Update on CAR T-Cells and Bispecific Antibody Therapy for Myeloma

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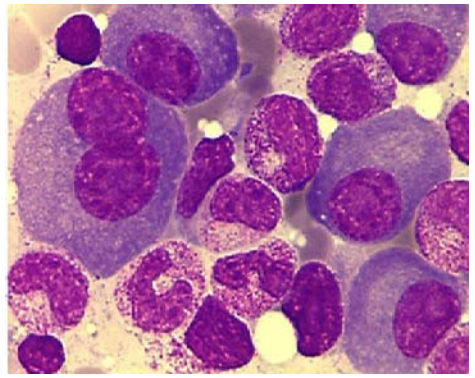
Professor of Internal Medicine
Director of Myeloma, Waldenstrom's, and Amyloidosis Program

Controversies in Hematologic Malignancies Symposium
MCW 3/2/24



UTSouthwestern Harold C. Simmons Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

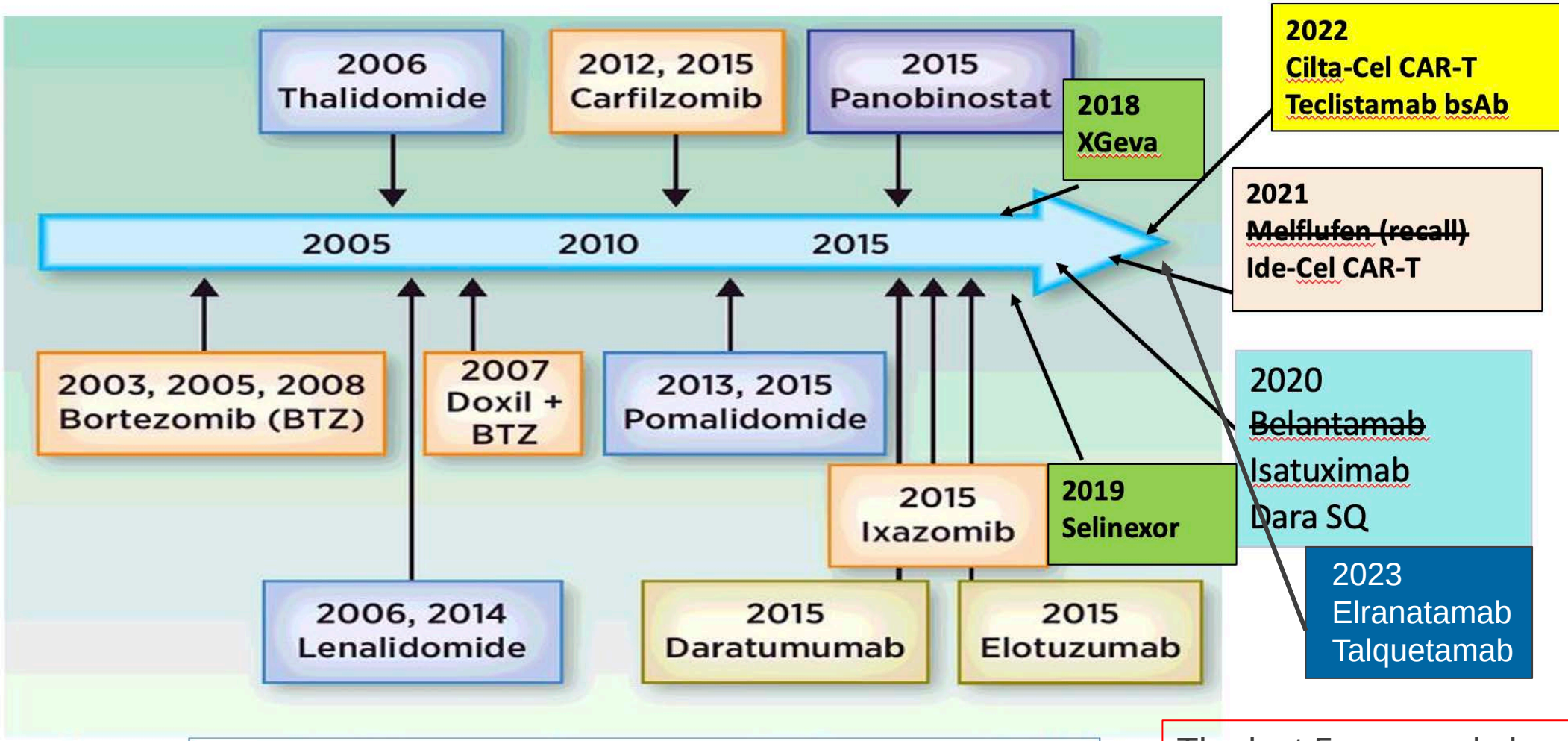
MYELOMA, WALDENSTROM'S & AMYLOIDOSIS PROGRAM
UTSouthwestern Medical Center

Conflicts of Interest

Advisory Board activities or Consultation with Honoraria:

Janssen, Celgene, BMS, Amgen, GSK, AbbVie, Beigene, Cellectar, Sanofi, Prothena

FDA APPROVALS IN MYELOMA



20 **drugs approved since 2000 !!!**
compared to only oral and iv Melphalan from 1960s to 2000

The last 5 approvals have all been Either CAR-T cells or BsAbs

OUTCOMES FOR TRIPLE CLASS EXPOSED RRMM Prior to Availability of CAR T-cell therapy options (The Unmet Need)

Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy

Gandhi, UH et al

Leukemia **33**, 2266–2275 (2019) | Cite this article

Monoclonal Antibodies in Multiple Myeloma: Outcomes after Therapy Failure, the MAMMOTH study)

- Overall response rate to first regimen after anti-CD38 Ab was 31% with median PFS 3.4 mo and median OS 9.3 months

Gandhi et al, Leukemia 2019.

Clinical Case

- 61 Female at Dx (age 71 now): Dx 7/2012 with Stage 3 Lambda Light Chain Myeloma (High risk double hit 17p deletion and add 1q)
- Progressed after at least 9 lines of therapy (w/ 2 SCT) over the course of 6 years:
- VRD + Auto SCT, Ixa, VRD, Dara/dex, Dara-CyBorD, Car/Pom/dex, Dara-CyBorD, 2nd Auto SCT, Dara-VRD –> Progression with Lambda in 500s in 5/2018
- Travelled from MN to TX to enroll on anti-BCMA CAR T-cell trial -> Leukapheresis 4/12/18 -> Bridging Dara/Pom/Cy/Dex -> LD Flu/Cy -> Day 0 CAR T-cell infusion 5/21/18
- Grade 1 Cytokine Release Syndrome (CRS) day 14 and 15 so d/c delayed until day 18. No Tocilizumab or steroids, No ICANS/NT
- Lambda FLC 580 mg/L (pre-CAR) -> 370 (d7) -> 138 (d14) (before fevers) -> 2.31 mg/L on 6/11/18 (d21). M-spike 0.03 at d28 but 0 by 3 mo (sCR)
- She remains in stringent CR at 5.5 + years (despite being OFF all therapy since 5/2018)
- Ongoing IVIG replacement due to Hypogammaglobulinemia

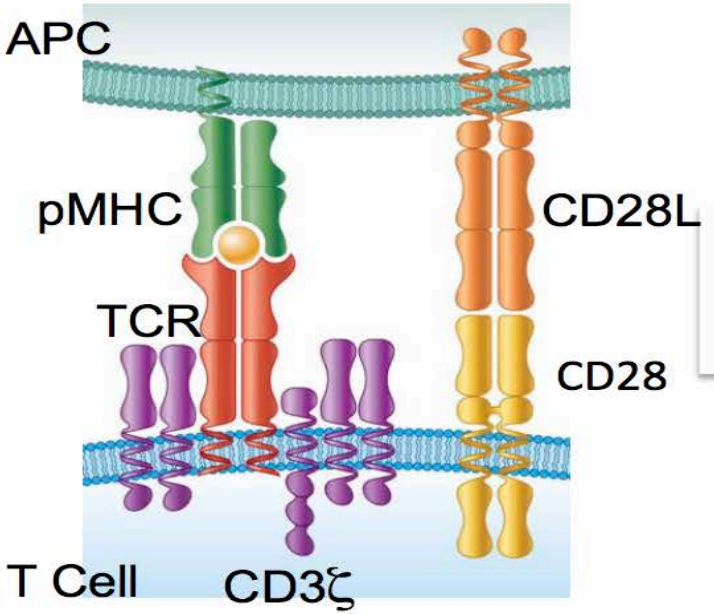
Types of Immunotherapy

- **Monoclonal antibodies**
  - Anti-CD20 mAb (Rituximab)
- **Checkpoint Inhibitors**
  - PD-1 inhibitors (Pembrolizumab), CTLA4 inhibitors (Ipilimumab)
- **Cancer Vaccines**
  - Peptide vs Protein vs Tumor cell vs Dendritic cell (Sipuleucel-T)
- **BITE (Bispecific T cell Engager that links T cell and cancer)** (Teclistamab for MM 10/22, Elrenatamab and Talquetamab 8/23)
  - Off the shelf, Blinatumomab approved for ALL (anti CD3/19)
- **Adoptive Cell Transfer Therapy (ACT)**
  - TIL: Tumor-Infiltrating Lymphocytes (limited success)
  - Genetically Engineered T-Cell Receptor therapy (Tumor Specific T-cell Receptor gene modification) (requires Ag presentation by MHC and requires separate costimulation)
  - Chimeric Antigen Receptor (CAR) T-cell Therapy (provides costimulation and no need for MHC presentation)

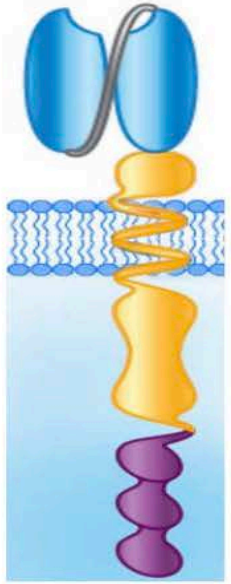
CAR Design: Critical Elements of T Cell Activation and Function in a Single Molecule

CAR T cells are genetically altered to express CAR on the cell surface.

T Cell Receptor



Chimeric Antigen Receptor



scFv: recognize tumor surface proteins

Costimulatory Signal 2:
CD28 or 4-1BB or OX40

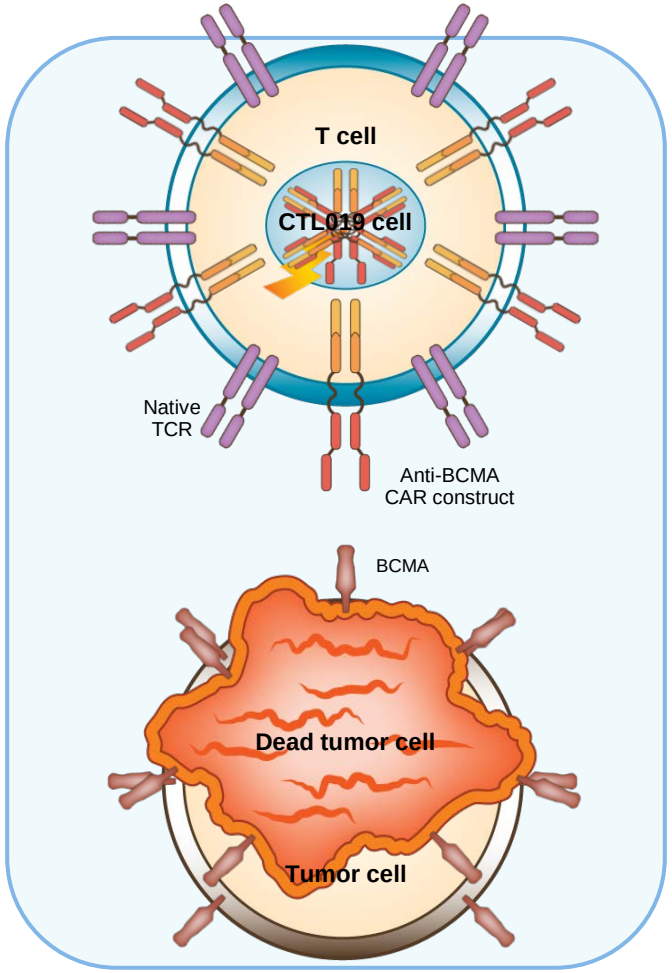
Essential Signal 1:
CD3ζ

Activation Independent of MHC
Limited to cell surface proteins

Graeber, 2018: Immunotherapy and the Race to Cure Cancer

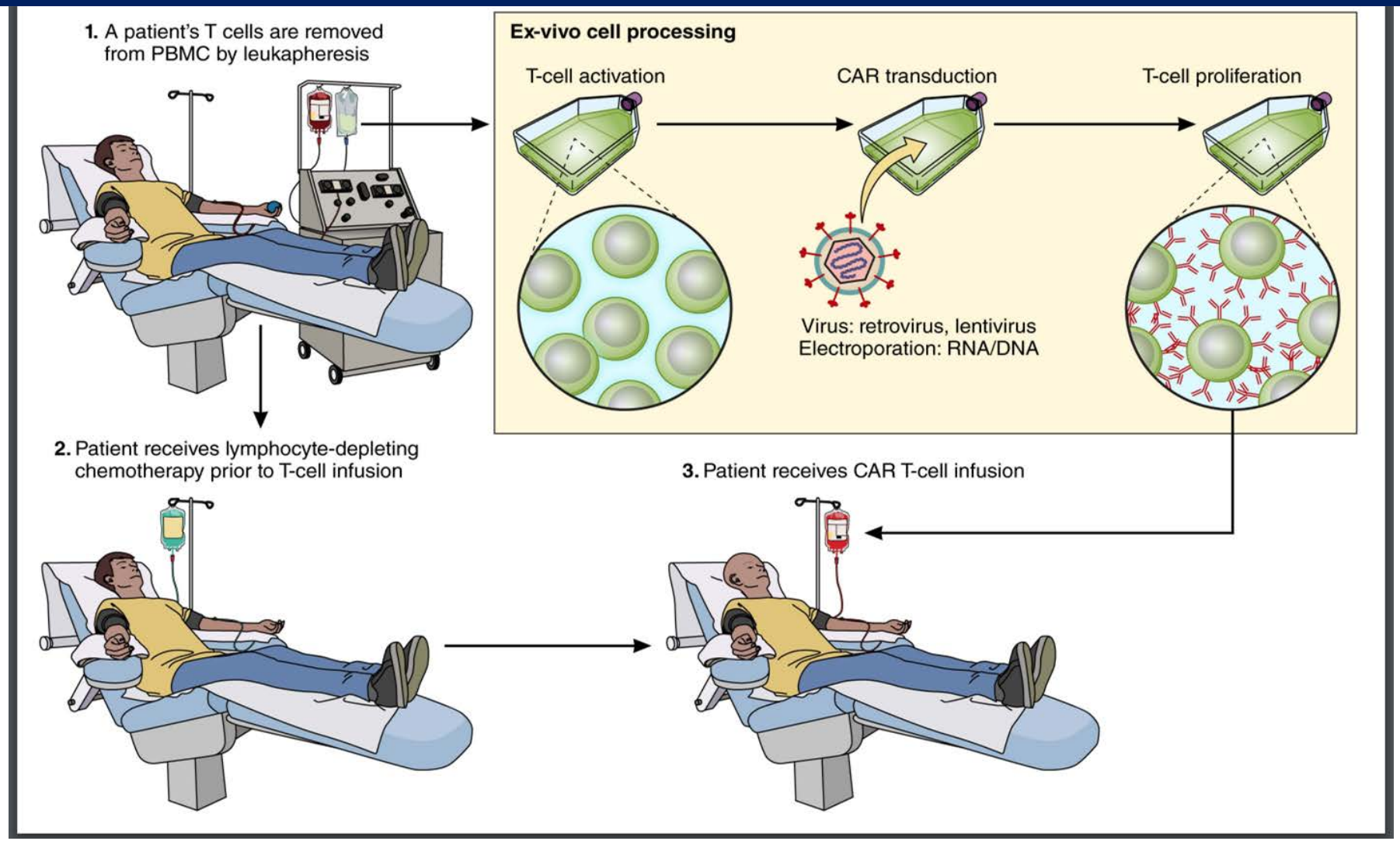
Redirecting T-Cell Specificity with **C**himeric **A**ntigen **R**eceptor (CAR) T cell therapy

- Gene transfer technology stably expresses CARs on T cells[1,2]
- Takes advantage of the cytotoxic potential of T cells, killing tumor cells in an *antigen-dependent* manner[1,3]
- Persistent CAR T cells consist of both effector (cytotoxic) and central memory T cells[3]
- **T cells are *non-cross resistant* to chemotherapy**



1. Milone MC, et al. *Mol Ther.* 2009;17:1453-1464.
2. Hollyman D, et al. *J Immunother.* 2009;32:169-180.
3. Kalos M, et al. *Sci Transl Med.* 2011;3:95ra73.

