2022 ASCO® ANNUAL MEETING

Abstract # 3005

A Phase 1 Study of TPST-1120 as a Single Agent and in Combination with Nivolumab in Subjects with Advanced Solid Tumors

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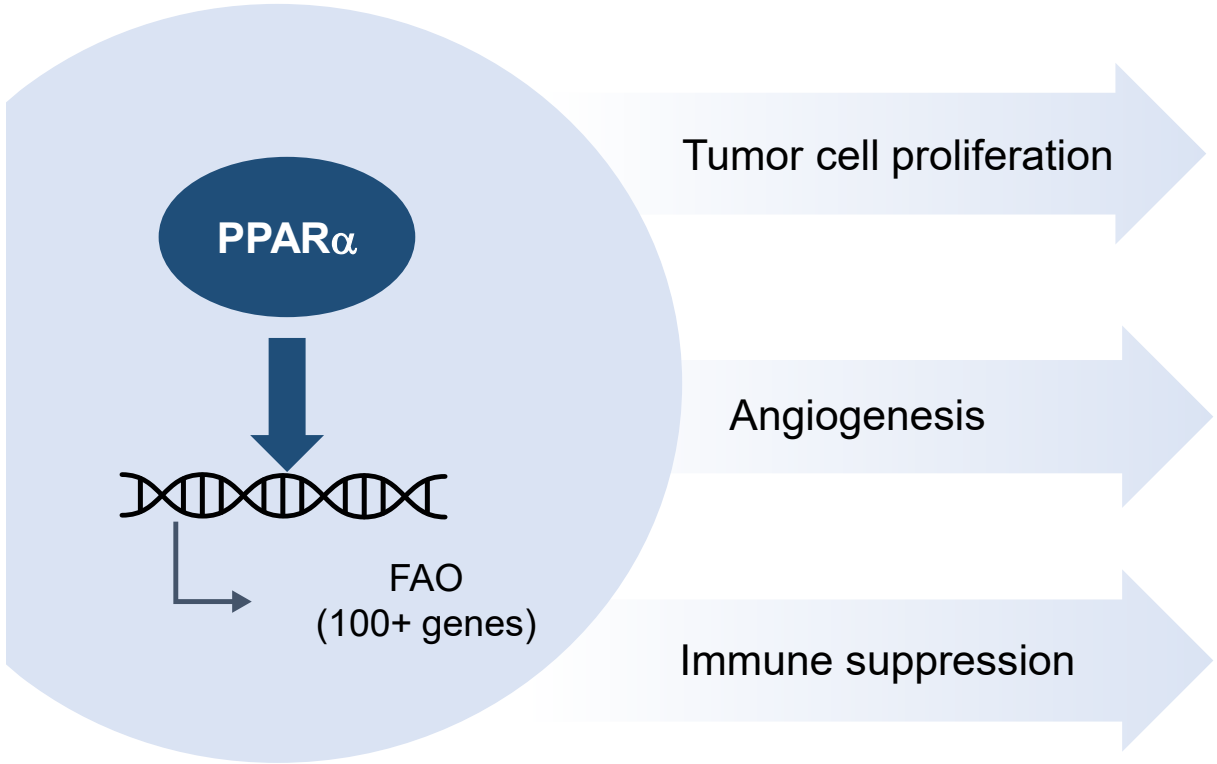
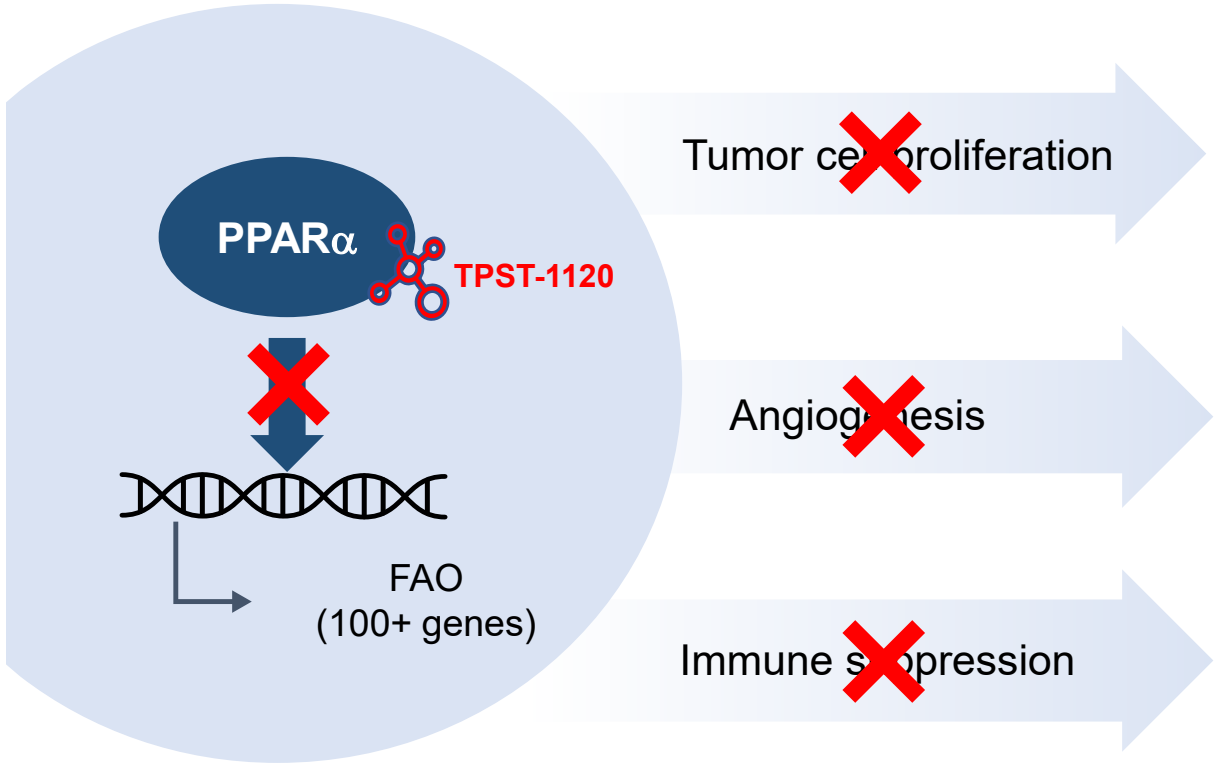
Fatty Acid Oxidation Supports Cancer Progression



- FAO is a key cancer metabolic adaptation that supports tumor growth and metastasis
- FAO is a principal metabolic pathway for immune suppressive cell types and FAO induces angiogenesis
- PPARα is a transcription factor and master regulator of FAO, controlling > 100 lipid metabolism genes
- Inhibiting PPARα to reduce FAO is a promising strategy to inhibit tumor growth and relieve immunosuppression

