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Multidisciplinary Approaches to Cancer Symposium

Management of Relapsing Myeloma

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Disclosures

- Consultant for Janssen and Sanofi.
- On the Speakers Bureau for Adaptive Biosciences, and Janssen.

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 Talquetamab, Mezigdomide, and 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:

- *Efforts to boost/increase diversity and inclusivity of patient participation in clinical trials for advanced multiple myeloma.*
- *Efforts to risk stratify patients not only by age but by functionality.*

Treatment at first relapse: Len refractoriness, mAb-based regimens, and beyond

Multiple therapeutic options for early relapse

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,l-n]	
Note: If a regimen listed for previously treated multiple myeloma was used as a primary induction therapy and relapse is >6 months, the same regimen may be repeated.	
Preferred Regimens for Early Relapses (1–3 prior therapies) *Order of regimens do not indicate comparative efficacy*	
• **Bortezomib/lenalidomide/dexamethasone** • **Carfilzomib/lenalidomide/dexamethasone (category 1)[o]** • **Daratumumab/bortezomib/dexamethasone (category 1)** • **Daratumumab/carfilzomib/dexamethasone (category 1)** • **Daratumumab/lenalidomide/dexamethasone (category 1)** • **Ixazomib/lenalidomide/dexamethasone (category 1)[o]** • **Isatuximab-irfc/carfilzomib/dexamethasone (category 1)**	• *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** ‣ **Pomalidomide/bortezomib/dexamethasone (category 1)** • *After two prior therapies including lenalidomide and a PI* ‣ **Isatuximab-irfc/pomalidomide/dexamethasone (category 1)** ‣ **Daratumumab/pomalidomide/dexamethasone (category 1)**
Other Recommended Regimens for Early Relapses (1–3 prior therapies)	
• **Bendamustine/bortezomib/dexamethasone** • **Bendamustine/lenalidomide/dexamethasone** • **Bortezomib/liposomal doxorubicin/dexamethasone (category 1)** • **Bortezomib/cyclophosphamide/dexamethasone** • **Carfilzomib/cyclophosphamide/dexamethasone** • **Carfilzomib (twice weekly)/dexamethasone (category 1)** • **Cyclophosphamide/lenalidomide/dexamethasone** • **Daratumumab/cyclophosphamide/bortezomib/dexamethasone** • **Elotuzumab/bortezomib/dexamethasone** • **Elotuzumab/lenalidomide/dexamethasone (category 1)** • **Ixazomib/cyclophosphamide/dexamethasone** • **Selinexor/bortezomib/dexamethasone (once weekly) (category 1)**	• *After two prior therapies including an IMiD and a PI and disease progression on/within 60 days of completion of last therapy* ‣ **Pomalidomide/carfilzomib/dexamethasone** ‣ **Pomalidomide/cyclophosphamide/dexamethasone** • *After two prior therapies including lenalidomide and a PI* ‣ **Elotuzumab/pomalidomide/dexamethasone**

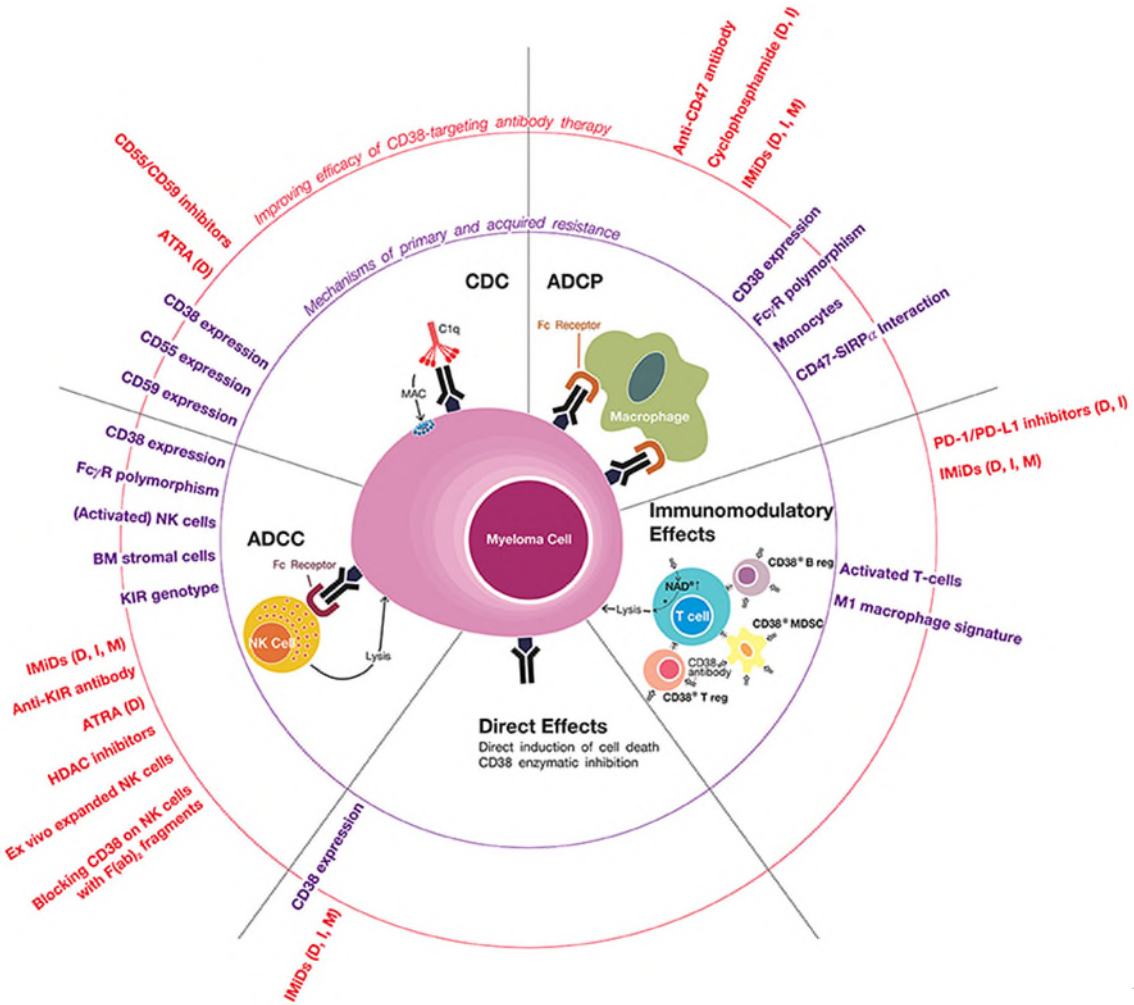
Most patients will have progressive-disease while on lenalidomide, therefore have len-refractory disease

At first relapse, lenalidomide-combinations are preferred in those NOT len-refractory

Trial(s)	ASPIRE*	POLLUX*	ELOQUENT-2	TOURMALINE-MM1*
Regimen	KRd vs. Rd	DRd vs. Rd	Elo-Rd vs. Rd	Ixa-Rd vs. Rd
Indication	RRMM with 1-3 LOT	RRMM ≥ 1 LOT	RRMM with 1-3 LOT	RRMM ≥ 1 LOT
ORR	87.1 vs. 66.7%	93 vs. 76%	79% vs. 66%	78% vs. 72%
DOR	28.6 vs. 21.2 mo	NR vs. 25.2 mo	21.9 vs. 17.1 mo	20.5 vs. 15.0 mo
PFS	mPFS – 26.3 vs. 17.6 mo; HR 0.69	mPFS – NR vs. 19.6 mo** HR 0.42 42-mo PFS 57.3% vs. 27.8%	mPFS – 19.4 vs. 14.9 mo HR 0.70	20.6 vs. 14.7mo HR
OS	mOS - 48.3 mo vs. 40.4 mo HR 0.79	mOS – 67.6 vs. 51.8mo HR 0.73	mOS – 48.3 vs. 39.6 mo HR 0.82	mOS – 53.6 vs. 51.6 mo HR 0.939 (NS)

