Emerging and Current Treatment of Multiple Myeloma: What Should We Know and What Should We Do

Kenneth Anderson, MD
Director, Jerome Lipper Multiple Myeloma Center
and LeBow Institute for Myeloma Therapeutics
Dana-Farber Cancer Institute
Kraft Family Professor of Medicine
Harvard Medical School

Disclosures

Advisory Role: Pfizer, Astrazeneca, Janssen, Oncopeptides

Board Membership: C4 Therapeutics, Dynamic Cell Therapies, Window, Starton

Ownership Interests: C4 Therapeutics, Oncopep, NextRNA, Dynamic Cell Therapies

Therapeutic Advances in Multiple Myeloma

Proteasome inhibitors: bortezomib, carfilzomib, ixazomib; immunomodulatory drugs: thalidomide, lenalidomide, pomalidomide; HDAC inhibitor: panobinostat; monoclonal antibodies: elotuzumab, daratumumab, and isatuximab; nuclear transport inhibitor: selinexor; Immunotoxin: belantomab mafodotin; CAR T cell: idecel, ciltacel; bispecific T cell engager: teclistamab

Target MM in the BM microenvironment, alone and in combination, to overcome conventional drug resistance *in vitro* and *in vivo*

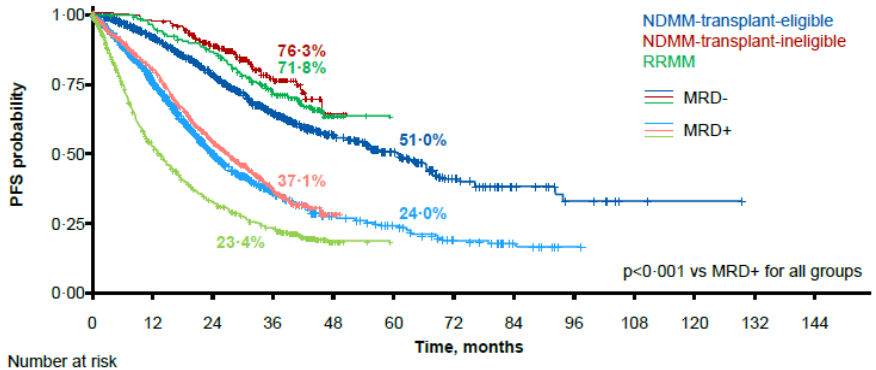
Effective in relapsed/refractory, relapsed, induction, consolidation, and maintenance therapy

31 FDA approvals (15 agents), median patient survival prolonged 3-4 fold, from 3 to at least 8-10 years, and MM is a chronic illness in many patients.

3 Eras of Progress: Transplant 1980-; Targeted Therapies 2000-; Immune Therapies 2020-

Minimal Residual Disease Negativity in Newly Diagnosed and Relapsed Refractory MM: Prolonged PFS and OS

PFS

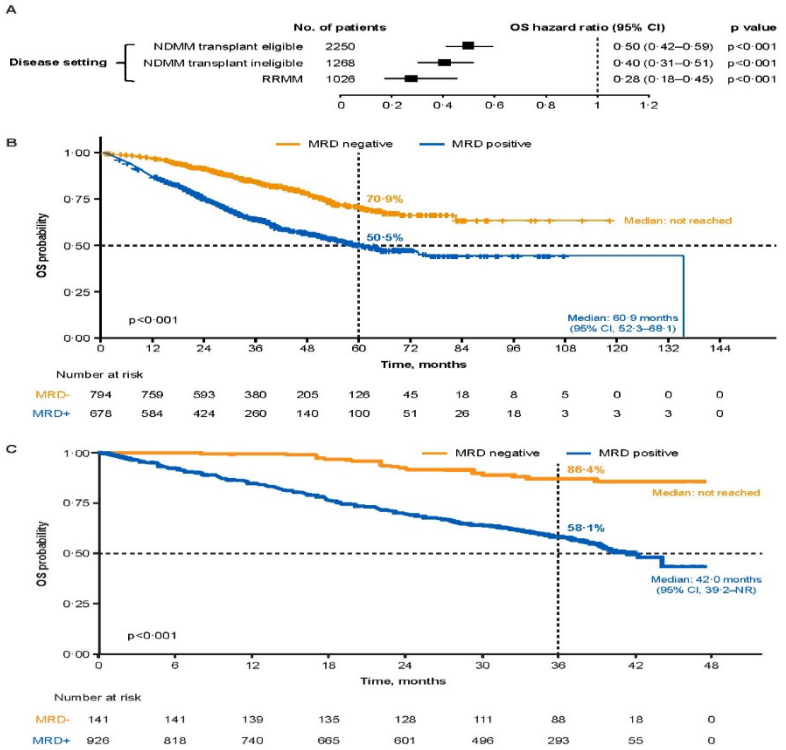


Number at risk

MRD-	1515	1055	589	332	164	95	47	22	10	3	1	0	0
MRD+	1180	719	317	153	72	50	30	13	2	0	0	0	0
MRD-	291	283	217	93	4	0							
MRD+	1328	983	516	133	5	0							
MRD-	164	155	135	97	10	0							
MRD+	960	456	269	179	11	0							

Munshi et al., Blood Adv 2020; 4: **5988-99**.

OS



NDMM Transplant -eligible

RRMM

Therapy for Newly Diagnosed MM Transplant Candidates

Triplets

Lenalidomide (R)/ Bortezomib (V)/ Dexamethasone (Dex) RVD
Cyclophosphamide (Cy)/Bortezomib/Dex CyBorD
Carfilzomib (K) RD if neuropathy KRD
Ixazomib RD all oral IRD
VRD equivalent to KRD in non high risk; KRD in high risk

Quadruplets

VTD-Daratumumab (Cassiopeia, MRD- responses, FDA approved)
RVD-Dara (Griffin, MRD- responses),
KRD-Dara (Forte, MRD- including high risk)
Elotuzumab RVD equivalent to RVD in high risk
Isatuximab KRD active in high risk
Ixazomib RD Dara under evaluation

Maintenance

R in standard risk; VR Bort, KR, Dara-R in high risk

DETERMINATION Phase 3 and IFM Study RVd vs RVd-ASCT with R to Progression (US) or Fixed Duration (IFM)

- Median age 57 y (RVd) and 55 y(RVd-ASCT), HR 19-20%, median 3 y for R maintenance

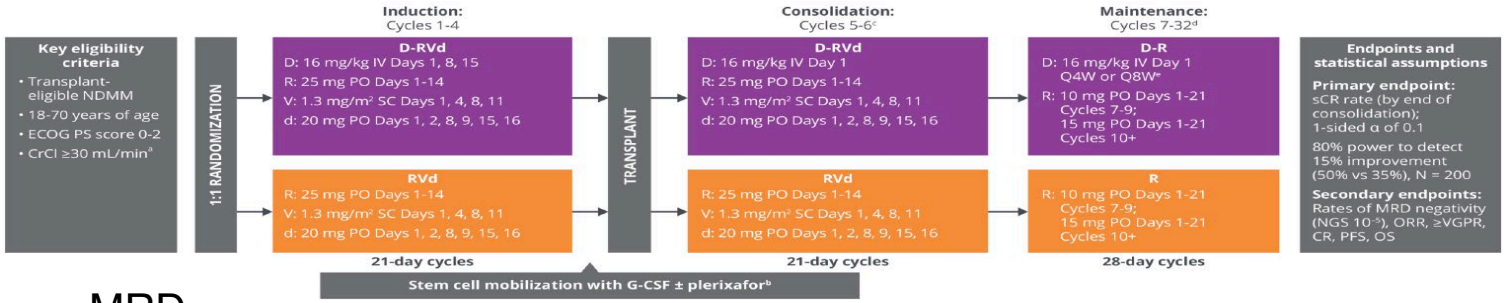
PFS: RVd RVd ASCT	5-y OS	PFS IFM 2009
• ITT 46.2 vs. 67.5 mo.	79.2 vs. 80.7 %	35.0 vs. 47.3 mo.
• HR 17.1 vs. 55.5 mo.	54.3 vs. 63.4 %	20.2 vs. 29.5 mo.
• SR 53.2 vs. 82.3 mo.	86.2 vs. 86.0 %	36.8 vs. 52.0 mo.

