Emerging and Current Treatment of Multiple Myeloma

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Disclosures

Consultant: Astrazeneca, Janssen, Pfizer

Board/ Stock Options: Dynamic Cell Therapies, C4 Therapeutics, Next RNA, Oncopep, Starton, Window

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; CAR T cell: idecel, ciltacel; bispecific T cell engager: teclistamab, elranatamab, talquetamab

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; now under evaluation earlier in disease course, SMM

Minimal residual disease negativity (MRD-) associated with prolonged PFS and OS in NDMM (transplant-eligible and -ineligible) and RRMM

32 FDA approvals (16 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

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

Doublets

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

Quadruplet

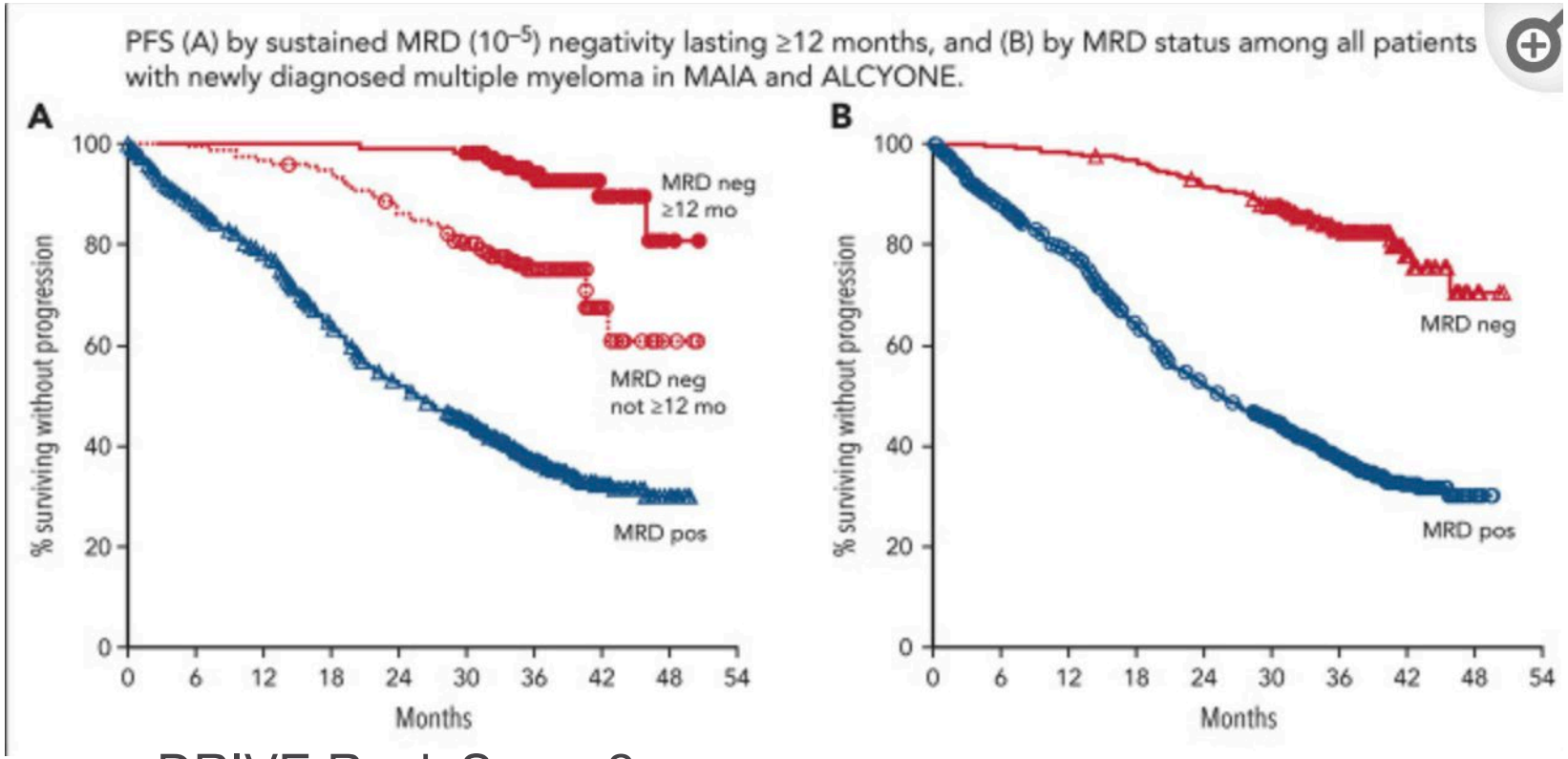
Daratumumab MPV (FDA approved but not used in USA); RVD lite,

R ixazomib D with or without MoAbs under evaluation

Maintenance

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

Sustained MRD- (10^{-5} NGS) In NDMM (MAIA and ACYONE)



DRIVE Rank Score 2

San-Miguel J et al Blood 2022; 139: 492-501

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

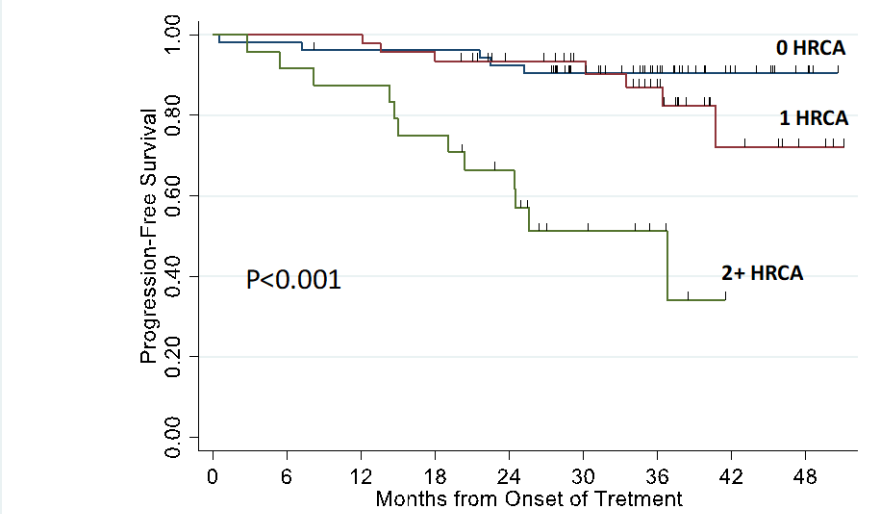
VTD-Daratumumab (MRD- responses)
RVD-Dara (MRD-including high risk)
KRD-Dara (MRD- including high risk)
Elotuzumab RVD equivalent to RVD in high risk
Isatuximab KRD active in high risk
Ixazomib RD Dara under evaluation

Maintenance

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

Daratumumab, Carfilzomib, Lenalidomide and Dexamethasone (Dara-KRd), ASCT, MRD Response-Adapted Consolidation and Treatment Cessation-MASTER Trial

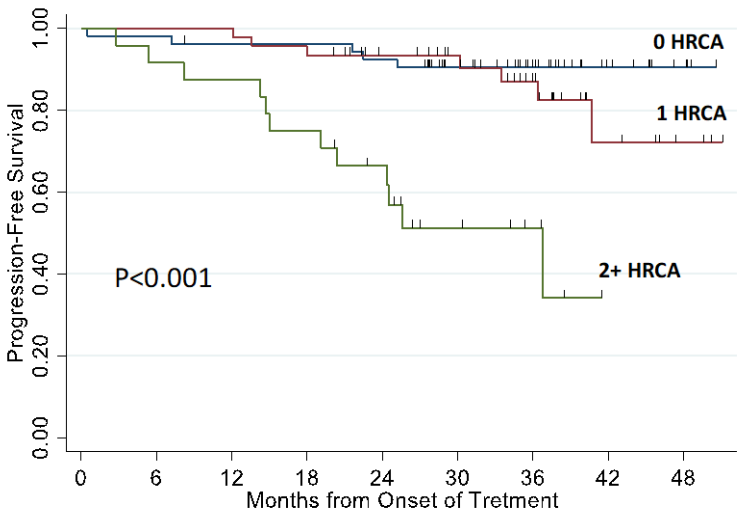
PFS – All Patients (N=123)



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	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

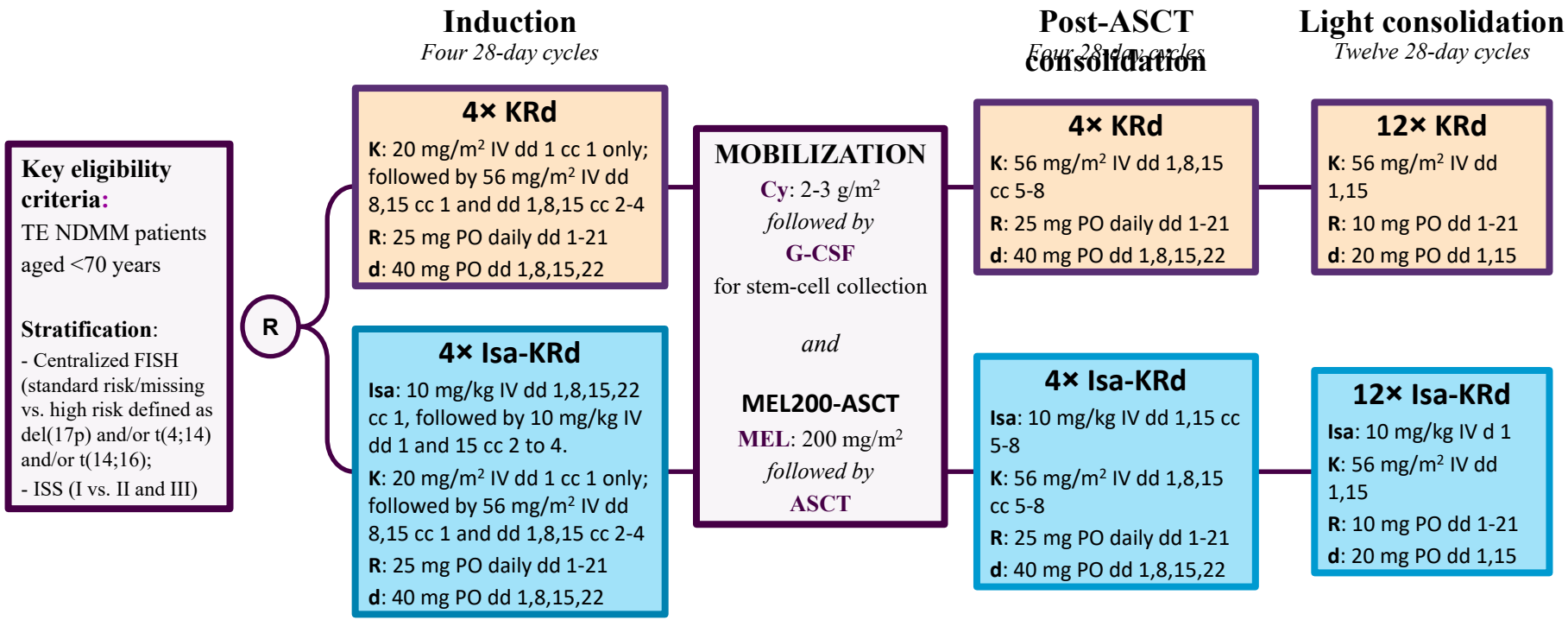
HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20), del(17p)

