Penn Medicine

TnMUC1-targeted CAR T cells

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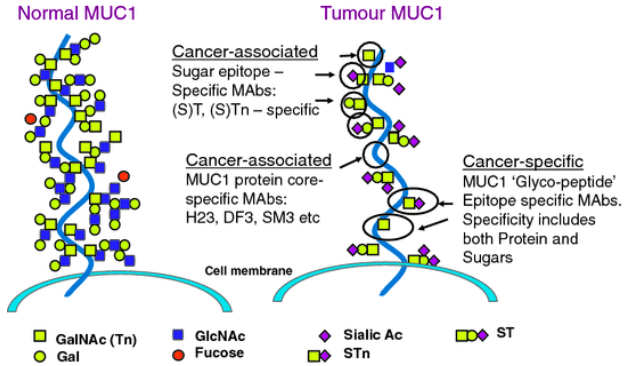
CAR T cells in solid cancers

- CAR T cell efficacy is limited in solid cancers
- Many barriers to effective translation of CAR T cells need to be overcome in order to demonstrate activity in solid cancers
  - CAR target selection
  - Trafficking and infiltration of CAR T cells in solid tumors
  - Immunosuppressive microenvironment
- An ideal target would be a tumor-specific cell surface protein
  - Most surface proteins on epithelial malignancies, however, are shared proteins with essential tissues throughout the body

Glycosylation of MUC1

- MUC1 is a glycoprotein commonly expressed on most simple glandular epithelial cells and some leukocytes
- In cancers arising from these tissues, MUC1 is commonly aberrantly glycosylated
  - Common forms of aberrant glycosylation include Tn and STn
- Tn and STn expression
  - Associated with worse prognosis in a variety of malignancies
  - Alter cell adhesion and motility
  - Increase tumorigenesis and metastatic potential

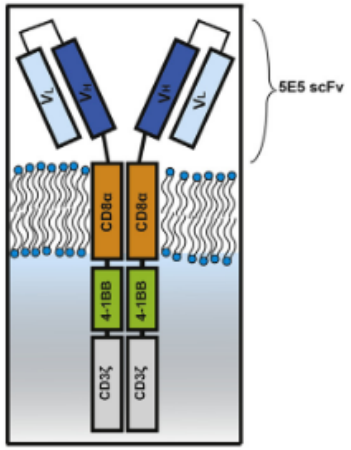


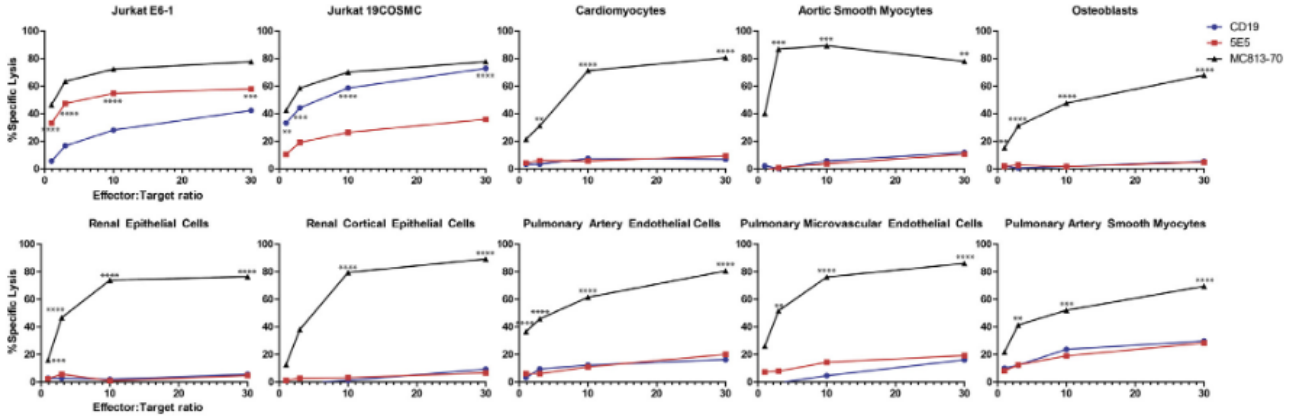
- TnMUC1 is overexpressed on multiple myeloma and breast, colon, lung, stomach, ovary, and pancreatic cancer cells
- TnMUC1 is recognized by the monoclonal antibody 5E5
  - 5E5 reacts with all Tn and STn glycoforms of MUC1, but not unglycosylated MUC1