In transplant eligible patients RVd-ASCT prolongs PFS, but not OS, to a greater extent with continuous than fixed maintenance. Benefit is much less in HR patients

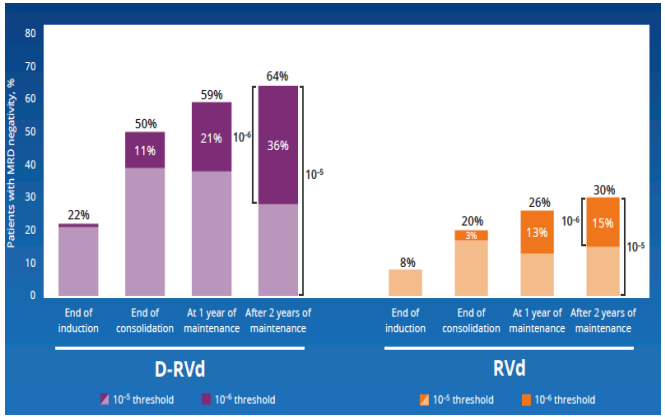
AA 18.5%; Asian 2.8%, Hispanic 5.9%
DRIVE Rank Score 5

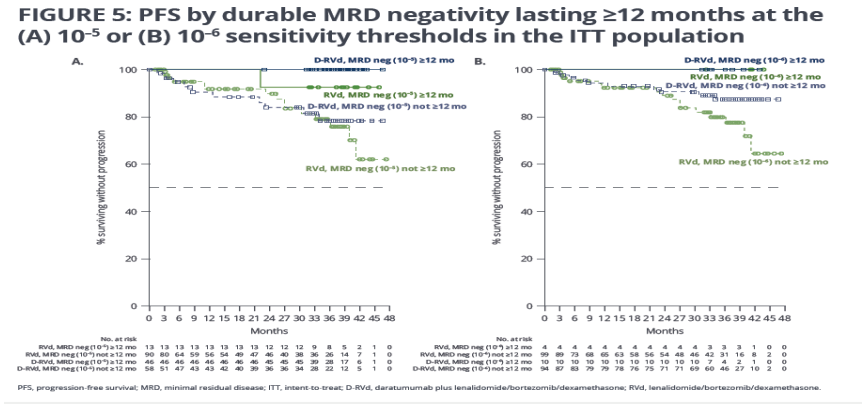
Richardson et al ASCO 2022, N Eng J Med 2022; 387: 132-47.
Attal et al NEJM 2017; 376: 1311-20
Perrot A et al Blood 2018; 132:2456-64; ASH 2020

Dara with RVD Griffin Study: Phase 2 Randomized Study



MRD-





Depth of Response Increases from Induction through Maintenance

Sustained MRd at 12m: 44.2% (DRVd) vs 12.6% (RVd) (10^{-5}) Associated with Prolonged PFS

Carfilzomib Induction, Consolidation, and Maintenance with or without ASCT In NDMM: Cytogenetic Subgroup Analysis of FORTE Clinical Trial

KRd x 4, melphalan ASCT, KRd x 4 vs KRd x 12 cycles vs KCd x 4, ASCT, KCd x 4

477 pts enrolled, 396 pts cytogenetic data

4- year PFS: 71% with 0 HRCA, 60% with 1 HRCA, 39% with $\geq$ 2 HRCA

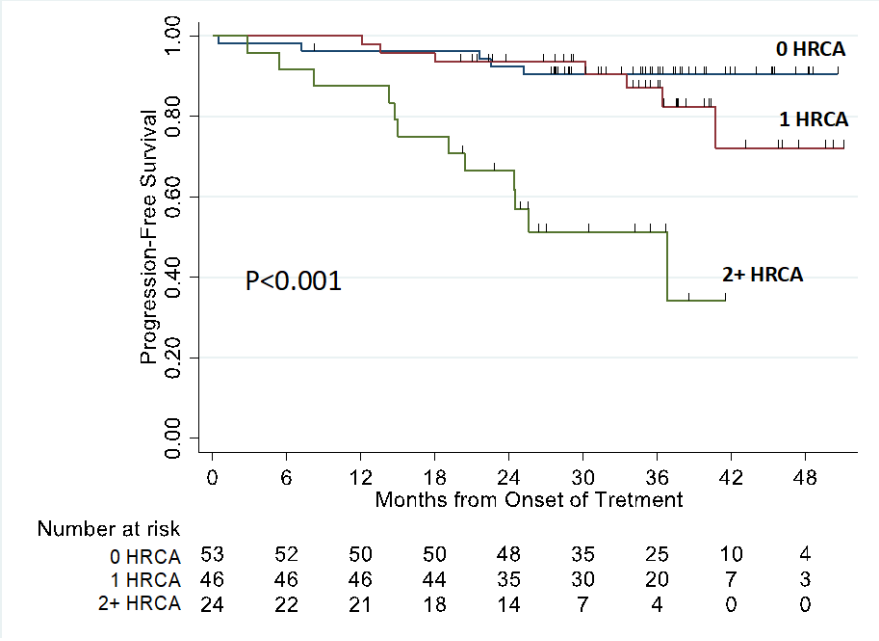
4-year OS: 94% with 0 HRCA, 83% with 1 HRCA, 63% with $\geq$ 2 HRCA

Conclusion: Carfilzomib based induction-intensification-consolidation regimens effective with 0 or 1 HRCA, but unmet need remains with $\geq$ 2 HRCA

Mina et al, Lancet Oncol 2023; 24: 64-76.

