Penn Medicine

HARVESTING KNOWLEDGE: THE NAPA SUMMIT ON MULTIPLE MYELOMA

Non-T-Cell Redirection Therapies: Current and Future Timing and Novel Products

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Non-T cell Redirecting Therapies for Myeloma

TOPICS

When to use and Why

General Approach

Standard and experimental options:

- belantamab mafodotin (back on the market)
- bcl2 inhibitors (venetoclax, sonrotoclax)
- cereblon modulators (mezigdomide)
- MMSET inhibitor (gintemetostat)
- p300 inhibitor (inobrodib)

Some of the studies reported in this presentation were presented as an abstract and/or presented at a conference. These data and conclusions should be considered to be preliminary until published in a peer-reviewed journal.

Who can benefit from non-T cell redirecting therapies

1) **Patients who want to avoid the need for close observation for CRS and ICANS**

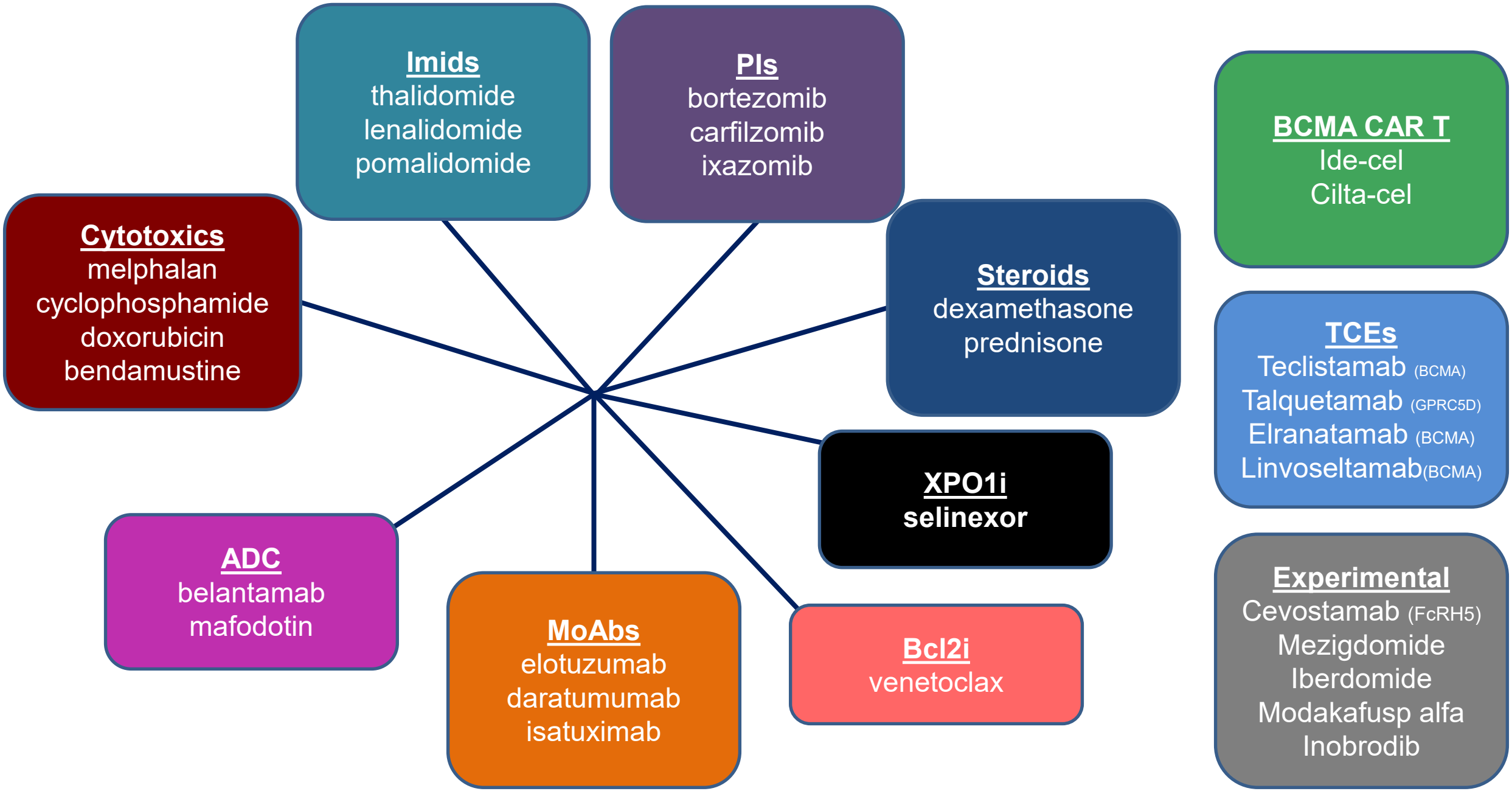
   e.g. live far away, dislike hospitalization, no one available to accompany

2) **Patients who want to avoid specific toxicities of T cell redirecting therapies**

   e.g. Parkinsonism from cilta-cel, dysgeusia from talquetamab

3) **Patients who have already progressed after T cell redirecting therapies**

   especially post-BCMA or post-TCE/pre-CAR-T


Imids
thalidomide
lenalidomide
pomalidomide
PIs
bortezomib
carfilzomib
ixazomib
BCMA CAR T
Ide-cel
Cilta-cel
Cytotoxics
melphalan
cyclophosphamide
doxorubicin
bendamustine
Steroids
dexamethasone
prednisone
TCEs
Teclistamab (BCMA)
Talquetamab (GPRC5D)
Elranatamab (BCMA)
Linvoseltamab(BCMA)
XPO1i
selinexor
ADC
belantamab
mafodotin
MoAbs
elotuzumab
daratumumab
isatuximab
Bcl2i
venetoclax
Experimental
Cevostamab (FcRH5)
Mezigdomide
Iberdomide
Modakafusp alfa
Inobrodib

Belantamab mafodotin

Antibody-drug conjugate targeting B cell maturation antigen (BCMA)

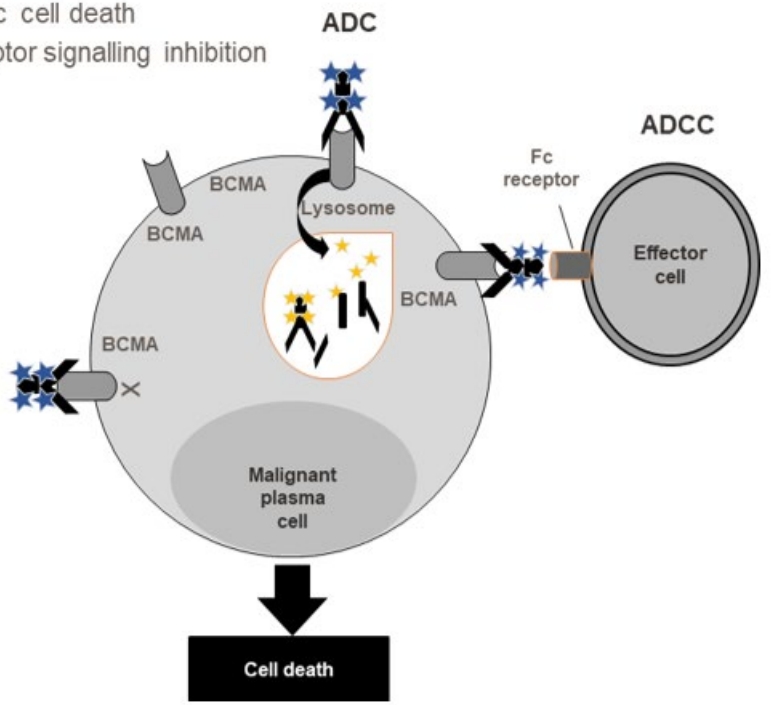
Approved August 2020 based on 31-34% overall response rate in CD38-refractory patients (phase 2 DREAMM-2)

Withdrawn from market 11/2022 after a randomized trial failed to show improved PFS compared to pomalidomide/dexamethasone

Approved again in 10/2025 in combination with bortezomib/dexamethasone based on trial showing improved PFS and OS

Four mechanisms of action:

1. ADC mechanism
2. ADCC mechanism
3. Immunogenic cell death
4. BCMA receptor signalling inhibition



Hungria V et al. N Engl J Med. 2024;391:393-407

DREAMM-7: Belantamab-Vd vs DVd

Eligibility criteria

- Age ≥18 years with MM
- ≥1 prior line of MM therapy and documented PD during or after the most recent therapy
- No prior treatment with anti-BCMA
- No disease refractory to or intolerance of daratumumab or bortezomib

