Cabozantinib, Nivolumab and Ipilimumab (CaNI) for advanced Renal Cell Carcinoma with Variant Histology

Background and Rationale

Renal cell carcinoma (RCC) with variant histology comprises a heterogeneous group of diseases with generally worse prognosis than clear cell RCC counterparts. Toxicity notable for 73% Grade 3 or 4 adverse events with triple therapy; only 58% of patients received all 4 doses of ipilimumab. This trial will explore the regimen in patients with RCC with variant histology decreasing initial cabozantinib dose to optimize ipilimumab.

Eligibility

- Locally advanced or metastatic RCC with variant histology
  - Papillary RCC, any type
  - Unclassified RCC
  - Translocation RCC
  - Chromophobe RCC
  - Collecting duct RCC
  - Medullary RCC
  - Renal cell carcinoma with 80% or more sarcomatoid features
  - Other variant histologies - ECOG performance status ≤ 1
  - No prior VEGF therapy
  - No prior immunotherapy or cabozantinib
  - No untreated CNS metastases
  - Anticoagulation with DOACs allowed

- Adequate Laboratory Function
  - Absolute neutrophil count ≥ 1,500/mCL
  - Platelets ≥100,000/mCL
  - Hemoglobin ≥9g/dL (transfusions allowed)
  - Total bilirubin ≤2.0 x institutional UNL
  - AST(SGOT)/ALT(SGPT) ≤2.5 x institutional UNL
  - Creatinine clearance ≥30 mL/min/1.73 m2 according to the Cockcroft-Gault equation.
  - Normal coagulation INR ≤ 1.5

Study Schema

**CAN-I** is a single arm phase 2 study evaluating cabozantinib, nivolumab and ipilimumab in patients with RCC with variant histology receiving ≤ 1 prior line of VEGF therapy

**NCT04413123**

37/40 enrolled

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Objective Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib</td>
<td>112</td>
<td>27%</td>
</tr>
<tr>
<td>Cabozantinib (papillary)</td>
<td>46</td>
<td>23%</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>165</td>
<td>26%</td>
</tr>
<tr>
<td>Nivolumab/Ipilimumab</td>
<td>52</td>
<td>19.6%</td>
</tr>
<tr>
<td>Atezolizumab/Bevacizumab</td>
<td>30</td>
<td>33%</td>
</tr>
<tr>
<td>Cabozantinib/Atezolizumab</td>
<td>40</td>
<td>47.5%</td>
</tr>
<tr>
<td>Cabozantinib/Nivolumab</td>
<td>40</td>
<td>47.6%</td>
</tr>
<tr>
<td>Lenvatinib/Pembrolizumab</td>
<td>82</td>
<td>47.6%</td>
</tr>
</tbody>
</table>

Study Treatment

Cabozantinib starting dose is 40 mg daily for first 40 patients

- Reductions to 20 mg daily or 20 mg every other day allowed
- For remaining 20 patients, starting dose reduced to 20 mg for triplet
  - Dose increase to 40 mg after triplet if tolerated

Nivolumab dosed at 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks for 4 cycles followed by nivolumab 480 mg IV every 4 weeks

- Dose reductions of Nivolumab or Ipilimumab are not permitted
- Delays up to 12 weeks are allowed

Nivolumab may be continued without Ipilimumab if toxicity attributed to ipilimumab

Objectives and Endpoints

- **Primary Endpoints**
  - Objective Response Rate (ORR) per RECIST 1.1

- **Secondary Endpoints**
  - Duration of Response
  - Progression Free Survival
  - Overall Survival
  - Safety (CTCAE v5)
  - Quality of life
  - FKSI-10, BFI with each CT

Study Assessments

- CT Chest, abdomen, pelvis in addition to MRI Brain is performed at baseline; bone scan performed as clinically indicated

- CT CAP +/- bone scan is performed at 12 weeks then every 8 weeks thereafter for 16 weeks before reverting to every 12 weeks

Statistical Analysis

A one-stage design is employed to enroll 40 eligible patients, which provides 93% power at 1-sided alpha of 0.09 to distinguish an ORR of 40% versus 20%. ≥ 12 responses required to deem treatment promising.

References

1. De Velasco et al, Clin Genitourinary Cancer 2017
5. Tykodi et al, ASCO GU 2021