Mezigdomide plus dexamethasone in relapsed/refractory multiple myeloma: results from the dose-expansion phase of the CC-92480-MM-001 trial

MM-360

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Introduction

- Mezigdomide (MEZI; CC-92480) is a novel, potent oral cereblon (CRBN) E3 ligase modulator (CELMoD™) with enhanced tumoricidal and immune-modulatory effects compared with immunomodulatory drugs (IMiDs®)[1]
  - Preclinical and translational data suggest a differentiated profile of MEZI from IMiD agents[2-4]
- MEZI was designed for maximal degradation of target proteins, including Ikaros and Aiolos, leading to increased apoptosis in myeloma cells and immune stimulation[1]
  - MEZI induces a closed, active state in 100% of CRBN molecules[5]
  - Ikaros and Aiolos are transcription factors that play a key role in the development and differentiation of hematopoietic cells[6,7]
- Preclinically, MEZI demonstrated synergy with dexamethasone (DEX), proteasome inhibitors (PIs), and anti-CD38 monoclonal antibodies (mAbs)[8]
- In phase 1 of the CC-92480-MM-001 trial, the recommended phase 2 dose (RP2D) of MEZI in combination with DEX was selected at 1 mg once daily (QD) for 21/28 days[9]
  - In phase 1, the overall response rate (ORR) at the RP2D was 54.5%[9]

Objective

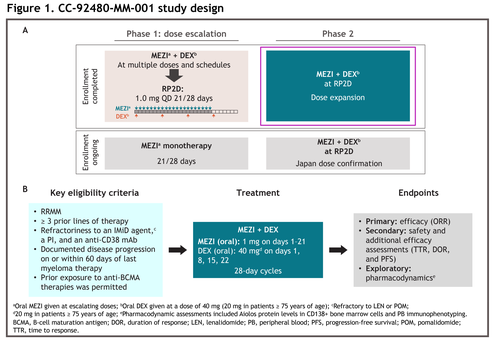
- To report efficacy and safety of the MEZI + DEX dose-expansion cohort of the CC-92480-MM-001 trial

Methods

Study design and treatment

- CC-92480-MM-001 is a phase 1/2 trial evaluating MEZI alone or in combination with DEX in patients with relapsed/refractory multiple myeloma (RRMM)[10] (**Figure 1**)

Figure 1. CC-92480-MM-001 study design



[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]Refractory to LEN or POM; [d]20 mg in patients ≥ 75 years of age; [e]Pharmacodynamic assessments included Aiolos protein levels in CD138+ bone marrow cells and PB immunophenotyping. BCMA, B-cell maturation antigen; DOR, duration of response; LEN, lenalidomide; PB, peripheral blood; PFS, progression-free survival; POM, pomalidomide; TTR, time to response.

Results

Patients

- At data cutoff (September 16, 2022), 101 patients had received MEZI + DEX at the RP2D
- Baseline characteristics are shown in **Table 1**, and prior therapies and refractory status are shown in **Table 2**
- Ten (9.9%) patients continued on treatment (**Table 3**)
  - Few patients discontinued due to adverse events (AEs), with minimal treatment-related mortality

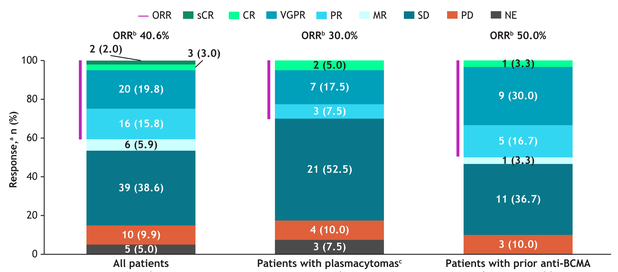
Safety

- Grade 3/4 treatment-emergent AEs (TEAEs) were mostly hematologic and were managed with granulocyte colony-stimulating factor and dose interruptions/reductions (**Figure 2**)
  - Neutropenia was the most common TEAE leading to dose reduction (16.8%) and interruption (36.6%)
- Only 1 patient discontinued treatment due to mortality from COVID-19 (**Table 4**)

MEZI + DEX demonstrates encouraging efficacy (ORR 40.6%) with a manageable safety profile in patients with RRMM, including in those with prior BCMA-targeted therapies and with extramedullary plasmacytomas

Figure 2. Efficacy (ORR) and safety of MEZI + DEX in patients with RRMM

A



Time to first response, median (range), months	
All patients	0.95 (0.89-12.92)
Patients with plasmacytomas[c]	2.17 (0.92-5.26)
Patients with prior anti-BCMA therapy	2.10 (0.89-10.16)

Follow-up time,[d] median (range), months	
All patients	5.46 (0.03-17.49)
Patients with plasmacytomas[c]	6.10 (0.03-15.98)
Patients with prior anti-BCMA therapy	5.46 (0.03-15.98)

