Mezigdomide in novel combinations for relapsed or refractory multiple myeloma: updated results from the CA057-003 trial

MM-552

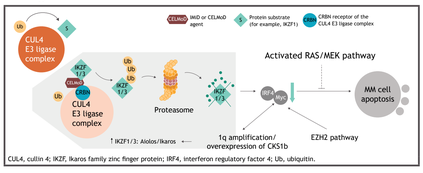
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Introduction

- Mezigdomide (MEZI) is an oral CELMoD™ agent with enhanced antitumor and immunostimulatory effects compared with immunomodulatory drug (IMiD®) agents, as well as a differentiated preclinical profile[1-3]
  - MEZI binds cereblon (CRBN) to induce the closed/active conformation, resulting in more efficient degradation of Ikaros and Aiolos[4]; it also enhances cytokine production and reverses T-cell exhaustion associated with the activation and proliferation of T cells[5]
- MEZI plus dexamethasone (DEX; MEZId) has shown promising clinical activity in patients with heavily pretreated relapsed/refractory multiple myeloma (RRMM),[6] providing a rationale for combining MEZI with other antimyeloma therapies
- EZH2 and RAS-RAF-MEK-ERK pathways and 1q/CKS1b amplification are associated with progressive disease (PD) and poor prognosis in MM[7-9]
  - CA057-003 (NCT05372354)[10,11] is a phase 1/2 trial evaluating all-oral, novel-novel targeted triplet combinations using a backbone of MEZId combined with the EZH2 inhibitor tazemetostat (TAZ), the BET inhibitor BMS-986158, and the MEK inhibitor trametinib (TRAM) in patients with RRMM who are intolerable to, or unsuitable for, available therapies (**Figure 1**)
  - Preclinical data show that MEZI combined with TAZ, BMS-986158, or TRAM increased apoptosis in MM cell lines[12]

Figure 1. MEZI mechanism of action: targeted protein degradation through CRBN[7,12,13]



CUL4, cullin 4; IKZF, Ikaros family zinc finger protein; IRF4, interferon regulatory factor 4; Ub, ubiquitin.

Objective

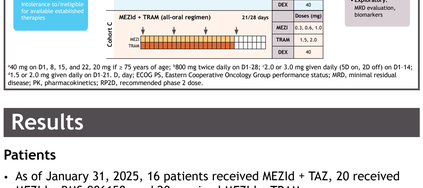
- To report results from the CA057-003 dose-finding cohorts of MEZId combined with TAZ, BMS-986158, or TRAM in RRMM as of January 31, 2025

Methods

Study design and treatment

- Key eligibility criteria, treatment, and endpoints are summarized in **Figure 2**

Figure 2. CA057-003 study design for cohorts A, B, and C



[a]40 mg on D1, 8, 15, and 22, 20 mg if ≥ 75 years of age; [b]800 mg twice daily on D1-28; [c]2.0 or 3.0 mg given daily (5D on, 2D off) on D1-14; [d]1.5 or 2.0 mg given on D1-21. D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; MRD, minimal residual disease; PK, pharmacokinetics; RP2D, recommended phase 2 dose.

Results

Patients

- As of January 31, 2025, 16 patients received MEZId + TAZ, 20 received MEZId + BMS-986158, and 20 received MEZId + TRAM
- Baseline characteristics are shown in **Table 1**
  - Median (range) age was 63 (37-83) years; time since initial diagnosis was 7.9 (1.2-18.4) years; more than one-third of patients (n = 20; 35.7%) had plasmacytomas

