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Preliminary Clinical Data from a Phase 1 Trial with CPI-818, A Selective ITK Inhibitor that Preferentially Blocks the Growth of T Lymphoma Cells

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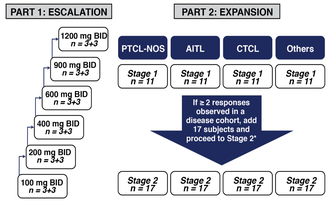
BACKGROUND

Introduction

ITK is a tyrosine kinase critical to T cell receptor (TCR) signaling. Overexpression of this gene has been reported in cutaneous T-cell lymphoma (CTCL) and peripheral T-cell lymphoma (PTCL). Genomic analyses have demonstrated the contribution of aberrant TCR signaling in the pathogenesis of T-cell lymphomas (TCL). RLK, a closely related kinase, is co-expressed with ITK in T and NK cells, and is partially functionally redundant with ITK signaling. Selective inhibition of ITK, but not other signal transduction components such as RLK, may be an effective strategy to treat TCL while preserving normal T and NK cell functions.

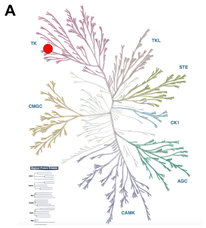
CPI-818 is an orally bioavailable, covalent inhibitor of ITK with >100-fold selectivity over RLK and BTK (Figure 1). It was well tolerated and exhibited anti-tumor activity in companion dogs with spontaneous TCL (2019 AACR Annual Meeting Abstract #1313). A phase 1/1b trial with CPI-818 in human TCL has been initiated (NCT03952078). Here we present preclinical evidence that CPI-818 inhibits the proliferation of human malignant T cells with relative sparing of normal lymphocytes, and we report early results from the clinical trial.

Design of Phase 1/1b Trial of CPI-818 in T-Cell Lymphoma

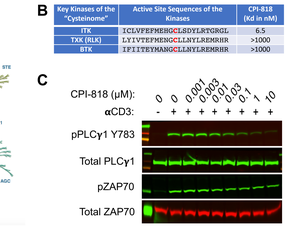


Others: Other types of T-cell lymphoma (NK/T-cell lymphoma, enteropathy associated T-cell lymphoma, hepato-splenic T-cell lymphoma, ALCL, ATL and T-PLL)
* Simon's Two-Stage design

CPI-818 Specifically Inhibits ITK and Downstream Signaling



Key Kinases of the "Cysteinome"	Active Site Sequences of the Kinases	CPI-818 (Kd in nM)
ITK	ICLVFEFMEHGCLSDYLRTGRGL	6.5
TXK (RLK)	LYIVTEFMENGCLLNYLREMRHR	>1000
BTK	IFIITEYMANGCLLNYLREMRHR	>1000

