Part 1 Results of a Dose Finding Study of Belantamab Mafodotin in Combination with Pomalidomide and Dexamethasone for the Treatment of Relapsed/Refractory Multiple Myeloma (RRMM)

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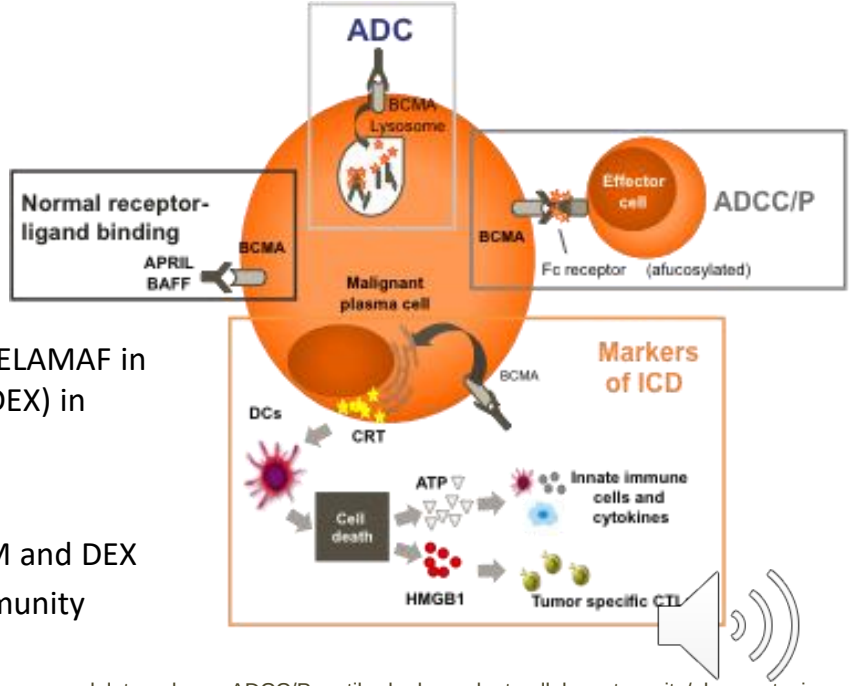
Disclosures

Disclosures: Trudel: *Takeda:* Honoraria; *Sanofi:* Honoraria; *Karyopharm:* Honoraria; *AstraZeneca:* Honoraria; *Pfizer:* Honoraria, Research Funding; *Janssen:* Honoraria, Research Funding; *GSK:* Consultancy, Honoraria, Research Funding; *Genentech:* Research Funding; *BMS:* Consultancy, Honoraria, Research Funding; *Amgen:* Consultancy, Research Funding. **McCurdy:** *Celgene:* Consultancy, Honoraria; *Amgen:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria; *Takeda:* Consultancy, Honoraria; *Sanofi:* Honoraria; *GSK:* Consultancy, Honoraria. **Sutherland:** *Amgen:* Consultancy; *Celgene:* Consultancy; *Takeda:* Consultancy, Honoraria; *Bristol Myers Squibb:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria. **Louzada:** *Takeda:* Consultancy, Honoraria; *Amgen:* Consultancy, Honoraria; *Pfizer:* Consultancy, Honoraria; *Celgene:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria. **Venner:** *Celgene, Amgen:* Research Funding; *Janssen, BMS/Celgene, Sanofi, Takeda, Amgen:* Honoraria. **White:** *Amgen:* Honoraria; *Celgene:* Honoraria; *Janssen:* Honoraria; *Sanofi:* Honoraria; *Karyopharm:* Honoraria; *Antengene:* Honoraria; *GSK:* Honoraria; *Takeda:* Honoraria. **Kotb:** *Merck:* Honoraria, Research Funding; *Karyopharm:* Current equity holder in publicly-traded company; *Celgene:* Honoraria; *Amgen:* Honoraria; *Janssen:* Honoraria; *Takeda:* Honoraria; *Sanofi:* Research Funding. **Mian:** *Takeda:* Consultancy, Honoraria; *Sanofi:* Consultancy; *Janssen:* Consultancy, Honoraria; *Amgen:* Consultancy, Honoraria; *Celgene:* Consultancy. **Camacho:** *Bausch-Health:* Consultancy; *Janssen:* Consultancy; *AbbVie:* Consultancy. **Reece:** *Otsuka:* Research Funding; *Celgene:* Consultancy, Honoraria, Research Funding; *Janssen:* Consultancy, Honoraria, Research Funding; *Takeda:* Consultancy, Honoraria, Research Funding; *Merck:* Research Funding; *BMS:* Research Funding; *Millenium:* ResearchFunding; *Amgen:* Consultancy, Honoraria; *Karyopharm:* Consultancy. **Othman:** *Celgene:* Honoraria; *Janssen:* Honoraria; *Sanofi:* Honoraria; *Novartis:* Honoraria; *Takeda:* Honoraria; *Roche:* Honoraria.

