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POSTER ABSTRACTS

651.MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS: BASIC AND TRANSLATIONAL

Preclinical and Translational Biomarker Analyses to Inform Clinical Development of Mezigdomide (CC-92480) in Combination with Dexamethasone and Daratumumab in Multiple Myeloma

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Introduction: Mezigdomide (MEZI) is a novel, oral cereblon (CRBN) E3 ligase modulator (CELMoD) that induces rapid and potent degradation of Ikaros and Aiolos. Reduction of these transcription factors results in direct tumoricidal and immunomodulatory effects in multiple myeloma (MM). MEZI showed promising efficacy and safety in combination with dexamethasone in the phase 1/2 CC-92480-MM-001 trial (NCT03374085) in Relapsed/Refractory MM. MEZI is currently being investigated in combination with daratumumab and dexamethasone (MEZI + DARA + DEX or MEZI-Dd) in the phase 1/2 CC-92480-MM-002 trial (NCT03989414). In MEZI-Dd cohort, MEZI is administered at three different schedules (B1 for 21/28 days; B2 for 14/21 days; B3 for 7/14 days), and at two different doses (0.3mg; 0.6mg). Here we report preclinical data and pharmacodynamic (PD) biomarker analyses from blood and bone marrow samples collected in CC-92480-MM-002 to support dose and schedule optimization of MEZI-Dd.

Methods: Preclinical studies on the pro-apoptotic effects of MEZI on daratumumab-mediated complement-dependent cytotoxicity (CDC) and peripheral blood mononuclear cell-based antibody-dependent cell-mediated cytotoxicity (ADCC) were performed in MM cell lines treated with MEZI-D in comparison to single-agent MEZI or DARA. Clinical PD biomarker analyses included peripheral blood samples collected on treatment Cycle (C)1 Day (D)1 and mid C1-C3 for the expression of Aiolos in T-cells and immunomodulation by flow cytometry. Bone marrow samples were collected for immunohistochemistry at screening and mid C2. Serum free light chain (sFLC) and soluble B-cell maturation antigen (BCMA) were analyzed as biomarkers for tumor burden from C1-C6.

Results: Preclinically, combinations of MEZI-D induced synergistic anti-tumor activity in MOLP-8 cells. The MEZI-D combination showed greater anti-MM activities across the dosing gradient than either single-agent DARA (~2-4.5 fold) or MEZI (~1.7-2.4 fold) in a CDC assay. MEZI-D also induced significantly more cell apoptosis than POM-D ($p<0.05$) in an ADCC assay. In the clinic, MEZI-Dd was sufficient to induce rapid Aiolos degradation in the peripheral blood T-cells for doses as low as 0.3mg MEZI, but 0.6mg MEZI was necessary to result in >50% substrate degradation, suggesting 0.6mg MEZI induced deeper substrate degradation. While 0.3mg MEZI-Dd decreased total CD56+/CD16+ NK-cell counts (Median -83.8%) by mid C1 via immunophenotyping analyses, the combination increased %Ki67+ proliferative NK-cell (Median 251.9%). 0.3mg MEZI-Dd also showed consistent trends of schedule-dependent PD immune effects by mid C3, including increased %Ki67+ proliferative CD3+ T-cell (Median B1: 113.1%, B2: 365.1%, B3: 37.4%), decreased CD45RA+CCR7+ naïve CD4+ T-cell (Median B1: -82.0%, B2: -62.3%, B3: -43.9%), increased CD45RO+CCR7- effector memory CD4+ T-cell (Median B1: 142.3%, B2: 82.9%, B3: 13.9%), and increased HLA-DR expressing CD4+ T-cell activation (Median B1: 149.3%, B2: 107.9%, B3: 17.1%). Thus, greater PD immune effects were observed with schedules of 21/28 and 14/21 days, compared to the 7/14 schedule. At 0.6mg MEZI-Dd, greater median changes of PD immune effects were induced with the 7/14 schedule, compared to 0.3mg MEZI-Dd. Conversely, at continuous dosing schedules longer than 7 days, MEZI-Dd PD immune effects of 0.6mg MEZI were similar to

0.3mg MEZI. In addition, greater reduction of tumor burden was observed at 0.6mg MEZI-Dd, compared to 0.3mg MEZI-Dd across different schedules, as assessed by sFLC and soluble BCMA analyses.
Conclusions: Our data show dose- and schedule-dependent PD effects of MEZI-Dd. PD analyses at 0.3mg MEZI suggest at least two weeks of continuous dosing may be needed for greater PD activities in combination with daratumumab, compared to one week of dosing. For continuous dosing of one week, a higher dose at 0.6mg MEZI may be needed to achieve greater PD activities. Further investigation of doses at 0.6mg and 1mg MEZI is underway to determine the optimal dose. Moreover, MEZI induction of NK-cell proliferation and/or activation may provide mechanistic rationale for possible MEZI-D synergy in the clinic.

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