City of Hope

Multidisciplinary Approaches to Cancer Symposium

Harnessing the Immune System to Fight Relapsed/Refractory Multiple Myeloma

Focus: CAR T-Cell Therapy

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City of Hope

Disclosures

- Consultant/Advisor for BMS, Janssen & Sanofi
- On the Speakers Bureau for Janssen, BMS

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

The off-label/investigational use of Teclistamab, Talquetamab, Ide-Cel, Cilta-Cel, Elranatamab, Mezigdomide, Iberdomide will be addressed.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

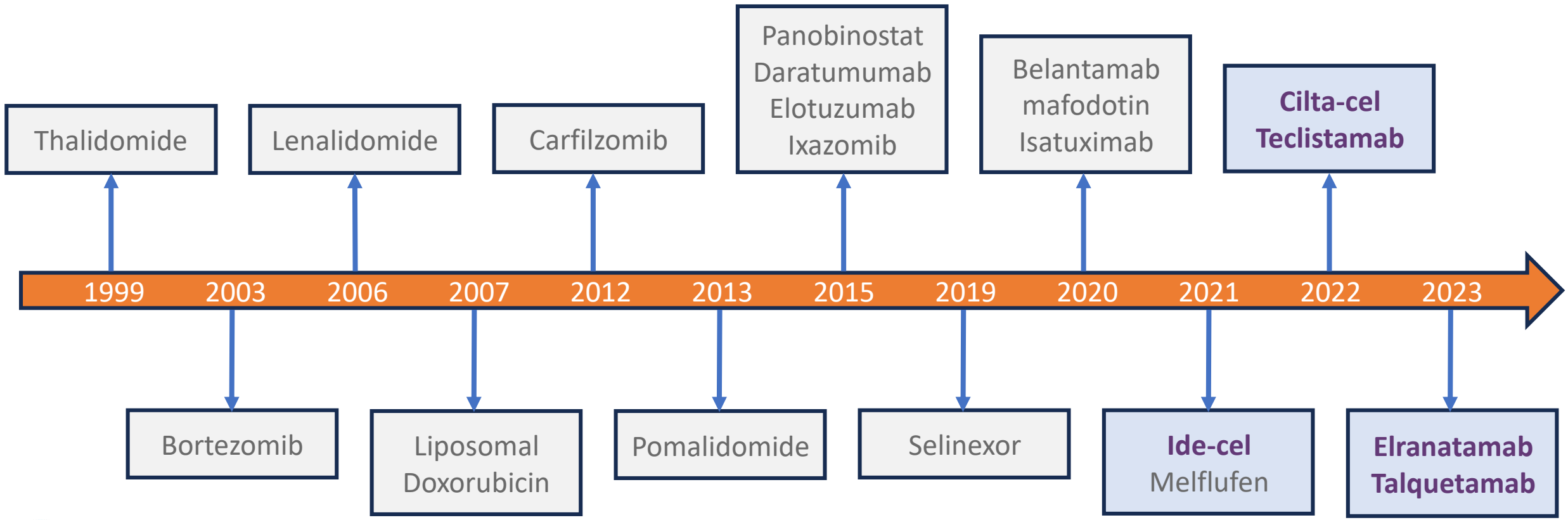
EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Inclusion of underrepresented minorities in clinical trials and generalizability to standard practice.*
- *Generalizability to elderly populations and inclusion in CAR T and bispecific trials*

A cornucopia of treatment options for RRMM



THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,l-o]
Relapsed/Refractory Disease After 1–3 Prior Therapies

Preferred Regimens*
Order of regimens does not indicate comparative efficacy

Anti-CD-38 Refractory	Bortezomib-Refractory	Lenalidomide-Refractory
• Carfilzomib/lenalidomide/dexamethasone (category 1) • Carfilzomib/pomalidomide/dexamethasone • Pomalidomide/bortezomib/dexamethasone (category 1) ***After two prior therapies including lenalidomide and a PI*** ▸ Elotuzumab/pomalidomide/dexamethasone ***After two prior therapies including an IMiD and a PI and with disease progression on/within 60 days of completion of last therapy*** ▸ Ixazomib/pomalidomide/dexamethasone	• Carfilzomib/lenalidomide/dexamethasone (category 1) • Daratumumab/carfilzomib/dexamethasone (category 1) • Daratumumab/lenalidomide/dexamethasone (category 1) • Isatuximab-irfc/carfilzomib/dexamethasone (category 1) • Carfilzomib/pomalidomide/dexamethasone ***After one prior therapy including lenalidomide and a PI*** ▸ Daratumumab/pomalidomide/dexamethasone (category 1) ***After two prior therapies including lenalidomide and a PI*** ▸ Isatuximab-irfc/pomalidomide/dexamethasone (category 1) ▸ Elotuzumab/pomalidomide/dexamethasone	• Daratumumab/bortezomib/dexamethasone (category 1) • Daratumumab/carfilzomib/dexamethasone (category 1) • Isatuximab-irfc/carfilzomib/dexamethasone (category 1) • Pomalidomide/bortezomib/dexamethasone (category 1) • Carfilzomib/pomalidomide/dexamethasone ***After one prior therapy including lenalidomide and a PI*** ▸ Daratumumab/pomalidomide/dexamethasone (category 1) ***After two prior therapies including lenalidomide and a PI*** ▸ Isatuximab-irfc/pomalidomide/dexamethasone (category 1) ▸ Elotuzumab/pomalidomide/dexamethasone ***After two prior therapies including an IMiD and a PI and with disease progression on/within 60 days of completion of last therapy*** ▸ Ixazomib/pomalidomide/dexamethasone

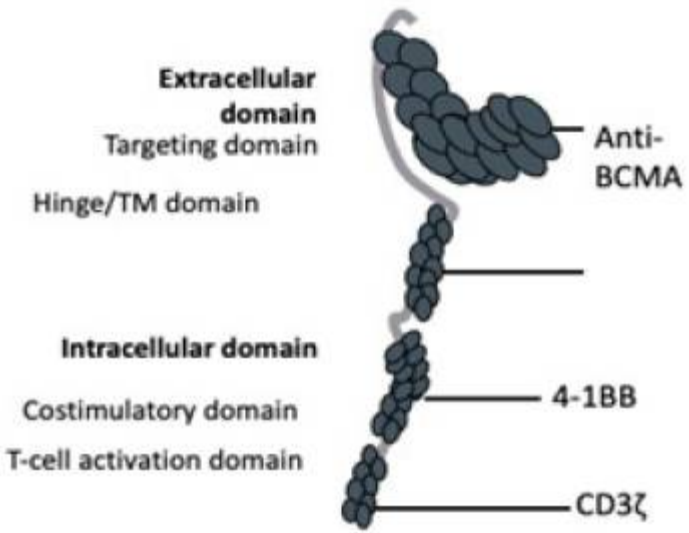
CAR T-Cell Therapy
After one prior line of therapy including IMiD and a PI, and refractory to lenalidomide
▸ Ciltacabtagene autoleucel (category 1)

After two prior lines of therapies including an IMiD, an anti-CD38 monoclonal antibody and a PI
▸ Idecabtagene vicleucel (category 1)