Background

- B cell maturation antigen (BMCA)
  - ✓ Selectively expressed on plasmablasts and plasma cells[1]
  - ✓ Requisite for long-lived plasma cell survival[1]
- Belantamab mafodotin (BELAMAF)
  - ✓ Humanized, afucosylated IgG1, antibody drug conjugate (ADC) targeting BMCA[2]
  - ✓ Multimodal mechanisms of action (MoA)[2]
  - ✓ Convenient IV 0.5-1 h outpatient infusion
- Algonquin Study (NCT03715478)
  - ✓ Multicentre Phase 1 trial evaluating the safety and activity of BELAMAF in combination with pomalidomide (POM) and dexamethasone (DEX) in patients with RRMM
- Study Rationale
  - ✓ urgent need to improve outcomes of patients treated with POM and DEX
  - ✓ the ability of IMiDs to augment T cell and NK cell-mediated immunity including ADCC/P forms the basis for combination[3]

BELAMAF mode-of-action



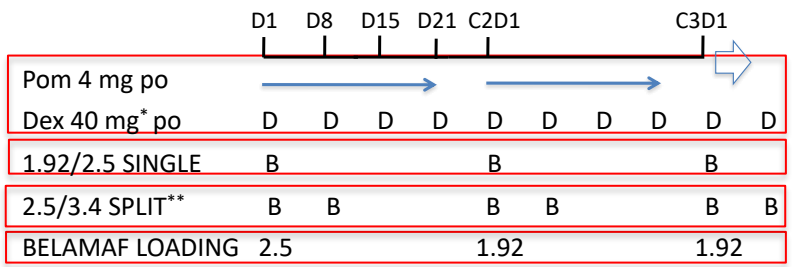
IMiDs, immunomodulatory drugs; ADCC/P, antibody dependent cellular cytoxocity/phagocytosis; NK, natural killer cells, DCs, dendritic cells; CTLs, cytotoxic T lymphocytes; [1]Cho, Front Immunol. 2018;9:1821; [2]Sheikh, Future Oncol. 2020; [3]Carral, J Immunol, 1999:163:380.

Trial design

Part 1 DLT 3+3

Part 1 RP2D Determination up to 12 patients/cohort

Part 2



BELAMF 1.92 SINGLE (cohort -1), 2.5 SINGLE/LOADING (cohort 1a) and SPLIT (cohort 1b) or 3.4 SPLIT (cohort 2) mg/kg IV; *20 mg ≥75 yo; **2.5 or 3.4 mg/kg, split equally on days 1 and 8 Q4W; treatment until PD or toxicity.

