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OVERCOMING TUMOR HETEROGENEITY – CLINICAL TRIAL ASSAYS TO PROSPECTIVELY ASSIGN PATIENTS CUSTOMIZED MULTIPLEXED TCR-T CELL THERAPY IN PHASE 1

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Background TCR-engineered T cell therapy has shown encouraging response rates in solid tumors, but complete responses are rare and partial responses are often short-lived. We submit that the primary reason underlying these results is that solid tumors exhibit heterogeneous target expression and HLA loss is common. Consequently, tumor cells that lack or lose the targeted antigen are resistant to single-targeted TCR-T therapies and drive relapse. To address these challenges, TScan has developed clinical trial assays to assess target expression and HLA loss in patient tumors. These assays enable prospective patient selection and assignment of treatment with multi-targeted TCR-T therapy. T-Plex is a multiplexed TCR-T cell product consisting of customized combinations of 2–3 TCR-T cell components selected from a pre-existing collection of TCR-Ts.

Methods To enable T-Plex, TScan is developing an Immuno-Bank of TCRs targeting MAGE-A1, HPV16, PRAME, and two additional undisclosed targets across multiple HLAs. TScan and Neogenomics have developed IHC and RNA-ISH assays to assess target expression in FFPE tumor samples. In addition, TScan and Tempus have developed a novel NGS-based pan-HLA-A/B/C Loss of Heterozygosity (LOH) algorithm to assess partial or clonal loss of HLA class I alleles in solid tumors.

Results Analysis of >150 tumor samples revealed the prevalence of MAGE-A1, HPV16, and PRAME across various solid tumor types. For example, PRAME expression was observed in 95% of melanoma samples, but only in 55% of NSCLC and HNSCC. Furthermore, the intensity and uniformity of expression varied considerably. H-scores for PRAME ranged from 66–300 (melanoma), 5–170 (NSCLC) and 2–135 (HNSCC). Similarly, MAGE-A1 expression was observed in 40% of melanomas and 20% of NSCLC and HNSCC. H-scores for MAGE-A1 varied considerably, ranging from 1–200 (melanoma), 1–50 (NSCLC) and 3–180 (HNSCC). Notably, co-expression of PRAME and MAGE-A1 was observed in ~31%, ~10% and ~9% of melanomas, NSCLC, and HNSCC, respectively. Heterogeneity of HLA expression was also observed. Data collected at Tempus showed that clonal and subclonal loss of HLA occurs in approximately 14% and 29% of melanomas, 23% and 16% of NSCLC, and 27% and 14% of HNSCC. Importantly, HLA-A/B/C alleles were almost always lost together, indicating that HLA loss most frequently occurs through haplotype loss, informing a strategy to direct multiplexed TCR-T to the remaining HLA haplotype.

Conclusions Overall, these data highlight the importance of a multiplexed TCR-T cell therapy targeting various intact tumor antigens presented on intact HLA alleles in order to effectively address solid tumors.

Ethics Approval The data presented in this abstract does not meet the definition of human subject research and animals were not used in this study.

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