BCMA CAR T Constructs

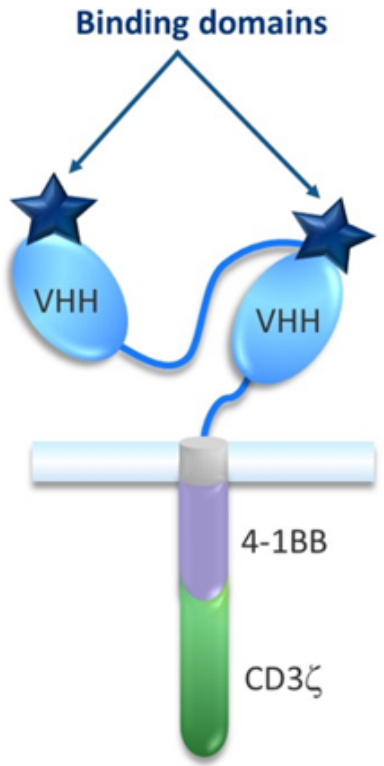
Idecabtagene Vicleucel

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



Ciltacabtagene Autoleucel

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



Martino M et al. *Cancers. 2021*

Driving CAR T Forward

ORIGINAL ARTICLE

Ide-cel or Standard Regimens in Relapsed and Refractory Multiple Myeloma

Paula Rodriguez-Otero, M.D., Ph.D., Sikander Ailawadhi, M.D., Bertrand Arnulf, M.D., Ph.D., Krina Patel, M.D., Michele Cavo, M.D., Ajay K. Nooka, M.D., M.P.H., Salomon Manier, M.D., Ph.D., Natalie Callander, M.D., Luciano J. Costa, M.D., Ph.D., Ravi Vij, M.D., Nizar J. Bahlis, M.D., Philippe Moreau, M.D., Scott R. Solomon, M.D., Michel Delforge, M.D., Jesus Berdeja, M.D., Anna Truppel-Hartmann, M.D., Zhihong Yang, Ph.D., Linda Favre-Kontula, Ph.D., Fan Wu, Ph.D., Julia Piasecki, B.A., Mark Cook, M.B., Ch.B., Ph.D., and Sergio Giralt, M.D.

ORIGINAL ARTICLE

Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma

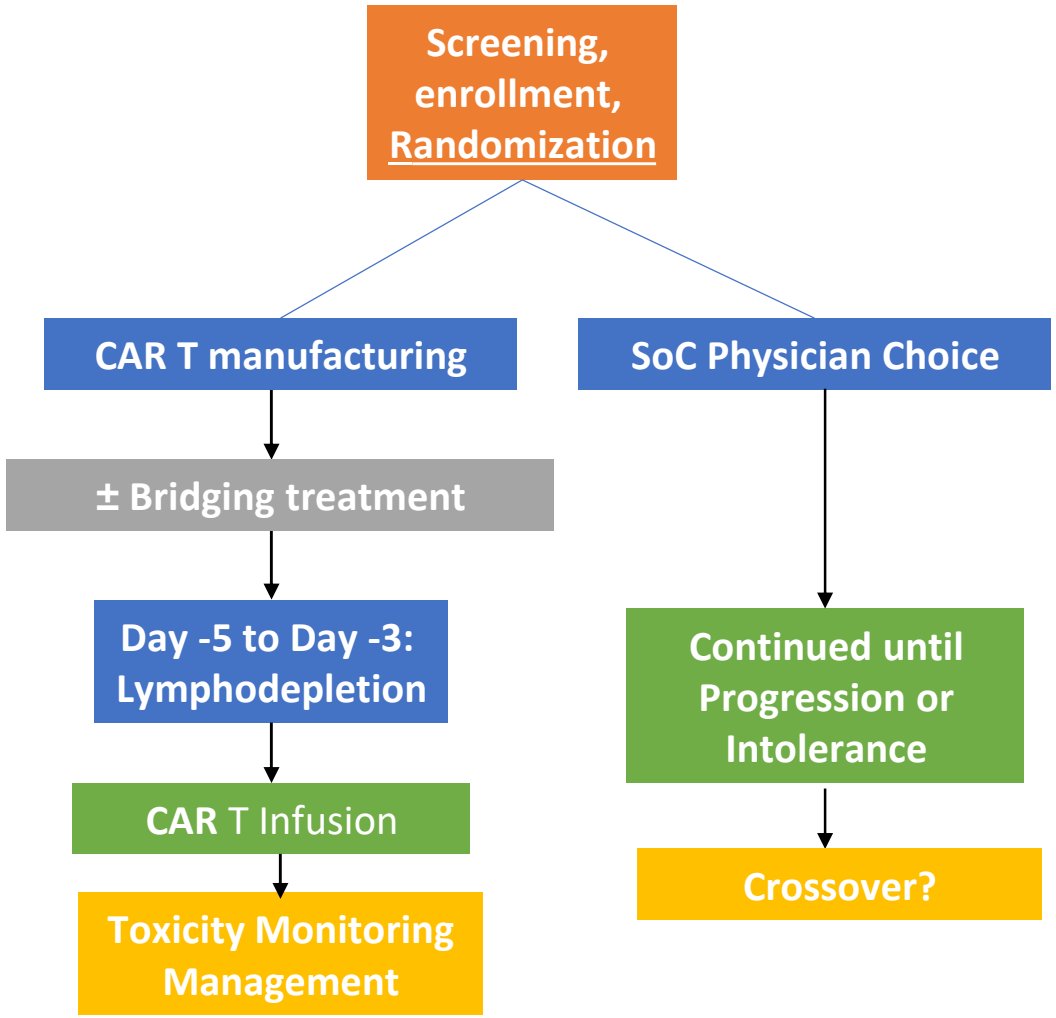
Jesús San-Miguel, M.D., Ph.D., Binod Dhakal, M.D., Kwee Yong, Ph.D., Andrew Spencer, M.D., Sébastien Anguille, M.D., Ph.D., María-Victoria Mateos, M.D., Ph.D., Carlos Fernández de Larrea, M.D., Ph.D., Joaquín Martínez-López, M.D., Philippe Moreau, M.D., Ph.D., Cyrille Touzeau, M.D., Xavier Leleu, M.D., Irit Avivi, M.D., Michele Cavo, M.D., Tadao Ishida, M.D., Ph.D., Seok Jin Kim, M.D., Ph.D., Wilfried Roeloffzen, M.D., Niels W.C.J. van de Donk, M.D., Ph.D., Dominik Dytfeld, M.D., Surbhi Sidana, M.D., Luciano J. Costa, M.D., Albert Oriol, M.D., Ph.D., Rakesh Popat, M.D., Ph.D., Abdullah M. Khan, M.B., B.S., Yaël C. Cohen, M.D., P. Joy Ho, M.B., B.S., D.Phil., James Griffin, Ph.D., Nikoletta Lendvai, M.D., Carolina Lonardi, Pharm.D., Ana Slaughter, Ph.D., Jordan M. Schecter, M.D., Carolyn C. Jackson, M.D., Kaitlyn Connors, B.S., Katherine Li, M.S., Enrique Zudaire, Ph.D., Diana Chen, M.S., Jane Gilbert, M.Sc., Tzu-min Yeh, M.S., Sarah Nagle, M.D., Erika Florendo, M.S., Lida Pacaud, M.D., Nitin Patel, B.M., B.Ch., Simon J. Harrison, Ph.D., and Hermann Einsele, M.D.

