJMoa2303379
Mateos et al., IMS 2024
FDA Carvykti ODAC Materials 15 Mar 2024
https://www.fda.gov/advisory-committees/advisory-committee-calendar/march-15-2024-meeting-oncologic-drugs-advisory-committee-meeting-announcement-03152024

Cilta-cel vs SOC safety



CAR+ lymphomas
Harrison et al., NEJM Feb 2025

Dhakal et al., ASCO 2023 LBA-106 & NEJM DOI: 10.1056/NEJMoa2303379
Mateos et al., IMS 2024

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Where is the sweet spot in the 1-4 prior lines window?

Overall Survival in KarMMa-3

Overall Survival in CARTITUDE-4

When crossover is permitted in next line of therapy, there is no OS advantage to earlier use.

Early OS trend may favor standard therapy in patients enrolled after 1 prior line of therapy.

FDA ODAC Materials 15 Mar 2024
https://www.fda.gov/advisory-committees/advisory-committee-calendar/march-15-2024-meeting-oncologic-drugs-advisory-committee-meeting-announcement-03152024

Conclusions from early-line CAR T cell studies

- **Efficacy**
  - CAR T cell therapy (cilta-cel) improves overall survival in multiple myeloma
  - Cilta-cel continues to appear more effective than ide-cel
  - Cilta-cel efficacy appears better in 1-3 PL vs 4+ PL but not transformational (no plateau)
  - Within early-line window (1-3 priors), not clear that earlier is better.
- **Safety**
  - CAR T cells appear safer in earlier lines compared to late-line (4+) usage.
    - No fatal CRS or neurologic toxicity
    - Less Parkinsonism
  - Infections are comparable to SOC (worse earlier, better later)
  - SPMs (including CAR+ lymphoma) appear higher with cilta-cel vs SOC
  - ~10% cilta-cel patients have long-lived and/or life-threatening toxicities (SPMs, neurologic)
- **Our practice:** cilta-cel in 3rd line for most patients, 2nd line for high-risk patients (not using much ide-cel)

Where does this leave bispecific antibodies?

- Patients who need rapid disease control
- Patients who do not want to bear risk of CAR T cell therapy
- Patients who cannot access CAR T cell therapy
- Older/frail patients who may not tolerate CAR T cell therapy
- Patients relapsing after CAR T cell therapy
- Bridging therapy to enable CAR T cell therapy

	Indication	ORR	PFS/DOR	Toxicity
Teclistamab[4,5]	FDA: 4+ prior lines of therapy NCCN: 4+ prior therapies	63%	12.5 m 24 m	• CRS/NT (unlikely severe) • Infection risk (perhaps higher) • Cytopenias (unlikely severe)
Elranatamab[6]		61%	~15 m NR	
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BCMA or GPRC5D bsAb after anti-BCMA CAR failure?

- Teclistamab (anti-BCMA) real-world analysis from US MM Immunotherapy Consortium (N=509)

	N = 236[1]
BCMA-directed agent(s) received	
Ide-cel	93 (39%)
Belantamab	59 (25%)
Ide-cel & Belantamab	32 (14%)
Other	31 (13%)
Cilta-cel	11 (4.7%)
Belantamab & Other	6 (2.5%)
Cilta-cel & Belantamab	2 (0.8%)
Ide-cel & Other	2 (0.8%)

	≥PR		≥VGPR	
	%	aOR	%	aOR
No prior BCMA	58%	---	51%	---
Prior BCMA >9M	56%	0.67 p=0.4	45%	0.47 p=0.11
Prior BCMA <9M	39%	0.37 p=0.02	30%	0.28 p=0.006

Razzo et al., Under review (please do not post)

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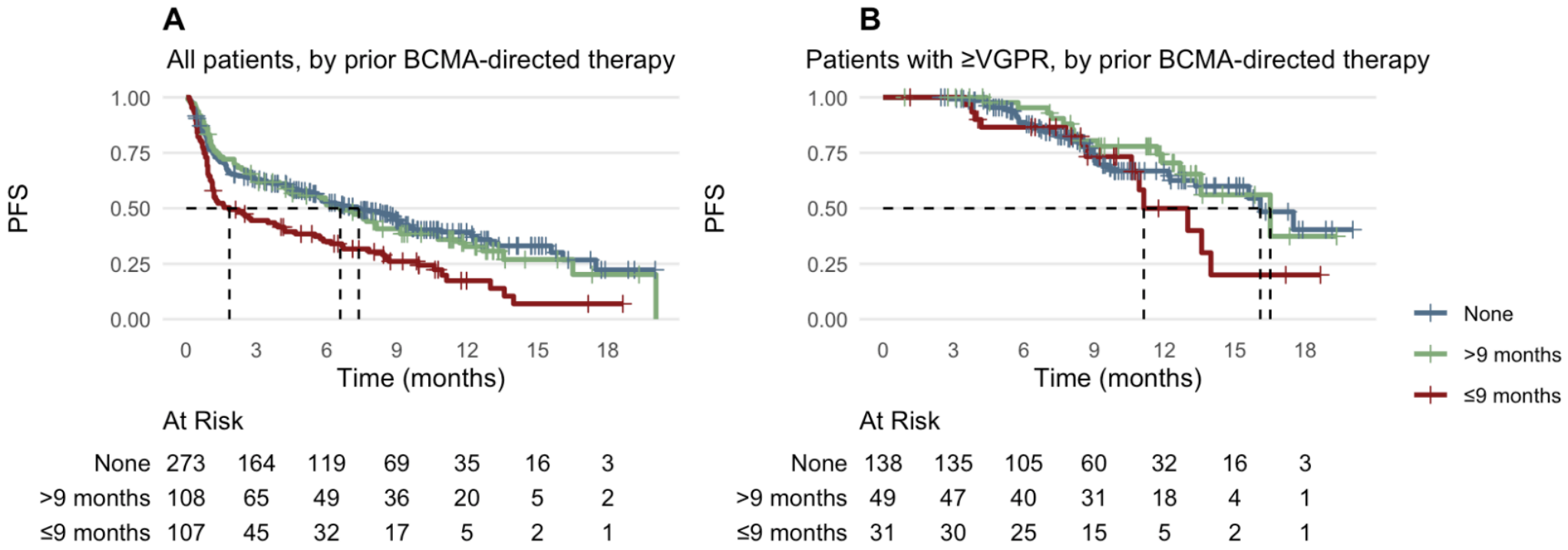

