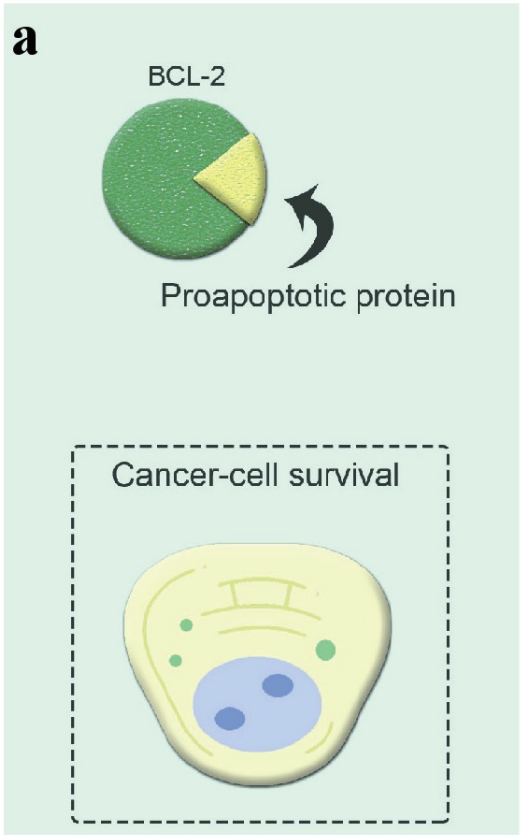
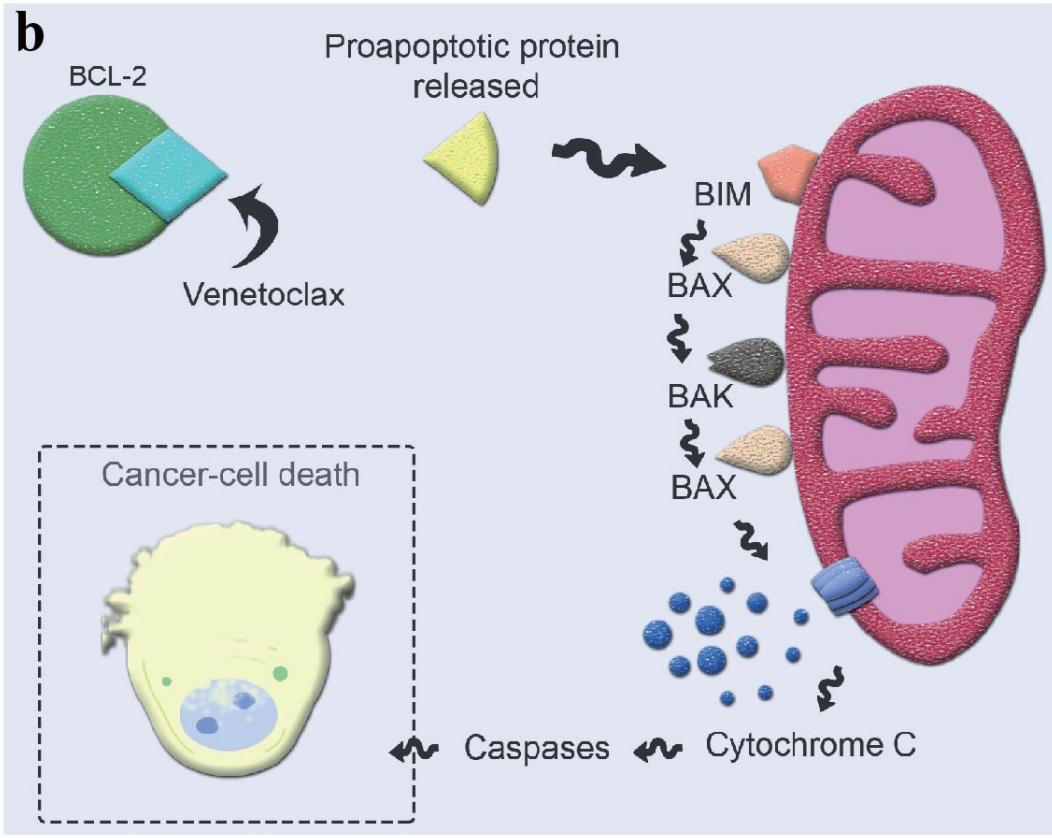
Novel Agents and Strategies Under Investigation in Multiple Myeloma

Muhamed Baljevic, MD, FACP
Assistant Professor of Medicine
Division of Hematology / Medical Oncology
University of Nebraska Medical Center
Dr_MBaljevic

Targeting Bcl-2 in Multiple Myeloma

- BCL-2 prosurvival family proteins preferentially dictate survival of human MM cells with t(11;14)
- ~ 20% of the patients with MM have t(11;14) with overexpression of BCL-2
- Resistance to venetoclax is mitigated by co-treatment with other agents such as glucocorticoids or PIs