KarMMa-3 Ide-Cel

- ≥18 years old, measurable disease
- ECOG 0-1
- **2-4 prior LoT including dara, IMID, PI**

- **Randomized 2:1 to ide-cel vs. SoC**
  - DPd, DVd, IRd, Kd, elo-Pd
  - Stratified by age, HR cyto, no. prior LOT

Crossover permitted



CARTITUDE-4 Cilta-Cel

- ≥18 years old, measurable disease
- ECOG 0-1
- **1-3 prior LoT**
- **Lenalidomide-refractory**

- **Randomized 1:1 to cilta-cel vs. SoC**
  - DPd or PVd
  - Stratified by regimen for SOC/bridging, ISS, no. prior LOT

Crossover not permitted

San-Miguel et al. (2023), Rodriguez-Otero et al. (2023)

Baseline Characteristics

Trial	KarMMa-3		CARTITUDE-4	
Arm	Ide-cel	SoC	Cilta-cel	SoC
N	254	132	208	211
Median age, y	63	63	61.5	61
Male, %	61	60	56	59
Extramedullary disease, %	24	24	21	17
ECOG-0 Performance Status, %	47	50	55	57
High-risk cytogenetics (w/o 1q), %	42	46	35	33
Prior LOT, median (range)	3 (2-4)	3 (2-4)	2 (1-3)	2 (1-3)
Penta-refractory, %	6	5	1	0.5
Triple-class refractory, %	65	67	14	16
Prior ASCT	84	86	NR	NR

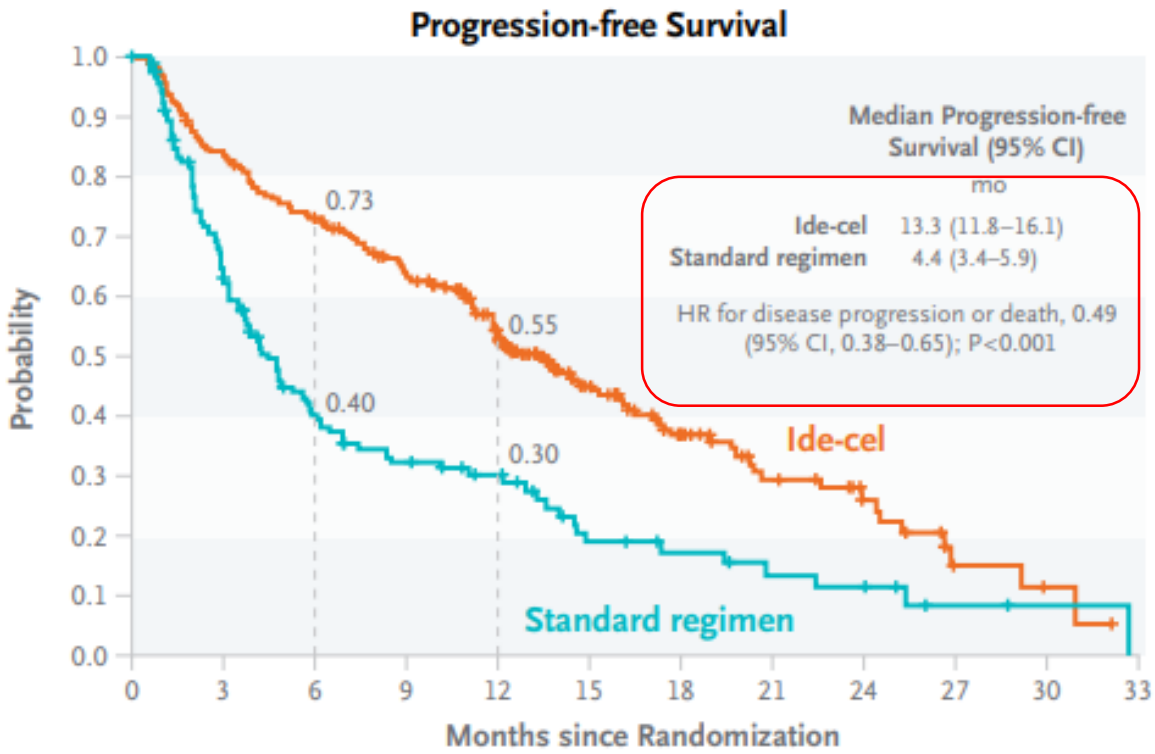
San-Miguel et al. (2023), Rodriguez-Otero et al. (2023)

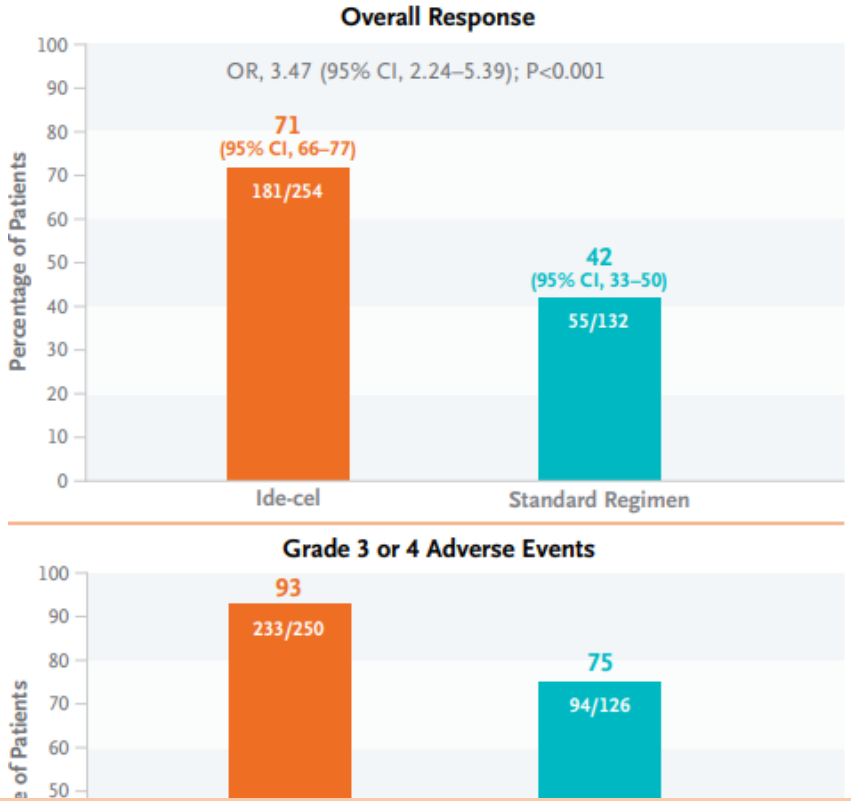
The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Ide-cel or Standard Regimens in Relapsed and Refractory Multiple Myeloma

