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

MM-520

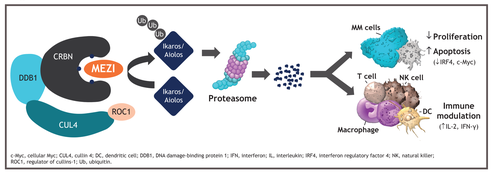
Albert Oriol,[1] Irwindeep Sandhu,[2] Marc S. Raab,[3] Darrell White,[4] Richard LeBlanc,[5] Noopur Raje,[6] Enrique M. Ocio,[7] Aurore Perrot,[8] Thierry Facon,[9] Cesar Rodriguez,[10] Ralph Waesch,[11] Michael Amatangelo,[12] Zehua Zhou,[12] Yue Wang,[12] Tiziana Civardi,[13] Phillip Koo,[12] Paulo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

[1]Catalan Institute of Oncology and Josep Carreras Institute, Hospital Germans Trias i Pujol, Badalona, Spain; [2]University of Alberta, Edmonton, AB, Canada; [3]Universitätsklinikum Heidelberg, Heidelberg, Germany; [4]Dalhousie University and Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada; [5]Hôpital Maisonneuve-Rosemont, Université de Montréal, Montreal, QC, Canada; [6]Massachusetts General Hospital, Boston, MA, USA; [7]Hospital Universitario Marqués de Valdecilla (IDIVAL), Santander, Spain; [8]Institut Universitaire du Cancer de Toulouse Oncopole, Toulouse, France; [9]Centre Hospitalier Universitaire (CHU) Lille, Service des Maladies du Sang, University of Lille, Lille, France; [10]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [11]Department of Medicine, University of Freiburg Medical Center, Freiburg, Germany; [12]Bristol Myers Squibb, Princeton, NJ, USA; [13]Celgene International Sàrl, a Bristol-Myers Squibb Company, Boudry, Switzerland; [14]Dana-Farber Cancer Institute, Boston, MA, USA

Introduction

- Mezigdomide (MEZI) is a novel, potent CELMoD™ agent purposefully designed for rapid and maximal degradation of Ikaros and Aiolos, leading to immune-modulatory effects and enhanced tumoricidal activity in myeloma cells[1-3] (**Figure 1**)
- In patients with relapsed/refractory multiple myeloma (RRMM), MEZI plus dexamethasone (DEX) had a manageable safety profile and promising activity[4]
- Preclinical studies have shown synergy between MEZI and DEX, proteasome inhibitors (PIs), and anti-CD38 monoclonal antibodies (mAbs)[5]
  - Preclinically, MEZI has also shown ability to enhance T-cell engager-mediated antitumor activity[6]
- MEZI showed promising efficacy and safety with DEX plus bortezomib (BORT) and DEX plus carfilzomib (CFZ) in patients with RRMM
  - In phase 1 of the CC-92480-MM-002 trial (NCT03989414; EudraCT: 2018-004767-31), a study evaluating MEZI with different treatment combinations in MM, a 1.0-mg dose plus BORT and DEX was selected for further investigation in a dose-expansion cohort[1,2]

Figure 1. Mechanism of action and downstream effects of MEZI



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

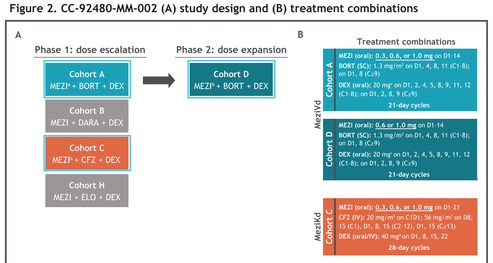
- To report updated results from the dose-escalation Cohorts A (MEZI + BORT + DEX [MeziVd]) and C (MEZI + CFZ + DEX [MeziKd]), and from the MeziVd dose-expansion Cohort D from the CC-92480-MM-002 trial