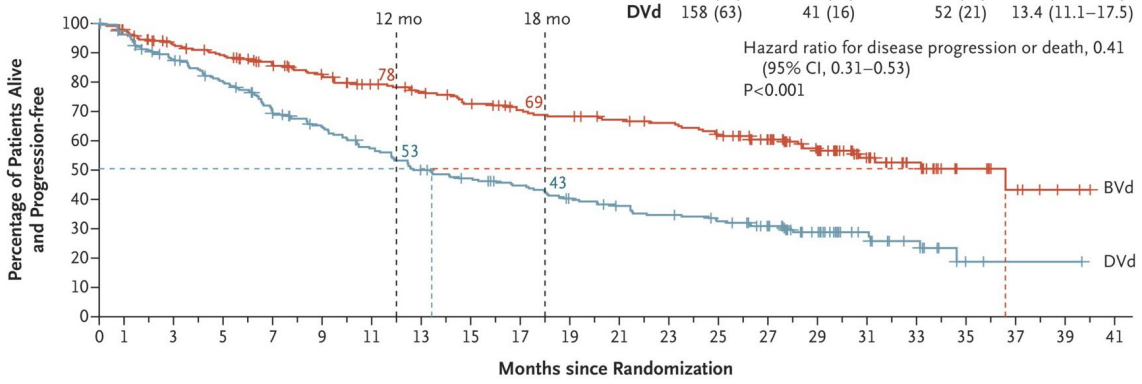
1:1 randomization

	Cycles 1-8	Cycle 9+
BVd	**Belantamab mafodotin** 2.5 mg/kg IV q3w + **bortezomib** + **dexamethasone**	**Belantamab Mafodotin monotherapy** 2.5 mg/kg IV q3w
DVd	**Daratumumab** 16 mg/kg IV cycles 1-3; qw and cycles 4-8; q3w + **bortezomib** + **dexamethasone**	**Daratumumab monotherapy** 16 mg/kg IV q4w

Progression-Free Survival

	Patients with an Event	Patients with Censored Data, Follow-up Ended	Patients with Censored Data, Follow-up Ongoing	Median Progression-free Survival (95% CI)
		no. (%)		*mo*
BVd	91 (37)	44 (18)	108 (44)	36.6 (28.4–NR)
DVd	158 (63)	41 (16)	52 (21)	13.4 (11.1–17.5)

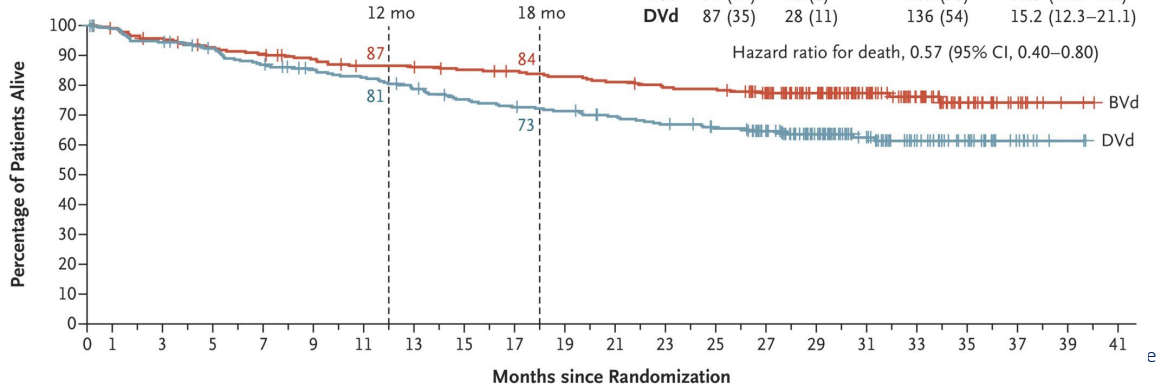
Hazard ratio for disease progression or death, 0.41 (95% CI, 0.31–0.53)
P<0.001



Overall Survival

	Patients with an Event	Patients with Censored Data, Follow-up Ended	Patients with Censored Data, Follow-up Ongoing	25th Percentile of Overall Survival (95% CI)
		no. (%)		*mo*
BVd	54 (22)	20 (8)	169 (70)	33.9 (21.9–NR)
DVd	87 (35)	28 (11)	136 (54)	15.2 (12.3–21.1)

Hazard ratio for death, 0.57 (95% CI, 0.40–0.80)



DREAMM-7: Belantamab-Vd vs DVd

Event	BVd (N=242)		DVd (N=246)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	no. of patients (%)			
Any adverse event	242 (100)	230 (95)	246 (100)	192 (78)
Blood and lymphatic system disorders				
Any	185 (76)	151 (62)	158 (64)	109 (44)
Thrombocytopenia†	167 (69)	134 (55)	122 (50)	87 (35)
Anemia‡	46 (19)	20 (8)	65 (26)	25 (10)
Infections and infestations				
Any	170 (70)	75 (31)	166 (67)	49 (20)
Pneumonia	44 (18)	28 (12)	22 (9)	10 (4)
Coronavirus disease 2019	58 (24)	14 (6)	49 (20)	11 (4)
Upper respiratory tract infection	48 (20)	0	49 (20)	0
Ocular events				
Any	191 (79)	82 (34)	72 (29)	7 (3)
Blurred vision	160 (66)	53 (22)	26 (11)	2 (1)
Dry eye	123 (51)	17 (7)	17 (7)	0
Photophobia	114 (47)	5 (2)	6 (2)	0
Eye irritation	103 (43)	12 (5)	13 (5)	0
Foreign-body sensation in eye	106 (44)	8 (3)	10 (4)	0
Eye pain	77 (32)	2 (1)	8 (3)	1 (<1)
Cataract	49 (20)	17 (7)	25 (10)	6 (2)

Table 4. Worsening of BCVA in Both Eyes among Patients in the BVd Group with Normal BCVA at Baseline.*

Measure	Worsening to 20/50	Worsening to 20/200
No. of patients with event/total no. (%)	82/242 (34)	5/242 (2)
First event		
Median time from start of treatment to onset of first event (range) — days	73.5 (16–753)	105 (47–304)
Improvement after first event — no./total no. (%)	80/82 (98)	5/5 (100)
Median time from onset of first event to improvement (range) — days	22 (6–257)	19 (8–26)
Resolution after first event — no./total no. (%)	77/82 (94)	4/5 (80)
Median time from onset of first event to resolution (range) — days	64 (8–908)	87 (22–194)
Last event		
Improvement after last event — no./total no. (%)	75/82 (91)	3/5 (60)
Median time from onset of last event to improvement (range) — days	22 (8–173)	19 (8–26)

Dimopoulos MA et al. N Engl J Med2024;391:408-421

DREAMM-8: Belantamab-Pd vs VPd

Eligibility criteria

- Adults with MM
- ≥1 prior line of MM therapy including LEN
- Documented PD during or after their most recent therapy
- No prior treatment with anti-BCMA or pomalidomide; not refractory/intolerant to bortezomib

N=302

1:1 randomization

BPd (Q4W)

Belantamab mafodotin
2.5 mg/kg IV (cycle 1) then 1.9 mg/kg IV Q4W from cycle 2 onward
+
Pomalidomide 4 mg orally on days 1-21 (28-day cycles)
+
Dexamethasone 40 mg[a] on days 1, 8, 15, and 22

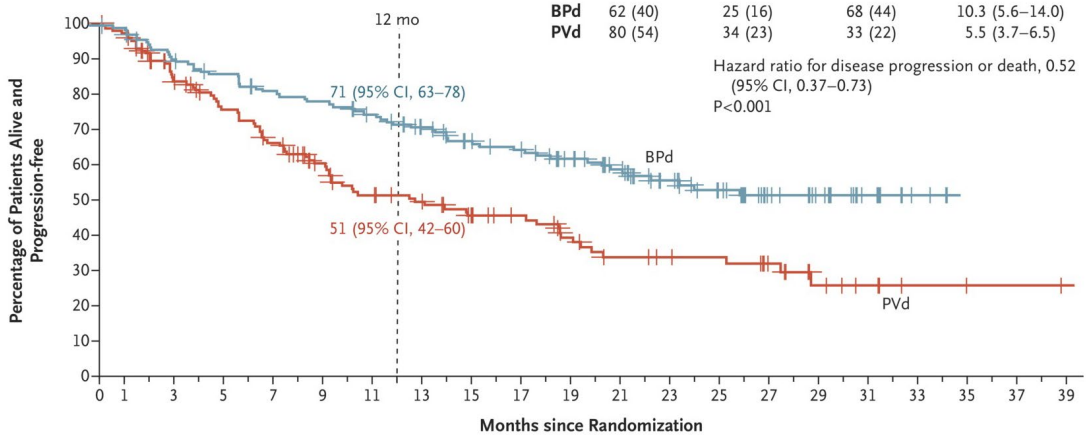
PVd (Q3W)

