Mezigdomide in novel combinations effectively reactivates immune system in patients with relapsed/refractory multiple myeloma including those after T cell redirecting therapies

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Objective

- To explore immune composition and changes associated with mezigdomide (MEZI)-based treatment combinations in patients with relapsed/refractory multiple myeloma (RRMM) with or without prior T cell redirecting therapies (TCRT) exposure

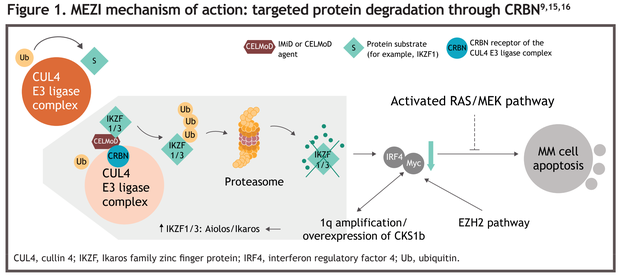
Conclusions

- MEZI-based novel combinations lead to activation of adaptive and innate immune populations in heavily pretreated patients with RRMM irrespective of prior TCRT exposure
  - Among patients who received prior TCRT, there was no significant difference between chimeric antigen receptor (CAR) T cell therapy and T cell engagers (TCEs) for T, B, and natural killer (NK) cells and proliferating T cells
- Dynamics of immune changes upon treatment with MEZI-based novel combinations is concordant with findings reported for the MEZI plus dexamethasone (DEX; MEZId) backbone[1]
- These results suggest that previous exposure to TCRT and the addition of novel agents do not affect the ability of MEZI to increase activation and proliferation of NK and T cells, supporting its use in combinations for patients with prior TCRT exposure
  - These effects are reproducible independently of combination of MEZI with tazemetostat (TAZ), BMS-986158, or trametinib (TRAM)

Introduction

- MEZI is an oral CELMoD™ agent with improved direct antitumor and immunostimulatory therapeutic effects compared with immunomodulatory drug (IMiD®) agents, as well as having greater immunostimulatory effects[2-5]
  - MEZI efficiently induces the closed/highly active conformation of cereblon (CRBN), resulting in more efficient proteasomal degradation of Ikaros and Aiolos[6]; it also enhances cytokine production and reverses T cell exhaustion associated with the activation and proliferation of T cells[7]
- MEZId has shown promising clinical activity in patients with heavily pretreated RRMM,[8] 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[9-11]
  - CA057-003 (NCT05372354)[12-14] is a phase 1/2 trial evaluating all-oral, novel targeted triplet combinations using a backbone of MEZId combined with the EZH2 inhibitor TAZ, the BET inhibitor BMS-986158, and the MEK inhibitor TRAM in patients with RRMM who are intolerable to, or unsuitable for, available therapies (**Figure 1**)
- Due to dual mechanism of action of MEZI, exploring the role of MEZI-based regimens in patients post TCRTs, such as CAR T cell therapy and TCEs is crucial given the potential for T cell exhaustion and immune dysregulation after treatment with TCRTs

Figure 1. MEZI mechanism of action: targeted protein degradation through CRBN[9,15,16]



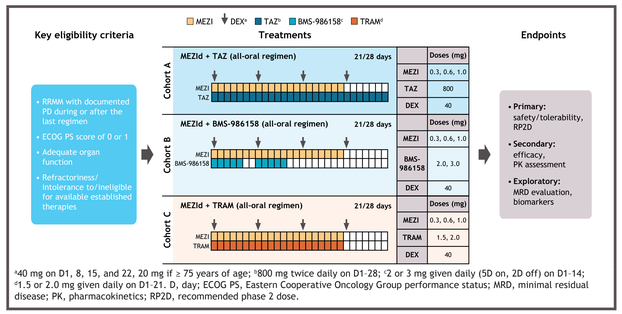
CUL4, cullin 4; IKZF, Ikaros family zinc finger protein; IRF4, interferon regulatory factor 4; Ub, ubiquitin.

