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POSTER ABSTRACTS

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

Mezigdomide Treatment in Relapsed-Refractory Myeloma Patients Shifts Bone Marrow NK and T Cell Populations from Exhaustion to Activation

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Background

The effect of immunomodulatory drugs (IMiDs) and novel cereblon E3 ligase modulators (CELMoDs) on the tumour microenvironment (TME) of multiple myeloma (MM) patients remains poorly understood. A recent multi-center phase 1/2 trial (CC-92480-MM-001) of CELMoD Mezigdomide (MEZI) demonstrated clinical response in triple-class refractory, heavily pre-treated MM patients (Richardson et al, EHA abstracts 2020). Here, we report results from high dimensional mass cytometry immune profiling of baseline and treatment samples from relapsed-refractory MM (RRMM) patients to understand the effect of MEZI on the bone marrow (BM) TME. In addition, we analyze baseline samples to evaluate BM immune phenotypes that may correlate with response to MEZI.

Methods

We identified 45 RRMM patients with paired bone marrow aspirate samples pre- (screening) and post- (cycle 2 onwards) MEZI treatment, and 32 additional patients with isolated screening samples. Of the 45 patients, 39 received a dose of 0.8-1.0mg daily for 14 or 21 days of a 28-day cycle, 6 received 0.2-0.6mg on varying schedules as part of the trial design. CD138-negative BM mononuclear cells were isolated from these patients and profiled at single-cell resolution using a previously described 39-marker TME CyTOF-panel (van Oekelen, ASH 2021). Both manual hierarchical gating and unsupervised computational workflows were used for CyTOF data analysis. Around 5 million total cells were analyzed and over 100 immune populations. Samples with <2500 total events were excluded for quality-control. Population frequencies used for comparison are reported as median percentage of the parent population. Statistical comparisons between groups were assessed using the Wilcoxon test.

Results

Upon MEZI treatment, both adaptive and innate BM immune compartments demonstrated a significant increase in activated populations and marked reduction in exhausted/senescent populations (Figure 1A). Total NK and NKT populations expanded on MEZI ($p<0.01$ for both). Both CD4 and CD8 T cell populations shifted towards an effector phenotype with significant increases in effector memory (CCR7-CD45RA-) populations ($p<0.001$ for both) and concurrent reductions of and naïve ($p<0.001$), central memory ($p<0.01$ for CD4, NS for CD8) and TEMRA populations ($p<0.001$). HLADR-expressing CD4, CD8

and NKT populations significantly increased on MEZI ($p<0.001$ for all) as did ICOS-expressing CD4 ($p<0.01$), NK ($p<0.001$) and NKT cells ($p<0.05$).
Senescent NK, NKT, CD4 and CD8 populations expressing KLRG1 decreased on MEZI treatment ($p<0.01$ for all) and CD57 positive CD8 and NKT cell populations also reduced ($p<0.05$). CD8, NK and NKT cells expressing the inhibitory checkpoint molecule TIGIT, showed a near 3-fold reduction of on treatment ($p<0.001$ for all). Although PD1-positive populations did not change on MEZI, PD1/TIGIT double-positive CD4 and CD8 populations showed significant reduction ($p<0.05$ for both). A dose-dependent reduction of TIGIT-expressing CD8 and NKT populations was seen at higher doses of MEZI ($p<0.05$ for both), suggesting a direct effect of MEZI on the BM TME.
We further correlated depth-of-response with baseline immune composition in 77 patients (Figure 1B). Patients with progression of disease (n=9) on MEZI, when compared to all other patients (n=68), were found to have higher frequencies of PD1 ($p<0.05$) and TIGIT ($p<0.001$) positive, as well as dual PD1 and TIGIT positive ($p<0.001$), CD8 and NKT populations. Number of prior lines (median = 6) and type of MM therapy prior to MEZI did not significantly affect baseline PD1 or TIGIT positive populations.

Conclusion

MEZI treatment leads to significant activation of adaptive and innate BM immune populations with concurrent reduction of exhausted and senescent populations. These findings are concordant with prior observations of IMiD-mediated immune-stimulation. Patients progressing through MEZI had higher levels of immune checkpoint expression at baseline, which may be helpful for patient selection for this novel CELMoD. These results also suggest that MEZI may be useful in combination with other agents for increasing immune activation and reducing immune exhaustion. Further analyses comparing the effect of different CELMoDs on the BM TME are ongoing.

