P867 TUMOR PROFILING OF IDECATAGENE VICLEUCEL (IDE-CEL; BB2121) PATIENTS IN KARMMA SHOWED COMPARABLE RESPONSES IN EXISTING MOLECULAR HIGH-RISK SUBSETS AND PRELIMINARY GENE SIGNATURE OF DURABLE RESPONSE

**Topic:** 13. Myeloma and other monoclonal gammopathies - Biology & Translational Research

Nathan Martin¹, Amy Xu**, Nicholas Stong**, Julie Rytlewski¹, Olivia Finney², Timothy Campbell¹, William Pierceall¹, Erin Flynt¹, Ethan Thompson¹, Shari Kaiser²

¹ Bristol Myers Squibb, Princeton, NJ, United States; ² seventy bio, Boston, MA, United States

**Background:** Multiple myeloma (MM) tumors exhibit increasing prevalence of high-risk/resistance (HR) features with each successive relapse, leading to poorer outcomes in late-line patients (pts). This may arise primarily as malignancy heterogeneity increases, and with selective pressure from successive treatment regimens. Idecatagene vicleucel (ide-CEL; bb2121) was the first approved anti-BCMA CAR T therapy in late-line relapsed/refractory MM (RRMM), and CAR Ts represent a novel mechanism of action (MOA) in the MM treatment landscape. In the KarMMa study (NCT03361748), high incidences of overall responses (OR) to ide-CEL were observed, including in the pt subgroup with HR cytogenetic features.

**Aims:** Assess baseline multi-omics molecular profiles in KarMMa pt tumors to characterize known and novel molecular features and ide-CEL outcomes. Evaluate post–ide-CEL tumor composition by analyzing paired pt specimens (pretreatment and at relapse).

**Methods:** Bone marrow aspirates were collected from KarMMa pts at pretreatment (n=97 RNA, n=68 DNA) and progression (n=64 RNA, n=33 DNA). RNA sequencing and whole genome sequencing was performed on CD138+ cells. Known molecular HR genomic (biallelic p53 inactivation, high cancer clonal fraction del17p, HR t(4,14), and cereblon mutation) and transcriptomic (MDMS8 gene signature) features were analyzed, and correlations with OR and progression-free survival (PFS) evaluated. BCMA mutation and copy number variation were evaluated. Differential gene expression and principal component analyses explored novel transcriptomic signatures and response.

**Results:** Molecular HR features were identified in 44% (43/97) of pts at pretreatment and 48% (31/64) at progression. Some tumors had multiple HR features consistent with heterogeneity in late-line RRMM. Paired pre/post–CAR T samples did not show dominant enrichment for ≥ 1 HR features at progression. OR and PFS were similar in those with vs. without each molecular HR feature analyzed. One principal component (PC4) was correlated with PFS (p=0.002). The top weighted genes in PC4 may be a novel signature associated with durable ide-CEL responses, and exploratory analyses of this signature are ongoing. Loss of one copy of BCMA was observed in 4% (3/68) and 12% (4/33) of pts at pretreatment and progression, respectively. Biallelic loss of BCMA at progression was observed in 6% (2/33) of pts, one of whom had single copy number loss pretreatment.

**Summary/Conclusion:** Baseline multi-omic-based tumor HR features were not associated with OR. This finding suggests ide-CEL activation and expansion remains a critical axis for OR that may not be substantially influenced by tumor intrinsic features. Biallelic loss of BCMA was not observed pretreatment and infrequently at progression, consistent with previous reports. Baseline HR features did not correlate with PFS, and a dominant selection for any one HR feature at progression was not noted. These observations were consistent with previous reports in non-molecularly defined HR subgroups from KarMMa and the hypothesis that CAR T MOA may have a broader spectrum of clinical activity across more diverse molecular subtypes of pts, especially existing HR subsets; this could be a consideration as CAR Ts are developed in earlier lines of therapy. A transcriptional signature was associated with more durable ide-CEL responses, which we postulate may outline a distinct suboptimal pretreatment feature in an ide-CEL context; further exploration of this preliminary signal is ongoing.
**Authors contributed equally to this abstract.**