A Phase 1 Study of TPST-1495 as a Single Agent and in Combination with Pembrolizumab in Subjects with Advanced Solid Tumors (NCT04344795)

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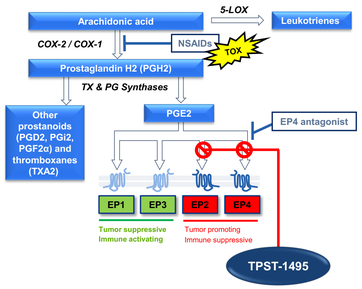
BACKGROUND

Figure 1. Prostaglandin E2 (PGE2) signaling

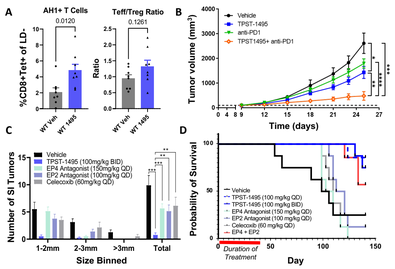


- COX-2/PGE2 implicated in development and progression of multiple cancer types[1,2]
- PGE2: tumor stimulation & immune suppressive signaling via **EP2** & **EP4** prostanoid receptors; immune-stimulation via EP1 & EP3 receptors
- Therapeutic COX inhibition blocks beneficial receptors and is associated with cardiovascular toxicity due to alterations in prostanoids, thromboxane, and leukotriene levels

TPST-1495

- Highly specific and potent dual EP2/EP4 antagonist
- Anti-tumor activity, reduced immune suppression, and activated immune effector responses in syngeneic tumor models
- Dual EP2/EP4 inhibition more active than single EP2 or EP4 antagonists or COX-2 inhibition

Figure 2. TPST-1495 anti-tumor activity and anti-PD1 synergy



(A) Tumor-specific CD8$^+$ T cell responses in CT26 BALB/c mice bearing 100 mm^3 CT26 tumors. (B) Synergistic anti-tumor activity with TPST-1495 + anti-PD1. (C) APC$^{min/+}$ tumor burden and (D) probability of survival with dual EP2/EP4 (TPST-1495) vs. EP4i, EP2i, or the COX-2 inhibitor celecoxib

METHODS

Study Design: First-in-human Phase 1a/1b, multicenter, open-label, dose-escalation, schedule & dose optimization and expansion study evaluating TPST-1495 as a single agent and in combination with pembrolizumab in patients with advanced solid tumors

Key Eligibility Criteria:

- Metastatic or unresectable cancer w/ no remaining standard therapy known to confer clinical benefit
- ECOG PS 0 or 1
- Measurable disease (RECIST v1.1)
- Excluded if intolerant to NSAIDs (including bleeding, ulcer), on anticoagulation therapy or at increased risk for bleeding, or experienced intolerable or unresolved immune-related adverse events (AEs) with prior checkpoint inhibitor therapy

Study Objectives:

1°: Safety & tolerability, MTD, RP2D & schedule

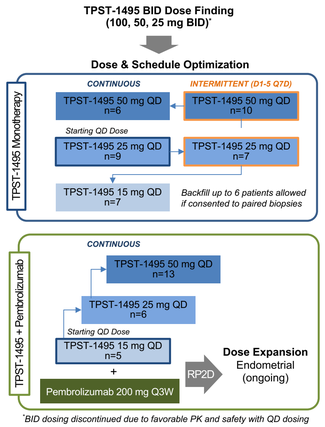
2°: Anti-tumor activity, PK

Exploratory: PD[a]

Efficacy Evaluable Population:
Treated patients who have baseline and evaluable on-treatment assessment, or discontinued treatment for objective disease progression, study drug-related toxicity, or disease-related death

Data Cutoff: April 17, 2023

Figure 3. Study schema



*BID dosing discontinued due to favorable PK and safety with QD dosing

[a]Immunomodulatory effects in blood, tumor; 30% of expansion cohort will have paired biopsy for PD evaluation

BID, twice daily; NSAID, nonsteroidal anti-inflammatory drug; PD, pharmacodynamics; PK, pharmacokinetics; QD, once daily; Q3W, once every 3 weeks; Q7D, once every 7 days

