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Abstract # 376

Introduction

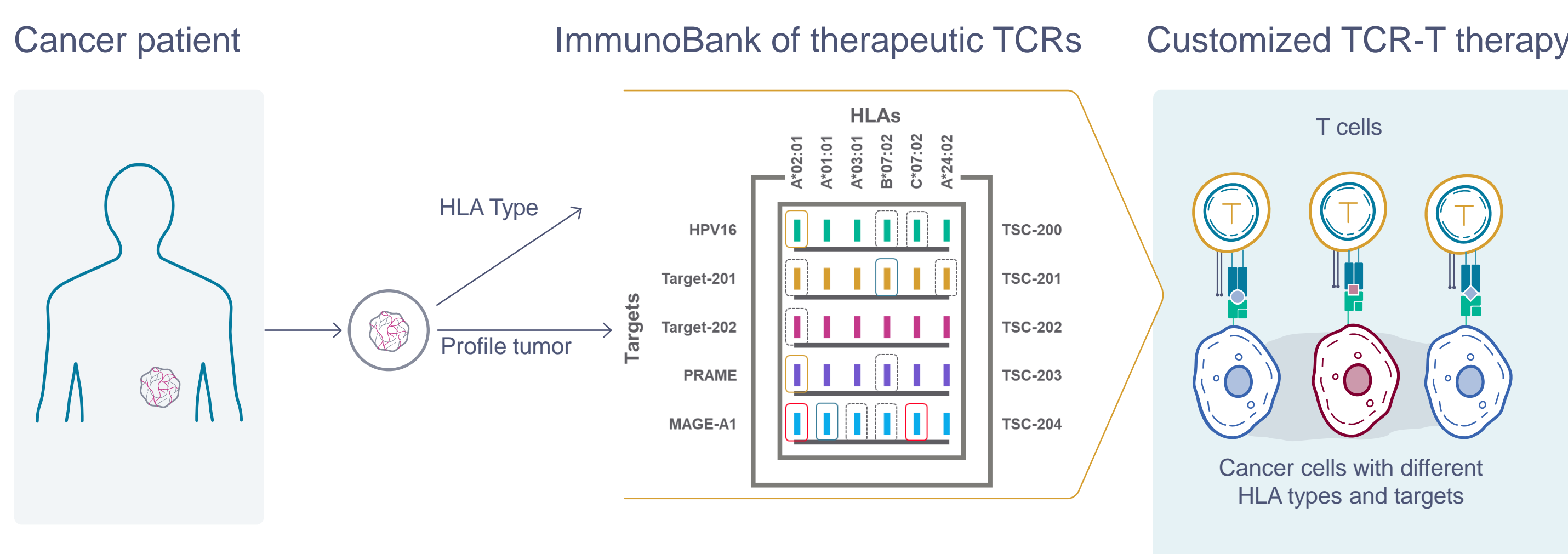
Background: TCR-engineered T cell therapy has shown encouraging response rates in solid tumors, but complete responses are rare and partial responses are often short-lived. We submit that the primary reason underlying these results is that solid tumors exhibit heterogeneous target expression, and HLA 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 ImmunoBank of TCRs targeting HPV16, PRAME, MAGE-A1, MAGE-C2, and 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 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). 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 ~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 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.