Methods

Study design and treatment

- **Figure 2** shows the study design of the CC-92480-MM-002 trial and treatment combinations received by patients in Cohorts A, D, and C
- Eligible patients had a diagnosis of MM with measurable disease, disease progression during or after the last antimyeloma therapy, and minimal response or better to ≥ 1 prior regimens
  - Patients in Cohorts A and C must have received 2–4 prior regimens; patients in Cohort D must have received 1–3 prior regimens; all patients must have received lenalidomide (LEN) for ≥ 2 consecutive cycles
- The primary endpoints were:
  - To assess the safety and preliminary efficacy (overall response rate [ORR]) of MEZI
  - To determine the recommended dose and regimen for Cohorts A and C

Figure 2. CC-92480-MM-002 (A) study design and (B) treatment combinations



*0.3, 0.6, or 1.0 mg; †1.0 mg: 20 mg if < 75 years of age; †10 mg if > 75 years of age.
C, cycle; D, day; DARA, daratumumab; ELO, elotuzumab; IV, intravenous; SC, subcutaneous.

Results

Patient characteristics and prior therapies

- As of July 6, 2023, 28 patients were included in Cohort A, 49 in Cohort D, and 27 in Cohort C (**Table 1**)
  - The median age and median time since diagnosis were similar between cohorts
  - For all cohorts, most patients had an ECOG PS score of 1 and high-risk cytogenetics were present in 42.9% (Cohort A), 55.1% (Cohort D), and 59.3% (Cohort C) of patients
  - Patients had received a median of 3 (Cohort A), 1 (Cohort D), and 2 (Cohort C) prior therapies
  - In all cohorts, most patients had been exposed to a PI and were IMiD-agent refractory

Table 1. Baseline characteristics, prior therapies, and refractory status

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]
Prior therapies, median (range), n (%)	3 (2-4)	1 (1-3)	2 (2-4)
Stem cell transplantation	6 (21.4)	14 (28.6)	5 (18.5)
PI	27 (96.4)	44 (89.8)	27 (100)
IMiD agent	28 (100)	49 (100)	27 (100)
Anti-CD38 mAb	14 (50.0)	19 (38.8)	22 (81.5)
IMiD-agent refractory, n (%)	24 (85.7)	31 (63.3)[g]	24 (88.9)[h]
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	4 (14.3)	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,[i] n (%)	9 (32.1)	1 (2.0)	10 (37.0)

[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]1/28 patients were missing or not evaluable; [e]2/49 patients were missing or not evaluable; [f]4/27 patients were missing or not evaluable; [g]6 of 31 patients was refractory to thalidomide; [h]4 of 24 patients was refractory to thalidomide; [i]defined as refractory to ≥ 1 IMiD agent, 1 PI, and 1 anti-CD38 mAb.
ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immune-modulatory drug; ISS, International Staging System; IXA, ixazomib; POM, pomalidomide.

Treatment disposition and treatment exposure

- By data cutoff, 89.3% (Cohort A), 67.3% (Cohort D), and 70.4% (Cohort C) of patients had discontinued treatment; few patients discontinued treatment due to AEs (**Table 2**)
- Patients had received median of 12.5 (Cohort A), 15.0 (Cohort D), and 12.0 (Cohort C) cycles, and MEZI dose reductions had occurred in 21.4% (Cohort A), 40.8% (Cohort D), and 29.6% (Cohort C) of patients (**Table 2**)

Table 2. Treatment disposition and 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]
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 (1-54)	15.0 (1-35)	12.0 (2-33)
Dose reduction of MEZI, n (%)	6 (21.4)	20 (40.8)	8 (29.6)
RDI of MEZI, % (range)	93.0 (43.0-639.0)	83.0 (42.0-1126.0)	82.0 (48.0-107.0)

[a]Data cutoff: July 6, 2023; [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, 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 chain 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 cutoff).
AE, adverse event; COVID-19, coronavirus disease 2019; PD, progressive disease; RDI, relative dose intensity.