Posey AD et al, 2016; Radhakrishnan P et al, 2014; Ren D et al, 2014; Cazet A et al, 2010; Sorenson AL et al, 2006; Andrulis M et al, 2014; Laverson K et al, 2013; Pinto R et al 2012

TnMUC1 as a target for CAR T cells

- The 5E5 scFv is an attractive targeting domain for CAR T cells
- 5E5 monoclonal antibody binding to normal tissues
  - Immunostain of normal tissue shows no binding of 5E5 mAb to most tissues
  - Tissue microarrays for stomach, lung, pancreas, and kidney did stain for 5E5 mAb, but stain was intracellular
- Intense binding of 5E5 in human breast cancer cells
- CAR T cells with the 5E5 scFv demonstrated no reactivity to normal human tissues by chromium release assays

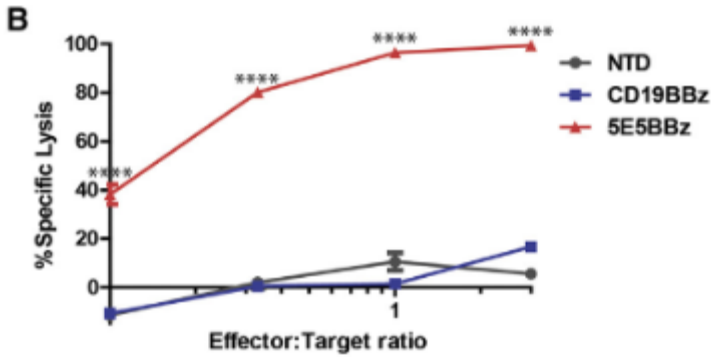


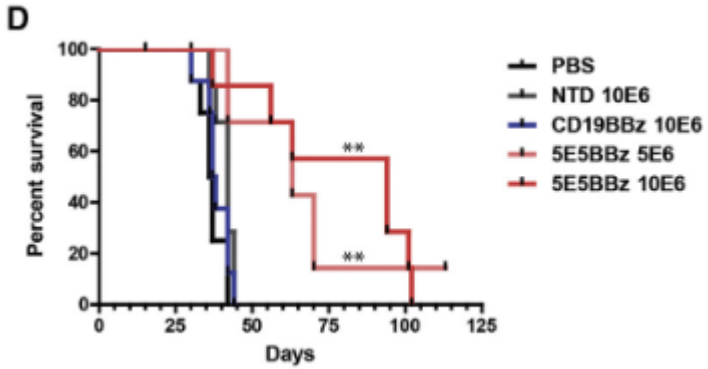


Posey AD et al, 2016

TnMUC1-directed CAR T cells

- TnMUC1-directed CAR T cells demonstrate potent cytotoxicity and improved survival



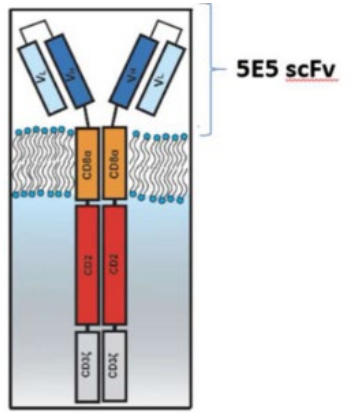


- TnMUC1-directed CAR T cells recognize multiple different cancer cell lines
  - Leukemia (Jurkat and K562)
  - Pancreas
  - Breast