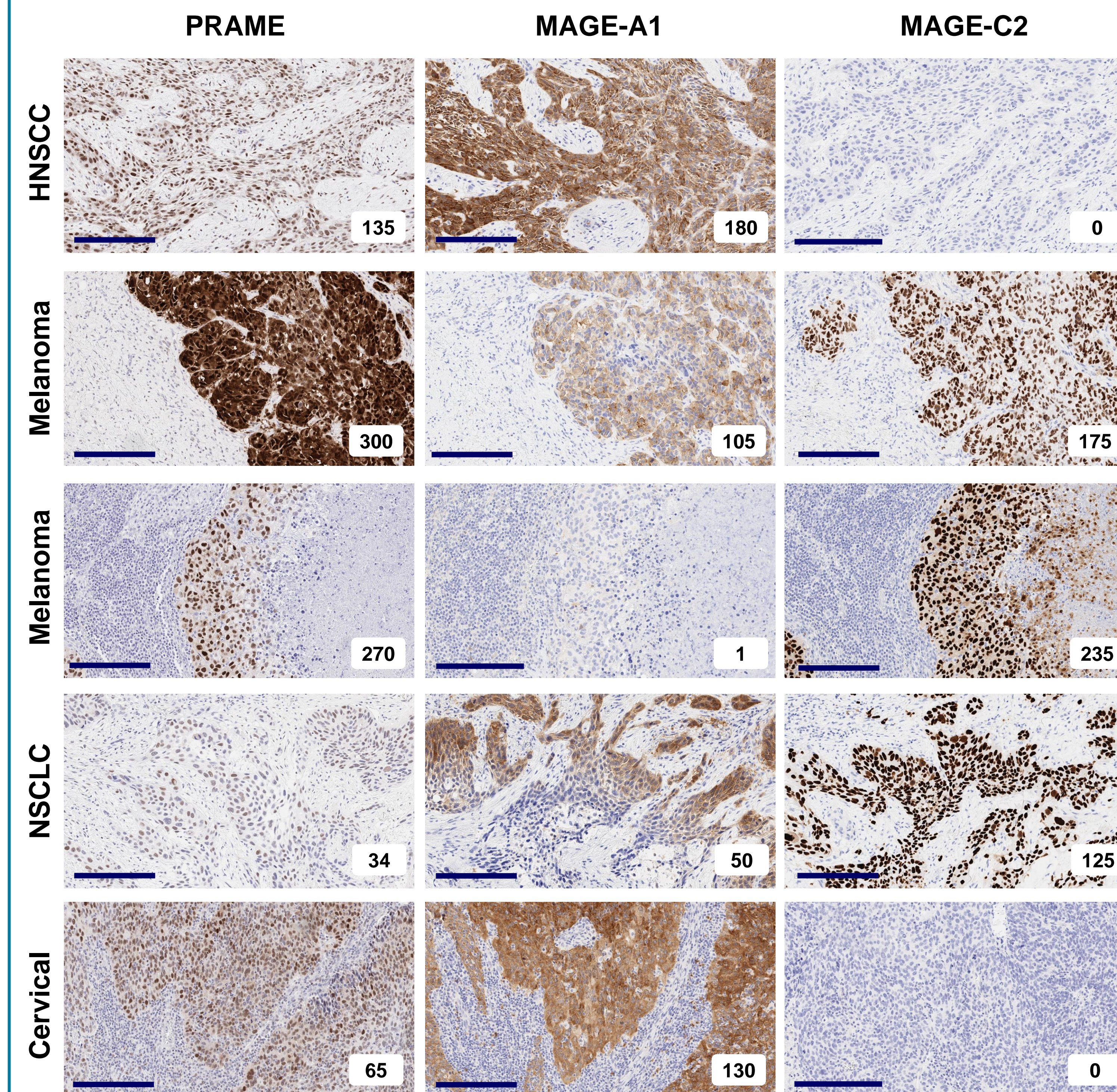
Conclusion: Overall, these data highlight the importance of developing multiplexed TCR-T cell therapy targeting multiple intact tumor antigens presented on intact HLA alleles in order to effectively address solid tumors.

TScan is building an ImmunoBank of TCRs to enable enhanced, multiplexed TCR-T cell therapy (T-Plex)



