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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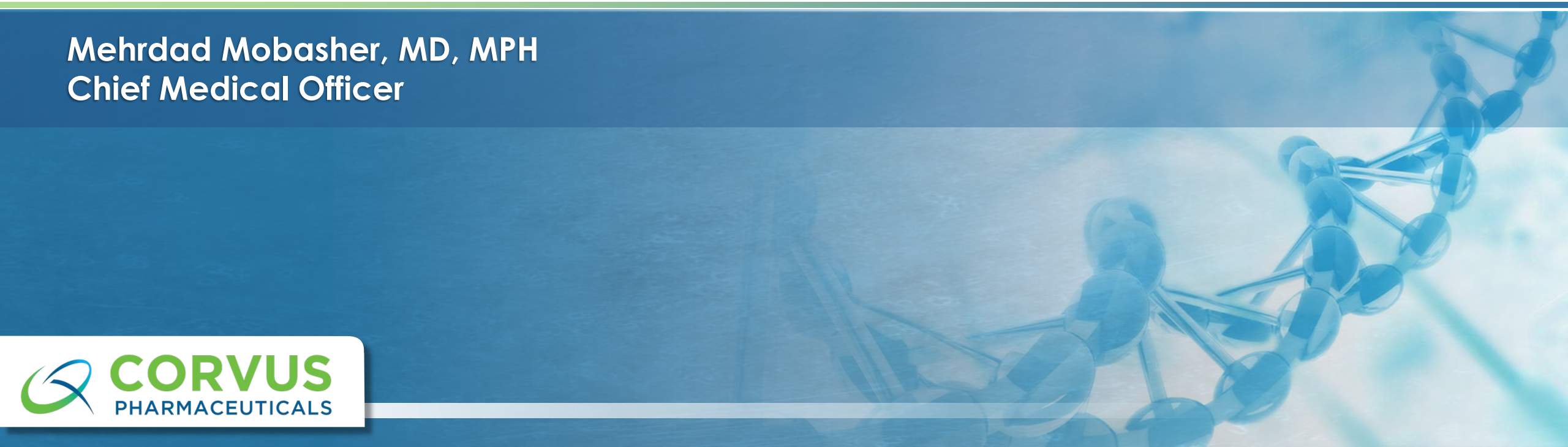
Chief Medical Officer



