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Optimal Patient Phenotype in Relapsed MM

CAR-T Therapy

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Conflict of Interest Disclosure

I hereby declare the following potential conflicts of interest concerning my presentation:

- Consultancy and Honoraria: Adaptive Biotechnologies, Amgen, Bristol Myers Squibb, Cellectar biosciences, GlaxoSmithKline, Janssen, K36 therapeutics, ONK therapeutics, Pfizer, Sanofi, and Takeda
- Research Funding: Aduro Biotech, Amgen, Arch Oncology, Bristol Myers Squibb, Cellectis, Cellectar, Genentech, GlaxoSmithKline, Janssen, Karyopharm, Kite Pharma, Merck, Pfizer, and Takeda Patents and Royalties:
- Discussion of off-label drug use: None

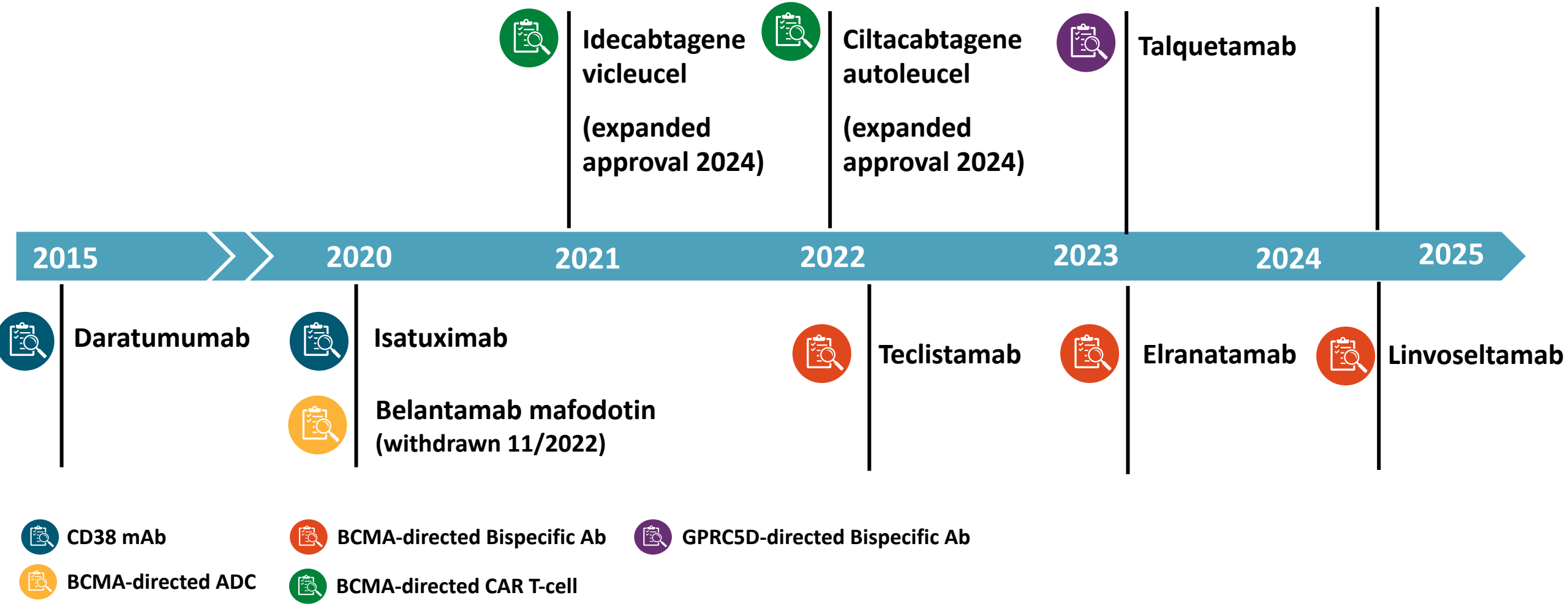
Dr. Joseph's strategy to win the debate

- **Efficacy data**
- **Safety data**
  - Rare toxicities
- **Cost**
- **Access**
- **Kill the audience with kindness**

Case

- 60-year-old Caucasian female with standard risk disease, R-ISS stage 2 IgG kappa multiple myeloma, diagnosed in 01/2022, with monosomy 13, IGH rearrangement with no evidence of high-risk translocations
- Induction therapy with daratumumab, bortezomib, lenalidomide and dexamethasone (D-RVd) for 4 cycles, achieving VGPR, underwent early autologous stem cell transplant in 05/2022 and started maintenance therapy with lenalidomide in 09/2022.
- She continued maintenance until 5/2025 when she presented with left forearm swelling and pain. Plain films showed a destructive mass, and a PET/CT confirmed plasmacytoma of the left radius, and other bone lesions. FNA confirmed a plasmacytoma. She received palliative radiation to left radius (20 Gy in 5 fractions) in 06/2025 to discuss relapse myeloma options.
- What is the most optimal therapy for this patient?