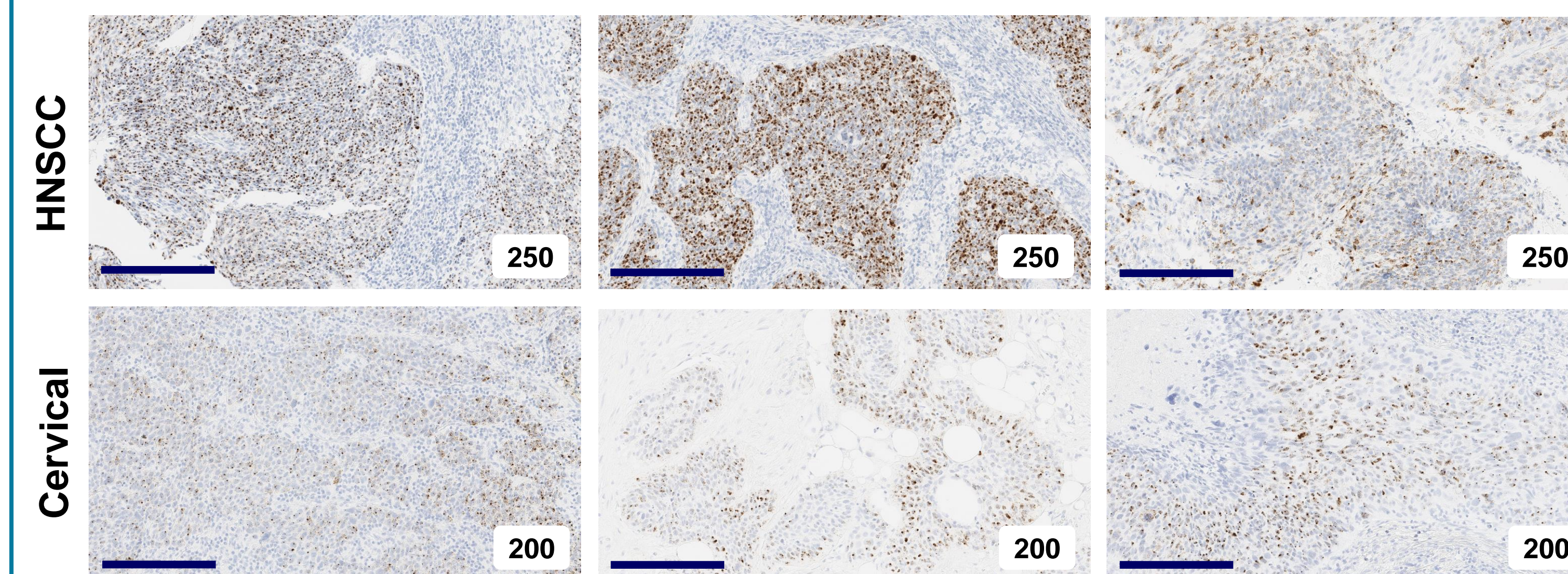
TScan is building an ImmunoBank- a collection of TCR-Ts targeting cancer-specific epitopes derived from HPV16, PRAME, MAGE-A1, MAGE-C2, and additional undisclosed targets, presented on common HLA class I molecules. T-Plex is a multiplexed TCR-T cell product consisting of customized combinations of 2-3 TCR-T cell components selected from the ImmunoBank.

Co-expression of Targets in Common Solid Tumor Types



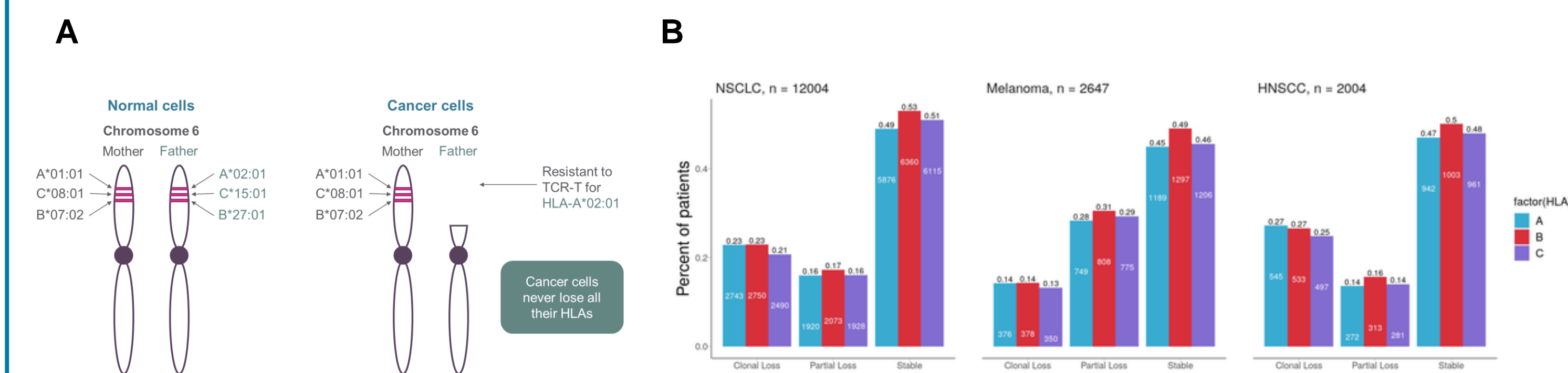
Tumors are frequently positive for multiple antigens supporting the rationale for multiplexed therapy. Represented images show co-expression of PRAME, MAGE-A1, and MAGE-C2 in the same tumor samples from Head and Neck Squamous Cell Carcinoma (HNSCC), Melanoma, Non-Small Cell Lung Carcinoma and Cervical cancer. Numbers on the bottom right of each panel indicate H-Scores. Scale bar represents 200 μm.

