T-Cell Exhaustion–Based Transcriptomic Signature Predicts Multiple Myeloma Survival and Reveals Montelukast as an Immunomodulatory Repositioning Candidate

A. TURUNC, MD[1] ; E. KALEMOGLU, MD, PhD[2] ; B. GUVENC, MD[1]

1. Çukurova University, Faculty of Medicine, Adana, Turkey
2. RUTGERS – Jersey City Medical Center, Jersey City, NJ, USA

SOHO 2026 · Poster MM-1088 · Multiple Myeloma (MM)

INTRODUCTION

- BCMA-directed cellular immunotherapy has transformed multiple myeloma (MM), yet a substantial proportion of patients fail to achieve durable responses.
- Pre-existing T-cell exhaustion within the bone marrow (BM) niche is increasingly recognised as a contributing factor.
- We assembled a literature-derived T-cell exhaustion gene signature, assessed its prognostic relevance in two large bulk transcriptomic MM cohorts, and applied LINCS L1000 connectivity analysis to identify clinically available agents capable of reversing this programme.

AIM

To determine whether a T-cell exhaustion transcriptomic signature carries prognostic information in multiple myeloma, and to identify clinically available compounds predicted to reverse that programme as candidates for microenvironment conditioning before BCMA-directed immunotherapy.

METHODS

- Signature. A 20-gene exhaustion signature (15 upregulated, 5 downregulated) constructed from published scRNA-seq studies of the MM BM compartment.
- Prognostic evaluation. Kaplan–Meier analysis via the KM Plotter platform in a pooled cohort of 1,152 patients with newly diagnosed MM (GSE24080 and GSE4204; CD138-enriched bone marrow plasma cells).
- Connectivity analysis. Signature genes queried against 1,165,466 perturbational profiles on clue.io (Touchstone v1.1.1.43).
- Prioritisation. Candidates ranked by normalised connectivity score (NCS ≤ −1.50) and filtered for clinical availability.

CONCLUSIONS

- A bulk T-cell exhaustion score carries prognostic information in MM independent of conventional risk factors.
- Single-gene checkpoint transcripts behave discordantly in bulk data, underlining that the composite score, not any individual gene, is the informative unit.
- Montelukast, an oral and FDA-approved agent that is entirely untested in MM, emerges as a biologically coherent and clinically tractable candidate for microenvironment conditioning prior to BCMA-directed immunotherapy.

RESULTS

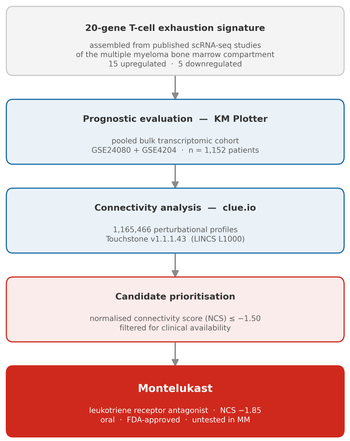

Figure 1. Analytical workflow, from signature construction to candidate prioritisation.

KEY NUMBERS

1,152
MM patients, two pooled cohorts

HR 0.76
composite score, overall survival (P = 0.025)

−1.85
NCS, leukotriene receptor antagonists

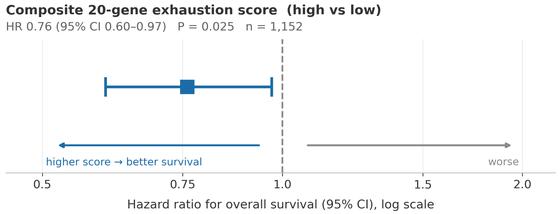

Figure 2. A higher composite exhaustion score was associated with improved overall survival in the pooled cohort (n = 1,152).

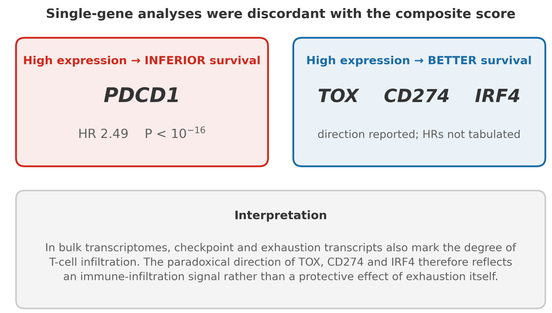

Figure 3. Single-gene associations were heterogeneous and, for TOX, CD274 and IRF4, directionally opposite to expectation.

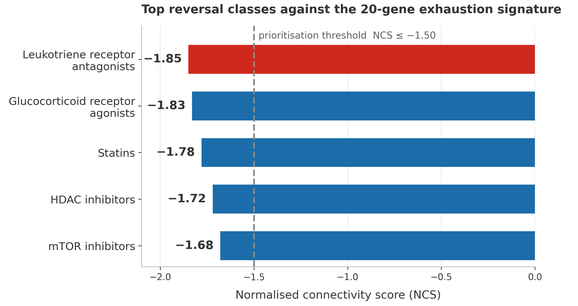

Figure 4. Compound classes predicted to reverse the exhaustion signature, ranked by normalised connectivity score.

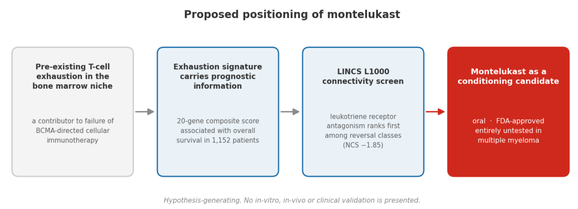

Figure 5. Rationale linking the prognostic signature to a clinically available conditioning candidate.

LIMITATIONS

- Both cohorts profile CD138-enriched bone marrow plasma cells, not the intact immune compartment. Exhaustion transcripts therefore represent residual non-plasma-cell signal, and the score should be read as an indirect marker of immune content.
- This directly explains the discordant single-gene directions, and means the signature indexes the microenvironment rather than measuring T-cell exhaustion itself.
- The cohorts predate routine BCMA-directed therapy, so the signature was not tested against the outcome it is proposed to inform.
- Connectivity analysis predicts transcriptional reversal in reference cell lines, not therapeutic benefit in the myeloma niche. No in-vitro, in-vivo or clinical validation of montelukast in MM is presented.

REFERENCES

1. Zhan F, Huang Y, Colla S, et al. The molecular classification of multiple myeloma. Blood. 2006;108(6):2020–2028. (GSE4204 source cohort)
2. Shi L, Campbell G, Jones WD, et al. The MicroArray Quality Control (MAQC)-II study of common practices for the development and validation of microarray-based predictive models. Nat Biotechnol. 2010;28(8):827–838. (GSE24080)
3. Nagy Á, Munkácsy G, Győrffy B. Pancancer survival analysis of cancer hallmark genes. Sci Rep. 2021;11(1):6047. (KM Plotter)
4. Subramanian A, Narayan R, Corsello SM, et al. A next generation connectivity map: L1000 platform and the first 1,000,000 profiles. Cell. 2017;171(6):1437–1452.
5. Munshi NC, Anderson LD Jr, Shah N, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. N Engl J Med. 2021;384(8):705–716.

CONTACT & ACKNOWLEDGEMENTS

Ali Turunc, MD
Department of Hematology, Çukurova University Faculty of Medicine, Adana, Turkey
aliturunc@cu.edu.tr

This analysis used publicly available de-identified transcriptomic data (GSE24080, GSE4204) and the LINCS L1000 resource. The authors thank the investigators who generated and deposited these datasets. This abstract was not industry supported.