Overview of CAR-T Cell Process

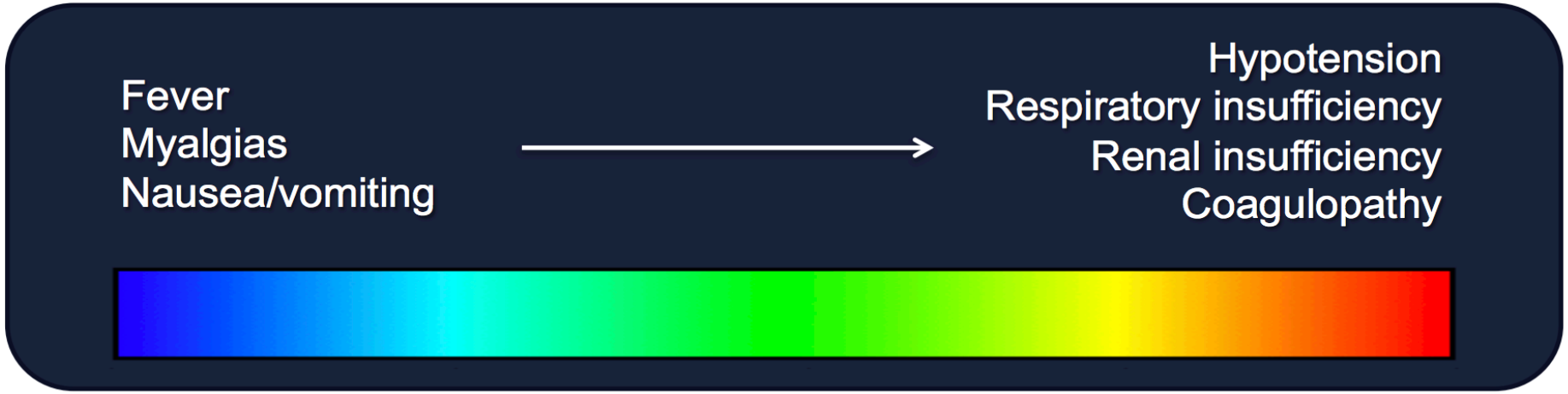


McGuirk J. *et al*, Cytotherapy 2017; 19:1015-1024

Cytokine Release Syndrome (CRS)

CRS is related to T-cell expansion and may be necessary for efficacy

- Symptoms typically occur 1-14 days after CAR T- cell infusion in ALL



- Severity scales with disease burden

- Inflammatory response from IL-6 and other cytokine production
- The more CAR-T triggering the more cytokine release (increases w/ dz burden)
- Low grade treated with symptom management (anti-pyretics)
- Higher grade or refractory treated with Tocilizumab +/- steroids

Neurotoxicity (ICANS) with CAR T-cell Therapy

- **CRES** = Cytokine Related Encephalopathy Syndrome
- **ICANS** = Immune effector Cell Associated Neurologic Syndrome
- Symptoms and signs: somnolence, encephalopathy, aphasia, seizures, confusion, delirium, tremors, paralysis of limbs, incontinence.
- Onset of neurotoxicity may be biphasic:
  - 1st phase (Days 0-5) – symptoms may appear with other CRS
  - 2nd phase (After day 5) – starts after CRS s/s have subsided
  - Neurotoxicity such as seizures may occur later even in 3rd or 4th week
- Neurotoxicity typically lasts 2-4 days, but may vary in duration from hours to few weeks. It is s generally reversible
- Corticosteroids treatment of choice in managing neurotoxicity, anakinra next
- Tocilizumab might reverse neurological toxicity during 1st phase only
- Seizure prophy with Keppra if high risk product or if ICANS symptoms (no driving for 2 months)
- Rare cases of delayed Parkinsonian movement disorder, motor neuropathy, and CN palsies, may be irreversible

Simplified Grading scales for CRS and Neurotoxicity (ICANS)

Biol Blood Marrow Transplant 25 (2019) 625–638

ELSEVIER

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Guideline

ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells

Daniel W. Lee[1,#], Bianca D. Santomasso[2,#], Frederick L. Locke[3], Armin Ghobadi[4], Cameron J. Turtle[5], Jennifer N. Brudno[6], Marcela V. Maus[7], Jae H. Park[8], Elena Mead[9], Steven Pavletic[6], William Y. Go[10], Lamis Eldjerou[11], Rebecca A. Gardner[12], Noelle Frey[13], Kevin J. Curran[14], Karl Peggs[15], Marcelo Pasquini[16], John F. DiPersio[4], Marcel R.M. van den Brink[8], Krishna V. Komanduri[17], Stephan A. Grupp[18,*], Sattva S. Neelapu[19,**]

FDA Approved CAR-T Therapies
A New Era in Immunotherapy

CD19

Tisagenlecleucel (Tisa-cel, Kymriah; Novartis)
FDA Approved 8/17 for r/r ALL (up to 25 y/o) (2018 for r/r DLBCL)

Axicabtagene ciloleucel (Axi-cel, Yescarta; Kite Pharma=Gilead)
FDA Approved 10/17 for R/R DLBCL, r/r FL 3/21, 2nd Line DLBCL 4/22

Brexucabtagene autoleucel (Brexu-cel, Tecartus; Kite = Gilead)
FDA approved for Relapsed MCL 7/20, for adult ALL 10/21
Uses same vector as axi-cel but w/ T-cell enrichment to avoid circulating blasts

Lisocabtagene maraleucel (Liso-cel, Breyanzi; BMS)
FDA Approved 2/21 for relapsed DLBCL, 7/22 for 2nd line DLBCL

BCMA

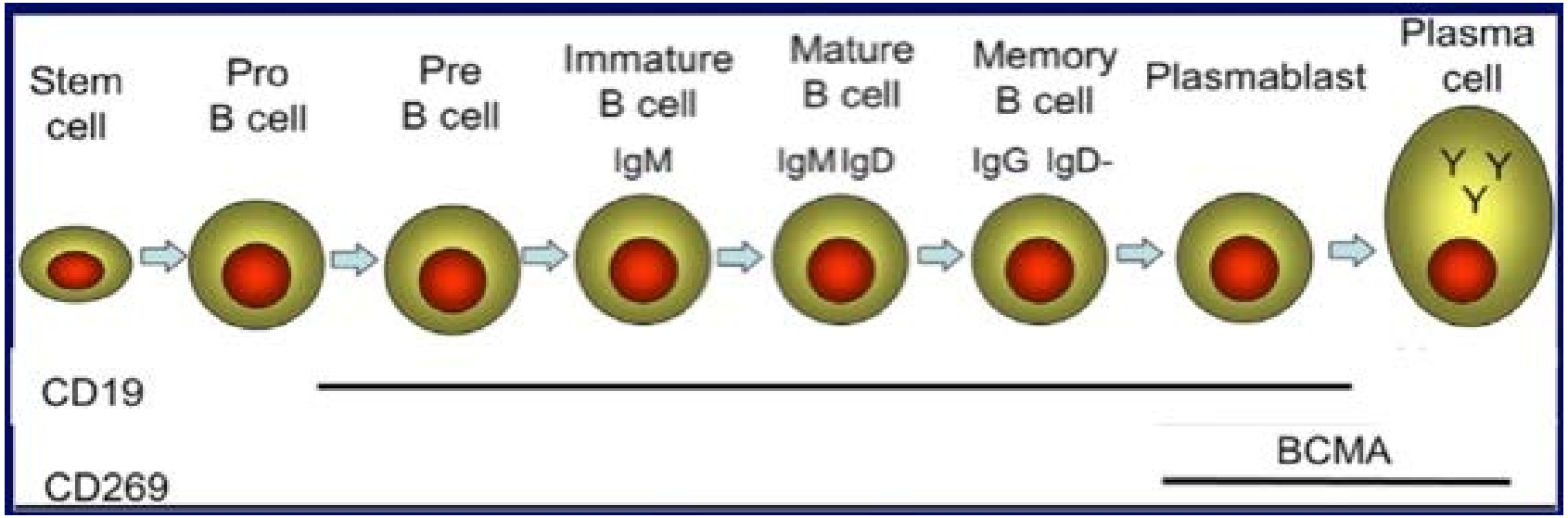
Idecabtagene vicleucel (Ide-cel, Abecma; BMS)
FDA approved for Rel/Ref Myeloma after 4 prior lines 3/26/21

Ciltacabtagene autoleucel (Cilta-cel, Karvyti; Janssen)
FDA approved for Rel/Ref Myeloma after 4 prior lines 2/28/22

Borgert R, AJMC 2021

BCMA as a Target for Myeloma CAR T-Cell Therapy

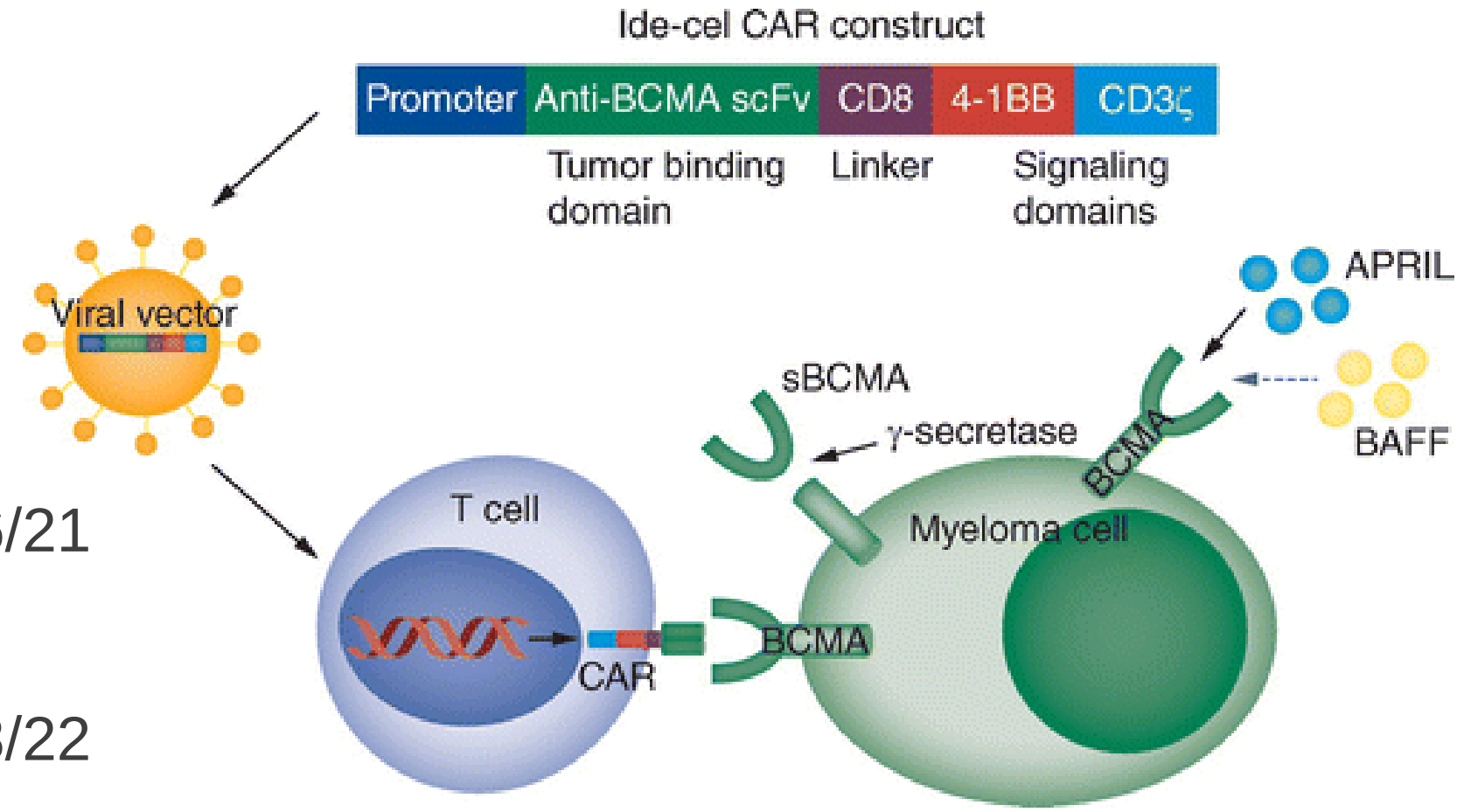
- **BCMA:** B Cell Maturation Antigen
- Receptor expressed on Myeloma tumor cells, nonmalignant plasma cells, and some late stage mature B-cells
- Cell lineage specific so avoids off target toxicity



Turning a Corner with CAR T

Ide-Cel
Approved 3/26/21

Cilta-Cel
Approved 2/28/22



Anderson LD Jr, *Future Oncology* 2022

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma

Nikhil C. Munshi, M.D., Larry D. Anderson, Jr., M.D., Ph.D.*, Nina Shah, M.D., Deepu Madduri, M.D., Jesús Berdeja, M.D., Sagar Lonial, M.D., Noopur Raje, M.D., Yi Lin, M.D., Ph.D., David Siegel, M.D., Ph.D., Albert Oriol, M.D., Philippe Moreau, M.D., Ibrahim Yakoub-Agha, M.D., Ph.D., Michel Delforge, M.D., Michele Cavo, M.D., Hermann Einsele, M.D., Hartmut Goldschmidt, M.D., Katja Weisel, M.D., Alessandro Rambaldi, M.D., Donna Reece, M.D., Fabio Petrocca, M.D., Monica Massaro, M.P.H., Jamie N. Connarn, Ph.D., Shari Kaiser, Ph.D., Payal Patel, Ph.D., Liping Huang, Ph.D., Timothy B. Campbell, M.D., Ph.D., Kristen Hege, M.D., and Jesús San-Miguel, M.D., Ph.D.

*Drs. Munshi and Anderson contributed equally to this article.

N Engl J Med 2021;384:705-16.
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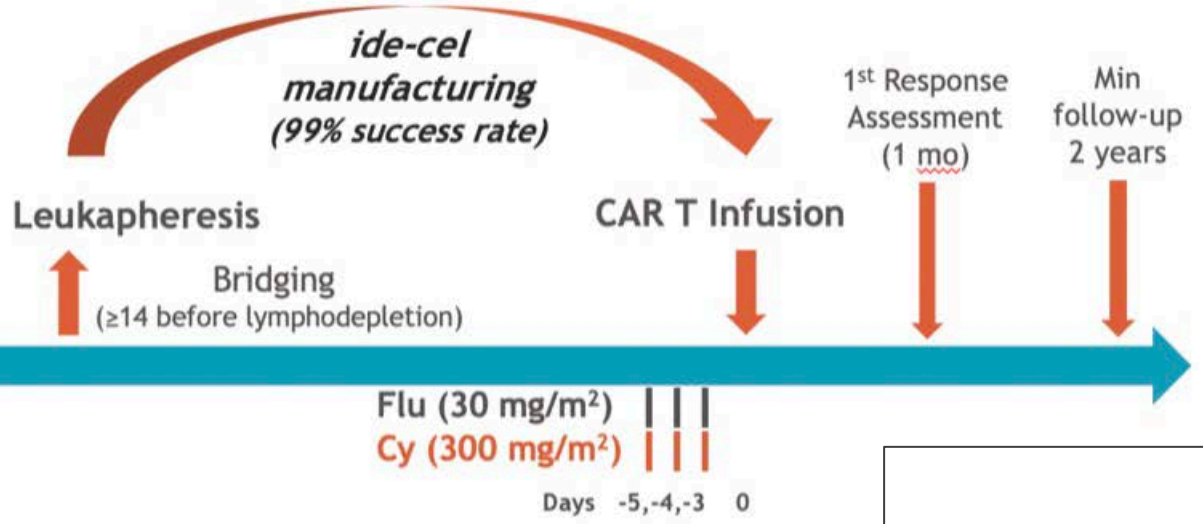
BCMA-Directed CAR-T Cells
Published 2/25/2021
FDA Approved 3/26/2021
ASCO Update 6/2021

Phase II KarMMa study of Ide-Cel in Relapsed/Refractory Myeloma

KarMMa™

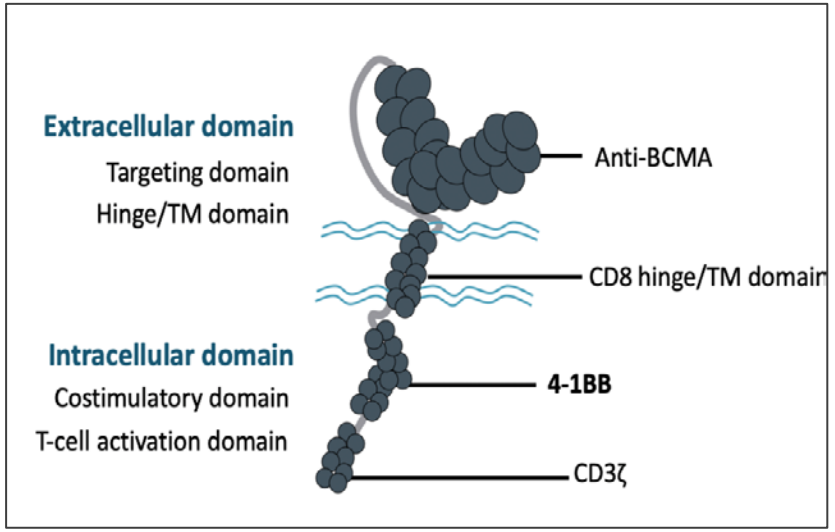
- RRMM
- ≥3 prior regimens with ≥2 consecutive cycles each (or best response of PD)
- Previously exposed to:
  - IMiD agent
  - Proteasome inhibitor
  - Anti-CD38 antibody
- Refractory to last prior therapy per IMWG