Table 1. Baseline characteristics

Characteristic	Total (N = 56)	MEZId + TAZ (n = 16)	MEZId + BMS-986158 (n = 20)	MEZId + TRAM (n = 20)
Age, median (range), years	63 (37-83)	63 (51-80)	64 (45-83)	63.5 (37-79)
Sex, male, n (%)	35 (62.5)	10 (62.5)	12 (60.0)	13 (65.0)
Race,[a] n (%)				
White	44 (78.6)	11 (68.8)	16 (80.0)	17 (85.0)
Black or African American	9 (16.1)	4 (25.0)	3 (15.0)	2 (10.0)
Asian	1 (1.8)	0	1 (5.0)	0
Time since initial diagnosis, median (range), years	7.9 (1.2-18.4)	8.9 (2.4-13.3)	7.7 (2.0-18.4)	7.5 (1.2-11.9)
ECOG PS score, n (%)				
0	14 (25.0)	2 (12.5)	5 (25.0)	7 (35.0)
1	42 (75.0)	14 (87.5)	15 (75.0)	13 (65.0)
ISS stage at study entry,[b] n (%)				
I	23 (41.1)	7 (43.8)	11 (55.0)	5 (25.0)
II	22 (39.3)	6 (37.5)	6 (30.0)	10 (50.0)
III	8 (14.3)	3 (18.8)	3 (15.0)	2 (10.0)
Presence of EMD,[c] n (%)	20 (35.7)	6 (37.5)	8 (40.0)	6 (30.0)
High-risk cytogenetics[d,e] n (%)	15 (26.8)	5 (31.3)	6 (30.0)	4 (20.0)

Data cutoff January 31, 2025. Percentages may not total 100% due to rounding. [a]Data were not collected/unknown for 1 (6.3%) patient (TAZ cohort), and 1 (5.0%) patient (TRAM cohort); [b]Data were unknown/not reported in 3 (15.0%) patients in the TRAM cohort; [c]Including parasseous lesions; [d]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; [e]9 (56.3%), 7 (35.0%), and 8 (40.0%) patients were not evaluated/tested in the TAZ, BMS-986158, and TRAM cohorts, respectively. EMD, extramedullary disease; ISS, International Staging System.

- Median (range) number of prior regimens in the total cohort was 5 (2-20) (**Table 2**)
- Prior treatments included IMiD agents (100%), PIs (100%), anti-CD38 mAbs (100%), ASCT (82.1%), and TCRT (55.4%); most patients (82.1%) had triple-class refractory disease

Table 2. Prior therapies and refractory status

Treatment characteristic	Total (N = 56)	MEZId + TAZ (n = 16)	MEZId + BMS-986158 (n = 20)	MEZId + TRAM (n = 20)
Prior therapies, median (range)	5 (2-20)	5 (3-14)	5 (2-20)	4 (2-9)
Prior therapies, n (%)				
ASCT	46 (82.1)	14 (87.5)	18 (90.0)	14 (70.0)
PI	56 (100)	16 (100)	20 (100)	20 (100)
Bortezomib	55 (98.2)	16 (100)	20 (100)	19 (95.0)
Carfilzomib	42 (75.0)	10 (62.5)	17 (85.0)	15 (75.0)
IMiD agent	56 (100)	16 (100)	20 (100)	20 (100)
Lenalidomide	55 (98.2)	16 (100)	19 (95.0)	20 (100)
Pomalidomide	44 (78.6)	13 (81.3)	17 (85.0)	14 (70.0)
Anti-CD38 mAb	56 (100)	16 (100)	20 (100)	20 (100)
TCRT	31 (55.4)	11 (68.8)	11 (55.0)	9 (45.0)
CAR T cell therapy	19 (33.9)	6 (37.5)	7 (35.0)	6 (30.0)
T-cell engager[a]	16 (28.6)	8 (50.0)	5 (25.0)	3 (15.0)
Refractory to prior therapies, n (%)				
PI	51 (91.1)	14 (87.5)	19 (95.0)	18 (90.0)
Bortezomib	39 (69.6)	10 (62.5)	13 (65.0)	16 (80.0)
Carfilzomib	33 (58.9)	8 (50.0)	13 (65.0)	12 (60.0)
IMiD agent	52 (92.9)	14 (87.5)	18 (90.0)	20 (100)
Lenalidomide	43 (76.8)	12 (75.0)	14 (70.0)	17 (85.0)
Pomalidomide	38 (67.9)	11 (68.8)	13 (65.0)	14 (70.0)
Anti-CD38 mAb	49 (87.5)	14 (87.5)	17 (85.0)	18 (90.0)
T-cell engager[a]	16 (28.6)	8 (50.0)	5 (25.0)	3 (15.0)
Triple-class refractory,[b] n (%)	46 (82.1)	13 (81.3)	15 (75.0)	18 (90.0)

Data cutoff January 31, 2025. [a]A bi-or tri-specific T-cell engager; [b]Refractory to an IMiD agent, a PI, and an anti-CD38 mAb. ASCT, autologous stem cell transplantation; CAR, chimeric antigen receptor; mAb, monoclonal antibody; PI, proteasome inhibitor; TCRT, T cell redirecting therapy.