Safety

- Grade 3/4 treatment-emergent AEs (TEAEs) were mostly hematologic, with few non-hematologic grade 3/4 TEAEs (**Table 3**)
  - The most common hematologic grade 3/4 TEAE was neutropenia, leading to dose reduction (6.7%) and interruption (21.2%)
  - The most common non-hematologic grade 3/4 TEAEs were infections

Table 3. TEAEs

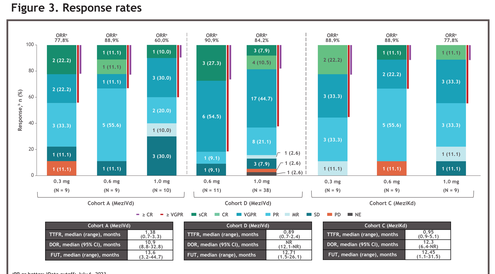
Most common (≥ 30% all grade) TEAEs and events of interest,[a] n (%)	All doses All grade	0.6 mg Grade 3/4	1.0 mg Grade 3/4
Cohort A (MeziVd)	N = 28	n = 9	n = 10
Hematologic TEAEs			
Neutropenia	15 (53.6)	1 (11.1)	7 (70.0)
Anemia	13 (46.4)	1 (11.1)	1 (10.0)
Thrombocytopenia	10 (35.7)	2 (22.2)	1 (10.0)
Non-hematologic TEAEs			
Peripheral sensory neuropathy	11 (39.3)	0	0
Dyspnea[b]	11 (39.3)	0	0
Insomnia	9 (32.1)	1 (11.1)	2 (20.0)
Diarrhea	13 (46.4)	1 (11.1)	2 (20.0)
Fatigue	5 (17.9)	1 (11.1)	0
Infections	20 (71.4)	3 (33.3)	0
COVID-19[c]	3 (10.7)	0	0
Pneumonia[d]	3 (10.7)	2 (22.2)	0
Cohort D (MeziVd)	N = 49	n = 11	n = 38
Hematologic TEAEs			
Neutropenia	38 (77.6)	7 (63.6)	22 (57.9)
Anemia	22 (44.9)	0	3 (7.9)
Thrombocytopenia	24 (49.0)	2 (18.2)	11 (28.9)
Non-hematologic TEAEs			
Peripheral sensory neuropathy	27 (55.1)	0	2 (5.3)
Dyspnea[b]	11 (39.3)	0	0
Insomnia	16 (32.7)	0	0
Diarrhea	22 (44.9)	0	4 (10.5)
Fatigue	17 (34.7)	0	2 (5.3)
Infections	39 (79.6)	2 (18.2)	14 (36.8)
COVID-19[c]	19 (38.8)	1 (9.1)	4 (10.5)
Pneumonia[d]	14 (28.6)	2 (18.2)	10 (26.3)
Cohort C (MeziKd)	N = 27	n = 9	n = 9
Hematologic TEAEs			
Neutropenia	15 (55.6)	5 (55.6)	6 (66.7)
Anemia	10 (37.0)	2 (22.2)	2 (22.2)
Thrombocytopenia	14 (51.9)	2 (22.2)	3 (33.3)
Non-hematologic TEAEs			
Peripheral sensory neuropathy	4 (14.8)	0	0
Dyspnea[b]	15 (55.5)	1 (11.1)	1 (11.1)
Insomnia	9 (33.3)	0	0
Diarrhea	13 (48.1)	3 (33.3)	0
Fatigue	9 (33.3)	0	2 (22.2)
Infections	19 (70.4)	3 (33.3)	3 (33.3)
COVID-19[c]	14 (51.9)	2 (22.2)	1 (11.1)
Pneumonia[d]	2 (7.4)	0	1 (11.1)

In Cohort A, there were 23 (≥ 30% grade 3/4 hematologic TEAEs reported, and few grade 3/4 non-hematologic TEAEs, the most common being infections (22.2%), at the 0.3 mg dose level. There is no 0.3 mg dose level in Cohort D. In Cohort C, there were no grade 3/4 hematologic and non-hematologic TEAEs reported at the 0.3 mg dose level.
[a]Data cutoff: July 6, 2023; [b]includes dyspnea exertional; [c]includes COVID-19-related pneumonia; [d]includes all preferred terms for pneumonia except COVID-19-related pneumonia.

