Integrando la inmunoterapia en el tratamiento del MM: 3º línea

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Conflict of interest disclosure

I have received honoraria from lectures and participation in advisory boards from: Celgene-BMS, Janssen, Sanofi, Kite Pharma, Abbvie, Oncopeptides, Amgen, Takeda and GSK.

Beyond 2-3 line

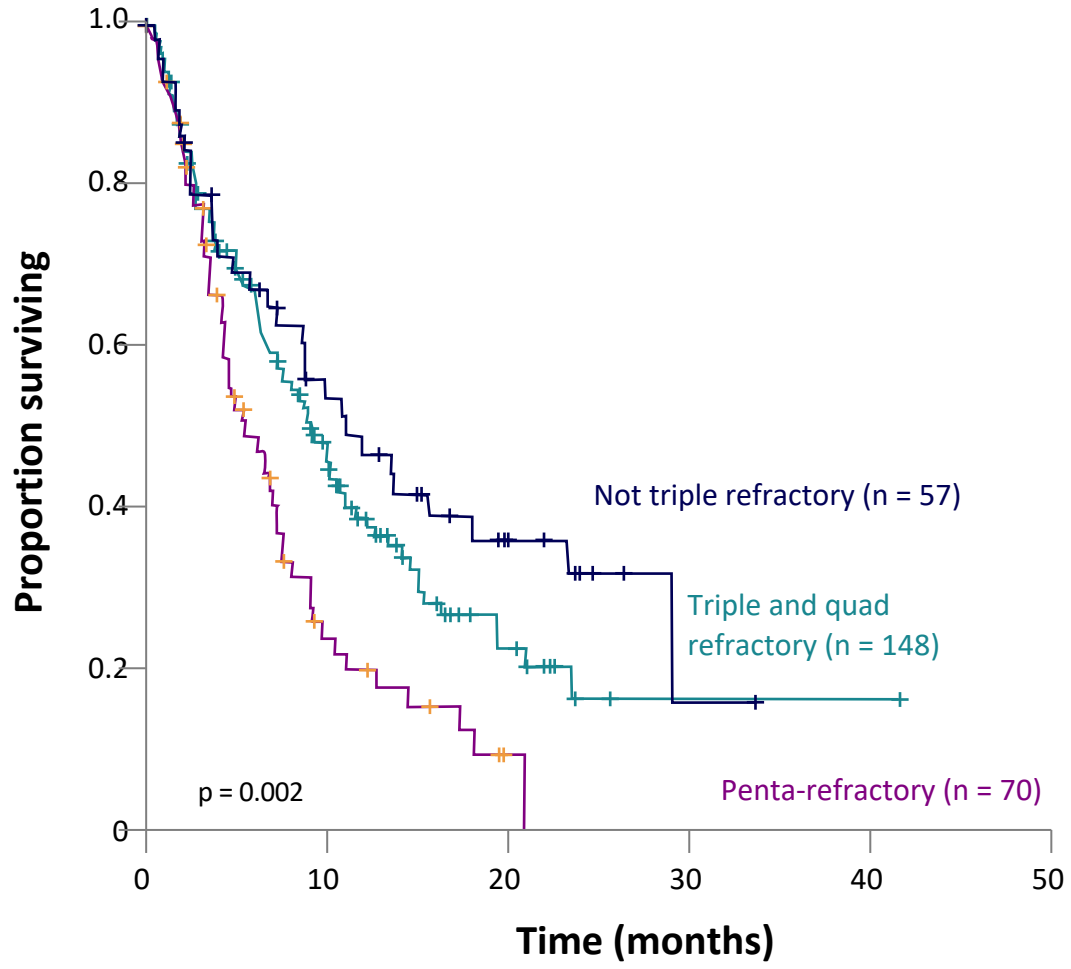
The issue of Triple-class exposed/refractory patients

Outcomes in triple-class refractory patients
MAMMOTH study

- 275 MM patients refractory to anti-CD38 mAbs
- mOS from refractoriness to CD38:
  - all patients: 8.6 months
  - "non-triple-refractory": 11.2 months
  - "triple- and quad-refractory": 9.2 months
  - "penta-refractory": 5.6 months

- 249 patients received further treatment:
  - mPFS: 3.4 months
  - mOS: 9.3 months

OS according to refractoriness



- Non-triple-refractory: refractory to 1 CD38 mAb, and not both PI and IMiD compound
- Triple- and quad-refractory: refractory to 1 CD38 mAb + 1 IMiD compound + 1 PI; or 1 CD38 mAb + 1 PI + 1 or 2 IMiD compounds; or 1 CD38 mAb + 1 or 2 PIs + 1 IMiD compound
- Penta-refractory: refractory to 1 CD38 mAb + 2 PIs + 2 IMiD compounds

mOS, median overall survival; mPFS, median progression-free survival.

Gandhi UH, et al. Leukemia. 2019;Mar 11 [Epub ahead of print].

Real-world outcomes in triple-class exposed RRMM
Prospective observational LocoMMotion study

Baseline Characteristics

Characteristics	N=225
Age, median (range) years	68.0 (41.0–89.0)
Time from initial MM diagnosis,[a] median (range) years	6.0 (0.3–22.8)
Follow-up time, median (range) months	3.7 (0–12.7)
Number of prior lines of therapy, median (range)	4.0 (2.0–13.0)
Triple-class exposed,[a] n (%)	225 (100)
Refractory status, n (%)	
Any PI	177 (78.7)
Any IMiD	212 (94.2)
Any anti-CD38 mAb	209 (92.9)
Triple-class refractory[b]	166 (73.8)
Refractory to last line of prior therapy, n (%)	208 (92.4)

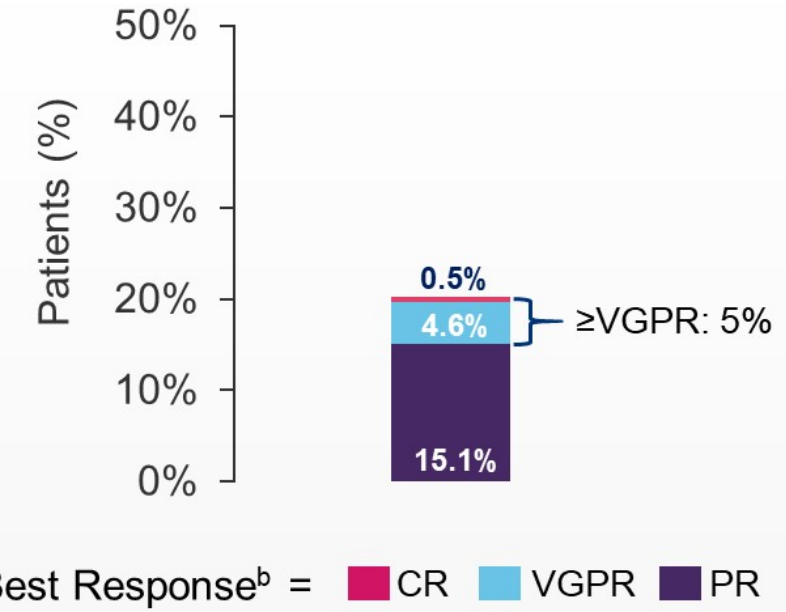
[a]Out of 222 patients at the time of analysis; [b]PI, IMiD, and anti-CD 38 mAb.

Antimyeloma SOC in Patients With RRMM Receiving ≥3 Prior Lines of Therapy

SOC Treatment[a], n(%)	N=225
Cytotoxic agents[b]	130 (57.8)
PI	124 (55.1)
IMiD	104 (46.2)
Anti-CD38 mAbs	23 (10.2)
HDAC inhibitors	11 (4.9)
Anti-SLAMF7 mAbs	8 (3.6)
Other[c]	11 (4.9)

[a]Only the most common classes of SOC treatment regimens are shown for brevity as there were >80 different regimens of SOC treatment in this patient population; [b]Includes alkylating agents, anthracyclines, topoisomerase inhibitors and mitotic inhibitors; [c]Includes venetoclax-based regimens, belantamab mafodotin–based regimens, selinexor-based regimens, and rituximab that was used in 1 patient in combination with bendamustine; additionally, 5 patients had a salvage ASCT.

ORR[a] Following Real-Life SOC Salvage Therapy = 20.1% (44/219)



Safety:
- **Treatment-emergent adverse events were reported in 148 (65.8%) patients, 95 (42.2%) were grade ≥3**
- **Fifteen patients (7%) died during the study due to treatment-emergent adverse events**

Mateos MV et al. ASCO 2021. Poster presentation. Abstract #8041

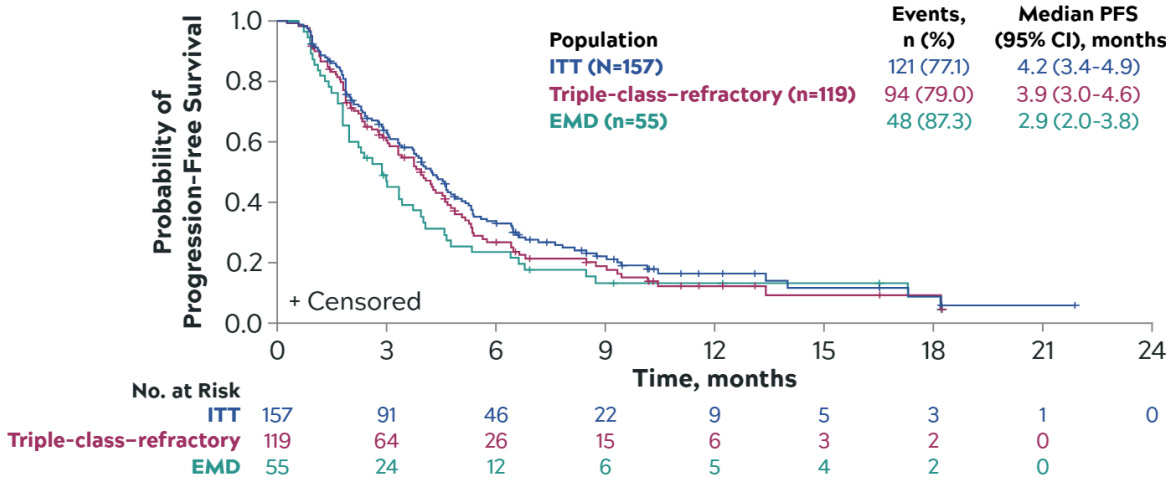
Phase 2 HORIZON (OP-106) Study of Melflufen + Dexamethasone in RRMM: *Updated Efficacy*

Key inclusion: ≥ 2 prior lines, refractory to last line. Refractory to Pom or Dara.

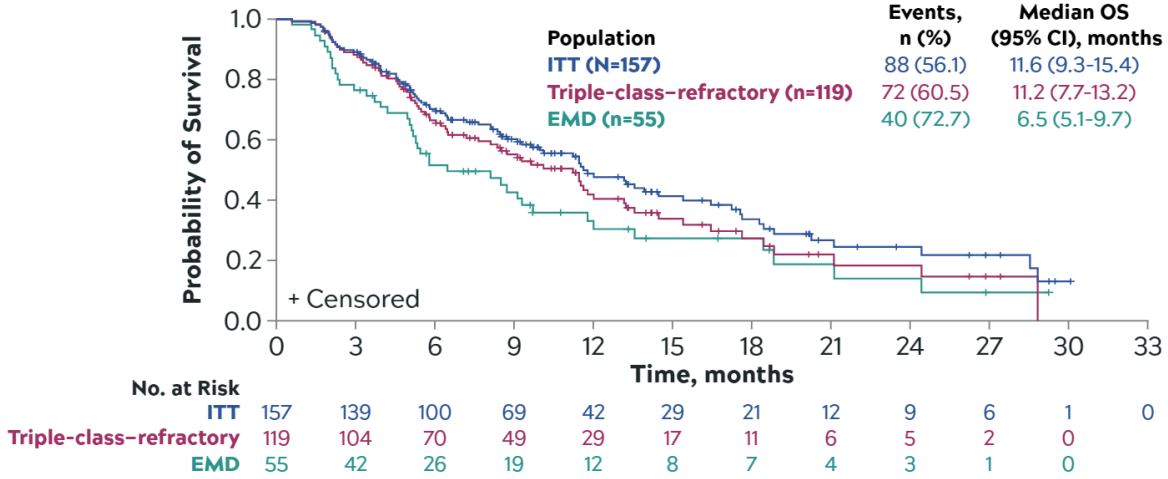
- Median age: 65 years
- Median 5 prior lines (2-12)
- 38% patients had high-risk cytogenetics
- **80%** refractory to **anti-CD38**
- **76% triple** refractory (**PI + IMiD + anti-CD38**); 59% refractory to prior alkylator therapy.

ORR: Overall 29%; Triple-class refractory 26%; EMD 24%

PFS



OS



Richardson P et al. EHA 2020. Presentation EP945

OCEAN (OP-103): Phase III study comparing Melflufen-Dex vs Pom-Dex in RRMM: *Top line results (n=495)*

Key inclusion: 2-4 prior lines. Prior exposure to Len and PI. Refractory to Len. Refractory to last line.

Treatment schedule:

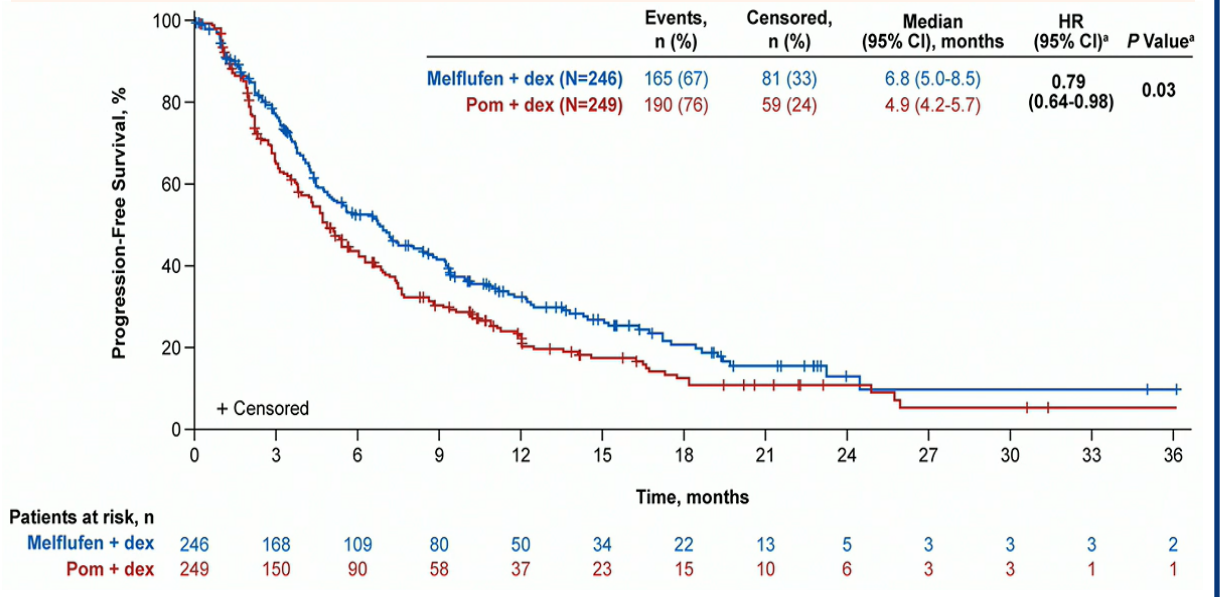
- Melflufen 40mg + weekly dex 40mg, Q4W
- Pom 4mg 1-21 day + Dex weekly 40mg Q4W.

