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Multimodal single-cell sequencing analysis reveals putative tumor-reactive population in lifileucel TIL products

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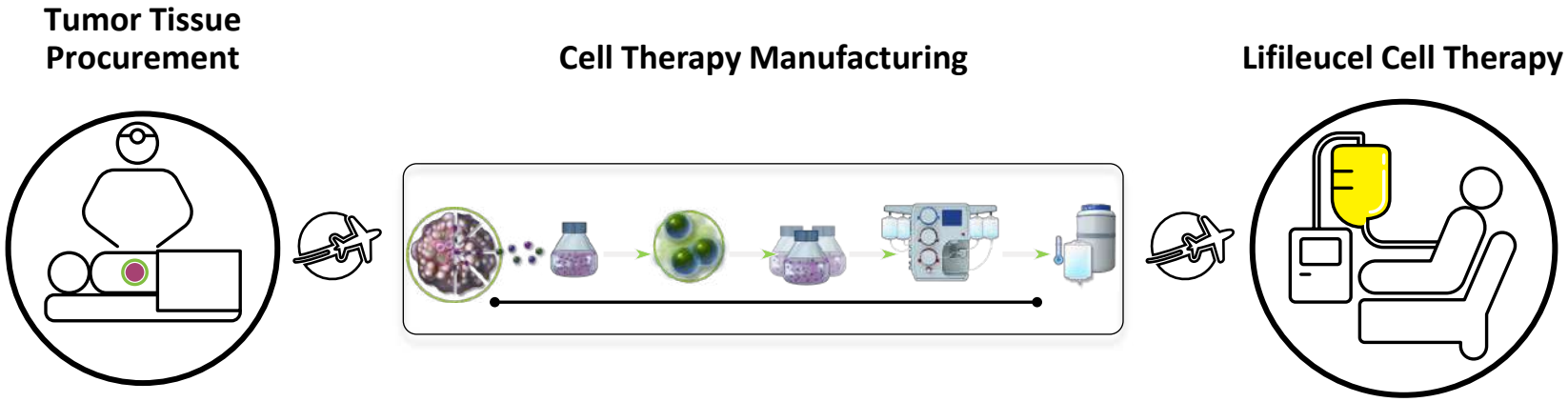
Disclosures

- Joe Dean, Joe Yglesias, Behzad Damirchi, Mark Ozeck, Kranthi Kunkalla, Brian Gastman, Rana Fiaz, Giri Sulur, Hequn Yin, Rongsu Qi: Iovance Biotherapeutics
- Theresa Medina: BioAtla, Bristol Myers Squibb, Checkmate, Day One Pharmaceutical, Exicure, Iovance Biotherapeutics, Merck, Moderna, Nektar, Pfizer, Regeneron, Replimune, Taiga, Xencor
- Amod Sarnaik: Blueprint Oncology Concepts, Gerson Lehrman Group, Guidepoint, Iovance Biotherapeutics, Provectus Biopharmaceuticals, Second City Science, Turnstone Biologics
- Jason Chesney: None to disclose
- Mike Cusnir: None to disclose

