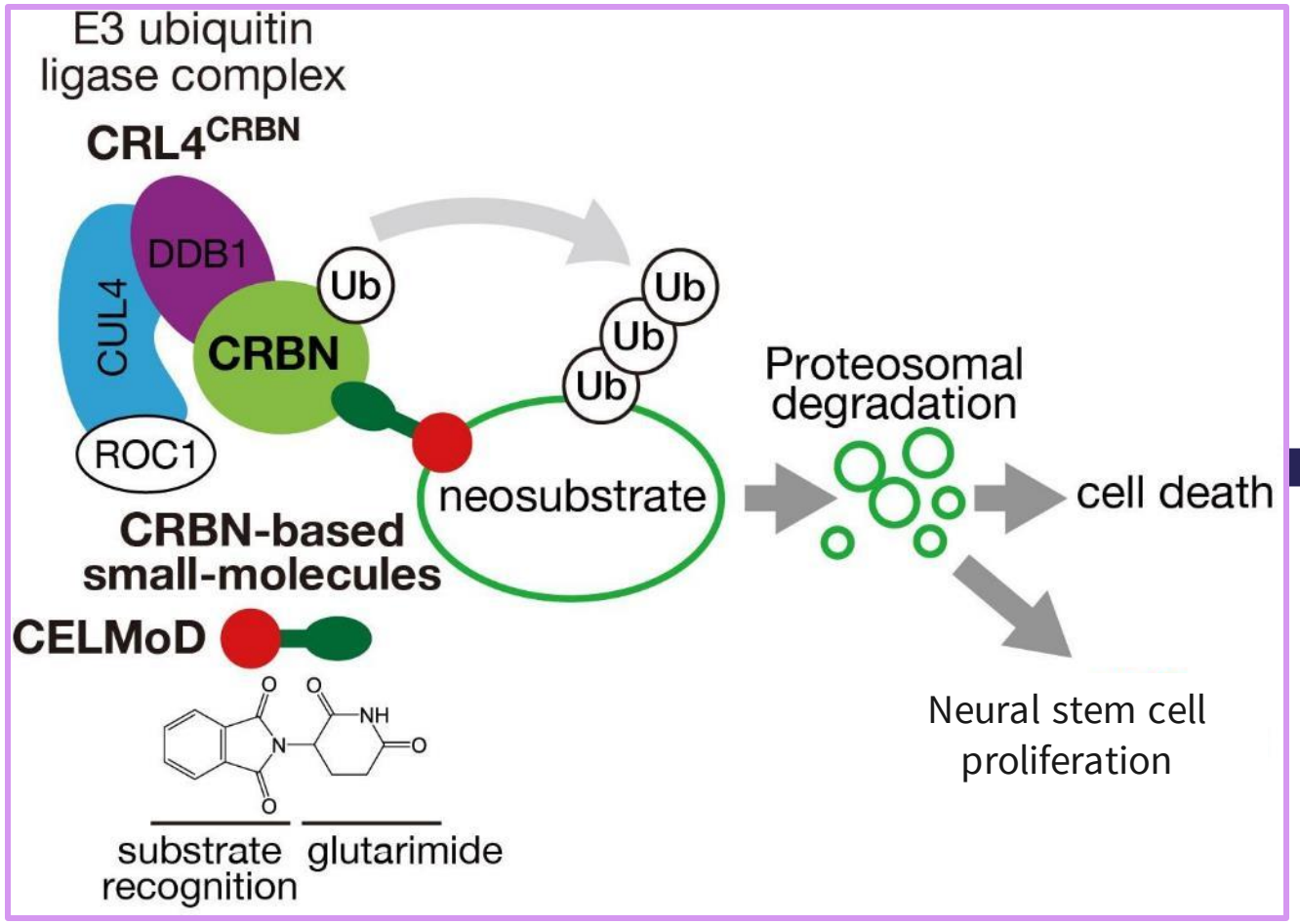
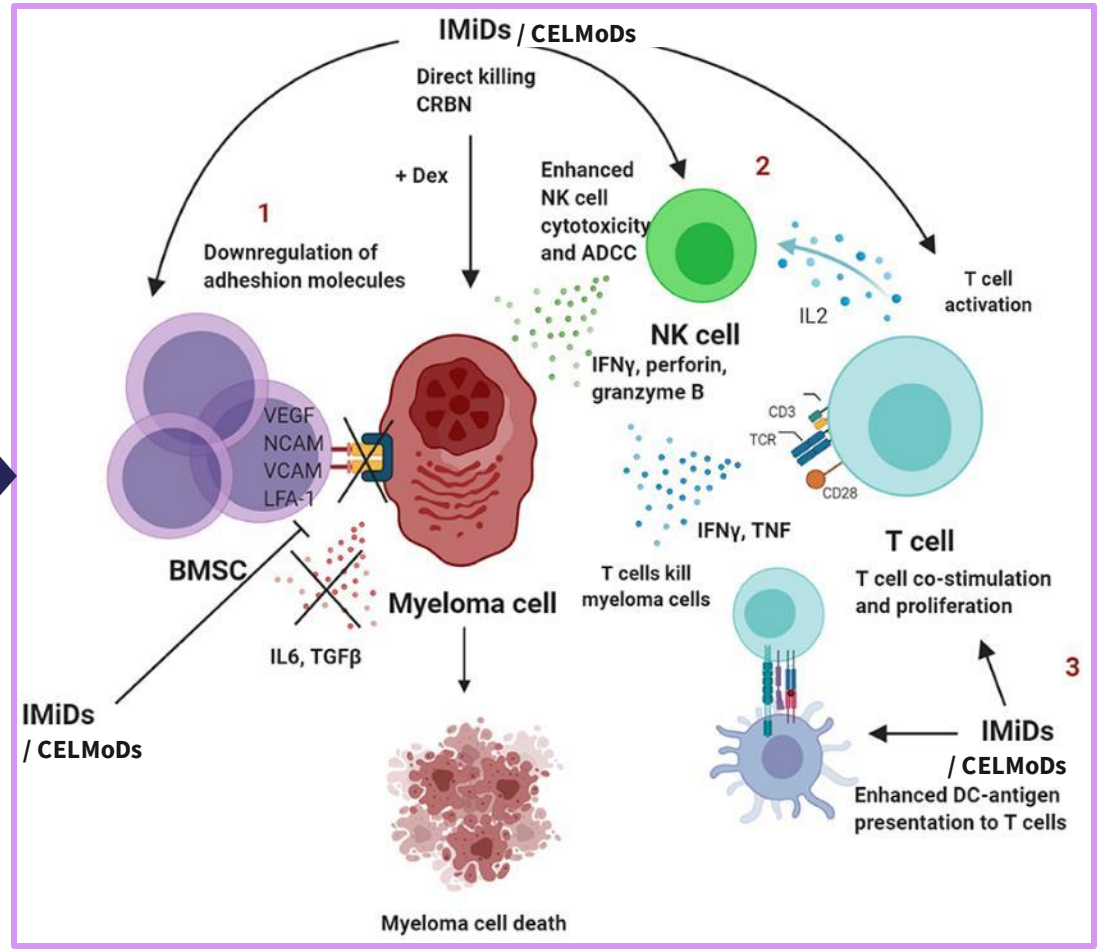
# Discussion topic 1: Patient case discussion on treating with CELMoDs