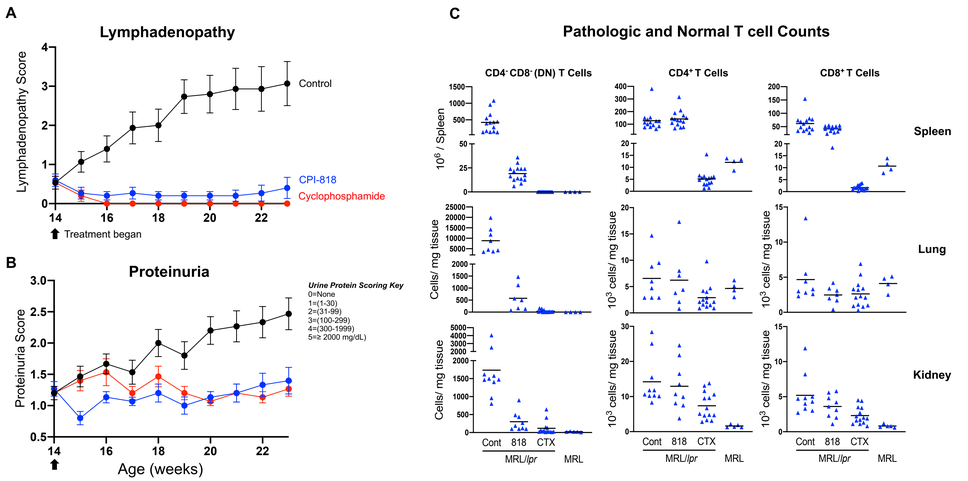


CPI-818 selectively inhibited ITK

CPI-818 inhibited phosphorylation of PLCγ1, but not ZAP70

Figure 1. (A, B) CPI-818 was tested against >400 kinases, only ITK was inhibited by >90% when tested at 1 μM. (C) Jurkat T cells incubated with CPI-818 at 37°C for 1 h were washed and stimulated with αCD3. The phosphorylation of molecules on the TCR signaling pathway were analyzed by Western Blotting after 30 seconds of stimulation.

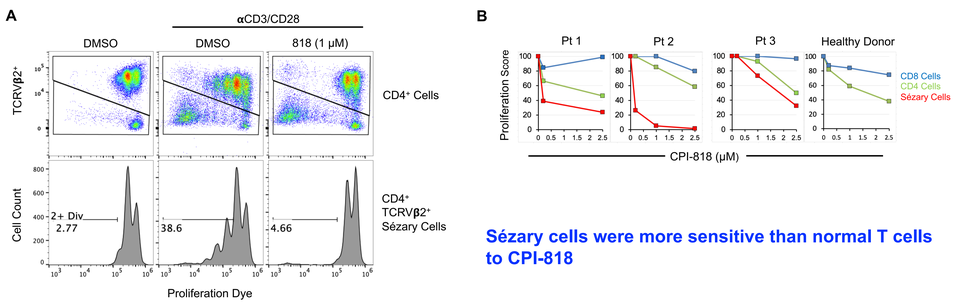
CPI-818 TREATS T-CELL LYMPHOPROLIFERATIVE DISEASE AND AUTOIMMUNITY IN MRL/*lpr* MICE



In animals with established disease, CPI-818 treatment led to marked regression of lymphadenopathy with minimal effect on normal CD4⁺ and CD8⁺ T cells, and prevented autoimmune glomerulonephritis

Figure 2. Fas-deficient MRL/*lpr* mice spontaneously develop lymphadenopathy and splenomegaly, and suffer from lung and kidney damage by infiltrating T cells. Mice (n = 15) were given control diet ± a daily gavage of cyclophosphamide (CTX, 15 mg/kg), or CPI-818-formulated diet (300 mg/kg/day) beginning at 14 weeks old. (A) 6 target lymph nodes were calipered weekly to monitor lymphadenopathy. (B) Protein in the urine was measured weekly. (C) At study termination, organs were harvested from MRL/*lpr* mice and five age-matched, Fas-sufficient MRL mice. The absolute cell count of each T cell subset within an organ was enumerated by flow cytometry.

CPI-818 DEMONSTRATES SELECTIVE ANTIPROLIFERATIVE EFFECT ON SÉZARY CELLS WITH LOWER IMPACT ON NORMAL T CELLS



Sézary cells were more sensitive than normal T cells to CPI-818

Figure 3. T cells purified from the blood of 3 Sézary syndrome patients and a healthy donor were labeled with proliferation dye and stimulated with αCD3/CD28 for 6 days in the presence of CPI-818. In flow cytometry analyses, Sézary cells were identified by antibodies to the clonal TCRVβ chain. Gating strategy is shown (A). The % Sézary or normal CD4⁺ T cells with ≥2 cell divisions, and CD8⁺ T cells with ≥4 cell divisions were converted to proliferation scores. The scores of cells from samples stimulated in the presence of DMSO were set to 100 (B).