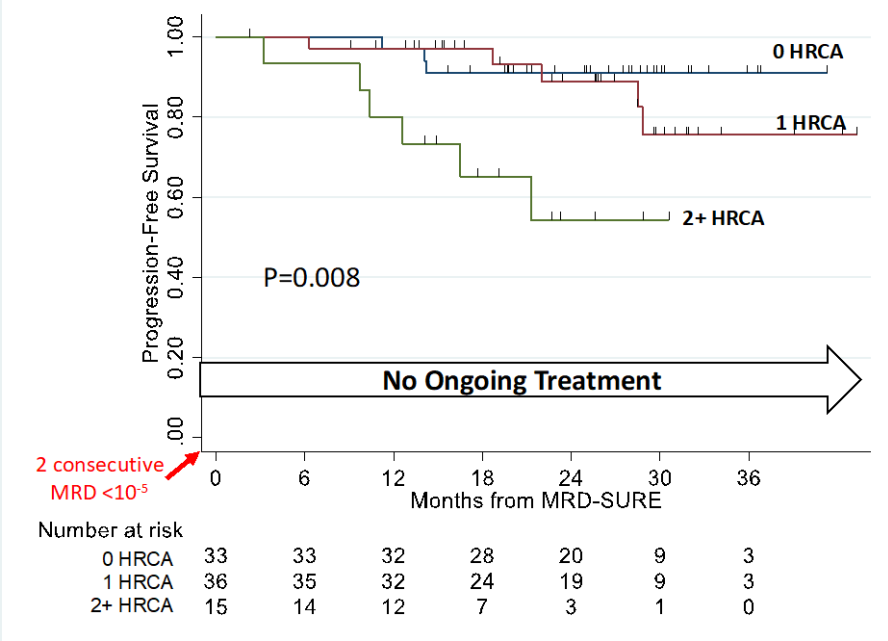
MRD-Guided Treatment Augmentation and Cessation- MASTER Trial

PFS – All Patients (N=123)



Number at risk									
0 HRCA	53	52	50	50	48	35	25	10	4
1 HRCA	46	46	46	44	35	30	20	7	3
2+ HRCA	24	22	21	18	14	7	4	0	0

PFS – Patients in MRD-SURE (N=84)



Number at risk							
0 HRCA	33	33	32	28	20	9	3
1 HRCA	36	35	32	24	19	9	3
2+ HRCA	15	14	12	7	3	1	0

HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20), del(17p)

Median follow up 34.1 mo, unpublished data, IMW.

Early relapses with 2+ HRCA

Costa et al. JCO 2022; 40: 2901-12

Therapy for Newly Diagnosed MM Transplant Ineligible

Triplets preferred at attenuated dose/schedule:

Lenalidomide (Len)/ Bortezomib (Bort)/ Dexamethasone (Dex) RVD Lite

Cyclophosphamide (Cy)/Bort/Dex CyBorD

Carfilzomib RD if neuropathy KRD

Ixazomib RD all oral regimen IRD

Daratumumab RD DRD (Maia, FDA approved)

Doublets

Frail patients, ie Bort/Dex or Len/Dex at reduced doses

Quadruplet

Daratumumab MPV (FDA approved but not used in USA); RVD lite,

R ixazomib D with or without MoAbs under evaluation

Maintenance

Len in standard risk, Bort or Len Bort in high risk, MoAbs under evaluation

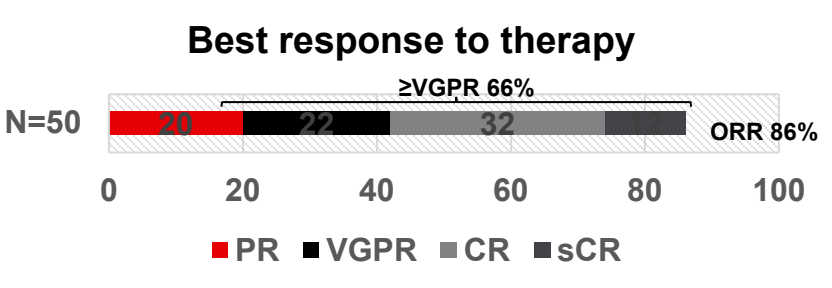
RVd-lite: Reduced-Intensity Triplet Regimen with Substantial Efficacy

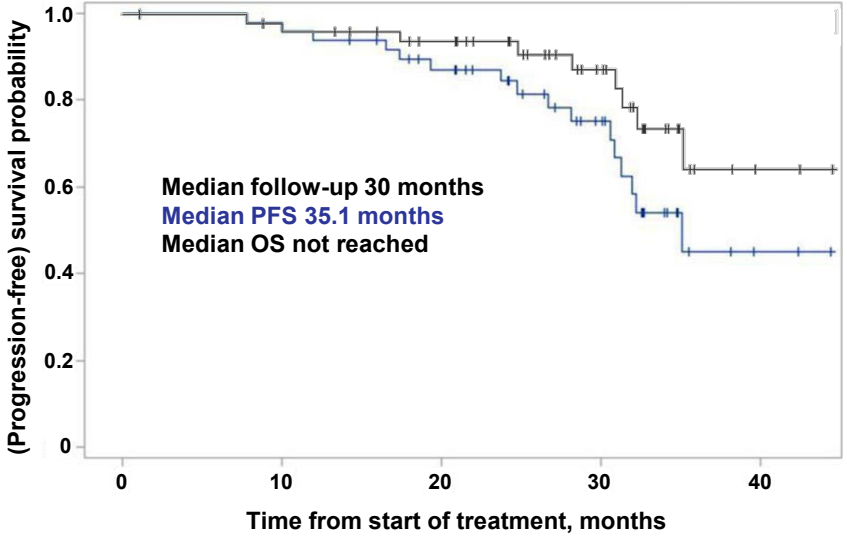
9 x 35-day induction cycles:

- Lenalidomide 15 mg, days 1-21
- Bortezomib 1.3 mg/m^2 SC, days 1, 8, 15, 22
- Dex 20 mg days 1, 2, 8, 9, 15, 16, 22, 23 (days 1, 8, 15, 22 only for patients aged >75 years)

6 x 28-day consolidation cycles

- Lenalidomide 15 mg, days 1-21
- Bortezomib 1.3 mg/m^2 SC, days 1, 15





Safety and tolerability

- Peripheral neuropathy 62% (2% grade 3)
- Median treatment duration was 15 cycles (64% completed all 15 cycles)
- 2 patients (4%) discontinued due to toxicity

O'Donnell EK, et al. Br J Haematol 2018;182(2):222–30.

Health-Related Quality of Life for Frail Transplant-Ineligible Patients With Newly Diagnosed Multiple Myeloma Treated With Daratumumab, Lenalidomide, and Dexamethasone (D-Rd) in MAIA (DRd vs Rd) Trial

The phase 3 MAIA study demonstrated that the triplet regimen D-Rd improved PFS (53%) and OS (66%) in newly diagnosed transplant ineligible patients.