PATIENTS

Table 1. Demographics and baseline characteristics

Parameters	TPST-1495 Monotherapy BID (n=11)	TPST-1495 Monotherapy QD Continuous (n=22)	TPST-1495 Monotherapy QD Intermittent (n=17)	TPST-1495 + Pembrolizumab (n=24)	All Patients (N=74)
Age, y, median (range)	58 (44-72)	62 (31-78)	60 (40-83)	60 (30-83)	60 (30-83)
Female, n (%)	2 (18)	8 (36)	7 (41)	12 (50)	29 (39)
Primary cancer type, n (%)					
Colorectal cancer	6 (55)	13 (59)	13 (76)	12 (50)	44 (59)
Endometrial	1 (9)	1 (5)	0	2 (8)	4 (5)
Pancreatic	1 (9)	3 (14)	0	0	4 (5)
Anal squamous cell carcinoma	1 (9)	1 (5)	0	1 (4)	3 (4)
Cholangiocarcinoma	1 (9)	0	1 (6)	0	2 (3)
Leiomyosarcoma	0	0	1 (6)	1 (4)	2 (3)
Squamous cell carcinoma	0	0	2 (12)	0	2 (3)
Other	1 (9)[a]	4 (18)[b]	0	8 (33)[c]	13 (18)
ECOG PS, n (%)					
0	1 (9)	13 (59)	9 (53)	15 (63)	38 (51)
1	10 (91)	9 (41)	8 (47)	9 (38)	36 (49)
Prior lines of therapy, median (range)	4 (2-8)	4 (2-7)	3 (2-11)	3 (1-7)	4 (1-11)

[a]1 prostate cancer; [b]1 each w/ sinonasal, head & neck, urothelial, uveal melanoma; [c]1 each w/ breast, fallopian tube, gastroesophageal junction, melanoma, hepatocellular carcinoma, ovarian, non-small cell lung cancer, ampulla of vater

SAFETY

Table 2. Safety summary

Category, n (%)	TPST-1495 Monotherapy BID (n=11)	TPST-1495 Monotherapy QD Continuous (n=22)	TPST-1495 Monotherapy QD Intermittent (n=17)	TPST-1495 + Pembrolizumab (n=24)
Any TEAE	11 (100)	21 (95)	14 (82)	23 (96)
Gr ≥3 TRAEs	5 (45)	1 (5)	2 (12)	2 (8)
DLTs	1 (9)[a]	1 (5)[b]	0	1 (4)[c]
TRAEs leading to dose interruption	6 (55)	7 (32)	2 (12)	2 (8)
TRAEs leading to dose reduction	2 (18)	2 (9)	0	1 (4)
TRAEs leading to discontinuation	4 (36)	1 (5)	1 (6)	0
TRAEs leading to death	0	0	0	0

DLT, dose-limiting toxicity; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event deemed related or possibly related to TPST-1495
[a]Gr 3 large intestinal hemorrhage; [b]Gr 3 esophageal varices hemorrhage; [c]Gr 3 AST increased

- Most common treatment-related AEs (TRAEs) were Grade 1-2 gastrointestinal disorders
- No Grade 4 or 5 TRAEs

Table 3. Treatment-related AEs occurring in ≥15% patients on TPST-1495 monotherapy

Treatment-related AE[a], n (%)	TPST-1495 BID (n=11)		TPST-1495 QD Continuous (n=22)		TPST-1495 QD Intermittent (n=17)	
	All Grades	Gr 3+	All Grades	Gr 3+	All Grades	Gr 3+
Any event	10 (91)	5 (45)	17 (77)	1 (5)	11 (65)	2 (12)
Diarrhea	5 (45)	0	3 (14)	1 (5)	3 (18)	0
Abdominal Pain	3 (27)	0	7 (32)	0	0	0
Fatigue	4 (36)	0	3 (14)	0	3 (18)	0
Nausea	1 (9)	0	4 (18)	0	4 (24)	0
Dyspepsia	4 (36)	0	2 (9)	0	1 (6)	0
Anemia	4 (36)	3 (27)	1 (5)	0	1 (6)	1 (6)
Edema peripheral	2 (18)	0	1 (5)	0	1 (6)	0
Vomiting	3 (27)	0	0	0	1 (6)	0
GI hemorrhage	2 (18)	0	0	0	0	0

[a]Deemed related or possibly related to TPST-1495

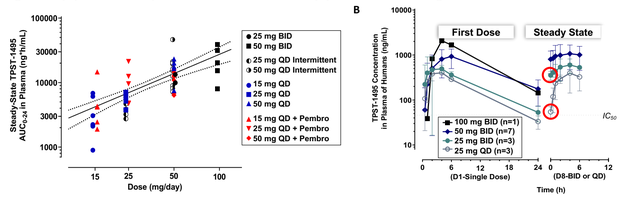
Table 4. Treatment-related AEs occurring in ≥15% patients on TPST-1495 + pembrolizumab