Novel Therapies in Multiple Myeloma

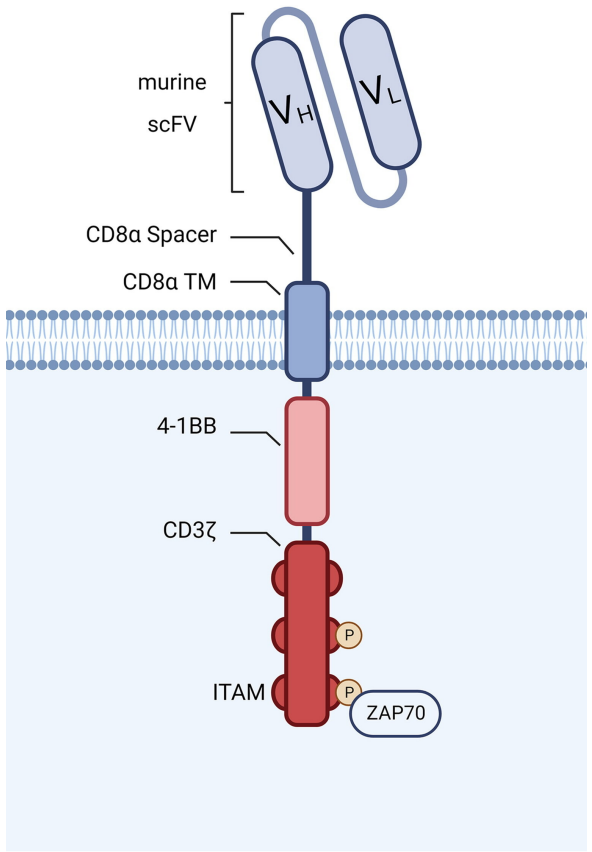


Progress with new targets/products

Target	Modality	NDMM	Early relapse	RRMM
CD38	Naked Ab			
SLAMF7	Naked Ab			
BCMA	ADC			
BCMA	CART			
BCMA	BsAb			
GPRC5D	BsAb			
GPRC5D	CART			
FcRH5	BsAb			

BCMA-Directed CAR-T in Multiple Myeloma

Ide-cel (ABECMA)



FDA Approved: Mar 26, 2021

KarMMa Trial

Phase II (n=128)

ORR: 72%

- 95% CI, 63.2 – 80.8
- ORR = sCR + VGPR + PR

mDOR: 22.6 months

- 95% CI, 14.39 – NE

mPFS: 11.3 months

- 95% CI, 10.3 – 15.3

mOS: 24.0 months

- 95% CI, 18.96 – NE

Cilta-cel (CARVYKTI)

FDA Approved: Feb 28, 2022

CARTITUDE-1 Trial

Phase Ib/II (n=97)

ORR: 98%

- 95% CI 92.7–99.7
- ORR = sCR + VGPR + PR

mDOR: 33.9 months

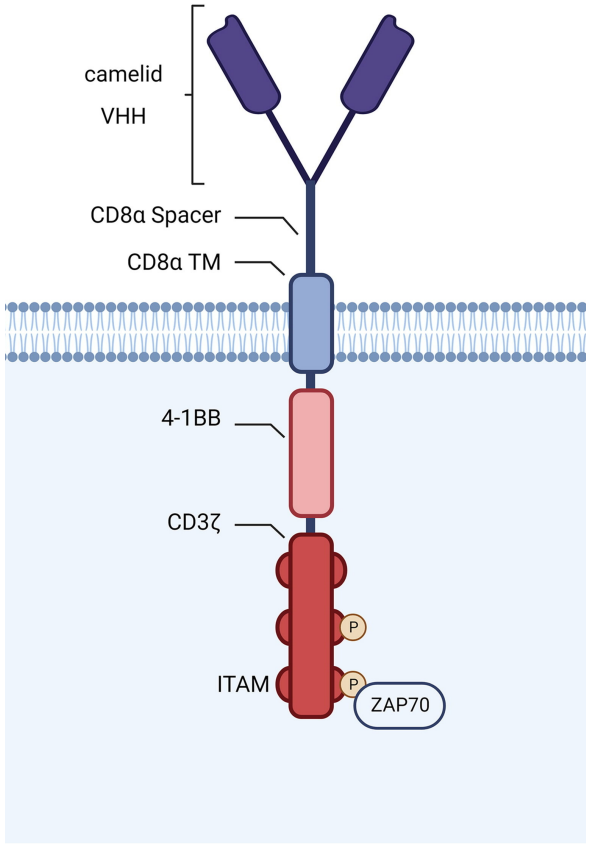
- 95% CI: 25.5 – NE

mPFS: 34.9 months

- 95% CI: 25.2 – NE

mOS: NR

- 62.9% OS at 36 months



https://www.abecmahcp.com/ (Accessed Feb 15, 2024); Yi Lin et al. *JCO* 41, 8009-8009 (2023).

The New York Times

From No Hope to a Potential Cure for a Deadly Blood Cancer

Multiple myeloma is considered incurable, but a third of patients in a Johnson & Johnson clinical trial have lived without detectable cancer for years after facing certain death.