Paul Richardson / All

## Novel, accessible, oral treatment options

# CELMoDs®: Iberdomide[1] and mezigdomide[2]




BMSC, bone marrow mesenchymal stem cells; CELMoD, cereblon E3 ligase modulatory drug; CRBN, cereblon; CRL4, cullin 4-RING ubiquitin ligase; CUL4, cullin-RING-based E3 ubiquitin-protein ligase; DDB1, damage-specific DNA-binding protein 1; Dex, dexamethasone; IFN, interferon; IL, interleukin; IMiD, immunomodulatory drug; NCAM, neural cell adhesion molecule; NK, natural killer; ROC1, regulator of cullins 1; TCR, T-cell receptor; TGF, transforming growth factor; Ub, ubiquitin; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor.

1. Lonial S, et al. *Lancet Haematol*. 2022;9(11):e822-e832; 2. Richardson PG, et al. *N Engl J Med*. 2023; doi: 10.1056/NEJMoa2303194.

Figures adapted from: (left) Sato T, et al. *Front Cell Dev Biol*. 2021;9:629326; (right) D'Souza C, et al. *Front Immunol*. 2021;12:632399.

# Iberdomide + Dex, Dara-Dex, Vd, or Kd in RRMM

## CC-220-MM-001: Iberdomide-Dex expansion cohorts[1–3]

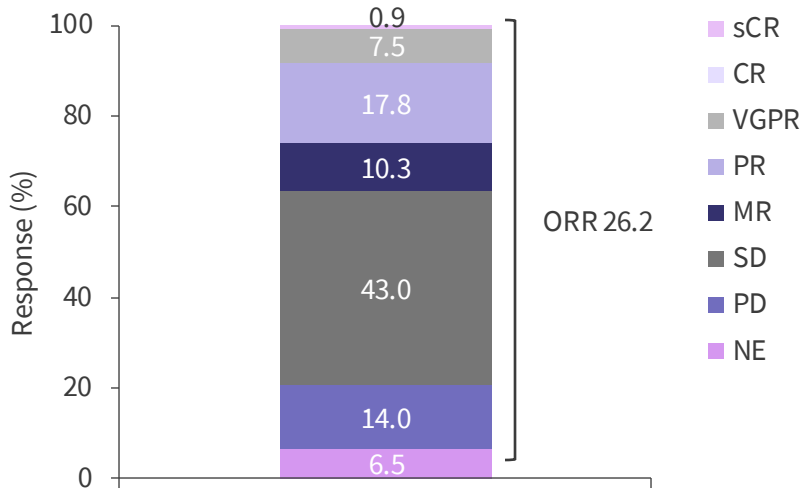
### Cohort D (N = 107)[1,2]

- 29.9% high-risk cytogenetics
- Median 6 prior therapies
- 100% IMiD-refractory
- 97.2% PI-refractory
- 100% anti-CD38 mAb-refractory
- 97.2% triple-class refractory
- Median duration of treatment: 4 cycles

### Cohort I (N = 38, BCMA-exposed)[3]

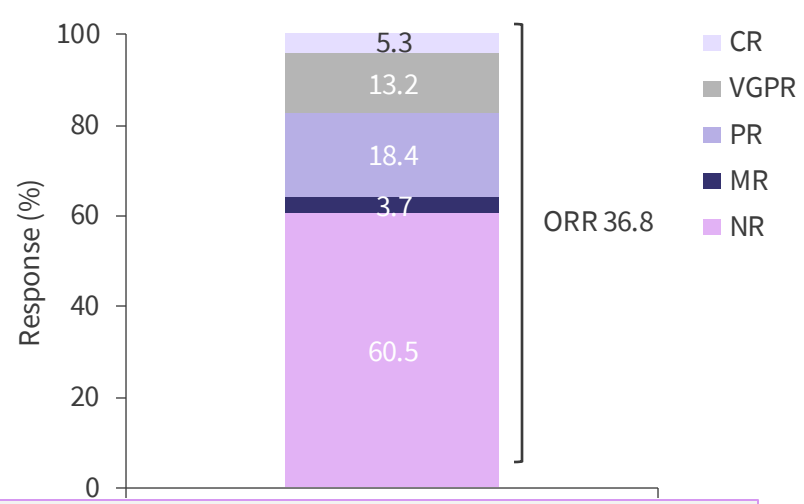
- 31.6% high-risk cytogenetics
- Median 7 prior therapies
- 100% triple-class exposed
- 100% exposed to BCMA-targeted therapy: 36.8% prior CAR T-cell therapy, 34.2% prior ADC, 23.7% prior T-cell engager
- Median duration of treatment: 3.5 cycles