Lifileucel tumor-infiltrating lymphocyte (TIL) cell therapy background

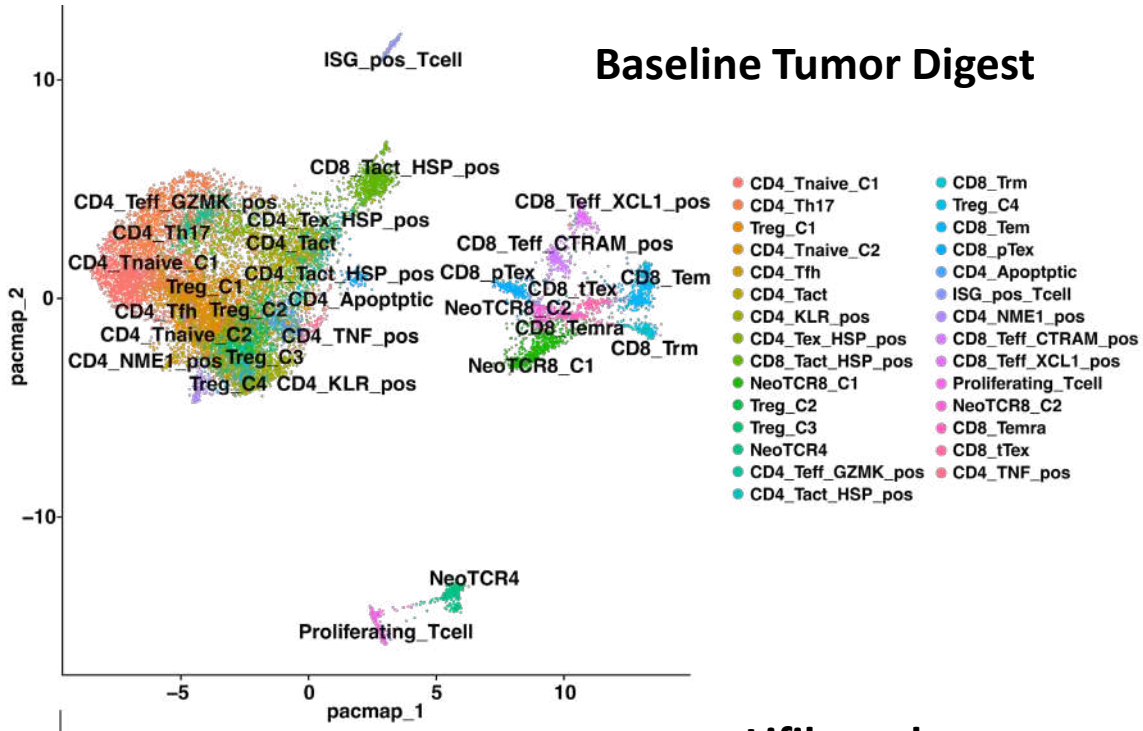


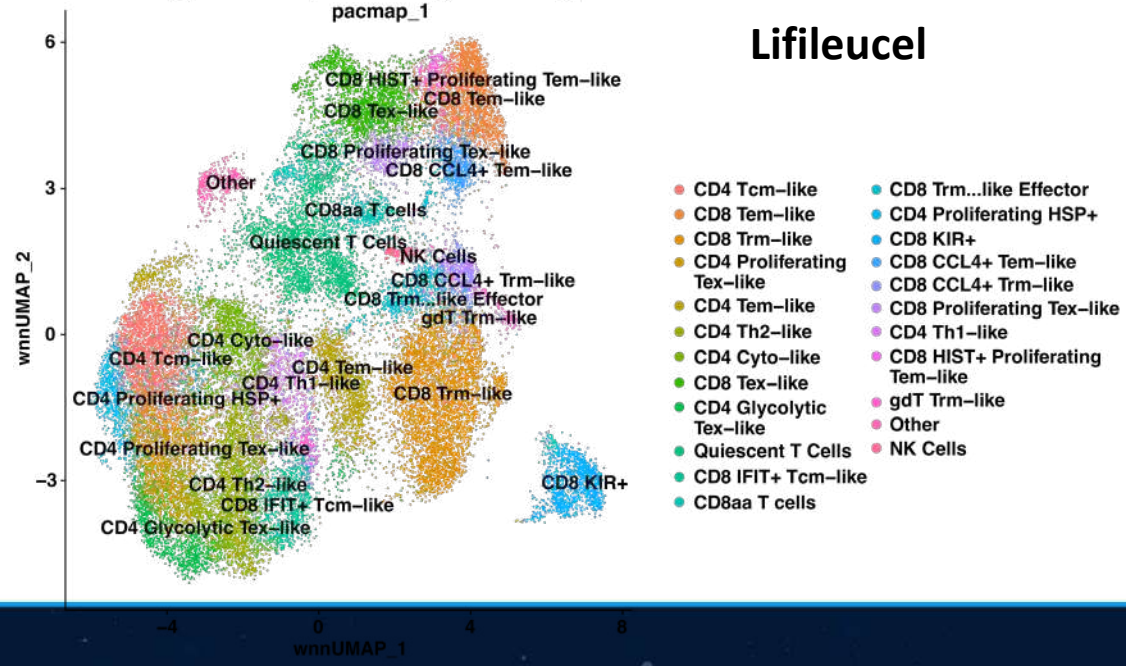
What are the potential cellular determinants of response to TIL cell therapy?