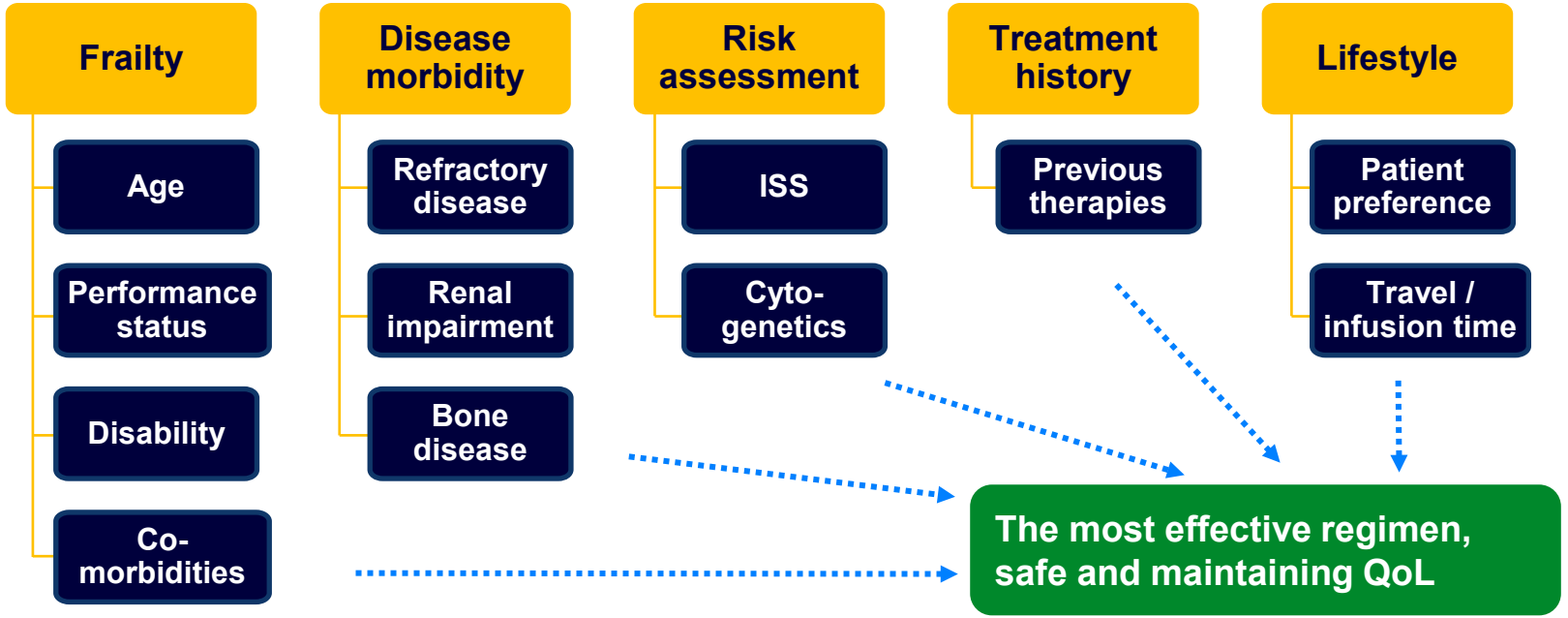
Additional updates of the MAIA study at ASH 2022 confirm superior outcomes with D-Rd vs Rd

- In an analysis of OS at a longer median follow-up (73.6 months) and an overall analysis of updated efficacy and safety after a median follow-up of 64.5 months
- In clinically important subgroups and in patients aged <70, <75, and ≥70 to <75 years both at a median follow-up of 64.5 months

Frail patients in MAIA showed improvements over time with D-Rd in Global Health Status (an overall HRQoL measure), in physical functioning, and reductions in pain.

Perrot et al ASH 2022

Disease and Patient Factors Influence Treatment Choices in Relapsed Refractory MM



Therapy for Relapsed MM

Active In Len and Bort refractory MM

Carfilzomib Pom Dex (no neuropathy)

Dara Pom Dex (FDA approved), Dara Carfilzomib Dex (deep responses, FDA approved)

Elo Pom Dex (well tolerated, FDA approved)

Isatuximab Pom Dex, Isa Carfilzomib Dex (FDA Approved)

Active in Bort refractory MM

Elotuzumab Len/Dex (indolent relapse), Ixazomib Len Dex (all oral), Carfilzomib Len Dex (no neuropathy), Dara Len dex (MRD- responses) (all FDA approved)

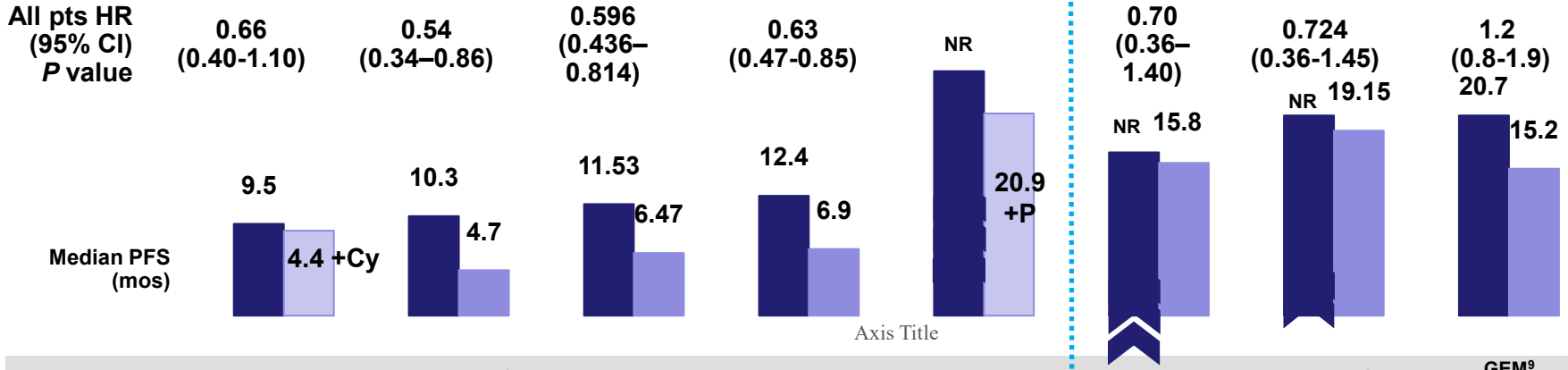
Active in Len refractory MM

Pom Bort Dex, Selinexor Bort Dex, Dara Bort Dex (MRD- responses)(FDA approved)

Active in Len, Pom, Bort, Carfil, Dara refractory MM

Selinexor (GI side effects), Belantomab mafodotin (keratopathy), Idecel and Ciltacel CAR T cells, Teclistamab bispecific T cell engager (all FDA approved)

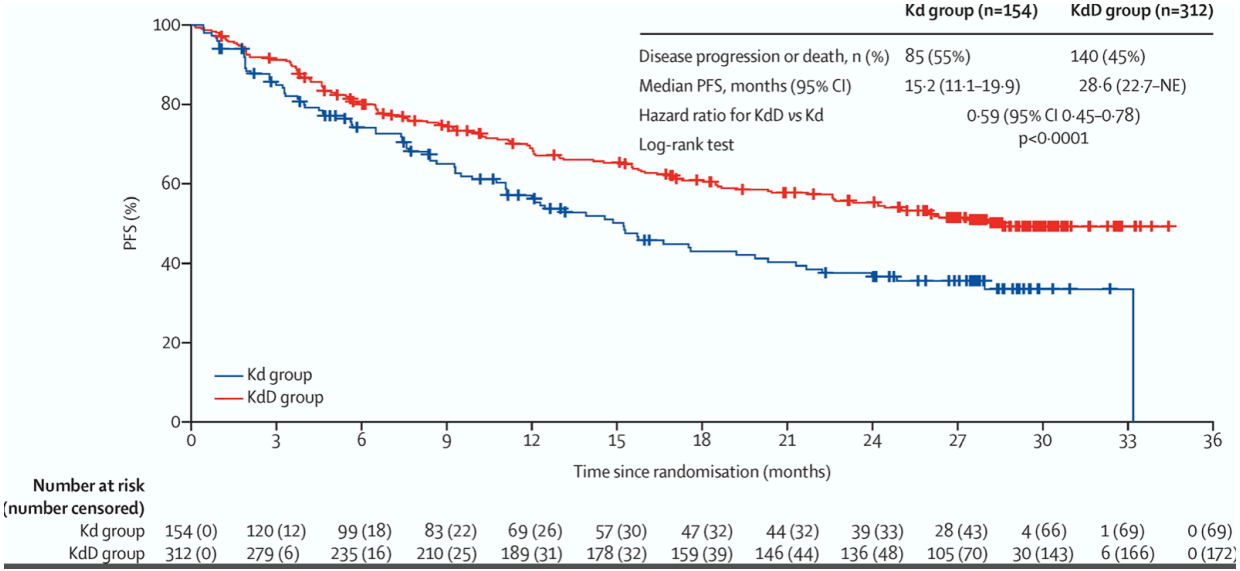
Pomalidomide/Carfilzomib Backbone Randomized Studies



