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ORAL ABSTRACTS

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

Evaluating Tumor-Intrinsic and Patient-Specific Mechanisms of Resistance to Teclistamab in Anti-BCMA Exposed and Naïve Multiple Myeloma

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Background: Teclistamab (Tec) is a CD3 x BCMA bispecific antibody granted accelerated FDA approval for treating relapsed/refractory (RR) multiple myeloma (MM) based off the results of the MajesTEC-1 trial (Usmani S, et al. *Lancet* 2021, Moreau P, et al. *N Engl J Med* 2022). However, patients with prior exposure to anti-BCMA therapies were excluded from this trial and there is no published data evaluating Tec efficacy in this setting. Additionally, little is known about tumor-intrinsic and patient-specific immunologic predictors of response to Tec.
Methods: We performed an IRB-approved analysis of clinical outcomes for 52 commercially treated Tec patients treated as of 07/28/2023 at our center. Results were correlated to pre-treatment BCMA expression measured by immunohistochemistry (IHC). We also profiled peripheral blood T-cells from pre-treatment peripheral blood mononuclear cell (PBMC) samples from a sub cohort of patients via high-dimensional spectral cytometry using a 37-color panel including lineage, exhaustion, and activation markers.
Results: Our commercial cohort was older (median age 70 vs 64), more heavily pretreated (median prior lines of therapy 7 vs 5) and had higher incidence of both high-risk cytogenetic abnormalities (33% vs 26%) and extramedullary disease (35% vs 17%) than the MajesTEC-1 population. Additionally, 52% had prior exposure to anti-BCMA therapies, including belantamab mafodotin (31%), anti-BCMA CAR T-cell therapies (37%), and anti-BCMA bispecific antibody therapies (4%), with some having exposure to multiple prior anti-BCMA therapies (17%). Among response evaluable patients (90%), with a median follow-up time of 100 days, the overall response rate (ORR) to Tec was 64% (36% ≥VGPR). Progression free survival (PFS) in patients without prior BCMA therapy was higher than in the anti-BCMA exposed population (median PFS NR vs 102 days, $p = 0.032$, **Figure Panel A**). However, the anti-BCMA therapy exposed population was more heavily pretreated (8 vs 5 median prior lines of therapy) and had more patients with high-risk cytogenetic abnormalities (46% vs 19%) and extramedullary disease (42% vs 27%) than the anti-BCMA therapy naïve cohort. No major differences in BCMA expression were noted between responding and non-responding patients or between anti-BCMA exposed and anti-BCMA naïve patients. However, two patients had absent BCMA expression following prior treatment with other BCMA targeting agents and did not respond to Tec. Cytokine release syndrome (CRS) during step-up dosing was strongly associated with Tec efficacy (median PFS NR vs 27 days, $p < 0.0001$), with a

100% ORR for patients with CRS. Immune profiling experiments **(Figure Panel B)** revealed that Tec responders had peripheral blood enriched for both CD8 $^+$ effector memory T-cells (TEM, >6-fold increase, $p = 0.0499$) and CD8 $^+$ effector memory T-cells re-expressing CD45RA (TEMRA, >5-fold increase, $p = 0.012$) when compared to Tec non-responders. Tec non-responders had peripheral blood enriched for TIGIT $^+$ regulatory T-cells (Tregs, 3-fold increase, $p = 0.03$) when compared to Tec responders. No differences in PD-1, CTLA-4, LAG-3 or TIM-3 expression were observed in Tec responders vs non-responders. Patients with recent relapse from non-BCMA targeting bispecific antibodies (including products targeting FcRH5 or GPRC5D) had peripheral blood enriched for $\gamma\delta$ T-cells with high TIGIT expression.

Conclusion: Tec is an effective therapy in RRMM with a slightly lower efficacy observed in patients with prior anti-BCMA therapy exposure. PFS reductions among these anti-BCMA exposed patients may be partly due to independent disease associated risk factors. A pre-Tec peripheral blood T-cell population enriched with highly cytotoxic effector T-cells was associated with response to therapy, while suppressive TIGIT $^+$Tregs were associated with nonresponse, suggesting a potential therapeutic role for TIGIT blockade or CD25 $^+$ cell depletion to enhance the therapeutic efficacy of bispecific antibodies. Clinical and translational data from additional patients will be presented at the meeting.

