Highlights from
IMS 20th meeting 2023

Renato Zambello, MD

Terapie del MM refrattario con nuovi agenti/classi di farmaci: CELMoDs (iberdomide e mezigdomide)

30-31 gennaio 2024
BOLOGNA, Royal Hotel Carlton

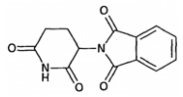
Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
GSK						x	
Janssen						x	
Menarini Stemline						x	
Amgen						x	
Sanofi						x	
Oncopeptides						x	

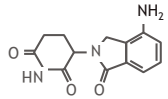
The purposefully designed CELMoD program

Based on a deep understanding of the cereblon pathway, we **purposefully designed the novel CELMoD program** to develop next-generation IMiD agents

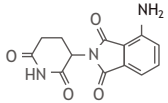
Thalidomide (1999)[1,2]



Lenalidomide (2006)[3]



Pomalidomide (2013)[4]

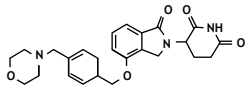


THAL, LEN and POM transformed MM treatment; however, the mechanisms of action were unknown[5,6]

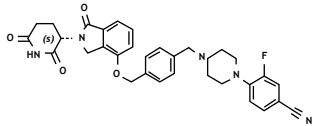
Discovery of cereblon* (2014)[5,6]

Novel CELMoD agents

Iberdomide (2019)[7]



Mezigdomide (2020)[8]



*Discovery that immunomodulators are dependent on cereblon to degrade target proteins (ie, Ikaros/Aiolos)

References: 1. Singhal S et al. *N Engl J Med*. 1999;341(21):1565-71. **2.** VanRhee F et al. *Blood*. 2008;112;(4):1035-1038. **3.** Chen C et al. *Br J Haematol*. 2009;146(2):164-170. **4.** San Miguel SJ et al. *Lancet Oncol*. 2013;14(11):1055-1066. **5.** Kronke J et al. *Science*. 2014;343(6168)301-305. **6.** Lu G et al. *Science*. 2014;343(6168)305-309. **7.** Lonial et al. Presented at the 61st Annual Meeting of the American Society of Hematology (ASH); December 7–10, 2019; Orlando, FL. Abstract 3119. **8.** Richardson PG et al. Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 29–31, 2020; Virtual Program.

Novel CELMoD agents co-opt cereblon with unique binding features and induce distinct conformational changes

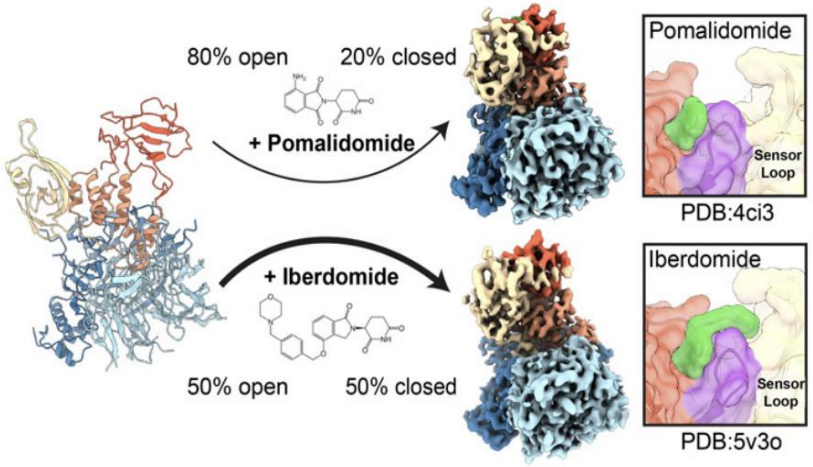
Classic IMiD agents exist as a mixture of S and R isomers, of which the R isomer is known to bind less efficiently to cereblon[1,2]

- Novel CELMoD agents IBER and MEZI are uniquely administered as a single S isomer and bind to cereblon with greater potency

Compound	CRBN Binding Affinity (IC_{50})
Lenalidomide	~1.5uM
Pomalidomide	~1.2uM
Iberdomide	~0.06uM
Mezigdomide	~0.03uM

- However, binding affinity is only part of the story

"Active" Conformation[3]



	LEN	POM	IBER	MEZI
Percent Closed	25%	20%	50%	100%

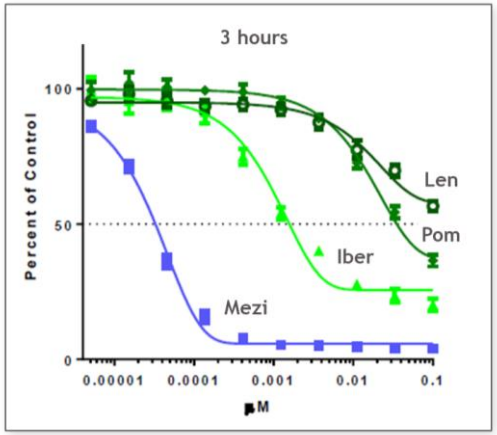
The ability to bind to cereblon and induce a closed conformation leads to substrate degradation and downstream anti-MM effects

References: **1.** Hansen JD, et al. *J Med Chem*. 2020 Jul 9;63(13):6648-6676. **2.** Matyskiela M, et al. *ACS*. 2018 Jan 25;61(2):535-542. **3.** Watson ER, et al. *Science*. 2022 Nov 4;378(6619):549-553. 4. Thieblemont C, et al. Oral presentation at ASH; December 10-13, 2022; New Orleans, LA. Abstract 232.

Unique biochemical features of novel CELMoDs offer enhanced activity over classic IMiD agents and a differentiated profile

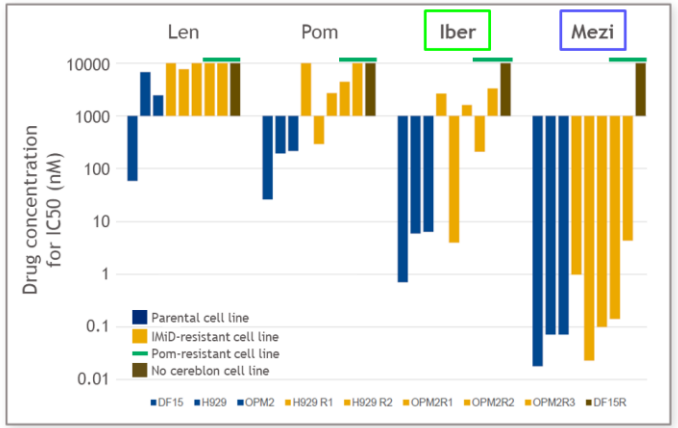
Protein degradation kinetics (Aiolos) [1,2]

In vitro, a lower concentration of IBER or MEZI are needed to degrade Aiolos to a similar extent than LEN and POM



Antiproliferative activity [3,4]

Iber and Mezi induce superior anti-proliferative activity including in IMiD-resistant cell lines



Faster substrate degradation results in increased direct anti-tumor activity, yet may not correlate with increased immune activation

References: **1.** Hansen JD, et al. *J Med Chem*. 2020 Jul 9;63(13):6648-6676. **2.** Matyskiela M, et al. *J Med Chem*. 2018;61(2):535-542.
3. Richardson PG et al. Presented at the ASCO Annual Meeting; May 29–31, 2020; Virtual Program. **4.** Lopez-Girona A., et al. *Blood*. 2019;134(suppl 1):1812.

CELMoDs at IMS 20th

Iberdomide	Mezigdomide
1 Oral	1 Oral
7 Posters	3 Posters

Iberdomide, bortezomib, and dexamethasone (IberVd) in transplant-ineligible newly diagnosed multiple myeloma: results from the CC-220-MM-001 trial

Darrell White,[1] Brea Lipe,[2] Mercedes Gironella Mesa,[3] Ruben Niesvizky,[4] Albert Oriol,[5] Anna Sureda Balari,[6] Manisha Bhutani,[7] Cristina Encinas,[8] Abdullah M. Khan,[9] Michael Amatangelo,[10] Kexin Jin,[10] Thomas Solomon,[10] Kevin Hong,[10] Alpesh Amin,[10] Paulo Maciag,[10] Niels W.C.J. van de Donk,[11] Sagar Lonial[12]

Iberdomide plus dexamethasone in patients with relapsed/refractory multiple myeloma: a safety analysis from the CC-220-MM-001 trial

Niels W.C.J. van de Donk,[1] Darrell White,[2] Brea Lipe,[3] Abdullah M. Khan,[4] Ruben Niesvizky,[5] Albert Oriol,[6] Mercedes Gironella Mesa,[7] Faiz Anwer,[8] Manisha Bhutani,[9] Brian McClune,[10] Seema Singhal,[11] Yiming Cheng,[12] Izumi Hamada,[12] Kexin Jin,[12] Thomas Solomon,[12] Kevin Hong,[12] Alpesh Amin,[12] Paulo Maciag,[12] Sagar Lonial[13]