### Cohort D, Iberdomide-Dex (N = 107)[1,2]




- Median DoR 7.0 months
- Median PFS 3.0 months
- Median OS 10.4 months
- Grade 3/4 neutropenia 25.2%/19.6%, anemia 28.0%/0%, thrombocytopenia 6.5%/15.0%, infections 24.3%/2.8% (COVID-19 4.7%/1.9%)

### Cohort I, Iberdomide-Dex (N = 38)[3]




- Median DoR 7.5 months
- Median PFS 2.4 months
- Grade 3/4 AEs in 78/9%, including neutropenia 50.0%, anemia 28.9%, leukopenia 23.7%, thrombocytopenia 21.1%, infections 23.7% (pneumonia 21.1%)
- No patients discontinued iberdomide due to AEs

ADC, Antibody-drug conjugate; AE, adverse event; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; Dara, daratumumab; Dex, dexamethasone; DoR, duration of response; IMiD, immunomodulatory drug; Kd, carfilzomib and dexamethasone; mAb, monoclonal antibody; MR, minimal response; NE, not evaluable; NR, no response; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PI, protease inhibitor; PR, partial response; RRMM, relapsed/ refractory multiple myeloma; sCR, stringent complete response; SD, stable disease; Vd, bortezomib-and dexamethasone; VGPR, very good partial response.

1. Lonial S, et al. *Blood.* 2021;138(suppl 1):Abstract 162; 2. Lonial S, et al. *Lancet Haematol.* 2022;9(11):e822-e832; 3. Lonial S, et al. *Blood.* 2022;140(suppl 1):Abstract 1918.

# Iberdomide + Dex, Dara-Dex, Vd, or Kd in RRMM

## CC-220-MM-001: Iberdomide + Dara-dex, Vd, or Kd[1]

### Iberdomide-Dara-Dex (N = 43)

- 16.3% EMD
- Median 4 prior therapies
- 95.3% IMiD-refractory
- 86.0% PI-refractory
- 37.2% anti-CD38 mAb-refractory
- 32.6% triple-class refractory
- Median duration of treatment: 4 cycles

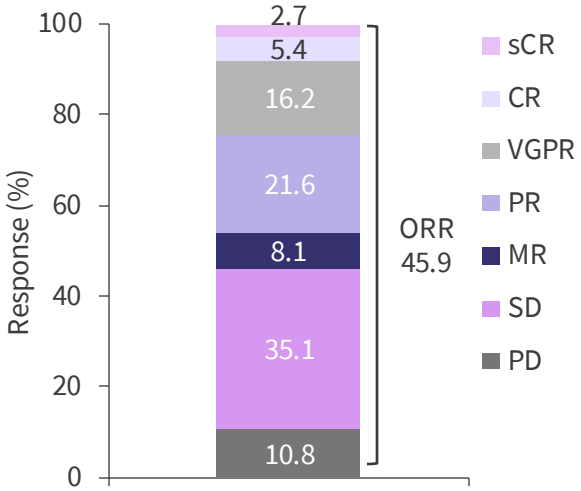
### Iberdomide-Vd (N = 25)

- 16.0% EMD
- Median 5 prior therapies
- 80.0% IMiD-refractory
- 68.0% PI-refractory
- 80.0% anti-CD38 mAb-refractory
- 48.0% triple-class refractory
- Median duration of treatment: 6 cycles

### Iberdomide-Kd (N = 9)

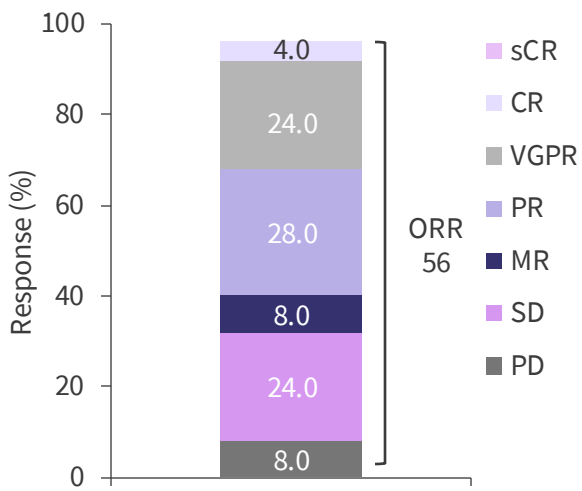
- 22.2% EMD
- Median 6 prior therapies
- 88.9% IMiD-refractory
- 66.7% PI-refractory
- 77.8% anti-CD38 mAb-refractory
- 55.6% triple-class refractory
- Median duration of treatment: 5 cycles

### Iberdomide-Dara-Dex (N = 43)



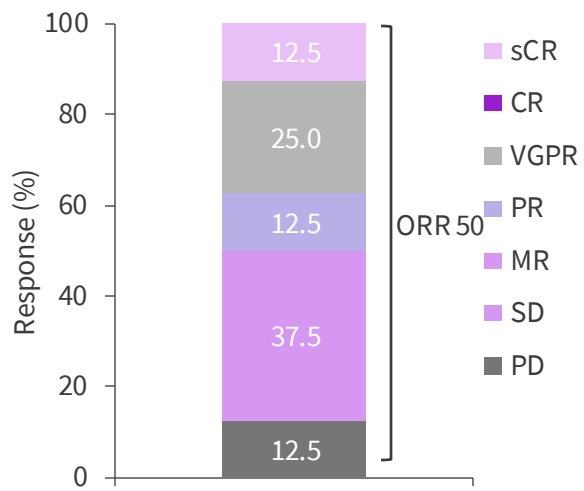

- Median DoR not reached
- Grade 3/4 hematologic AEs: neutropenia 12.8%/53.8%, anemia 20.5%/0%, thrombocytopenia 7.7%/5.1%
- Grade 3 nonhematologic AEs: fatigue 2.6%, diarrhea 2.6%
- Infections 59.0% (Grade 3/4: 10.3/5.1%)

