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# POSTER ABSTRACTS

## 652.MULTIPLE MYELOMA: CLINICAL AND EPIDEMIOLOGICAL

### T-Cell Exhaustion Signature Predicts Early Relapse after Autologous Stem Cell Transplant for Multiple Myeloma: BMT CTN 0702 Secondary Immune Analysis

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*Introduction*: Autologous stem-cell transplant (ASCT) is standard-of-care for the treatment of multiple myeloma (MM), but most patients eventually relapse. Patients with early relapse, within 12-24 months of ASCT, have a lower overall survival that is not fully explained by conventional high-risk disease features, such as frailty, extramedullary disease, and cytogenetics. In this study, we performed high-dimensional flow cytometry-based immune phenotyping of the T-cell compartment of MM patients to identify features predictive of early relapse.
*Methods*: Peripheral blood samples collected at 90 days post-ASCT from participants in BMT CTN 0702 comprised two cohorts: an early relapse cohort (ER), defined as relapse within 24 months from ASCT, and a long-term responder cohort (LR) defined as not relapsed at >4 years from ASCT. We performed 28-color flow cytometry to explore differences in T-cell subset frequency and activation state between cohorts. A total of 96 patients from the ER (n=51) and LR (n=45) cohorts were analyzed. We manually gated on live, CD3+ events and integrated all patient samples. High-dimensional flow cytometry analysis was conducted using the FlowSOM algorithm, which identified 20 cell clusters. We manually annotated each cluster based on CD45RA and CCR7 expression into separate CD4 and CD8 effector and memory subsets. Differential expression analysis was performed with empirical Bayesian testing, controlling for batch effect and treatment modality, followed by effect size estimates with Cohen's *d*.
*Results*: We observed 2 out of 20 cell clusters with a significant difference in proportion between groups. For ER patients, there were two CD45RA $^{-}$, CCR7 $^{+}$, CD25 $^{+}$, CCR4 $^{+}$ CD4 $^{+}$ clusters with a 29% (log fold change (LFC) = -0.628, p-value < 0.001) and 54% relative decrease in cell number (LFC = -1.25, p-value < 0.001), suggesting an absence of activated central memory CD4 T cells with early relapse. Analysis of positive and negative costimulatory molecules revealed upregulation of PD1, CD38, and TIGIT, with corresponding decreased expression of granzyme B, CD28, and CD27 within multiple CD4 and CD8 clusters among the ER group (Figure 1A). By differential expression testing, early relapse was most strongly associated with CD28 downregulation by effector memory (CD45RA $^{-}$, CCR7 $^{-}$) CD8 T cells (LFC = -0.016, p-value < 0.001), increased PD1 expression by effector memory CD8 T cells (LFC = 0.022, p-value < 0.001), increased TIGIT expression by central memory (CD45RA $^{-}$, CCR7 $^{+}$) CD8 T cells (LFC = 0.038, p-value < 0.001), and decreased granzyme B among T regulatory (FoxP3 $^{+}$, CD25 $^{+}$) cells (LFC = -0.030, p-value < 0.001) (Figure 1B).

*Conclusion*: Distinct signatures of T-cell exhaustion and depletion are present in the early post-ASCT period among individuals relapsing within 24 months. Peripheral blood immune phenotyping may identify functionally high-risk patient populations in need of alternative treatment approaches to maintain durable disease control.

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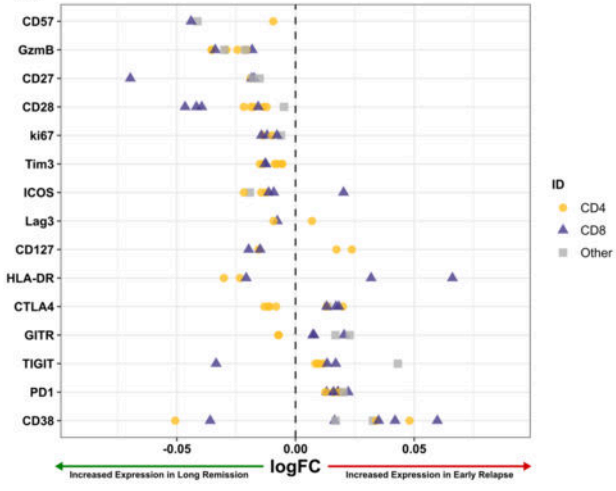
A




B

| Cluster | Marker | LFC | Effect size | p-value |
|---|---|---|---|---|
| EM CD8 2 | PD1 | 0.022 | 0.064 | $1.03 \times 10^{-4}$ |
| EM CD8 2 | CD28 | −0.016 | −0.053 | $1.05 \times 10^{-3}$ |
| Tregs 2 | CD27 | −0.018 | −0.050 | $7.82 \times 10^{-6}$ |
| EM CD8 2 | GITR | 0.008 | 0.041 | $1.21 \times 10^{-2}$ |
| Tregs 2 | GzmB | −0.030 | −0.041 | $1.37 \times 10^{-4}$ |
| EM CD8 2 | CD38 | 0.016 | 0.037 | $2.37 \times 10^{-2}$ |
| EM CD8 2 | CD27 | −0.018 | −0.035 | $2.96 \times 10^{-2}$ |
| CM CD8 1 | TIGIT | 0.017 | 0.033 | $7.82 \times 10^{-6}$ |
| Naive CD8 2 | GITR | 0.020 | 0.030 | $1.97 \times 10^{-4}$ |
| Tregs 2 | GITR | 0.017 | 0.029 | $5.69 \times 10^{-3}$ |

**Figure 1**

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