Venetoclax

CELMoDs

non-BCMA-directed bispecific antibodies

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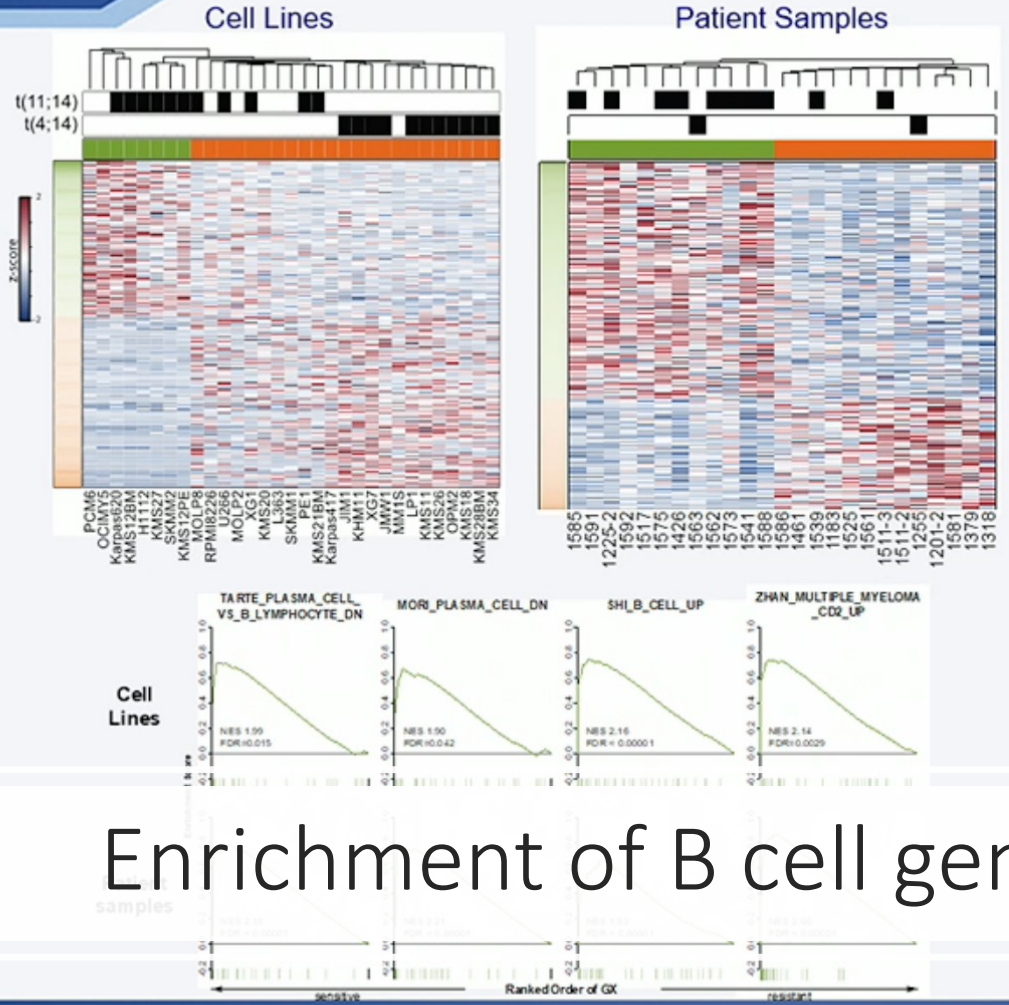
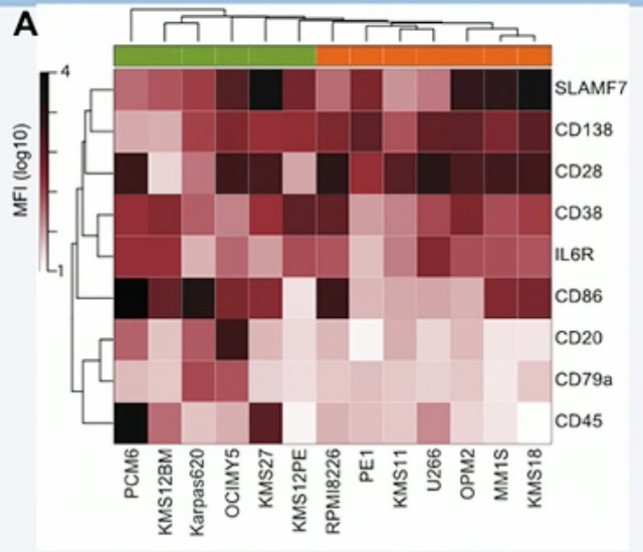
Enrichment of B cell genes in venetoclax sensitive samples.
Flow cytometry of cell surface markers predicts venetoclax sensitivity.

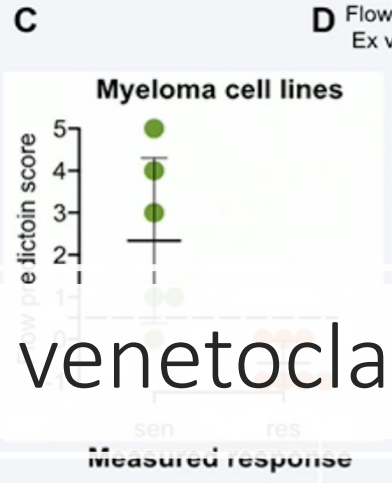


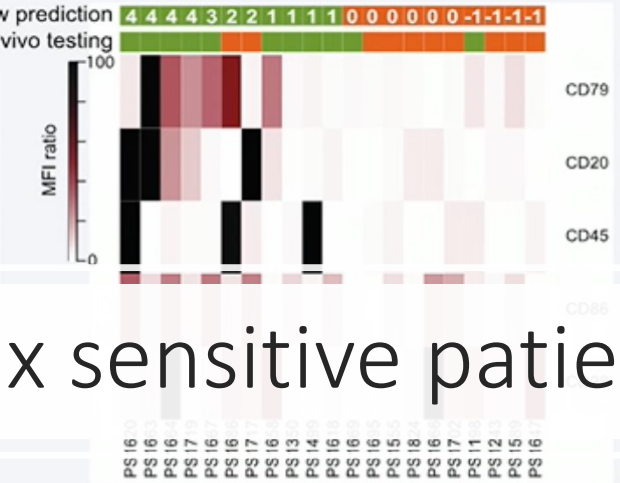


B

Marker	Score
CD79a	+2
CD20	+2
CD45	+1
CD86	+1
CD28	-1

Sensitive	Resista...
≥1	≤0





82% Sensitivity
80% Specificity
p=0.0089

Enrichment of B cell genes in venetoclax sensitive patients

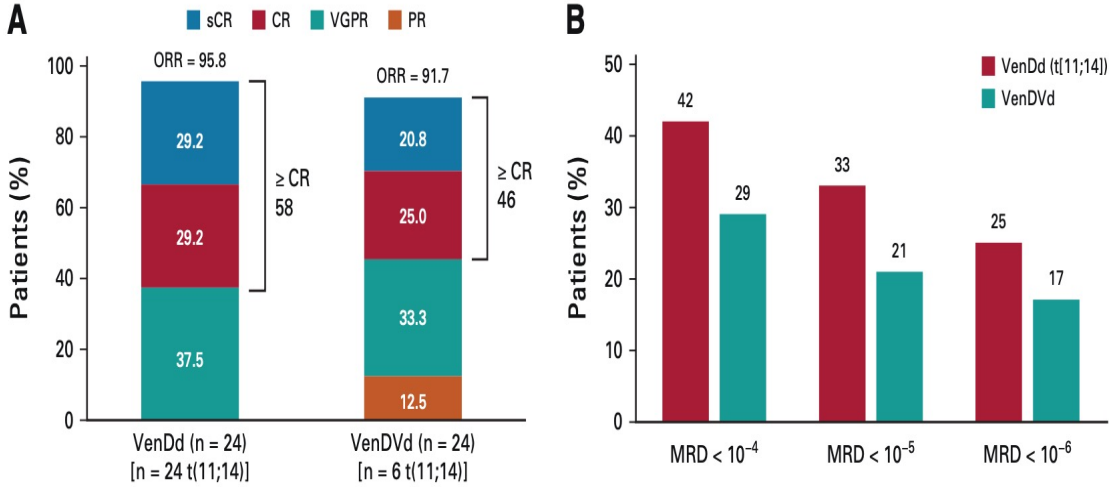
BELLINI: a renaissance for an era of precision therapy in multiple myeloma

