Abstract
TPS2696

Trial-in-Progress: A Phase 1 Study of TPST-1495 as a Single Agent and in Combination with Pembrolizumab in Subjects with Solid Tumors

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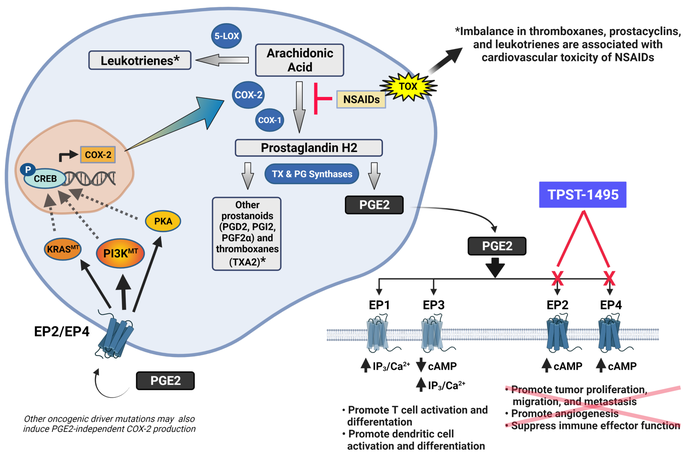
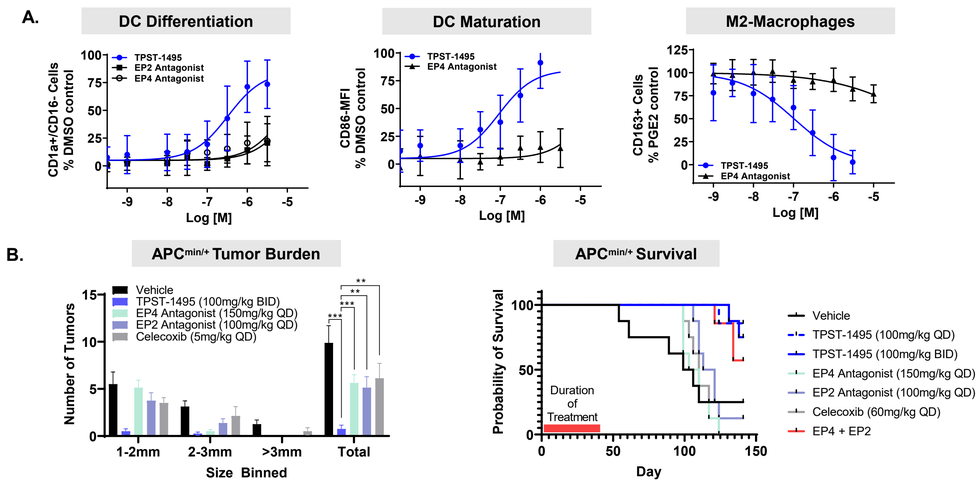
PROSTAGLANDIN E2 (PGE2) SIGNALING



- **PGE2 supports tumor progression through diverse tumor-specific and immune-mediated mechanisms[1,2]**
- ***Pro-tumor and immune suppressive signaling* is mediated by EP2 and EP4 receptors, while EP1 and EP3 are generally *immune stimulating***
- **Targeting upstream COX enzymes for cancer therapy results in loss of beneficial receptor activity and is associated with cardiovascular toxicity due to alterations in related bioactive lipids**
- **Activation of oncogenic driver genes such as PI3K and KRAS is associated with upregulation of COX-2 and PGE2 and may be a predictive biomarker for benefit from PGE2 inhibitors[3]**
- **TPST-1495 is a highly specific and potent inhibitor of *only* the tumor-promoting EP2 and EP4 receptors and is being evaluated in a first-in-human Phase 1 clinical trial described here**