Treatment-related AE[a], n (%)	TPST-1495 + Pembrolizumab: TPST-1495 dose 15 mg (n=5)		25 mg (n=6)		50 mg (n=13)	
	All Grades	Gr 3+	All Grades	Gr 3+	All Grades	Gr 3+
Any event	4 (80)	0	5 (83)	0	8 (62)	2 (15)
Nausea	2 (40)	0	1 (17)	0	4 (31)	0
Diarrhea	1 (20)	0	2 (24)	0	2 (15)	0
Fatigue	0	0	2 (34)	0	3 (23)	1 (8)
Anemia	1 (20)	0	1 (17)	0	2 (15)	0
Abdominal pain	2 (40)	0	0	0	1 (8)	0
Dyspepsia	2 (40)	0	1 (17)	0	0	0
Abdominal distension	0	0	1 (17)	0	1 (8)	0
AST increased	0	0	0	0	2 (15)	1 (8)
Blood creatinine increased	0	0	0	0	2 (15)	0
Dizziness	0	0	1 (17)	0	1 (8)	0
Pruritus	1 (20)	0	0	0	1 (8)	0
Vomiting	0	0	2 (34)	0	0	0

AST, aspartate aminotransferase
[a]Deemed related possibly related to TPST-1495

PHARMACOKINETICS

Figure 4. (A) Relationship between dose and AUC. (B) BID vs. QD dosing: concentration-time curve



- Linear PK (slope = 0.99 [95% CI: 0.55, 1.09]), with dose-dependent increase in exposure
- No changes in PK parameters with addition of pembrolizumab
- Steady state trough was higher for BID vs. QD dosing (red circles, Figure 4B) and was associated with reduced tolerability (Tables 2 and 3)

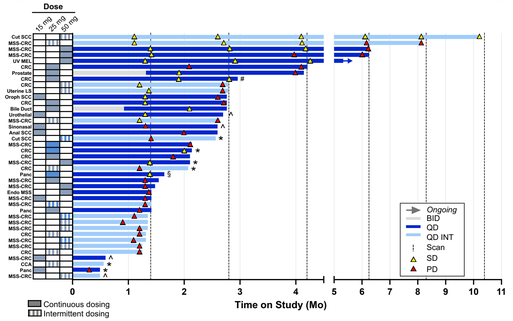
EFFICACY

TPST-1495 MONOTHERAPY

Responses

- BID: Stable disease (SD) in 3/8 patients; disease control rate (DCR: complete response + partial response [PR] + SD [at least 1 scan]) of 37.5%: 2/2 in 25 mg cohort, 1/5 in 50 mg cohort
- QD Intermittent: SD in 5/15 patients; DCR of 33.3%: 2/6 (25 mg cohort), 3/9 (50 mg cohort)
- QD Continuous: SD in 11/21 patients; DCR of 52.3%: 3/6 (15 mg cohort), 4/9 (25 mg cohort), 4/6 (50 mg cohort)

Figure 5. TPST-1495 monotherapy: time on study (41 patients treated[a], 1 ongoing)



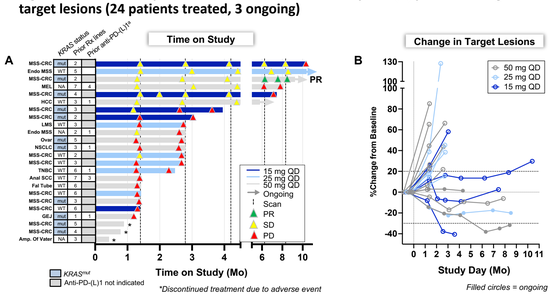
*Discontinued treatment for other than PD: *Adverse event, ^Withdrawal of consent, ^Investigator decision, ^Other (tumor marker rise without objective progression)*
[a]Including 2 BID pts who switched to QD dosing within the first 1.5 months of treatment

COMBINATION: TPST-1495 + PEMBROLIZUMAB

Responses

- 1 PR (MSS colorectal carcinoma [CRC] patient in 50 mg cohort) + 8 SD = 40.9% DCR
- SDs in 3/5 patients in 15 mg cohort, 2/6 in 25 mg cohort, 3/11 in 50 mg cohort