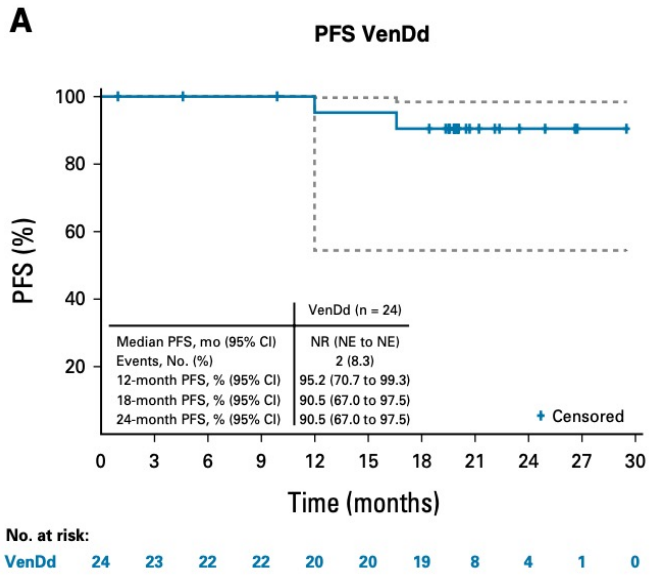
Venetoclax or placebo in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI): a randomised, double-blind, multicentre, phase 3 trial

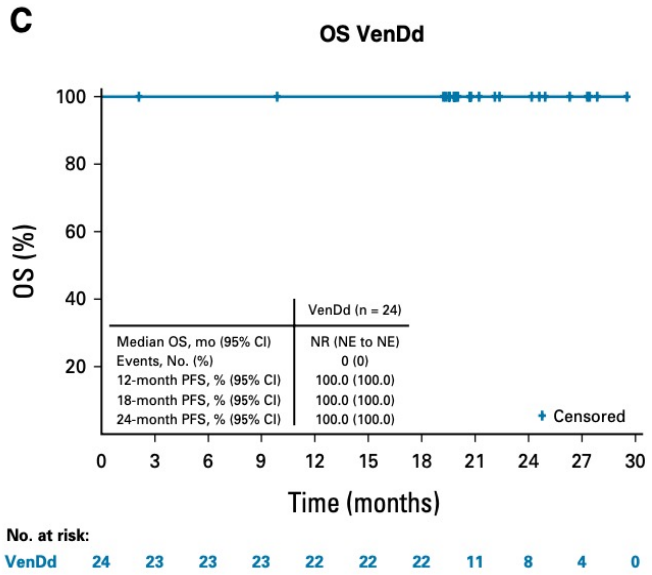
Shaji K Kumar [1], Simon J Harrison [2], Michele Cavo [3], Javier de la Rubia [4], Rakesh Popat [5], Cristina Gasparetto [6], Vania Hungria [7], Hans Salwender [8], Kenshi Suzuki [9], Inho Kim [10], Elizabeth A Punnoose [11], Wan-Jen Hong [11], Kevin J Freise [12], Xiaoqing Yang [12], Anjla Sood [12], Muhammad Jalaluddin [12], Jeremy A Ross [12], James E Ward [12], Paulo C Maciag [12], Philippe Moreau [13]

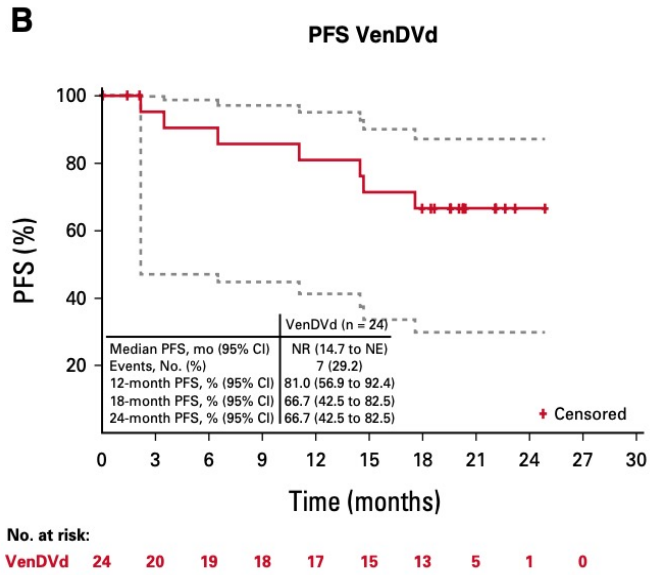
VenDaraDex and VenDaraBorDex

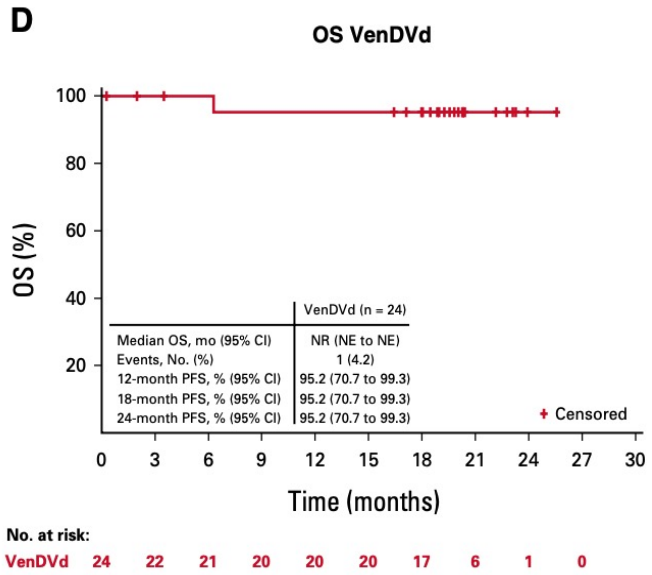
- Bahlis JCO 2021











CANOVA

- The primary end point is PFS
- Enrollment 244 patients
- At least 1 proteasome inhibitor and have disease that is refractory to lenalidomide