### Iberdomide-Vd (N = 25)




- Median DoR 35.7 weeks
- Grade 3/4 hematologic AEs: neutropenia 20%/8%, anemia 12%/0%, thrombocytopenia 4%/20%
- Grade 3 nonhematologic AEs: diarrhea 4%, rash 4%
- Infections 68% (Grade 3/4: 16/4%)

### Iberdomide-Kd (N = 8)

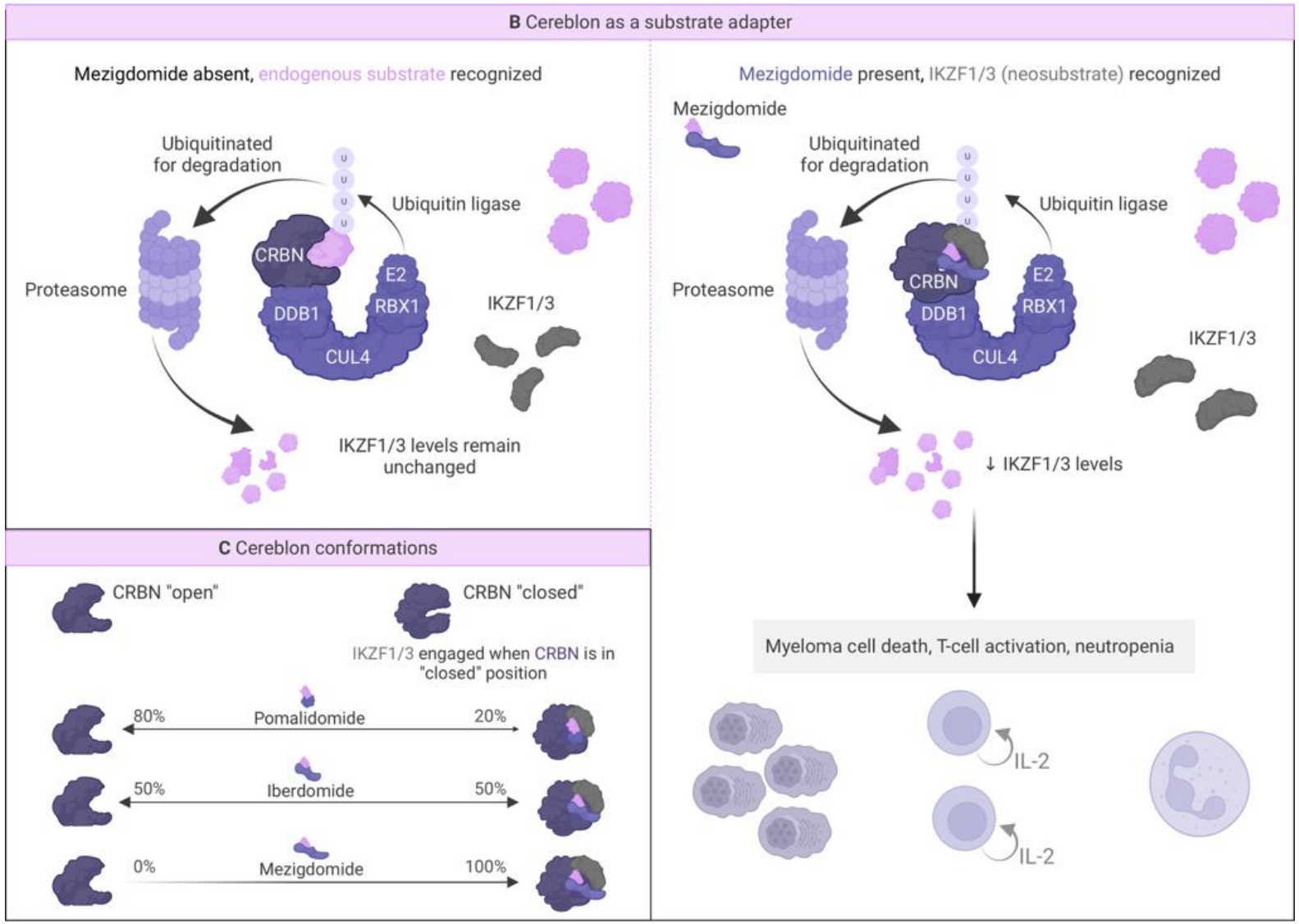



- Median DoR not reached
- Grade 3/4 hematologic AEs (N = 9): neutropenia 22.2%/11.1%, anemia 0%, thrombocytopenia 0%/11.1%
- Grade 3 non-hematologic AEs: fatigue 11.1%
- Infections 77.8% (Grade 3/4: 22.2/11.1%)

AE, adverse event; Dara, daratumumab; Dex, dexamethasone; DoR, duration of response; EMD, extramedullary disease; IMiD, immunomodulatory drug; Kd, carfilzomib and dexamethasone; mAb, monoclonal antibody; MR, minimal response; NE, not evaluable; NR, no response; ORR, overall response rate; PD,pomalidomide and dexamethasone; PI, protease inhibitor; PR, partial response; RRMM, relapsed/ refractory multiple myeloma; sCR, stringent complete response; SD, stable disease; Vd, bortezomib and dexamethasone; VGPR, very good partial response.