Persistent MRD- Allows Maintenance Discontinuation with 0-1, but not 2+ HRCA

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

IsKia EMN24 Study Design

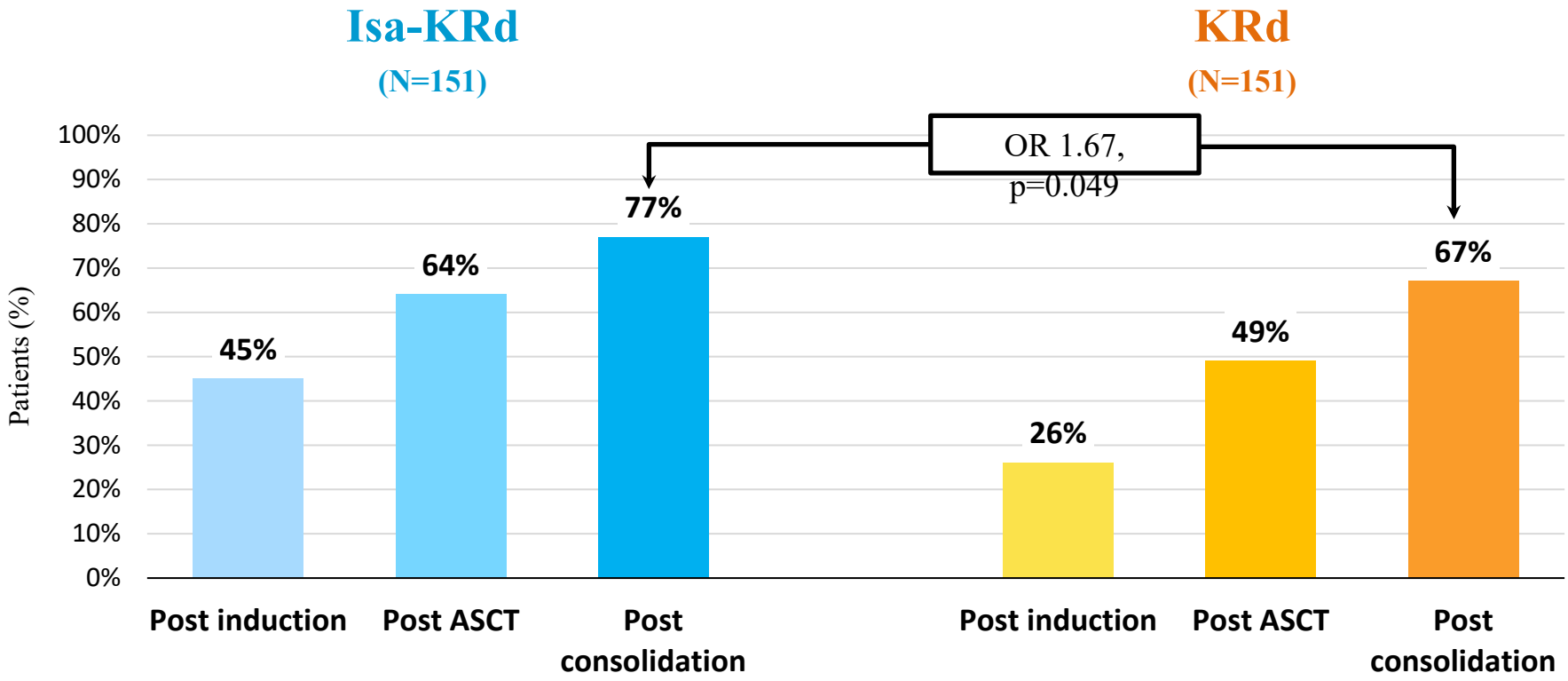
42 active sites; enrollment: Oct 7, 2020 – Nov 15, 2021



DRIVE Rank Score 2

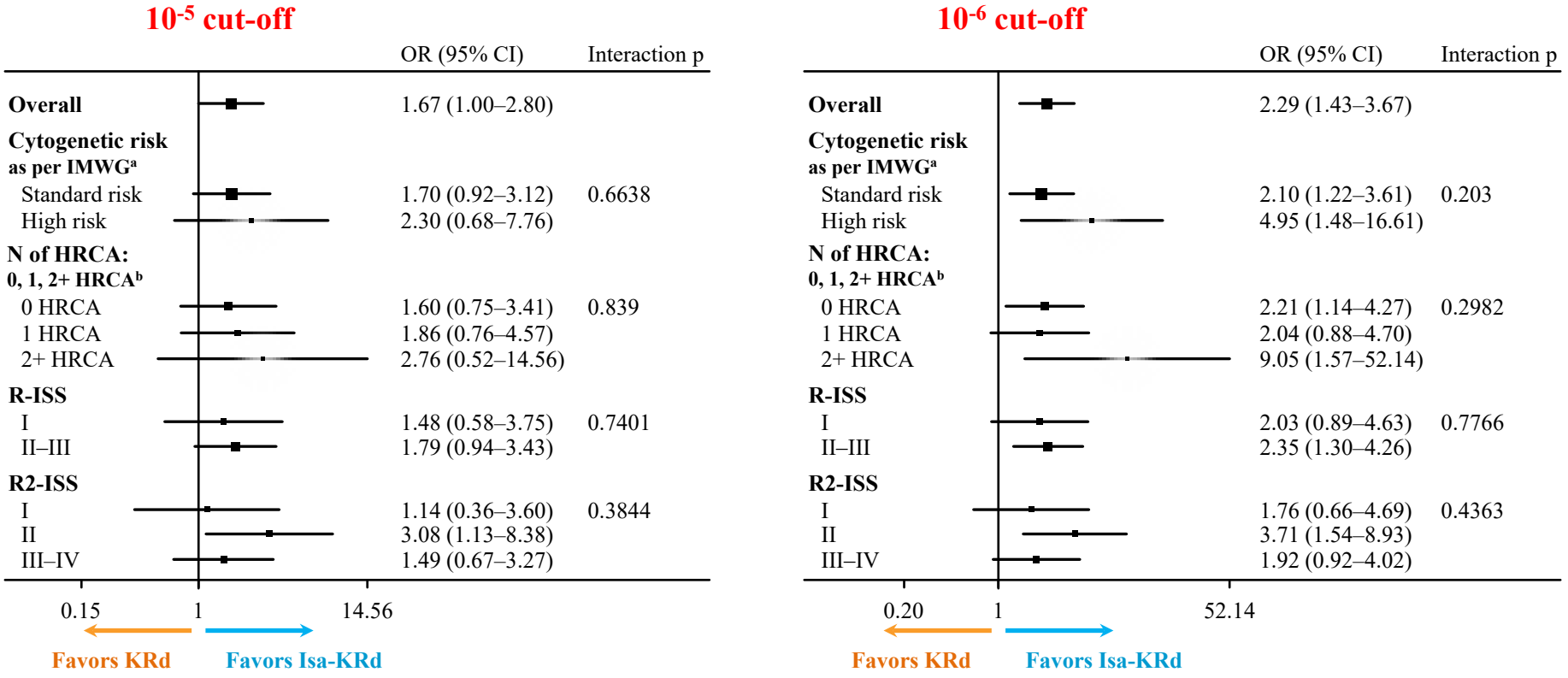
Gay et al, ASH (abstr) 2023

MRD Negativity Rates Over Time (10^{-5})



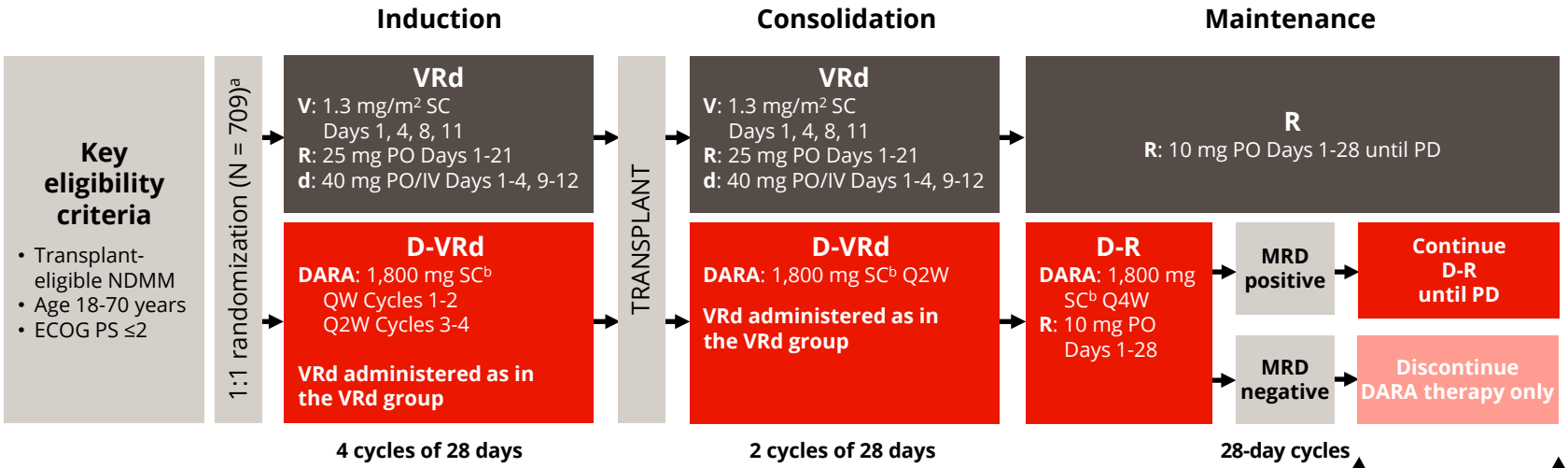
Gay et al, ASH (abstr) 2023

Post-Consolidation MRD Negativity by NGS



Gay et al, ASH (abstr) 2023

PERSEUS: Study Design



Primary endpoint: PFS[c]

Key secondary endpoints: Overall ≥CR rate,[c] overall MRD-negativity rate,[d] OS

Discontinue DARA therapy only after ≥24 months of D-R maintenance for patients with ≥CR and 12 months of sustained MRD negativity

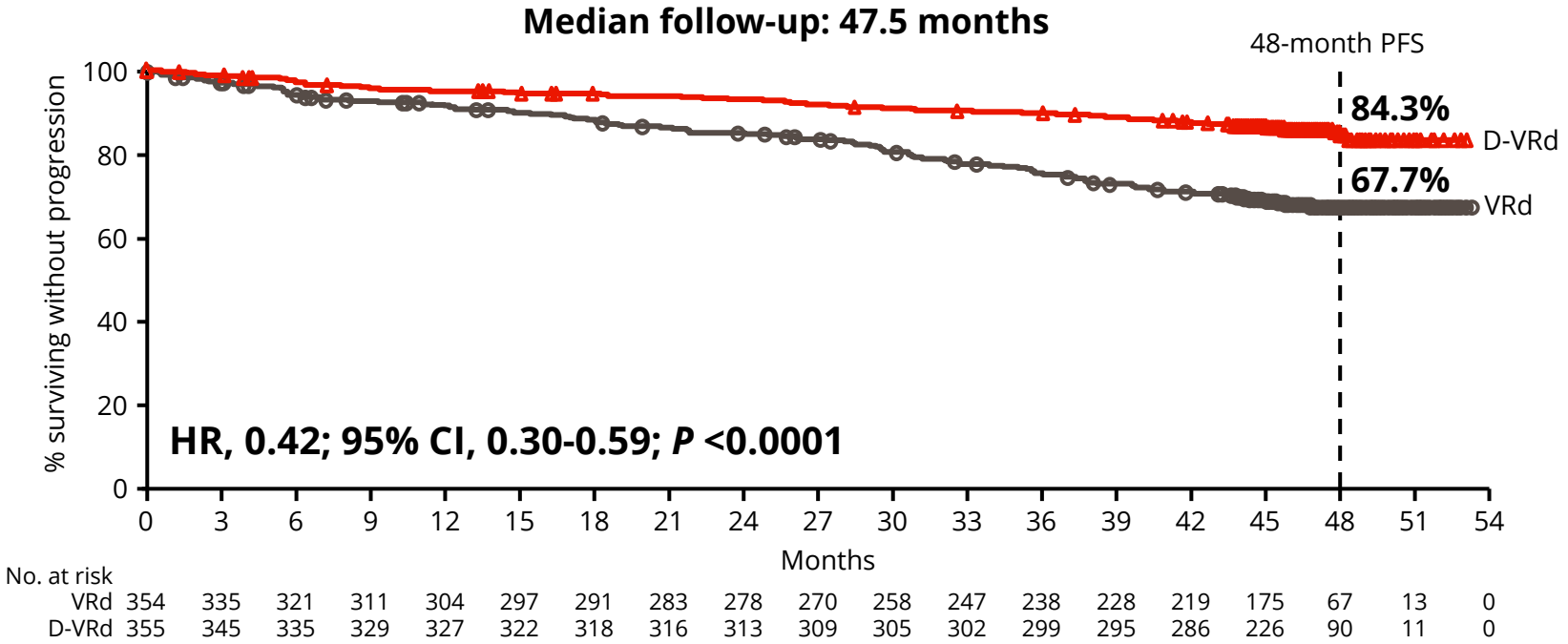
Restart DARA therapy upon confirmed loss of CR without PD or recurrence of MRD

DRIVE Rank Score 2

Sonneveld et al ASH (abstr) 2023

Presented by P Sonneveld at the 65th American Society of Hematology (ASH) Annual Meeting; December 9-12, 2023; San Diego, CA, USA

PERSEUS: Progression-Free Survival



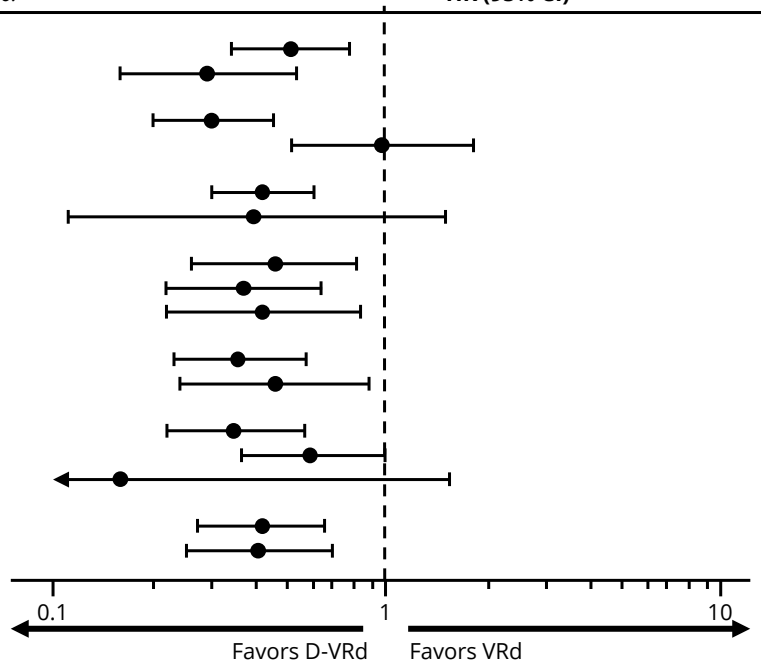
- **58% reduction in the risk of progression or death in patients receiving D-VRd**