RP2D N=23 (+12 in Part 1 = 35 evaluable for ORR)

PRIMARY OUTCOMES:

PART 1
✓to determine the MTD and/or RP2D

PART 2:
✓ORR (% of patients with ≥PR by IMWG 2016 criteria)

KEY SECONDARY OUTCOMES:

✓Efficacy: PFS, OS, DoR
✓Safety, including ocular findings (slit lamp exam + BCVA (snellen test) ➡ graded by KVA scale)

ELIGIBILITY CRITERIA:

- ✓ Measurable disease by IMWG 2016 criteria
- ✓ ECOG PS 0–2
- ✓ ≥ 1 prior lines of therapy
- ✓ Refractory to lenalidomide (LEN) and proteaosme inhibitor (PI) exposed or refractory
- ✓ Progressed on or within 60 days of last MM therapy
- ✓ Patients with mild/moderate renal impairment and grade 2 cytopenias were permitted
- ✓ Prior POM therapy excluded

PD, prrogressive diisease; DLT, dose limiting toxicity; RP2D, recommended part 2 dose; yo, years old; ORR, overall response rate; MTD, maximum tolerated dose; PFS, progression free survival; OS, overall survival; DoR, duration of response; BCVA, best corrected visual acuity; KVA, keratophy and visual acuity scale.

Baseline demographics and disease characteristics

Canadian Myeloma RESEARCH GROUP

Characteristic	n=37 (%)
Age, median (range), years	64 (36-81)
ISS Stage I/II/III	17 (45.9%)/16 (43.2%)/1 (2.7%)
High-risk cytogenetics*	9/19 (47%)
Number of prior lines of therapy, median (range)	3 (1-5)
Autologous Stem Cell Transplant (ASCT)	24 (64.9%)
LEN exposed LEN refractory	37 (100%) 33 (89.2%)
PI exposed Bortezomib Carfilzomib PI refractory	37 (100%) 36 (97.3%) 13 (35.1%) 30 (81.1%)
DARA exposed DARA refractory	16 (43.2%) 16 (43.2%)
LEN and PI refractory	27 (73%)
LEN, PI, and DARA refractory	13 (35.1%)

Data cut-off as of Nov 1, 2020

*Patients with any of the following genetic abnormalities were considered high-risk del17p13, t(4;14), t(14;16), 1 q gain

Patient disposition and treatment status

Patient Disposition	Total (N=37)
Dose Cohort	
-1 (Q4W): 1.92 mg/kg SINGLE	12
1a (Q4W): 2.5 mg/kg SINGLE	7
2.5 mg/kg LOADING	5
1b (Day 1,8): 2.5mg/kg SPLIT	8
2 (Day 1,8): 3.4 mg/kg SPLIT	5
Ongoing, n (%)	28 (76)
Discontinued, n (%)	9 (24)
Progression	7 (19)
Patient decision	1 (3)
Toxicity	1 (3)
Number of treatment cycles, median (range)	9 (2-23)
Duration of follow-up, median (range), months	7.8 (1.9-20.3)

2.5 mg/kg combined, n=20

Data cut-off as of Nov 1, 2020

Safety overview

	N=37 (%)
Any AE	36 (97.3%)
Treatment related AEs	34 (91.9%)
Grade 3-4 AEs	28 (75.7%)
Serious AEs (SAEs)	16 (43.2%)
Treatment related	9 (24.3%)
Fatal SAE	0
SAEs occurring in ≥ 2 patients (treatment related)	
Fever	4 (10.8%)
Lung infection	2 (5.4%)
Neutropenia	2.(5.4%)
AE leading to permanent discontinuation of study treatment	1 (2.7%)
AE leading to dose reduction	14 (37.8%)
AE leading to dose interruption/delay	27 (73%)

Dose Cohort	Dose Limiting Toxicity
2.5 mg/kg SINGLE	G3 keratopathy
3.4 mg/kg SPLIT	G3 keratopathy + G3 decrease BCVA
3.4 mg/kg SPLIT	G3 keratopathy + G4 decrease BCVA

MTD established as BELAMAF 2.5 mg/kg (Day 1) and 2.5 SPLIT (1.25 mg/kg Day 1 and 8) Q4W in combination with standard dosing of POM and DEX.