Median nº PL: 3 in each group
51% prior ASCT in Melf-Dex vs 48% Pd

ORR Melf-Dex 33% vs Pom-Dex 27%

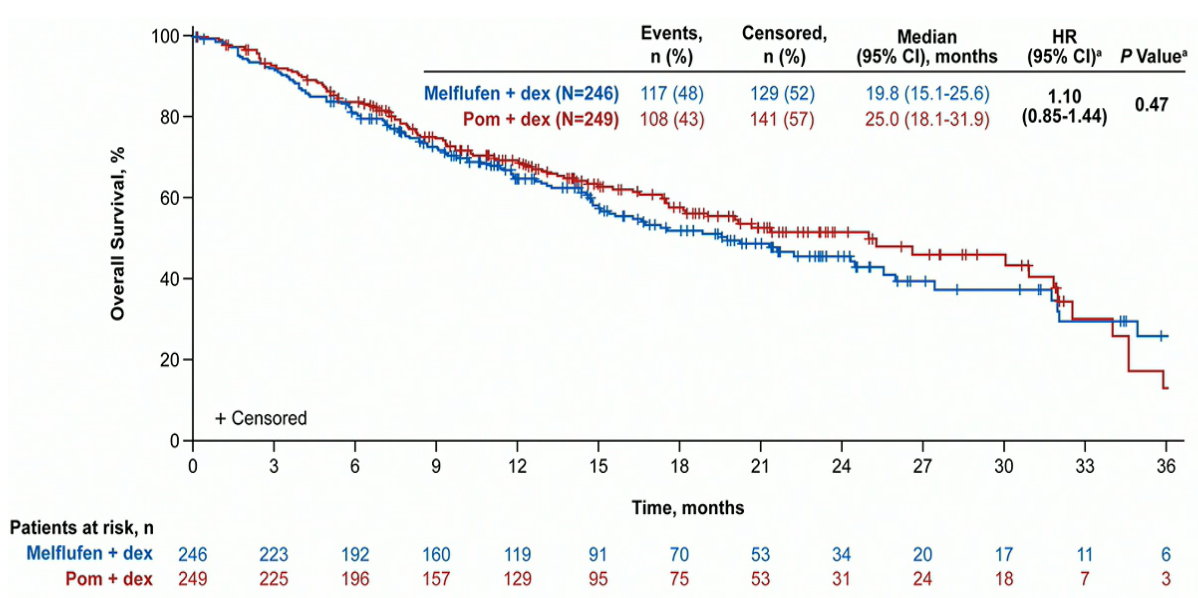
Primary endpoint: PFS
mPFS 6.8 m (melf) vs 4.9m (Pd)

Median FUP: 15.5 m (melf-d) and 16.3 m (Pd)



Key secondary endpoint: OS
mOS 19.8 m (melf) vs 25m (Pd)

HR 1.1 (0.85 – 1.44) p-value= 0.47



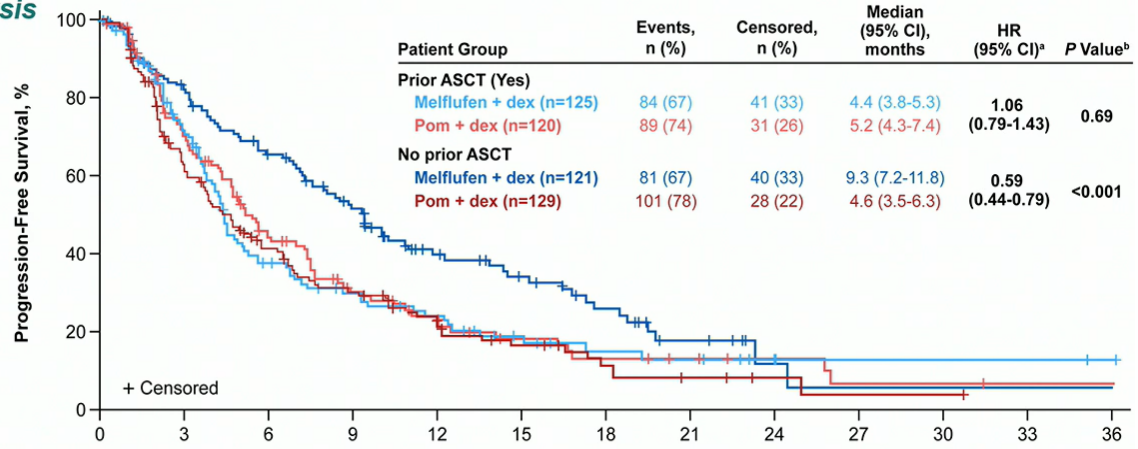
- Schjesvold F et al, IMW 2021 #OAB50

OCEAN (OP-103): Phase III study comparing Melflufen-Dex vs Pom-Dex in RRMM: *Top line results (n=495)*

Key secondary endpoint: OS
mOS 19.8 m (melf) vs 25m (Pd)
HR 1.1 (0.85 – 1.44) p-value= 0.47

PFS by prior ASCT
mPFS 9.3 m (melf) vs 4.0m (Pd) in NON-Prior ASCT
mPFS 4.4m (melf) vs 5.2m (Pd) in Prior ASCT

nalysis

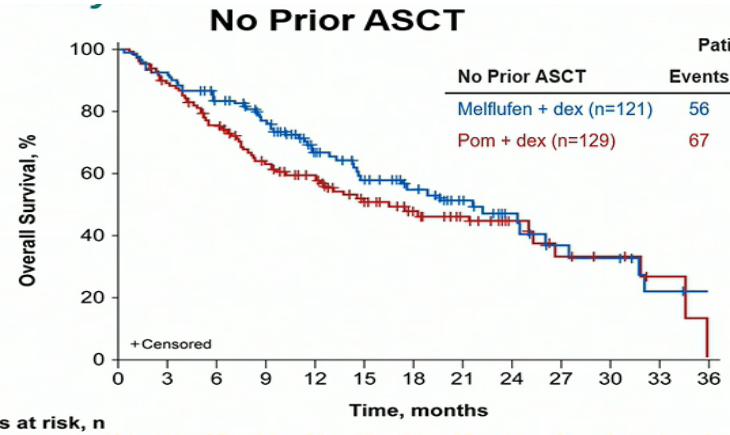


Patient Group	Events, n (%)	Censored, n (%)	Median (95% CI), months	HR (95% CI)[a]	*P* Value[b]
Prior ASCT (Yes)					
Melflufen + dex (n=125)	84 (67)	41 (33)	4.4 (3.8-5.3)	1.06 (0.79-1.43)	0.69
Pom + dex (n=120)	89 (74)	31 (26)	5.2 (4.3-7.4)		
No prior ASCT					
Melflufen + dex (n=121)	81 (67)	40 (33)	9.3 (7.2-11.8)	0.59 (0.44-0.79)	<0.001
Pom + dex (n=129)	101 (78)	28 (22)	4.6 (3.5-6.3)		

Patients at risk, n

Prior ASCT (Yes)													
Melflufen + dex	74	36	26	19	11	7	6	3	2	2	2	1	0
Pom + dex	77	45	26	18	11	8	6	4	2	2	1	1	1
No prior ASCT													
Melflufen + dex	94	73	54	31	23	15	7	2	1	1	1	1	0
Pom + dex	73	45	32	19	12	7	4	2	1	1	0	0	0

No Prior ASCT

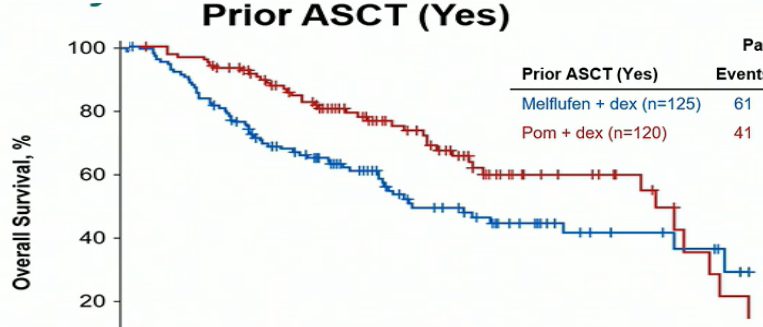


No Prior ASCT	Patients, n: Events	Censored	Median (95% CI), months	HR (95% CI)[a]; *P* Value[b]
Melflufen + dex (n=121)	56	65	21.6 (14.6-26.0)	0.78 (0.55-1.12) *P*=0.1766
Pom + dex (n=129)	67	62	16.5 (10.3-25.3)	

Patients at risk, n

Melflufen + dex	121	111	97	84	55	45	34	25	14	9	8	4	3
Pom + dex	129	112	91	70	59	43	32	24	13	8	6	2	0

Prior ASCT (Yes)



Prior ASCT (Yes)	Patients, n: Events	Censored	Median (95% CI), months	HR (95% CI)[a]; *P* Value[b]
Melflufen + dex (n=125)	61	64	16.7 (14.8-32.0)	1.61 (1.09-2.40) *P*=0.0170
Pom + dex (n=120)	41	79	31.0 (20.2-34.1)	

In conclusion, results from OCEAN suggest that Melflufen-Dex may become a potential treatment for patients with Len-Ref RRMM who have received 2-4 prior lines and who have not received prior ASCT.

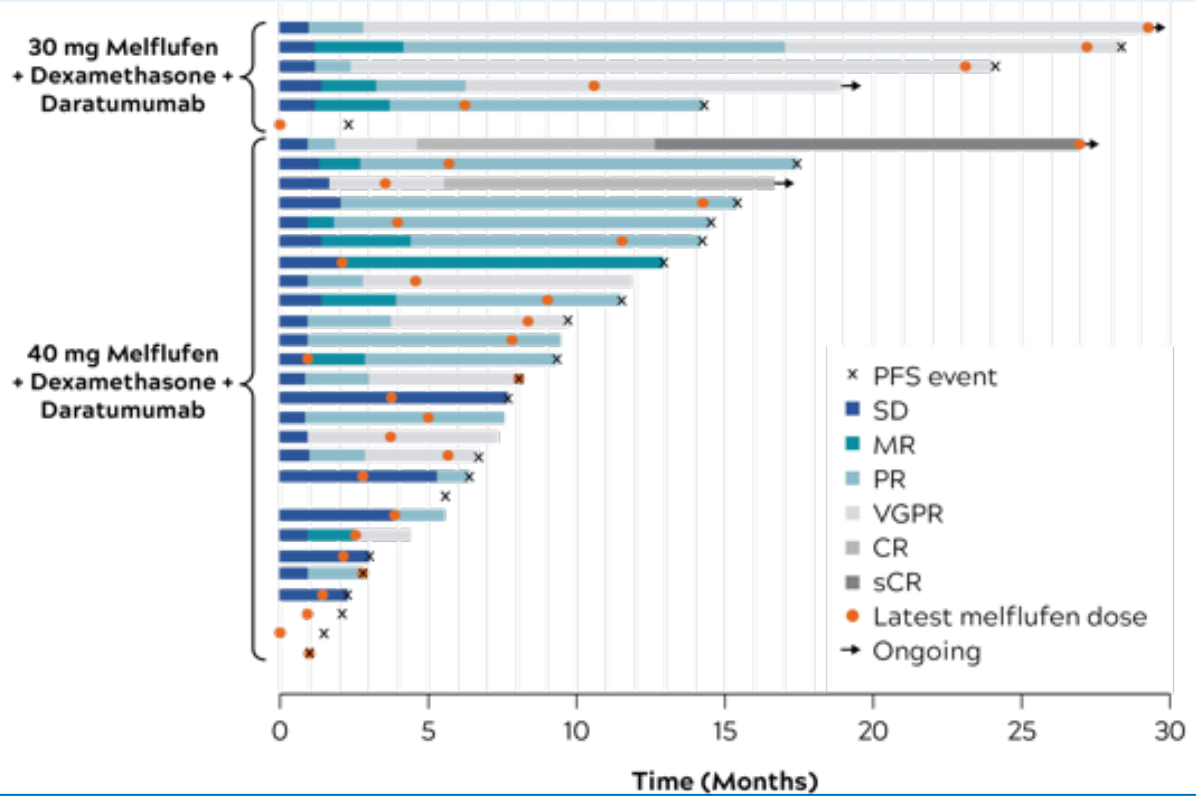
- Schjesvold F et al, IMW 2021 #OAB50

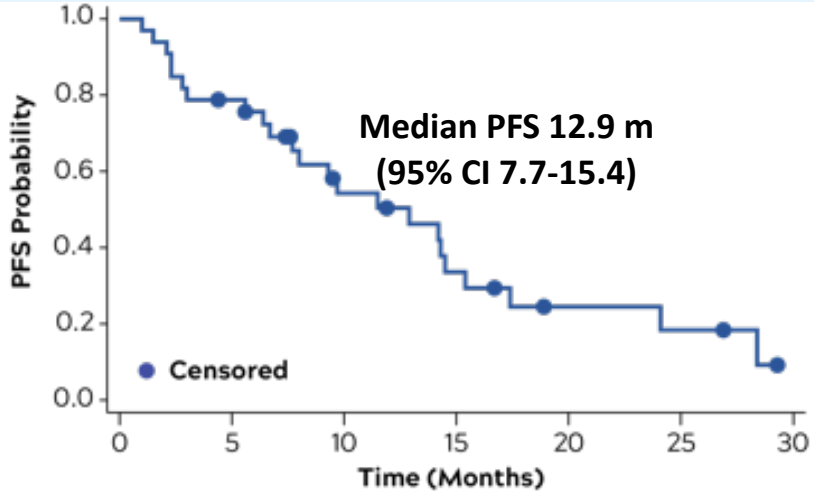
Phase 2 ANCHOR study: Melflufen in combination with Daratumumab (N=33) Median FUP 18.4 m.

Key inclusion: 1-4 prior lines. Refractory (or intolerant) to PI and IMID. No prior anti-CD38 therapy.

- Median age: 63 y (35-78)
- 54% patients had high-risk cytogenetics
- **Median nº of 2 PL: 64% were IMID-Ref; 45% PI-Ref and 36% Double refractory**

ORR 73% (at the dose of 30mg: 83%)





The OS data were immature at the median follow-up of 18.4 months

- Grade ≥3 TRAEs were present in 88% of the patients. Most frequent grade ≥3 TREAEs were: Thrombocytopenia (73%) and Neutropenia (67%)
- 15 patients (45%) experienced SAEs, most commonly pneumonia (12%)
- 4 AEs with fatal outcome.

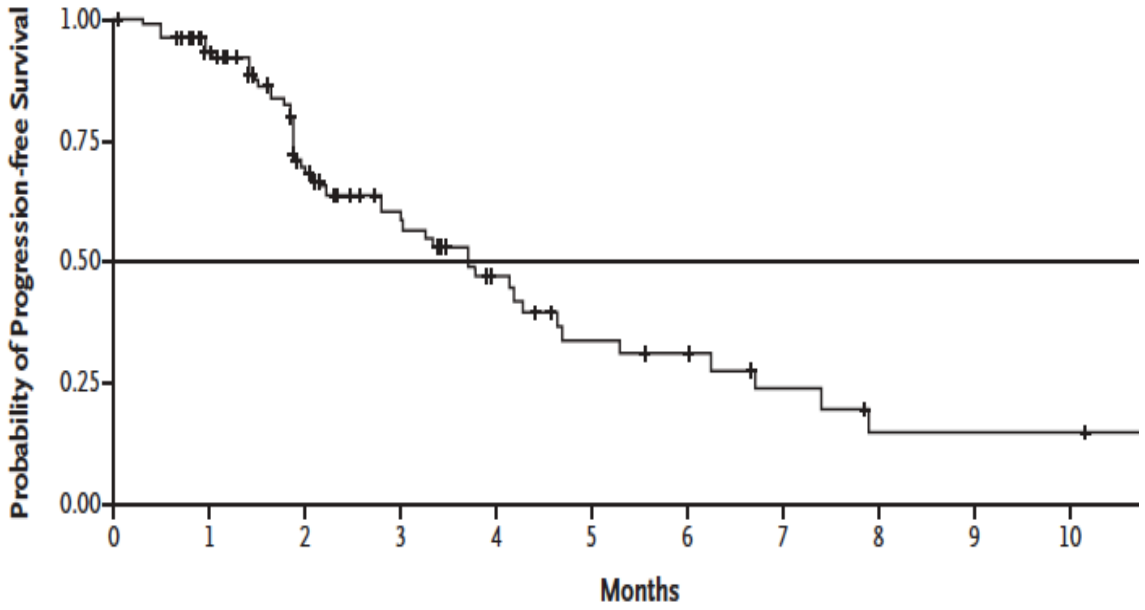
Ocio EM et al. ASH 2020. Abstract

Selinexor + dexamethasone in penta-refractory RRMM
phase 2 STORM study (n=122)

