Background There is an urgent unmet medical need for patients with advanced unresectable and/or metastatic carcinomas. Mucin 1 (MUC1) is a well-characterized heterodimeric glycoprotein that is overexpressed on many epithelial-derived tumors and consists of non-covalently linked N-terminal (MUC1-N) and C-terminal (MUC1-C) monomers. The MUC1-C epitope is selectively seen in epithelial-derived solid tumors such as breast, colorectal, ovarian, gastric, lung carcinoma and others. MUC1-C is also expressed broadly and accessibly throughout tumor tissue due to the loss of cell polarity, one of the hallmarks of tumorigenesis. P-MUC1C-ALLO1 is a fully allogeneic CAR-T targeting the MUC1-C epitope and is manufactured using non-viral transposon-based integration (piggyBac® DNA Delivery System) that results in a highly enriched T stem cell memory (TSCM) product. It contains 3 transgenes: an anti-MUC1-C humanized scFv-based CAR, a DHFR drug selection gene to improve product homogeneity, and an iCasp9-based safety switch gene to allow for rapid ablation of the CAR-T if required. The cells are gene edited using the Cas-CLOVER™ Site-Specific Gene Editing System to eliminate expression of endogenous T cell receptors in all cells via knockout of the T cell receptor beta chain 1 gene to prevent graft-vs-host (GvH) response, and the β2-microglobulin gene to eliminate expression of MHC class I to attenuate host-vs-graft responses. Preclinical efficacy was observed with P-MUC1C-ALLO1 in murine models of triple negative breast cancer and ovarian cancer, providing rationale for this first-in-human (FIH) Phase 1 trial.

Methods This is a Phase 1, multi-center, open-label, FIH, 3+3 design to evaluate P-MUC1C-ALLO1 in patients with advanced or metastatic epithelial-derived cancers measurable by RECIST 1.1 and refractory/ineligible to standard of care therapy. Up to 100 patients will be enrolled into 4 arms of single and cyclic administrations using two different lymphodepletion (LD) regimens (cyclophosphamide/fludarabine ± rituximab). Planned dose escalation in each arm ranges from 0.75 to 15 x 10^6 cells/kg.

Primary objectives for this study include defining maximum tolerated dose (MTD), evaluation of overall safety and tolerability, preliminary efficacy, and disease response. Exploratory endpoints will include MUC1-C tumor expression and correlation to response, P-MUC1C-ALLO1 cell kinetics, and bio-marker analysis including MUC1 related tumor markers CA15-3 and CA27-29 and CTCs.

Results To date, three patients have been treated with P-MUC1C-ALLO1 (esophageal adenocarcinoma, colorectal adenocarcinoma, and breast cancer). P-MUC1C-ALLO1 treatment to date has been well tolerated, with no dose limiting toxicities, CRS, or GvH disease observed. This study continues to recruit subjects and updated data will be presented.

Trial Registration NCT05239143

Ethics Approval Ethics approvals have been obtained from the clinical sites enrolling patients: Sarah Cannon Research Institute Denver CO (IORG0010151); NEXT Oncology San Antonio TX (IORG0005674); University of California, San Francisco, CA (IORG0000135)