Highlights from
IMS 20th meeting 2023

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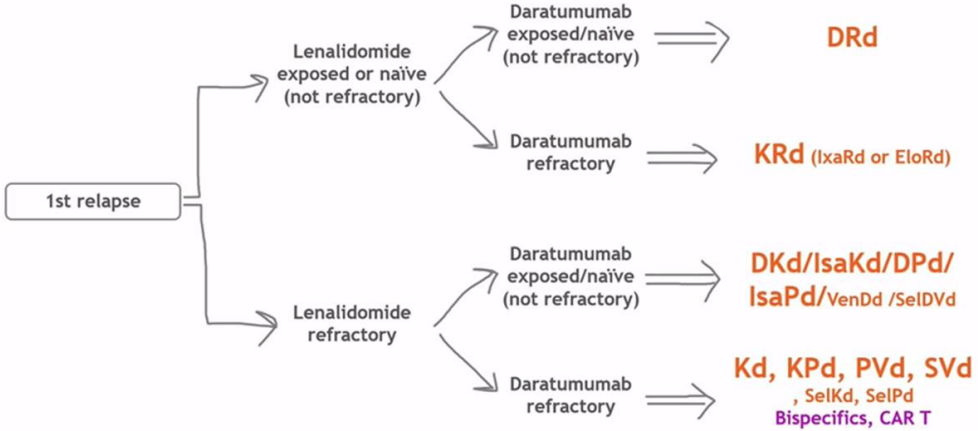
Paziente con refrattarietà a 2-3 classi di farmaci dopo 1-2 precedenti terapie: dati disponibili e possibili opzioni

30-31 gennaio 2024
BOLOGNA, Royal Hotel Carlton

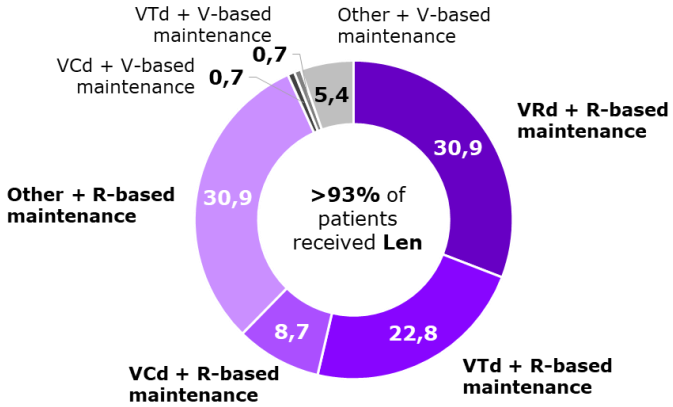
One strategy for approaching a relapsed patient



The data presented are provided for ease of viewing information from multiple trials. Direct comparison between trials is not intended and should not be inferred.
BelaPd, belantamab mafodotin + pomalidomide + dexamethasone; IsaPd, Isatuximab + pomalidomide + dexamethasone; KPd, carfilzomib + pomalidomide + dexamethasone; SelDVd, selinexor + daratumumab + bortezomib , + dexamethasone; SelKd, selinexor + carfilzomib + dexamethasone; SelPd, selinexor + pomalidomide + dexamethasone; VenDd, venetoclax + daratumumab + dexamethasone.
Cartoon representation courtesy of Rodriguez P.
Based on: Dimopoulos MA, et al. Ann Oncol. 2021;32:309-22. Kaufman J et al. Blood. 2019;134:abstract 1866. Avet-Loiseau H, et al. Blood Cancer J 2020;10:111. Siegel DS, et al. J Clin Oncol 2018;36:728-34.

S. Lonial, IMS 2023

Induction and maintenance regimens in Te NDMM in France, Germany, Spain and Italy (N=149)[1]



1. Weisel K, et al. Eur J Haematol 2022;109:388–97

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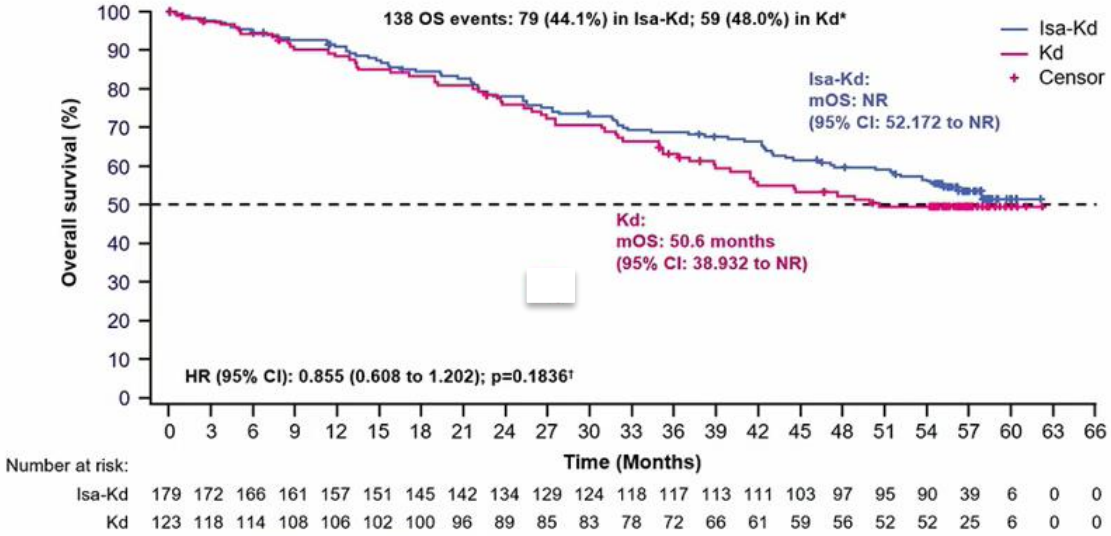
OS analysis

32% L-refractory
31% PI-refractory



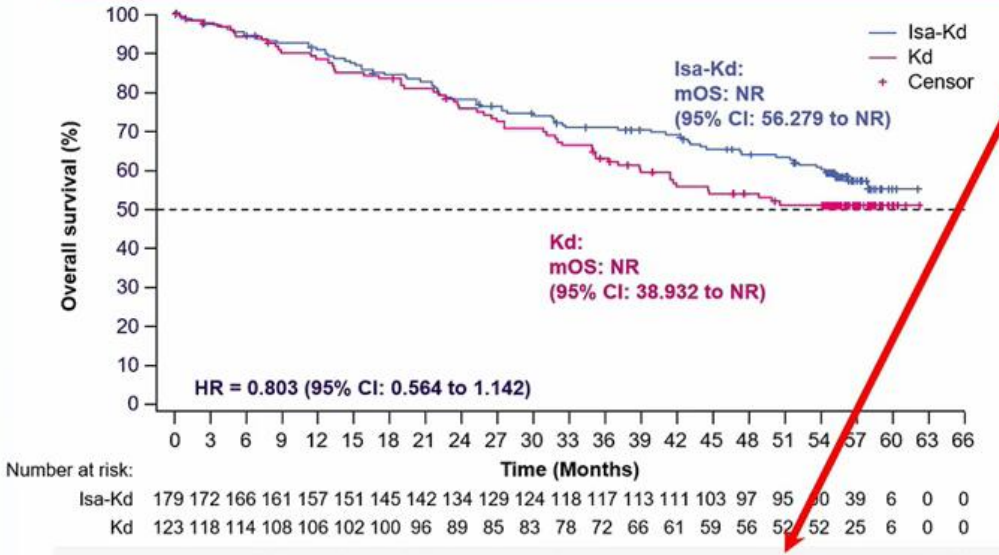
Extrapolating the current observed trend for an additional 12 months of follow-up, the mOS estimate for Isa-Kd arm is **63 months** (95% CI: 59–69)

This corresponds to an estimated 1-year difference in mOS

After a median follow-up of 56.6 months, mOS was not reached in the Isa-Kd arm. The extrapolated mOS estimate of 63 months for Isa-Kd corresponds to an estimated 1-year difference in mOS versus Kd

*Cutoff date for OS analysis: February 7, 2023.
†Nominal one-sided p-value.
CI, confidence interval; HR, hazard ratio; d, dexamethasone; Isa, isatuximab; K, carfilzomib; mOS, median OS; NR, not reached; OS, overall survival.

COVID infection and response is a complication of CD38 related treatment



n (%)	Isa-Kd (n=179)	Kd (n=123)
Deaths due to COVID-19, n (%)	8* (4.5)	2† (1.6)
Deaths‡ included in the sensitivity analysis, n (%)	71 (39.7)	57 (46.3)

*3 patients during study treatment and 5 in the follow-up period;
†1 patient during study treatment and 1 in the follow-up period

	HR (95% CI)
OS analysis (ITT)	0.855 (0.608–1.202)
Sensitivity analysis censoring death due to COVID-19	0.803 (0.564–1.142)

Results of the sensitivity analysis show that COVID-19 disproportionately impacted OS in the Isa-Kd arm

Cutoff date: February 7, 2023.
‡In the Isa-Kd arm, there were 12 deaths during study treatment (COVID-19, n=3; pneumonia, n=2; and 1 each due to cardiac failure, health deterioration due to progression of disease, large intestine perforation, severe asthma attack, cardiac decompensation, atypical lower lobe pneumonia, and polytrauma) and 66 during follow-up (progressive disease, n=43; adverse event of *Pneumocystis jirovecii* pneumonia, n=1; other, n=22). In the Kd arm, there were 6 deaths during study treatment (COVID-19, acute myocardial infarction, septic shock, unknown, cardiac failure, and health deterioration due to progression of disease) and 53 during follow-up (progressive disease, n=43; other, n=10).
CI, confidence interval; HR, hazard ratio; d, dexamethasone; Isa, isatuximab; ITT, intent to treat; K, carfilzomib; mOS, median OS; NR, not reached; OS, overall survival.

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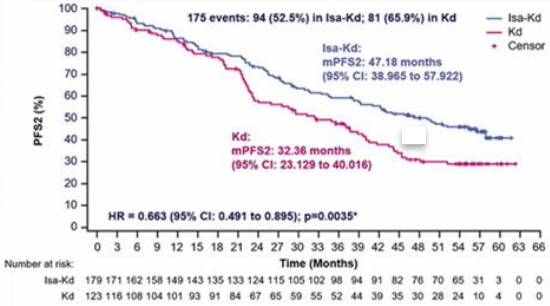
PFS2 (time from randomization to PD on subsequent therapy or death)



ITT population	PFS2 HR (95% CI)
At final PFS analysis Median follow-up: 43.96 months	0.683 (0.496–0.941)
At OS analysis Median follow-up: 56.6 months	0.663 (0.491–0.895)

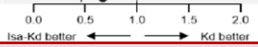
The PFS benefit of Isa-Kd versus Kd is maintained after the first subsequent therapy

*Nominal, one-sided p-value.
CI, confidence interval; d, dexamethasone; HR, hazard ratio; Isa, isatuximab; ITT, intention-to-treat; K, carfilzomib; m, median; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, second PFS.

