A phase Ib/II study (IMMCO-1) of atezolizumab plus tivozanib in immunologically cold pancreatic, gallbladder, and biliary cancers

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BACKGROUND

- Checkpoint inhibition (CPI) represents a significant advance in cancer care however it is not effective in the treatment of several immunologically cold tumors including pancreatic, gallbladder, and biliary cancers where checkpoint inhibitors have produced objective response rates of <5%.
- VEGF is thought to play a key role in modulating the anti-tumor immune response. Secreted by tumors, it leads to endothelial cell proliferation, vascular permeability, and vasodilation that together leads to the development of an abnormal vasculature with excessive permeability and poor blood flow, thus limiting immune surveillance.
- In addition, VEGF inhibits dendritic cell differentiation, limiting the presentation of tumor antigens to CD4 and CD8 T cells. Through the inhibition of VEGF, it may be possible to potentiate the effect of immune checkpoint blockade.
- Combined use of a VEGF tyrosine kinase inhibitor (TKI) and checkpoint inhibitor is already standard of care in advanced kidney, cervical and endometrial cancers. There has been suggestion that such a combination may have clinical activity in some microsatellite stable (MSS) GI malignancies.
- This signal seeking study aims to build upon those observations by incorporating a pan-VEGF axis inhibitor (tivozanib) with CPI (atezolizumab).

METHODS

- This is an open-label non-randomized phase Ib/II signal seeking basket study in multiple immunologically cold tumors.
- The co-primary endpoints are safety and efficacy of the combination of the VEGF-TKI tivozanib and CPI atezolizumab.
- Key eligibility criteria include~~s~~ patients with MSS pancreatic, biliary (cholangiocarcinoma and gallbladder), well-differentiated grade 2 and 3 neuroendocrine tumors, ovarian and vulvar cancer, soft tissue sarcoma, castrate resistant prostate cancer, and HER2 positive hormone receptor negative breast cancer, that is metastatic and progressed on at least one line of therapy.
- Key exclusion criteria will include patients with known mismatch repair deficiency, microsatellite instability, or high tumor mutational burden.

Table 1. Phase 1b 3+3 Dose De-escalation Design

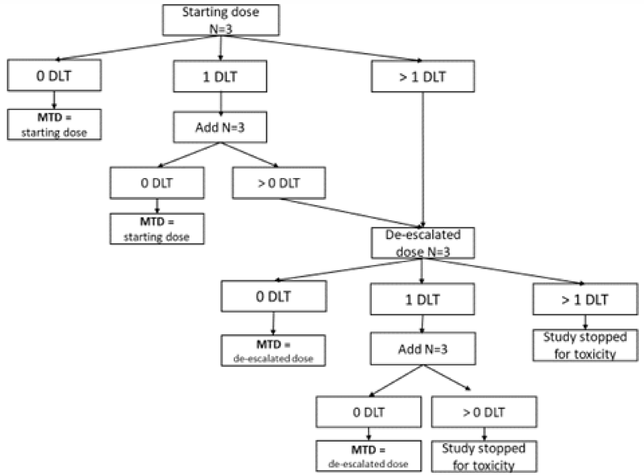
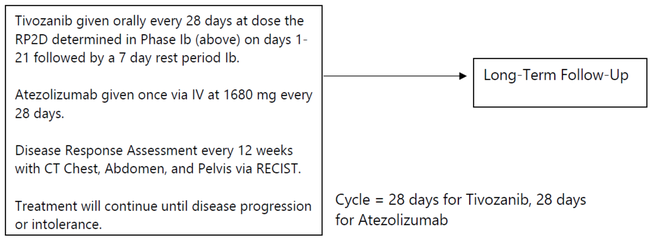


Table 2. Phase 2 Simon Two-Stage Design



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STATISTICAL PLAN

- The phase Ib portion will assess the safety profile of the combination of tivozanib and atezolizumab with a potential dose de-escalation of tivozanib using a 3+3 study design to yield a recommended phase 2 dose (RP2D).
- Starting doses include tivozanib 1.34 mg per day (dose level 0) for 21 days of each 28-day cycle and atezolizumab 1680 mg on day 1 of every 28-day cycle. Tivozanib dose level -1 will be 0.89 mg per day for 21 days of each 28-day cycle.
- The phase II portion will enroll up to 26 additional patients using the RP2D using the Simon two-stage design of recruitment. Accounting for a 20% dropout rate, up to 33 patients are planned to be enrolled. Cohort enrollment caps will be used to ensure maximum histologic diversity.
- This signal seeking study is looking to confirm the best objective response rate for evaluable patients increasing from < 7% (null hypothesis) to 25% (one-sided alpha = 0.05; 80% power).
- Disease response assessments are every 12 weeks with CT Chest, Abdomen, and Pelvis via RECIST 1.1.
- Treatment will continue until progression or intolerance.

TRIAL STATUS

- Active enrollment continues.
- No unexpected toxicities have thus far been identified.
- NCT05000294

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