Treatment disposition

- At data cutoff, 3 (18.8%) patients continued treatment in the MEZId + TAZ cohort, 3 (15.0%) in the MEZId + BMS-986158 cohort, and 9 (45.0%) in the MEZId + TRAM cohort; the main reason for discontinuation in all cohorts was PD
- Median (range) follow-up was 7.0 (1.3-16.1) months (MEZId + TAZ), 4.6 (1.0-15.7) months (MEZId + BMS-986158), and 8.2 (2.1-20.3) months (MEZId + TRAM)

Safety

- The most frequent grade 3/4 treatment-emergent adverse event (TEAE) overall was neutropenia (56.3%-85.0%) (**Table 3**), which was manageable with dose interruptions, granulocyte colony-stimulating factor, and dose reductions as clinically indicated
- Other than infections, rates of grade 3/4 non-hematologic TEAEs were low
- Of evaluable patients, 8 had dose-limiting toxicities (DLTs) (**Table 4**); all combinations and dose levels were tolerated except DL3 of MEZId + BMS-986158

Table 3. TEAEs

Most common (≥ 25% all grade) TEAEs and events of interest, n (%)	MEZId + TAZ (n = 16)		MEZId + BMS-986158 (n = 20)		MEZId + TRAM (n = 20)	
	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4
Any TEAE	16 (100)	11 (68.8)	20 (100)	17 (85.0)	20 (100)	18 (90.0)
Hematologic TEAEs						
Neutropenia	11 (68.8)	9 (56.3)	15 (75.0)	13 (65.0)	17 (85.0)	17 (85.0)
Leukopenia	1 (6.3)	0	4 (20.0)	1 (5.0)	6 (30.0)	5 (25.0)
Anemia	4 (25.0)	3 (18.8)	12 (60.0)	7 (35.0)	14 (70.0)	5 (25.0)
Thrombocytopenia	4 (25.0)	1 (6.3)	14 (70.0)	8 (40.0)	11 (55.0)	4 (20.0)
Non-hematologic TEAEs						
Fatigue	8 (50.0)	1 (6.3)	6 (30.0)	2 (10.0)	11 (55.0)	1 (5.0)
Cough	5 (31.3)	0	2 (10.0)	0	4 (20.0)	0
Diarrhea	4 (25.0)	0	8 (40.0)	0	12 (60.0)	1 (5.0)
Rash	2 (12.5)	0	0	0	4 (20.0)	0
Arthralgia	3 (18.8)	0	6 (30.0)	0	2 (10.0)	0
Nausea	2 (12.5)	0	2 (10.0)	0	6 (30.0)	0
Hypocalcemia	0	0	1 (5.0)	0	9 (45.0)	2 (10.0)
Hypomagnesemia	0	0	2 (10.0)	0	7 (35.0)	0
Hypokalemia	1 (6.3)	1 (6.3)	1 (5.0)	0	6 (30.0)	3 (15.0)
Constipation	2 (12.5)	0	1 (5.0)	0	6 (30.0)	0
Infections	11 (68.8)	4 (25.0)	11 (55.0)	4 (20.0)	18 (90.0)	8 (40.0)
URTI	6 (37.5)	0	3 (15.0)	0	6 (30.0)	0
Pneumonia	3 (18.8)	2 (12.5)	1 (5.0)	1 (5.0)	4 (20.0)	4 (20.0)

Data cutoff January 31, 2025. URTI, upper respiratory tract infection.

