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Clonal CD8⁺ T-cell expansion is associated with complete response to elranatamab in refractory multiple myeloma

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Article Summary :

Bispecific T cell engagers lead to T cell depletion and frequent subsequent infections.

We report the case of a patient with clonal CD8 T cell proliferation associated with response to treatment in refractory multiple myeloma.

Author's contributions: Conceptualization: RK, SB, and XM; data curation and formal analysis: RK, SB, SHBA and XM; writing-original draft: RK and XM; writing-review & editing: all authors.

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Data availability: Data will be made available upon request to the corresponding author.

Bispecific T cell engagers (TCEs) recognizing CD3 and BCMA represent new powerful therapeutic options recently approved by FDA and EMA agencies in refractory multiple myeloma (MM) patients. Although TCEs in MM achieve high clinical response rates, the precise immunological mechanisms that underlie long-term clinical response, primary resistance, and secondary failure as well as the overall impact of TCEs on T cell compartment remain poorly understood.

In a recent article, Friedrich et al¹ analysed the link between inter-individual differences in the immune repertoire and clinical response to BCMAxCD3 TCEs in relapsed/refractory MM (RRMM) patients. By applying scRNA-Seq transcriptome analysis of immune cells and scRNA/VDJ-Seq TCR tracing coupled to clonotype mapping of bone marrow (BM) and peripheral T cell populations, the authors concluded that in RRMM patients treated by TCEs : (i) the TCEs-induced clinical response is driven by *CX3CR1*-expressing CD8+ T cell effectors ; (ii) in clinical responders, BM and peripheral blood T cell repertoire respond with overlapped clonal expansion of CD8+ (but not CD4+) effector T cells with persistent expansion of specific TCR family(ies)/clone(s) and contraction of others; (iii) the abundance of the CD8+ T cells bearing exhausted-type transcriptional signature *PDCD1/LAG3/TOX* predicts response failure. We report the clinical and immunological analysis of a patient that represents a striking exaggeration of the observations made by Friedrich et al.

The patient was a 74-year-old man with Lambda light chain relapsing refractory MM diagnosed 11 years prior and previously treated with nine lines including two autologous hematopoietic stem-cell transplantations. He was penta-refractory. The patient provided informed consent for this report. Treatment with sc Elranatamab (another BCMAxCD3 TCE), 76 mg weekly was started due to relapse with initiation of dialysis because of MM-related

end stage renal insufficiency. As previously described for TCE^{2,3}, the patient initially presented with severe lymphopenia starting days after the first exposure (Figure 1A). A month post treatment, the patient started to show increase in total lymphocyte counts that reached between 4,000 and 9,500/mm³ two months after the start of the TCE (Figure 1A). The serum free lambda light chains (sFLC) were measured at 12,700 mg/L at relapse and the patient was in complete response at two months of treatment with sFLC at 12 mg/L. This response remains unchanged eight months later at the last follow up. Elranatamab was decreased to one injection every other week. The patient presented with two episodes of severe *Campylobacter jejuni* infection that occurred after the rise of the lymphocytosis (Figure 1 A). Moreover, the lymphocytosis persisted after successful treatment of this infection. Thus, we do not think that infections may have played a role in the lymphocyte expansion.

Phenotyping of the T cell populations was made at 4 months post starting the TCE and showed important CD8+ T cells lymphocytosis (87% of CD3+ T cells, 5,910/mm³), normal peripheral CD4+ T cell count (12% of CD3+ T cells, 823/mm³) and undetectable circulating CD19+ B cell pool despite no administration of B cell depleting agents. Flow cytometric assessment of T cell receptor (TCR)-V β repertoire of peripheral CD8+ T cell compartment revealed a bi-clonal CD8 lymphocytosis with major expansions within TCRV β 22 and TCRV β 3 families (35.4% and 35.6% of the total circulating CD8+ T cell repertoire, respectively) and a consequently underrepresentation of several families within the remaining TCRV β repertoire (Figure 1B). Immunophenotypic analysis showed circulating CD8+ T cell pool almost entirely composed of cells with CD45RO+CD27+CCR7- effector memory (TEM) and CD45RA+CD27-CCR7- terminally differentiated (TEMRA) phenotype (55% and 45% of CD8+ T cells, respectively) highly expressing activation markers HLA-DR and CD38. A small fraction of bi-

clonal (TCRV β 22/TRBV2+ and TCRV β 3/TRBV28+) CD3^{high}CD8^{high} T cells with blastic/cycling phenotype was also present. Interestingly, pools of CD8+ T cells expressing either exhaustion marker PD-1 or senescence marker CD57 were not increased (27 and 24% positive cells, respectively) in striking contrast to the not-expanded CD4+ T cell population dominated by hyperactivated CD45RO+CD27+CCR7-CD7^{low}/- TEM effectors expressing PD-1 (83%), CD57 (41%) and HLA-DR (91% positive cells). CD4+ T cell pool was more polyclonal but presented two clear expansions (TCRV β 8/TRBV12-3/TCRBV12-4+ and TCRV β 13.1/TRBV6-5/TRBV6-6/TRBV6-9+) (Figure 1C).

The bi-clonal CD8+ T cell expansion, CD8+ and CD4+ T cell phenotypic changes reflecting cell activation as well as CD8+ T cell repertoire alterations persisted at 8-month follow-up albeit at lesser degree (total lymphocytosis at 5,482/mm³ and CD8+ T cells lymphocytosis at 4,640/mm³) likely in response to diminished dosing of Elranatamab every two weeks. The absence of pretreatment phenotyping of T-cell populations is a limitation of this study since we cannot rule out that these T cell clones were present before treatment.