Mezigdomide plus dexamethasone and bortezomib or carfilzomib in patients with relapsed/refractory multiple myeloma: results from the CC-92480-MM-002 trial

Albert Oriol,[1] Irwindeep Sandhu,[2] Marc S. Raab,[3] Darrell White,[4] Richard LeBlanc,[5] Noopur Raje,[6] Enrique M. Ocio,[7] Aurore Perrot,[8] Thierry Facon,[9] Cesar Rodriguez,[10] Ralph Waesch,[11] Michael Amatangelo,[12] Zehua Zhou,[12] Yue Wang,[12] Tiziana Civardi,[13] Phillip Koo,[12] Paulo Maciag,[12] Yue Zhu,[12] Jessica Katz,[12] Paul G. Richardson[14]

Mezigdomide monotherapy in relapsed/refractory multiple myeloma: results from the CC-92480-MM-001 trial

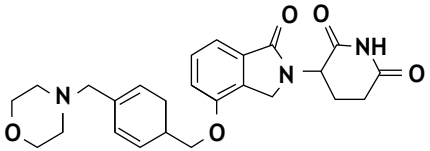
Scott R. Goldsmith,[1] Albert Oriol,[2] Pekka Anttila,[3] Nizar J. Bahlis,[4] Jesús G. Berdeja,[5] Andrew J. Cowan,[6] Meletios A. Dimopoulos,[7] Laahn H. Foster,[8] Jens Hillengass,[9] Martha L. Louzada,[10] Ka Lung Wu,[11] Tracy T. Chow,[12] Wencong Chen,[12] Yue Wang,[12] Alessia Spirli,[13] Phillip Koo,[12] Paulo Maciag,[12] Yue Zhu,[12] Jessica Katz,[12] Paul G. Richardson[14]

Emerging data suggest an interesting clinical profile for IBER

Iberdomide

Properties enable **combinability, enhanced anti-MM activity,** and **favorable tolerability** needed to achieve long-term disease control[1,2]

Unique **immune-stimulation profile** (T and NK cells) and potential for no dose modifications in RI[3,4]



Clinical insights on IBER

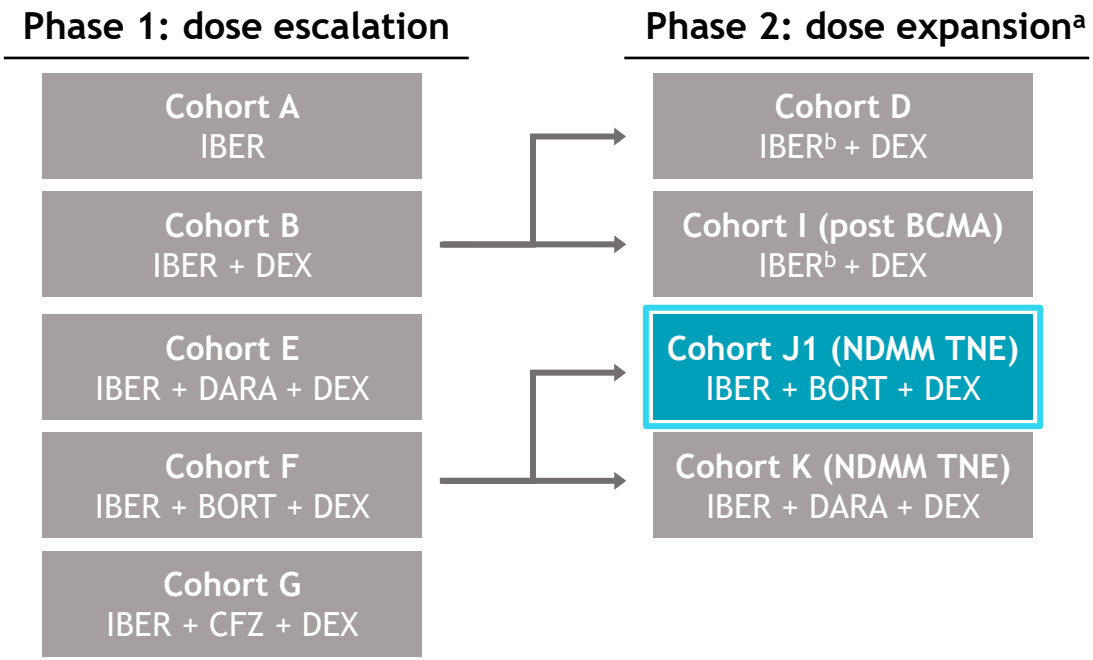
- Activity and tolerability with IBER+DEX, +Vd, +Kd, and +Dd regimens suggest a high potential for combinability[1,2]
- Consistent safety profile and no dose adjustments anticipated for patients with mild-to-moderate renal impairment[3]
- Multiple dose strengths, and a unique T and NK cell signal, without reaching the MTD[4]
- Activity as IBER monotherapy being evaluated as maintenance post-ASCT[5,6]
- Data at ASH 2022 demonstrate continued clinical activity in patients with prior BCMA therapy[7]
- Ongoing research program evaluating IBER as monotherapy and in combination for HRSMM, NDMM, maintenance, and RRMM[5,6,8-10]

D=Darzalex (daratumumab); d=dexamethasone; DARA=Darzalex (daratumumab); IBER=iberdomide; LEN=REVLIMID (lenalidomide); MEZI=mezigdomide; MTD=maximum tolerated dose; POM=POMALYST/IMNOVID (pomalidomide); RI=renal impairment.

References: 1. Lonial S et al. *Lancet Haematol*. 2022; S2352-3026(22)00290-3. **2.** Lonial S et al. Oral presentation at the EHA Virtual Meeting; June 9-17, 2021. Abstract S187. **3.** van de Donk NWCJ et al. Presented at the IMS Annual Meeting; August 25-27, 2022; Los Angeles, CA, USA. **4.** Amatangelo M et al. Presented at the International Myeloma Society Hybrid Congress 2022, August 25-27, Los Angeles, CA, USA. **5.** ClinicalTrials.gov identifier: NCT04564703. Updated August 18, 2022. Accessed June 21, 2023. https://www.clinicaltrials.gov/study/NCT04564703. **6.** ClinicalTrials.gov identifier: NCT05827016. Updated June 7, 2023. Accessed June 21, 2023. https://www.clinicaltrials.gov/study/NCT05827016. **7.** Lonial S et al. Presented at 64th American Society of Hematology (ASH) Annual Meeting; December 10-13, 2022. New Orleans, LA. **8.** ClinicalTrials.gov identifier: NCT04776395. Updated June 12, 2023. Accessed June 21, 2023. https://www.clinicaltrials.gov/study/NCT04776395. **9.** ClinicalTrials.gov identifier: NCT05558319. Updated September 28, 2022. Accessed June 21, 2023. https://www.clinicaltrials.gov/study/NCT05558319. **10.** ClinicalTrials.gov identifier: NCT04975997. Updated June 2, 2023. Accessed June 21, 2023. https://www.clinicaltrials.gov/study/NCT04975997.

CC-220-MM-001 study design and objective

- Phase 1/2 trial evaluating IBER with different treatment combinations in MM[1,2]
- **Objective**: to report the first results from the dose-expansion cohort of the CC-220-MM-001 trial evaluating IberVd in patients with NDMM who are TNE or not receiving ASCT as their first therapy



[a]Cohorts C (IBER monotherapy expansion) and J2 (IBER + BORT + DEX in patients with NDMM who are TE) were planned but not opened; [b]1.6 mg on D1–21 of 28-day cycles.
ASCT, autologous stem cell transplant; BCMA, B-cell maturation antigen; CFZ, carfilzomib; D, day; TE, transplant eligible; TNE, transplant ineligible.
1. ClinicalTrials.gov: NCT02773030; 2. EudraCT number: 2016-000860-40.

White D et al. Presentation OA-41

CC-220-MM-001 eligibility, treatments, and endpoints

Key eligibility criteria

- NDMM
- Previously untreated symptomatic MM[a]
- No ASCT planned for initial therapy or ASCT-ineligible[b]
- Measurable disease

Treatments

IBER + BORT + DEX

IBER (oral): 1.0, 1.3, or 1.6 mg on D1–14 in C1-8, and D1-21 in C≥9

BORT (SC): starting at 1.3 mg/m^2 on D1, 4, 8, and 11 in C1-8

DEX (oral): 20 mg[c] on D1, 2, 4, 5, 8, 9, 11, and 12 in C1-8, and 40 mg[d] weekly in C≥9

21-day cycles (C1-8)
28-day cycles (C≥9)

Endpoints

- **Primary:** efficacy and safety
- **Secondary:** additional efficacy parameters (including DOR and PFS)
- **Exploratory:** Pharmacodynamics assessment, MRD evaluation

[a]Radiotherapy, bisphosphonates, or a single short course of steroids were permitted; [b]Patients ineligible for ASCT due to age (≥ 65 years of age) or severe comorbidities; [c]DEX was given at a dose of 10 mg in patients > 75 years of age; [d]DEX was given at a dose of 20 mg in patients > 75 years of age.
C, cycle; DOR, duration of response; MRD, minimal residual disease; PD, progressive disease; PFS, progression-free survival; SC, subcutaneous.