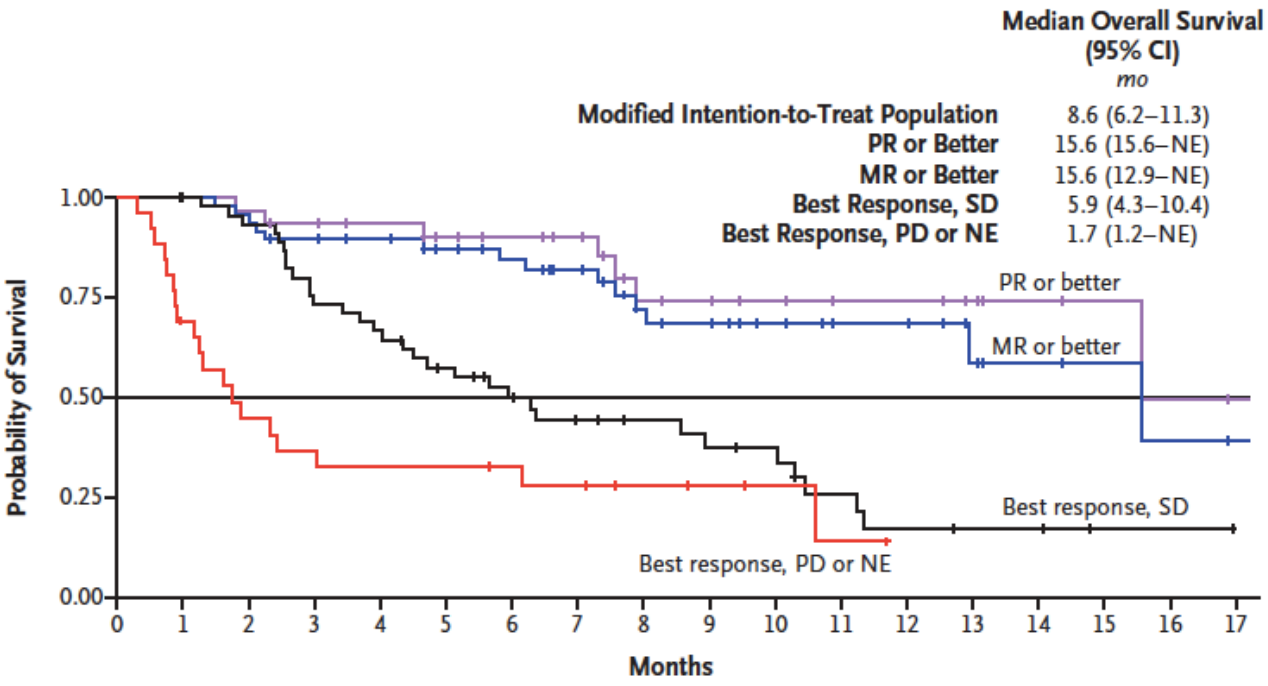
Key inclusion: Penta-exposed. Triple-class refractory and refractory to last line.
Median nº PL: 7

ORR 26% and CBR (≥MR) 39%(95% CI, 31 to 49).

Progression-free survival
mPFS 3.7 m(95% CI, 3.0 to 5.3)



Overall survival by response



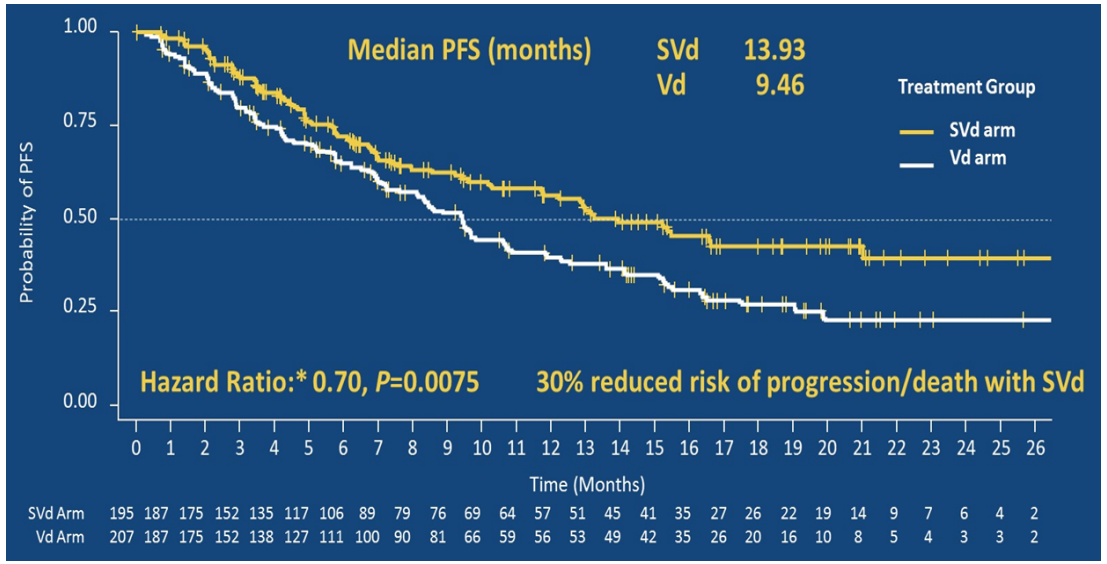
- The most common TEAEs: thrombocytopenia (73%, fatigue (73%), nausea (72%), and anemia (in 67%)
- **Most common G3-4 TEAEs: thrombocytopenia (59%), anemia (44%), hyponatremia (22%), and neutropenia(21%).**
- AEs are generally reversible and manageable with dose modification and standard supportive care agents

Chari A et al. N Engl J Med. 2019 Aug 22;381(8):727-738.

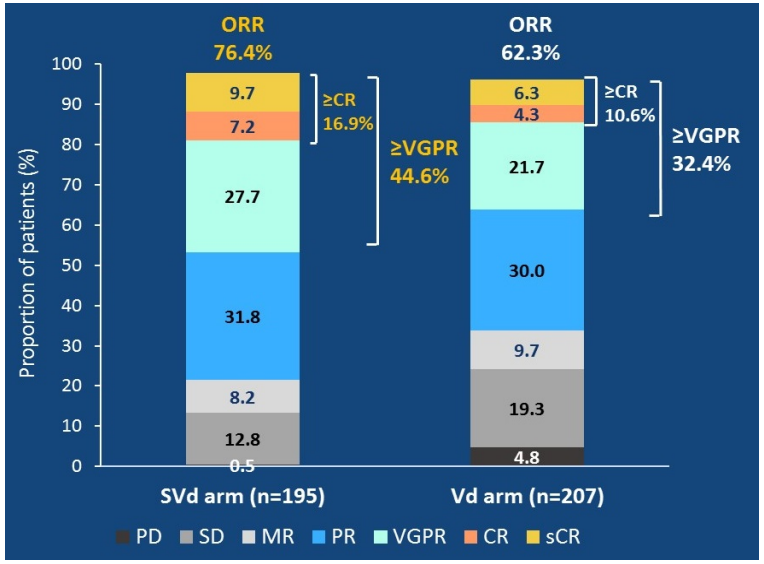
Phase 3 BOSTON Study: Selinexor + bortezomib-dex in RRMM – Efficacy

- Median age: 66 years (SVd) vs 67 years (Vd)
- 2 prior lines: 33% vs 31%; 3 prior lines: 16% vs 21
- High-risk cytogenetics: 50% vs 46%
- Lenalidomide exposed: 39.5% vs 37.2%

Progression-free survival (IRC-assessed)



Response



- Median follow-up: 13.2 vs 16.5 months

More frequent AEs with SVd:

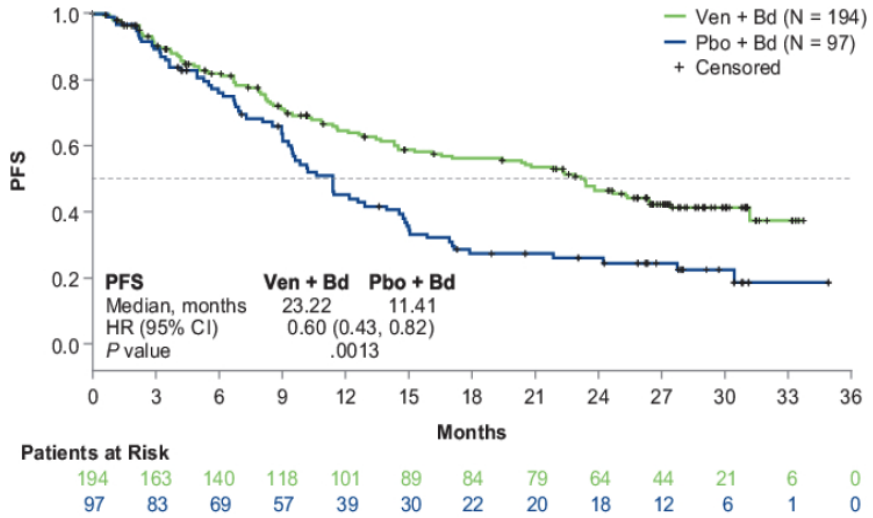
- Thrombocytopenia 60% (grade ≥3: 39.5%). Grade 3 + bleeding: 8.7%
- Neutropenia 14.9% (grade ≥ 3: 8.7%). Febrile neutropenia 0.5%
- Nausea 50.3% (grade ≥3 7.7%). Diarrhea 32.2% (grade ≥3 6.2%

Dimopoulos MA, et al. ASCO 2020; abstract 8501

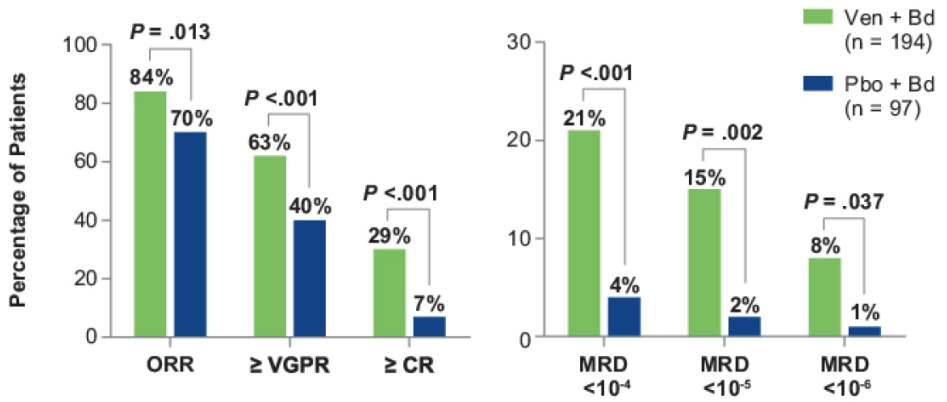
Phase 3 BELLINI Study: Venetoclax+ bortezomib-dex in RRMM: Efficacy

- Median age: 66 years vs 65 years
- High BCL-2 expression: 78% (Ven-Vd) vs 81% (Pbo-Vd)
- 1 prior line: 47% vs 45%; 2–3 prior lines: 53% vs 55%

Progression-free survival



Response rates



- Median OS: 33.5 months vs NR;
  HR: 1.460 (95% CI: 0.912-2.237); p=0.112

Hazard ratios for PFS and OS by *BCL2* gene expression and cytogenetic risk

Group		PFS HR (95% CI)	OS HR (95% CI)
A	t(11;14) or *BCL2*^{high} with standard-risk cytogenetics	0.32 (0.17-0.59)	0.90 (0.36-2.27)
B	t(11;14) or *BCL2*^{high} with high-risk cytogenetics	0.23 (0.04-1.21)	0.95 (0.12-7.49)
C	Non-t(11;14) and *BCL2*^{low} with standard-risk cytogenetics	0.71 (0.43-1.15)	1.35 (0.68-2.66)
D	Non-t(11;14) and *BCL2*^{low} with high-risk cytogenetics	1.88 (0.64-5.49)	6.01 (0.76-47.23)

Bd, bortezomib-dexamethasone; CI, confidence interval; CR, complete response; HR, hazard ratio; MRD, minimal residual disease; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; VGPR, very good partial response

Kumar SK, et al. EHA 2020; abstract EP939

CC-92480 (CELMoD) in combination with Dex in RRMM
Ph I dose escalation study (n=76) – Study design & Patients characteristics

CC-92480-MM-001

CC-92480-MM-001 phase 1 trial (NCT03374085): study design

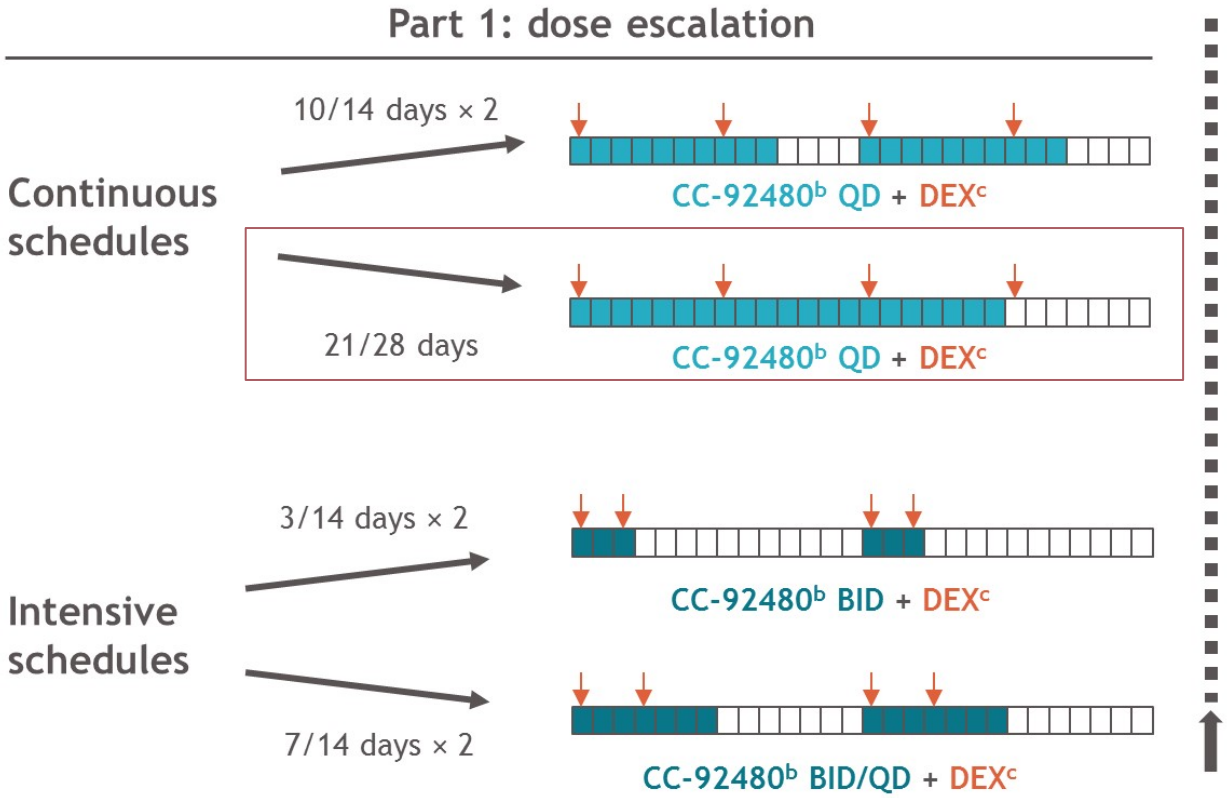
Median nº of prior lines: 6
36.8% EMD
Triple-Refractory: 50%

Key eligibility criteria

- RRMM
- Resistant or intolerant to, or not otherwise candidates for currently available therapies[a]
- Progression on or within 60 days of last antimyeloma therapy

Study endpoints

- **Primary:** assess PK, safety, and define the MTD/RP2D
- **Secondary:** assess preliminary efficacy



Part 2: cohort expansion

MTD: 10mg QD 10/14 days x 2 and 21/28 days schedules.

RP2D: 1mg QD 21/28 days

[a]Including LEN, POM, a PI, a glucocorticoid, and/or anti-CD38 mAb, according to local availability; [b]Administered orally; [c]DEX given at a dose of 40 mg (20 mg in patients aged ≥ 75 years).

BID, twice daily; DEX, dexamethasone; LEN, lenalidomide; MTD, maximum tolerated dose; PD, pharmacodynamics; PK, pharmacokinetics; QD, once daily; RP2D, recommended phase 2 dose; RRMM, refractory/relapsed multiple myeloma.