Richardson et al. (2021); Dimoppolous et al. (2023); Moreau et al. (2021); Facone et al. (2016); Bahlis et al. (2020); Stewart et al. (2017)

Given that most are len-refractory, CD38 monoclonal antibodies are the current backbone of RRMM treatment



Van de Donk and Usmani. (2018)

CD38 mAb plus Kd for early relapse

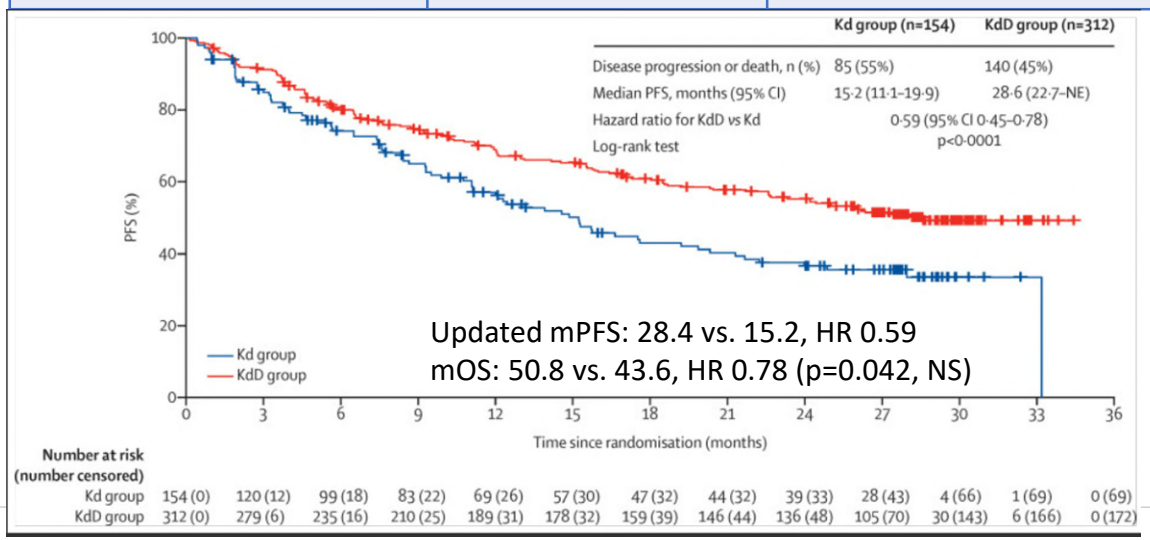
- CANDOR – Dara plus Kd vs. Kd
  - Dara(IV) + carf (56mg/m^2 twice weekly 3 of 4 weeks) +dex 40mg wk
  - 1-3 line of prior therapy
  - Cardio/pulmonary and severe renal disease excluded
  - 2:1 randomization
  - Continued to disease progression/intolerance

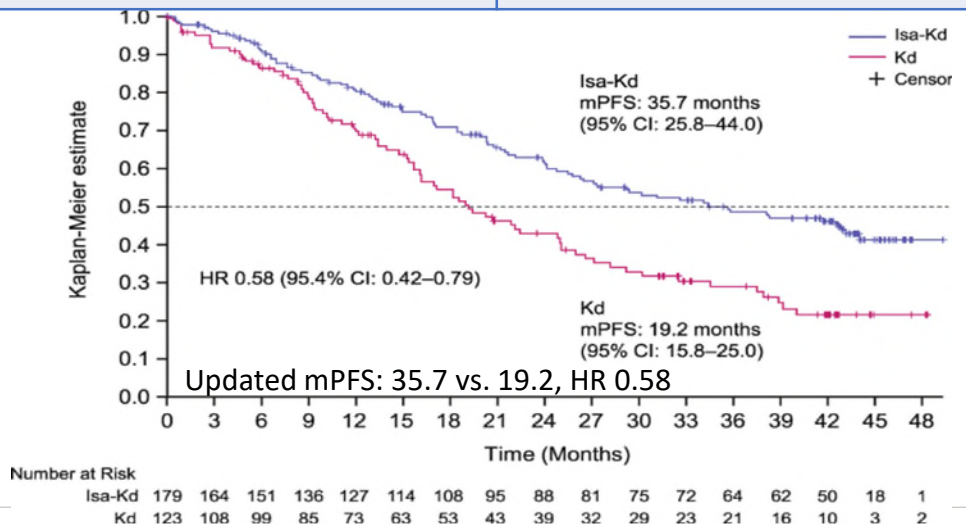
- IKEMA – Isa plus Kd vs. Kd
  - Isa(IV) + carf (56mg/m^2 twice weekly 3 of 4 weeks) +dex 40mg wk
  - 1-3 line of prior therapy
  - Cardiac and severe renal disease excluded
  - 3:2 randomization
  - Continued to disease progression/intolerance

Usmani et al. (2022); Moreau et al. (2022); Moreau et al. (2021)

Dara and Isa, when combined with Kd, improve outcomes over Kd alone

	CANDOR – DKd vs. Kd		IKEMA- IKd vs. Kd	
Age– med (range)	64 (57-71)		64 (33-90)	
Prior lines – med (range)	2 (1-3) – 29% BTZ-ref, 33% len-ref		2 (1-4) – 21% double refractory	
High Risk Cyto	16%		24% (42% gain 1q)	
Arm	**DKd**	**Kd**	**IKd**	**Kd**
ORR, %, (95% CI)	84 (80-88)	75 (67-81)	86.6 (80.7-91.2)	82.9 (75.1-89.1)
CR, %	28	10	44.1	28.5





Usmani et al. (2023); Martin et al. (2023); Moreau et al. (2021)

Dara or Isa combined with Kd increase risk of respiratory infections

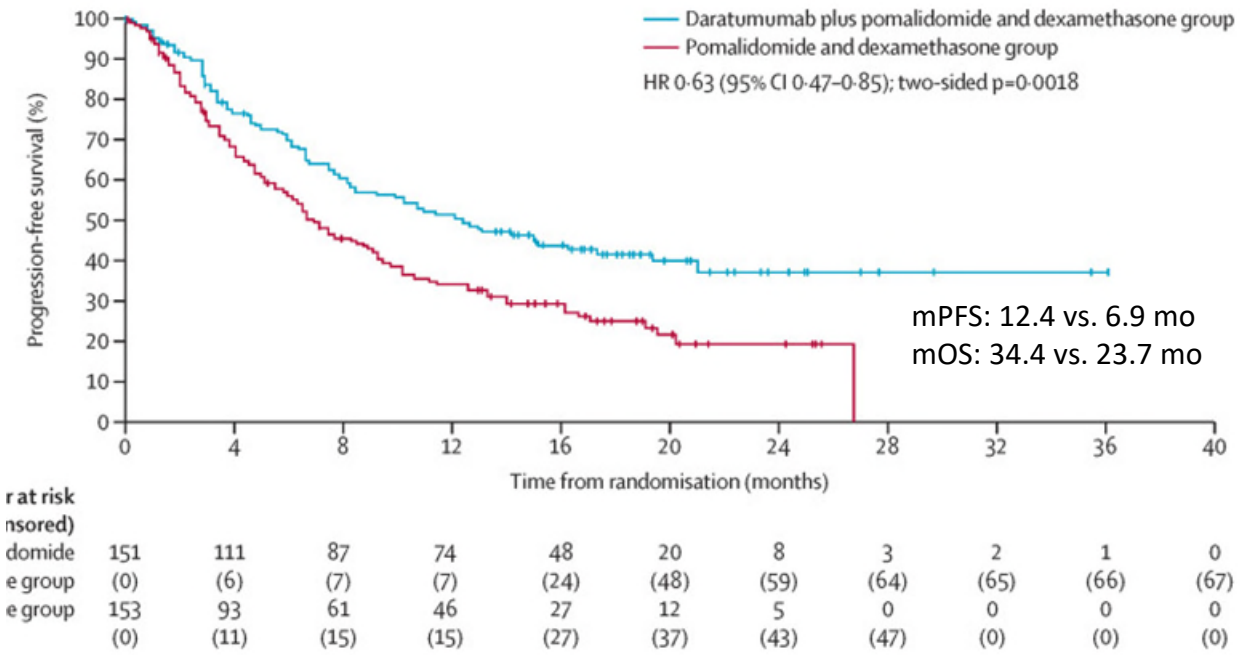
- Do not appear to increase risk of cardiac complications