Bortezomib
1.3 mg/m² SC on days 1, 4, 8, and 11 of cycles 1-8 then days 1 and 8 (21-day cycles)
+
Pomalidomide 4 mg orally on days 1-14 (21-day cycles)
+
Dexamethasone 20 mg[a] on the day of and day after bortezomib

Progression-Free Survival

	Patients with an Event	Patients with Censored Data, Follow-up Ended	Patients with Censored Data, Follow-up Ongoing	25th Percentile of Progression-free Survival (95% CI)
	no. (%)	*no. (%)*	*no. (%)*	*mo*
BPd	62 (40)	25 (16)	68 (44)	10.3 (5.6–14.0)
PVd	80 (54)	34 (23)	33 (22)	5.5 (3.7–6.5)

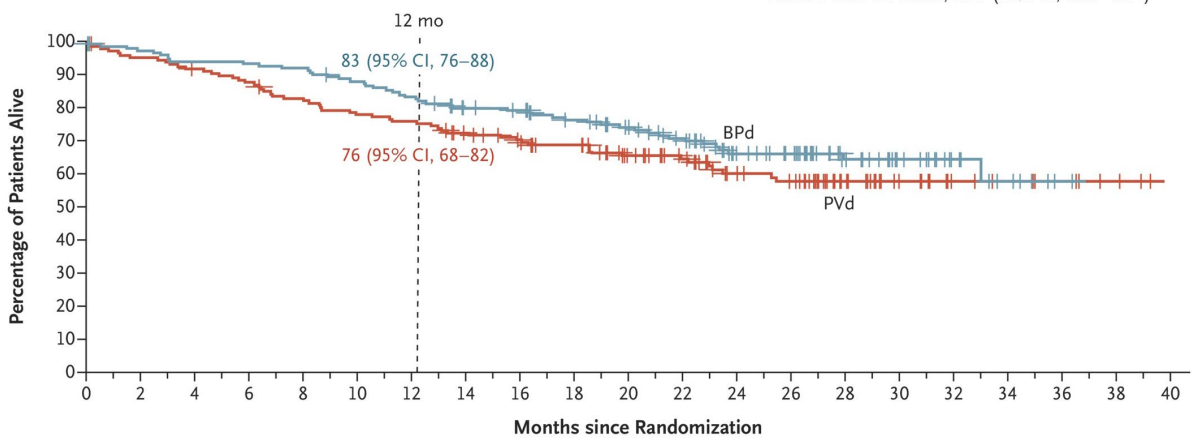
Hazard ratio for disease progression or death, 0.52 (95% CI, 0.37–0.73)
P<0.001



Overall Survival

	Patients with an Event	Patients with Censored Data, Follow-up Ended	Patients with Censored Data, Follow-up Ongoing	25th Percentile of Overall Survival (95% CI)
	no. (%)	*no. (%)*	*no. (%)*	*mo*
BPd	49 (32)	12(8)	94 (61)	19.0 (12.2–23.3)
PVd	56 (38)	7(5)	84 (57)	12.7 (8.0–18.5)

Hazard ratio for death, 0.77 (95% CI, 0.53–1.14)

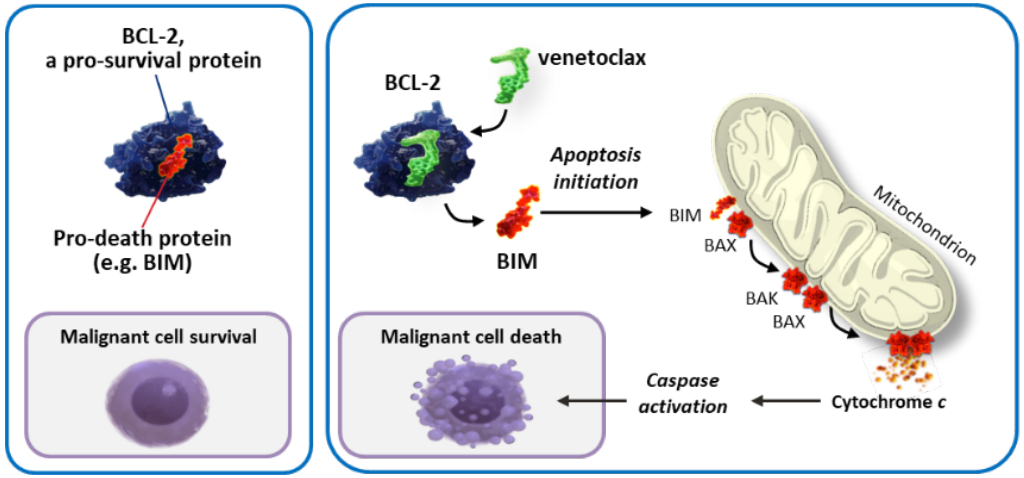


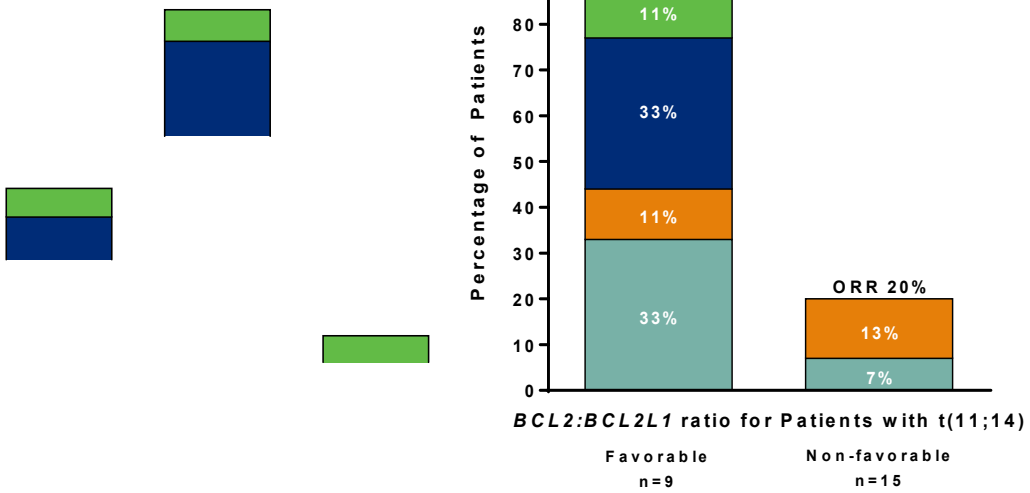
(Re)Learning to use belantamab mafodotin

USE, DOSING, AND TOXICITY MANAGEMENT

- Who will benefit from belantamab?
  - —Patients who want to avoid the immune suppression and hospitalization of CAR T cells or TCEs
  - —Patients relapsed after other BCMA-directed therapies who still have BCMA expression
- Dosing
  - —Almost no one stays at 2.5 mg/kg
  - —Almost no one stays at q3 weeks
  - —Liberal dose reductions and dose holds, especially in responding patients
- Consider combination with pomalidomide/dex
  - —(or single-agent)
- Partner with any ophthalmologist
- Corneal Toxicity
  - —Counsel patients: reversible and recurrent, mostly annoying, sometimes interferes with ADLs
  - —Eye exam prior to each dose required
  - —REMS program required
  - —Can dose adjust based on symptoms
  - —Use lubricating drops; topical steroids not helpful
  - —Dose holds up to q3-6 months
  - —Dose reductions 1.9 → 1.4 → 1.1 mg/kg
- Thrombocytopenia
  - —Hold and/or reduce dose for platelets <50
- 1st dose delayed infusion reactions
  - —Fever/chills
  - —Hours to days after 1st dose