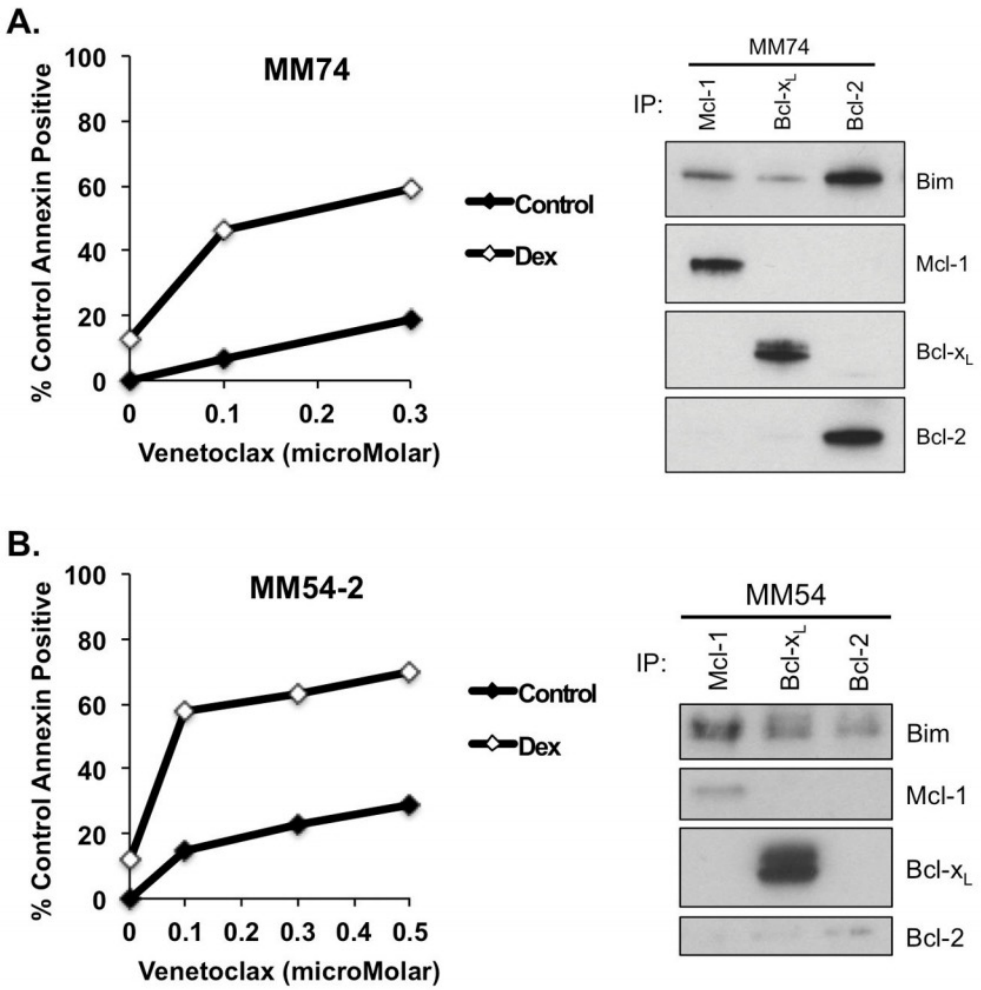


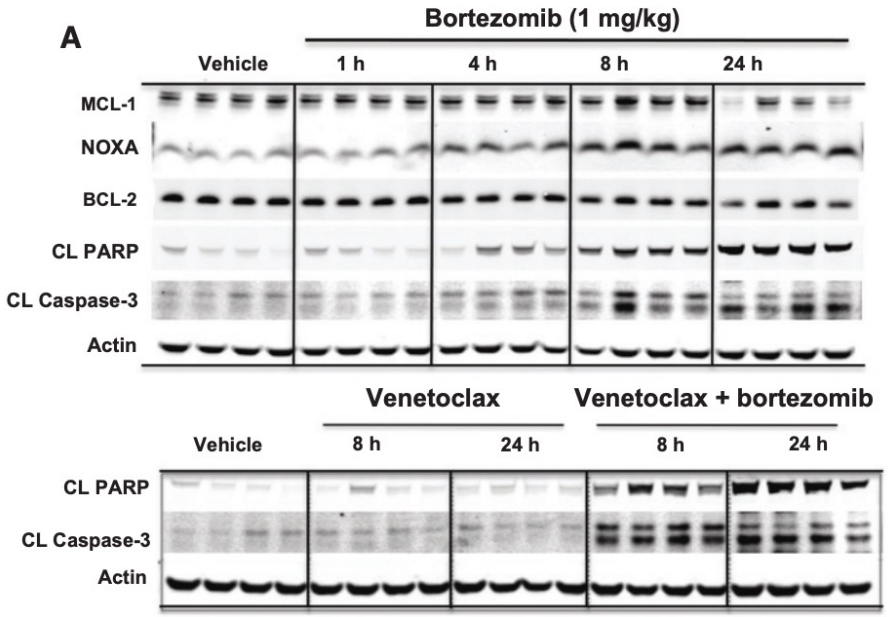


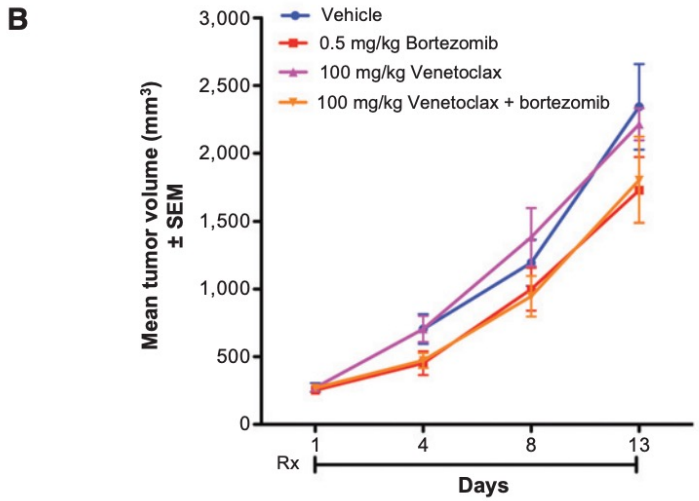
J Hematol. 2021 Jun;10(3):89-97.

Venetoclax Synergy with Dexamethasone or Bortezomib

Plasma Cells From MM Patients







Matulis. Leukemia. 2016;30:1086; Mol Cancer Ther. 2016 May;15(5):1132-44.

Selected Completed Venetoclax Studies in R/R MM

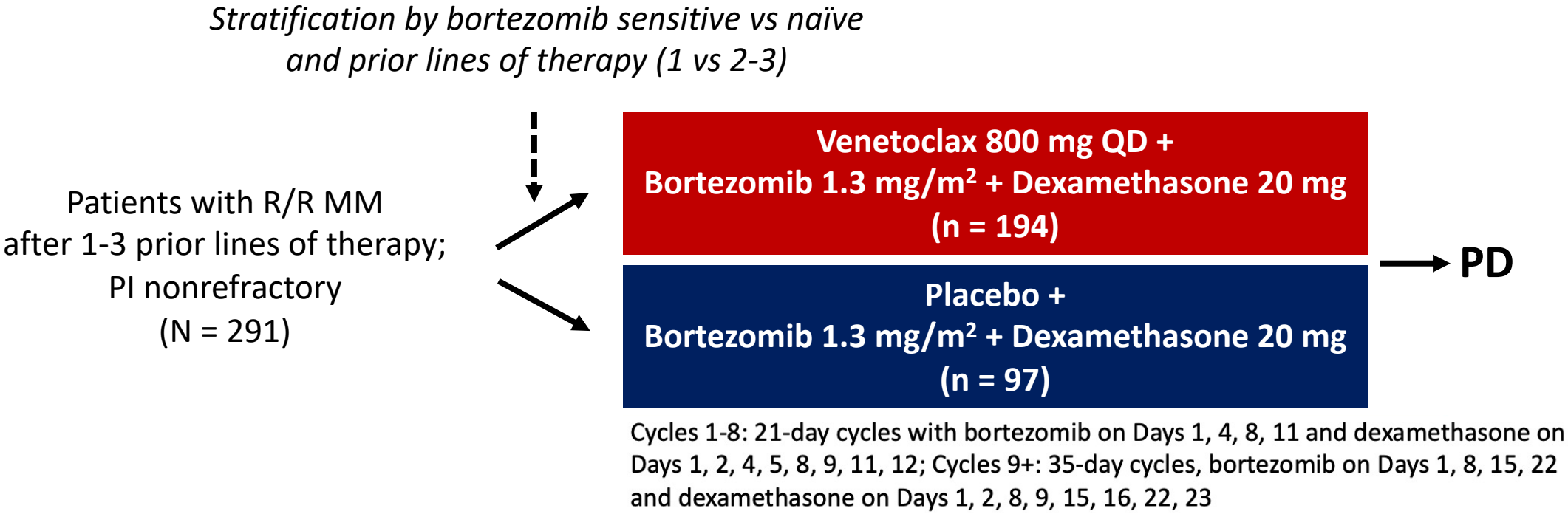
Author, year	Study type	Number of patients	Prior lines of therapy, median (range)	Cytogenetics t (11;14)	Regimens	ORR
Kumar et al, 2017 [12]	Phase I	66	5 (1 - 15)	46%	VEN	
Moreau et al, 2017 [14]	Phase Ib	66	3 (1 - 13)	14%	VEN + V + Dex	
Costa et al, 2018 [16]	Phase II	42	1 (1 - 3)	23%	VEN + K + Dex	
Kaufman et al, 2019 [13]	Phase I/II	Phase I: 20 Phase II: 31	Phase I: 2.5 (1 - 7) Phase II: 5 (1 - 9)	Phase I: 100%	VEN + Dex	65%
Sidiqi et al, 2019 [18]	Retrospective	56	6 (1 - 15)	75%	VEN ± Dex VEN + Dex + PI ± IMiDs	
Basali et al, 2020 [20]	Prospective	10	6 (2 - 19)	100%	VEN + V + Dex	78%
Kaufman et al, 2020 [17]	Phase I/II	Part 1: 24 Part 2: 24	Part 1: ≥ 1 Part 2: (1 - 3)	Part 1: 100% Part 2: 25%	VEN + D + Dex ± V	96% 96%
Kambhampati et al, 2020 [19]	Retrospective	43	7 (2 - 13)	38%	A: VEN + PI B: VEN + PI + Dex	
Kumar et al (BELLINI trial), 2020 [15]	Phase III	VEN: 194 Pbo: 97	(1 - 3)	11%	VEN + V + Dex	

VEN: venetoclax; PI: proteasome inhibitor; V: bortezomib; K: carfilzomib; D: daratumumab; Dex: dexamethasone; Pbo: placebo; IMiDs: immunomodulatory drugs.