TPST-1120 – First-in-Class PPARα Antagonist



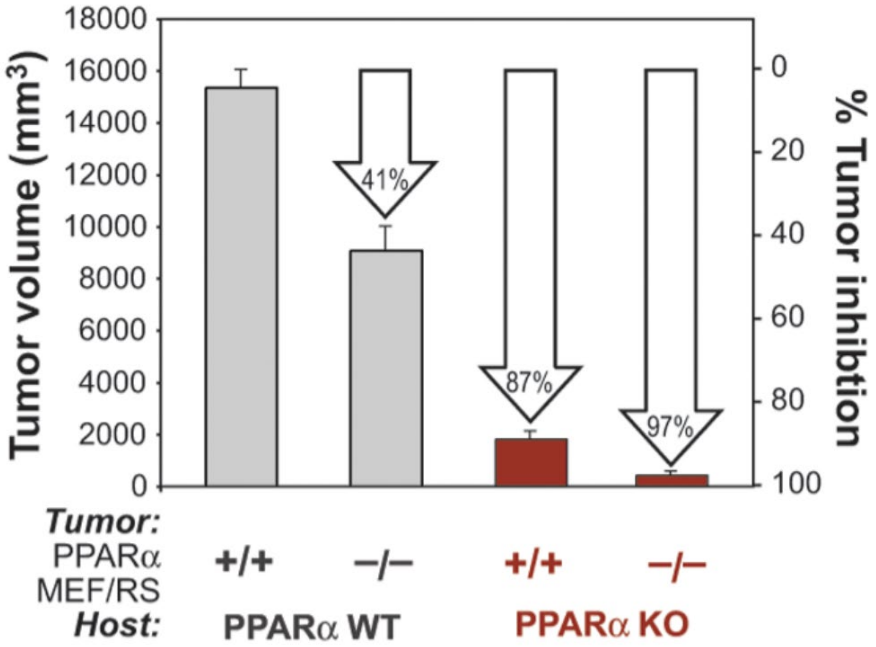
PPAR Inhibition* IC_{50} (μM)		
Isoform	**Species**	
PPAR-	Human	Mouse
α	**0.052**	**0.42**
β/δ	13	29
γ	33	30

**Luciferase Reporter*

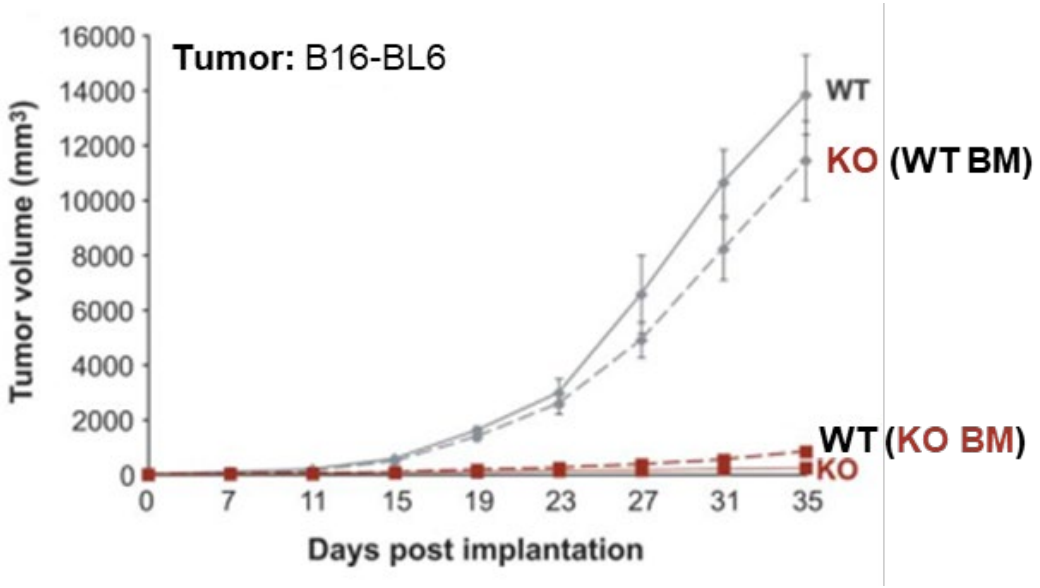
Genetic Validation for Targeting PPARα

PPARα and FAO Are Required to Sustain Tumor Growth

PPARα KO Prevents Tumor Growth



PPARα Inhibition in Immune Cells Enhances Antitumor Immunity



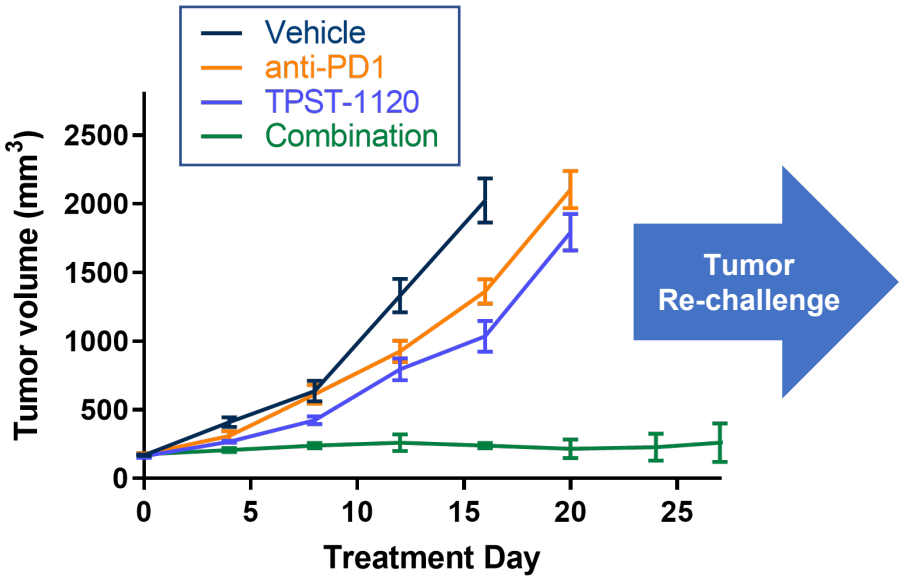
Bone Marrow Transplantation Confers Transplant Phenotype

Kaipainen et al., PLoS ONE 2007, 2(2): e260

TPST-1120 and anti-PD-1 Synergize and Confer Durable Immunity

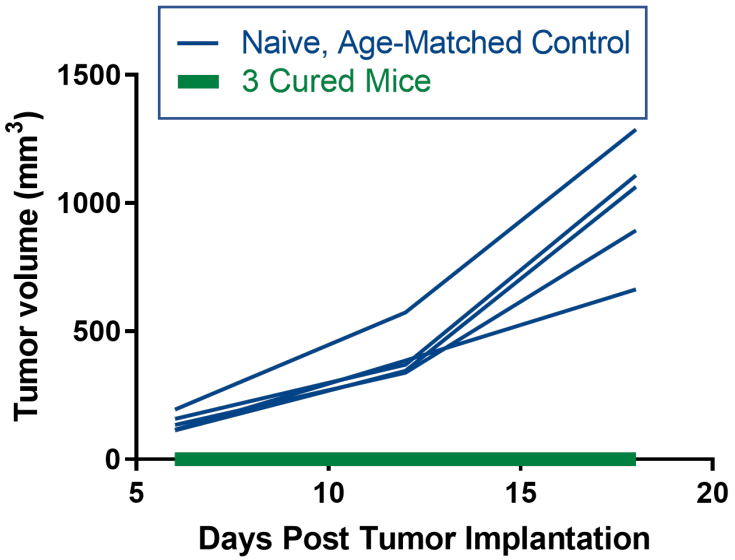
MC38 colorectal cancer tumor model, C57BL/6 immunocompetent mice