GMP, Good Manufacturing Practice; IL-2, interleukin-2; TIL, tumor infiltrating lymphocyte.

Dataset and methods

- Single-cell (sc) RNA sequencing and sc T-cell receptor (TCR) sequencing
  - 10x genomics 5’ immune profiling
- C-144-01 metastatic melanoma dataset[a]
  - Lifileucel, N=27
  - Matched tumor digest (CD45 enriched) and lifileucel, N=7
- High-resolution annotation of clusters
  - Baseline tumor T-cell subsets
  - Lifileucel CITE-seq informed reference map
- Putative tumor-reactive T-cell tracking based on the TCR clones expressed by NeoTCR8 cluster[1]

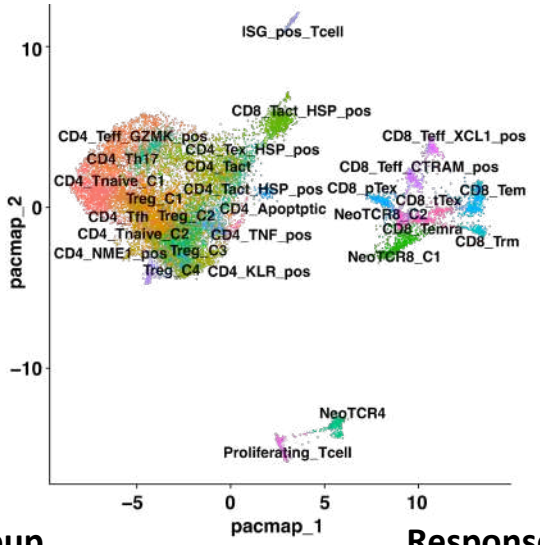




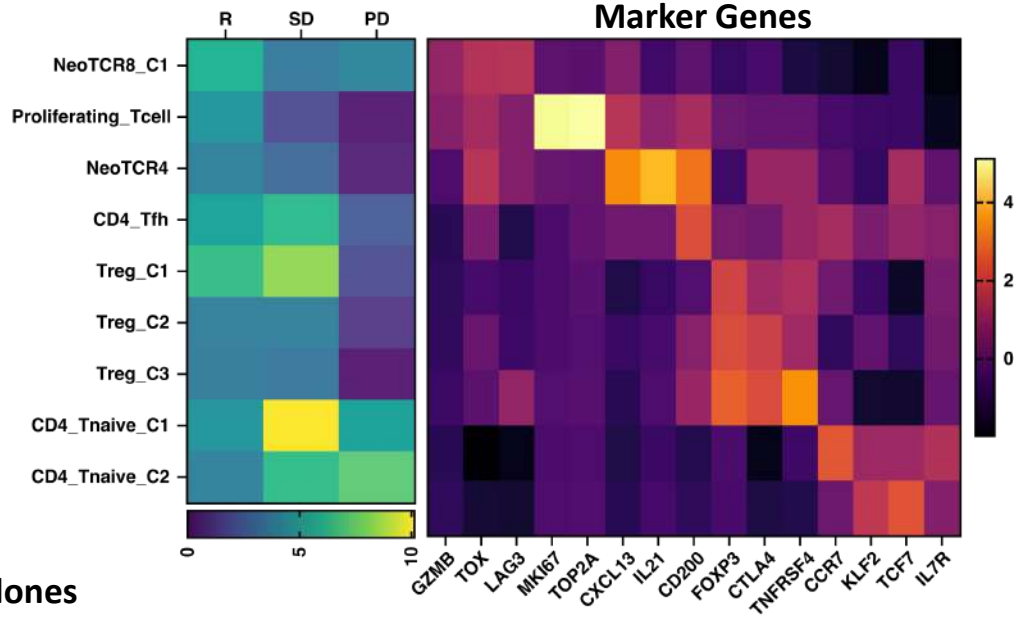
[a]**ClinicalTrials.gov ID:** NCT02360579. 1. Lowery FJ, et al. *Science.* 2022;375(6583):877–884.
CITE-seq, cellular indexing of transcriptomes and epitopes by sequencing; TCR, T-cell receptor.