32% L-refractory
31% PI-refractory

PFS2 subgroup analysis

Subgroup		Isa-Kd Events/total	Kd Events/total	Hazard ratio (95% CI)
All patients		80/179	73/123	0.683 (0.494-0.946)
Age	<65	42/88	37/66	0.802 (0.515-1.248)
	>65	38/91	36/57	0.579 (0.366-0.914)
Baseline eGFR (MDRD)	>60 mL/min/1.73 m²	51/122	54/93	0.692 (0.471-1.016)
	<60 mL/min/1.73 m²	21/43	10/183	0.706 (0.329-1.512)
ISS staging at study entry	I	26/89	39/71	0.496 (0.305-0.807)
	II	34/63	17/31	0.894 (0.456-1.601)
	III	18/26	16/20	0.852 (0.434-1.671)
High-risk cytogenetic status	Yes	26/42	22/31	0.850 (0.479-1.507)
	No	42/114	41/77	0.611 (0.397-0.940)
1q21+	Yes	40/75	35/52	0.702 (0.446-1.109)
	No	30/84	27/55	0.670 (0.398-1.128)
Number of prior lines of therapy	1	27/80	24/55	0.721 (0.415-1.252)
	>1	53/99	49/68	0.661 (0.448-0.975)
Prior PI treatment	Yes	40/81	29/47	0.774 (0.480-1.249)
	No	40/98	44/76	0.596 (0.388-0.917)
Prior IMiD treatment	Yes	37/81	40/62	0.610 (0.390-0.955)
	No	43/98	33/61	0.783 (0.485-1.262)
Refractory to lenalidomide	Yes	38/57	33/42	0.737 (0.462-1.176)
	No	40/81	40/122	0.639 (0.414-0.986)
Refractory to lenalidomide at last prior regimen	Yes	24/36	24/31	0.761 (0.432-1.342)
	No	56/143	49/92	0.674 (0.456-0.989)



- **Subgroup analyses of PFS2 show a consistent treatment effect for Isa-Kd across subgroups**

CI, confidence interval; d, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; Isa, isatuximab; ISS, International Staging System; K, carfilzomib; MDRD, Modification of Diet in Renal Disease; PFS2, second PFS.

Phase III APOLLO: PFS With Dara-Pd vs Pd in R/R MM

R/R MM patients previously treated with ≥1 prior line with both lenalidomide and PI (N = 304)

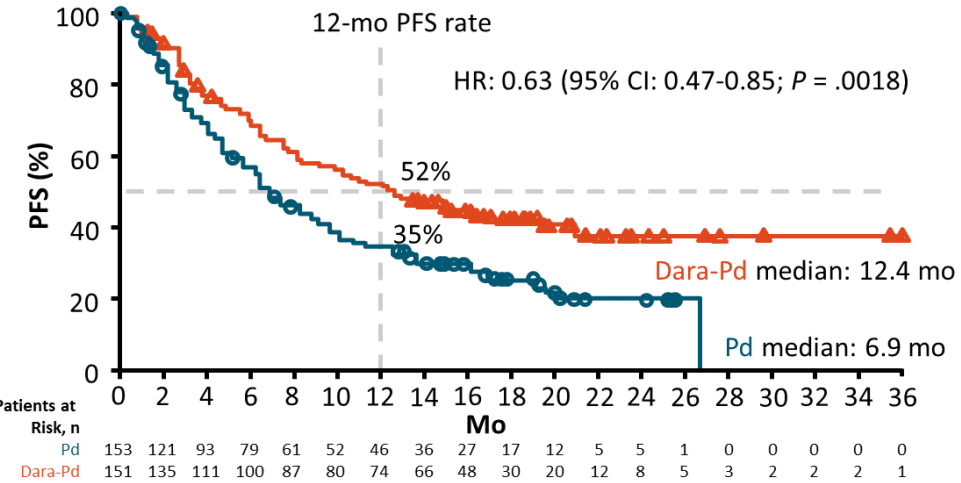
Daratumumab + Pomalidomide + Dexamethasone (Dara-Pd) (n = 151)

Pomalidomide + Dexamethasone (Pd) (n = 153)

Dosing (28-day cycles): Dara: 1800 mg SC* QW in C1-2, Q2W C3-6, then Q4W; P: 4 mg PO days 1-21; dex: 40 mg PO QW.

Response, %	Dara-Pd (n = 151)	Pd (n = 153)
ORR	69	46
≥ VGPR	51	20
≥ CR	25	4
MRD negative	9	2

- Dara-Pd significantly improved ORR, rates of ≥ VGPR, ≥ CR, and MRD negativity (all *P* ≤.0102)
- For those refractory to Len, mPFS was 9.9 mo with Dara-Pd vs 6.5 mo with Pd



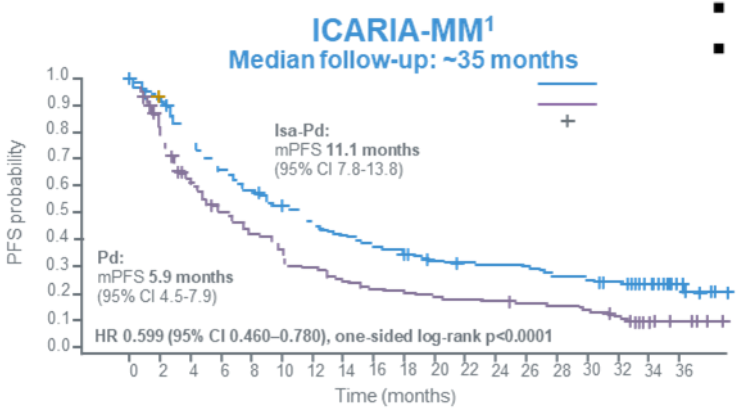
*Patients received Dara 16 mg/kg IV prior to protocol amendment, patients who initially received IV dosing switched to SC dosing on Day 1 of any cycle from cycle 3+.

Dimopoulos. Lancet Oncol. 2021;22:801.

Phase III ICARIA-MM

Isa-Pd group

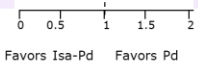
- 3 prior lines of therapy
- 94% Len refractory (60% in last line)
- 77% PI refractory
- 72% double refractory



ICARIA-MM: Isa-Pd vs Pd in RRMM

PFS by refractory status (median follow-up 11.6 months)

	Median PFS, months		Hazard ratio (95% CI)
	Isa-Pd	Pd	
Refractory status			
Len-refractory	11.40	5.59	0.593 (0.431; 0.816)
Len-refractory at last line	11.60	5.70	0.50 (0.34; 0.76)
PI-refractory	11.40	5.59	0.578 (0.405; 0.824)
Len- and PI-refractory	11.20	4.76	0.579 (0.401; 0.835)



PFS benefit was maintained with Isa-Pd regardless of Len-refractory status

Bringhen S, et al. Leuk Res 2021;104:106576

The potential use of anti-CD38 mAb therapy upfront adds additional considerations to second-line treatment

What should the treatment strategy be at relapse after continuous DRd?

- **Include a PI**
- **Triplets are preferred**
- **What options are there?**
  - **PVd**
  - **XVd**
  - **Kd**

- **Len-based regimens**

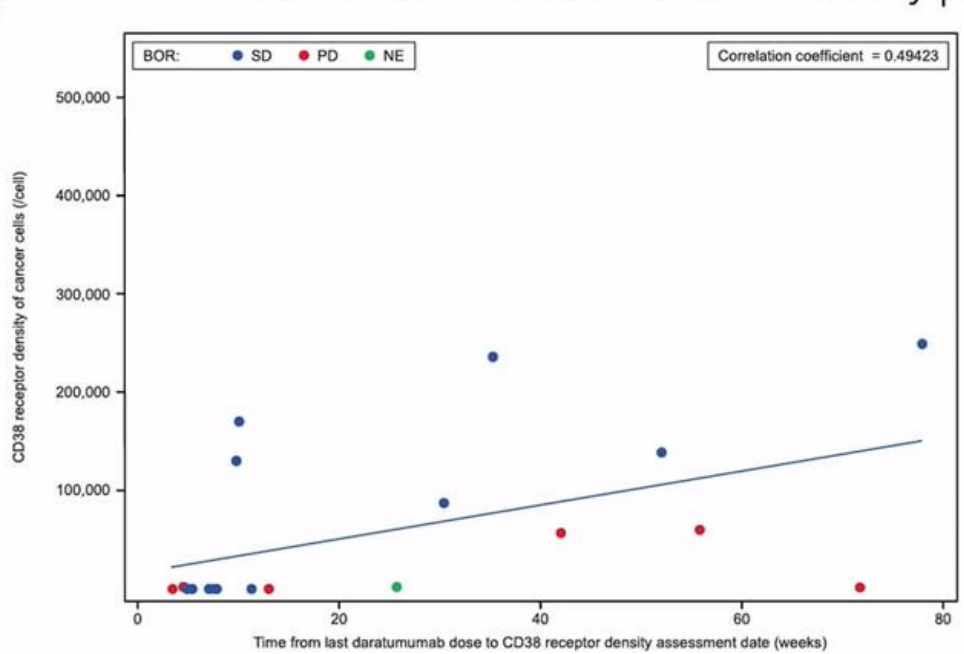
- **In which circumstances can CD38-mAb-based regimens be adopted?**

d, dexamethasone; D, daratumumab; K, carfilzomib; mAb, monoclonal antibody; P, pomalidomide; PI, proteasome inhibitor; R, lenalidomide; V, bortezomib; X, selinexor

F. Schjesvold, IMS 2023

Refractoriness to anti-CD38 antibodies

Retreatment with Isatuximab in Daratumumab refractory patients?

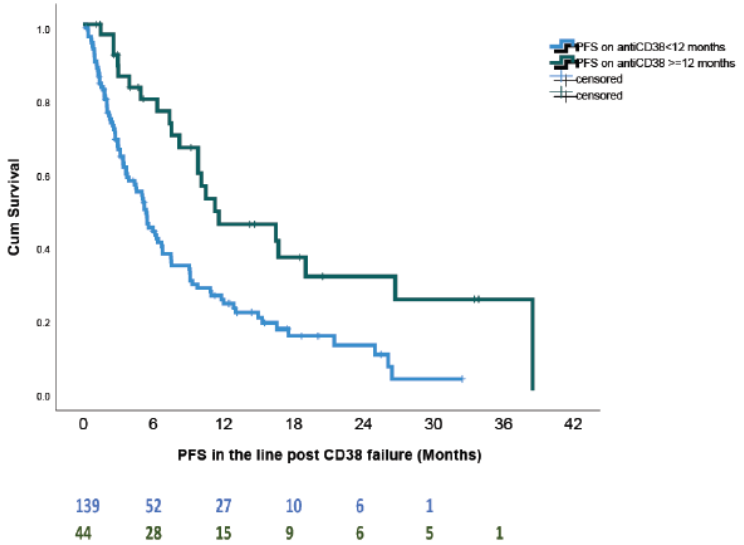


Mikhael et al. Blood Cancer Journal 2021; 11:89
Kikushi T et al Annals of Hematology 2023 102:1477–1483
Nooka A et al Cancer 2019 125: 2991–3000

International Myeloma Society

Management and Outcomes of Anti-CD38 Refractory Patients: The Impact of Retreatment and of Subsequent Therapies

Kastritis E et al. Hemasphere 2023

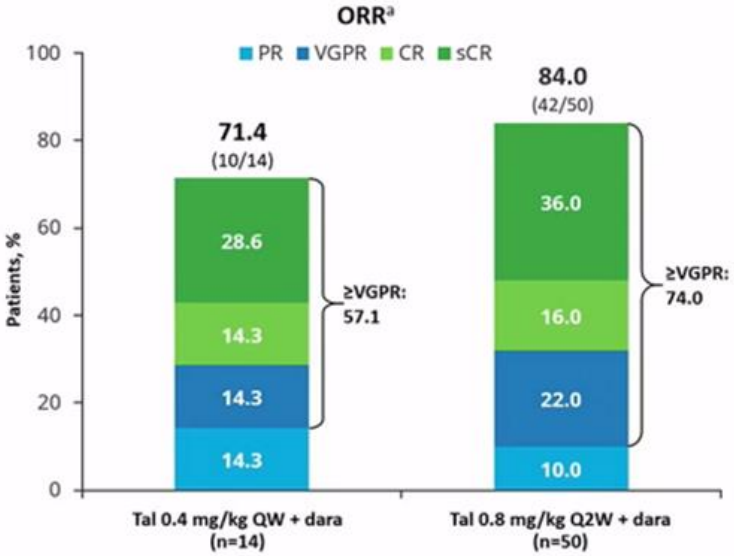


Post-CD38 failure regimen		PFS	OS
PI-containing	40%	6.4 (4.8–8)	22.9 (19.9–25.9)
Carfilzomib-containing	23%	6.7 (2.6–10.9)	22.7 (20.1–24.6)
Pomalidomide-based	30%	4.5 (2.6–6.5)	20.9 (12.4–29.4)
Anti-CD38-based	23%	4 (1.7–6.1)	16.6 (6.8–29.9)
Belantamab	15%	9.1 (4.3–13.9)	24.5. (17.5–31.5)
Selinexor ± PI	5%	3.7 (1–11.8)	30 (NE)
Triplet	50%	6(4.6–7.3)	17.9 (11.1–27.3)
Doublet/monotherapy	50%	6.8 (3.2–10.5)	17.3 (12.6–29.3)