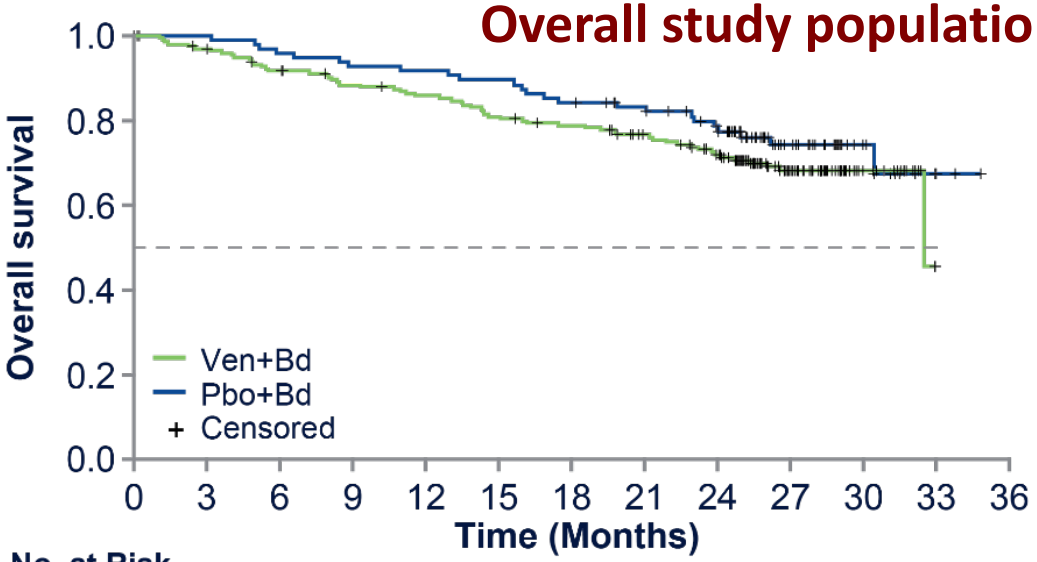
Venetoclax in t(11;14) myeloma





Kumar, ASH 2016, Abstract 488
Harrison, ASH 2019, Abstract 142
Kumar, Lancet Oncology 2020;21(12):1630-1642

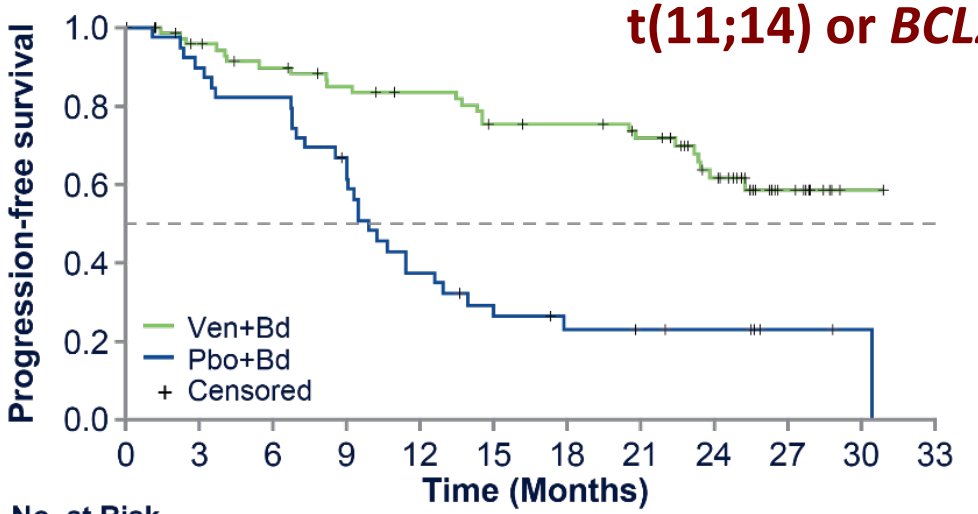
Overall study population



No. at Risk

194	186	174	165	159	150	144	133	118	62	18	0
97	95	91	88	87	85	80	75	66	33	12	2	0

t(11;14) or *BCL2*^{high}



No. at Risk

74	65	59	54	51	45	44	40	29	11	1	0
40	35	32	25	14	10	7	6	5	2	1	0

Sonrotoclax (bcl2-inhibitor) with carfilzomib/dex

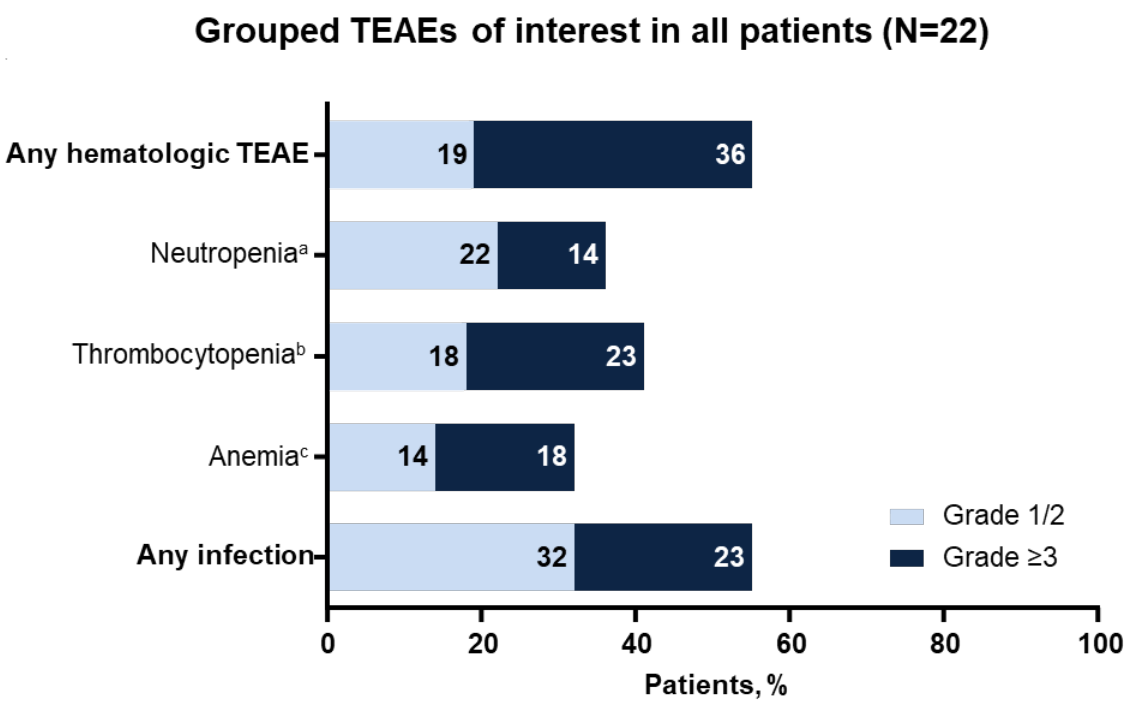
Key eligibility criteria

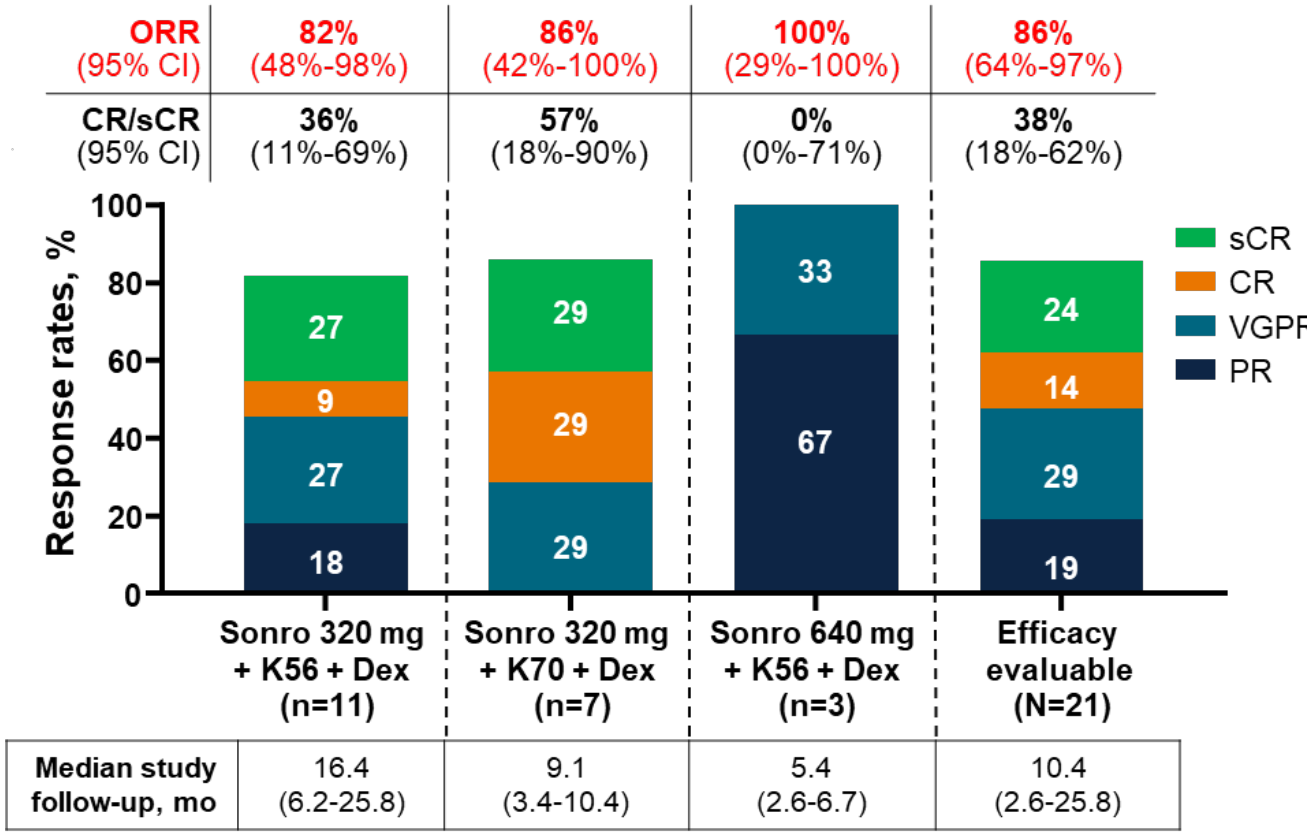
- Confirmed MM with t(11;14) translocation
- At least 3 prior lines of therapy including PI, IMiD and anti-CD38 monoclonal antibody[a]
- No more available approved therapies