Sonneveld et al ASH (abstr) 2023

Presented by P Sonneveld at the 65th American Society of Hematology (ASH) Annual Meeting; December 9-12, 2023; San Diego, CA, USA

PERSEUS: PFS in Prespecified Subgroups

Subgroup	D-VRd (no. of progression events or deaths/total no.)	VRd (no. of progression events or deaths/total no.)	HR (95% CI)
Sex			
Male	36/211	61/205	0.51 (0.34-0.77)
Female	14/144	42/149	0.29 (0.16-0.53)
Age			
<65 y	30/261	84/267	0.30 (0.20-0.46)
≥65 y	20/94	19/87	0.97 (0.52-1.81)
Race			
White	47/330	95/323	0.42 (0.30-0.60)
Other	3/25	8/31	0.40 (0.11-1.50)
ISS stage			
I	18/186	35/178	0.46 (0.26-0.81)
II	19/114	43/125	0.37 (0.22-0.64)
III	13/55	25/50	0.42 (0.22-0.83)
Type of MM			
IgG	28/204	58/185	0.36 (0.23-0.57)
Non-IgG	13/78	31/96	0.46 (0.24-0.88)
Cytogenetic risk			
Standard risk	25/264	62/266	0.35 (0.22-0.56)
High risk	24/76	38/78	0.59 (0.36-0.99)
Indeterminate	1/15	3/10	0.16 (0.02-1.56)
ECOG PS			
0	28/221	60/230	0.42 (0.27-0.66)
≥1	22/134	43/124	0.41 (0.25-0.69)

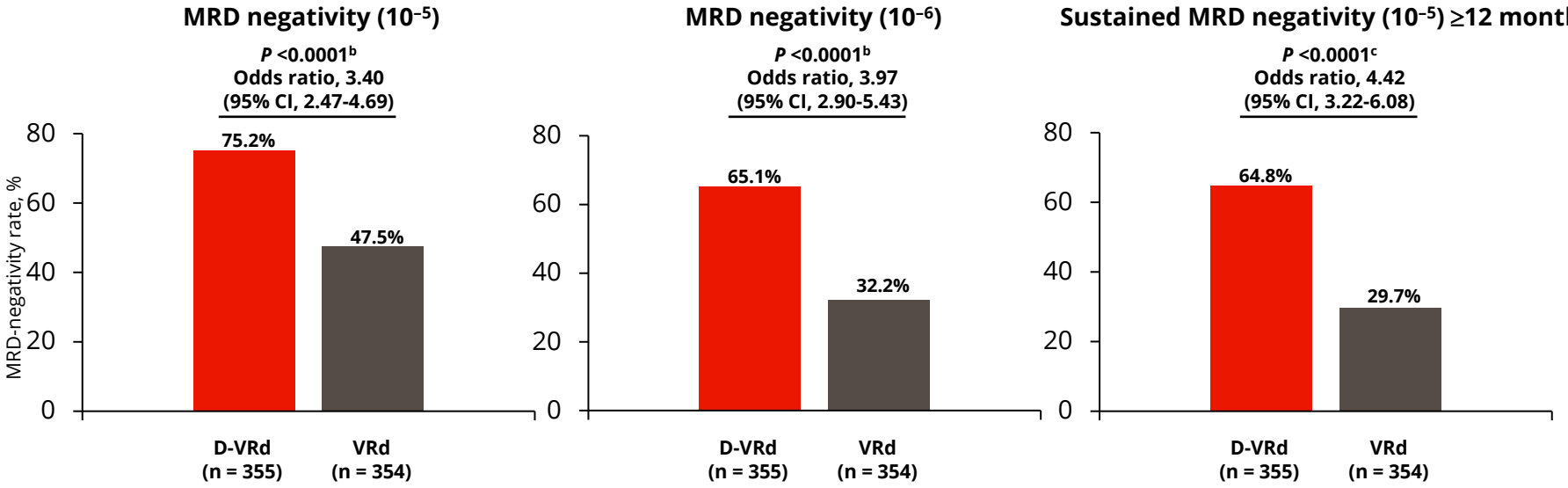


- **PFS was improved with D-VRd versus VRd across clinically relevant subgroups**

Sonneveld et al ASH (abstr) 2023

Presented by P Sonneveld at the 65th American Society of Hematology (ASH) Annual Meeting; December 9-12, 2023; San Diego, CA, USA

PERSEUS: Overall and Sustained MRD-Negativity Rates[a]



- **Deep and durable MRD negativity was achieved with D-VRd**
- **64% (207/322) of patients receiving maintenance in the D-VRd group discontinued DARA after achieving sustained MRD negativity per protocol[d]**

Sonneveld et al ASH (abstr) 2023

Presented by P Sonneveld at the 65th American Society of Hematology (ASH) Annual Meeting; December 9-12, 2023; San Diego, CA, USA

Iberdomide Maintenance after ASCT in NDMM: First Results of Phase 2 EMN26 Study

- Iberdomide maintenance improved response after IMiD/PI-based +/- anti-CD38 antibody induction and ASCT:
- Iberdomide demonstrated at least 50% improvement of response at cycle 12
- Lenalidomide demonstrated 31% improvement of response at cycle 12 in the EMN02 trial
- Conversion to MRD-negativity during maintenance is an important outcome post-ASCT, and promising data with iberdomide were observed
- Iberdomide showed a manageable safety profile with few grade 3-4 non-hematologic adverse events
- These data support the investigation of iberdomide versus lenalidomide maintenance in the ongoing phase 3 registrational Excaliber maintenance trial

DRIVE Rank Score 2

Van de Donk ASH (abstr) 2023

Therapy for Relapsed MM

Active In Len and Bort refractory MM

Carfilzomib Pom Dex (no neuropathy)

Dara Pom Dex, Dara Carfilzomib Dex (deep responses)

Elo Pom Dex (well tolerated)

Isatuximab Pom Dex, Isa Carfilzomib Dex

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)

Active in Len refractory MM

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

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

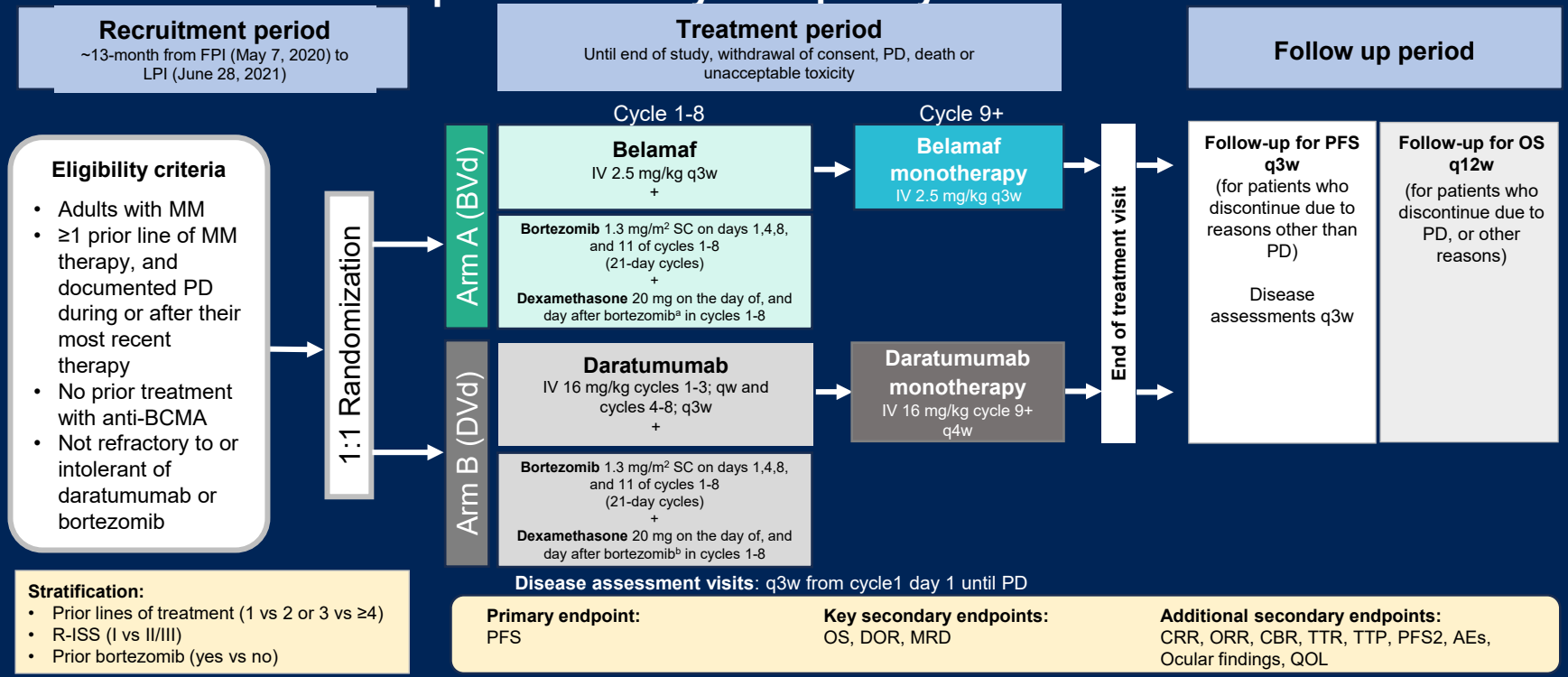
Selinexor (GI side effects), Belantomab mafodotin (keratopathy), Idecel and Ciltacel CAR T cells; Teclistamab, Elranatamab, Talquetamab bispecific T cell engagers

Mezigdomide (MEZI)

- E3 Ligase Modulator with greater cytotoxic immunomodulatory effects compared with IMiDs
- MEZI in combination with DARA or ELO promising efficacy in RRMM
  - ORR with MeziDd was 82.6%
    ORR with MeziEd was 45.0%
- The safety profile of MEZI plus mAbs was manageable
- Most grade 3/4 TEAEs hematologic; neutropenia most common grade 3/4 TEAE and was managed with G-CSF and dosing schedule adjustments
- MEZI was immune-stimulatory in combination with DARA and ELO at all schedules and dose levels tested
- These data support further evaluation of MEZI with immunotherapies including CD38, SLAMF7, BCMA, and GPRC5D-targeting approaches.

Hansen et al. J Med Chem 2020;63:6648–76; Richardson et al ASH (abstr) 2023

Results from the randomized phase 3 DREAMM-7 study of belantamab mafodotin plus bortezomib and dexamethasone vs daratumumab, bortezomib and dexamethasone in relapsed/refractory multiple myeloma



Stratification:
- Prior lines of treatment (1 vs 2 or 3 vs ≥4)
- R-ISS (I vs II/III)
- Prior bortezomib (yes vs no)

Disease assessment visits: q3w from cycle1 day 1 until PD

Primary endpoint: PFS

Key secondary endpoints: OS, DOR, MRD

Additional secondary endpoints: CRR, ORR, CBR, TTR, TTP, PFS2, AEs, Ocular findings, QOL

AE, adverse event; CBR, clinical benefit rate; CRR, complete response rate; DOR, duration of response; FPI, first-patient-in; IV, intravenous; LPI, last-patient-in; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; q3w, every 3 weeks; q4w, every 4 weeks; q12w, every 12 weeks; qw, every week; QOL, quality of life; R-ISS, Revised International Staging System; SC, subcutaneous; TTP, time to progression; TTR, time to response.

[a] Reduce starting dose of dexamethasone to 10 mg for patients >75 years of age, who have a body-mass index <18.5, who had previous unacceptable side effects associated with glucocorticoid therapy, or who are unable to tolerate the starting.

