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POSTER ABSTRACTS

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

RRMM and Post-BCMA Treated Subjects from the CC-220-MM-001 Study Show Increased Genomic Aberrations Associated with High-Risk and Significant Dysfunction in CD4+ T-Cell Compartment Compared to NDMM Subjects

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Introduction

Outcomes for patients with multiple myeloma (MM) have improved significantly through development of novel therapeutics, including immunomodulatory agents (IMiDs ®), proteasome inhibitors, anti-CD38 monoclonal antibodies and new BMCA targeting T-cell redirecting therapies. While most MM patients respond well to initial therapy, over time their disease relapses, requiring several subsequent lines of treatment. However, how patient tumors and immune profiles evolve over lines of treatment and how this may impact the efficacy of subsequent treatment regimens remains poorly understood. CC-220-MM-001 is a multicohort, phase 1/2 trial (NCT02773030) studying the efficacy of iberdomide (CC-220; a cereblon [CRBN] E3 ligase modulator) as monotherapy, and in combination with other treatments in subjects with newly diagnosed MM (NDMM) or relapsed/refractory MM (RRMM), including patients who have received prior BCMA targeting agents. This study allows uniform comparison of immune and tumor biomarkers across these clinical patient segments.

Methods

Baseline samples collected in the CC-220-MM-001 study prior to iberdomide treatment included peripheral blood for immunophenotyping, bone marrow biopsies for immunohistochemistry and CD138+ enriched bone marrow aspirates for genomic analysis. Biomarkers were evaluated for differences between NDMM subjects and subjects refractory to IMiD agents, proteasome inhibitors, anti-CD38 antibodies, and BCMA targeting CAR-T and T-cell engager therapies.

Results

Analysis of immune profiles showed NDMM subjects had a less immunodeficient profile compared to RRMM subjects, particularly in the CD4+ compartment, with significantly more total and naïve CD4+ T-cells ($p<0.001$) and significantly lower proportion of PD-1+ CD4+ T-cells ($p=0.002$) and CD4+ Tregs ($p=0.005$). RRMM subjects had median levels of several immune cells well below the lower limit of normal (LLN) reference range for healthy individuals, including low B cells, NK-cells, and total CD3+ and CD4+ (but not CD8+) T-cells. Median number of CD4+ T-cells was approximately half of the LLN (500 cells/mL) and median ratio of CD4+ to CD8+ T-cells was ˜0.75. Phenotypic assessment of immune cells in RRMM subjects showed evidence of immune stimulation with >30% T-cells expressing activation markers (HLA-DR+ and ICOS+) and exhibiting a memory phenotype (CD45RO+). In contrast, a low proportion of pre-treatment T-cells were observed to be in a proliferative state (Ki-67+; median 6.2% of CD3+) despite evidence of activation, and more than 1/3 of both CD4+ and CD8+ cells in RRMM subjects expressed PD-1, together suggesting T-cell dysfunction and/or exhaustion. These results were mostly consistent regardless of prior refractoriness to IMiDs and PIs. Conversely, subjects post anti-CD38 had lower levels of NK and CD38+ T-cells ($p<0.001$) and subjects post-BCMA T-cell redirecting therapies ($n=22$) trended to have lower absolute levels of both CD4+ and CD8+ T-cells and increased proportion of T-cells expressing activation markers than other RRMM patient segments. Analysis of the bone marrow compartment showed that while CRBN protein was quantifiably detectable in CD138+ cells in almost all samples, including in subjects coming off IMiD based regimens, 40% of RRMM subjects had evidence of molecular dysregulation of CRBN including, loss of COPS7b/COPS8, high CRBN-del-exon10 expression, CRBN

LOH or CRBN mutation. A wide range of CRBN protein levels was observed, however, differences in protein levels did not correlate with refractory status to any therapy. Notably, median CRBN expression levels were 2× higher in NDMM subjects. Prevalence of translocations, hyperdiploidy, CNAs and other mutations in RRMM subjects showed 31% of subjects had KRAS mutations, 28% had Amp1q, 23% were hyperdiploid, 21% had del17p, 12% had t(11;14), 11% had NRAS mutations and 9% had t(4;14).

Conclusions

These data illustrate that late-line RRMM subjects have appreciable immunosuppression compared to NDMM subjects, with particular dysfunction in the CD4+ helper T-cell compartment, suggesting that the efficacy of immunotherapies in late line myeloma may benefit from combinations with agents that improve CD4+ T-cell function. These data also show enrichment of molecular high-risk segments and CRBN-related genomic aberrations in RRMM subjects in the CC-220-MM-001 study.

Disclosures Amatangelo: *Bristol Myers Squibb:* 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. **Flynt:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company. **Stong:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company. **Ortiz:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company. **Ray:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company; *The University of Texas at Dallas:* Ended employment in the past 24 months; *Doloromics, Inc:* Current equity holder in private company. **Wang:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company. **van de Donk:** *Servier:* Membership on an entity's Board of Directors or advisory committees; *Adaptive:* Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Membership on an entity's Board of Directors or advisory committees; *Pfizer:* Membership on an entity's Board of Directors or advisory committees; *Bayer:* Membership on an entity's Board of Directors or advisory committees; *Roche:* Membership on an entity's Board of Directors or advisory committees; *Takeda:* Membership on an entity's Board of Directors or advisory committees; *Bristol Myers Squibb:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Cellectis:* Research Funding; *Novartis:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Celgene:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Amgen:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Janssen:* Membership on an entity's Board of Directors or advisory committees, Research Funding. **Lonial:** *TG Therapeutics Inc:* Other: Board of Directors with Stock; *Janssen:* Research Funding; *Bristol-Myers Squibb Company, Janssen Biotech Inc, Novartis, Takeda Pharmaceuticals USA Inc.:* Other: Contracted Research, Research Funding; *AbbVie Inc, Amgen Inc, Bristol-Myers Squibb Company, Celgene Corporation, Genentech, a member of the Roche Group, GlaxoSmithKline, Janssen Biotech Inc, Novartis, Pfizer Inc, Takeda Pharmaceuticals USA Inc:* Consultancy, Other: Advisory Committee; *Novartis:* Research Funding. **Raval:** *Arcus Biosciences:* Divested equity in a private or publicly-traded company in the past 24 months, Ended employment in the past 24 months; *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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