Listen to this article · 7:33 min Learn more

Share full article

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Efficacy of CAR-T as earlier lines of therapy

KarMMa-3[1]

Screening

Key inclusion criteria:

- Aged ≥18 years with MM
- **2-4 prior LOT (including IMiD + PI + Anti-CD38 mAB)**
- **Refractory to the last regimen**
- ECOG PS 0-1

Randomization

2:1 Randomization

Stratified by:

- Age (<65 vs ≥ 65 years)
- Number of prior LOT (2 vs 3 or 4)
- High-risk cytogenetics (yes vs no/unknown)

Apheresis → **Optional Bridging**
DPd, DVd, IRd, Kd, or EPd
≤1 cycle

LDC → **Ide-cel infusion**
150 to 450 x 10^6
CAR+ T cells

Standard Regimens
DPd, DVd, IRd, Kd or EPd

Ide-cel allowed after confirmed PD

Cross Over

CARTITUDE-4[2]

Screening

Key inclusion criteria:

- Aged ≥18 years with MM
- **1-3 prior LOT (including PI + IMiD)**
- **LEN Refractory**
- ECOG PS 0-1

Randomization

1:1 Randomization

Stratified by:

- Choice of PVd/DPd
- ISS Stage
- Number of prior LOT

Apheresis → **Bridging**
PVd or DPd
≥1 cycle

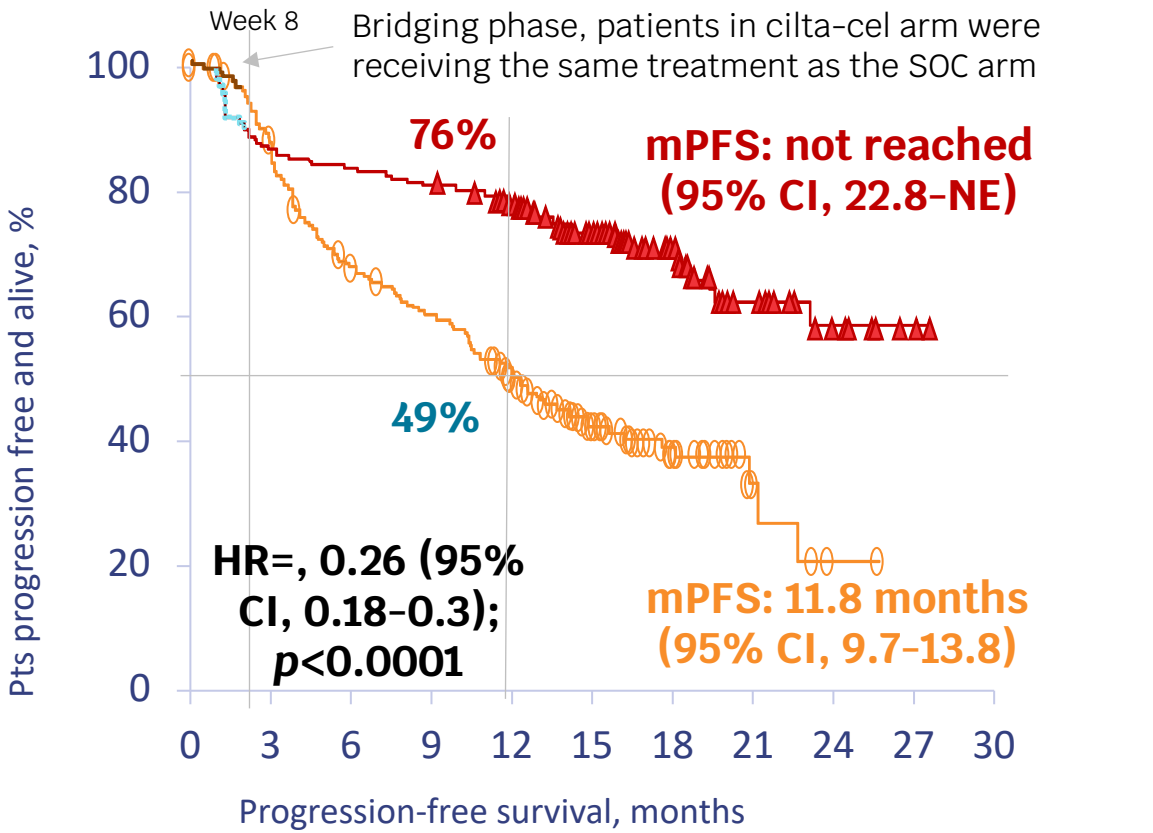
LDC → **Cilta-cel infusion**
(Target: 0. 75x10^6
CAR+ T cells/kg)