J Hematol. 2021 Jun;10(3):89-97.

BELLINI Phase III Trial in R/R MM

- Double-blind, randomized 2:1, placebo-controlled Phase III trial



- Primary endpoint: PFS (per IRC)
- Key secondary endpoints: ORR, ≥VGPR, OS, QoL/PRO parameters

Kumar et al. ASCO 2020; Abstract 8509.

BELLINI: Patient Characteristics

Characteristic	Ven + Vd (n = 194)	Pbo + Vd (n = 97)
Median age, yrs (range)	66 (36-87)	65 (44-83)
▪ ≥ 65 yrs, n (%)	108 (56)	52 (54)
Male, n (%)	97 (50)	55 (57)
Multiple myeloma ISS,* n (%)		
▪ Stage 1	81 (42)	48 (50)
▪ Stage 2	69 (36)	32 (33)
▪ Stage 3	39 (20)	13 (13)
ECOG PS,* n (%)		
▪ 0	101 (52)	47 (49)
▪ 1 or 2	92 (48)	49 (51)
No. of prior lines of therapy, n (%)		
▪ 1	91 (47)	44 (45)
▪ 2 or 3	103 (53)	53 (55)
Prior stem cell transplant, n (%)	116 (60)	57 (59)

Characteristic, n (%)	Ven + Vd (n = 194)	Pbo + Vd (n = 97)
Prior exposure to PI	135 (70)	68 (70)
Prior exposure to IMiD	131 (68)	65 (67)
Cytogenetics		
▪ High-risk†	31 (17)	18 (19)
▪ Standard-risk‡	141 (78)	72 (77)
▪ Unknown/missing§	22 (11)	7 (7)
t(11;14) status*		
▪ Positive	20 (10)	15 (16)
▪ Negative	152 (84)	74 (79)
▪ Unknown§	22 (11)	8 (8)
BCL-2 expression (IHC)*		
▪ High	93 (78)	47 (81)
▪ Low	26 (22)	11 (19)

*Percentage calculated by excluding patients with missing data.
† t(4;14) or t(14;16) or del(17p).
‡ No high-risk cytogenetics.
§ Sample tested but results inconclusive.

Kumar et al. ASCO 2020; Abstract 8509.

BELLINI: Efficacy and Safety

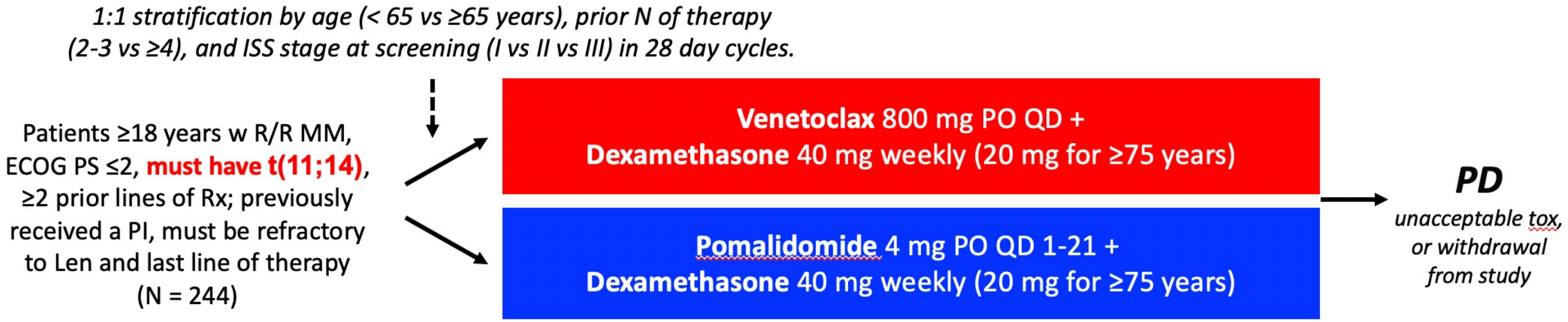
Outcome	Ven + Vd (n = 194)	Pbo + Vd (n = 97)	Significance (95% CI)
Median PFS, mos	23.22	11.41	HR: 0.60 (0.43-0.82); *P* = .0013
Median OS, mos	33.5	NR	HR: 1.46 (0.91-2.33); *P* = .112
▪ ≥ VGPR	63	40	*P* < .001
▪ ≥ CR	29	7	*P* < .001
▪ MRD % < 10^{-4}	21	4	*P* < .001
▪ MRD % < 10^{-5}	15	2	*P* < .002
▪ MRD % < 10^{-6}	8	1	*P* = .037
Median DoR, mos	NR	12.8	HR: 0.46 (0.30-0.71); *P* <.001
Median TTP, mos	NR	12.2	HR: 0.55 (0.38-0.79); *P* = .001

Group, HR (95% CI)	PFS	OS
t(11;14) or *BCL2*^{high} with standard-risk cytogenetics	0.32 (0.17-0.59)	0.90 (0.36-2.27)
t(11;14) or *BCL2*^{high} with high-risk cytogenetics	0.23 (0.04-1.21)	0.95 (0.12-7.49)
Non-t(11;14) or *BCL2*^{low} with standard-risk cytogenetics	0.71 (0.43-1.15)	1.35 (0.68-2.26)
Non-t(11;14) or *BCL2*^{low} with high-risk cytogenetics	1.88 (0.64-5.49)	6.01 (0.76-47.23)

Deaths, n (%)	Ven + Vd (n = 193)	Pbo + Vd (n = 96)
All	63 (33)	24 (25)
Treatment emergent	12 (6)	1 (1)
Within 30 days of last dose	14 (7)	1 (1)
> 30 days after last dose	49 (25)	23 (24)

Kumar et al. ASCO 2020; Abstract 8509.

CANOVA Phase III Trial in R/R MM



The primary endpoint: **PFS** per IRC assessment based on IMWG criteria.
The final PFS analysis will be performed when approximately 147 PFS events per IRC are observed.
Secondary endpoints: RR, PROs, OS, DOR, TTTR and TTTP, MRD(-)rate, safety, and Ven pharmacokinetics.