Parameters	Total (N=22)
Age, median (range), y	65.0 (44-77)
Male, n (%)	16 (73)
ECOG PS 0 or 1, n (%)	22 (100)
R-ISS stage at initial diagnosis, n (%)	
I	3 (14)
II	9 (41)
III	4 (18)
High cytogenetic risk[a], n (%)	3 (14)
Prior lines of systemic therapy, median (range)	4.0 (2-8)
Prior lines of systemic therapy, n (%)	
2	1 (5)
3	7 (32)
≥4	14 (64)
Triple-class[c] exposed, n (%)	19 (86)
Refractory status, n (%)	
PI	14 (64)
IMiD	19 (86)
Anti-CD38 antibody	13 (59)
Triple-class[c] refractory	9 (41)
Prior ASCT, n (%)	14 (64)

Quach, ASH 2025, Abstract 633

Sonrotoclax with carfilzomib/dex



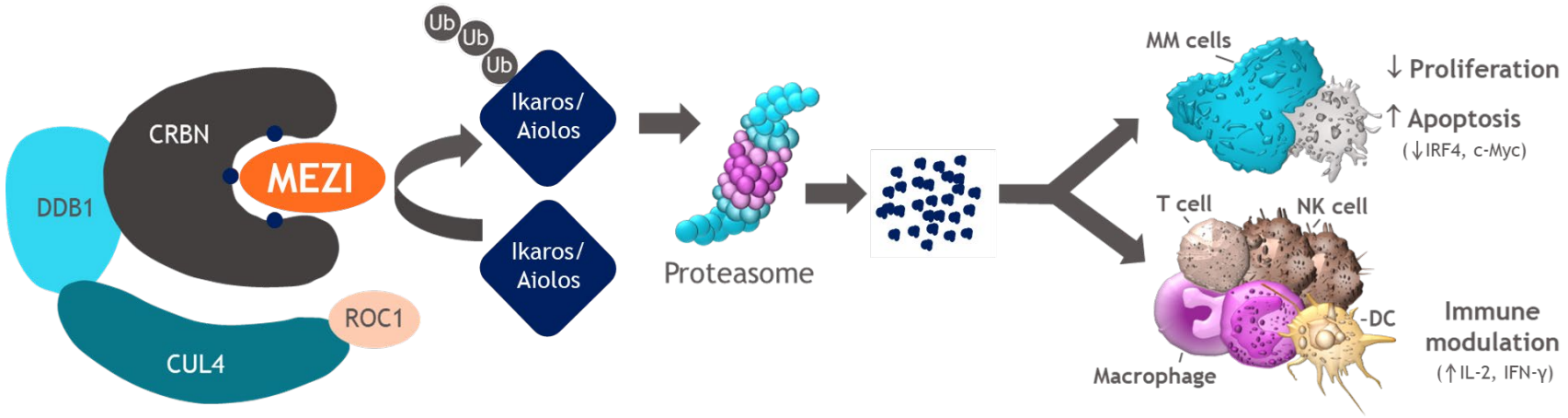


Median study follow-up, mo	16.4 (6.2-25.8)	9.1 (3.4-10.4)	5.4 (2.6-6.7)	10.4 (2.6-25.8)

Quach, ASH 2025, Abstract 633

Mezigdomide

- MEZI is a novel, oral CELMoD agent that is a potent inducer of Ikaros and Aiolos degradation, resulting in immune-modulatory effects and enhanced tumoricidal activity in myeloma cells[1-3]
- In patients with triple-class RRMM, MEZI + DEX had a manageable safety profile and a promising ORR of 41%[4]



BORT, bortezomib; CD, cluster of differentiation; CFZ, carfilzomib; c-Myc, cellular Myc; CRBN, cereblon; CUL4, cullin 4; DC, dendritic cell; DDB1, DNA damage-binding protein 1; DEX, dexamethasone; IFN, interferon; IL, interleukin; IRF4, interferon regulatory factor 4; mAb, monoclonal antibody; MEZI, mezigdomide; MM, multiple myeloma; NK, natural killer; ORR, overall response rate; PI, proteasome inhibitor; ROC1, regulator of cullins-1; RRMM, relapsed/refractory multiple myeloma; Ub, ubiquitin.

1. Hansen JD, et al. *J Med Chem* 2020;63:6648–6676. 2. Lu G, et al. *Science* 2014;343:305–309. 3. John LB, Ward AC. *Mol Immunol* 2011;48:1272–1278. 4. Richardson PG, et al. *N Engl J Med* 2023;389:1009–1022. 5. Wong L, et al. *Blood* 2019;134(suppl 1). Abstract 1815. 6. ClinicalTrials.gov. NCT03989414. 7. Richardson PG, et al. *Blood* 2021;138(suppl 1). Abstract 2731. 8. Oriol A, et al. Oral presentation at the International Myeloma Society (IMS) Annual Meeting; September 27–30; 2023; Athens, Greece. Abstract OA-49.

Mezigdomide plus Dexamethasone in Relapsed and Refractory Multiple Myeloma

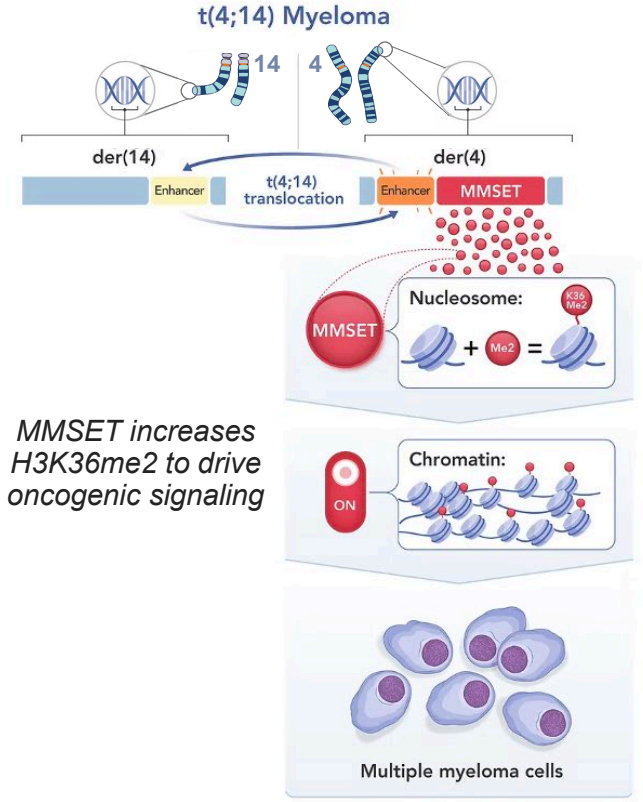
Variable	Dose-Escalation Cohort			Dose-Expansion Cohort		
	All Patients (N=77)	10-Day Schedule, Repeated† (N=10)	21-Day Schedule‡ (N=11)	All Patients (N=101)	Patients with Plasmacytomas§ (N=40)	Patients with Previous Anti-BCMA Therapy (N=30)
	number of patients (percent)					
Overall response¶	19 (25)	4 (40)	6 (55)	41 (41)	12 (30)	15 (50)‖
Stringent complete response	0	0	0	2 (2)	0	0
Complete response	1 (1)	0	1 (9)	3 (3)	2 (5)	1 (3)
Very good partial response	9 (12)	2 (20)	3 (27)	20 (20)	7 (18)	9 (30)
Partial response	9 (12)	2 (20)	2 (18)	16 (16)	3 (8)	5 (17)
Minimal response	4 (5)	1 (10)	1 (9)	6 (6)	0	1 (3)
Stable disease	34 (44)	4 (40)	4 (36)	39 (39)	21 (52)	11 (37)
Progressive disease	17 (22)	1 (10)	0	10 (10)	4 (10)	3 (10)
Response could not be evaluated**	3 (4)	0	0	5 (5)	3 (8)	0