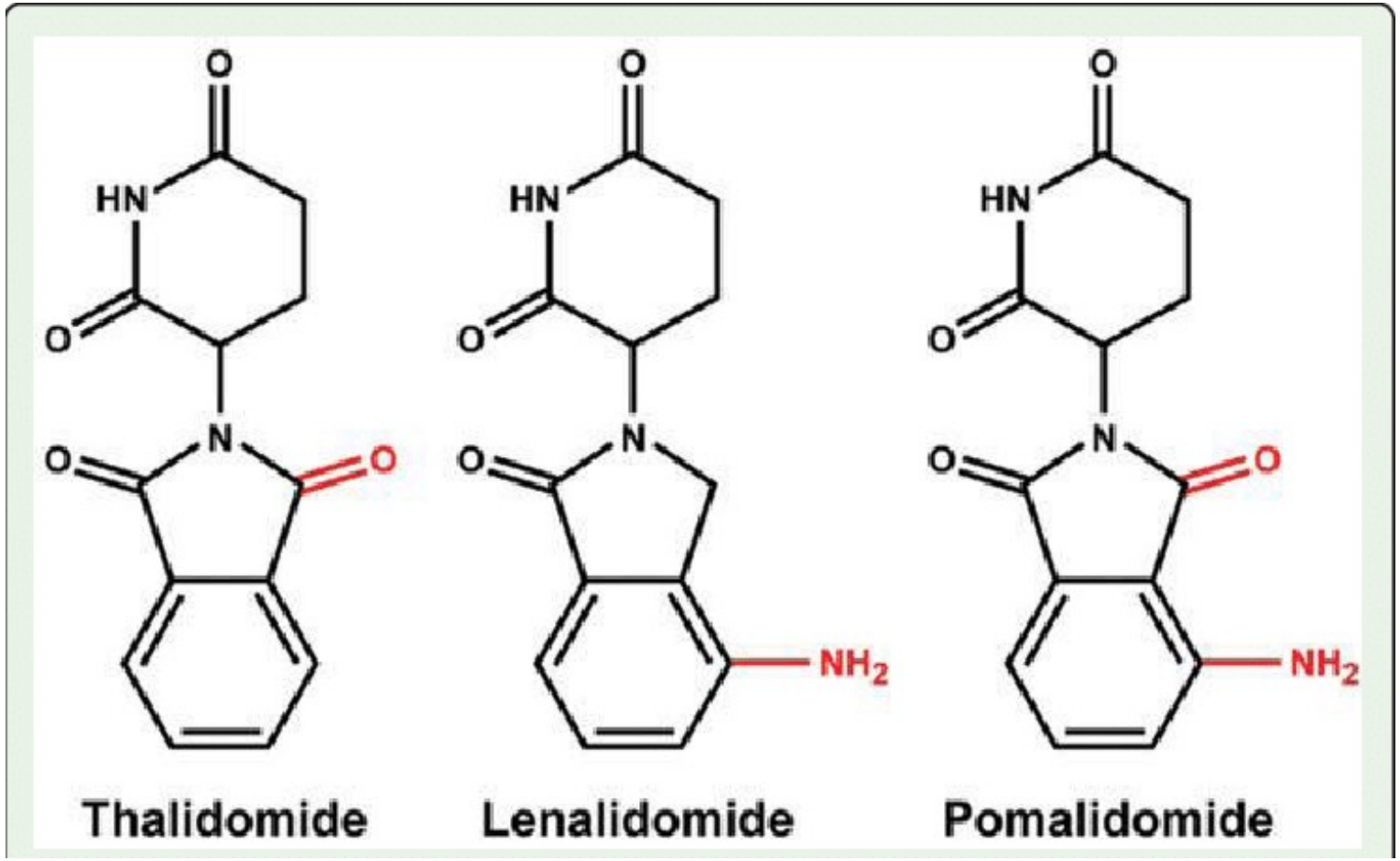
A phase III, randomized, multicenter, open-label study of venetoclax or pomalidomide in combination with dexamethasone in patients with t(11;14)-positive relapsed/refractory multiple myeloma.

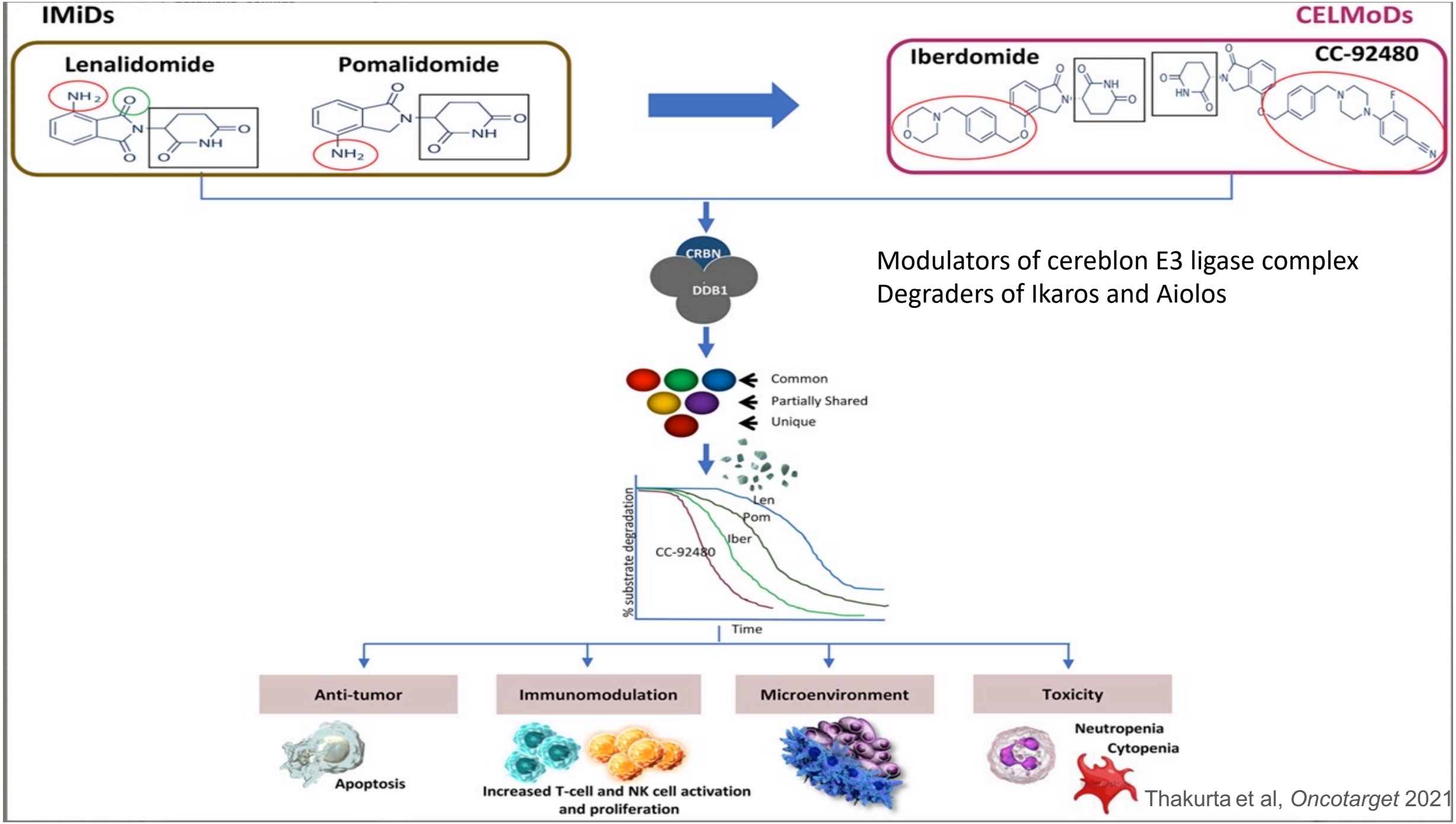
Presentations ASH 2021

- Final Overall Survival Results from BELLINI, a Phase 3 Study of Venetoclax or Placebo in Combination With Bortezomib and Dexamethasone in Relapsed/Refractory Multiple Myeloma: **Saturday, December 11, 9:45 a.m. CT**

- Safety and Preliminary Efficacy From the Expansion Cohort of a Phase 1/2 Study of Venetoclax Plus Daratumumab and Dexamethasone vs Daratumumab Plus Bortezomib and Dexamethasone in Patients With t(11;14) Relapsed/Refractory Multiple Myeloma: **Monday, December 13, 3:30 p.m.**

The First Family of IMIDS



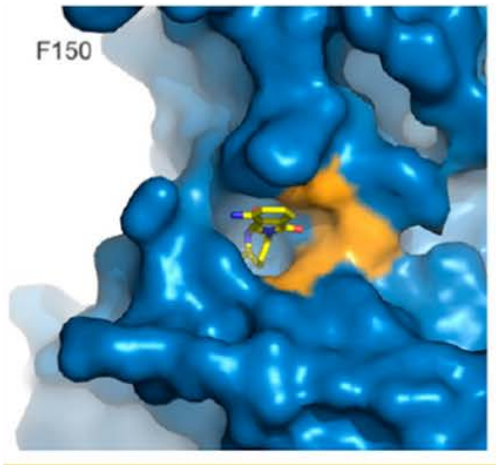


Modulators of cereblon E3 ligase complex
Degraders of Ikaros and Aiolos

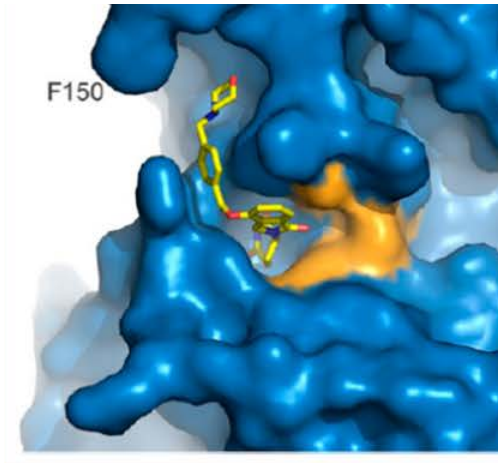
Thakurta et al, *Oncotarget* 2021

- IBER binds to CRBN with higher affinity and degrades the **target proteins Ikaros and Aiolos more potently** compared with LEN and POM[1]