Immunomodulatory effects of anti-CD38 MoAb

TRIMM-2 (Tal + Dara): Deep and durable Responses in Daratumumab refractory patients

Daratumumab depletion of CD38-expressing Tregs may enhance BCMA and GPRC5D bispecific antibodies-mediated killing of myeloma cells

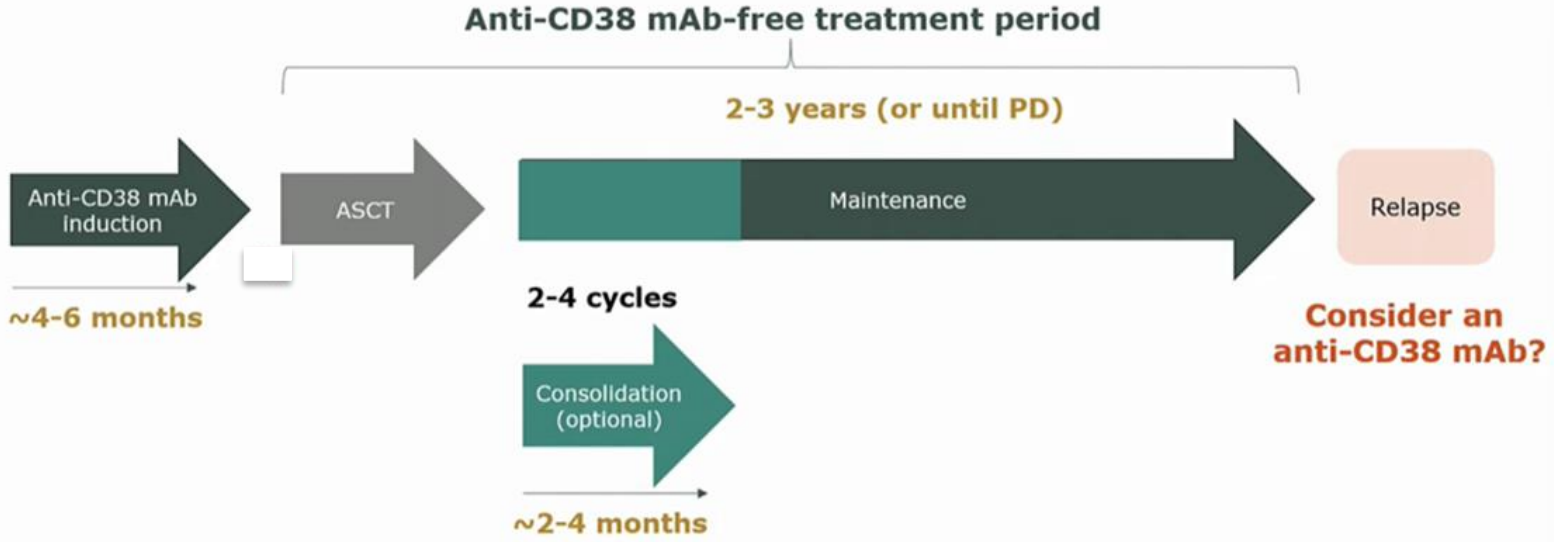


Parameter	Tal 0.4 mg/kg QW + dara (n=14)	Tal 0.8 mg/kg Q2W + dara (n=51)
Median (range) follow-up, mo	16.8 (1.9–31.0)	15.0 (1.0–23.3)
Median (range) time to first response, mo	1.0 (0.9–2.4)	1.0 (0.9–8.3)
ORR in anti-CD38, n (%)		
Naïve	3/3 (100.0)	5/5 (100.0)
Exposed	7/11 (63.6)	37/45 (82.2)
Refractory	7/11 (63.6)	32/40 (80.0)
ORR in T-cell redirection therapy[b] exposed, n (%)	4/6 (66.7)[c]	15/19 (78.9)
CAR-T	1/2 (50.0)	8/9 (88.9)
BsAb	4/5 (80.0)	7/10 (70.0)

International Myeloma Society

Bahlis N et al. European Hematology Association (EHA) 2023 Hybrid Congress; June 8–11, 2023; Frankfurt, Germany

Can an anti-CD38 mAb be considered in 2L if an anti-CD38 mAb was given during induction only?

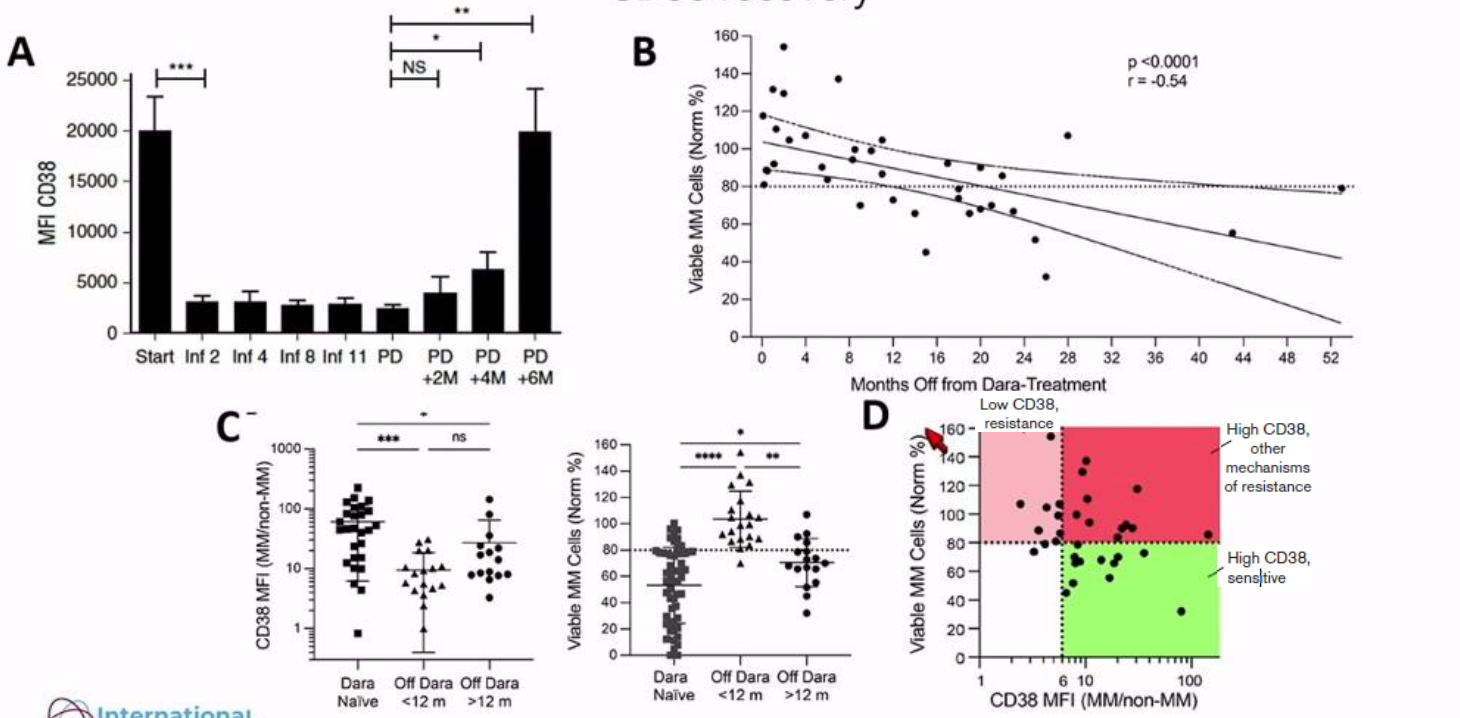


2L, second-line; ASCT, autologous stem cell transplant; mAb, monoclonal antibody; PD, disease progression

F. Schjesvold, IMS 2023

Is refractoriness to anti-CD38 antibodies reversible?

CD38 recovery



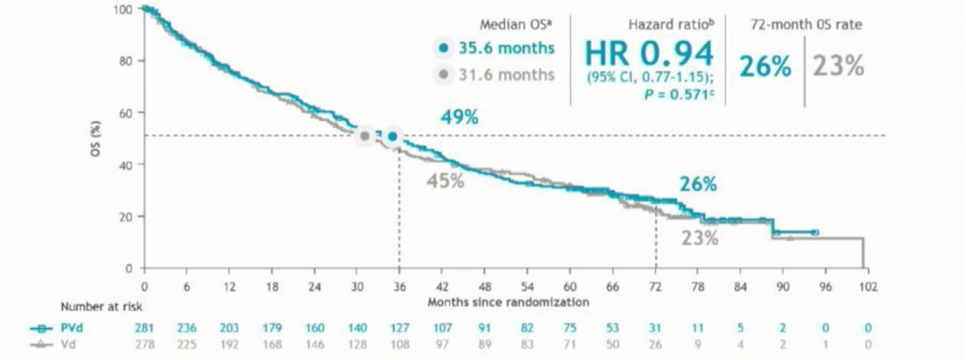
International Myeloma Society

Nihjov I et al Blood 2016, 128:959-970
Perez de Acha et al Blood Adv, 2023

OPTIMISMM: PVD *vs* VD

OPTIMISMM PVd final OS

OS: ITT population



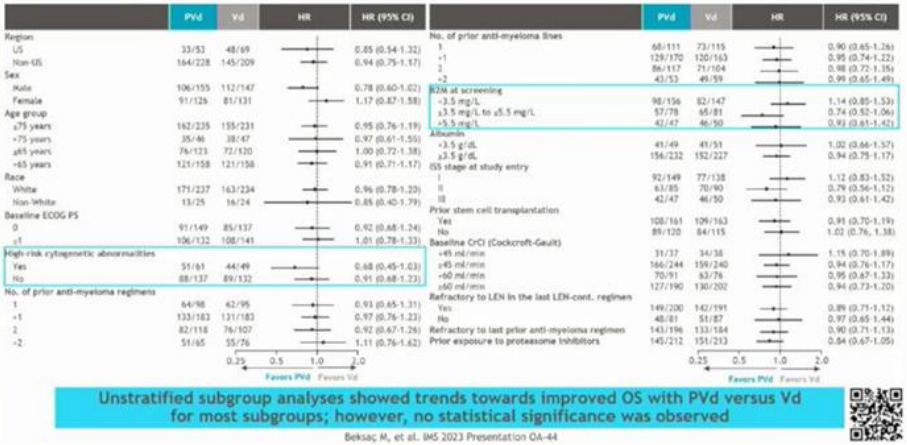
Median OS was numerically longer for PVd versus Vd, but this difference was not statistically significant

Median follow-up: 64.5 months. Square and triangle symbols indicate censoring.
[a]Based on Kaplan-Meier estimate; [b]Based on Cox proportional hazards model, comparing the hazard functions associated with treatment groups, stratified by age (≤ 75 vs > 75 years), prior number of antimyeloma regimens (1 vs >1), and B2-microglobulin at screening (< 3.5 vs ≥ 3.5 to ≤ 5.5 vs > 5.5 mg/L); [c]Based on a stratified log rank test with stratification factors as above Cox model.

