1319 NEXT-GENERATION TCR BISPECIFICS (TCER®) TARGETING PEPTIDE-HLA ANTIGENS FOR THE TREATMENT OF PATIENTS WITH SOLID TUMORS

[1]Sebastian Bunk*, [1]Martin Hofmann, [1]Gabriele Pszolla, [1]Meike Hutt, [1]Felix Unverdorben, [1]Frank Schwoebel, [1]Nadine Aschmoneit, [1]Claudia Wagner, [1]Maike Jaworski, [1]Christoph Schraeder, [1]Heiko Schuster, [1]Sarah Missel, [2]Toni Weinschenk, [1]Dominik Maurer, [2]Carsten Reinhardt. [1]*Immatics Biotechnologies GmbH, Tuebingen, Germany*; [2]*Immatics N. V., Tuebingen, Germany*

Background T cell engaging bispecifics have emerged as a promising therapeutic opportunity for patients with solid cancers. However, challenges related to target specificity and drug safety profiles remain and many efforts are being made to generate optimized molecules with improved pharmacodynamic characteristics while reducing T cell engager-associated toxicities. We have developed a pipeline of novel bispecific molecules comprising a T cell receptor (TCR) for giving access to intracellular tumor antigens presented as peptide-HLA molecules and a unique T cell recruiting antibody aiming at conferring a favorable safety profile.

Methods We designed a novel TCR-incorporating bispecific format, called T cell engaging receptor (TCER®). TCER® molecules targeting different peptide-HLA antigens and using different recruiting moieties were generated and assessed for preclinical characteristics such as *in vitro* efficacy, *in vitro* safety and anti-tumor responses in tumor xenograft models.

Results Based on comparative preclinical testing of different TCR bispecific formats and T cell recruiting antibodies, we have developed a next-generation bispecific (TCER®) consisting of a high-affinity TCR capable of targeting tumor-specific peptide antigens and a low-affinity T cell recruiter designed to maximize efficacy while minimizing toxicity. The TCER® format harbors an effector function-silenced Fc part for the extension of serum half-life and improved manufacturability. For the development of different TCER® candidates, TCRs with promising functional avidity and high target-specificity are identified from the human repertoire and matured via yeast surface display to enhance TCR stability and to increase TCR affinity towards the target-peptide by at least 1,000-fold while retaining the target-specific binding pattern. TCER® molecules built with the maturated TCRs show *in vitro* activity at picomolar concentrations against tumor cell lines presenting the target peptide at similar copy numbers as found on patient tumors. Further, the TCER® molecules demonstrate consistent tumor regression including complete remissions in tumor xenograft models in mice and thereby also uncovered an essential role for the type of T cell recruiting antibody. For our clinical lead TCER® candidates we confirmed a favorable *in vitro* safety profile with a broad therapeutic window between tumor and normal cell reactivity against more than 20 different human normal tissue cell types.

Conclusions We have developed a next-generation, half-life extended TCR Bispecific format that in preclinical tests demonstrated higher potency than multiple other established formats. By incorporating an innovative T cell recruiter we aim to reduce the risk for toxicities, specifically CRS, in patients. For each TCER® candidate we generate a robust preclinical data package before entering clinical development.

http://dx.doi.org/10.1136/jitc-2022-SITC2022.1319