American Society of Hematology 2022, Poster 3993

ITK Inhibitor Induces Dose-Dependent Th1 Skewing in Normal T Cells and is Active in Refractory T Cell Lymphomas

Ryan Wilcox, MD, PhD
Section Head, Lymphoma & Myeloma
Associate Professor, Department of Internal Medicine, Division of Hematology/Oncology
University of Michigan

Yuqin Song[1], Ning Ding[1], Dok Hyun Yoon[2], John Reneau[3], Ryan Wilcox[4], Won Seog Kim[5], Youn Kim[6], Michael Khodadoust[6], Tatyana Feldman[7], Costas K Yannakou[8], Pratyush Giri[9], Jonathan Brammer[3], Lih-Yun Hsu[10], Hongwei Yuan[10], Erik Verner[11], Suresh Mahabhashyam[10], Richard Miller[10,11]

[1]Peking University Cancer Hospital & Institute, Beijing, China; [2]Asan Medical Center, Seoul, South Korea; [3]The Ohio State University and Wexner Medical Center, Columbus, OH, USA; [4]University of Michigan, Ann Arbor, MI, USA; [5]Samsung Medical Center, Seoul, South Korea; [6]Stanford Cancer Institute, Stanford, CA, USA; [7]John Theurer Cancer Center at HMH, Hackensack, NJ, USA; [8]Epworth HealthCare, Melbourne, Victoria, Australia; [9]Royal Adelaide Hospital, Adelaide, South Australia, Australia; [10]Corvus Pharmaceuticals Inc, Burlingame, CA, USA; [11]Angel Pharmaceuticals Co., Ltd, Jiaxing, China

Introduction

- ITK (IL-2 inducible T cell kinase) is expressed in T cells with an important role in T cell receptor signaling and T helper cell differentiation.
- Resting lymphocyte kinase (RLK) is a closely related kinase involved in the differentiation of naïve T cells into Th1 T cells
- ITK-/- mice exhibit defects in Th2 differentiation while retaining the ability to differentiate into Th1 cells that secrete INFγ
- Th1 cells are involved in cytotoxic T cell functions such as destruction of tumor cells; Th2 cells play a role in various inflammatory processes.
- CPI-818 is a covalent inhibitor of ITK (KD 2.5nM) with > 100 fold selectivity over RLK
- CPI-818 is being evaluated in an ongoing phase 1 trial in refractory peripheral T cell lymphomas

ITK Plays Critical Roles in T Helper Cell Differentiation

ITK involved in many diseases

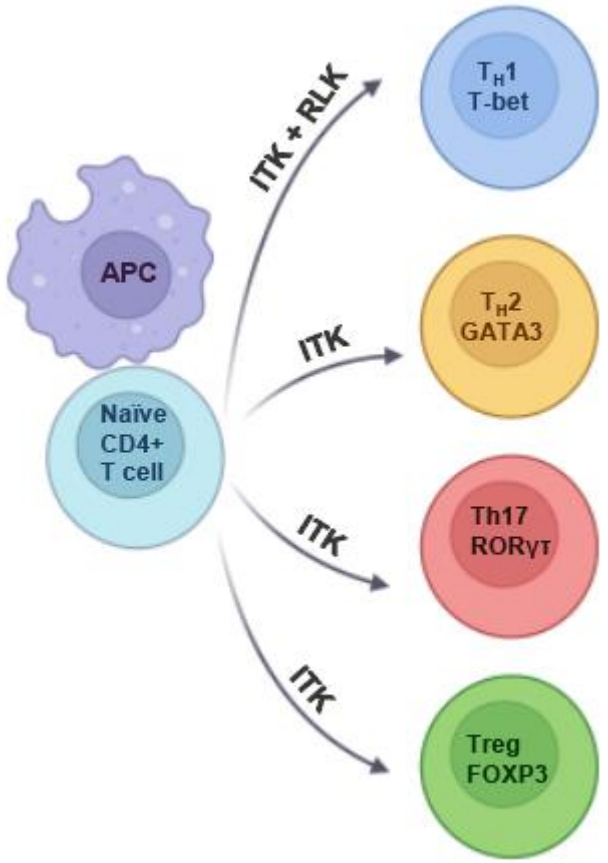
CPI-818 is selective for ITK

Closely related Tec Kinases

	CPI-818 K_D* (nM)
ITK	2.5
BLK	4700
BMX	9100
BTK	1200
EGFR	>10000
ERBB2	>10000
ERBB4	>10000
JAK3	2800
MKK7	>10000
TEC	540
RLK	2700

* Dissociation constants

ITK blockade leads to increase in Th1 and reduction in Th2, Th17



Th1 cells play a role in cancer cell and viral elimination

Th2 and Th17 cells are involved in autoimmune, inflammatory, fibrotic and allergic diseases