Methods

Study design and treatment

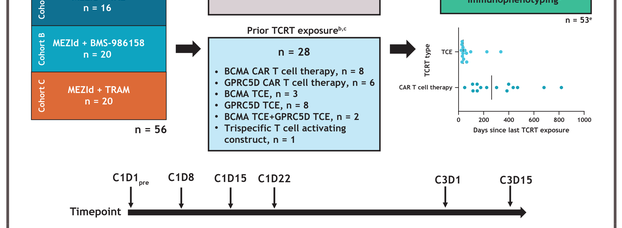
- Key eligibility criteria, treatment, and endpoints are summarized in **Figure 2** and the assessment plan is shown in **Figure 3**

Figure 2. CA057-003 study design



[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 or 3 mg given daily (5D on, 2D off) on D1-14; [d]1.5 or 2.0 mg given daily on D1-21. D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; MRD, minimal residual disease; PK, pharmacokinetics; RP2D, recommended phase 2 dose.

Figure 3. Assessment plan



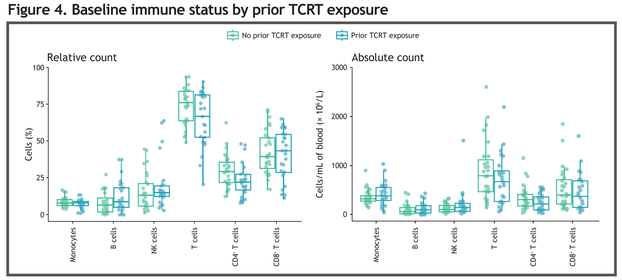
[a]Eligible patients had a median (range) number of prior regimens of 5 (2-20); prior treatments included IMiD agents (100%), proteasome inhibitors (100%), anti-CD38 monoclonal antibodies (100%), autologous stem cell transplantation (82.1%), and TCRT (55.4%); most patients (82.1%) had triple-class refractory disease; [b]Patients were considered to have prior TCRT exposure if they had received TCRT in the last regimen immediately prior to MEZI; [c]Of the 28 patients who had prior TCRT exposure, 4 achieved a stringent complete response, 1 a complete response, 8 a very good partial response, 3 a partial response, 1 a minimal response, 3 had stable disease, and 7 progressive disease (1 patient had unknown response); [d]T, B, NK cells subpopulations, activation, and proliferation status had been assessed; 384 populations analyzed in 4 panels; [e]From the 56 patients enrolled, 53 were profiled: 16 patients from Cohort A, 18 patients from Cohort B, and 19 patients from Cohort C. BCMA, B-cell maturation antigen; C, cycle; $C1D1_{pre}$, C1D1 before the MEZI dosing; GPRC5D, G protein-coupled receptor class C group 5 member D.

Results

Impact of prior TCRT exposure on immune status

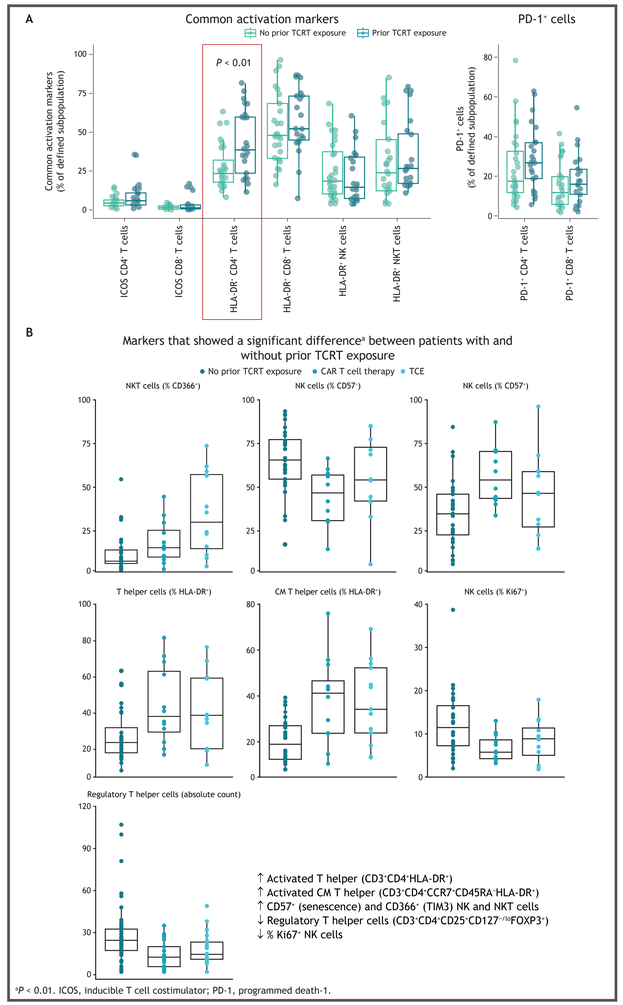
- When comparing the baseline immune status of patients who received and did not receive prior TCRT, the abundance of different immune subsets appears similar as assessed by relative or absolute numbers of $CD4^+$ and $CD8^+$ T-cells, T, B, and NK cells, and by levels of $Ki67^+$, $CD4^+$, and $CD8^+$ T cells (**Figure 4**)