LEN[2]



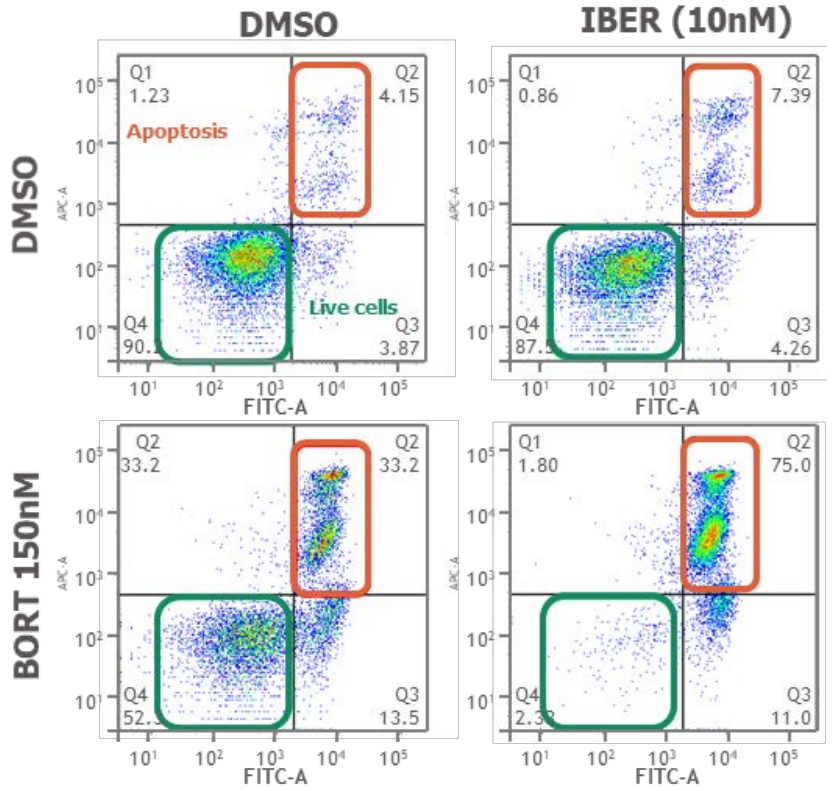
IBER[2]



EC_{50}, nM^2	Ikaros	Aiolos
LEN	67	87
POM	24	22
IBER	1	0.5

- IBER has marked synergistic tumoricidal and immune-stimulatory effects in combination with BORT or DARA in preclinical MM models[3-6]

Synergy with BORT

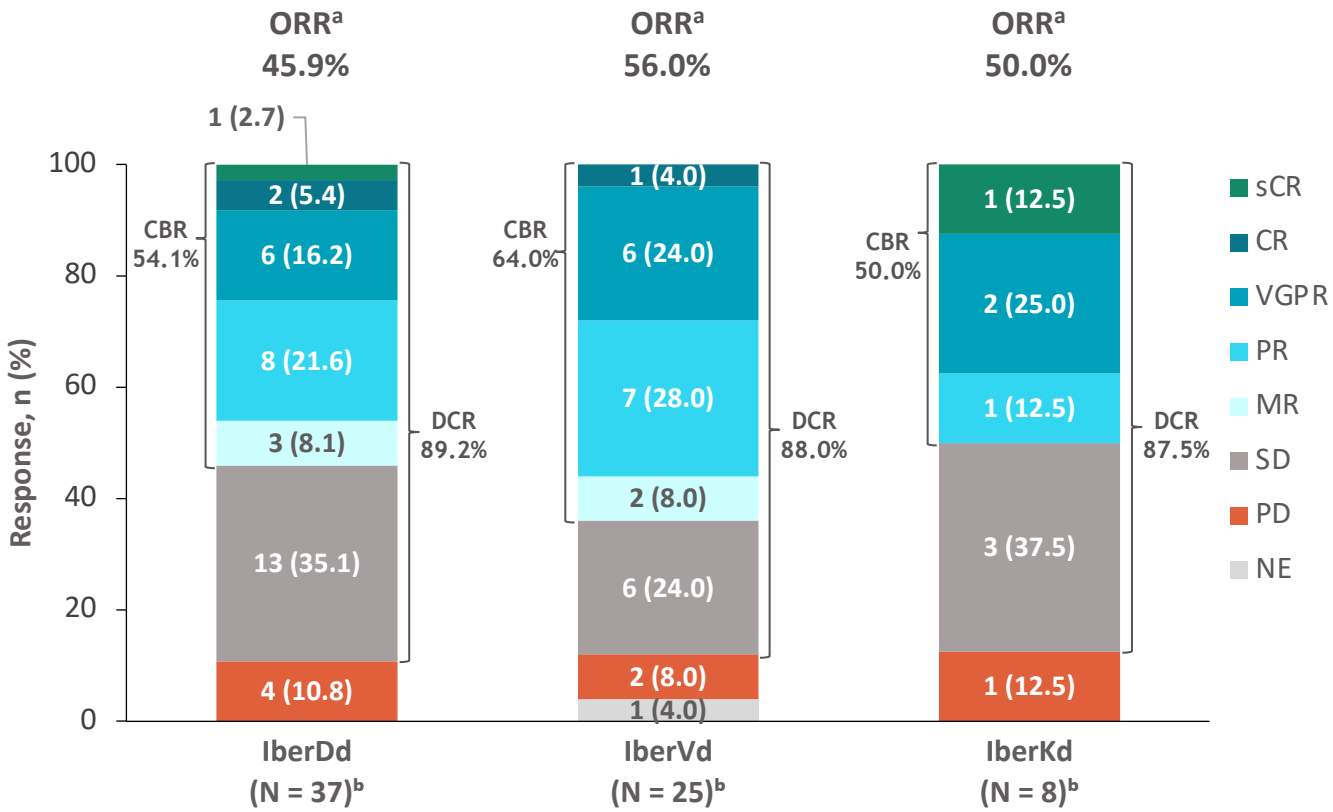


- BORT, bortezomib; DARA, daratumumab; DMSO, dimethyl sulfoxide; EC50, half-maximal effective concentration; FITC, fluorescein isothiocyanate.
- 1. Bjorklund CC, et al. *Leukemia* 2020:34:1197–1201. 2. Adapted with permission from Matyskiela ME, et al. *J Med Chem* 2018;61:535-542 © 2018 American Chemical Society. 3. Amatangelo M, et al. *Blood* 2018; 132:1935; 4. Lonial S, et al. *Blood* 2019;134:3119. 5. Amatangelo M, et al. Presented at ASH 2020; December 5-8. Abstract 1358. 6. Amatangelo M, et al. Presented at ASH 2020; December 5-8. Abstract 1359.

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

Sagar Lonial, et al.