SOC arm
PVd or DPd

1. Rodriguez-Otero P et al. NEJM 2023;389 (11): 1002-1014. 2. San-Miguel J et al. NEJM 2023;389(4): 335-347

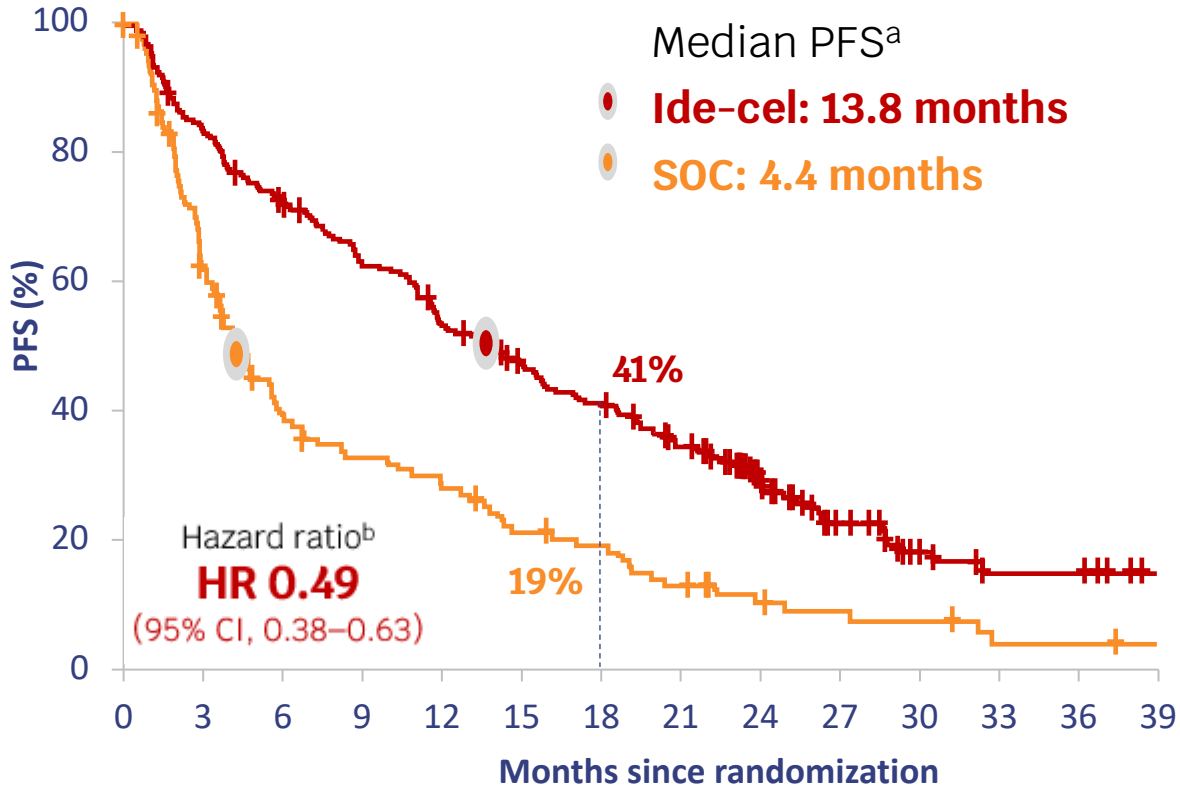
Efficacy of CAR-T as an earlier LoT

CARTITUDE-4: Primary Endpoint- PFS (ITT Population)



FDA APPROVED AFTER 1L AS OF 4/5/24

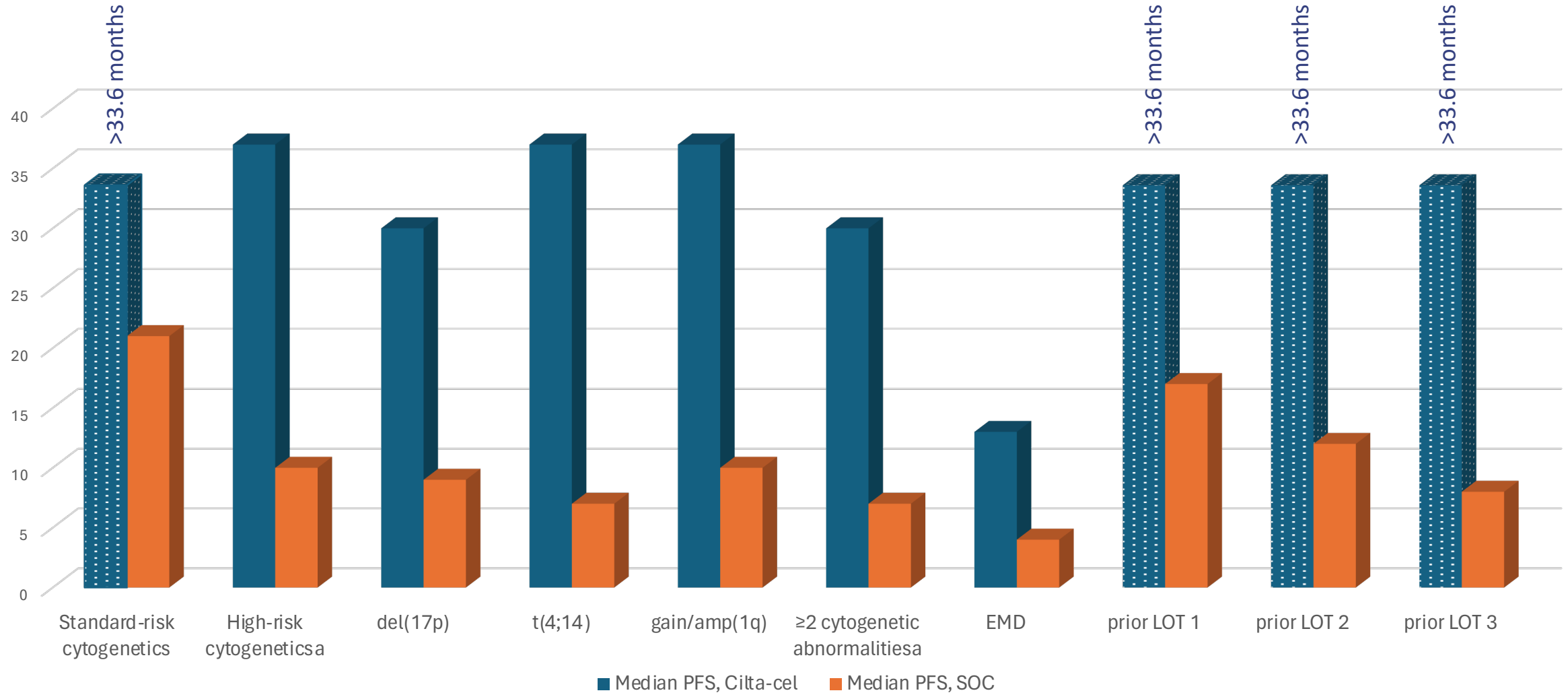
KarMMa-3 Primary Endpoint: PFS analysis (ITT)