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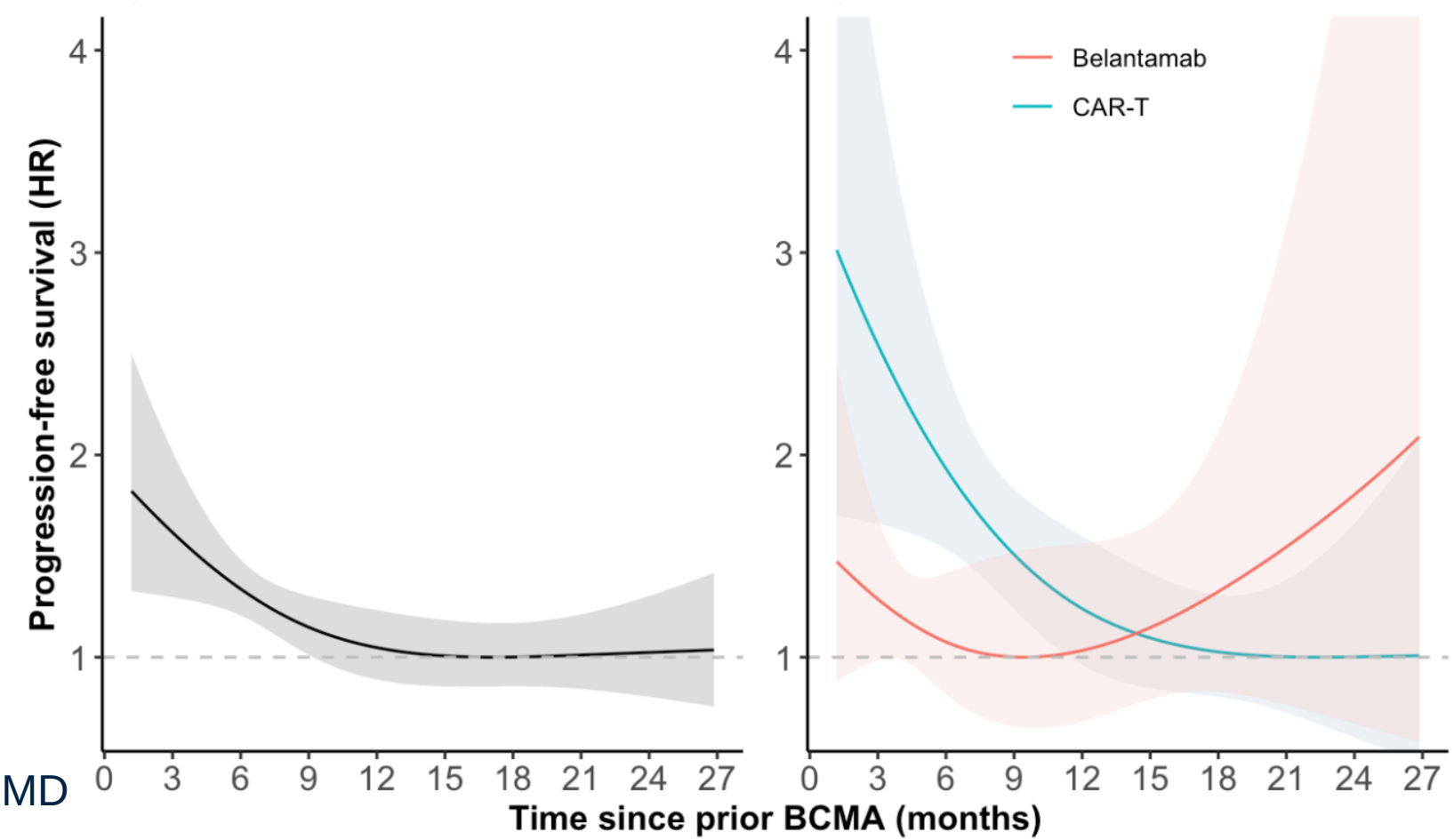

Andrew Portuguese MD
FHCRC

Razzo et al., Under review (please do not post)

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MonumenTAL: Phase 1/2 Talquetamab Monotherapy

Median follow-up 9-15 mos

Select patient characteristics

Cohort	0.4 mg/kg (n=143)	0.8 mg/kg (n=145)	Prior TCR (n=51)
Median age, years	67	67	61
EMD (%)	23	25	31
High-risk cytogenetic (%)	31	29	41
ISS stage III (%)	20	24	18
Median prior LoTs, n (range)	5 (2–13)	5 (2–17)	6 (3–15)
TCR (%)	74	69	84

Key efficacy outcomes

ORR (%)	74	72	65
Patients achieving ≥CR (%)	34	39	35
mDoR, mo (95% CI)	9.5 (6.7–13.3)	NR (13.0–NE)	11.9 (4.8–NE)
12-mo DoR in patients achieving ≥CR (%)	79	91	81
12-mo PFS rate (%)	35	54	38
12-mo OS rate (%)	76	77	63
Patients achieving ≥CR (%)	34	39	35

Key safety outcomes

AEs, n (%)	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
CRS	113 (79.0)	3 (2.1)	108 (74.5)	1 (0.7)	39 (76.5)	1 (2.0)
Dysgeusia	103 (72.0)	NA	103 (71.0)	NA	39 (76.5)	NA
Infections	84 (58.7)	28 (19.6)	96 (66.2)	21 (14.5)	37 (72.5)	14 (27.5)
Skin related	80 (55.9)	0	106 (73.1)	1 (0.7)	35 (68.6)	0
ICANS	10.7%	NA	8.3%	NA	2.9%	NA
Discontinuations due to AEs	4.9%		8.3%		7.8%	

Schinke CD et al. ASCO 2023. Abstract 8036.

BCMA or GPRC5D bsAb after anti-BCMA CAR failure?

- If late relapse after anti-BCMA CAR T cells, our data would support preference for anti-BCMA bispecific (avoids GPRC5D toxicity, similar responses as BCMA-naïve patients).

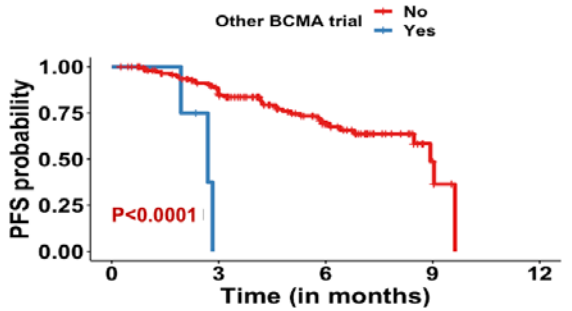
- For early relapse, would prefer talquetamab, but anti-BCMA bispecific is not futile (30% VGPR).

Does bsAb therapy preclude future CAR T cell therapy?

- Reports of both ide-cel and cilta-cel after prior bsAb suggest poor response
- Numbers are small, and these were primarily patients who **had not responded** to prior bsAb.

Real world ide-cel
Median PFS: 2.7 months

BCMA bispecific antibody on trial, N = 4



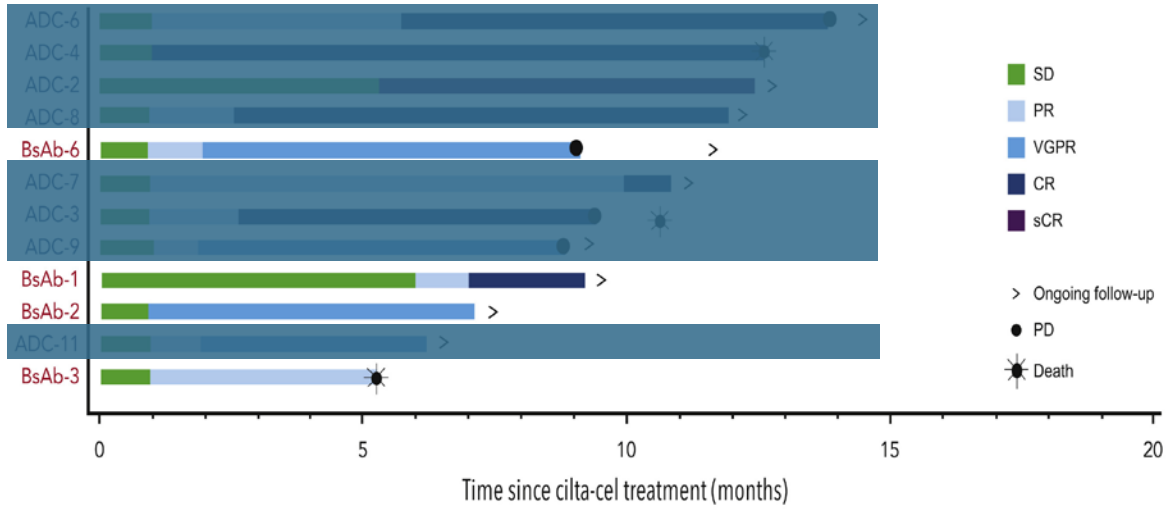
Median PFS: 2.7 months (95% CI, 1.9 to NR)
Median PFS: 8.9 months (95% CI, 8.5 to NR)

