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

MM-099

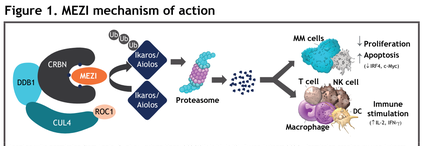
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Introduction

- Mezigdomide (MEZI) is an oral CELMoD™ agent that binds cereblon (CRBN) and modulates its activity to induce proteasomal degradation of Ikaros and Aiolos, leading to higher multiple myeloma (MM) cell killing and immune stimulation versus immunomodulatory drug (IMiD®) agents (**Figure 1**)[1-3]
- In patients with triple-class relapsed/refractory MM (RRMM), MEZI + dexamethasone (DEX) had a manageable safety profile and a promising overall response rate (ORR) of 41%[4]
- In preclinical studies, MEZI has shown marked synergy in combination with other antimyeloma therapies, including DEX, proteasome inhibitors (PIs), and anti-CD38 monoclonal antibodies (mAbs)[5]

Figure 1. MEZI mechanism of action



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c-Myc, cellular Myc; CUL4, cullin 4; DC, dendritic cell; DDB1, DNA damage-binding protein 1; IFN, interferon; IL, interleukin; IRF4, interferon regulatory factor 4; NK, natural killer; ROC1, regulator of cullins-1; Ub, ubiquitin.

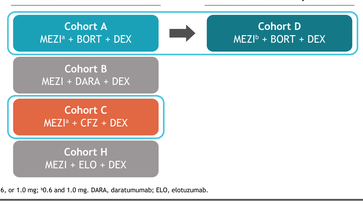
Objective

- To report updated results with longer follow-up from the phase 1/2 CC-92480-MM-002 trial (NCT03989414, EudraCT: 2018-004767-31)[6-9] from the MEZI + DEX + bortezomib (BORT; MeziVd) and MEZI + DEX + carfilzomib (CFZ; MeziKd) dose-escalation cohorts (A and C) and the MeziVd dose-expansion cohort (D)

Methods

- CC-92480-MM-002 is an open-label, multicenter, phase 1/2 dose-finding and dose-expansion clinical trial[6,7] evaluating MEZI + DEX in combination with different treatments in patients with MM (**Figure 2**)

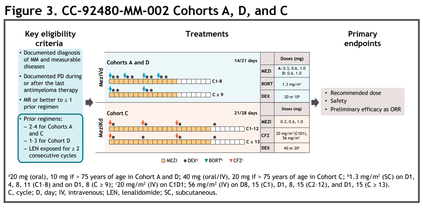
Figure 2. CC-92480-MM-002 study design



[a]0.3, 0.6, or 1.0 mg; [b]0.6 and 1.0 mg. DARA, daratumumab; ELO, elotuzumab.

- Eligible patients with RRMM received 2–4 (Cohorts A and C) or 1–3 (Cohort D) prior regimens, experienced progressive disease (PD) during/after last therapy, and had minimal response (MR) or better to ≥ 1 prior regimen
- MEZI was administered at escalating (Cohort A) or selected (Cohort D) doses with BORT + DEX, or at escalating doses with CFZ + DEX (Cohort C) (**Figure 3**)

Figure 3. CC-92480-MM-002 Cohorts A, D, and C



*20 mg (oral), 10 mg if > 75 years of age in Cohort A and D; 40 mg (oral/IV), 20 mg if > 75 years of age in Cohort C; †1.3 mg/m² (SC) on D1, 4, 8, 11 (C1-8) and on D1, 8 (C ≥ 9); ‡20 mg/m² (IV) on C1D1; 56 mg/m² (IV) on D8, 15 (C1), D1, 8, 15 (C2-12), and D1, 15 (C ≥ 13). C, cycle; D, day; IV, intravenous; LEN, lenalidomide; SC, subcutaneous.

Results

- Among all cohorts, the median age of patients and median time since diagnosis were similar, and approximately half of all patients had high-risk cytogenetics (**Table 1**)

Table 1. 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)
Female sex, n (%)	16 (57.1)	16 (32.7)	18 (66.7)
Time since initial diagnosis, median (range), years	4.8 (1.9-17.1)	4.2 (0.9-20.5)	5.4 (0.7-15.7)
ECOG PS score, 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)	6 (12.2)	3 (11.1)
High-risk cytogenetics,[c] n (%)	12 (42.9)[d]	26 (53.1)[e]	16 (59.3)[f]

[a]Data cutoff: June 28, 2024; [b]including extramedullary soft tissue-only disease as well as soft tissue bone-related plasmacytomas. Scans are required if plasmacytoma is only accessible radiographically; [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: cutoff values: t(4,14) – 15%; t(14,16) – 15%; amplification 1q21 – 3%; [d]11/28 patients were missing or NE; [e]10/49 patients were missing or NE; [f]8/27 patients were missing or NE. ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; NE, not evaluable.

