PRE-CLINICAL DEVELOPMENT OF CT-1119, A MESOTHELIN TARGETING CHIMERIC ANTIGEN RECEPTOR MACROPHAGE (CAR-M), FOR SOLID TUMOR IMMUNOTHERAPY

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Background Despite significant success in treating hematological malignancies, adoptive cell therapies have yielded limited efficacy in solid tumors. Macrophages are myeloid cells of the innate immune system and are naturally recruited to solid tumors, where they have the potential to phagocytose tumor cells, activate the tumor microenvironment (TME), and prime a broad anti-tumor adaptive immune response via T cell recruitment and activation. We have previously developed chimeric antigen receptor macrophages (CAR-M) targeting HER2 and showed efficacy in a variety of pre-clinical models, with a Phase I clinical trial ongoing. Mesothelin is overexpressed in a variety of solid tumors, including mesothelioma, lung, pancreatic, and ovarian cancers. Here, we present preclinical data summarizing the development of CT-1119, a mesothelin targeted CAR-M for solid tumors.

Methods Using the chimeric adenoviral vector Ad5f35, we engineered primary human macrophages to express a CAR comprising a human scFv targeted against human mesothelin. To assess the activity of CT-1119, in vitro cell based assays and in vivo murine xenograft models were utilized. Donor-matched untransduced (UTD) macrophages served as controls.

Results Primary human CAR-M engineered with an Ad5f35 vector demonstrated high CAR expression, high viability, upregulated M1 (anti-tumor) macrophage markers, and downregulated M2 (pro-tumor) macrophage markers. CT-1119 demonstrated increased resistance to repolarization by M2 (pro-tumor) polarizing cytokines as compared to donor matched UTD macrophages. CT-1119 specifically bound mesothelin and binding was not impacted by mesothelin shedding. CT-1119 specifically phagocytosed multiple mesothelin expressing tumor cell lines in a CAR-dependent and antigen-dependent manner. CT-1119 demonstrated robust in vitro killing of the relevant tumor cell lines A549 and MES-OV expressing mesothelin. CAR engagement also induced the release of pro-inflammatory cytokines such as TNFα following stimulation with mesothelin in both cell-free and cell-based contexts in a dose-dependent manner. In vivo, CT-1119 significantly reduced tumor burden in a murine xenograft model of lung cancer. Similarly, human monocytes targeting mesothelin were successfully generated using the same Ad5f35 vector and demonstrated specific activity against mesothelin positive tumor cells.

Conclusions The presented results demonstrate that CT-1119, an autologous human anti-mesothelin CAR-M, can cause phagocytosis, tumor cell killing, and pro-inflammatory cytokine release in response to stimulation with mesothelin. These results show that CAR-M is a feasible approach for the treatment of mesothelin expressing solid tumors via the potential for induction of a systemic anti-tumor response.

REFERENCES

Ethics Approval All studies involving animals were approved by the IACUC of the Wistar Institute (protocol 201364).