As of January 21, 2020: 28 patients have been randomized (from 19 sites in 12 countries) and enrollment is ongoing.
Estimated Study Completion Date: March 24. 2024

Selected Ongoing Venetoclax Studies in R/R MM

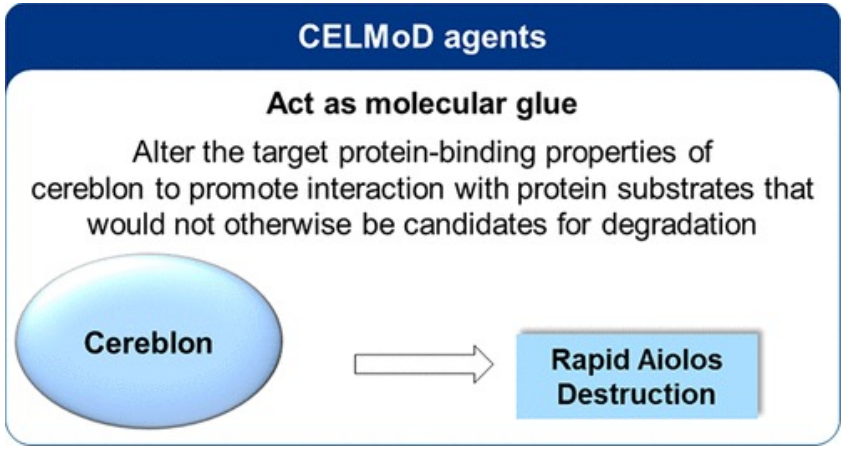
NCT ID	Phase	Population	Regimen	Estimated completion
NCT02899052	II	RRMM	VEN + carfilzomib + dexamethasone	2025
NCT03539744	III	t (11;14)-positive RRMM	VEN + dexamethasone vs. pomalidomide + dexamethasone	2024
NCT03312530	I/II	RRMM	VEN + cobimetinib ± atezolizumab	2020
NCT03567616	II	RRMM	VEN + pomalidomide + dexamethasone	2020
NCT03314181	II	t (11;14)-positive RRMM	VEN + daratumumab + dexamethasone ± bortezomib	2024
NCT01794520	I/II	t (11;14)-positive RRMM	VEN + dexamethasone	2021
NCT02265731	I/II	RRMM	VEN	2021
NCT03732703	I/II	t (11;14)-positive RRMM	VEN + ixazomib + pomalidomide + dexamethasone	2022

[a]Only clinical trials registered on https://clinicaltrials.gov/ are listed. RRMM: relapsed refractory multiple myeloma; VEN: venetoclax; NCT: national clinical trial.

J Hematol. 2021 Jun;10(3):89-97.

Cereblon E3 Ligase Modulators (CELMoDs)

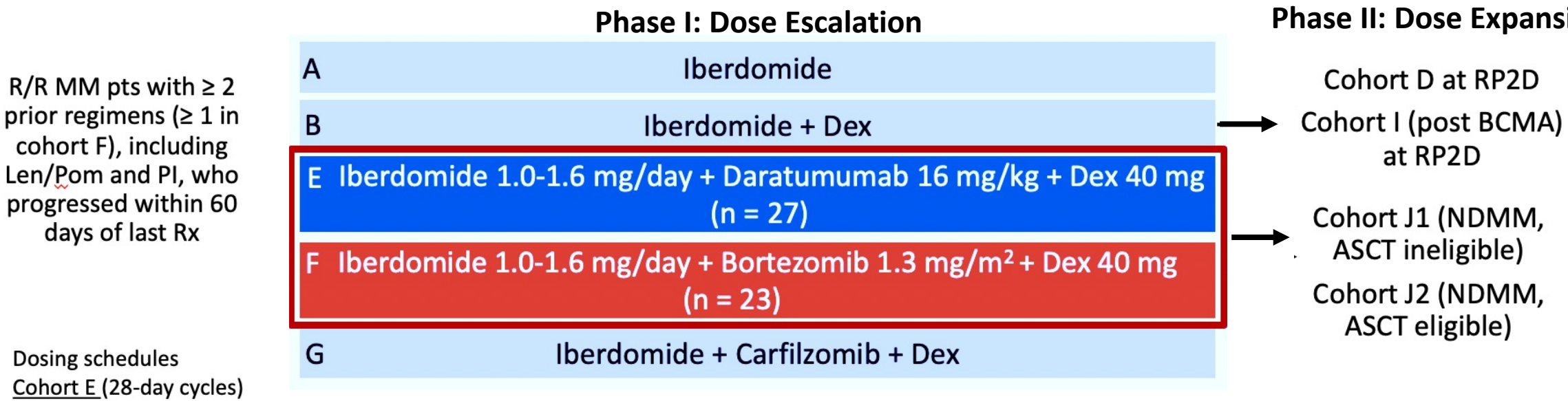
- Immunomodulatory drugs (IMiDs) are cornerstone agents in the treatment of all phases of MM; however, IMiD-relapsed and/or refractory MM is unfortunately common
- Iberdomide (CC-220): a novel small molecule inhibitor of *cereblon E3 ligase modulator*
  - Binding to cereblon induces degradation of target proteins, including *Ikaros* and *Aiolos*
  - Binds cereblon with 20X higher affinity than Lenalidomide and Pomalidomide
  - In preclinical models: demonstrated direct anti-MM and IMiD activity
  - Exhibits *enhanced apoptosis* and Ab-dependent cellular toxicity *synergistically* with Bortezomib and Daratumumab



Matyskiela. J Med Chem. 2018;61:535; Bjorklund. ASH 2016. Abstr 1591; Amatangelo. Blood. 2018;132:Abstr 1935; J Med Chem. 2020 Jul 9;63(13):6648-6676.

CC-220-MM-001 Phase I/II Study Design: Iberdomide + Dd or Vd in R/R MM

Open label dose-escalation/dose-expansion trial



Dosing schedules
Cohort E (28-day cycles)
Iberdomide D1-21
Dexamethasone D1,8,15,22
Daratumumab C1-2: D1,8,15,22; C3-6: D1,15; C7+: D1
Cohort F (21-day cycles)
Iberdomide D1-14
Dexamethasone D1,8,15
Bortezomib C1-8: D1,4,8,11; C9+: D1,8

- Primary endpoints: Identify MTD and RP2D, efficacy
- Secondary endpoint: Safety
- RP2D of 1.6 mg/day determined for iberdomide with Dex; cohorts E, F continuing enrollment with 1.6 mg/day dose

Van De Donk NWCJ et al. ASH 2020; Abstract 724.

CC-220-MM-001 Phase I/II Study: Iberdomide + Dd or Vd in R/R MM Efficacy

Best Response, n (%)	Iber + Dd (n = 27)	Iber + Vd (n = 23)
ORR	11 (42.3)	14 (60.9)
▪ sCR	1 (3.8)	0
▪ CR	2 (7.7)	1 (4.3)
▪ VGPR	2 (7.7)	5 (21.7)
▪ PR	6 (23.1)	8 (34.8)
MR	2 (7.7)	2 (8.7)
SD	10 (38.5)	4 (17.4)
PD	3 (11.5)	2 (8.7)
NE	0	1 (4.3)
CBR (MR or better)	13 (50)	16 (69.6)
DCR (SD or better)	23 (88.5)	20 (87.0)
Median time to response, wks (range)	4.1 (4.0-12.0)	3.6 (3.0-13.1)

- **<u>Iber + Dd patient characteristics (Cohort E)</u>**
  26/27 IMiD refractory
  15/27 Daratumumab refractory
  13/27 Triple-class refractory
  4/27 Daratumumab refractory pts achieved PR

- **<u>Iber + Vd patient characteristics (Cohort F)</u>**
  18/23 IMiD refractory
  15/23 PI refractory
  9/23 Bortezomib refractory
  9/23 Triple-class refractory
  Durable responses in PI exposed or refractory pts

- Addition of Dara or BTZ to Iber + Dex showed minimal effect on pharmacodynamics

Van De Donk NWCJ et al. ASH 2020; Abstract 724.

