Background
Tumor cells rely on glucose consumption via glycolytic pathways. However, alternative metabolic pathways can be critical for the maintenance of tumor growth, survival, and dissemination. PPARα is a nuclear receptor that regulates the expression of genes involved in fatty acid metabolism, glucose metabolism, and inflammation. PPARα antagonists were shown to inhibit tumor growth in preclinical studies. TPST-1120 is a selective PPARα antagonist that blocks transcription of PPARα target genes leading to a metabolic switch from fatty acid oxidation (FAO) to glycolysis which supports both tumor growth and suppressive immune cells in the tumor microenvironment (TME). Increasing FAO usage facilitates tumor growth and suppressive immune cells. TPST-1120 leads to intracellular metabolism shift from FAO to glycolysis which inhibits tumor growth and facilitates an antitumor immune response.

Methods
This is a single-arm, open-label dose escalation study intended to establish MTD and the recommended phase 2 dose (RP2D). TPST-1120 is administered orally in 3 cycles, with a 7-day washout period between cycles. TPST-1120 will be dosed once daily in the morning to achieve plasma concentrations in the range of 3-4 nM with a >35 fold selectivity over other PPAR isoforms. TPST-1120 is administered in 2-stage expansion design. This trial will consist of 4 monotherapy arms and 4 combination arms in which TPST-1120 is combined with nivolumab, docetaxel, or cetuximab. TPST-1120 in combination with anti-PD1 or anti-EGFR monoclonal antibody leads to intracellular metabolism shift from FAO to glycolysis which inhibits tumor growth and facilitates an antitumor immune response. Indication for TPST-1120 includes treatment-naive and pretreated advanced solid tumors expressing high PPARα gene expression.

The primary objectives are to 1) evaluate safety and tolerability of TPST-1120 in patients with advanced solid tumors 2) evaluate antitumor activity in various solid tumors 3) characterize the PK of TPST-1120 and 4) characterize the PD of TPST-1120.

The secondary objectives are to 1) assess the correlation between gene expression profiling of PPARα-associated genes and immune activation genes 2) evaluate immune response in peripheral blood and tumor biopsies 3) evaluate gene expression changes following dose escalation and combination therapy.

Eligibility
Patients must have histologically or cytologically confirmed advanced solid tumors with at least one of the following characteristics: primary tumor of the breast, urothelial, pancreatic, cholangiocarcinoma, gastro-esophageal, non-small cell lung, hepatocellular, renal cell, or triple-negative breast cancer. Patients must have received at least 1 but not more than 4-5 prior regimens for advanced or recurrent disease. Patients must have received at least 1 line of therapy with at least 4 weeks of agents that target the same pathway. Patients must be able to provide informed consent. Patients must be free of moderate or severe active non-malignant disease or are free of significant cardiovascular, gastrointestinal, or pulmonary disease. Patient must be able to provide sample for IHC for CD8+ tumor-infiltrating lymphocytes.

BIOMARKER PLAN
TPST-1120 cell lines and tumors are PI3K and mTOR pathway active and support TPST-1120 activity but do not show resistance to TPST-1120. Gene expression profiling of PPARα-associated genes and immune activation genes will be performed to determine TPST-1120 activity in various solid tumors. This trial will be initiated in May 2018 and is currently enrolling into the monotherapy and combination arms.

SUMMARY
TPST-1120 targets tumor growth and suppressive immune cells in the TME facilitating tumor cell death and support of effector immune cells. TPST-1120 is a potent, selective, and oral PPARα antagonist that blocks transcription of PPARα target genes leading to a metabolic switch from FAO to glycolysis. Increasing FAO usage facilitates tumor growth and suppressive immune cells. TPST-1120 leads to intracellular metabolism shift from FAO to glycolysis which inhibits tumor growth and facilitates an antitumor immune response. TPST-1120 is administered orally in 3 cycles, with a 7-day washout period between cycles. TPST-1120 will be dosed once daily in the morning to achieve plasma concentrations in the range of 3-4 nM with a >35 fold selectivity over other PPAR isoforms. TPST-1120 is administered in 2-stage expansion design. This trial will consist of 4 monotherapy arms and 4 combination arms in which TPST-1120 is combined with nivolumab, docetaxel, or cetuximab. TPST-1120 in combination with anti-PD1 or anti-EGFR monoclonal antibody leads to intracellular metabolism shift from FAO to glycolysis which inhibits tumor growth and facilitates an antitumor immune response. The objectives are to 1) evaluate safety and tolerability of TPST-1120 in patients with advanced solid tumors 2) evaluate antitumor activity in various solid tumors 3) characterize the PK of TPST-1120 and 4) characterize the PD of TPST-1120.