

Iberdomide in combination with dexamethasone and daratumumab, bortezomib, or carfilzomib in patients with relapsed/refractory multiple myeloma

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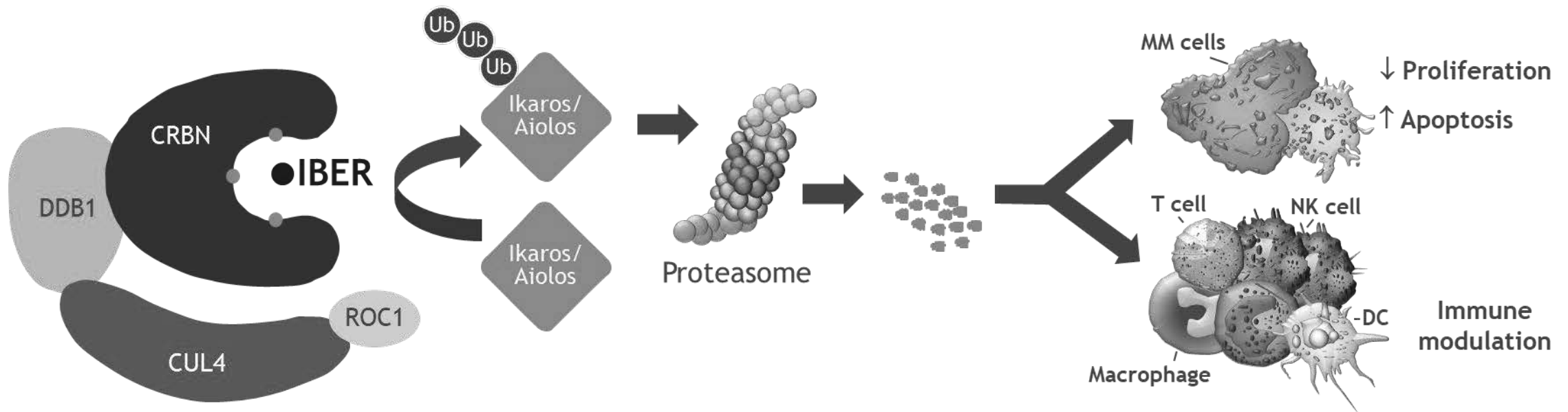
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Disclosures

- Consultancy and honoraria
 - Bristol Myers Squibb; Celgene, a Bristol-Myers Squibb Company
- Other
 - Bristol Myers Squibb; Celgene, a Bristol-Myers Squibb Company

Introduction

- IBER is an oral, potent novel CRBN E3 ligase modulator (CELMoD[®]) compound that co-opts CRBN to enable enhanced degradation of target proteins, including Ikaros and Aiolos^{1,2}
 - IBER induces potent direct antimyeloma and immune-stimulatory activity in preclinical models¹
 - IBER is active in LEN- and POM-resistant myeloma cell lines and enhances cell-mediated killing through immune stimulation^{1,2}
 - IBER has marked synergistic tumoricidal and immune-stimulatory effects in combination with PIs or anti-CD38 mAbs, preclinically and clinically³⁻⁶



CRBN, cereblon; CUL4, cullin 4; DC, dendritic cell; DDB1, DNA damage-binding protein 1; IBER, iberdomide; LEN, lenalidomide; mAb, monoclonal antibody; MM, multiple myeloma; NK, natural killer; PI, proteasome inhibitor; POM, pomalidomide; ROC1, regulator of cullins-1; E3, ubiquitin protein ligase; Ub, ubiquitin.

1. Matyskiela ME, et al. *J Med Chem* 2018;61:535-42; 2. Bjorklund CC, et al. *Leukemia* 2020;34:1197-1201; 3. Amatangelo M, et al. *Blood* 2018;132(suppl 1). Abstract 1935; 4. Lonial S, et al. *Blood* 2019;134(suppl 1). Abstract 3119; 5. Amatangelo M, et al. *Blood* 2020;136(suppl 1). Abstract 1358; 6. Amatangelo M, et al. *Blood* 2020;136(suppl 1). Abstract 1359.