NeoTCR8 T-cell proportion in tumor appears to be associated with response

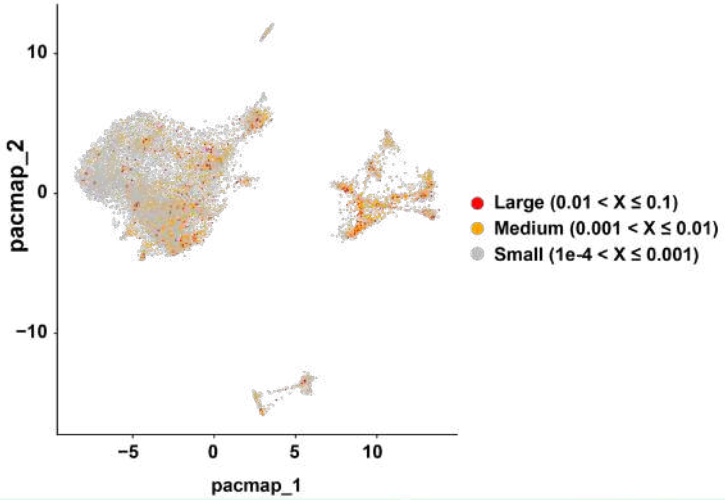
Baseline Tumor scRNA Cluster



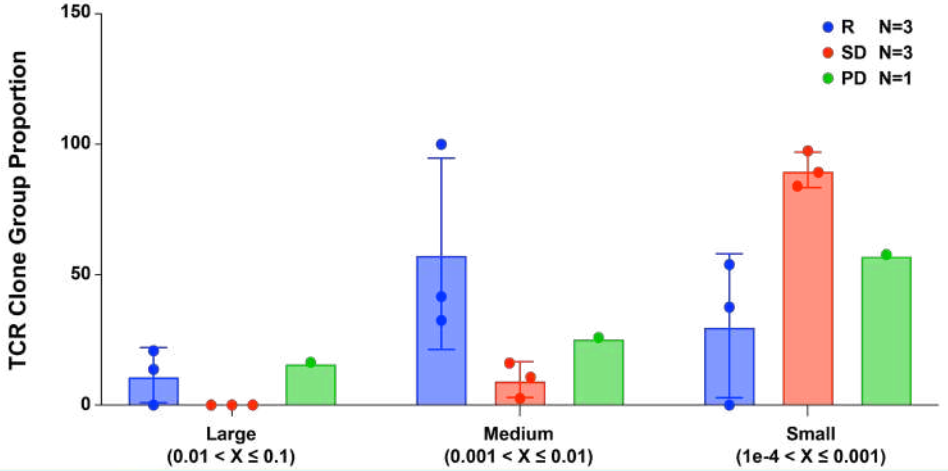
Marker Genes



Baseline Tumor scTCR Clone Group

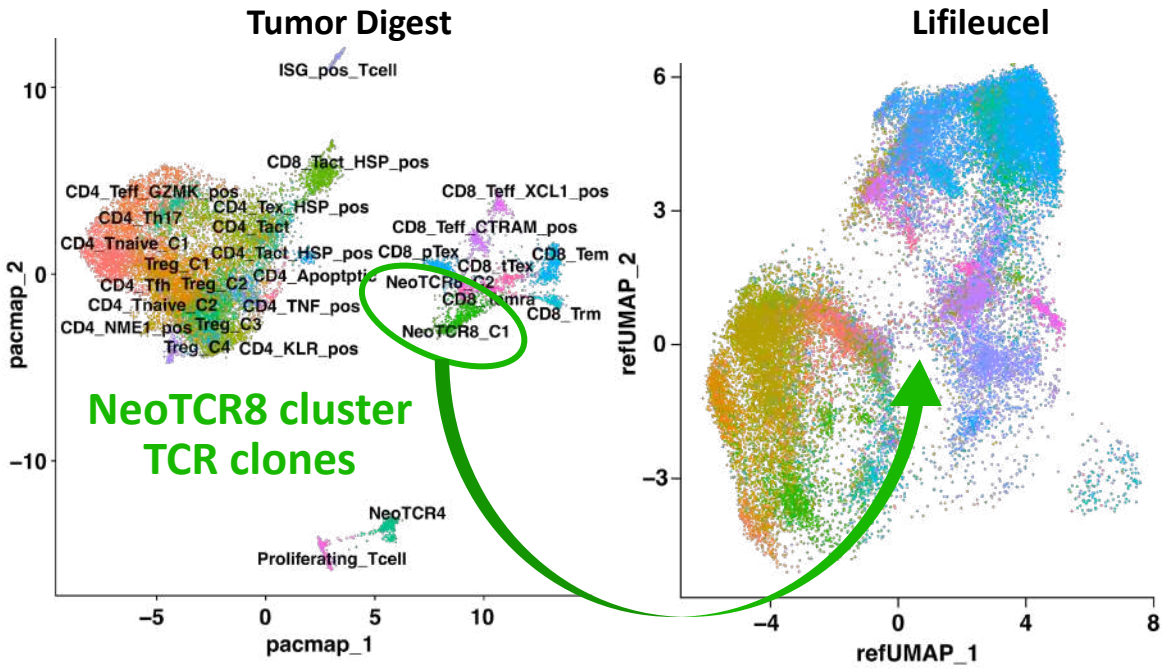


