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POSTER ABSTRACTS

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

Iberdomide Enhances Dara Mediated Cytotoxicity through Upregulation of CDC Activity and Elevated NK Cell Mediated ADCC

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Background: Multiple Myeloma (MM) is an incurable hematological malignancy with current treatments comprising combination regimens, typically featuring immunomodulatory agents (IMiDs) due to their potent anti-tumor activity and immunomodulatory effects. Clinical studies utilizing the combination of IMiD agents and daratumumab (DARA), an anti-CD38 monoclonal antibody, have shown improved patient outcomes for MM. However, patients ultimately relapse demonstrating the need for novel therapies. Iberdomide (IBER) is a novel cereblon E3 ligase modulator. It promotes faster and deeper degradation of the substrate targets compared to IMiDs, resulting in enhanced anti-proliferative, pro-apoptotic and immune stimulatory activity. In early clinical studies, IBER has been shown to overcome resistance to IMiDs and in the ongoing Phase 3 EXCALIBER study (NCT04975997) is being explored for treatment of newly diagnosed (ND) and relapsed/refractory (RR) MM in combination with DARA and dexamethasone. Here, we investigate the potential mechanisms of synergy between IBER and DARA in preclinical models.

Methods: Complement dependent cytotoxicity (CDC) of DARA was assessed with 15% human serum for human complement components and assays were performed by titrating either single agent or combinations in a tritiated thymidine assay. Antibody dependent cellular cytotoxicity (ADCC) was performed by co-culturing MM cells with varying expression levels of CD38 and effector cells and assessing target cell viability with annexin-v/topro-3 flow. A humanized PBMC adoptive transfer mouse model, utilizing human PBMC engraftment 14 days prior to implantation, was used to assess in vivo activity of IBER, DARA and IBER + DARA.

Results: In CDC assays, we observed variable sensitivity of MM cells to complement-specific CDC in the presence of DARA (0.1-1 μg/ml), regardless of cell surface CD38 expression. Notably, IBER treatment resulted in upregulation of CD38 surface expression in 60% of MM cell lines tested. LP1 and MOLP8 displayed susceptibility to DARA-mediated CDC. DARA showed a dose-dependent increase in CDC activity in both cell lines. Notably, IBER+DARA also showed ~35% more synergistic CDC activity in both cell lines, than the single agents. In ADCC assays, we observed pretreatment of PBMC with IBER (vs. DMSO) significantly increased DARA mediated ADCC in H929 and LP-1 cells. To confirm that this effect was directed by NK cells, we cultured NK cells for 24 hr in supernatants from stimulated PBMC in presence of IBER prior to co-culture with MM cells. We noted that IBER-treated PBMC supernatant significantly enhanced the NK ADCC activity of DARA suggesting that IBER enhancement of cytokine secretion from PBMC increases NK cell mediated ADCC. Orthogonally, we pre-treated MM cells with IBER or DMSO prior to co-culture in ADCC assay. Notably, IBER treatment of MM cells, without treating immune cells, also increased DARA-mediated ADCC, indicating that IBER directly increases sensitivity to DARA-directed ADCC.

To investigate the MOA of IBER-DARA synergy in ADCC, we analyzed gene expression and cell surface changes of a panel of NK-specific receptor ligands on MM cells following treatment with IBER. We observed IBER-induced upregulation of MICA mRNA levels (~2x) and surface expression (~40%) in MM target cells. We used RNAi to knock down Ikaros, an IBER substrate, which resulted in increased MICA expression (~3x) in MM cells. Furthermore, we observed that RNAi knock down of MICA in MM cells resulted in a significant decrease (60%, $p<0.0001$) in MM cell killing by NK cells, suggesting IBER-enhanced sensitivity of MM cells to NK-cell killing was in part, due to the upregulation of MICA through degradation of Ikaros.

Lastly, we examined the anti-MM effects of IBER in a humanized xenograft model with a lenalidomide resistant cell line. Longitudinal analysis identified persistence of human PBMC engraftment and activation of immune subsets (NK cells and T-

cells) that were increased upon IBER treatments, consistent with clinical observations. The combination of IBER/DARA resulted in ~22% tumor growth inhibition (TGI) in comparison to single agents, DARA and IBER and ~37% TGI in comparison to vehicle. **Conclusion:** Taken together, these data demonstrate that IBER and DARA work synergistically in preclinical models primarily through enhancement of both ADCC and CDC. This combination has the potential to improve outcomes in MM.

Disclosures Ma: *Bristol Myers Squibb:* Ended employment in the past 24 months. **Sridharan:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company. **Wollerman:** *Bristol Myers Squibb:* Ended employment in the past 24 months. **Dutta:** *Biocon Bristol Myers Squibb:* Current Employment. **Singh:** *Biocon Bristol Myers Squibb:* Current Employment. **Mukherjee:** *BMS:* Current Employment. **Bjorklund:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company. **Hagner:** *BMS:* Current Employment, Current equity holder in publicly-traded company. **Amatangelo:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company. **Gandhi:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company.

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