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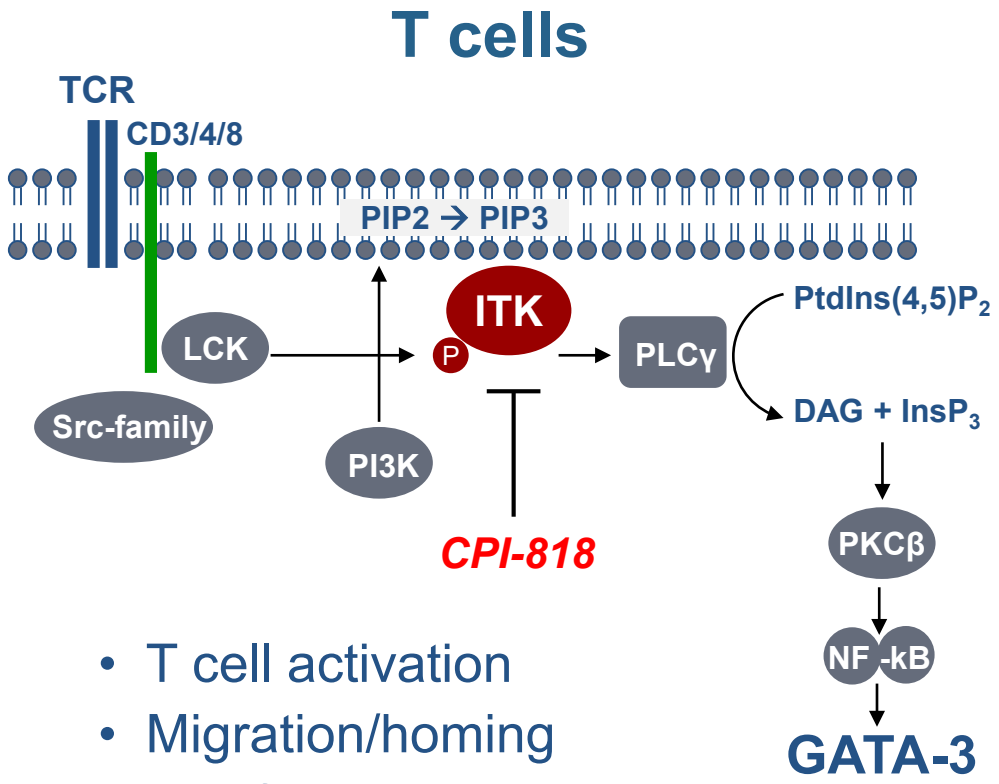
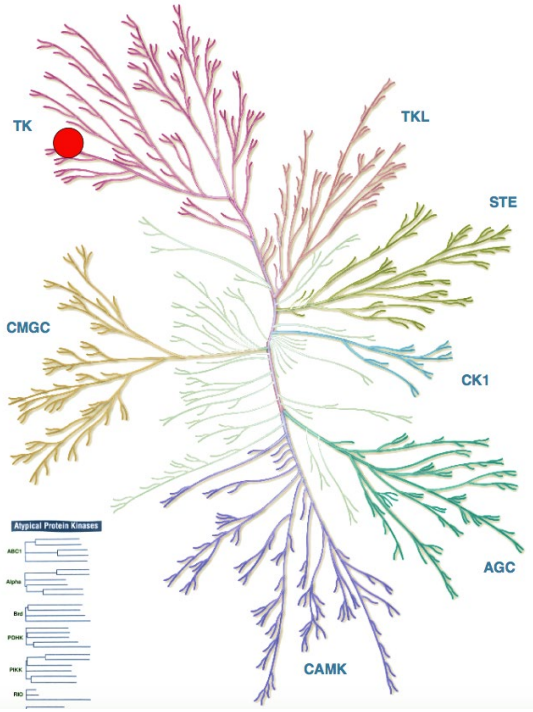
Inhibition of ITK for T Cell Lymphoma

- 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_H2-driven malignancies
- CPI-818 is a selective, covalent inhibitor of ITK
- Clinical activity observed in canines with CTCL and PTCL



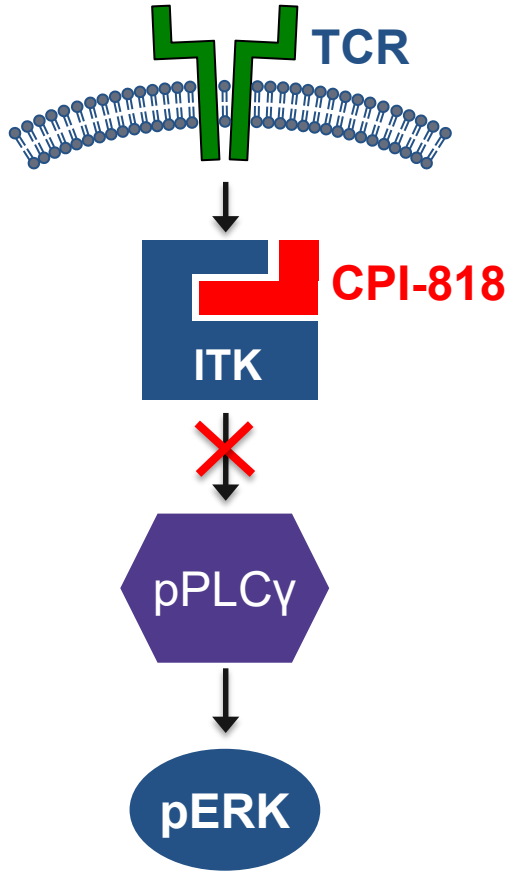
CPI-818 Selectivity Inhibits ITK and Blocks Cellular Signaling

