## 850 DUAL BLOCKADE OF THE EP2 AND EP4 PGE2 RECEPTORS WITH TPST-1495 IS AN OPTIMAL APPROACH FOR DRUGGING THE PROSTAGLANDIN PATHWAY

[1]Brian Francica*, [1]Justine Lopez, [1]Anja Holtz, [1]Dave Freund, [2]Dingzhi Wang, [1]Amanda Enstrom, [1]Sam Whiting, [1]Chan Whiting, [1]Thomas Dubensky. *[1]Tempest Therapeutics, Berkeley, CA, USA; [2]MUSC, Charleston, SC, USA*

**Background** Prostaglandin E2 (PGE2) is a bioactive lipid produced by tumor cells that drives disease progression through stimulating tumor proliferation, enhancing angiogenesis and suppressing immune function in the TME.[1] PGE2 is also a mediator of adaptive resistance to immune checkpoint inhibitor therapy via the upregulation of cyclooxygenase-2 (COX-2). While the role of PGE2 signaling in cancer is clear, how best to inhibit PGE2 for cancer treatment remains under investigation. Inhibition of COX-1 and/or COX-2 has shown promising results in observational studies and meta-analyses, but inconsistent results in prospective studies. PGE2 signals through four receptors, EP1-4, that are variably expressed on tumor and immune cells and have distinct biological activities. The EP2/EP4 receptors signal through cAMP and drive pro-tumor activities, while EP1/EP3 receptors signal through calcium flux and IP3 and drive immune activation and inflammation. While COX-2 and single EP inhibitors continue to be developed, the nature of PGE2 signaling supports our rationale to inhibit PGE2 by dual antagonism of the pro-tumor EP2/EP4 receptors, while sparing the pro-immune EP1/EP3 receptors.

**Methods** We utilized human and murine whole blood to perform in vitro characterization of PGE2/inhibitor activity. In vivo, CT26 tumors and APCmin/+ mice were used to model CRC and measure immune endpoints.

**Results** In mouse and human whole blood assays, dual blockade of EP2 and EP4 receptors with TPST-1495 reversed PGE2-mediated suppression of LPS induced TNF-α, while EP4 receptor antagonists were unable to block suppression at higher PGE2 concentrations. Similarly, in murine and human T cells in vitro, TPST-1495 inhibited PGE2-mediated suppression, resulting in a significant increase of IFN-γ production in response to stimulation with cognate peptide Ag. In vivo, TPST-1495 therapy alone also significantly reduced tumor outgrowth in CT26 tumor bearing mice, correlated with increased tumor infiltration by NK cells, CD8+ T cells, AH1-specific CD8+ T cells, and DCs. The induced NKp46+CD4-CD8- cell population appeared to have an important role in TPST-1495 efficacy, as significant anti-tumor activity was observed in murine models lacking T Cells, particularly CT26 tumor-bearing RAG2-/- mice. TPST-1495 monotherapy demonstrated a decrease of both the intestinal tumor size and number in Adenomatous Polyposis (APCmin/+) mice, as compared to a single EP4 antagonist.

**Conclusions** TPST-1495 is a potent inhibitor of PGE2 mediated immune suppression and is currently being evaluated in an ongoing Phase 1 first-in-human study (NCT04344795) to characterize PK, PD, safety, and to identify a recommended phase 2 dose for expansion cohorts in key indications and biomarker selected patients.

### REFERENCE

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