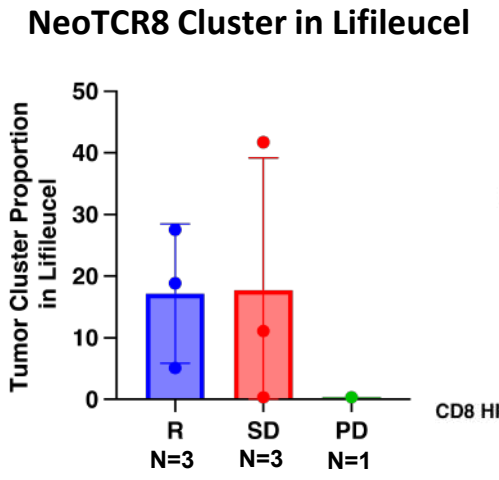
Response by Proportion of TCR Clones

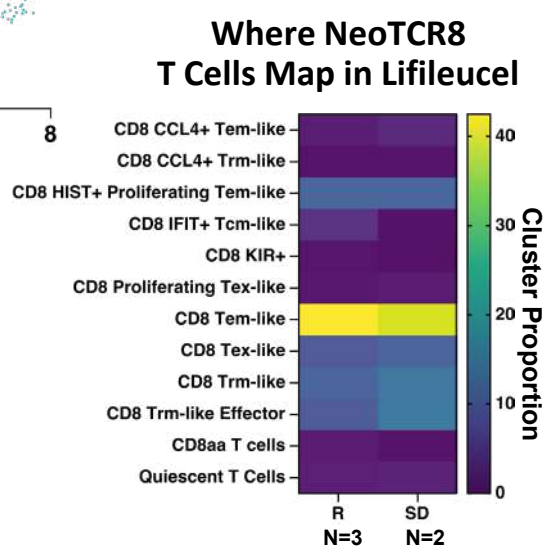


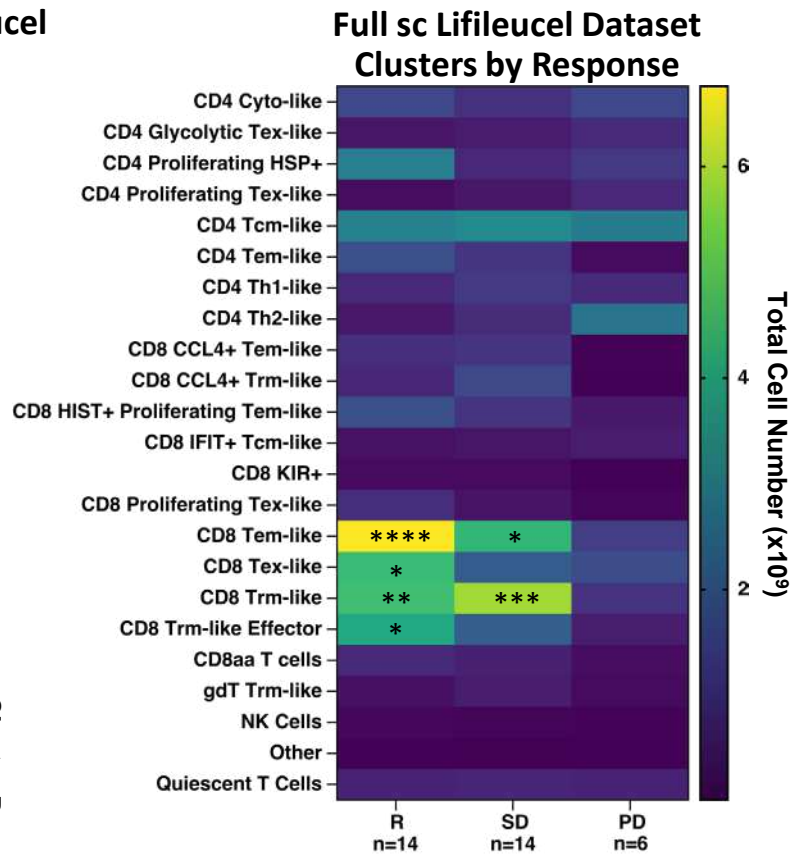
PD, progressive disease; R, responder; SD, stable disease; scRNA, single-cell RNA; scTCR, single-cell T-cell receptor; Treg, regulatory T cells.