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Baseline characteristics

Characteristic[a]	IberVd TNE NDMM (N = 18)
Age, median (range), years	77.5 (57–84)
Sex, n (%)	
Male	12 (66.7)
Race, n (%)	
White	17 (94.4)
Not collected or reported	1 (5.6)
Time since diagnosis, median (range), years	0.1 (0.0–0.4)
ECOG PS, n (%)	
0	3 (16.7)
1	11 (61.1)
2	4 (22.2)
ISS stage at study entry, n (%)	
I	7 (38.9)
II	9 (50.0)
III	2 (11.1)
High-risk cytogenetics,[b] n (%)	11 (61.1)[c]

At follow up 14 months, only 1 patient discontinued treatment due to an AE of peripheral neuropathy

[a]Data cutoff: June 23, 2023; [b]Defined as the presence of any abnormality for del(17p), and/or translocation t(4,14), and/or translocation t(14,16), and/or amplification 1q21; [c]2/18 patients were not evaluable.
ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System.

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TEAEs

Most common (≥ 25% all grade) TEAEs and events of interest,[a] n (%)	IberVd TNE NDMM (N = 17)[b]		
	All grade	Grade 3	Grade 4
Hematologic TEAEs			
Neutropenia	6 (35.3)	2 (11.8)	2 (11.8)
Thrombocytopenia	5 (29.4)	1 (5.9)	1 (5.9)
Anemia	4 (23.5)	1 (5.9)	0
Lymphopenia	4 (23.5)	0	0
Non-hematologic TEAEs			
Peripheral edema	11 (64.7)	1 (5.9)	0
Peripheral sensory neuropathy	11 (64.7)	1 (5.9)	0
Constipation	10 (58.8)	1 (5.9)	0
Insomnia	8 (47.1)	1 (5.9)	0
Fatigue	7 (41.2)	2 (11.8)	0
Pain in extremity	6 (35.3)	0	0
Dyspnea	6 (35.3)	0	0
Decreased appetite	6 (35.3)	0	0
Agitation	5 (29.4)	0	0
Dysgeusia	5 (29.4)	0	0
Infections	13 (76.5)	5 (29.4)	1 (5.9)
COVID-19	5 (29.4)	1 (5.9)	0
Pneumonia	3 (17.6)	2 (11.8)	1 (5.9)

[a]Data cutoff: June 23, 2023; [b]1 patient was enrolled but not included in the safety population due to self-withdrawal (appointment absence).
COVID-19, coronavirus disease 2019.

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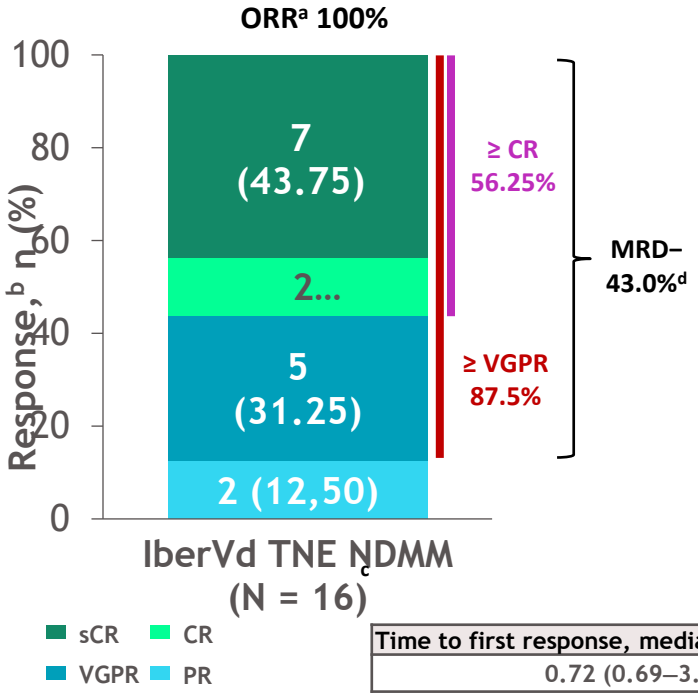
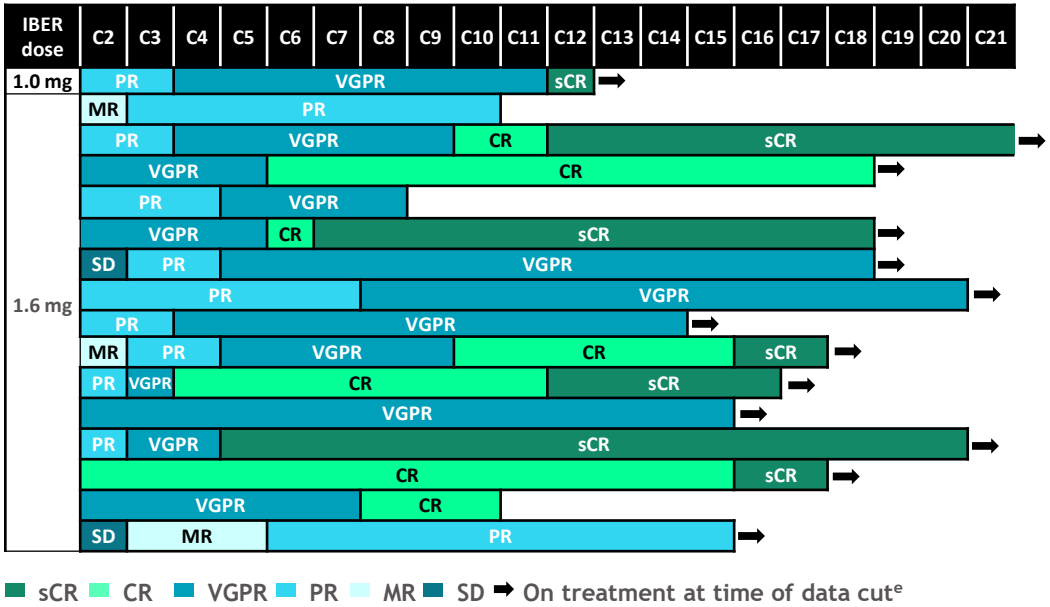
Response rates





Time to first response, median (range), months	Follow-up,[f] median (range), months
0.72 (0.69–3.91)	12.63 (3.91–16.43)

ORR was 100% in the efficacy-evaluable population

[a]ORR (PR or better); [b]Data cutoff: June 23, 2023; [c]Efficacy-evaluable population; [d]At a threshold of 10^{-5}; [e]BORT was administered during C1–8 only; [f]From univariate analysis for all responders without adjusting for censoring.
CR, complete response; MR, minimal response; ORR, overall response rate; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