Tregs involved in immune suppression

Methods and Trial Design

IN VITRO AND PRECLINICAL STUDIES

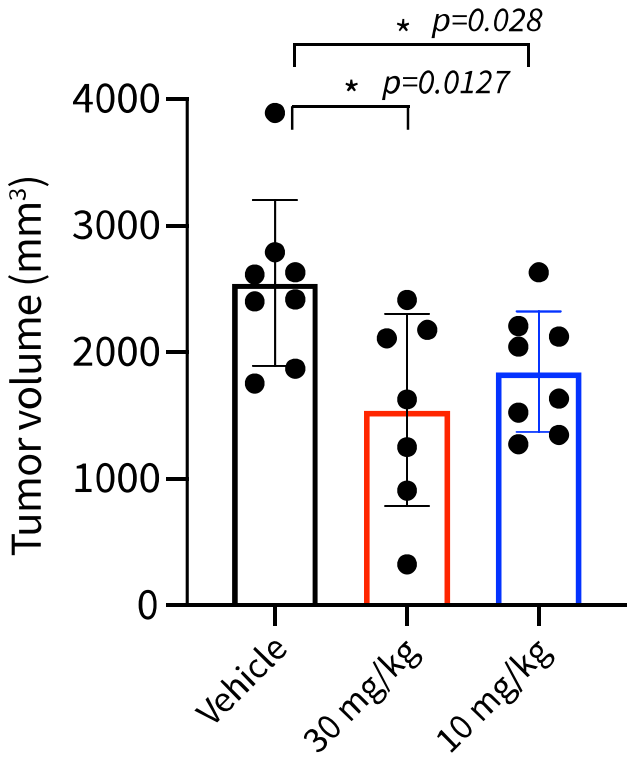
- **Serum cytokines** measured using MSD immunoassay format
- **Lymphocyte subsets** enumerated using flow cytometry on peripheral blood and tumor biopsy specimens using antibodies to CD3, 4, 8, 183, 196, 197 and 45RA
- C57BL/6 mice with established EL4 murine T cell lymphoma (CD4+/CD8-) were treated with CPI-818

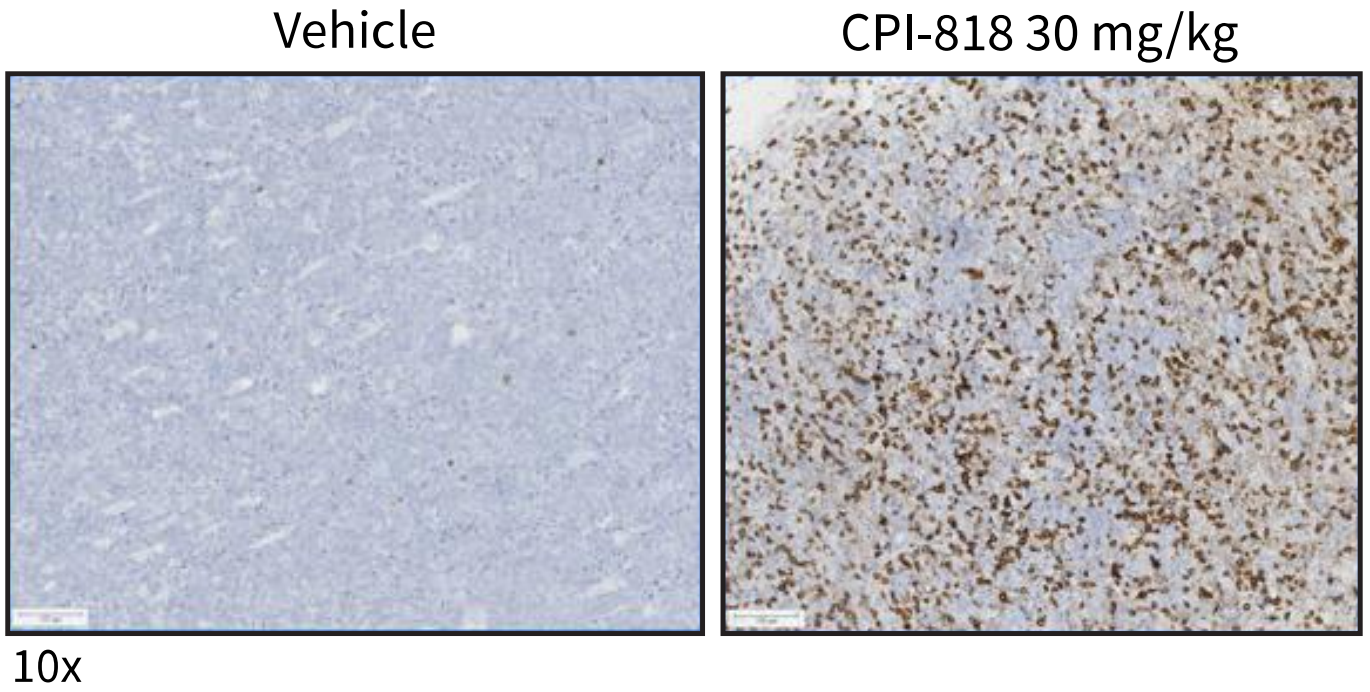
PHASE 1 CLINICAL TRIAL IN REFRACTORY PERIPHERAL T CELL LYMPHOMAS

- **Eligibility:** failed all standard prior therapies
- **Histologies:** cutaneous T-cell lymphoma (CTCL), angioimmunoblastic T-cell lymphoma (AITL), peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), anaplastic large-cell lymphoma (ALCL), and extranodal natural killer/T-cell lymphoma (ENKTCL)
- **Design:** successive cohorts of patients received CPI-818 100 mg, 200 mg, 400 mg, or 600 mg PO BID
- **Endpoints:** safety, immunologic activity and tumor response