Beksaç M, et al. IMS 2023 Presentation OA-44

OPTIMISMM PVd final OS

OS: subgroup analysis



Unstratified subgroup analyses showed trends towards improved OS with PVd versus Vd for most subgroups; however, no statistical significance was observed

Beksaç M, et al. IMS 2023 Presentation OA-44

Pre-planned OS by Cox proportional hazards model using time-dependent covariates

Subsequent therapy	PVd	Vd
POM Subsequent Therapy (%)	19.2	58.3
≥1 Subsequent antimyeloma therapy received (%)	68.3	79.1

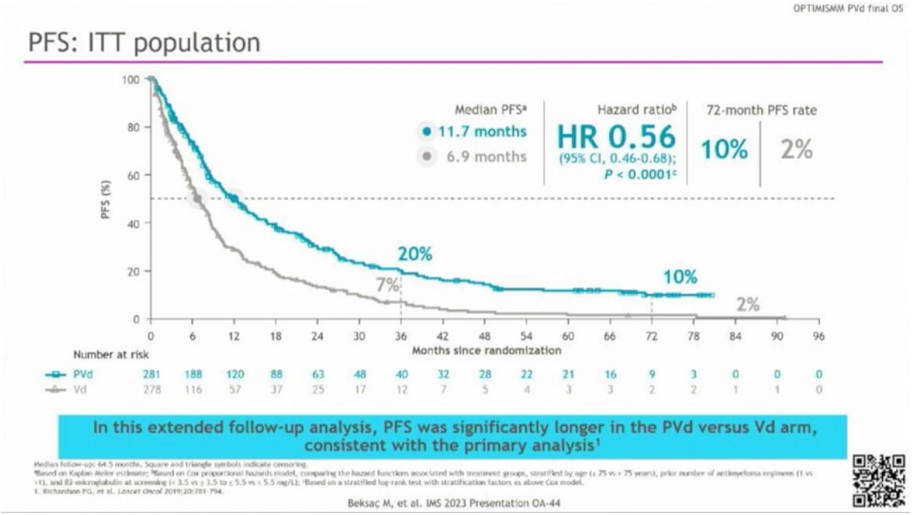
- With subsequent therapy as a time-dependent covariate and adjusting for stratification factors, a statistically significant improvement in OS was observed with PVd versus Vd (P = 0.008)

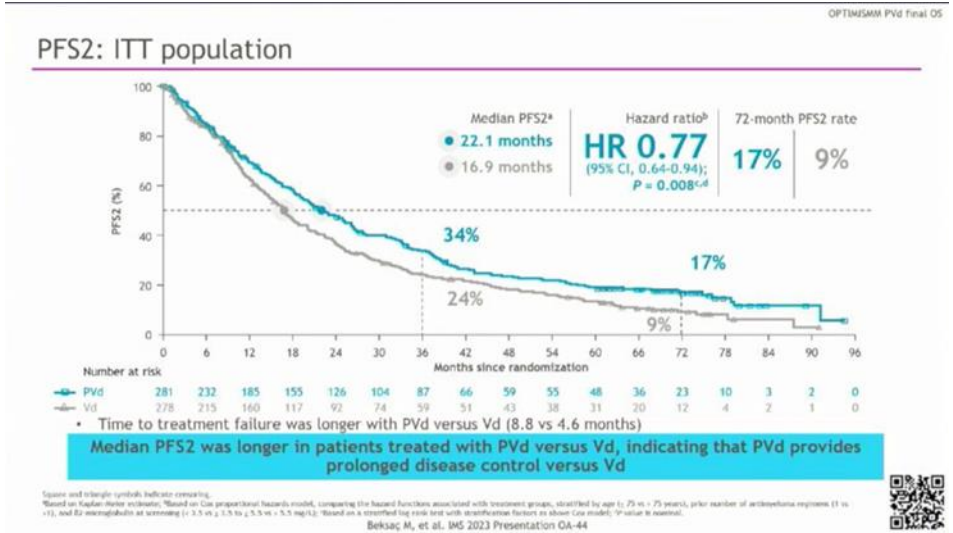
Model parameter	HR	95% CI lower bound	95% CI upper bound	*P* value[a]
Treatment arm: PVd versus Vd	0.759	0.619	0.931	0.008
Age: ≤ 75 versus > 75 years	0.970	0.747	1.258	0.817
Number of prior antimyeloma regimens: 1 versus >1	0.668	0.540	0.827	< 0.001
B2-microglobulin: ≤ 5.5 versus > 5.5 mg/L	0.365	0.285	0.466	< 0.001
Subsequent antimyeloma therapy: yes versus no (time dependent)	0.319	0.247	0.413	< 0.001

[a]Based on the Cox proportional hazard model comparing the hazard functions associated with the model parameter.

Beksaç M, et al. IMS 2023 Presentation OA-44

OPTIMISMM: PVD *vs* PD





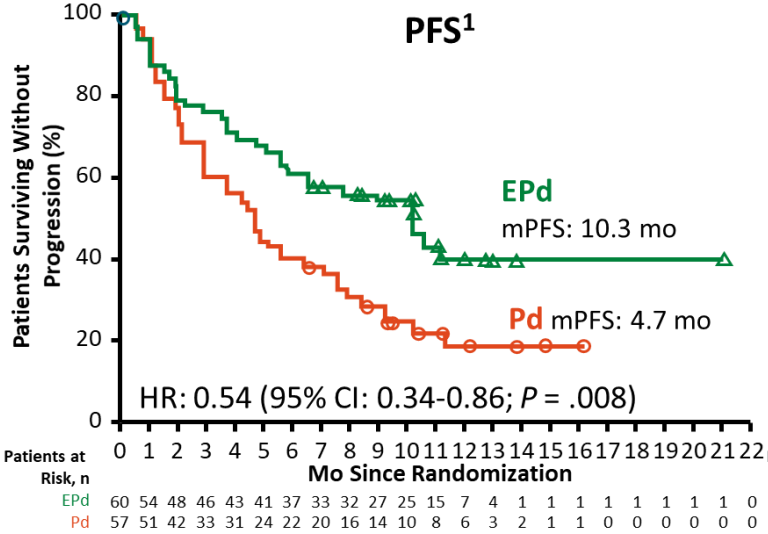
Phase II ELOQUENT-3: Elotuzumab + Pd vs Pd in R/R MM

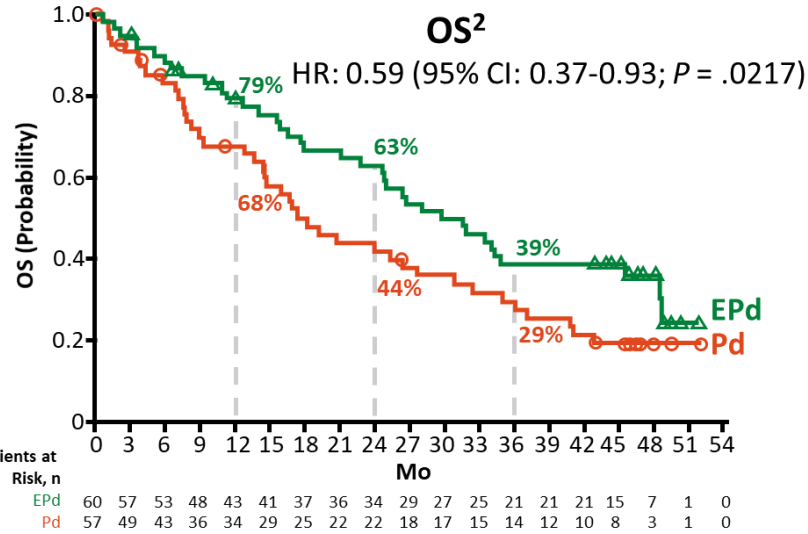
R/R MM patients previously treated with ≥2 lines of tx, including Len and a PI (N = 117)

- **Elotuzumab + Pomalidomide + Dexamethasone (Elo-Pd)** (n = 60)
- **Pomalidomide + Dexamethasone (Pd)** (n = 57)

Dosing (28-day cycles): Elo: 10 mg/kg IV QW in C1-2, then 20 mg/kg Q4W; P: 4 mg PO Days 1-21; dex: 40 mg PO QW (20 mg if ≥75 yr of age).

ORR: 53% with EPd vs 26% with Pd[1]



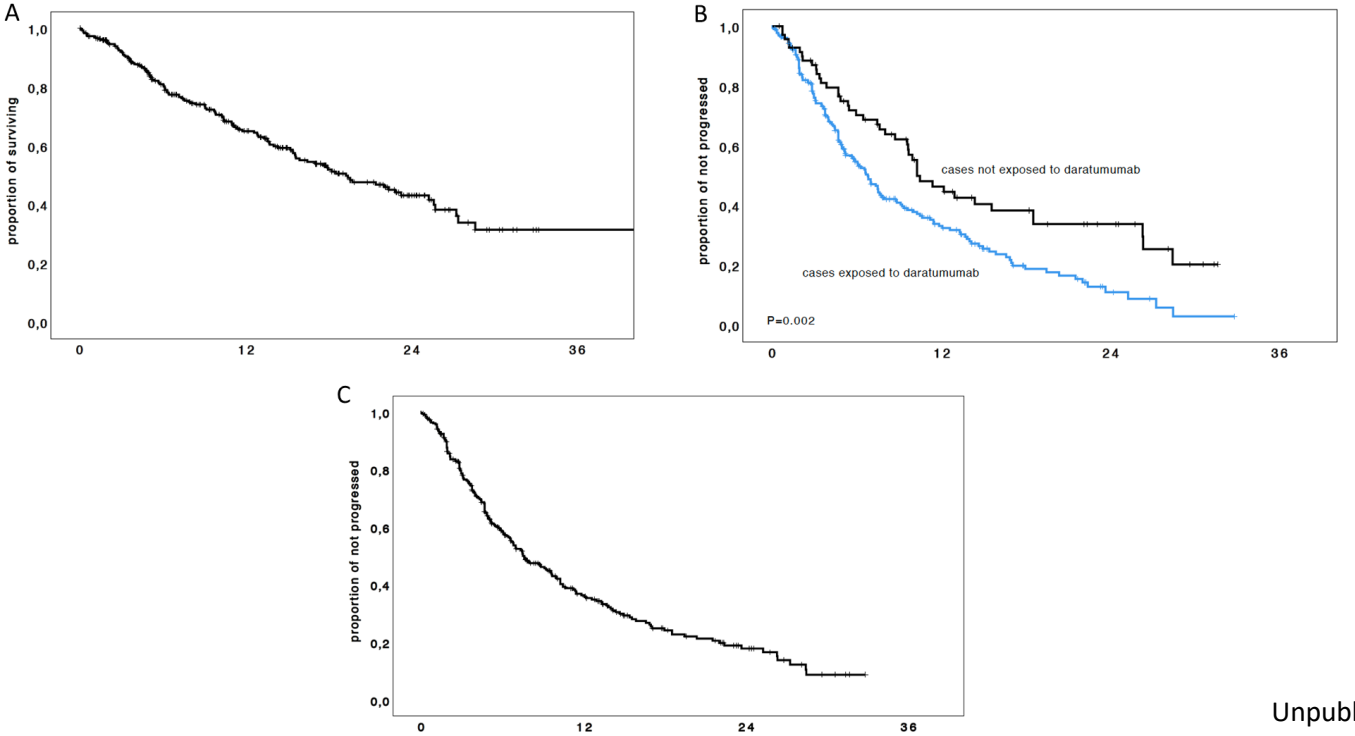


1. Dimopoulos. NEJM. 2018;379:1811. 2. Dimopoulos. JCO. 2022;[Epub].

EloPD in rrMM: extended follow-up of a multicenter, retrospective real-world experience with 305 cases outside of controlled clinical trials

