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 T_{H}2-driven malignancies

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

- Clinical activity observed in canines with CTCL and PTCL

**T cells**

- **TCR**
- **CD3/4/8**
- **ITK**
- **CPI-818**
- **LCK**
- **PI3K**
- **Src-family**
- **PLCγ**
- **PtdIns(4,5)P_2** → **PIP3**
- **DAG + InsP_3**
- **PKCβ**
- **NF-κB**
- **GATA-3**

- **T cell activation**
- **Migration/homing**
- **Proliferation**
CPI-818 Selectivity Inhibits ITK and Blocks Cellular Signaling

Kinome Profile and Kinases with Cys-442

- Kᵢ < 10 nM
- 468 Kinases Profiled

<table>
<thead>
<tr>
<th>Kinase</th>
<th>CPI-818 Kd in 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>

ITK, BLK, BMX, BTK, MGK, CMGC, CAMK, AGC, CK1, TEC, RLK, TCR, pPLC, ITK, pPLCγ, pERK, X, αCD3, CD3, PLCγ, pERK

pPLCγ1 Suppression

CPI-818 (µM):
- αCD3: - + + + + + + +
- pPLCγ1 Y783
- Total PLCγ1

pERK Suppression

MFI Fold Change (over unstim)
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.
CPI-818 Preferentially Inhibits Sézary Cells

In collaboration with Drs. Y Kim and M Khodadoust, Stanford University

• Sézary cells were more sensitive than normal CD4+ or CD8+ T cells to the anti-proliferative effect of CPI-818
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

**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

AITL

Stage 1
n=11

CTCL

Stage 1
n=11

Others*

n=28

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

Stage 2
n=17

Stage 2
n=17

Stage 2
n=17

* Other types include NKTCL, ALCL, ATLL, etc
**CPI-818-001 Study**

**Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>CPI-818 100mg BID (N=4)</th>
<th>CPI-818 200mg BID (N=3)</th>
<th>CPI-818 400mg BID (N=5)</th>
<th>CPI-818 600mg BID (N=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs), median (range)</strong></td>
<td>51 (29, 75)</td>
<td>59 (57, 60)</td>
<td>69 (42, 80)</td>
<td>69 (34, 74)</td>
</tr>
<tr>
<td><strong>Gender, male N (%)</strong></td>
<td>3 (75%)</td>
<td>1 (25%)</td>
<td>3 (60%)</td>
<td>2 (50%)</td>
</tr>
<tr>
<td><strong>No. of prior therapies, median (range)</strong></td>
<td>3 (2, 4)</td>
<td>3 (2, 6)</td>
<td>7 (3, 10)</td>
<td>5 (4, 8)</td>
</tr>
<tr>
<td><strong>Histologies</strong></td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Adult T cell leukemia/lymphoma</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral T cell lymphoma- NOS</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Angioimmunoblastic T cell lymphoma</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Anaplastic large cell lymphoma</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CTCL (Sézary syndrome)</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>CTCL (Mycosis fungoides)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
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</table>

*Data cut off date: 27Jan2020*
<table>
<thead>
<tr>
<th>Adverse Events N (%)</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>

*Data cut off date: 27Jan2020; 600 mg patients not included as the cohort opened recently*
• 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
Preliminary Patient Status in Dose Escalation
CPI-818-001 Study

Histology (No. of Prior Lines)

- AITL (4)
- PTCL-NOS (3)
- ALCL (4)
- ATLL (2)
- PTCL-NOS (2)
- CTCL SEZARY (3)
- AITL (6)
- CTCL SEZARY (3)
- CTCL SEZARY (5)
- CTCL SEZARY (9)
- CTCL MF (9)
- CTCL SEZARY (7)
- AITL (8)
- CTCL MF (6)
- PTCL-NOS (4)
- PTCL-NOS (5)

Treatment Cycles

- wk1
- wk2
- wk3

Histology occupancy:
- AITL
- PTCL-NOS
- ALCL
- ATLL
- PTCL-NOS
- CTCL SEZARY
- AITL
- CTCL SEZARY
- CTCL SEZARY
- CTCL MF
- CTCL SEZARY
- AITL
- CTCL MF
- PTCL-NOS
- PTCL-NOS

Trough ITK Occupancy:
- 100 mg
- 200 mg
- 400 mg
- 600 mg
- Ongoing
- PD
- SD
- Nodal CR

TBD%
58%
76%
88%

median time on treatment to 55 days
CTCL/SS Patient on 200mg Cohort with Nodal CR

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 $5.6 \times 10^9$/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 sézary 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:

United States
- UCSF
- Stanford Cancer Center
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- University of Michigan
- Ohio State University
- Washington University
- University of Pittsburgh
- University of Pennsylvania
- Dartmouth
- Memorial Sloan Kettering Cancer Center

South Korea
- National Cancer Centre
- Seoul National University Hospital
- Asan Medical Center
- Seoul St Mary Hospital
- Samsung Medical
- Gil Medical Center
- Gachon University

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

• The patients and their families
• Colleagues at Corvus