No prior bispecific N=155

Cilta-cel after prior BCMA-directed therapy (CARTITUDE-2)

Among 7 prior bsAb patients who received cilta-cel:
- 5 had not responded to the prior bsAb
- 4 responded to cilta-cel

Responders had longer time from prior bsAb to CAR



Hansen DK et al. *J Clin Oncol*. 2023;41(11):2087-97; Cohen AD et al. *Blood*. 2023;141(3):219-30.
Ferreri et al., Blood Cancer Journal, 13:177(2023)

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Does bsAb therapy preclude future CAR T cell therapy?

- Reports of both ide-cel and cilta-cel after prior bsAb suggest poor response
- Numbers are small, and these were primarily patients who **had not responded** to prior bsAb.
- Longer time from prior anti-BCMA therapy may help

Cilta-cel real-world data

Sidana et al., IMS 2024; Blood 2024 (https://doi.org/10.1182/blood.2024025945)

Where does this leave bispecific antibodies?

- Patients who need rapid disease control
- Patients who do not want to bear risk of CAR T cell therapy
- Patients who cannot access CAR T cell therapy
- Older/frail patients who may not tolerate CAR T cell therapy
- Patients relapsing after CAR T cell therapy
- **Bridging therapy to enable CAR T cell therapy**

	Indication	ORR	PFS/DOR	Toxicity
Teclistamab[4,5]	FDA: 4+ prior lines of therapy NCCN: 4+ prior therapies	63%	12.5 m 24 m	• CRS/NT (unlikely severe) • Infection risk (perhaps higher) • Cytopenias (unlikely severe)
Elranatamab[6]		61%	~15 m NR	
Talquetamab[7,8]		~72%	~12m NR	• Oral/taste toxicity (potentially severe) • Skin and nail toxicity

Talquetamab bridging therapy

50 cilta-cel; 15 ide-cel

	N=12
Age, median years	61 (50-75)
Male, sex	5 (42)
ECOG >=2	2 (17)
High risk disease/EM disease	7 (58)/5 (42)
Median prior lines	6 (4-10)
Median time from Tal dose to apheresis, days	94 (28-174)
Response to Talquetamab	11/12 (92)
CAR-T infusion	8/12 (67)
Reasons for not infusion	Manufacturing failure (2)*, PD (1), OOS (1)

Dhakal et al., ASH 2024

Talquetamab bridging therapy

	N=65	
	All grades	Grade 3/4
CRS	47 (72%)	2 (3%)
ICANS	7 (10%)	1 (2%)
Delayed neurotoxicity	1 (1.5%) (CN VII palsy)	0
Infections	16 (27%)	6 (9%)
Second malignancies	1 (1.5%) (AML TP53 and DNMT3A)	NA
Severe cytopenia (day+60)	7 (10%)	7 (10%)