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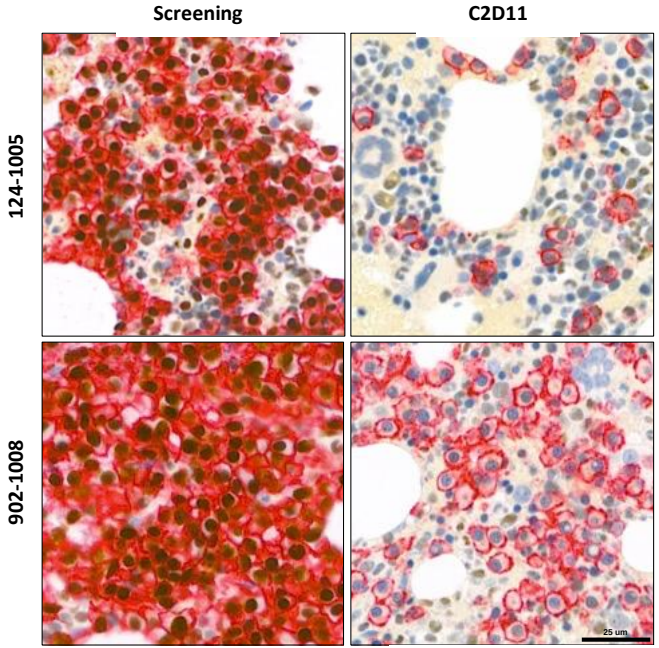
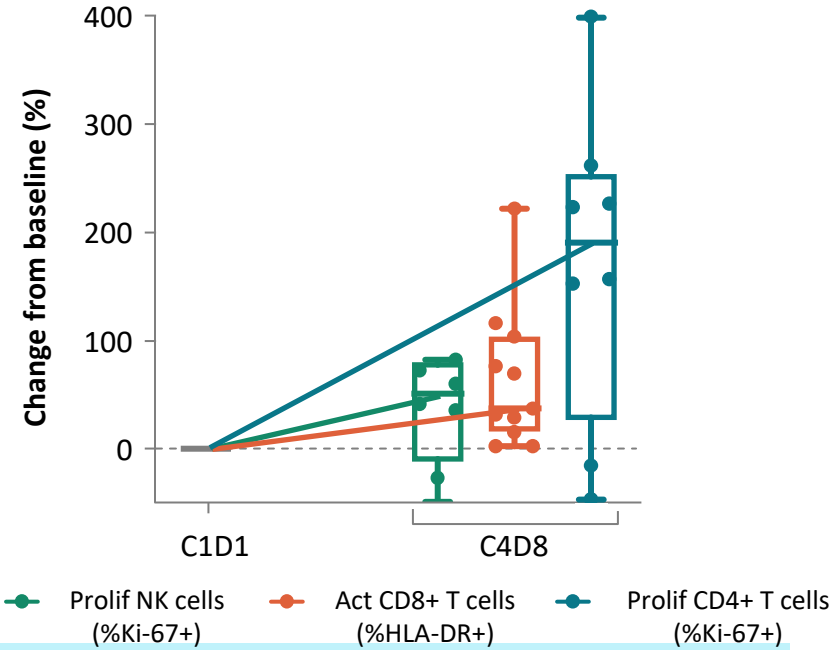
Pharmacodynamics

Degradation of Aiolos in BM



CD138 (red); Aiolos (brown)

Induction of T/NK-cell stimulation in PB



Pharmacodynamic data showed that IBER treatment led to robust substrate degradation (median > 50% decrease) and immune stimulation (177% median increase in T-cell proliferation) when combined with Vd

Act, activated; BM, bone marrow; HLA-DR, human leukocyte antigen – DR isotype; PB, peripheral blood; Prolif, proliferating.

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Conclusions

- In this cohort of mostly older patients with TNE NDMM, IberVd showed high efficacy with deep, ongoing responses
  - The ORR in the efficacy-evaluable population was 100%, with 87.5% of patients achieving VGPR or better, and 56.25% of patients achieving CR or better
  - Among patients who achieved ≥ VGPR, 6/14 (43%) patients were MRD-negative at 10^{-5}
  - 68.8% of patients responded in < 6 weeks
  - At data cutoff, no events of documented PD or death were reported
- The safety profile was manageable with no new safety signals
  - Most grade 3/4 TEAEs were hematologic and the occurrence of other grade 3/4 non-hematologic TEAEs was low
  - Only 1 patient discontinued treatment due to an AE of peripheral neuropathy
- IBER induced robust Aiolos degradation and immune stimulation in combination with Vd
- These data support further assessment of IBER combinations in the frontline setting

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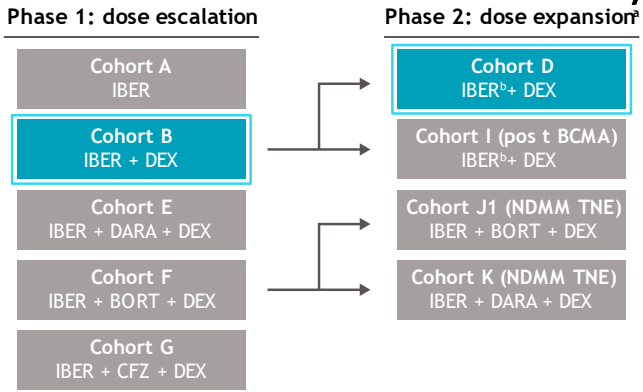
Study design

CC -220 MM- 001 trial

A



Objective

To assess the kinetics of the most common TEAEs and impact on clinical outcomes (using ER analyses) in patients with RRMM treated with IBER + DEX in Cohorts B and D of the CC-220-MM-001 trial

B

Key eligibility criteria

- RRMM
- ≥ 2 prior therapies[c] (Cohort B) or ≥ 3 prior therapies[d] (Cohort D)
- PD on or within 60 days of last antimyeloma therapy
- Refractory to an IMiD agent, a PI, a glucocorticoid, and a CD38 mAb (Cohort D only)

Treatments

IBER + DEX[e]

IBER (oral): 0.3-1.6 mg (Cohort B) or 1.6 mg (Cohort D) on days 1-21

DEX (oral): 40 mg[f] on days 1, 8, 15, 22

28-day cycles

Endpoints

- **Primary:** determine MTD/RP2D (Cohort B) and efficacy as ORR (Cohort D)
- **Secondary:** PK, safety, and additional efficacy parameters

ClinicalTrials.gov: NCT02773030
EudraCT: 2016-000860-40

[a]Cohorts C (IBER monotherapy expansion) and J2 (IBER + BORT + DEX in patients with NDMM TE) were planned but not opened; [b]1.6 mg on days 1-21 of 28-day cycles; [c]Including LEN, POM, a PI, and a glucocorticoid; [d]Including LEN, POM, a PI, a glucocorticoid, and a CD38 mAb; [e]Prophylactic use of G-CSF and/or epoetin was permitted, except during the cycle 1 DLT evaluation period for Cohort B; [f]20 mg if > 75 years of age.

BCMA, B-cell maturation antigen; CFZ, carfilzomib; DLT, dose-limiting toxicity; G-CSF, granulocyte colony-stimulating factor; LEN, lenalidomide; mAb, monoclonal antibody; MTD, maximum tolerated dose; NDMM, newly diagnosed MM; PD, progressive disease; PI, proteasome inhibitor; POM, pomalidomide; RP2D, recommended phase 2 dose; TE, transplant eligible; TNE, transplant non-eligible.

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CC -220 MM- 001 trial

Patients

- As of June 2, 2021, 197 patients had received IBER + DEX (90 in Cohort B, 107 in Cohort D)
- Cohort D was particularly heavily pretreated, with 97.2% being triple-class refractory

Safety

- Grade 3/4 TEAEs occurred in 75 (83.3%) patients in Cohort B, and 88 (82.2%) patients in Cohort D
- AEs were largely related to myelosuppression and most grade 3/4 TEAEs were hematologic
  - Grade 3/4 infections occurred in 23 (25.6%) patients in Cohort B and 29 (27.1%) patients in Cohort D
  - The incidence of grade 3/4 non-hematologic TEAEs was < 3%

Discontinuation due to TEAE was 6.7 (cohort B) and 4.7 (cohort D)

TEAEs of interest,[a] n (%)	Cohort B IBER + DEX dose escalation (N = 90)		Cohort D IBER + DEX dose expansion (N = 107)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any event	89 (98.9)	75 (83.3)	107 (100)	88 (82.2)
Hematologic TEAEs				
Neutropenia	43 (47.8)	38 (42.2)	64 (59.8)	48 (44.9)
Febrile neutropenia	3 (3.3)	3 (3.3)	5 (4.7)	5 (4.7)
Anemia	35 (38.9)	24 (26.7)	44 (41.1)	30 (28.0)
Thrombocytopenia	18 (20.0)	13 (14.4)	38 (35.5)	23 (21.5)
Leukopenia	14 (15.6)	12 (13.3)	30 (28.0)	22 (20.6)
Non-hematologic TEAEs				
Fatigue	33 (36.7)	2 (2.2)	25 (23.4)	3 (2.8)
Insomnia	29 (32.2)	1 (1.1)	15 (14.0)	1 (0.9)
Diarrhea	21 (23.3)	1 (1.1)	25 (23.4)	1 (0.9)
Rash	17 (18.9)[b]	0	21 (19.6)[c]	3 (2.8)[c]
Venous thromboembolism	4 (4.4)	2 (2.2)	5 (4.7)	2 (1.9)
Infections	56 (62.2)	23 (25.6)	62 (57.9)	29 (27.1)
Pneumonia	14 (15.6)[d]	12 (13.3)[d]	13 (12.1)[e]	9 (8.4)[e]
Respiratory tract infection	21 (23.3)[f]	5 (5.5)[f]	15 (14.0)[g]	4 (3.7)[g]

AE, adverse event; DEX, dexamethasone; IBER, iberdomide; TEAE, treatment-emergent adverse event.

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CC -220 MM- 001 trial

Authors' conclusions

- The all-oral regimen of IBER + DEX showed a tolerable safety profile in patients with RRMM
- TEAEs were manageable with dose modifications, dose interruptions, and G-CSF
  - Few patients discontinued IBER due to TEAEs
- AEs were largely related to myelosuppression
- Higher IBER PK exposure was associated with a higher probability and earlier occurrence of grade ≥ 3 neutropenia and grade ≥ 3 thrombocytopenia
- These safety data support further development of IBER in combination with other agents in patients with RRMM

AE, adverse event; DEX, dexamethasone; G-CSF, granulocyte colony-stimulating factor; IBER, iberdomide; MM, multiple myeloma; RR, relapsed/refractory; TEAE, treatment-emergent AE.