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

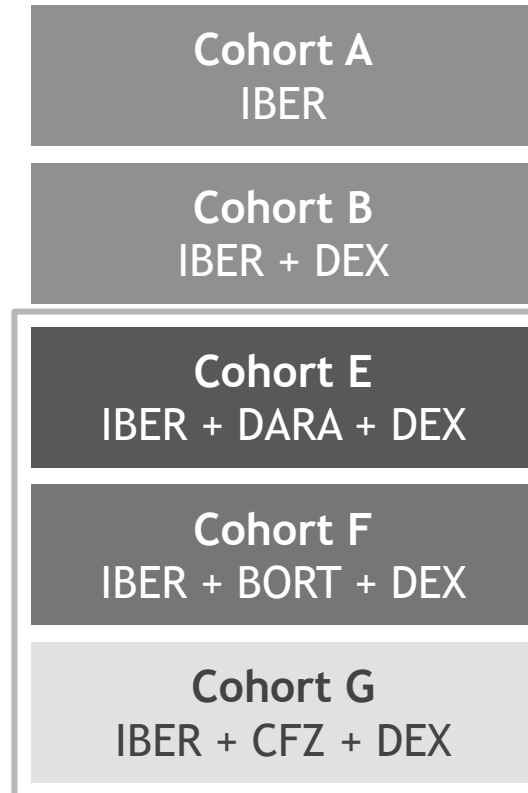
Key eligibility criteria (Cohorts E, F, and G)

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

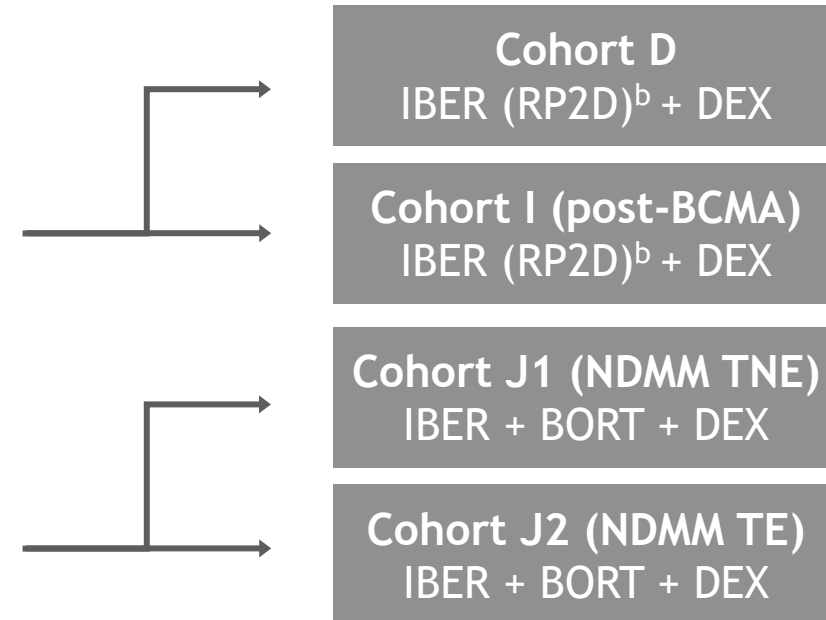
Study endpoints

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

Phase 1: dose escalation



Phase 2: dose expansion^a



Objective: To present safety and efficacy of IBER + DARA + DEX (IberDd; Cohort E), IBER + BORT + DEX (IberVd; Cohort F), and IBER + CFZ + DEX (IberKd; Cohort G)

^aCohort C (IBER monotherapy expansion) was planned, but not opened; ^b1.6 mg QD.

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

CC-220-MM-001: doses and schedule

	Cohort A IBER	Cohort B IBER + DEX ^a	Cohort E <i>IberDd</i> IBER + DARA + DEX ^a	Cohort F <i>IberVd</i> IBER + BORT + DEX ^b	Cohort G <i>IberKd</i> IBER + CFZ ^c + DEX ^a
Phase 1	21/28-day cycles	21/28-day cycles	21/28-day cycles	14/21-day cycles	21/28-day cycles
	0.30 mg QD	0.30 mg QD			
	0.45 mg QD	0.45 mg QD			
	0.60 mg QD	0.60 mg QD			
	0.75 mg QD	0.75 mg QD			
	0.90 mg QD	0.90 mg QD			
	1.0 mg QD	1.0 mg QD	1.0 mg QD	1.0 mg QD	
		1.1 mg QD	1.1 mg QD	1.1 mg QD	1.1 mg QD
		1.2 mg QD	1.2 mg QD		
		1.3 mg QD	1.3 mg QD	1.3 mg QD	1.3 mg QD
	1.6 mg QD (RP2D)	1.6 mg QD	1.6 mg QD	↓	
Phase 2		Cohort D IBER 1.6 mg + DEX ^a			
		Cohort I (post-BCMA) IBER 1.6 mg + DEX ^a			