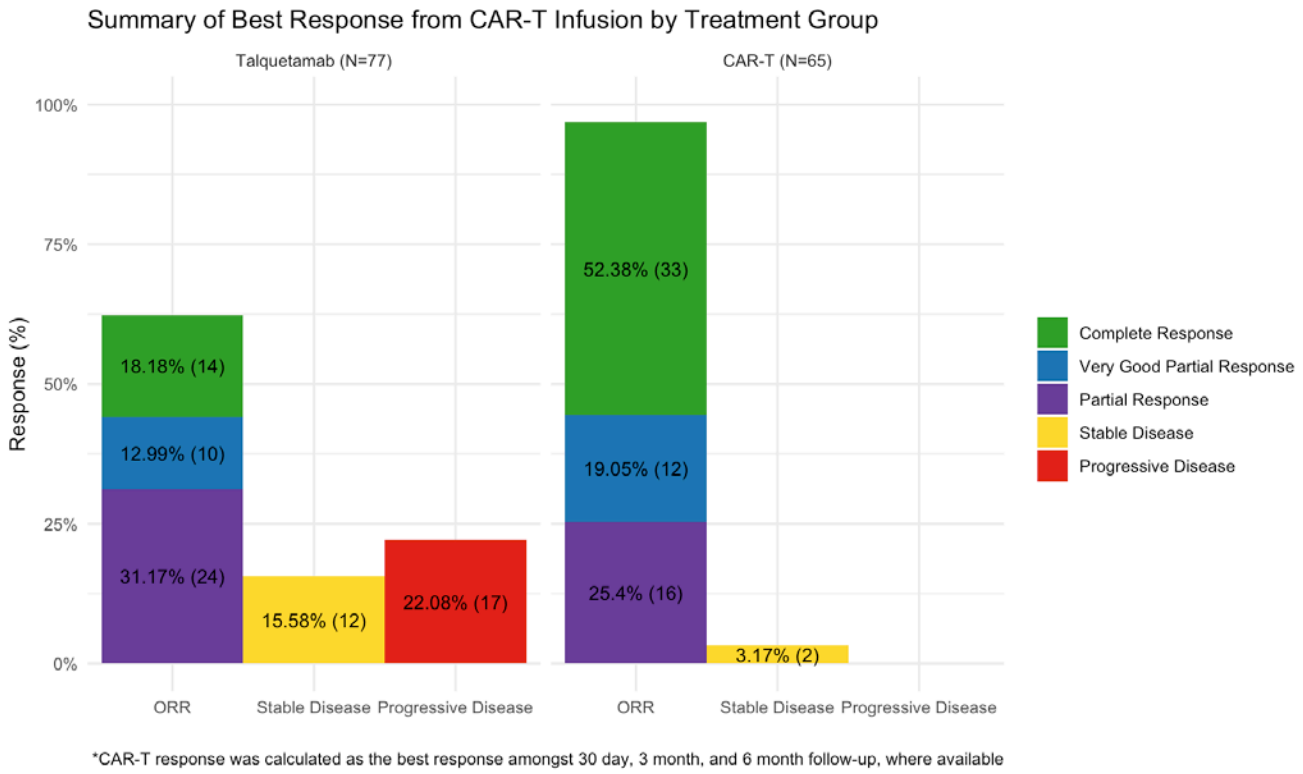
Total deaths overall: 16

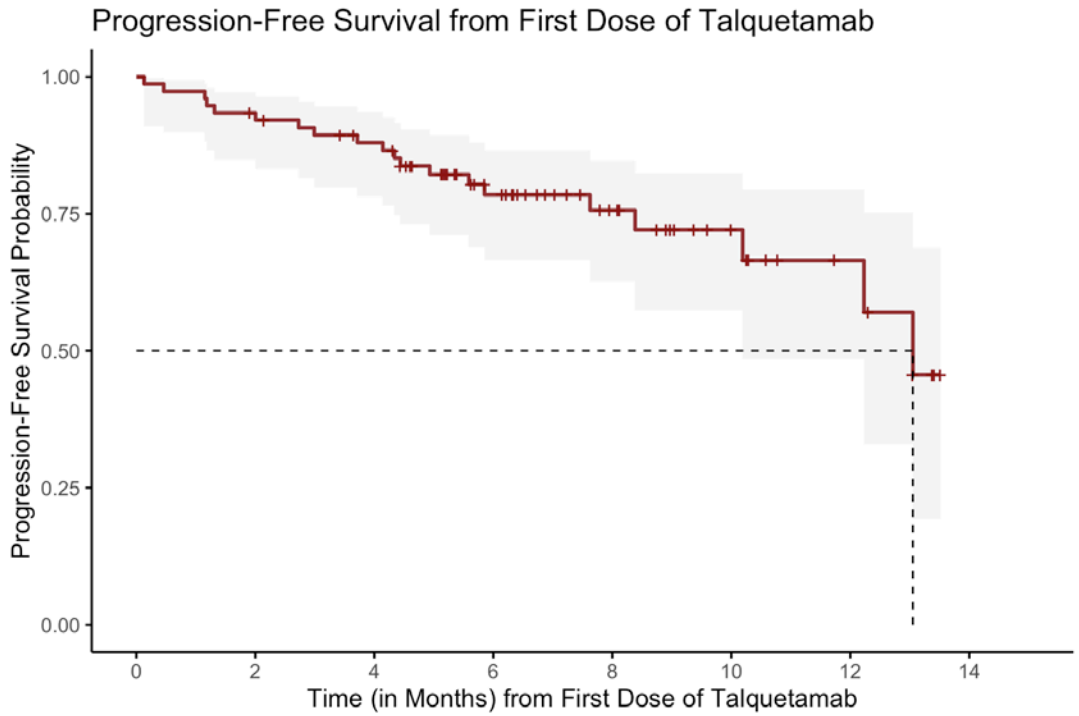
Total deaths after CAR-T infusion: 8

Non relapse mortality after CAR:3 (2 sepsis/shock and 1 AML/MDS)

Dhakal et al., ASH 2024

Talquetamab bridging therapy





Dhakal et al., ASH 2024

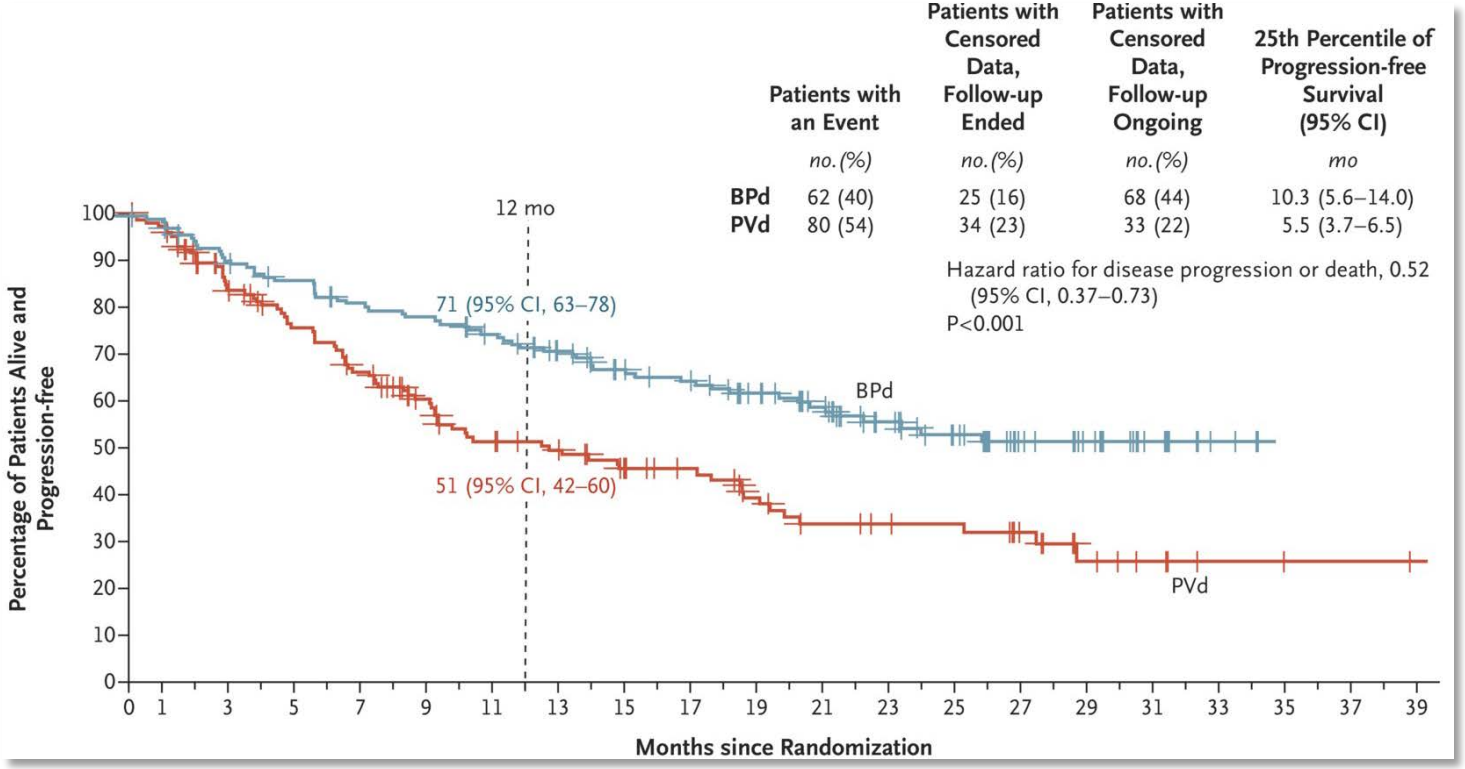
Outline

- What we do now and why?
  - CAR T cells: how early?
  - Sequencing of CAR T cells, bispecific antibodies, and targets

- **Where are we going?**
  - Role for belantamab
  - Fixed-duration bispecific antibody therapy
  - New agents (trispecifics, anito-cel, etc)
  - Ongoing first- and early-line trials

Belantamab mafadotin + pomalidomide (BPd vs VPd (DREAMM-8)

≥1 prior lines, lenalidomide-exposed



Response	BPd (N=155)	PVd (N=147)
≥PR	77%	72%
≥VGPR	64%	38%
≥CR	40%	16%
MRD-neg ≥CR	24%	5%
Sustained (12m) MRD-neg ≥CR	8%	1%