1. Lonial S, et al. *HemaSphere*. 2021;5(S2):49-50; Abstract S187.

# Mezigdomide (CC-92480) and multiple myeloma




CRBN, cereblon; CUL4, cullin 4; DDB1, damage-specific DNA-binding protein 1; E2, ubiquitin-conjugating enzyme ; IKZF1/3, Ikaros family zinc finger proteins 1/3 ; IL-2, interleukin-2; RBX1, RING box protein

Figure adapted from: Shortt J. *N Engl J Med.* 2023;389:1046-1050.

# Mezigdomide + Dex in RRMM

## First-in-human phase 1 trial: Mezigdomide + Dex

### Dose escalation

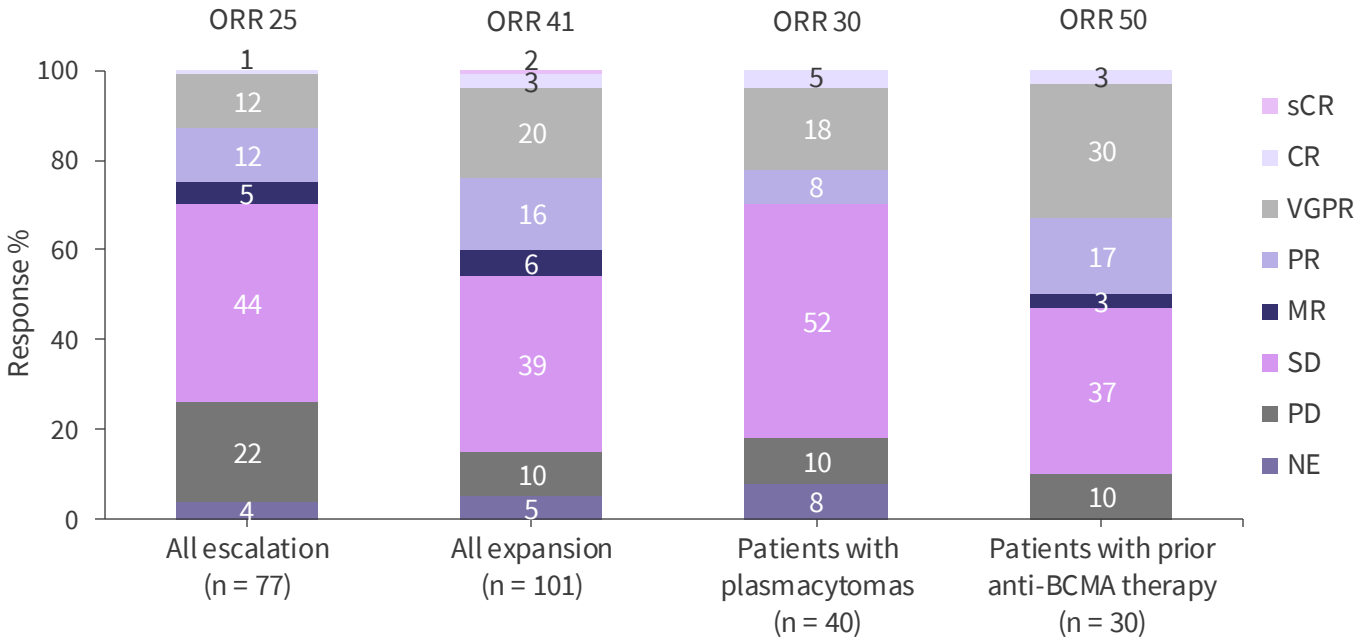
- 77 heavily pretreated RRMM patients
- 30% high-risk cytogenetics, 35% EMD
- Median 6 prior therapies
- 56% triple-class-refractory

### Dose expansion at RP2D

- 101 heavily pretreated RRMM patients
- 37% high-risk cytogenetics, 40% EMD
- Median 6 prior therapies
- 100% triple-class-refractory

### Efficacy in dose-expansion cohort

- Median DoR 7.6 months
- Median PFS 4.4 months
- In patients with prior anti-BCMA therapy, median DoR 6.9 months and median PFS 5.4 months




### Safety in dose escalation/expansion cohorts

- Grade 3/4 neutropenia 71%/76%, anemia 38%/36%, thrombocytopenia 24%/28%, febrile neutropenia 9%/15%
- Infections 74%/65% (Grade 3/4 40%/35%)
- Treatment discontinuation due to AEs NR/6%

