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

Bispecific T-cell engagers (TCE) recognizing CD3 and BCMA represent new powerful therapeutic options recently approved by the Food and Drug Administration and European Medicines Agency in refractory multiple myeloma (MM) patients. Although TCE 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 TCE on the T-cell compartment remain poorly understood.

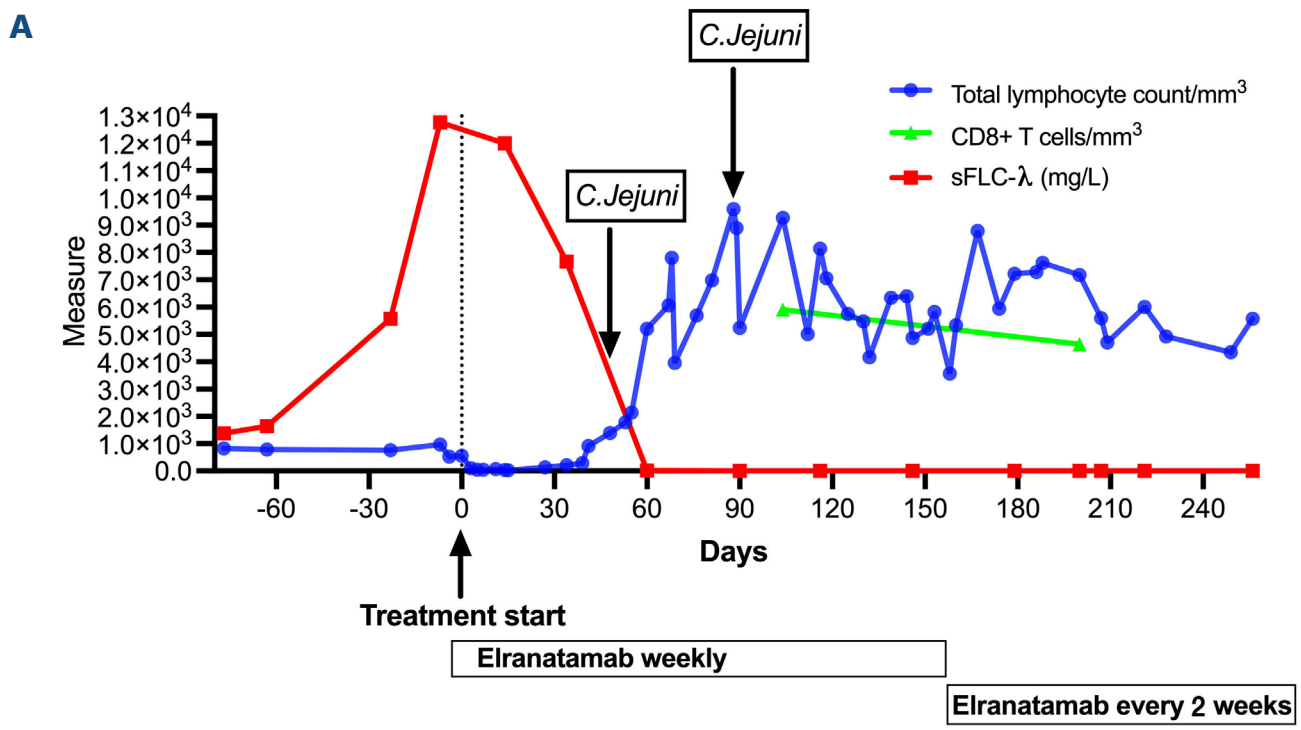
In a recent article, Friedrich *et al.*[1] analyzed the link between inter-individual differences in the immune repertoire and clinical response to BCMAxCD3 TCE in relapsed/refractory MM (RRMM) patients. By applying single-cell RNA sequencing (scRNA-Seq) transcriptome analysis of immune cells and scRNA/VDJ-Seq T-cell receptor (TCR) tracing coupled to clonotype mapping of bone marrow (BM) and peripheral T-cell populations, the authors concluded that in RRMM patients treated by TCE : (i) the TCE-induced clinical response is driven by *CX3CR1*-expressing CD8$^+$ T-cell effectors; (ii) in clinical responders, BM and the 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 who represents a striking exaggeration of the observations made by Friedrich *et al.*