Treatment of Murine EL4 T Cell Lymphoma with CPI-818

Tumor growth inhibition and increases in CD8+ T cell infiltration



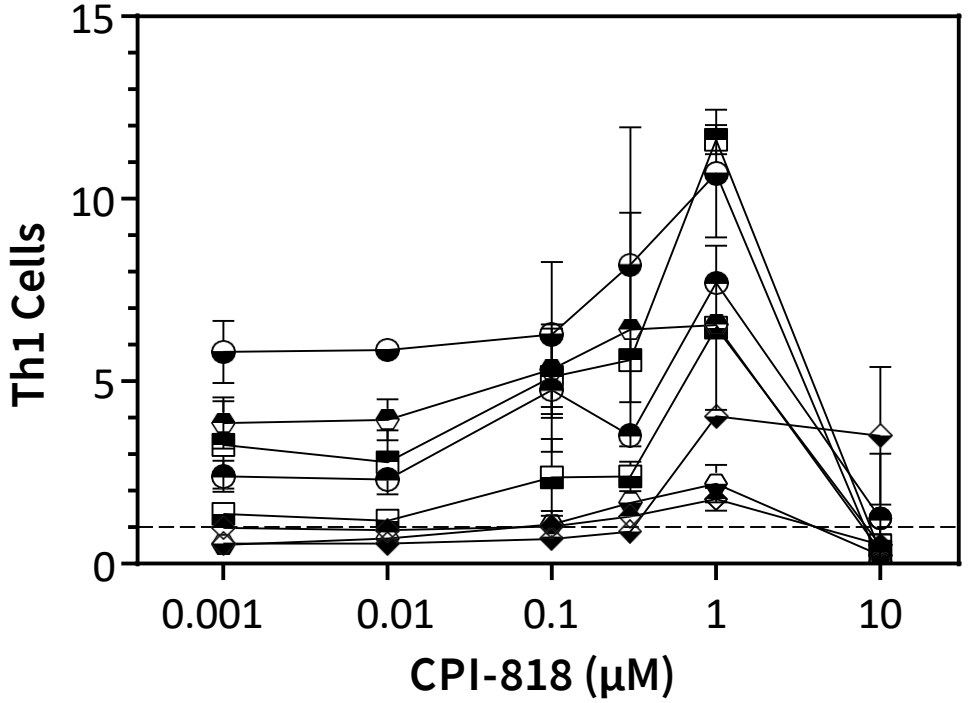


Mice with established EL4 tumors (CD4+) were treated with CPI-818 10, 30 mg/kg or vehicle daily for 7 days and tumor measurements/excision were made at Day 22 (3 days after dosing). Treatment groups were compared to control. Tumors were removed and immunohistochemistry was performed to enumerate infiltrating CD8+ normal T cells.

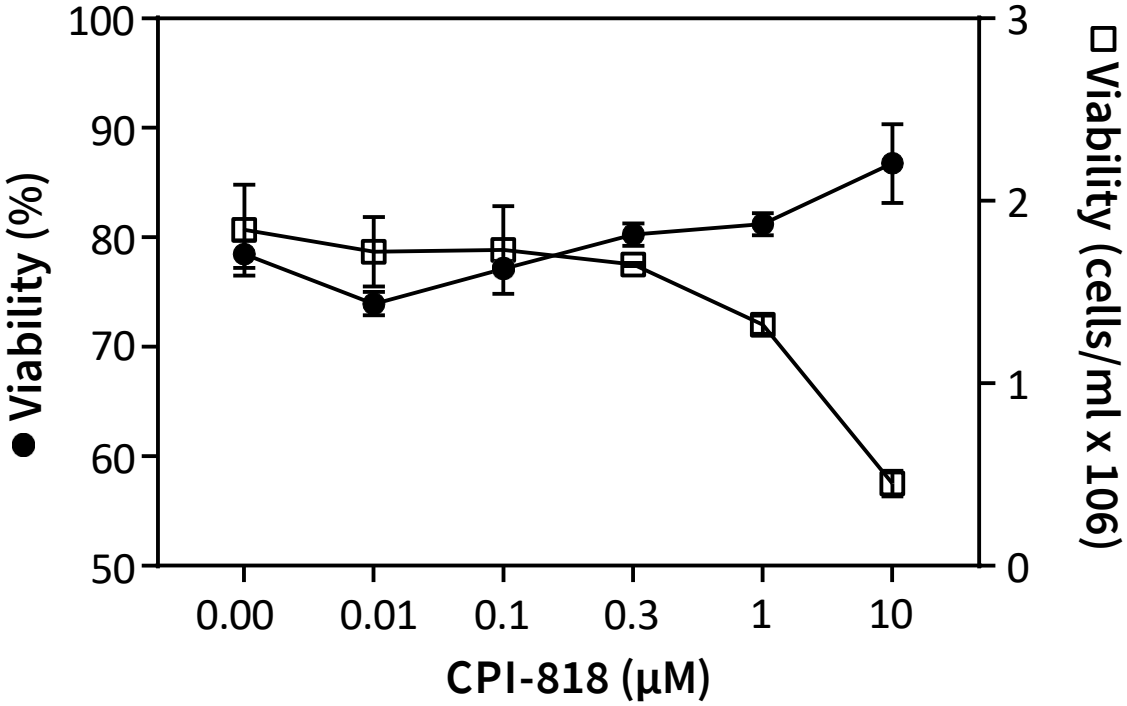
CPI-818 induces Th1 skewing *in vitro* in Normal PBMC