Disclosures Amatangelo: *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company. **Chow:** *BMS:* Current Employment, Current equity holder in private company, Current equity holder in publicly-traded company, Current holder of *stock options* in a privately-held company, Divested equity in a private or publicly-traded company in the past 24 months. **Kurtova:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company. **Gooding:** *Bristol Myers Squibb:* Research Funding. **Jagannath:** *Karyopharm:* Consultancy; *Janssen:* Consultancy; *Bristol Myers Squibb:* Consultancy; *Regeneron:* Consultancy; *Sanofi:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Legend Biotech:* Consultancy; *Caribou:* Consultancy. **Flynt:** *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. **Thakurta:** *Antenegene, Bristol Myers Squibb:* Consultancy, Current Employment, Current equity holder in publicly-traded company, Current holder of *stock options* in a privately-held company, Honoraria, Research Funding. **Parekh:** *Caribou Biosciences:* Research Funding; *Grail, LLC:* Membership on an entity's Board of Directors or advisory committees; *Karyopharm Therapeutics:* Research Funding; *Celgene/BMS Corporation:* Research Funding; *Amgen:* Research Funding.

Figure 1.

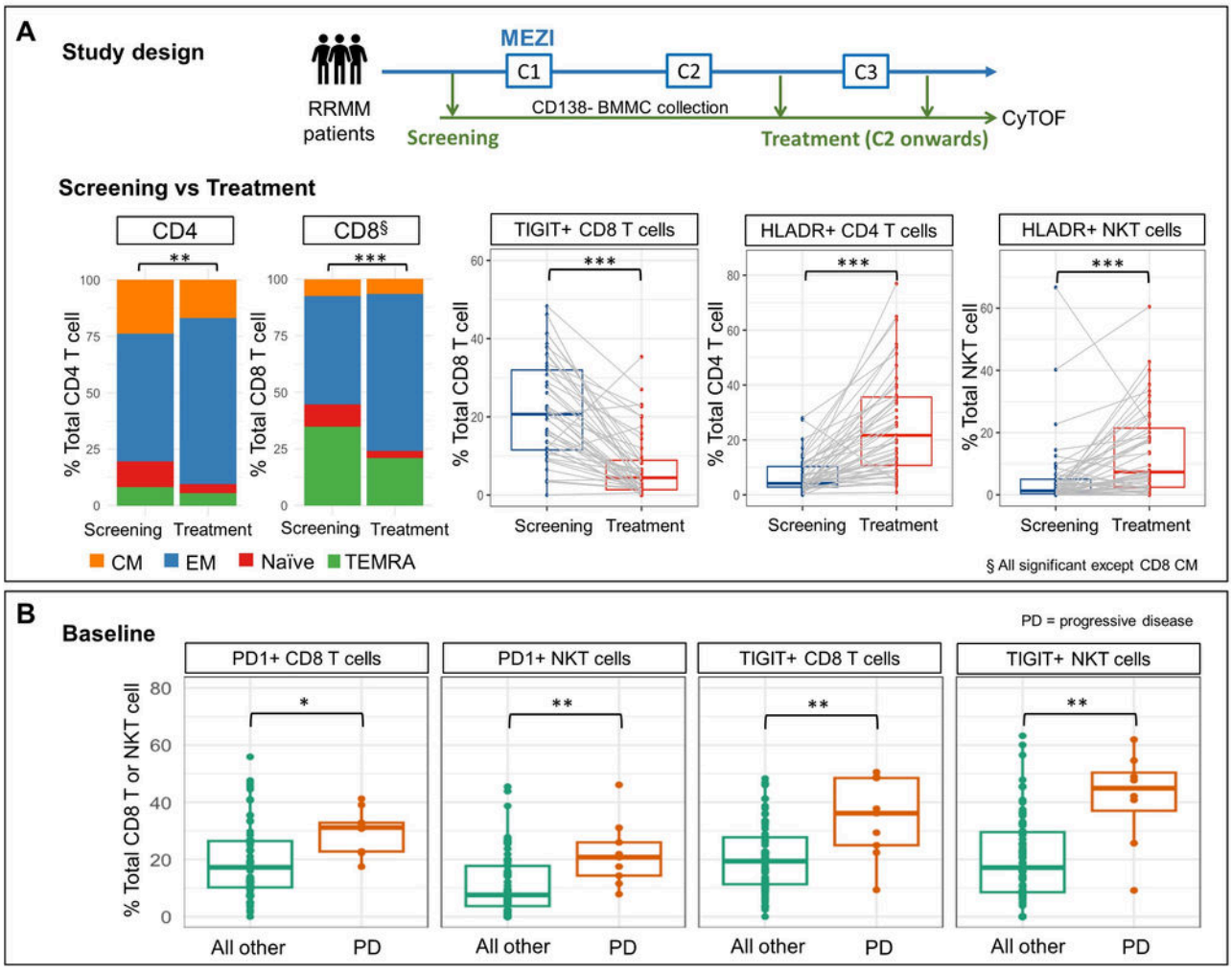

Figure 1

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