Table 4. DLTs

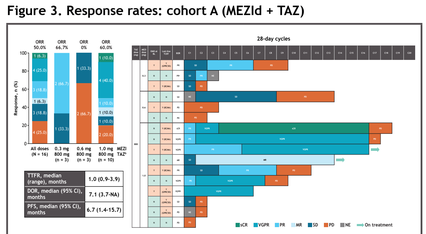
	MEZId + TAZ[a] (n = 16)			MEZId + BMS-986158[b] (n = 20)			MEZId + TRAM[c] (n = 20)			
	DL1 (n = 3)	DL2 (n = 3)	DL3 (n = 10)	DL1 (n = 8)	DL2 (n = 7)	DL3 (n = 5)	DL1 (n = 3)	DL2 (n = 4)	DL3 (n = 7)	DL4 (n = 6)
DLT-evaluable patients,[d] n (%)	15 (93.8)			18 (90.0)			19 (95.0)			
Per dose level, n (%)	3 (100)	3 (100)	9 (90.0)	6 (75.0)	7 (100)	5 (100)	3 (100)	4 (100)	6 (85.7)	6 (100)
Patients with ≥ 1 DLT,[e] n (%)	1 (6.7)			5 (27.8)			2 (10.5)			
Per dose level, n (%)	0	0	1 (11.1)	1 (16.7)	0	4 (80.0)	0	0	1 (16.7)	1 (16.7)
DLTs by dose level, n										
Thrombocytopenia	0	0	1	1	0	3	0	0	0	0
Neutropenia	0	0	0	0	0	1	0	0	1	0
Febrile neutropenia	0	0	0	0	0	1	0	0	0	1
Fatigue	0	0	0	0	0	1	0	0	0	0
Left ventricular dysfunction	0	0	0	0	0	0	0	0	1	0
Diarrhea	0	0	0	0	0	0	0	0	0	1
Staphylococcal infection	0	0	0	0	0	0	0	0	0	1

Data cutoff January 31, 2025. [a]Defined as 0.3 mg MEZI (DL1), 0.6 mg MEZI (DL2), or 1.0 mg MEZI (DL3) plus 800 mg TAZ and 40/20 mg DEX; [b]Defined as 0.3 mg MEZI (DL1), 0.6 mg MEZI (DL2), or 1.0 mg MEZI (DL3) plus 2.0 mg BMS-986158 and 40/20 mg DEX; [c]Defined as 0.3 mg MEZI (DL1), 0.6 mg MEZI (DL2), or 1.0 mg MEZI (DL3) plus 1.5 mg TRAM, or 1.0 mg MEZI plus 2.0 mg TRAM (DL4), in combination with 40/20 mg DEX; [d]DLT-evaluable population defined as all patients from the safety population who met the minimum exposure criterion and had sufficient safety evaluations, or who had experienced a DLT during the first treatment cycle; [e]Individual patients may have experienced multiple DLT events. DL, dose level.

Efficacy

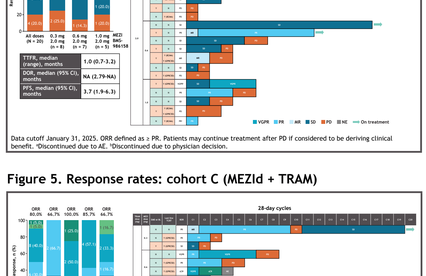
- In the efficacy-evaluable population, overall response rate (ORR) was 50% with MEZId + TAZ (**Figure 3**), 35% with MEZId + BMS-986158 (**Figure 4**), and 80% with MEZId + TRAM (**Figure 5**)
- Deeper responses (≥ VGPR) were observed with 1.0 mg MEZI in the MEZId + TAZ and MEZId + BMS-986158 cohorts, and with ≥ 0.6 mg MEZI in the MEZId + TRAM cohort

Figure 3. Response rates: cohort A (MEZId + TAZ)



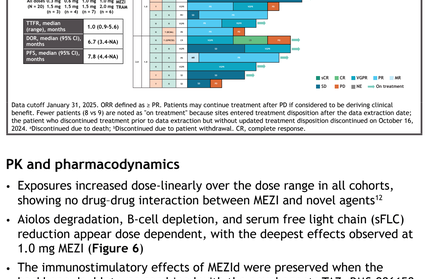
Data cutoff January 31, 2025. Percentages may not total 100% due to rounding. ORR defined as ≥ PR. Fewer patients (2 vs 3) are noted as "on treatment" because sites entered treatment disposition after the data extraction date; the patient who discontinued treatment prior to data extraction but without updated treatment disposition discontinued on January 8, 2025. [a]Discontinued due to physician decision. [b]800 mg twice daily. [c]Discontinued due to death, BCMA, B-cell maturation antigen; BL, baseline; BOR, best overall response; C, cycle; CI, confidence interval; DOR, duration of response; GPRC5D, G protein-coupled receptor class C group 5 member D; MR, minimal response; NA, not available; NE, not evaluable; PFS, progression-free survival; PR, partial response; sCR, stringent complete response; SD, stable disease; TTFR, time to first response; VGPR, very good PR.