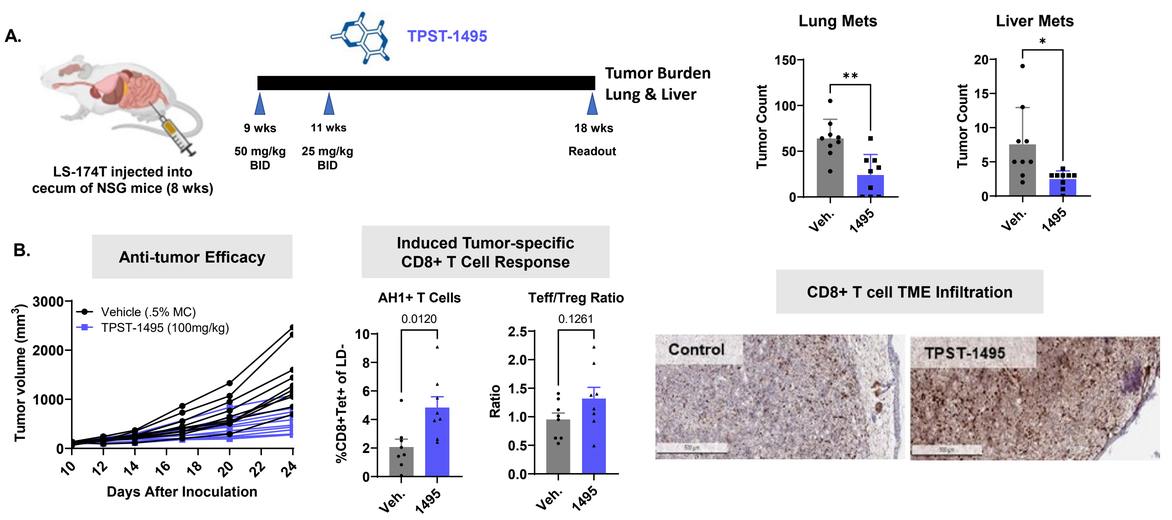
OPTIMAL ACTIVITY WITH DUAL EP2/EP4 ANTAGONISM

Figure 2. In vitro and in vivo comparison of dual EP2/4 inhibition by TPST-1495 versus single EP2 or EP4 receptor inhibition.
(A) Activity in primary human monocytes cultured with GMCSF + IL4 + PGE2 + EP receptor antagonist. (B) Activity in APC$^{min/+}$ model.



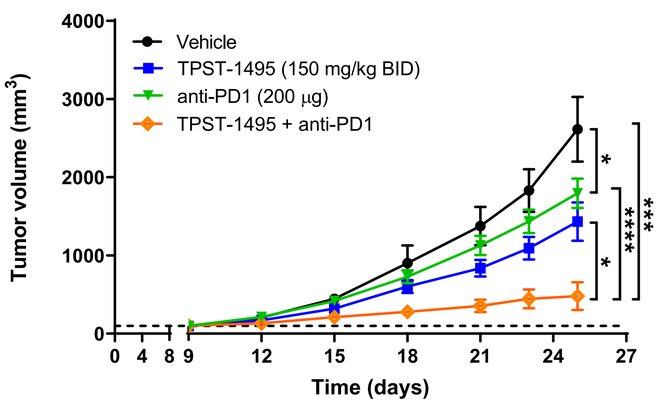
ANTI-TUMOR ACTIVITY IS BOTH DIRECT AND IMMUNE-MEDIATED

Figure 3. Direct inhibition of tumor cell growth (A) and immunomodulatory activity (B) mediated by TPST-1495. (A) Activity in NSG mice bearing orthotopic LS-174T human tumor cells. (B) Treatment of CT26 Balb/c mice bearing 100 mm3 established tumors.



RATIONALE FOR COMBINATION WITH CHECKPOINT INHIBITOR

Figure 4. Synergistic efficacy with TPST-1495 and anti-PD1 combination



- PGE2 is a potent suppressor of immune function in the TME
- COX-2 upregulation is associated with both primary and secondary (adaptive) resistance to immune checkpoint inhibitor therapy
- TPST-1495 blocks the immunosuppressive signaling of PGE2 and stimulates anti-cancer immune function
- COX-2 and PD-L1 are induced by non-redundant signals and represent independent and potentially complimentary therapeutic targets

TPST-1495-001 STUDY DESIGN (NCT04344795)