Expression of HPV16 E6 and E7 mRNA by RNA-ISH

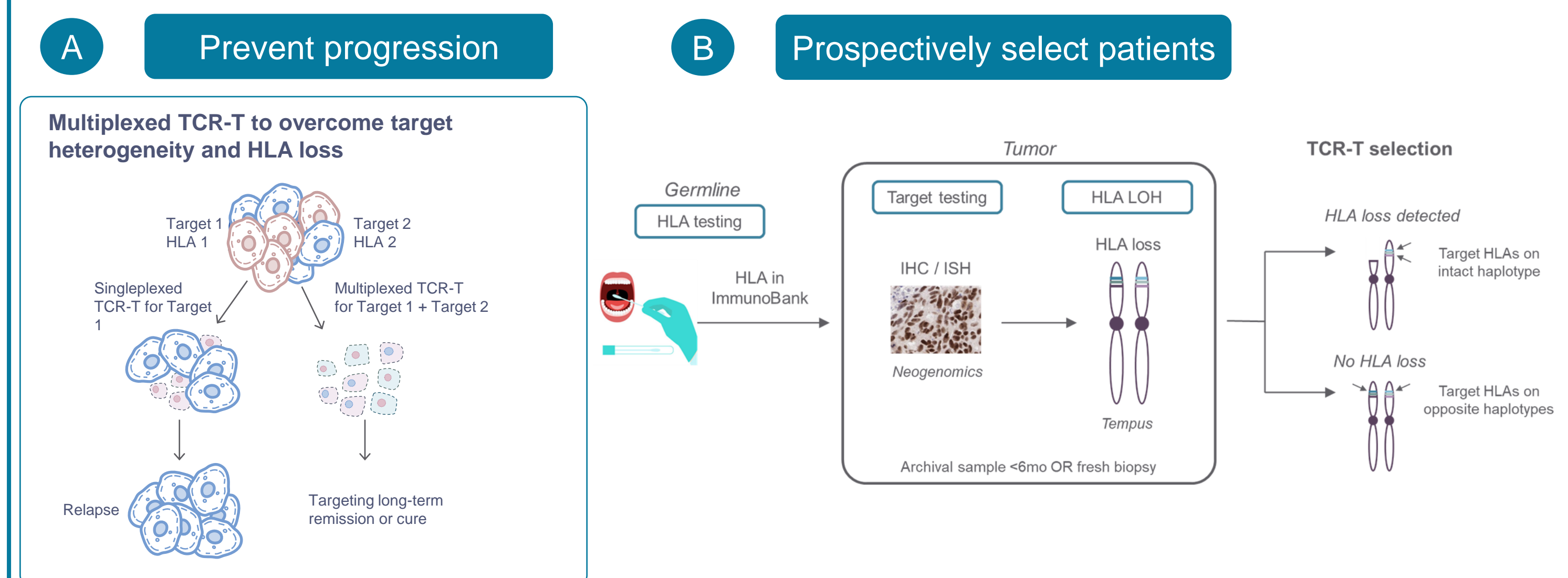


Representative images show expression of HPV16 E6 and E7 mRNA by RNA-ISH in individual Head and Neck Squamous Cell Carcinomas (HNSCC) and Cervical cancers. TSC-200-A0201 targets an HPV16 E7-derived epitope presented on HLA-A*02:01. Numbers on the bottom right of each panel indicate H-Scores. Scale bar represents 200 μm.