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DREAMM-7: baseline demographics and clinical characteristics

Baseline characteristics	ITT population	
	BVd (N=243)	DVd (N=251)
Age, median (range), years	65.0 (34-86)	64.0 (32-89)
<65, n (%)	121 (50)	126 (50)
65 to <75, n (%)	85 (35)	95 (38)
≥75, n (%)	37 (15)	30 (12)
Male/female, n (%)	128 (53)/115 (47)	144 (57)/107 (43)
White/Black or African American/other, n (%)[a]	206 (85)/8 (3)/ 28 (12)	203 (81)/12 (5)/34 (14)
ECOG PS ≤1, n (%)	232/242 (96)	235/246 (96)
R-ISS stage at screening, n (%)		
I	102 (42)	103 (41)
II	130 (53)	132 (53)
III	9 (4)	14 (6)
Unknown	2 (<1)	2 (<1)
Years since diagnosis, median (range)	4.28 (0.2-26.0)	3.94 (0.1-23.4)
Cytogenetic abnormalities, n (%)		
High risk[b]	67 (28)	69 (27)
Standard risk[c]	175 (72)	175 (70)
Missing or non-evaluable	1 (<1)	7 (3)
Extramedullary disease, n (%)		
Yes	13 (5)	25 (10)
No	230 (95)	226 (90)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; ITT, intent-to-treat.
[a] "Other" for the BVd arm included Asians only; for the DVd arm included Asians (n=33) and mixed/multiple races (n=1). [b] High-risk cytogenetics were defined as the presence of ≥1 of the following: t(4;14), t(14;16), or del(17p13).
[c] Standard risk cytogenetics were defined as having negative results for all high-risk abnormalities: t(4;14), t(14;16), or del(17p13).

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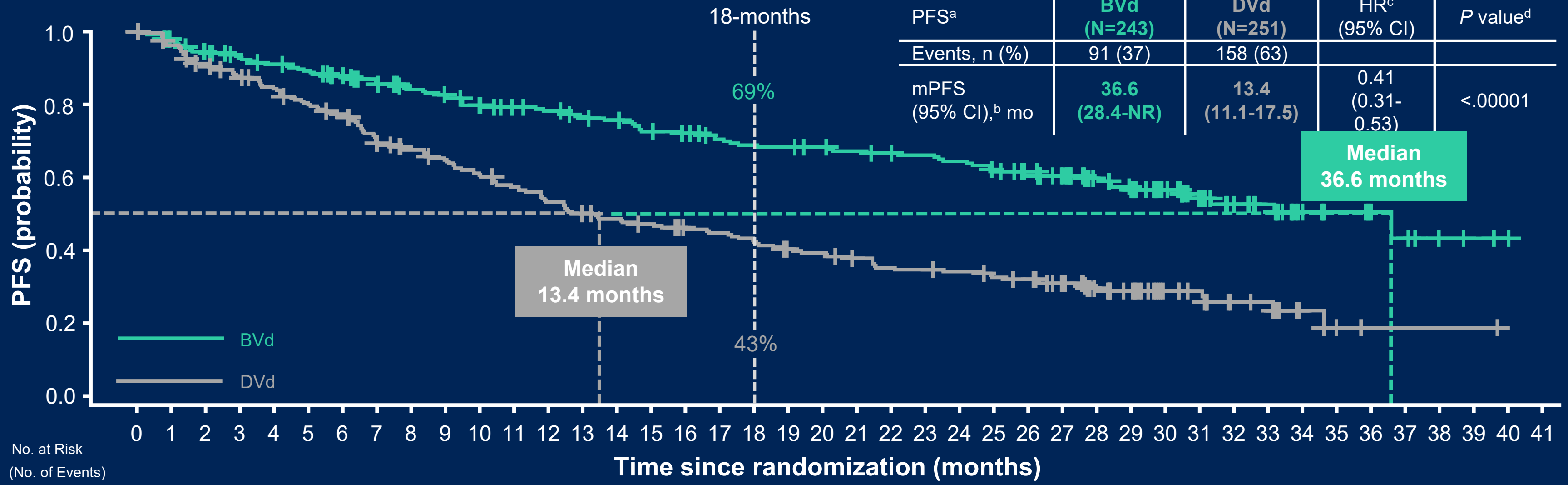
DREAMM-7: BVd led to a significant increase in PFS vs DVd

PFS[a]	BVd (N=243)	DVd (N=251)	HR[c] (95% CI)	*P* value[d]
Events, n (%)	91 (37)	158 (63)		
mPFS (95% CI),[b] mo	**36.6 (28.4-NR)**	**13.4 (11.1-17.5)**	0.41 (0.31-0.53)	<.00001



No. at Risk (No. of Events)

	0	1	2	3	4	5	6	7	8	9	10	11	12	13
BVd	243 (0)	230 (6)	220 (13)	211 (17)	205 (21)	200 (25)	192 (28)	183 (32)	175 (36)	171 (39)	163 (45)	158 (46)	155 (48)	150 (51)
DVd	251 (0)	230 (9)	214 (22)	205 (29)	194 (37)	183 (47)	176 (53)	155 (71)	148 (75)	141 (81)	132 (90)	124 (97)	115 (106)	107 (113)

	14	15	16	17	18	19	20	21	22	23	24	25	26	27
BVd	147 (53)	140 (59)	137 (60)	131 (63)	128 (66)	127 (67)	125 (67)	122 (69)	120 (70)	118 (71)	115 (74)	110 (78)	105 (79)	94 (81)
DVd	103 (116)	99 (119)	94 (121)	91 (124)	87 (128)	80 (133)	78 (135)	73 (138)	68 (143)	67 (144)	65 (145)	61 (148)	59 (149)	52 (151)

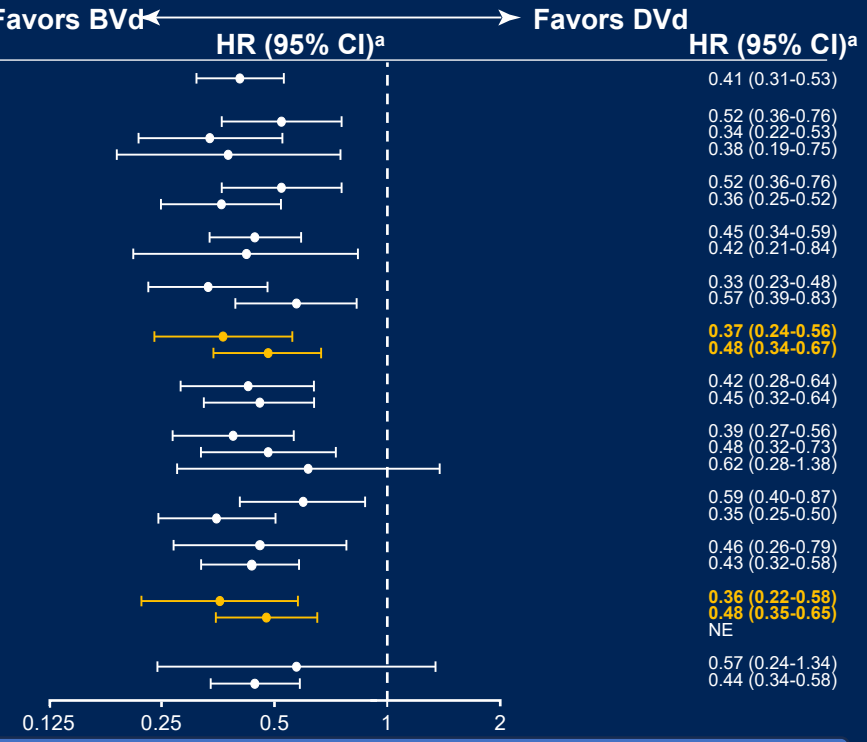
	28	29	30	31	32	33	34	35	36	37	38	39	40	41
BVd	79 (82)	72 (86)	56 (86)	41 (88)	31 (89)	25 (89)	15 (90)	11 (90)	8 (90)	6 (91)	3 (91)	2 (91)	1 (91)	0 (91)
DVd	39 (153)	33 (154)	22 (154)	19 (154)	12 (156)	11 (156)	5 (157)	2 (158)	1 (158)	1 (158)	1 (158)	1 (158)	0 (158)	0 (158)

BVd demonstrated a statistically significant and clinically meaningful IRC-assessed PFS benefit with a median PFS that was 23 months longer than DVd (36.6 vs 13.4 months)

HR, hazard ratio; IRC, independent review committee; mPFS, median PFS; NR, not reached.
[a] Two patients in the ITT population were randomized, not treated, re-screened, and re-randomized. They are counted as 4 unique patients in this output. [b] CIs were estimated using the Brookmeyer Crowley method. [c] HRs were estimated using a Cox proportional hazards model stratified by the number of lines of prior therapy (1 vs 2 or 3 vs ≥4), prior bortezomib, and R-ISS at screening (I vs II/III), with a covariate of treatment. [d] *P* value from 1-sided stratified log-rank test.

DREAMM-7: prespecified subgroup analysis of IRC-assessed PFS

Categories	BVd n/N	DVd n/N	HR (95% CI)[a]
All Subjects (Stratified)[b]	91/243	158/251	0.41 (0.31-0.53)
Number of Prior LOT (1 vs 2 or 3 vs ≥4)			
1	46/125	76/125	0.52 (0.36-0.76)
2 or 3	30/88	62/99	0.34 (0.22-0.53)
≥4	15/30	20/27	0.38 (0.19-0.75)
Number of Prior LOT (1 vs >1)			
1	46/125	76/125	0.52 (0.36-0.76)
>1	45/118	82/126	0.36 (0.25-0.52)
Prior Bortezomib			
Yes	79/210	132/211	0.45 (0.34-0.59)
No	12/33	26/40	0.42 (0.21-0.84)
Prior Lenalidomide			
Yes	44/127	88/130	0.33 (0.23-0.48)
No	47/116	70/121	0.57 (0.39-0.83)
Refractory to Lenalidomide			
Yes	**33/79**	**64/87**	**0.37 (0.24-0.56)**
No	**58/164**	**94/164**	**0.48 (0.34-0.67)**
Revised ISS Staging at Screening			
I	37/102	64/103	0.42 (0.28-0.64)
II/III	53/139	94/146	0.45 (0.32-0.64)
Age			
<65 years	42/121	84/126	0.39 (0.27-0.56)
65-<75 years	37/85	61/95	0.48 (0.32-0.73)
≥75 years	12/37	13/30	0.62 (0.28-1.38)
Gender			
Female	48/115	59/107	0.59 (0.40-0.87)
Male	43/128	99/144	0.35 (0.25-0.50)
Time to Relapse After Completion of 1L Treatment			
≤12 months	23/49	31/50	0.46 (0.26-0.79)
>12 months	68/194	127/201	0.43 (0.32-0.58)
Cytogenetics Risk			
High Risk[c]	**26/67**	**48/69**	**0.36 (0.22-0.58)**
Standard Risk[d]	**65/175**	**106/175**	**0.48 (0.35-0.65)**
Missing or Not Evaluable	0/1	4/7	NE
Extramedullary Disease at Baseline			
Yes	8/13	18/25	0.57 (0.24-1.34)
No	83/230	140/226	0.44 (0.34-0.58)



PFS benefit consistently favored BVd vs DVd across prespecified subgroups, including patients with lenalidomide refractory or high-risk cytogenetic MM

IVRS, interactive voice response system; NE, not evaluable.
[a] HRs for subgroups were only plotted if number of the events was ≥20 in total across both treatments. HRs for subgroups were estimated using Cox proportional hazards model, without adjustment for stratification variables. [b] Stratified by the number of lines of prior therapy (1 vs 2 or 3 vs ≥4), prior bortezomib (no, yes) and R-ISS at screening (I vs II/III) according to IVRS strata, with a covariate of treatment. [c] A patient was considered as high risk if the subject had any of the following cytogenetics: t(4;14), t(14;16) or del(17p13). [d] A patient was considered standard risk if the subject has negative results for all high-risk abnormalities: t(4;14), t(14;16) or del(17p13).