- IBER + DEX in combination with DARA or BORT or CFZ showed a favorable safety profile in patients with heavily pretreated RRMM; TEAEs were mainly hematologic and well manageable
- The RP2D was determined at 1.6 mg in the IberDd cohort, while dose evaluation continues in the IberVd and IberKd cohorts
- Promising efficacy was observed even among patients refractory to IMiD® agents, DARA, and PIs



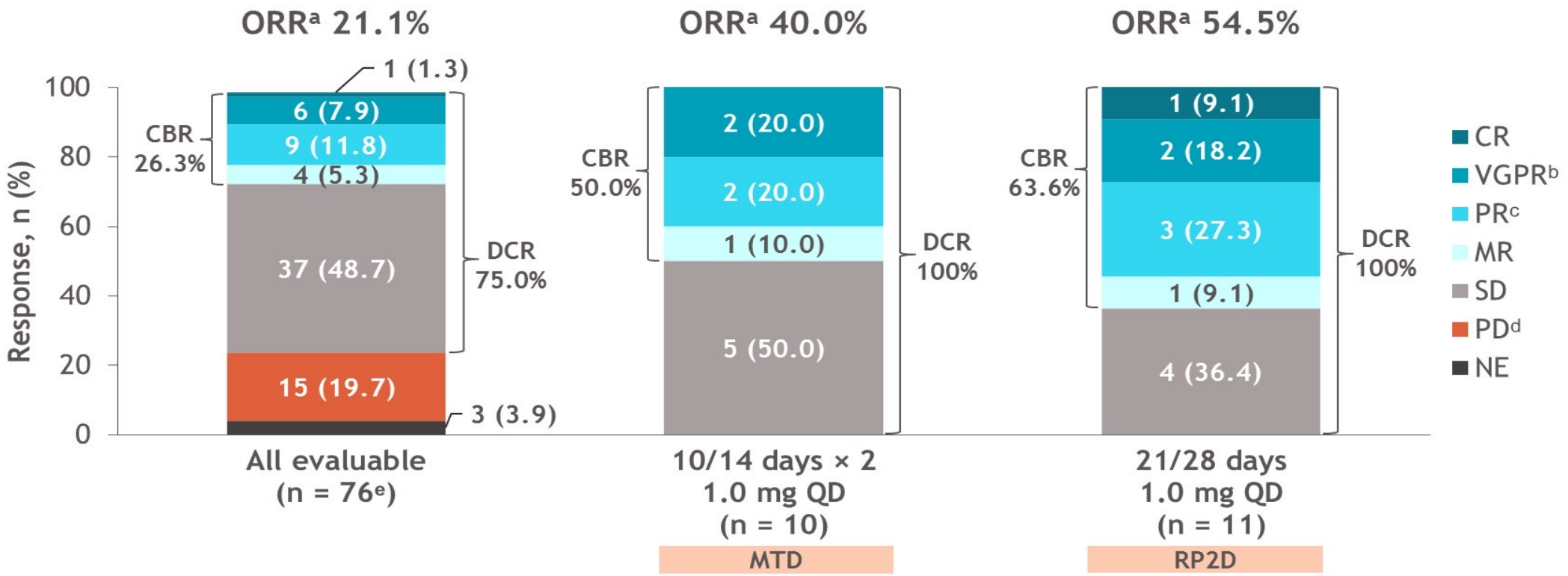
[a]PR or better; [b]Excludes treated patients who did not reach any post-baseline efficacy assessment and were still on treatment at the time of cutoff.

BORT, bortezomib; CBR, clinical benefit rate; CFZ, carfilzomib; CR, complete response; DARA, daratumumab; DCR, disease control rate; DEX, dexamethasone; IBER, iberdomide; IberDd, IBER+DARA+DEX; IberKd, IBER+CFZ+DEX; IberVd, IBER+BORT+DEX; IMiD, immunomodulatory drug; MR, minimal response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PI, proteasome inhibitor; PR, partial response; RP2D, recommended phase 2 dose; RRMM, relapsed/refractory multiple myeloma; sCR, stringent complete response; SD, stable disease; TEAE, treatment-emergent adverse event; VGPR, very good partial response.

New CELMoD- CC92480

CC-92480-MM-001

Best response



- At the RP2D 1.0 mg QD 21/28 days, 7 out of 11 patients were triple-class-refractory[f]
  - 1 patient had CR, 1 VGPR, 2 PR, and 1 MR

[a]PR or better; [b]1 patient in the 21/28-day 1.0 mg QD cohort had an unconfirmed VGPR as of the data cutoff date; [c]2 patients in the 21/28-day 0.8 mg QD cohort had an unconfirmed PR as of the data cutoff date; [d]1 patient in the 21/28-day 0.8 mg QD cohort had an unconfirmed PD as of the data cutoff date; [e]1 patient had a pending response assessment at data cutoff date; [f]Defined as refractory to ≥ 1 IMiD agent, 1 PI, and 1 anti-CD38 mAb.

CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; MR, minimal response; MTD, maximum tolerated dose; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; QD, once daily; RP2D, recommended phase 2 dose; SD, stable disease; VGPR, very good partial response.

Responses in patients with EMP

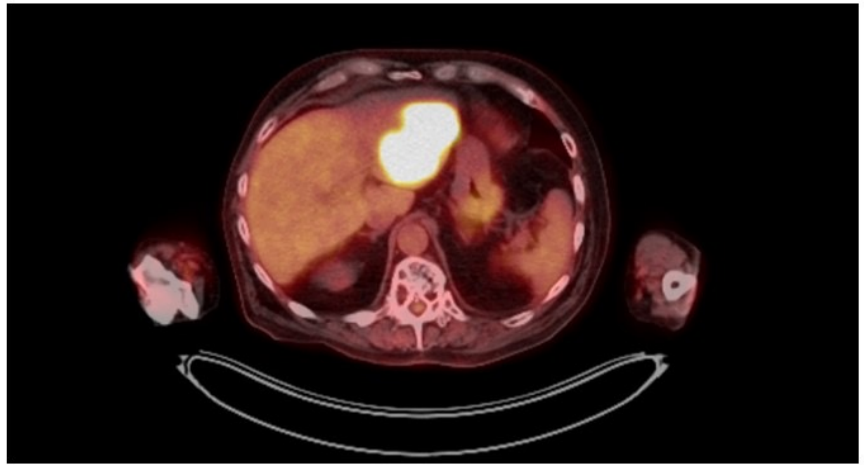
- Only patients on continuous schedules are shown

Dosing schedule[a]	Dose level	C2	C3	C4	C5	C6	C7	C8	C9	C10
10/14 days × 2	0.1 mg QD	SD	PD							
	0.2 mg QD	PD								
	0.3 mg QD	SD	PD							
		PD								
	0.6 mg QD	PD								
		SD	PD							
21/28 days	0.8 mg QD	SD								
		SD								
		SD	PD							
		PR								
		SD								
10/14 days × 2	1.0 mg QD	MR	PR			VGPR				
		SD								
		SD			PR					
21/28 days	1.0 mg QD	PR		PD						
		SD	PR	VGPR						
		PR		VGPR		CR				
		PR (case study)								
		SD								

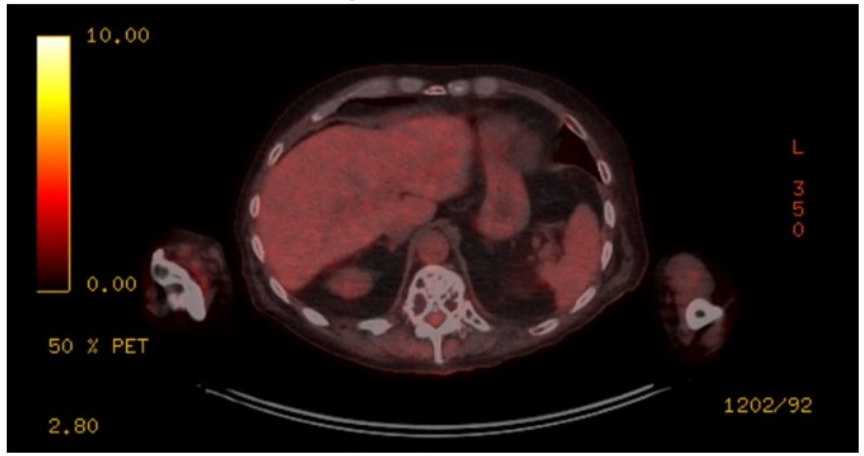
CR
VGPR[a]
PR[b]
MR
SD
PD[c]
On treatment at time of data cut