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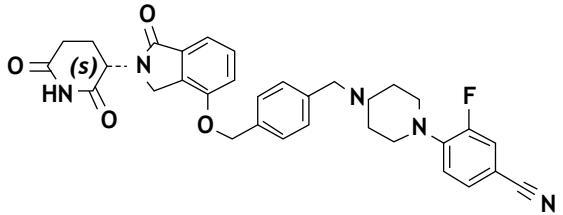
Emerging data suggest an interesting clinical profile for MEZI

Mezigdomide

Optimized for **rapid and maximal degradation of target proteins**, induces **tumor cell apoptosis** and responses needed **to regain control** with tolerability[1,2]

Stimulates the immune system and maintains the potential **to treat advanced disease** in combination regimens[1,2]



MEZI Clinical insights

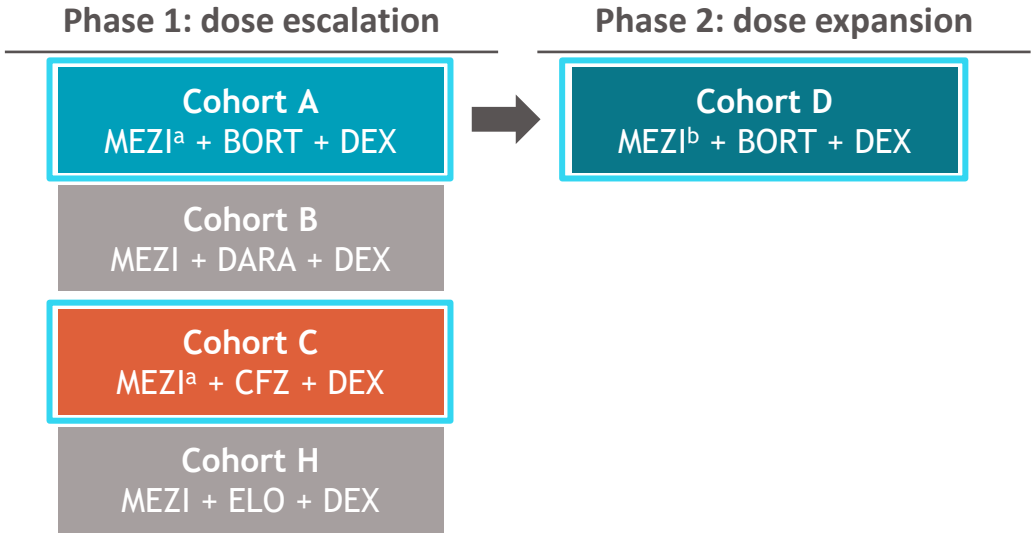
- The most potent cereblon-modulating agent with rapid substrate degradation and apoptosis induction[1,2]
- Activity in combination with PIs in DARA- and REV-refractory patients[3]
- Manageable safety profile with neutropenia as the most frequent TEAE[1-4]
- Potential for deep tissue distribution and activity in the presence of plasmacytomas[1]
- Data at ASH 2022 demonstrates the activity and safety of MEZI + DEX in heavily pretreated patients[4]
- Ongoing research program evaluating MEZI-based regimens in RRMM[5,6]

DARA=Darzalex (daratumumab); EMP=extramedullary plasmacytoma; LEN=REVLIMID (lenalidomide); MEZI=mezigdomide; POM=POMALYST/IMNOVID (pomalidomide); TEAE=treatment emergent adverse events.

References: 1. Richardson PG et al. Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 29-31, 2020; Virtual Program. **2.** Amatangelo M et al. Presented at the IMS Annual Meeting; August 25-27, 2022; Los Angeles, CA, USA. Abstract P-230. **3.** Richardson PG et al. Presented at the IMS Annual Meeting; August 25-27, 2022; Los Angeles, CA, USA. Abstract OAB-053. **4.** Richardson PG et al. Presented at 64th American Society of Hematology (ASH) Annual Meeting; December 10-13, 2022. New Orleans, LA. **5.** ClinicalTrials.gov identifier: NCT05519085. Updated June 13, 2023. Accessed June 21, 2023. https://www.clinicaltrials.gov/study/NCT05519085. **6.** ClinicalTrials.gov identifier: NCT05552976. Updated June 18, 2023. Accessed June 21, 2023. https://www.clinicaltrials.gov/study/NCT05552976.

CC-92480-MM-002 study design and objective

- Phase 1/2 study evaluating MEZI with different treatment combinations in MM[1,2]
- **Objective**: to report updated results from the MEZI + BORT + DEX (MeziVd) and MEZI + CFZ + DEX (MeziKd) dose-escalation cohorts, and the MeziVd dose-expansion cohort



[a]0.3, 0.6, or 1.0 mg; [b]0.6 and 1.0 mg.
DARA, daratumumab; ELO, elotuzumab; ISA, isatuximab.
1. ClinicalTrials.gov: NCT03989414; 2.EudraCT number: 2018-004767-31.

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CC-92480-MM-002 Cohorts A, C, and D

Key eligibility criteria

- Documented diagnosis of MM and measurable disease
- Documented disease progression during or after the last antimyeloma therapy
- MR or better to ≥ 1 prior regimen
- Prior regimens:
  - 2–4 for Cohorts A and C
  - 1–3 for Cohort D
  - LEN for ≥ 2 consecutive cycles

Treatments

MeziVd

Cohort A

MEZI (oral): 0.3, 0.6, or 1.0 mg on D1–14
BORT (SC): 1.3 mg/m^2 on D1, 4, 8, 11 (C1–8); on D1, 8 (C≥9)
DEX (oral): 20 mg[a] on D1, 2, 4, 5, 8, 9, 11, 12 (C1–8); on D1, 2, 8, 9 (C≥9)
21-day cycles

Cohort D

MEZI (oral): 0.6 or 1.0 mg on D1–14
BORT (SC): 1.3 mg/m^2 on D1, 4, 8, 11 (C1–8); on D1, 8 (C≥9)
DEX (oral): 20 mg[a] on D1, 2, 4, 5, 8, 9, 11, 12 (C1–8); on D1, 2, 8, 9 (C≥9)
21-day cycles

MeziKd

Cohort C

MEZI (oral): 0.3, 0.6, or 1.0 mg on D1–21
CFZ (IV): 20 mg/m^2 on C1D1; 56 mg/m^2 on D8, 15 (C1), D1, 8, 15 (C2–12), D1, 15 (C≥13)
DEX (oral/IV): 40 mg[b] on D1, 8, 15, 22
28-day cycles

Primary endpoints

- Recommended dose and regimen (Cohorts A and C)
- Safety
- Preliminary efficacy as ORR

[a]10 mg if > 75 years of age; [b]20 mg if > 75 years of age.
C, cycle; D, day; IV, intravenous; LEN, lenalidomide; MR, minimal response; ORR, overall response rate; SC, subcutaneous.

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CC-92480-MM-002 Cohorts A, C, and D

Baseline characteristics

Characteristic[a]	Cohort A MeziVd (N = 28)	Cohort D MeziVd (N = 49)	Cohort C MeziKd (N = 27)
Age, median (range), years	65.5 (46–86)	64.0 (43–83)	68.0 (41-76)
Sex, n (%)			
Female	16 (57.1)	16 (32.7)	18 (66.7)
Time since initial diagnosis, median (range), years	4.8 (1.9-17.1)	4.4 (0.9-20.5)	5.4 (0.7-15.7)
ECOG PS, n (%)			
0	11 (39.3)	22 (44.9)	10 (37.0)
1	15 (53.6)	25 (51.0)	15 (55.6)
2	2 (7.1)	2 (4.1)	2 (7.4)
ISS stage at study entry, n (%)			
I	20 (71.4)	34 (69.4)	21 (77.8)
II	6 (21.4)	9 (18.4)	3 (11.1)
III	2 (7.1)	6 (12.2)	3 (11.1)
Presence of plasmacytomas,[b] n (%)	5 (17.9)	5 (10.2)	3 (11.1)
High-risk cytogenetics,[c] n (%)	12 (42.9)[d]	27 (55.1)[e]	16 (59.3)[f]

[a]Data cutoff: July 6, 2023; [b]Including extramedullary soft tissue-only disease as well as soft tissue bone-related plasmacytomas; [c]Defined as the presence of any abnormality for del(17p), and/or translocation t(4,14), and/or translocation t(14,16), and/or amplification 1q21; [d]11/28 patients were missing or not evaluable; [e]12/49 patients were missing or not evaluable; [f]9/27 patients were missing or not evaluable.
ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System.