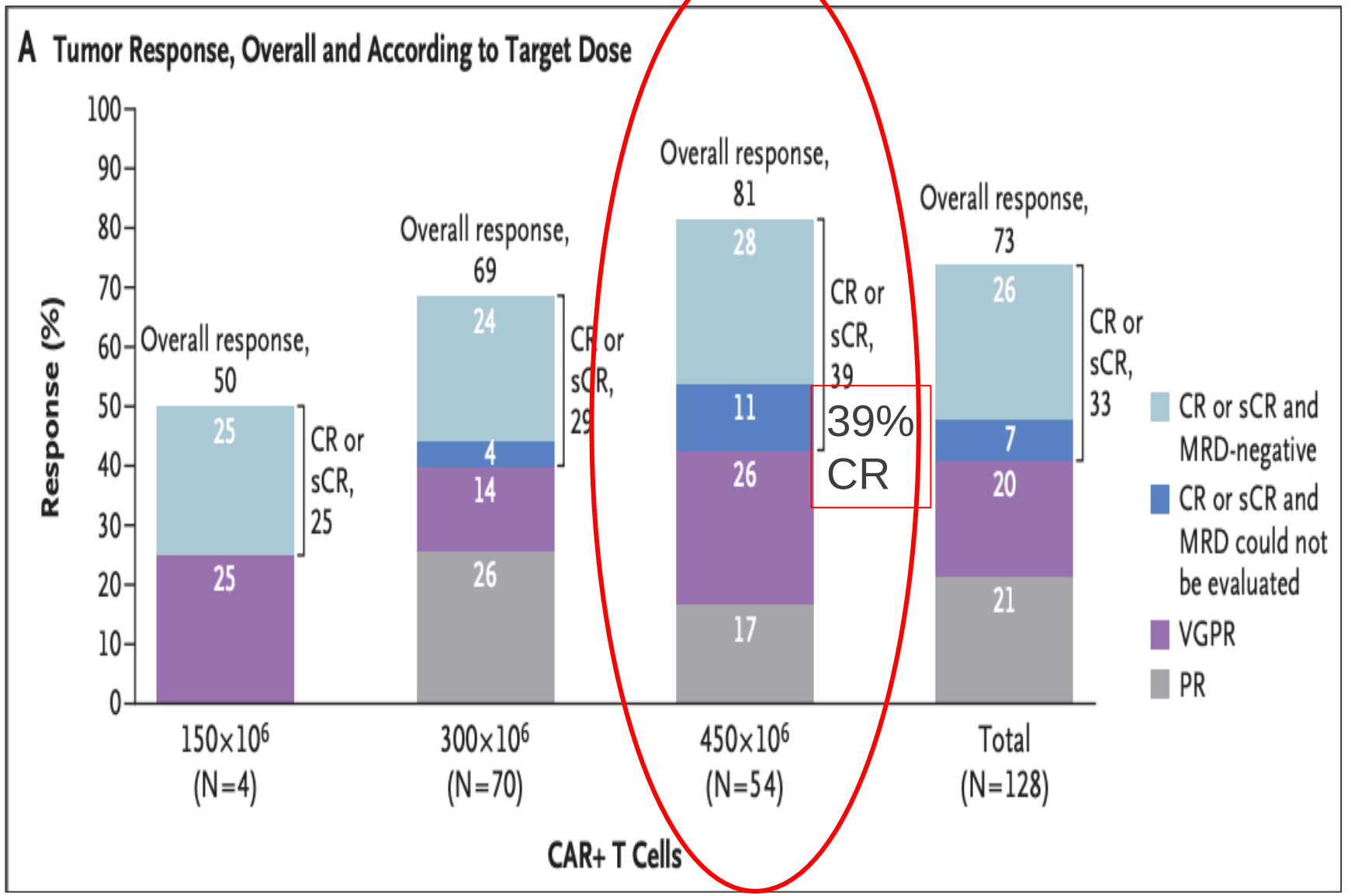
Endpoints

- **Primary**: ORR (null hypothesis ≤50%)

Median 6 Prior Lines of Rx
Expected response rate 25-30%, PFS 3-4 mo
Based on other recently approved products in Triple class exposed MM

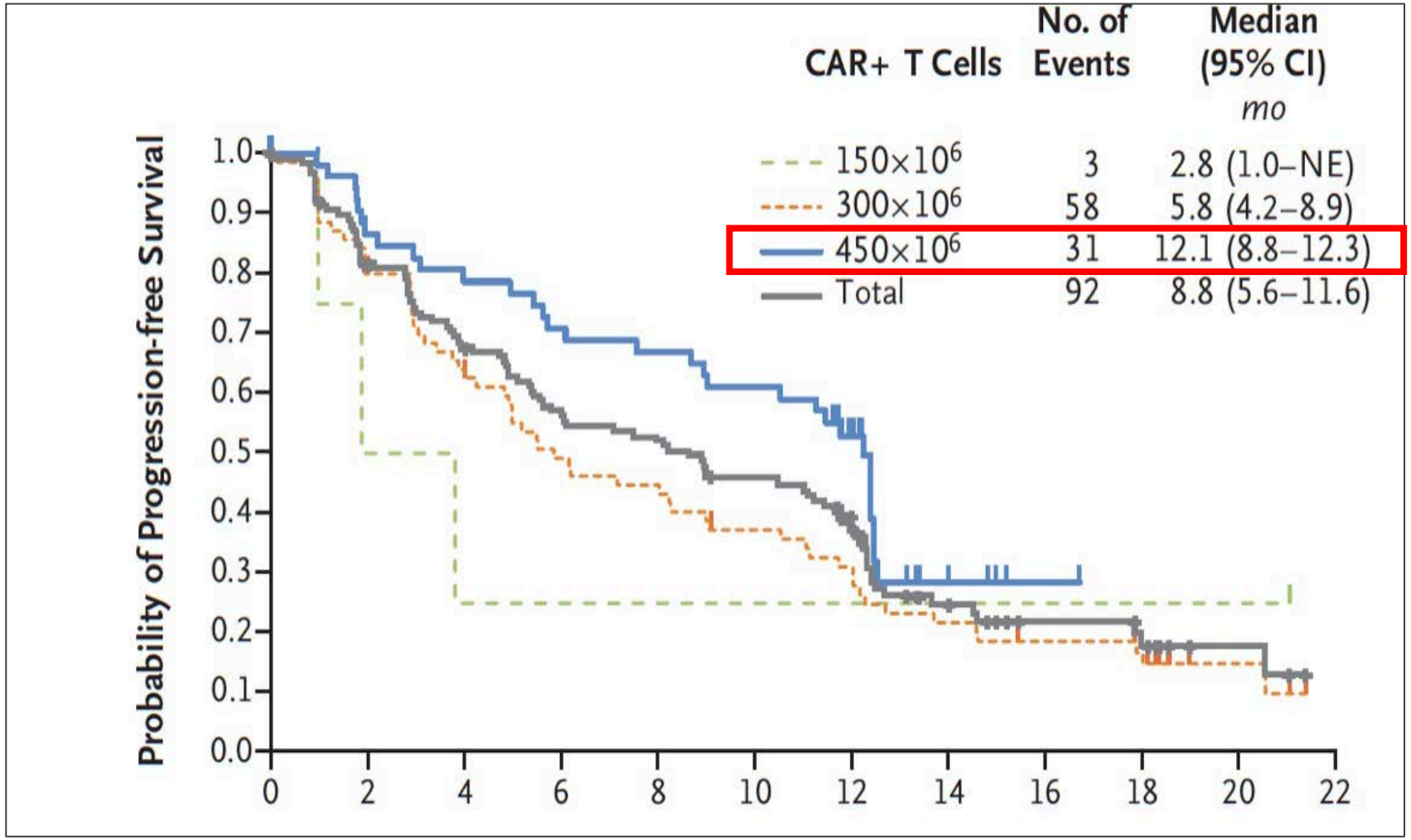


Munshi & Anderson et al, NEJM 2021
Anderson LD Jr et al, ASCO 2021



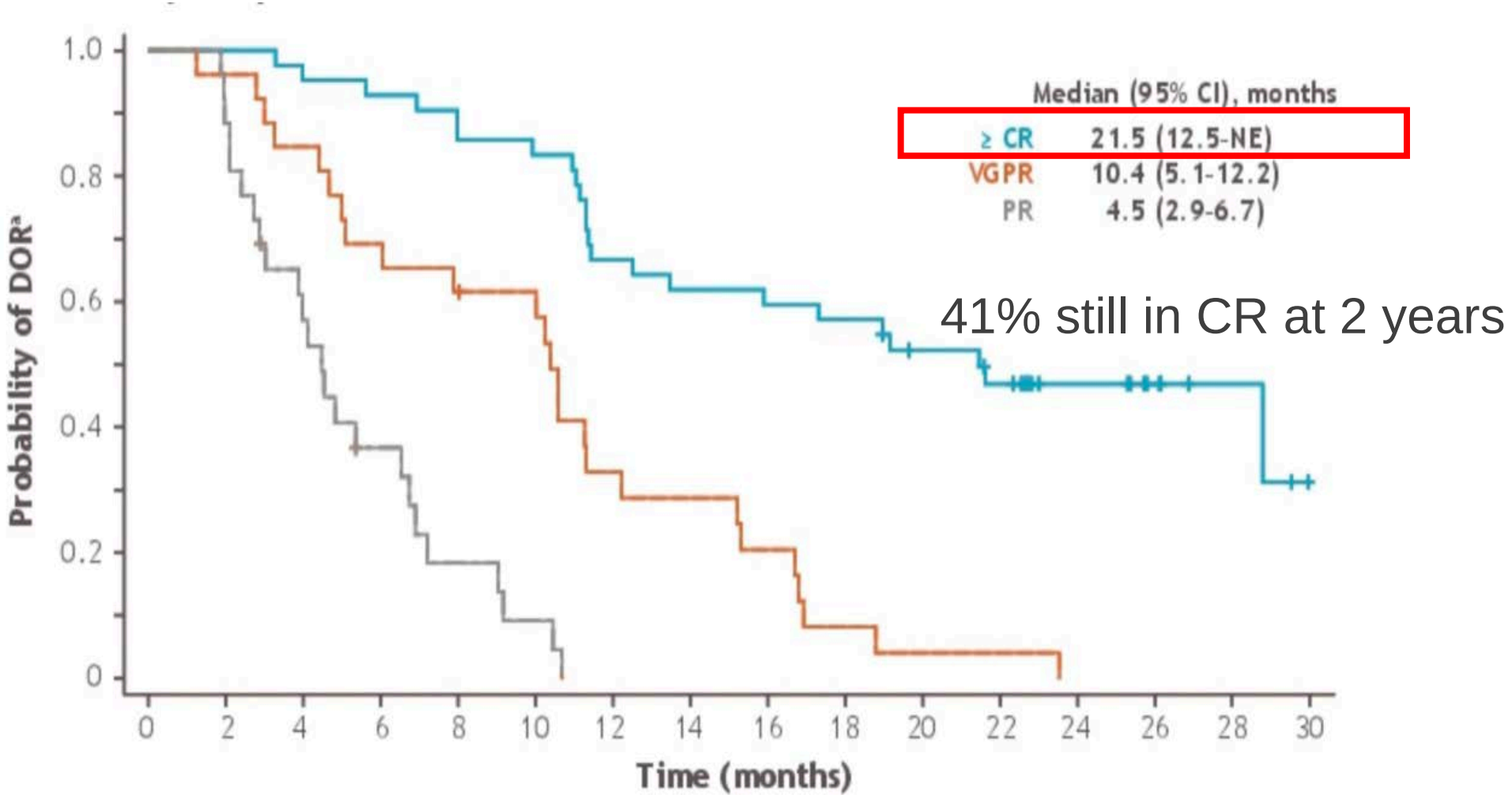
Munshi N & Anderson LD Jr et al, NEJM 2021

KarMMa Trial PFS According to Target Dose



Munshi and Anderson et al, NEJM 2021

KarMMa Trial DOR by Level of Response



41% still in CR at 2 years

Anderson LD Jr et al, ASCO 2021 and IMW 2021

Summary of KarMMa (Ide-Cel) Outcomes

- ORR 81% for $450x10^6$ target dose
- PFS 12.2 mo for $450x10^6$ target dose
- Median OS 24.8 mo (expected 9 mo in this population)
- Median OS >20 mo in several high-risk subgroups
- Those in CR had PFS 20.2 mo and DOR 21.5 mo
- 84% CRS but mostly low grade and brief, only 5% grade 3-4 CRS, 1 fatality from CRS
- Median time to onset of CRS was 1 day
- Neurotoxicity all grades only 18%, only 4% grade 3-4
- 52% required Toci, 15% required steroids, 48% supportive care (Tylenol)

Anderson LD Jr, et al. ASCO 2021

Idecabtagene vicleucel (Ide-cel)
FDA APPROVED 3/26/2021

- First CAR-T Cell therapy approved for Multiple Myeloma
- Approved for Relapsed or Refractory Myeloma after at least 4 Prior Lines of Therapy including an IMiD, PI, and CD38 mAb
- Requires REMS program, and pt must live within 2 hrs of CAR-T center for 1 mo and no driving for 2 mo
- Limited to tertiary BMT & Cell Therapy centers due to toxicity
- Now trials are exploring earlier lines of therapy in KarMMa 2, 3, 4 (More functional T cells?)
- Testing culture with PI3k inhibitor to enrich memory T cells (bb21217)

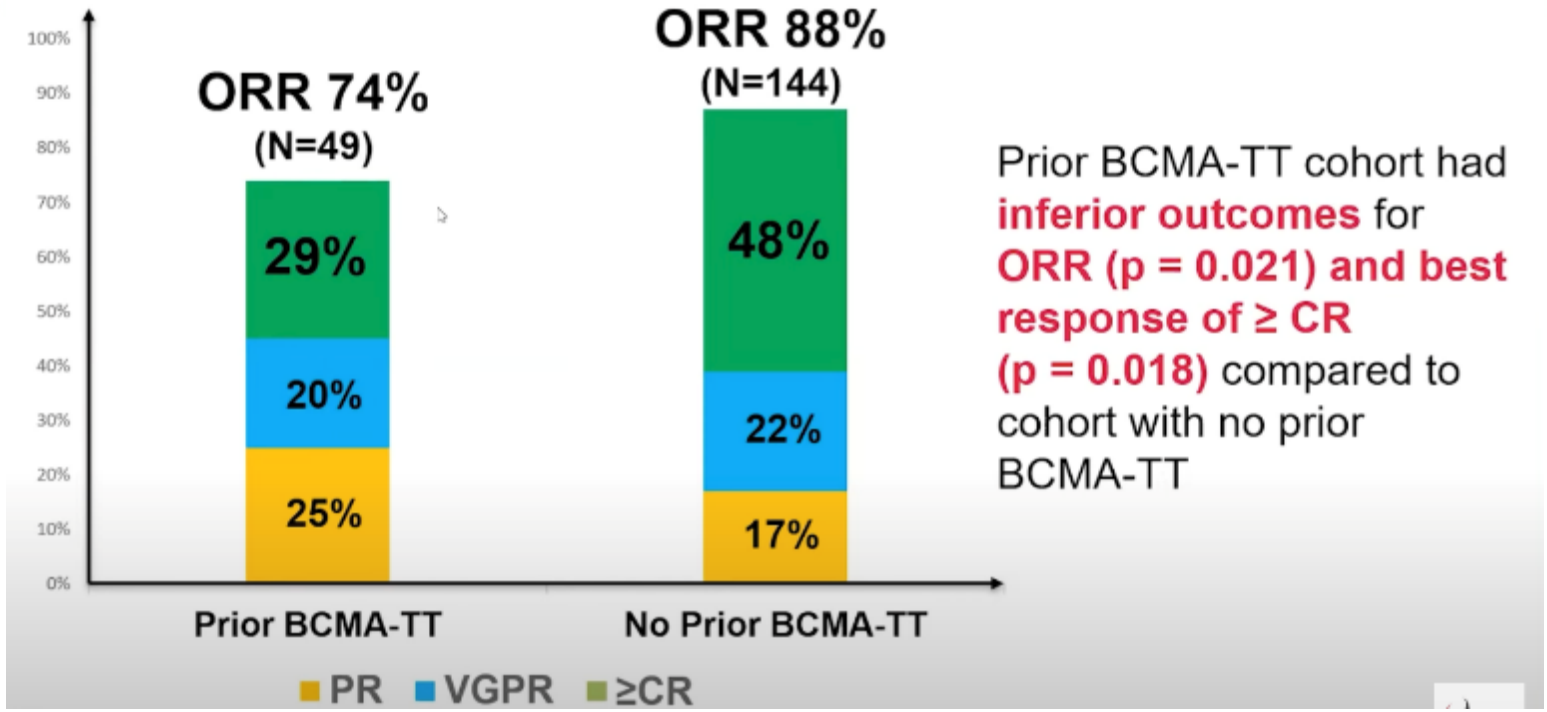
Idecabtagene Vicleucel for Relapsed/Refractory Multiple Myeloma: Real-World Experience From the Myeloma CAR T Consortium

- 159 MM pts from 11 US institutions with intent to receive SOC ide-cel
- 75% of infused patients would have been **ineligible** for participation in the KarMMa trial due to comorbidities
- CRS occurred in 82% with 3% grade ≥ 3
- Neurotoxicity rate 18% with 6% grade ≥ 3
- ORR 84%, and 42% ≥ CR (slightly better responses despite sicker patients)
- At a median follow-up of 6.1 mo from CAR T infusion, median PFS was 8.5 mo
- Patients with previous exposure to BCMA-targeted therapy, high-risk cytogenetics, ECOG ≥ 2, and younger age had inferior PFS on multivariable analysis
- Even older patients and those with comorbidities did well with ide-cel in the real world