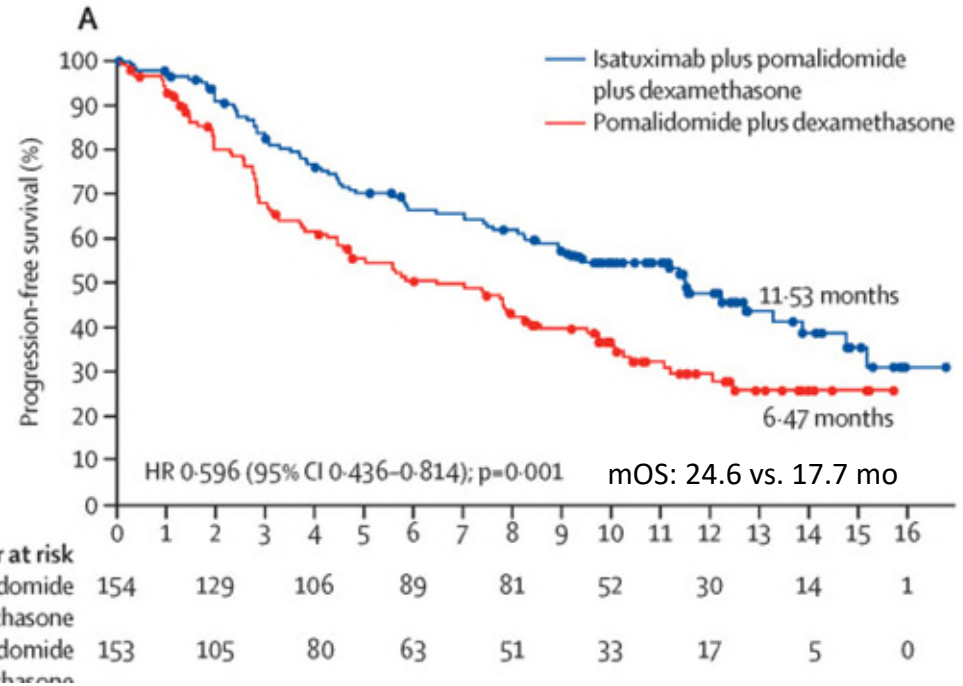
Arm	DKd	Kd	IKd	Kd
Grade ≥3, %	87	76	77	67
Hypertension	21	15	20	20
Pneumonia	17	9	23	14
Thrombocytopenia	25	16	30	24
Cardiac Failure	3	2	4	4
Fatal, %	9	5	3	3
Cardiac	2	0	NR	NR
Infections	5	3	NR	NR
Respiratory	1	1	NR	NR

Usmani et al. (2022); Moreau et al. (2022); Moreau et al. (2021)

CD38 mAb plus Pd for len-refractory MM

	APOLLO – DPd vs. Pd		ICARIA-MM – IPd vs. Pd	
Age– med (range)	67 (42-86)		67 (36-86)	
Prior lines – med (range)	**2 (1-5); 80% len ref, 48% PI-ref, 42% double**		**3 (2-11); 93% len-ref, 76% PI-ref, 73% double-refractory**	
High Risk Cyto	35%		20%	
Arm	**DPd**	**Pd**	**IPd**	**Pd**
ORR, %, (95% CI)	69 (61-76)	46 (38-55)	86.6 (80.7-91.2)	82.9 (75.1-89.1)
CR, %	25	4	44.1	35





Dimopolous et al. 2022; Richardson et al. 2022; Richardson et al. 2022

Daratumumab regimens for RRMM

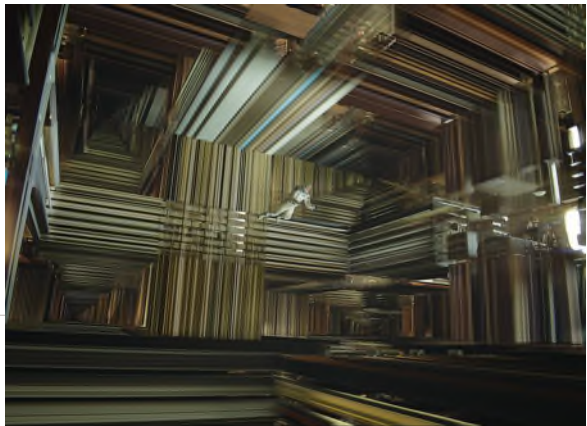
Trial(s)	SIRIUS GEN501	POLLUX	EQUULES APOLLO	CASTOR	EQUULES CANDOR
Regimen	Monotherapy	DRd vs. Rd	DPd DPd vs. Pd	DVd vs. Vd	DKd vs. Kd
Indication	• ≥3 lines OR • PI/IMID refractory	• ≥1 line	• ≥2 line (approved) • ≥1 line (off-label)	• ≥1 line	• ≥1-3 line
ORR	29.2% (20.8-38.9) 36% (21.6 – 52)	92.9% vs. 76.4%	60% APOLLO: ≥VGPR 51.0% vs. 19.6%	85% vs. 63%	84% 84% vs. 75%
DOR	7.4 mo (5.5 – NE)	NR	EQUULES: 6 mo: 85% 12 mo: 68%	NR	NE vs. 16.6
PFS	3.7 mo (2.8 – 4.6)	44.5 vs. 17.5 mo	APOLLO: 12.4 vs. 6.9 mo	16.7 vs. 7.1 mo	CANDOR: 18-month PFS 62% vs. 43%
OS	17.5 mo (13.7 – NE)	42-month OS rate: 65% vs. 57%	APOLLO: HR for OS 0.91 (95% CI 0.6-1.4)	NR	CANDOR: HR for OS 0.75 (95% CI 0.49-1.13)

My general strategy for early relapse (1-3 prior lines) – "mixing and painting with the right colors"

- Clinical trial if available
- Generally choose a triplet regimen – repeatedly shown to have superior efficacy to doublets
- Choose regimens based on the following
  - Which agents are they refractory to (progression while on or within 60 days of completing treatment) – This is different than exposure
  - What is current performance status and comorbidities – i.e. cardiac disease is thinking carfilzomib, respiratory illnesses if considering anti-CD38
  - How did they tolerate specific agents and drug classes in the past? – i.e. bad rash or cytopenias from IMiDs previously, ongoing neuropathy from PIs
- Lean toward Dara-containing regimens in general, Len-containing regimens if not refractory