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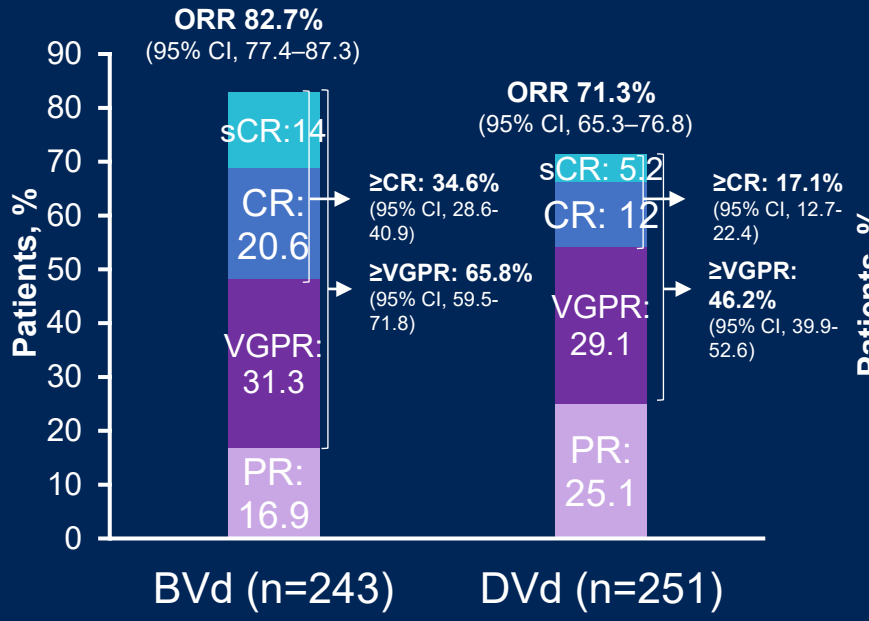
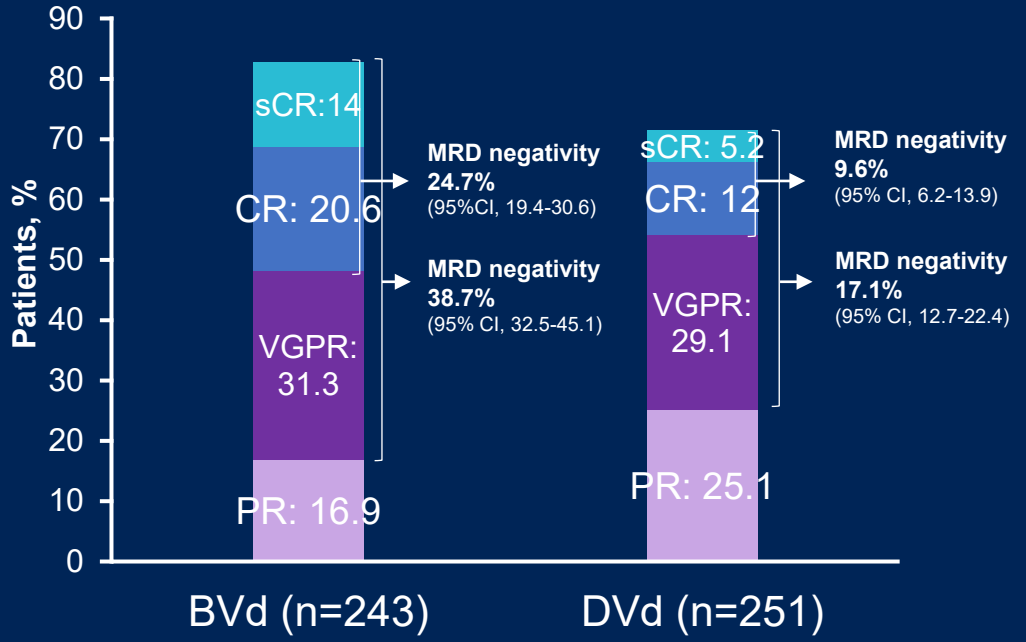
DREAMM-7: deeper IRC assessed responses with BVd vs DVd[a]



BVd was associated with ≥CR rate double that with DVd



MRD negativity (sensitivity of 10^{-5})[a] with BVd more than double with DVd (*P* value <.00001)

DREAMM-7: changes in best corrected visual acuity

Normal Vision (20/20)

Blurred Vision (20/50)

Vision Impaired (20/200)

BVd	Blurred Vision (20/50)[a]	Vision Impaired (20/200)[a]
Patients, n/N (%)	82/242 (34)	5/242 (2)
Time to onset of first event, median (range), days	73.5 (16-753)	105 (47-304)
Duration of first event, median (range), days	22 (6-257)	19 (8-26)
First event resolved,[b] n (%)	80 (98)	5 (100)

44% of patients had dose reductions, 78% had dose delays/interruptions, and 9% discontinued due to any ocular event

[a] Only patients with baseline visual acuity of 20/25 or better in at least one eye with on-study worsening to 20/50 or 20/200 in each eye at the same visit. [b] "Resolved" was defined as achieving grade 1 or baseline visual acuity.
Shi C, et al. *bioRxiv*. Published online May 22, 2018.

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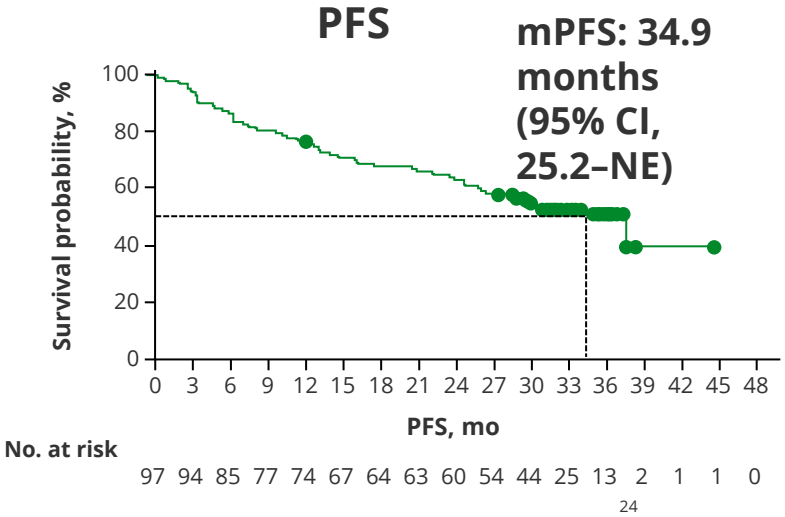
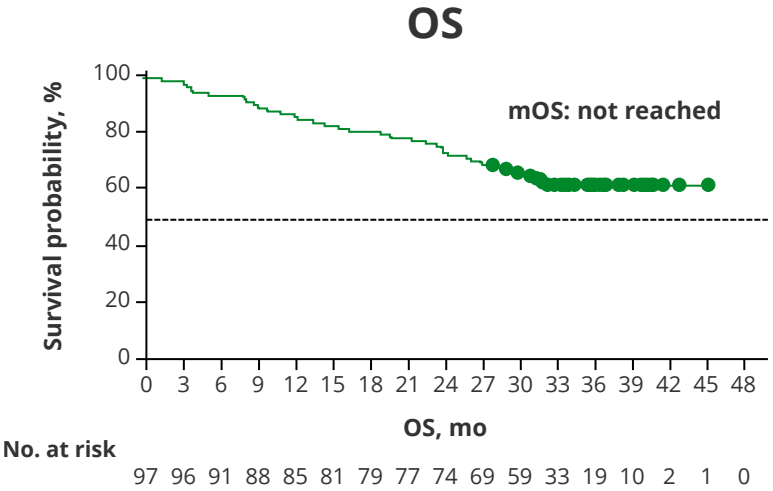
Ciltacel CAR T Cells in RRMM

Final Results CARTITUDE-1 : Time-to-Event Outcomes (3-Year F/U)





Median DOR: 33.9 months (95% CI, 25.5–NE)

Estimated 62.9% of patients were alive at 3-year follow-up

Berdeja JG, et al. Lancet 2021;398:314-24; Martin T, et al. J Clin Oncol 2023;41:1265-74; Munshi N, et al. EHA;2023.

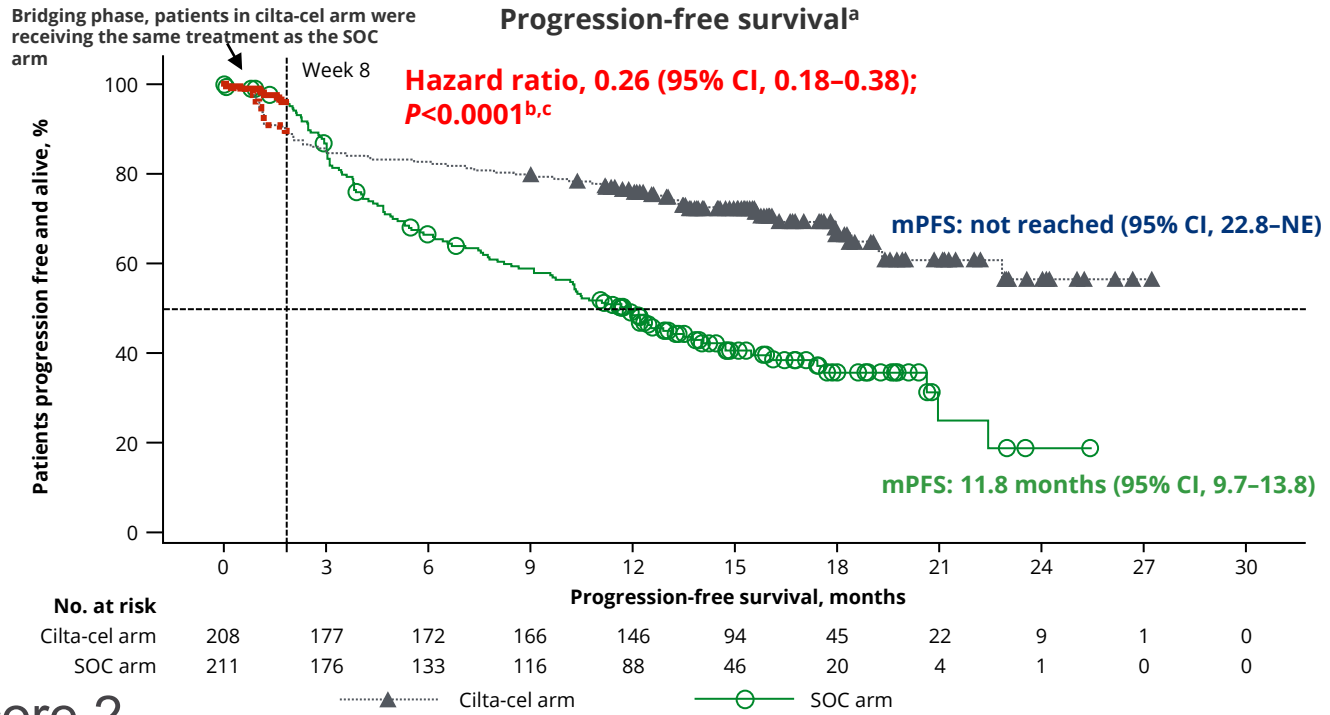
CARTITUDE-4: 1 to 3 Prior Therapies
Primary Endpoint – PFS (ITT Population)

Cilta-cel vs SOC

Len Refractory

SOC Dara Pom Dex or Dara Vel Dex

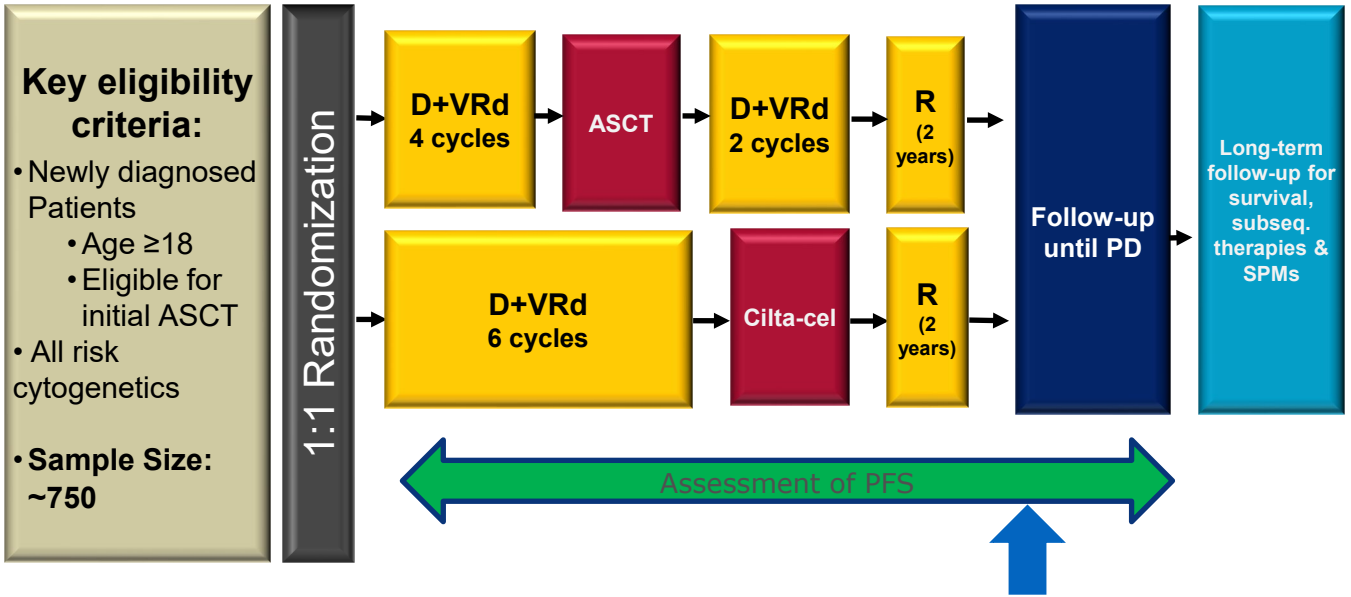
12-month PFS rate: 76% vs 49%



DRIVE Rank Score 2

San Miguel J, et al. ASCO;2023. Abstract LBA106. San Miguel J, et al. EHA;2023. San Miguel J, et al. NEJM 2023; 389: 335-47.