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CC-92480-MM-002 Cohorts A, C, and D

Prior therapies and refractory status

Treatment characteristic[a]	Cohort A MeziVd (N = 28)	Cohort D MeziVd (N = 49)	Cohort C MeziKd (N = 27)
Prior therapies, median (range), n	3 (2-4)	1 (1-3)	2 (2-4)
Stem cell transplantation, n (%)	6 (21.4)	14 (28.6)	5 (18.5)
PI, n (%)	27 (96.4)	44 (89.8)	27 (100)
IMiD® agent, n (%)	28 (100)	49 (100)	27 (100)
Anti-CD38 mAb, n (%)	14 (50.0)	19 (38.8)	22 (81.5)
IMiD agent refractory, n (%)	24 (85.7)	31 (63.3)[b]	24 (88.9)[c]
LEN refractory, n (%)	23 (82.1)	31 (63.3)	21 (77.8)
POM refractory, n (%)	13 (46.4)	0	12 (44.4)
PI refractory, n (%)	14 (50.0)	8 (16.4)	14 (51.9)
IXA refractory, n (%)	6 (21.4)	2 (4.1)	2 (7.4)
BORT refractory, n (%)	4 (14.3)	1 (2.0)	13 (48.1)
CFZ refractory, n (%)	7 (25.0)	5 (10.2)	0
Anti-CD38 mAb refractory, n (%)	14 (50.0)	17 (34.7)	20 (74.1)
Triple-class refractory,[d] n (%)	9 (32.1)	1 (2.0)	10 (37.0)

Most patients had been exposed to a PI and were IMiD-agent refractory

[a]Data cutoff: July 6, 2023; [b]1/31 patients was refractory to thalidomide; [c]1/24 patients was refractory to thalidomide; [d]Defined as refractory to ≥ 1 IMiD agent, 1 PI, and 1 anti-CD38 mAb.
IMiD, immunomodulatory drug; IXA, ixazomib; POM, pomalidomide.

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CC-92480-MM-002 Cohorts A, C, and D

Treatment exposure

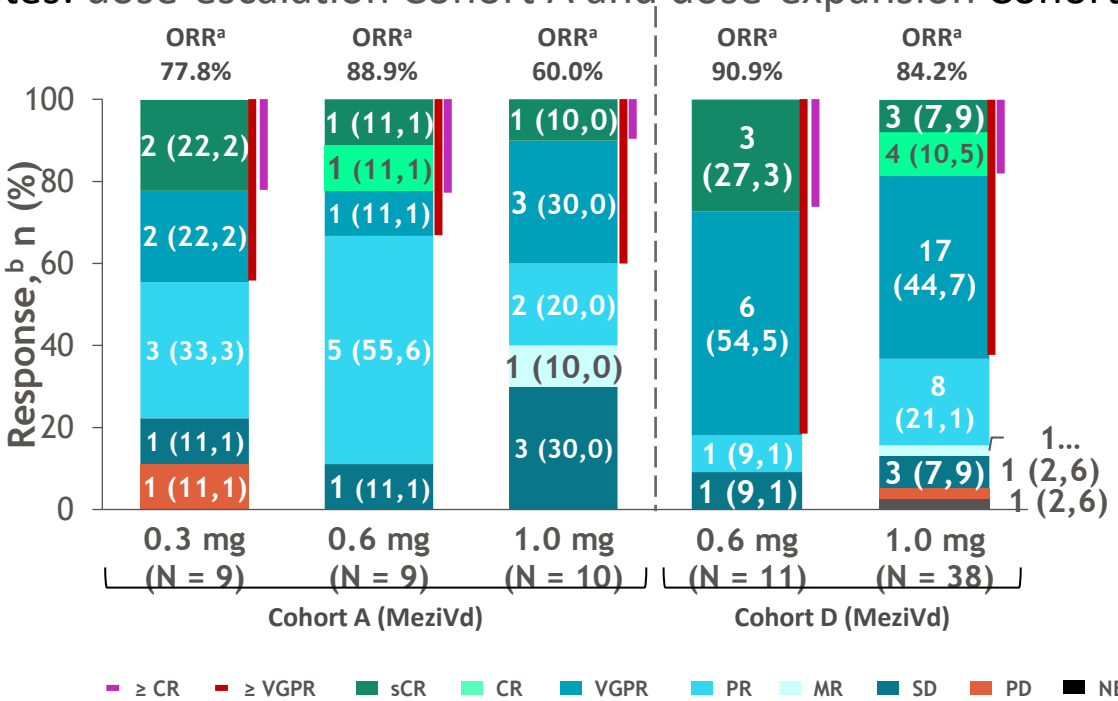
Patient disposition,[a] n (%)	Cohort A MeziVd (N = 28)	Cohort D MeziVd (N = 49)	Cohort C MeziKd (N = 27)
Ongoing	3 (10.7)	16 (32.7)	8 (29.6)
Discontinued	25 (89.3)	33 (67.3)	19 (70.4)
PD	18 (64.3)	21 (42.9)	10 (37.0)
AE	2 (7.1)[b]	7 (14.3)[c]	4 (14.8)[d]
Physician decision	2 (7.1)	0	0
Withdrawal	1 (3.6)	2 (4.1)	2 (7.4)
Death	0	2 (4.1)	1 (3.7)
Other	2 (7.1)[e]	1 (2.0)[f]	2 (7.4)[g]

Few patients discontinued due to AEs

[a]Data cutoff: July 6, 2023; [b]1 malignant neoplasm progression and 1 dysgeusia; [c]1 Guillain-Barre syndrome, 1 *Pneumocystis jirovecii* pneumonia, 1 orthostatic hypotension, 1 dyspnea, 1 decreased appetite, 1 neutropenia, and 1 neuromyelitis optica spectrum disorder; [d]1 COVID-19 pneumonia, 1 COVID-19, 1 diarrhea, and 1 fatigue; [e]1 patient came off treatment due to PD based upon serum free light chains and 1 patient did not want to continue therapy; [f]Patient's decision; [g]1 patient did not want to continue therapy due to ongoing abdominal issues/weight loss as well as social circumstances, and 1 patient came off treatment due to unknown reasons (the reason for discontinuation was changed to PD after the data cut-off).
AE, adverse event; COVID-19, coronavirus disease 2019; PD, progressive disease; RDI, relative dose intensity.

Response rates: dose-escalation Cohort A and dose-expansion Cohort D (MeziVd)

Cohort A (MeziVd)	
TTFR, median (range), months	1.38 (0.7-3.3)
DOR, median (95% CI), months	10.9 (8.8-32.8)
FUT, median (range), months	13.6 (3.2-44.7)



Cohort D (MeziVd)	
TTFR, median (range), months	0.89 (0.7-2.4)
DOR, median (95% CI), months	NR (12.1-NR)
FUT, median (range), months	12.71 (1.5-26.1)

MeziVd showed efficacy at all dose levels tested

- [a]ORR (PR or better); [b]Data cutoff: July 6, 2023.
- CI, confidence interval; CR, complete response; DOR, duration of response; FUT, follow-up time; NR, not reached; PR, partial response; sCR, stringent CR; SD, stable disease; TTFR, time to first response; VGPR, very good PR.

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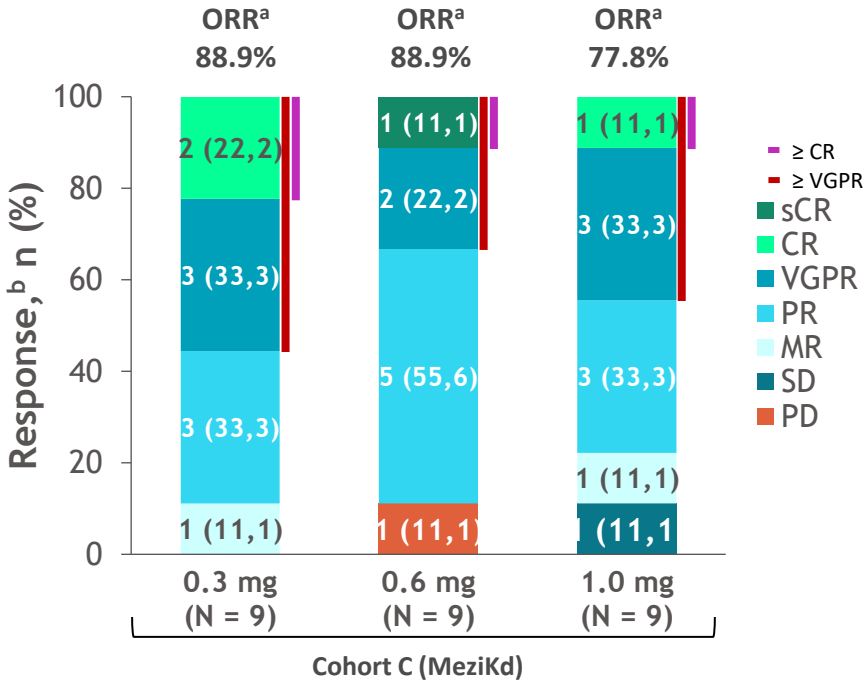
Response rates: dose-escalation Cohort C (MeziKd)



Cohort C (MeziKd)	
TTFR, median (range), months	0.95 (0.9-5.1)
DOR, median (95% CI), months	12.3 (6.4, NR)
FUT, median (range), months	12.45 (1.1-31.5)

MeziKd showed efficacy at all dose levels tested

[a]ORR (PR or better); [b]Data cutoff: July 6, 2023.