Hansen DK et al, J Clin Oncol 2023

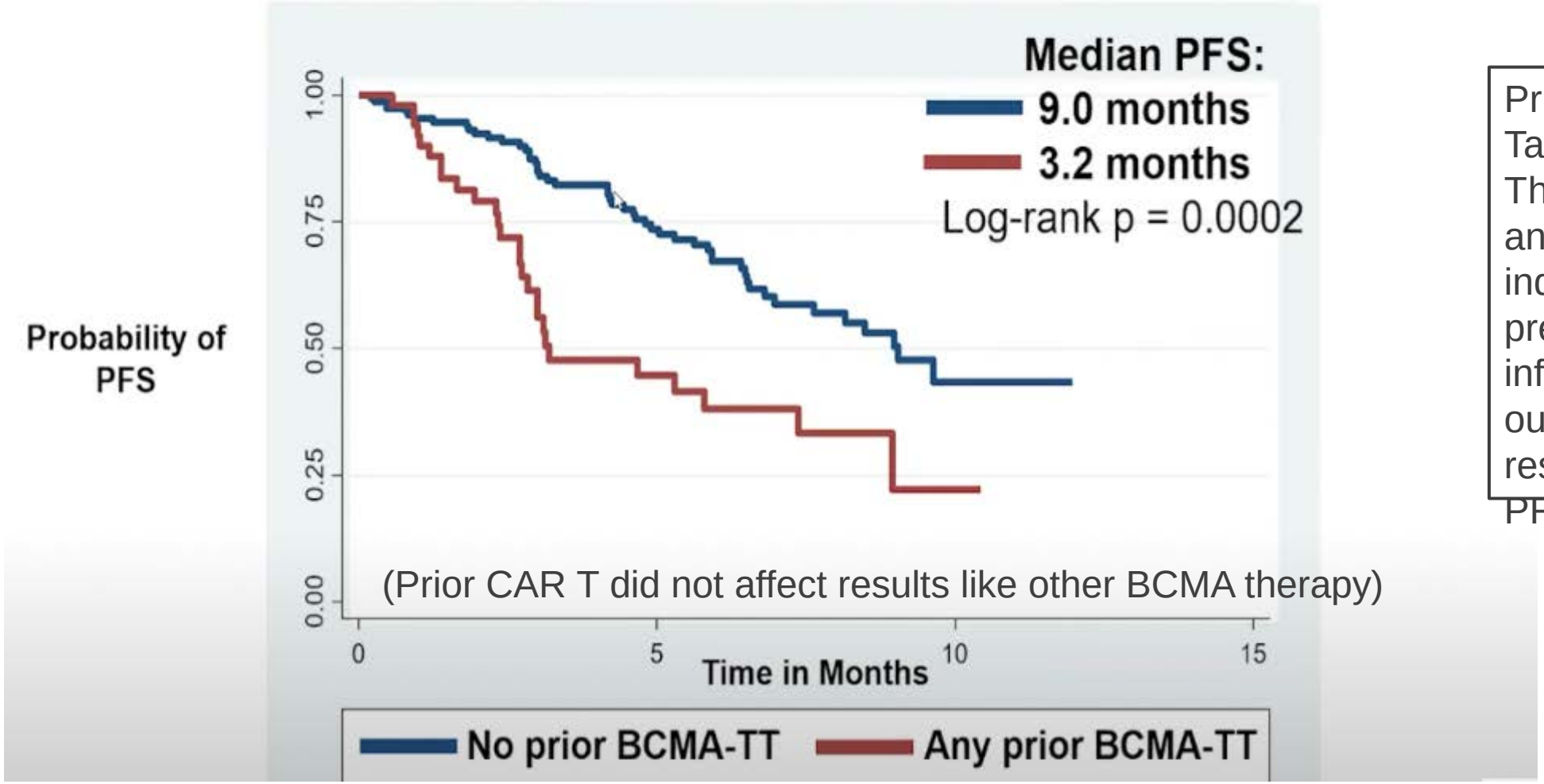
Real-world experience of patients with multiple myeloma receiving ide-cel after a prior BCMA-targeted therapy

Christopher J. Ferreri[1,15], Michelle A. T. Hildebrandt[1,15], Hamza Hashmi[2], Leyla O. Shune[3], Joseph P. McGuirk[3], Douglas W. Sborov[4], Charlotte B. Wagner[4], M. Hakan Kocoglu[5], Aaron Rapoport[5], Shebli Atrash[6], Peter M. Voorhees[6], Jack Khouri[7], Danai Dima[7], Aimaz Afrough[8], Gurbakhash Kaur[8], Larry D. Anderson Jr.[8], Gary Simmons[9], James A. Davis[2], Nilesh Kalariya[1], Lauren C. Peres[10], Yi Lin[11], Murali Janakiram[12], Omar Nadeem[13], Melissa Alsina[10], Frederick L. Locke[10], Surbhi Sidana[14], Doris K. Hansen[10,15], Krina K. Patel[1,15]✉ and Omar Alexis Castaneda Puglianini[10,15]



Blood Cancer Journal (2023) 13:117

PFS Outcomes: Prior BCMA-TT versus no prior BCMA-TT

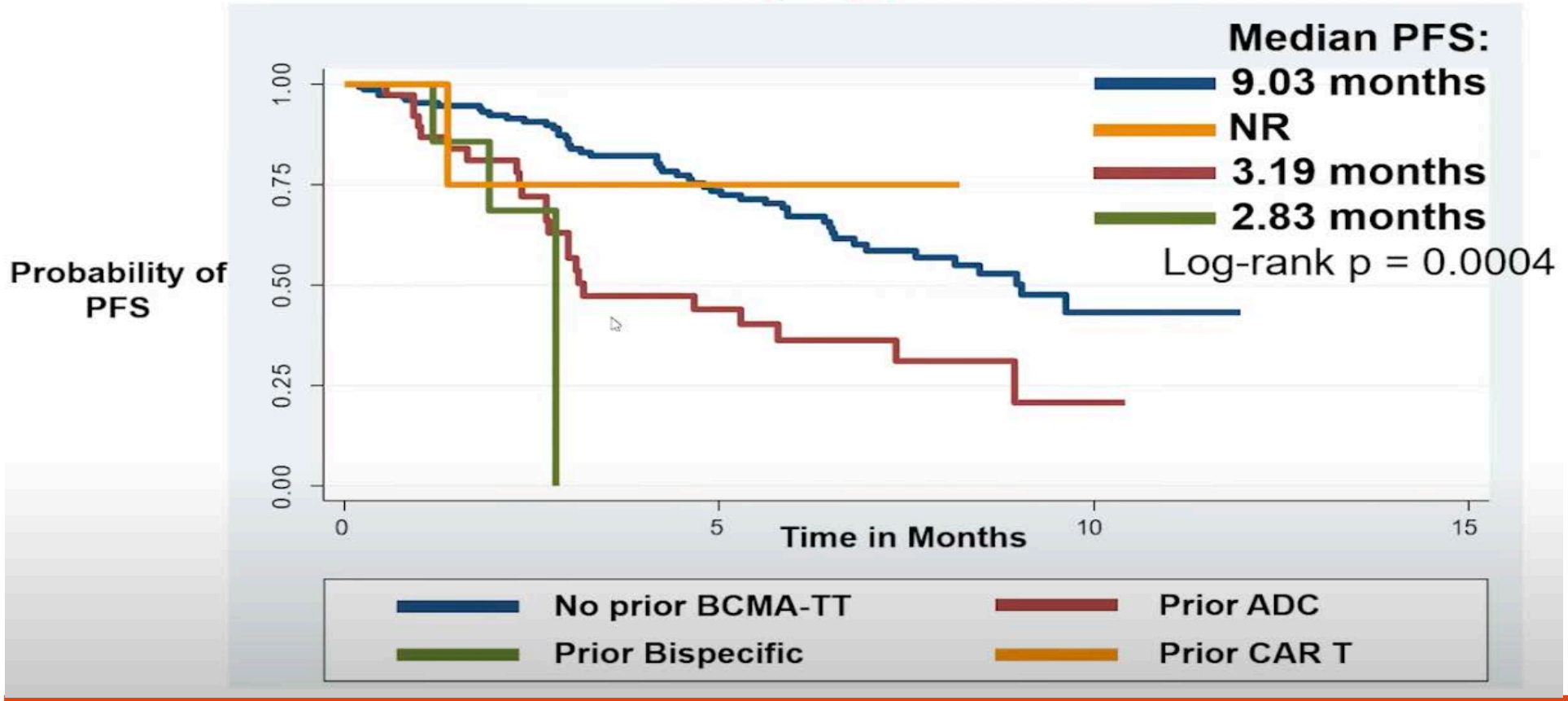


(Prior CAR T did not affect results like other BCMA therapy)

Prior BCMA Targeted Therapy is an independent predictor of inferior outcomes for response, PFS, and OS

Ferreri et al, Blood Cancer Journal 2023, US Myeloma CAR T Consortium

PFS Outcomes By Type of Prior BCMA-TT



Prior BCMA Targeted Therapy is an independent predictor of inferior outcomes for response, PFS, and OS

PFS by Previous BCMA-TT	Prior BCMA-TT	No Prior BCMA-TT	*P* Value
Median PFS, mo	3.2	9.0	.0002

PFS by Type of Previous BCMA-TT	ADC	Bispecific	CAR T-Cell	No BCMA-TT	*P* Value
Median PFS, mo	3.19	2.83	NR	9.03	.0004

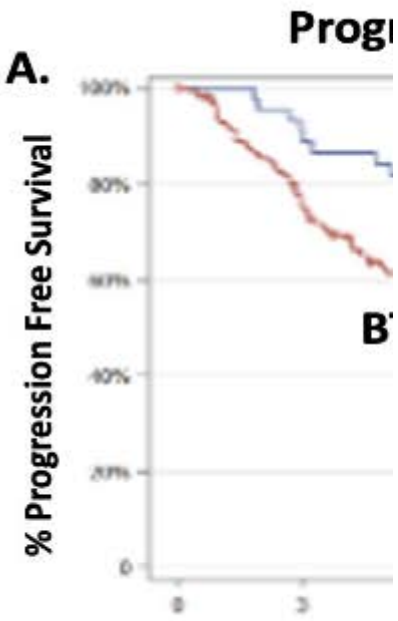
Ferreri et al, Blood Cancer Journal 2023, US Myeloma CAR T Consortium

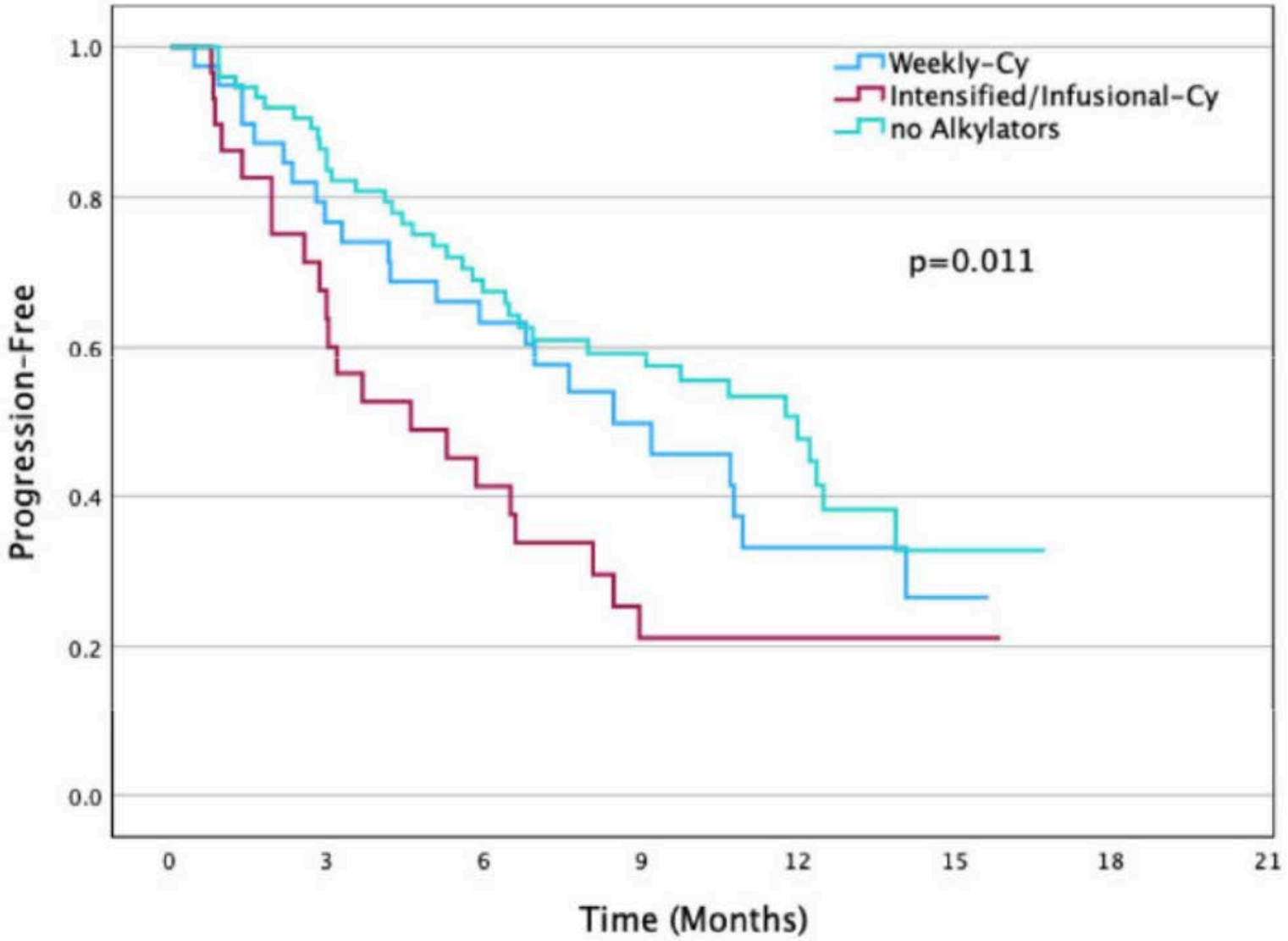
Impact of Bridgi
with Ide-cel CAR

Aimaz Afrough MD,[1*] Hamza
Puglianini MD,[3] Mehmet H.
Ferreri MD,[10]

e Myeloma (RRMM)
na CAR T Consortium

eeman MD, PhD,[3] Omar Castaneda
glas W. Sborov MD,[9] Christopher J.
@ Yi Lin MD, PhD.[12#]





Effect on PFS and OS mostly due to "Subgroup with Alkylator BT" in Heavily Refractory RRMM (especially infusional) and no effect of IMID/mAb so Earlier use of CAR T may help overcome this

Afrough A, et al ASCO 2023, IMS 2023, Blood Cancer Journal 2024 In Press

UT Southwestern
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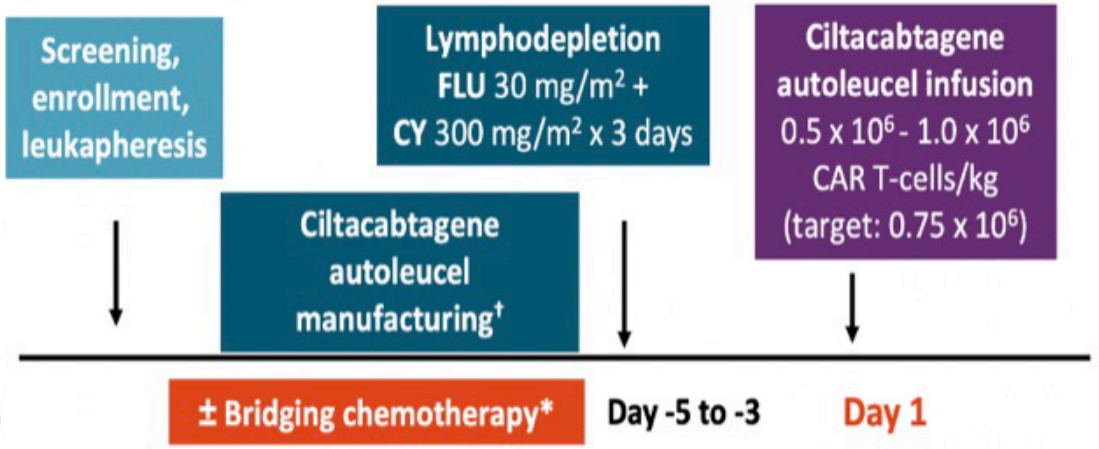
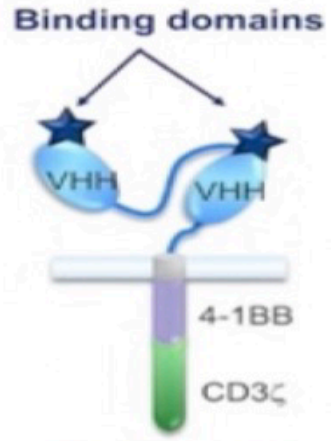
CARTITUDE-1 Phase Ib/II Study of Ciltacabtagene Autoleucel: BCMA-Directed CAR T-Cells in R/R MM

- Phase Ib/II trial conducted in the United States

Patients with R/R MM
ECOG PS ≤ 1; ≥ 3 prior therapies including PI, IMiD, and anti-CD38 therapy, or double refractory to PI and IMiD
(N = 113)



*73 patients received bridging therapy with previously used agents to maintain
†0 patients d/c due to manufacturing failure.