Efficacy

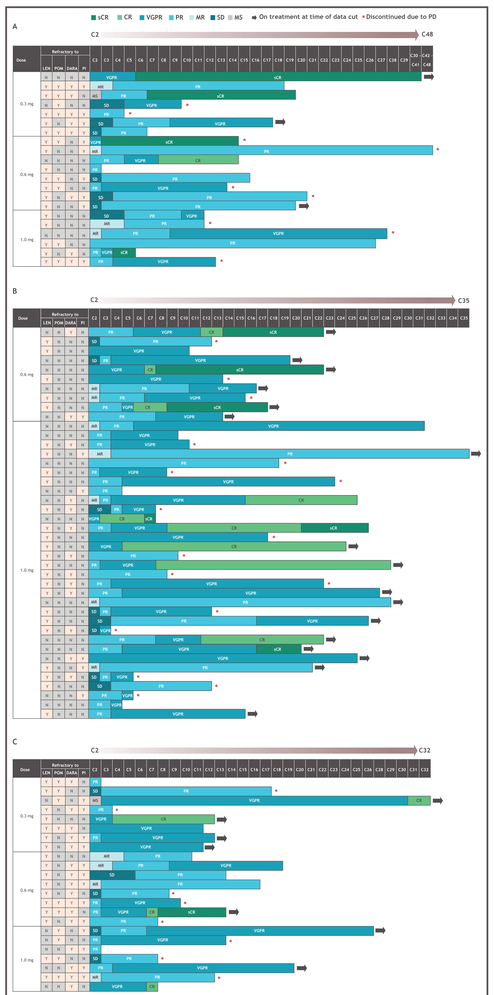
- MeziVd and MeziKd showed efficacy (ORR ≥ 60%) at all dose level tested (**Figure 3**)
  - Overall, responses were deep and durable, with 3 patients from Cohort A, 17 from Cohort D, and 7 from Cohort C patients still on treatment at the time of data cut (**Figure 4**)
- MEZI remained active in patients refractory to POM and to both LEN and anti-CD38 mAbs (**Figure 5**)

Figure 3. Response rates



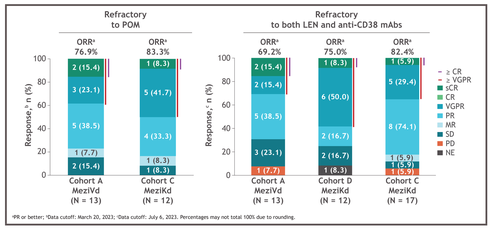
¹PR or better; ²Data cutoff: July 6, 2023.
CI, confidence interval; CR, complete response; DOR, duration of response; FUT, follow-up time; NE, not estimable; NR, not reached; PR, partial response; sCR, stringent CR; SD, stable disease; TTFR, time to first response; VGPR, very good PR. Percentages may not total 100% due to rounding.

Figure 4. Swimmer plot for responders in (A) Cohort A (MeziVd), (B) Cohort D (MeziVd), and (C) Cohort C (MeziKd)



Last best response is shown for each patient.
MS, missing.

Figure 5. Response rates by refractoriness to prior therapies

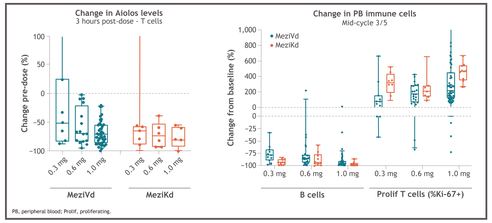


¹PR or better; ²Data cutoff: March 20, 2023; ³Data cutoff: July 6, 2023. Percentages may not total 100% due to rounding.

Pharmacodynamics summary

- MEZI showed pharmacodynamic activity with BORT or CFZ at all doses tested, with 1.0 mg inducing the greatest substrate degradation and immune-modulation across cohorts (**Figure 6**)
  - These data also demonstrate that MEZI activity is not inhibited in the presence of PIs

Figure 6. Pharmacodynamic activity of MEZI



PB, peripheral blood; Prolif, proliferating.

Conclusions

- With longer follow-up, MEZI in combination with either BORT or CFZ continued to show promising efficacy at all dose levels tested, consistent with previous reports[6,7]
  - 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 granulocyte colony-stimulating factor
  - 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 phase 3 SUCCESSOR studies, SUCCESSOR-1 (NCT05519085; MeziVd vs POM plus BORT), and SUCCESSOR-2 (NCT05552976; MeziKd vs CFZ), which are currently enrolling

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