Phase IB/II trial of Ipilimumab, Nivolumab, and Ciforadenant (adenosine A2a receptor antagonist) in first-line advanced RCC

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Conflicts of Interest

• Research funding to the Institution Laboratory Research: Aravive, BMS-LCFA-IASLC YIA grant, Pionyr, Arsenal

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• Consultant: Alpine Immune Sciences, Aravive, AstraZeneca, Aveo, BMS, Exelexis, Merck, Sanofi, Seagen
Rationale for the combination of checkpoint inhibition and A2AR antagonist

- Anti-PD-(L)1 antibodies are approved for treatment of RCC but most patients progress.

- Adenosine blocks T-cell activation and promotes myeloid suppression.\(^a,b,c\)

- Resistance to PD-1 blockade is associated with an immunosuppressive myeloid signature.\(^c,d\)

- CPI-444 is a oral small molecule antagonist of the adenosine 2A receptor (A2AR) that has shown efficacy in animal models and is associated with T cell activation.\(^c,e\)

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\(^a\) Vijayan et al, Nature Reviews, 2017  
\(^b\) Ohta and Stitkovsky et al, PNAS, 2006  
\(^c\) Willingham et al, Cancer Immunology Research, 2018  
\(^d\) Mc Dermott et al, Nature Medicine, 2018  
\(^e\) Leago et al, Cancer Immunology Immunotherapy, 2018
A2AR blockade in refractory RCC

3rd or 4th line refractory RCC trial demonstrate safety and efficacy

<table>
<thead>
<tr>
<th></th>
<th>Ciforadenant monotherapy</th>
<th>Ciforadenant + Atezolizumab</th>
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<tbody>
<tr>
<td>ORR</td>
<td>3%</td>
<td>11%</td>
</tr>
<tr>
<td>PFS</td>
<td>4.1 mos</td>
<td>5.8 mos</td>
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<tr>
<td>OS</td>
<td>69% at 16 mos</td>
<td>&gt;90% at 25 mos</td>
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<tr>
<td>6 month DCR</td>
<td>17%</td>
<td>39%</td>
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(Fong et al., 2020)
Eligibility
- Newly diagnosed or recurrent stage IV clear cell RCC
- No prior systemic therapy
- ECOG 0, 1
- Measurable Disease
- Tumor sample for histologic confirmation & biomarker assessment
- Adequate Organ Function

Phase IB
Ipilimumab 1 mg/kg IV q3w
+ Nivolumab 3 mg/kg IV q3w
+ Ciforadenant 100 mg PO BID

N=8

❖ Primary Endpoint: Safety, tolerability, and anti-tumor
❖ If rate of adverse events > 45%, then decrease ciforadenant to 50 mg BID will occur

Phase II
Ipilimumab 1 mg/kg IV q3w
+ Nivolumab 3 mg/kg IV q3w
+ Ciforadenant 100 mg PO BID

N=42

(Simon Two Stage <7/28 stop for futility)

❖ Primary Endpoint: Increasing percentage of patient who achieve depth of response of >50% tumor reduction from historical control of 32% to 48%
❖ Secondary Endpoint: ORR, PFS, irAE
❖ Exploratory: Gene expression signatures, systemic peripheral blood analysis on therapy
Primary Endpoint Discussion

Primary Endpoints:
• The Phase 1b primary endpoint will be safety as determined through assessment of dose limiting toxicities using CTCAE 5.0 criteria.
• The Phase 2 primary endpoint will be percentage of patients who achieve a depth of tumor burden reduction >50% by RECIST1.1 criteria.

Secondary Endpoints:
• The secondary endpoints will include: ORR, DOR, PFS, and treatment related adverse event rate.

Exploratory Endpoints:
• The exploratory endpoints will include assessment of gene expression signatures and pharmacodynamic markers in relation to clinical response on therapy.