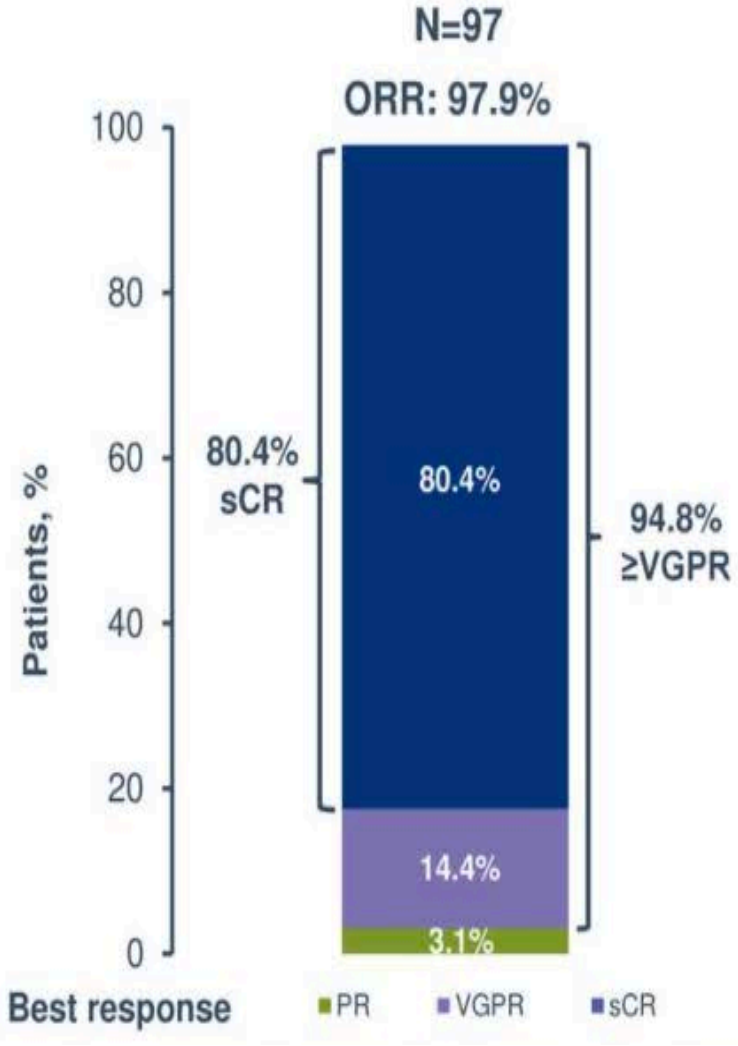


(Cilta-Cel)

- Of 113 patients enrolled, 97 received ciltacabtagene autoleucel; phase Ib (n = 29); phase II (n = 68); median administered dose: 0.71 x 106 (0.51–0.95 x 106) CAR+ viable T-cells/kg
- Primary endpoints: safety and RP2D (phase Ib), efficacy (phase II)

Usmani SZ et al, ASCO 2021.
Berdeja JG et al, Lancet 2021

CARTITUDE-1: Overall Response Rate

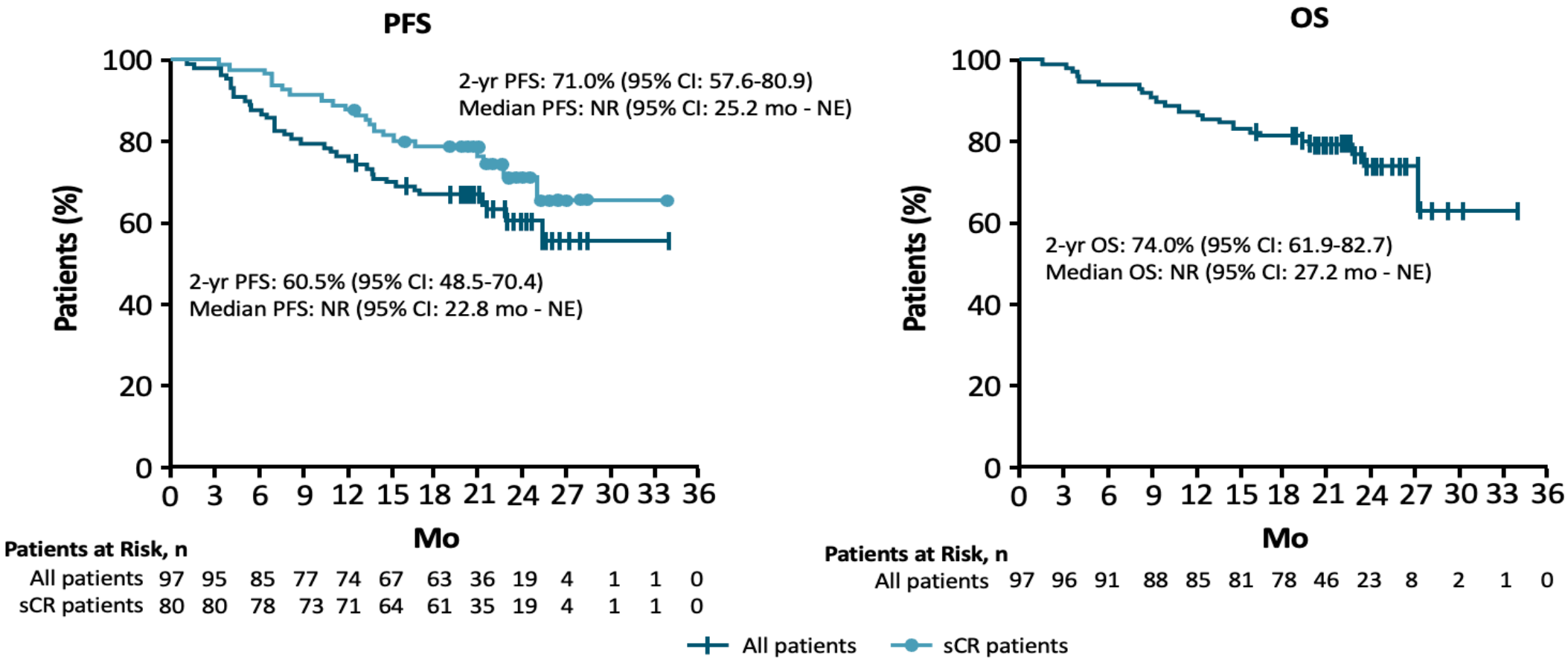


With longer follow-up, responses deepened with increasing rate of sCR

- Median time to first response: 1 month (range, 0.9–10.7)
- Median duration of response: 21.8 months (95% CI, 21.8–NE); not reached in patients with sCR
- Response rates were comparable (range, 95–100%) across different subgroups (eg, number of prior lines of therapy, refractoriness, extramedullary plasmacytomas, and cytogenetic risk)[a]
- 91.8% of 61 evaluable patients were MRD negative[b]
  - Median time to MRD 10^{-5} negativity: 1 month (range, 0.8–7.7)

Martin et al ASH 2021,
Usmani SZ et al, ASCO 2021.
Berdeja JG et al, Lancet 2021

CARTITUDE-1: PFS and OS



Martin. ASH 2021. Abstr 549.

Martin et al ASH 2021

CARTITUDE-1: Safety

- CRS
  - 94.6% of patients experienced low-grade CRS (n=92)
  - Median time to onset of 7 days (range, 1-12)
  - Median duration of 4 days (range, 1-97)[b] and resolved in 91 (98.9%) patients within 14 days of onset
- Neurotoxicity
  - 20.6% of patients experienced neurotoxicity in total with overlap between ICANS and Other Neurotoxicities (Grade ≥3: 10.3%)
    - ICANS observed in 16.5% (Grade ≥3: 2.1%)
    - Other Neurotoxicities[c] observed in 12.4% (Grade ≥3: 9.3%)
- 6 treatment-related deaths as assessed by the investigator[d]

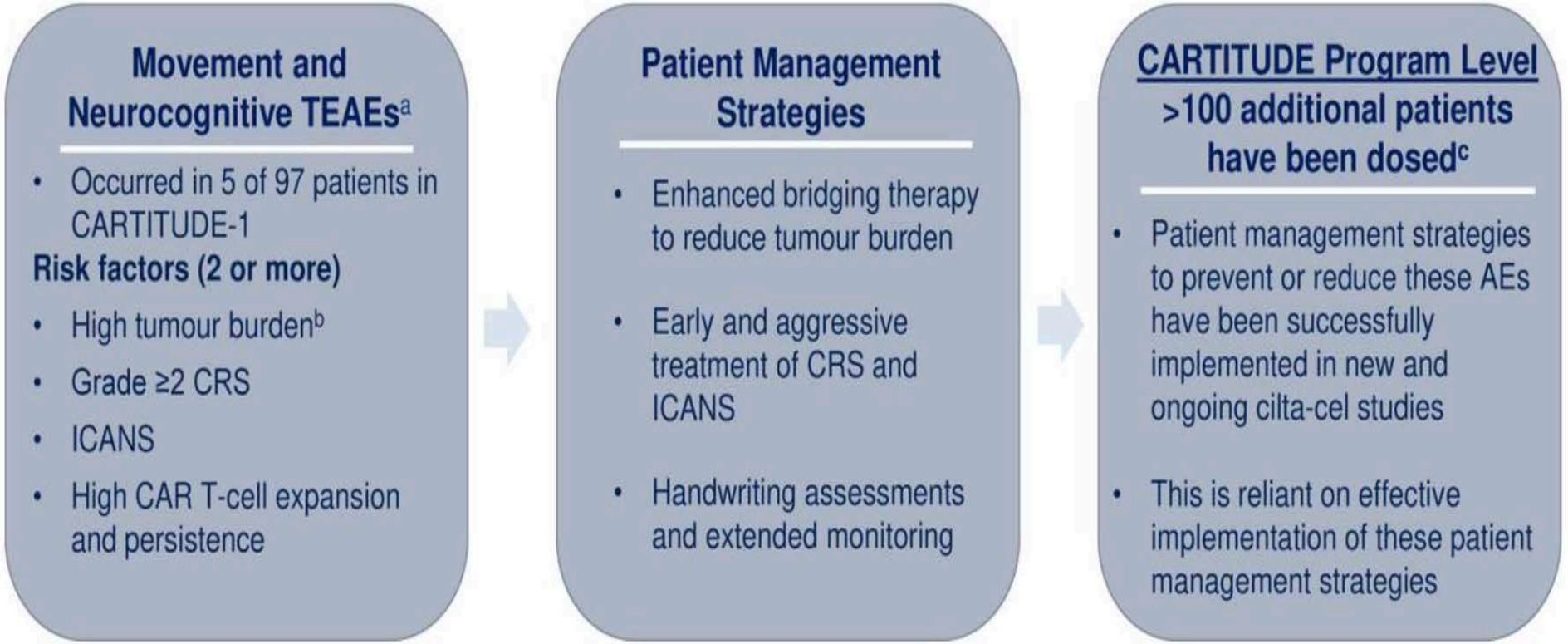
5 Movement and/or Neurocognitive/ Parkinsonian
7 Nerve Palsy or motor neuropathy

FDA Approved 2/28/2022

Usmani SZ et al, ASCO 2021.
Berdeja JG et al, Lancet 2021

CARTITUDE Program: Safety

Successful new patient management strategies have been implemented in the CARTITUDE program to prevent and reduce the incidence of neurotoxicity[1-3]



Usmani SZ et al, ASCO 2021

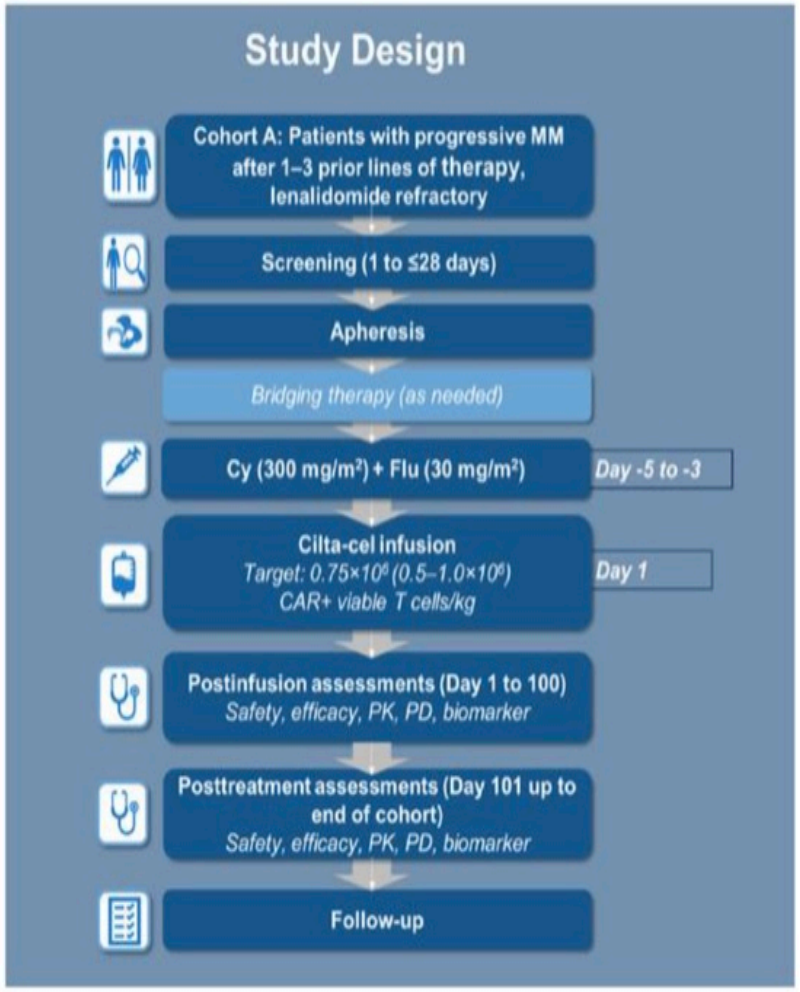
CARTITUDE-2: Multicohort Study
Cohort A: 1 – 3 prior lines, lenalidomide refractory RRMM

- CARTITUDE-2 is a phase 2, multicohort, open-label study assessing the efficacy and safety of cilta-cel in patients with multiple myeloma in various clinical settings

Cohort A:
- Cohort A patients had progressive MM after 1–3 prior lines of therapy, and were refractory to lenalidomide
- Despite advances continued unmet need with mPFS of 9.9 months (DPd)[1]

Primary objectives
- Minimal residual disease (MRD) 10^{-5} negativity

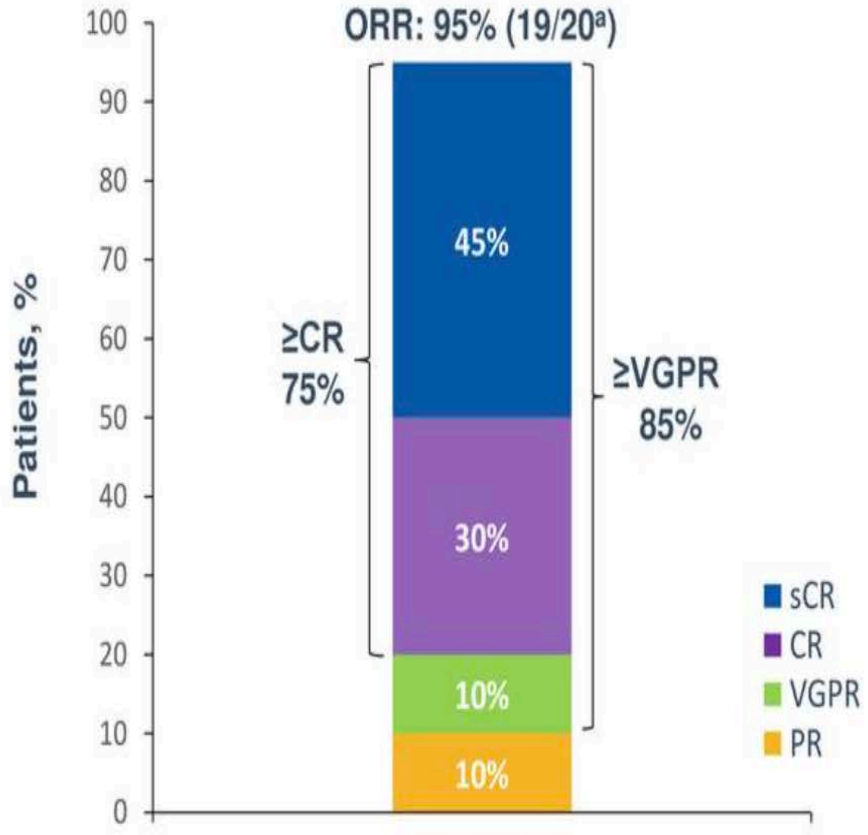
Secondary objectives
- ORR, duration of response, time and duration of MRD negativity, and incidence and severity of adverse events



Agha ME et al, ASCO 2021

CARTITUDE-2: Phase 2 Multi-Cohort Study

- Cohort A included 20 patients who had progressive MM after 1–3 prior lines of therapy and were refractory to lenalidomide
- Median prior lines of therapy: 2 (range, 1-3); 1 patient treated in an outpatient setting



- No progression of disease at median follow-up of 5.8 months (range 2.5-9.8)
- All patients (n=4) with MRD-evaluable[b] samples at the 10^{-5} threshold were MRD negative at data cut-off
- The safety profile was manageable
  - CRS occurred in 85% (n=17); mostly grades 1/2; median time to CRS onset was 7 days (range, 5–9)
  - Neurotoxicities occurred in 20% (n=4) of patients; no grade ≥3; no incidence of movement and neurocognitive TEAEs
  - 1 death occurred 100 days after infusion due to COVID-19 (assessed as tx related by the investigator)

Cohen et al ASH 2021 abstract now shows All responses VGPR or better in 19/20
1 grade 2 facial paralysis but no Parkinsonian

Agha ME et al, ASCO 2021
Cohen et al, ASH 2021/ASTCT 2022

Myeloma CAR T-Cell Therapy

	Idecabtagene vicleucel (Ide-Cel)(BMS)	Ciltacabtagene autoleucel (Cilta-Cel)(Janssen)
Pivotal trial	Phase II KARMMa (N = 128)	Phase Ib/II CARTITUDE-1 (N = 97)
Prior therapy	≥ 3 prior lines	≥ 3 prior lines
Median (range)	6 lines (3–16)	6 lines (4-8)
CAR T-cell dose	150–450 x 10^6 cells	Median: 0.75 x 10^6 cells/kg
Grade ≥ 3 CRS	5%	4%
Grade ≥ 3 NT	3%	9% (+ some non-CNS NT)
ORR	73% (81% at target dose)	97%
CR	33% (39% at target dose)	67% (80% sCR at update)
PFS	Median PFS: 8.8 mo (12.2 mo)	24 mo 61%
OS	Median 24.8 mo	24-mo OS 74%
FDA	Approved 3/26/2021	Approved 2/28/2022

