Overcoming tumor heterogeneity – Clinical trial assays to prospectively assign patients multiplexed TCR-T cell therapy in Phase 1


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Motor: To enable T-Plex, TScan is developing an ImmunoBank of TCRs targeting HPV16, PRAME, MAGE-A1, MAGE-C2, and additional undisclosed targets across multiple HLAAs. 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 HPV16, PRAME, MAGE-A1, and MAGE-C2 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). Notably, co-expression of PRAME and MAGE-A1 was observed in ~38%, ~13% 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 HNSCC, respectively. Importantly, HLA-A/B/C alleles were almost always lost together, indicating that HLA loss most frequently occurs through haplotype loss, in a strategy to direct multiplexed TCR-T to the remaining HLA haplotype.

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

Multiplexed TCR-T cell therapy (T-Plex) can effectively address tumor heterogeneity and HLA LOH

(A) HLA loss of heterozygosity (LOH) generally occurs through loss of one HLA haplotype on chromosome 6. (B) Novel pan-HLA LOH detection algorithm using tumor/normal comparisons of Tempus tumor data indicate that clonal and sub-clonal loss of HLA occurs in ~15-30% of common solid tumors. Tumors that have lost the target HLA cannot respond to single-targeted TCR-Ts.

Multifocal TCR-T cell therapy targets a combination of targets and incorporates a TCR-T selection algorithm to overcome HLA LOH.

Prevent Relapse: First-generation TCR-Ts targeting single antigens on single HLA types often result in partial responses and rapid progression. Multiplexed TCR-T targeting different targets on different HLA types has the potential to induce more durable or even complete responses.

Prospectively select patients: Germline HLA typing is followed by testing tumors for target antigens and HLA LOH. TCR-T selection can be used to overcome HLA LOH.

Screening Protocol Pre-Identifies Patients for Treatment

Patients with melanoma, non-small cell lung cancer, head and neck, ovarian, cervical, and anogenital cancers are screened while they are receiving standard-of-care therapy. Screening includes germline HLA typing (blood swab) and archival tumor testing for antigen expression and HLA LOH. Upon progression, patients that meet the specified criteria may enroll in the treatment protocol. In the treatment protocol, patients first receive lymphodepletion, followed by one or two doses of T-Plex. Treatment at dose levels (DL) 1 and 2 consists of 1 dose of a single TCR-T cell component. Treatment at DL3 and DL4 consists of two doses of T-Plex, comprising a customized combination of 2 different TCR-T components, administered 28 days apart.

For more information on TScan’s clinical trial design and dose-escalation scheme or TScan’s ImmunoBank:
1. Abstract # 358: Discovery of a novel MAGE2-specific TCR-T cell therapy candidates to expand multiplex therapy of solid tumors
2. Abstract # 354: Tumor progression and clinical trial design for T-Plex, a multiplexed, enhanced T cell receptor-engineered T cell therapy for solid tumors
3. Abstract # 356: Discovery of novel MAGE-A1-specific TCR-T cell therapy candidates to expand multiplex therapy of solid tumors

Abstract # 376: Discovery of a novel MAGE-A1-specific TCR-T cell therapy candidates to expand multiplex therapy of solid tumors