FDA APPROVED AFTER 2L AS OF 4/5/24

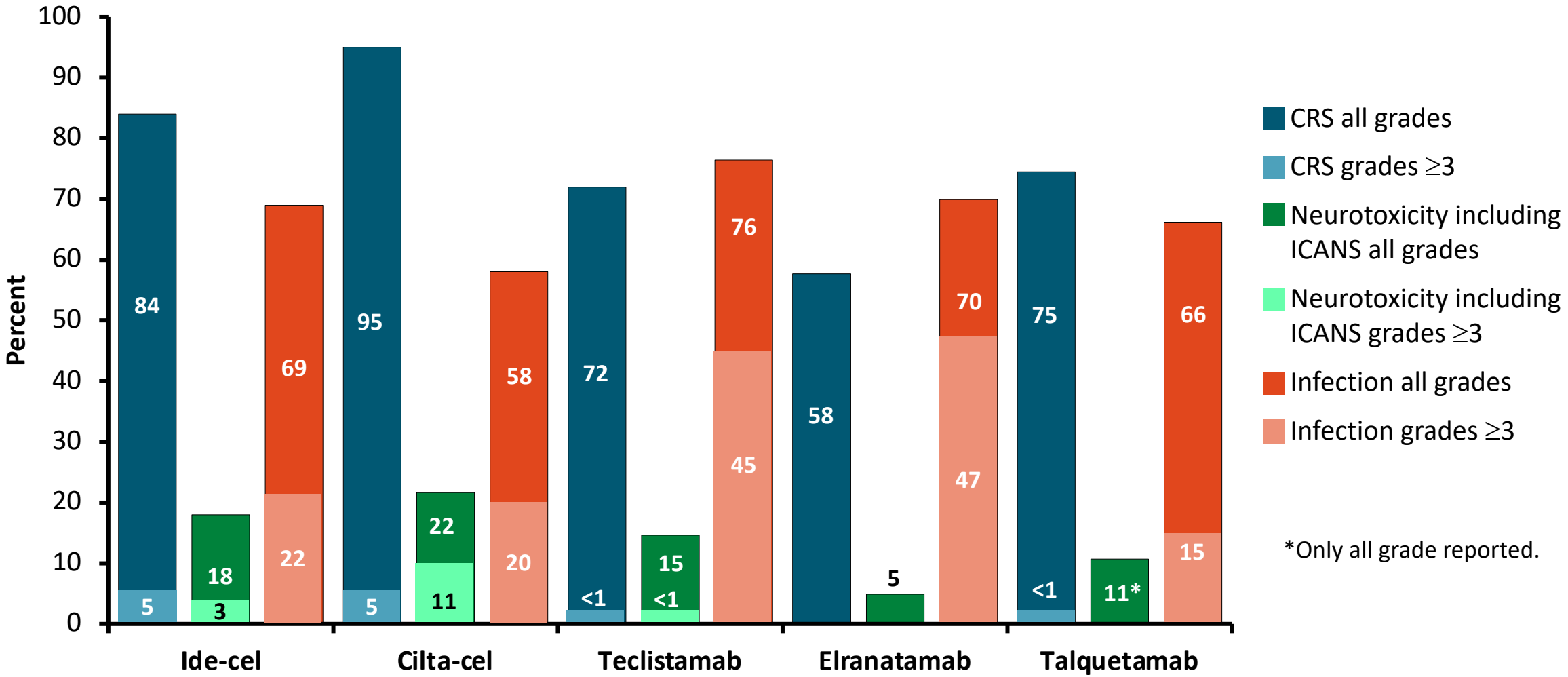
Dhakal et. al. ASCO 2023. J Clin Oncol 41, 2023 (suppl 17; abstr LBA106)

Median PFS by subgroups (CARTITUDE-4)



Sidana S, Martinez-Lopez J, Khan AM, Oriol A, Spencer A, Dhakal B, et al. Ciltacabtagene autoleucel (cilta-cel) vs standard of care (SOC) in patients (pts) with relapsed/refractory multiple myeloma (MM): CARTITUDE-4 survival subgroup analyses. Journal of Clinical Oncology. 2025;43(16_suppl):7539-.

