TPS2665: Phase 1/1b Multicenter Trial of TPST-1120, a Peroxisome Proliferator-Activated Receptor Alpha (PPARα) Antagonist as a Single Agent (SA) or in Combination in Patients with Advanced Solid Tumors

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ABSTRACT

Background

Tumor cells initially favor glucose metabolism via aerobic glycolysis. As tumors rapidly proliferate and metastasize, glucose stores are depleted and metabolic reprogramming shifts intracellular metabolism(IcM) towards fatty acid oxidation (FAO). Fatty acids support the metabolism of suppressive immune cells in the TME in addition to tumor growth. PPARα is a ligand-activated nuclear transcription factor which regulates lipid metabolism and FAO. TPST-1120 is a first in class, oral, selective PPARα antagonist that blocks transcription of PPARα target genes leading to an IcM shift from FAO to glycolysis. Reduction of fatty acids in the TME leads to direct killing of tumor cells dependent on FAO and facilitates the cytotoxicity of immune effector cells. TPST-1120 also restores thrombospondin-1, a known natural inhibitor of angiogenesis, to homeostatic levels within the TME. Preclinical studies in multiple tumor models demonstrate efficacy of TPST-1120 as monotherapy and in combination(combo) with an anti-PD1 monoclonal antibody (mAb) and chemotherapy.

Methods

We have initiated a phase 1/1b multicenter, open label Dose Escalation (DEs) and Dose Expansion (DEx) trial to evaluate TPST-1120 as a SA and in combo with nivolumab, an anti-PD1 mAb; docetaxel, a chemotherapeutic agent and cetuximab, an anti-EGFR mAb. Objectives are to 1) evaluate safety and tolerability of continuous dosing of TPST-1120 2) identify a recommended phase 2 dose (RP2D) and 3) evaluate efficacy. Eligibility: 1) patients with select advanced solid tumors who have failed 1 but not more than 5 prior therapies. This phase 1/1b adaptive design has 4 DEs arms, 1 SA arm and 3 combination arms in which TPST-1120 is combined with nivolumab, docetaxel or cetuximab. The RP2D of TPST-1120 to proceed to DEx will be determined by safety and biomarkers during DEs. The DEx arms have 8 histology-specific cohorts, 4 SA arms and 4 combo arms and will follow a 2-stage expansion design. Biomarker analyses include gene expression profiling of PPARα-associated genes, tumor markers of immune modulation and serum lipid profiling. The total sample size is up to 338 pts. This trial is accruing at U.S sites.

BACKGROUND

- Aerobic glycolysis is the metabolic pathway favored by proliferating tumor cells
- As tumor proliferate and metastasize, glucose stores are depleted in context of hypoxic TME
- Metabolic reprogramming shifts intracellular metabolism toward fatty acid oxidation (FAO)
- **PPARα:** peroxisome proliferator-activated receptor alpha is transcription factor that regulates FAO and inflammation
- **TPST-1120** is a 'first in class' oral selective PPARα antagonist that blocks transcription of PPARα target genes
  - TPST-1120 leads to intracellular metabolism shift from FAO to glycolysis
  - TPST-1120 has an IC_{50} of 0.04 nM with > 35 fold selectivity over other PPAR isoforms
  - Preclinical models shows efficacy of TPST-1120 as a single agent and in combination with an anti-PD1 antibody and chemotherapy

FIGURE 1: PPARα Regulates Fatty Acid Oxidation (FAO) and inflammation in TME

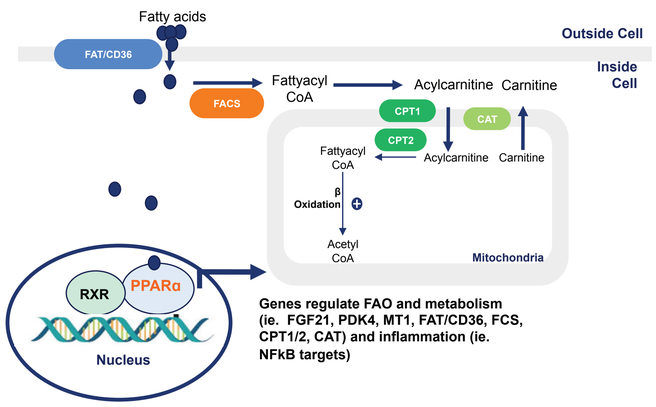
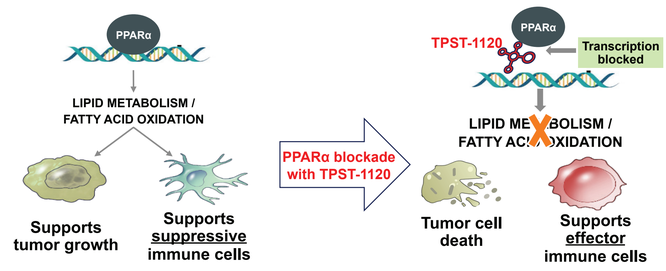


Figure 1: PPARα regulates key genes involved in FAO, metabolism and inflammation. Upon ligand binding, PPARα heterodimerizes with RXR, stimulates gene transcription of target genes involved in FAO and lipid metabolism. PPARα also negatively modulate gene transcription by inhibiting DNA-binding of several other transcription factors, such as NF-κB.