^aDEX given at a dose of 40 mg (20 mg in patients aged ≥ 75 years) on days 1, 8, 15, and 22 of each 28-day cycle; ^bDEX given at a dose of 40 mg (20 mg in patients aged ≥ 75 years) on days 1, 8, and 15 of each 21-day cycle; ^cCFZ given at a dose of 56 mg/m² on days 1, 8, 15, and 22 of each 28-day cycle.

Baseline characteristics

Characteristic	IberDd (N = 43)	IberVd (N = 25)	IberKd (N = 9)
Age, median (range), years	67 (40-80)	64 (47-81)	61 (36-73)
Male, n (%)	21 (48.8)	18 (72.0)	6 (66.7)
Time since initial diagnosis, median (range), years	7.35 (1.1-19.1)	7.10 (3.0-16.0)	6.70 (2.4-13.5)
Eastern Cooperative Oncology Group performance status, n (%)			
0	19 (44.2)	9 (36.0)	3 (33.3)
1	23 (53.5)	15 (60.0)	6 (66.7)
2	1 (2.3)	1 (4.0)	0
International Staging System at study entry, n (%) ^a			
Stage I	25 (58.1)	14 (56.0)	7 (77.8)
Stage II	11 (25.6)	9 (36.0)	1 (11.1)
Stage III	5 (11.6)	2 (8.0)	1 (11.1)
Presence of extramedullary plasmacytoma, n (%)	7 (16.3)	4 (16.0)	2 (22.2)
Creatinine clearance, n (%)			
< 60 ml/min	11 (25.6)	4 (16.0)	3 (33.3)
≥ 60 ml/min	32 (74.4)	21 (84.0)	6 (66.7)

Median time since diagnosis was > 6.5 years

^aValues missing for 2 patients in the IberDd cohort due to inclusion immediately before data cutoff.

Prior therapies and refractory status

Characteristic	IberDd (N = 43)	IberVd (N = 25)	IberKd (N = 9)
Prior therapies, median (range), n	4 (2-13)	5 (1-14)	6 (2-8)
ASCT, n (%)	34 (79.1)	22 (88.0) ^a	9 (100) ^b
IMiD [®] agent, n (%)	43 (100)	25 (100)	9 (100)
POM	28 (65.1)	19 (76.0)	8 (88.9)
PI, n (%)	43 (100)	25 (100)	9 (100)
BORT	41 (95.3)	24 (96.0)	9 (100)
Anti-CD38 mAb, n (%)	21 (48.8)	23 (92.0)	9 (100)
IMiD-refractory, ^c n (%)	41 (95.3)	20 (80.0)	8 (88.9)
POM	28 (65.1)	14 (56.0)	5 (55.6)
PI-refractory, n (%)	37 (86.0)	17 (68.0)	6 (66.7)
BORT	17 (39.5)	11 (44.0)	4 (44.4)
CFZ	25 (58.1)	9 (36.0)	5 (55.6)
Ixazomib	13 (30.2)	4 (16.0)	0
Anti-CD38 mAb-refractory, n (%)	16 (37.2)	20 (80.0)	7 (77.8)
Triple-class refractory, ^d n (%)	14 (32.6)	12 (48.0)	5 (55.6)

More than one-third of patients in all 3 cohorts were triple-class refractory

^a4 patients received both autologous and allogenic stem cell transplant; ^b1 patient received both autologous and allogenic stem cell transplant; ^cDefined as refractory to LEN or POM; ^dDefined as refractory to ≥ 1 IMiD agent, 1 PI, and 1 anti-CD38 mAb.

ASCT, autologous stem cell transplant; CD, cluster of differentiation; IMiD, immunomodulatory imide drug.