- Patients in Cohorts A and C were heavily pretreated, and all patients were exposed to IMiD agents (**Table 2**)
  - Most patients were IMiD agent refractory

Table 2. 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 (%)	17 (60.7)	35 (71.4)	19 (70.4)
PI, n (%)	27 (96.4)	44 (89.8)	27 (100)
BORT	23 (82.1)	36 (73.5)	27 (100)
CFZ	10 (35.7)	13 (26.5)	2 (7.4)
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)	24 (88.9)
LEN refractory	23 (82.1)	31 (63.3)	21 (77.8)
POM refractory	13 (46.4)	0	12 (44.4)
PI refractory, n (%)	14 (50.0)	8 (16.3)	14 (51.9)
IXA refractory	6 (21.4)	2 (4.1)	2 (7.4)
BORT refractory	3 (10.7)	1 (2.0)	13 (48.1)
CFZ refractory	7 (25.0)	5 (10.2)	0
Anti-CD38 mAb refractory, n (%)	14 (50.0)	17 (34.7)	20 (74.1)
Triple-class refractory,[b] n (%)	9 (32.1)	1 (2.0)	10 (37.0)

[a]Data cutoff: June 28, 2024; [b]Defined as refractory to ≥ 1 IMiD agent, 1 PI, and 1 anti-CD38 mAb. IXA, ixazomib; POM, pomalidomide.

- At data cutoff, 89.3% (Cohort A), 81.6% (Cohort D), and 81.5% (Cohort C) of patients had discontinued treatment (**Table 3**)
  - Most patients discontinued because of PD, with few due to AEs
- MEZI exposure was > 80% RDI (**Table 3**)

Table 3. Patient disposition and treatment exposure

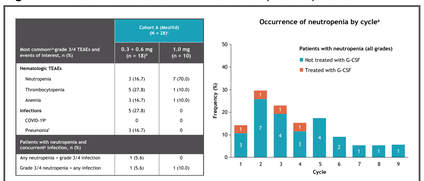
	Cohort A (MeziVd) (N = 28)	Cohort D (MeziVd) (N = 49)	Cohort C (MeziKd) (N = 27)
Ongoing treatment,[a] n (%)	3 (10.7)	9 (18.4)	5 (18.5)
Discontinuation of treatment,[a] n (%)	25 (89.3)	40 (81.6)	22 (81.5)
PD	18 (64.3)	26 (53.1)	13 (48.1)
AE	2 (7.1)[b]	8 (16.3)[c]	4 (14.8)[d]
Physician decision	2 (7.1)	1 (2.0)	0
Withdrawal	1 (3.6)	2 (4.1)	2 (7.4)
Death	0	2 (4.1)	2 (7.4)
Other	2 (7.1)[e]	1 (2.0)[f]	1 (3.7)[g]
Treatment exposure[a]			
Doses tested, mg	0.3, 0.6, 1.0	0.6, 1.0	0.3, 0.6, 1.0
Cycles received, median (range), n	12.5 (1.0-54.0)	15.0 (1.0-46.0)	12.0 (2.0-44.0)
Dose reductions/interruptions of MEZI, n (%)	23 (82.1)	48 (98.0)	24 (88.9)
RDI of MEZI,[h] median (range), %	93.0 (48.0-100.0)	81.0 (36.0-108.0)	86.0 (48.0-107.0)
RDI of BORT,[h] median (range), %	82.0 (22.0-101.0)	72.0 (31.0-101.0)	-
RDI of CFZ,[h] median (range), %	-	-	85.5 (15.0-113.0)
RDI of DEX,[h] median (range), %	67.0 (22.0-115.0)	72.0 (33.0-105.0)	70.0 (16.0-100.0)

[a]Data cutoff: June 28, 2024; [b]1 malignant neoplasm progression and 1 dysgeusia; [c]1 Guillain-Barré syndrome, 1 *Pneumocystis jirovecii* pneumonia, 1 orthostatic hypotension, 1 dyspnea, 1 decreased appetite, 1 neutropenia, 1 neuromyelitis optica spectrum disorder, and 1 fatigue; [d]1 COVID-19 pneumonia, 1 COVID-19, 1 diarrhea, and 1 fatigue; [e]1 patient came out of 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; [h]data cutoff: October 30, 2024. AE, adverse event; RDI, relative dose intensity.

