Phase 1 Study of P-MUC1C-ALLO1 Allogeneic CAR-T Cells in Patients With Epithelial-Derived Cancers

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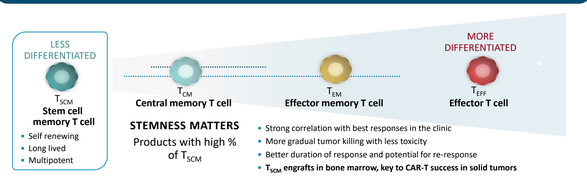
BACKGROUND

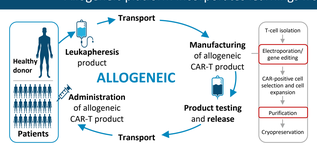
- There is a high unmet medical need in the treatment of advanced unresectable and metastatic solid cancers even though many different treatment options are available.
- Most solid tumors are of epithelial origin and express mucin 1 (MUC1) and MUC1-C (MUC1, cell surface associated, C-terminal), such as breast, ovarian, prostate, colorectal, pancreatic, gastric, esophageal, nasopharyngeal, as well as non-small cell lung cancer, renal cell carcinoma, head-and-neck squamous cell carcinoma, and others.
- There have been multiple clinical-stage therapeutics against the MUC1 epitope, including chimeric antigen receptor (CAR)-T therapies, antibody-drug conjugates, and bispecific T-cell engagers which have thus far demonstrated little evidence for "on-target, off-tumor" toxicity.[1-3]
- MUC1-C is expressed broadly and accessibly throughout tumor tissue due to the loss of cell polarity, one of the hallmarks of tumorigenesis.
- We have developed a fully allogeneic CAR-T cell therapy, called P-MUC1C-ALLO1, targeting the MUC1-C epitope that is manufactured using non-viral transposon-based integration (piggyBac® DNA Delivery System), resulting in a highly enriched T stem cell memory (T_{SCM}) product. Previously, P-MUC1C-ALLO1 administration resulted in complete elimination of solid tumors in murine models.
- This first-in-human Phase 1 clinical trial is evaluating a CAR-T in epithelial-origin tumors.

P-MUC1C-ALLO1 is highly enriched for T stem cell memory CAR-Ts

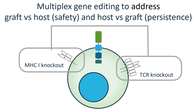


- Strong correlation with best responses in the clinic
- More gradual tumor killing with less toxicity
- Better duration of response and potential for re-response
- **T_{SCM} engrafts in bone marrow, key to CAR-T success in solid tumors**

Allogeneic platform incorporates learnings from our autologous experience



FULLY ALLOGENEIC
Multiplex gene editing to address graft vs host (safety) and host vs graft (persistence)



Unique allogeneic platform

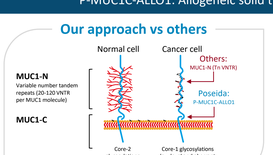
- Preserve/improve **high T_{SCM}**
- **Optimized dosing** regimens
- **Healthy donor** material
- **Robust manufacturing**
- Dramatic **cost reductions**
  - Up to **100s of doses**

Booster molecule

Our patented technology is designed to overcome the "allo tax" and **significantly increase production yield** while **preserving desirable T_{SCM} attributes** of P-MUC1C-ALLO1.

P-MUC1C-ALLO1: Allogeneic solid tumor CAR-T with broad potential

Our approach vs others



Tumor type	Total MUC1 expression, %*	Poseida MUC1-C IHC frozen tissue data, %†
Breast	91	92
Ovarian	83	93

*American Cancer Society, 2017; †Positive samples defined as: Frequency: +, occasional cells; ++, few cells; +++, many cells Intensity: 2, mild; 3, moderate; 4, heavy staining

Breast

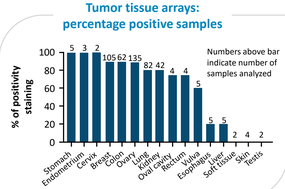
Ovarian

- MUC1 is normally expressed on the apical surface of epithelium. On cancer cells, an aberrant form is expressed, and polarity is lost.
- The P-MUC1C-ALLO1 targets MUC1-C, which is retained on the cell surface following cleavage of MUC1-N.
- **P-MUC1C-ALLO1** potentially addresses patients populations in **multiple solid tumor indications** including many epithelial-derived cancers.
  - Breast, ovarian, non-small cell lung, colorectal, pancreatic, and others.
- **High representation of P-MUC1C-ALLO1 epitope** in breast and ovarian cancer.