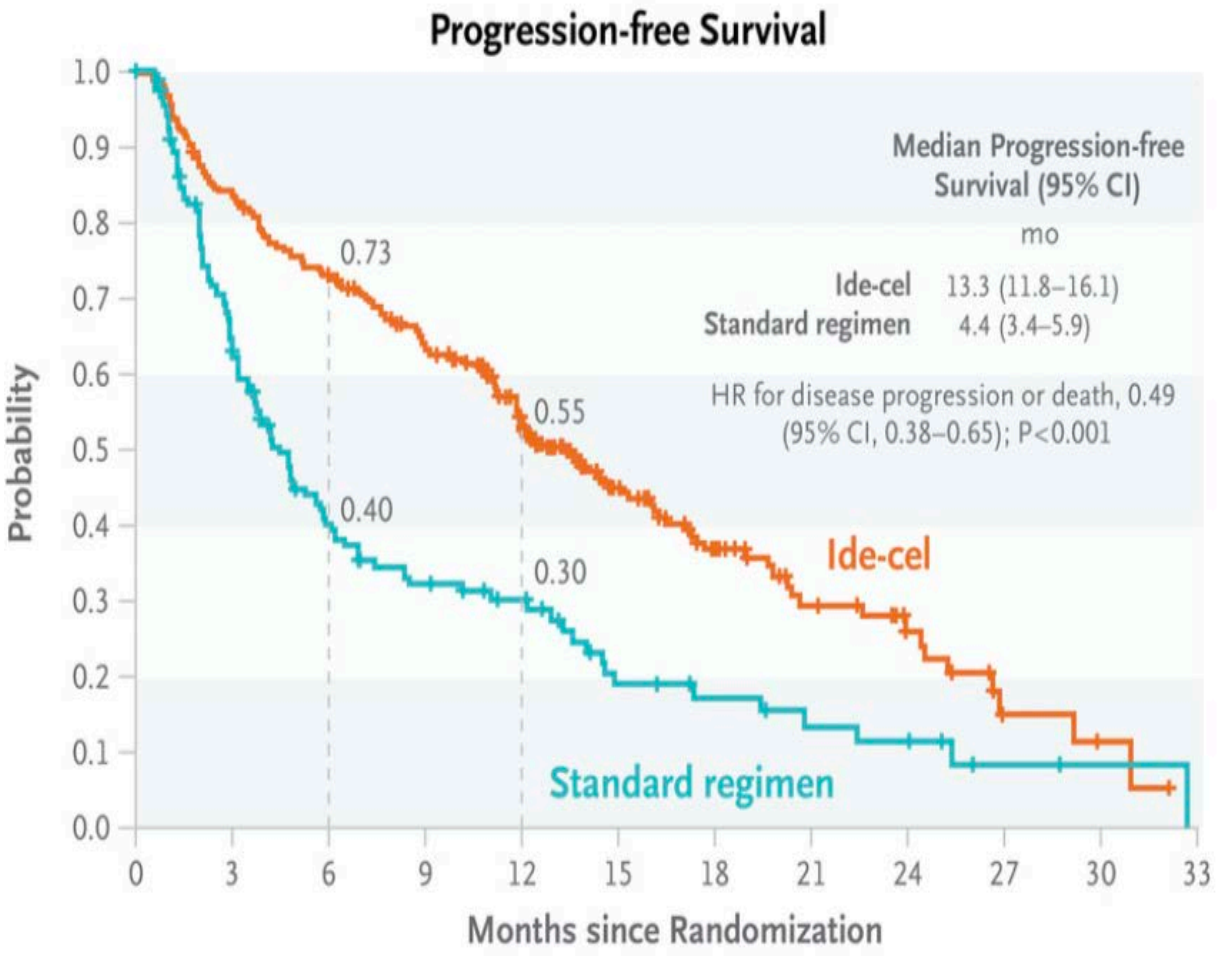
- Several other products are being tested (human CAR, ddBCMA, etc)
- Now looking at non-BCMA targets like GPRC5D and combination targets

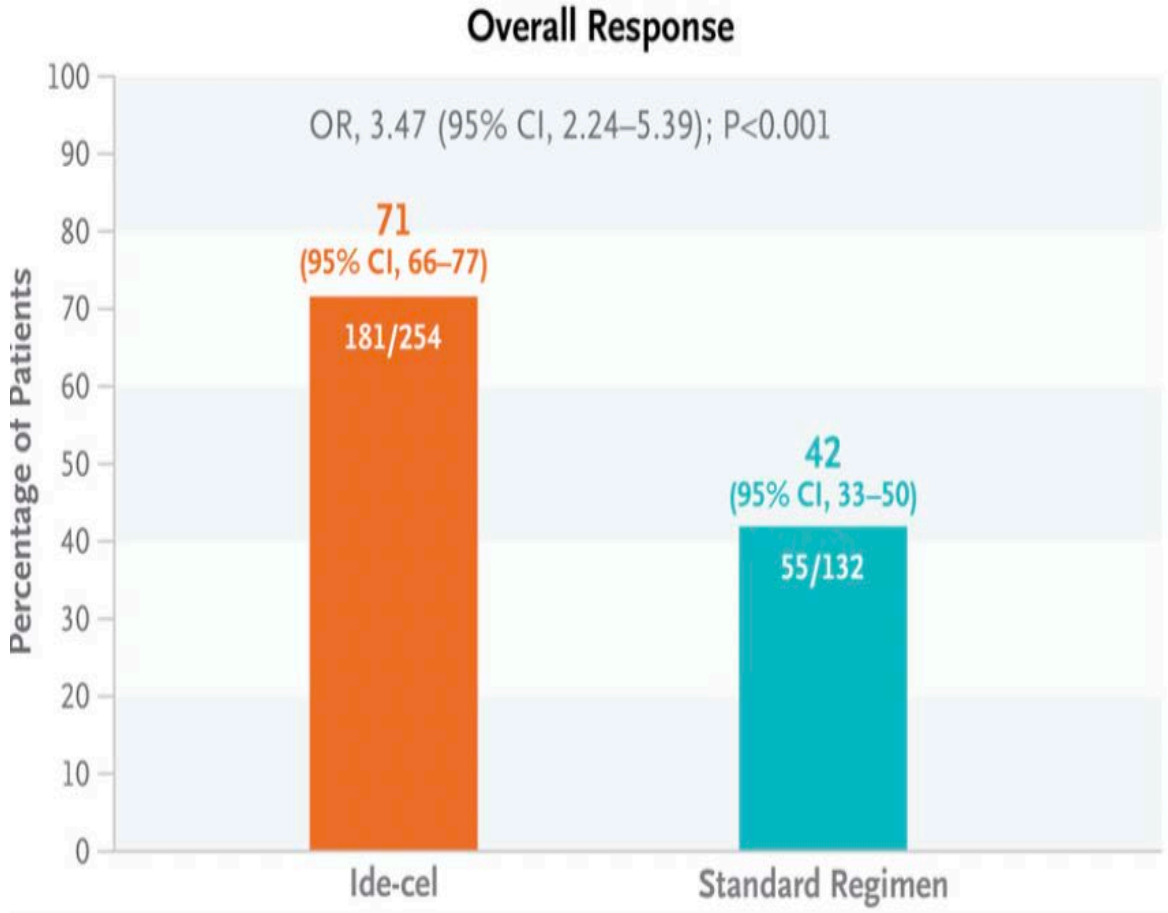
Munshi and Anderson et al NEJM 2021; Berdeja et al. *Lancet.* 2021; Usmani et al ASCO 2021

KarMMa-3 (2-4 prior lines of therapy, Ide-cel vs SOC (DPd, DVd, Ird, Kd, or EPd), NEJM 2023

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

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

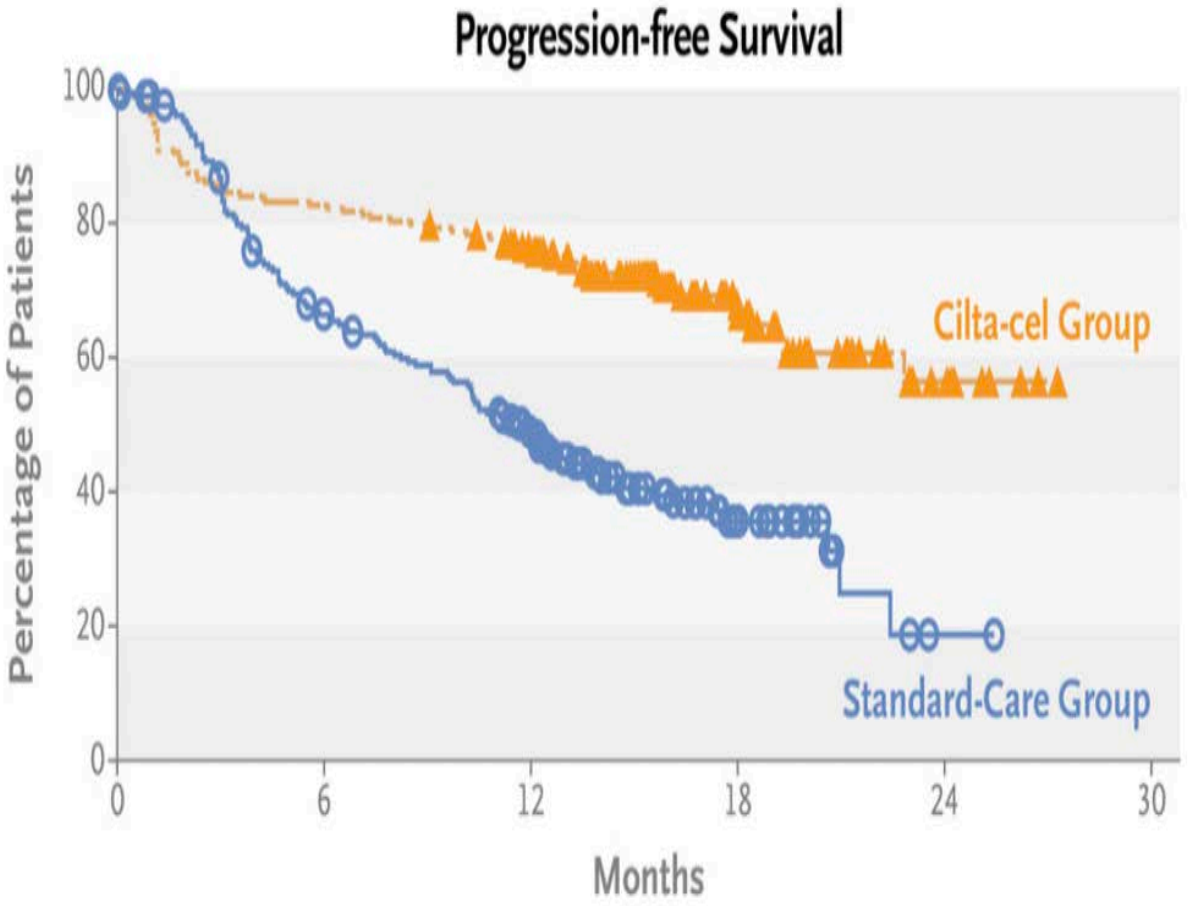


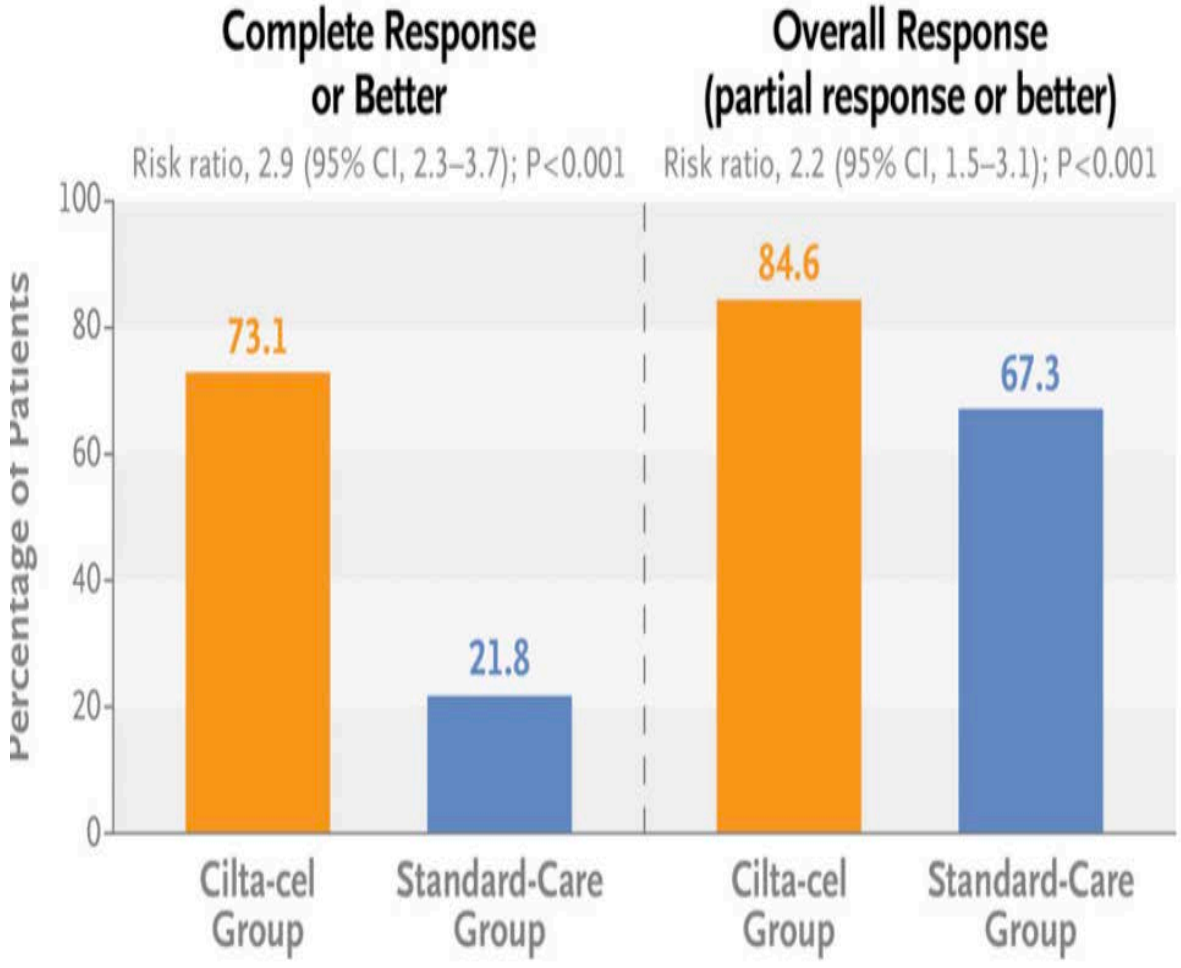


Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma

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

CARTITUDE-4 (1-3 prior lines of therapy, Cilta-cel vs SOC (DPd or PVd)





Results of Randomized KarMMa-3 and CARTITUDE-4 trials of Early Line CAR T

	KarMMa-3 [7]		CARTITUDE-4 [6, 83]	
	Ide-Cel	SOC	Cilta-Cel	SOC
Study Design				
Inclusion Criteria	2-4 prior lines including PI + IMiD + Dara		1-3 prior lines, Len refractory	
Therapy given	CAR T	Choice: DPd, DVd, IRd, Kd, or EPd	CAR T	Choice: DPd or PVd
CAR T-Cell Dose, median (range)	445x106 ($175\text{-}529x10^6$)	N/A		
Baseline Characteristics				
No of pts Randomized	254	132		
Median Prior Lines (range)	3 (2-4)	3 (2-		
Refractory to anti-CD38 Ab	242 (95) **	123 (9		
Triple Class Refractory (%)	164 (65) **	89 (6		
Efficacy (intent-to-treat)				
ORR (%)	181 (71)	55 (4		
≥ CR (%)	98 (39)	7 (5		
≥ VGPR (%)	153 (60)	20 (1		
MRD Negative 10^{-5} (%)	51/254 (20)	1 (1		
ORR for infused pts (%)	NR	NR		
Median DOR, months	14.8	9.7		
Median PFS, months	13.3	4.4		
Median OS, months	Not reached	Not reac		

	KarMMa-3 [7]		CARTITUDE-4 [6, 83]	
	Ide-Cel	SOC	Cilta-Cel	SOC
Safety (for treated pts only)	N=225	N=126	N=176	N=176
Infections Any Grade	146 (58)	68 (54)	129/208 (62)	148/208 (71)
Infections Grade 3-5	72 (28)	26 (20)	56/208 (27)	51/208 (25)
CRS any grade (%)	197 (88)	N/A	134/176 (76)	N/A
CRS grade ≥ 3 (%)	11 (5)	N/A	2 (1)	N/A
Median days to CRS (range)	1 (1-14)	N/A	8 (1-23)	N/A
Neurotoxicity any grade (%)	34 (15)	N/A	(4.5)	N/A
ICANS grade ≥ 3 (%)	7 (3)	N/A	0 (0)	N/A
Non-ICANS Neurotoxicity (%)	0 (0)	N/A	30 (17%) ** 1 Parkinsons, 18 CN Palsy, 5 PN	N/A

Non-BCMA CAR T for Myeloma (Targeting GPRC5D)