CLINICAL STUDY

Eligibility and Study Objectives

Eligibility

- T-cell lymphoma (TCL) with measurable disease
- Progressed on, refractory to, relapsed, or intolerant to ≥2 standard therapies
- ECOG status 0-1 with adequate organ function

Primary Objectives

- To establish the safety and tolerability profile of CPI-818
- To establish the MTD/MAD of CPI-818 to select the expansion cohort dose

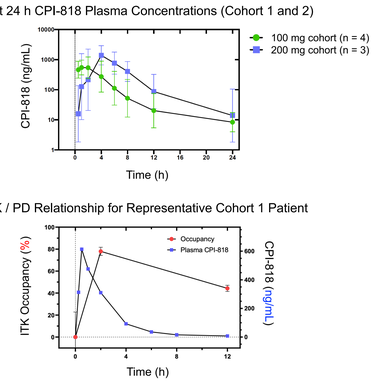
Secondary Objectives

- To evaluate the pharmacokinetics and pharmacodynamics of CPI-818
- To assess the anti-tumor activity of CPI-818
- To evaluate potential predictive biomarkers associated with anti-tumor activity in tumor tissue and blood samples

Patient Characteristics and Safety Findings

- 7 patients with advanced relapsed/refractory TCL have been enrolled into the 100 mg BID cohort (n = 4) and 200 mg BID cohort (n = 3).
- Histologies: PTCL-NOS (n=2), CTCL (n=1), AITL (n=2), ALCL (n=1), ATLL (n=1)
- Treatment was well-tolerated with no treatment related grade 3-5 AEs or DLTs.

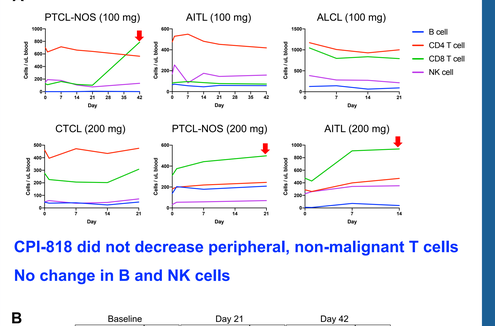
Pharmacokinetic and Pharmacodynamic Analyses



BID dosing achieved significant but incomplete ITK inhibition that persisted after drug clearance

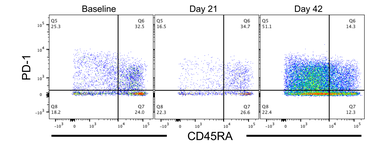
Figure 4. (A) CPI-818 plasma concentration was measured using standard LC-MS methods. (B, C) Active site occupancy of PBMC ITK by CPI-818 was measured using an irreversible, biotinylated probe in an electrochemiluminescence immunosorbent assay. The values were normalized to protein concentration in the sample and expressed as % of the pre-treated occupancy value.

Peripheral Blood B, T, and NK Cell Counts



CPI-818 did not decrease peripheral, non-malignant T cells

No change in B and NK cells



Increased normal CD8⁺ cells in 3 patients (), one of which has an activated, memory phenotype

Figure 5. Flow cytometry analysis of patient whole blood. (A) Quantification of B cells (CD19⁺), CD3⁺ CD4⁺ T cells, CD3⁺ CD8⁺ T cells, and NK cells (CD3⁻ CD16/CD56⁺) was done by normalizing to counts of a standard bead. (B) A phenotypic staining that included CD3, CD4, CD8, CD45RA and PD-1 was also performed.

CONCLUSIONS

- CPI-818 is a covalent, selective ITK inhibitor that results in sustained blockade of ITK.
- CPI-818 treatment led to marked regression of lymphadenopathy in MRL/*lpr* mice, with minimal impact on normal CD4⁺ and CD8⁺ T cells, and no effect on other immune cells.
- CPI-818 prevented autoimmune nephritis in MRL/*lpr* mice.
- In vitro studies showed that malignant Sézary cells were more sensitive to the antiproliferative effect of CPI-818 than normal T cells.
- The initial two dose-escalation cohorts of the Phase 1/1b trial have been enrolled. No DLTs or treatment related grade 3-5 AEs have been reported. Treatment of 2 out of 3 patients in the second cohort is ongoing. Occupancy studies revealed significant but incomplete ITK inhibition.
- Consistent with preclinical data, CPI-818 did not decrease normal T, B, or NK cell counts. Normal CD8⁺ T cells increased in 3 patients.

ACKNOWLEDGMENTS

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- For further information, please visit poster #4030 or contact Corvus at CPI818_communications@corvuspharma.com
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PosterCast