1.0 mg dose active in EMP

PET scan pretreatment



PET scan post-CC-92480 C3D1

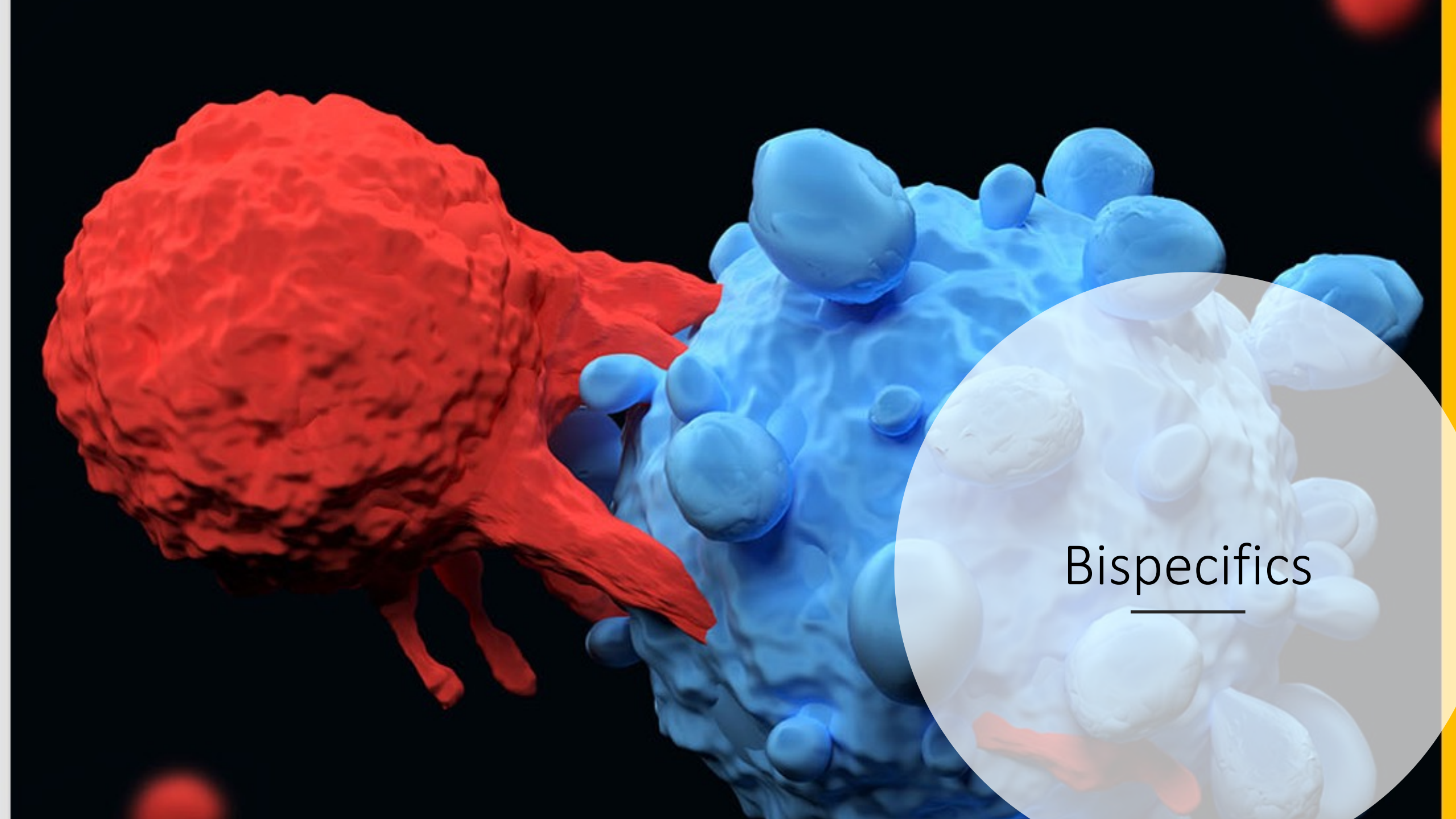


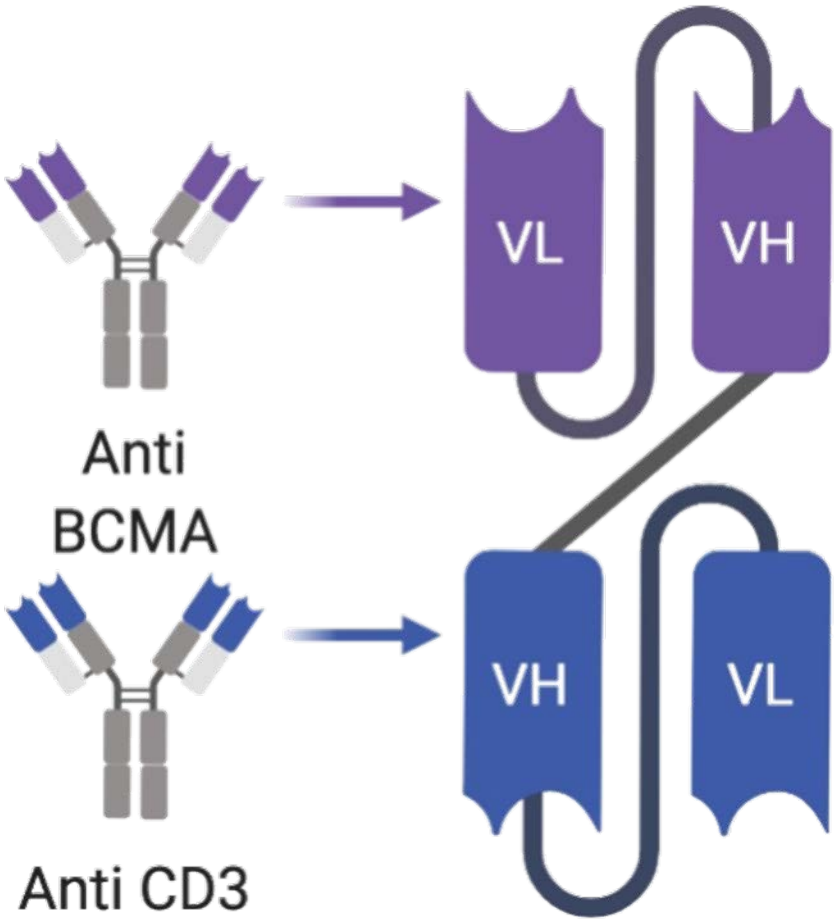
[a]1 patient in the 21/28-day 1.0 mg QD cohort had an unconfirmed VGPR as of the data cutoff date;
[b]1 patient in the 21/28-day 0.8 mg QD cohort had an unconfirmed PR as of the data cutoff date;
[c]1 patient in the 21/28-day 0.8 mg QD cohort had an unconfirmed PD as of the data cutoff date.

