Phase 2 trial of Cabozantinib with Nivolumab and Ipilimumab in advanced RCC with variant Histology CaNI (NCT04413123)

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RCC with variant Histology an Unmet Need

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Objective Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib(^1)</td>
<td>112</td>
<td>27%</td>
</tr>
<tr>
<td>Cabozantinib (papillary)(^2)</td>
<td>46</td>
<td>23%</td>
</tr>
<tr>
<td>Pembrolizumab(^3)</td>
<td>165</td>
<td>26%</td>
</tr>
<tr>
<td>Nivolumab/Ipilimumab(^4)</td>
<td>52</td>
<td>19.6%</td>
</tr>
<tr>
<td>Atezolizumab/Bevacizumab(^5)</td>
<td>40</td>
<td>26%</td>
</tr>
<tr>
<td>Cabozantinib/Atezolizumab(^6)</td>
<td>30</td>
<td>33%</td>
</tr>
<tr>
<td>Cabozantinib/Nivolumab(^7)</td>
<td>40</td>
<td>47.5%</td>
</tr>
<tr>
<td>Lenvatinib/Pembrolizumab(^8)</td>
<td>82</td>
<td>47.6%</td>
</tr>
</tbody>
</table>

1. Martinez Chanza et al, Lancet Oncology 2019
2. Pal et al, Lancet 2021
4. Tykodi et al, ASCO GU 2021
5. McGregor et al, Journal Clinical Oncology 2020
6. Pal et al, Lancet Oncology 2021
7. Lee et al, Journal of Clinical Oncology 2022
8. Albige et al, ESMO 2022
CaN-I in Variant Histology RCC

Metastatic ncRCC
N=40
Papillary
Chromophobe
Collecting Duct
Medullary
Translocation
>80% Sarcomatoid
Unclassified

Cabozantinib 40 mg daily
Ipilimumab 1 mg/kg q3 weeks x 4
Nivolumab 3 mg/kg q3 weeks x 4

Cabozantinib 40 mg daily
Nivolumab 480 mg IV q4 weeks

Biopsy
Biopsy (if initial response)

Primary Objective
ORR

Secondary Objectives
Toxicities
Duration of responses

37 enrolled!

NCT04413123
Toxicities

Summary of Adverse Events (Safety Population)

<table>
<thead>
<tr>
<th>Treatment-related adverse event</th>
<th>Cabo+Nivo+Ipi (N=426)</th>
<th>Pbo+Nivo+Ipi (N=424)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3–4</td>
</tr>
<tr>
<td>Any event, %</td>
<td>99</td>
<td>73</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>46</td>
<td>26</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>44</td>
<td>20</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>41</td>
<td>4</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia</td>
<td>28</td>
<td>3</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>24</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23</td>
<td>8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td>Amylase increased</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Rash</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Pruritus</td>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>

- Grade 5 TRAEs occurred in 3 patients (1%) with Cabo+Nivo+Ipi (gastrointestinal hemorrhage, hepatic failure, and respiratory failure) and 3 patients (1%) with Pbo+Nivo+Ipi. Patients had grade 5 TRAEs with Cabo+Nivo+Ipi (immune-mediated hepatitis and acute hepatic failure) and one additional patient with Pbo+Nivo+Ipi (perforated ulcer).
- Use of high-dose corticosteroids

Only 58% received all 4 doses of ipilimumab

1. Choueiri et al, EMSO 2022
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#KCRS22