Cartitutude 6: Randomized Phase 3 study in Newly Diagnosed, Transplant Eligible Patients vs ASCT (Initiated in Fall 2023)



Stratification factors:

a) ISS staging
b) Cytogenetics
c) Age

Dual Primary endpoints:
PFS and Sustained MRD neg CR

European Myeloma Network

Real World Outcomes with Idecabtagene Vicleucel (Ide-cel) CAR-T Therapy for Relapsed/Refractory Multiple Myeloma

- Largest real-world study CAR-T cell therapy in patients with RRMM (N=821).
- Heavily pre-treated population and co-morbidities that would have made a majority of patients ineligible for KarMMa clinical trial.
- Ide-cel demonstrated a favorable safety and efficacy profile, comparable to trial population and previously reported real-world data for ide-cel.
- Overall response rate of 73% and median PFS of 9 months with median 7 prior LOT.
- Key adverse prognostic factors for PFS: Extramedullary disease, high-risk cytogenetics, high disease burden, ISS stage III, prior BCMA therapy within 6 months and bendamustine lymphodepletion.

Sidana et al ASH (abstr) 2023

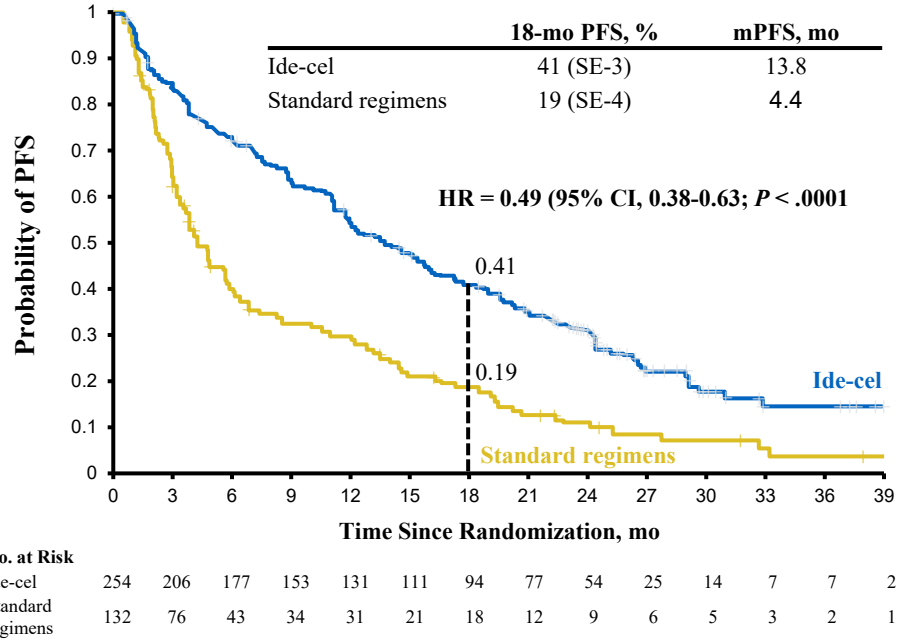
DRIVE Rank Score 5

KarMMa-3 Ide-Cel Vs Standard Regimens in RRMM (1-3 prior lines)

Final PFS Analysis

- Significantly longer PFS was maintained with ide-cel
- PD or death risk reduced by 51%
- CRR with ide-cel increased since the IA, indicating a deepening response, but were unchanged with std regimens
- A single ide-cel infusion vs continuous treatment with std regimens resulted in longer median TTNT and PFS2

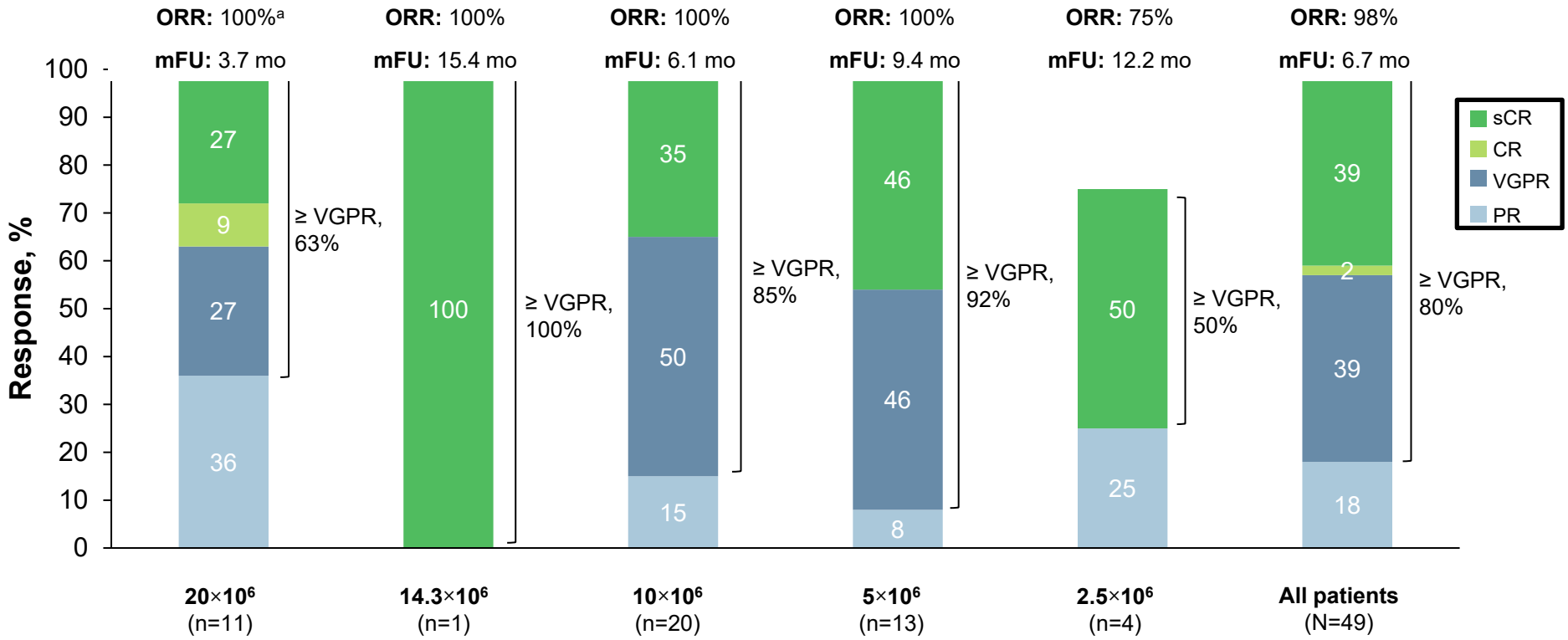
PFS (ITT Population)



Otero P et al. ASH 2023 (abstract 1028)

DRIVE Rank Score 2

PHE885 BCMA-Directed CAR-T Cell Therapy Manufactured in <2 Days



- All but 1 patient at the dose of 2.5×10^6 achieved a clinical response[b]

Sperling AS, et al. J Clin Oncol. 2023;41(16_suppl):8004.

PHE885: Clinical Responses Deepen Over Time

- **MRD negativity rate[a]:**

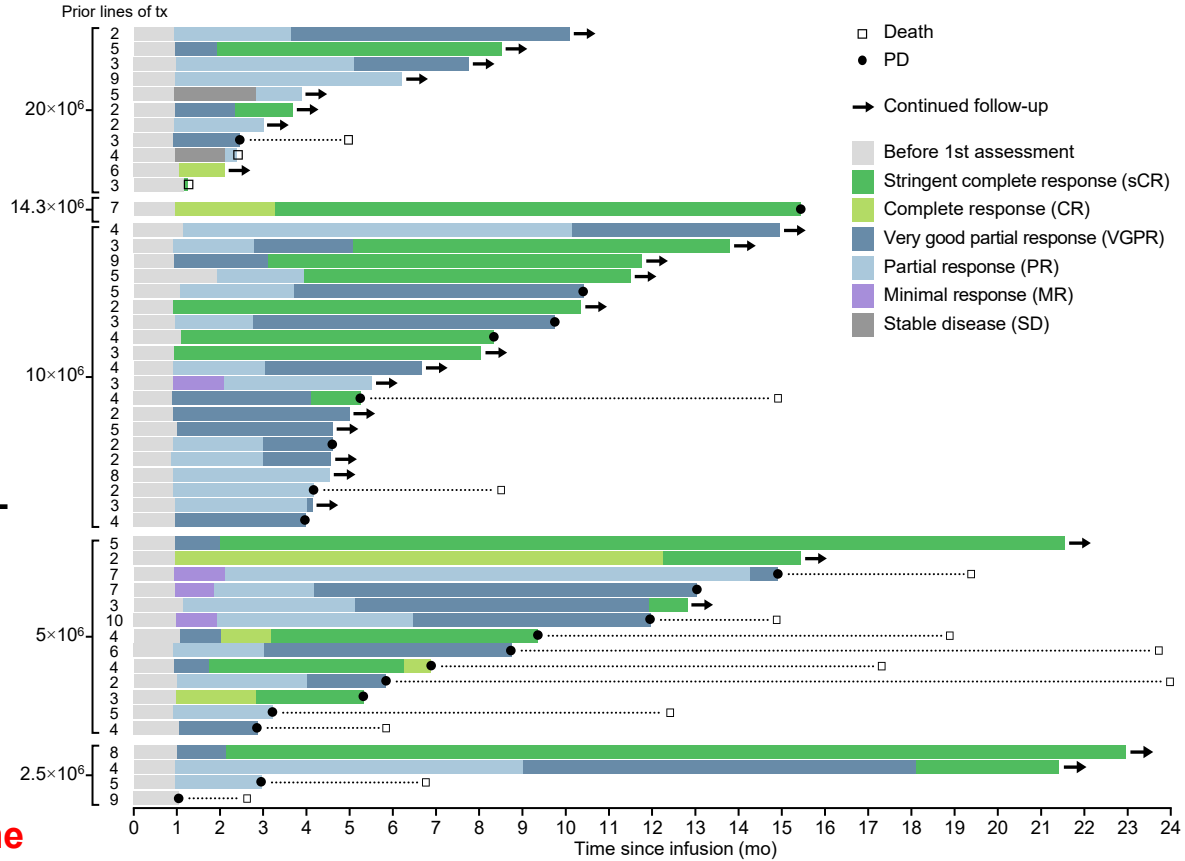
Dose	Month 3	Month 6
20×10⁶	4/5 (80%)	3/3 (100%)
14.3×10⁶	1/1 (100%)	1/1 (100%)
10×10⁶	7/13 (54%)	5/7 (71%)
5×10⁶	6/11 (55%)	5/7 (71%)
2.5×10⁶	0/2 (0%)	0/1 (0%)
All doses	18/32 (56%)	14/19 (74%)

Median time to first response 0.95 (0.89-2.83) months and median time to best response 2.76 (0.92-18.1) months

Conversion to CR/sCR occurred as late as 18 months after infusion

In vivo expansion and persistence

Median time of last detectable transgene 6 months



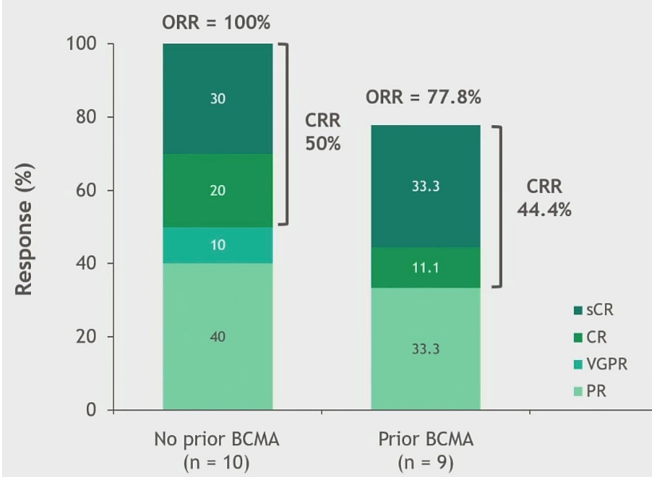
Sperling AS, et al. J Clin Oncol. 2023;41(16_suppl):8004

[a]MRD assessed by NGS with a sensitivity of 10^{-5} in all MRD-evaluable patients.

CC-95266 GPRC5D-Targeting CAR-T Cell Therapy: Response

ORRa

ORR in patients with and without prior BCMA-targeting therapy



- ICANS-type neurotoxicity was infrequent, low grade and reversible with steroid treatment: Any grade 2 (6%), none were grade 3/4
- DLTs: prolonged neutropenia and/or thrombocytopenia, 2 patients (25 x 10^6 and 75 x 10^6 CAR-T cells)
- MTD has not been reached
- No deaths related to study treatment (1 death prior to treatment)

Berdeja J, et al. ASH;2022 (abstr).

