A phase I trial targeting advanced or metastatic pancreatic cancer using a combination of standard chemotherapy and adoptively transferred nonengineered, multiantigen specific T cells in the first-line setting (TACTOPS)

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Introduction

To explore the benefit of immunotherapy to solid tumors, we have developed a non-engineered T cell therapy with single T cell lines that simultaneously target the tumor-associated antigens (TAAs) PRAME, SSX2, MAGEA4, NY-ESO-1 and Survivin, and administer these T cells to patients with pancreatic adenocarcinoma (**Figure 1**) in a Phase I clinical trial. Treated patients reported here had unresectable/metastatic disease that was responding to standard first line chemotherapy. These patients began to receive monthly T cell infusions in month 4, while continuing the same chemotherapy (**Figure 2**). The primary study objectives are safety and feasibility with assessment of progression-free and overall survival as secondary outcome measures.

Figure 1

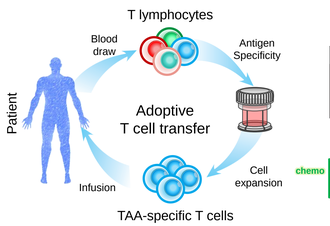
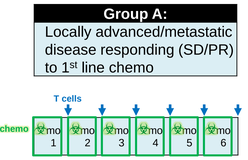


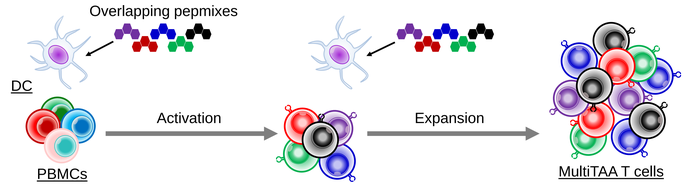
Figure 2



Manufacture of mTAA-T cells

Multiantigen-targeted T cells are generated by culturing autologous PBMCs in the presence of a Th1-polarizing/pro-proliferative cytokine cocktail, and adding autologous pepmix-loaded dendritic cells as antigen presenting cells (**Figure 3**). The use of whole antigen overcomes the HLA restriction imposed by the use of transgenic TCRs specific for single peptides, while targeting multiple antigens simultaneously should reduce the risk of tumor immune evasion.

Figure 3



Characteristics of mTAA-T cells

To date, we have generated 54 clinical-grade multiTAA T cell lines, comprising CD3+ T cells (mean 95.7±1.2%) with a mixture of CD4+ (mean 47.4±3.5%)) and CD8+ (mean 39.0±3.1%)) T cells (**Figure 4**) that recognize the targeted antigens PRAME, SSX2, MAGEA4, NY-ESO-1 and Survivin (range 0-2570, 0-721, 0-1385, 0-208 and 0-44 SFU/2x10^5, respectively in IFNγ ELIspot) (**Figure 5**). None of the lines reacted against non-malignant autologous cells (3±0.5% specific lysis; E:T 20:1) (**Figure 6**).

Phenotype

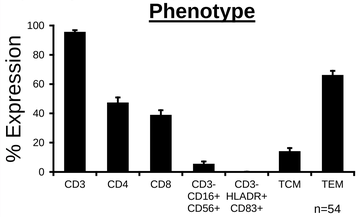


Figure 4

Specificity

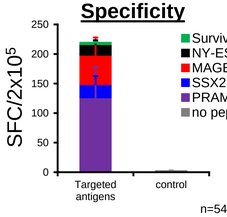


Figure 5

Safety

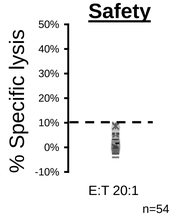


Figure 6

Treatment summary

- We treated 13 patients, each of whom received up to 6 monthly infusions of 1x10^7 multiTAA-T cells/m^2 in conjunction with ongoing first line chemotherapy and without prior protocol-associated lymphodepletion.
- For 12/13 patients, we generated sufficient cells for all 6 planned doses; 2 doses were available for the remaining patient.
- Patients had the following outcomes while on study treatment:
  - 2 patients had disease progression,
  - 1 patient had a mixed response,
  - 10 patients had ongoing radiographic stable disease or tumor responses (6-19 month duration), including one radiographic complete response.
- **Figures 7-10** show patients 7 (complete responder), 1, 3 and 12 (partial responders), with radiographic scans showing post-multiTAA T cell benefit that was associated with an increase in the circulating frequency of T cells directed against a spectrum of both targeted and non-targeted tumor associated antigens.
- **Figure 11** summarizes the outcomes of all patients treated
- For 9/13 patients, cancer control was maintained for a longer than expected duration, compared to historical controls
- Five additional patients underwent procurement for T cell product creation, but never received cells and are not included in response reporting:
  - 2 patients had disease progression and died from their disease prior to enrollment
  - 1 patient had disease progression and initiated a second line of chemotherapy prior to enrollment
  - 2 patients had an inadequate number of doses of T cells created. For each of these patients, 1 dose of the T cells were created and they could have gone onto the trial to receive the single dose. After discussion, these patients opted not to pursue trial therapy.

