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Learning from relapse: how MajesTEC-1 immune profiling points the way to next-generation bispecific strategies

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Vishwamitra and colleagues describe immune determinants to anti-BCMA bispecific antibody Teclistamab from a longitudinal analysis from the MajesTEC-1 trial, using a multi-platform interrogation including flow cytometry, CyTOF and soluble BCMA quantitation of longitudinal samples collected at baseline, on treatment, and critically, at relapse. Prior work from this group established that baseline immune fitness and regulatory T cell burden were important determinants of response [1].

They further expand on this theme by demonstrating that responding patients exhibit greater and more rapid T cell margination early (within 24 hours of the first step-up dose), followed by more robust peripheral T cell recovery and earlier T cell activation on CD8+ T cells by Cycle 1 Day 1, while non-responders show attenuated margination, failure of T cell count recovery, and delayed T cell activation. Non-responders additionally had a T cell phenotype of elevated coinhibitory checkpoint marker expression on both CD4+ and CD8+ T cells through Cycle 3, accompanied by higher and sustained proportions of immunosuppressive CD38+ regulatory T cells. Additionally, bone marrow regulatory T cells at relapse show upregulation of PD-1 and TIGIT, potentially enhancing their immunosuppressive capacity within the tumor microenvironment. At relapse, CyTOF analyses of paired baseline and progression samples reveal a shift in the peripheral and bone marrow T cell compartment toward markers associated with exhaustion, impairment, and senescence. Complementing the immune data, BCMA receptor density on bone marrow plasma cells is significantly reduced at relapse relative to baseline, without a corresponding change in the proportion of BCMA-positive cells.

The findings from this manuscript have direct clinical and translational implications. First, the CD38+ Treg signal that is elevated at baseline in non-responders, sustained on treatment, enriched at relapse makes a strong mechanistic argument for teclistamab-daratumumab combinations. Daratumumab depletes CD38-expressing immune regulatory cells while also targeting myeloma directly. Results from the TRIMM-02 and MajesTEC-9 trials confirm positive outcomes from the addition of anti-CD38 antibody to Teclistamab [2, 3].

Second, the immune checkpoint expression make a case for revisiting rational combination of bispecifics with immune checkpoint inhibitors. Whether adding these agents to a bispecific backbone can reinvigorate dysfunctional T cells or the combination may suggest use of T cell reinvigorating agents such as CeLMODs may have a space for combination to enhance outcomes from bispecific antibody therapy.

Third, these data support earlier deployment of teclistamab, utilizing greater immune fitness by treating patients earlier in their disease course. The findings from BCMA receptor density analysis add an important complementary dimension. Soluble BCMA falls at relapse indicating reduced overall tumor burden from initial response which is matched by the reduction of membrane-bound BCMA receptor density on bone marrow plasma. The proportion of BCMA-positive cells does not change appreciably, suggesting this is not straightforward antigen loss in the classical sense, but rather downregulation of surface density on persisting cells potentially causing a partial antigen escape. The question remains whether this reflects transcriptional reprogramming, selective pressure eliminating BCMA-high clones, or emerging mutational escape which will require larger genomic datasets to fully dissect. These findings also impact the clinical decision around sequential use of anti-BCMA therapeutics.

There are a few considerations to keep in mind in the interpretation of this data- (a) functional studies are required to definitively validate the T cell dysfunction hypothesis. Implementation of

proliferation assays, cytokine secretion, tumor cell killing in patient samples at the relevant time points would strengthen this argument. (b) Longitudinal tumor burden assessment integrated with immune profiling would clarify immune-intrinsic from tumor-burden-driven dynamics would. (c) Larger datasets validating the changes in antigen expression along with genomic characterization of the BCMA locus are needed to understand the relative contributions of both towards tumor drivers of clinical relapse. Finally, prospective biomarker-stratified trials to test whether the immune features identified here can predict and ultimately be used to improve clinical outcomes.

Vishwamitra and colleagues have commendably generated a large translational immune dataset with clinically impactful findings for myeloma beyond teclistamab and other bispecific antibodies. Their results help productively shape the next generation of translational questions in BCMA-directed myeloma therapy.

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