Rodriguez-Otero P et al. DOI: 10.1056/NEJMoa2213614





KarMMa-3 update [ASH 2023] – Ide-cel vs SOC

Median FU – 30.9 mo

Improvement in CR rate 44% (95% CI 38-50) vs. 5% (95% CI 2-9)

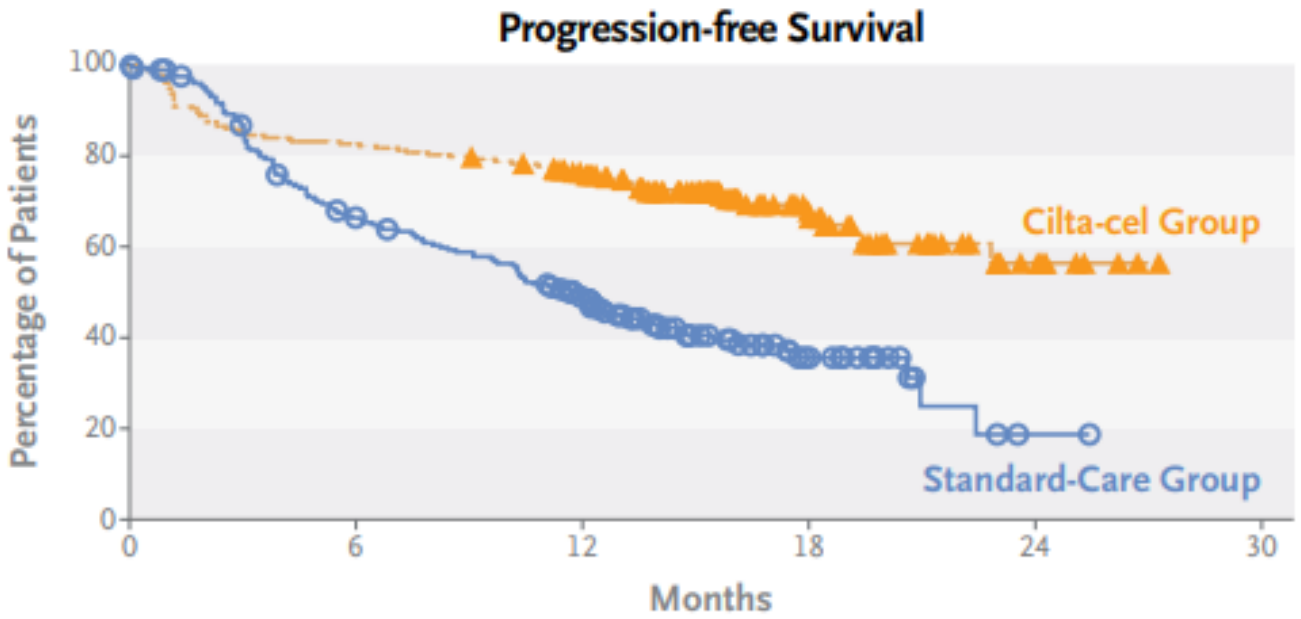
Prespecified sensitivity analyses adjusting for crossover showed a median OS of 41.4 months for Abecma (95% CI: 30.9-NR) and 23.4 months (95% CI: 17.9-NR) for standard regimens (95% CI: 0.45-1.09; HR: 0.69), trend for OS