Kinome Profile and Kinases with Cys-442

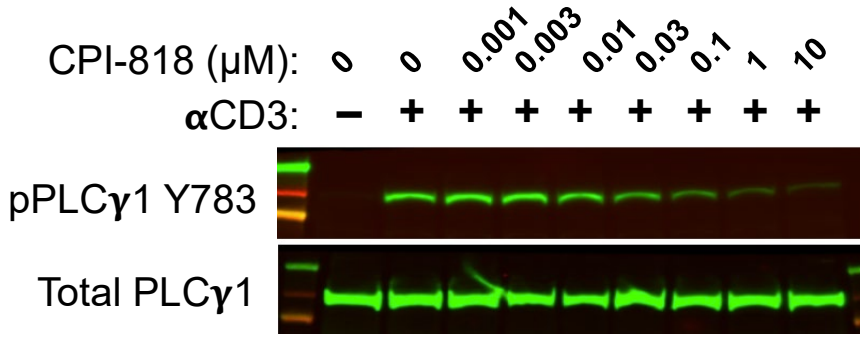


K_i < 10 nM
468 Kinases Profiled

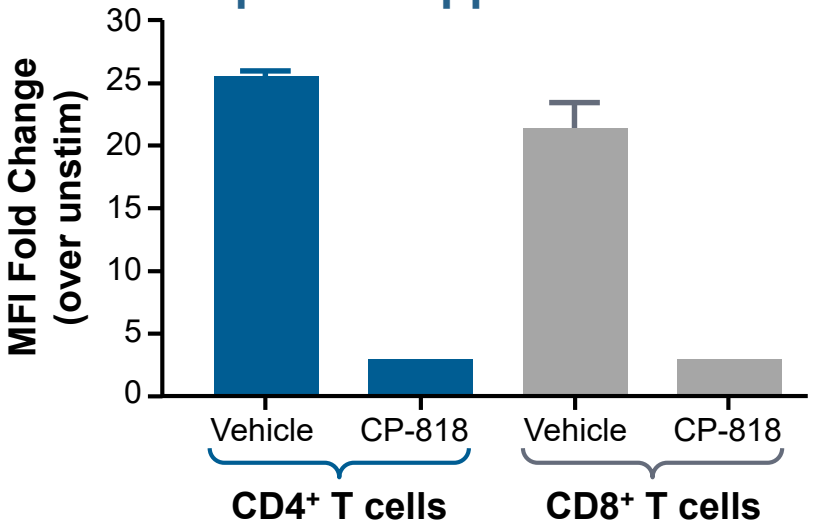
	CPI-818 Kd in nM
ITK	2.5
BLK	4700
BMX	9100
BTK	1200
EGFR	>10000
ERBB2	>10000
ERBB4	>10000
JAK3	2800
MKK7	>10000
TEC	540
RLK	2700