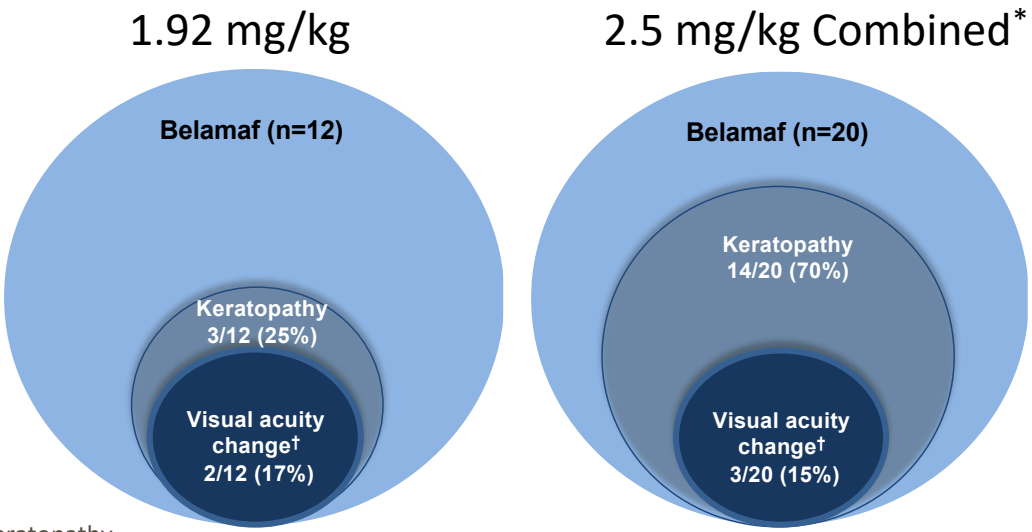
AEs, adverse events; BCVA, best corrected visual acuity; MTD, maximum tolerated dose; POM, pomalidomide; DEX, dexamethasone

AEs (Any Grade ≥ 25%)

TEAE	Any Grade	≥ Grade 3
Keratopathy	28 (75.7%)	19 (51.4%)
Neutropenia	21 (56.8%)	15 (40.5%)
Thrombocytopenia	18 (48.6%)	12 (32.4%)
Decreased visual acuity	17 (45.9%)	6 (16.2%)
Fatigue	15 (40.5%)	4 (10.8%)
Fever	13 (35.1%)	1 (2.7%)
Cataract	13 (35.1%)	1 (2.7%)
Constipation	12 (32.4%)	0
Diarrhea	11 (29.7%)	0
Infusion related reaction	11 (29.7%)	2 (5.4%)

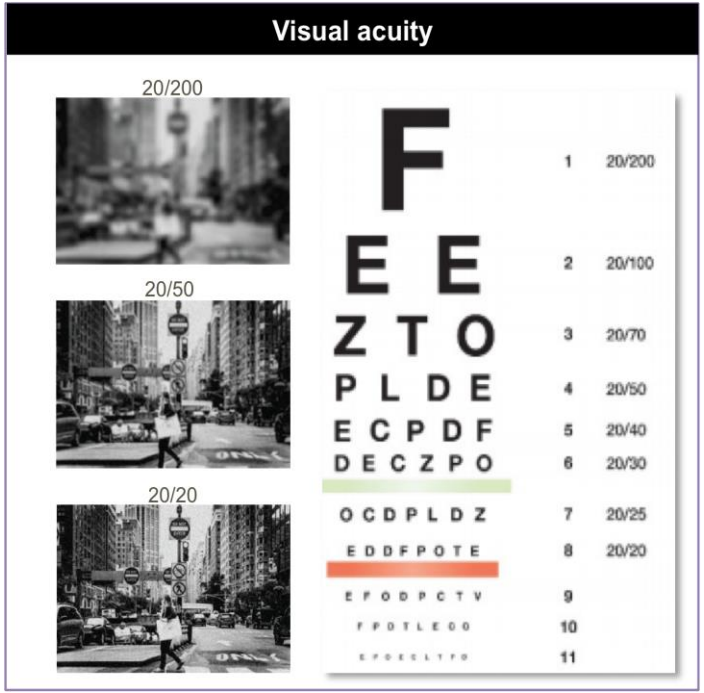
- Most frequent ≥Grade 3 AEs were keratopathy (51.4%), neutropenia (40.5%) and thrombocytopenia (32.4%)
- Infusion-related reactions (29.7%) mostly grade 1/2
- One patient discontinued treatment for grade 4 decreased visual acuity that recovered to grade 3 within 7 days