NeoTCR8 T-cell proportion in lifileucel appears to be associated with response









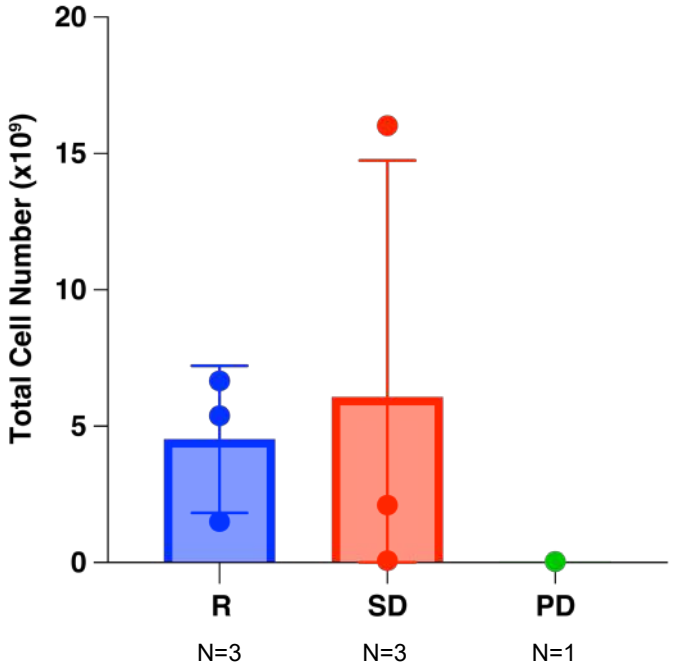
- The TIL drug product (DP) received by the patient with best overall response of PD lacks this putative tumor-reactive T-cell population
- NeoTCR8 T cells map to CD8 TEM-like cluster in TIL DP
- Number of CD8 TEM-like cells in lifileucel is significantly higher in responders in this limited data set

PD, progressive disease; R, responder; SD, stable disease.