CC-220-MM-001 Phase I/II Study: Iberdomide + Dd or Vd in R/R MM Safety

TEAEs of interest, n (%)	IBER + DARA + DEX (N = 27)		
	All grade	Grade 3	Grade 4
Hematologic TEAEs			
Neutropenia	19 (70.4)	4 (14.8)	14 (51.9)
Febrile neutropenia	1 (3.7)	0	1 (3.7)
Thrombocytopenia	11 (40.7)	3 (11.1)	1 (3.7)
Anemia	10 (37.0)	7 (25.9)	1 (3.7)
Non-hematologic TEAEs			
Fatigue	9 (33.3)	0	0
Diarrhea	6 (22.2)	1 (3.7)	0
Constipation	6 (22.2)	0	0
Rash	3 (11.1)	0	0
Peripheral neuropathy	2 (7.4)	0	0
Infusion-related reaction	1 (3.7)	0	0
Thrombotic event	0	0	0
Infections	21 (77.8)	3 (11.1)	2 (7.4)
Upper respiratory tract infection	10 (37.0)	0	0

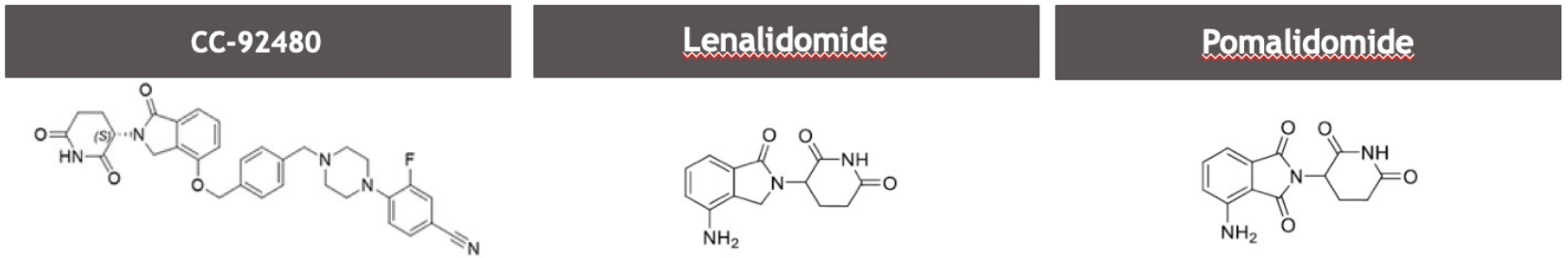
No incidence of VTE events (including PE or DVT) reported in either cohort

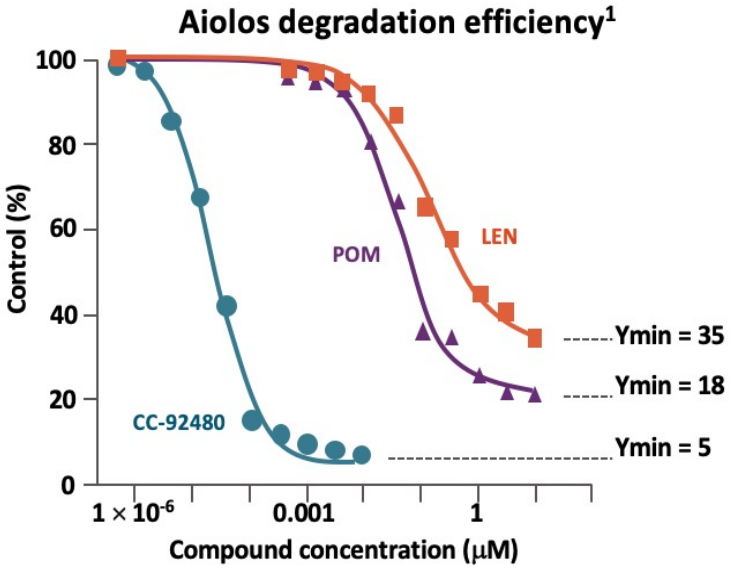
TEAEs of interest, n (%)	IBER + BORT + DEX (N = 23)		
	All grade	Grade 3	Grade 4
Hematologic TEAEs			
Neutropenia	8 (34.8)	5 (21.7)	1 (4.3)
Febrile neutropenia	0	0	0
Thrombocytopenia	8 (34.8)	1 (4.3)	5 (21.7)
Anemia	5 (21.7)	3 (13.0)	0
Non-hematologic TEAEs			
Peripheral neuropathy	7 (30.4)	0	0
Diarrhea	7 (30.4)	1 (4.3)	0
Decreased appetite	7 (30.4)	0	0
Fatigue	6 (26.1)	0	0
Rash	6 (26.1)	1 (4.3)	0
Myalgia	5 (21.7)	0	0
Insomnia	5 (21.7)	0	0
Pruritus	5 (21.7)	0	0
Constipation	5 (21.7)	0	0
Thrombotic event	0	0	0
Infections	14 (60.9)	3 (13.0)	0
Upper respiratory tract infection	7 (30.4)	2 (8.7)	0

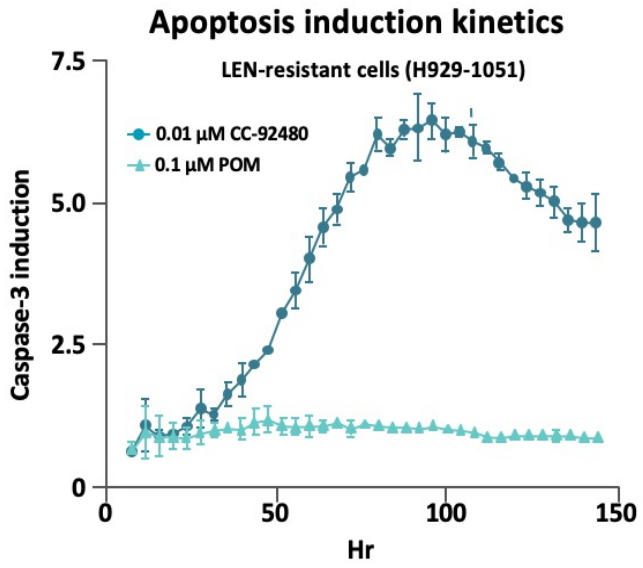
Van De Donk NWCJ et al. ASH 2020; Abstract 724.

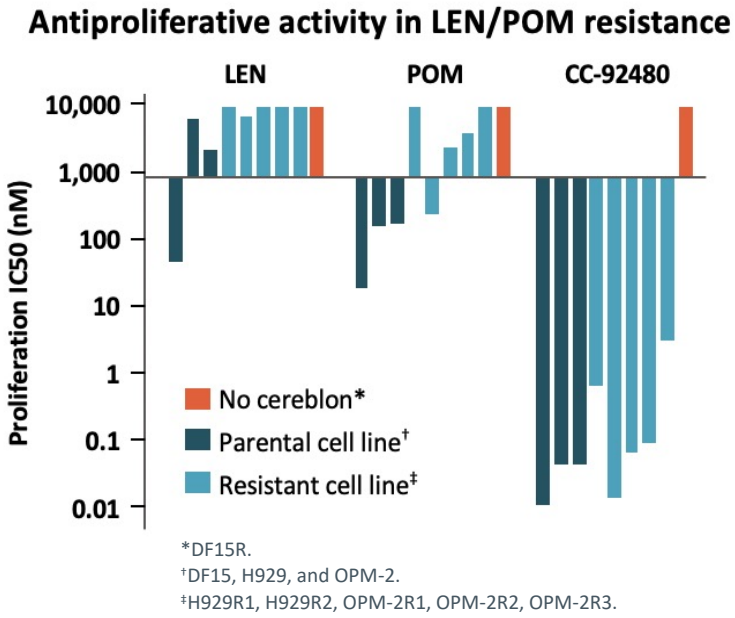
CC-92480 is a Novel CELMoD

- Designed for rapid protein degradation
- Resulting efficient substrate degradation leads to apoptosis + potent activity in Lenalidomide and Pomalidomide resistant MM









*DF15R.
†DF15, H929, and OPM-2.
‡H929R1, H929R2, OPM-2R1, OPM-2R2, OPM-2R3.