M. Gentile et al EMN 2024

235/305 pts (77%) dara exposed



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Phase III BOSTON: PFS With SVd vs Vd in R/R MM

Prior Therapies, n (%)

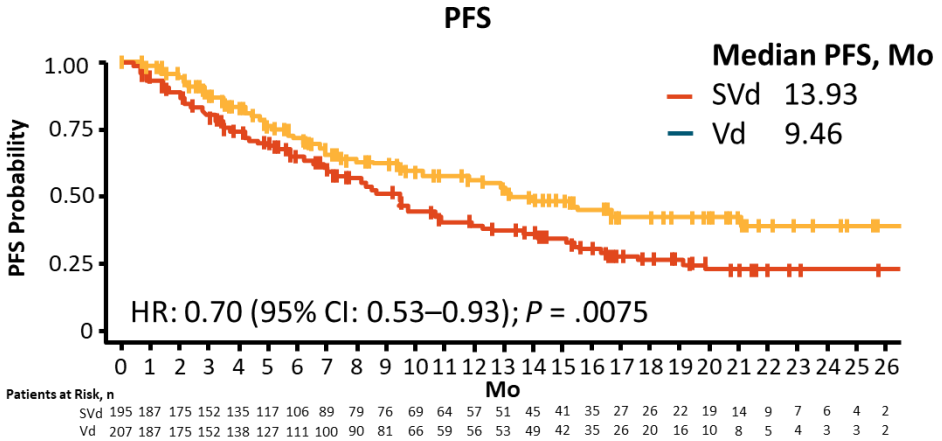
Bortezomib	134 (69)
Carfilzomib	20 (10)
Daratumumab	11 (6)
Lenalidomide	77 (39)
Pomalidomide	11 (6)
Ixazomib	6 (3)
Stem cell transplant[1]	76 (39)

Selinexor + Bortezomib + Dexamethasone (SVd)*
(n = 195)

Bortezomib + Dexamethasone (Vd)‡
(n = 207)

*Dosing (35-day cycles): Seli 100 mg PO D1,8,15,22,29; Bort 1.3 mg/m2 SC Days 1,8,15,22; Dex 20 mg PO twice weekly. ‡Crossover to SVd or Sd permitted if IRC confirmed PD.

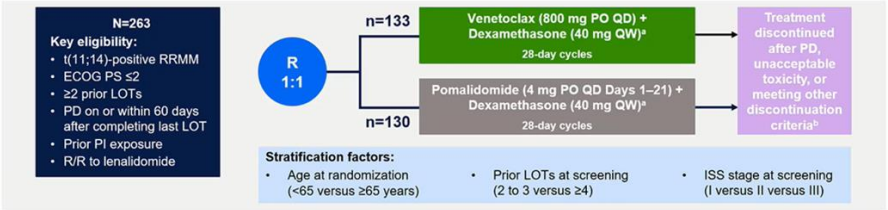
Parameter, %	SVd (n = 195)	Vd (n = 207)
ORR	76.4	62.3
Stringent CR	10	6
CR	7	4
VGPR	28	22
SD	13	19
PD	1	5
MRD negative	5	4



1. Dimopoulos. ASCO 2020. Abstr 8501. 2. Grociski. Lancet. 2020;396:1563.

CANOVA: VenD *vs* PD

CANOVA is an ongoing, randomized, global, multicenter, open-label Phase 3 study of VenDex versus PomDex in t(11;14)-positive RRMM



- **Primary Endpoint**
  - PFS per IRC in the ITT population
- **Analysis Populations**
  - ITT population: all randomized patients
  - Safety analysis set: all patients who received ≥1 dose of study drug
- **Key Secondary Endpoints**
  - ORR and ≥VGPR per IRC (based on IMWG 2016)
  - OS
  - MRD negativity rate ($<10^{-5}$)
  - PRO parameters (**Supplemental Materials**; scan Conclusions slide QR code)
    - Time to deterioration of disease symptoms[c]
    - Time to deterioration of physical functioning[d]

[a]Patients aged ≥75 years received dexamethasone 20 mg QW. Dexamethasone could be administered IV when PO was not possible. [b]Patients who discontinued treatment due to PD were followed for survival and postreatment information; those who discontinued treatment due to a reason other than PD remained on study and continued disease assessments until confirmed PD, death, or withdrawal of consent. [c]As measured by the EORTC QLQ Multiple Myeloma Module 20 disease symptom domain. [d]As measured by the EORTC QLQ Core 30 physical functioning domain.
ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; IMWG, International Myeloma Working Group; IRC, independent review committee; ISS, International Staging System; ITT, intent to treat; LOT, line of therapy; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PI, proteasome inhibitor; PO, oral; PomDex, pomalidomide and dexamethasone; PRO, patient-reported outcome; QD, once daily; QW, once weekly; R, randomized; R/R, relapsed/refractory; RRMM, R/R multiple myeloma; VenDex, venetoclax and dexamethasone; VGPR, very good partial response.

Patient baseline demographics and clinical characteristics

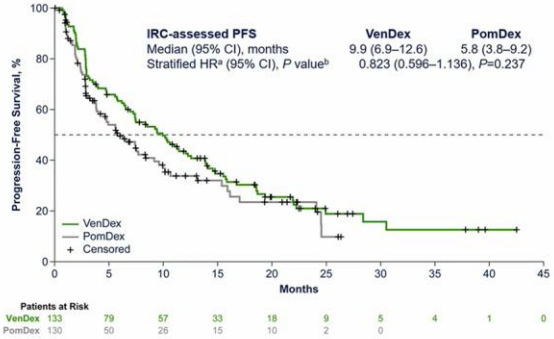
Baseline characteristic	VenDex (n=133)	PomDex (n=130)
Median age (range), years	67 (39–85)	66 (37–89)
<65 years, n (%)	56 (42)	58 (45)
≥65 years, n (%)	77 (58)	72 (55)
≥75 years, n (%)	29 (22)	23 (18)
Male, n (%)	81 (61)	69 (53)
Race, n (%)[a]		
Asian	40 (31)	40 (31)
Black or African American	1 (1)	2 (2)
White	88 (68)	85 (66)
Hispanic or Latino ethnicity, n (%)[a]	6 (5)	4 (3)
ECOG PS, n (%)		
0 to 1	118 (89)	124 (95)
2	15 (11)	6 (5)
IMWG consensus risk[a,b]		
Standard risk, n (%)	91 (93)	88 (92)
High risk, n (%)	7 (7)	8 (8)
Missing, n	35	34
Cytogenetic risk factors, n/N (%)		
del(17p)	14/66 (21)	15/66 (23)
gain(1q) (≥3 copies)	13/51 (25)	17/47 (36)

Baseline characteristic	VenDex (n=133)	PomDex (n=130)
ISS stage at screening, n (%)		
I	67 (50)	60 (46)
II	40 (30)	46 (35)
III	26 (20)	24 (18)
Median number of prior LOTs (range)	3 (2–8)	2 (2–8)
Prior LOTs at screening, n (%)		
2 to 3	98 (74)	97 (75)
2	58 (44)	72 (55)
3	40 (30)	25 (19)
≥4	35 (26)	33 (25)
Prior ASCT, n (%)[a]	69 (97)	74 (99)
Refractory to PI, n (%)	109 (82)	95 (73)
Refractory to IMiD, n (%)	128 (96)	127 (98)
Refractory to lenalidomide	128 (96)	125 (96)
Refractory to anti-CD38 mAb, n (%)	47 (35)	50 (38)
Refractory to PI + IMiD, n (%)	105 (79)	94 (72)
Refractory to PI + IMiD + anti-CD38 mAb, n (%)	40 (30)	42 (32)

[a]Percentages were based on the number of patients with available data. Race information was missing for 6 patients (VenDex, n=4; PomDex, n=2), ethnicity for 2 patients in the VenDex arm, and prior stem cell transplant information was missing for 117 patients (VenDex, n=62; PomDex, n=55). [b]High risk was defined as ISS stage II/III and del(17p) per IMWG consensus on risk stratification (Chng WJ, et al. *Leukemia*. 2014;28(2):269-277).
ASCT, autologous stem cell transplant; ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; ISS, International Staging System; LOT, line of therapy; mAb, monoclonal antibody; PI, proteasome inhibitor; PomDex, pomalidomide and dexamethasone; VenDex, venetoclax and dexamethasone.

The primary endpoint of IRC-assessed PFS was longer with VenDex versus PomDex but did not meet statistical significance

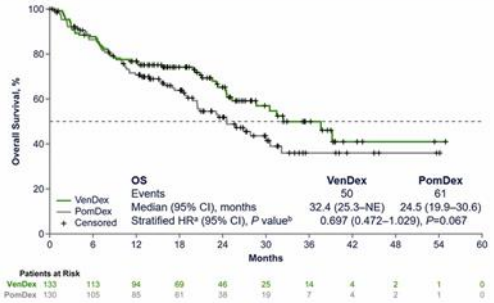
- The median follow-up time was 24.9 months for VenDex and 25.6 months for PomDex
- The concordance[c] between IRC- and investigator-assessed PFS was 94%



[a]HR for PFS was determined by a stratified Cox proportional hazard model. [b]P value was determined by stratified log-rank test. [c]The overall concordance rate was defined as the percentage of patients who had PD by both IRC and investigator and patients who were non-PD by both IRC and investigator among all patients.
HR, hazard ratio; IRC, independent review committee; PD, progressive disease; PFS, progression-free survival; PomDex, pomalidomide and dexamethasone; VenDex, venetoclax and dexamethasone.

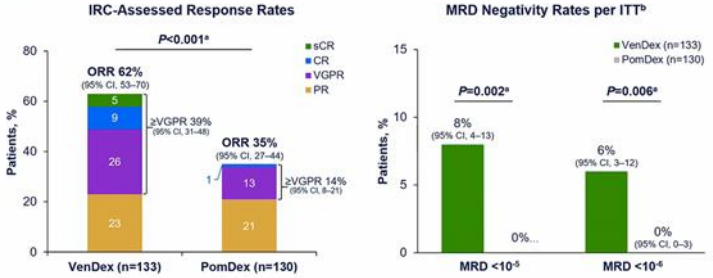
VenDex resulted in numerically longer OS versus PomDex after a median 24.9 months of follow-up

- 62 patients (47%) in the VenDex arm and 78 (60%) in the PomDex arm went on to receive subsequent anti-MM therapy
- The types of posttreatment anti-MM therapies received were generally balanced between VenDex and PomDex (**Supplemental Materials**; scan Conclusions slide QR code)



[a]HR for OS was determined by a stratified Cox proportional hazard model. [b]P value was determined by stratified log-rank test and is presented for descriptive purposes only.
HR, hazard ratio; MM, multiple myeloma; NE, not evaluable; OS, overall survival; PomDex, pomalidomide and dexamethasone; VenDex, venetoclax and dexamethasone.

