CPI-818, an Oral Interleukin-2-Inducible T-Cell Kinase Inhibitor

Pre-clinical Characterization and Interim Results of a Phase I/Ib Dose-Escalation Trial in Patients with Relapsed/Refractory T-Cell Lymphoma

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Chief Medical Officer
Inhibition of ITK for T Cell Lymphoma

• Rationale for Targeting ITK Signaling in Lymphomas
  – TCR signaling is maintained in most T cell lymphomas
  – Analogous to BCR and B cell lymphomas; ITK is the T cell homologue of BTK and is widely expressed in T cell malignancies
  – Activation of ITK drives NF-κB which drives GATA-3 and survival
  – CTCL and certain PTCLs are thought to be Th2-driven malignancies

• CPI-818 is a selective, covalent inhibitor of ITK

• Clinical activity observed in canines with CTCL and PTCL
CPI-818 Selectivity Inhibits ITK and Blocks Cellular Signaling

Kinome Profile and Kinases with Cys-442

<table>
<thead>
<tr>
<th>Kinase</th>
<th>K_i (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITK</td>
<td>2.5</td>
</tr>
<tr>
<td>BLK</td>
<td>4700</td>
</tr>
<tr>
<td>BMX</td>
<td>9100</td>
</tr>
<tr>
<td>BTK</td>
<td>1200</td>
</tr>
<tr>
<td>EGFR</td>
<td>&gt;10000</td>
</tr>
<tr>
<td>ERBB2</td>
<td>&gt;10000</td>
</tr>
<tr>
<td>ERBB4</td>
<td>&gt;10000</td>
</tr>
<tr>
<td>JAK3</td>
<td>2800</td>
</tr>
<tr>
<td>MKK7</td>
<td>&gt;10000</td>
</tr>
<tr>
<td>TEC</td>
<td>540</td>
</tr>
<tr>
<td>RLK</td>
<td>2700</td>
</tr>
</tbody>
</table>

K_i < 10 nM
468 Kinases Profiled

pPLCγ1 Suppression

CPI-818 (µM):
- 0.001
- 0.003
- 0.01
- 0.03
- 0.1
- 1
- 10

αCD3:
- -
+ + + + + + + +

pPLCγ1 Y783

Total PLCγ1

pERK Suppression

<table>
<thead>
<tr>
<th>Condition</th>
<th>CD4+ T cells</th>
<th>CD8+ T cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td><img src="Vehicle" alt="Bar Chart" /></td>
<td><img src="Vehicle" alt="Bar Chart" /></td>
</tr>
<tr>
<td>CP-818</td>
<td><img src="CP-818" alt="Bar Chart" /></td>
<td><img src="CP-818" alt="Bar Chart" /></td>
</tr>
</tbody>
</table>
Fas-/- MRL/lpr mice spontaneously develop lymphoproliferative disease from uncontrolled growth of T cells.

CPI-818 treatment led to marked regression of lymphadenopathy, with little effect on normal CD4+ and CD8+ T cells.
Sézary cells were more sensitive than normal CD4+ or CD8+ T cells to the anti-proliferative effect of CPI-818.

In collaboration with Drs. Y Kim and M Khodadoust, Stanford University.
Spontaneous T Cell Lymphoma in Companion Animals
Evaluation of CPI-818 by Prof. Douglas Thamm (CSU)

CTCL Patient
11 year old, Male
Golden Retriever

4 months
CPI-818-001 Phase 1/1b Clinical Trial Design

Dose escalation

Dose Escalation

- 1200mg BID  
  \( n = 3+3 \)
- 900mg BID  
  \( n = 3+3 \)
- 600mg BID  
  \( n = 3+3 \)
- 400mg BID  
  \( n = 3+3 \)
- 200mg BID  
  \( n = 3+3 \)
- 100mg BID  
  \( n = 3+3 \)

Design

- Initial enrollment in dose escalation with 3+3 (+ optional 3) design
- Up to 6 ascending dose levels of CPI-818
- Enroll patients with various types of T-cell lymphoma (PTCL and CTCL) who have progressed on, refractory to, relapsed, or intolerant to at least 2 standard therapies
- Patients will receive CPI-818 orally BID continuously up to sixteen 21-day cycles, until progression or unacceptable toxicity

Objectives

- Primary: To establish Safety/ tolerability and determine MTD or MAD, as well as Expansion Cohort Dose
- Secondary: PK/PD, biomarkers and efficacy

Biomarker Assessments

- ITK in peripheral blood, tissue, cytokines, etc.
CPI-818-001 Trial
Dose expansion

Dose Expansion

- PTCL-NOS
  - Stage 1
    - n=11
  - Stage 2
    - n=17

- AITL
  - Stage 1
    - n=11
  - Stage 2
    - n=17

- CTCL
  - Stage 1
    - n=11
  - Stage 2
    - n=17

- Others*
  - n=28

If ≥ 2 response observed in a disease cohort, add 17 subjects and proceed to Stage 2