Richardson PG et al. N Engl J Med 2023;389:1009-1022

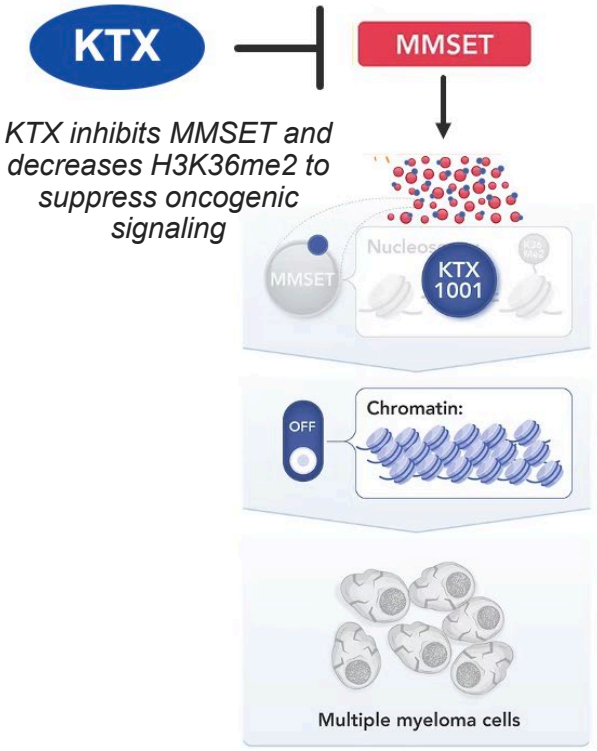
The NEW ENGLAND JOURNAL of MEDICINE

KTX-1001 (MMSET inhibitor)

- MM with t(4;14), present in approximately 10-15% of newly diagnosed patients, represents a distinct biological subtype with unique clinical characteristics[1-3]
- t(4;14) results in overexpression of **MMSET (also known as NSD2)** and has been associated with poor clinical outcomes in MM patients[1-3]
- KTX-1001, named as gintemetostat, is an oral, first-in-class, potent, and selective inhibitor of MMSET[4]
- KTX-1001 **binds to and inhibits the catalytic SET domain** of MMSET resulting in epigenetic reprogramming of MM cells via decreased H3K36me2 and downregulation of oncogenic signaling[4-6]



MMSET increases H3K36me2 to drive oncogenic signaling



KTX inhibits MMSET and decreases H3K36me2 to suppress oncogenic signaling

1. Morgan, G et al. *Nat Rev Cancer.* 2012;12:335-348. 2. Keats JJ, et al. *Leuk Lymphoma*. 2006;47:2289-2300. 3. Chesi, M et al. *Blood*. 1998;92:3025-3034. 4.Bories P, et al. *Blood.* 2024;144 (Supplement 1): 3370. 5. Lewis C, et al. *J Biol Chem.* 2025; 301(7):110382. 6. Azagra A, et al. *Int J Mol Sci.* 2022;23(19):11075.

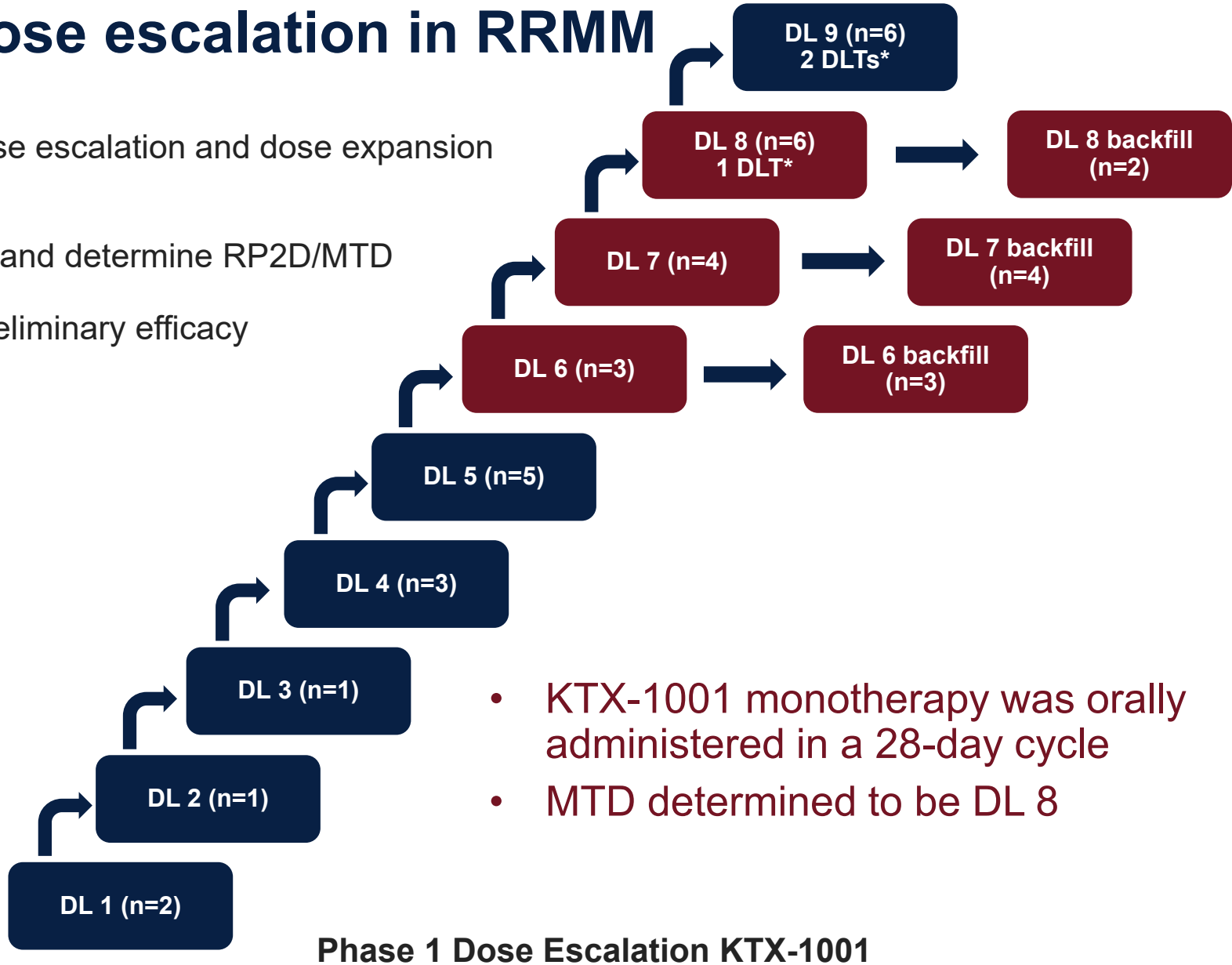
H3K36me2: histone 3 lysine 36 dimethylation; MM: multiple myeloma; MMSET: MM SET domain protein; NSD2: nuclear receptor binding SET domain protein 2.

KTX-1001 Study Design: Dose escalation in RRMM

- Ongoing open label, multi-center Phase 1 dose escalation and dose expansion study in RRMM (NCT 05651932)
- Primary objectives: assess safety, tolerability and determine RP2D/MTD
- Secondary objectives: assess PK, PD and preliminary efficacy

KEY INCLUSION CRITERIA

- ≥ 18 years of age
- RRMM pts who received ≥3 prior therapies, including a proteasome inhibitor, an immunomodulatory drug and an anti-CD38 monoclonal antibody
- Measurable disease
- ECOG ≤ 1



- KTX-1001 monotherapy was orally administered in a 28-day cycle
- MTD determined to be DL 8

Phase 1 Dose Escalation KTX-1001

Data as of 13 June 2025.

*DLT in DL 8 was due to thrombocytopenia grade 4 . Two patients in the DL 9 experienced 3 DLT events (grade 4 thrombocytopenia in 2 subjects, grade 3 epistaxis).DL: dose level, DLT: dose limiting toxicities, ECOG: Eastern Cooperative Oncology Group, MTD: maximum tolerated dose, RP2D: recommended phase 2 dose, RRMM: relapsed/refractory multiple myeloma, PD: pharmacodynamics, PK: pharmacokinetics.