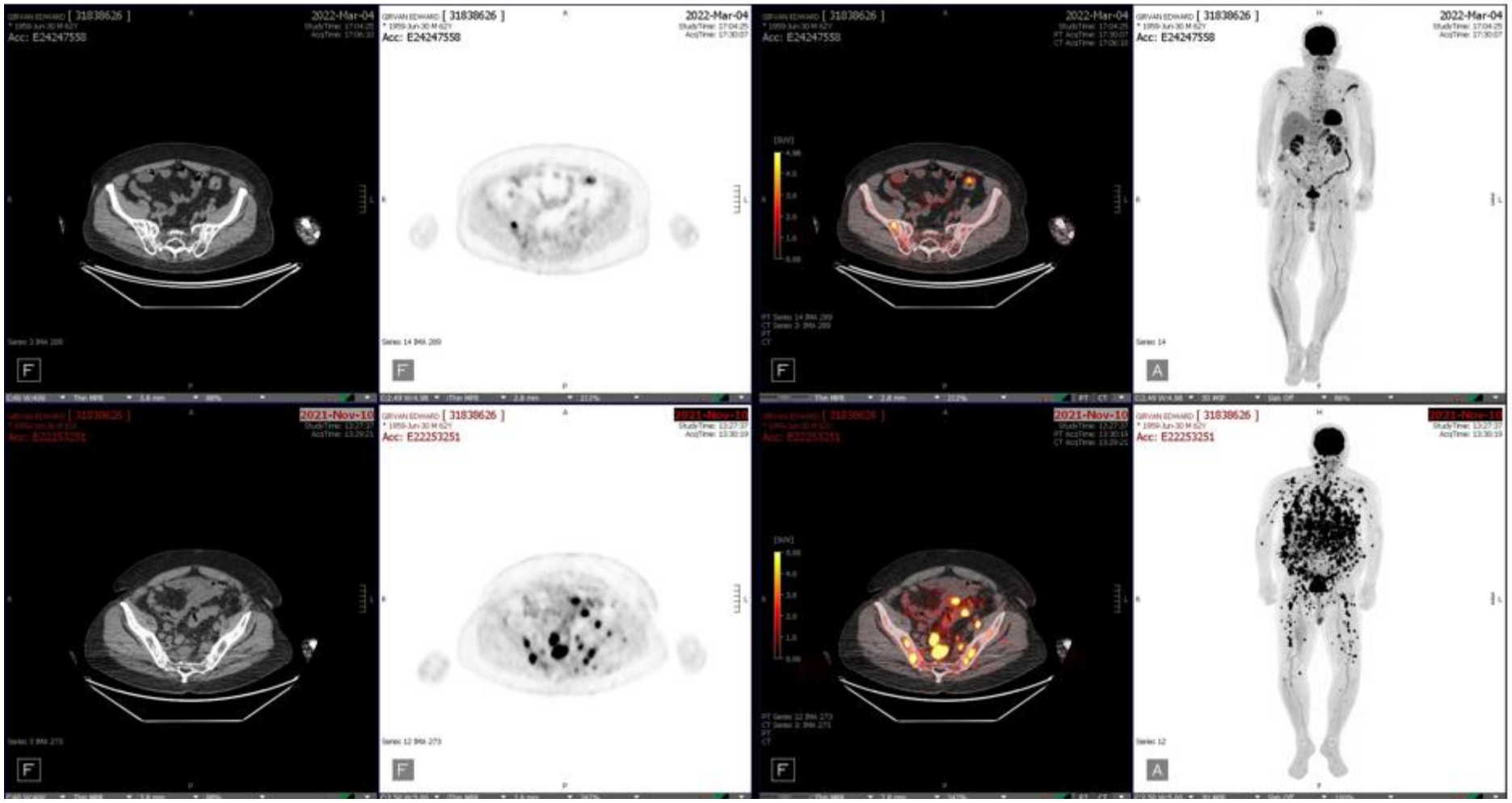
AE, adverse event; BCMA, B-cell maturation antigen; Dex, dexamethasone; DoR duration of response; EMD, extramedullary disease; NE, not evaluable; NR, no response; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; RP2D, recommended phase II dose; RRMM, relapsed/ refractory multiple myeloma; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

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

# Plasmacytomas/EMD: responses to mezigdomide (CC92480) + Dex in RRMM

**After 4 months of 480/Dex**

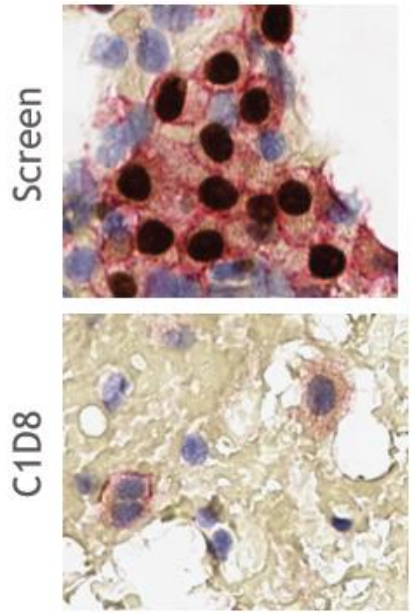
**Treatment start at study entry**




Dex, dexamethasone; EMD, extramedullary disease; RRMM, relapsed/ refractory multiple myeloma.
Richardson PG, et al. Abstract #568. Presented at: 65th ASH Annual Meeting & Exposition; Dec 10-13, 2022; New Orleans, US.

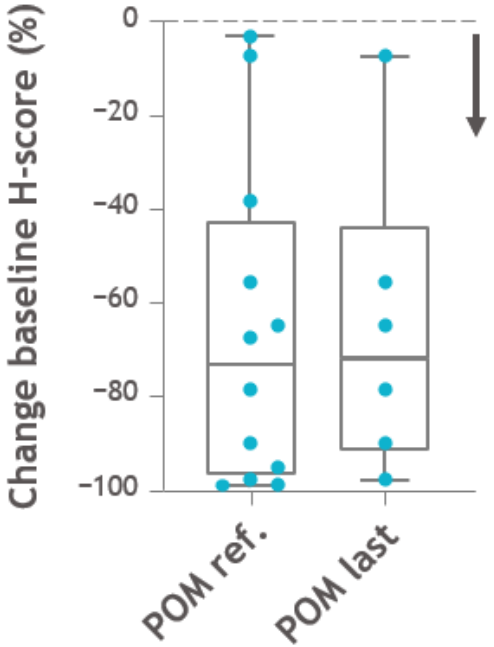
# Pharmacodynamics summary: Mezigdomide in RRMM

