HLA-A*02:01/p53 R175H pHLA complex with exquisite specificity. It effectively activated T cells and lysed tumor cells both in vitro and in vivo. This approach could in theory be used to target cancers containing mutations that are difficult to target in conventional ways.

Acknowledgements We thank Surojit Sur, Nicolas Wyhs, Ashley Cook, Marco Dal Molin, Richard L. Blosser, Lilian Dasko-Vincent, Christopher Thoburn, Jianhong Cao, and José Rodríguez Molina for assistance with this study.

Trial Registration NA

Ethics Approval NA

Consent NA

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http://dx.doi.org/10.1136/jitc-2020-SITC2020.0629

630 PD-L1/CD47 TUMOR DIRECTED B-BODYTM BISPECIFIC ANTIBODIES DEMONSTRATING SIGNIFICANT ANTI-TUMOR ACTIVITY WITH NO TOXICITY IN PRECLINICAL MODELS

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Background Tumor cells have been shown to utilize both innate and adaptive checkpoints to evade anti-tumor immune responses. CD47 and PD-L1 are two targets widely expressed on the cell surface of tumor cells and are predicted to coordinately suppress innate and adaptive sensing respectively to evade immune control. PD-L1 dampens T cell-mediated tumor killing (via PD-L1/PD-1 signaling) while CD47 protects tumor cells from phagocytosis (via CD47/SIRP-alpha signaling). Targeting each of the above pathways with monoclonal antibodies has shown promise with PD-L1/PD-1 inhibition showing durable responses and extended overall survival for several approved products, whereas the molecules targeting CD47 pathway are in early clinical trials. Given that a significant number of patients are either resistant or relapse on PD-L1/PD-1 therapy, combinations with anti-CD47 antibodies are being explored. However, the expression of CD47 on many normal cells such as hematopoietic cells, red blood cells (RBCs) and platelets provides a widespread antigen sink which impacts the PK and adverse event profile of these agents.

Methods Here, we describe the generation and testing of a large panel of bispecifics with combinations of different affinities to PD-L1 and CD47 using the B-Body™ bispecific screening platform. The bispecific antibodies were screened in various in vitro activity and developability assays. Selected leads from the screen were tested in multiple in vivo models with differential expression of CD47 and PD-L1.

Results The lead bispecific antibodies showed significant blockade of SIRPa/CD47 and PD-L1/PD-1 signaling in vitro and tumor growth inhibition in vivo. The studies also showed no significant binding to RBCs and induced minimal RBC phagocytosis in vitro. A summary of screened candidates and characterization of a lead candidate being developed further will be presented.

Conclusions We have identified multiple CD47/PD-L1 bispecific antibodies with favorable efficacy and safety profiles. Selection of a lead for further IND and clinical development is underway.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0630

631 DEVELOPMENT OF HIGHLY EFFICACIOUS AND SAFE TARGETED CANCER IMMUNOTHERAPY VIA IL12-BASED TMEKINE™ PLATFORM

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Background We developed tumor microenvironment-targeting immunocytokine or TMEkine™ utilizing strong anti-tumoral effect of interleukin 12 (IL-12). In this effort, we created a bi-specific 1+1 antibody fusion with conventional knob-in-hole technology where anti-CD20 was paired with IL-12 fc fusion arm. A couple of IL-12 muteins were used in our therapeutic molecules to reduce systemic toxicity. IL-12 has been known for a key orchestrator in immune response. The main actions of IL-12 include the induction of CD4+ Th0 cells toward Th1 type and enhancement of IFN-γ production, stimulation of cytotoxicity and growth of natural killer (NK) cells and CD8+ T cells. For these reasons, IL-12 has long been considered as a potential therapeutic molecule for treating cancers by enhancing immune activity toward tumor cells. However, systemic administration of IL-12 showed poor efficacy and severe adverse effects. With our therapeutic approach of tumor targeting and attenuated IL-12 mutein, we expect that our IL12-based TMEkine™ holds great promise for the future of cancer immunotherapy.In this study, we targeted CD-20 expressing cancers such as B-cell lymphoma with our anti-CD20/IL-12 mutein TMEkine. We evaluated the biological activity of our molecules with in vitro and in vivo efficacy and safety.

Methods The target specific binding to CD20 and IL-12 receptor was analyzed by FACS and ELISA. Biological activities as signaling transduction and T cell activation were confirmed in vitro using HEKblue IL12 cell line, primary human T cells and NK cells. The anti-tumor efficacy of TMEkine (CD20-IL-12) was assessed in A20 lymphoma syngeneic mouse model. To demonstrate long term protection to A20, the cured five mice after TMEkine administration were re-challenged with A20 and 4T1 cells.

Results First, we analyzed the specific binding of our TMEkine molecules to CD20 expressing B-cell lymphoma cell lines (such as Raji). We showed that TMEkine (CD20-IL-12) binds to Raji and Ramos, which express CD20, but not to Jurkat, which does not express CD20. We also showed that TMEkine molecules bind to IL-12 receptor in a dose-dependent manner. pSTAT4 alphaLISA assay revealed that TMEkine (CD20-IL-12) transduces STAT4 signaling. In our IL-12 mutein, key residues for heparin binding were mutated. The biological activity of our mutein molecule was attenuated due to this change in human PBMC. In addition, our TMEkine molecules significantly induced IFN-γ secretion from primary human T cells and NK cells. An A20 B-cell lymphoma syngeneic mouse model was utilized to investigate the anti-tumor activity of TMEkine (CD20-IL-12). TMEkine molecules were injected three times with Q3D intraperitoneally. Tumor growth was