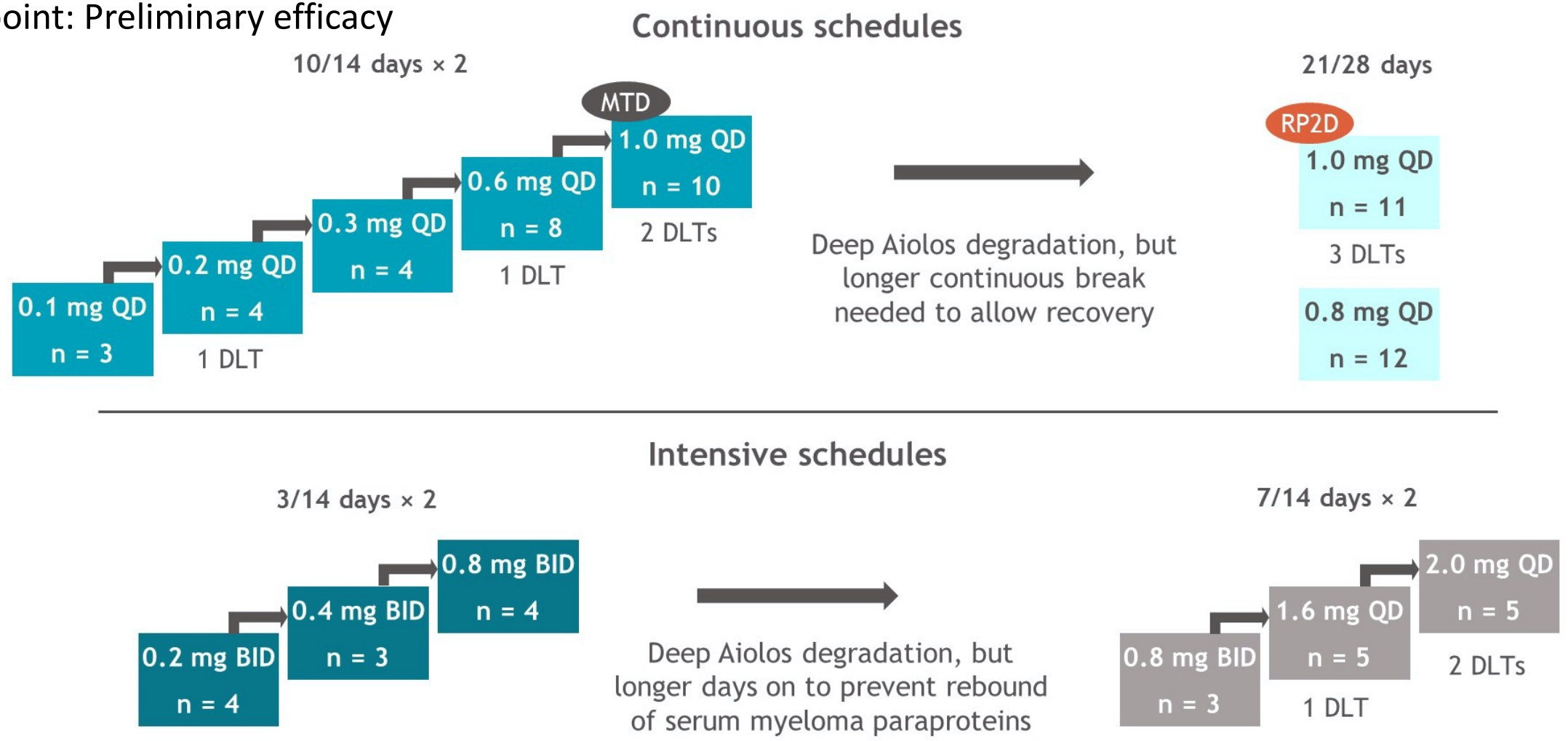
Hansen et al. J Med Chem 2020;63:6648; Wong et al. ASH 2019; Abstract 1815; Richardson et al. ASCO 2020; Abstract 8500.

CC-92480-MM-1 Phase I Trial: CC-92480 + Dex in R/R MM

(First in human, multicenter, dose escalation/expansion)

1° endpoints: PK, safety, MTD/RP2D

2° endpoint: Preliminary efficacy

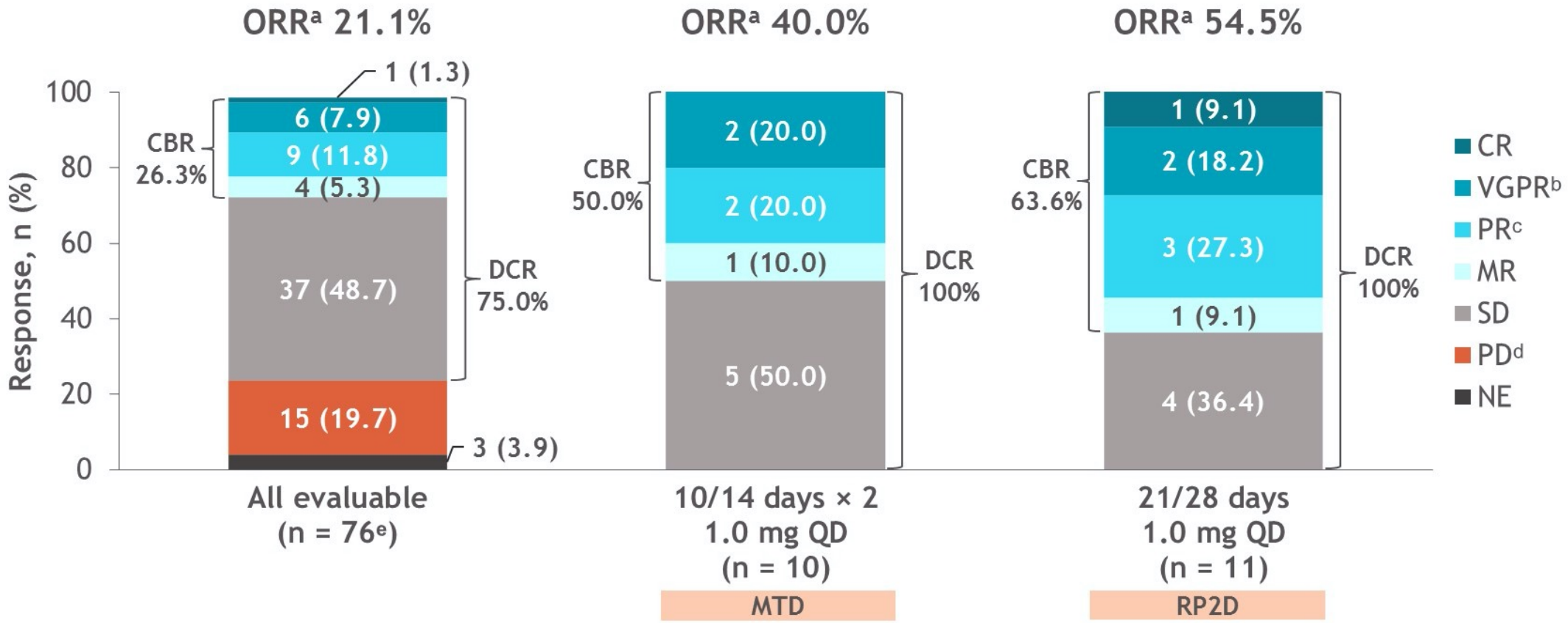


As of February 24, 2020 data cut.