Treatment disposition

Patient disposition, ^a n (%)	IberDd (N = 43)	IberVd (N = 25)	IberKd (N = 9)
Ongoing	22 (51.2)	6 (24.0)	5 (55.6)
Discontinued	21 (48.8)	19 (76.0)	4 (44.4)
Progressive disease	15 (34.9)	10 (40.0)	2 (22.2)
Withdrawal	1 (2.3)	2 (8.0)	1 (11.1)
Physician decision ^b	4 (9.3)	5 (20.0)	0
Adverse event	1 (2.3) ^c	2 (8.0) ^d	1 (11.1) ^e
Dose reduction of IBER	17 (43.6) ^f	9 (36.0)	3 (33.3)
Treatment exposure			
Cycles received, median (range), n	4 (1-25)	6 (1-29)	5 (1-20)

- No deaths occurred on study

Few patients discontinued due to adverse events

^aData cutoff: April 08, 2021; ^bDue to unconfirmed disease progression; ^cGrade 3 pneumonia; ^dGrade 2 pelvis pain and grade 2 intermittent presyncope; ^eGrade 3 bipolar disorder; ^fBased on the safety population.

TEAEs all cycles: IberDd cohort

TEAEs of interest, n (%)	IberDd (N = 39) ^a		
	All grade	Grade 3	Grade 4
Hematologic TEAEs			
Neutropenia	27 (69.2)	5 (12.8)	21 (53.8)
Febrile neutropenia ^b	2 (5.1)	1 (2.6)	1 (2.6)
Thrombocytopenia	13 (33.3)	3 (7.7)	2 (5.1)
Anemia	12 (30.8)	8 (20.5)	0
Non-hematologic TEAEs			
Fatigue	11 (28.2)	1 (2.6)	0
Diarrhea	7 (17.9)	1 (2.6)	0
Constipation	5 (12.8)	0	0
Infusion-related reaction	4 (10.3)	0	0
Peripheral neuropathy ^c	3 (7.7)	0	0
Rash	3 (7.7)	0	0
Thrombotic event ^d	0	0	0
Infections	23 (59.0)	4 (10.3)	2 (5.1)
Upper respiratory tract infection	11 (28.2)	0	0

^a4 patients were enrolled but not treated at the time of data cutoff; ^bIncludes neutropenic sepsis; ^cIncludes peripheral sensory neuropathy; ^dIncludes pulmonary embolism and deep vein thrombosis. TEAE, treatment-emergent adverse event.

TEAEs all cycles: IberVd cohort

TEAEs of interest, n (%)	IberVd (N = 25)		
	All grade	Grade 3	Grade 4
Hematologic TEAEs			
Neutropenia	9 (36.0)	5 (20.0)	2 (8.0)
Febrile neutropenia ^a	0	0	0
Thrombocytopenia	9 (36.0)	1 (4.0)	5 (20.0)
Anemia	6 (24.0)	3 (12.0)	0
Non-hematologic TEAEs			
Peripheral neuropathy ^b	8 (32.0)	0	0
Fatigue	8 (32.0)	0	0
Decreased appetite	7 (28.0)	0	0
Diarrhea	6 (24.0)	1 (4.0)	0
Constipation	5 (20.0)	0	0
Myalgia	5 (20.0)	0	0
Insomnia	5 (20.0)	0	0
Pruritus	5 (20.0)	0	0
Rash	4 (16.0)	1 (4.0)	0
Thrombotic event ^c	0	0	0
Infections	17 (68.0)	4 (16.0)	1 (4.0)
Upper respiratory tract infection	9 (36.0)	2 (8.0)	0

^aIncludes neutropenic sepsis; ^bIncludes peripheral sensory neuropathy; ^cIncludes pulmonary embolism and deep vein thrombosis.