* Other types include NKTCL, ALCL, ATLL, etc
### Patient Characteristics

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Age (yrs), median (range)</th>
<th>Gender, male N (%)</th>
<th>No. of prior therapies, median (range)</th>
<th>Histologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPI-818 100mg BID</td>
<td>51 (29, 75)</td>
<td>3 (75%)</td>
<td>3 (2, 4)</td>
<td>Adult T cell leukemia/lymphoma 1</td>
</tr>
<tr>
<td>CPI-818 200mg BID</td>
<td>59 (57, 60)</td>
<td>1 (25%)</td>
<td>3 (2, 6)</td>
<td>Peripheral T cell lymphoma- NOS 1</td>
</tr>
<tr>
<td>CPI-818 400mg BID</td>
<td>69 (42, 80)</td>
<td>3 (60%)</td>
<td>7 (3, 10)</td>
<td>Angioimmunoblastic T cell lymphoma 1</td>
</tr>
<tr>
<td>CPI-818 600mg BID</td>
<td>69 (34, 74)</td>
<td>2 (50%)</td>
<td>5 (4, 8)</td>
<td>Anaplastic large cell lymphoma 1</td>
</tr>
</tbody>
</table>

*Data cut off date: 27Jan2020*
### All Adverse Events

No grade 3/4 AEs

*Data cut off date: 27Jan2020; 600 mg patients not included as the cohort opened recently*

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>100mg (N=4)</th>
<th>200mg (N=3)</th>
<th>400mg (N=5)</th>
<th>Total (N=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any TEAE</td>
<td>4 (100%)</td>
<td>3 (100%)</td>
<td>3 (60%)</td>
<td>10 (83.3%)</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>1 (25.0%)</td>
<td>0</td>
<td>0</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (25.0%)</td>
<td>0</td>
<td>0</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (25.0%)</td>
<td>0</td>
<td>1 (20%)</td>
<td>2 (16.7%)</td>
</tr>
<tr>
<td>Retching</td>
<td>1 (25.0%)</td>
<td>0</td>
<td>0</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (25.0%)</td>
<td>0</td>
<td>0</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Chills</td>
<td>1 (25.0%)</td>
<td>0</td>
<td>0</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>0</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>0</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Skin wound (trauma)</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>0</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>1 (25.0%)</td>
<td>0</td>
<td>0</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1 (25.0%)</td>
<td>0</td>
<td>0</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Hypercalcaemia</td>
<td>1 (25.0%)</td>
<td>0</td>
<td>0</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Hyperuricaemia</td>
<td>1 (25.0%)</td>
<td>0</td>
<td>0</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Hypomagnesaemia</td>
<td>1 (25.0%)</td>
<td>0</td>
<td>0</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>0</td>
<td>0</td>
<td>1 (20%)</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>0</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1 (25.0%)</td>
<td>0</td>
<td>0</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Cough</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>0</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Rash erythematous</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>0</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>1 (25.0%)</td>
<td>0</td>
<td>0</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Skin Pain</td>
<td>1 (25.0%)</td>
<td>0</td>
<td>0</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1 (25.0%)</td>
<td>1 (33.3%)</td>
<td>0</td>
<td>2 (16.7%)</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>1 (20%)</td>
<td>2 (16.7%)</td>
</tr>
</tbody>
</table>
• No DLTs observed so far and MTD not reached

• 100mg cohort:
  – No treatment related Grade ≥ 2 AEs or SAEs
  – Treatment related AEs: diarrhea, nausea, retching (all n=1; Grade 1).
  – Other AEs: abdominal pain, vomiting, chills, weight decreased, decreased appetite, hypercalcemia, hyperuricemia, hypomagnesemia, anxiety, hyperhidrosis, pain in skin, pruritus in the setting of disease progression (all n=1)

• 200mg cohort:
  – No treatment related Grade ≥ 2 AEs or SAEs
  – Treatment related AEs: fatigue, rash (all n=1; Grade 1)
  – Other AEs: soft tissue injury, pyrexia, headache, cough, pruritus, rash erythematous due to steroid discontinuation (all n=1)

• 400mg cohort:
  – 4 DLT evaluable pts with no AEs
  – Treatment related AEs: nausea (n=1; Grade 1), Grade 2 rash in DLT unevaluable patient (treatment hold - 13 days)
  – Other AE: Musculoskeletal pain (n=1; Grade 1)
PK and Occupancy Summary from Cohorts 1, 2 and 3

Occupancy is increasing as a function of dose, BID Dosing Required

Rapid absorption and clearance drives
~ 80% ITK occupancy near Cmax
~ 50% occupancy at 12hr

The Pharmacokinetic profile of CPI-818 and ITK Occupancy in PBMCs following a 100 QD dose

Trough ITK Occupancy for Cycle 1 with BID Dosing of CPI-818
Preliminary Patient Status in Dose Escalation
CPI-818-001 Study

Histology (No. of Prior Lines)