Common TEAEs were Primarily Hematologic and Manageable

Common TEAEs (> 20% all grade)

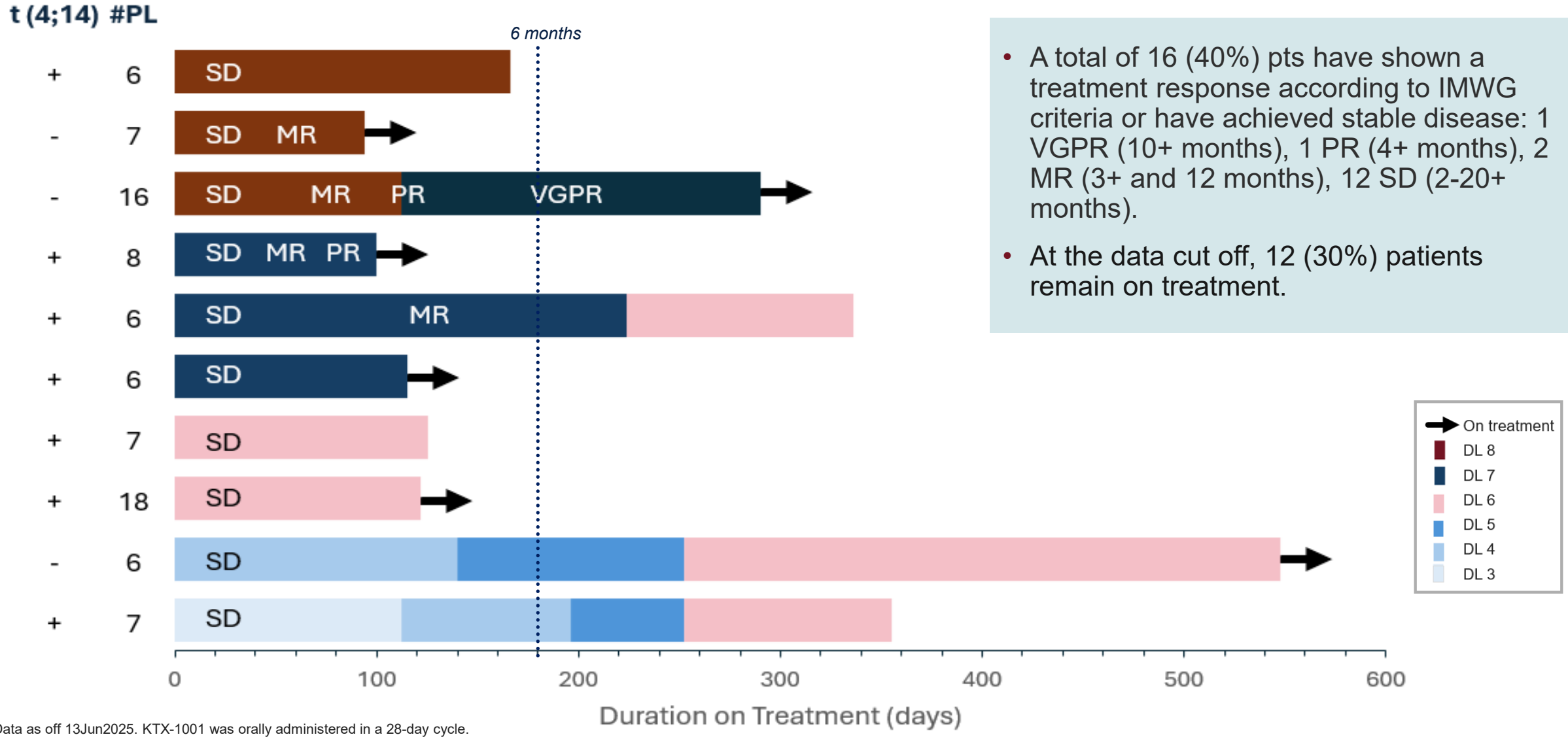
Common TEAEs (> 20% all grade), n (%)	All treated patients (n=40)		
	All Grade	Grade 3	Grade 4
Any TEAEs	39 (97.5)	19 (47)	10 (25)
Hematologic TEAEs	25 (62.5)	12 (30)	9 (22.5)
Thrombocytopenia	18 (45)	4 (10)	8 (20)
Anemia	14 (35)	10 (25)	0
Neutropenia	13 (32.5)	10 (25)	2 (5.0)
Febrile Neutropenia	2 (5.0)	2 (5.0)	0

Common TEAEs (> 20% all grade), n (%)	All treated patients (n=40)		
	All Grade	Grade 3	Grade 4
Non - hematologic TEAEs			
Infections	16 (40)	**5 (12.5)**	0
Fatigue	13 (32.5)	4 (10)	0
Diarrhea	10 (25)	0	0
Pyrexia	9 (22.5)	0	0
Headaches	9 (22.5)	0	0

- 4 DLT events: one patient at DL 8 had thrombocytopenia Grade 4 . Two patients at DL 9 experienced 3 DLT events (Grade 4 thrombocytopenia in 1 patient, Grade 4 thrombocytopenia and Grade 3 epistaxis in 1 patient).
- 2 patients experienced Grade 5 (respiratory failure in 1 patient, pleural effusion in 1 patient), unrelated to KTX-1001.

Data as off 13Jun2025. DL: dose level; DLT: dose limiting toxicity; TEAE: treatment emergent adverse event.

Exposure and Clinical Response in the Dose-Escalation Cohort on Treatment ≥ 3 Cycles



- A total of 16 (40%) pts have shown a treatment response according to IMWG criteria or have achieved stable disease: 1 VGPR (10+ months), 1 PR (4+ months), 2 MR (3+ and 12 months), 12 SD (2-20+ months).
- At the data cut off, 12 (30%) patients remain on treatment.

Data as off 13Jun2025. KTX-1001 was orally administered in a 28-day cycle.
CBR: clinical benefit rate (CR + VGPR + PR + MR+ >6 month SD); DL: dose level; MR: minimal response; ORR: overall response rate; PD: progressive disease; PL: prior lines; PR: partial response; SD: stable disease; VGPR: very good partial response

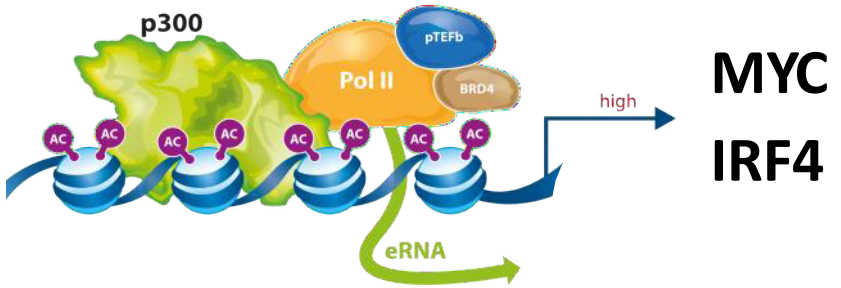
Inobrodib with pomalidomide and dexamethasone

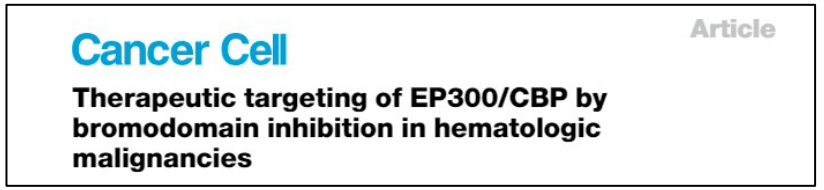
Inobrodib: First-in-class, oral, potent and specific bromodomain inhibitor of p300/CBP, two transcriptional coactivators with key roles in hematological cancers

Strong scientific rationale for targeting p300/CBP in myeloma

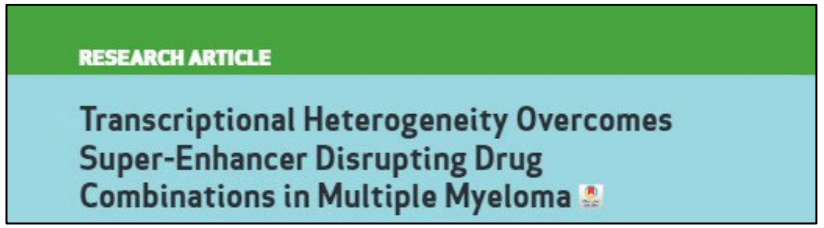
- selective displacement of p300/CBP from 10% of binding sites[1]
- inhibition of key oncogenic drivers IRF4 and MYC
- exquisite synergy with IMiDs[2]

Clinical activity has been observed in patients with relapsed and refractory myeloma when given as a monotherapy (ORR 25%)[3]