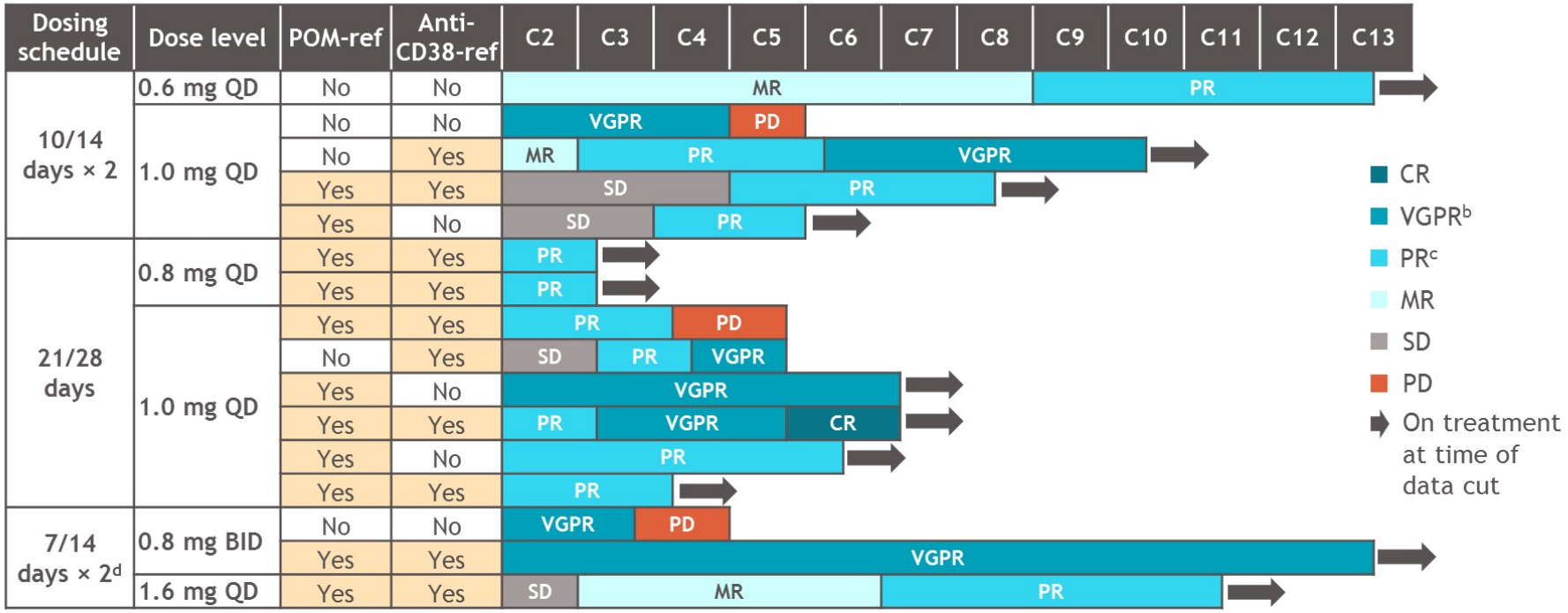
Richardson P et al, ASCO 2020. Abstract 8500.

CC-92480 (CELMoD) in combination with Dex in RRMM
Phase I dose escalation study in RRMM (n=76) – Efficacy

- **ORR all evaluable (n=76): 21.1 %. CBR 26.3%**
- MTD (10/14 days x 2 1.0 mg QD): 40.0% (CBR 50%)
- **RP2D (21/28 days 1mg QD) (n=11): 54.5% (CBR 63.6%)**

Median nº of prior lines: 6
36.8% EMD
Triple-Refractory: 50%

- Majority of responders were dual-IMiD-refractory[a] (10 out of 16 patients [63%])



[a] Refractory to both LEN and POM; [b]1 patient in the 21/28 1.0 mg QD cohort had an unconfirmed VGPR as of the data cutoff date; [c]2 patients in the 21/28 0.8 mg QD cohort had an unconfirmed PR as of the data cutoff date; [d]No response at 2.0 mg QD 7/14 days × 2.

C, cycle; CR, complete response; IMiD, immunomodulatory drug; MR, minimal response; PD, progressive disease; PR, partial response; QD, once daily; ref, refractory; SD, stable disease; VGPR, very good partial response.

Safety ➔ Main TEAEs (myelosupression)
- Neutropenia all grade 73.3% (G3 30.3%/G4 34%)
- Febrile neutropenia all grade 7.9% (G3 5.3%)

Richardson P et al, ASCO 2020. Abstract 8500.

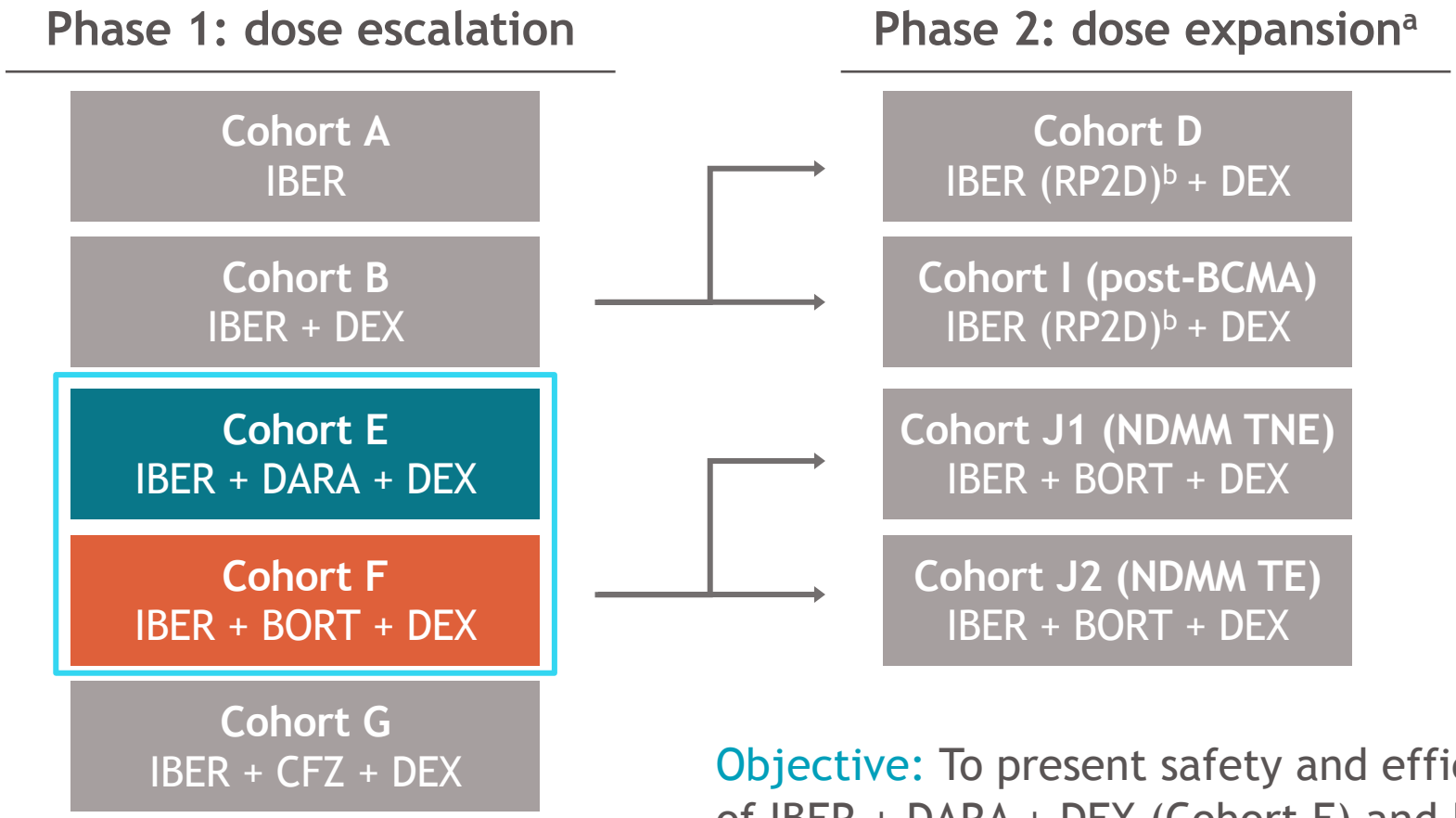
CC-220-MM-001: study design and objective

Key eligibility criteria (Cohorts E and F)

- 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:** to determine MTD/RP2D and efficacy
- **Secondary:** to assess safety



Objective: To present safety and efficacy of IBER + DARA + DEX (Cohort E) and IBER + BORT + DEX (Cohort F)

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

BCMA, B cell maturation antigen; CFZ, carfilzomib; DEX, dexamethasone; MTD, maximum tolerated dose; NDMM, newly diagnosed multiple myeloma; PI, proteasome inhibitor; qd, once daily; RP2D, recommended phase 2 dose; RRMM, relapsed/refractory multiple myeloma; TE, transplant eligible; TNE, transplant non-eligible.

ClinicalTrials.gov: NCT02773030
EudraCT: 2016-000860-40

van de Donk NWCJ, et al. ASH 2020. Abstract 724.

Iberdomide (CC-220) in combination with Dex in RRMM
Phase 1/2 study design – Cohort B (Iber + Dex) n=76

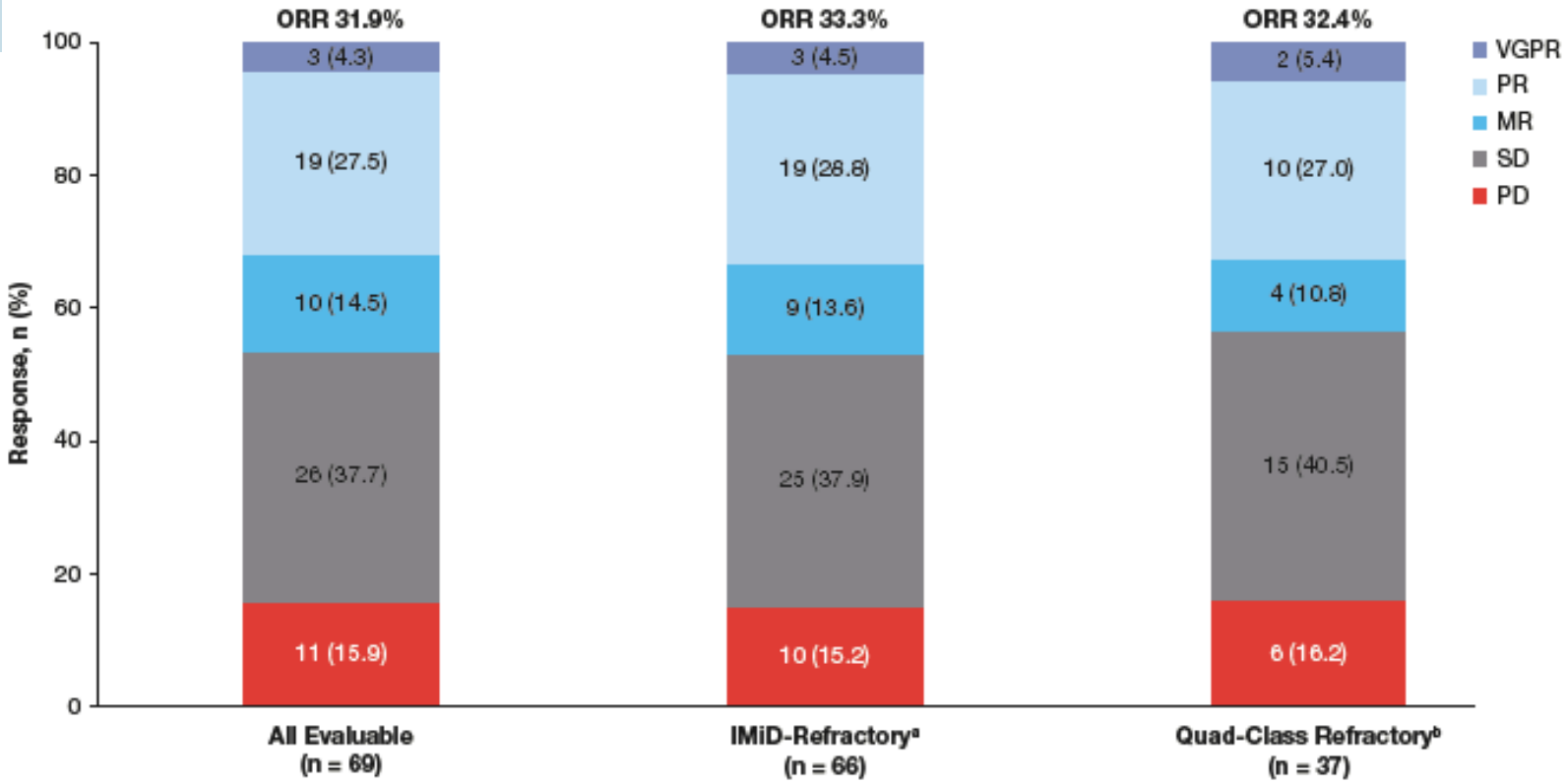
Key inclusion criteria:

- **RRMM**
- **≥2 prior lines, exposed to IMID and PI and refractory to the last line.**

Median nº of prior lines: 6

Prior therapies: ASCT (79%), LEN (100%), POM (71%), PI (100%), Dara (74%), BCMA (8%).

RP2D: 1.6mg QD 21/28 days



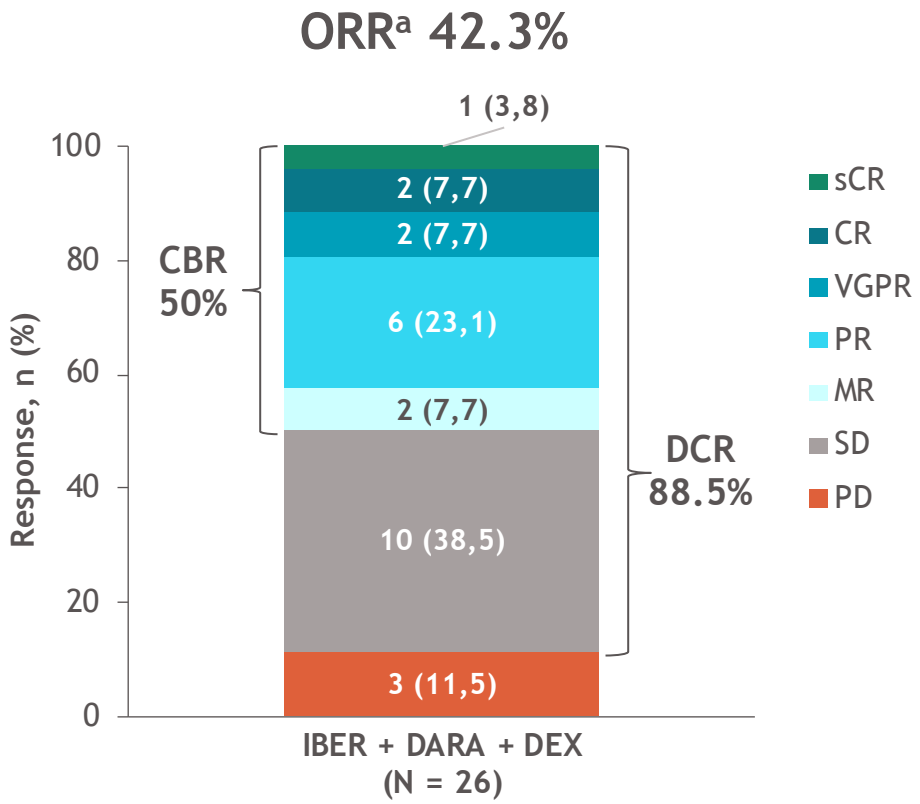
Safety ➔ Overall excelent safety profile