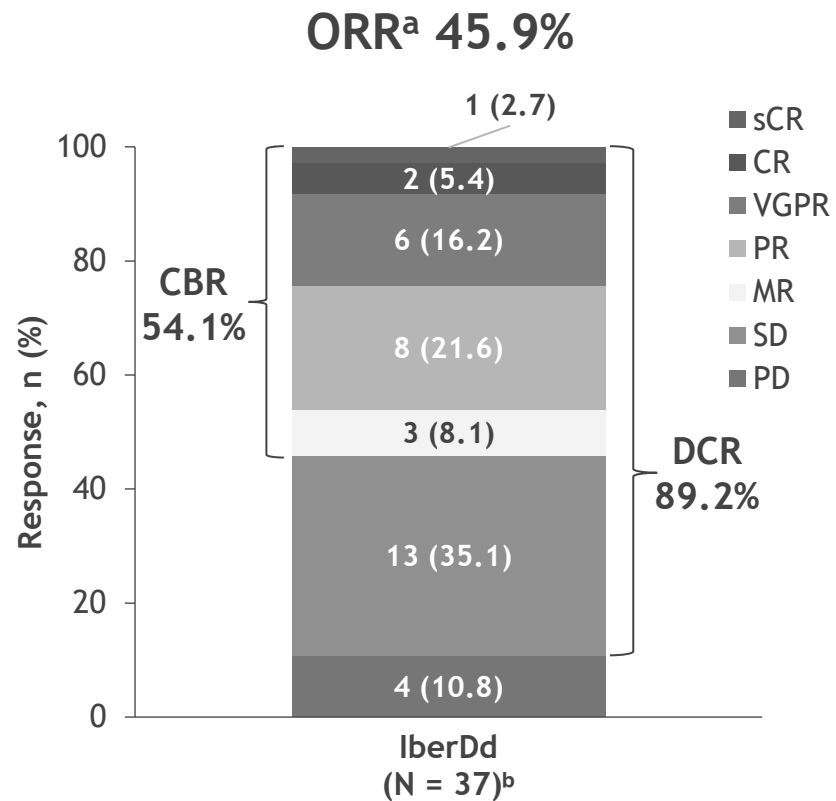
TEAEs all cycles: IberKd cohort

TEAEs of interest, n (%)	IberKd (N = 9)		
	All grade	Grade 3	Grade 4
Hematologic TEAEs			
Neutropenia	3 (33.3)	2 (22.2)	1 (11.1)
Febrile neutropenia ^a	0	0	0
Thrombocytopenia	2 (22.2)	0	1 (11.1)
Anemia	2 (22.2)	0	0
Non-hematologic TEAEs			
Diarrhea	3 (33.3)	0	0
Abdominal pain	3 (33.3)	0	0
Fatigue	3 (33.3)	1 (11.1)	0
Insomnia	3 (33.3)	0	0
Peripheral neuropathy ^b	2 (22.2)	0	0
Thrombotic event ^c	0	0	0
Infections	7 (77.8)	2 (22.2)	1 (11.1)
Upper respiratory tract infection	2 (22.2)	0	0

- No cardiovascular events or hypertension were observed

^aIncludes neutropenic sepsis; ^bIncludes peripheral sensory neuropathy; ^cIncludes pulmonary embolism and deep vein thrombosis.

Best response: IberDd cohort



- While the median duration of response was not reached, responses were ongoing in 14/17 responders
- Median time to response was 4.1 (range 4.0-12.0) weeks

Dose level	Prior reg, n	Prior DARA	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15	C16	C17	C18	C19	C20	C21	C22	C23	C24	C25
1 mg	4	Ref	PD																							
	3	Ref	SD	SD					PD																	
	7	Ref	SD	PD																						
1.1 mg	11	Ref		MR				NE		PD																
	8	Ref	SD	PD																						
1.2 mg	2	Naïve		PR						VGPR															sCR	
	4	Ref	SD	PD																						
	3	Naïve	SD	PD																						
	5	Naïve	SD							PD																
1.3 mg	4	Ref		MR				PD																		
	2	Naïve	MR		PR					VGPR																
	3	Naïve		PR				VGPR																	CR	
	5	Ref		PR																						
	11	Exp		MR						PR																
	2	Naïve	SD	PR		VGPR					CR															
	13	Ref	PD																							
	6	Ref	MR		PR						PD															
	5	Exp	SD	PD																						
	5	Ref		PR		PD																				
	2	Naïve	PR								VGPR															
1.6 mg	6	Naïve	SD	PD																						
	3	Ref	PD																							
	3	Naïve		PR																						
	4	Naïve		SD																						
	3	Ref	SD	PD																						
	3	Naïve		PR																						
	4	Ref	SD	PD																						
	12	Ref		PR							PD															
	5	Naïve									VGPR															
	3	Naïve		VGPR																						
	2	Naïve		VGPR																						
4	Naïve		SD																							
3	Naïve		VGPR																							
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3	Naïve		SD																							
5	Ref	PD																								

