Predictive response and resistance factors of Duruvalumab and Tremelimumab neoadjuvant combination immunotherapy in head and neck cancer

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Abstract

Predictors of immune checkpoint inhibitor (ICI) response among cancer patients are unclear despite active research into their tumor microenvironment. Moreover, mechanisms of combinatory ICI treatment are not understood leading to ineffective clinical trials. There is currently an urgent need to stratify and select cancer patients for implementing successful immunotherapy. In this study we leverage the advantages of neoadjuvant immunotherapy, to collect paired samples of Durvalumab or Durvalumab and Tremelimumab treated head and neck cancer patients. Single-cell multi-omics profiling of TCR and RNA was performed for 57 biopsies including paired baseline prior to ICI treatment and were annotated for early response. Samples were analyzed using state-of-the-art bioinformatic approaches using transformer-based foundation model, non-negative matrix factorization (NMF), and cell-type specific gene networks. We found signatures associated with ICI sensitivity and immune activation that predict ICI response at baseline, validated using foundation model pretrained on millions of single cells. Moreover, we report that Tremelimumab therapy effect is inhibited via upregulation of IL2 signaling by 4-1BB+ (TNFRSF9+) regulatory T cells, with non-response distinguished by TNFRSF9-TNFSF9 interaction with dysfunctional CD8+ T cells. Importantly, we identified reinvigoration of tumor-specific exhausted subset (Tex) to precursor exhausted (Tpex) state determining therapy response, highlighting the plasticity of exhausted T cells during early stages of ICI treatment. Our findings provide important mechanistic insights into enhancing combination therapy efficacy and provide immunological bases for predicting response via tumor-CD8+ T cell axis. Evidence of transcriptional regulation governing reinvigoration of Tex necessitates future development of clinical strategies for maintaining ICI response and suppressing relapse.

Key words: Head and Neck Cancer; Neoadjuvant Immunotherapy; Duruvalumab; Tremelimumab; scRNA-seq; scTCR-seq; Single-cell network biology; Foundation model; Multi-omics