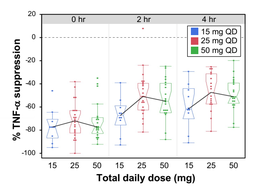
Figure 6. TPST-1495 + pembrolizumab: (A) time on study and (B) percent change in target lesions (24 patients treated, 3 ongoing)



Discontinued treatment due to adverse event
Filled circles = ongoing
[a]Patients with prior anti-PD-(L)1 treatment discontinued their most recent anti-PD-(L)1 regimen due to disease progression except for the GEJ patient who discontinued for initiation of local therapy

PHARMACODYNAMICS & BIOMARKERS

Figure 7. Reversal of PGE2-induced immune suppression with TPST-1495

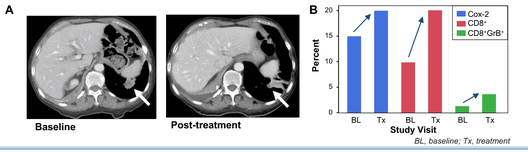


- Whole blood samples collected prior to and 2- or 4-hours following TPST-1495 were incubated with LPS + PGE2 overnight before measuring TNF-α secretion
- TPST-1495 reversed PGE2-induced TNF-α suppression at 2- and 4-hours post-dose, with higher potency at 25 and 50 mg
- Patients receiving TPST-1495 QD showed trends of dose-dependent urinary prostaglandin E2 metabolite (PGEM) elevation by Day 2, extending through Day 22 (data not shown)

CASE STUDIES

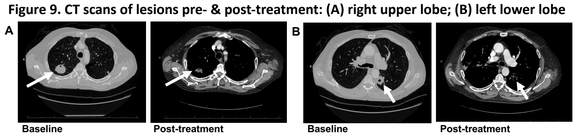
- **Case Study #1:** 78-year-old female with Stage IV metastatic MSS endometrial cancer and lung mets, 5 prior therapies in metastatic setting; TPST-1495 25 mg QD + pembrolizumab
- Best overall response: SD (-22.5% tumor shrinkage)
- Paired biopsies show high baseline COX-2 expression and increased CD8$^+$ and CD8$^+$GrB$^+$ T cell infiltration
- 270+ days on treatment

Figure 8. (A) CT scans (lower left lobe) at baseline and after 4 cycles. (B) Quantitative IHC differences in biomarkers pre- and post-treatment (Day 42)



- **Case Study #2:** 60-year-old male with Stage IV metastatic MSS CRC with lung mets and rectal wall thickening, 3 prior therapies in metastatic setting; TPST-1495 50 mg QD plus pembrolizumab
- Achieved PR at Day 190, confirmed on Day 253. Response ongoing at time of data cutoff

Figure 9. CT scans of lesions pre- & post-treatment: (A) right upper lobe; (B) left lower lobe



CONCLUSIONS & FUTURE DIRECTIONS

- TPST-1495 is a novel inhibitor of PGE2 signaling that specifically antagonizes the tumor-promoting and immune-suppressing EP2 and EP4 prostanoid receptors. In this first-in-human Phase 1 study conducted in patients with treatment-refractory solid tumors, predominantly MSS CRC, TPST-1495 demonstrated:
  - Disease control activity with tumor shrinkage and prolonged SD in both monotherapy and in combination with pembrolizumab as well as a durable confirmed PR in a combination therapy patient with MSS CRC, an indication not normally responsive to immuno-oncology (IO) therapy
  - Manageable safety profile on the QD schedule with related AEs being predominantly grade 1-2 (and no Grade 4/5), gastrointestinal in nature, and on-target for the prostaglandin pathway. No signal of cardiovascular or renal toxicity was noted
  - Linear PK and both immune-specific and PGE2-specific pharmacodynamic activity. The RP2D is 50 mg QD for monotherapy and in evaluation at 25 mg QD and 50 mg QD for the combination with pembrolizumab
- Next steps include TPST-1495 + pembrolizumab in a 20-patient endometrial cancer cohort (now enrolling) and initial exploration of TPST-1495 monotherapy to treat the inherited cancer syndrome familial adenomatous polyposis (FAP)

REFERENCES: 1. Pelly et al. *Cancer Discov*. 2021; 11(10):2602-2619; 2. Tury et al. *Oncotarget* 2016;7(51):85124-85141

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