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Monoclonal Gammopathies & Multiple Myeloma

TUMOR BURDEN AND IMMUNE MICROENVIRONMENT INFLUENCE RESPONSE TO ANTI-BCMA BISPECIFIC ANTIBODIES IN RELAPSED/REFRACTORY MULTIPLE MYELOMA

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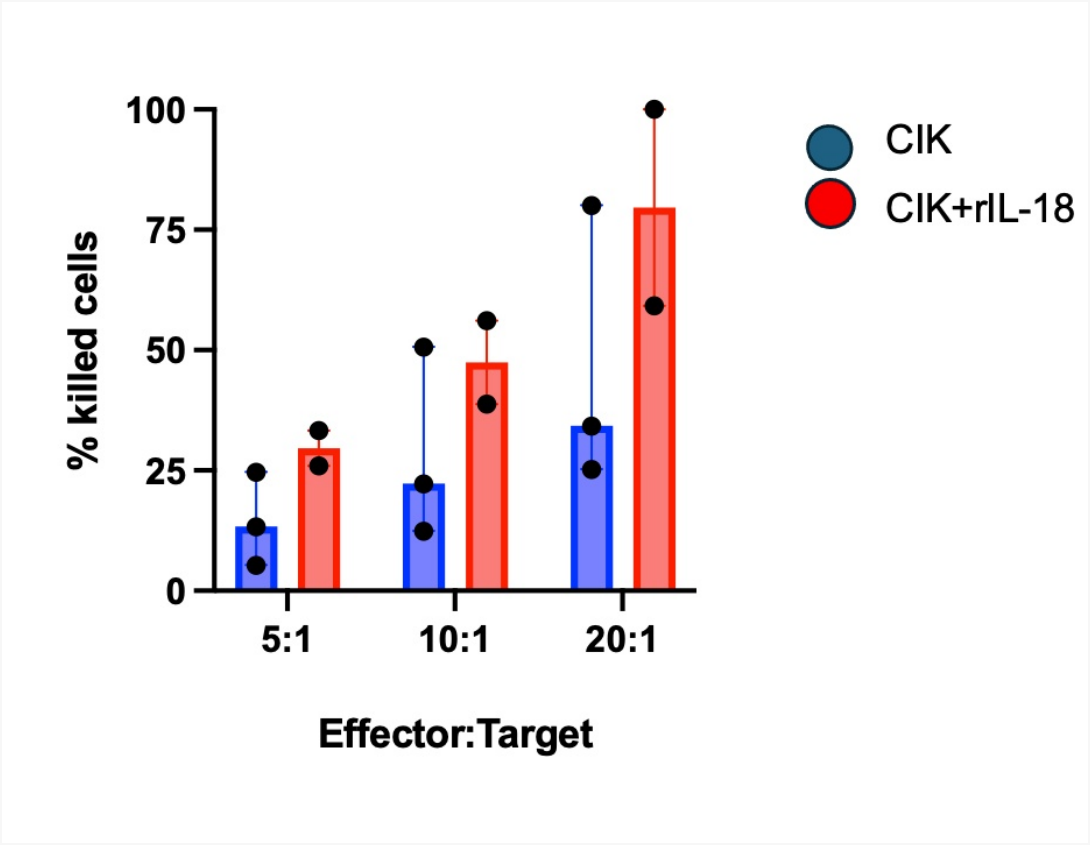
Patients with triple-class refractory relapsed/refractory multiple myeloma (RRMM) face extremely poor outcomes, with median overall survival rarely exceeding 4–8 months despite intensive therapy. Against this dismal background, the advent of bispecific antibodies (BsAbs) has dramatically improved prognosis, producing deep and durable responses even in heavily pretreated individuals. Nevertheless, approximately 30–40% of patients exhibit primary resistance, underscoring the urgent need to identify predictive biomarkers of response to guide treatment selection and minimize unnecessary toxicity and cost.

We conducted a retrospective study approved by the Ethics Committee of the University Hospital of Palermo to explore immunological and transcriptional determinants of response to new anti-MM BsAbs. In a cohort of 18 triple class exposed/refractory MM patients (7 treated with Teclistamab, 7 with Elranatamab, and 4 with Talquetamab), we integrated clinical, laboratory, and, where available single-cell RNA-seq/CITE-seq (SC) data to identify features associated with treatment resistance.

Comparative analysis of 20 hematochemical parameters and 5 derived indices revealed that non responder patients presented an increased ISS stage (p=0.001), disease burden in term of monoclonal component (p=0.039), and a reduced Hemoglobin level (p:0.03). Interestingly, responders patients experienced a strong lymphocytes reduction between pre and post step-up dose (p<0.001). The latter in particular was associated with a significantly longest PFS (p=0.001, no events experienced after 18 months follow-up). To deeply understand changes in BM microenvironment, we performed a single-cell analysis of BMMCs from a subset of 10 patients at baseline, uncovering distinct immunological configurations between responders and non-responders. We analyzed a total of 39195 single cells were we found little to no deifferences in term of population abundances except with B cells (strongly reduced in non responders p<0.01). In term of transcriptome profile, we observed that responders displayed a more enhanced intrinsic anti-tumor immunity. In contrast, non-responders exhibited enrichment of exhausted T cells expressing HAVCR2 (TIM-3) and genes linked to oxidative stress and immune dysfunction, coupled with tolerogenic monocytes and upregulation of immunosuppressive pathways, including TLR signaling and myeloid chemotaxis.

Functional pathway analysis confirmed a pronounced divergence between the two groups: responders engaged adaptive and effector immune programs, whereas non-responders displayed immunologically suppressed profiles.

In conclusion, integrating clinical and single-cell data reveals that BsAb efficacy in RRMM is critically shaped by both tumor burden and baseline immune competence. These insights support the implementation of pre-treatment strategies aimed at lowering tumor burden and enhancing the effector-to-target ratio, thereby optimizing responses to bispecific antibody therapies.


100
75
50
25
0
% killed cells
5:1
10:1
20:1
Effector:Target
CIK
CIK+rIL-18