Posey AD et al, 2016

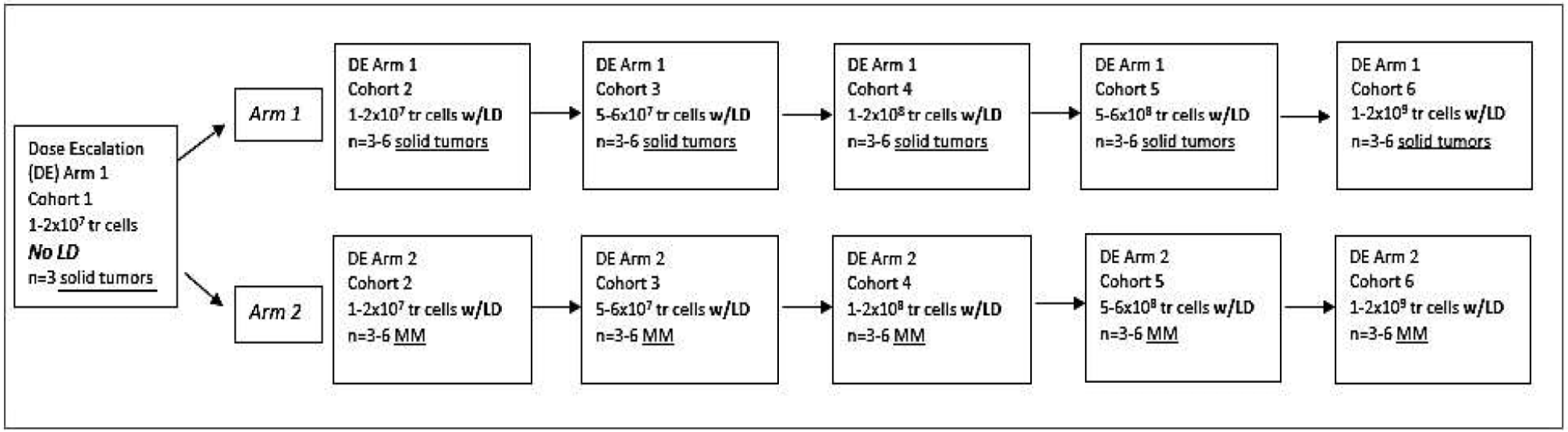
Phase I open-label multicenter first in human study of TnMUC1-targeted genetically modified CAR T cells in patients with advanced TnMUC1-positive solid tumors and multiple myeloma

- First in human phase 1 trial with dose escalation using a TnMUC1-directed CAR
- Main Inclusion/Exclusion Criteria
  - Confirmed diagnosis of one of the following
    - Metastatic epithelial ovarian cancer
    - Metastatic pancreatic adenocarcinoma
    - Metastatic triple negative breast cancer
    - Metastatic non small cell lung cancer
    - Relapsed/refractory multiple myeloma
  - TnMUC1+ disease as assessed by central testing on prior or archival tissue
  - Evaluable disease
  - Adequate vital organ function and performance status
  - No active autoimmune disease or significant concurrent infections
  - No concurrent systemic steroid use