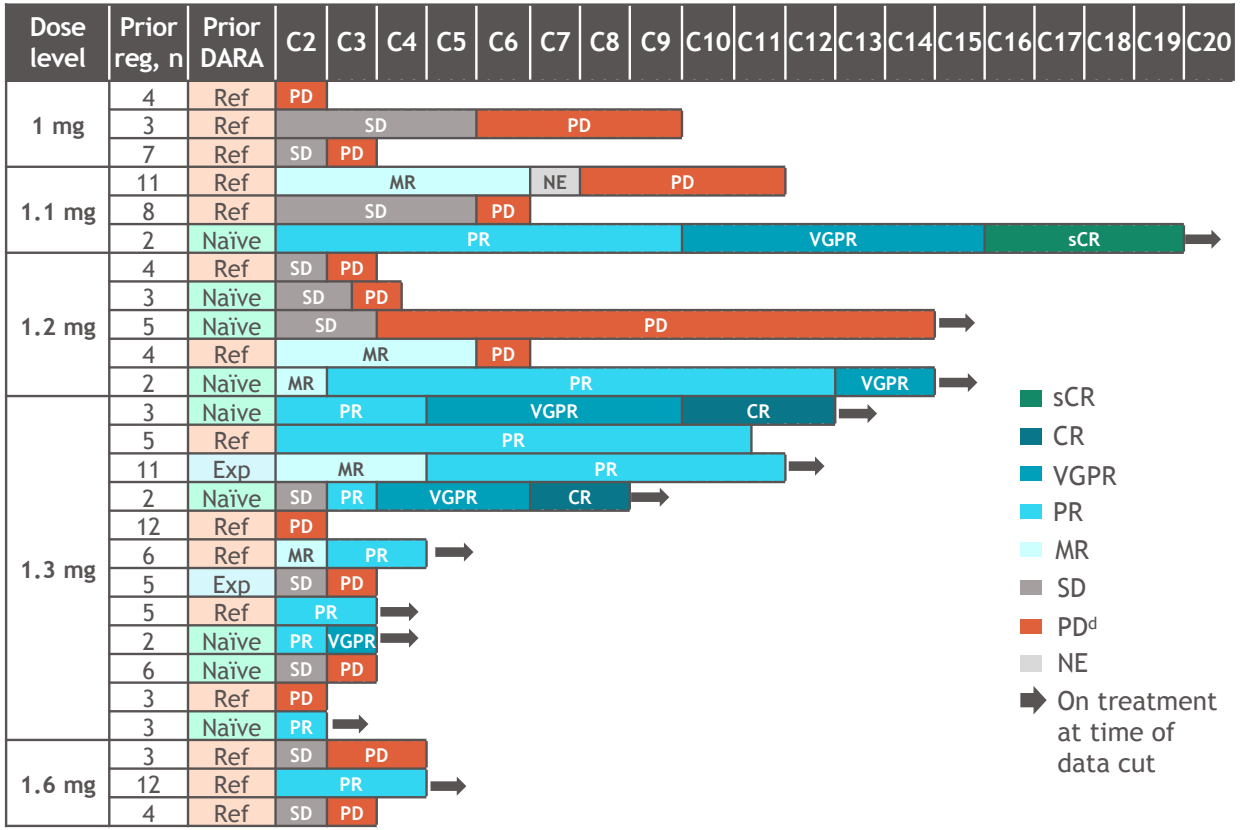
- Neutropenia all grade 40% (G3 17.3%/G4 16%)
- Thormbocytopenia 17.3% (G3 4%/ G4 6.7%)

Lonial S et al, ASH 2019 poster Abstract 3119.

CC-220-MM-001 Cohort E Phase 1 dose escalation: Iber-Dara-Dex Key data (n= 26)

- Median age 66 y-o
- Median nº PL: 4 (2-12). IMID Ref: 96.3% (Pom Ref: 77.8%); PI-Ref 77.8%; **Dara-Ref 77.8%; Triple-class Ref: 48.1%.**





- Median time to response was 4.1 (range 4.0–12.0) weeks

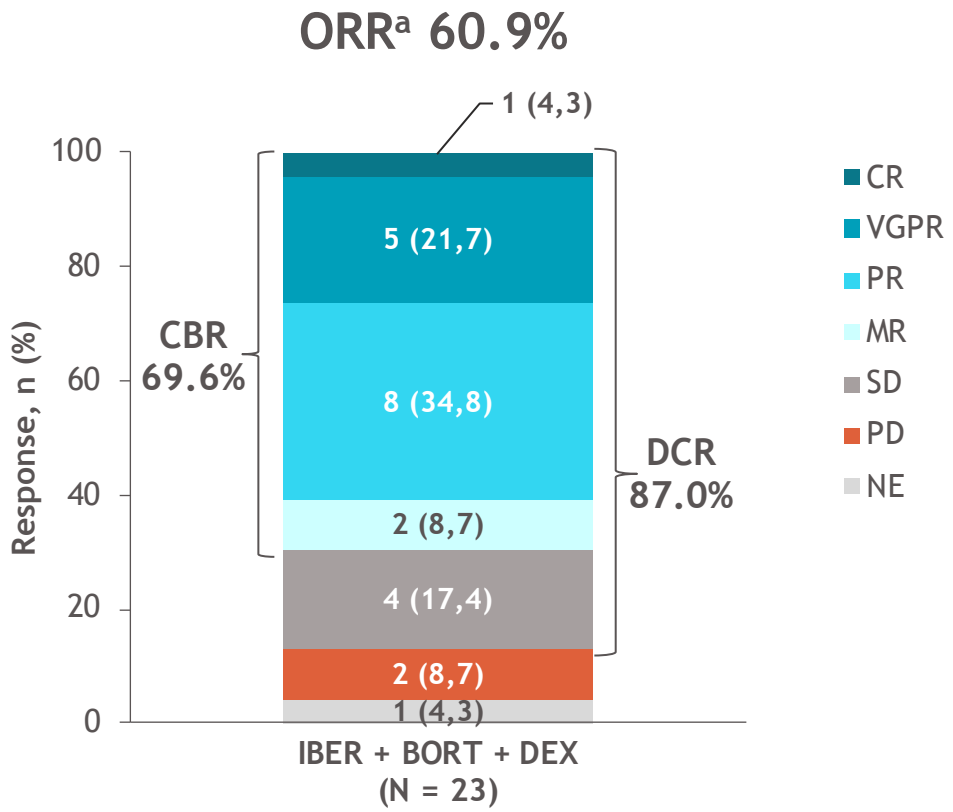
- **Most frequent TRAEs were**: Neutropenia 70.4% [G3 14.8%, G4 51.9%] [Febrile neutropenia 1 patient]; Thrombocytopenia 40.7% [G3 11.1%, G4 3.7%] and Infections 77.8% [G3 in 5 patients].
- **No discontinuation due to AEs**

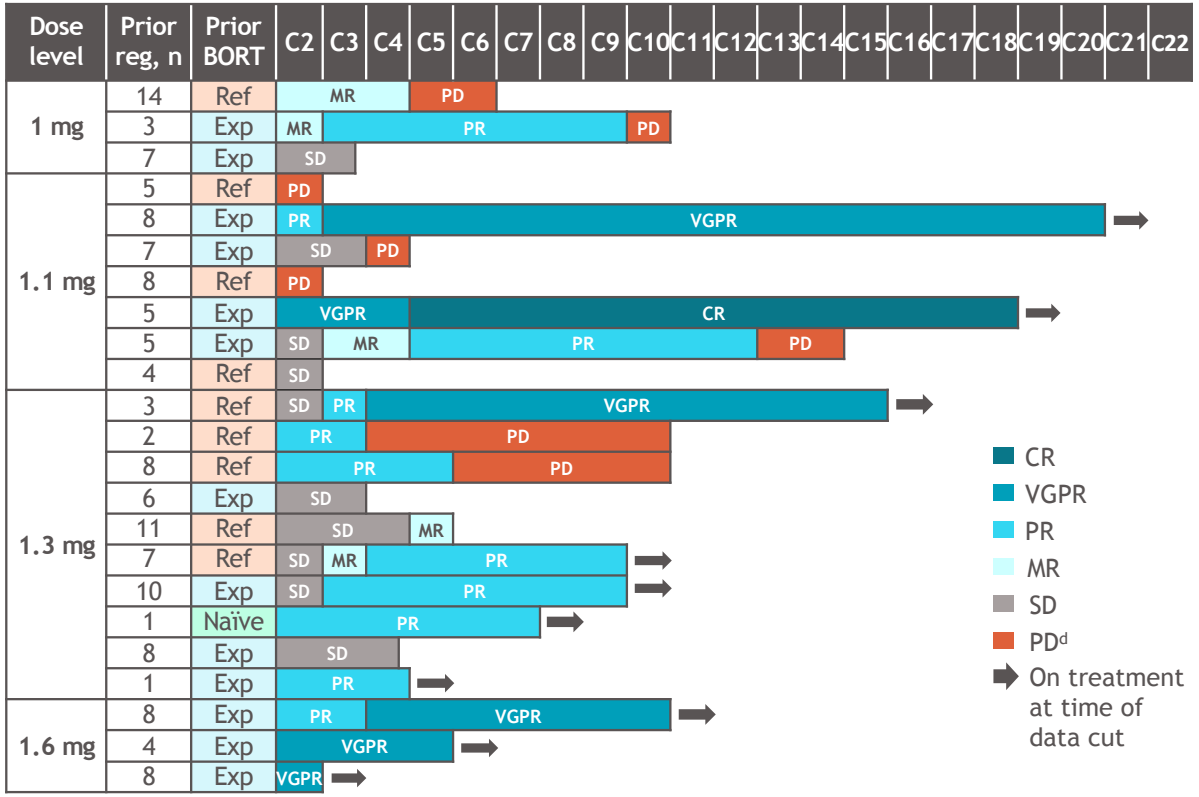
[a]PR or better. [b]Full analysis population (N = 27). [d]1 patient in the 1.2 mg group and 2 patients in the 1.3 mg group had an unconfirmed PD as of the data cutoff date.

van de Donk NWCJ, et al. ASH 2020. Abstract 724.

CC-220-MM-001 Cohort F Phase 1 dose escalation: Iber-Bortezomib-Dex Key data (n= 26)

- Median age 63 y-o
- Median nº PL: 6 (1-14). IMID Ref: 78.3% (Pom Ref: 52.2%); **PI-Ref 65.2% (Bortezomib-Ref 39.1%);** Dara-Ref 73.9%; **Triple-class Ref: 39.1%.**





- Median time to response was 3.6 (range 3.0–13.1) weeks

- **Most frequent TRAEs were**: Neutropenia 34.8% [G3 21.7%, G4 4.3%];Thrombocytopenia 34.8% [G3 1pt]; Peripheral neuropathy 30.4% [no G3-4], Diarrhea 30.4% [no G3-4] and Infections 60.9% [G3 13%].
- **Discontinuation due to AEs in 2 patients (8.7%)**

[a]PR or better. [b]Full analysis population (N = 23). [c]Defined as refractory to ≥ 1 IMiD, 1 PI, and 1 anti-CD38 mAb. [d]1 patient in the 1.1 mg group had an unconfirmed PD as of the data cutoff date.

van de Donk NWCJ, et al. ASH 2020. Abstract 724.

BCMA-targeted therapies: a new platform for drug development

Comparison of BCMA-targeted modalities in MM

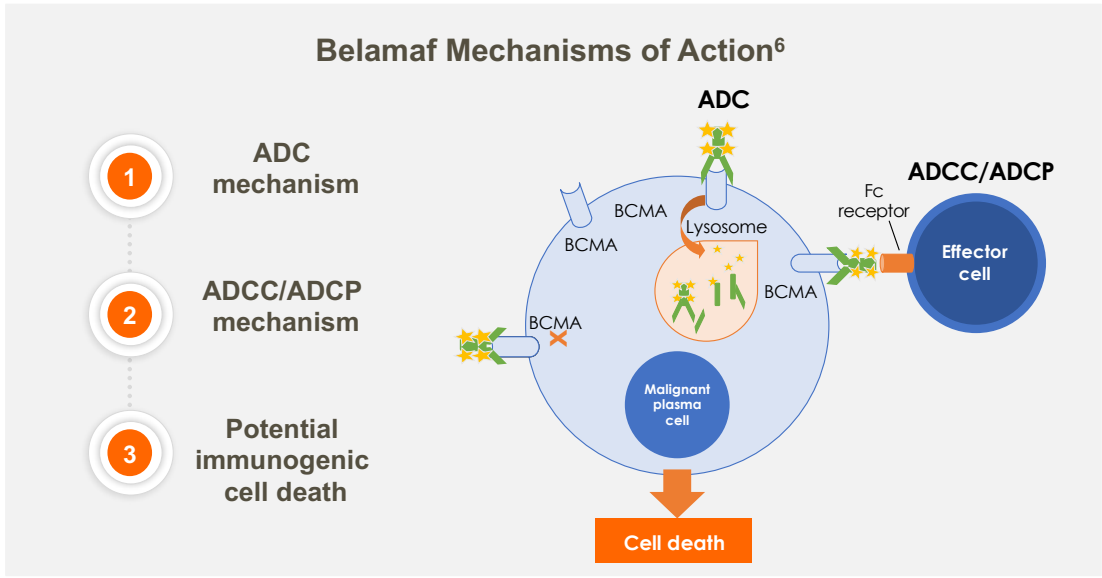
	ADCs	Bispecific antibodies/BiTEs	CAR T cells
Off the shelf	Yes	Yes	No*
Logistics/ease of administration	Easiest, outpatient dosing†	More difficult, requires hospitalization for initial dosing, familiarity with CRS/neurotoxicity management	Most difficult, requires leukapheresis, specialty center with CAR T expertise, delays owing to manufacturing, hospitalization, familiarity with CRS/neurotoxicity management
Repeated dosing required	Yes	Yes	No
Dependent on patient T-cell "fitness"	No	Yes	Yes
Unique toxicities	Infusion reactions, toxin dependent	CRS, neurotoxicity	CRS, neurotoxicity
Toxicity duration	Ongoing	Ongoing	Usually 7-21 d
Durable clinical activity seen	Yes	Yes	Yes

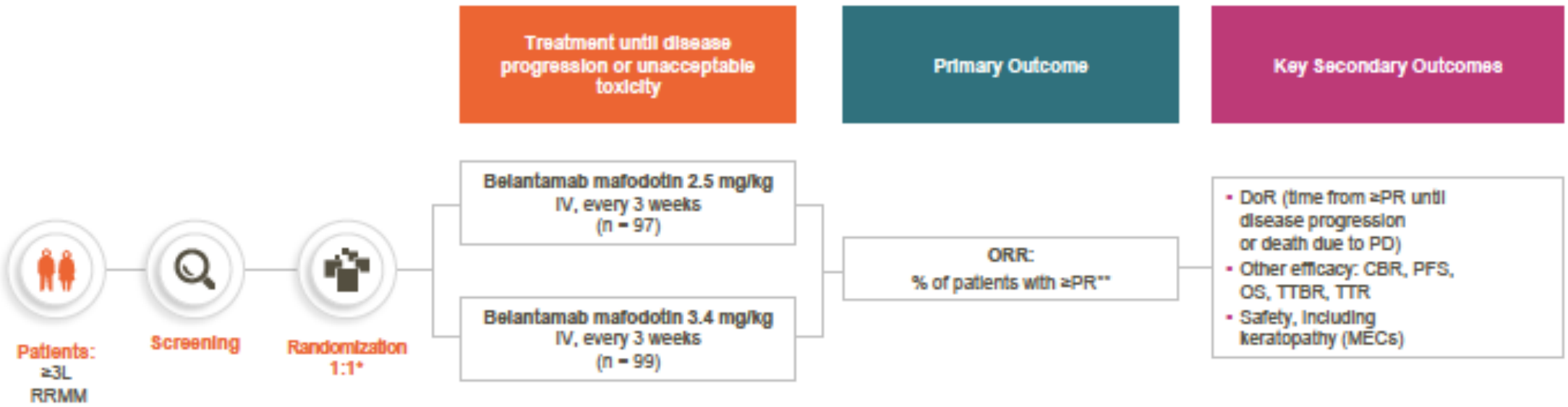
*Allogenic "off-the-shelf" CAR T cells are in development for MM, but no clinical data are available yet.
†The anti-BCMA ADC GSK2857916 does require dose monitoring with an ophthalmologist owing to corneal toxicity; other non-MMAF-containing ADCs should not have this issue.

ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; BiTEs, bispecific T-cell engagers; CAR, chimeric antigen receptor; CRS, cytokine release syndrome.

Cohen A, et al. ASH 2019. Educational session.

