Clinical Activity of Adenosine A2A Receptor (A2aR) Inhibitor CPI-444 is Associated with Tumor Expression of Adenosine Pathway Genes and Tumor Immune Modulation

Drew Hotson1, John Powderly2, Leisha Emens3, Patrick Forde3, Matthew Hellmann4, Lawrence Fong5, Ben Markman6, Brett Hughes7, Jonathan Goldman8, Mario Szno9, Daruka Mahadevan10, Shivaani Kummar11, Joshua Brody12, Philip Bonomi13, Jason Luke14, Matthew Riese15, Taofeek Owonikoko16, Sherene Loi17, Amy Wiese18, Robert Doebele19, James Lee20, Chunyan Gu1, Stephen Willingham1, Ginna Laport1, Richard Miller1 and Ian McCaffery1

1Corvus Pharmaceuticals, Burlingame, CA; 2Carolina BioOncology Institute, Huntersville, NC; 3Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD; 4Memorial Sloan Kettering Cancer Center, New York City, NY; 5University of California, San Francisco, San Francisco, CA; 6Monash Medical Centre, Clayton, Australia; 7Royal Brisbane and Women’s Hospital, Herston, Australia; 8University of California, Los Angeles, Los Angeles, CA; 9Yale University School of Medicine, New Haven, CT; 10University of Arizona Cancer Center, Tucson, AZ; 11Stanford University School of Medicine, Stanford, CA; 12Icahn School of Medicine at Mount Sinai, New York City, NY; 13Rush University Medical Center, Chicago, IL; 14University of Chicago Medical Center, Chicago, IL; 15Medical College of Wisconsin, Milwaukee, WI; 16Emory University Hospital, Atlanta, GA; 17Peter MacCallum Cancer Centre, Melbourne, Australia; 18Karmanos Cancer Institute/Wayne State University, Detroit, MI; 19University of Colorado Anschutz Medical Campus, Aurora, CO; 20University of Pittsburgh Medical Center Hillman Cancer Center, Pittsburgh, PA.
Disclosures

Consultancy
7 Hills, Actym, Amgen, Array, AstraZeneca, BeneVir, Bristol-Myers Squibb, Castle, CheckMate, EMD Serono, Gilead, Janssen, Novartis, Merck

Clinical Trial Support to Institution
AbbVie, Boston Biomedical, Bristol-Myers Squibb, Celldex, Corvus, Delcath, Five Prime, Genentech, Immunocore, Incyte, Intensity, MedImmune, Macrogenics, Novartis, Pharmacyclics, Merck, Tesaro

Funding for CPI-444 clinical trial provided by Corvus
Background

- Anti-PD-(L)1 antibodies are approved for treatment of several cancers but a small proportion of patients benefit.

- Mechanisms of anti-PD-(L)1 resistance are not well understood and no agents are approved to overcome resistance.

- Adenosine pathway mediates tumor immunosuppression; may be a resistance mechanism to anti-PD-(L)1 therapy.

- CPI-444 is an oral, small molecule inhibitor of A2AR that has shown anti-tumor activity in anti-PD-(L)1 resistant/refractory, and PDL-1 negative patients.

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1Fong, ASCO 2017; 2Beavis et al., Can Immun Res 2015; 3Sharma et al., Cell 2017
Phase 1/1b Clinical Study with Oral Drug CPI-444

**Eligibility**

- Prior anti-PD-(L)1 allowed
  - **Resistant:** SD or better > 3 months of treatment
  - **Refractory:** progression within 3 months
- Must have progressive disease on prior therapy
- No selection for PD-L1 expression
Prior Anti-PD-(L)1 Treatment Increases A2AR, CD73 and CD39

Adenosine pathway is a potential mechanism of resistance

Exposure to anti-PD-(L)1 therapy (> 3 months) increases A2AR, CD73, and CD39 expression
Adenosine Pathway Expression is Higher in RCC and NSCLC Pre-Treatment Biopsies

A2AR

- p < 0.0001
- p = 0.05

CD73

- p = 0.03
- p < 0.0001

CD39

- p < 0.0001
- p = 0.0002

Other = bladder, colorectal, triple-negative breast, melanoma, prostate
## Renal Cell Cohorts Expanded

### Patient characteristics

<table>
<thead>
<tr>
<th>Prior anti-PD-(L)1 exposure</th>
<th>Renal Cell Cancer (N=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naïve</td>
<td>16 (31%)</td>
</tr>
<tr>
<td>Resistant/Refractory</td>
<td>35 (69%)</td>
</tr>
</tbody>
</table>

| PD-L1 Negative (archival) * | 91%                     |

| Median time since IO agent, months (range) | 1.6 (1 – 71)            |

<table>
<thead>
<tr>
<th>Histology</th>
<th>Renal Cell Cancer (N=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 (98%) Clear cell</td>
<td>64 (44-70)</td>
</tr>
<tr>
<td>1 (2%) Papillary</td>
<td>25/26</td>
</tr>
</tbody>
</table>

| Median age, years (range)      | 1 (1-5)                 |
| No. of patients: single agent /combination | 3 (1-5)                 |

