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POSTER ABSTRACTS

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

Integrative Analysis of the Tumor and Microenvironment to Model the Molecular Heterogeneity Underlying the Response to Cevostamab in Relapsed/Refractory Multiple Myeloma

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Background: Cevostamab is an FcRH5xCD3 bispecific antibody that facilitates T-cell directed killing of myeloma cells and has shown promising activity and a favorable safety profile as monotherapy in patients with relapsed/refractory multiple myeloma (RRMM) in the ongoing Phase I GO39775 trial (NCT03275103; Trudel et al. ASH 2021). We performed an integrative analysis of peripheral blood (PB) and bone marrow aspirate (BMA) samples collected at baseline from patients in GO39775 to understand the heterogeneity of patients with RRMM and potential correlations with clinical outcome.
Methods: PB and BMA samples were collected at baseline from 100 patients in GO39775. Patients who had less than 25% missingness in any data layer were selected from the single-step (3.6/90-252mg dose levels [n=49] and 3.6/90mg tocilizumab premedication group [n=14; Trudel et al. ASH 2022]) and double-step (0.3-1.2/3.6-7.2/60-160mg dose levels [n=37]) dose-escalation and dose-expansion cohorts. To characterize immune cells, samples were profiled at a central laboratory by 8-color flow cytometry. Cytokine profiling was performed on baseline plasma samples via electrochemiluminescence and digital ELISA. Serum B-cell maturation antigen (sBCMA) levels were quantified using hybrid immunoaffinity capture by liquid chromatography with tandem mass spectrometry. For the unbiased integrative analysis, a Similarity Network Fusion algorithm was applied to preprocessed flow cytometry data from PB and BMA samples, and to baseline characteristics including demographics, prior therapies, and selected clinical laboratory analytes. Data were imputed in samples with less than 25% missingness using a random forest algorithm.
Results: Initial findings from unsupervised machine learning-based integrative clustering analysis of baseline samples from multiple immunological and clinical data types revealed three patient subpopulations with unique biological features, illustrating the molecular heterogeneity of patients with RRMM. Each cluster was characterized by distinct patterns of immune cell proportions and activation states. Interestingly, these immunologically defined clusters also corresponded to clinical outcomes. Cluster 1 had the strongest response to cevostamab, followed by Cluster 2 and Cluster 3.
Conclusions: Our novel, unbiased, machine learning, integrative clustering approach not only revealed unique molecular subtypes that illustrate the heterogeneity of patients with RRMM, but also identified immunological features associated with potentially reduced response to cevostamab therapy, which could provide direction for future research.

Disclosures Hamidi: *Genentech:* Current Employment, Current equity holder in publicly-traded company. **Nakamura:** *F. Hoffmann La Roche Ltd:* Current equity holder in publicly-traded company; *Genentech, Inc.:* Current Employment. **Roy:** *Amgen Inc:* Current equity holder in publicly-traded company, Ended employment in the past 24 months; *Genentech, Inc.:* Current Employment, Current equity holder in publicly-traded company. **Rajasekaran:** *Genentech, Inc.:* Current Employment; *Genentech, Inc., F. Hoffmann La Roche Ltd:* Current holder of *stock options* in a privately-held company. **Diaz:** *Genentech, Inc., F. Hoffmann-La Roche Ltd:* Current Employment, Current equity holder in publicly-traded company. **Dos Santos:** *Genentech:* Current Employment, Current equity holder in publicly-traded company. **Sumiyoshi:** *Genentech, Inc.:* Current Employment; *F. Hoffmann La Roche Ltd:* Current equity holder in publicly-traded company.

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