Safety Cohort A and Cohort D (MeziVd)

- Neutropenia was the most common grade 3/4 treatment-emergent AE (TEAE), and it was managed with granulocyte colony-stimulating factor (G-CSF) treatment in all cohorts
  - In Cohort A, only 1 patient with neutropenia had a grade 3/4 infection within 1 week before/after the start date of neutropenia (**Figure 4**)

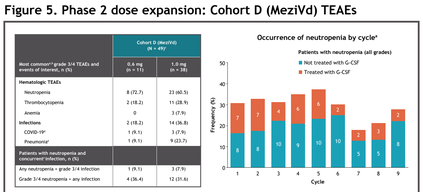
Figure 4. Phase 1 dose escalation: Cohort A (MeziVd) TEAEs



[a]Data cutoff: June 28, 2024; [b]Grade 3/4 TEAEs observed in ≥ 25% of patients. Toxicities may be managed by dose reductions or interruptions; [c]Median number of prior therapies = 3; 0.3 mg: n = 9, 0.6 mg: n = 9; [d]Includes COVID-19-related pneumonia; [e]Includes all preferred terms for pneumonia except COVID-19-related pneumonia; [f]Concurrent infection is infection within 1 week before/after the occurrence of neutropenia, and before/on the end date of any neutropenia.

- In Cohort D, fewer than 10% of patients with any neutropenia had grade 3/4 infections within 1 week before/after the start date of neutropenia (**Figure 5**)

Figure 5. Phase 2 dose expansion: Cohort D (MeziVd) TEAEs

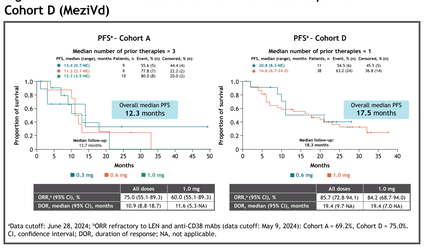


[a]Data cutoff: June 28, 2024; [b]Grade 3/4 TEAEs observed in ≥ 25% of patients. Toxicities may be managed by dose reductions or interruptions; [c]Median number of prior therapies, n = 1; [d]Includes COVID-19-related pneumonia; [e]Includes all preferred terms for pneumonia except COVID-19-related pneumonia; [f]Concurrent infection is infection within 1 week before/after the occurrence of neutropenia, and before/on the end date of any neutropenia.

Efficacy Cohort A and Cohort D (MeziVd)

- MeziVd showed durable efficacy at all dose levels tested with an overall median progression-free survival (PFS) > 1 year (17.5 months in Cohort D) (**Figure 6**)

Figure 6. PFS in dose-escalation Cohort A and dose-expansion Cohort D (MeziVd)



[a]Data cutoff: June 28, 2024; [b]ORR refractory to LEN and anti-CD38 mAbs (data cutoff: May 9, 2024): Cohort A = 69.2%, Cohort D = 75.0%. CI, confidence interval; DOR, duration of response; NA, not applicable.

- Responses in Cohort D were deep and durable, with some responses ongoing at the time of data cutoff (**Figure 7**)

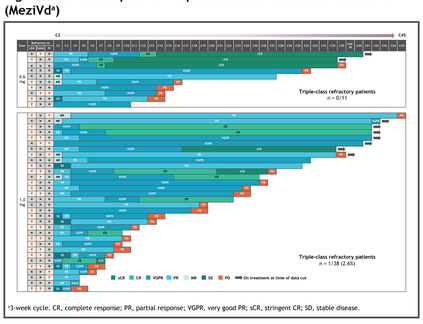
Safety Cohort C (MeziKd)

- Neutropenia was the most common grade 3/4 TEAE
  - Neutropenia was managed with G-CSF treatment and was associated with few grade 3/4 infections (**Figure 8**)

Efficacy Cohort C (MeziKd)

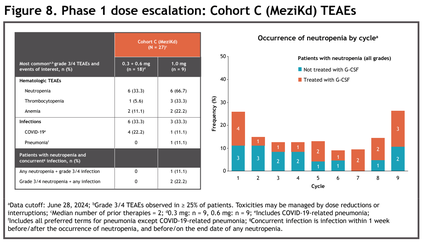
- MeziKd showed efficacy at all dose levels tested with an overall median PFS of 13.5 months (**Figure 9**)
- Responses in Cohort C were deep and durable, even in triple-class refractory patients, with some responses ongoing at data cutoff (**Figure 10**)

Figure 7. Swimmer plot for responders: dose-escalation Cohort D (MeziVd[a])



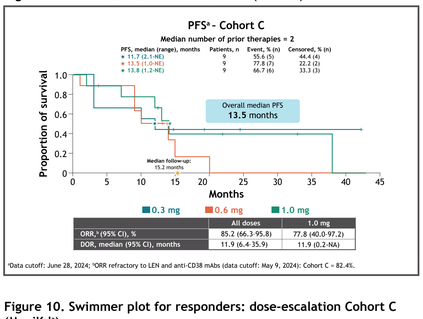
[a]3-week cycle. CR, complete response; PR, partial response; VGPR, very good PR; sCR, stringent CR; SD, stable disease.