Of note, despite the large clonal burden of activated T cells effectors in the peripheral blood and the high tumour burden, the patient did not present any immunological severe adverse events (irAEs) such as cytokine release syndrome (CRS), neurotoxicity or cytopenias.

The putative antigenic specificity of expanded clones as well as bone marrow tracking of the expanded clones have not been addressed in this case. However, considering the spectacular clinical response (complete remission within 2 months) in this patient with an explosive refractory disease, we hypothesize that the CD8+ T cell clonal expansion was driven by primed or recall-type response to MM cells-associated tumor antigen(s). Although transient

proliferation (Ki67+ cells) of T cells in peripheral blood has been described in safety profile description of Elranatamab⁴⁵, no case of CD8+ T cell clonal lymphoproliferation in response to Elranatamab has been reported yet. Expansion of few immunodominant CD8+ T cell clones private to the treated cancer have been described following immunotherapy^{6,7}. Collectively, study by Friedrich et al and our report emphasize the role of TCRV β repertoire perturbations within CD8+ T cell compartment as a potential consequence associated with TCEs-based therapy and show the interest of T cell clonality assessment in these patients, especially in the case of peripheral T cell lymphocytosis. Since current TCE designs target the CD3 ϵ chain also present in CD3 dimers (CD3 $\delta\epsilon$, CD3 $\gamma\epsilon$) associated with TCR $\gamma\delta$ receptors, the activation and potential expansion of BM resident TCR $\gamma\delta$ T cells might be involved in direct killing of MM tumor cells should also be analysed and monitored, in addition to TCR $\alpha\beta$ T cell pool. Also, persistent clonal expansion of terminally differentiated CD8+ T cell effectors or the presence of exhausted CD4+ T cell pool does not necessarily predict an upcoming treatment failure as shown by this patient. Finally, whether vigorous clonal expansion of CD8+ and/or CD4+ T cell effectors correlates with disease control and prolonged progression-free and overall survival in BCMAxCD3 TCEs-treated MM patients remains to be established in large cohort studies.

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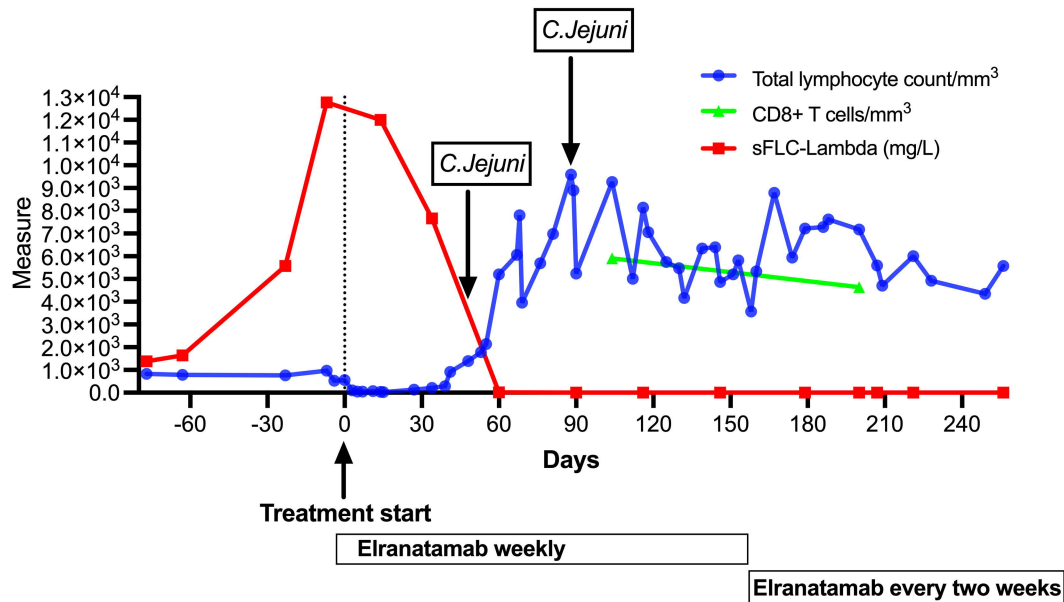
Figure 1: Bi-clonal CD8+ T cell expansion and complete clinical remission in response to Elranatamab in a patient with relapsed/refractory MM.

A) Data plots for total peripheral lymphocyte count, CD8+ T cell count and serum free Lambda light chains (sFLC) levels

B) Bi-clonal pattern (TCRV β 3+ and TCRV β 22+) of expanded peripheral CD8+ T cell pool

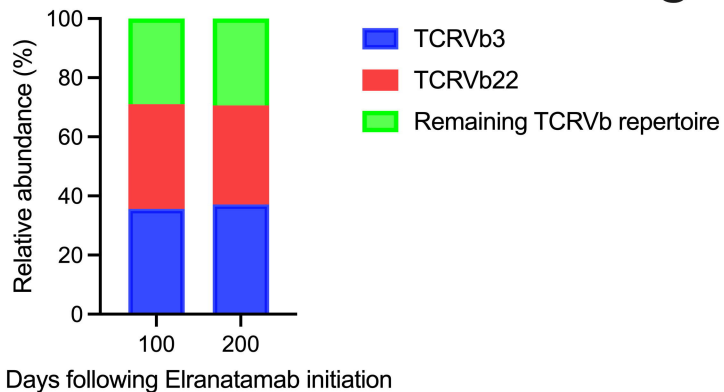
C) Characteristics of TCRV β repertoire of the non-expanded peripheral CD4+ T cell pool

A



B

Circulating CD8+ T Cell pool



C

Circulating CD4+ T Cell pool