TPST-1120 + anti-PD1 treatment

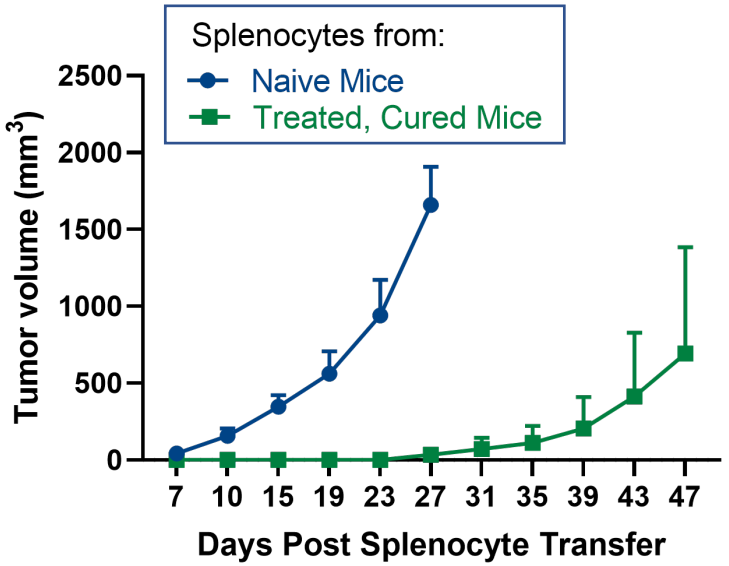


C57BL/6 mice bearing 150 mm^3 MC38 flank tumors treated with TPST-1120 30 mg/kg BID and 200 µg anti-PD-1 Q3D

Tumor re-challenge



Splenocyte adoptive transfer followed by tumor cell challenge



Adoptive transfer of splenocytes from naïve C57BL/6 mice or MC38 tumor-bearing mice cured with TPST + anti-PD-1 into naïve C57BL/6 mice, followed by challenge with 1 x 10^6 MC38 tumor cells

Source: Dipak Panigrahy, Harvard

TPST-1120-001 Phase 1 Study Design

NCT03829436

Key Eligibility Criteria

Inclusion:

- Advanced/metastatic solid tumor
- ECOG PS 0-1
- Adequate renal, hepatic and hematologic function
- No standard therapy available
- Archived or fresh tumor Bx, paired Bx optional

Exclusion:

- Immunosuppressive meds
- Autoimmune disease
- Fibrates within 28 days of enrollment

Part 1: TPST-1120 Monotherapy Dose Escalation

Solid Tumors
3+3 Design
TPST-1120 up to 600 mg BID

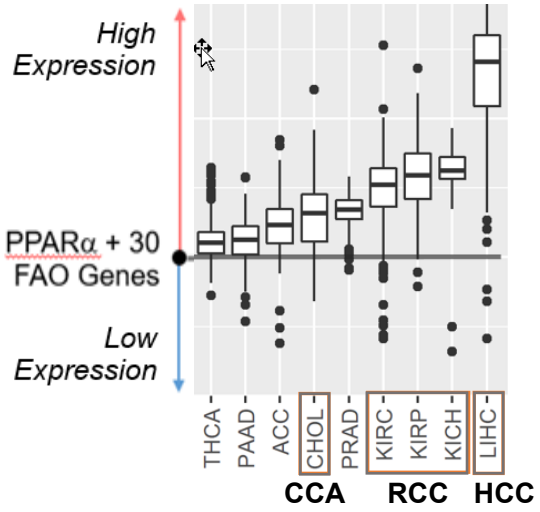
Part 2: TPST-1120 Combination with α-PD-1 Dose Escalation

HCC, RCC, Cholangiocarcinoma
3+3 Design
TPST-1120 up to 600 mg BID
Full dose nivolumab

Endpoints

- Safety
- MTD and/or OBD of TPST-1120
- Pharmacokinetics
- Preliminary efficacy

TCGA gene expression profile



ECOG PS - Eastern Cooperative Oncology Group Performance Status; Bx biopsy; BID twice daily; RCC renal cell carcinoma; HCC hepatocellular carcinoma; CCA cholangiocarcinoma; MTD maximal tolerated dose; OBD optimal biologic dose; DLT dose limiting toxicity

PRESENTED BY:
Mark Yarchoan, MD

Demographics and Patient Characteristics

Baseline Characteristics		TPST-1120 Monotherapy (N=20)	TPST-1120 + Nivolumab (N=18)
Age [median (range)]		65 (41-78)	64 (43-84)
Female [n (%)]		10 (50)	9 (50)
TPST-1120 Dose [n (%)]	100 mg BID	3 (15)	-
	200 mg BID	4 (20)	3 (17)
	300 mg BID	3 (15)	3 (17)
	400 mg BID	4 (20)	3 (17)
	600 mg BID	6 (30)	9 (50)
Primary Cancer Type [n (%)]	Castration Resistant Prostate Cancer	1 (5.0)	-
	Cholangiocarcinoma	5 (25)	9 (50)
	Colorectal Cancer	4 (20)	-
	Hepatocellular Carcinoma	1 (5.0)	4 (22)
	Non-small-cell Lung Cancer	1 (5.0)	-
	Pancreatic Cancer	8 (40)	-
	Renal Cell Carcinoma		5 (28)
Prior systemic regimens	Median (range)	3 (2-9)	3 (1-6)
	Prior α-PD-1/α-PD-L1* [n (%)]	6 (30)	10 (56)
ECOG PS [n (%)]	0	5 (25)	8 (44)
	1	15 (75)	10 (56)

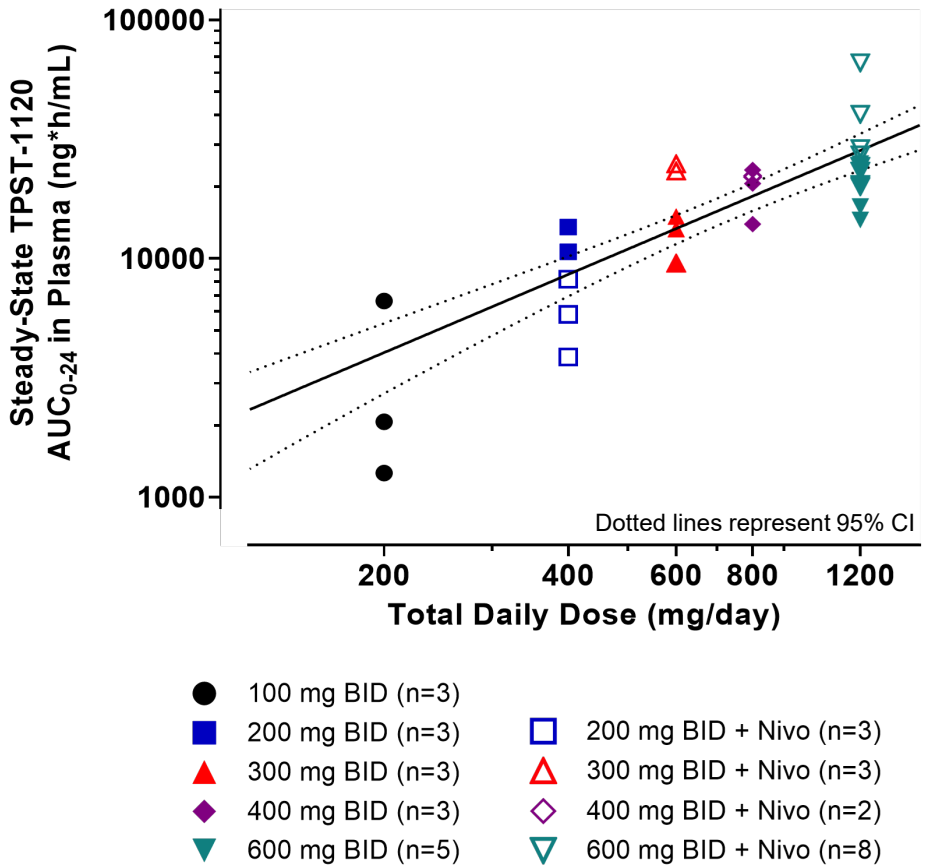
N is safety population, Data cut: April 15, 2022

