PRECLINICAL EVALUATION AND ANTI-TUMOR ACTIVITY OF AZD6422, A CLDN18.2 TARGETING ARMORED CAR-T FOR GASTRIC, ESOPHAGEAL AND PANCREATIC CANCERS

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Background CLDN18 is a well-characterized cell surface membrane protein involved in the formation of tight junctions. Two different isoforms, CLDN18.1 and CLDN18.2, have been identified. Expression of CLDN18.2 has been observed in pancreatic, gastric and esophageal cancers, whereas normal tissue expression of CLDN18.2 is mostly restricted to differentiated gastric mucosal epithelial cells. This has led to extensive exploration of CLDN18.2 as a clinical target for multiple therapeutic modalities, including chimeric antigen receptor T cells (CAR-T). While CAR-T are showing clinical promise, a challenge faced in development of CAR-T therapy for solid tumors will be to overcome the immunosuppressive tumor microenvironment (TME) which includes presence of immune and stromal cells secreting high levels of TGFβ.

Methods Herein we report preclinical development of a novel second-generation CLDN18.2 targeting CAR-T in antigen positive gastric, esophageal and pancreatic models. We evaluated inclusion of a dominant negative TGFβRII armoring in the lentiviral construct, with both the CAR and the dominant negative receptor driven from a single promoter, as well as use of a cell manufacturing process designed to generate a less differentiated final CAR-T product in a shorter time frame.

Results In vitro characterization of the dnTGFβRII armored CLDN18.2 targeted CAR-T, AZD6422, demonstrated specific cytotoxic activity across a range of antigen expression levels in cancer cell lines. Further, serial restimulation assays established superior persistence and cytolytic function of AZD6422 as compared to the unarmored CAR-T over multiple rounds of coculture with tumor cells. Importantly, AZD6422 exhibited superior in vivo anti-tumor activity and tolerability following a single CAR-T infusion in multiple patient derived xenograft models with varied CLDN18.2 and TGFβ levels as determined by IHC.

Conclusions Taken together, the selection of CAR-T design which provided therapeutic margin in relevant murine models, addition of armoring and optimization of manufacturing enabled generation of a lead molecule which provides efficacy in relevant cell line and patient derived xenograft models of gastric, pancreatic and esophageal cancers and supports further clinical development of AZD6422.

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