Corneal AEs overview



G3/4 keratopathy
Visual acuity change 20/50 or worse in better seeing eye

	1.92 mg/kg SINGLE	2.5 mg/kg Combined
Median dose holds/subject, n (range)	1 (0, 8)	5 (0, 16)

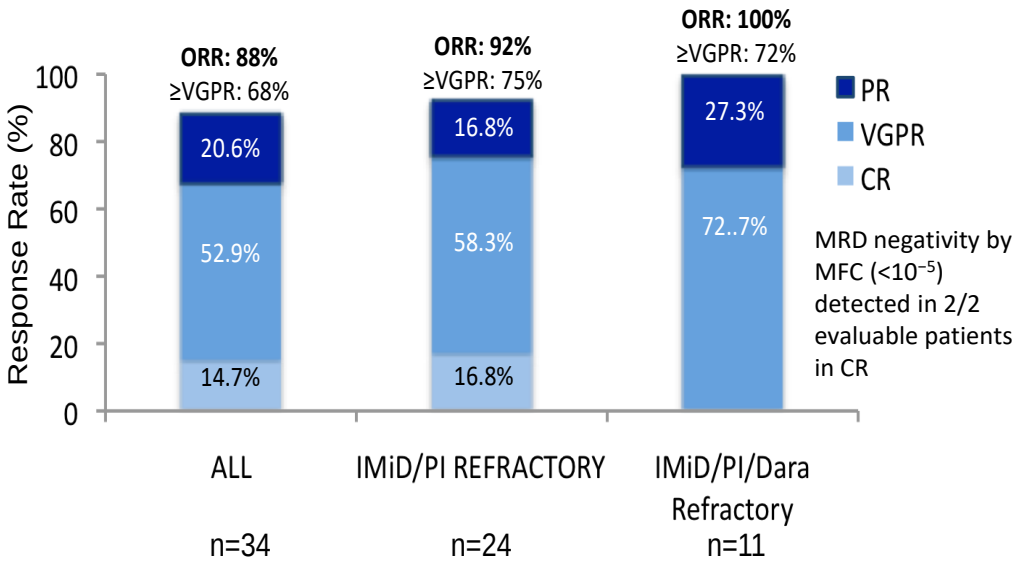


*2.5 mg/kg SINGLE, LOADING and SPLIT

Best overall response* and PFS

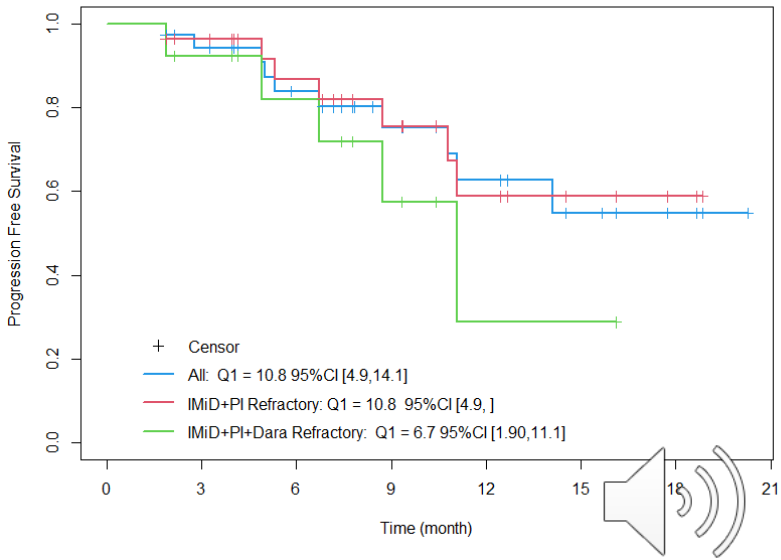
Outcome (median)	All	IMiD/PI Refractory	IMiD/PI/Dara Refractory
Follow-up, months (range)	7.8 (1.9, 20.3)	7.8 (1.9, 18.9)	7.4 (2.1, 16.1)
PFS, months (95% CI)	NR (10.8, -)	NR (10.8, NR)	11.1 (4.9, NR)