PRECLINICAL RATIONALE

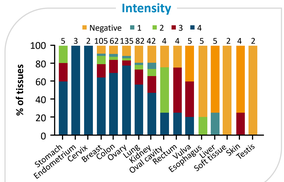
P-MUC1C-ALLO1 epitope highly prevalent in solid tumor indications

Tumor tissue arrays: percentage positive samples



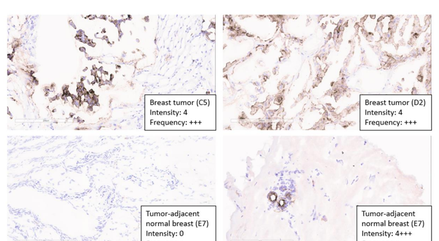
- A high percentage of tumor samples tested positive for staining with scFv binder used by P-MUC1C-ALLO1 CAR.
  - ~90% of breast and colon tumors were positive, as were 88% of ovary, 81% of lung, and 81% of renal tumors.
- Expression profile was consistent with what has been widely reported for full-length MUC1.

Intensity



- Percentage of positive samples was similar for breast, colon, ovary, lung, and renal tumors, but intensity of staining varied between indications.
- 77% of ovarian vs 47% of renal tumors scoring 4 on a scale of – (0), 1, 2, 3, or 4, with 4 being the highest intensity.

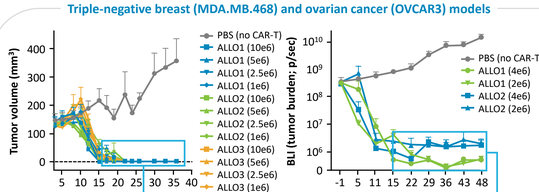
Representative IHC staining using MUC1C-scFv



- **100% of normal tissue staining was in the apical aspect** of the acinar/ ductular glandular epithelium, extending to involve the luminal surface **vs tumor staining, which was global**
- T-cell access to luminal surfaces of normal tissues is highly regulated under normal circumstances
- Likely contributes to excellent safety record of >40 MUC1-targeting drugs in clinical development

P-MUC1C-ALLO1 CAR-T demonstrated potent in vivo activity

Triple-negative breast (MDA.MB.468) and ovarian cancer (OVCAR3) models



Four animals per group.
Error bars SEM.

100% tumor elimination after ~2 weeks

CLINICAL STUDY METHODS AND DESIGN

Topic	Detail
Study information	This was a Phase 1, dose escalation, and expanded cohort study of P-MUC1C-ALLO1 in adults with advanced or metastatic solid tumors (NCT05239143). The study will include 15 years of follow-up and evaluate the safety, MTD, and antitumor effect of P-MUC1C-ALLO1.
Study design	Part 1: Standard 3+3 design of dose-escalating cohorts **Arm A (SA)**: single dose after cy/flu lymphodepletion **Arm B (CYC)**: multiple doses in cycles Q2W after cy/flu lymphodepletion with ≤2 additional lymphodepletion in cycles ≤6-week intervals **Arm C (SA-RIT)**: singe dose after cy/flu plus rituximab lymphodepletion **Arm D (CYC-RIT)**: multiple doses in cycles Q2W after cy/flu/rit lymphodepletion with ≤2 additional lymphodepletion in cycles ≤6-week intervals Part 2: RP2D at ≤MTD in groups of up to 15 patients with defined characteristics
Study patient population	Adults with confirmed unresectable, locally advanced or metastatic epithelial-derived solid tumors refractory to standard-of-care therapy or ineligible or refused another existing treatment option
Proposed sample size	Up to 100 patients
Evaluation criteria: efficacy, safety, and other variables	Safety/feasibility: AEs, labs, CRS, neurotoxicity, and MAS/HLH[4] Efficacy: RECIST v1.1 and secondarily iRECIST; ORR, TTR, DOR, PFS, OS, CTCs, P-MUC1C-ALLO1 cells (vectors/clonality)
Exploratory	MUC1-C expression in tumor biopsies. P-MUC1C-ALLO1 cell kinetics and phenotype including B2m expression; immunogenicity in context of patient-donor match metrics. Cytokine correlates of lymphodepletion, safety, and efficacy.