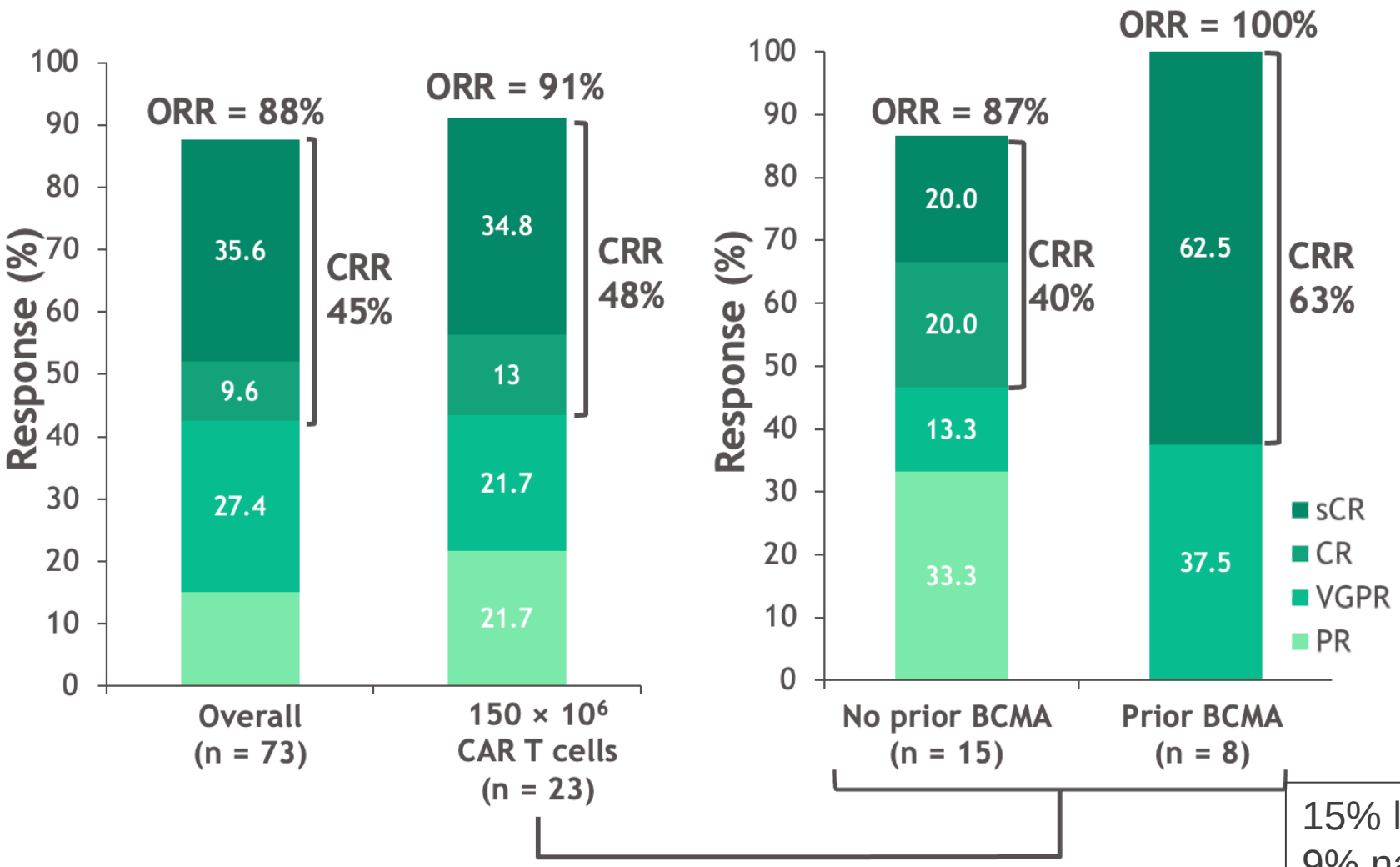
BMS-986393 (CC-95266), a G protein–coupled receptor class C group 5 member D (GPRC5D)–targeted chimeric antigen receptor (CAR) T-cell therapy for relapsed/refractory multiple myeloma: updated results from a phase 1 study

Susan Bal,[1] Myo Htut,[2] Omar Nadeem,[3] Larry D. Anderson, Jr,[4] M. Hakan Koçoğlu,[5] Tara Gregory,[6] Adriana C. Rossi,[7] Tom Martin,[8] Daniel N. Egan,[9] Luciano J. Costa,[1] Hongxiang Hu,[10] Yanping Chen,[10] Shaoyi Li,[10] Lisa M. Kelly,[10] Naomey Sarkis,[10] Safiyyah Ziyad,[10] Wei-Ming Kao,[10] Allison J. Kaeding,[10] Michael R. Burgess,[10] Jesus G. Berdeja[11]

GPRC5D, an orphan receptor expressed on MM cells with limited expression in other tissues (hair follicles, tongue, nail beds), is a promising therapeutic target

Bal et al, ASH 2023

BMS-986393 in RRMM: high response rates irrespective of prior BCMA-targeted treatment or EMD[a]



High response rates in subgroups of interest

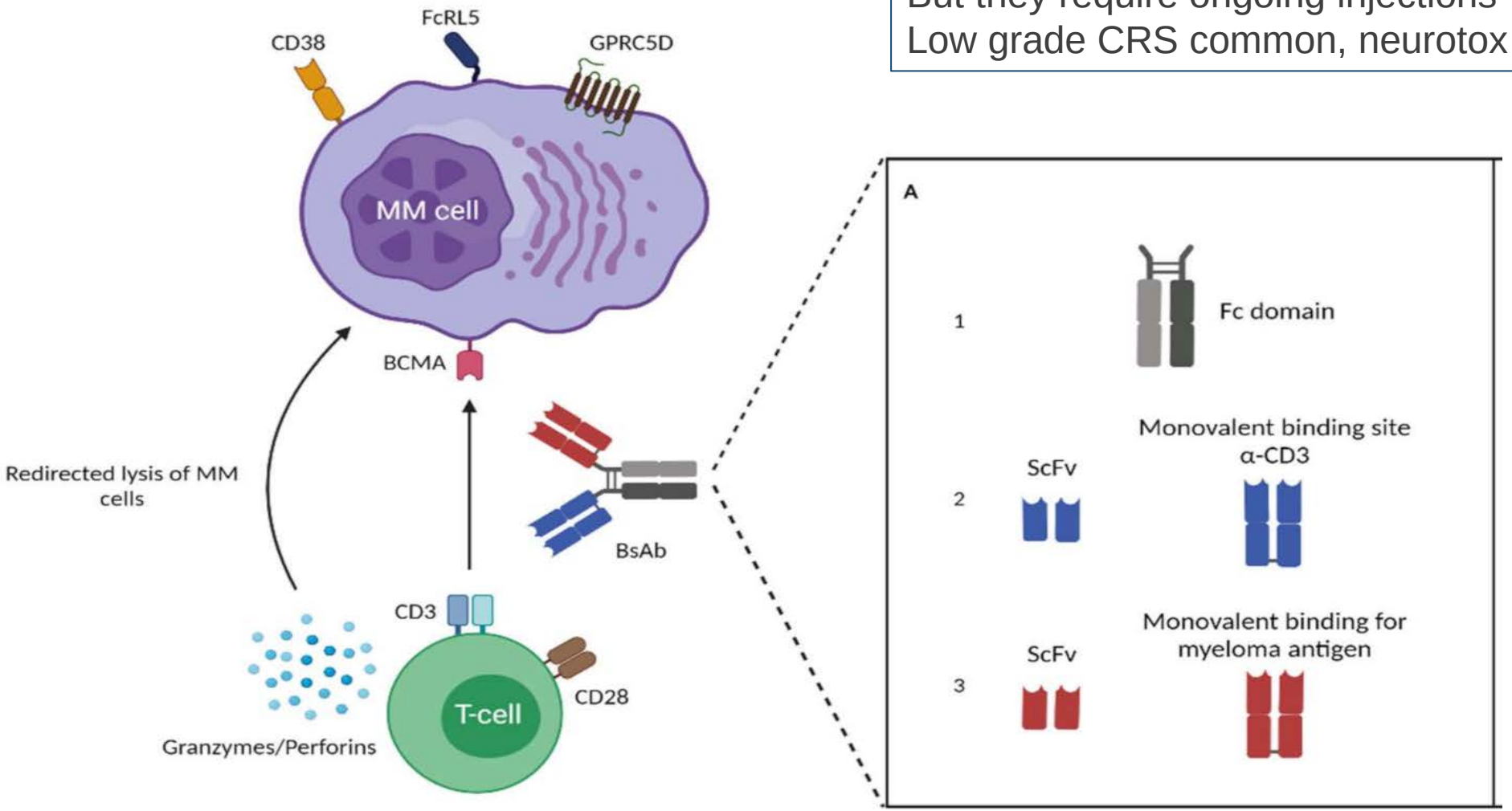
Disease characteristic	ORR (CRR)	
	With	Without
EMD	84% (32%)	91% (55%)
Prior BCMA-targeted therapy	78% (44%)	95% (46%)
del(17p)	XX	XX

15% low grade dysgeusia, 6% ICANS, 9% nail changes , 30% skin (self limited rash)

Bal et al, ASH 2023

Bispecific T Cell Engaging Abs (TCE BsAbs)

Response rates approaching CAR T
But they require ongoing injections
Low grade CRS common, neurotox less common



Hosny *et al, J. Clin. Med.* **2021**

MajesTEC-1 Study: Teclistamab, a BCMA x CD3 Bispecific Antibody, in Relapsed/Refractory Myeloma

- First-in-human, open-label, dose-escalation/dose-expansion phase I/II trial
  - Median follow-up: 7.8 mo (range: 0.5+ to 18); data cutoff: September 7, 2021

Patients with R/R MM who received ≥3 prior lines of therapy and were triple-class exposed (ie, received IMiD, PI, and anti-CD38 mAb); no prior BCMA therapy (N = 165)

→ **Week 1**: **Teclistamab** step-up doses of 0.06 and 0.3 mg/kg SC — Days 1 and 4

→ **Cycles 1+**: **Teclistamab** 1.5 mg/kg SC once weekly — Day 7+

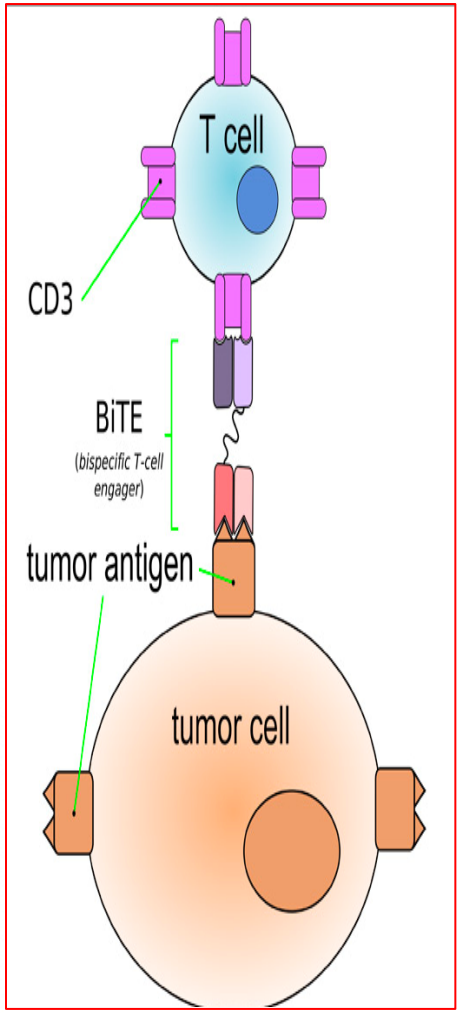
→ *Continue until PD, intolerance, withdrawal, physician decision, or death*

F/u 2 yr after LPI

- Primary endpoint: ORR

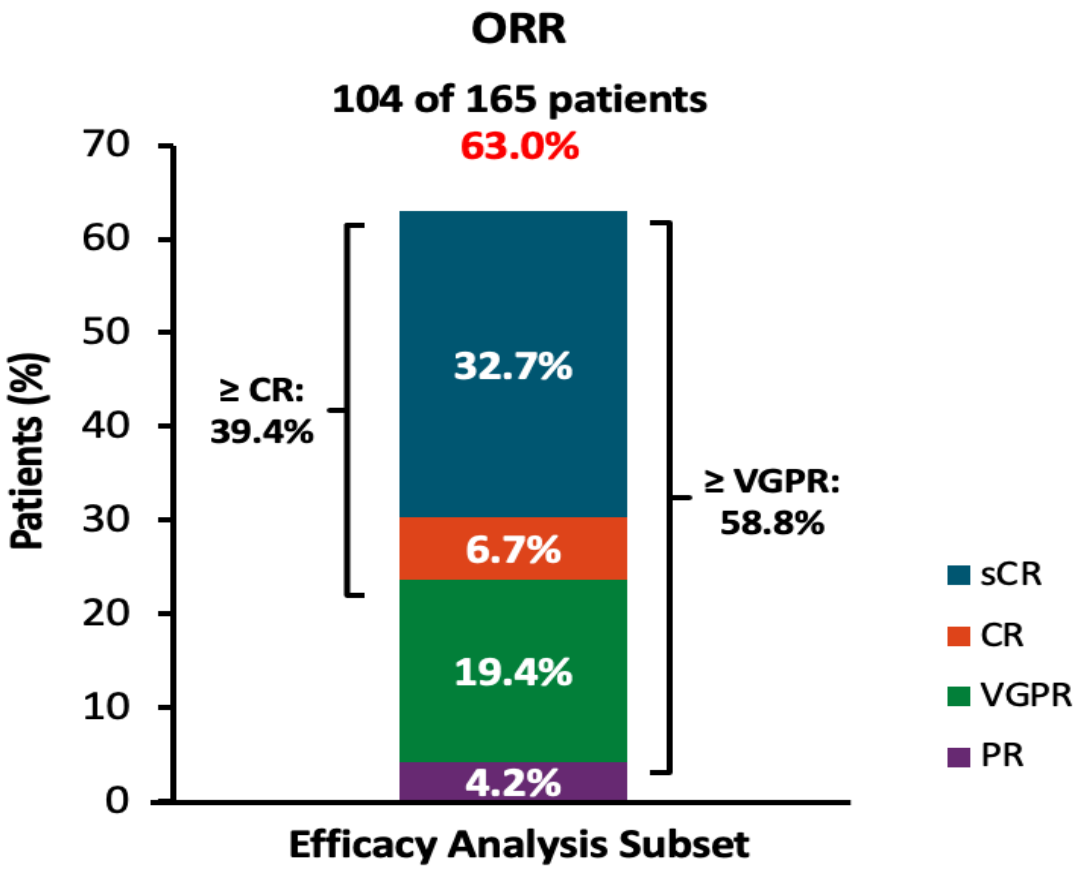
Moreau. ASH 2021. Abstr 896. NCT03145181. NCT04557098.

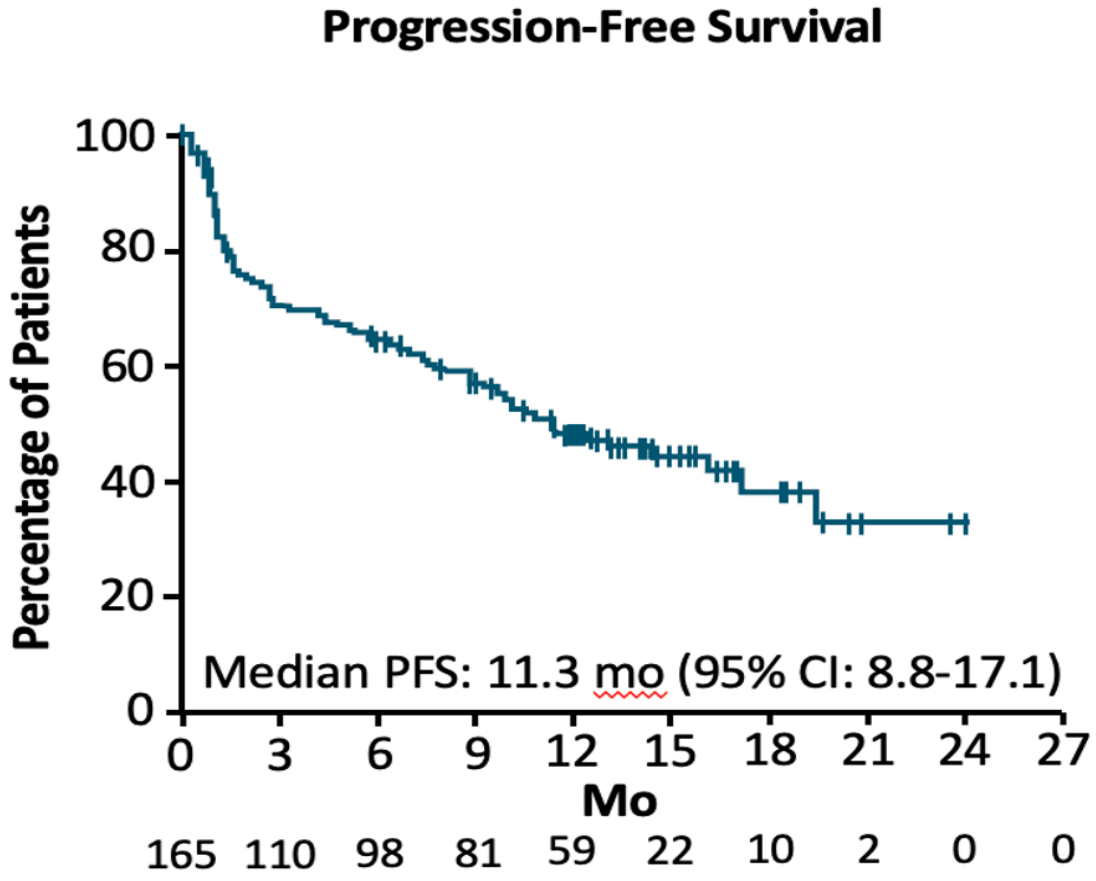
Bispecific anti-CD3/BCMA Dual Ab



MajesTEC-1: Response

Teclistama FDA APPROVED 10/25/22
4 or more prior lines including IMID/PI/CD38





- Median follow-up: 14.1 mo (range: 0.3-24.4)
- Median treatment duration: 8.5 mo (range: 0.2-24.4)
- Median relative dose intensity: 93.7%

72% CRS, only 1 grade 3, 36% Toci, 8% steroids
3% ICANS, all concurrent with CRS and resolved

Nooka. ASCO 2022. Abstr 8007. Moreau. NEJM. 2022;[Epub].