Concentration dependent effects

Th1 cells (ratio IFNg:IL-4) dose response effect in vitro



High concentrations block T cell proliferation in vitro



Normal PBMC from 12 healthy donors were stimulated in vitro with anti-CD3/CD28 in the presence of various concentrations of CPI-818. Intracellular interferon gamma and IL-4 were measured using flow cytometry and Th1 skewing was determined by interferon gamma:IL-4 ratio. Effects on cell proliferation and viability were also determined. These results indicate that concentrations >0.01 and <10 µM induce Th1 skewing with anti-proliferative effects seen ≥1 µM.

Phase I Trial Pharmacokinetic Analysis

Dose of 200mg achieves levels needed for Th1 skewing

In vivo CPI-818 Plasma Concentration mM*

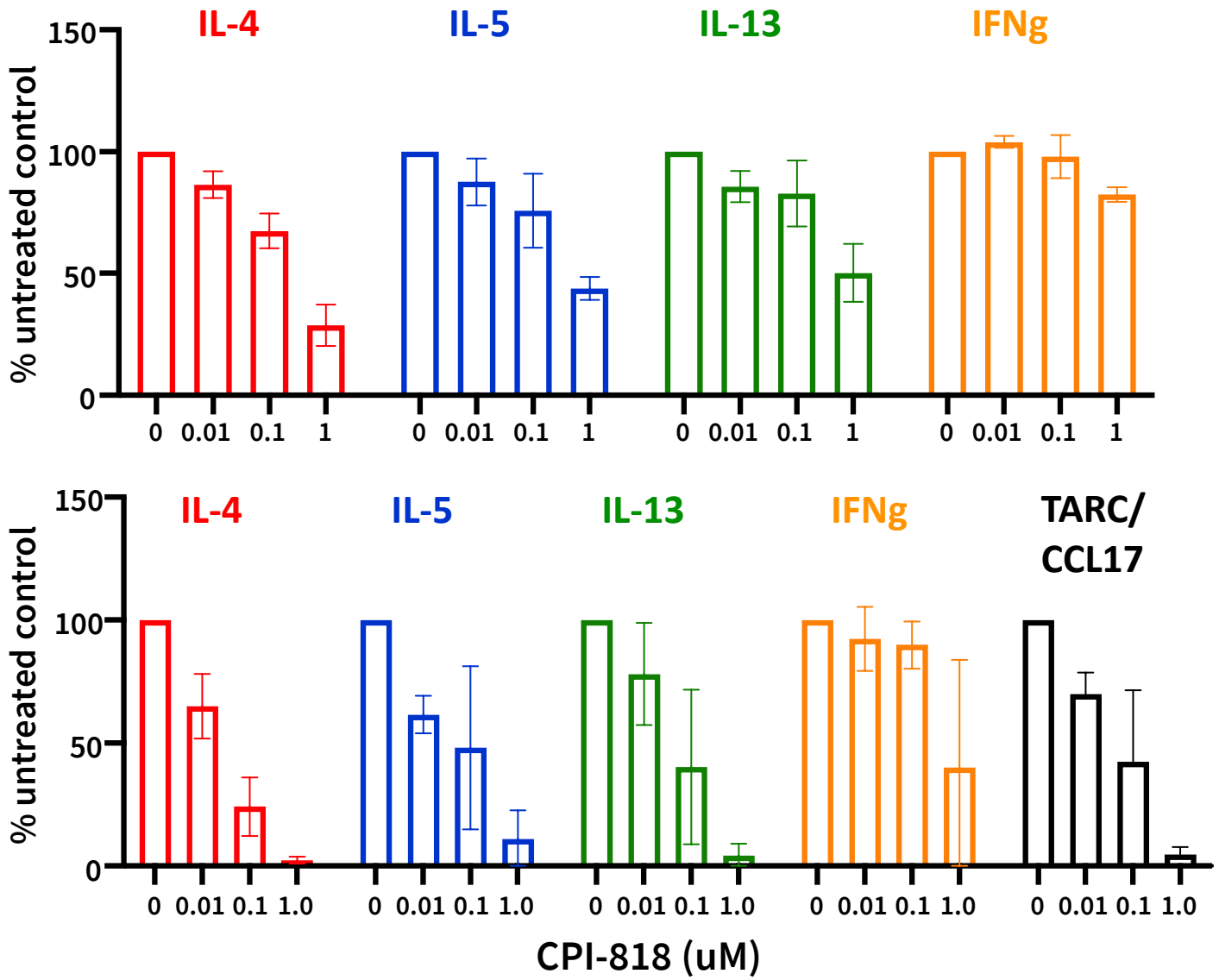
Dose (mg)	C_{max} (Std Dev)	C_{min} (Std Dev)
100 (N=4)	1.3 (1.0)	0.04 (0.1)
200 (N=5)	2.3 (1.9)	0.09 (0.2)
400 (N=5)	4.0 (2.3)	0.5 (1.1)
600 (N=11)	5.5 (4.7)	0.4 (0.6)