Teclistamab Alone and with SC Daratumumab and Lenalidomide in RRMM

– Teclistamab BCMA×CD3 bispecific antibody (Tec) FDA approved 165 pts 76% refractory to IMiD, PI, CD 38 Ab; median 5 lines prior therapy

– ORR 63%, CR 39%, 26% MRD-; Median PFS 11.3 mo, DOR 18.4 mo

– CRS 72.1% (0.6% grade 3); 64.2%, 37%, and 21.2% ≥ grade 3 low WBC, Hct, and Plts

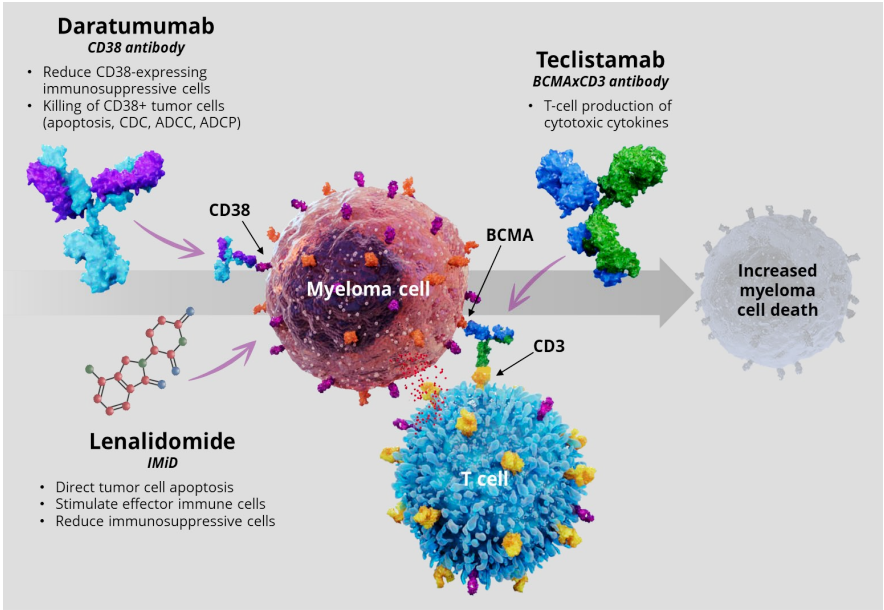
– Infections 76.4% (44.8% grade 3)

Lenalidomide stimulates CTL/NK cells, downregulates Tregs; Daratumumab expands CTLs

– Tec/Len/Dara: 93.5% ORR, 54.8% CR; 90.3% ≥ VGPR including Dara and/or Len refractory MM; 25/31 (80.6%) progression-free on treatment

– CRS 81% (no grade 3); 90.6% ≥ grade 3 AEs including low WBC, Hct, and Plts in 78.1%, 15.5%, and 12.5%

– Patients w > 1 infection 90.6% (37.5% grade ≥ 3, 2 deaths)



Combinations with immunogenic cell death inducers

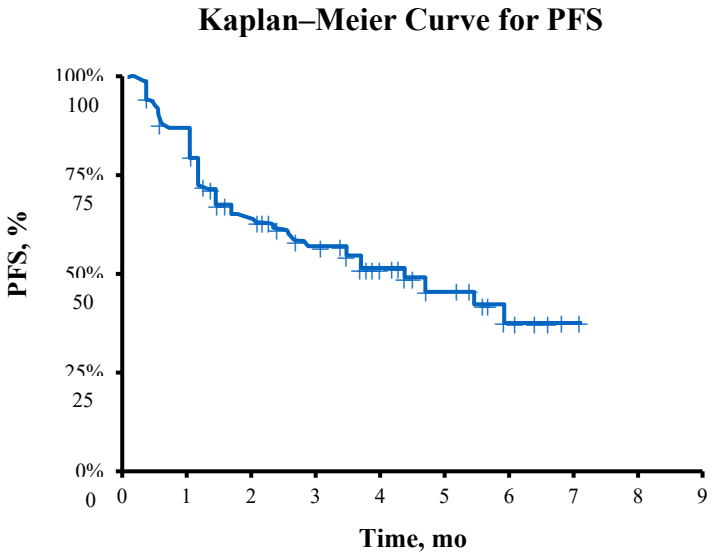
DRIVE Rank Score 2

Nooka A, et al. ASCO 2022 (abstr); Moreau P, et al. N Engl J Med. 2022; 387:495. Searle E, et al. ASH 2022 (abstr).

Real-World Experience With Teclistamab

US Myeloma Innovations Research Collaborative (5 academic centers, 102 RRMM Pts)

Efficacy Outcomes	n (%)
ORR (n = 102)	65 (64)
PR	18 (18)
VGPR	18 (18)
sCR/CR	29 (28)
	ORR
Age >70 (n = 33)	23 (70)
Non-Hispanic Black (n = 25)	17 (68)
Ineligible for MajesTEC-1 trial (n = 83)	49 (59)
R-ISS III (n = 25)	13 (52)
High-risk cytogenetics (n = 55)	34 (62)
EMD (n = 44)	20 (45)
CrCl <40 mL/min (n = 13)	7 (54)
Four or less prior LOT (n = 23)	18 (78)
More than four prior LOT (n = 79)	47 (59)
Triple refractory (n = 94)	58 (62)
Penta refractory (n = 68)	45 (66)
BDT refractory (n = 56)	32 (57)
Prior belantamab mafodotin (n = 23)	15 (65)
Prior BCMA directed CAR-T (n = 42)	25 (60)
≥2 prior BCMA directed therapies (n = 13)	9 (69)



- **Overall teclistamab was well tolerated with no major safety concerns, despite worse PS and cytopenias than the MajestTEC-1 trial population**

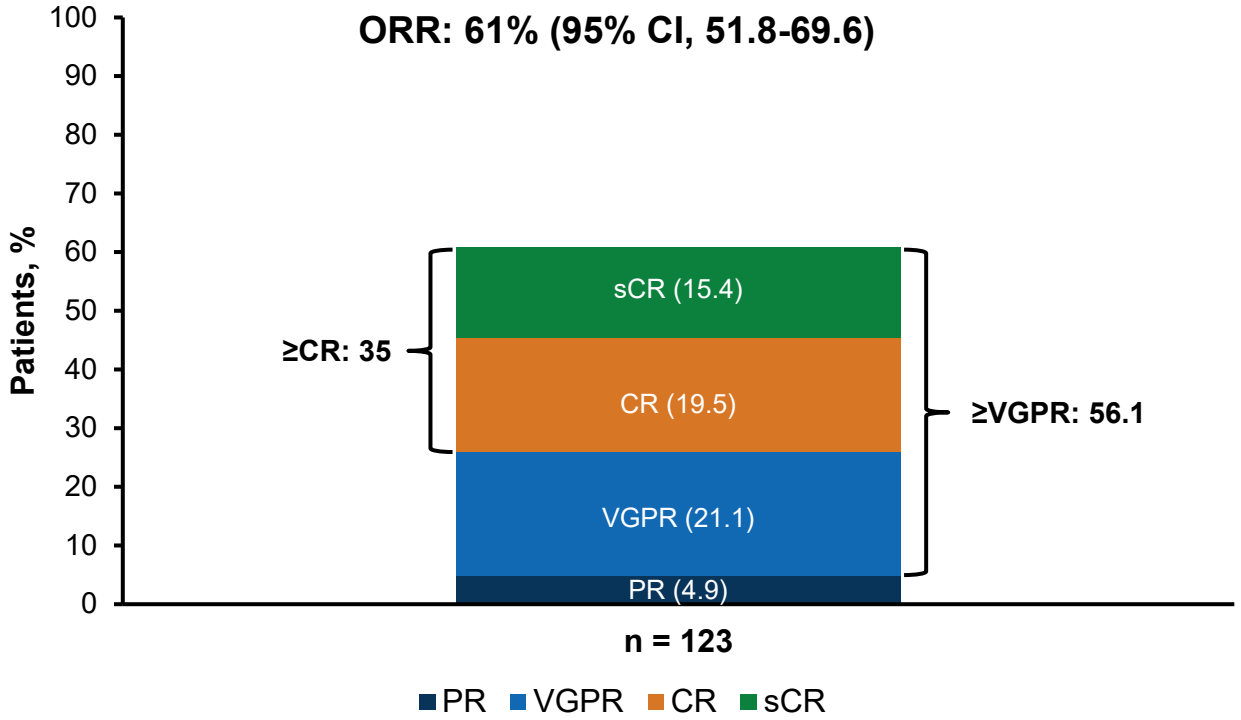
DRIVE Rank Score 5

Dima D et al. ASH 2023 (Abstr 91)

MagnetisMM-3 : Elranatamab in Patients With RRMM

SC administration of elranatamab in RRMM (N = 123, cohort A, BCMA-naïve patients)[1]

- Median number of prior regimens was 5; 91% were TCR
- **ORR: 61%**
- MRD negativity of 10^{-5} was achieved by 90.9% of evaluable patients

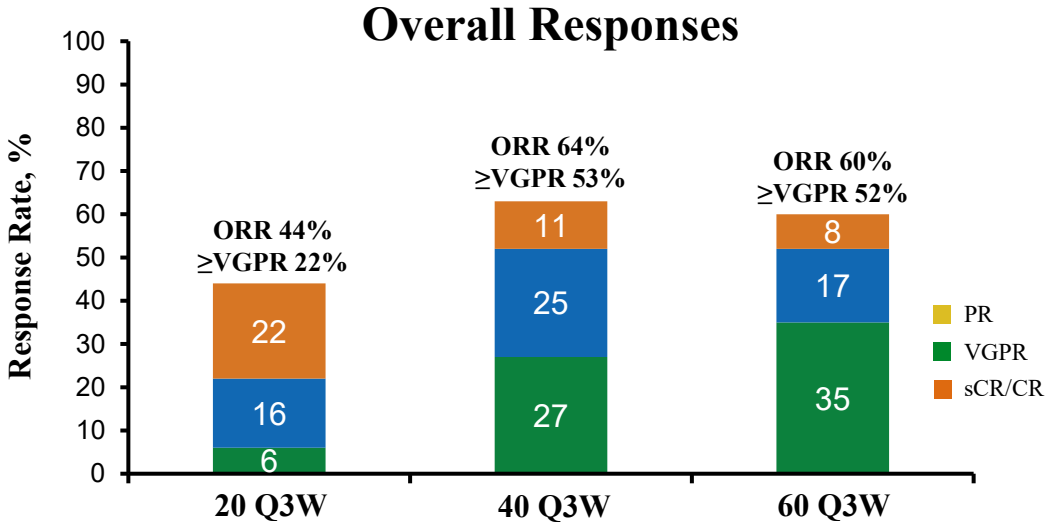


DRIVE Rank Score 2

Lesokhin A et al. Nat Med. 2023; 29: 2259-67.

ABBV-383 in RRMM

ABBV-383 IV Q3W at 20 mg, 40 mg and 60 mg dose levels



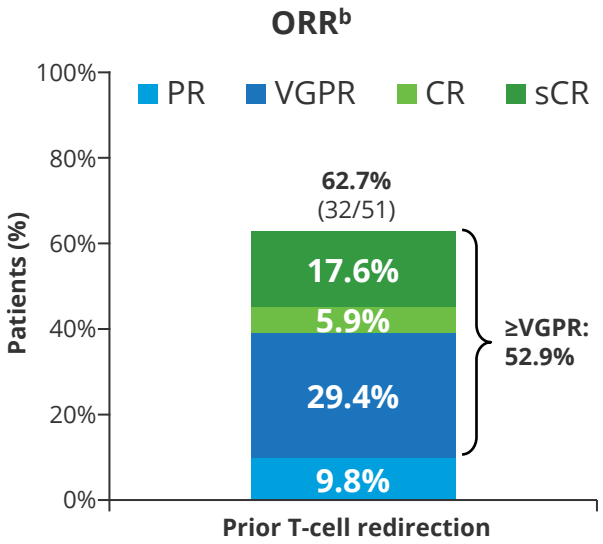
Vij R et al. ASH 2023 (abstr 3378)

Talquetamab GRRC5D BiTE in Patients with Prior T-Cell Redirection

- Median 6 (3–15) prior lines of therapy
- 70.6% (n=36) prior CAR-T cell therapy
- 35.3% (n=18) prior bispecific antibody therapy
- 3 patients both
- 7.8% (n=4) refractory to belantamab
- Most patients received QW (n=43) vs Q2W (n=8) talquetamab dosing

– ORR 62.7%
  - 72.2% ORR (26/36) prior CAR-T therapy
  - 44.4% ORR (8/18) prior BiTE treatment
– Median DOR: 12.7 months at median F/U 11.8 months

Combinations of BCMA and GPRC5D BiTEs may enhance response and avoid/delay resistance