Dimopoulos et al., N Engl J Med 2024;391:408-421

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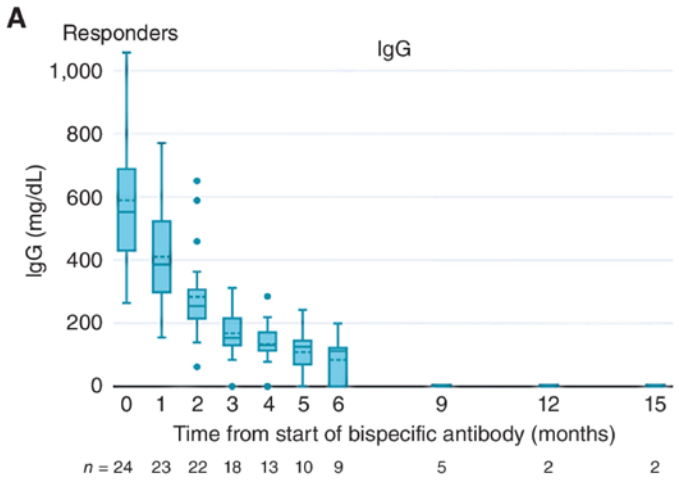
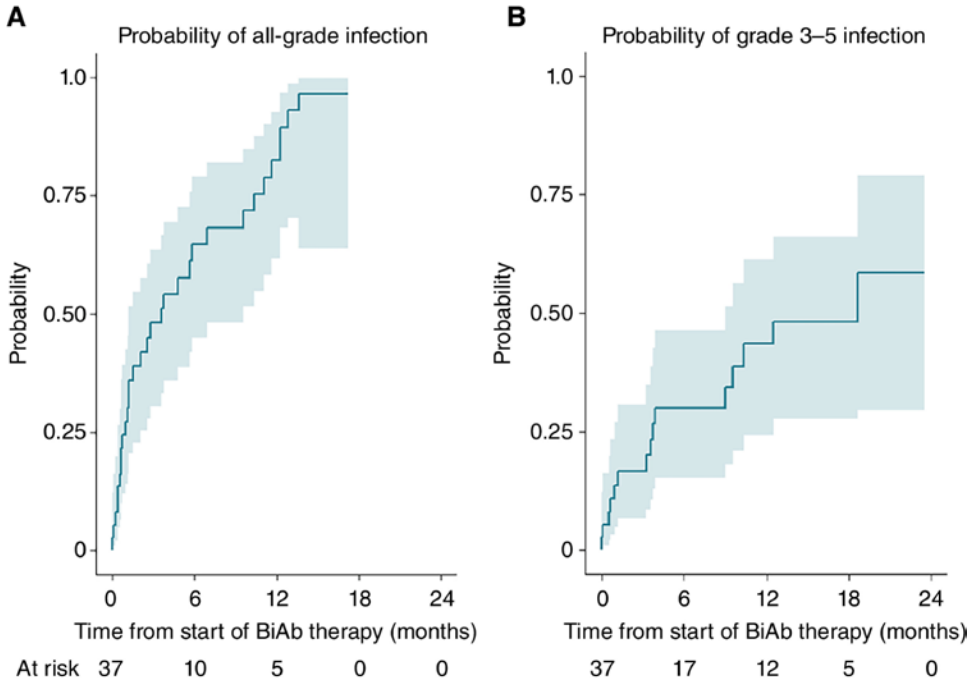
Fixed duration bispecific antibody therapy

- Continuous anti-BCMA bsAb therapy has significant infection risk.
- Anecdotal reports of long-term responses to fixed duration therapy.
- In early lines, continuous therapy could extend many years and be quite burdensome.





Lancman et al., *Blood Cancer Discov* (2023) 4 (6): 440–451.

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Fixed duration bispecific antibody therapy

- Continuous anti-BCMA bsAb therapy has significant infection risk.
- Anecdotal reports of long-term responses to fixed duration therapy.
- In early lines, continuous therapy could extend many years and be quite burdensome.

Limited-duration Teclistamab

ClinicalTrials.gov ID NCT05932680

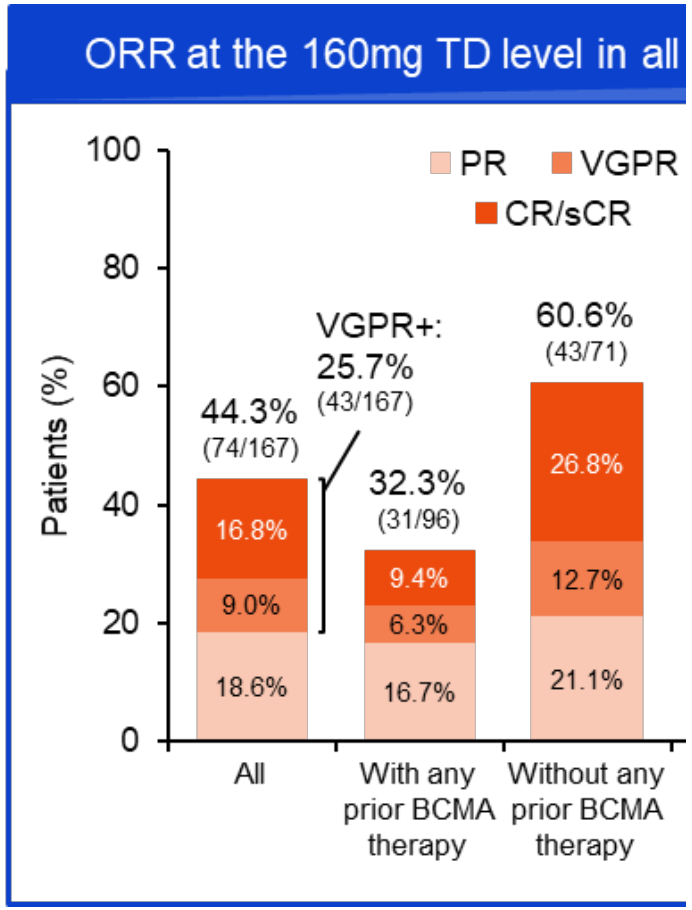
Sponsor Abramson Cancer Center at Penn Medicine

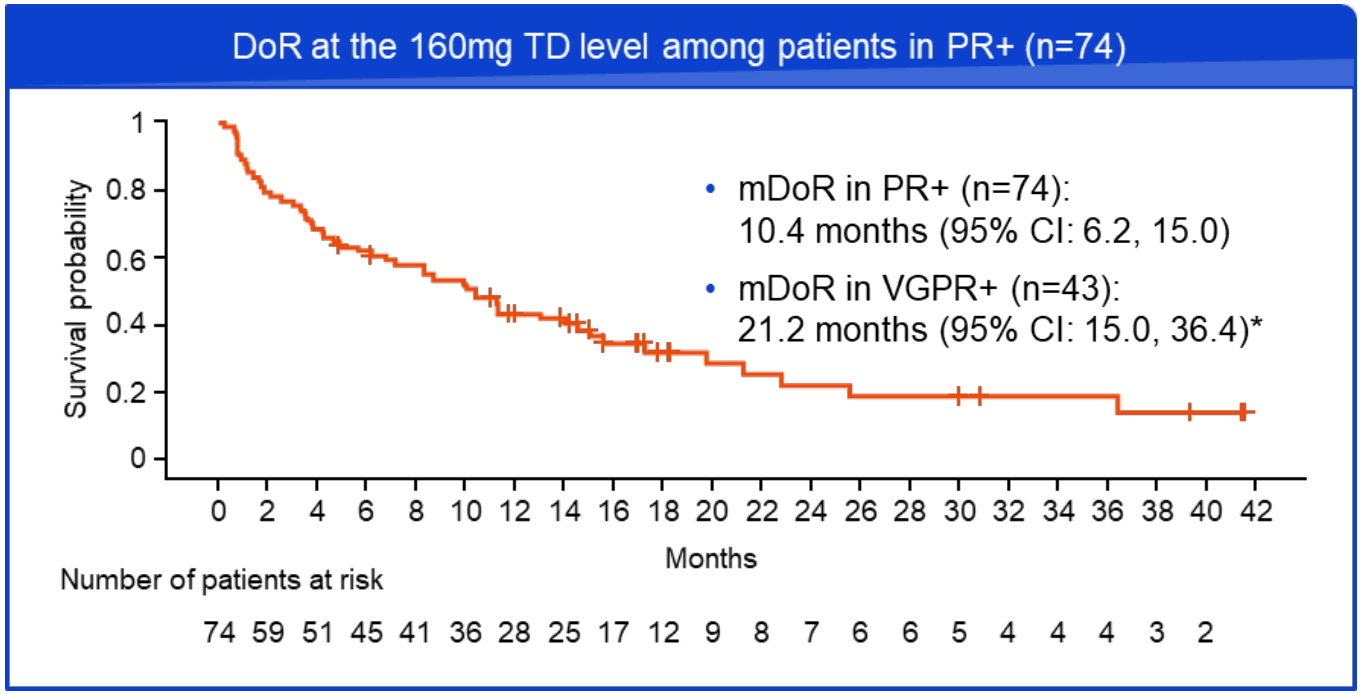
Information provided by Abramson Cancer Center at Penn Medicine (Responsible Party)