**Aiolos IHC**

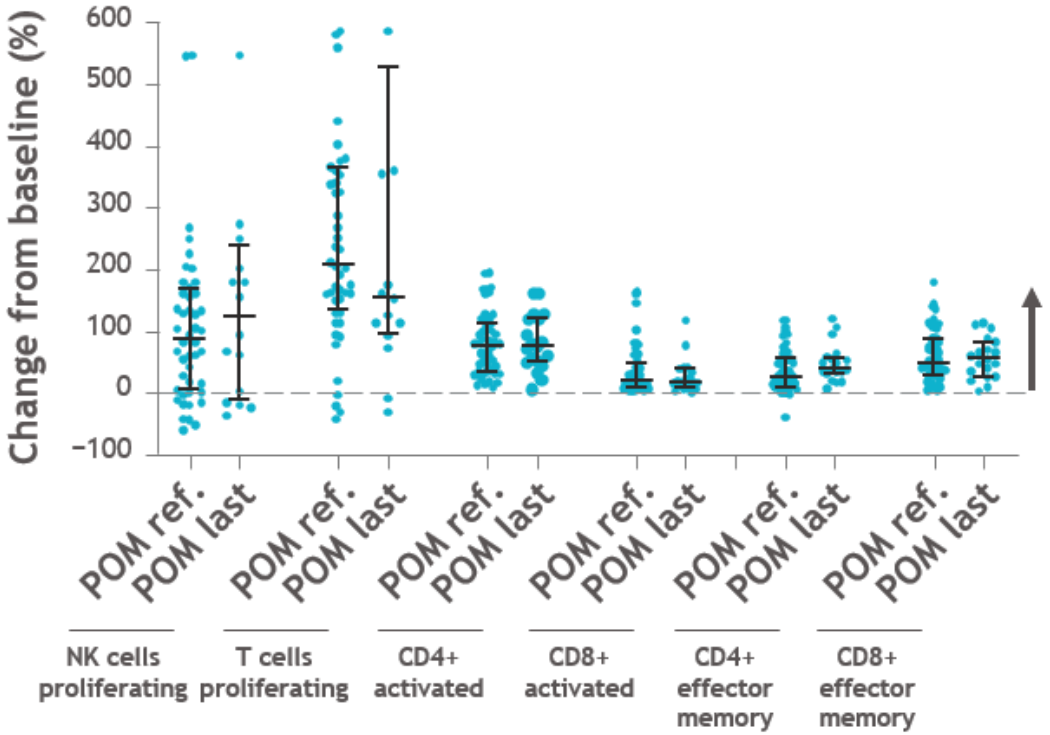



Last prior regimen:
ISA POM DEX

**Change in tumor Aiolos**
by prior POM status




**Change in PB immunophenotyping**
by prior POM status




**Mezigdomide is pharmacodynamically active in patients who were refractory to POM or had received POM in the last regimen**

C1D8, cycle 1, day 8; Dex, dexamethasone; IHC, immunohistochemistry; ISA, isatuximab; NK, natural killer; PB, peripheral blood; POM, pomalidomide; ref, refractory.

Richardson PG, et al. Abstract #568. Presented at: 65th ASH Annual Meeting & Exposition; Dec 10-13, 2022; New Orleans, US; Richardson PG, et al. *N Engl J Med.* 2023;389:1009-1022.

# Mezigdomide + Vd or Kd in RRMM

## CC-92480-MM-002 Phase I/II study: Mezigdomide + Vd / Kd[1]

### Mezigdomide + Vd (N = 28)

- 39.3% high-risk cytogenetics
- Median 3 prior therapies
- 85.7% R-refractory
- 50.0% PI-refractory
- 50.0% anti-CD38 mAb-refractory
- Median duration of treatment: 9 cycles

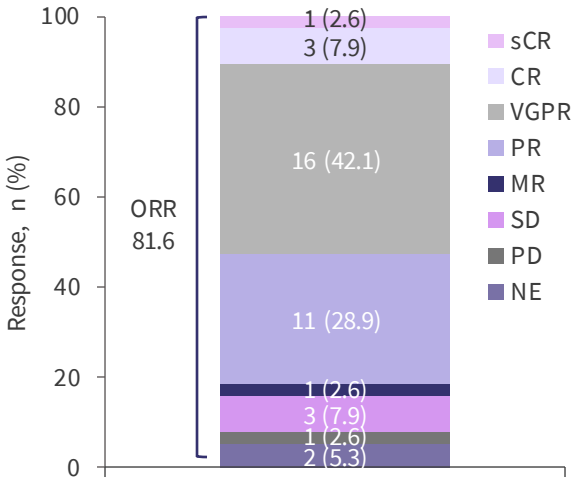
### Mezigdomide + Vd 1.0 mg (N = 38)

- 34.2% high-risk cytogenetics
- Median 1 prior therapy
- 65.8% R-refractory
- 18.4% PI-refractory
- 36.8% anti-CD38 mAb-refractory
- Median duration of treatment: 8 cycles

### Mezigdomide + Kd (N = 26)

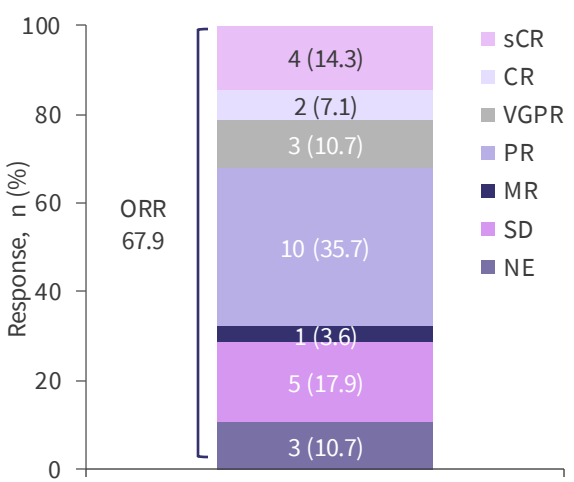
- 53.8% high-risk cytogenetics
- Median 2 prior therapies
- 80.8% R-refractory
- 50.0% PI-refractory
- 73.1% anti-CD38 mAb-refractory
- Median duration of treatment: 5 cycles