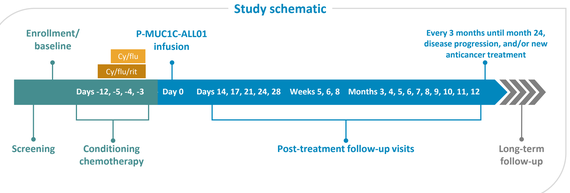
Major inclusion criteria

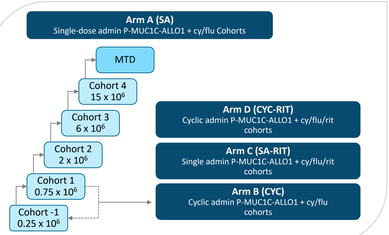
- Must have a confirmed diagnosis (histological or cytological confirmation) of unresectable, locally advanced or metastatic epithelial-derived cancer (including but not limited to breast, ovarian, non-small cell lung, colorectal, pancreatic, and other cancers)
- Measurable disease per RECIST v1.1
- Refractory to standard of care treatment or ineligible/refused other existing treatment options
- ANC ≥1000/μL, platelets 50,000/μL, Hb >8 h/dL
- Ferritin ≤5000 ng/mL
- Creatinine ≤1.5 mg/dL, ALT and AST ≤1.5 x ULN
- LVEF ≥45% within 4 weeks of screening
- Patients must have tissue available or be willing to consent to a biopsy collection for retrospective and exploratory biomarker testing. Archived or fresh tumor core biopsy is required.

Major exclusion criteria

- Active second primary malignancies
- Active autoimmune disease
- Active systemic infections
- Significant CNS, liver or heart disease
- Has known CNS metastases or symptomatic CNS involvement (including leptomeningeal carcinomatosis, cranial neuropathies or mass lesions that cause spinal cord compression).
- Has a history of or active hepatitis B (HBV) or hepatitis C (HCV). Must test negative for HBsAg, HBcAb, HBV DNA, HCV RNA.
- Has a history of or active infection with human immunodeficiency virus (HIV) 1 or 2 or human T lymphotropic virus (HTLV I/II). Must test negative for HIV and HTLV.
- Has a history of significant liver disease or active liver disease not related to metastatic tumor (e.g., including but not limited to fibrosis, cirrhosis, or disease involving the hepato-biliary tract that could worsen or may require treatment during the study). The medical monitor will determine whether a disease meets this exclusion criterion.
- Has a history of or known genetic predisposition to HLH/MAS.

STUDY SCHEMATIC





*Doses are weight-based (cells/kg); currently dosing in Cohort 2.

Planned dose escalation*

If the maximum tolerated dose (MTD) has not been reached following completion of cohort 4, the dose of P-MUC1C-ALLO1 may be increased by 5-10 x10^6 cells/kg for the subsequent dose levels as agreed upon with the safety committee and the FDA.

SUMMARY

- MUC1-C epitope is highly expressed across common epithelial cancers and is apically restricted in normal tissues.
- Potent antitumor activity was seen in triple-negative breast cancer and ovarian xenograft models.
- The Phase 1 trial for P-MUC1C-ALLO1 was initiated in Feb 2022 with the first patient treated in May 2022 and is estimated to treat up to 100 patients.
- As of the data cut-off of 29 Sep 2022, we are continuing dose escalation and are currently enrolling in cohort 2 at dose level 2 x 10^6 cells/kg.
- Cohort 1 was completed without dose-limiting toxicities, CRS, or graft vs host disease observed.

PARTICIPATING STUDY CENTERS

KU Medical Center – The University of Kansas
next ONCOLOGY
UC San Diego
Sarah Cannon – Fighting Cancer Together
The University of Texas MD Anderson Cancer Center
UCSF Helen Diller Family Comprehensive Cancer Center
Memorial Sloan Kettering Cancer Center

ACKNOWLEDGMENTS: The authors and Poseida Therapeutics, Inc., thank the patients, caregivers, investigators, and study site staff for their involvement in this study. This study was funded by Poseida (San Diego, CA). Editorial support funded by Poseida was provided by Keng Jin Lee, PhD, and Joe Alling, BSc, of Core Medica (Knutsford, UK).

ABBREVIATIONS: AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; B2M = beta-2-microglobulin; BLI = bioluminescent imaging; CNS = central nervous system; CRS = cytokine release syndrome; CTC = circulating tumor cell; cy = cyclophosphamide; CYC = cyclic administration; DOR = duration of response; FDA = US Food and Drug Administration; Hb = hemoglobin; flu = fludarabine; HLH = hemophagocytic lymphohistiocytosis; ICANS = immune effector cell–associated neurotoxicity; LVEF = left ventricular ejection fraction; MAS = macrophage activation syndrome; MTD = maximum tolerated dose; ORR = overall response rate; OS = overall survival; PBS = phosphate-buffered saline; PFS = progression-free survival; Q2W = every 2 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; RIT = rituximab; RP2D = recommended Phase 2 dose; SA = single ascending; TTR = time to response; ULN = upper limit of normal.

REFERENCES: 1. Taylor-Papadimitriou J et al. *Biochem Soc Trans.* 2018;46(3):659-668. 2. Gutierrez R et al. *J Clin Oncol.* 2021;39(suppl 15). 3. Specht J et al. *J Clin Oncol.* 2021;39(suppl 15). 4. Lee DW et al. *Biol Blood Marrow Transplant.* 2019:25(4):625-638.