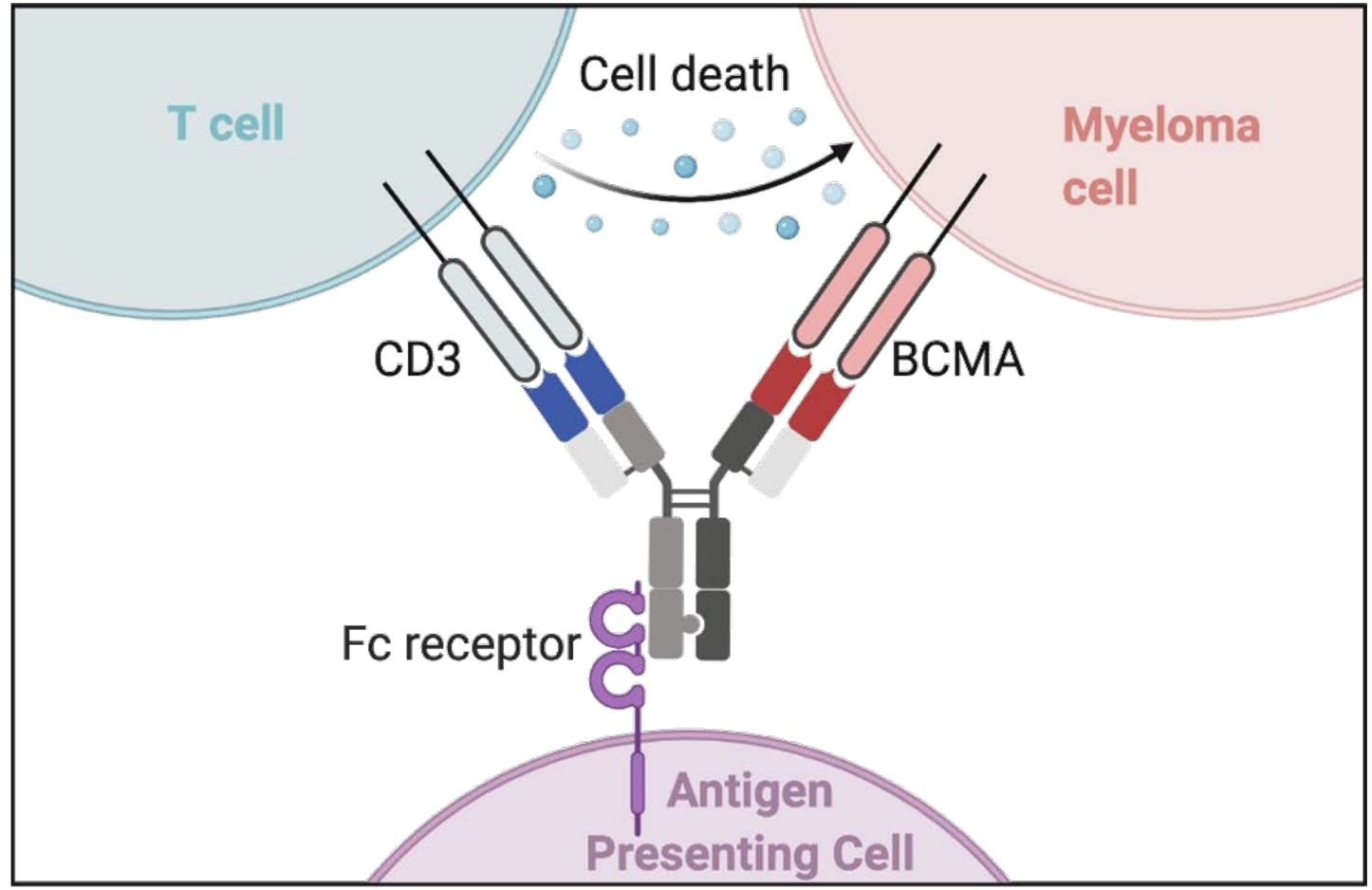
C, Cycle; CR, complete response; D, Day; EMP, extramedullary plasmacytoma; MR, minimal response; PD, progressive disease; PET, positron emission tomography; PR, partial response; QD, once daily; SD, stable disease; VGPR, very good partial response.

Iberdomide presentations in ASH 2021

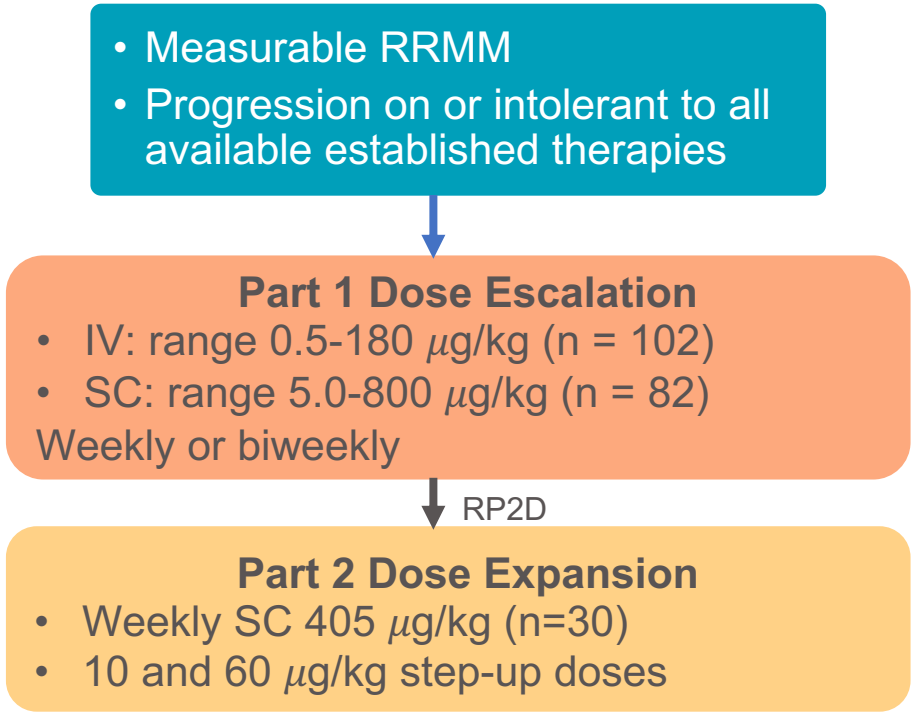
IBER in Combination with Dexamethasone (DEX) in Patients (pts) with Relapsed/Refractory Multiple Myeloma (RRMM): Results from the Dose-Expansion Phase of the CC-220-MM-001 Trial	Sagar Lonial	Oral Abstract #162	653. Myeloma and Plasma Cell Dyscrasias: Clinical-Prospective Therapeutic Trials: Novel Targets and Amyloid	Saturday, December 11, 1:15 PM
CC-92480, a Potent, Novel Cereblon E3 Ligase Modulator (CELMoD) Agent, in Combination with Dexamethasone (DEX) and Bortezomib (BORT) in Patients (pts) with Relapsed/Refractory Multiple Myeloma (RRMM): Preliminary Results from the Phase 1/2 Study CC-92480-MM-002	Paul Richardson	Poster Abstract #2731	653. Myeloma and Plasma Cell Dyscrasias: Clinical-Prospective Therapeutic Trials: Poster II	Sunday, December 12 6:00 - 8:00 PM
Large-Scale Mass Cytometry Reveals Significant Activation of Innate and Adaptive Immunity in Bone Marrow Tumor Microenvironment of Iberdomide-Treated Myeloma Patients	Oliver Van Oekelen	Oral Abstract #730	651. Multiple Myeloma and Plasma Cell Dyscrasias: Basic and Translational: The Myeloma Immune Microenvironment	Monday, December 13, 3:30 PM


Bispecifics


Anti
BCMA
VL
VH
Anti CD3
VH
VL


T cell
Cell death
Myeloma
cell
CD3
BCMA
Fc receptor
Antigen
Presenting Cell

MonumenTAL-1 (TALQUETAMAB) DESIGN AND CHARACTERISTICS



NCT03399799

Key objectives

- **Part 1:** Identify RP2D
- **Part 2:** Safety and tolerability
- Antitumor activity, pharmacokinetics, pharmacodynamics

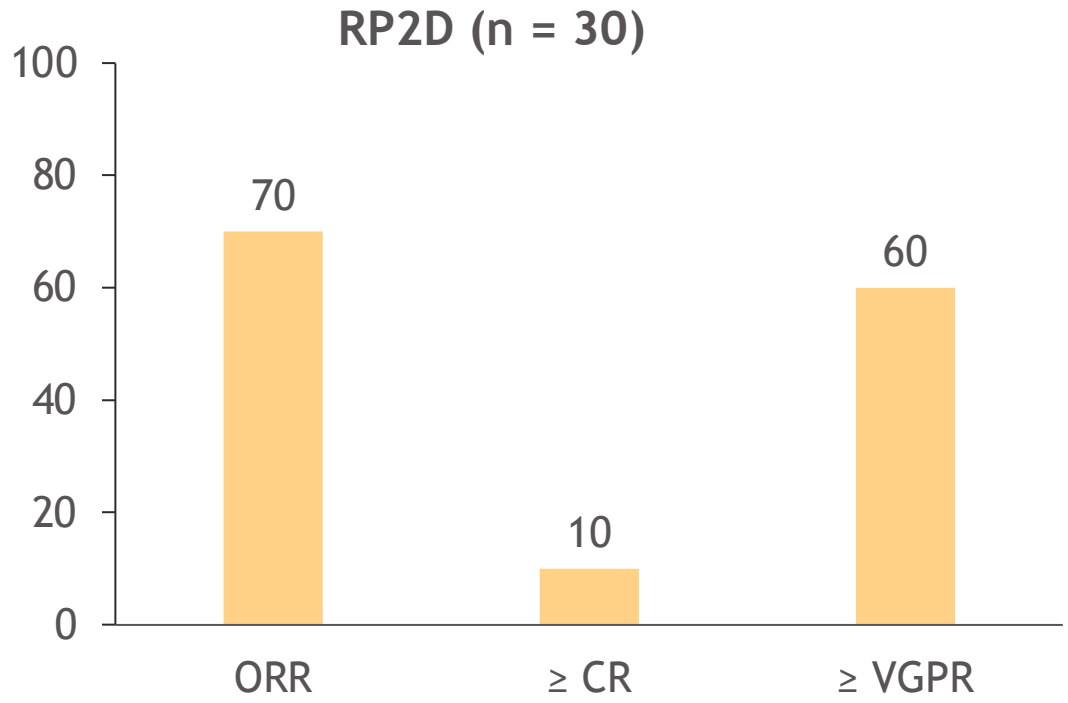
Characteristic	RP2D (n = 30)
Age, median (range), y	61.5 (46-80)
Prior LoT, median (range)	6.0 (2-14)
Triple-class/penta-drug exposed, %	100/80
Triple-class/penta-drug refractory, %	77/20
Refractory to last LoT, %	87
Prior BCMA-directed therapy, %	27
Duration of follow-up, median (range), mo	6.3 (1.4-12.0)