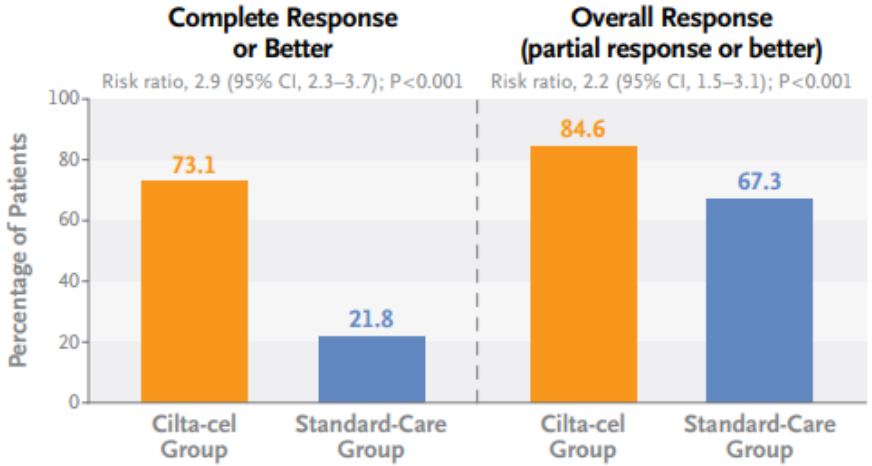
The NEW ENGLAND JOURNAL of MEDICINE

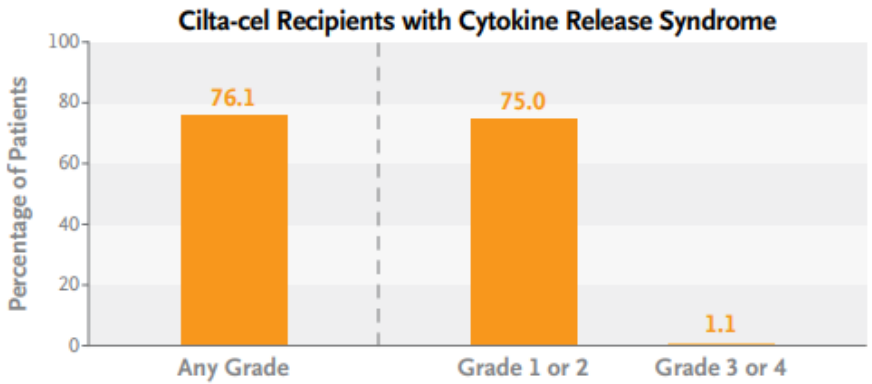
RESEARCH SUMMARY

Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma

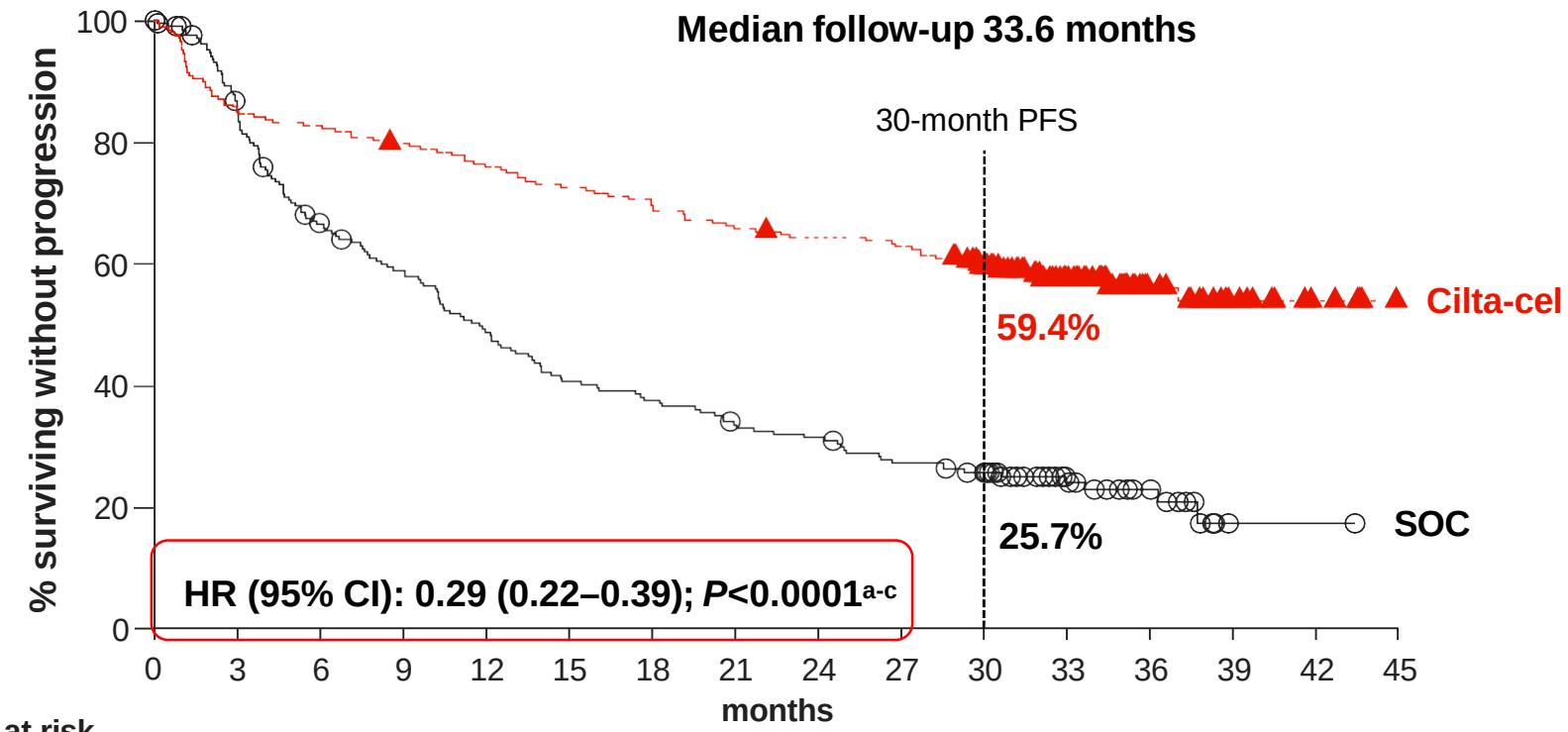
San-Miguel J et al. DOI: 10.1056/NEJMoa2303379







Long-Term CARTITUDE-4 Update (34 Months): Cilta-cel Maintained Significant Improvement in Progression-Free Survival

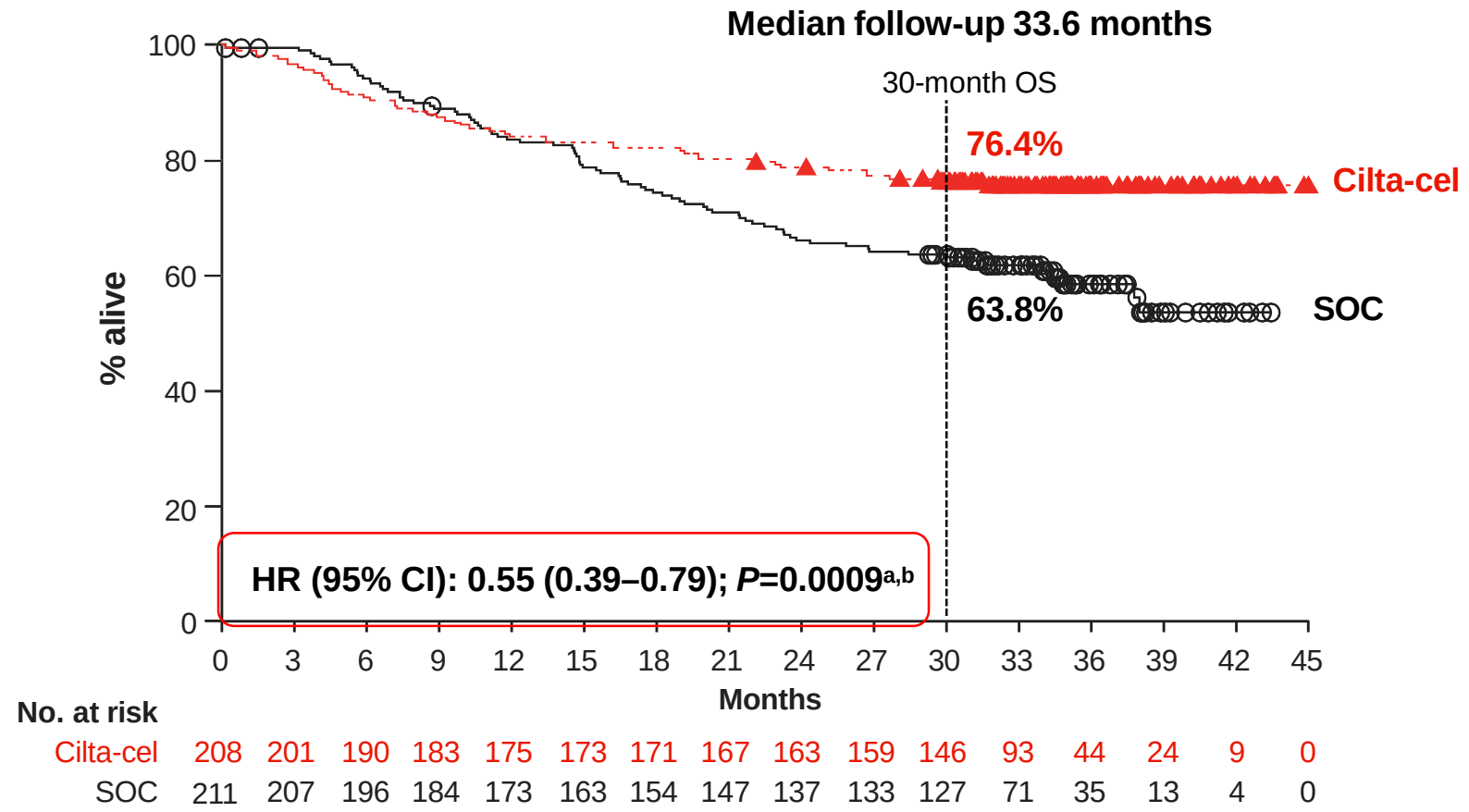


~70% reduction in the risk of progression or death in patients who received cilta-cel and mPFS has not been reached

[a]Constant piecewise weighted log-rank test. [b]HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable, including only PFS events that occurred >8 weeks post randomization.
[c]Nominal *P* value.
Cilta-cel, ciltacabtagene autoleucel; HR, hazard ratio; mPFS, median progression-free survival; PFS, progression-free survival; SOC, standard of care.