[1]*Nicosia et al, Cancer Cell 2023*



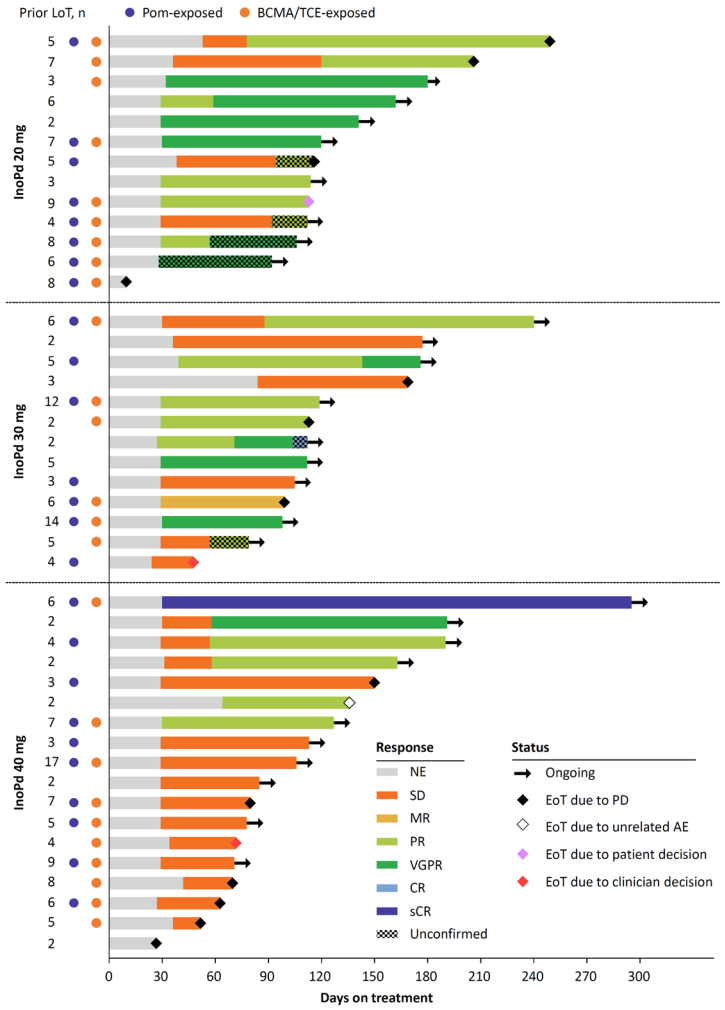
[2]*Welsh et al, Blood Cancer Discovery 2024*

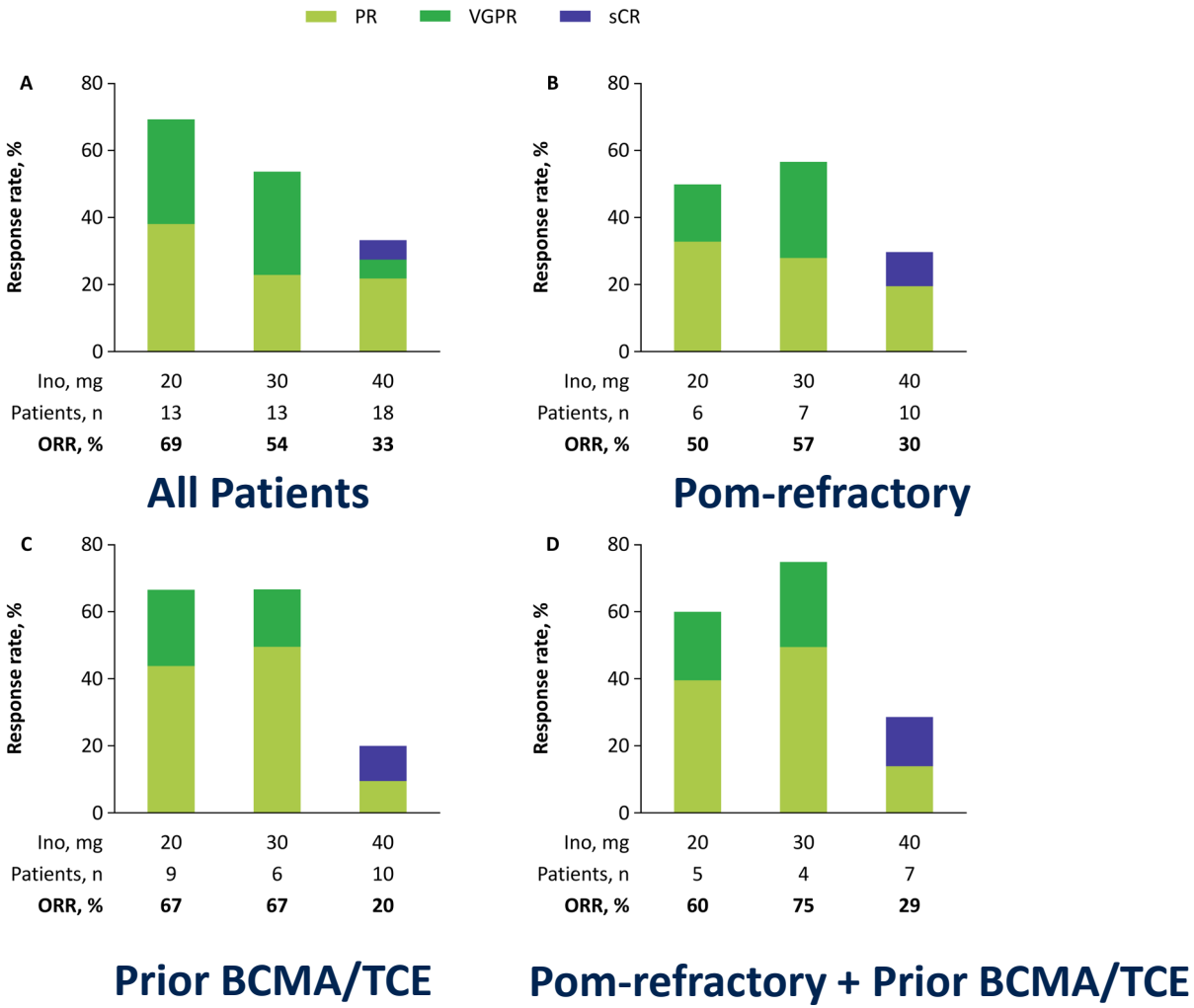
Inobrodib with pom/dex

Patients with TEAE, n (%)[a]	InoPd 20 mg (n=21)		InoPd 30 mg (n=19)		InoPd 40 mg (n=21)		Total (N=61)	
	Any-grade	Grade 3/4	Any-grade	Grade 3/4	Any-grade	Grade 3/4	Any-grade	Grade 3/4
Hematologic								
Thrombocytopenia	8 (38)	5 (24)	10 (53)	6 (32)	14 (67)	11 (52)	32 (53)	22 (36)
Neutropenia	8 (38)	5 (24)	9 (47)	8 (42)	13 (62)	8 (38)	30 (49)	21 (34)
Anemia	8 (38)	4 (19)	6 (32)	4 (21)	9 (43)	4 (19)	23 (38)	12 (20)
Leukopenia	1 (5)	1 (5)	5 (26)	3 (16)	11 (52)	5 (24)	17 (28)	9 (15)
Non-hematologic								
Fatigue	12 (57)	2 (10)	9 (47)	3 (16)	8 (38)	1 (5)	29 (48)	6 (10)
Diarrhea	2 (10)	0	4 (21)	1 (5)	7 (33)	2 (10)	13 (21)	3 (5)
Muscle spasms	4 (19)	0	6 (32)	0	3 (14)	0	13 (21)	0
Hyperglycemia	2 (10)	0	6 (32)	0	4 (19)	2 (10)	12 (20)	2 (3)

Patients, n (%)	InoPd 20 mg (n=21)	InoPd 30 mg (n=19)	InoPd 40 mg (n=21)	Total (N=61)
Dose modification				
Reduction of ino / pom	1 (5) / 6 (29)	3 (16) / 7 (37)	9 (43) / 6 (29)	13 (21) / 19 (31)
Interruption of ino / pom	7 (33) / 6 (29)	9 (47) / 10 (53)	11 (52) / 12 (57)	27 (44) / 28 (46)

Inobrodib with pom/dex





Current clinical trials at Penn

FOR RELAPSED/REFRACTORY MYELOMA

Anti-GPRC5D antibody/drug conjugate, phase 1

MMSET inhibitor for t(4;14) myeloma, phase 1

Inobrodib (p300/CBP inhibitor) with pomalidomide and dexamethasone, phase 2

Allogeneic (off-the-shelf) BCMA-directed CAR T cells, phase 1

Trispecific BCMAxGPRC5DxCD3 T cell engaging antibody, phase 2

Triple-targeted (BCMA, GPRC5D, FcRH5) mRNA-encoded bispecifics

limited-duration teclistamab (LimiTEC)

Support Civic Health

Our Government Affects Our Health

- Funding for research
- Medicare and Medicaid funding
- Regulation of drugs and devices
- Regulation of vaccines
- Regulation of private insurance
- Telemedicine

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- Talk to your patients about voting

To register and request a mail-in ballot:
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or text “VOTE PENN” to 34444.

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