Last Update Posted 2023-07-27

Cevostamab (FcRH5 x CD3 bsAb) phase 1 update

At RP2D (160mg q3wks IV x 17 cycles)
Median 6 lines, 96% triple-class refractory
58% prior BCMA tx



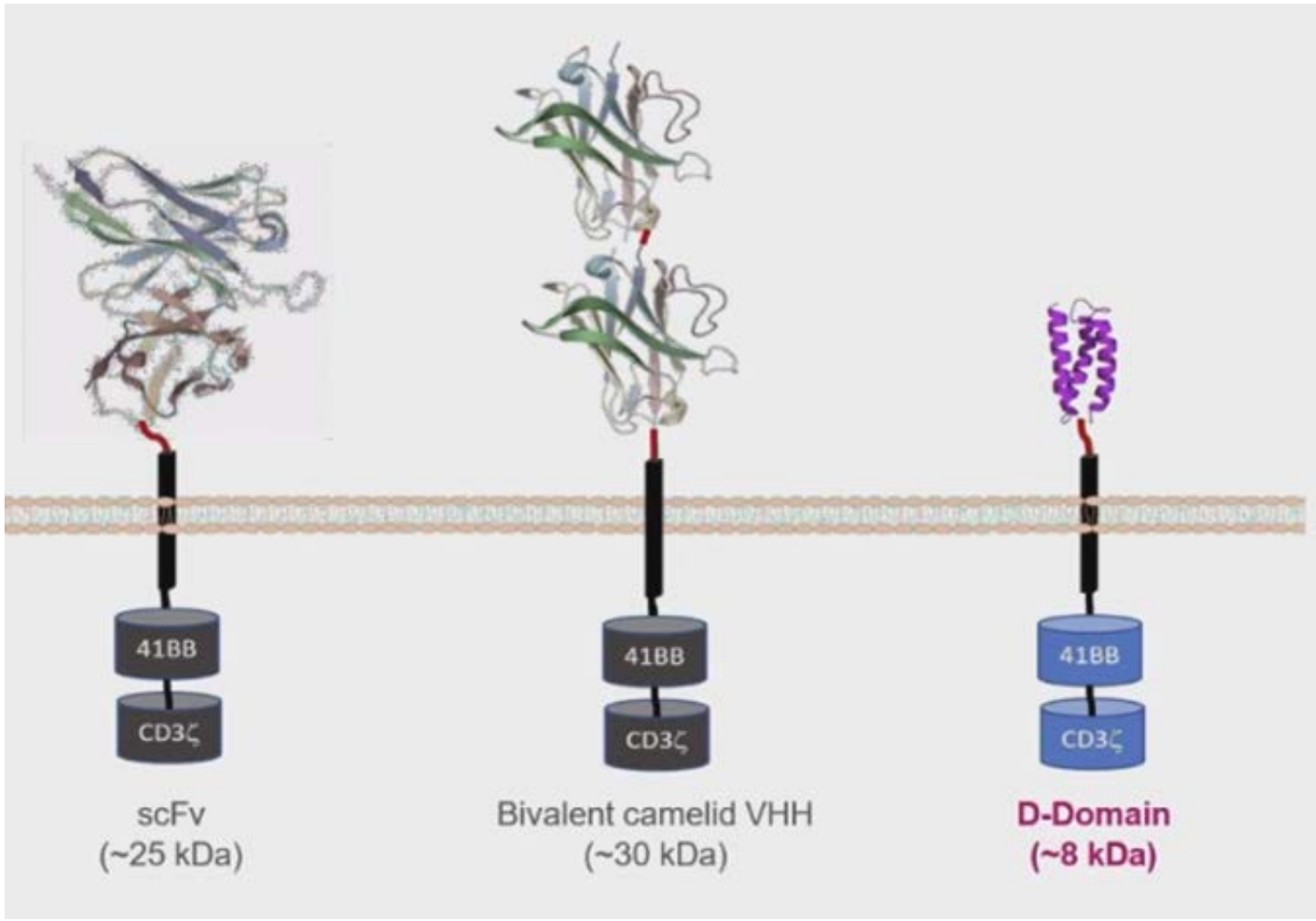


At RP2 step-up (n=30):
CRS 63% (0% Gr 3-4)

N (%) of patients	n=167
AE of infection	91 (54.5)
Gr 3–5 AE of infection	32 (19.2)
Gr 3	24 (14.4)
Gr 4	2 (1.2)
Gr 5 (fatal)	6 (3.6)
SAE of infection	37 (22.2)
AE of infection leading to treatment discontinuation	10 (6.0)

Richter et al, ASH 2024, #1021

Anito-cel (CART-ddBCMA) for rel/ref MM



Anito-cel phase 1 in RRMM

Bishop et al, ASH 2024, #4825

No delayed neurotoxicity

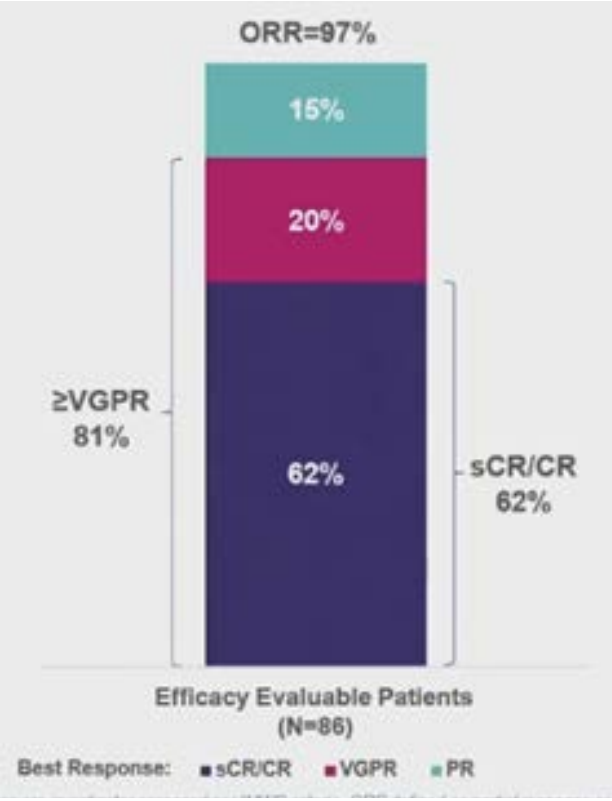
Freeman et al, ASH 2024, #1031

Anito-cel (CART-ddBCMA) for rel/ref MM

iMMagine-1 Phase 2 registration study

Median 4 lines, 87% triple-class refractory, 0% BCMA tx

Median f/up = 9.5 months



	PFS Rate (%) (95% CI)	OS Rate (%) (95% CI)
6-Month	93.3% (84.4%, 97.2%)	96.5% (89.6%, 98.9%)
12-Month	78.5% (63.5%, 87.9%)	96.5% (89.6%, 98.9%)