Presented by M-V Mateos at the 21st International Myeloma Society (IMS) Annual Meeting; September 25–28, 2024; Rio de Janeiro, Brazil

Long-Term CARTITUDE-4 Update (34 Months): Cilta-cel Significantly Improved Overall Survival

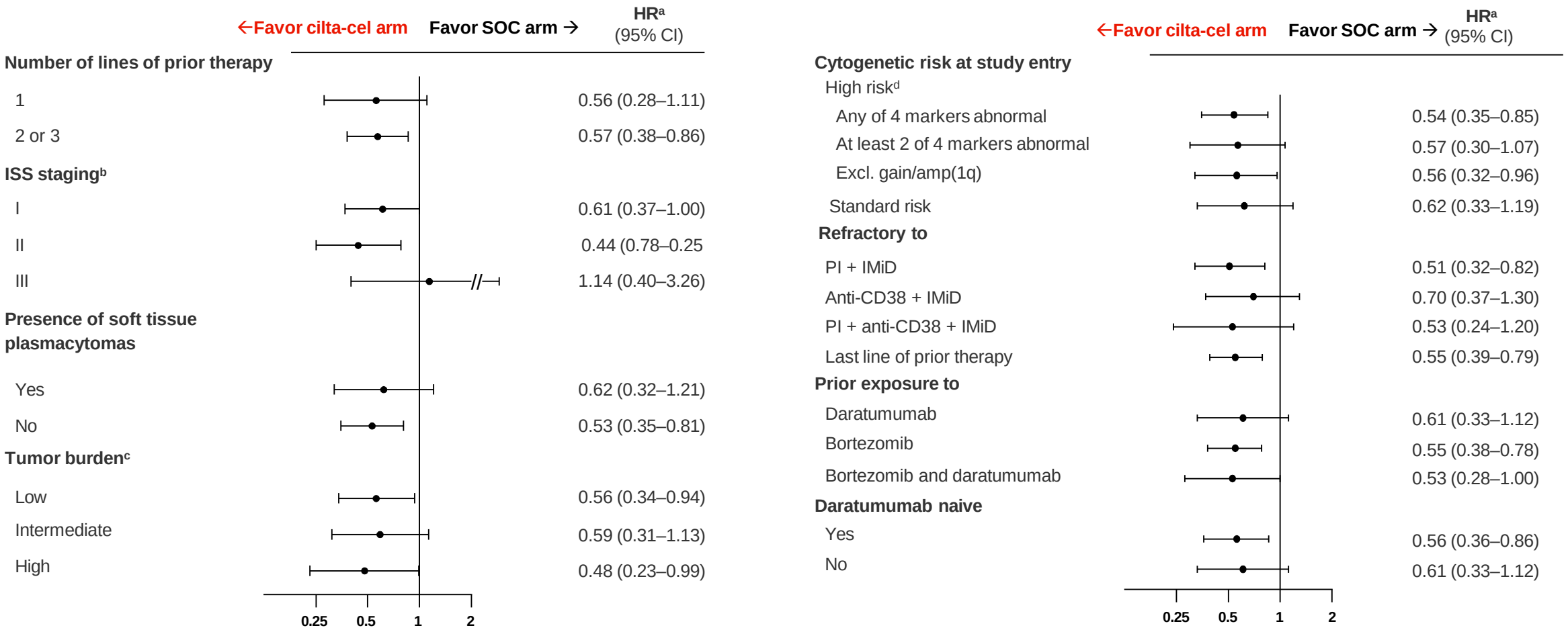


First CAR-T to demonstrate overall survival benefit in multiple myeloma

[a]Log-rank test. *P*-value, 0.0009, crossed the prespecified boundary of 0.0108 as implemented by the Kim-DeMets spending function with parameter=2. [b]Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable.
CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; HR, hazard ratio; OS, overall survival; SOC, standard of care.

Presented by M-V Mateos at the 21st International Myeloma Society (IMS) Annual Meeting; September 25–28, 2024; Rio de Janeiro, Brazil

Long-Term CARTITUDE-4 Update (34 Months): Consistent Overall Survival Benefit for Cilta-cel Across Prespecified Subgroups