Later relapse – Painting in 4 dimensions

Early referral to Myeloma Specialist can help optimize treatment strategy

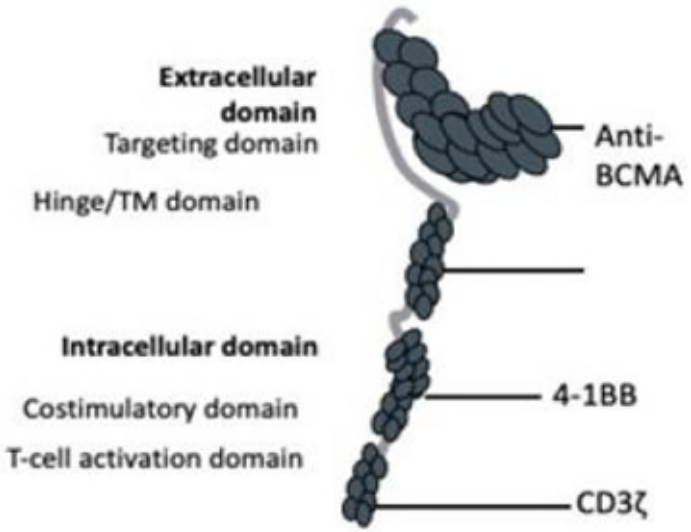


Harnessing the power of the immune system to fight later relapsed MM

BCMA CAR T construct differences

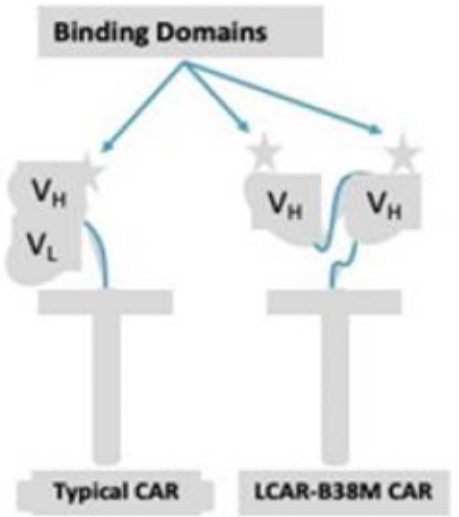
Idecabtagene Vicleucel

- 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



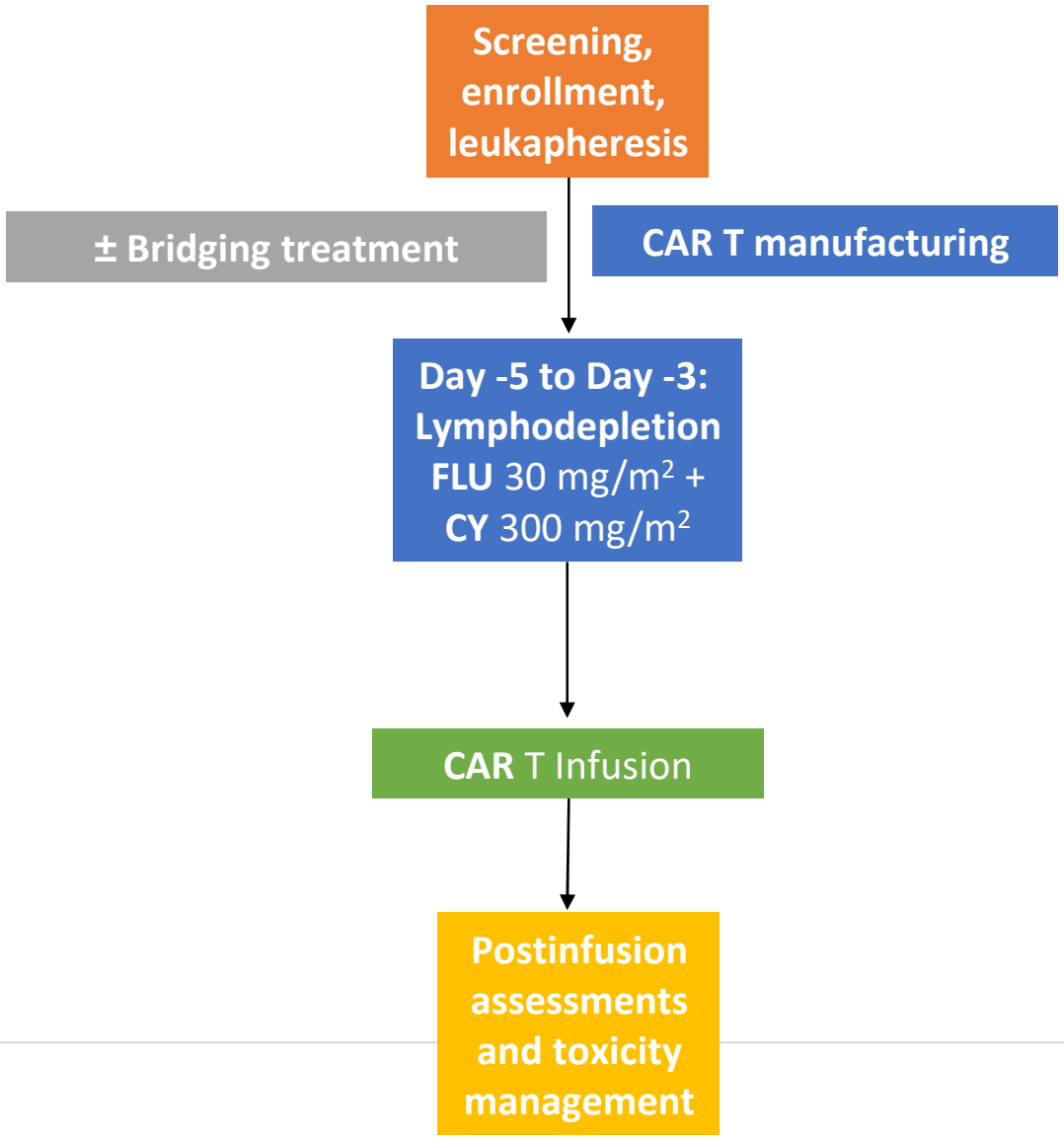
Ciltacabtagene Autoleucel

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



Martino M et al. *Cancers.*

KarMMa and CARTITUDE-1 Study Designs

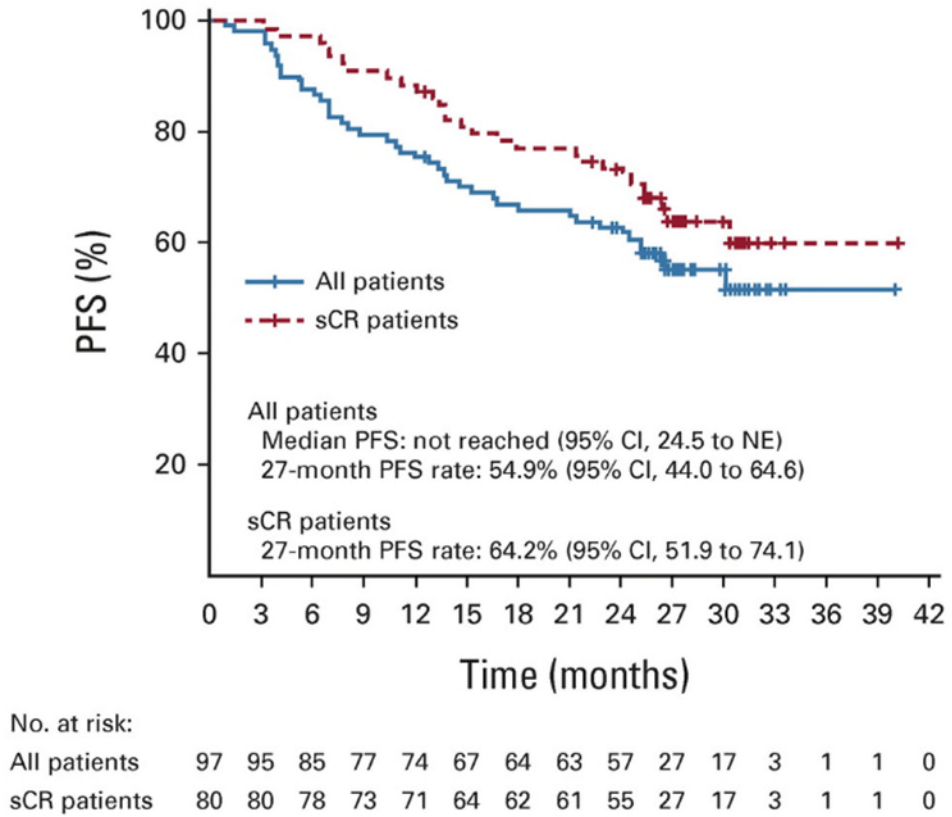


BCMA CAR T Trials - Baseline Characteristics

Trial	KarMMa	CARTITUDE-1
CAR T product	Ide-cel	Cilta-cel
N	128	97
Median age, y	61	61
Male, %	76	59
Extramedullary disease, %	39	13
ECOG-0 Performance Status, %	45	40
ISS Stage III, %	16	14
High-risk cytogenetics, %	35	24
Prior LOT (median)	6	6
Penta-refractory, % Triple-class refractory, %	26 84	42 88

Munshi et ak. (2021); Berdeja et al. (2021)

CARTITUDE-1 Efficacy

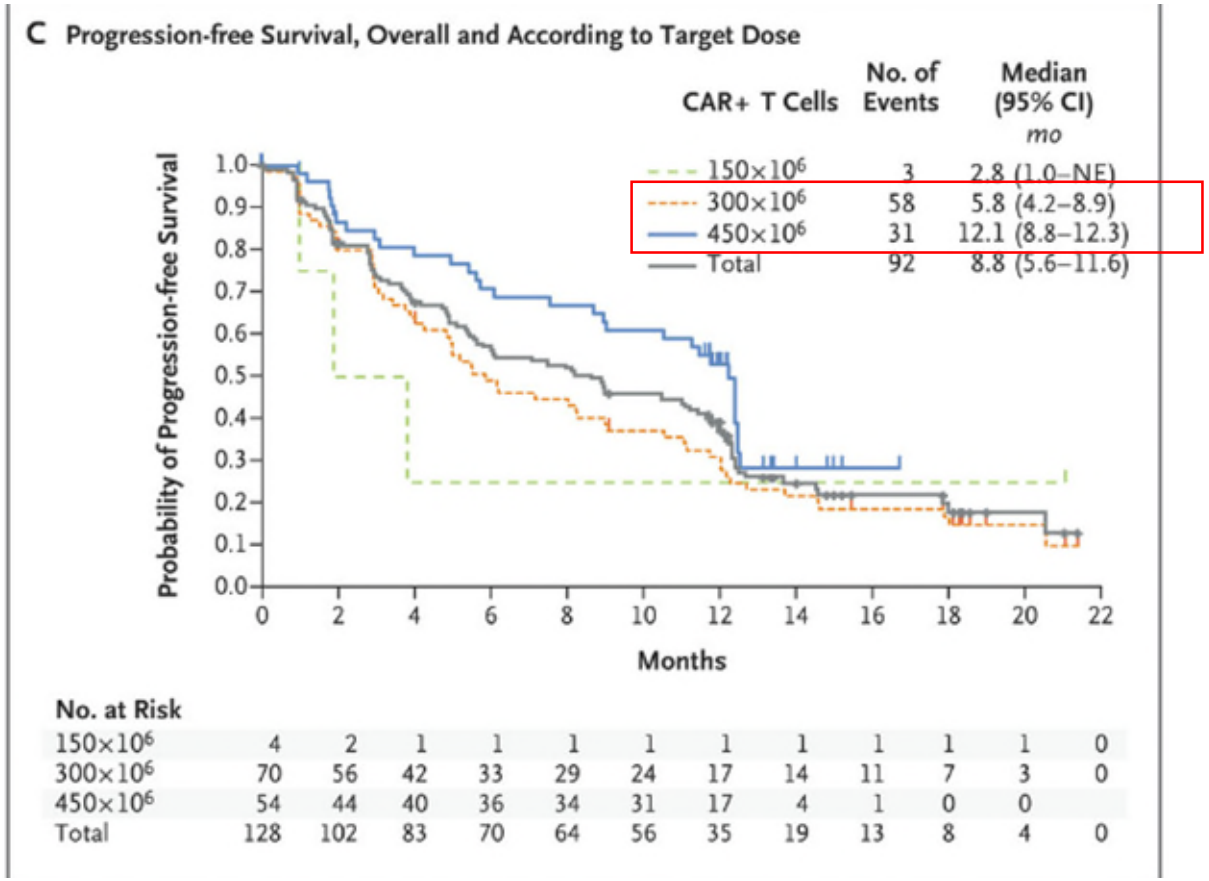


Subgroup	n	mPFS (95% CI), mo	30-mo PFS rate	36-mo PFS rate