HLA loss of heterozygosity (LOH) is prevalent and overlooked in solid tumors

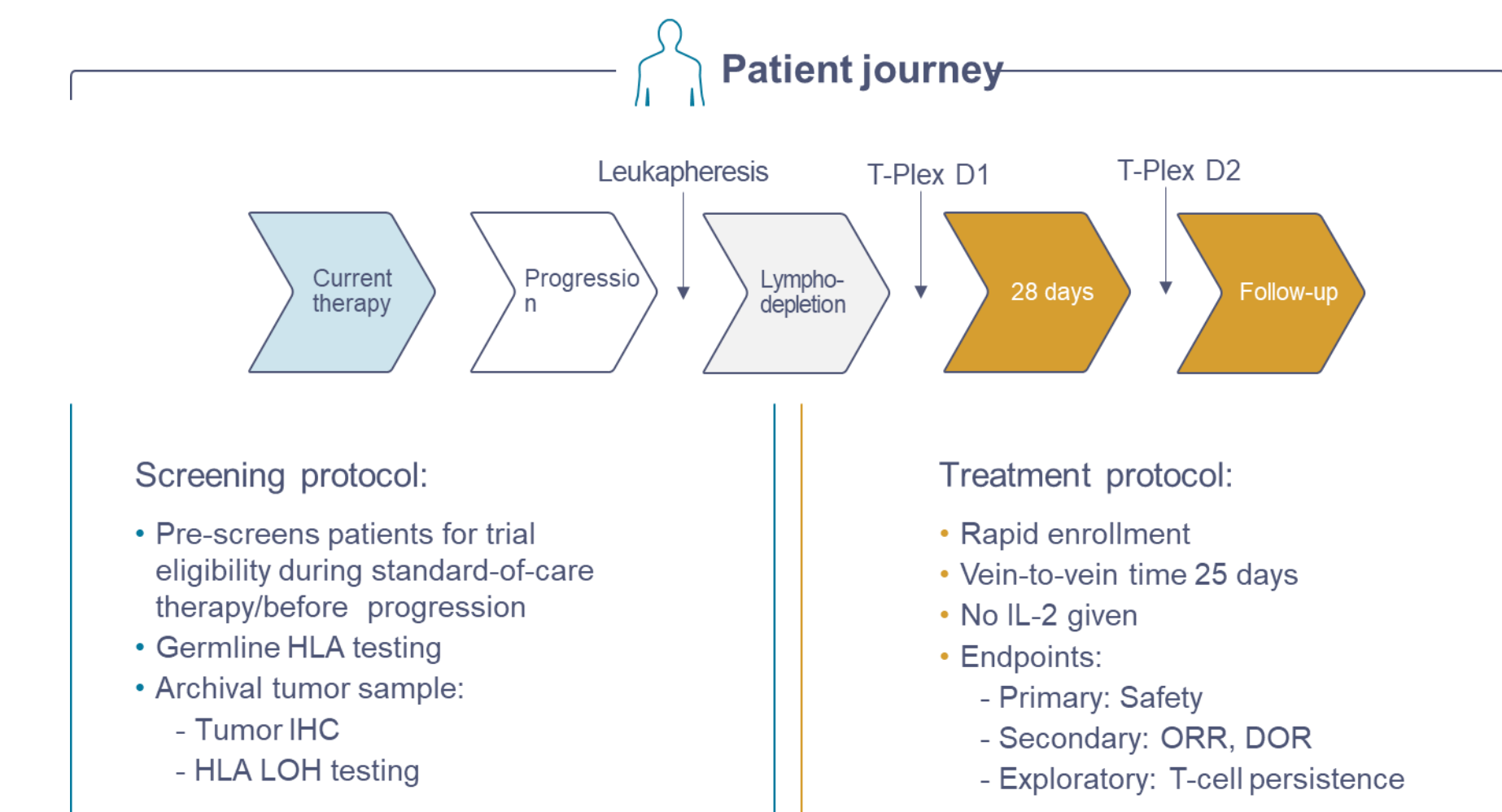


Multiplexed TCR-T cell therapy (T-Plex) can effectively address tumor heterogeneity and HLA LOH



(A) 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 target antigens on different HLA types has the potential to induce more durable or even complete responses **(B) 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, or anogenital cancers are screened while they are receiving standard-of-care therapy. Screening includes germline HLA typing (buccal 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 TCR-T. 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 individual 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 #709: Trial in progress: Product characteristics and clinical trial design for T-Plex, a multiplexed, enhanced T cell receptor-engineered T cell therapy for solid tumors
2. Abstract # 364: Non-clinical development of T-Plex component TSC-200-A0201: A natural HPV16 E7-specific TCR-T cell therapy for the treatment of HPV16-positive solid tumors.
3. Abstract # 390: Discovery of MAGE-A1-specific TCR-T cell therapy candidates to expand multiplex therapy of solid tumors
4. Abstract # 357: Discovery of a novel MAGEC2 epitope for TCR-T adoptive cell therapy from expanded T cell clones of TIL therapy products