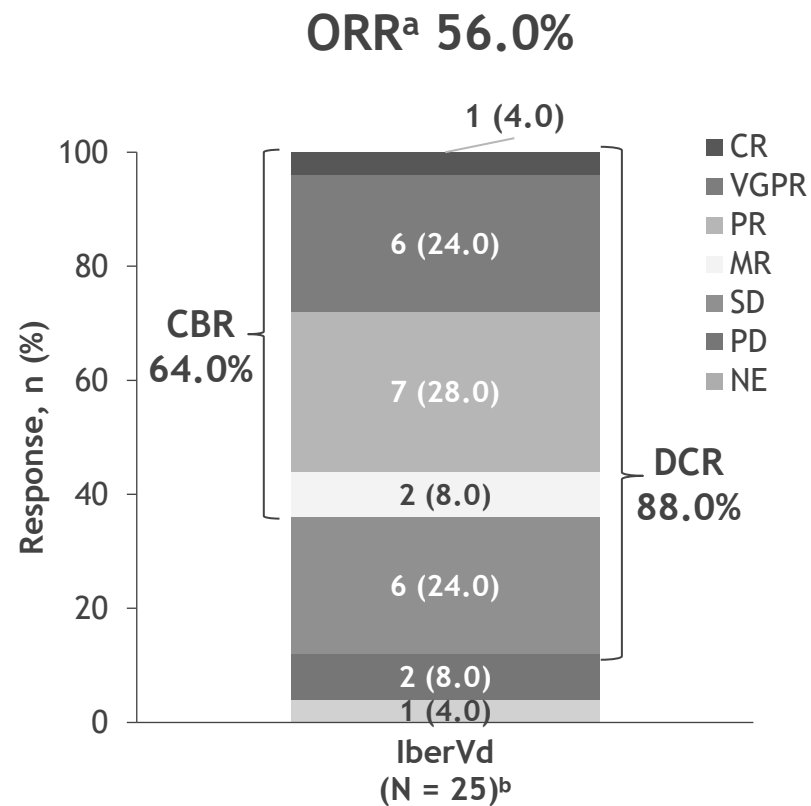
Legend:

- sCR
- CR
- VGPR
- PR
- MR
- SD
- PD
- NE
- ➔ On treatment at time of data cut

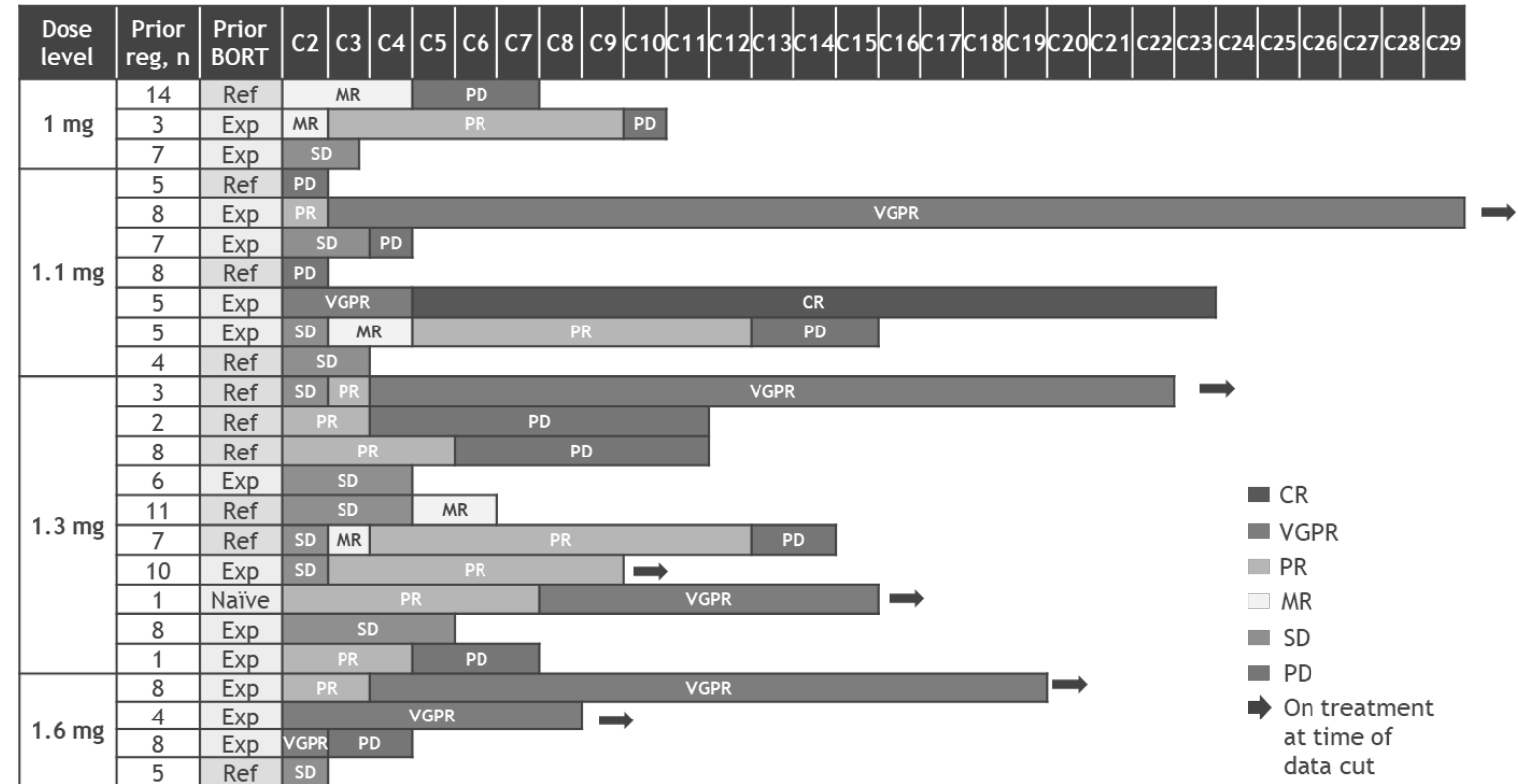
^aPR or better; ^bExcludes treated patients who did not reach any post-baseline efficacy assessment and still on treatment at the time of cutoff.