<table>
<thead>
<tr>
<th>Adverse Prognostic Factors (%)</th>
<th>Renal Cell Cancer (N=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visceral metastases</td>
<td>88%</td>
</tr>
<tr>
<td>Hepatic metastases</td>
<td>20%</td>
</tr>
<tr>
<td>Anemia</td>
<td>45%</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>21%</td>
</tr>
</tbody>
</table>

* PD-L1 status determined using FDA-approved assay (SP142, cutoff = 5%)

Data cutoff 10/26/17
CPI-444 Anti-Tumor Activity in Renal Cell Cancer

Responses with single agent and combination

Data cutoff 10/26/17

Partial Responses in RCC

Single agent CPI-444 (atezolizumab-refractory)

Combination CPI-444 + atezolizumab

- Resistant to prior IO
- Refractory to prior IO
- Naïve to prior IO
Renal Cell Cancer
Response rate and disease control rate in evaluable patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Objective Response Rate</th>
<th>Disease Control Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPI-444</td>
<td>2*/14 (14%)</td>
<td>4/14 (29%)</td>
</tr>
<tr>
<td>CPI-444 + atezolizumab</td>
<td>2/16 (13%)</td>
<td>11/16 (69%)</td>
</tr>
</tbody>
</table>

*1 unconfirmed

Drug Treatment (months)

Data cutoff 10/26/17
## Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>Adverse Events (Gr1/2) &gt; 5% Frequency (n=210)</th>
<th>CPI-444 (%)</th>
<th>CPI-444/Atezolizumab (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>21</td>
<td>29</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Pruritus</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Anemia</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

### Grade ≥ 3 Serious Adverse Events

**CPI-444 (n=1)**
- Gr 3 nausea/vomiting/diarrhea

**CPI-444/Atezolizumab (n=5)**
- Gr 3 immune related hepatitis, dermatitis, mucositis, pneumonitis
- Gr 3 autoimmune hemolytic anemia
- Gr 3 increased ALT/AST
- Gr 3 thrombocytopenia/ Gr 4 encephalitis
- Gr 3 pneumonitis

Data cutoff 10/26/17
Screening A2AR and CD73 Associated with Response

**Double positive A2AR, CD73 may be predictive**

A2AR

- **Neg**
- **Pos**

CD73

- **Neg**
- **Pos**

A2AR+/CD73+

- **Neg**
- **Double Positive**

**Tumor Response (Best % Change)**

- **p=0.01**
- **p=0.09**
- **p=0.0006**

**CRC (MSI-H)**

**NSCLC**

**RCC**

**Tissue not available for all PRs**

**Partial Responses**

n = 35        n = 32

n = 16        n = 51

n = 49        n = 24
Screening A2AR, CD73 Associated with Disease Control Rate

*Double positive A2AR, CD73 may be predictive*

<table>
<thead>
<tr>
<th></th>
<th>Negative</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A2AR</strong></td>
<td>4/39 (10%)</td>
<td>10/34 (29%)</td>
</tr>
<tr>
<td><strong>CD73</strong></td>
<td>2/22 (9%)</td>
<td>12/51 (24%)</td>
</tr>
<tr>
<td><strong>A2AR + CD73</strong></td>
<td>4/49 (8%)</td>
<td>10/24 (42%)*</td>
</tr>
</tbody>
</table>

* *p=0.0007
In CD73+ Tumors, Single Agent CPI-444 Induces Expression of T cell Activation Markers in Post-Dose Biopsies

<table>
<thead>
<tr>
<th>Infiltration</th>
<th>Inflammation</th>
<th>IFNγ Induction</th>
<th>Effector</th>
<th>Checkpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD8 (IHC)</td>
<td>PD-L1 (IHC)</td>
<td>CXCL9</td>
<td>GZMA</td>
<td>IDO1</td>
</tr>
<tr>
<td>p = 0.005</td>
<td>p = 0.15</td>
<td>p = 0.02</td>
<td>p = 0.07</td>
<td>p = 0.01</td>
</tr>
</tbody>
</table>

CD73 Expression (in Screening Biopsies)
Summary

- Tumor expression of A2AR, CD73 and CD39 are increased in patients that are resistant to prior treatment with anti-PD-(L)1
- RCC and NSCLC have high tumor expression of adenosine pathway genes A2AR, CD73 and CD39
- CPI-444 has anti-tumor activity in RCC
  - Responses seen in anti-PD-(L)1 resistant/refractory patients
  - A2AR and CD73 expression in screening biopsies is associated with response to therapy
- CPI-444 increases CD8+ infiltration in tumors and induces expression of IFNγ-dependent genes and Th1 activation
- This study continues to enroll patients with RCC and NSCLC in expansion cohorts
Acknowledgements

Patients and their Families

Clinical Investigators and their staff

Colleagues at Corvus