PRECLINICAL DEVELOPMENT AND CHARACTERIZATION OF ALLOGENEIC CAR T CELLS TARGETING CLAUDIN18.2-POSITIVE TUMORS

Zhe Li*, Barbra Sasu, Siler Panowski. Allogene Therapeutics, South San Francisco, CA, USA

Background Claudin18.2 (CLDN18.2) has emerged as a promising therapeutic target, with high expression in many types of epithelial cancers including stomach, esophagus, pancreatic, and ovarian cancers. Multiple CLDN18.2-directed monoclonal antibodies and autologous CAR T cell therapies have entered clinical trials and demonstrated promising results. Here, we describe the preclinical development of a novel allogeneic, off-the-shelf CLDN18.2 CAR T product candidate with the potential to provide clinical benefit with a single treatment and overcome many of the challenges facing autologous CAR T cells.

Methods A panel of allogeneic fully human scFv-based CAR T cells targeting both human and murine CLDN18.2 were generated. To enable off-the-shelf use, TALEN® gene editing was used to KO the TRAC locus; CD52 was also eliminated to permit CD52-directed lymphodepletion regimens. Binding specificity was studied utilizing cell lines and candidates were characterized using a variety of in vitro functional assays and in vivo xenograft mouse models. Rituximab-based off switches to provide control over CAR T function were also evaluated.

Results A subset of CARs showed highly specific binding to CLDN18.2 and evaluation of these CARs in multiple rituximab off-switch formats identified candidates with potent activity in both short-term and repeat stimulation in vitro cytotoxicity assays. Lead allogeneic CAR T cell candidates exhibited cytokine release upon target exposure and displayed robust antitumor activity at low cell doses in vivo against both subcutaneous and intraperitoneal gastric cancer models. Safety evaluation was also performed, including body weight measurement. Taken together, these data support the existence of a therapeutic window and the potential to target CLDN18.2 with allogeneic off-the-shelf CAR T cells.

Conclusions These efficacy and safety data suggest that allogeneic CLDN18.2 CARs may be an effective and clinically valuable treatment for patients with CLDN18.2-positive cancers.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0283