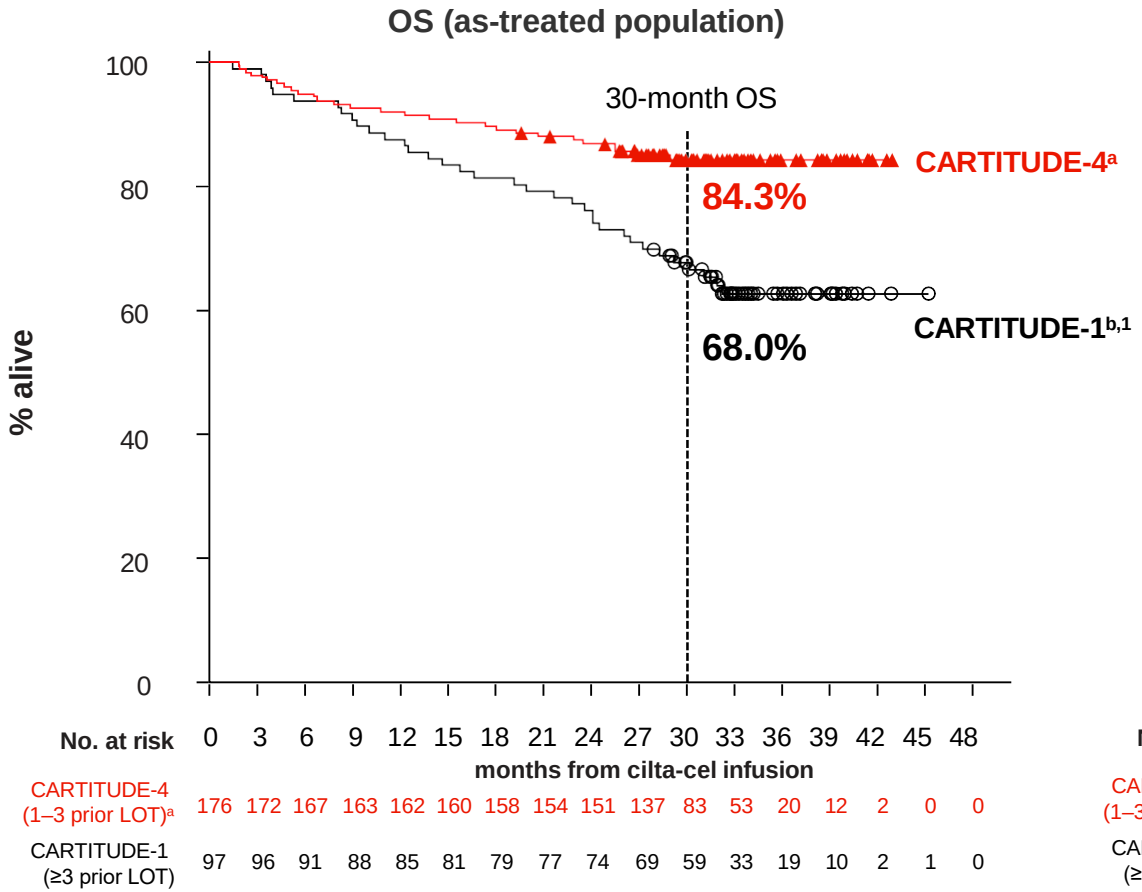


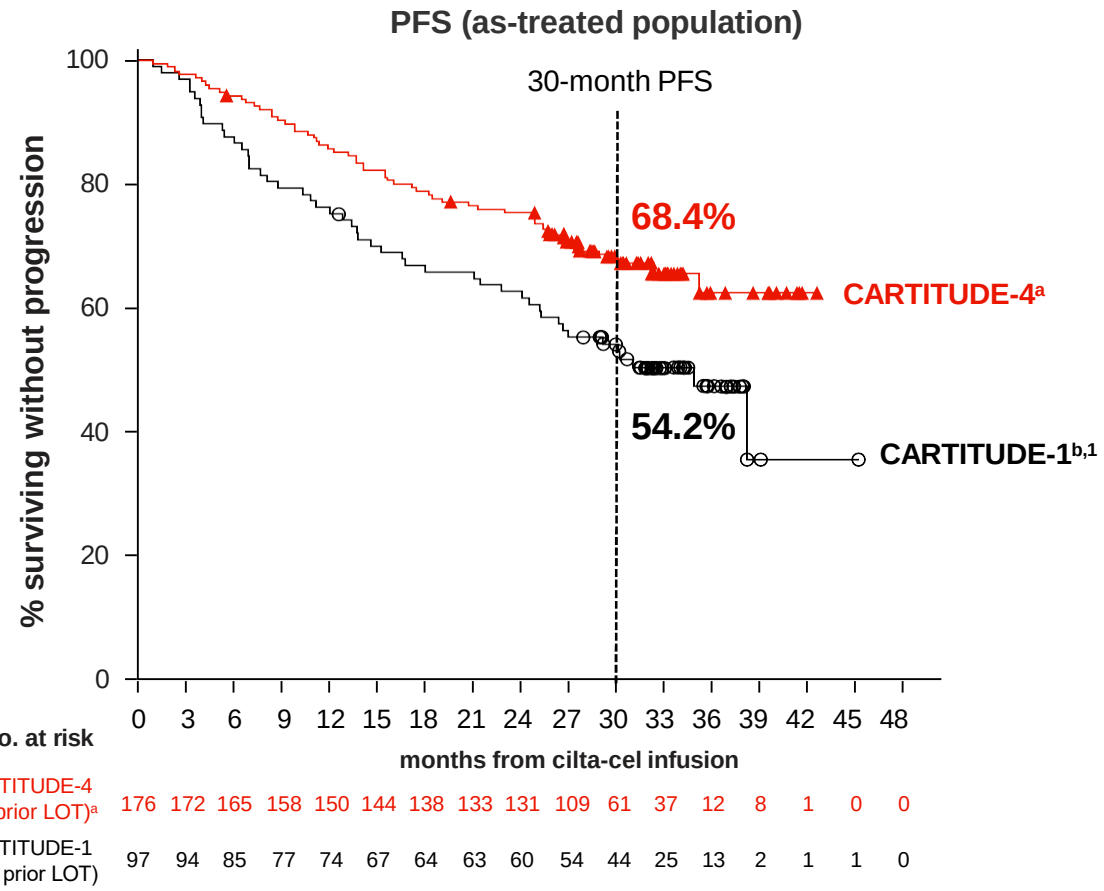
Consistent reduction in risk of death across prespecified subgroups[e]

[a]HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable. HR <1 indicates an advantage for the cilta-cel arm. [b]Based on serum β_2-microglobulin and albumin. [c]Low tumor burden defined as meeting all following parameters (as applicable): bone marrow % plasma cell <50%, serum M-protein <3 g/dL, serum free light chain <3000 mg/L; high tumor burden defined as meeting any of the following parameters: bone marrow % plasma cell ≥80%, serum M-protein ≥5 g/dL, serum free light chain ≥5000 mg/L; intermediate tumor burden did not fit either criteria of high or low tumor burden. [d]Positive for del(17p), t(14;16), t(4;14), and/or gain/amp(1q) by fluorescence in situ hybridization testing. Protocol-defined high-risk cytogenetics refers to "Any of 4 markers abnormal". [e]Except ISS stage III, which had n=12 in cilta-cel arm and n=14 in SOC arm. Cilta-cel, ciltacabtagene autoleucel; HR, hazard ratio; IMiD, immunomodulatory drug; ISS, International Staging System; OS, overall survival; PI, proteasome inhibitor; SOC, standard of care.

Presented by M-V Mateos at the 21st International Myeloma Society (IMS) Annual Meeting; September 25–28, 2024; Rio de Janeiro, Brazil

Long-Term CARTITUDE-4 Update (34 Months): Numerically Higher Overall and Progression-Free Survival Rates Versus CARTITUDE-1





Cilta-cel use in earlier lines demonstrated numerically higher rates of overall and progression-free survival

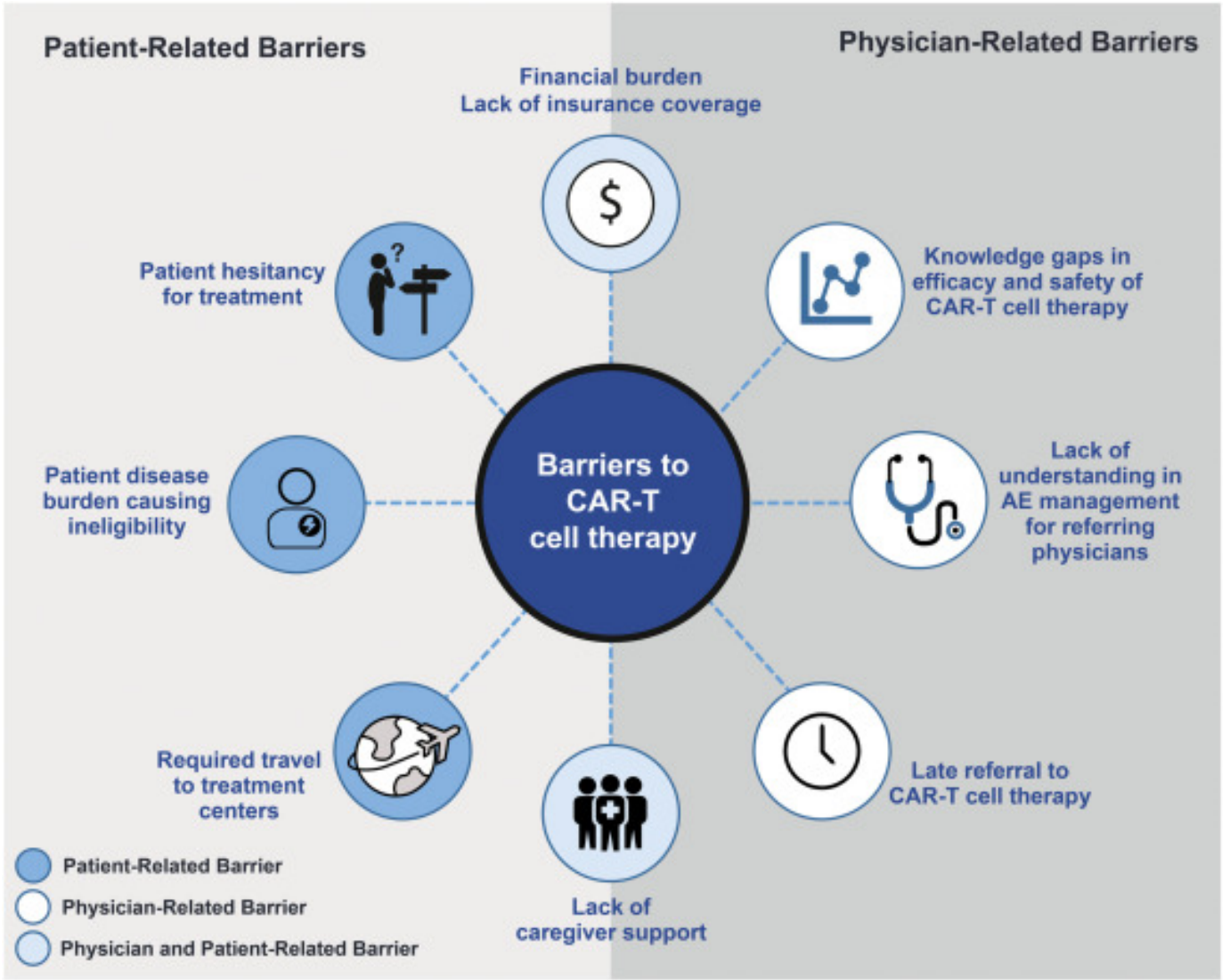
[a]Re-baselined to begin at time of cilta-cel infusion for patients who received cilta-cel as study treatment, with median follow-up of 30.5 months. [b]33.4-month median follow-up.
Cilta-cel, ciltacabtagene autoleucel; LOT, line of therapy; OS, overall survival; PFS, progression-free survival; SOC, standard of care.
1. Lin et al. Abstract 8009, presented at ASCO; June 2–6, 2023; Chicago, IL, USA & Virtual.