	PomCyDex vs PomDex+Cy[1]	ELOQUENT-3[2] EPd vs Pd	ICARIA-MM[4] Isa-Pd vs Pd	APOLLO[5] D-Pd vs Pd	DCdP vs DCd+P[6]	CANDOR[7] DKd vs Kd	IKEMA[8] IsaKd vs Kd	GEM[9] KyCydex vs Kydex
Total N	34 vs 36	60 vs 57	154 vs 153	151 vs 153	61 vs 59	312 vs 154	179 vs 123	97 vs 101
No. prior lines	4	3	3	2	2	2	2	1
Len refractory (%)	100	90 vs 84	94 vs 92	79.6	97	32 vs 36	31.8 vs 34.1	33 vs 36
PI refractory (%)	78 vs 71	78 vs 82	77 vs 75	48	93			92
mFU (months)		9.1	11.6	16.9	25.3 (8.9 mo after +P in Arm B)	16.9 vs 16.3	20.7	15.6
≥CR (%)	3 vs 3	8 vs 2	5 vs 1	24.5 vs 3.9		29 vs 10	39.7 vs 27.6	18 vs 20
OS HR	0.63 (0.32-1.22)	NR	NR	0.91 (0.61-1.35)	NR			P=0.9
Missing Molecular Data (%)			18 vs 26			51 vs 49	12.8 vs 11.4	24.7 vs 21.7

1. Baz RC et al. Blood (2016) 127 (21): 2561–2568; 2. Dimopoulos MA et al. N Engl J Med. 2018;379:1811; 3. Richardson et al. Lancet Oncol. 2019;20:781-794; 4. Attal M et al. *Lancet.* 2019;394:2096;
5. Dimopoulos MA et al. ASH 2020; 6. Sebag M et al. ASH 2020. 7. Dimopoulos M et al. Lancet. 2020;396:186; 8. Moreau P et al. Presented at the 25th European Hematology Association Annual Meeting; June 2020. Abstract LB2603.
9. Mateos MV et al. ASH 2020.

Carfilzomib, Dexamethasone, and Daratumumab versus Carfilzomib and Dexamethasone For RRMM (Candor)

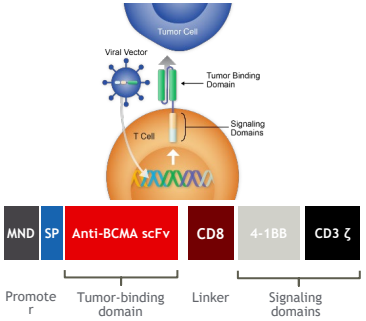


At median FU 27.8 mo: median PFS 28.6 mo in KdD and 15.2 mo in Kd cohort. HR 0.59, p<0.0001)

Grade ≥ 3 treatment emergent adverse events: 87% pts KdD vs 76% pts in Kd cohort

Usmani et al Lancet Oncol 2022; 23: 65-76.

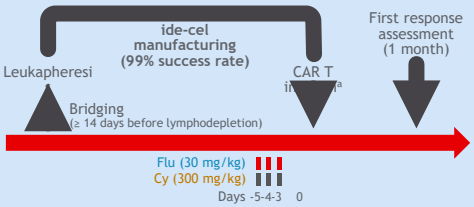
Phase 2 KarMMa Study: Ide-cel in Relapsed Refractory Multiple Myeloma



Endpoints[2,3]

- **Primary:** ORR (null hypothesis ≤ 50%)
- **Secondary:** CRR (key secondary; null hypothesis ≤ 10%), safety, DOR, PFS, OS, PK, MRD[c], QOL, HEOR
- **Exploratory:** Immunogenicity, BCMA expression/loss, cytokines, T-cell immunophenotype, GEP in BM

- RRMM
- ≥ 3 prior regimens
- Previously exposed to:
  - IMiD® agent
  - Proteasome inhibitor
  - Anti-CD38 Ab
- Refractory to last prior therapy per IMWG[b]



Patient characteristics[2]

Time since initial diagnosis, median (range) in yrs		6 (1–18)
No. of prior antimyeloma regimens, median (range)		6 (3–16)
Prior autologous SCT, %	1 > 1	94 34
Any bridging therapies for MM, %		88
Refractory status, %	Anti-CD38 Ab refractory Triple refractory	94 84

Study status as of 14 January 2020

Screened N = 158

Leukapheresed N = 140

Treated N = 128 (Target dose CAR T cells)
150 × 10⁶

n = 4
300 × 10⁶

n = 70

Median follow-up (months)
150 × 10⁶

18.0
300 × 10⁶

15.8
450 × 10⁶

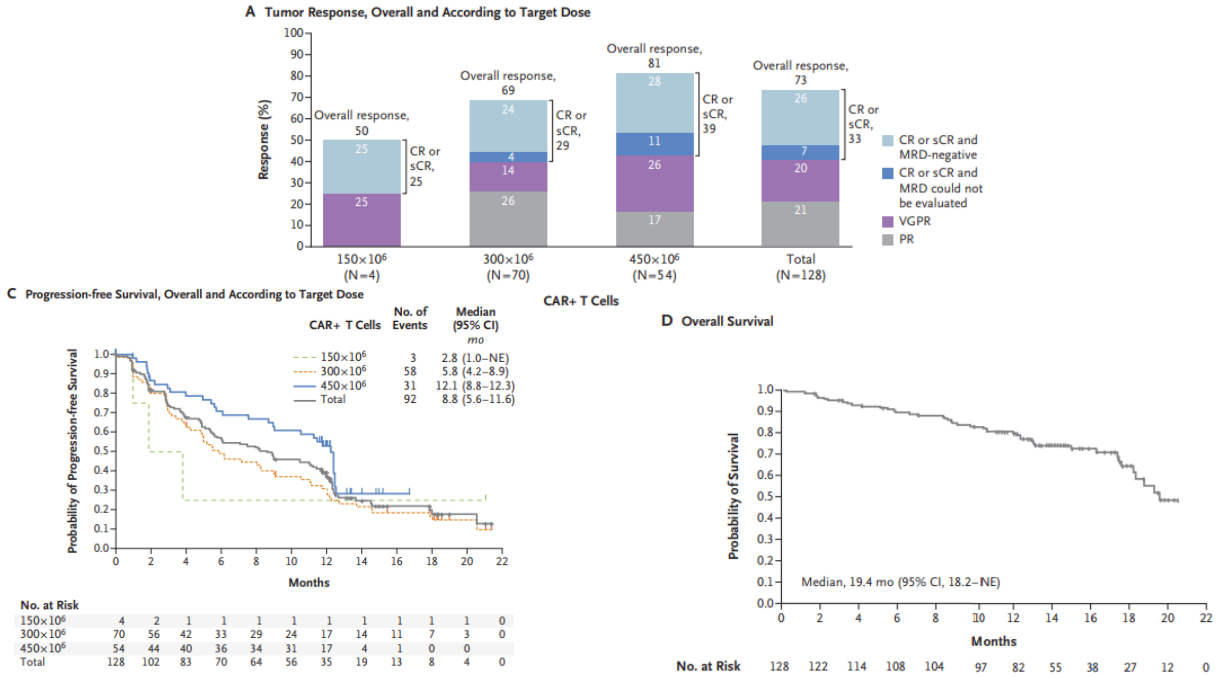
12.4
Total

13.3

FDA Approved for RRMM with ≥ 4 lines prior therapy

Munshi et al NEJM 2021; 384: 705-16.