*All enrolled NSCLC, HCC, and RCC patients had prior treatment with at least one approved α-PD-1 or α-PD-L1

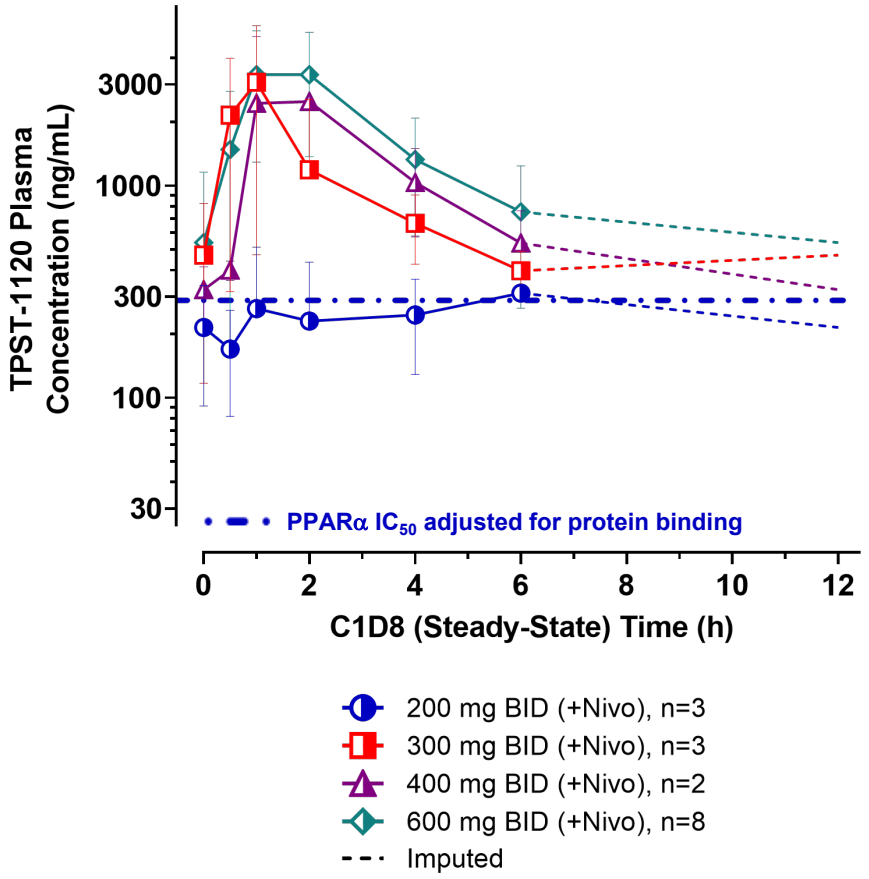
TPST-1120 Pharmacokinetics

Exposure Increases Linearly With Dose

Dose-Exposure Relationship



Steady-State Profile (Combination)



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Safety Summary

TPST-1120 Monotherapy and Combination with Nivolumab

Treatment-related adverse events occurring in ≥ 2 patients

AE, n (%)	TPST-1120 Monotherapy (N=20)	
	Any Grade	Grade 3
Any AE	10 (50.0)	1 (5.0)†
Nausea	4 (20.0)	-
Fatigue	3 (15.0)	-
Diarrhoea	2 (10.0)	-

†Hypertension

AE, n (%)	TPST-1120 + Nivolumab (N=18)	
	Any Grade	Grade 3
Any AE*	15 (83.3)	3 (16.7)^
Fatigue	6 (33.3)	-
Diarrhoea	4 (22.2)	-
Nausea	3 (16.7)	-
Abdominal pain	2 (11.1)	-

*Related to either TPST-1120 or nivolumab
^Arthralgia, Hepatic enzyme increased, Muscle spasms

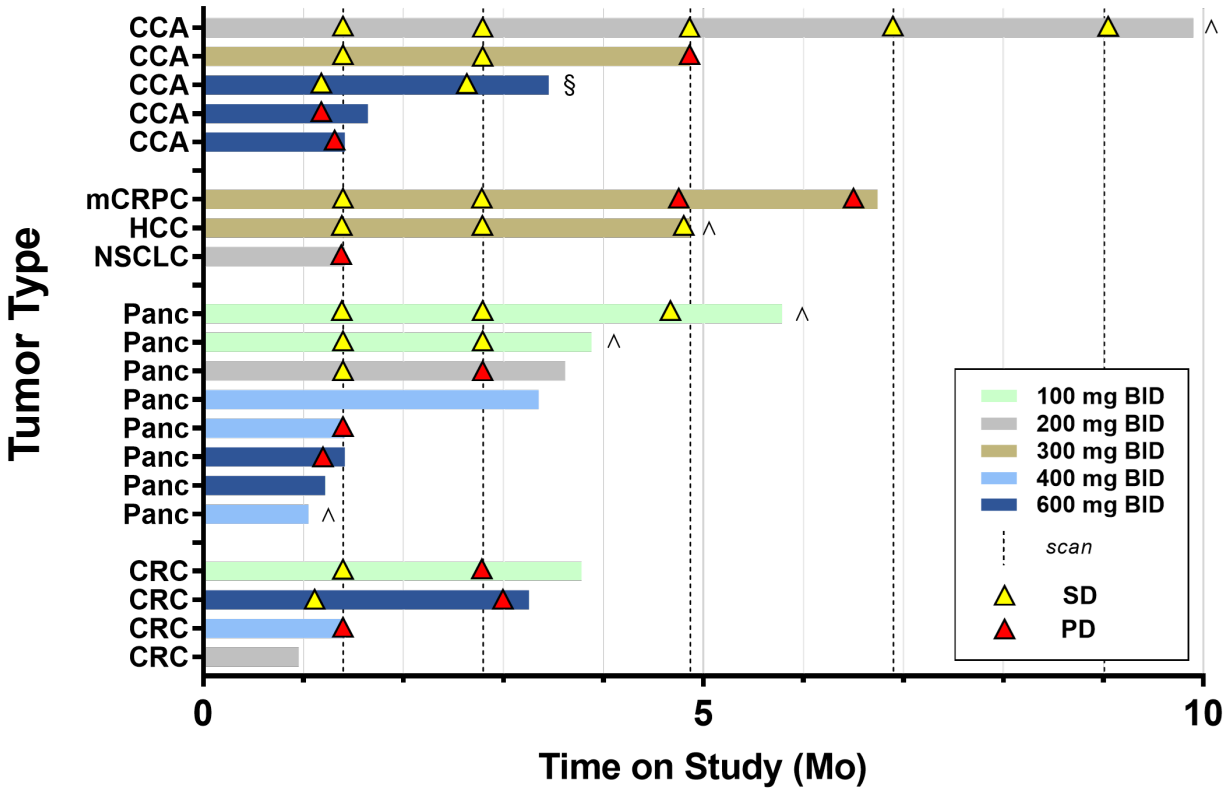
- TPST-1120 showed tolerable safety profile as monotherapy and in combination with nivolumab
- Most common treatment-related AEs were nausea, fatigue and diarrhea
- No DLTs during dose escalation
- RP2D 600 mg PO BID for monotherapy and combination