Figure 8. Phase 1 dose escalation: Cohort C (MeziKd) TEAEs



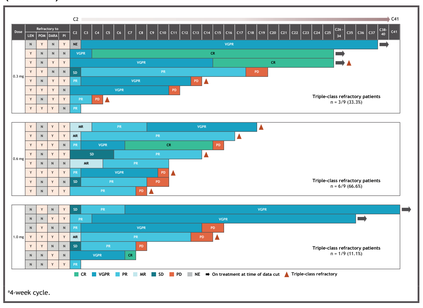
[a]Data cutoff: June 28, 2024; [b]Grade 3/4 TEAEs observed in ≥ 25% of patients. Toxicities may be managed by dose reductions or interruptions; [c]Median number of prior therapies = 2; 0.3 mg: n = 9, 0.6 mg: n = 9; [d]Includes COVID-19-related pneumonia; [e]Includes all preferred terms for pneumonia except COVID-19-related pneumonia; [f]Concurrent infection is infection within 1 week before/after the occurrence of neutropenia, and before/on the end date of any neutropenia.

Figure 9. PFS in dose-escalation Cohort C (MeziKd)



[a]Data cutoff: June 28, 2024; [b]ORR refractory to LEN and anti-CD38 mAbs (data cutoff: May 9, 2024): Cohort C = 82.4%.

Figure 10. Swimmer plot for responders: dose-escalation Cohort C (MeziKd[a])

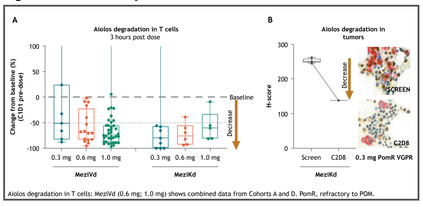


[a]4-week cycle.

Pharmacodynamics

- MEZI showed pharmacodynamic activity with BORT or CFZ at all doses tested (**Figure 11A**) and induced substrate degradation in the presence of PIs in tumors (**Figure 11B**)

Figure 11. Pharmacodynamics



Aiolos degradation in T cells: MeziVd (0.6 mg; 1.0 mg) shows combined data from Cohorts A and D. PomR, refractory to POM.

Conclusions

- MEZI is an oral CELMoD agent that induces proteasomal degradation of Ikaros and Aiolos, resulting in enhanced cytotoxic effects in MM cells and direct T-cell and NK-cell immunostimulatory activities[10,11]
- Proteasome inhibition does not abrogate the substrate degradation induced by MEZI
- MEZI demonstrated dose-dependent linear pharmacokinetics, with no difference in exposure between Cohorts A, D, or C[12]
- MeziVd and MeziKd in RRMM confirmed promising efficacy at all dose levels tested, including at the 1.0-mg dose, in patients with RRMM previously exposed to IMiD agents, PIs, and anti-CD38 mAbs
  - Responses were deep and durable (ORR Cohort A: 75.0%; Cohort D: 85.7%; Cohort C: 85.2%), with median PFS of ≥ 1 year in all cohorts (Cohort A: 12.3 months; Cohort D: 17.5 months; Cohort C: 13.5 months)
  - PFS was longer in the MeziVd dose-expansion cohort (Cohort D) with 1 median prior line of therapy, than in the dose-escalation cohort (Cohort A) with 3 median prior lines of therapy
- Among all cohorts, MEZI demonstrated a manageable safety profile with no cumulative toxicity
  - Neutropenia was the most common grade 3/4 TEAE, occurred infrequently with grade 3/4 infections, and was manageable with G-CSF and dose interruption/reduction
  - Non-hematologic grade 3/4 TEAEs were uncommon
- These results support the investigation of MEZI in phase 3 trials of patients with RRMM:
  - SUCCESSOR-1 (NCT05519085): MeziVd versus POM + BORT + DEX (PVd); eligible patients had MM and measurable disease, received 1–3 antimyeloma regimens, and achieved ≥ MR to ≥ 1 therapy
  - SUCCESSOR-2 (NCT05552976): MeziKd versus CFZ + DEX (Kd); eligible patients had MM and measurable disease with documented disease progression after the last myeloma regimen, received ≥ 1 prior antimyeloma therapy, received prior LEN treatment and ≥ 2 cycles of an anti-CD38 mAb, and achieved ≥ MR to ≥ 1 therapy

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12. BMS. Data on file.

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