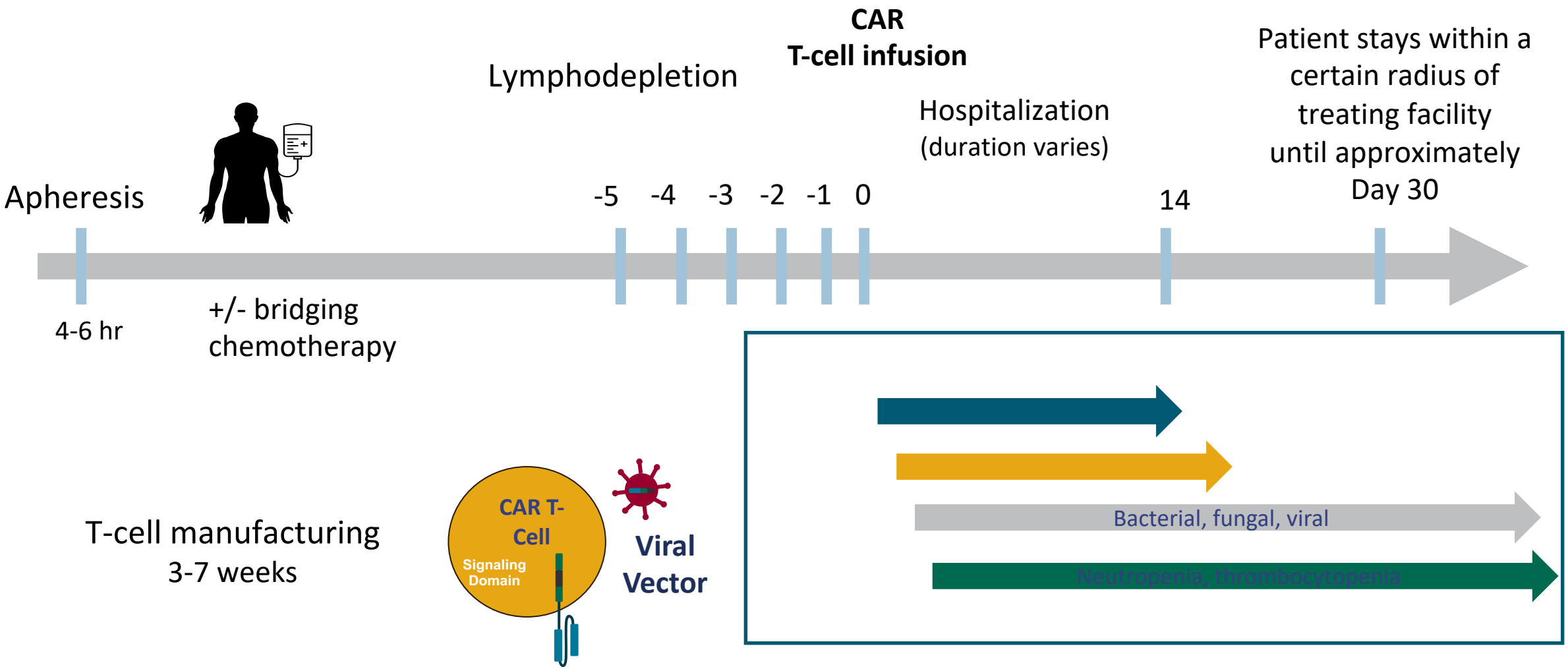
Safety - CAR T-Cell Therapy vs Bispecific Antibodies in RRMM



- Results are from different clinical trials/populations and should not be used for cross-comparison

Ludwig. Lancet Oncol. 2023;24:e255. Munshi. NEJM. 2021;384:705. Martin. JCO. 2023;41:1265. Moreau. NEJM. 2022;387:495. Tomasson. ASH 2023. Abstr 3385. Schinke. ASCO 2023. Abstr 8036.