Data cut: April 15, 2022

TPST-1120 Monotherapy

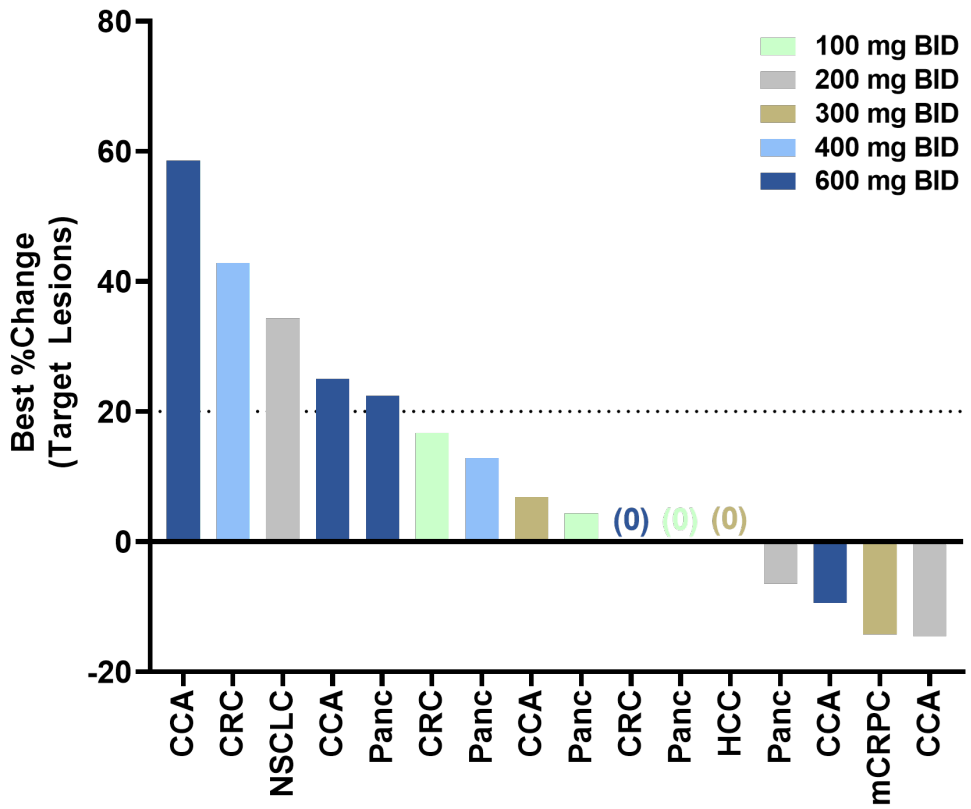
Prolonged Disease Control and Tumor Shrinkage in Late Line Patients

20 Enrolled



Discontinuation for other than disease progression: ^Clinical Deterioration, §Consent withdrawn

TPST-1120 Monotherapy (N=19[a]): 53% DCR



[a]Response-evaluable patients include pts with a postbaseline scan or discontinued treatment due to disease progression

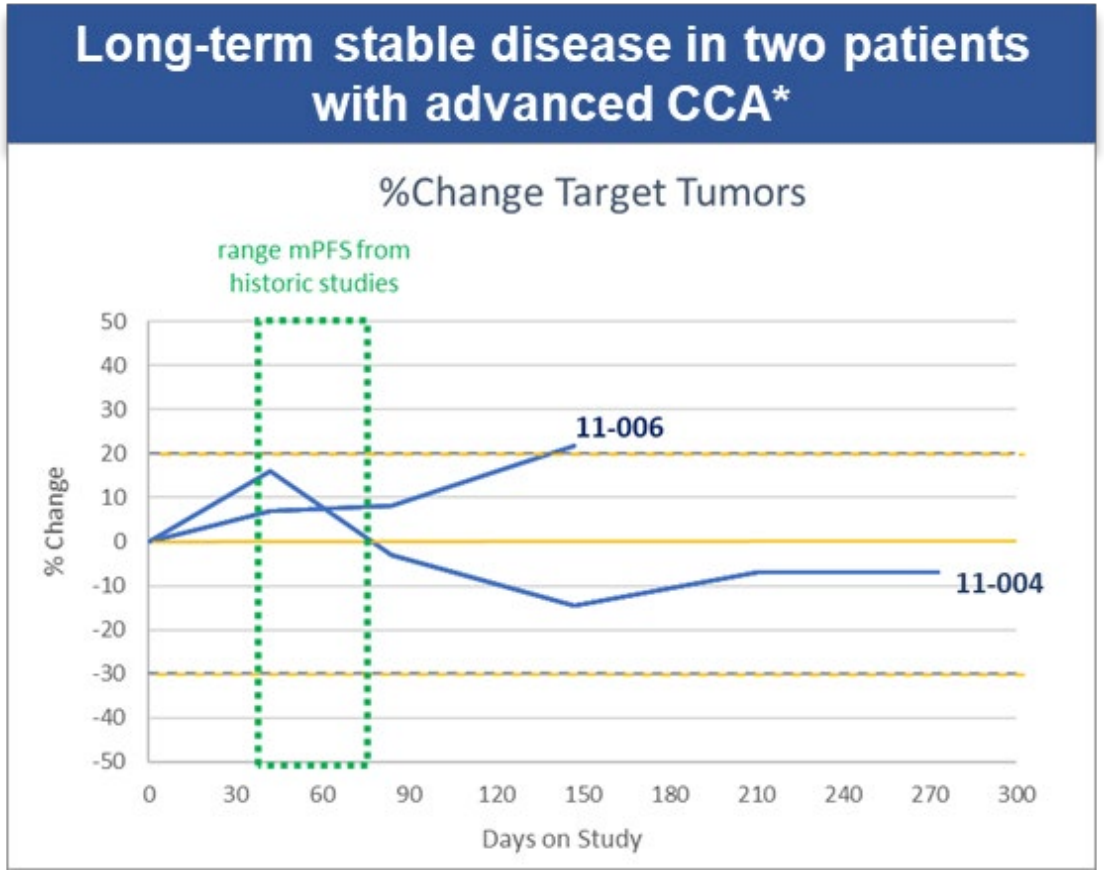
DCR, disease control rate = complete response + partial response + stable disease; mCRPC metastatic Castration resistant prostate cancer; NSCLC Non small cell lung cancer; Panc Pancreatic cancer; CRC Colorectal cancer