B

Most frequent (≥ 20% all grade) TEAEs and events of interest,[a] n (%)	MEZI + DEX (N = 101)		
	All grade	Grade 3	Grade 4
Hematologic TEAEs			
Neutropenia	78 (77.2)	22 (21.8)	54 (53.5)
Anemia	53 (52.5)	35 (34.7)	1 (1.0)
Thrombocytopenia	43 (42.6)	14 (13.9)	14 (13.9)
Febrile neutropenia	15 (14.9)	13 (12.9)	2 (2.0)
Non-hematologic TEAEs			
Infections	66 (65.3)	29 (28.7)	6 (5.9)
Pneumonia[e]	22 (21.8)[f]	13 (12.9)[g]	3 (3.0)[h]
COVID-19	17 (16.8)	7 (6.9)	0
Fatigue	36 (35.6)	5 (5.0)	0
Diarrhea	31 (30.7)	3 (3.0)	0
Constipation	24 (23.8)	0	0
Dyspnea	22 (21.8)	5 (5.0)	0
Nausea	21 (20.8)	1 (1.0)	0
Decreased appetite	21 (20.8)	1 (1.0)	0
Arthralgia	21 (20.8)	2 (2.0)	0
Insomnia	20 (19.8)	1 (1.0)	0

[a]Data cutoff: September 16, 2022; [b]PR or better; [c]Including extramedullary soft tissue only disease as well as soft tissue bone-related plasmacytomas; [d]From univariate analysis for all responders without adjusting for censoring; [e]Including all preferred terms for pneumonia; [f]9 pneumonia NOS, 6 *Pneumocystis jirovecii* pneumonia, 2 COVID-19 pneumonia, 2 viral pneumonia, 1 bacterial pneumonia, 1 *Haemophilus* pneumonia, and 1 *Pseudomonas* pneumonia. [g]6 pneumonia NOS, 2 *Pneumocystis jirovecii* pneumonia, 2 COVID-19 pneumonia, 1 viral pneumonia, 1 *Haemophilus* pneumonia, and 1 *Pseudomonas* pneumonia; [h]1 pneumonia NOS, 2 *Pneumocystis jirovecii* pneumonia. MR, minimal response; NE, not evaluable; NOS, not otherwise specified; PD, progressive disease; SD, stable disease; VGPR, very good partial response.

Table 1. Baseline characteristics

Characteristic	MEZI + DEX (N = 101)
Age, median (range), years	67 (42-85)
Sex, n (%)	
Male	55 (54.5)
Time since initial diagnosis, median (range), years	7.4 (1.1-37.0)
ECOG PS, n (%)	
0	35 (34.7)
1	57 (56.4)
2	9 (8.9)
ISS stage at study entry, n (%)	
Stage I	39 (38.6)
Stage II	41 (40.6)
Stage III	21 (20.8)
Presence of plasmacytomas,[a] n (%)	40 (39.6)
High-risk cytogenetics,[b] n (%)	37 (36.6)[c]

[a]Including extramedullary soft tissue only disease as well as soft tissue bone-related plasmacytomas; [b]Defined as the presence of any abnormality for del(17p), and/or translocation t(4;14), and/or amplification 1q21; [c]36/101 patients were not evaluable.
ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System.

Table 2. Prior therapies and refractory status

Treatment characteristic	MEZI + DEX (N = 101)
Prior lines of therapies, median (range), n	6 (3-15)
Stem cell transplantation, n (%)	78 (77.2)
IMiD agents, n (%)	101 (100)
POM	101 (100)
LEN	101 (100)
PIs, n (%)	101 (100)
Anti-CD38 mAb, n (%)	101 (100)
Anti-BCMA therapy, n (%)	30 (29.7)
Antibody-drug conjugate	22 (21.8)
T-cell engager	8 (7.9)
CAR T cell therapy	3 (3.0)
Refractory status, n (%)	
IMiD agents[a]	101 (100)
POM	97 (96.0)
LEN	89 (88.1)
PIs	101 (100)
Anti-CD38 mAb	101 (100)
Triple-class refractory[b]	101 (100)

[a]Defined as refractory to LEN or POM; [b]Defined as refractory to ≥ 1 IMiD agent, 1 PI, and 1 anti-CD38 mAb.
CAR, chimeric antigen receptor.

Table 3. Patient disposition and treatment exposure

Patient disposition	MEZI + DEX (N = 101)
Follow-up, median (range), months	7.46 (0.5-21.9)
Ongoing, n (%)	10 (9.9)
Discontinued, n (%)	91 (90.1)
Progressive disease	61 (60.4)
Withdrawal	11 (10.9)
Death	8 (7.9)[a]
Due to AE	5 (5.0)[a]
AE	6 (5.9)[b]
Other	5 (5.0)[c]
Treatment exposure	
Cycles received, median (range), n	4 (1-20)
Relative dose intensity of MEZI (range)	0.88 (0.3-1.1)
Patients with ≥ 1 dose interruption of MEZI, n (%) Due to AE	89 (88.1) 77 (76.2)
Patients with ≥ 1 dose reduction of MEZI, n (%) Due to AE	32 (31.7) 30 (29.7)

[a]See Table 4 for further details; [b]1 grade 4 pseudomonal sepsis, 1 grade 4 hypertransaminasemia, 1 grade 3 pyrexia, 1 grade 1 ischemic colitis, 1 grade 4 neutropenia and grade 4 thrombocytopenia, and 1 grade 3 peripheral sensory neuropathy; [c]1 investigator's decision due to lack of response, 1 investigator's decision due to worsening of general condition, and 3 clinical progression.