BID, twice daily; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; QD, once daily; RP2D, recommended phase 2 dose.

Richardson PG et al. ASCO 2020; Abstract 8500.

Phase I Trial of CC-92480: Efficacy

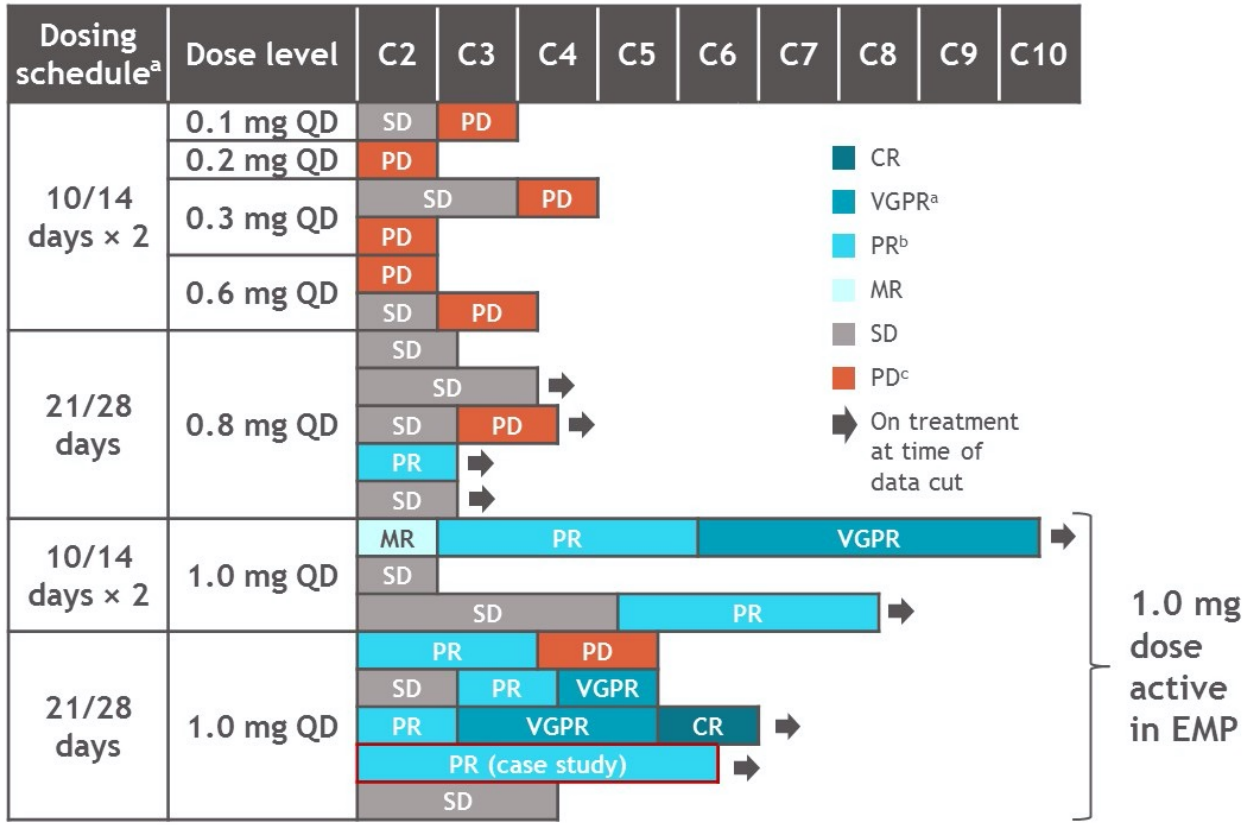


- 7/11 patients at RP2D of 1 mg QD 21/28 days were triple-class refractory (to ≥1 IMiD, 1 PI, and 1 anti-CD38 mAb)
- Of these: 1 CR, 1 VGPR, 2 PR, 1 MR

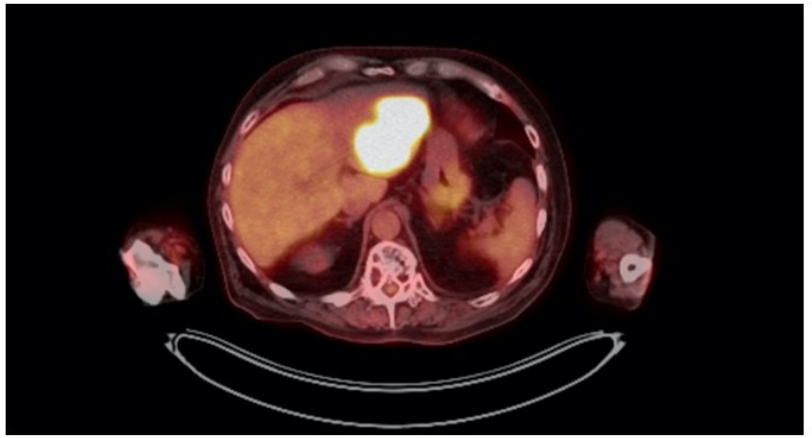
Richardson PG et al. ASCO 2020; Abstract 8500.

Phase I Trial of CC-92480: Efficacy/Safety in HR Extramedullary Myeloma

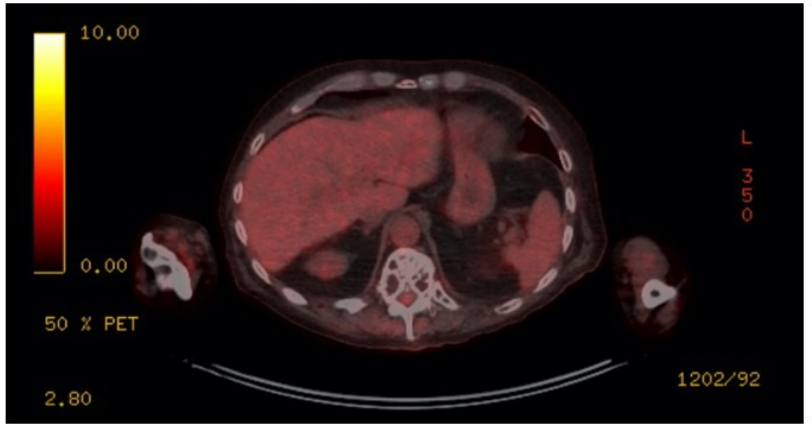
- Only patients on continuous schedules are shown



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.

Treatment-related adverse events were mainly related to myelosuppression

Richardson PG et al. ASCO 2020; Abstract 8500.