Response Rate and PFS to Idecel in Relapsed and Refractory Multiple Myeloma



Munshi et al NEJM 2021; 384: 705-16

Ide-cel or Standard Regimens in RRMM

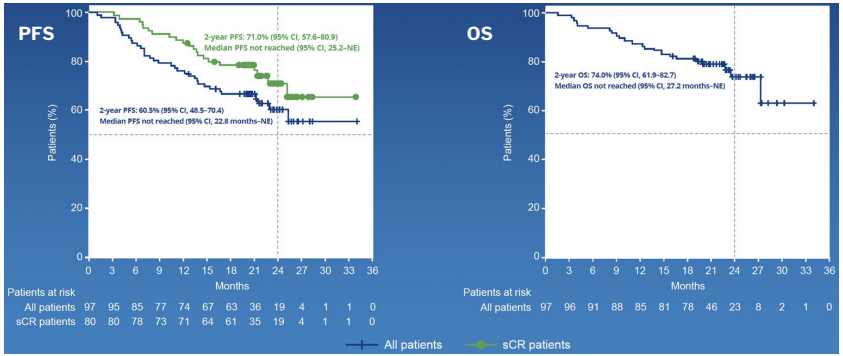
Phase III trial in RRMM after 2-4 regimens (IMiDs, PIs, Dara), refractory to last regimen
Randomized 2:1 to Ide-Cel or 1 of 5 standard regimens

Results:
254 pts Ide-cel and 132 to standard regimen
66% triple refractory, 95% Dara refractory

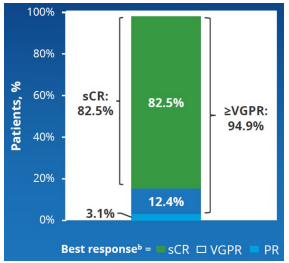
At median 18.6 mos followup: PFS 13.3 mo Ide-cel vs 4.4 mo standard regimen HR 0.49, $p<0.001$); OS not mature
ORR: 71% Ide-cel vs 42% standard therapy ($p<0.001$)
Adverse events Grade $\geq$ 3: 93%% Idecel vs 75% standard therapy
Idecel: CRS 88%, 5% grade $\geq$ 3; Neurotoxocity 15%, 3% grade $\geq$ 3

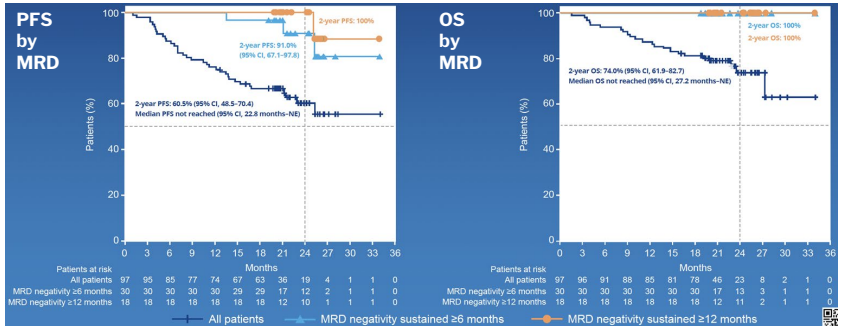
Rodriguez-Otero P et al NEJM 2023, in press

Updated Results From the CARTITUDE-1 Phase 1/2 Study of Cilta-cel CART in RRMM



ORR (by IRC): 97.9% (95/97)





Efficacy		
Best response of sCR by median follow-up, %	1 year	67
	2 years	83
Median time to __ (range), months	First response	1 (0.9-10.7)
	Best response	2.6 (0.9-17.8)
	≥CR	2.9 (0.9-17.8)
Median DOR (range), months		NE (21.8-NE)
MRD-negative (10^{-5}) [n=61], %		92

Martin T, et al. ASH 2021. Abstract 549

Cartitude 2: Ciltacel in Early Relapse (within one year of ASCT, or within one year in those without ASCT)

n=19 pts
ORR 100%, 90% CR, 95% VGPR
12 mo PFS 90%
84% CRS, ICANs grade 4 1 pt

van de Donk ASCO 2022

Cartitude 2 : Ciltacel for Relapse after 1-3 prior therapies

n=20 pts
ORR 95%, 75% CR/sCR, 85% VGPR
Median DOR not reached
CRS 85%, 10% grade ¾
3 pts ICANS grades 1-2

Agha et al ASCO 2022

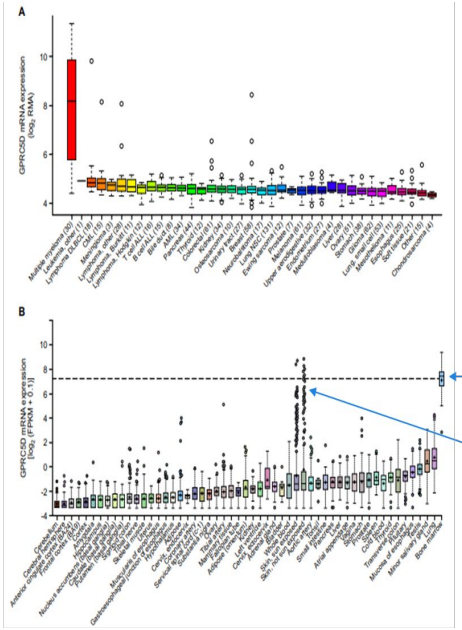
CRS/NT Events With BCMA CAR T-Cell Therapies

- CRS and NT events were primarily grade 1/2 and manageable

	KarMMa[1] N = 128	CARTITUDE-1[2] N = 97
≥ 1 CRS event, n (%)	107 (84)	92 (95)
Grade 1/2	100 (78)	87 (95)
≥ Grade 3	7 (5)	5 (5)
Median onset (range), days	1 (1 – 12)	7 (1 – 12)
Median duration (range), days	5 (1 – 63)	4 (1 – 97)
≥ 1 NT event, n (%)	23 (18)	20 (21)
Grade 1/2	18 (12)	10 (10)
≥ Grade 3	5 (4)	10 (10)
ICANS any grade, %	-	17