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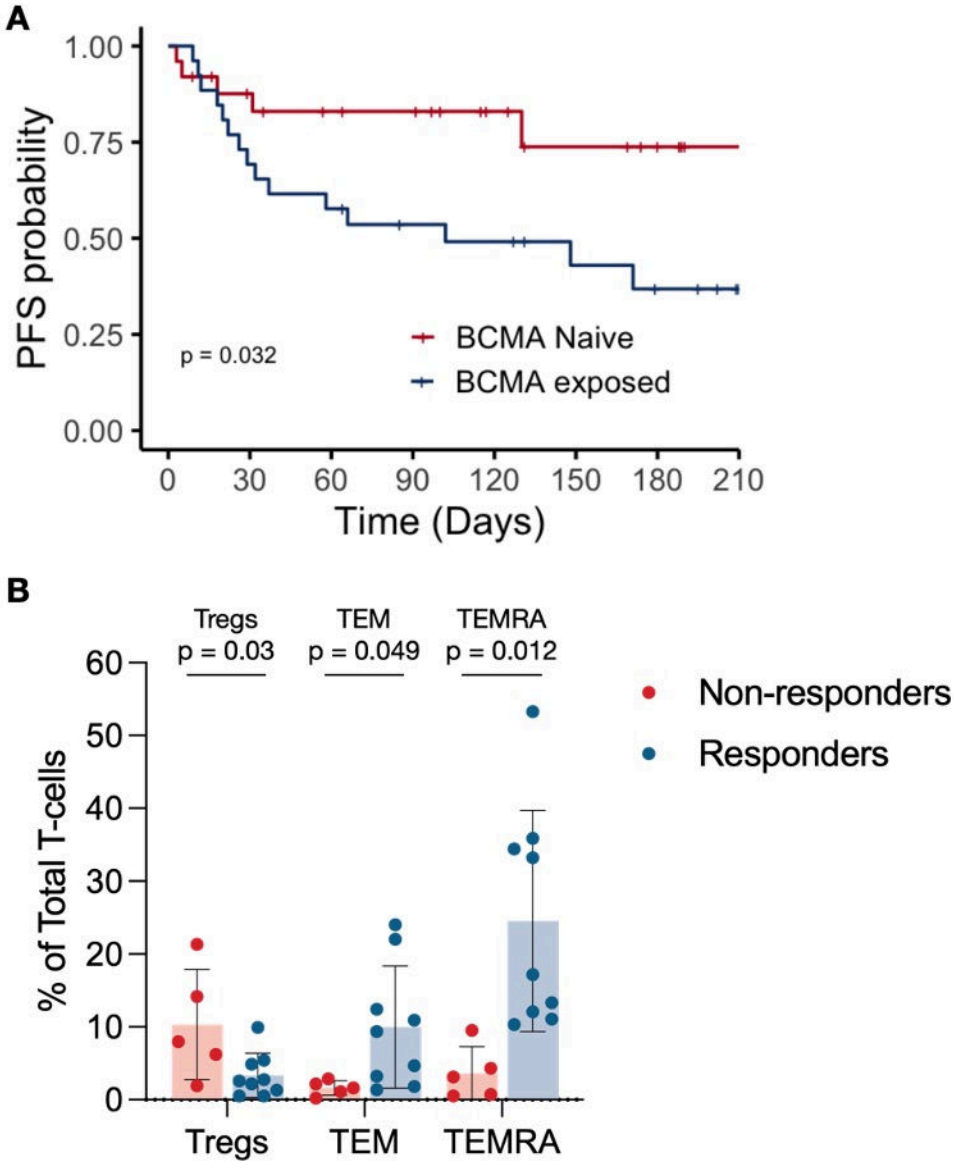

Figure 1: (A) PFS for patients with prior anti-BCMA therapy exposure (blue) is slightly reduced compared to PFS for anti-BCMA therapy naive (red) patients (p = 0.032). **(B)** Pre-treatment peripheral blood immune profiling via high-dimensional spectral cytometry showed elevated regulatory T-cells in Tec non-responders, and elevated CD8+ TEM and TEMRA cells in Tec responders.

Figure 1

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