All pts	97	34.9 (25.2–NE)	54.2%	47.5%
≥CR	76	38.2 (34.9–NE)	66.8%	59.8%
6-mo sustained MRD negativity[a]	34	32.2 (25.1–NE)	68.6%	45.7%
12-mo sustained MRD negativity[a]	26	NR (NE–NE)	74.9%	NE
12-mo sustained MRD-negative CR[a]	20	NR (NE–NE)	78.5%	NE

[a]≥2 MRD-negative assessments, 6 or 12 mo apart, with no MRD-positive samples in that interval.

Martin et al. (2022); Lin et al. 2023

KarMMa Efficacy



Munshi et al. 2021

Efficacy Outcomes of BCMA CAR T

Trial	KarMMa	CARTITUDE-1
CAR T product	Ide-cel	Cilta-cel
N	128	97
ORR, %	73	97.9
PFS (median)	8.6	34.9
OS (median)	24.8	NR (3-year OS 62.9%)
MRD negativity, %	26	92

Munshi et al. (2023); Anderson et al. (2021); Lin et al. 2023

Safety Outcomes of Late BCMA CAR T

Trial	KarMMa	CARTITUDE-1
CAR T product	Ide-cel	Cilta-cel
N	128	97
TEAE, any/≥Gr 3,%	100/99	100/94
CRS, Any, %	84	95
Gr 3/4	5	4
Gr 5	<1	1
Median onset, d	1	7
Median duration, d	5	4
NT, Any, %	18	21 (ICANS 17%, other NT 12%)
Gr 3/4	4	9 (ICANS 2%, other NT 8%)
Gr 5	0	1
Median onset, d	2	ICANS 8, Other 27
Median duration, d	5	ICANS 4, Other 74.5

Munshi et ak. (2021); Berdeja et al. (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