Munshi et al. NEJM 2021; 384(8):705-716. Berdeja et al. Lancet 2021; 398:314

GPRC5D Targeted CAR T Cell Therapy in Relapsed Refractory Multiple Myeloma



Smith EL. et al. Science Translational Medicine 2019

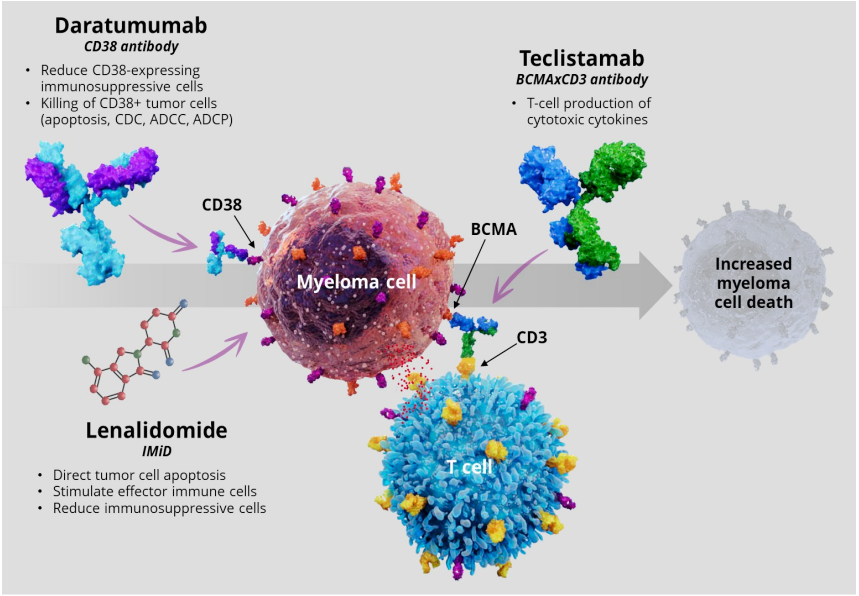
Response	25 X10^6 CAR+ T cells (n=3)	50 X10^6 CAR+ T cells (n=3)	150 X10^6 CAR+ T cells (n=5)	450 X10^6 CAR+ T cells (n=5)	Total (N=16)
PR or better, n (%)	1 (33)	3 (100)	2 (40)	5 (100)	11 (69)
VGPR or better, n (%)	1 (33)	2 (67)	0 (0)	4 (80)	7 (44)
CR or better (%)	0 (0)	1 (33)	0 (0)	3 (60)	4 (25)
MRD negativity, n (%)	2 (67)	2 (67)	2 (40)	2 (50)	8 (50)

Response	Prior BCMA therapy (n=10)	Prior CAR T therapy (n=8)
Partial Response or better, n (%)	8 (80)	6 (75)
Complete Response or better	3 (30)	3 (38)
BM MRD negativity*, n (%)	5 (50)	2 (25)

Mailankody et al ASH 2021; N Engl J Med 2022; 387: 1196-1206.

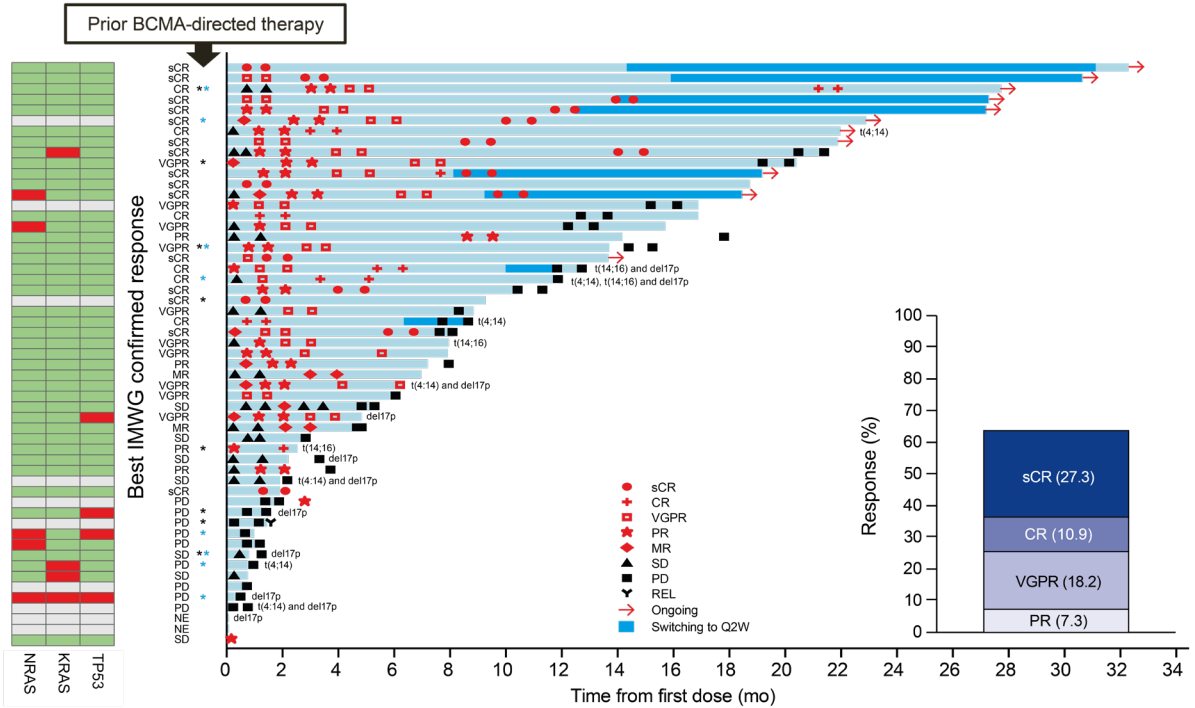
Teclistamab With SC Daratumumab and Lenalidomide in RRMM MajesTEC-2, Phase 1b, Multicohort Study

- **Teclistamab BCMA×CD3 bispecific antibody FDA approved (ORR, 63%)** for patients with ≥ 4 lines heavily pretreated RRMM
- Len stimulates CTL/NK cells, downregulates Tregs; Dara expands CTLs
- **Tec/Len/Dara93.5% ORR, 54.8% CR; 90.3% ≥ VGPR** including Dara and/or Len refractory MM
- 25/31 (80.6%) patients remain progression-free on treatment
- Grade 3/4 AEs occurred in 29 (90.6%) patients, cytopenias and pneumonia most common, **infectious deaths**



Nooka A et al. ASCO 2022; Moreau P et al. NEJM 2022; 387:495: Searle et al ASH 2022

Elranatamab, a BCMA Targeted T-cell Engaging Bispecific Antibody, Induces Durable Clinical and Molecular Responses in RRMM



- **Median duration of follow-up 12.0 months (range 0.3–32.3)**
- **ORR 64% (95% CI, 50–75) and CR/sCR rate 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)**