Dose & Schedule Optimization Modified 3+3 Design

N = up to ~75

MONOTHERAPY
Multiple dose levels
BID vs QD administration
D1-5 Q7D versus QD dosing
Enrolling

RP2D&S

PEMBROLIZUMAB COMBINATION
Multiple dose levels
QD administration
D1-5 Q7D versus QD dosing
Enrolling

Dose Expansion Cohorts

N = ~90

Endometrial
SCCHN

PIK3CA Basket
CRC, Breast, NSCLC, urothelial, gastroesophageal, anal SCC, cervical SCC

RP2D&S

MSS CRC
Endometrial
SCCHN

PIK3CA Basket
Breast, NSCLC, urothelial, gastroesophageal, anal SCC, cervical SCC

PIK3CA: 100% of basket cohort and 40% of each disease specific expansion will have documented pathogenic PIK3CA mutation
PAIRED BIOPSIES: 30% of each expansion cohort will have paired biopsy for PD evaluation

Study Objectives	1°: Safety, tolerability, determine MTD and/or RP2D and schedule 2°: Evaluate anti-tumor activity, PK Exploratory: PD; immunomodulatory effects in blood, tumor

KEY GENERAL ELIGIBILITY

Inclusion

- Metastatic or unresectable cancer with no remaining standard therapy known to confer clinical benefit
- Measurable disease per RECIST v1.1
- ECOG PS 0 or 1

Exclusion

- Intolerance to NSAIDs (including bleeding/ulcer)
- On anticoagulation therapy or considered to be at increased risk of bleeding
- If prior exposure to checkpoint inhibitor therapy (CPI), must not have
  a. Permanently discontinued CPI due to irAE
  b. Any unresolved irAE > G1 with prior CPI
  c. Use of immunosuppression other than corticosteroids for AE management, AE recurrence if re-challenged, requirement of maintenance doses of >10 mg prednisone or equivalent per day

DISEASE-SPECIFIC I/E

Endometrial – Inclusion/*Exclusion*

- ≥2 prior lines of therapy (adv/met), including a platinum-based regimen unless contraindicated
- If MSI-H/dMMR or TMB high disease, must have received anti-PD-1/L1 therapy
- *Uterine sarcoma and carcinosarcoma*

SCCHN – Inclusion/*Exclusion*

- ≥1 prior line of therapy (adv/met), and must have received platinum-based therapy and anti-PD-1/L1 therapy (alone or together) unless contraindicated or intolerant
- *Nasopharyngeal carcinoma and non-squamous histology*

CRC – Inclusion/*Exclusion*

- ≥2 prior lines of systemic therapy
- Confirmed MSS status (combination cohort only)
- *Neuroendocrine histology*

NOTE: Full eligibility criteria provided in protocol

SUMMARY

- **Prostaglandin E2 stimulates tumor cell growth and suppresses anti-cancer immunity through the EP2 and EP4 receptors**
- **TPST-1495 is a first-in-class, potent and selective, dual antagonist of EP2 and EP4 which does not inhibit the immune stimulating EP1 and EP3 receptors**
- **TPST-1495 has immune independent and immune dependent anti-tumor activity in preclinical models and overcomes PGE2-mediated immune suppression more effectively than single antagonists of either EP2 or EP4, or the COX-2 inhibitor celecoxib**
- **Enrollment is ongoing in the first-in-human TPST-1495-001 Phase 1 clinical study to determine the optimal dose and schedule of administration, safety profile, pharmacokinetics, pharmacodynamic and immunomodulatory activity, and to evaluate anti-tumor activity of TPST-1495 as monotherapy and in combination with pembrolizumab**
- **Expansion cohorts are planned at the RP2D in key tumor indications and in a biomarker-selected cohort supported by PGE2 biology and medical literature, including MSS CRC, SCCHN, Endometrial cancer, and PIK3CA-mutated tumors.**

REFERENCES: 1. Pelly et al. *Cancer Discov*. 2021; 11(10):2602-2619. 2. Tury et al. *Oncotarget* 2016;7(51):85124-85141. 3. Zelenay et al. *Cell* 2015;162(6):1257-1270.
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