RETROSPECTIVE TUMOR MICROENVIRONMENT ANALYSIS FROM A PERSONALIZED NEOTCR-T CELL THERAPY CLINICAL TRIAL AND ITS POTENTIAL APPLICATIONS FOR OFF-THE-SHELF HPV TCRS

Eric Stawiski*, Chad Smith, Tyler Borrman, Zheng Pan, Stefanie Mandl, Vinnu Bhardwaj.
PACT Pharma, South San Francisco, CA, USA

Background We have developed a state-of-the-art approach to validate predicted neoepitopes (neoEs) and their cognate T cell receptors (neoTCRs) by capturing neoepitope-specific T cells from peripheral blood. This neoTCR discovery and validation process is being applied in a phase I clinical trial (NCT03970382) evaluating personalized neoTCR-T cell therapy to treat patients across eight solid tumor types. We have since expanded our mission to discover off-the-shelf TCRs against recurrent epitopes including HPV+ cancers. The tumor microenvironment (TME) has been shown to critically influence responses to immunotherapy making it paramount to explore in the context of adoptive cell therapy.

Methods Using bulk RNA-seq data from biopsies, we examined the TME of both our clinical cohort (n=137) as well as TCGA H&N samples (n=485). To do this we measured 29 gene expression signatures that capture specific aspects of largely pro or anti-tumor infiltrates that were previously described as being predictive to response to immunotherapy. These signatures were used for K-means clustering with 4 distinct subsets, Immune Enriched (IE), Depleted (D), Fibrotic (F), Immune Enriched/Fibrotic (IE/F) across 6 different cancer types.

Results TME subtypes were predictive of response to ICI in a previously published Melanoma data set (p=0.04).1 Screening biopsies from patients enrolled in our clinical trial consisted of 22% D, 30% F, 23% IE and 25% IE/F (n=137) across 6 solid tumor types. Amongst samples screened for autologous TCRs (n=64), TME subtype did not affect our ability to isolate TCRs from patients with a median of 2 TCRs for D and IE, 3 for F and 0 for IE/F (ranges 0-10) (p-value = 0.62). We observed a significant positive correlation between ovarian TCR capture and MHCII presentation as well as Treg and Th2 Trafficking (p<0.001), which may be general markers for inflammation. Amongst samples that were ultimately dosed with autologous TCRs, 2/3 had unfavorable TME’s (D=7, F=3). TCGA H&N samples that were HPV- (n=414) had 19% IE, 21% IE/F, 28% D, and F 31%. In contrast HPV+ cancers (n=71) showed a significant enrichment for IE samples (61%) and depletion of D and F subtypes (16% and 5% respectively).

Conclusions Retrospective analysis shows no correlation with TME subtype and our ability to isolate autologous TCRs from those patients. The current trial shows lower levels of immunotherapy favorable subtypes. In contrast HPV+ cancers show high levels of immunotherapy responsive subtypes suggesting it may be a favorable cancer indication for adoptive cell therapy.

REFERENCE