Abstract: P903

Title: MEZIGDOMIDE (MEZI), TAZEMETOSTAT (TAZ), AND DEXAMETHASONE (DEX) IN PATIENTS (PTS) WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM): PRELIMINARY RESULTS FROM THE CA057-003 TRIAL

Abstract Type: Poster Presentation

Topic: Myeloma and other monoclonal gammopathies - Clinical

Background:

The CA057-003 phase 1/2 trial (NCT05372354) is evaluating oral, novel-novel targeted triplet combination regimens using a MEZI+DEX backbone in pts with RRMM who are refractory to, intolerant to, nor are candidates for established MM therapies. MEZI, a novel CELMoD™ agent with enhanced tumoricidal and immune-modulatory effects compared with classic IMiD® agents, induces rapid and maximal degradation of Ikaros/Aiolos leading to increased apoptosis in MM cells. The third agent in each combination intervenes on a** key oncogenic pathway upregulated in RRMM, as identified by The Myeloma Genome Project: 1) EZH2 inhibitor TAZ for PRC2 complex dysregulation; 2) BET inhibitor BMS-986158 for CKS1b (located on chromosome 1q) amplification; 3) MEK inhibitor trametinib for RAS-RAF-MEK-ERK activation.

Aims:

To report results from the CA057-003 dose-finding cohort of MEZI+TAZ+DEX in pts with RRMM.

Methods:

Eligible pts had RRMM with documented progressive disease (PD) during or after the last regimen and ECOG performance status score ≤1, and were refractory or intolerant to, or ineligible for, available established therapies. Oral MEZI was given at 3 different escalating doses on days (D) 1–21 of each 28-day cycle with oral TAZ (800mg) twice daily on D1–28 and weekly oral DEX (40mg; 20mg if >75 y of age). Primary objectives are to define the RP2D and dosing schedule, and to evaluate safety; secondary objectives are to assess efficacy and pharmacokinetics.

Results:

As of January 2, 2024, 12 pts received MEZI+TAZ+DEX (3 pts 0.3mg; 3 pts 0.6mg; 6 pts 1.0mg). Median (range) age was 68 (51–80) y and median time since initial diagnosis was 7.1 (2.4–12.3) y; extramedullary plasmacytomas were present in 5 (41.7%) pts. Median number of prior regimens was 5 (3–14), 10 (83.3%) pts were triple-class refractory (to an IMiD agent, proteasome inhibitor, and anti-CD38 monoclonal antibody), and 8 (66.7%) pts had received prior T-cell–redirecting therapy, including anti-BCMA.

At data cutoff, 7 (58.3%) pts continued treatment; 4 pts discontinued due to PD and 1 pt due to physician's decision. Median number of cycles received was 3 (1–9). Median follow-up was 3.19 (1.2–8.3) mo and median MEZI treatment duration was 10.7 (4.0–37.0) wk.

Overall, 8 (66.7%) pts experienced a grade (Gr) 3/4 treatment-emergent adverse event (TEAE); the most common hematologic TEAEs were neutropenia (33.4%) and anemia (16.7%). Most common (reported in >1 pt) non-hematologic Gr 3/4 TEAEs included infections (16.7%) and dyspnea (16.7%). No dose-limiting toxicities were observed. No TEAEs led to MEZI dose reduction or discontinuation. At data cutoff there were no deaths due to TEAEs.

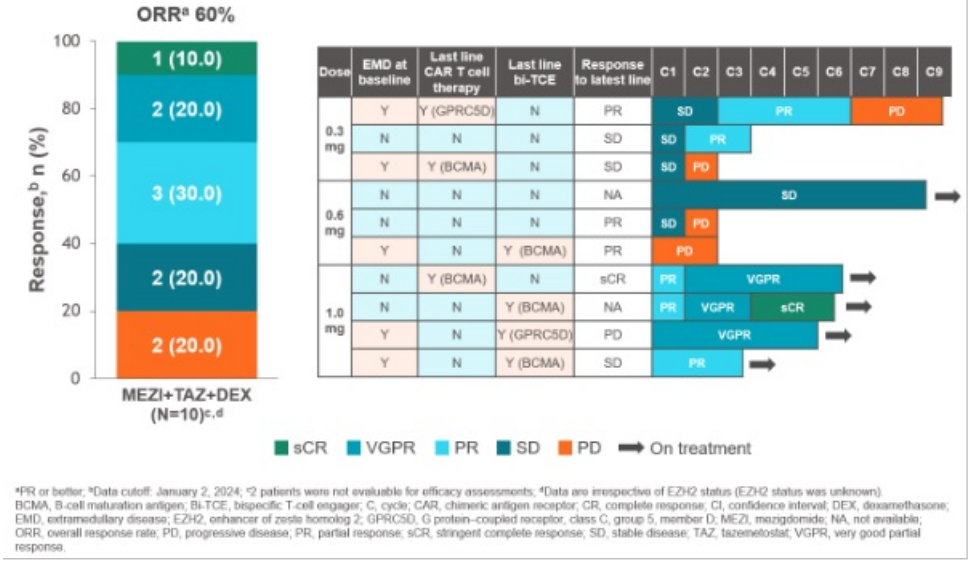
In evaluable pts (N=10), overall response rate was 60% (95% CI, 26.2–87.8) with 1 stringent complete response, 2 very good partial responses, and 3 partial responses (Figure); the median time to response was 1.8 (0.9–3.8) mo. There were responses among pts who had T-cell–redirecting therapies as their last line and deeper responses were observed at the highest MEZI dose.

Exposure (Cmax and area under the curve) increased in a more than dose-linear manner over the dose range. There was no pharmacological interaction between MEZI and TAZ. MEZI remained pharmacodynamically active, inducing Ikaros/Aiolos degradation and B cell reduction with TAZ at all dose levels, with the greatest effect observed at MEZI 1.0mg.

Summary/Conclusion:

MEZI+TAZ+DEX showed promising preliminary efficacy and safety in pts with RRMM, with no new safety concerns. These results provide rationale for further exploration of this novel all-oral combination. Updated results will be presented at the meeting.

Figure: Response rates to MEZI+TAZ+DEX in patients with RRMM



[a]PR or better; [b]Data cutoff: January 2, 2024; [c]2 patients were not evaluable for efficacy assessments; [d]Data are irrespective of EZH2 status (EZH2 status was unknown).
BCMA, B-cell maturation antigen; Bi-TCE, bispecific T-cell engager; C, cycle; CAR, chimeric antigen receptor; CR, complete response; CI, confidence interval; DEX, dexamethasone; EMD, extramedullary disease; EZH2, enhancer of zeste homolog 2; GPRC5D, G protein–coupled receptor, class C, group 5, member D; MEZI, mezigdomide; NA, not available; ORR, overall response rate; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; TAZ, tazemetostat; VGPR, very good partial response.

Keywords: Immunomodulation, Myeloma, Clinical trial, EZH2