Belantamab-Mafodotin (BCMA-ADC): First-in-class BCMA-ADC approved
Mechanism of action and study design





*Patients stratified based on number of previous lines of therapy (≤4 vs >4) and presence or absence of high-risk cytogenetic features
**According to International Myeloma Working Group 2016 criteria

Lonial S et al. The Lancet Oncology 2019, Lonial S, et al. EHA 2020; abstract EP937. Lonial S et al ASCO 2020 Abstract 8536

DREAMM-2 phase 2 pivotal study (n=196, 1:1 randomization)
Efficacy _ Response rate

Key inclusion: > 3 PL, refractory to PI and IMIDs and refractory/Intolerant to Dara.
Median nº prior lines: 7 (2.5 mg/kg) and 6 (3.4 mg/kg). 45% HR CA.

Independent Review Committee-assessed Response*	Belantamab Mafodotin 2.5 mg/kg (N = 97)	Belantamab Mafodotin 3.4 mg/kg (N = 99)
Overall response rate,† n (%) (97.5% CI)	31 (32) (21.7-43.6)	35 (35) (24.8–47.0)
Best response, n (%)		
Stringent complete response	2 (2)	2 (2)
Complete response	5 (5)	3 (3)
Very good partial response	11 (11)	18 (18)
Partial response	13 (13)	12 (12)
Minimal response	4 (4)	5 (5)
Stable disease	27 (28)	22 (22)
Clinical benefit rate‡ (95% CI)	35 (36) (26.6–46.5)	40 (40) (30.7–50.7)

	Belantamab Mafodotin 2.5 mg/kg (N = 97)	Belantamab Mafodotin 3.4 mg/kg (N = 99)
Median DoR, months (95% CI)[1]	11 (4.2-NR)	6.2 (4.8-NR)
Median PFS, months (95% CI)[1]	2.8 (1.6-3.6)	3.9 (2.0-5.8)
Median OS, months (95% CI)[1]	13.7 (9.9-NR)	13.8 (10.0-NR)

At the 2.5 mg/kg dose, 32% of the patients responded with 16/31 (58%) achieving a ≥VGPR. Responses were durable with a median DoR of 11 m in the 2.5 mg/kg cohort.

Lonial S et al. The Lancet Oncology 2019, Lonial S, et al. EHA 2020; abstract EP937. Lonial S et al ASCO 2020 Abstract 8536

Bela-Maf _ DREAMM-2 phase 2 pivotal study
Adverse events of Special Interest (13-month Follow-up)

Adverse Events of Special Interest*	Belantamab Mafodotin 2.5 mg/kg (N = 95)	Belantamab Mafodotin 3.4 mg/kg (N = 99)
Thrombocytopenia	36 (38)	56 (57)**
IRRs	20 (21)	16 (16)
Keratopathy (MECs)	68 (72)	76 (77)
Median time to onset of first MEC, days	37.0	22.5
Percent recovered from first event	77	73
Percent recovered from last event	48	47
Other Corneal Events		
Blurred vision†	24 (25)	33 (33)
Dry eye†	14 (15)	25 (25)
BCVA decline to 20/50 or worse in better-seeing eye	17 (18)	20 (20)

*Values expressed as n (%) unless otherwise noted
**Events include 2 Grade 5 events in the 3.4 mg/kg cohort only
†For events of any grade

- Median time to onset of first occurence: 37 days (19-143)
- Median duration of first event: 86.5 days (8-358)
- All patients recovered from kertopathy

Grade 3/4 symptoms were less common: dry eye (1% and 0% in the 2.5 and 3.4-mg/kg groups) and blurred vision (4% in both groups).

AE = adverse event; BCVA = best-corrected visual acuity; IRR = infusion-related reaction; MEC = microcyst-like epithelial change.

Lonial S, Lee HC, Badros A, et al. Pivotal DREAMM-2 study: single-agent belantamab mafodotin (GSK2857916) in patients with relapsed/refractory multiple myeloma (RRMM) refractory to proteasome inhibitors (PIs), immunomodulatory agents, and refractory and/or intolerant to anti-CD38 monoclonal antibodies (mAbs). Poster presented at: American Society of Clinical Oncology Annual Meeting; May 29-June 2, 2020; Virtual.

Bela-Maf _ DREAMM-2 phase 2 pivotal study
Dose modifications and discontinuations

n (%)	Belantamab Mafodotin 2.5 mg/kg (N = 95)	Belantamab Mafodotin 3.4 mg/kg (N = 99)
AEs leading to dose delays	51 (54)	61 (62)
Dose delays due to keratopathy (MECs)	45 (47)	52 (53)
AEs leading to dose reductions	33 (35)	44 (44)
Dose reductions due to keratopathy (MECs)	24 (25)	30 (30)
AEs leading to permanent treatment discontinuation	9 (9)	12 (12)
Discontinuation due to keratopathy (MECs)	1 (1)	3 (3)
Discontinuation due to patient-reported AEs/symptoms	2 (2)*	0

*Blurred vision or change in BCVA (n = 1 each)

Dose modifications were common due to AEs, but events were generally manageable and few patients permanently discontinued treatment

Most dose delays and reductions were due to keratopathy (MECs). Adverse Events were manageable, and patients recovered with supportive care along with recommended dose modifications

Responses were maintained or even deepened over time despite dose modifications and treatment interruptions.

AE = adverse event; BCVA = best-corrected visual acuity; IRR = infusion-related reaction; MEC = microcyst-like epithelial change.

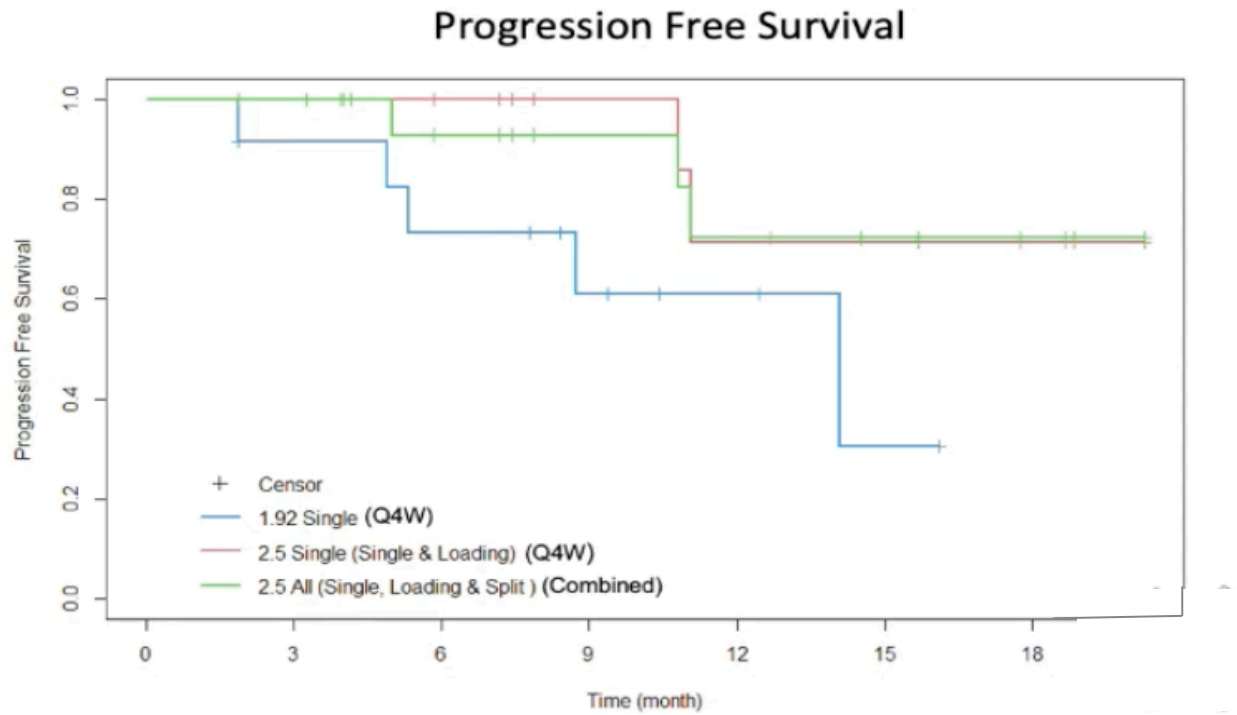
Lonial S, Lee HC, Badros A, et al. Pivotal DREAMM-2 study: single-agent belantamab mafodotin (GSK2857916) in patients with relapsed/refractory multiple myeloma (RRMM) refractory to proteasome inhibitors (PIs), immunomodulatory agents, and refractory and/or intolerant to anti-CD38 monoclonal antibodies (mAbs). Poster presented at: American Society of Clinical Oncology Annual Meeting; May 29-June 2, 2020; Virtual.

Belantamab-Pom-dex (BPd) in RRMM: Ph1-2 Algonquin study

- Key inclusion: ≥ 1 prior lines, LENALIDOMIDE REFRACTORY
- **RP2D: Belamaf 2.5 mg/kg day 1 (or Split day 1 and 8) Q4W + Pd standard dose**

Median nº of prior lines: 3 (1 – 5). Len-R 89.2% - PI-Ref 81.1%. Dara-Ref 43.2%. Triple-Class Ref 35.1%
HR-CA (including 1q): 47%. Median age: 64 years.

ORR 2.5mg combined: 95% // ≥ VGPR 74% // ≥ CR: 26%
Median PFS for the 2.5 mg combined cohort was NR with a median FUP of 7.6 months



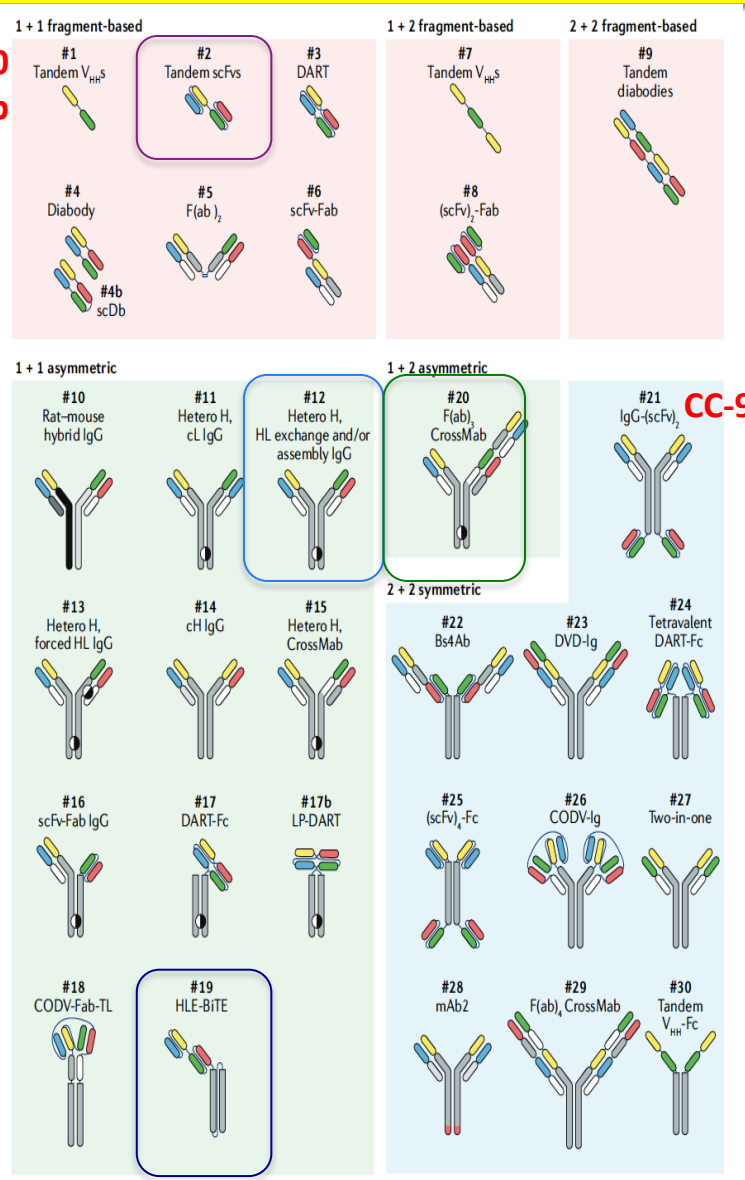
DREAMM-8 trial
(Phase 3 comparing BelaPd vs PVd is ongoing)

- **<u>Most frequent grade ≥3 TRAEs</u>**: Keratopathy 51.4%; Neutropenia 40.5% and Thrombocytopenia 32.4%.
- Visual acuity change 15% whilst keratopathy (any grade) 70%

Trudel S et al. ASH 2020. Abstract #725

Bispecific antibodies: a platform for drug development

AMG-420
Blinatumomab



Non-Ig like
- Short half live
- Better tissue penetration
- Better access to epitopes

64007957 (BCMA-CD3)

CC-93269 (BCMA-CD3)

Ig Like (retain Fc Fraction)
- Longer half life (intermittent infusions)
- Lower tissue penetration

AMG-701

Trudel S, et al. Lancet Oncol. 2018;19:1641-53. Trudel S, et al. Blood Cancer J. 2019;9:37.
Adapted from Mackall CL, et al. Nat Rev Clin Oncol. 2014;11:693-703.

Different BCMA-TCE under evaluation in clinical trials
Patient populations

ORR ranging between 26% - 80%. Deep responses. mDOR NR so far.

	Teclistamab[1] (N = 149)	REGN5428[2] (N = 49)	AMG701[3] (N = 85)	PF-3135[4] (N = 30)	TNB-383B[5] (N = 58)	Cevostamab[6] (N = 53)
Abstract #	**180**	**291**	**181**	**3206**	**293**	**292**
Median follow-up (range)	3.9 months @ RP2D	2.6 (0.5-13.4)	6.5 (1-2.7) in responders	Not reported	Not reported	10.3 (2.7-19.5) in responders
Median prior LoT (range)	6 (2-14)	5 (2-17)	6 (2-25)	8 (3-15)	6 (3-15)	6 (2-15)
Refractory to last line of therapy	91%	61%	Not reported	Not reported	81%	94%
Triple refractory	**81%**	**100%**	**62%**	**Not reported**	**64%**	**72%**
Extramedullary disease	12%	Not reported	25%	Not reported	Not reported	17%
High-risk cytogenetics	32%	Not reported	Not reported	26.7%	Not reported	88%

* n=22. LoT, lines of therapy; mDOR, median duration of response; MRD, minimal residual disease; NR, not reported; ORR, overall response rate; R2PD, recommended phase 2 dose; TCE, T-cell engager; VGPR, very good partial response.

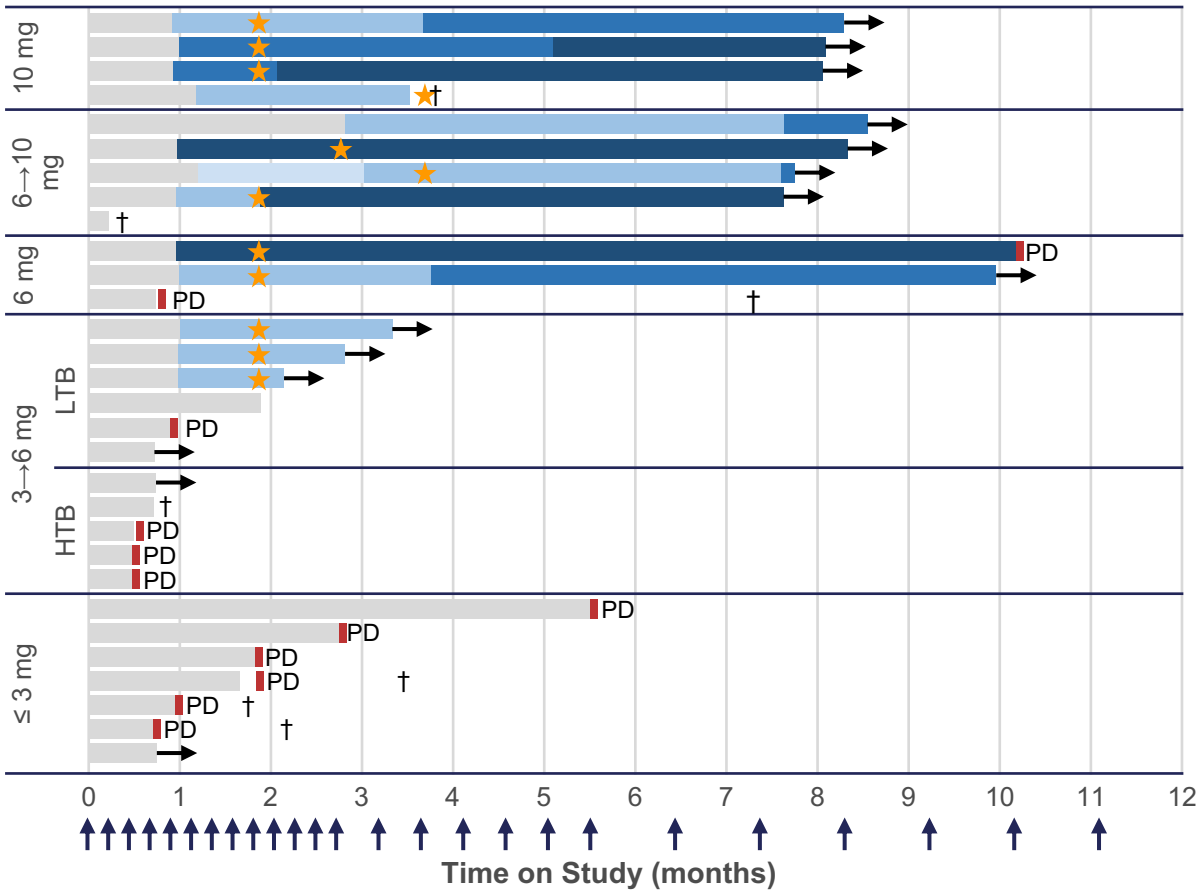
This table is provided for ease of viewing. Cross trials comparison are not intended and should not be inferred.