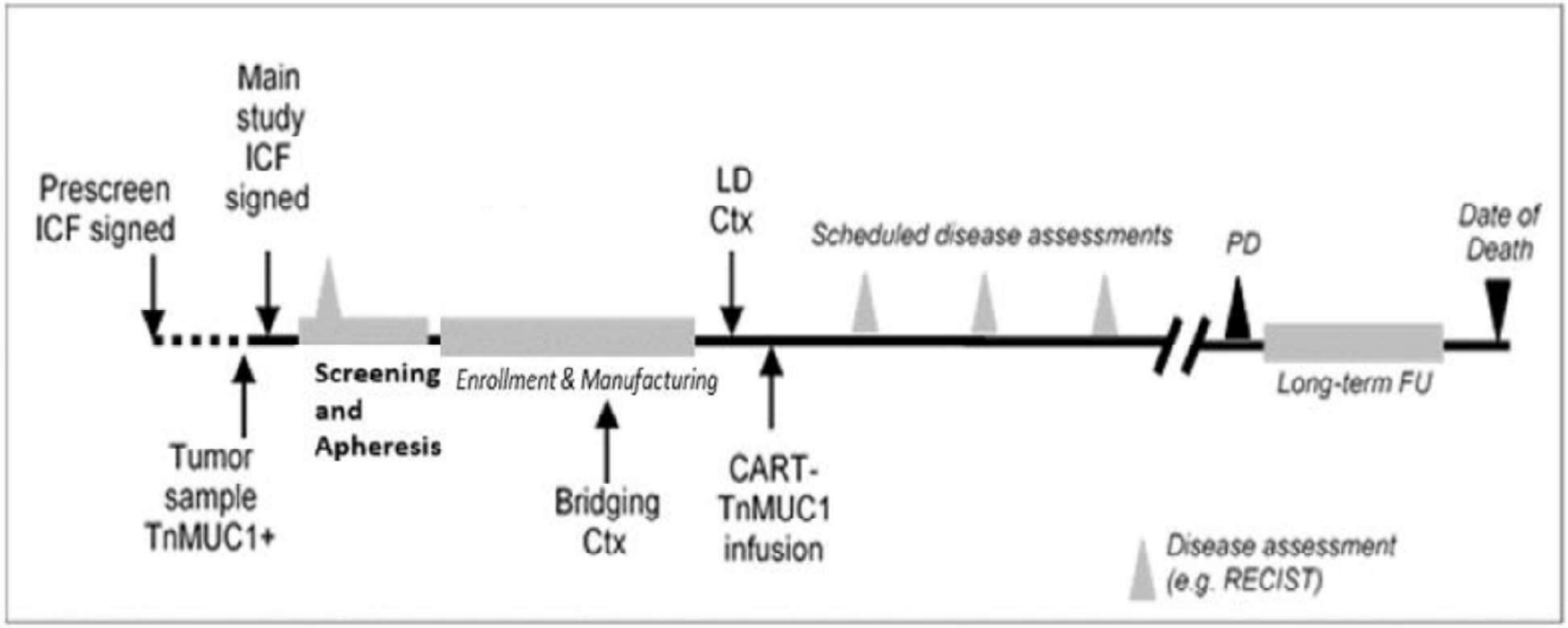
Phase I trial: CART-TnMUC1

- Two Dose Escalation arms are being assessed
  - Arm 1: solid cancers (pancreatic, NSCLC, breast cancer, ovarian cancer)
  - Arm 2: multiple myeloma
- Planned dose expansion in each malignancy once the RP2D is achieved



Phase I trial: CART- TnMUC1 cells

- Patient treatment pathway



Phase I trial: TnMUC1 CART-TnMUC1 cells

- Primary Objectives
  - Dose escalation arms: identify a RP2D of CART-TnMUC1 cells
  - Expansion phase: estimate the overall response rate of CART-TnMUC1 cells in patients with TnMUC1+ tumors
- Secondary Objectives
  - Assess safety, tolerability, and feasibility of CART-TnMUC1 cells
  - Evaluate preliminary efficacy of CART-TnMUC1 cells by measuring ORR, DOR, TTR, PFS, and OS
- Exploratory Objectives
  - Characterize peripheral blood for persistence and activity of CART-TnMUC1 cells, levels of cytokines and other soluble biomarkers, and identify anti-CAR immune responses
  - Evaluate the tumor and tumor microenvironment in pre- and post-treatment biopsies to evaluate mechanism of response and/or resistance to CART-TnMUC1 cells

Phase I trial: TnMUC1 CART-TnMUC1 cells

- The trial (NCT04025216) is currently enrolling at 2 sites and will expand to 8 sites
- Data on tolerability and potential efficacy will be updated in the future

Conclusions

- TnMUC1 is an attractive target for CAR T cell therapy in solid malignancies
- The 5E5 monoclonal antibody against TnMUC1 has specificity for TnMUC1+ tumor cells and limited binding to the cell surface of normal tissue
  - 5E5 is the scFv for the CART-TnMUC1 cells
- Preclinical work with CART-TnMUC1 cells demonstrates promising activity in TnMUC1+ malignancies
- An ongoing multicenter Phase 1 trial is exploring the use of CART-TnMUC1 cells in combination with lymphodepleting chemotherapy in patients with multiple myeloma or pancreatic, ovarian, non small cell lung, or triple negative breast cancers

Thank you

- Patients and their families

- CART-TnMUC1 Team at Penn
  - Al Garfall
  - Payal Shah
  - Charu Aggarwal
  - Reenie Martin
  - CCI team
  - Tmunity team