Data cut: April 15, 2022

Monotherapy Tumor Control in Late-Line Cholangiocarcinoma

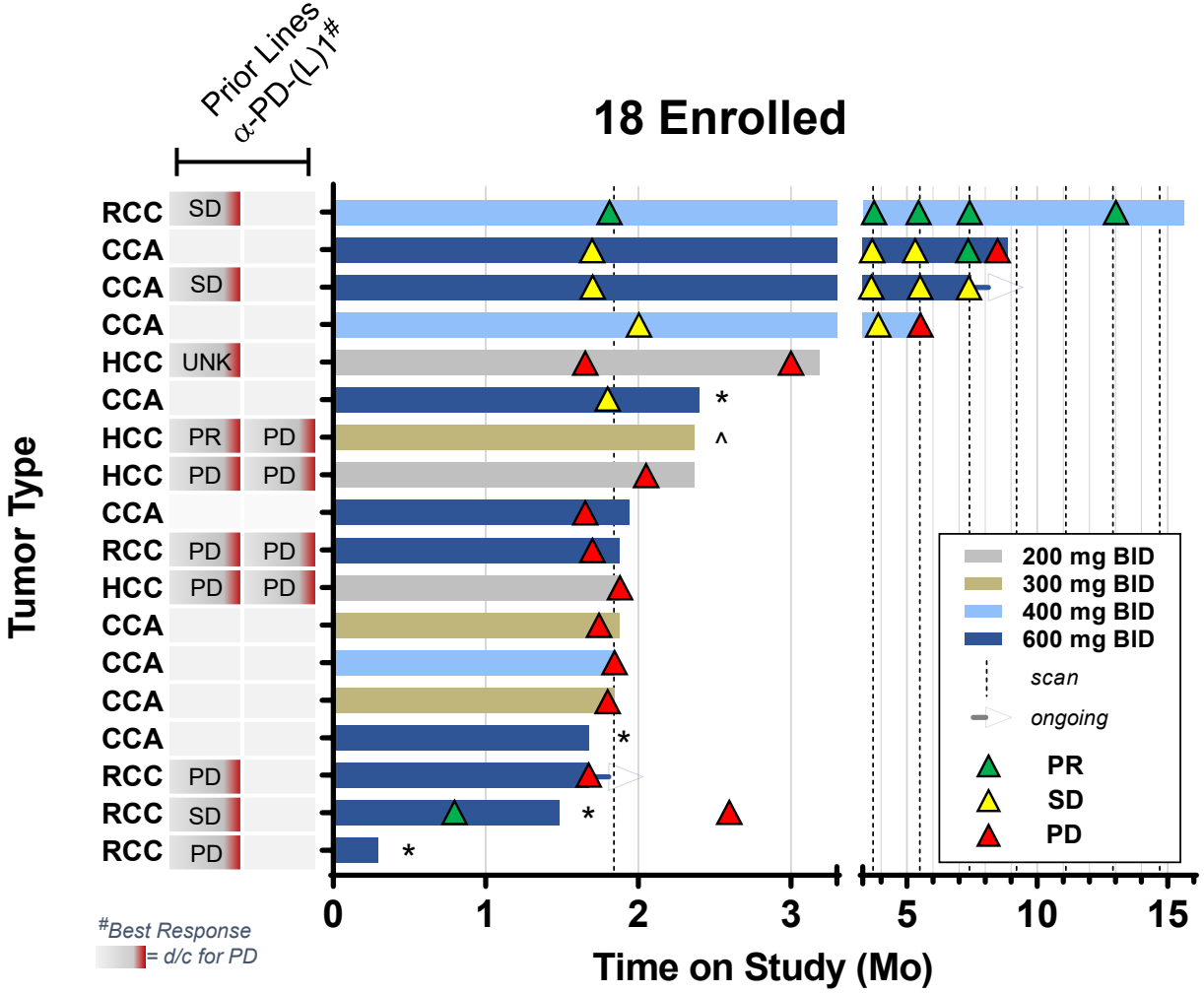
11-004
- 4 prior systemic therapies
  - Carboplatin/taxol
  - Gemcitabine
  - Oxaliplatin/5-FU
  - IDOi/investigational anti-PD-1
    discontinued due to progression
- IDH1 mutation

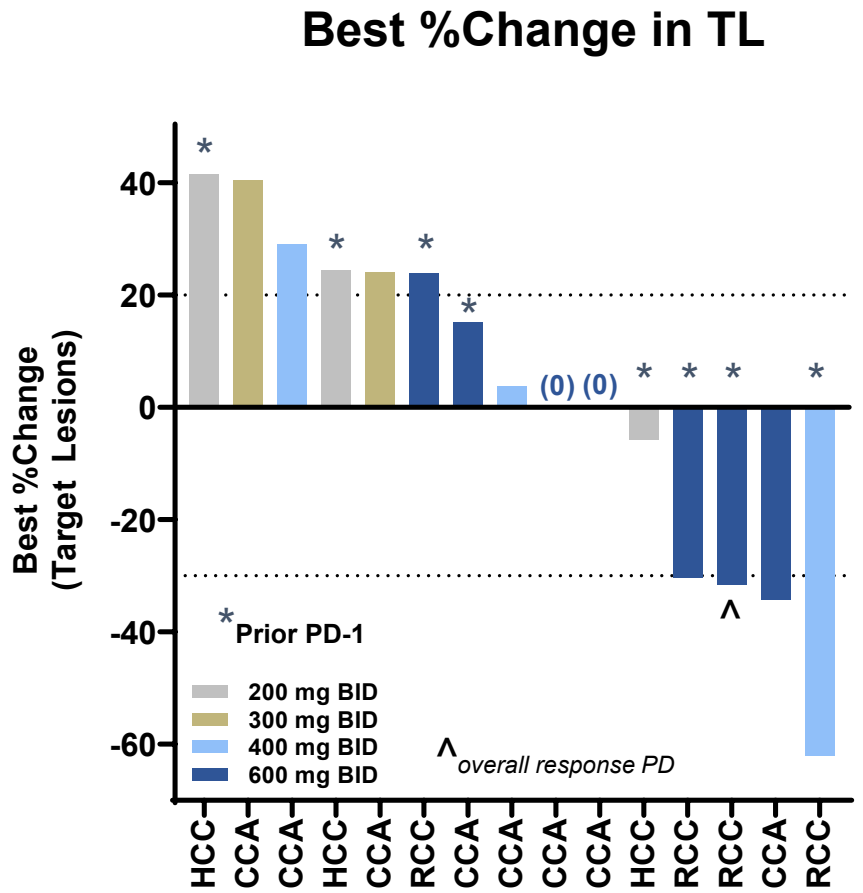
11-006
- 3 prior systemic therapies
  - Cisplatin/gemcitabine
  - Investigational TKI
  - Investigational anti-PD-1
    discontinued due to progression
- IDH1 mutation