Logistics/access - CAR T-Cell Treatment Schema

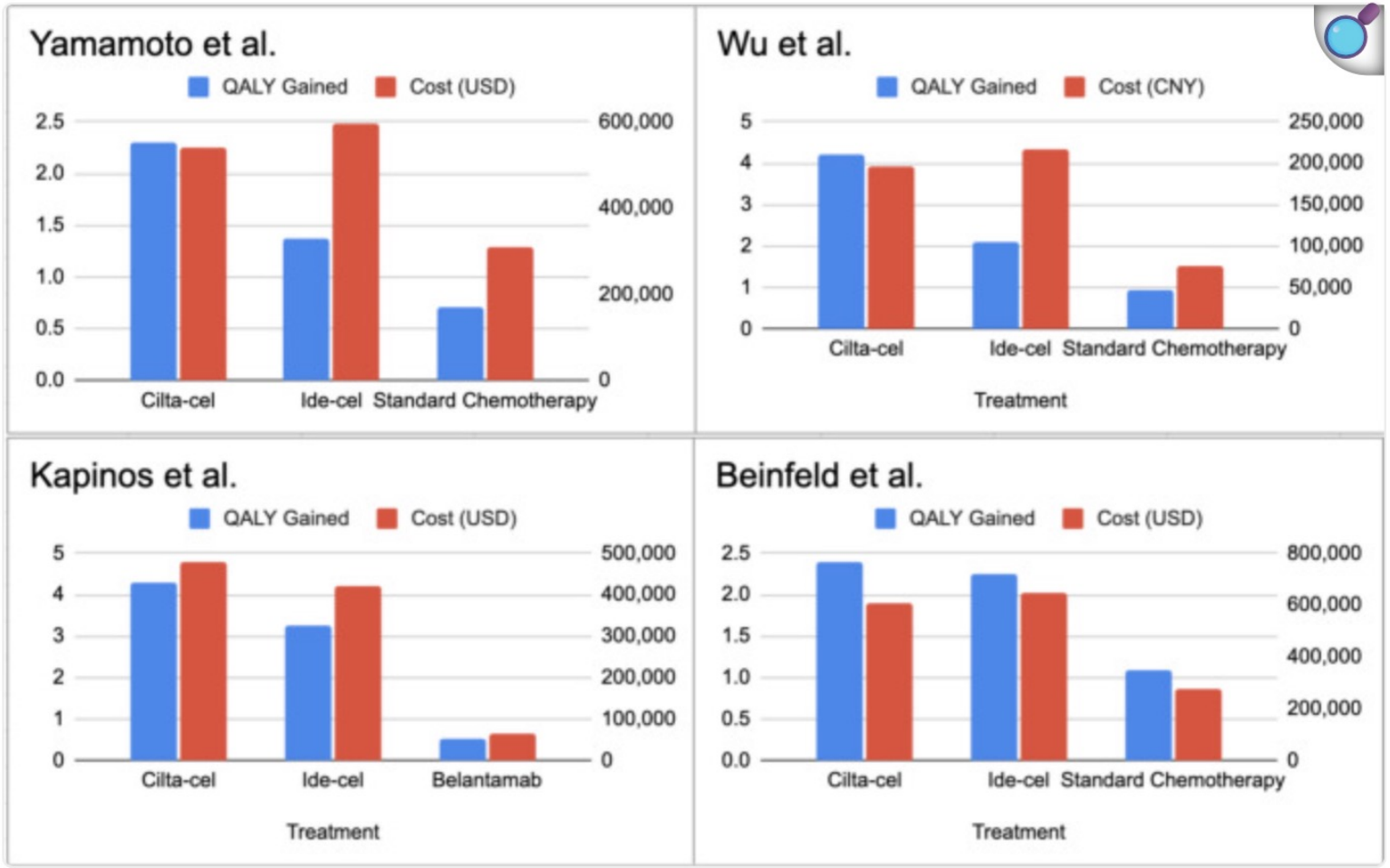


Beaupierre. J Adv Pract Oncol. 2019;10(suppl 3):29. Cho. Front Immunol. 2018;9:1821.
Ciltacabtagene autoleucel PI. Idecabtagene vicleucel PI. Perica. Biol Blood Marrow Transplant. 2018;24:1135.

Cost – CART vs BsAb

Approximate Annual Drug Cost for the regimen (USD)

CAR-T		
2nd Line	Cilta-Cel	$507,687
3rd Line	Ide-Cel	$503,455
T-cell engagers		
5th line	Belantamab	$371,658
5th line	Elranatamab	$486,506
5th line	Teclistamab	$234,963
5th line	Talquetamab	$372,380



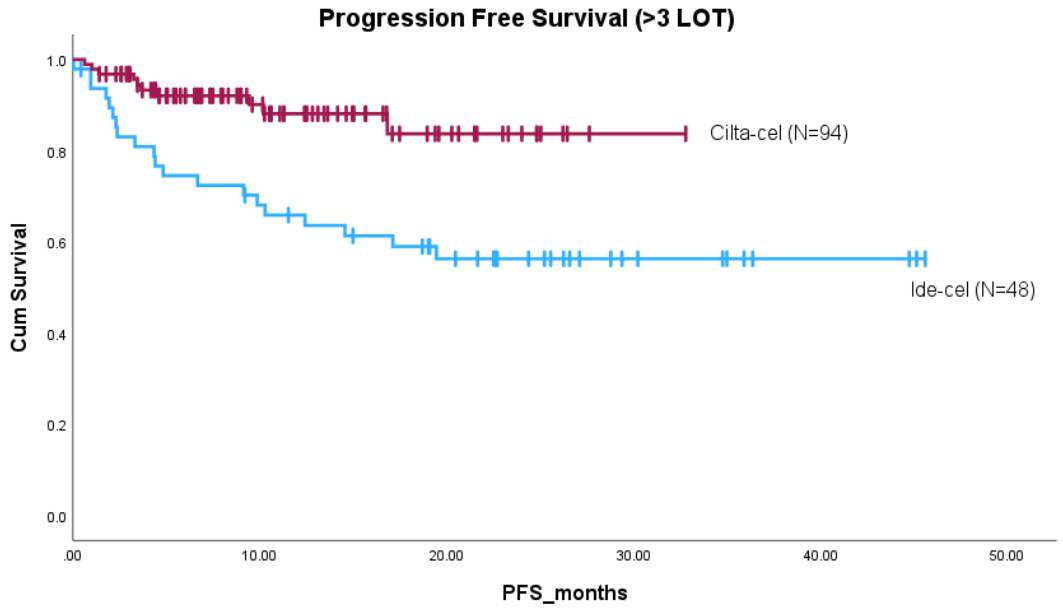
Conclusion: CAR-T used in earlier LOT and combined with a longer PFS are likely to be cost effective

