Immune correlates of resistance to BCMAxCD3 bispecific antibodies in multiple myeloma

Translational

Hematology

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ABSTRACT

Introduction

Bispecific antibodies (BsAbs) that redirect T cells toward malignant plasma cells—particularly BCMA×CD3 agents—have transformed the treatment of relapsed/refractory multiple myeloma (RRMM). The FDA-approved BsAbs teclistamab and elranatamab induce high response rates even in heavily pretreated patients. Nonetheless, many individuals experience incomplete or short-lived responses, and mechanisms of primary or acquired resistance remain insufficiently understood. Early evidence suggests that pre-existing T-cell composition and functionality may shape BsAb activity, yet the prognostic contribution of other immune cell types and the nature of T-cell remodeling during therapy remain unclear. To address these gaps, we performed an in-depth longitudinal profiling of the bone marrow (BM) and peripheral blood (PB) immune landscapes in patients treated with teclistamab or elranatamab.

Methods

We studied samples from the ResisTec trial (NCT05945524), a multicenter real-world IFM cohort of 100 RRMM patients receiving teclistamab or elranatamab. BM aspirates were collected at baseline and month 3; PB was collected monthly. Single-cell RNA sequencing (scRNA-seq) of CD45$^+$ cells was integrated using standardized workflows to evaluate transcriptional states, immune composition, and T-cell clonal dynamics. A 40-marker spectral flow cytometry panel validated and extended key observations.

Results

Baseline BM CD4$^+$ and CD8$^+$ T-cell frequencies lacked predictive value, whereas the PB immune landscape was more informative: higher circulating CD4$^+$ and CD8$^+$ T-cell levels correlated with better clinical responses. Early on-treatment remodeling was even more discriminative. During the first two cycles, responders showed a strong expansion of cytotoxic CD8$^+$ T cells and a marked reduction in regulatory T cells (Tregs), yielding a pronounced increase in the CD8/Treg ratio. Non-responders exhibited neither CD8$^+$ cytotoxic expansion nor sufficient Treg contraction.

Transcriptional profiling did not reveal significant T-cell exhaustion. Expression of exhaustion-associated genes (PDCD1, TOX, LAG3, CTLA4, HAVCR2) remained low across time points in both groups, arguing against exhaustion as a main resistance mechanism.

Clonal analyses highlighted key mechanistic features. Responders demonstrated robust PB clonal expansion during treatment, whereas non-responders showed minimal or absent expansion. Notably, many expanding clones in responders were undetectable in PB at baseline but were present in the BM. These BM-resident clones displayed an interferon-responsive signature before therapy, then proliferated under teclistamab pressure, acquired cytotoxic effector profiles (GZMB, PRF1), and recirculated into PB. In contrast, terminally differentiated cytotoxic clones pre-existing in PB tended to contract regardless of clinical outcome.

Conclusions

Teclistamab activity is associated with a favorable baseline lymphoid milieu, early PB immune remodeling characterized by CD8$^+$ cytotoxic expansion and Treg depletion, and the mobilization of BM-resident interferon-responsive T-cell clones that gain cytotoxicity during treatment. These findings identify dynamic clonal recruitment—rather than static phenotypes or exhaustion—as a major driver of response, and point toward new biomarkers and combination strategies aimed at overcoming BsAb resistance.

SCIENTIFIC IMPACT

This study provides the first comprehensive longitudinal profiling of immune remodeling in RRMM patients treated with BCMA×CD3 bispecific antibodies. By integrating scRNA-seq, spectral cytometry, and clonal analyses, we uncover that treatment efficacy depends not on baseline T-cell phenotypes or exhaustion, but on early immune reprogramming and the mobilization of BM-resident interferon-responsive T-cell clones that acquire cytotoxicity under therapy. These findings redefine the mechanisms of action of T-cell–engaging BsAbs and identify dynamic clonal recruitment as a key determinant of response. Our work establishes new biomarkers for predicting treatment outcome and highlights rational combination strategies—such as Treg modulation or approaches that enhance BM-resident T-cell priming—to overcome resistance and improve patient survival.

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