* Geometric mean

- **PK studies indicate 200 mg dose provides optimum plasma concentration for Th1 skewing.**
- **Other studies on peripheral blood T cells showed that doses of 200 mg and higher provide maximal ITK target occupancy.**

Effects of CPI-818 on In Vitro T Cell Cytokine Production

CPI-818 inhibits Th2 cytokine production from normal CD4+ and Sezary cells



FACS-sorted CD4+ T cells from healthy controls (n=3; top panel) or from Sezary patients (n=2; bottom panel) were activated with anti-CD3/CD28/CD2-coated beads in the absence or presence of varying concentrations of CPI-818 for 72 hours. Supernatants were collected and Th2-associated cytokines, IFNg, and TARC (CCL17) were measured.

Interim Phase 1 Trial Results

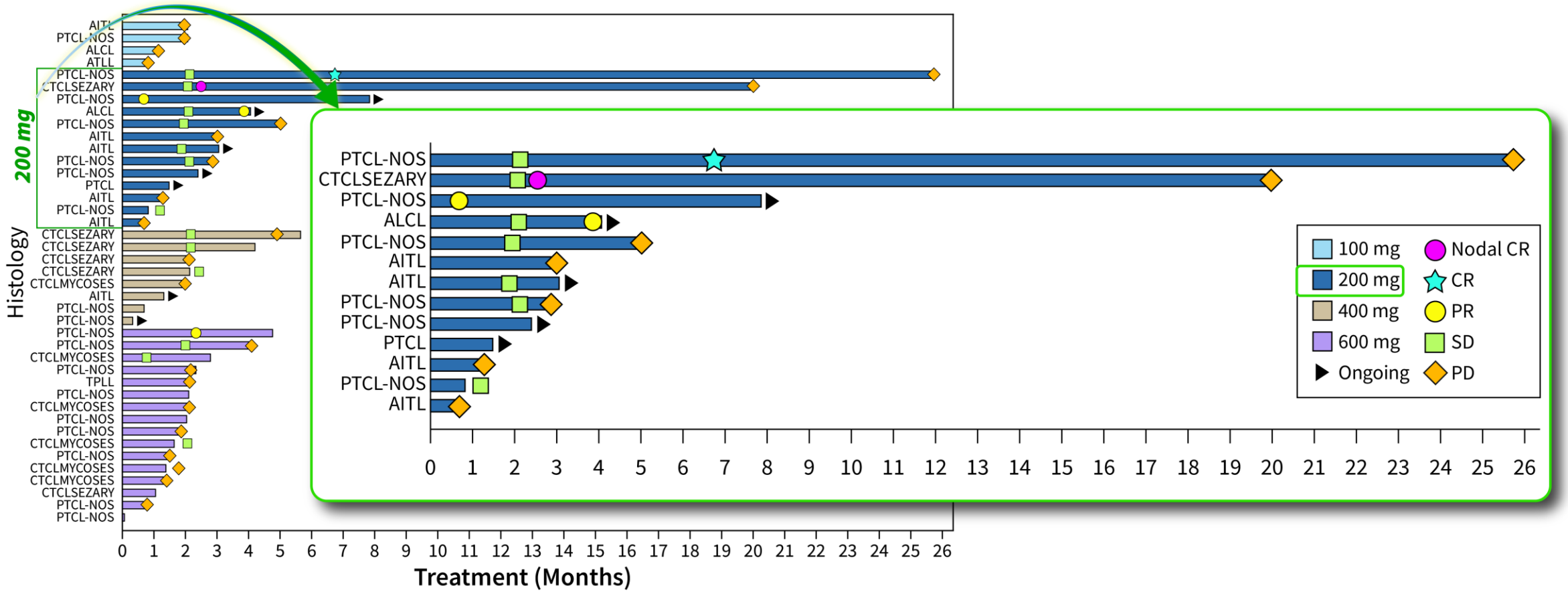
Patient characteristics and adverse event summary