<table>
<thead>
<tr>
<th>Histology</th>
<th>No. of Prior Lines</th>
</tr>
</thead>
<tbody>
<tr>
<td>AITL</td>
<td>4</td>
</tr>
<tr>
<td>PTCL-NOS</td>
<td>3</td>
</tr>
<tr>
<td>ALCL</td>
<td>4</td>
</tr>
<tr>
<td>ATLL</td>
<td>2</td>
</tr>
<tr>
<td>PTCL-NOS</td>
<td>2</td>
</tr>
<tr>
<td>CTCL SEZARY</td>
<td>3</td>
</tr>
<tr>
<td>AITL</td>
<td>6</td>
</tr>
<tr>
<td>CTCL SEZARY</td>
<td>3</td>
</tr>
<tr>
<td>CTCL SEZARY</td>
<td>5</td>
</tr>
<tr>
<td>CTCL SEZARY</td>
<td>9</td>
</tr>
<tr>
<td>CTCL MF</td>
<td>9</td>
</tr>
<tr>
<td>CTCL SEZARY</td>
<td>9</td>
</tr>
<tr>
<td>AITL</td>
<td>8</td>
</tr>
<tr>
<td>CTCL MF</td>
<td>6</td>
</tr>
<tr>
<td>PTCL-NOS</td>
<td>4</td>
</tr>
<tr>
<td>PTCL-NOS</td>
<td>5</td>
</tr>
</tbody>
</table>

Treatment Cycles

1 2 3 4 5 6 7 8
wk1 wk2 wk3 wk1 wk2 wk3 wk1 wk2 wk3 wk1 wk2 wk3 wk1 wk2 wk3 wk1

Histology by Treatment Cycles:

- wk1: AITL, PTCL-NOS, ALCL, ATLL, PTCL-NOS, CTCL SEZARY, AITL, CTCL SEZARY, CTCL SEZARY, CTCL MF, CTCL SEZARY, AITL, CTCL MF, PTCL-NOS
- wk2: AITL, PTCL-NOS, ALCL, ATLL, PTCL-NOS, CTCL SEZARY, AITL, CTCL SEZARY, CTCL SEZARY, CTCL MF, CTCL SEZARY, AITL, CTCL MF, PTCL-NOS
- wk3: AITL, PTCL-NOS, ALCL, ATLL, PTCL-NOS, CTCL SEZARY, AITL, CTCL SEZARY, CTCL SEZARY, CTCL MF, CTCL SEZARY, AITL, CTCL MF, PTCL-NOS

Trough ITK Occupancy

- 58%
- 76%
- 88%
- TBD%

Median time on treatment to 55 days
Summary

• 60 year old Caucasian female with SS
• FDG avid adenopathy in cervical, axillary, inguinal nodes bilaterally at diagnosis in 2017
• Enrolled in 200mg BID cohort since 21 Oct, 2019
• Screening PET: Small mediastinal (Paratracheal, subcarinal, hilar) and mandibular lymph nodes with moderate FDG avidity
• C4D1 PET Dec 2019: Interval reduction in the mediastinal nodes with no focus of FDG activity
• Last Visit = C5D1 (13-Jan) remains stable
• mSWAT stable, Sézary cells stable
CTCL/SS Patient on 400mg cohort with Skin Improvement

Summary

• 80 year old Caucasian male CTCL (Sézary Syndrome)

• Started C1D1 on 400mg BID cohort on 25-Nov-2019

• Screening: no visceral disease or target lesions on CT, absolute Sézary count 5.6x10⁹/L

• Patient reported decreased skin redness with start of treatment after treatment

• C4D1 response assessment: There has been a clinical improvement (mSWAT 92->71)

• Lymphocytosis stable
Conclusion

• CPI-818 is a selective, covalent inhibitor of ITK (sparing RLK and BTK)
• Blocks signal transduction in endpoints downstream of T-cell activation
• Inhibits lymphoproliferative disease in MRL mouse model
• Preferentially inhibits the proliferation of malignant cells sparing normal T cells in blood isolated from sédary patients
• In a companion animal study in dogs with PTCL and CTCL, CPI-818 was well tolerated with evidence for clinical responses
• Interim data from dose escalation part of CPI-818-001 trial shows 100 mg, 200 mg and 400 mg BID doses were well tolerated. Early signs of clinical activity is observed.
• Dose escalation continues
Acknowledgements

• Participating Centers and Investigators:

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- UCSF
- Stanford Cancer Center
- University of Michigan
- Ohio State University
- Washington University
- University of Pittsburgh
- Hackensack University Medical Center
- MD Anderson
- University of Nebraska
- Virginia Commonwealth University

South Korea
- National Cancer Centre
- Seoul National University Hospital
- Asan Medical Center
- Seoul St Mary Hospital
- Gachon University
- Gil Medical Center
- Pusan National
- Inje University Busan-Paik Hospital

Australia
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- Royal Hobart Hospital
- Liverpool Hospital
- Epworth Healthcare
- Peter McCallum
- Concord Repatriation Linear Clinical Research

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