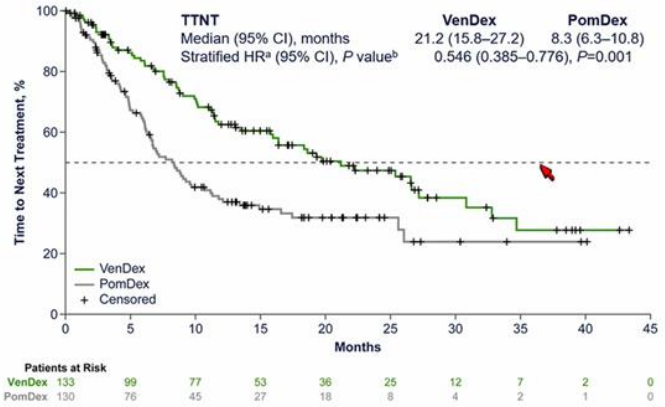
VenDex resulted in higher and deeper responses compared with PomDex



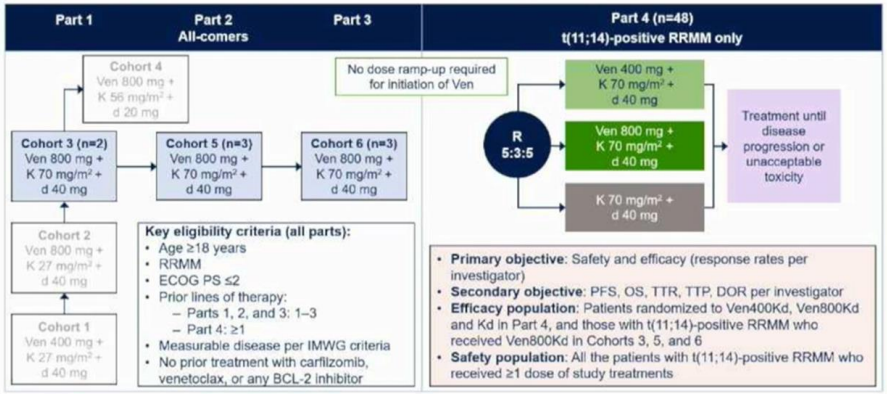
- The median DOR per IRC was 13.8 months (95% CI, 10.1–18.4) with VenDex versus 13.0 months (95% CI, 8.3–23.6) with PomDex

[a]P values were determined by stratified Cochran-Mantel-Haenszel test and are presented for descriptive purposes only. [b]MRD was assessed by NGS (ClonoSEQ assay) in 19 patients (VenDex, n=18; PomDex, n=1) who achieved a best response sCR or CR per IRC assessment. CR, complete response; DOR, duration of response; IRC, independent review committee; ITT, intent to treat; MRD, minimal residual disease; ORR, overall response rate; PomDex, pomalidomide and dexamethasone; PR, partial response; sCR, stringent CR; VenDex, venetoclax and dexamethasone; VGPR, very good PR.

The time to next treatment was longer with VenDex versus PomDex



Ongoing, open-label, multicenter Phase 2 study of venetoclax in combination with Kd in patients with RRMM (NCT02899052)



Ven was administered orally once daily on Days 1–28, with no dose ramp-up. K was administered once weekly on Days 1, 8, and 15 as a 30-minute infusion or per institutional guidelines. Dexamethasone was administered once weekly on Days 1, 8, 15, and 22 (patients aged ≥75 years could receive 20 mg). Antimicrobial prophylaxis included acyclovir for prevention of herpes zoster infection and trimethoprim/sulfamethoxazole while receiving treatment and levofloxacin for the first 90 days of the study and after development of Grade 4 neutropenia.
DOR, duration of response; ECOG PS Eastern Cooperative Oncology Group performance status; IMWG, International Myeloma Working Group; IV, intravenous; Kd, carfilzomib + dexamethasone; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; R, randomization; RRMM, relapsed/refractory multiple myeloma; TTP, time to progression; TTR, time to response; Ven400Kd, venetoclax 400 mg + carfilzomib + dexamethasone; Ven800Kd, venetoclax 800 mg + carfilzomib + dexamethasone

VenKD

Patient baseline characteristics were well balanced between treatment groups

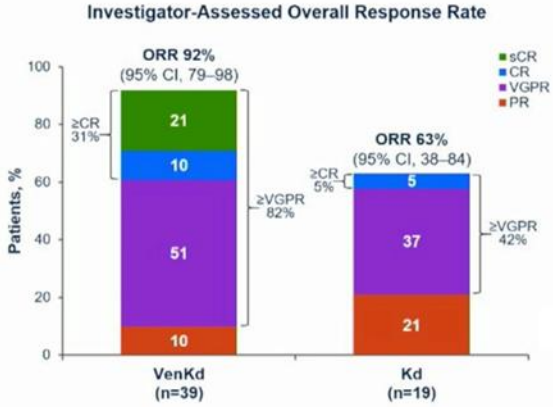
Characteristic (N=58)	Ven400Kd (n=19)	Ven800Kd (n=20)[a]	Kd (n=19)
Median age (range), years	71 (45–84)	71 (47–78)	73 (57–83)
≥65, n (%)	12 (63)	13 (65)	14 (74)
Male, n (%)	10 (53)	11 (55)	10 (53)
Race, n (%)			
White	17 (89)	18 (90)	15 (79)
Black or African American	2 (11)	2 (10)	4 (21)
Other	0	0	0
Geography, n (%)			
North America	6 (32)	12 (60)	12 (63)
Europe	11 (58)	6 (30)	6 (32)
ECOG PS, n (%)			
0	9 (47)	10 (50)	7 (37)
1-2	10 (53)	10 (50)	12 (63)
Median time from initial diagnosis (range), years[b]	4.1 (0.2–17.9)	4.1 (0.4–12.9)	3.4 (0.6–14.1)
ISS stage, n (%)			
I	5 (26)	9 (45)	6 (33)
II	5 (26)	6 (30)	8 (44)
III	8 (42)	5 (25)	2 (11)

Characteristic (N=58)	Ven400Kd (n=19)	Ven800Kd (n=20)[a]	Kd (n=19)
IMWG cytogenetic risk, n (%)			
High risk	3 (16)	3 (15)	3 (16)
Standard risk	11 (58)	15 (75)	7 (37)
Unknown	5 (26)	2 (10)	9 (47)
High-risk cytogenetics, n (%)			
del(17p)	4 (21)	4 (20)	6 (32)
gain(1q) (≥3 copies)	3 (16)	9 (45)	2 (11)
gain(1q) and/or del(17p)	7 (37)	11 (55)	7 (39)
Median number of prior lines of therapy (range)	2 (1–4)	2 (1–5)	2 (1–5)
Prior exposure to PI, n (%)	18 (95)	18 (90)	16 (89)
Refractory to PI	10 (53)	14 (70)	10 (56)
Prior exposure to IMiD, n (%)	17 (89)	17 (85)	16 (89)
Refractory to IMiD	16 (84)	14 (70)	14 (78)
Refractory to lenalidomide	12 (63)	13 (65)	13 (72)
Prior exposure to anti-CD38 mAb, n (%)	4 (21)	6 (30)	9 (50)
Refractory to daratumumab	4 (21)	6 (30)	8 (44)
Refractory to PI + IMiD, n (%)	8 (42)	9 (45)	6 (33)
Refractory to PI + IMiD + anti-CD38 mAb, n (%)	3 (16)	2 (10)	4 (22)

[a]Includes 6 patients treated during Parts 1–3 of the study and 12 patients treated during Part 4. [b]Median time from initial diagnosis to first study drug dose for patients enrolled in Parts 1–3 or randomization for patients enrolled in Part 4.
ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulating drug; IMWG, International Myeloma Working Group; ISS, International Staging System; Kd, carfilzomib + dexamethasone; mAb, monoclonal antibody; PI, proteasome inhibitor; Ven400Kd, venetoclax 400 mg + carfilzomib + dexamethasone; Ven800Kd, venetoclax 800 mg + carfilzomib + dexamethasone

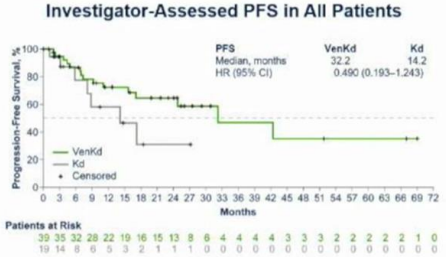
VenKD

Addition of venetoclax to Kd produced an overall response rate of 92% in patients with t(11;14)-positive RRMM



CR, complete response; Kd, carfilzomib + dexamethasone; ORR, overall response rate; PR, partial response; RRMM, relapsed/refractory multiple myeloma; sCR, stringent CR; Ven400Kd, venetoclax 400 mg + carfilzomib + dexamethasone; Ven800Kd, venetoclax 800 mg + carfilzomib + dexamethasone; VenKd, venetoclax + carfilzomib + dexamethasone; VGPR, very good PR.

Addition of venetoclax to Kd resulted in longer median PFS vs Kd alone, and median OS has not yet been reached in any group



	VenKd (n=39)	Kd (n=19)
Median follow-up, months (range)	22.6 (1.8–69.7)	16.8 (0.0–35.4)
Median DOR, months (95% CI)	41.5 (23.9–NE)	16.3 (6.5–NE)
Median TTR, months (95% CI)	1.0 (1.0–1.1)	1.3 (1.0–4.2)
Median TTP, months (95% CI)	32.2 (17.1–NE)	17.2 (5.8–NE)

DOR, duration of response; HR, hazard ratio; Kd, carfilzomib + dexamethasone; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival; TTP, time to progression; TTR, time to response; VenKd, venetoclax + carfilzomib + dexamethasone.

The majority of patients are becoming triple-class (PI + IMiD + CD38) refractory after 2-3 lines of therapy!!

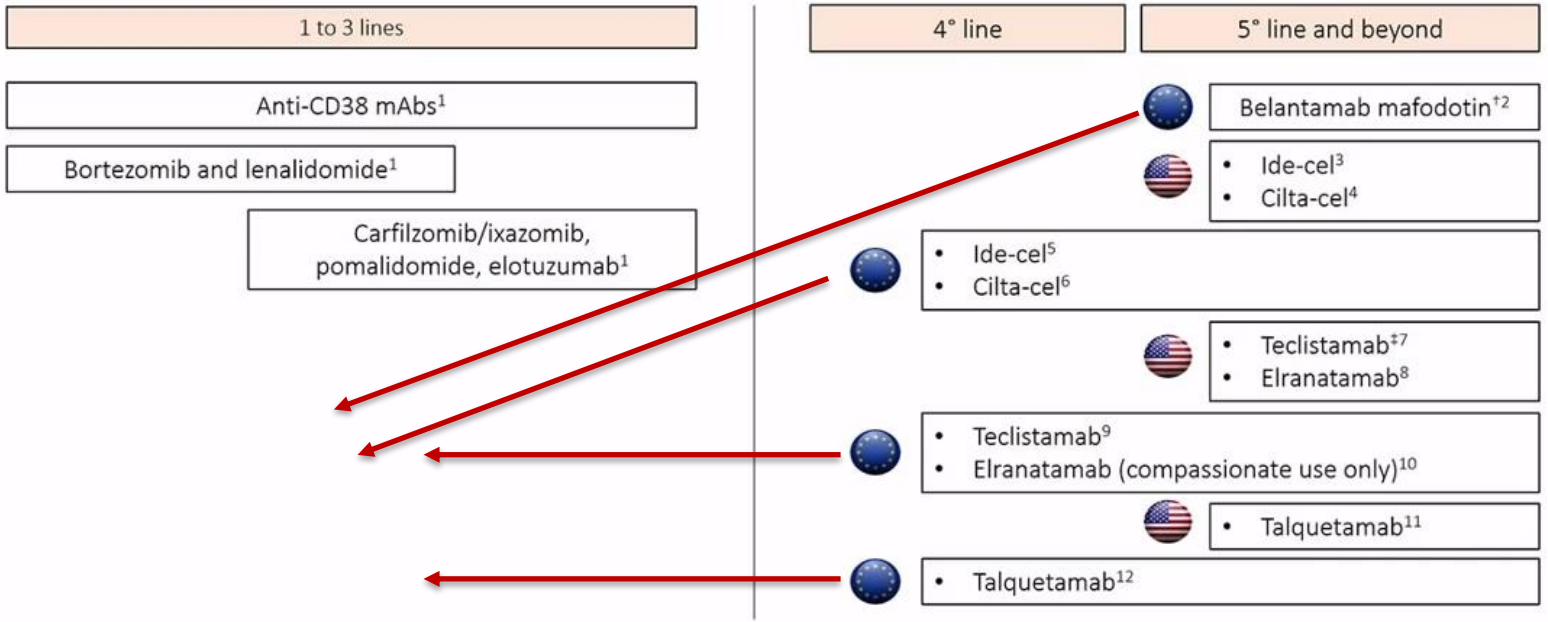
1st line: VRD/VTD-auto-len maintenance until PD

2nd line : Isa-Kd until PD

→ Len + K + CD38 refractory after 2 lines!

