## 1331 DUAL BLOCKADE OF THE EP2 AND EP4 PGE2 RECEPTORS WITH TPST-1495 IS AN OPTIMAL APPROACH FOR DRUGGING THE PROSTAGLANDIN PATHWAY

[1]Justine Lopez, [1]Anja Holtz, [1]Dave Freund, [1]Dara Burdette, [2]Dingzhi Wang, [2]Raymond Duboise, [1]Sam Whiting, [1]Thomas Dubensky, [1]Brian Francica*. [1]*Tempest Therapeutics, South San Francisco, 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. 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. 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. To our knowledge, TPST-1495 is the first clinical-stage dual inhibitor of both the EP2 and EP4 receptors.

**Methods** We utilized in vitro murine and human whole blood assays to isolate individual effects of EP inhibitors, as well as multiple syngeneic, xenograft, and GEM models to elucidate the effects of PGE2 pathway antagonism in vivo.

**Results** In mouse and human blood assays, dual blockade of EP2 and EP4 receptors with TPST-1495 reversed PGE2-mediated suppression of T cells and monocytes, while single receptor antagonists were unable to block suppression at higher PGE2 concentrations. In vivo, TPST-1495 monotherapy significantly reduced tumor outgrowth in five of seven syngeneic, xenograft and genetically engineered mouse models. CT26-bearing mice treated with TPST-1495 showed significant increases immune cell infiltration by CD8+, CD4+ and NK cells, and increased M1:M2 ratio among macrophages. APC-min/+ mice treated with TPST-1495 displayed almost complete reduction in tumor burden, which was not observed with other PGE2 pathway inhibitors, and increased in immune cell presence as demonstrated by histopathology. Transcriptional analysis of resected tumors demonstrated an increase in interferon gamma signature, as well as an increase in a gene profile associated with PGE2 inhibition.

**Conclusions** These results demonstrate the redundancy of EP2 and EP4 receptor signaling and the requirement for EP2 and EP4 to be blocked to achieve full therapeutic effect of PGE2 inhibition in tumors. The data further define the simultaneous effect of TPST-1495 on immune and non-immune compartments that lead to tumor regression. TPST-1495 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.

### REFERENCES

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**Ethics Approval** All murine studies were performed in accordance with human animal protocols guided by an IACUC.

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