Immunobiology, Preliminary Safety and Efficacy of CPI-006, an Anti-CD73 Antibody with Immune Modulating Activity, in a Phase 1 Trial in Advanced Cancers


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*Currently at University of Pittsburgh Medical Center
Adenosine in the tumor microenvironment is immunosuppressive

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

Ciforadenant (CPI-444) is an adenosine 2A receptor (A2AR) antagonist with anti-tumor activity in animals and in human clinical trials
- Adenosine gene signature in tumor correlates with response

*Resta & Thompson, Cell Signaling, 1997
CPI-006 Blocks CD73 Enzymatic Activity

**CD73 Catalytic Activity**

AMP → Adenosine + Phosphate

- isotype
- CPI-006
- 1mM APCP

**MDA-MB-231 Xenograft**

Dosed with 10 mg/kg CPI-006 daily

- PBS
- isotype
- CPI-006

Tumor Volume (mm³)

Day of Treatment

- Day 0
- Day 5
- Day 10
- Day 15
- Day 20

**MDA-MB-231: Human TNBC Xenograft Model**

- CD73 IHC (Non-Competitive Anti-CD73)
- CD73 IHC (Competitive Anti-CD73)

Immunomodulatory Activities of CPI-006 are Adenosine Independent

- Healthy donor PBMC treated overnight
- Flow cytometry analysis of surface markers on B cells (CD19^{POS}CD3^{NEG})

• Lymphocyte markers are consistent with activation of B cells as well as other antigen presenting cell populations, e.g., APCs
Clinical Trial Design

Design
- Phase 1/1b open label, 3 + 3 dose escalation/dose expansion
- CPI-006 given as 1 hour IV infusion every 3 weeks; fixed dose of ciforadenant (100 mg po BID) for combo

Eligibility
- Advanced cancers progressed on 1-5 prior therapies
- ECOG status 0 or 1
- 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
- Effects on CD73 expression in tumors
- Peripheral blood lymphocyte subsets
- Antibody occupancy of target
- Serum cytokines

Cohorts studied to date

DOSE ESCALATION

Arm 1a: CPI-006
- 24 mg/kg
- 18 mg/kg
- 12 mg/kg
- 6 mg/kg
- 3 mg/kg
- 1 mg/kg

Arm 1b: CPI-006 + Ciforadenant
- 24 mg/kg
- 18 mg/kg
- 12 mg/kg
- 6 mg/kg
- 3 mg/kg
- 1 mg/kg

Arm 1c: CPI-006 + Pembrolizumab
- 24 mg/kg
- 18 mg/kg
- 12 mg/kg
- 6 mg/kg
- 3 mg/kg
- 1 mg/kg

DOSE EXPANSION

- RCC
- NSCLC
- NHL
- Others
## Patient Characteristics

### Baseline Demographics

<table>
<thead>
<tr>
<th>Description</th>
<th>CPI-006 (N=12)</th>
<th>CPI-006 + ciforadenant (N=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs), median (range)</td>
<td>62 (46, 78)</td>
<td>64 (36, 86)</td>
</tr>
<tr>
<td>Gender, male n (%)</td>
<td>10 (83)</td>
<td>8 (100)</td>
</tr>
<tr>
<td>No. of prior therapies, median (range)</td>
<td>4 (1, 5)</td>
<td>4 (3, 7)</td>
</tr>
<tr>
<td><strong>Histologies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder Cancer</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Head and Neck Cancer</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Renal Cell Cancer</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Sarcoma</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=12)</th>
<th>CPI-006 + Ciforadenant (N=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Subjects with any TEAE</td>
<td>8 (66.7)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (8.3)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (8.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (25.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Chills</td>
<td>4 (33.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (16.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>2 (16.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (16.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (16.7)</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

Serum Pharmacokinetics

Peripheral CD8 Receptor Occupancy

- Exposure increases and clearance decreases with increasing dose
- CPI-006 detectable for 21 days after a single dose of 6 mg/kg or higher
- Total cell surface CD73 unchanged; CPI-006 epitope blocked
• Colorectal patient treated with 12 mg/kg CPI-006
• Tumor biopsy of retroperitoneal lesion obtained at trough pre-dose 3

- Tumor biopsy demonstrates presence of CD73 which is occupied by CPI-006
- CPI-006 saturates CD73 and inhibits enzymatic activity
Disease Assessment

Cycle = 21 days
Disease assessment every 3-4 cycles

- Higher doses appear to be providing longer term disease control with monotherapy
- Combination appears to improve disease control
Treatment Induces Rapid Changes in PBMCs