CRS 83% (≥Gr3=1%)

ICANS 9% (≥Gr3=1%)

3 deaths:

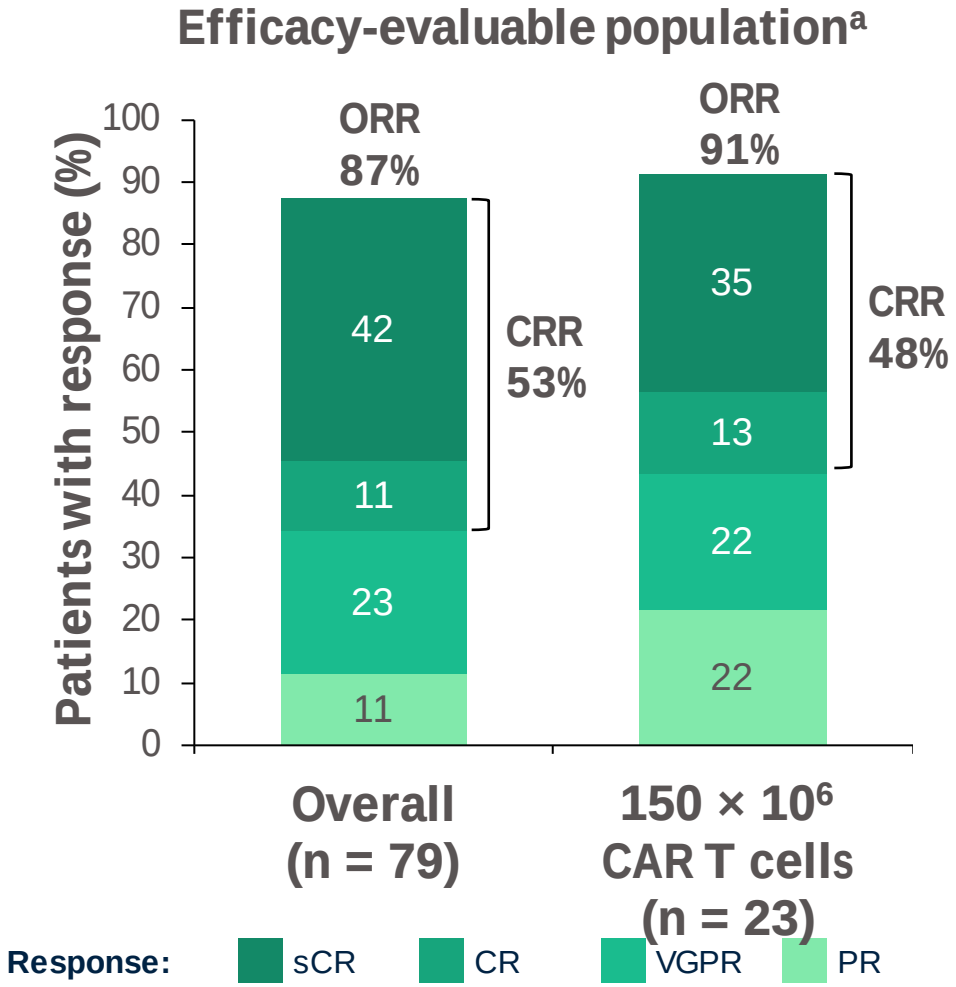
-HLH/hemorrhage, CRS, fungal infections

No delayed neurotoxicity

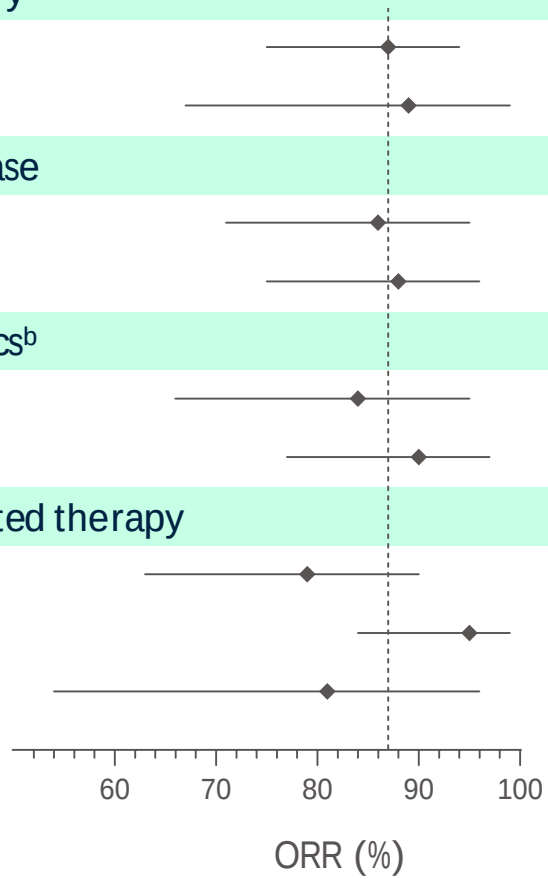
Phase 3 anito-cel vs SOC in 1-3 priors opened late 2024

Freeman et al, ASH 2024, #1031

Arlo-cel (anti-GPRC5D CAR)



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)



Bal et al., ASH 2024 #922

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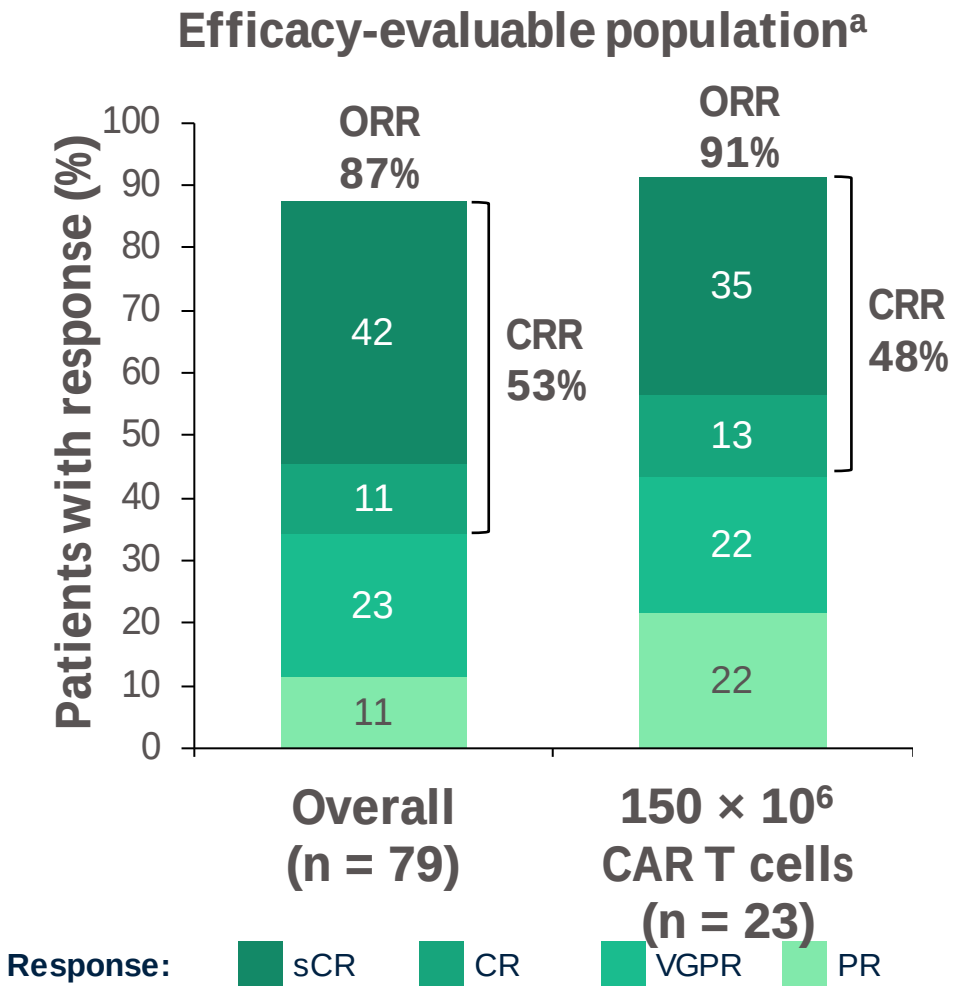
Arlo-cel (anti-GPRC5D CAR)