pPLCγ1 Suppression

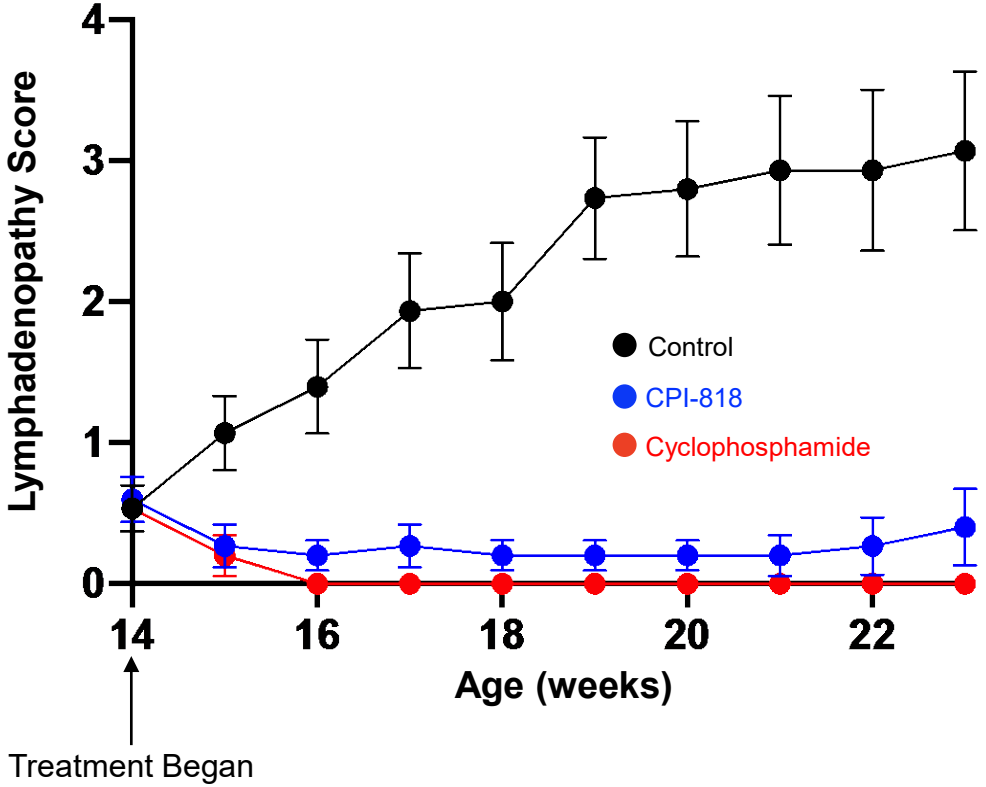


pERK Suppression

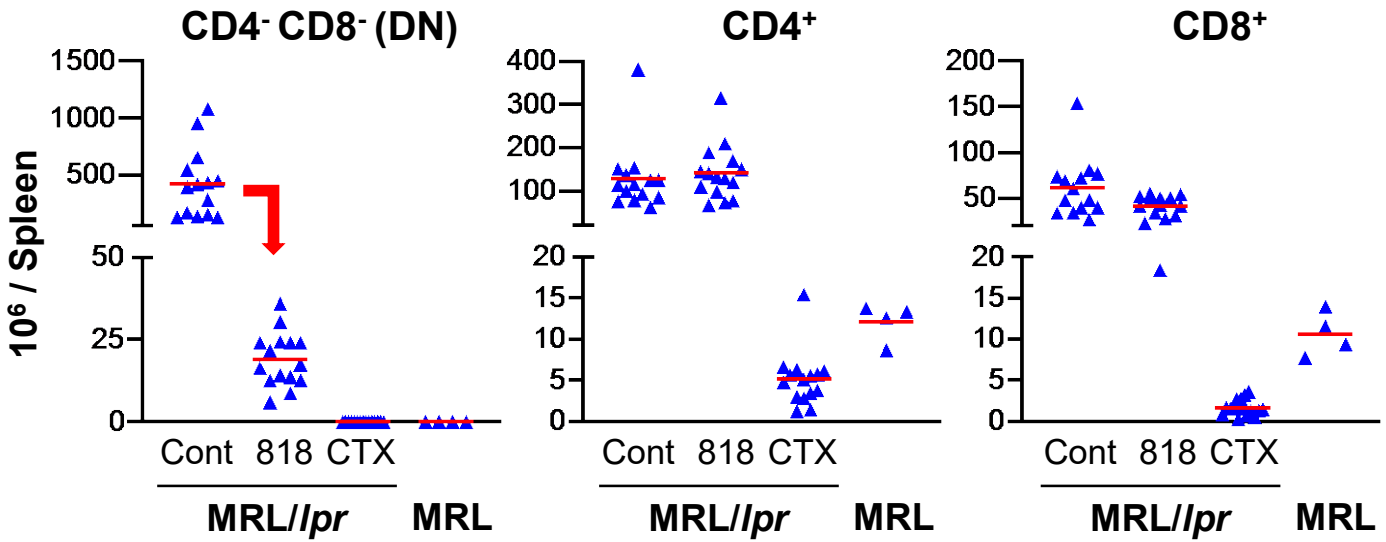