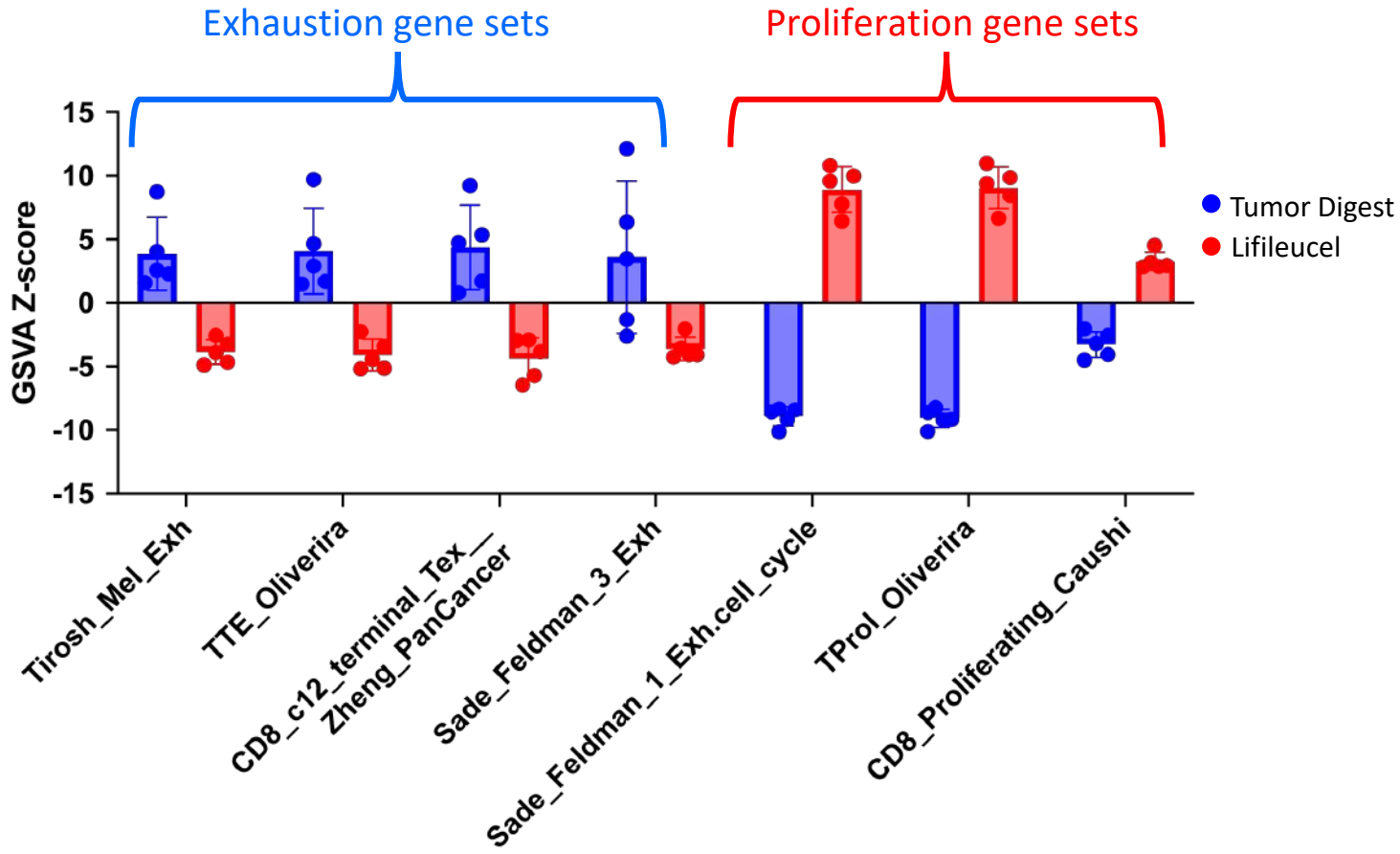
Lifileucel manufacturing process shifts phenotype of NeoTCR8 T cells

- NeoTCR8 T cells expand into the billions in lifileucel
- Upon expansion, NeoTCR8 T cells downregulate exhaustion and upregulate proliferation

NeoTCR8 Cluster in Lifileucel



Gene Signature Analysis Comparing NeoTCR8 T Cells in Tumor vs Lifileucel



PD, progressive disease; R, responder; SD, stable disease.

Conclusions

- Preliminary results suggest the tumor immune infiltrate from patients with SD and PD contains more bystander T cells, while responders have more putative tumor-reactive TIL
- The lifileucel manufacturing process shifts the phenotype of putative tumor-reactive TIL from exhausted to proliferating T cells
- Putative tumor-reactive TIL, post-REP, map to the CD8 T_{EM}-like cluster in the final drug product
- The proportion and total number of cells in the CD8 T_{EM}-like cluster appears to be associated with response to TIL cell therapy

Take-home message

- The current analysis suggests that the capture, expansion, and reinvigoration of putative tumor-reactive T cells may be important for efficacy of TIL cell therapy and may help guide future development of TIL drug products

Acknowledgments

Iovance

- Joe Yglesias, Behzad Damirchi, Mark Ozeck, Kranthi Kunkalla, Rana Fiaz, Giri Sulur, Hequn Yin, Rongsu Qi

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- Theresa Medina, Amod Sarnaik, Jason Chesney, Mike Cusnir

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Q&A