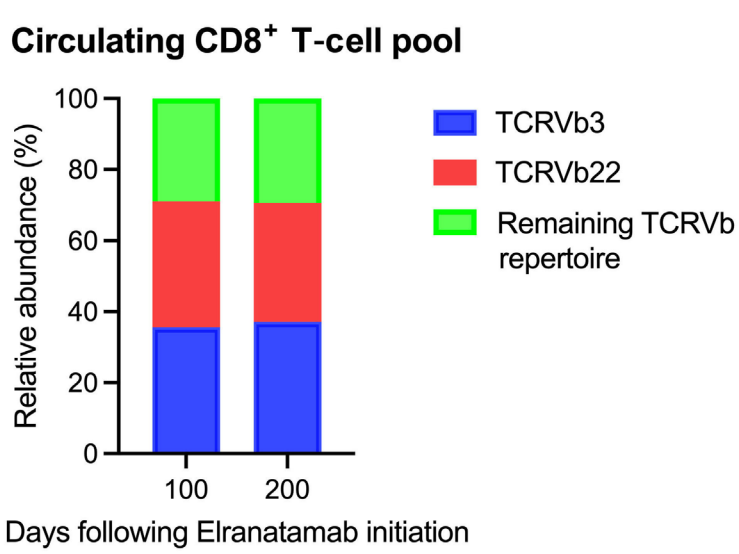
The patient was a 74-year-old man with λ light chain RRMM diagnosed 11 years prior and previously treated with nine lines including two autologous hematopoietic stem-cell transplantations. He was penta-refractory. The patient provided informed consent for this report. Treatment with subcutaneous elranatamab (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). One month post treatment, the patient started to show an increase in total lymphocyte counts that reached between 4.0x10^9/L and 9.5x10^9/L (convert values to x10^9/L) 2 months after the start of the TCE (Figure 1A). The serum free λ light chains (sFLC) were measured at 12,700 mg/L at relapse and the patient was in complete response at 2 months of treatment with sFLC at 12 mg/L. This response remains unchanged 8 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 1A). Moreover, the lymphocytosis persisted after successful treatment of this infection. Thus, we do not think that this infection may have played a role in the lymphocyte expansion.

Phenotyping of the T-cell populations was made at 4 months after starting the TCE and showed important CD8$^+$ T cells lymphocytosis (87% of CD3$^+$ T cells, 5.9x10^9/L), normal peripheral CD4$^+$ T cell count (12% of CD3$^+$ T cells, 0.8x10^9/L) and undetectable circulating CD19$^+$ B-cell pool despite no administration of B-cell depleting agents. Flow cytometric assessment of the TCRVβ repertoire of peripheral CD8$^+$ T-cell compartment revealed a bi-clonal CD8 lymphocytosis with major expansions within TCRVβ22 and TCRVβ3 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 TCRVβ 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 (TCRVβ22/TRBV2$^+$ and TCRVβ3/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 non-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). The CD4$^+$ T-cell pool was more polyclonal but presented two clear expansions (TCRVβ8/TRBV12-3/TCRBV12-4$^+$ and TCRVβ3.1/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 5.5x10^9/L and CD8$^+$ T-cell lymphocytosis at 4.6x10^9/L) likely in response to diminished dosing of elranatamab every 2 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-cell effectors in the peripheral blood and the high tumour burden, the patient did not present any immunological severe adverse events such as cytokine release syndrome, neurotoxicity or cytopenias.





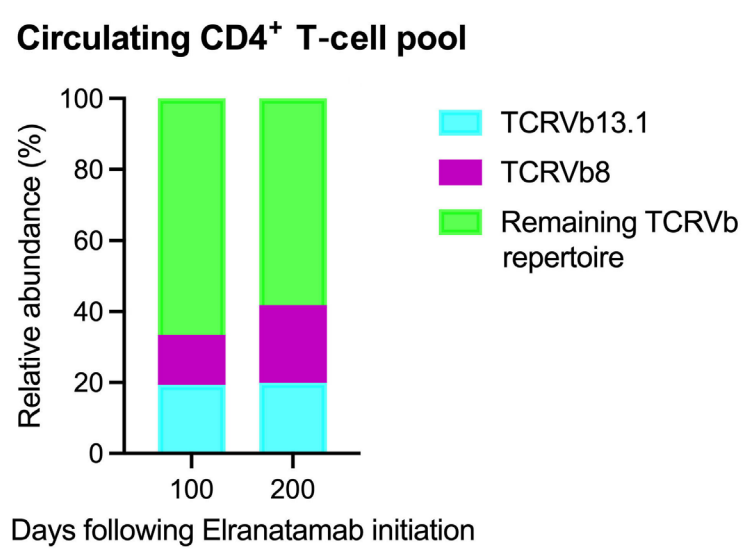


Figure 1. Bi-clonal CD8⁺ T-cell expansion and complete clinical remission in response to elranatamab in a patient with relapsed/refractory multiple myeloma. (A) Data plots for total peripheral lymphocyte count, CD8⁺ T-cell count and serum free λ light chains (sFLC) levels. (B) Bi-clonal pattern (TCRVβ3⁺ and TCRVβ22⁺) of expanded peripheral CD8⁺ T-cell pool. (C) Characteristics of TCRVβ repertoire of the non-expanded peripheral CD4⁺ T-cell pool.

The putative antigenic specificity of expanded clones as well as BM 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 cell-associated tumor antigen(s). Although transient proliferation (Ki67⁺ cells) of T cells in peripheral blood has been described in safety profile description of elranatamab,[4,5] 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, the study by Friedrich *et al*. and our report emphasize the role of TCRVβ repertoire perturbations within CD8⁺ T-cell compartment as a potential consequence associated with TCE-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 CD3ε chain also present in CD3 dimers (CD3γε, CD3δε) associated with TCRγδ receptors, the activation and potential expansion of BM resident TCRγδ T cells might be involved in direct killing of MM tumor cells should also be analyzed and monitored, in addition to TCRαβ 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 BCMAx-CD3 TCE-treated MM patients remains to be established in large cohort studies.

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Data-sharing statement

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

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