C, cycle; CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; Exp, exposed; MR, minimal response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; Ref, refractory; reg, regimen; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

Best response: IberVd cohort



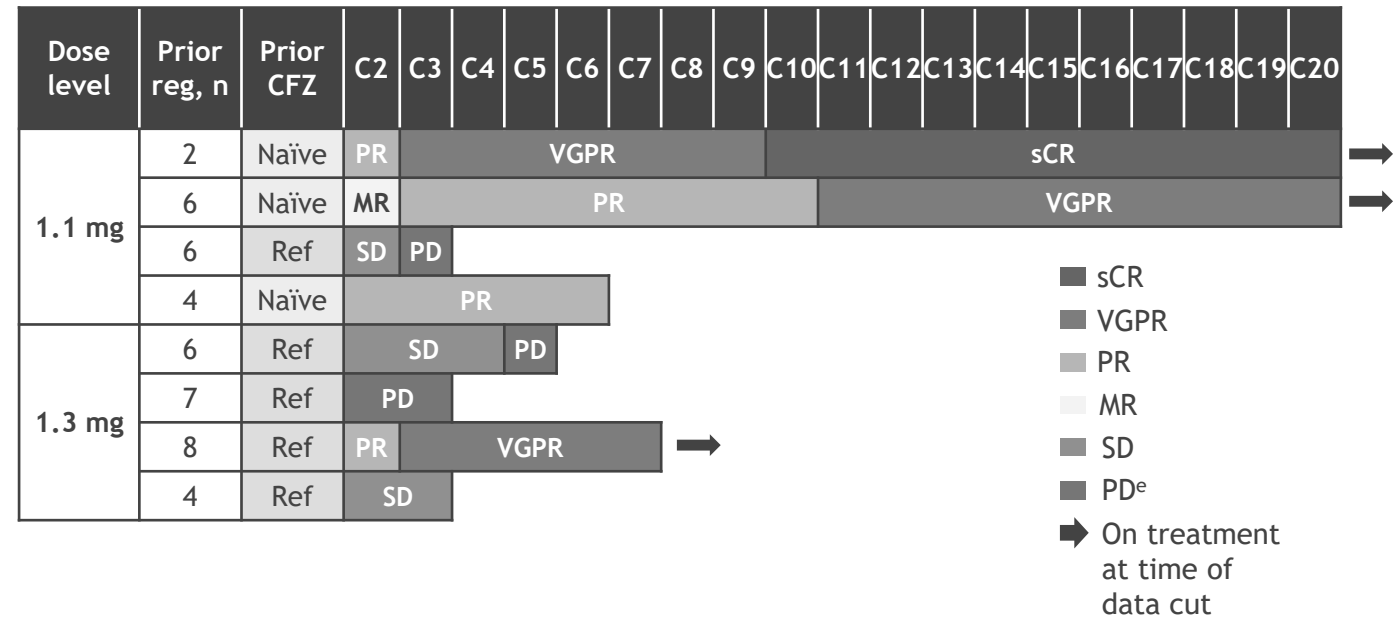
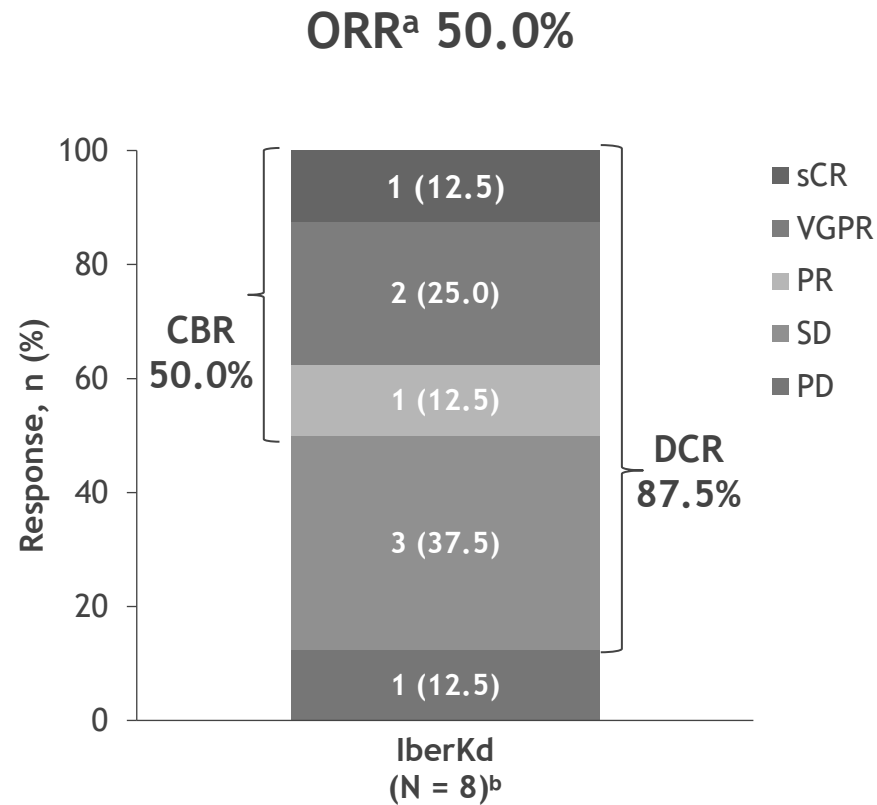
- Median duration of response was 35.7 weeks, and responses were ongoing in 7/14 responders



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

^aPR or better; ^bExcludes treated patients who did not reach any post-baseline efficacy assessment and still on treatment at the time of cutoff.

Best response: IberKd cohort



- While the median duration of response was not reached, responses were ongoing in the 4 responders
- Median time to response was 4.1 (range 4.1-8.1) weeks

^aPR or better; ^bExcludes treated patients who did not reach any post-baseline efficacy assessment and still on treatment at the time of cutoff.

Conclusions

- IBER in combination with DEX and DARA or BORT or CFZ showed a favorable safety profile in patients with heavily pretreated RRMM, with promising efficacy even among patients refractory to IMiD agents, DARA, and PIs
- Occurrence of non-hematologic TEAEs was low, with very few grade 3/4 fatigue, rash, and gastrointestinal disorders
- The RP2D was determined at 1.6 mg in the IberDd cohort, while dose evaluation continues in the IberVd and IberKd cohorts
- These results support further development of IBER-based regimens in MM, including initiation of phase 3 combination studies

Patient and site contributions

We would like to thank the patients and their families who are making the study possible, and the investigators and nurses for their contribution to the CC-220-MM-001 study



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Acknowledgments

- The clinical study teams who participated
- This study was supported by Celgene, a Bristol-Myers Squibb Company
- All authors contributed to and approved the presentation; writing and editorial assistance were provided by Mauro Locati, PhD, of Excerpta Medica, funded by Bristol Myers Squibb