Figure 4. Response rates: cohort B (MEZId + BMS-986158)



Data cutoff January 31, 2025. ORR defined as ≥ PR. Patients may continue treatment after PD if considered to be deriving clinical benefit. [a]Discontinued due to AE. [b]Discontinued due to physician decision.

Figure 5. Response rates: cohort C (MEZId + TRAM)

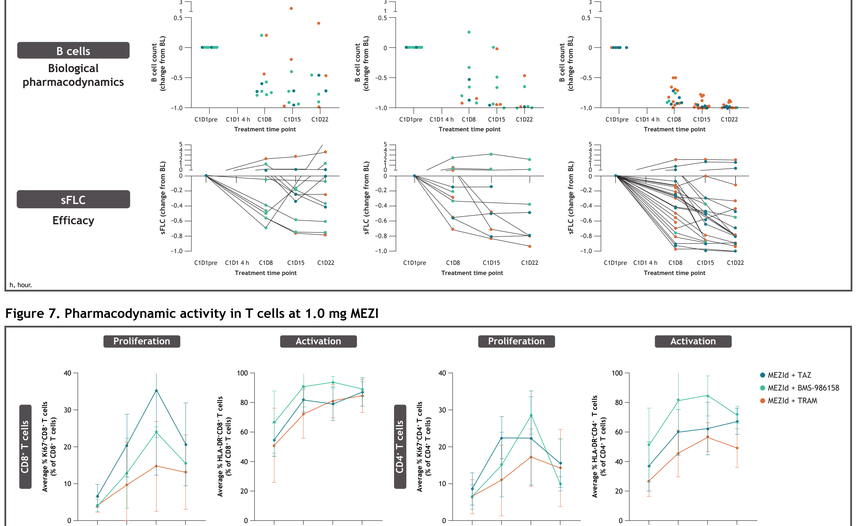


Data cutoff January 31, 2025. ORR defined as ≥ PR. Patients may continue treatment after PD if considered to be deriving clinical benefit. Fewer patients (8 vs 9) are noted as "on treatment" because sites entered treatment disposition after the data extraction date; the patient who discontinued treatment prior to data extraction but without updated treatment disposition discontinued on October 16, 2024. [a]Discontinued due to death; [b]Discontinued due to patient withdrawal. CR, complete response.

PK and pharmacodynamics

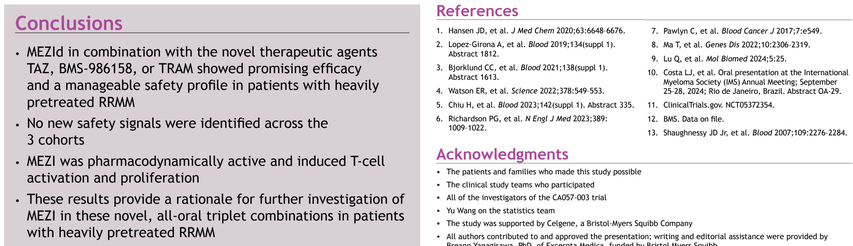
- Exposures increased dose-linearly over the dose range in all cohorts, showing no drug-drug interaction between MEZI and novel agents[12]
- Aiolos degradation, B-cell depletion, and serum free light chain (sFLC) reduction appear dose dependent, with the deepest effects observed at 1.0 mg MEZI (**Figure 6**)
- The immunostimulatory effects of MEZId were preserved when the backbone doublet was combined with the novel agents TAZ, BMS-986158, or TRAM (**Figure 7**)

Figure 6. Pharmacodynamic activity by MEZI dose level



h, hour.

Figure 7. Pharmacodynamic activity in T cells at 1.0 mg MEZI



Data shown are mean ± standard deviation. MEZI 1.0 mg + TAZ: n = 8; MEZI 1.0 mg + BMS-986158: n = 5; MEZI 1.0 mg + TRAM: n = 12.

Conclusions

- MEZId in combination with the novel therapeutic agents TAZ, BMS-986158, or TRAM showed promising efficacy and a manageable safety profile in patients with heavily pretreated RRMM
- No new safety signals were identified across the 3 cohorts
- MEZI was pharmacodynamically active and induced T-cell activation and proliferation
- These results provide a rationale for further investigation of MEZI in these novel, all-oral triplet combinations in patients with heavily pretreated RRMM

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