ELSEVIER

Blood 142 (2023) 1927–1928

The 65th ASH Annual Meeting Abstracts

# POSTER ABSTRACTS

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

### Immune Dynamics Associated with Patient Outcomes Identified By Multimodal Single-Cell Analysis in Multiple Myeloma Patients Receiving Talquetamab Monotherapy

*Tarek H. Mouhieddine, MD[1], Junia Vieira dos Santos, MD PhD[2], Yogita Ghodke-Puranik, PhD[2], Adolfo Aleman, MPA[3], David Melnekoff, MS[2], Bhaskar Upadhyaya, PhD[1], Adeeb Rahman, PhD[4], Shaked Afik, PhD[4], Hadas Lewinsky, PhD[4], Santiago Thibaud, MD[1], Adriana C Rossi, MD MSc[1], Shambavi Richard, MD[1], Cesar Rodriguez, MD[1], Joshua Richter, MD[3], Hearn Jay Cho, MD[5], Larysa Sanchez, MD[3], Sundar Jagannath, MD[6], Ajai Chari, MD[7,8], Alessandro Lagana, PhD[1], Samir Parekh, MD[1]*

[1] Department of Medicine, Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York
[2] Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY
[3] Department of Medicine, Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY
[4] ImmunAI, New York, NY
[5] Department of Medicine, Hematology and Medical Oncology, Tisch Cancer Institute, Tisch Cancer Institute, New York, NY
[6] Mount Sinai Medical Center, New York, NY
[7] Icahn School of Medicine at Mount Sinai, New York, NY
[8] at the time that the work was performed, Mount Sinai School of Medicine, New York, NY

**Background:** Talquetamab (Tal) is a CD3xGPRC5D bispecific antibody (BiAb) that redirects endogenous T cells to mediate killing of GPRC5D-expressing multiple myeloma (MM) cells. In the recent phase I/II MonumenTAL-1 trial (NCT03399799), Tal showed ≥ 70% response rate when given at the recommended phase 2 doses (RP2D) in heavily pretreated MM patients (Chari A et al., NEJM 2022). However, there is still a need to identify predictive biomarkers and better understand the immune dynamics associated with treatment response and durability with this novel agent.

**Methods:**We identified 30 patients who received Tal monotherapy and had bone marrow (BM) and peripheral blood (PB) samples collected at baseline and PB collected at cycle 3 day 1 (C3D1). Cellular indexing of transcriptomes and epitopes (CITE)-seq was performed to understand transcriptional changes and cell surface proteomics. Total cells were isolated by Ficoll separation from PB and BM samples and were then analyzed separately and only samples of good quality were included in the analysis. Samples were filtered for good quality based on total cell count: at least 1000 cells with more than 500 unique molecular identifiers (UMIs) or genes and less than 4-5 standard deviations above median for UMI, genes and mitochondrial transcripts. A total of 60,851 BM cells (15 pts at baseline) and 299,996 PB cells (23 pts at baseline and 17 pts on C3D1) were analyzed. Downstream analysis was performed using the Seurat R package. All patients included in this study had signed consent for an IRB-approved institutional sub-study (GCO # 18-00456).

**Results:** The 30 patients had a median age of 66.2 years and 57% were female. They received a median of 6 prior lines of therapy, with 83% being triple-class refractory and 50% penta-drug refractory. Only 2 patients were previously treated with anti-BCMA CAR-T cell therapy and none were treated with other BiAbs. 43% of patients had high-risk cytogenetics (including t(4;14), t(14;16) and 17p deletion) and 13% had extramedullary disease at time of initiating therapy. Ten patients (30%) received the recommended phase 2 dose (RP2D) of Tal (0.4 mg/kg weekly or 0.8 mg/kg every other week). Patients were followed for a median of 32.5 months and had a median progression-free survival (PFS) of 6.7 months. 22/30 patients (73%) achieved a partial response (PR) or better, and 14 patients had a short PFS of <150 days.

