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. Secreting 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 includes patients with MSS pancreatic, gallbladder, and biliary cancers, 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 neuroendocrine tumors, ovarian and vulvar cancer, soft tissue sarcoma, castrate resistant prostate cancer, and HER2 positive hormone receptor negative breast.

• 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>
<thead>
<tr>
<th>Dose Level</th>
<th>TKI Dose</th>
<th>CPI Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.34 mg</td>
<td>1680 mg</td>
</tr>
<tr>
<td>1</td>
<td>1.8 mg</td>
<td>1680 mg</td>
</tr>
<tr>
<td>2</td>
<td>2.1 mg</td>
<td>1680 mg</td>
</tr>
</tbody>
</table>

Cycle = 28 days for Tivozanib. 28 days for Atezolizumab.

STARTING Dose:

• Tivozanib given orally every 28 days at the RP2D determined in Phase Ib (above) on days 1 and 21 followed by a 7-day rest period.

• Atezolizumab given once IV at 1680 mg every 28 days.

Disease Response Assessment every 12 weeks with CT Chest, Abdomen, and Pelvis via RECIST 1.1.

Treat ment will continue until disease progression or intolerance.

Table 2. Phase 2 Simon Two-Stage Design

<table>
<thead>
<tr>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Cycle 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Progression</td>
<td>12 patients</td>
<td>12 patients</td>
<td>24 patients</td>
</tr>
<tr>
<td>Progression</td>
<td>16 patients</td>
<td>24 patients</td>
<td></td>
</tr>
</tbody>
</table>

TRIAL STATUS

• Active enrollment continues.

• No unexpected toxicities have thus far been identified.

• NCT05000294

REFERENCES


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