CPI-818 Inhibits Lymphoproliferative Disease in Mice

Lymphadenopathy



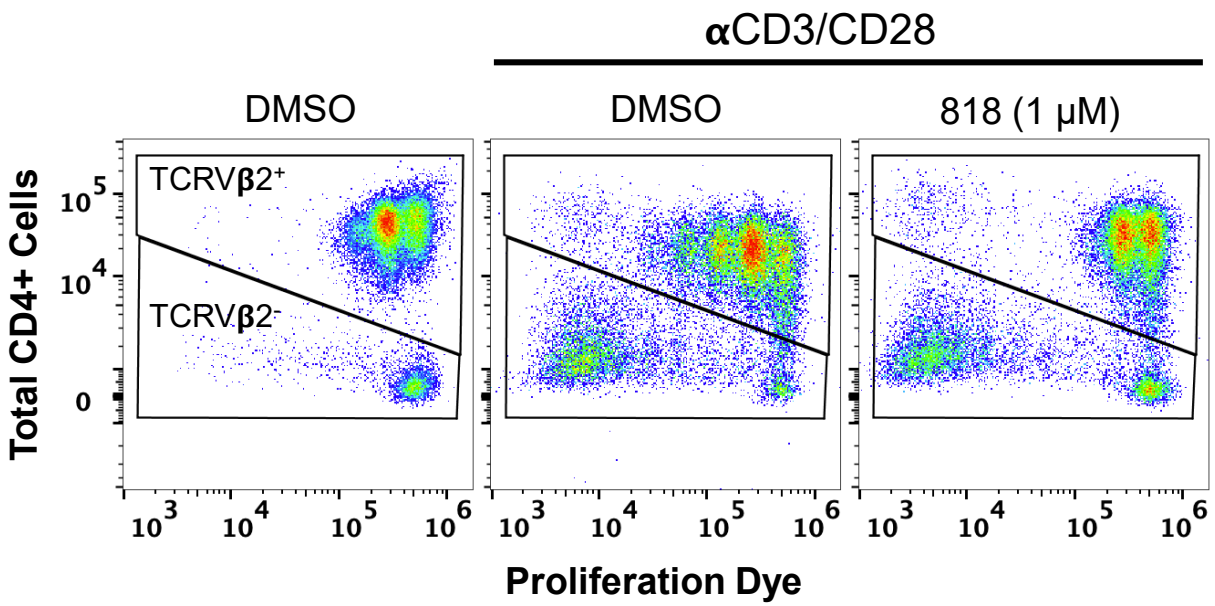
Pathologic and Normal T cells in Spleens