There was no association between the prevalence of different immune cell subsets and depth of response, but rather with PFS. In the baseline BM, a longer PFS was associated with a higher percentage of CD8+ cytotoxic T cells (central memory p=0.00031, effector memory p=0.0022, EMRA p=0.014) and a trend towards higher CD4+ cytotoxic T cells (p=0.072). Of note, we did not find the same associations in the baseline PB samples, which may indicate that the PB may not always reflect the tumor microenvironment in the BM.

When we next looked at immune changes in the PB of patients with longer PFS, we found that they exhibited higher percentage of NK cells (p=0.0018 for CD56 $^{low}$, p=0.04 for CD56 $^{high}$) and Gamma Delta T cells (p=0.04) at C3D1. Gamma Delta T cells are novel players that warrant further investigation, as they only constitute 1-5% of the T cell repertoire yet are involved in early immune response and do not require major histocompatibility complex (MHC) antigen presentation to function. Profiling of activation and exhaustion markers of these immune subsets is underway.

**Conclusion:** Our findings highlight that the baseline BM immune repertoire and the PB immune changes during Tal treatment may predict long term outcomes. Further *in vitro* mechanistic studies of T cell function and fitness and validation of these results in independent cohorts will be critical to develop these into predictive biomarkers of long-term response to Tal.

**Disclosures Mouhieddine:** *Legend Biotech:* Consultancy. **Rahman:** *ImmunAI:* Current Employment. **Afik:** *ImmunAI:* Current Employment. **Lewinsky:** *ImmunAI:* Current Employment. **Rossi:** *BMS:* Membership on an entity's Board of Directors or advisory committees; *JNJ:* Membership on an entity's Board of Directors or advisory committees; *Sanofi:* Membership on an entity's Board of Directors or advisory committees; *Adaptive:* Membership on an entity's Board of Directors or advisory committees. **Richard:** *Heidelberg Pharma:* Research Funding; *C4 Therapeutics:* Research Funding; *Bristol Myers Squibb:* Honoraria; *Janssen:* Honoraria. **Rodriguez:** *Janssen, Takeda, Bristol Myers Squibb, Amgen, Karyopharm Therapeutics:* Membership on an entity's Board of Directors or advisory committees. **Richter:** *Karyopharm:* Membership on an entity's Board of Directors or advisory committees; *Pfizer:* Consultancy; *Astra Zeneca:* Membership on an entity's Board of Directors or advisory committees; *Takeda:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Genentech:* Consultancy; *Sanofi:* Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Consultancy; *Adaptive Biotechnologies:* Membership on an entity's Board of Directors or advisory committees; *Bristol-Meyers-Squibb:* Membership on an entity's Board of Directors or advisory committees; *Celgene:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Janssen:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau. **Cho:** *Takeda, Inc.:* Research Funding; *Bristol Myers-Squibb:* Research Funding. **Sanchez:** *Janssen Pharmaceuticals:* Consultancy, Honoraria. **Jagannath:** *Caribou:* Consultancy; *Karyopharm:* Consultancy; *Regeneron:* Consultancy; *Sanofi:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Legend Biotech:* Consultancy; *Janssen:* Consultancy; *Bristol Myers Squibb:* Consultancy. **Chari:** *Glaxo Smith Kline:* Other: Advisory Board; *AbbVie:* Other: Advisory Board; *Millenium/Takeda:* Consultancy, Research Funding; *Seattle Genetics:* Other: Advisory Board, Research Funding; *Amgen:* Consultancy, Other: Advisory Board, Research Funding; *BMS:* Consultancy, Other: Advisory Board, Research Funding; *Janssen:* Consultancy, Other: Advisory Board, Research Funding; *Sanofi:* Other: Advisory Board; *Antengene:* Consultancy; *Shattuck Labs:* Other: Advisory Board; *Genentech:* Other: Advisory Board; *Karyopharm:* Other: Advisory Board; *Secura Bio:* Consultancy, Other: Advisory Board. **Parekh:** *Amgen:* Research Funding; *Celgene/BMS Corporation:* Research Funding; *Grail, LLC:* Membership on an entity's Board of Directors or advisory committees; *Caribou Biosciences:* Research Funding; *Karyopharm Therapeutics:* Research Funding.

https://doi.org/10.1182/blood-2023-185308