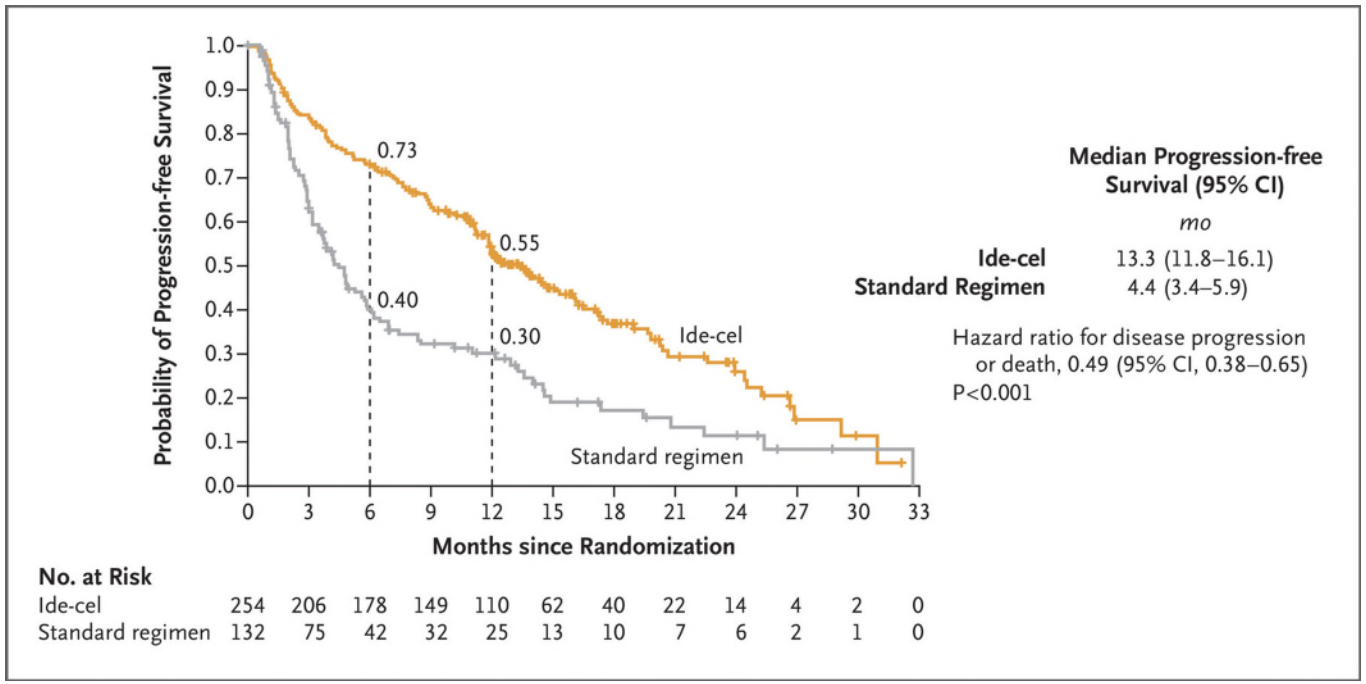
Jesús San-Miguel, M.D., Ph.D., Binod Dhakal, M.D., Kwee Yong, Ph.D., Andrew Spencer, M.D., Sébastien Anguille, M.D., Ph.D., María-Victoria Mateos, M.D., Ph.D., Carlos Fernández de Larrea, M.D., Ph.D., Joaquín Martínez-López, M.D., Philippe Moreau, M.D., Ph.D., Cyrille Touzeau, M.D., Xavier Leleu, M.D., 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.

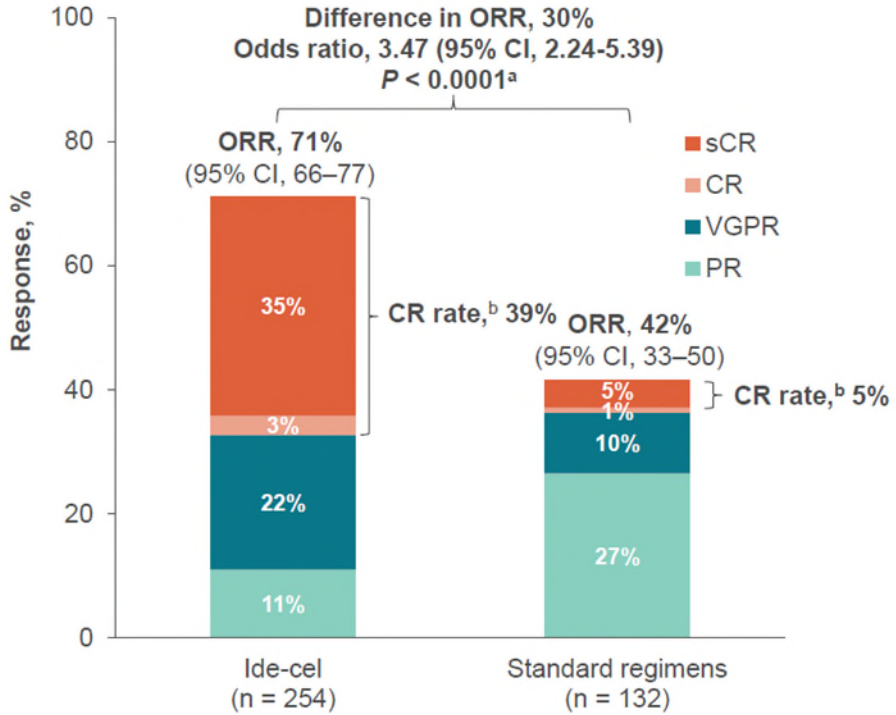
Baseline Characteristics

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, %	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

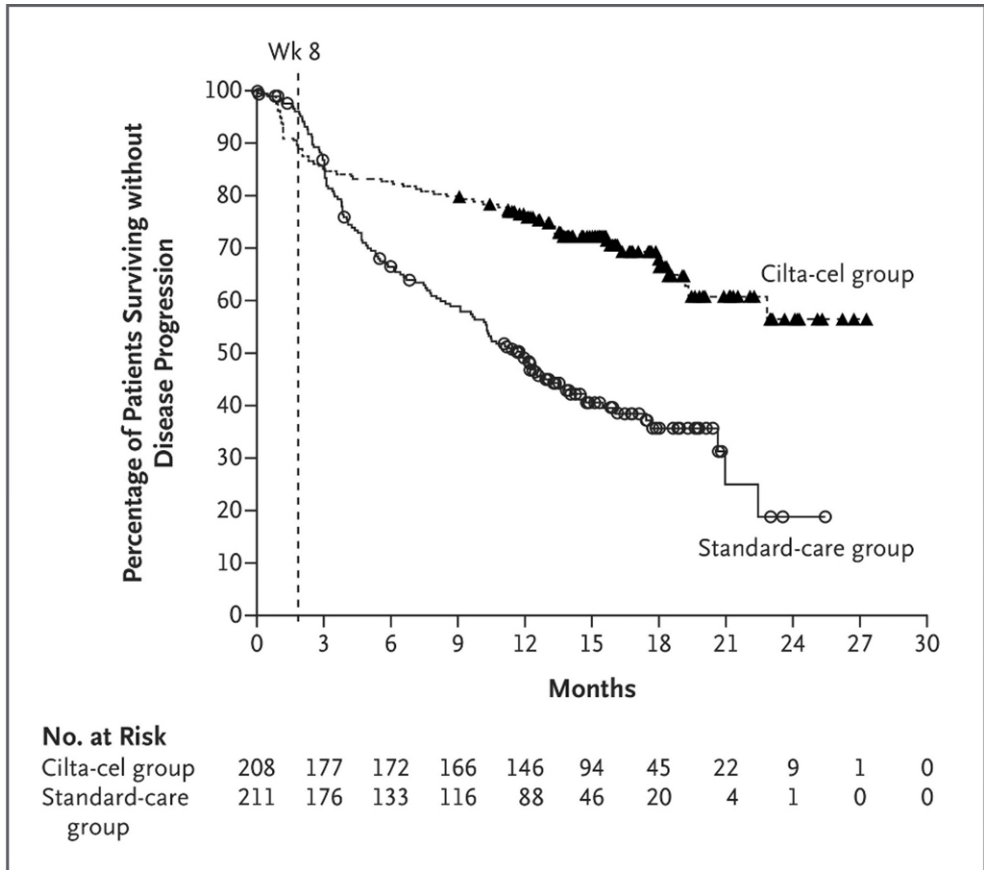
San-Miguel et al. (2023), Rodriguez-Otero et al. (2023)