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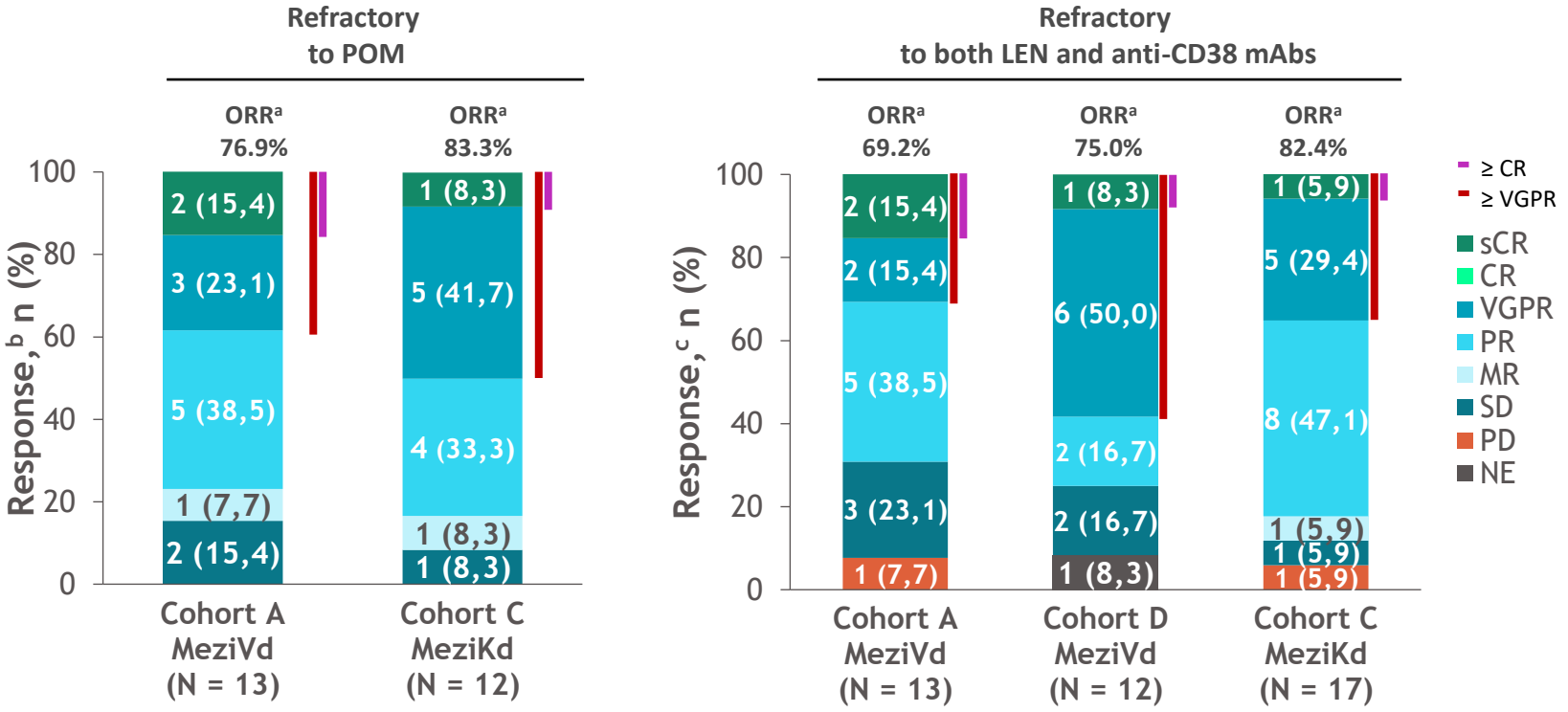
Response rates by refractoriness to prior therapies



MEZI was active in patients refractory to prior therapies

[a]PR or better; [b]Data cutoff: March 20, 2023; [c]Data cutoff: July 6, 2023.

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Conclusions

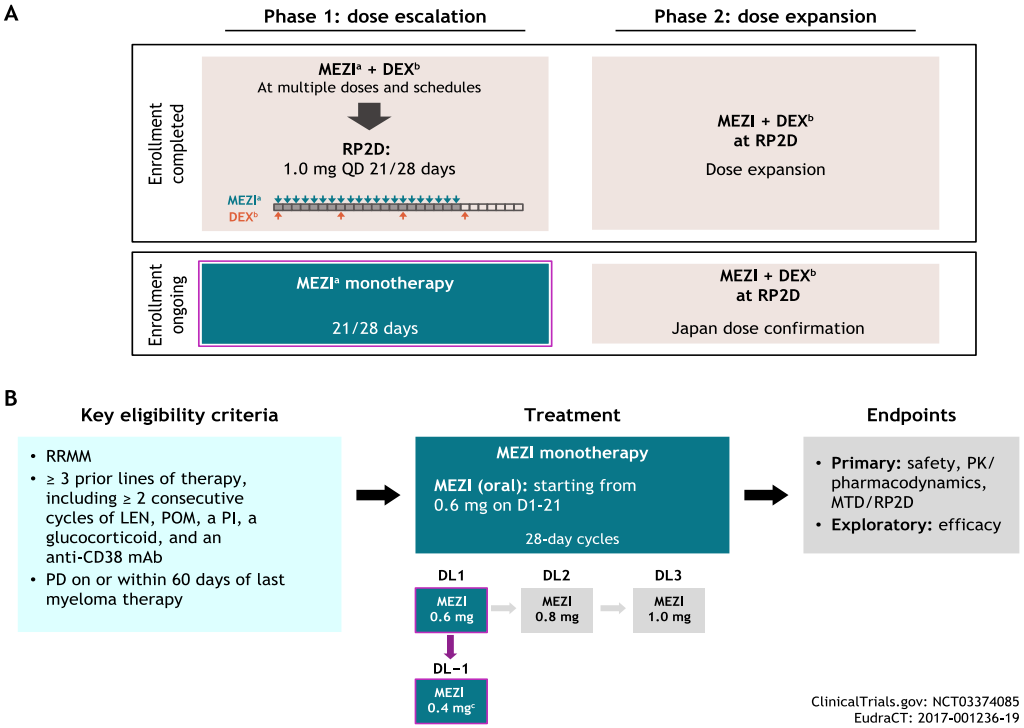
- With longer follow-up, MEZI in combination with either Vd or Kd continued to show promising efficacy at all dose levels tested, consistent with previous reports[1,2]
  - Responses were deep and durable, with many patients remaining on treatment after 1 year
  - MEZI was active in patients refractory to POM and both LEN and anti-CD38 mAbs
  - MEZI was pharmacodynamically active with BORT and CFZ at all dose levels tested
- MEZI was well tolerated with a manageable safety profile
  - The most common grade 3/4 TEAE was neutropenia, which was managed with dose interruptions and G-CSF
  - Non-hematologic grade 3/4 TEAEs were uncommon
  - Discontinuation due to TEAEs was low
- Clinical activity was observed in all cohorts and dose optimization of MEZI plus DEX in combination with PIs continues to be explored
  - These data support further investigation of MEZI in the phase 3 studies SUCCESSOR-1 (MeziVd vs POM plus Vd) and SUCCESSOR-2 (MeziKd vs Kd)

G-CSF, granulocyte-colony stimulating factor; Kd, CFZ + DEX; Vd, BORT + DEX.

1. Richardson PG, et al. *Blood* 2021;138(suppl 1). Abstract 2731; 2. Richardson PG, et al. *Clin Lymphoma Myeloma Leuk* 2022;22(suppl):S33.

CC-92480-MM-001 trial

Study design and Objective



To report, for the first time, the safety and efficacy results from the dose-escalation cohort of the CC-92480-MM-001 trial evaluating MEZI monotherapy in patients with RRMM

[a]Oral MEZI given at escalating doses; [b]Oral DEX given at a dose of 40 mg (20 mg in patients ≥ 75 years of age); [c]De-escalation to 0.4 mg was performed for dose exploration and was not in fulfillment of any DLT criteria.
DL, dose level; LEN, lenalidomide; mAb, monoclonal antibody; MTD, maximum tolerated dose; PD, progressive disease; PI, proteasome inhibitor; PK, pharmacokinetics; POM, pomalidomide; QD, daily; RP2D, recommended phase 2 dose.