TPST-1120 Combination with Nivolumab

RECIST Responses in RCC and Cholangiocarcinoma





Data cut: April 15, 2022

*Discontinuation for other than disease progression: *Adverse Event, ^Clinical Deterioration*

15 response-evaluable patients include pts with a postbaseline scan or discontinued treatment due to disease progression

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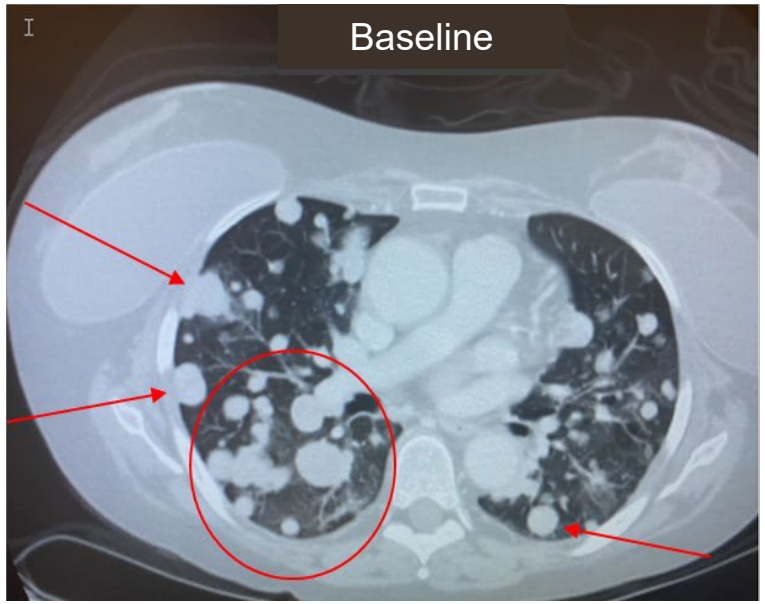
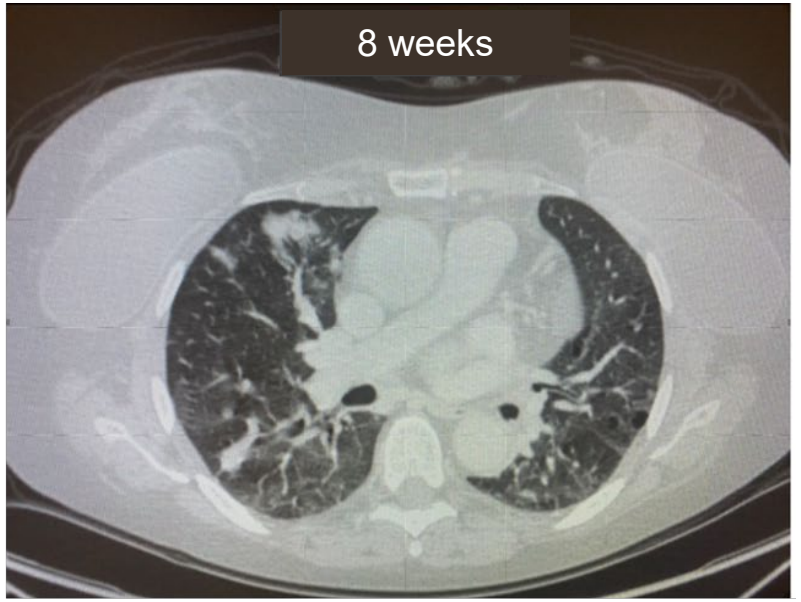
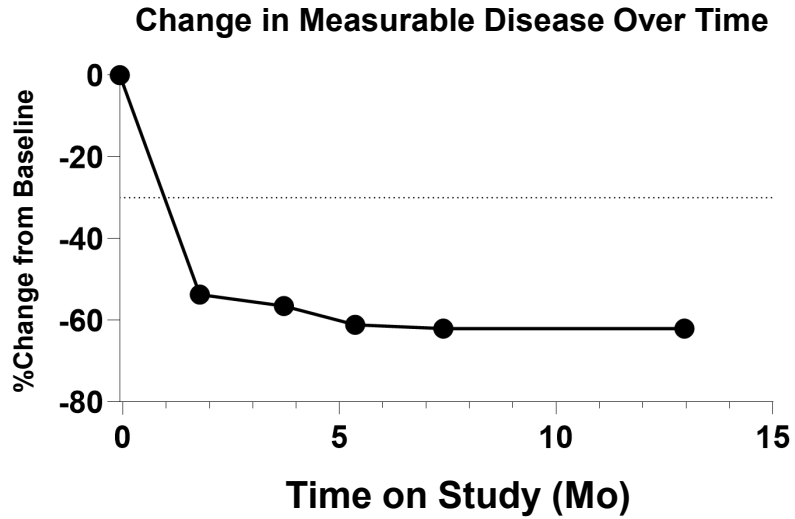
Case Study 1: PR in 53 yo F with Metastatic ccRCC







*Baseline SLD: **108 mm***

Treatment History

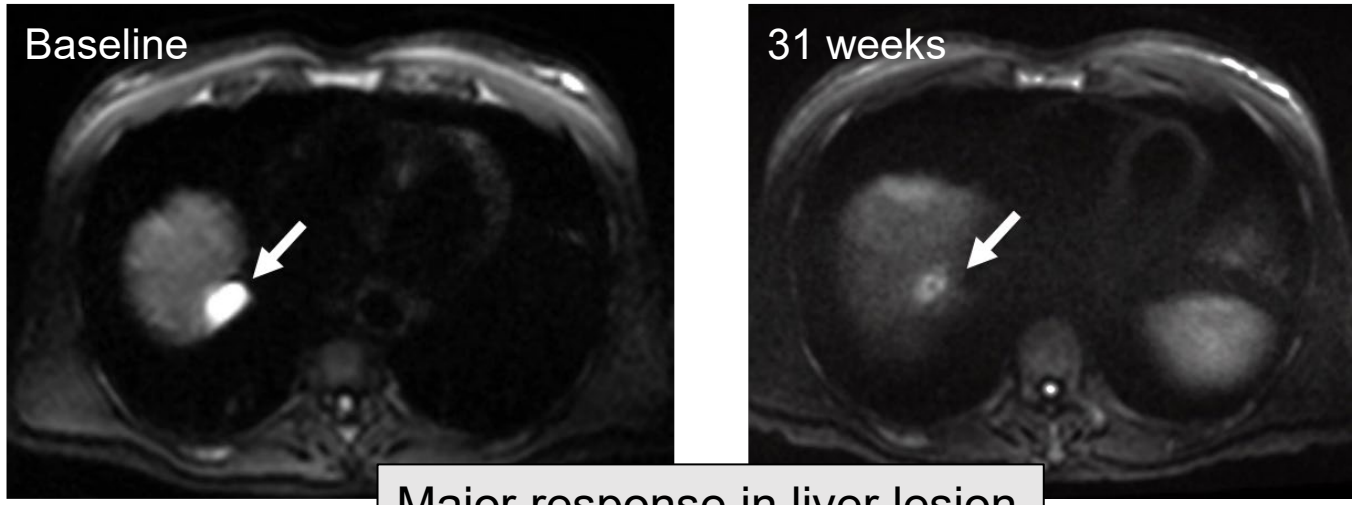
Prior Regimen	Best Response	Reason for Discontinuation
Ipilimumab/Nivolumab	SD	Progressive Disease
Cabozantinib	SD	Progressive Disease
Everolimus	SD	Progressive Disease