Berdeja J et al. ASCO 2021. Oral Presentation 8008.

MonumenTAL-1 (TALQUETAMAB) EFFICACY

Outcome	RP2D (n = 30)
Median time to first confirmed response (range), mo	1.0 (0.2-3.8)
ORR in triple-class refractory pts (n=23), %	65.2
ORR in penta-drug refractory pts (n=6), %	83.3
Median DOR, months	NR

- Of 6 evaluable pts across all cohorts, 4 with CR/sCR were MRD-negative at 10^{-6}, including 1 patient in the RP2D cohort
- MRD negativity was sustained 7 months post CR in 1 evaluable patient



Berdeja J et al. ASCO 2021. Oral Presentation 8008.

MonumenTAL-1 (TALQUETAMAB) SAFETY AND CONCLUSIONS

Adverse Events	RP2D (n = 30)
CRS (Gr 3), %	73 (3)
Time to onset, median (range), d	2 (1-22)
Duration, median (range), d	2 (1-3)
Neutropenia (Gr 3/4), %	67 (60)
Anemia (Gr 3/4), %	57 (27)
Dysgeusia (Gr 3/4), %	60 (NA)
Infections (Gr 3/4), %	37 (3)
Neurotoxicity (Gr 3/4), %	7 (0)
Skin-related AEs (Gr 3/4), %	77 (NR)
Nail disorders, %	27

- No DLTs at the RP2D
- No deaths due to AEs at the RP2D

[a] 400 µg/kg selected as final dosing concentration in phase 2 for operational convenience.

Berdeja J et al. ASCO 2021. Oral Presentation 8008.

Authors' Conclusions

- Talquetamab is an off-the-shelf T-cell redirecting, GPRC5D targeting agent that requires limited steroid use and has a manageable safety profile at a dose of 405 µg/kg SC QW
- Additional patients and longer follow-up support the RP2D
  - A high response rate (70% ORR) was observed
  - High response rate was maintained in triple-refractory and penta-refractory patients (65% and 84%, respectively)
  - Responses were durable and continued to deepen over time
  - Pharmacokinetic and pharmacodynamic data continue to support the RP2D
- Talquetamab showed encouraging efficacy in heavily pretreated patients with RRMM
  - A phase 2 expansion study of talquetamab at the RP2D[a] is in progress (NCT04634552)

Bispecific antibodies clinical data summary

	MagnetisMM Elranatamab	*MajesTEC* Teclistamab	AMG-701	REGN5458	TNB-383B	*MonumenTAL* Talquetamab	Cevostamab
Targets	BCMA	BCMA	BCMA	BCMA	BCMA	GPRC5D	FcRH5
Follow-up, median (range)		6.1 mos. (1.2–12.2)	6.5 mos.	2.6 mos.		6.3 (1.4-12.0)	8.1 mos. (0.2-30.4)
Prior LoT, median (range)	Txs: 8 (3–15)	5 (2-11)	6 (2-25)	5 (2-17)	6 (3-15)	6 (2-14)	6 (2-15)
Refractory to last LoT		83%		61%	81%	87%	94%
Triple refractory	87%	83%	62%	100%	64%	77%	72%
Prior anti-BCMA tx	23%					27%	
Extramedullary disease		20%	25%			33%	17%
ORR	70% at ≥ 215 µg/kg	65%	83% at RP2D	62% at RP2D	80% at 40-60 mg	70%	53%
≥CR	30%	40%	9.8%	42%	13% at 40-60 mg	**10%**	**18% at ≥3.6/20**
MRD negative	3/4 pts with prior anti-BCMA tx	10^{-6}: 5/6 pts with CR/sCR	6/7 pts tested	4/7 pts	3 out of 4	10^{-6}: 1 pt with CR/sCR	6/7 ≥ VGPR
All grade/grade ≥3 infections		45%/23%	NR / 17%	47% / 18%	21% / 14%	37%/3%	
CRS, all grade/grade ≥3	73% / 0%	70%/0	65%/9%	39% / 0%	45% / 0%	**73% / 3%**	**76% / 2%**
Median onset, d (range)	1 (1–3)	2 (1–6)		18 hrs (6-382)	<24hrs	2 (1-22)	12hrs
Median duration, d (range)	3 (1–10)	2 (1–8)		11 hrs (0-77)	24hrs	2 (1-3)	
Toci/Steroid use	30%/10%	35%/13%	29%/17%	32% / 21%	25% / 17%	60%/3%	25% / 17%

158 Updated Phase 1 Results from MonumenTAL-1: First-in-Human Study of Talquetamab, a G Protein-Coupled Receptor Family C Group 5 Member D x CD3 Bispecific Antibody, in Patients with Relapsed/Refractory Multiple Myeloma

Program: Oral and Poster Abstracts
Type: Oral
Session: 653. Myeloma and Plasma Cell Dyscrasias: Clinical-Prospective Therapeutic Trials: Novel Targets and Amyloid
Hematology Disease Topics & Pathways:
Clinical Trials, Biological, Bispecific Antibody Therapy, Clinical Research, Plasma Cell Disorders, Diseases, Therapies, Immunotherapy, Lymphoid Malignancies

Saturday, December 11, 2021: 12:15 PM

157 Cevostamab Monotherapy Continues to Show Clinically Meaningful Activity and Manageable Safety in Patients with Heavily Pre-Treated Relapsed/Refractory Multiple Myeloma (RRMM): Updated Results from an Ongoing Phase I Study

Program: Oral and Poster Abstracts
Type: Oral
Session: 653. Myeloma and Plasma Cell Dyscrasias: Clinical-Prospective Therapeutic Trials: Novel Targets and Amyloid
Hematology Disease Topics & Pathways:
Biological, Bispecific Antibody Therapy, Diseases, Therapies, Lymphoid Malignancies

Saturday, December 11, 2021: 12:00 PM

Suzanne Trudel, MD[1], *Adam D Cohen, MD*[2], *Amrita Y. Krishnan, MD*[3], *Rafael Fonseca*[4], *Andrew Spencer*[5], *Jesús G. Berdeja*[6], *Alexander Lesokhin, MD*[7], *Peter A Forsberg*[8], *Jacob P. Laubach*[9*], *Luciano J. Costa, MD, PhD*[10], *Paula Rodriguez-Otero*[11*], *Rayan Kaedbey*[12], *Joshua Richter, MD*[13], *Maria-Victoria Mateos*[14], *Sheeba K Thomas, MD, MS*[15], *Chihunt Wong*[16*], *Mengsong Li*[16*], *Voleak Choeurng*[16*], *Anjali Vaze*[16*], *Divya Samineni*[16*], *Teiko Sumiyoshi*[16*], *James Cooper*[16*] *and Simon J Harrison, MD*[17]