Raje et al, ASH 2022

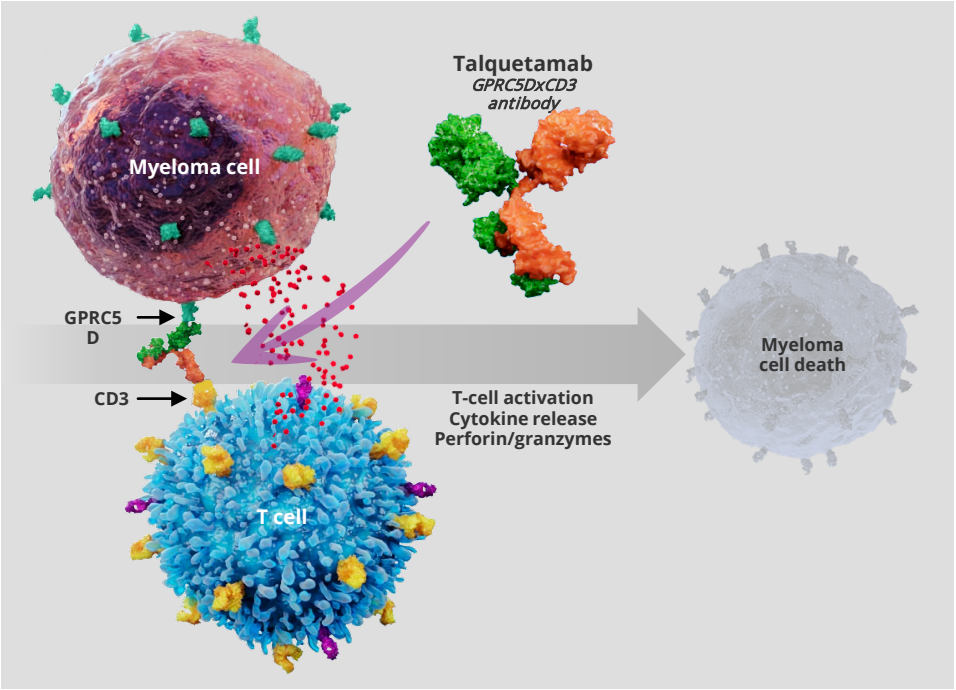
Response to Bites correlate with expansion of TCR+ MM CD8+ CTLs and decreased T cell exhaustion; conversely, loss of TCR+ CD8+ CTL and increased T cell exhaustion underlies relapse.

Monitoring both disease response and immune profile can inform optimal dose and schedule.

Neri, Rabb et al IMW 2022

Talquetamab, a G Protein-Coupled Receptor Family C Group 5 Member D × CD3 Bispecific Antibody in RRMM: Phase 1/2 Results From MonumenTAL-1

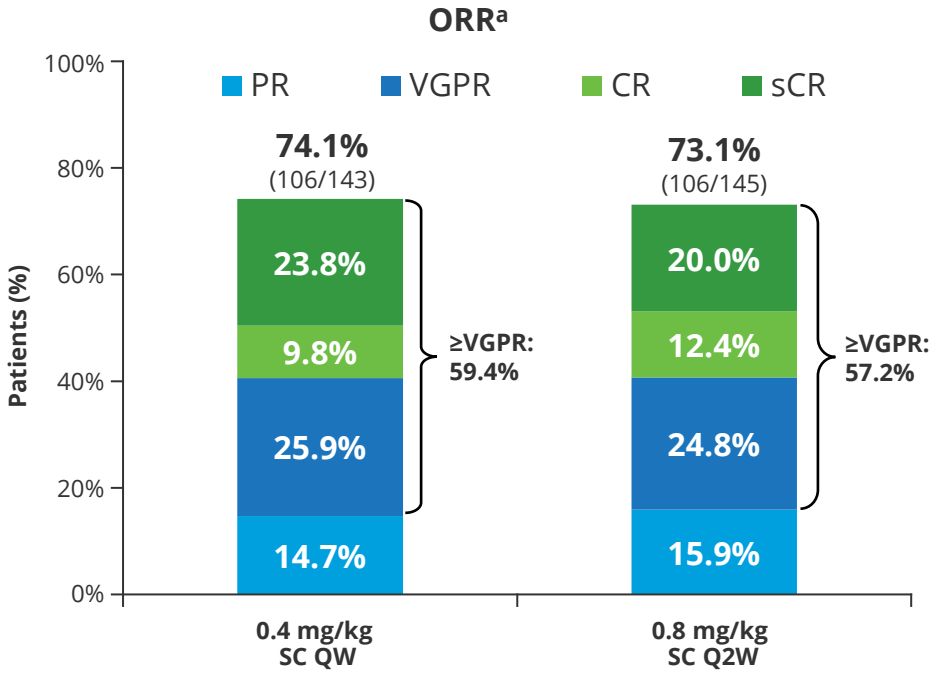
- **Talquetamab is a novel first-in-class, off-the-shelf, T-cell redirecting bispecific antibody** directed against a new antigen target called GPRC5D[1,2]
- **GPRC5D is a novel antigen target in myeloma** that is highly expressed on malignant plasma cells with limited expression in normal human tissues,[3-6] including hematopoietic stem cells[7]
- **Talquetamab has shown an ORR of 64–70%** with QW and Q2W dosing in the phase 1 MonumenTAL-1 study (NCT03399799)[8]



AA7.3%, Asian 2.4% Drive Rank Score 0

Chari et al ASH 2022

MonumenTAL-1: Overall Response Rate



ORR similar for QW and Q2W schedules

- **Triple-class refractory: 72.6% and 71.0%**
- **Penta-drug refractory: 71.4% and 70.6%**

Most common AEs were CRS, skin and nail-related events, and dysgeusia

At 0.4 mg/kg QW and 0.8 mg/kg Q2W:

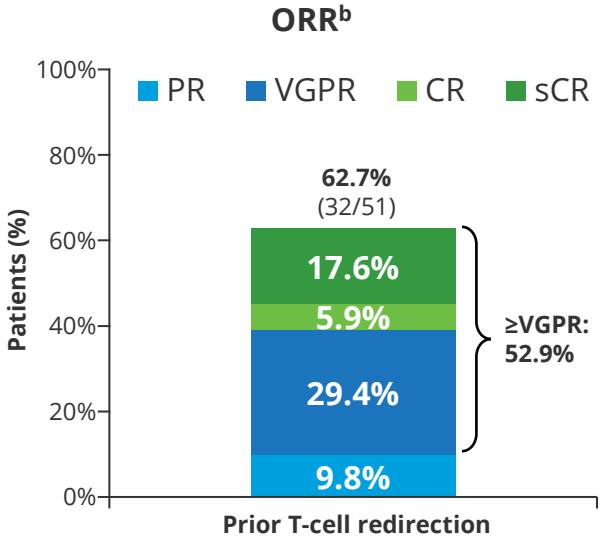
Infections occurred in 57.3% and 50.3%

- **Grade 3/4 in 16.8% and 11.7%**

Chari et al ASH 2022

Talquetamab ORR in Patients With Prior T-Cell Redirection

- **Patients enrolled in cohort of prior T-cell redirection therapy:**
  - **Were younger** and had a **higher prevalence of high-risk cytogenetics**
  - **Median of 6 prior lines of therapy** (range, 3–15)
  - 70.6% (n=36) received prior CAR-T cell therapy and 35.3% (n=18) prior bispecific antibody therapy; 3 patients received both
  - 7.8% (n=4) were refractory to belantamab
  - Most patients received QW (n=43) vs Q2W (n=8) talquetamab dosing
- **ORR was 62.7%**
  - **72.2% ORR** (26/36) in patients with **prior CAR-T therapy**
  - **44.4% ORR** (8/18) in patients with **prior bispecific antibody treatment**
- **Median DOR was 12.7 months** (range, 3.7–NE) at a median follow-up of 11.8 months (range, 1.0[a]–25.4)



Chari et al ASH 2022

1980- Stem cell transplant
2000- Novel agents
2020- Immune therapies

In the future, Dara RVD will achieve high rates of response NDMM; ASCT will be Compared with CAR T cells and/or BiTEs to both achieve durable MRD- responses and restore memory anti-MM immunity, allowing patients to be disease free and off all therapy.

"Cure is Growing Old and Dying from Something Else"

Francesca Thompson, MD
1986