KarMMa-3: Efficacy





CARTITUDE-4 Efficacy



- More PD or death in first 8 weeks in Cilta-cel arm

Overall PFS

- HR 0.26 (95% CI 0.18-0.38), P<0.001
- 12 mo PFS 75.9% vs. 48.6%

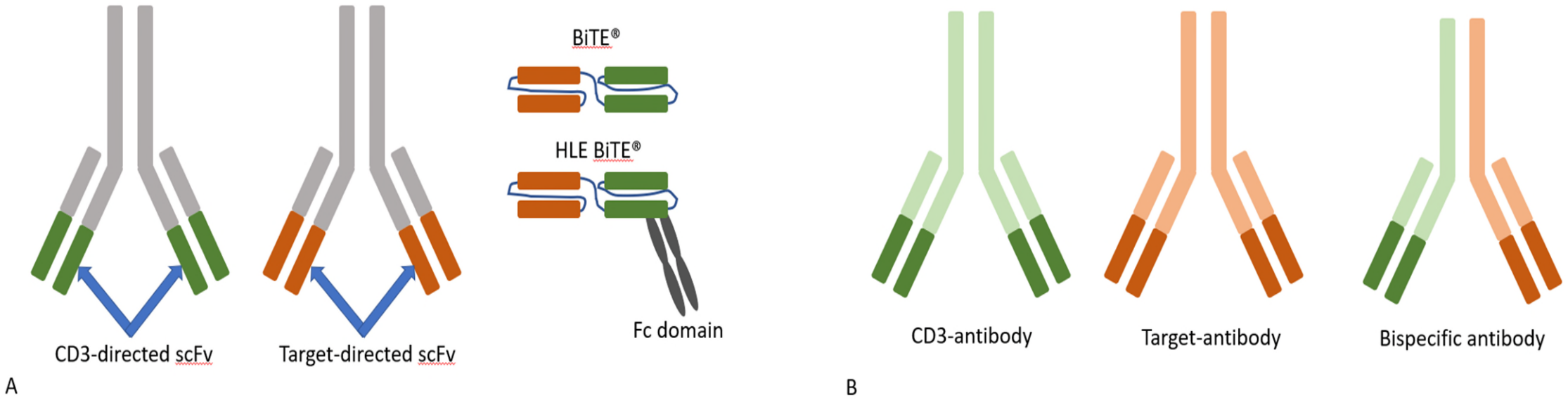
- Response
  - CR+ rate – 73.1% vs. 21.8%
  - ORR – 84.6% vs. 67.3%
  - 12 mo DOR –a 84.7% vs. 63%

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 995,%	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)

Bispecific Constructs Provide Off-the-Shelf T-cell Redirection to Combat Myeloma

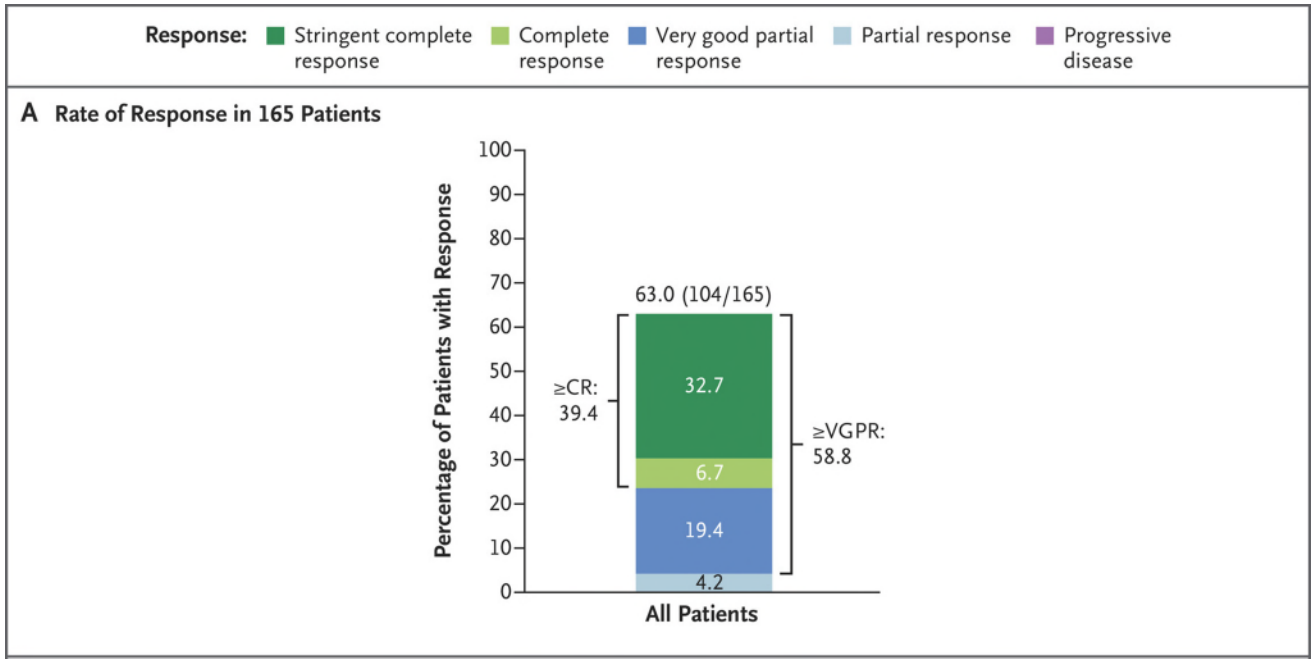


Goldsmith et al. (2022)

ORIGINAL ARTICLE

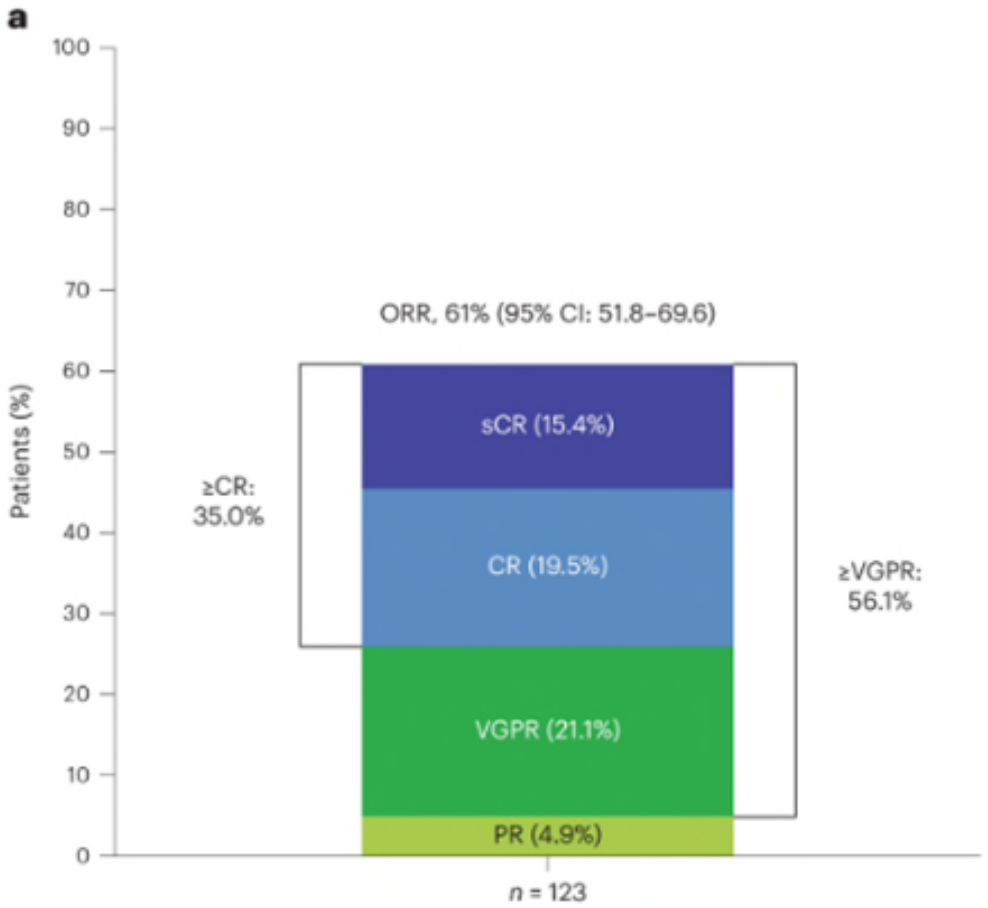
Teclistamab in Relapsed or Refractory Multiple Myeloma