Response Rates



MRD negativity by MFC ($<10^{-5}$) detected in 2/2 evaluable patients in CR

Progression Free Survival

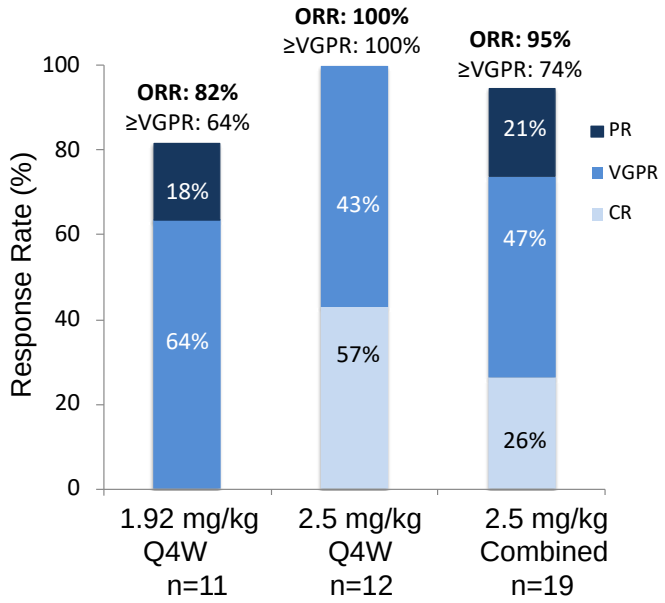


*by IMWG uniform response criteria 2016; PFS, progression free survival; DoR, duration of response;
**Combined-2.5 mg/kg SINGLE, LOADING, SPLIT; MFC, multiparameter flow cytometry CCOD: Nov 1, 2020

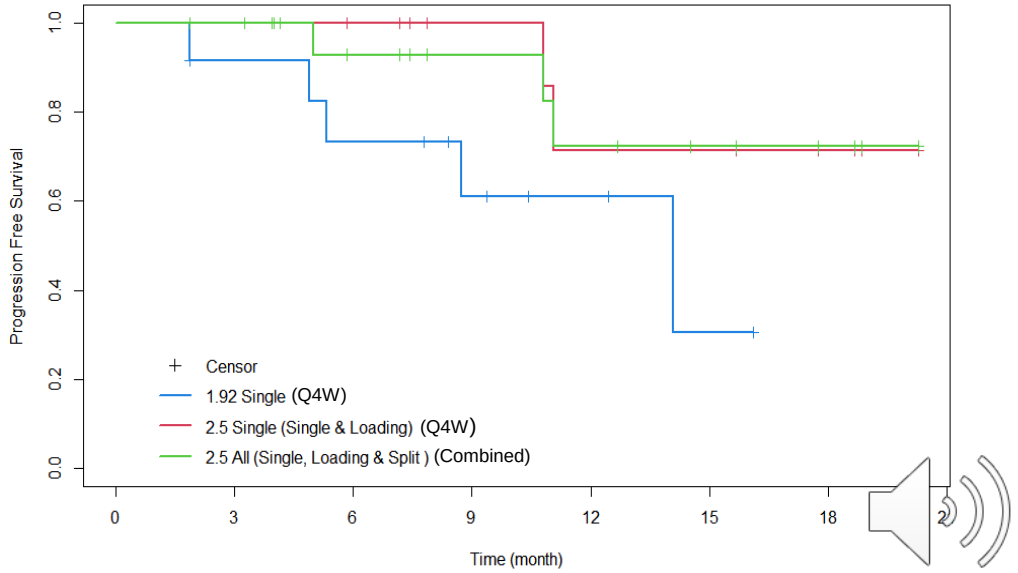
ORR* and PFS by dosing

Outcome (median)	1.92 mg/kg Q4W	2.5 mg/kg Q4W	2.5 mg/kg Combined**
Follow-up, months (range)	8.6 (1.9, 16.1)	13 (4.1, 20.3)	7.6 (1.9, 20.3)
PFS, months (95% CI)	14.1 (4.9, -)	NR (10.8, -)	NR (10.8, -)

