Immunobiology and Clinical Activity of CPI-006, an Anti-CD73 Antibody with Immunomodulating Properties in a Phase 1/1b Trial in Advanced Cancers

Disclosures

Jason J. Luke: University of Pittsburgh Medical Center, Pittsburgh

The following relationships exist related to this presentation:

- **Data and Safety Monitoring Board**: TTC Oncology
- **Scientific Advisory Board**: 7 Hills, Actym, Alphamab Oncology, Mavu, Pyxis, Springbank, Tempest
- **Consultancy**: Abbvie, Akrevia, Array, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Compugen, EMD Serono, Ideaya, Immunocore, Incyte, Janssen, Leap, Merck, Mersana, Novartis, RefleXion, Silicon, Vividion
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- **Travel**: Akrevia, AstraZeneca, Bayer, Bristol-Myers Squibb, EMD Serono, Immunocore, Incyte, Janssen, Merck, Mersana, Novartis, RefleXion
- **Patents**: (both provisional) Serial #15/612,657 (Cancer Immunotherapy), PCT/US18/36052 (Microbiome Biomarkers for Anti-PD-1/PD-L1 Responsiveness: Diagnostic, Prognostic and Therapeutic Uses Thereof)

*Corvus Pharmaceutical Inc. is the sponsor of this study.*
Background

**CPI-006 is an Anti-CD73 with Adenosine Independent Immunomodulatory Properties**

- CD73 is an ectoenzyme present on many tissues including subsets of T and B cells
  - Converts AMP to adenosine
  - Functions in lymphocyte adhesion, migration and activation
- CPI-006 is a humanized IgG1 Fcγ receptor deficient anti-CD73 with unique properties
  - Blocks catalytic activity
  - Has agonistic immunomodulatory activity on CD73 positive cells that are **adenosine independent**
  - Increases expression of CD69, HLA-DR, etc. on APC
- Early results from Ph1 dose escalation trial demonstrate lymphocyte activation and effects on trafficking
- Ciforadenant (CPI-444) is an adenosine 2A receptor (A2AR) antagonist with reported anti-tumor activity in mCRPC, RCC and NSCLC
  - Adenosine gene signature in tumor correlates with response in RCC

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1. Resta & Thompson, Cell Signaling, 1997
3. Fong et al, Cancer Discovery, In Press
CPI-006 is an Anti-CD73 with Unique Properties

*CPI-006 induces B cell differentiation: isotype switching and immunoglobulin secretion in vitro*

- CPI-006 activates B cells, resulting in morphological and surface marker changes consistent with B cell differentiation and isotype class switching.
- Comparison to adenosine blocking anti-CD73 antibody (CPX-016) demonstrates unique CPI-006 property.
**CPI-006-001 Clinical Trial Design**

### Design
- Phase 1/1b dose escalation/dose expansion in disease specific cohorts
- CPI-006 every 3 weeks; fixed dose of ciforadenant

### Eligibility
- Cancers progressed on 1-5 prior therapies
- CD73 expression: required in expansion, not in dose escalation
- Adenosine gene signature not used to select patients

### Objectives
- Primary: Safety and tolerability
- Secondary: PK/PD, efficacy, biomarkers

### Biomarker Assessments
- Tumor markers, cytokines, etc.

#### Dose Escalation
- **CPI-006**
  - 24 mg/kg
  - 18 mg/kg
  - 12 mg/kg
  - 6 mg/kg
  - 3 mg/kg
  - 1 mg/kg
- **CPI-006 + Ciforadenant**
  - 24 mg/kg
  - 18 mg/kg
  - 12 mg/kg
  - 6 mg/kg
  - 3 mg/kg
  - 1 mg/kg
- **CPI-006 + Pembrolizumab**
  - 18 mg/kg
  - 12 mg/kg
- **CPI-006 + Ciforadenant + Pembrolizumab**
  - 18 mg/kg
  - 12 mg/kg

#### Dose Expansion
- **mCRPC**
- **RCC**
- **NSCLC**
- **Others**

Doses explored to date & planned doses

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See Poster P434, Saturday Nov 9th

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34th Annual Meeting & Pre-Conference Programs

#SITC2019
## Patient Characteristics

<table>
<thead>
<tr>
<th>Total Patients N=40</th>
<th>CPI-006 (N = 24)</th>
<th>CPI-006 + Ciforadenant (N=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs), median (range)</strong></td>
<td>62 (46, 78)</td>
<td>67 (36, 86)</td>
</tr>
<tr>
<td><strong>Gender, male N (%)</strong></td>
<td>18 (75)</td>
<td>12 (75)</td>
</tr>
<tr>
<td><strong>No. of prior therapies, median (range)</strong></td>
<td>4 (1, 6)</td>
<td>4 (2, 7)</td>
</tr>
<tr>
<td><strong>Histologies</strong></td>
<td><strong>N</strong></td>
<td><strong>N</strong></td>
</tr>
<tr>
<td>Renal Cell Cancer</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Head and Neck Cancer</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Bladder Cancer</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
## Adverse Events