### Mezigdomide + Vd 1.0 mg (N = 38)



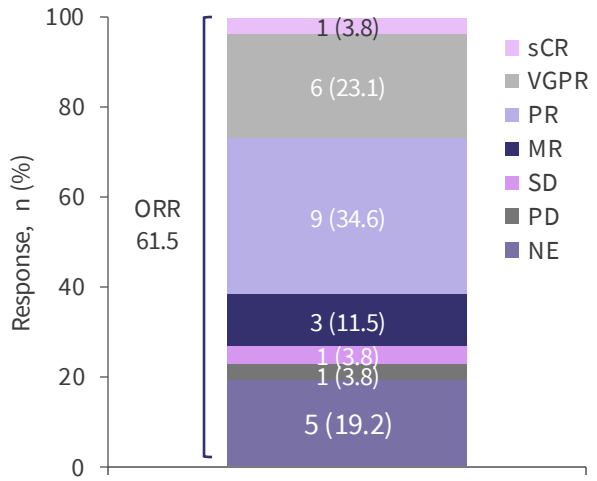

- Median DoR 14.5 months
- Grade 3/4 neutropenia 32.1%
- Grade 3/4 thrombocytopenia 21.4%
- Grade 3 anemia 14.3%
- Grade 3 diarrhea, insomnia 10.7%
- Infections 53.6%

### Mezigdomide + Vd 1.0 mg (N = 38)




- Median DoR not reached
- Grade 3/4 neutropenia 52.6%
- Grade 3/4 thrombocytopenia 26.3%
- Grade 3 anemia 7.9%
- Grade 3 diarrhea 10.5%
- Infections 65.8%

### Mezigdomide + Kd (N = 26)

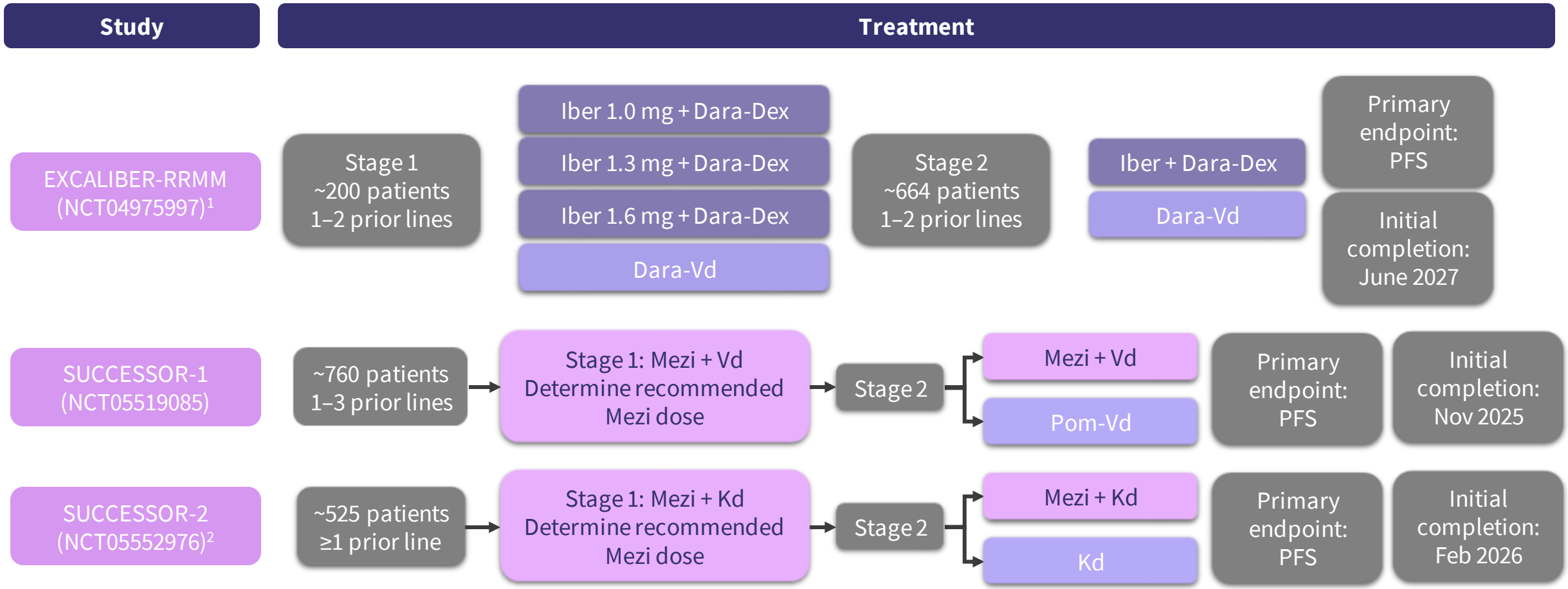



- Median DoR 11.9 months
- Grade 3/4 neutropenia 34.6%
- Grade 3/4 thrombocytopenia 11.5%
- Grade 3 anemia 7.7%
- Grade 3 diarrhea 7.7%
- Infections 42.3%

DoR, duration of response; Kd, carfilzomib and dexamethasone ; mAb, monoclonal antibody; MR, minimal response; NE, not evaluable; NR, no response; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PI, protease inhibitor; PR, partial response; RRMM, relapsed/ refractory multiple myeloma;sCR, stringent complete response; SD, stable disease; Vd, bortezomib and dexamethasone; VGPR, very good partial response.

1. Richardson PG, et al. Abstract #OAB-053. Presented at: 19th International Myeloma Society (IMS) Annual Meeting. Aug 27, 2022; Los Angeles, US.

# Phase 3 studies of CELMoDs in RRMM




CELMoD, cereblon E3 ligase modulatory drug; Dara, daratumumab; Dex, dexamethasone; Kd, carfilzomib and dexamethasone; iber, iberdomide; Mezi, mezigdomide; PFS, progression-free survival; Pom, pomalidomide; RRMM, relapsed/ refractory multiple myeloma; Vd, bortezomib and dexamethasone.

1. Lonial S, et al. *J Clin Oncol*. 2023;41(16_suppl):Abstract TPS8069; 2. Richardson PG, et al. *J Clin Oncol*. 2023;41(16_suppl):Abstract TPS8070.