Background Several peptide-HLA targets for T cell receptor (TCR)-based immunotherapies are currently being evaluated in the field; however, many are limited by their overall low prevalence, low copy numbers or relevant expression in healthy tissues. A T cell target with nearly ideal properties has high, homogenous and prevalent expression across multiple cancers in the absence of significant safety/toxicity liabilities. Here, we describe the in-depth characterization of an HLA-A*02:01-presented peptide derived from the cancer germline antigen preferentially expressed antigen in melanoma (PRAME) that opens an avenue of new opportunities for patients with solid cancers which we aim to leverage by two distinct TCR-based therapeutic modalities, TCR-engineered T cells (ACTengine® IMA203) and TCR Bispecifics (TCRer® IMA402).

Methods PRAME target peptide presentation and mRNA expression in tumor and normal tissues was assessed by quantitative mass spectrometry (MS) and transcriptomics. In situ hybridization was used to analyze target homogeneity. We compare target prevalences based on IMADetect® qPCR testing of screening biopsies from clinical trial patients with prevalences based on a PRAME target tailored, MS-based mRNA expression threshold applied to a large RNA sequencing dataset.

Results PRAME RNA expression is elevated across many tumor types and only minimal in some normal tissues except testis. As demonstrated by MS, RNA expression does not translate into relevant peptide presentation on normal tissues. Peptide copy numbers range from 100 to 1,000 peptide copies per cell (target density) in the majority of tumor tissues as measured by highly sensitive MS-based AbsQuant® technology. Histologic analysis of PRAME RNA in different solid tumors demonstrates homogenous expression of PRAME with a high frequency of positive tumors cells. PRAME shows a prevalence between 80-100% in uterine and ovarian carcinoma, sarcoma subtypes, cutaneous and uveal melanoma and high prevalence in many other solid cancer types, such as cholangiocarcinoma, lung, kidney, breast, head and neck, esophageal, bladder and hepatocellular carcinoma. Prevalence numbers obtained during patient screening in our clinical trials match predicted prevalences. Interim phase 1a data from the IMA203 TCR-T trial (cut-off Oct 05, 2021) showed clinical responses in head and neck carcinoma, synovial sarcoma, uveal melanoma, and cutaneous melanoma.

Conclusions Here, we demonstrate comprehensive target characterization and validation data supporting the nearly ideal target properties of PRAME that can be exploited for the benefit of patients: PRAME is highly cancer-associated, homogenously expressed, presented at high target density, highly prevalent across many solid cancers and clinically validated, underlining its potential to reach a large cancer patient population.

Trial Registration NCT03686124

Ethics Approval The study was approved by the institutional review board/ethics committee as required for each participating site.