Bal et al., ASH 2024 #922

Arlo-cel (anti-GPRC5D CAR)

Select TRAEs	All treated patients (N = 84) Any grade	Grade 3/4
CRS, n (%)	69 (82)	3 (4)
ICANS, n (%)	8 (10)	2 (2)
Other select neurotoxicity,[a] n (%)	10 (12)	6 (7)
MAS/HLH, n (%)	0	3 (4)
On-target/off-tumor skin, nail, and/or oral event		
Skin		
Patients with an event, n (%)	25 (30)	0
Patients with resolved event(s), n (%)	22 (88)	
Median time to resolution[b]	26 days	
Nail		
Patients with an event, n (%)	16 (19)	0
Patients with resolved event(s), n (%)	12 (75)	
Median time to resolution[b]	98 days	
Oral, including dysgeusia and dysphagia		
Patients with an event, n (%)	27 (32)	0
Patients with resolved event(s), n (%)	19 (70)	
Median time to resolution[b]	66 days	

- CRS was predominantly grade 1 or 2
  - One patient had grade 5 CRS at the 450 × 10^6 DL
- Most patients with skin, nail, and/or oral on target off tumor toxicity did not require intervention (79%)
- Five patients experienced weight loss
- Other select neurotoxicity episodes occurred at the 150–450 × 10^6 DLs
  - Defined as dizziness, ataxia, neurotoxicity, dysarthria, and/or nystagmus
  - None were grade 4/5; median time to onset was 30.5 days
- No cases of parkinsonism, Guillain-Barré syndrome, or cranial nerve palsy

Dizziness, ataxia, neurotoxicity, dysarthria, and/or nystagmus

Data cutoff: August 23, 2024. [a]Preferred CTCAE terms of dizziness, ataxia, neurotoxicity, dysarthria, and/or nystagmus. [b]Calculated from all resolved episodes, including separately considering individual episodes that occurred in 1 patient. AE, adverse event; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; DL, dose level; HLH, hemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; TRAE, treatment-related adverse event.

Bal et al., ASH 2024 #922

Dual-target approaches

- T&T: ORR 80%, EMD ORR 61%, 86% of responses ongoing @ 18M

- BCMA/GPRC5DxCD3 trispecific (JNJ-79635322)

ORIGINAL ARTICLE

Talquetamab plus Teclistamab in Relapsed or Refractory Multiple Myeloma

Authors: Yael C. Cohen, M.D., Hila Magen, M.D., Moshe Gatt, M.D., Michael Sebag, M.D., Ph.D., Kihyun Kim, M.D., Chang-Ki Min, M.D., Enrique M. Ocio, M.D., Ph.D., +16, for the RedirecTT-1 Investigators and Study Group* Author Info & Affiliations

Published January 8, 2025 | N Engl J Med 2025;392:138-149 | DOI: 10.1056/NEJMoa2406536 | VOL. 392 NO. 2

Characterization of JNJ-79635322, a Novel BCMAxGPRC5DxCD3 T-Cell Redirecting Trispecific Antibody, for the Treatment of Multiple Myeloma

Ram Pillarisetti, Danlin Yang, Jianhong Yao, Melissa Smith, Leopoldo Luistro, Peter Vulfson, James Testa, Jr., Kathryn Packman, Scott Brodeur, Ricardo M. Attar, Yusri Elsayed, Ulrike Philippar

Blood (2023) 142 (Supplement 1): 456.

https://doi.org/10.1182/blood-2023-174941

Dual-target approaches

- ISB 2001: CD38/BCMAxCD3 trispecific. Phase 1 ORR 75%

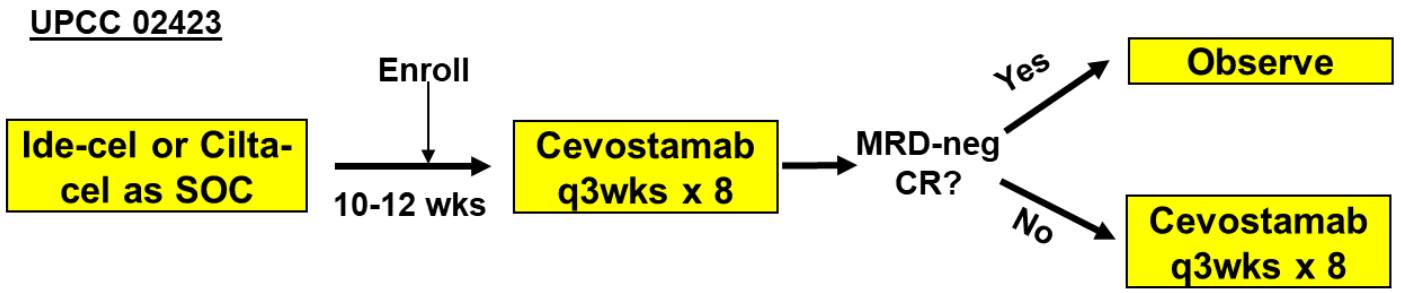
1026 First Results of a Phase 1, First-in-Human, Dose Escalation Study of ISB 2001, a BCMAxCD38xCD3 Targeting Trispecific Antibody in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

Program: Oral and Poster Abstracts
Type: Oral
Session: 654. Multiple Myeloma: Pharmacologic Therapies: Into the Future: New Drugs and Combinations in Multiple Myeloma
Hematology Disease Topics & Pathways:
Drug development, Bispecific Antibody Therapy, Treatment Considerations, Biological therapies

Monday, December 9, 2024: 5:45 PM

Hang Quach, MD, FRACP, FRCPA, MBBS[1], Bradley Augustson, MBBS, FRACP, FRCPA[2], Hanlon Sia, MBBS FRACP FRCPA[3*], Nishi Shah, MBBS, MPH[4], Eben I Lichtman, MD[5], Michaela Liedtke, MD[6], Camille Martinet[7*], Vinu Menon[8*], Andrew Garton, PhD[9*], Maria Pihlgren[10*], Beata Holkova, MD[11], Cyril Konto, MD[8], Lida Pacaud, MD[12*] and Amit Khot, MD, FRACP, FRCPath, MBBS, MRCP[13*]*

- CAR/bispecific combination approaches



Cohen et al, Blood 2023;142(Suppl 1):3389

Ongoing early-line studies

- (will update later)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