Figure 4. Baseline immune status by prior TCRT exposure



- Prior TCRT exposure appeared to increase immune subsets related to persistent activation, including activated T helper ($CD3^+CD4^+HLA\text{-}DR^+$) and activated central memory (CM) T helper cells ($CD3^+CD4^+CCR7^+CD45RA^-HLA\text{-}DR^+$), and increased numbers of $CD57^+$ and $CD366^+$ NK and NKT cells
- TCRT exposed patients had lower absolute counts of regulatory T cells ($CD3^+CD4^+CD25^+CD127^{-/lo}FOXP3^+$) and relative percent of $Ki67^+$ NK cells (**Figure 5A**)
- Among immune subsets that differed significantly between patients who received and did not receive prior TCRT, there was no significant difference between CAR T cell therapy and TCEs for T, B, and NK cells and proliferating T cells among patients who received prior TCRT (**Figure 5B**)

Figure 5. Distribution of common immune activation markers by prior TCRT exposure (A) and by TCRT type (B)



[a]$P < 0.01$. ICOS, inducible T cell costimulator; PD-1, programmed death-1.

Treatment with MEZI-based regimens

- Upon treatment with MEZI-based regimens, patients who received and did not receive TCRT showed increased levels of proliferation and enhanced activation of $CD4^+$ and $CD8^+$ T cells (**Figure 6**)
- In both patient populations, treatment with MEZI allowed a shift toward an exhausted/effector memory (EM) phenotype ($CCR7^-CD45RA^-$) in $CD8^+$ T cells with subsequent reduction of naive ($CCR7^+CD45RA^-$), CM ($CCR7^+CD45RA^+$), and EM T cells re-expressing CD45RA (TEMRA; $CCR7^-CD45RA^+$) populations in both $CD4^+$ and $CD8^+$ T cells upon treatment with MEZI-based regimens (**Figure 7**)

Figure 6. Proliferation and activation of $CD4^+$ and $CD8^+$ T cells following treatment with MEZI-based regimens

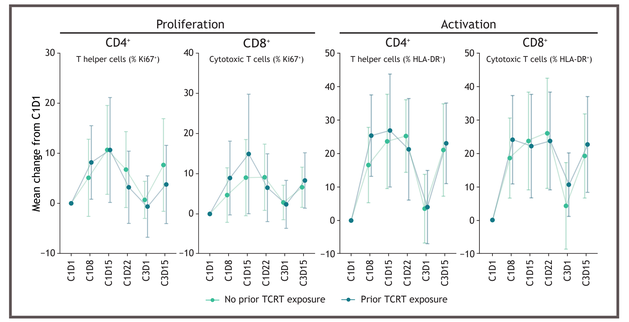
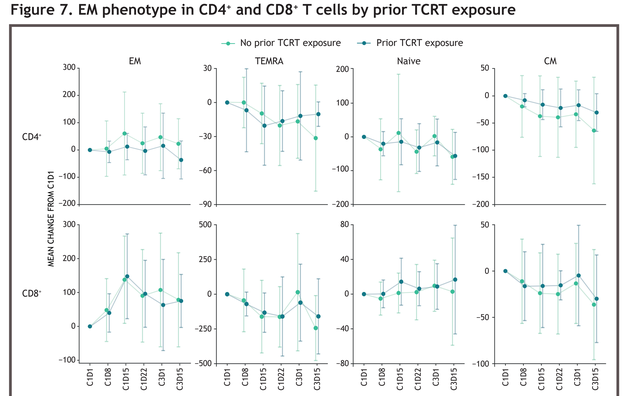


Figure 7. EM phenotype in $CD4^+$ and $CD8^+$ T cells by prior TCRT exposure



CM phenotype ($CCR7^+CD45RA^-$); EM phenotype ($CCR7^-CD45RA^-$); Naive phenotype ($CCR7^+CD45RA^+$); TEMRA ($CCR7^-CD45RA^+$).

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