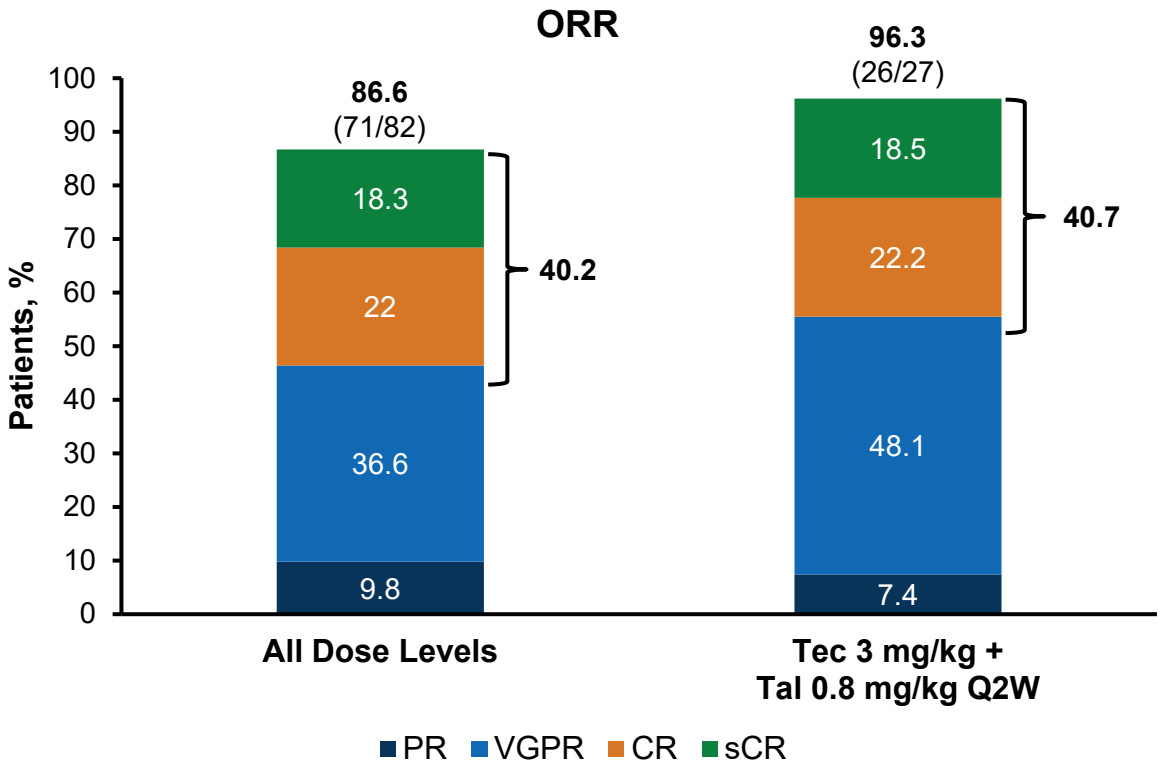


Chari et al ASH 2022 (abstr)

Bahlis N, et al. ASH 2022 (abstr).

RedirecTT-1: Dual Targeting of BCMA and GPRC5D in RRMM

- First results from the phase 1b trial of teclistamab + talquetamab showed a safety profile consistent with each of the monotherapies
- 96% ORR across at RP2R
- 86% ORR in extramedullary disease subgroup (RP2R)



Mateos M-V et al. EHA 2023 (abstract S190); Cohen YC et al. ASCO 2023 (Abstr 8002).

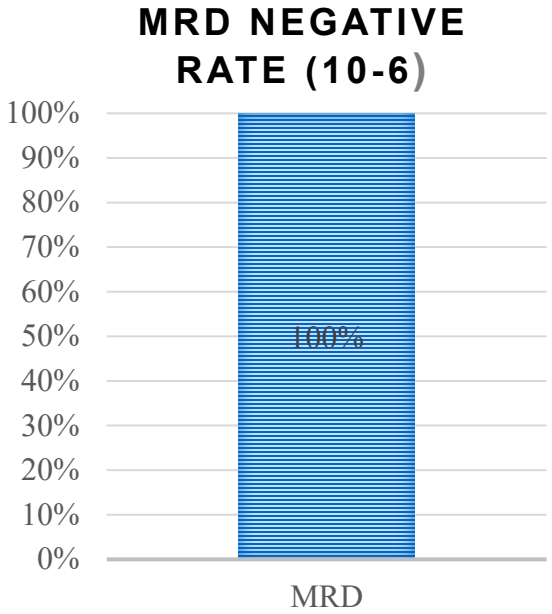
Efficacy in Teclistamab Arm in High Risk SMM , N=12

TEC-treated Cohort (12 patients)

Best response	n	%
CR	10	83
VGPR	2	17
Overall response rate	12	100

- No patients have progressed on treatment.
- Stem cell collection was successful in all eligible patients with an average stem cell yield of 8.94 x 10^6 CD34+ cells/kg.

Nadeem et al ASH 2023 (abstr)



MRD-negativity rate at 10^{-5} is 100%

MRD-negativity rate at 10^{-6} is 100%

Average time to MRD-4.25 cycles

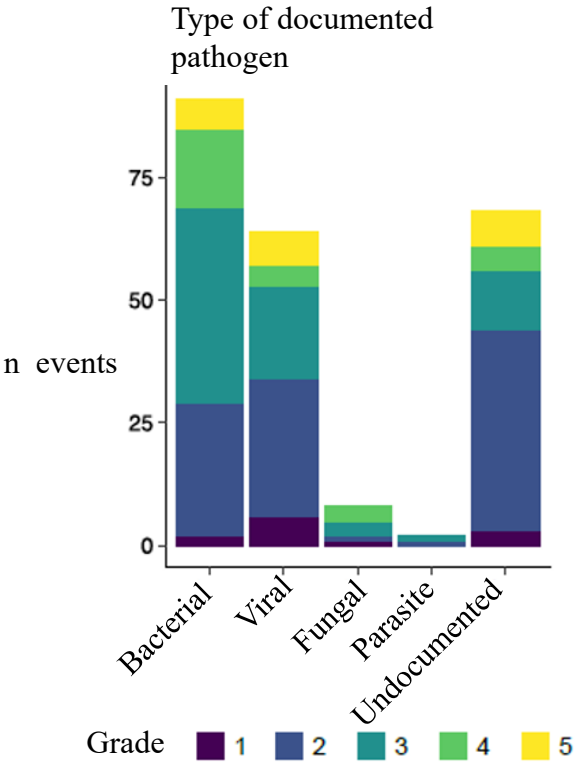
Infections requiring treatment, delay in treatment or hospitalisation in RRMM patients treated with anti BCMA or anti GPRC5D bispecific antibodies

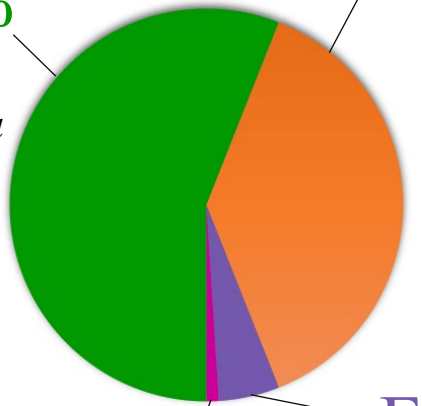
Variables	Total (n=229)	BCMA-targeting BsAb[a] (n=200)	GPRC5D-targeting BsAb[b] (n=29)
Variables	**Total (n=229)**	**BCMA-targeting BsAb[a] (n=200)**	**GPRC5D-targeting BsAb[b] (n=29)**
All-grade CRS (%)	60 %	60 %	66 %
All-grade ICANS (%)	5 %	5 %	7 %
Corticosteroids for CRS/ICANS (%)	**16 %**	**19 %**	**0 %**
Tocilizumab for CRS/ICANS (%)	25 %	23 %	41 %
≥ 1 week of neutropenia < $0.5x10^9$/L during BsAb treatment (%)	17 %	17 %	20 %

Cellerin et al ASH (abstr) 2023

Occurrence and characteristics – all infections

Documented infections 70%





Bacterial 56%

Enterobacteriaceae
Pseudomonas aeruginosa

Viral 38%

Respiratory viruses
Covid 19 n=21
CMV n=8
JC virus n=2

Parasites 1%

Toxoplasma gondii n=1
Giardia intestinalis n=1

Fungal 5%

Aspergillus spp n=6
Pneumocystis jirovecii n=1

Cellerin et al ASH (abstr) 2023

Mitigation Strategies

All infections :

First 6 weeks after beginning of treatment

Severe (grade ≥ 3)

Mostly Bacterial

Unusual Opportunistic infections

Importance of prophylactic measures

- HSV/VZV, Pneumocysitis jirovecii
- Anti-bacterial prophylaxis

First infections

High cumulative incidence, 70%

Associated variables with higher infectious risk
- Use of Corticosteroids for CRS/ICANS

Strategies to mitigate the risk of infections

- Immunoglobulin replacement
- Spaced injections

Ludwig and al, The Lancet, 2023
Lancman and al, Blood cancer discovery, 2023

Cellerin et al ASH (abstr) 2023

Mechanisms of Antigen Escape from BCMA- or GPRC5D-Targeted Immunotherapies in Multiple Myeloma

Combined bulk and SC WGS and CNV analysis of 30 patients treated with anti-BCMA and/or anti-GPRC5D CAR T/TCE therapy:

2 relapse by expansion of existent BCMA-clones with focal biallelic deletions
5 relapse by newly detected, nontruncating, missense mutations or in-frame deletions in ECM domain of BCMA, despite detectable surface BCMA
4 relapse with biallelic mutations of GPRC5D, 2 convergent evolution where multiple subclones lost GPRC5D through somatic events.

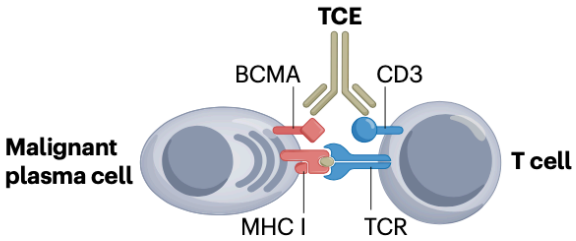
Immunoselection of BCMA- or GPRC5D-negative or mutant clones drives relapse post-targeted therapies.

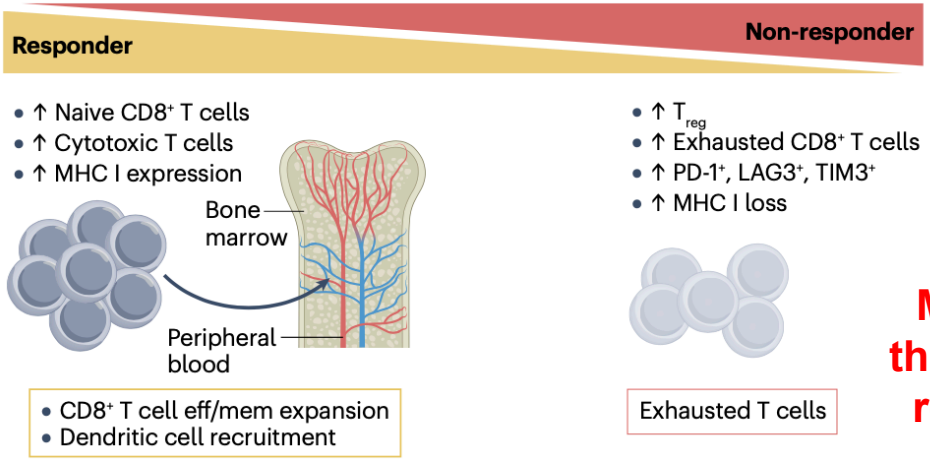
Mutational events on BCMA confer distinct sensitivities toward different anti-BCMA therapies.

Profiling tumor antigen landscape for optimal design and selection of targeted immunotherapies in MM.

Lee H et al Nat Med 2023; 29: 2295-2306.

T Cell Landscape Determines Response to Bispecific T Cell Engagers (TCE) in Multiple Myeloma





Single-cell TCR tracing identifies conserved T cell responses to TCEs

Clonal expansion of effector CD8+ T cells is a driver of TCE therapy response

Naive T cells require additional MHC class I signal and differentiate upon TCE activation

The abundance of exhausted CD8+ clones predicts response failure

Monitoring immune profile before and during therapy can inform schedule of TCE to optimize response and limit T cell exhaustion, relapse, and increased risk of infection.

Friedrich MJ, et al. Cancer Cell. 2023;41:711-725.e6.
Midha S, Anderson KC. Nat Rev Clin Oncol. 2023;20:505-506.

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

Alfred Goldberg (1943-2023)
Described proteasomal protein degradation, PS-341 (bortezomib)

In the future, targeted and immune therapies Including CART/BiTEs will be incorporated into initial treatment of MM to 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