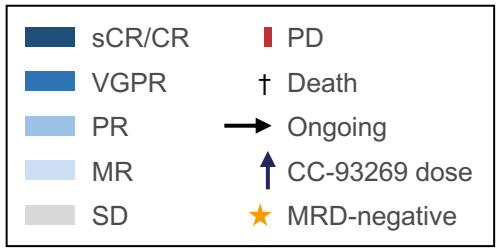
1. Garfall AL, et al. ASH 2020; abstract 180 (oral presentation). 2. Madduri D, et al. ASH 2020; abstract 291 (oral presentation). 3. Harrison SJ, et al. ASH 2020; abstract 181 (oral presentation). 4. Lesokhin AM, et al. ASH 2020; abstract 3206 (oral presentation).
5. Rodriguez C, et al. ASH 2020; abstract 293 (oral presentation). 6. Cohen AD, et al. ASH 2020; abstract 292 (oral presentation).

CC-93269 (2+1 IgG_1 TCE) Phase 1 dose escalation trial
Summary of efficacy data

Key inclusion: RRMM, 3 or more prior lines. Refractory to last line. No prior BCMA.
Median nº prior lines: 5 (3 – 13)
80% IMID refractory. 80% antiCD38 refr. 76.7% PI-refractory. **66.7% Triple-class refractory**

In all patients (n = 30), the ORR was 43.3% with a sCR/CR of 16.7%
Among patients receiving 10 mg (n = 9), the ORR was 88.9% with a sCR/CR of 44.4%





AEs	All grade	G ≥3
Anemia, n(%)	13 (43.3)	11 (36.7)
Neutropenia, n(%)	35 (46.7)	30 (43.3)
Thrombocyt, n(%)	9 (30%)	5 (16.7%)
CRS, n(%)	**23 (76.7%)**	1 (3.3%)
Infections, n(%)	**17 (56.7%)**	9 (30%)

Costa L. et al. ASH 2019. Abstract 143. Oral presentation

Data as of October 28, 2019.
[a] MRD negativity by Euroflow analysis was reported only if a minimum sensitivity of ≤ 1 tumor cell in 10^5 nucleated cells was achieved and in patients who had ≥ 1 baseline and ≥ 1 post-baseline MRD assessment. HTB, high tumor burden (defined as > 50% bone marrow plasma cells or > 5 extramedullary lesions); LTB, low tumor burden (defined as ≤ 50% bone marrow plasma cells and ≤ 5 extramedullary lesions); MR, minimal response.

Teclistamab: BCMA x CD3 Bispecific DuoBody® Antibody (n= 157)

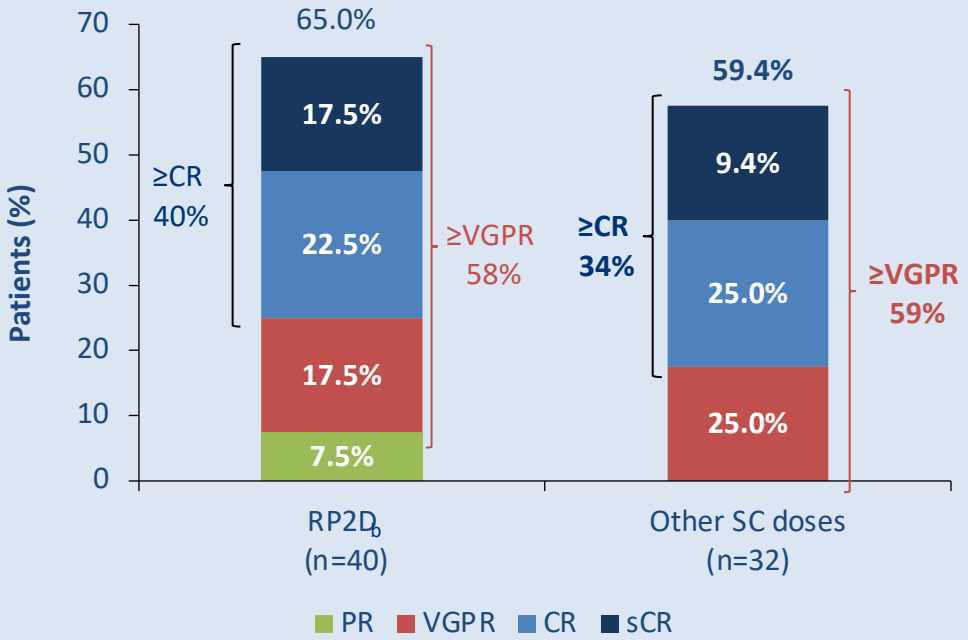
Summary of Key data at the RP2D

Key inclusion: RRMM intolerant to established therapies.
Median nº prior lines: 6 (5 PL at the RP2D)
32% patients with HR-CA. 81% Triple-class refractory.

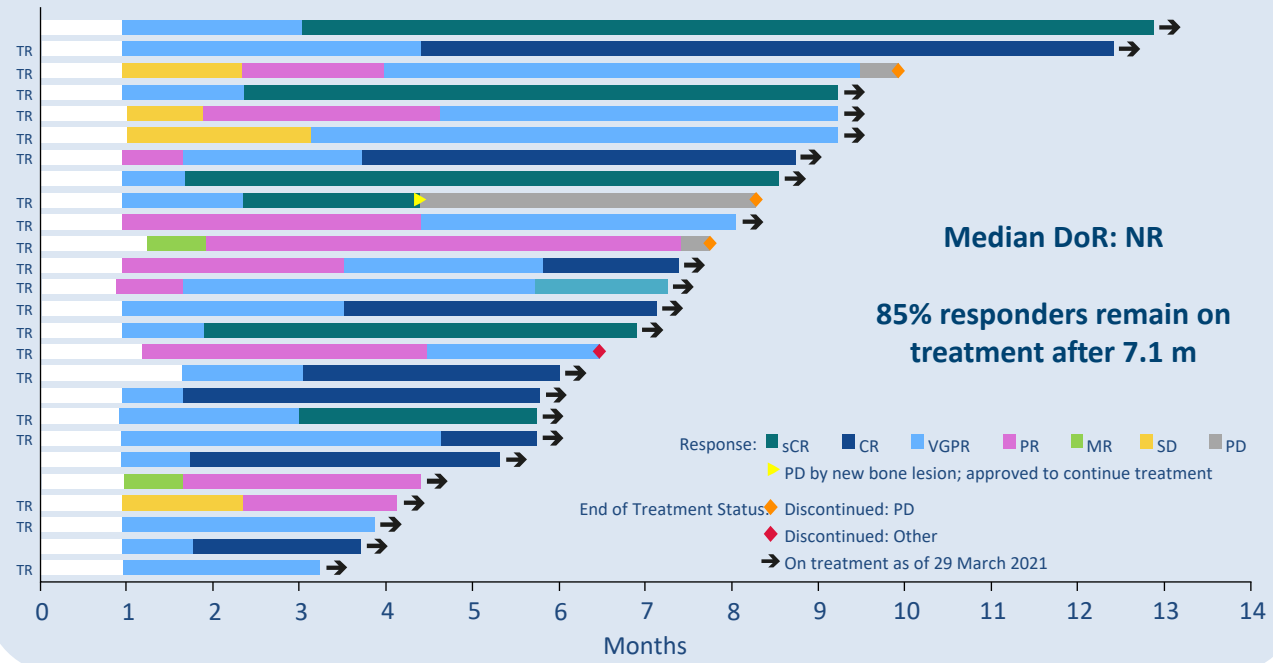
Total patients treated: 157
Most active doses: ***270-720 ug/kg IV*** *and 720-3000 ug/kg SC;* ***RP2D: 1500ug/kg (N=73)***
- ***ORR 69% (47/68)****; ≥ VGPR 59%;* ***≥CR 26%***
- ***67% (18/27) ORR*** *in IV (270-720 ug/kg) and* ***ORR 71% (29/41) in SC*** *(720-3000ug/kg)*

Similar efficacy and safety profile.

ORR[a]



Duration of Response at RP2D (1500 µg/kg SC QW)[a]



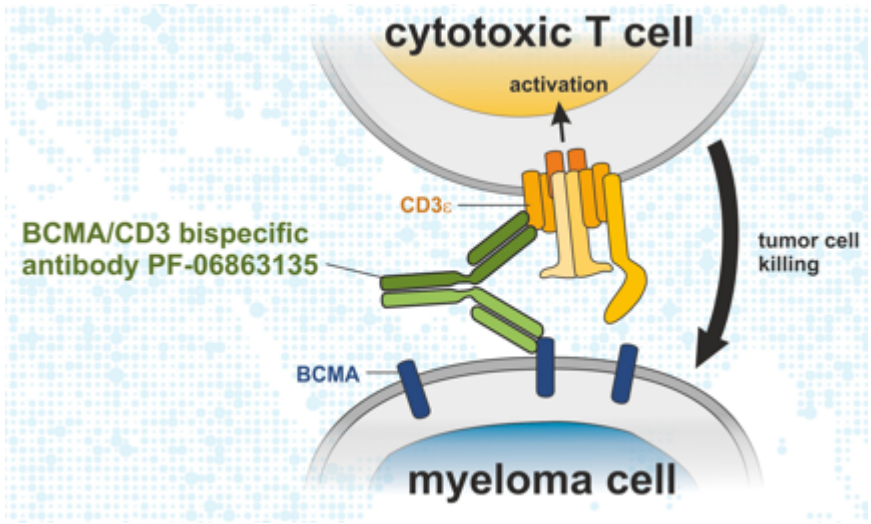
Most frequent TRAEs: overall (grade ≥3) at the RP2D

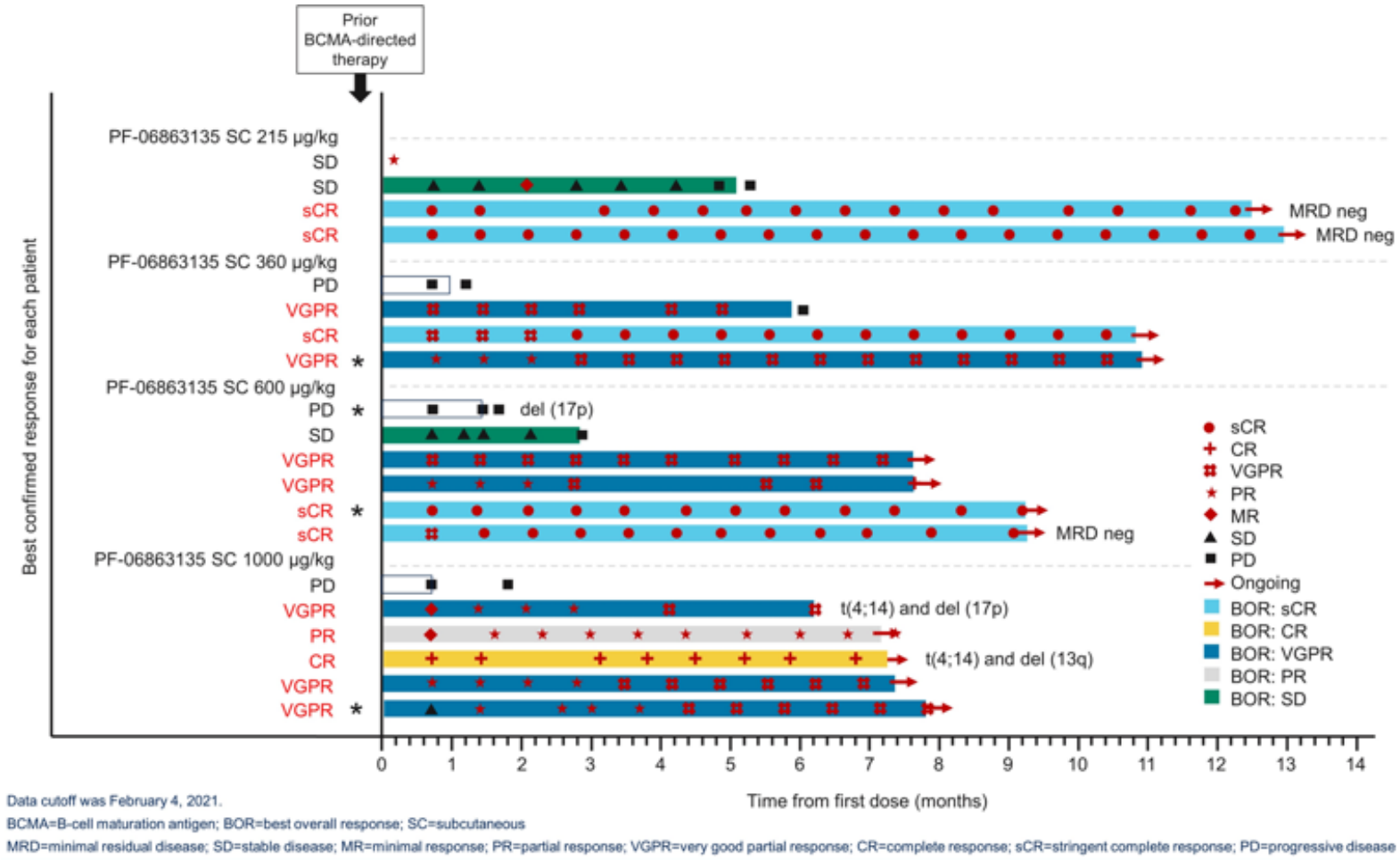
- **Neutropenia** 65% (40%)
- **Anemia** 50% (28%)
- **Thrombocytopenia** 45% (20%)
- **CRS 70% (0%)**
- **Infections in 45% of patients at RP2D (23% grade ≥3)**

Van de Donk N et al. EHA 2021 Oral presentation. Abstract#s193
Krishnan A et al. ASCO 2021. Oral presentation. Abstract #8007

Elranatamab

MAGNETISMM-1





Data cutoff was February 4, 2021.

BCMA=B-cell maturation antigen; BOR=best overall response; SC=subcutaneous

MRD=minimal residual disease; SD=stable disease; MR=minimal response; PR=partial response; VGPR=very good partial response; CR=complete response; sCR=stringent complete response; PD=progressive disease

- Median age: 63 years
- High risk: 23.3
- Triple class refractory: 86.7
- CRS: no grade >2 events

- RP2D 1,000 µg/kg: ORR 83.3%
- All doses: ORR 70.0%
- 3/4 patients BCMA-targeted therapy exposed: 2 VGPR, 1 sCR

Elranatamab is in further development as a monotherapy and in combination with other agents

Bahlis N et al. ASCO 2021; abstract 8006 (oral presentation)

Costello C et al. EHA 2021; abstract S192 (oral presentation)

Common toxicity profile between CAR T-cell and TCE: focus on bispecific antibodies

CRS
=60% (mostly G1-2)

Mitigation strategies
Dex premedication
Step-up dosing
Toci-premedication

Neurologic toxicities
(Immune effector cell associated neurotoxicity Sd –ICANS-)
<10%
(Grade 1-2)

Cytopenia
≈50% neutropenia
(G3 = 20-30%)
Transient (C1 & C2)
Responsive to supportive care

Infections
≈50% but Grade 3-4 not very frequently

On target Off tumor
Immuneparesis
Skin/Nail Tox
(GPRc5d)

CAR, chimeric antigen receptor; CRS, cytokine release syndrome; Dex, dexamethasone; TCE, T-cell engager; Toci, tocilizumab.

