CF33-CD19 T ONCOLYTIC VIRUS (ONCARLYTICS) IN COMBINATION WITH OFF-THE-SHELF ALLOGENEIC CYCART-19 T CELLS TARGETING DE NOVO CD19+ SOLID TUMORS

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Background Autologous chimeric antigen receptor (CAR) T cell therapy has shown impressive clinical responses against CD19+ B-cell hematological malignancies and is being actively explored in the treatment of solid tumors. However, several barriers have precluded therapeutic responses in solid tumors, including limited tumor-restricted CAR targets and the immunosuppressive tumor microenvironment. We have recently reported the successful combination immunotherapy using a novel chimeric vaccinia-based oncolytic virus (OV), called onCARlytics (Imugene Limited), that is engineered to express a non-signaling, truncated CD19 (CD19t) antigen for tumor-selective delivery, enabling de novo targeting of tumor cells by autologous CD19-CAR T cells. One of the field’s unanswered questions is whether treatment-naïve allogeneic CAR T cells are superior to cancer patient-derived T cells for product manufacturing to improve overall responses against solid tumors.

Methods Here, we evaluated this combination strategy using two allogeneic CAR T cell products generated from peripheral blood mononuclear cells (PBMC) and placental T cells, respectively. PBMC-derived CAR-T cells were manufactured from normal, healthy donors. CYCART-19 (Celularity, Inc.) cells were derived from postpartum human placental T cells that are genetically modified to express the CD19 CAR followed by CRISPR-Cas9- mediated knockout of the endogenous TCR and expanded to produce multiple doses of allogeneic “off the shelf” treatment. For preclinical testing, we utilized in vitro co-culture assays. We evaluated tumor cell killing and T cell activation using flow cytometry and cytokine assays. Xenograft mouse models were used to evaluate anti-tumor activity of the combination in vivo.

Results CYCART-19 T cells induced potent cytoltyic activity against solid tumor cells infected with onCARlytics. Interestingly, while we observed comparable anti-tumor activity between PBMC-derived CD19-CAR T cells and CYCART-19, significant differences in cytokine secretion were detected. This warrants the possibility that the placental-derived CAR T product may elicit reduced CRS potential in patients with maintained or improved efficacy. This combination approach demonstrated impressive in vivo anti-tumor response in human tumor xenograft models.

Conclusions In summary, our results have demonstrated that further development of this combination immunotherapy for the potential treatment of a wide array of solid tumors is warranted.