Real-World Safety and Efficacy of Teclistamab for Patients with Heavily Pretreated Relapsed-Refractory Multiple Myeloma

Danai Dima, James A. Davis, Nausheen Ahmed, Xuefei Jia, Aishwarya Sannareddy, Hira Shaikh, Leyla Shune, Gurbakhash Kaur, Jack Khouri, Aimaz Afrough, Christopher Strouse, Jonathan Lochner, Zahra Mahmoudjafari, Shahzad Raza, Jason Valent, Larry D. Anderson, Jr, Faiz Anwer, Al-Ola Abdallah, **Hamza Hashmi**

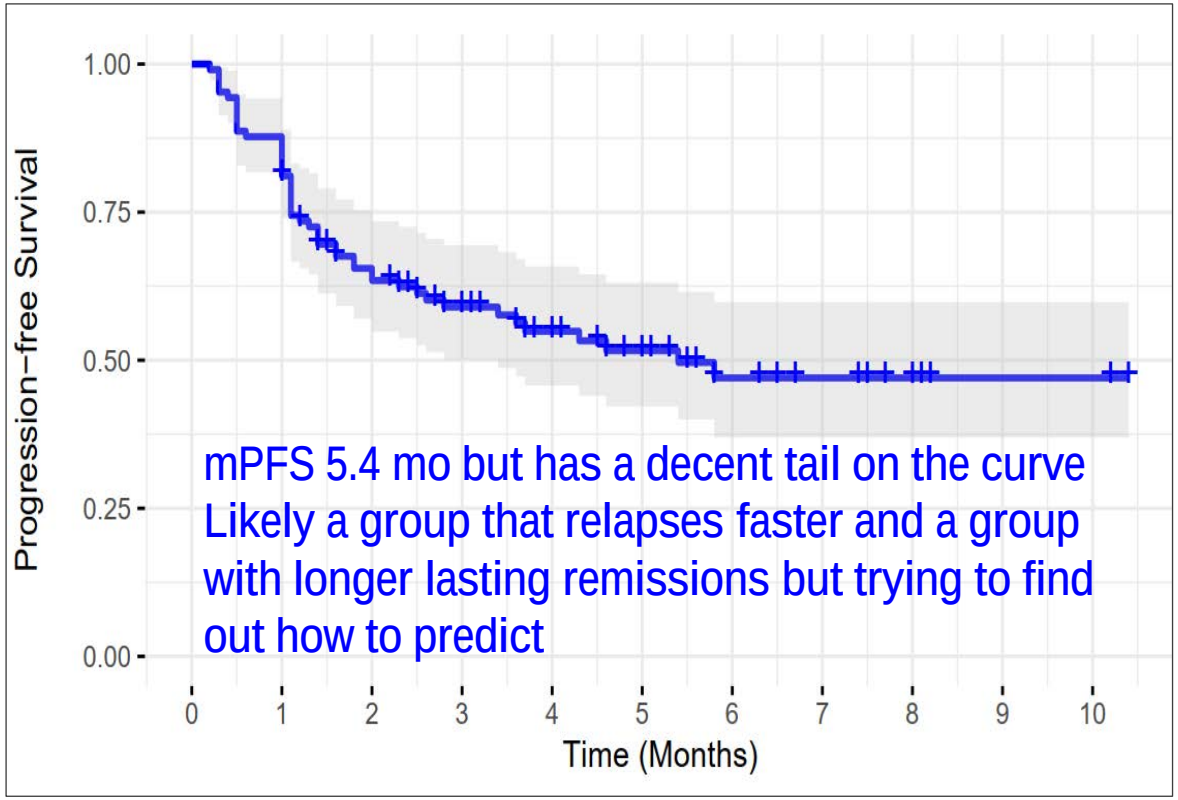
- This is retrospective analysis of RRMM patients who received teclistamab under a commercial FDA label between 8/9/22 and 8/15/23.
- Patients from 5 academic centers in the U.S. (UTSW, Cleveland Clinic, Univ Iowa,
- The safety and efficacy populations for this analysis included all the patients who had received at least one full dose of teclistamab, as of July 15, 2023.
- The median PFS for the entire cohort was 5.4 months (compared to 11.3 mo in Majestecc-1 so shorter PFS despite same ORR)

Response (Full Cohort) N (%)	RWE cohort N=104	MajesTec-1 N=165
Overall response rate	70 (66)	104 (63)
Complete response or better	31 (29)	65 (39.4)
Very good partial response	18 (17)	32 (19.4)
Partial response	21 (20)	7 (4.2)
Minimal response	0	2 (1.2)
Stable disease	10 (9.5)	27 (16.4)
Progressive disease	26 (24.5)	24 (14.5)
Not evaluable	0	8 (4.8)

Dima *et al, ASH 2023 and TCT 2024. (USMIRC Consortium)*

REAL WORLD TECLISTAMAB

Subgroups of Interest	ORR, N (%)
Age>70 (n=34)	24 (71)
Non-Hispanic Black (n=28)	20 (71)
Pts ineligible for MajestEC-1 trial (n=88)	53 (60)
High-risk cytogenetics (n=56)	35 (63)
Triple Refractory (n=97)	62 (64)
Penta refractory (n=68)	46 (68)
Prior BCMA therapy	33 (59)
R-ISS III (n=25)	13 (52)
EMD (n=45)	21 (47)
Four or less prior LOT (n=26)	21 (81)
>4 lines of prior therapy (n=80)	49 (61)

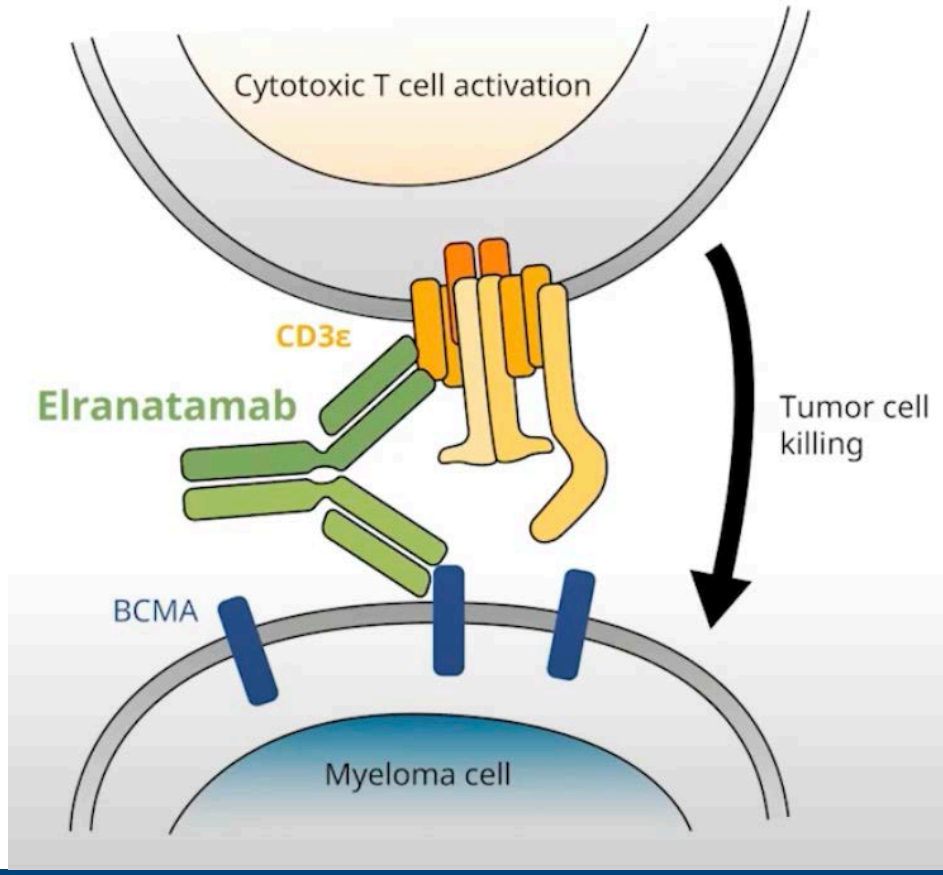


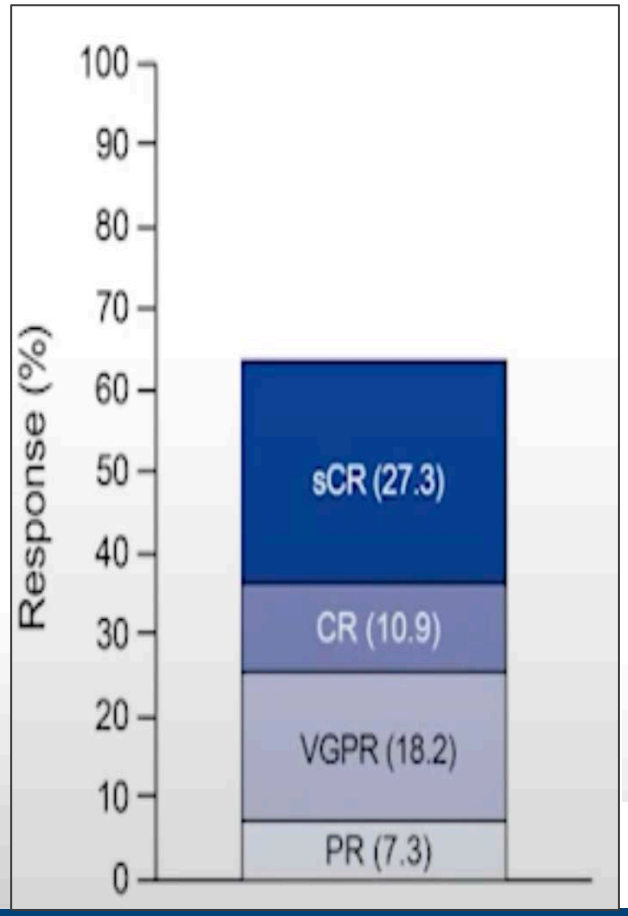
- The incidence of severe CRS and ICANS was low, suggesting possibly feasible outpatient teclistamab step-up dosing and use in the community practice after the initial step-up dosing.
- Cytopenias and infections remain a challenge, therefore, close monitoring, prophylactic antimicrobials, growth factors,, IVIG and vaccinations are important.

Dima *et al, ASH 2023 and TCT 2024*

Elranatamab, a BCMA Targeted T-cell Engaging Bispecific Antibody, Induces Durable Clinical and Molecular Responses for Patients With Relapsed or Refractory Multiple Myeloma (MagnetisMM-1 Trial)

FDA Approved 8/2023





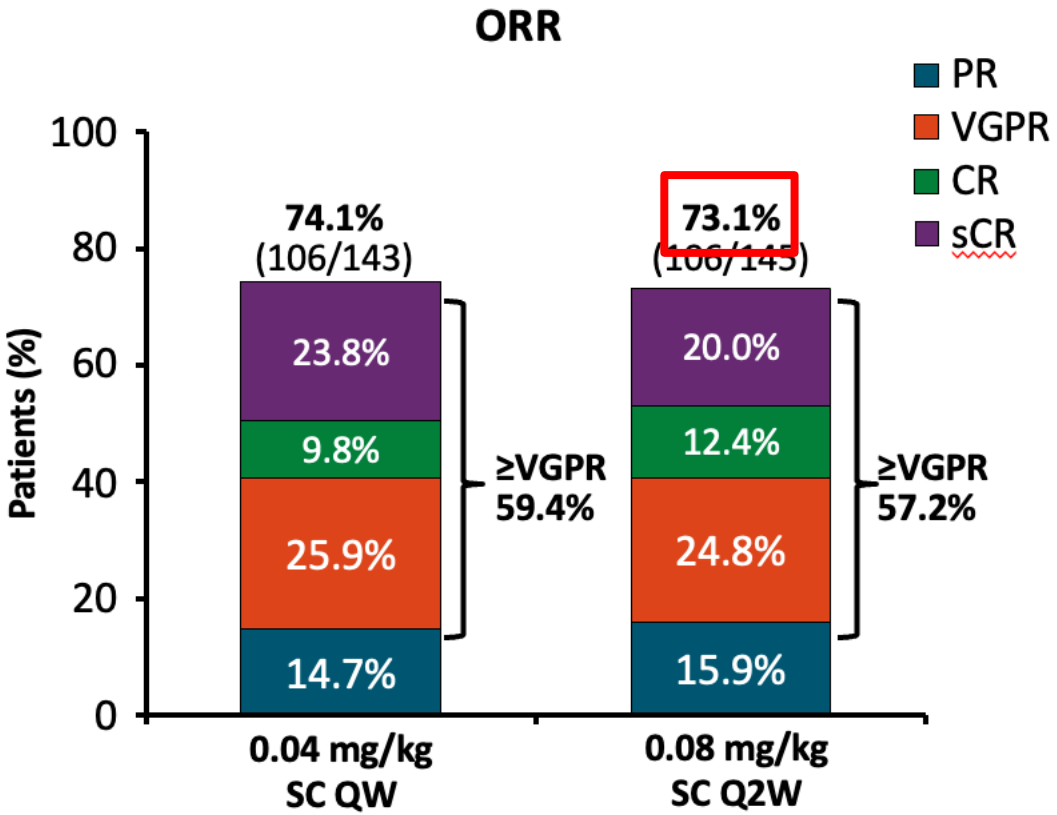
- Median duration of follow-up was 12.0 months (range 0.3–32.3)
- ORR was 64% (95% CI, 50–75) and CR/sCR rate was 38% (21/55)
- 54% (7/13) of patients with prior BCMA-directed therapy achieved response
- For responders (n=35), median time to response was 36 days (range 7–262)
- PFS 11.8 mo, DOR 17.1 mo

Raje et al, ASH 2022, Bahlis et al Nature Med 2023

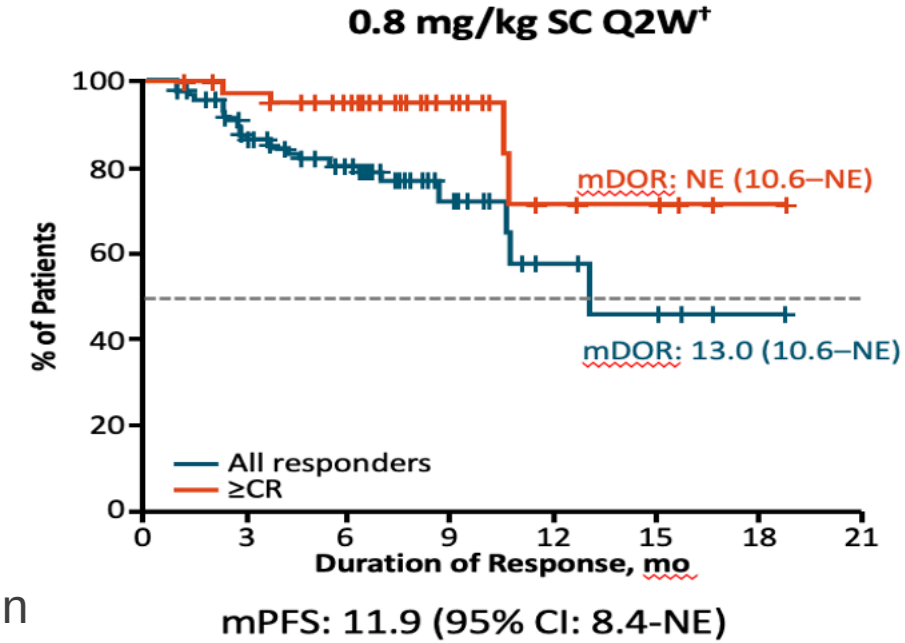
Novel Bispecifics with non-BCMA Targets (GPRC5D)

MonumenTAL-1: ORR

Talquetamab: first-in-class bispecific IgG4 antibody binding GPCR5D and CD3 receptors



- Similar ORR among all subgroups except for patients with EM plasmacytoma
- ORR was similar for both dosing schedules
  - Triple-class refractory: 72.6% (63.1-80.9) QW and 71.0% (61.1–79.6) Q2W
  - Penta-drug refractory: 71.4% (55.4–84.3) QW and 70.6% (52.5–84.9) Q2W



mPFS: 11.9 (95% CI: 8.4-NE)

FDA Approved 8/2023

Skin and nail changes in 75%. Dysgeusia common

Chari et al ASH 2022 Abstr 157

BCMA Therapeutics – Advantages/Disadvantages

	CAR T-cells	Bispecific antibody
Advantages	Personalized	Off the shelf
	Targeted immuno-cytotoxicity	Targeted immuno-cytotoxicity
	Single infusion ("one and done")	No lymphodepletion Minimal steroids
	Potentially persistent	
Disadvantages	Fact accredited center required (hospitalization likely required)	Initial hospitalization required
	CRS and Neurotoxicity; requires ICU and Neurology services	CRS and Neurotoxicity possible
	Dependent on T-cell health (manufacturing failures)	Dependent on T-cell health (T-cell exhaustion)
	Requires significant support social – caregiver required	Requires continuous administration
	$$$$	$$$

SUMMARY and CONCLUSIONS

- 2 Different CAR T-Cell products (Ide-Cel and Cilta-Cel) have been FDA approved for Myeloma after at least 4 prior lines including an IMID/PI/CD38
- KarMMa-3 and Cartitude-4 show improved PFS and ORR for both ide-cel and cilta-cel compared to SOC in earlier line relapsed Myeloma but awaiting FDA review
- CC95266 anti-GPRC5D CAR T-cells are effective in relapsed/refractory Myeloma
- 3 T-Cell Engaging BsAbs have been FDA approved (all for triple exposed and 4 prior lines) (2 anti-BCMA and 1 GPRC5D) (Teclistamab, Elranatamab, and Talquetamab)
- Real world data shows similar response to Ide-cel similar to KarMMa despite sicker pts
- Real World Data shows prior BCMA Bispecific Ab therapy is detrimental to ide-cel CAR T response and PFS, so sequencing is not straightforward
- Real world data shows similar response to Teclistamab but shorter remissions
- Can BsAbs replace CAR T for less cost and less toxicity, or is “one and done” CAR T better? (or could BsAbs better bridge/cytoreduce prior to CAR T to decrease risk?)
- Next steps include: CARTITUDE-6 (Frontline Cilta-cel vs Auto SCT in newly Dx MM) and Majestec-7 (frontline Teclistamab combination vs SOC in newly Dx MM)

Myeloma/PCD Specialists at UTSW

Larry Anderson

Gurbakhash Kaur

Aimaz Afrough

Adeel Khan

THANK YOU!
@ldandersonjr

UTSouthwestern
Harold C. Simmons
Comprehensive Cancer Center

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