Teclistamab: BCMA x CD3 Bispecific DuoBody® Antibody

Safety profile

AEs (≥20% of Total) n (%)	Total N=149		1500 µg/kg SC (RP2D) n=33	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Hematologic				
Neutropenia	85 (57)	69 (46)	17 (52)	11 (33)
Anemia	82 (55)	47 (32)	13 (39)	7 (21)
Thrombocytopenia	59 (40)	32 (22)	11 (33)	4 (12)
Leukopenia	41 (28)	21 (14)	11 (33)	6 (18)
Nonhematologic				
CRS	82 (55)	0	21 (64)	0
Pyrexia	45 (30)	0	6 (18)	0
Diarrhea	34 (23)	1 (1)	4 (12)	0
Nausea	33 (22)	1 (1)	6 (18)	0
Fatigue	33 (22)	2 (1)	8 (24)	1 (3)
Headache	32 (22)	0	4 (12)	0
Cough	31 (21)	3 (2)	1 (3)	0

- **Infections in 52% of patients; 27% at RP2D**
  - 15% had Gr ≥3 infections across all doses
  - 6% had Gr ≥3 infections at RP2D
- **Injection-site reactions in 32% of patients; 36% at RP2D (all Gr 1–2)**
- **1 TRAE leading to death; none at RP2D**
  - Gr 5 pneumonia at 80 µg/kg IV

Parameter, n (%)	Total (N=149)	IV (n=84)	SC (n=65)
Patients with CRS	82 (55)	45 (54)	37 (57)
Median time to CRS onset[a] (range), days	2 (1–5)	1 (1–3)	2 (1–5)
Median duration of CRS (range), days	2 (1–8)	1 (1–7)	2 (1–8)
Patients with supportive measures to treat CRS[b]	76 (51)	43 (51)	33 (51)
Tocilizumab	35 (23)	22 (26)	13 (20)
Steroids	19 (13)	15 (18)	4 (6)
Low flow oxygen	9 (6)	6 (7)	3 (5)
Single low-dose vasopressor	1 (1)	1 (1)	0

- No treatment discontinuations due to CRS
- CRS was generally confined to step-up and first full doses
- Step-up dosing to mitigate risk of severe CRS
- No grade ≥3 CRS events
- **Neurotoxicity in 7 patients (5%); 1 (3%) at RP2D**
  - 2 Gr ≥3 events with IV dosing; none with SC

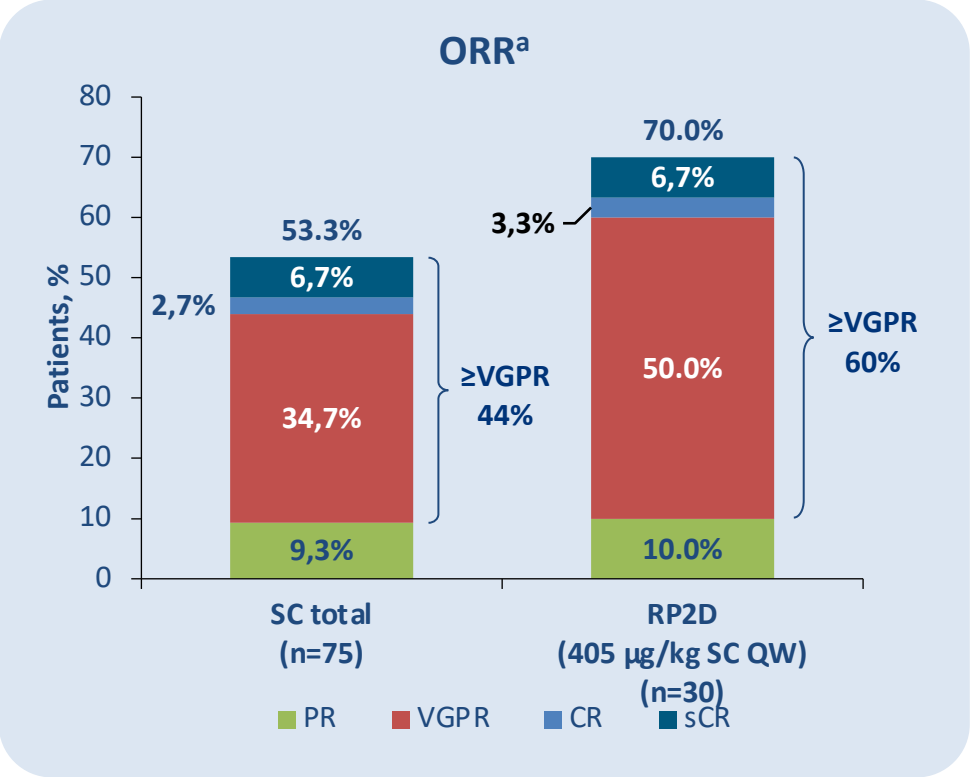
Garfall A et al. ASH 2020. Abstract #180

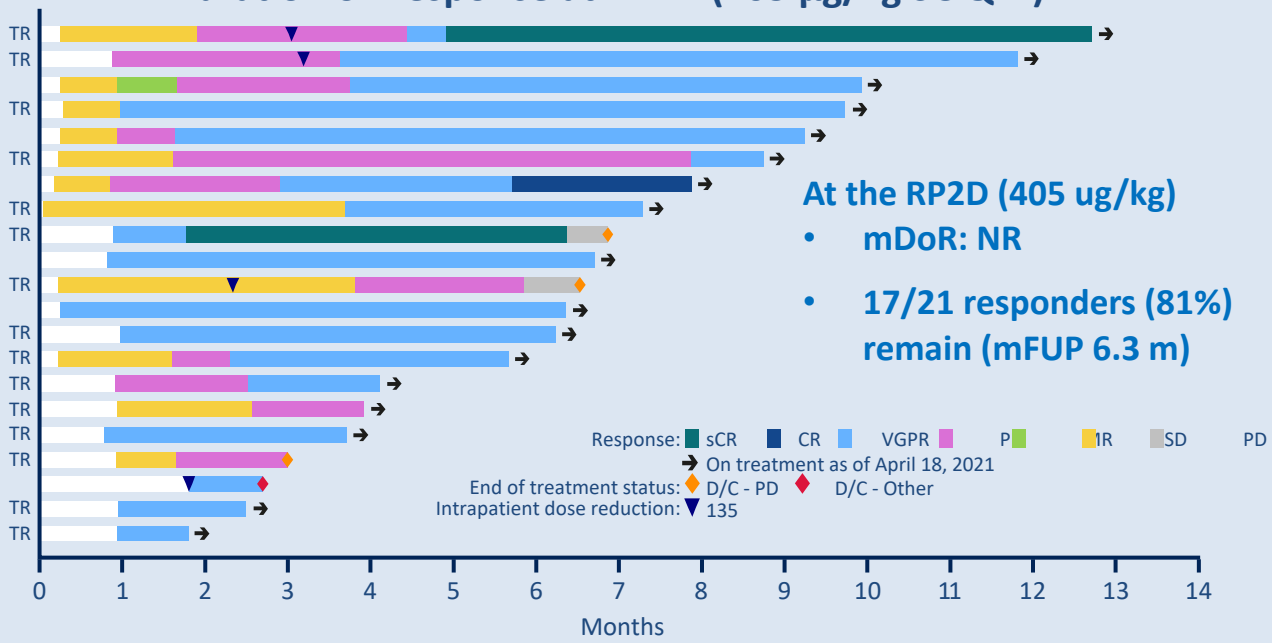
Talquetamab: GPRC5D x CD3 Bispecific DuoBody® Antibody (n=184)

Summary of Key data at the RP2D (405 ug/kg)

Key inclusion: RRMM intolerant to established therapies.
Median nº prior lines: 6 (4.5 PL at the RP2D)
13% patients with HR-CA. 82% Triple-class refractory.

Total patients treated: 184
*At most active doses: **20-180 µg/kg IV** and **135-800 µg/kg SC**; **RP2D 405ug/kg SC***
*- ORR **66**% (33/50); ≥ VGPR 42%*
*- **67%** (12/18) ORR in IV (270-720 ug/kg) and ORR **66%** (21/32) in SC*
Similar efficacy and safety profile.





Most frequent TRAEs: overall (grade ≥3)

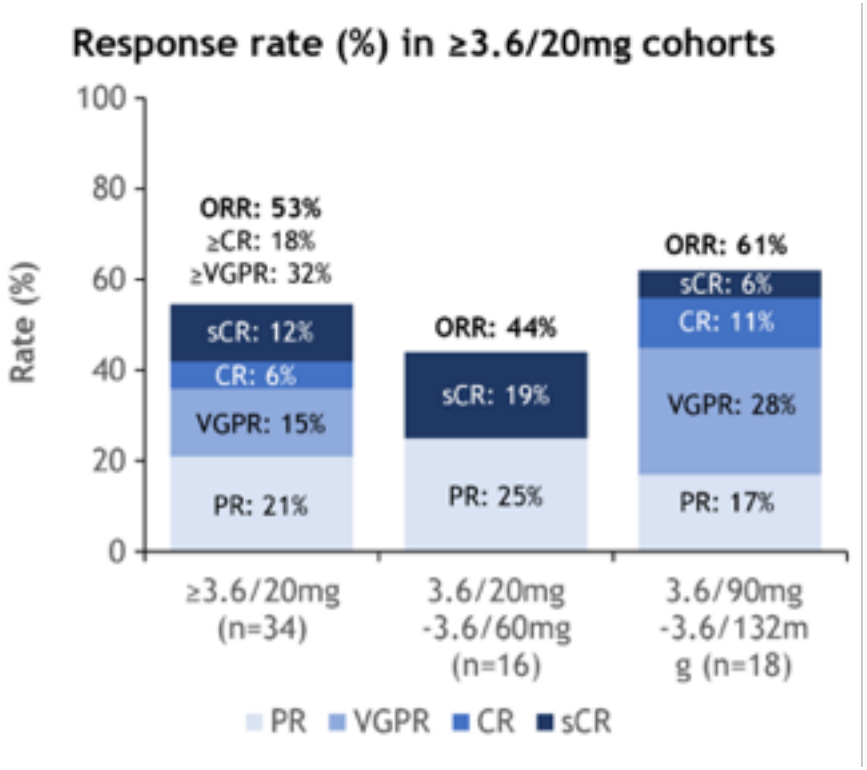
- **Anemia** 57% (27%)
- **Neutropenia** 67% (60%)
- **Lymphopenia** 37% (27%)
- **CRS 73% (2%)**

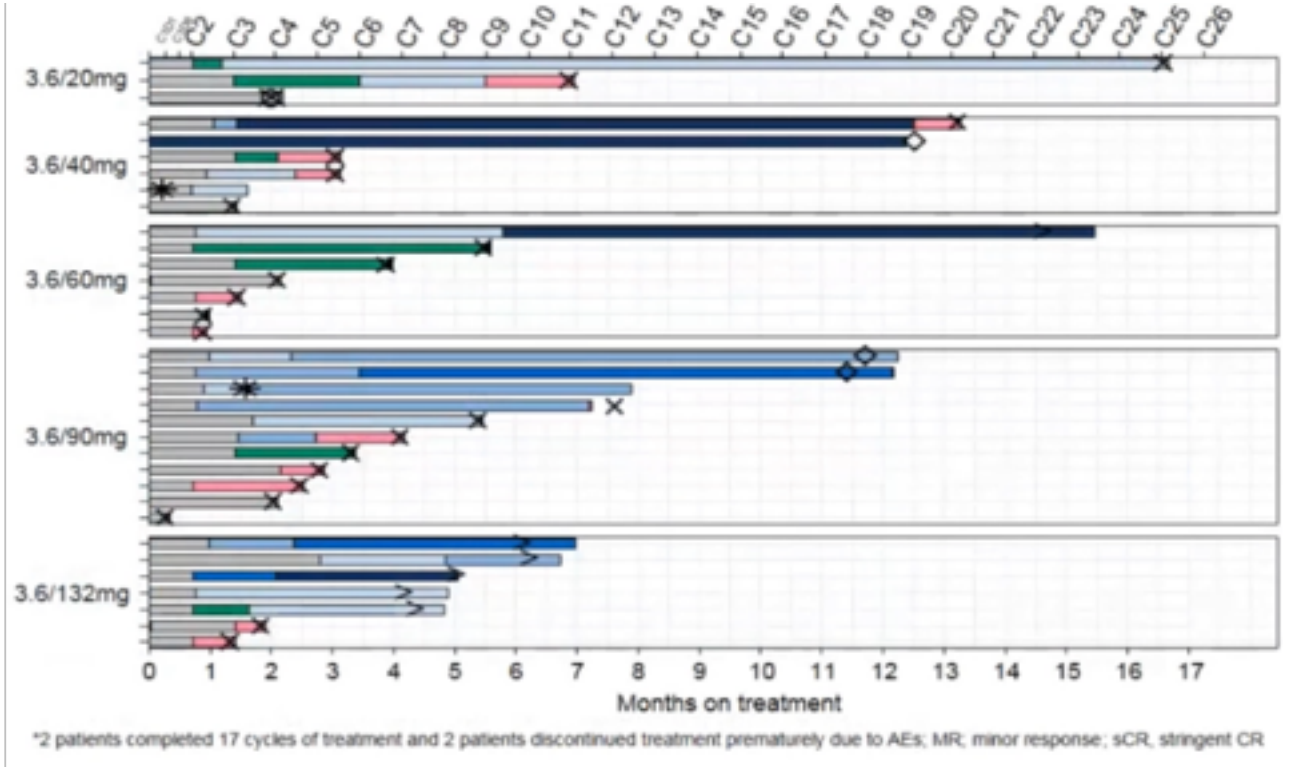
- **Skin-related AEs in 77% at RP2D (majority Grade 1/2)**
- **Infections in 38% of patients; 16% at RP2D**
  - **3% had Gr ≥3 infections at RP2D**

Krishnan A et al. EHA 2021. Oral presentation. #S191 . Berdeja J et al. ASCO 2021. Oral presentation

Cevostamab: BFCR4350A: FcRH5/CD3 Bispecific Antibody in RRMM
Summary of key data (n=157)

Key inclusion: RRMM intolerant to established therapies.
Median nº prior lines: 6 (2-15). RP2D not yet stablished
88% patients with HR-CA. 72% Triple-class refractory.





Most frequent TRAEs: overall (grade ≥3)

- **Thrombocytopenia 32**% (25%)
- **Anemia** 28% (19%)
- **Neutropenia** 17% (15%)
- **CRS 76% (2%)**

Cohen A et al. ASH 2020. Abstract #292

Closing remarks

- Despite continuous improvement in survival thanks to the incorporation of novel treatments, patients with MM still relapse, and survival after failure to IMiDs compounds, Pis and MoAb remains poor. Therefore, there is a **need for new treatment strategies in these patients**
- **New agents such as Melflufen, Iberdomide or Selinexor** are being combined with SoC agents showing encouraging efficacy in late-stage Myeloma.
- Development of **Belantamab-based combinations for patients failing SoC therapies**, particularly patients progressing on Dara.
- **Data on biespecifc TCE are promising with high efficacy and manageable safety profile, challenging the widespread use of CAR-T cell therapy.**
- **There is life beyond BCMA:** new targets on the block with Cevostamab (FcRH5-CD3 bispecific TCE) and Talquetamab (GPRC5D-CD3) as alternatives to BCMA-directed therapy.
- **CAR-T cells continue to show very high efficacy in late-stage patients.** Cilta-cel updated results are promising with long duration of response although there are questions regarding toxicity that remain unanswered. New manufacturing systems (virus-free) and allo-CAR are in the way to facilitate some aspects of CAR T cell therapy.