	100mg (N=4)	200mg (N=13)	400mg (N=10)	600mg (N=16)
Age (yrs), median (range)	51 (29, 75)	59 (29, 81)	66.5 (36, 80)	63.5 (34, 84)
Gender, male N (%)	3 (75)	4 (31)	6 (60)	8 (50)
No. of prior therapies, median (range)	3.5 (2, 4)	3 (1, 6)	4 (2, 15)	5 (1, 9)
Histologies				
PTCL- NOS	1	7	3	9
Angioimmunoblastic T cell lymphoma	1	4	2	0
Adult T cell leukemia/lymphoma	1	0	0	0
Anaplastic large cell lymphoma	1	1	0	0
T-PLL	0	0	0	1
CTCL (Sézary syndrome)	0	1	4	1
CTCL (Mycosis fungoides)	0	0	1	5

Most common (≥ 10%, all causality) AEs: nausea, chills, vomiting, fatigue, pyrexia, decreased appetite, pruritus, and rash. Treatment-related Grade 3+ AEs: anemia (1), lymphocytosis (1), WBC decreased (1) and neutropenia (1).

Anti-tumor Activity in Various Dosing Cohorts

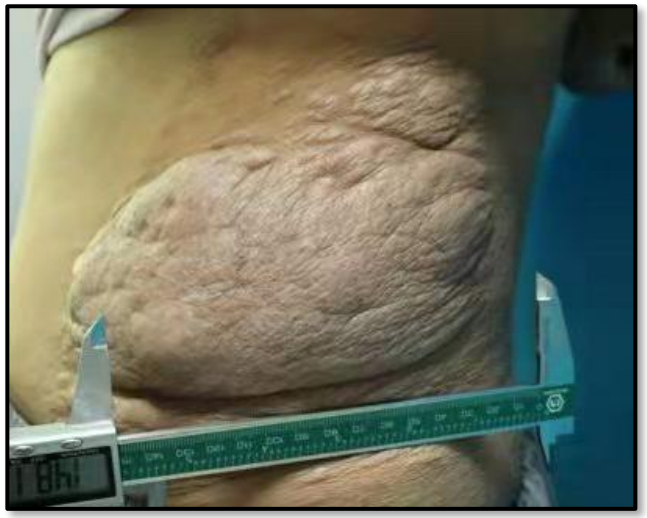
200 mg BID identified as optimal dose with ORR of 4/11 evaluable



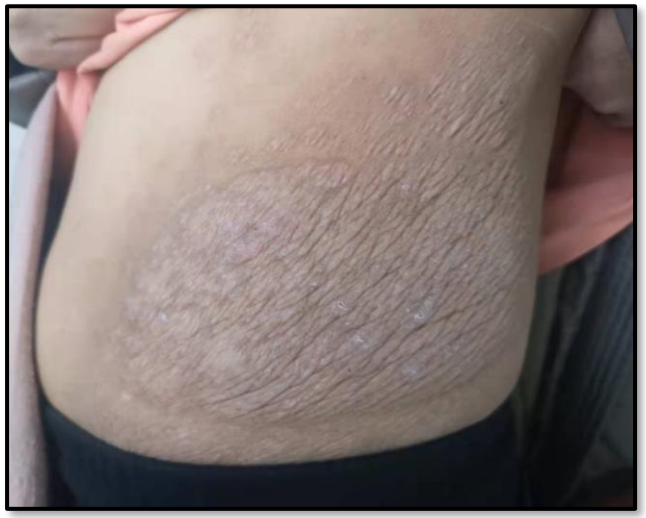
Data cut-off: September 2022

Anti-tumor Activity in Refractory Disease

Regression of large tumor masses observed



Screening



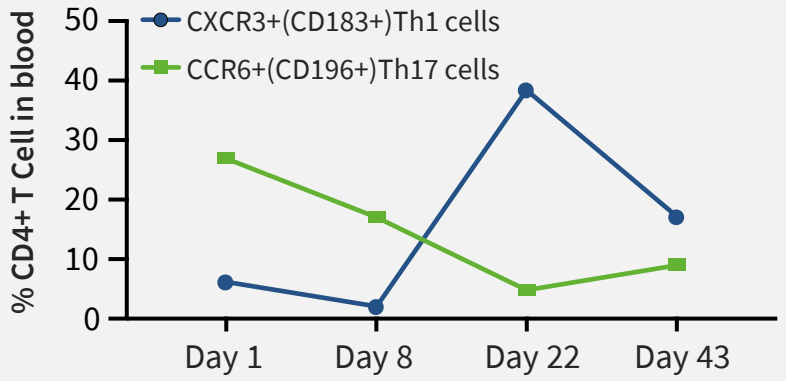
Day 15

- PTCL-NOS patient failed CHOEP, GDP, HDACi, and anti-PD1.
- Large subcutaneous mass on abdomen.
- Has PR 8+ months duration in all sites of disease (bone marrow, skin, lymph node, and spleen) on CPI-818.