<table>
<thead>
<tr>
<th>Adverse Events N (%)</th>
<th>CPI-006 Monotherapy (N=24)</th>
<th>CPI-006 + Ciforadenant (N= 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Patients with any TEAE</td>
<td>18 (75.0)</td>
<td>4 (16.7)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (4.2)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>2 (8.3)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Colitis</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (4.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (16.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (12.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Chills</td>
<td>11 (45.8)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (12.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2 (8.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>3 (12.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Liver enzymes increased (AST &amp; ALP)</td>
<td>1 (4.2)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>WBC decreased</td>
<td>1 (4.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1 (4.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>1 (4.2)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Tumor pain</td>
<td>2 (8.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (8.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (8.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (4.2)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Treatment related adverse events: Any grade 3 or 4 events, or 2 or more all grades
Pharmacokinetics and Receptor Occupancy

- Sustained CD73 occupancy of peripheral blood at ≥ 6 mg/kg
- Full tumor occupancy observed at ≥ 18 mg/kg
Treatment Induces Rapid Changes in Blood B and T Cells

- Changes in B cells (but not T cells) appear to be CD73 expression dependent
- B cell numbers partially return by 21 days; T cells fully return
Increase in Memory B Cells in Returning Lymphocytes

**Peripheral Blood Gated on CD19+ and CD20+ B Cells**

- Pre-treatment
- 30 min (Reduced B cells)
- Day 21 (Returning B cells: Memory Phenotype)

- Increased % class-switch memory cells
- No change in % class-switch memory cells
- Increased % class-switch memory cells

**Increased Memory B Cells at Day 21**

- At 0.5 hours no change in proportion of naïve and memory B cells; returning cells have a greater proportion of memory B cells
- These findings are consistent with a humoral adaptive response
Significant Expansion of New B and T cell Clones

Differential Abundance Plots of B cell Clonal Expansion

New B cell clones on treatment present at high frequencies (up to 1:100)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Number of Patients with B Cell Expansion</th>
<th>Number of Patients with T Cell Expansion</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPI-006 monotherapy</td>
<td>5 of 7</td>
<td>2 of 4</td>
</tr>
<tr>
<td>CPI-006 + ciforadenant</td>
<td>2 of 4</td>
<td>1 of 4</td>
</tr>
<tr>
<td>Total</td>
<td>7 of 11</td>
<td>3 of 8</td>
</tr>
</tbody>
</table>

- Generation of prevalent B and T cell clones on therapy
- Consistent with antigen-driven clonal selection
- No change in serum immunoglobulins observed
Response Assessments

• Response assessments in patients receiving ≥ 6 mg/kg dose
Tumor Reduction in a Prostate Cancer Patient

*CPI-006 monotherapy*

- 72 year old man with widely metastatic prostate cancer; previous therapies include leuprolide/bicalutamide, abiraterone, enzalutamide and docetaxel
- Decrease in target lesion in patient receiving 6 mg/kg monotherapy, treatment ongoing through 19 cycles
Responding Pulmonary Metastases in RCC Patient

CPI-006 6 mg/kg plus ciforadenant combination

- 36 year old male presented in 2015 with renal mass and bone metastases

- Failed TKI, nivo and nivo/ipi with increase pulmonary mets

- Regression of multiple biopsy proven pulmonary metastases on CPI-006 + ciforadenant
Model for CPI-006 Effects on Cells

**Blood**

- **Naïve B cell**
  - IgD+
  - CD19+
  - CD20+
  - CD27-
  - CD73+

- **CPI-006**

- **Memory B cell**
  - IgD-
  - CD19+
  - CD20+
  - CD27+
  - CD73+

- **Activated B cell**
  - CD19+
  - CD20+
  - CD25+
  - CD69+
  - CD83+
  - HLA-DR↑ CD73+

**Lymph node**

- **Plasmablast**
  - IgM,G secreted
  - IgD-
  - CD19+
  - CD20-
  - CD27+
  - CD38+
  - HLA-DR- CD73-
Conclusions

- CPI-006 has novel immunomodulatory activities:
  - Induces differentiation of B cells, class switching, secretion of immunoglobulin (in vitro), and generation of memory B cells
  - Increases expression of CD69 and other markers consistent with increased antigen presentation by APCs
- The optimum and well tolerated dose of CPI-006 is 18 mg/kg
- Treatment with CPI-006 induces redistribution of T and B cells with an increase in returning memory B cells and expansion of new B cell clones
- Changes in lymphocytes are consistent with induction of adaptive humoral immunity
- Tumor regression observed in RCC and prostate
- Treatment with CPI-006 may represent an opportunity to identify novel anti-tumor antibodies
Acknowledgements

• The patients and their families

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• Colleagues at Corvus