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CC-92480-MM-001 trial

- **Patients**
- At data cutoff (July 6, 2023), **17** patients had received MEZI
- prior therapy and refractory status are shown in **Table**
  - All patients were exposed to IMiD agents, anti-CD38 mAbs, and PIs
- Median follow-up was 3.7 (0.4-mg dose) and 5.8 (0.6-mg dose) months, and median treatment duration was 13.1 (0.4-mg dose) and 19.0 (0.6-mg dose) weeks
- Discontinuation was mainly due to PD, reported in 4/5 (80.0%) patients (0.4-mg dose) and 7/12 (58.3%) patients (0.6-mg dose), and 2 (11.8%) patients continued on treatment at the 0.6-mg dose
- Three (25.0%) patients at the 0.6-mg dose required MEZI dose reductions

Prior therapies and refractory status[a]	MEZI 0.4 mg (N = 5)	MEZI 0.6 mg (N = 12)
Prior antimyeloma therapies, median (range), n	3 (3–5)	6.5 (4–10)
ASCT, n (%)	2 (40.0)	10 (83.3)
T-cell therapy, n (%)	0	7 (58.3)
TCE	0	7 (58.3)
CAR T	0	1 (8.3)
Anti-BCMA	0	3 (25.0)
Triple-class exposed,[b] n (%)	5 (100)	12 (100)
Triple-class refractory,[b] n (%)	5 (100)	9 (75.0)
IMiD agent refractory,[c] n (%)	5 (100)	10 (83.3)
POM	4 (80.0)	10 (83.3)
LEN	5 (100)	7 (58.3)
PI refractory, n (%)	5 (100)	10 (83.3)
CFZ	5 (100)	8 (66.7)
BORT	2 (40.0)	8 (66.7)
Anti-CD38 mAb refractory, n (%)	5 (100)	12 (100)
DARA	5 (100)	12 (100)
ISA	0	1 (8.3)
BCMA therapy refractory, n (%)	0	3 (25.0)

IMiD, immunomodulatory drug; mAb, monoclonal antibody; MEZI, mezigdomide; PD, progressive disease; PI, proteasome inhibitor.

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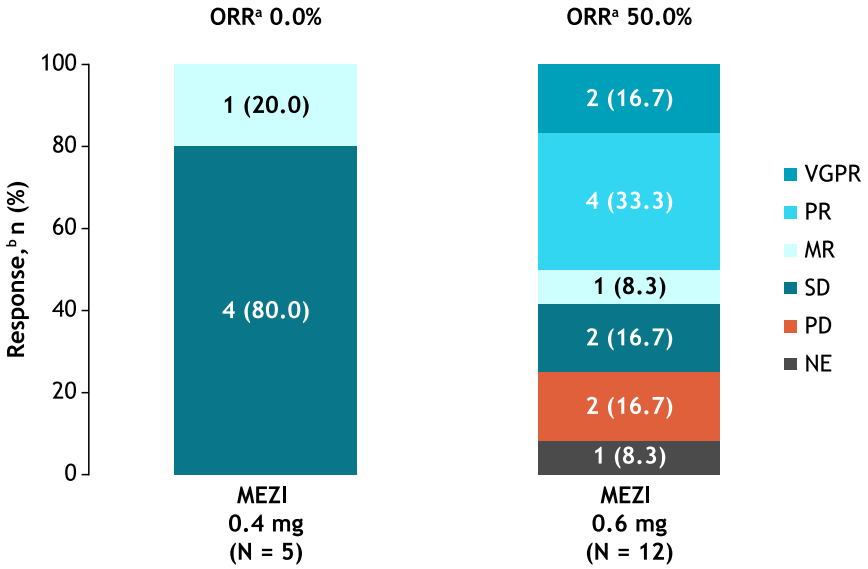
CC-92480-MM-001 trial

Overall response



- Response (PR or better) was reported in 6 of 12 patients (50.0%) at the 0.6-mg dose, including 2 VGPRs and 4 PRs
- There were no responses (0/5) at the 0.4-mg dose
  At the 0.6-mg dose, the VGPR or better rate was 16.7%
- Patients treated with the 0.6-mg dose had durable responses
- The median duration of response was not yet mature
- The median progression-free survival was 2.8 (95% CI, 1.9-4.6) months in the 0.4-mg cohort, and 5.7 (95% CI, 2.4–not available) months in the 0.6-mg cohort

[a]ORR (PR or better); [b]Data cutoff: July 6, 2023.
CR, complete response; MR, minimal response; NE, not evaluable; SD, stable disease.

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CC-92480-MM-001 trial

Safety

- Grade 3/4 TEAEs occurred in 5/5 (100%) patients (0.4-mg dose) and 11/12 (91.7%) patients (0.6-mg dose) (The most frequent hematologic grade 3/4 TEAEs were neutropenia (80.0% at the 0.4-mg dose, 83.3% at the 0.6-mg dose), anemia (40.0% at the 0.4-mg dose, 41.7% at the 0.6-mg dose), and leukopenia (60.0% at the 0.4-mg dose, 16.7% at the 0.6-mg dose)
  - Grade 3/4 infections were reported in 1/5 (20.0%) patients (0.4-mg dose) and 2/12 (16.7%) patients (0.6-mg dose)
  - The incidence of other grade 3/4 non-hematologic TEAEs was low
- Overall, 12 (70.6%) and 3 (16.6%) patients had MEZI dose interruptions and reductions due to TEAEs, respectively
- No patient discontinued MEZI due to TEAEs
- Of the 15 evaluable patients, 1 had a DLT in the 0.6-mg cohort (due to neutropenia lasting more than 5 days)

DLT, dose-limiting toxicity; MEZI, mezigdomide; TEAE, treatment-emergent adverse event.

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CC-92480-MM-001 trial

Authors' conclusions

- In patients with heavily pretreated RRMM, MEZI monotherapy at the 0.6-mg dose demonstrated an ORR of 50.0%, similar to that of MEZI + DEX (40.6%)
- In a non-randomized, heterogeneous population, MEZI was pharmacodynamically active with no new safety signals
- With dose modifications, MEZI was tolerable
  - Consistent with the profile of a CRBN-modulating drug, neutropenia was common, but manageable
  - The occurrence of grade 3/4 non-hematologic TEAEs was relatively low
- To date, the MTD/RP2D has not been reached; the 0.6-mg MEZI dose was safe and higher doses could be possibly explored in the future
- MEZI preliminary safety, efficacy, and pharmacodynamic profile support further development as a corticosteroid-sparing approach in MM

DEX, dexamethasone; MEZI, mezigdomide; MM, multiple myeloma; MTD, maximum tolerated dose; ORR, overall response rate; RP2D, recommended phase 2 dose; RR, relapsed/refractory; TEAE, treatment-emergent adverse event.

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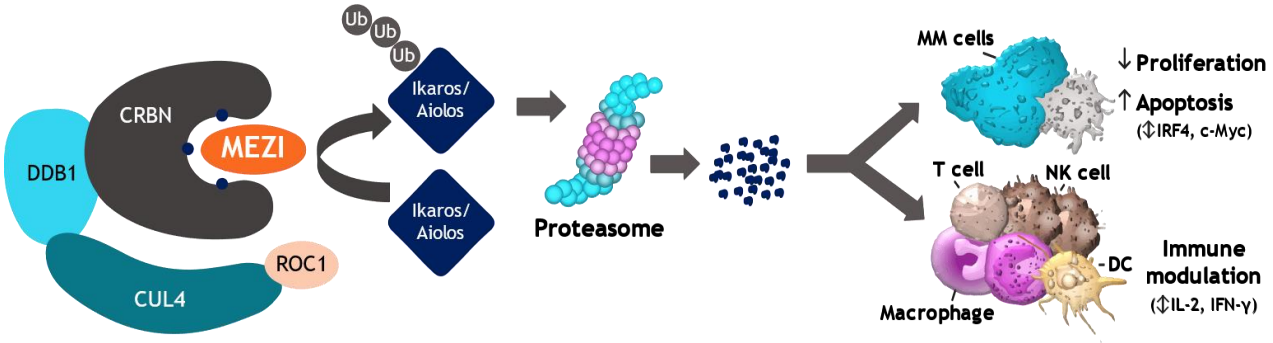
Take home

- Novel CELMoD agents demonstrate efficacy in IMID agent-resistant relapsed/refractory Myeloma
- Efficacy is increased in combination study to date
- Ongoing Studies will help define the optimal future role of IBER and MEZI in treatment of Myeloma patients



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