Presented by M-V Mateos at the 21st International Myeloma Society (IMS) Annual Meeting; September 25–28, 2024; Rio de Janeiro, Brazil

Safety Outcomes of Earlier BCMA CAR T

Trial	KarMMa-3	CARTITUDE-4
CAR T product	Ide-cel	Cilta-cel
N	250	208
AEs, any/Gr 3-4/Gr 5,%	99/93/14	100/97/NR
CRS, Any, %	88	76.1
Gr 3/4	4	2
Gr 5	1	0
Median onset, d	1	8
Median duration, d	3.5	3
NT, Any, %	34	20.5 (4.5 ICANS, 17 other, 0.6 MNT)
Gr 3/4	7	2.8 (0.1 ICANS, 2.3 other, 0 MNT)
Gr 5	0	0
Median onset, d	3	ICANS 9.5, other 21, MNT 85
Median duration, d	2	ICANS 2

Rodriguez-Otero et al. (2023); Berdeja et al. (2021)



Overcoming Barriers to Referral for Chimeric Antigen Receptor T Cell Therapy in Patients with Relapsed/Refractory Diffuse Large B Cell Lymphoma Hoffmann, Marc S. et al.Transplantation and Cellular Therapy, Volume 29, Issue 7, 440 - 448

First relapse

- Early interaction with the community oncologist is key to getting patients into CAR-T cell therapy at the appropriate time
- Educate community oncologists on eligibility criteria for CAR-T cell therapy to help obtain early referrals and quicker treatment
- Provide community oncologists with a direct line of communication (via personal cell phone) with treatment center physicians to facilitate timely referral

Leukapheresis

- Early, direct communication between the community oncologist and the leukapheresis center is key to optimizing the manufacturing process
- Prior to leukapheresis, educate community oncologists about the negative effects bendamustine and other therapies can have on T-cell fitness
- Leukapheresis material can be collected and cryopreserved, which may be optimal for some patients. Keep community oncologists apprised throughout the leukapheresis process to facilitate collaboration

Bridging therapy

- Educate community oncologists about appropriate bridging therapy options to maintain disease control and ensure CAR-T cell therapy eligibility

Infusion

- Keep the community oncologist apprised of the infusion process and the state of the patient following infusion
- Monitor patients for the first 7 days after infusion for possibility of adverse events
- Instruct patients to remain within proximity of certified healthcare facility for at least 4 weeks

Return to the community

- Clear, direct handoff of the patient back to the community oncologist for follow-up care is important

Long-term follow-up

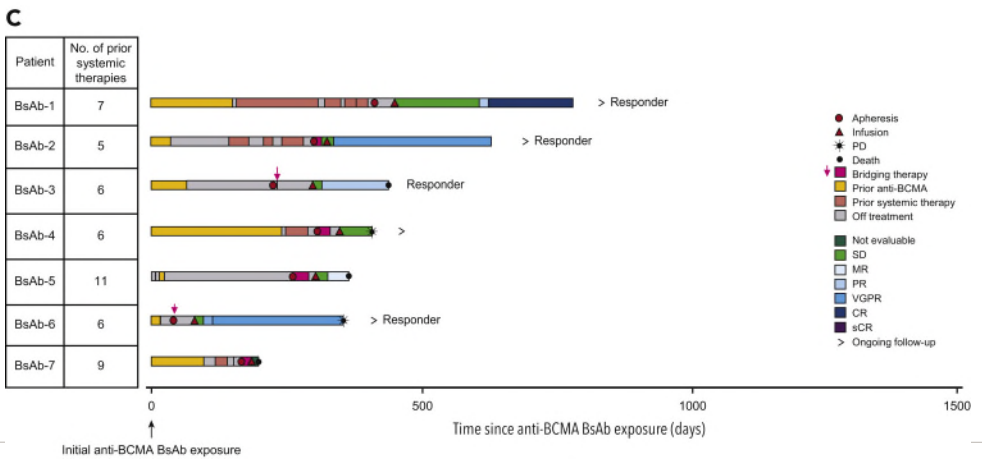
- Perform imaging following infusion to identify early relapses; educate the community oncologist on signs to monitor. Real world follow-up protocol for imaging is evolving and based on the remission status of the patient
- Long-term follow-up care is essential for management of cytopenias and B-cell aplasia, and to monitor for rare late relapses
- Community oncologists should monitor the patient for long-term immune reconstitution

Overcoming Barriers to Referral for Chimeric Antigen Receptor T Cell Therapy in Patients with Relapsed/Refractory Diffuse Large B Cell Lymphoma Hoffmann, Marc S. et al.Transplantation and Cellular Therapy, Volume 29, Issue 7, 440 - 448

Sequencing CAR T and Bispecifics?

- Mechanisms of resistance
  - CAR T
    - Infrequent genetic events (6% biallelic loss of BCMA leading to loss of antigen expression)
    - Anti-CAR antibodies - >50% in ide-cel
    - Loss of CAR T persistence
  - Bispecifics
    - More frequent mutations leading to antigen loss (~43% BCMA BsAb)
    - T-cell exhaustion from tonic signaling (could impact subsequent CAR T production)

Data, MoR, experience, and FDA approvals favor using BCMA CAR T therapy earlier than Bispecific Antibodies



Lee et al. *Nat Med.* 2023; Cohen et al. *Blood.* 2023; Liu et al. *ASCO Post*. 2024; Hansen et al. *JCO*. 2023