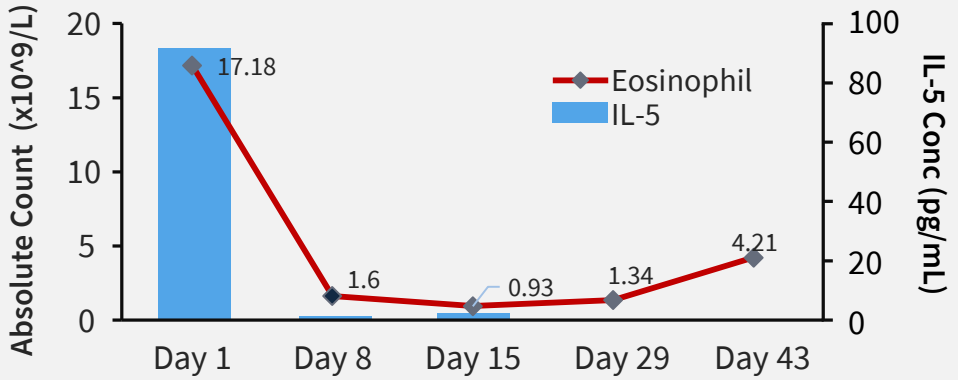
Immunologic Effects in Treated Patient

Optimum dose induces Th1 skewing and Th2 blockade

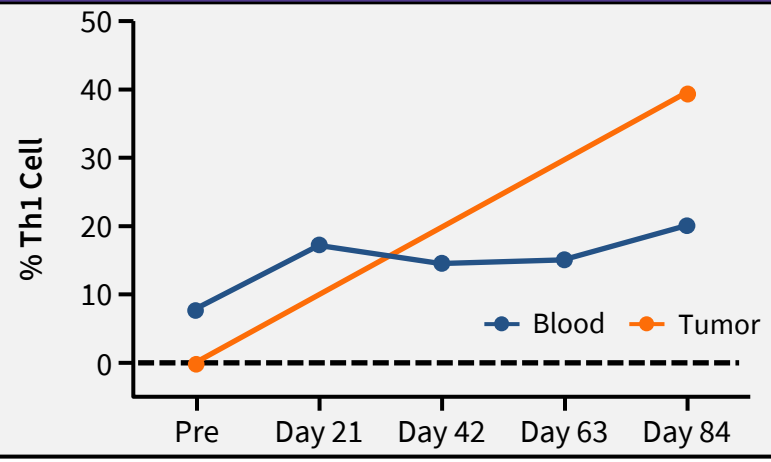
Frequency of Th1 & Th17 CD4 cells in Blood