Response Rates (%)



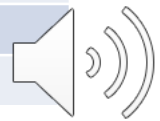
Progression Free Survival



*by IMWG uniform response criteria 2016; PFS, progression free survival; DoR, duration of response;
**Combined-2.5 mg/kg SINGLE, LOADING, SPLIT; 2.5 mg/kg Q4W (SINGLE+LOADING); CCOD: Nov 1, 2020

Belamaf+Pd compares favourably to other Pd Triplets

	N	Prior lines, median (range)	≥VGPR (%)	Median PFS, months (95% CI)
Pd (MM-003)[1]	455 (Pd arm 302)	Not stated	6	4.0 (3.6–4.7)
Anti CD38 naïve				
P Cyclo d[2]	34	4 (2–9)	9	9.5 (4.6–14)
Bortezomib + Pd (OPTIMISMM)[3]	559 (Bor + Pd 281)	2 (1–2)	52.7	11.20 (9.66–13.73)
Carfilzomib + Pd (NCT01464034)[4]	32	6 (2-12)	16	7.2 (3–9)
Isatuximab + Pd (ICARIA-MM)[5]	307 (Isa + Pd 154)	3 (2–4)	32	11.5 (8.9–13.9)
Daratumumab + Pd (APOLLO)[6]	304 (Dara + Pd 151)	2 (1–5)	50.9	12.4 (0.47-0.85)
Elotuzumab + Pd (ELOQUENT-3)[7]	117 (Elo + Pd 60)	3 (2–8)	20	10.3 (5.6–NR)
Anti CD38 exposed				
Selinexor +Pd (STOMP)[8]	51	4 (1–13)	15	10.4 (n=46 pts)
Belamaf 1.9 mg/kg + Pd	12	3 (1–5)	64	14.1 (4.9–)
Belamaf 2.5 mg/kg + Pd	20	3 (1–5)	74	NR (10.8–)



1, San Miguel J, et al. *Lancet Oncol* 2013;(11):1055–1066; 2 Baz RC et al, Blood 2016;127(21);2561, 3.Richardson P, et al. Lancet Oncol. 2019;20:781–94. 5. Shah J, et al. Blood. 2015;126:2284–90; 6. Attal M, et al. *Lancet* 2019;394(10214):2072; 7. Dimopulos MA, et al. Blood 2020,136 (Sup. 1): 5–6;; 8 Dimopoulos MA, et al. *N Engl J Med* 2018;379:1811–22; 9 Chen C, et al. EHA 2019, Poster PF587. Bor, Bortezomib; CI, confidence interval; Dar, Daratumumab; Elo, elotuzumab; IQR, interquartile range; Isa, isatuximab; NR, not reached; Pd, pomalidomide and dexamethasone; Cyclo Cyclophosphamide.

Conclusions….Too early….

- With PIs, IMiDs, anti-CD38, BMCA-targeted agents are the 4th pillar of MM treatment
- BELAMAF is the only anti-BMCA treatment, available for all patients with 30 minute outpatient infusion
- Bela-Pd demonstrates exceptional efficacy (≥ VGPR 72%) in patients that are IMiD/PI/Dara refractory

- BELAMAF 1.92 mg/kg Q4W
  - ≥ VGPR 64% and median PFS 14.1 months
  - Grade 3/4 keratopathy in 25% and ≤ 20/50 BCVA 17%
- BELAMAF 2.5 mg/kg (SINGLE Loading, SPLIT)
  - ≥ VGPR 74% (100% for the 2.5 mg/kg Q4W) and not yet reached
  - Grade 3/4 keratopathy in 70% and ≤ 20/50 BCVA 15%
- Alternative dosing schedules are under evaluation to further optimize efficacy/safety profile

PIs, proteosome inhibitors, IMiDs, immunomodulatory agent; BCVA,best corrected visual acuity; VGPR, very good partial response; NR, not reached

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