Background TPST-1120 is a first-in-class, small molecule antagonist of peroxisome-proliferator-activated receptor-alpha (PPAR-α), a transcriptional regulator of fatty acid oxidation and mediator of immune suppression. TPST-1120 was well tolerated and showed signs of activity in a phase 1 trial as monotherapy (53% disease control rate) and in combination with nivolumab (NCT03829436). In combination cohorts the objective response rate (ORR) was 23%, including 30% (3/10, all partial responses) in subjects treated at the two highest TPST-1120 doses. Responses included two subjects with renal cell carcinoma previously refractory to anti-PD-1 and one subject with late line cholangiocarcinoma. We assessed gene expression changes in post-treatment whole blood and performed baseline mutational analysis on ctDNA to identify potential biomarkers.

Methods Differential expression of 780 genes in 30 subjects receiving 100 mg to 600 mg TPST-1120 BID was assessed using the nCounter® PanCancer Immune Profiling panel (NanoString Inc.) supplemented with 30 PPAR-α target genes. Associations between expression change magnitudes and TPST-1120 exposure levels on study day 8 were calculated, and genes exhibiting a False Discovery Rate p-value < 0.05 and effect size > 0.5 were categorized as potential pharmacodynamic biomarkers. Putative clinical response biomarkers were identified using linear discriminant analysis (LDA) with best objective response as categorical discriminants to identify genes differentially expressed by partial response (PR) patients (p<0.05 by Mann-Whitney U Test). Mutational analysis of ctDNA was performed using the PredicineCARE™ assay (Predicine Inc.).

Results Seven of 780 genes assessed were modulated by TPST-1120 exposure (p<0.05), including genes associated with enhanced immune responsiveness (CXCL16, TNFRSF1A), monocytes or macrophages (ITGAX, FCGR2A) and PPAR-α blockade (NCF4). Similar TPST-1120 exposure-biomarker associations were observed among monotherapy and combination therapy patients. LDA performed on combination therapy patients revealed that those with PR demonstrated significant elevations (p<0.05) in multiple genes including those associated with Th17 development (RORC), lipid transport (APOE) and down-regulation of CD155, a TIGIT ligand. Mutational analysis revealed that patients with PR or stable disease were more likely to bear mutations in isocitrate dehydrogenase (IDH) and phosphatase and tensin homolog (PTEN) compared to patients with progressive disease.

Conclusions TPST-1120 induces pharmacodynamic changes in circulating blood consistent with PPAR-α blockade and reversal of PPAR-α immune suppressive activities. Patients with PR demonstrated gene expression changes that implicate immune activation and alleviation of immune suppression as potential biomarkers of clinical benefit. Increased frequencies of responding patients bearing PI3K pathway or IDH mutations may reveal populations likely to benefit from treatment with TPST-1120.