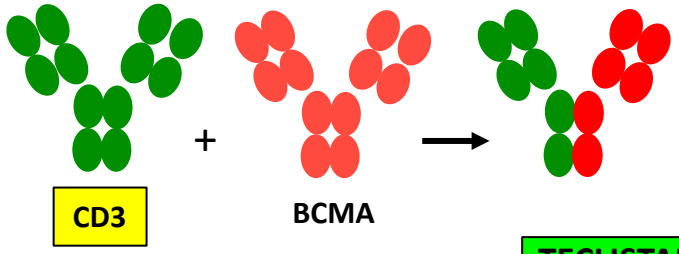
Unmet Need in R/R MM

Poor prognosis for ≥ triple class R/R MM: ORR ~30%, mPFS ~3 mo, mOS 6-11 mo

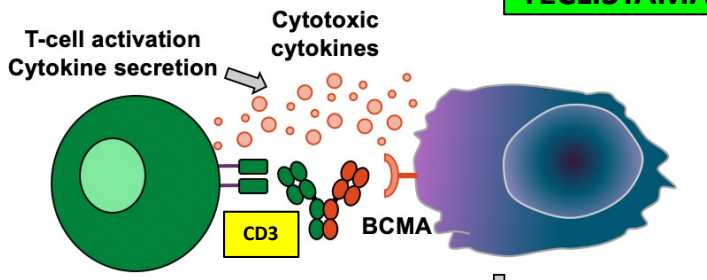
Treatment	CAR T	ADC	BiTE	DuoAb
Logistics	FDA approved; delivered in large/specialized centers; 4-5 weeks of generation (auto); bridging Rx	FDA approved; community feasible; off-the-shelf	not approved yet; more community feasible; off-the-shelf; continuous Rx	not approved yet; more community feasible; off-the-shelf;
Duration of Rx	~ 1-2 mo	likely more limited	likely prolonged need longer $t_{1/2}$	
Toxicities	CRS, NT, HLH, cytopenias marrow failure (rare)	corneopathies; TCP	CRS, infections	IRs, CRS, infections
Financials	evolving ~ $400,000 lump	$24,000/mo	unclear; long-term financial toxicity	

Ghandi et al. Leukemia 2019;33:2266.

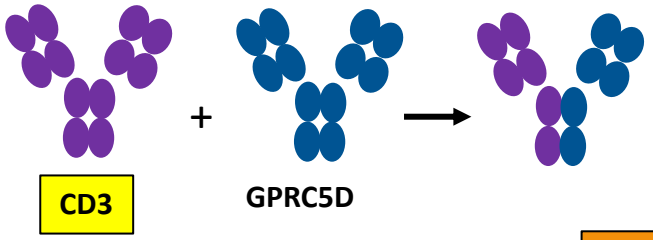
Emerging Bispecific Antibodies in R/R MM



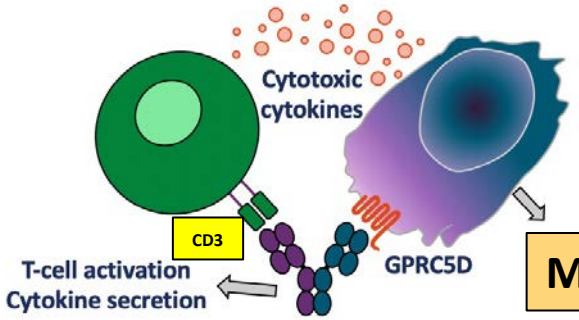
TECLISTAMAB



Myeloma Cell Death



TALQUETAMAB

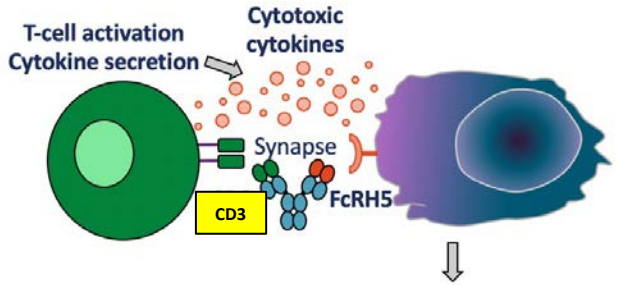


Myeloma Cell Death

Anti-CD3 Fab region

Anti-FcRH5 Fab region

CEVOSTAMAB



Myeloma Cell Death

Summary of Bispecific Antibodies in R/R MM

Drug	Target	Median Rx Lines (range)	Dosing	ORR	CRS	NT	Comments
Teclistamab[1] (n = 40 RP2D)	**BCMA**	5 (2-11)	SC QW for RP2D	65% @RP2D ≥CR 40%	70% @RP2D (no G3)	1% (0% in other SC doses)	TTR 1 mo SC dosing
Elranatamab[2] (n = 30)	**BCMA**	8 (3-15)	SC QW	83% @RP2D 1000 µg/kg 30% CR/sCR	73%	20%	SC dosing
Talquetamab[3] (n = 82 all SC, 30 RP2D)	**GPRC5D**	6 (2-17)	SC QW RP2D: 450 µg/kg	53% all SC doses (70% @ RP2D)	67% all SC (73% @RP2D) (3% G3 @RP2D)	5% all SC (7% @RP2D)	27% @RP2D BCMA-refr SC dosing, TTR 1 mo G3 skin rash, oral tox
Cevostamab[4] (n = 53, 34)	**FcRH5**	6 (2-15)	Q3W IV	61%, highest dose (n = 18) 63% in BCMA-refr (n = 8)	76% (2% G3)	28%	21% in BCMA-refr
TNB-383B[5] (n = 58, 15)	BCMA	6 (3-15)	Q3W	80% @higher doses (n = 15)	45% (no G3)	0%	Q3W tested in CrCl 30 cc/min
REGN-5458[6] (n = 49, 8)	BCMA	5	Q2W	63% @highest doses (n = 8)	39 (no G3)	12%	
Pavurutamab (AMG-701)[7] (n = 85, 6)	BCMA	6 (2-25)	QW	83% @highest doses (n = 6)	64% (9% G3)	3.8%	

1. Krishnan. ASCO 2021. Abstr 8007. 2. Bahlis. ASCO 2021. Abstr 8006. 3. Berdeja. ASCO 2021. Abstr 8008. 4. Cohen. ASH 2020. Abstr 292. 5. Rodriguez. ASH 2020. Abstr 293. 6. Madduri. ASH 2020. Abstr 291.
7. Harrison. ASH 2020. Abstr 181.

Take Homes

- NDMM Rx strategies evolving to deepen the response (MRD-) and prolong PFS, hopefully OS
- Rapidly expanding array of treatment options in R/R MM, with novel MoAs
- Paradigm shifts with single agent ORR in highly R/R MM: 20-30%s ---> 60%s!
- Approach to sequencing of therapies becoming even more complicated
- Increasing relevance of long-term: QoL, PROs, financial tox, accessibility
- Search for the cure: every decade brings us closer!

Clinical Case #1

- A 50-year-old man diagnosed with R-ISS stage I IgG Kappa MM. Bone marrow 50% plasma cells; PET/CT with diffuse skeletal lesions, no EMM. Normal cytogenetics, FISH t(11,14)(q13;q32). Normal kidney and renal functions at diagnosis.
- Induction with VRd q21 x 4 with VGPR, followed by Mel200 AHSCT with sCR at day +100
- Len maintenance 10-15 mg 21-28/28.
- Relapse with IgG Kappa MM after 28 mo: marrow 20% PCs, FISH t(11,14)(q13;q32), PET/CT negative.
- Salvaged with SPd x 4 with CR, followed by second AHSCT with sCR, Pom maintenance
- PD after 9 months, salvage with Seli-Kd on trial with VGPR, PD after 9 mo
- Marrow 15% PCs, FISH still t(11,14)(q13;q32)
- Salvaged with Venetoclax-Dex with VGPR after 2 cycles, ongoing response 4+ mo