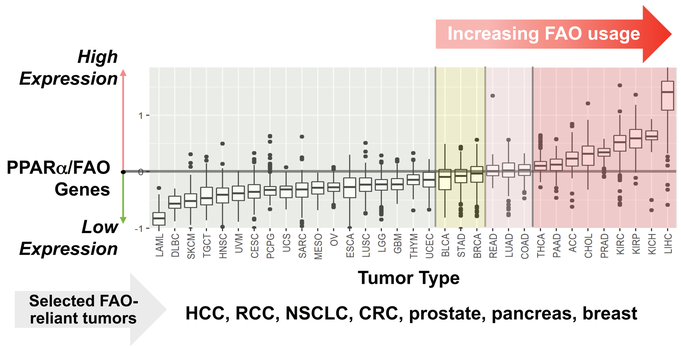
PPARα INHIBITS FATTY ACID METABOLISM

FIGURE 2



- Fatty acids within the TME support tumor growth and suppressive immune cells (Tregs, MDSCs, M2 macrophages)
- PPARα blockade inhibits FAO ➔ direct tumor cell death and facilitates effector immune cells

FIGURE 3: TCGA-based Metabolic Profiling Demonstrates Upregulation of PPARα and FAO Genes in DiverseTumors



OBJECTIVES

- **Primary**
  - To evaluate safety/tolerability of TPST-1120 as monotherapy and in combination with systemic anti-cancer therapies
  - To determine MTD and/or optimal biologic dose of TPST-1120 as monotherapy and in combination with systemic anti-cancer therapies
- **Secondary**
  - Characterize the PK of TPST-1120
  - To evaluate anti-tumor activity of TPST-1120 as monotherapy and in combination with systemic anti-cancer therapies
  - Explore effects of TPST-1120 on expression of PPARa including its FAO target genes, lipids, immune changes, TSP-1 and FGF21.

ELIGIBILITY

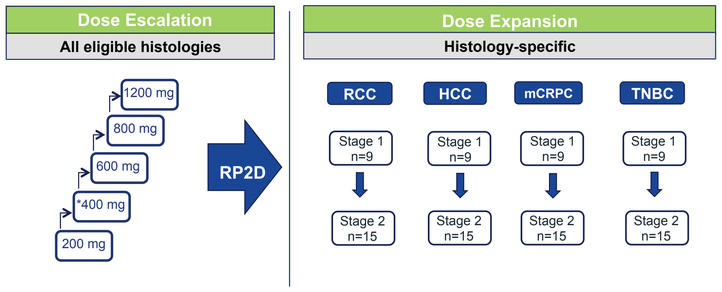
- ECOG performance status of 0 or 1
- Life expectancy > 12 weeks
- Adequate organ function
- Must have received at least 1 but nor more than 4-5 prior regimens for advanced or recurrent disease
- Eligible histologies
  - Monotherapy Dose Escalation: RCC, HCC, mCRPC, TNBC, pancreatic, cholangioca, sarcoma, UBC, NSCLC, MSS CRC, Gastroesophageal, SCCHN
  - Monotherapy Dose Expansion: RCC, HCC, mCRPC, TNBC
  - Combination Escalation/Expansion: HCC, NSCLC, MSS CRC, mCRPC
- Prior PD1/L1 or CTLA-4 agents allowed
- Paired tumor biopsies required

TPST-1120-001: PHASE 1/1b DOSE ESCALATION/ DOSE EXPANSION TRIAL

- **Dose Escalation**
  - One monotherapy arm
  - Three combination arms in which TPST-1120 is combined with nivolumab, docetaxel or cetuximab
- **Dose Expansion**
  - Eight histology specific cohorts following 2-stage expansion design
    - 4 monotherapy arms
    - 4 combination arms

FIGURE 4: MONOTHERAPY ARMS

Traditional 3+3 Design



RP2D: recommended phase 2 dose

FIGURE 5: COMBINATION ARMS

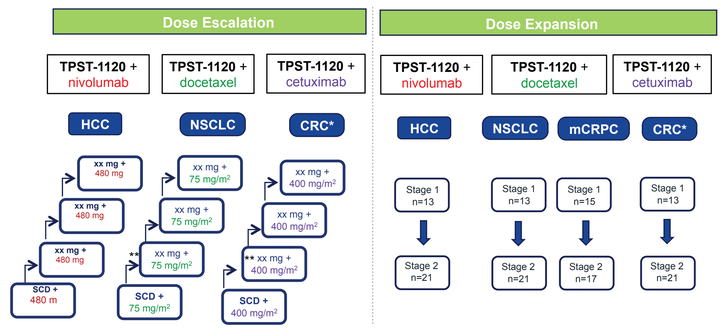


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Figure 5: **SCD** (starting combination dose) of TPST-1120 will be **400 mg** if the 600 mg dose level is cleared. However, this dose may be lower if MTD in monotherapy arm is lower than 600 mg.

**Subsequent doses of TPST-1120 in combination arms above will depend on SCD determined in TPST-1120 monotherapy arm

BIOMARKER PLAN

- **Peripheral blood**
  - Gene expression profiling of PPARα-associated genes and immune activation genes
  - Serum lipid profiling
  - Plasma levels of TSP-1(thrombospondin-1) and FGF21
- **Tumor**
  - Gene expression profiling of PPARα-associated genes and immune activation genes
  - IHC for CD8+ and other immune tumor infiltrating lymphocytes