### CD73^POS^ B cells

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CD73^POS^ B cells (Percentage of Lymphocytes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td><img src="#" alt="Graph showing CD73^POS^ B cells before treatment" /></td>
</tr>
<tr>
<td>0.5 Hour</td>
<td><img src="#" alt="Graph showing CD73^POS^ B cells at 0.5 hour" /></td>
</tr>
</tbody>
</table>

**Changes in PBMCs at 0.5 Hour**

- *Consistent with*
  - Trafficking of CD73^POS^ B cells out of the blood
  - Redistribution of T cells & monocytes (CD73^NEG^)
- Increase in CD4/CD8 ratios – including CD73^NEG^ subsets

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**Pre Treatment vs. 0.5 Hour**

- 1mg/kg: Red
- 3mg/kg: Orange
- 6mg/kg: Green
- 12mg/kg: Blue

**Fold Change in Cell Frequency**

- $p < 0.0001$
Changes in Blood B Cells Over Time

Changes in CD73\textsuperscript{POS} B cells

- CD73\textsuperscript{POS} B cells drop with each infusion and partially return reaching new steady state
- Consistent with redistribution of B cells to lymphoid tissue
- Increased expression of HLA-DR

Changes in HLA-DR Expression
6 mg/kg Monotherapy cohort

- HLA-DR ratio on B cells
- Colorectal
- SCC Head/Neck
- Prostate
Changes in CD73\textsuperscript{POS} B Cells & Tumor Reduction in a Prostate Cancer Patient

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 11 cycles
Treatment Induces Cytokines Consistent with Immune Activation

Rapid induction of inflammatory cytokines
Subsequent induction of C-reactive protein and serum amyloid A
These findings are consistent with early inflammatory response

<table>
<thead>
<tr>
<th>Serum Analytes</th>
<th>N=3, 6mg/kg Cohort</th>
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<tbody>
<tr>
<td>TNF-α</td>
<td></td>
</tr>
<tr>
<td>TNF-β</td>
<td></td>
</tr>
<tr>
<td>MIP-1α</td>
<td></td>
</tr>
<tr>
<td>MIP-1β</td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td></td>
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<tr>
<td>IL-10</td>
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<td>IL-8</td>
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<tr>
<td>IP-10</td>
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<tr>
<td>MCP-1</td>
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<td>MCP-2</td>
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<td>IL-1Ra</td>
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<td>GRO-α</td>
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<td>MIP-3α</td>
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<td>TNF-R1</td>
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<td>IL-27</td>
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<td>Fractalkine</td>
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<td>YKL-40</td>
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<tr>
<td>MDC</td>
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<td>SAA</td>
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<td>CRP</td>
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<tr>
<td>MMP-3</td>
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<tr>
<td>Angiopoietin 1</td>
<td></td>
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<tr>
<td>Osteoactivin</td>
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<tr>
<td>Thrombomodulin</td>
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</tbody>
</table>

Log₂ Fold Change

2 hr  Day 8  Day 15

Inflammatory Cytokines

CRP and SAA
Proposed Model for CPI-006 Immunomodulatory Activity

**Blood**

- CPI-006
- CD73
- Adenosine
- AMP
- B cell
- B cell Activation
- BTK
- ERK

**Lymphoid tissue**

- Migration to and retention in lymph nodes.
- Increased antigen presentation.

- CPI-006
- CD69
- S1P1
- Adenosine
- AMP

- APCs
- Dendritic Macrophage B Cell
  - CPI-006 mimics ligand (agonist)
  - CD73
  - TCR
  - CD73
  - MHC
  - Ligand?
Conclusions

• CPI-006 has novel immunomodulatory activity with dual mechanisms of action:
  – Affects B cell trafficking and increases expression of CD69 and other markers consistent with increased antigen presentation by APCs
  – Complete inhibition of CD73 enzyme activity without internalization

• CPI-006 is safe as monotherapy at least to doses of 12 mg/kg and in combination with ciforadentan to 6 mg/kg. No DLTs reported and MTD not reached.

• Doses of 12 mg/kg achieve:
  – Sustained occupancy of PBL
  – Target saturation and complete inhibition of enzyme activity in tumor biopsies

• Treatment with CPI-006 induces serum cytokines that mediate inflammatory response

• Preliminary data suggest increasing disease control with higher doses and enhancement with combination therapy

• Enrollment in this study continues with both monotherapy and combination in dose escalation
Acknowledgements

• The patients and their families

• Participating Centers: Carolina BioOncology Institute, University of Chicago, Medical College of Wisconsin, Roswell Park Cancer Institute, Yale University, Mount Sinai, Icahn School of Medicine, Dana Farber Cancer Institute, Mary Crowley Cancer Center, University of Miami, City of Hope, Sarah Cannon Research Institute, University of Oklahoma, Monash Health

• Colleagues at Corvus