Philippe Moreau, M.D., Alfred L. Garfall, M.D., Niels W.C.J. van de Donk, M.D., Ph.D., Hareth Nahi, M.D., Ph.D., Jesús F. San-Miguel, M.D., Ph.D., Albert Oriol, M.D., Ph.D., Ajay K. Nooka, M.D., Thomas Martin, M.D., Laura Rosinol, M.D., Ajai Chari, M.D., Lionel Karlin, M.D., Lotfi Benboubker, M.D., et al.



- BCMA-targeting bispecific antibody
- Long-term follow-up with median follow-up of 23 months
  - mDOR of 21.6 mo
  - Depth of response improved ≥CR 46.4%
- Toxicity with longer follow-up
  - CRS in 72%, 0.6% Gr 3, usually during step-up or first dose
  - ICANS in 6%, all Gr 1/2
  - **Infections in 80%, 55.2% Gr 3/4**

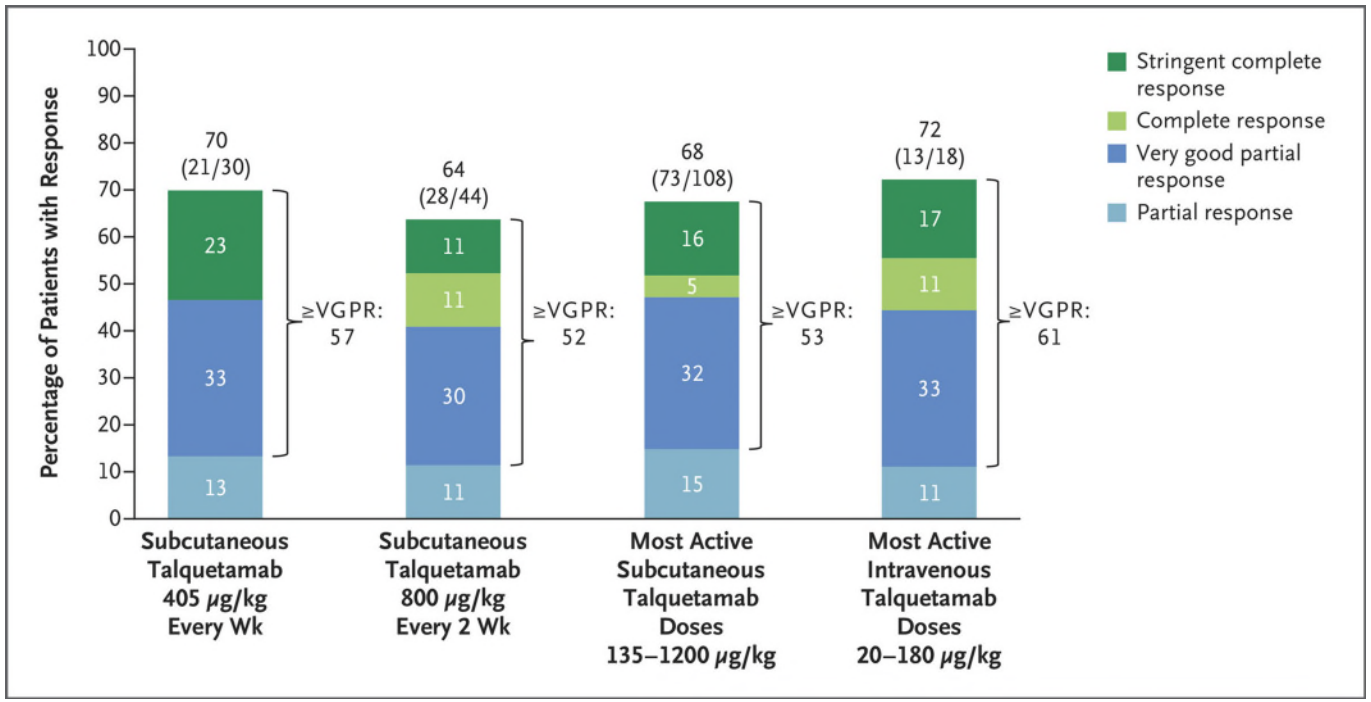
Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results



- BCMA-targeting bispecific antibody
- Median follow-up 14.7mo
  - 61% ORR, 35% ≥CR, consistent across subgroups
  - mDOR NR, 15mo estimated DOR 71.5% and PFS 50.9%
- Toxicity
  - CRS in 56.3%, all Gr 1/2, most in first 3 doses
  - ICANS in 3.4%, all Gr 1/2; 17.1% motor neuropathy, 1 Gr 3 event
  - **Infections in 69.9%, 39.8% Gr ¾, 6.5% Gr 5**

ORIGINAL ARTICLE

Talquetamab, a T-Cell–Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma



- GPRC5D is an orphan receptor on plasma cells and keratinized epithelial cells, independent of BCMA
- Pivotal cohorts - tal 0.4 mg/kg QW (n = 143) or 0.8 mg/kg Q2W (n = 145), and 51 pts with prior T-cell redirection therapy
  - ORR 74%, 73%, and 63%, respectively
  - mPFS 7.5, 11.9, and 5.1mo, respectively
- Toxicity
  - Common AEs included CRS (79%, 75%, 77%), skin-related AEs (56%, 71%, 69%), nail-related AEs (54%, 53%, 61%), and **dysgeusia** (50%, 48%, 61%)
  - **ICANS occurred in 11%, 11%, and 3%**
  - **Infections occurred in 58%, 65%, and 71% (grade 3/4: 22%, 16%, 26%)**

Chari et al. 2022; Schinke et al. 2023

CELMoDs overcome IMiD resistance

- Iberdomide
  - Enhanced tumoricidal and immunostimulatory effects
  - 20x greater affinity to CRBN than Len and Pom
  - 25-50% ORR in various combinations among heavily-pretreated patients
- Mezigdomide
  - Rapid degradation of Ikaros and Aiolos
  - 48% ORR in combination with dexamethasone
  - 75% ORR in combination with bortezomib
  - Responses regardless of IMiD refractoriness

Lonial et al. (2021); Richardson et al. (2021); Richardson et al. (2023)

Conclusions and Future Directions

- Multitude of standard and investigational options for RRMM
- Lack of head-to-head data and data on best sequence of therapies
- Choice of therapy influenced by prior therapy, comorbidities, pace of relapse, trial eligibility
- Early referral to and co-management with myeloma specialist important to expand options
- Novel agents will move toward frontline, requiring further innovation for those with RRMM

Thank you

- COH CME
- Dept. of Heme/HCT
- Patients and Families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