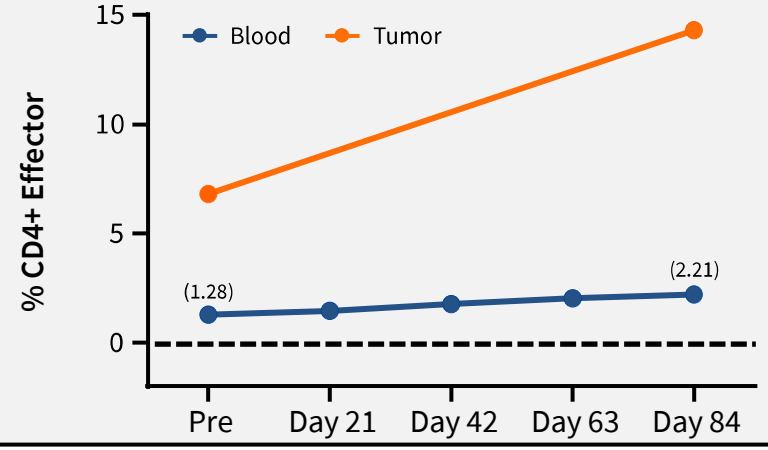


Effects on Eosinophils and Serum IL-5



Th1 and CD4+ Effector Cells Increase in Blood and Tumor During CPI-818 Treatment

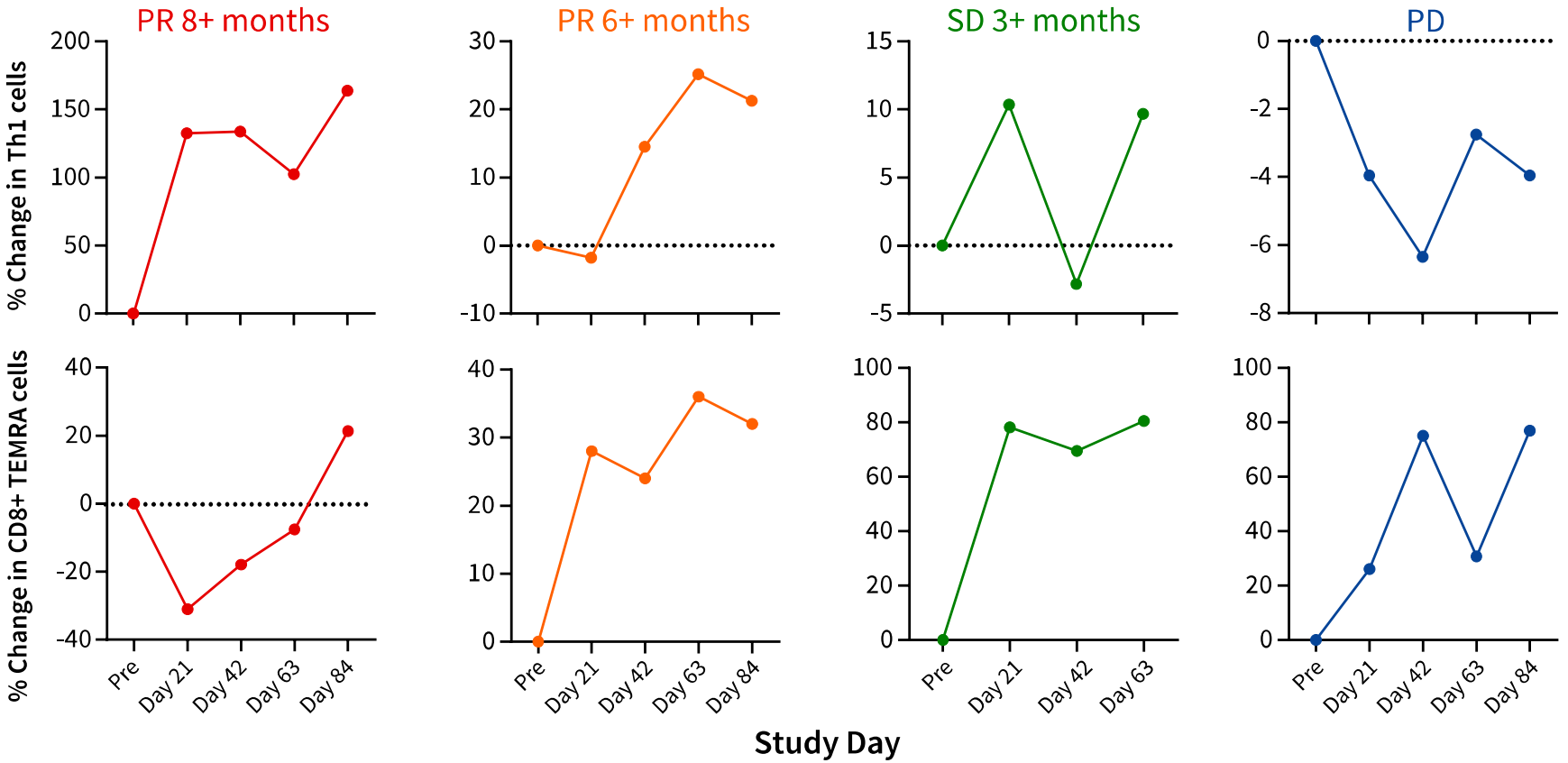




PBMC and tumor samples were analyzed at various timepoints and demonstrate increase in blood Th1, decrease in blood Th17, reduction of both eosinophil count and IL-5 consistent with Th1 skewing and Th2 blockade. Baseline and on treatment tumor biopsy and blood show increase in Th1 and terminally differentiated T effector memory cells.

Effects of CPI-818 on Differentiation of Th1 and CD8+ TEMRA Cells

Percent Change in Th1 and CD8+ TEMRA Cells from Baseline



Peripheral blood from four patients were collected at various timepoints and T cell subsets evaluated by flow cytometry. Plots show percent change from baseline for Th1 (CD3+/CD4+/CD8-/CD183+/CD196-) and for CD8+ TEMRA (CD3+/CD4-/CD8+/CD197-/CD45RA+). Two PR patients and SD patient show increases in Th1 and TEMRA cells while on treatment with CPI-818. Of note, the SD and PD patients were lymphopenic at baseline (<1000 ALC).

Conclusions

- CPI-818 is a selective ITK inhibitor that at optimal concentrations induces Th1 skewing and blockade of Th2 function and related cytokine production (e.g., IL-4, IL-5, IL-13, TARC).
- In an ongoing international Phase 1 trial:
  - Durable objective responses seen (1 CR, 25 mo; 1 nodal CR, 19 mo; 2 PRs, 6+, 8+ mo) in 11 evaluable patients at optimum dose.
  - Doses up to 600 mg po BID have been well-tolerated with no DLT.
  - Treatment induces Th1 skewing and Th2/Th17 blockade in vivo.
  - Baseline and on-treatment blood and tumor biopsy specimens show increases in both Th1 cells (CD3+/CD4+/CD8-/CD183+/CD196-) and in terminally differentiated T effector memory cells (TEMRA: CD3+/CD4-/CD8+/CD197-/CD45RA+).
- The increases in Th1 cells and TEMRA CD8+ cells in humans and preclinical data suggest that anti-tumor activity is due to induction of a host anti-tumor response.
- Selective ITK inhibition may have the potential to enhance anti-tumor immunity and also could be useful in the therapy of Th2-mediated autoimmune/allergic diseases.
- A Phase 2 trial in refractory peripheral T cell lymphomas is planned.

Acknowledgements

- **Participating Centers and Investigators**:

We thank the patients and their families.