P. Moreau, IMS 2023

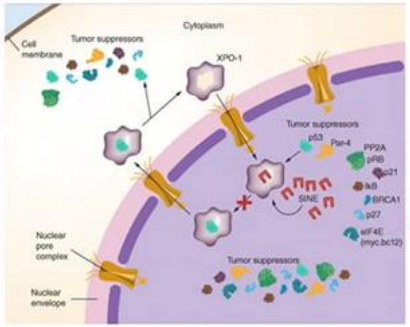
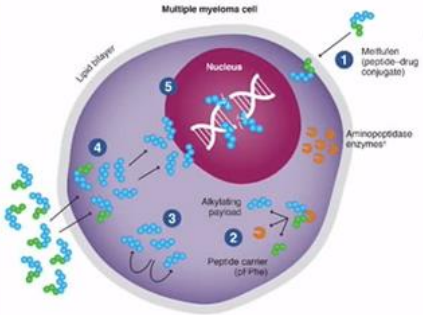
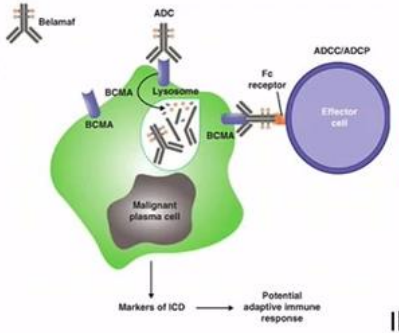
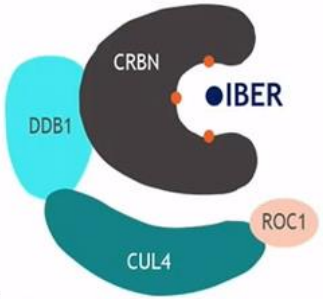
Treatment approach to triple-class exposed MM in the "T-cell redirecting" era*



*Please note that not all treatments shown on this slide are currently approved in this setting for the allocated geographical region; †The EMA's human medicine committee recommended to not renew Blenrep's conditional marketing authorization in September 2023[13]; ‡In the US, patients receiving teclistamab should be hospitalised for 48 hours after administration of all doses within the dosing schedule.[7]
BCMA, B-cell maturation antigen.

1. Dimopoulos MA, et al. Ann Oncol 2021;32:309–322; 2. Blenrep EU SmPC, June 2023; 3 Abecma US PI, March 2021; 4. CARVYKTI US PI, February 2023; 5. Abecma EU SmPC, October 2021; 6. CARVYKTI EU SmPC, July 2023; 7. TECVAYLI US PI, November 2022; 8. ELREXFIO US PI, August 2023; 9. TECVAYLI EU SmPC, August 2023; 10. Pfizer filing acceptance press release. Available at: https://www.pfizer.com/news/press-release/press-release-detail/pfizers-elranatamab-receives-fda-and-ema-filing-acceptance (last accessed August 2023); 11. TALVEY US PI, August 2023; 12. TALVEY EU SmPC, September 2023; 13. Press release. Available at: https://www.ema.europa.eu/en/news/ema-recommends-non-renewal-authorisation-multiple-myeloma-medicine-blenrep (last accessed September 2023).

Novel drugs for the treatment of RRMM. Beyond T-cell redirecting therapies

SELINEXOR	MELFLUFEN	BELANTAMAB-MAFODOTIN	CELMODS
			
mPFS 3.7 m (95% CI 3.0 – 5.3 m)	ORR: 29%; mPFS 4.2m	**mPFS in 2.8 m (95% CI 1.6–3.6)**	**ORR 26.2% (post-BCMA)** **ORR 40.6% post BCMA 50%**
			Iber Mezi
	Not approved in the US	Not approved in the US	Not approved

Recycling of agents or combination chemotherapy options

CC-220-MM-001: study design and objective

Key eligibility criteria (Cohorts E, F, and G)

- RRMM
- ≥ 2 prior regimens (≥ 1 in Cohort F) including LEN/POM and PI
- Disease progression on or within 60 days of last antimyeloma therapy

Study endpoints

Primary:

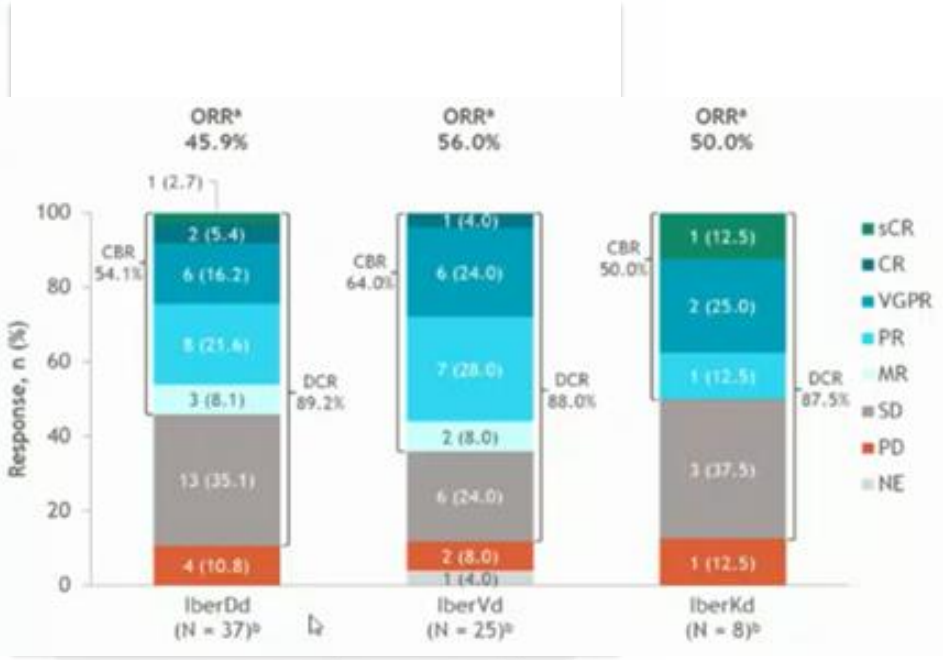
- Determine MTD/RP2D

Secondary:

- Assess safety and preliminary efficacy

Phase 1: dose escalation

- **Cohort A** IBER
- **Cohort B** IBER + DEX
- **Cohort E** IBER + DARA + DEX
- **Cohort F** IBER + BORT + DEX
- **Cohort G** IBER + CFZ + DEX



Iberdomide (IBER) is an investigational agent, currently not approved by any regulatory agency.

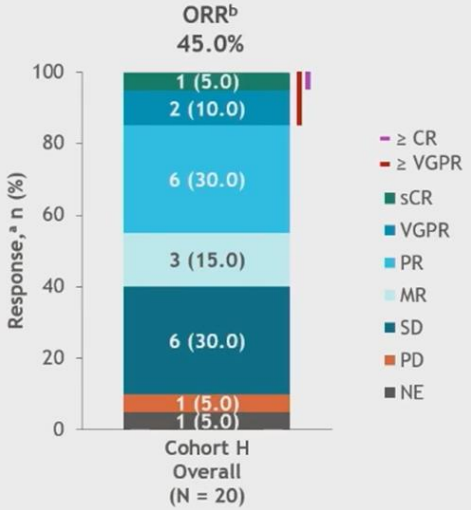
[a]Cohort C (IBER monotherapy expansion) was planned, but not opened; [b]1.6 mg QD.

BORT, bortezomib; CFZ, carfilzomib; DARA, daratumumab; MTD, maximum tolerated dose; NDMM, newly diagnosed MM; PI, proteasome inhibitor; RP2D, recommended phase 2 dose; TE, transplant-eligible; TNE, transplant non-eligible.

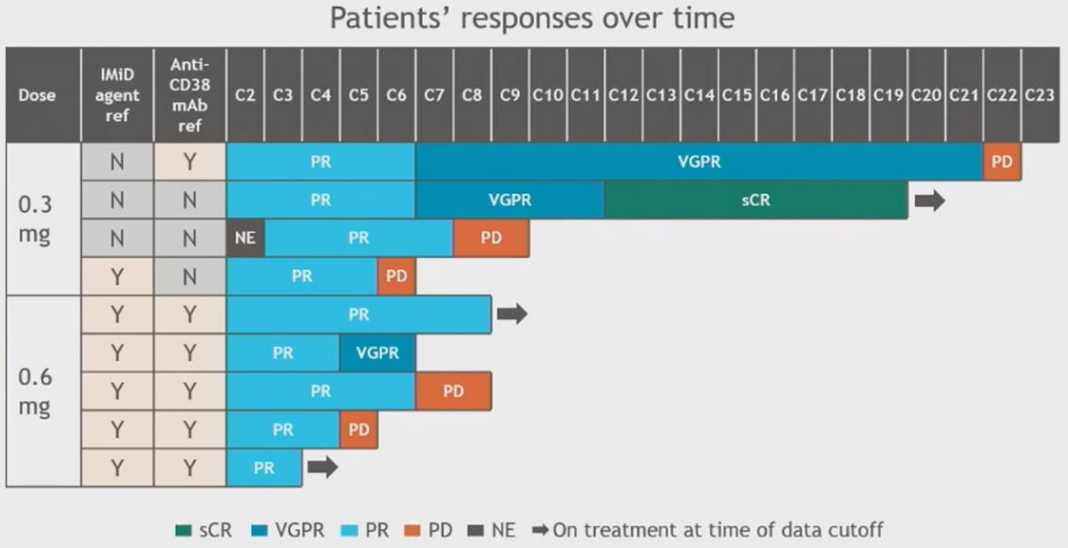
Lonial S, et al. Presented at EHA 2021. HemaSphere. 2021;5 Suppl 2:abstract S187. NCT02773030; Available from https://clinicaltrials.gov/, Accessed May 2023.

CC-92480-MM-002

Efficacy: Cohort H (MeziEd) CC-92480-MM-002 phase 1/2 trial



Median time to first response (range),[c] months	0.95 (0.9-2.8)
Median DOR (95% CI),[c] months	5.0 (3.7-NR)
Median follow-up time (range),[d] months	7.1 (2.0-21.7)



Sixteen (80%) patients were refractory to anti-CD38 mAbs
≥ 2 prior LOT, R refr 70%, PI refr 45%, TCE 30%

[a]Data cutoff: July 6, 2023; [b]PR or better; [c]Data derived from the safety population; [d]Data derived from the full analysis population.
Ref, refractory.