Sites of baseline metastatic disease:

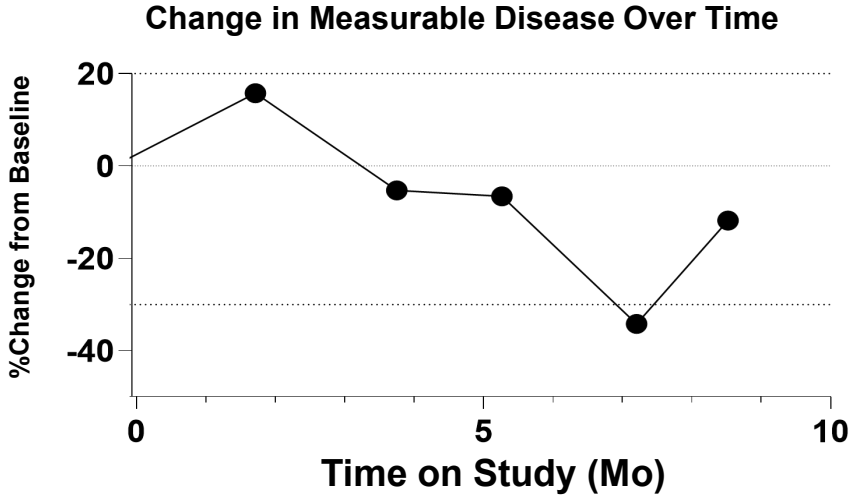
- Large volume pulmonary
- Multiple soft tissue (chest, peri-renal, peri-vaginal)
- Multiple Bone

ccRCC clear cell renal cell carcinoma; SLD Sum of longest diameters

Case Study 2: PR in 84 yo M with Extrahepatic CCA

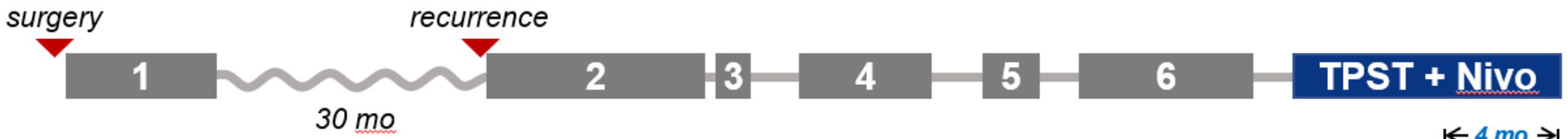


Major response in liver lesion



Baseline SLD: ***76 mm***
Target lesion sites: ***liver, lymph node, peritoneum***

Treatment History



	Prior Regimen	Reason for Discontinuation
1	Gemcitabine	Adjuvant therapy
2	Gemcitabine + Cisplatin + Trastuzumab	Completed
3	Capecitabine + RT	Completed
4	Trastuzumab	Progressive Disease
5	Gemcitabine + Trastuzumab	Progressive Disease
6	FOLFOX	Progressive Disease

RT Radiation therapy

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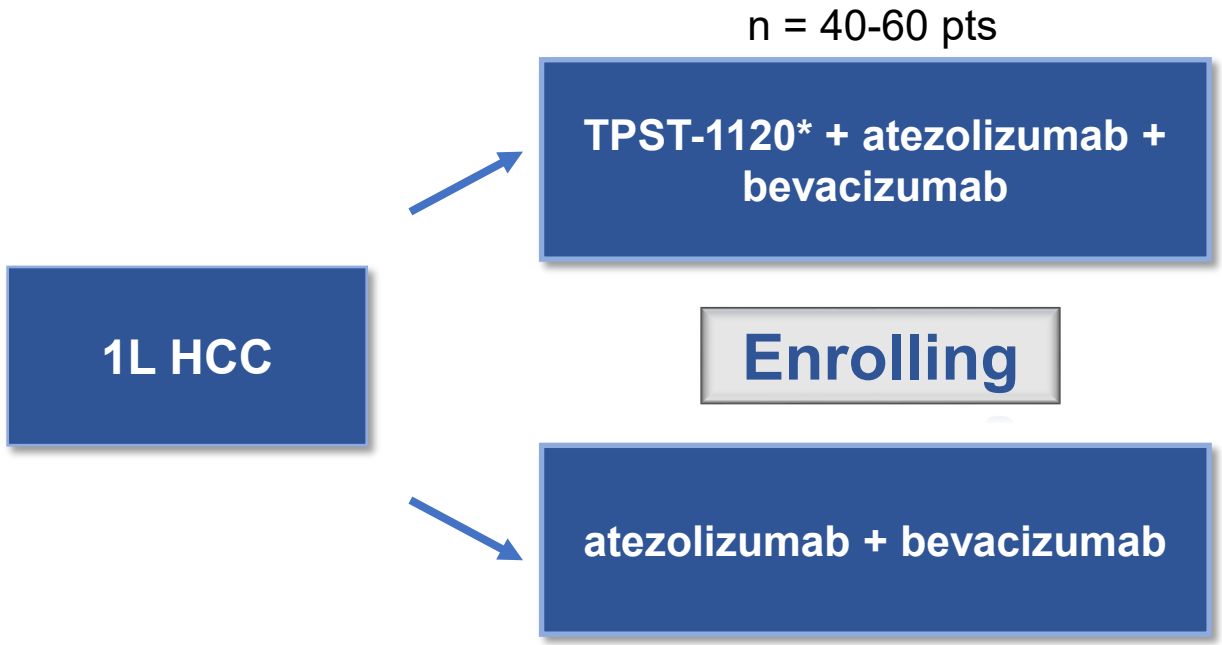
TPST-1120 Development: Next Step

Morpheus Liver Study Randomized Phase 1b/2 (NCT04524871)



Primary Endpoint: ORR
Secondary Endpoints (include): PFS, OS

Global study: US, EU, Asia

Operationalized by Roche

*Other investigational agents being evaluated include: tiragolumab, tocilizumab, RO7247669

Conclusions

- TPST-1120 is a first-in-class antagonist of the FAO regulator PPARα
- TPST-1120 demonstrated a tolerable safety profile in patients as monotherapy and in combination with nivolumab
- TPST-1120 demonstrated disease control as monotherapy and promising responses in combination with nivolumab
- Responses in patients previously refractory to anti-PD-(L)1 are consistent with PPARα mechanism targeting T-cell exhaustion and immune suppressive cells
- TPST-1120 in combination with atezolizumab and bevacizumab randomized against atezolizumab and bevacizumab is now enrolling in 1L HCC

Acknowledgements

- We humbly thank all of the patients and their families who supported this research

- We thank our fellow investigators and their dedicated site staff

Marina Gelman, PhD, provided editorial support for this presentation