Table 4. Mortality leading to treatment discontinuation

Patient disposition	MEZI + DEX (N = 101)
Deaths leading to treatment discontinuation, n (%)	8 (7.9)
AEs	5 (5.0)
Pneumocystis jirovecii pneumonia	2 (2.0)
Pneumonia	1 (1.0)
COVID-19	1 (1.0)
Septic shock	1 (1.0)
Disease progression	2 (2.0)
Unknown causes	1 (1.0)

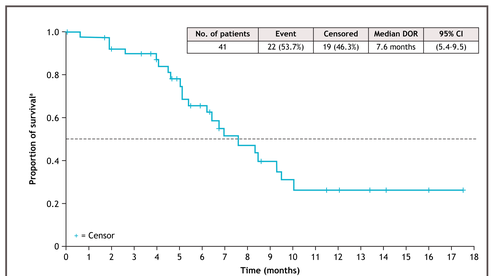
Efficacy

- Response (≥ partial response [PR]) was reported in 41 of 101 patients (40.6%), including 2 stringent complete responses (sCR, 2.0%) and 3 complete responses (CR, 3.0%) (**Figure 2**)
  - Responses were also observed in patients with plasmacytomas and in patients who had prior anti-BCMA therapy
- Median DOR was 7.6 (95% confidence interval [CI], 5.4-9.5) months (**Figure 3**), median PFS was 4.4 (95% CI, 3.0-5.5) months (**Figure 4**)

Pharmacodynamics

- There was near complete loss of Aiolos after MEZI treatment in CD138+ cells of a patient who received POM in their last line of therapy
- Median Aiolos degradation of > 60% was observed across patients who were either POM-refractory or received POM in their last line of therapy
- MEZI retained potent immune-stimulatory activity in patients who were POM-refractory or received POM in their last line of therapy, with MEZI treatment inducing ≈ 2-fold induction in proliferating (Ki-67+) and activated (HLA-DR+) natural killer (NK) and T cells in these patients

Figure 3. Duration of response

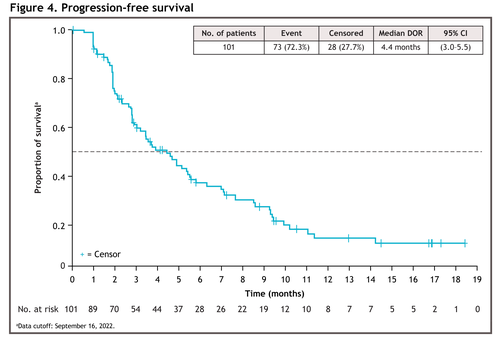


No. of patients	Event	Censored	Median DOR	95% CI
41	22 (53.7%)	19 (46.3%)	7.6 months	(5.4-9.5)

DOR for ≥ VGPR, median (95% CI), months	DOR for PR, median (95% CI), months
9.2 (6.4-NR)	5.1 (2.6-8.3)

[a]Data cutoff: September 16, 2022; data are not yet mature. NR, not reached.

Figure 4. Progression-free survival



No. of patients	Event	Censored	Median DOR	95% CI
101	73 (72.3%)	28 (27.7%)	4.4 months	(3.0-5.5)

[a]Data cutoff: September 16, 2022.

Conclusions

- MEZI is a potent novel CELMoD compound with a differentiated preclinical profile from IMiD agents
- MEZI + DEX showed notable clinical activity in patients with triple-class refractory RRMM (ORR 40.6%), including patients with prior BCMA-targeted therapies (ORR 50.0%) and with extramedullary plasmacytomas (ORR 30.0%)
  - MEZI also showed pharmacodynamic activity directly after POM-based therapies
- MEZI + DEX had a manageable safety profile
  - Few patients discontinued treatment due to AEs (5.9%), with 1 patient discontinuing due to hematologic TEAEs (grade 4 neutropenia and grade 4 thrombocytopenia)
- MEZI is currently being evaluated in combination with standard therapies in MM as part of a large, ongoing phase 1/2 trial (NCT03989414)
  - Preliminary results show that MEZI in combination with bortezomib + DEX (Vd) or carfilzomib + DEX (Kd) was safe and well tolerated with promising efficacy in patients with RRMM[11]
- Phase 3 trials evaluating MEZI in combination with Vd and Kd are currently enrolling (SUCCESSOR-1 [NCT05519085] and SUCCESSOR-2 [NCT05552976])
  - Both trials will include a dose-optimization phase to define the optimal dose of MEZI

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