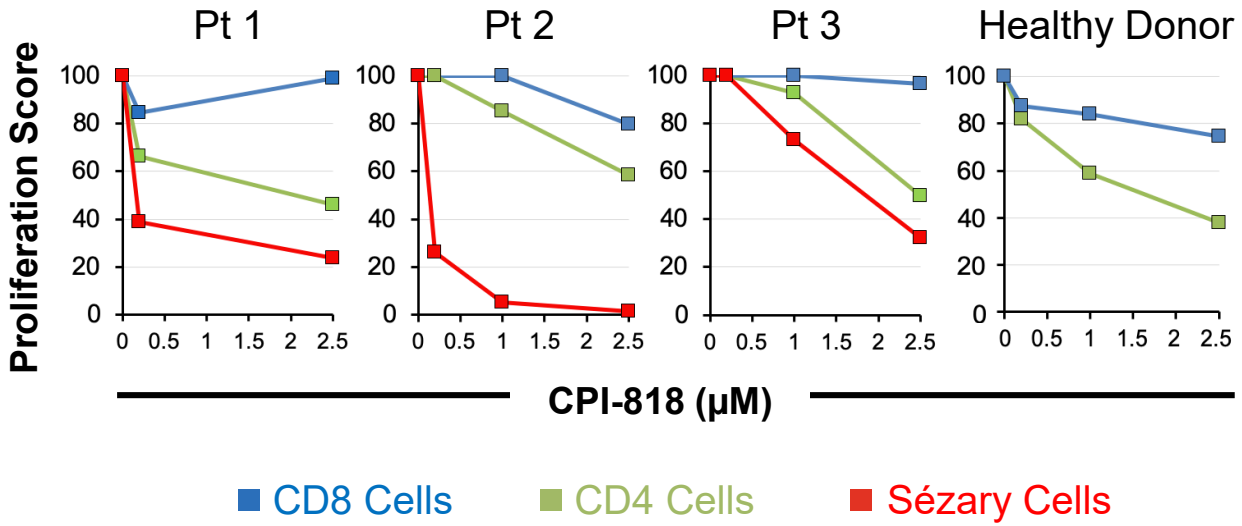
- Fas-/- MRL/lpr mice spontaneously develop lymphoproliferative disease from uncontrolled growth of T cells.
- CPI-818 treatment led to marked regression of lymphadenopathy, with little effect on normal CD4+ and CD8+ T cells.

CPI-818 Preferentially Inhibits Sézary Cells

Gating Strategy



Inhibition of Cell Division



- 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)