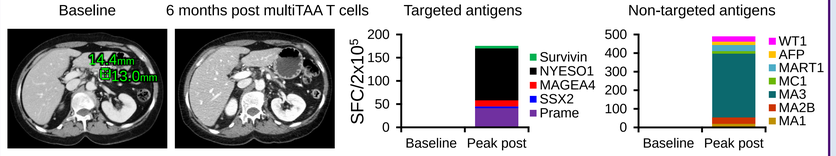


Figure 7-Radiographic response and antigen frequency pt#7

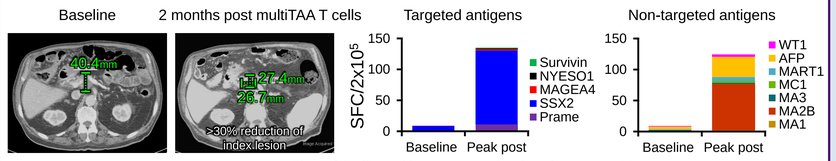


Figure 8-Radiographic response and antigen frequency pt#1

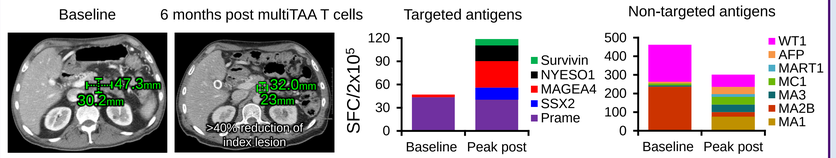


Figure 9-Radiographic response and antigen frequency pt#3

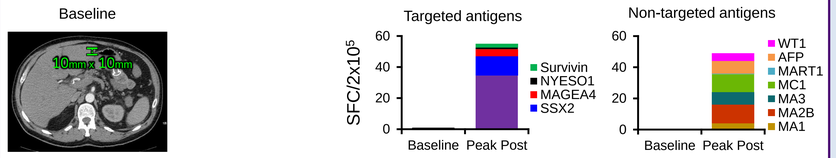
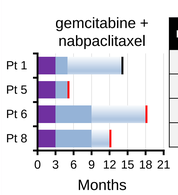
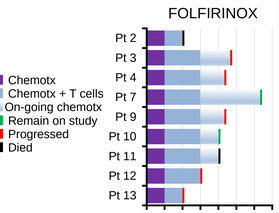


Figure 10- Radiographic metastatic disease and antigen frequency pt#12

Responses in patients



Patient	Best RECIST response on T cell therapy
1	Partial Response
5	Progressive Disease
6	Stable Disease
8	Stable Disease



Patient	Best RECIST response on T cell therapy
2	Mixed response
3	Partial Response
4	Stable Disease
7	Radiographic CR
9	Stable Disease
10	Stable Disease
11	Stable Disease
12	Partial Response
13	Progressive Disease

Figure 11: MultiTAA T cells + Chemo Summary

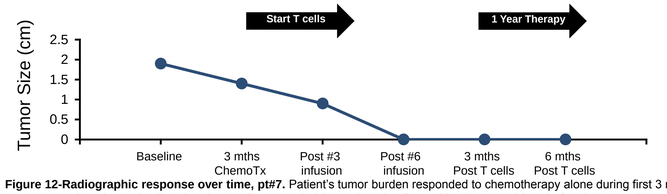


Figure 12-Radiographic response over time, pt#7. Patient's tumor burden responded to chemotherapy alone during first 3 months; response continued over the time that the T cells were administered, and radiographic CR was achieved after the 9 month assessment, when all 6 doses of T cells had been administered

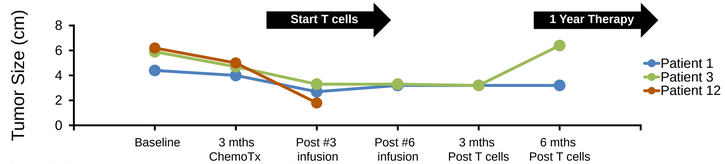


Figure 13-Radiographic responses over time, pts#1, 3, 12. The rate of these patients' tumor responses were enhanced with the addition of T cells to standard chemotherapy, starting with month 4

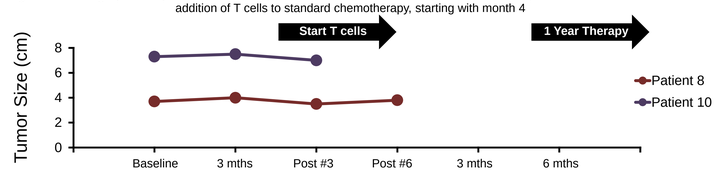


Figure 14-Radiographic responses over time, pts#8, 10. There appeared to be a degree of tumor progression during the initial 3 months of Standard of care chemotherapy, even though per RECIST, this would be defined as stable disease. With the introduction of T cells with month 4, these patients' tumors demonstrated a reversal in that trend and began to respond and shrink

Conclusions

Autologous, TAA cytotoxic T-cells can reliably be generated and safely administered to patients with advanced pancreatic cancer, in conjunction with standard of care chemotherapy. In some patients, addition of T-cells may extend duration of first line therapy cancer control and induce additional tumor responses. Clinical benefit has correlated with the detection of tumor-reactive T cells in patient peripheral blood. T cells have exhibited activity against targeted antigens as well as non-targeted TAAs indicating induction of antigen/epitope spreading. Notably, no patient had infusion-related systemic- or neuro-toxicity. Exploration in a higher phase study is warranted.