Richardson PG, et al. ASH 2023 [Abstract #1013]

ALGONQUIN

≥ 1 LOT, RP2D BM 2.5 mg every 8W

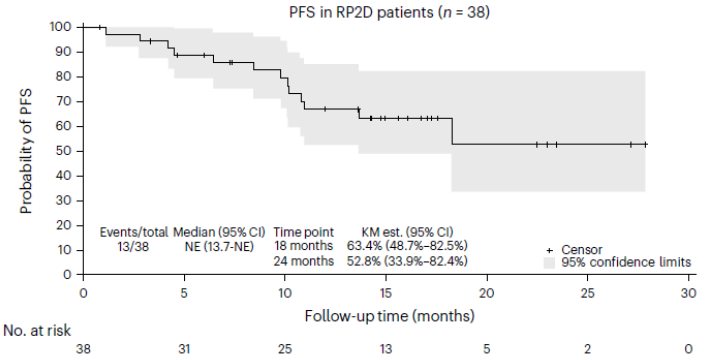
Belantamab mafodotin, pomalidomide and dexamethasone in refractory multiple myeloma: a phase 1/2 trial

nature medicine January 2024

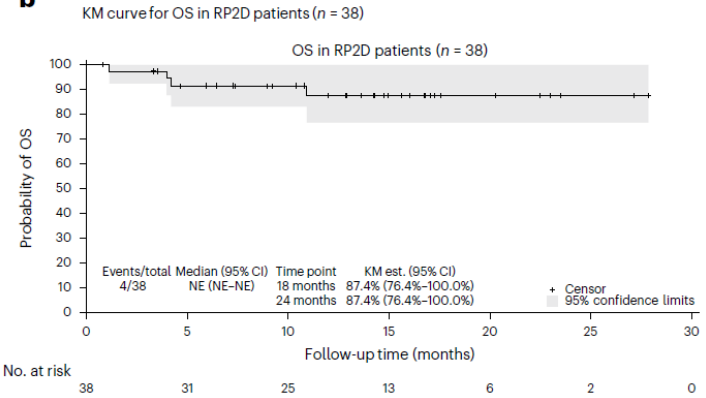
≥ 1 LOT (median 3; range 1-6)

Refractory to, n (%)			
Lenalidomide	58 (95.1)	36 (94.7)	84 (96.6)
PI	53 (86.9)	32 (84.2)	75 (86.2)
Anti-CD38	36 (59.0)	30 (78.9)	58 (66.7)
Triple-class refractory, n (%)	30 (49.2)	24 (63.2)	48 (55.2)

Efficacy outcomes	Part 1	RP2D	All
	n=61	*n*=38	*N*=87
ORR, *n*/*N* (%)	53/59 (89.8)	29/34 (85.3)	71/81 (87.7)
CR/sCR, *n*/*N* (%)	20/59 (33.9)	11/34 (33.3)	27/81 (33.3)
VGPR, *n*/*N* (%)	24/59 (40.7)	14/34 (42.4)	32/81 (39.5)
PR, *n*/*N* (%)	9/59 (15.3)	4/34 (11.8)	12/81 (14.8)
mPFS, months (95% CI)	20.0 (15.7–30.0)	NYR (13.7 to NYR)	21.8 (17.8- 32.5)
mOS, months (95% CI)	34.0 (24.0 to NYR)	NYR (NYR to NYR)	34.0 (24.4 to NYR)
Median follow-up, months (range)	17.1 (0.9–42.5)	13.9 (1.1–28.2)	14.5 (0.9–42.5)



b

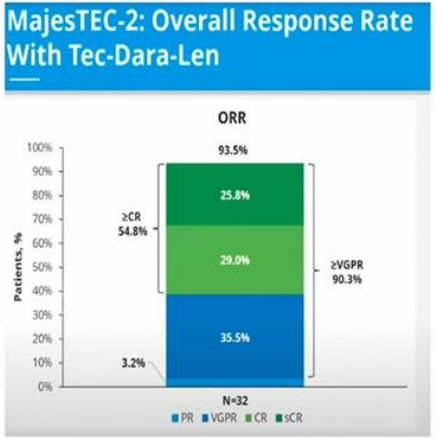


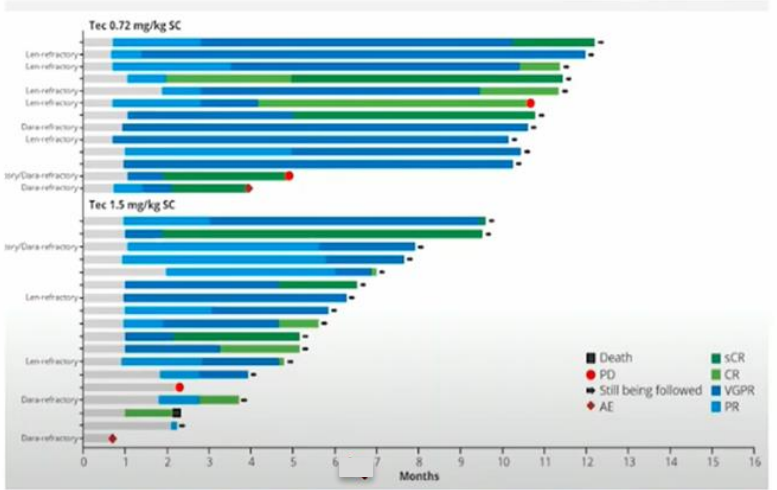
AEs, maximum grade	RP2D
	n=38
Keratopathy, grade 2, *n* (%)	4 (10.5)
Keratopathy, grade 3–4, *n* (%)	20 (52.6)
Keratopathy recovery from grade ≥2 to grade 1, *n*/*N* (%)	13/24 (54.2)
Decrease in BCVA, grade 2, *n* (%)	9 (23.7)
Decrease in BCVA, grade 3–4, *n* (%)	21 (55.3)
BCVA recovery from grade ≥2 to grade 1, *n*/*N* (%)	15/30 (50.0)
Blurred vision (patient reported), grade 2, *n* (%)	2 (5.3)
Blurred vision (patient reported), grade 3–4, *n* (%)	5 (13.2)
Other ocular toxicity, grade 2, *n* (%)	4 (10.5)
Other ocular toxicity, grade 3–4, *n* (%)	0 (0.0)

Teclistamab

Median (range) prior LOT	2 (1–3)	2 (1–3)
Prior stem cell transplant, n (%)	8 (61.5)	18 (94.7)
Prior proteasome inhibitor, n (%)	13 (100)	19 (100)
Prior immunomodulatory drug, n (%)	13 (100)	19 (100)
Prior anti-CD38 mAb, n (%)	5 (38.5)	5 (26.3)
Refractory status, n (%)		
To lenalidomide	6 (46.2)	3 (15.8)
To an anti-CD38 mAb[b]	3 (23.1)	3 (15.8)

BCMA bispecifics in earlier relapsed MM (1-3 prior lines)





81% of responders (n=31) progression free at med f/up 8 months

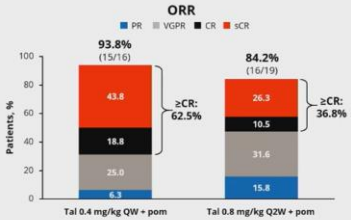
Searle et al, ASH 2022, #160

Penn Medicine

Key eligibility criteria[a]

- Measurable MM
- ≥2 prior lines of therapy including a PI and an IMiD
- ECOG PS 0–1
- Prior pomalidomide and prior T-cell redirection therapy (CAR-T and BsAb) permitted
- No prior GPRC5D therapy

MonumenTAL-2 (Tal+Pom): High ORR With Rapid and Deep Responses



	Tal 0.4 mg/kg QW + pom (n=16)	Tal 0.8 mg/kg Q2W + pom (n=19)
Median follow-up, months (range)	15.0 (1.2–19.0)	11.1 (1.2–14.8)
Median time to first response, months (range)	1.7 (0.9–3.3)	1.2 (0–4.8)

- ORRs were consistent across patient subgroups
  - 100% (3/3) in CAR-T–exposed patients in the QW cohort (no patients had CAR-T exposure in Q2W)
  - 100% (5/5 in QW, 3/3 in Q2W) in pomalidomide-exposed patients in both cohorts
  - 50% (1/2 in QW) and 67% (2/3 in Q2W) in patients with EMD
  - 80% (4/5 in QW) and 75% (3/4 in Q2W) in patients with high-risk cytogenetics

Data cut-off date: October 11, 2023.
CAR, chimeric antigen receptor; CR, complete response; EMD, extramedullary disease; ORR, overall response rate; pom, pomalidomide; PR, partial response; Q2W, every other week; QW, weekly; sCR, stringent complete response; tal, talquetamab; VGPR, very good partial response.

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

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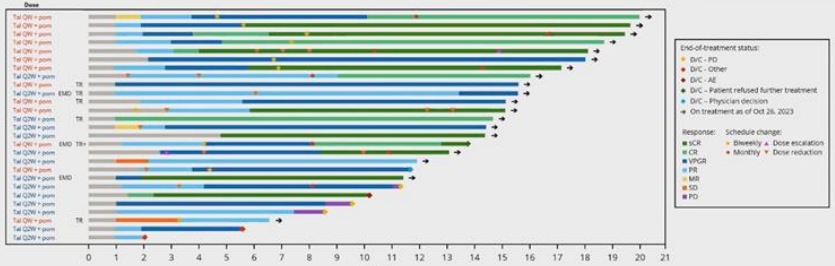
MonumenTAL-2 (Tal+Pom): Responses Deepened Over Time



	Tal 0.4 mg/kg QW + pom	Tal 0.8 mg/kg Q2W + pom
Median PFS, mo (95% CI)	NR (14.09–NR)	NR (7.43–NR)
9-month PFS rate, % (95% CI)	93.8 (63.2–99.1)	75.5 (46.4–90.3)
Median DOR, mo (95% CI)	NR (12.0–NR)	NR (7.4–NR)
9-month DOR rate, % (95% CI)	100.0 (100.0–100.0)	83.9 (49.4–95.7)

Due to open inquiries on response data, 4 patients were excluded from the swimmer plot. Data cut-off date: October 11, 2023.
AE, adverse event; CR, complete response; D/C, discontinue; DOR, duration of response; EMD, extramedullary disease patient; MR, minimal residual; NR, not reached; PD, progressive disease; PFS, progression-free survival; PR, partial response; pom, pomalidomide; Q2W, every other week; QW, weekly; sCR, stringent complete response; SD, stable disease; tal, talquetamab; TR+, penta-refractory patient; TR, triple-refractory patient; VGPR, very good partial response.

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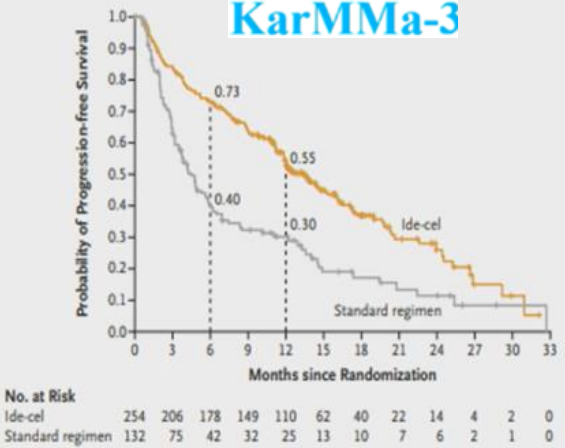
Talquetamab

BCMA CAR T Cells in Earlier Lines of Treatment

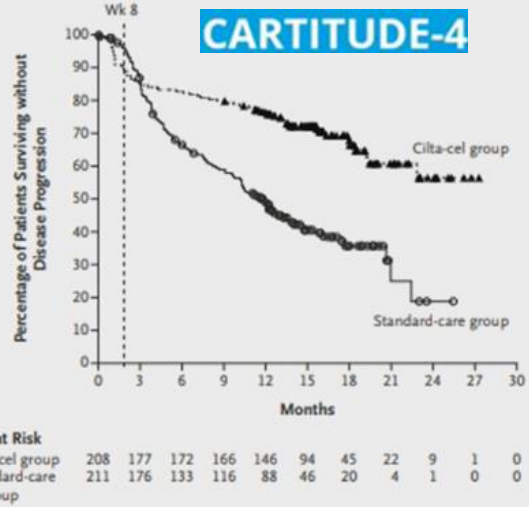
KarMMa-3



Median PFS: 13.3 vs. 4.4 months

2-4 prior lines, 2/3 TCR, 42% HR

CARTITUDE-4



Median PFS: Not reached vs. 11.8 months

1-3 prior lines, R 100%, PI 49%, Dara 23%, TCR 11%, HR 59%

Rodriguez-Otero et al. NEJM 2023; San-Miguel et al. NEJM 2023