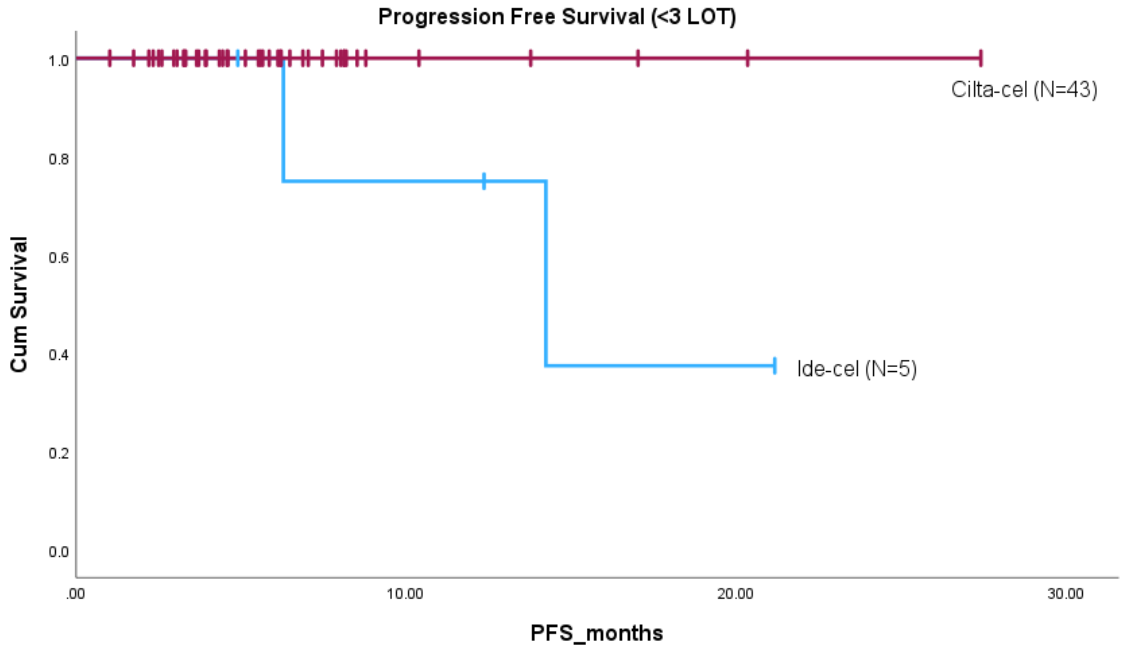
Keesari PR, Samuels D, Vegivinti CTR, Pulakurthi YS, Kudithi R, Dhar M, Janakiram M. Navigating the Economic Burden of Multiple Myeloma: Insights into Cost-effectiveness of CAR-T and Bispecific Antibody Therapies. Curr Hematol Malig Rep. 2025 Jan 4;20(1):3.

Congratulations! On behalf of the International Myeloma Society, I am pleased to inform you that you have been selected as one of the recipients of the IMS Young Investigator Award for Exemplary Abstract for the following abstract:

Shree Allada, Oyinda Adisa, Vikas A Gupta, Craig C Hofmeister, Jonathan L Kaufman, Sagar Lonial, Ajay K Nooka, Nisha S Joseph

Abstract title: Optimizing the use of Chimeric Antigen Receptor T-cell (CART) therapy for relapsed/refractory myeloma





Optimal Patient Phenotype for CART in Relapsed MM

- Good organ functions that could withstand CRS
  - Age less of an issue
- Disease control until patient is able to get to CART
  - Bridging therapy is crucial
  - Bispecific antibodies as bridging are not an absolute contraindication
- Selected patients for early relapse myeloma
  - High-risk phenotypes, functionally high-risk with early relapses, EMD
- Healthy T-cell repertoire
  - Earlier the better, when T-cells are less beaten up
- Absence of contraindications (relative)
  - Infectious history, CNS disease, neurological history etc.

Case continued

- This 60-year-old female with functional high-risk disease had a non-secretory relapse with biopsy-confirmed left radial plasmacytoma. Serum immunologic and bone marrow with no evidence of M-spike at this time. She is s/p palliative radiation
- Given the short PFS1 and the non-secretory relapse, recommended T-cell collection and initiation of bridging therapy with daratumumab, carfilzomib and dexamethasone (DKd) per CANDOR trial. While the trial used DKd regimen until progression, I am inclined to use DKd as a bridge to CAR-T (Cilta-cel) to use in early-relapsed setting.
- She underwent T-cell collection on 6/5/2025; started Flu/Cy on 7/23/25 with planned CART infusion on 7/28/2025

Label: The FDA has approved cilta-cel on 4/5/2024 for the treatment of patients with relapsed or refractory multiple myeloma who have received at least one prior line of therapy, including a PI and an IMiD, and who are refractory to lenalidomide

Conclusions

- CART therapies (ide-cel and cilta-cel) have demonstrated unprecedented activity in RRMM
- More recently, they have demonstrated proven activity as early lines of therapy compared to SOC options
- High-risk patients (biological, functional) do get benefitted with CART despite the fact the benefit may not be on par with standard risk patients
- CRS and neurotoxicity, cytopenias and infections are predictable and manageable, and concern for toxicities should not limit these life saving therapies be offered to relapsed myeloma patients

Dr. Joseph's strategy to win the debate

- **Efficacy data – not all products are the same (CART>BsAb)**
- **Safety data – justified (CART>BsAb)**
  - Rare toxicities – are just rare
- **Cost – justified (CART>BsAb)**
- **Access – send them all, we can offer them CART**
- **Kill the audience with kindness**

Myeloma team at Emory – always available for a call about your patient

Sagar Lonial

Ajay Nooka

Jonathan Kaufman

Nisha Joseph

Amy Langston

Craig Hofmeister

Vikas Gupta

Nishi Shah

Richa Parikh