**BACKGROUND**

- Therapeutic antibodies that block the programmed death-1 (PD-1) – programmed death-ligand 1 (PD-L1) pathway can induce robust and durable responses in patients with various cancers. However, these responses only occur in a subset of patients. Elucidating the determinants of response and resistance is key to improving outcomes and developing new treatment strategies.

- Stromal signature regulated by TGF-β pathway is one of the major mechanisms of tumor immune surveillance, leading to resistance to immune checkpoint inhibitors (IC). This occurred particularly in patients with tumors, which showed elevation of CD8+ T cells from the tumor parenchyma that were instead found in the fibroblast- and collagen-rich peritumoral stroma. Moreover, TGF-β responsive signatures (TBRS) of stromal cells have been associated with poor prognosis.

- Vactosertib (TGFBRI-I-IR) is a potent, highly selective, oral inhibitor of TGF-β type-I receptor (TGFβRI) that has shown promise as a drug candidate for the treatment of various solid tumors and hematologic malignancies.

**METHODS**

- A total of 36 patients aged 18 and older with histologically confirmed locally advanced or metastatic solid tumors were enrolled in a phase I/II dose-escalation study (NCT03181186).

- Vactosertib was orally administered at the dose range of 20–340 mg QD and 200mg BID for 5 days with 2 days off every week.

- Evaluation of peripheral blood mononuclear cells (PBMCs) was evaluated during Cycle 1.

- RNA sequencing of pretreatment tumor samples in 10 patients were analyzed to evaluate F-TBRS defined as geometric mean values of 171 corresponding gene expressions.

**RESULTS**

- Table 3: List of treatment-related adverse events (TRAEs)

- Figure 11: F-TBRS levels and clinical score

- Summary & Conclusion

- Vactosertib, a potent and highly selective oral TGFβRI inhibitor, was safe and well tolerated and the maximum tolerated dose was not determined.

- In per-protocol analysis, 6 out of 17 patients who received ≥140 mg achieved stable disease (35.3%) and showed higher F-TBRS levels than those with progressive disease.

- Based on PK profiles observed, a BID dosing regimen would allow for better maintenance of plasma levels of vactosertib in the biologically active range and enhance the potential for antitumor activity. Therefore, the proposed RDQs are 100 mg BID or 200 mg BID which now are being evaluated in combination with other therapeutic options in multiple solid tumors and hematologic malignancies.

- Since high F-TBRS levels are well recognized as one of the main mechanisms related to resistance to ICs, vactosertib would be an ideal therapeutic strategy in combination with ICs or conventional anti-tumor therapies for solid tumors with high F-TBRS levels.

**REFERENCES**

For more information, please contact us at therapeutics@pdx.net. phone: +88-10-732-3936

**ACKNOWLEDGMENTS**

- This study was financially supported by National Cancer Center (R01-2019-0153), Korea.