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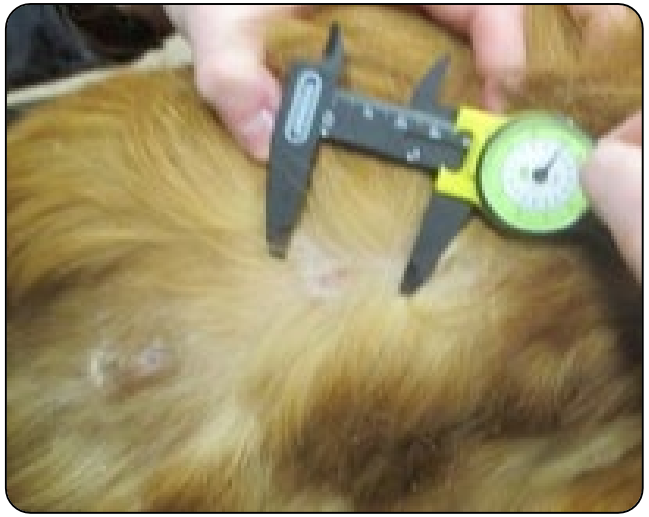
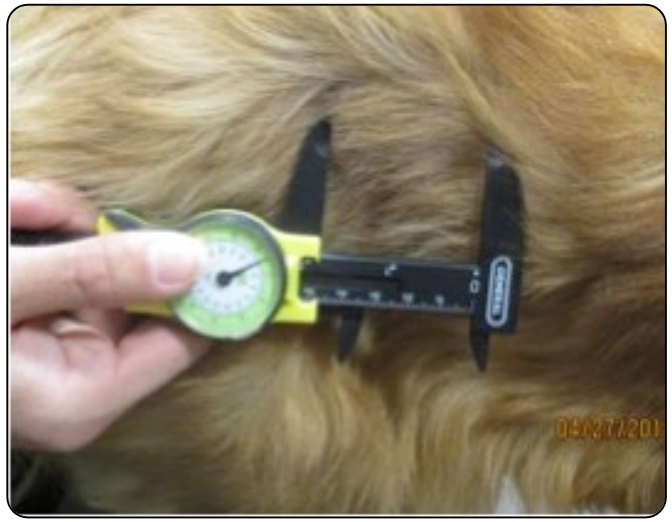
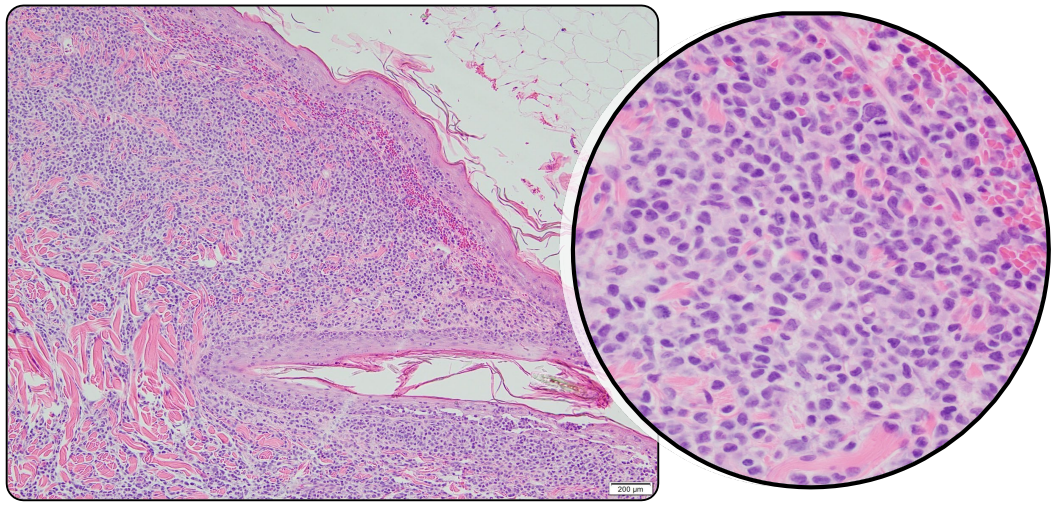
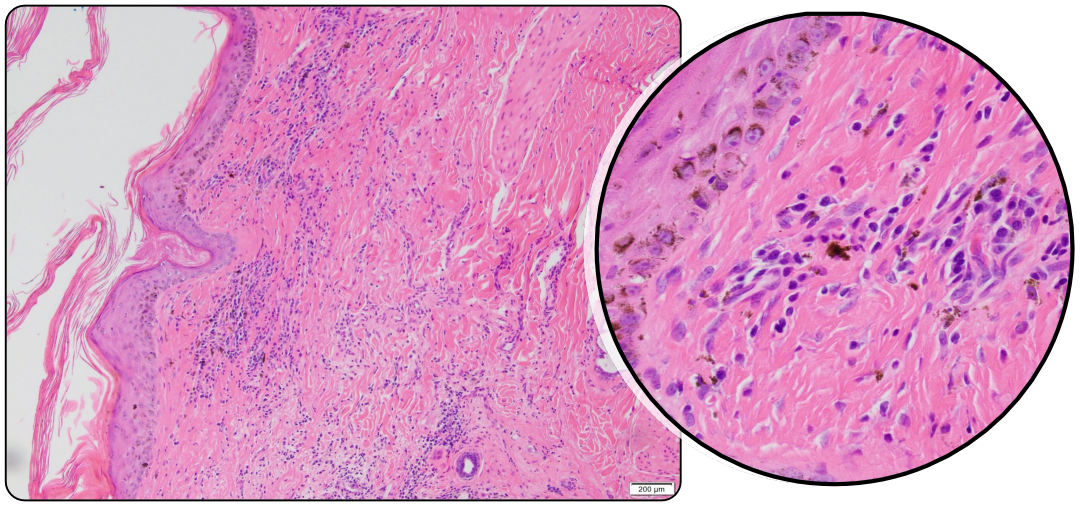


CTCL Patient
11 year old, Male
Golden Retriever

4 months

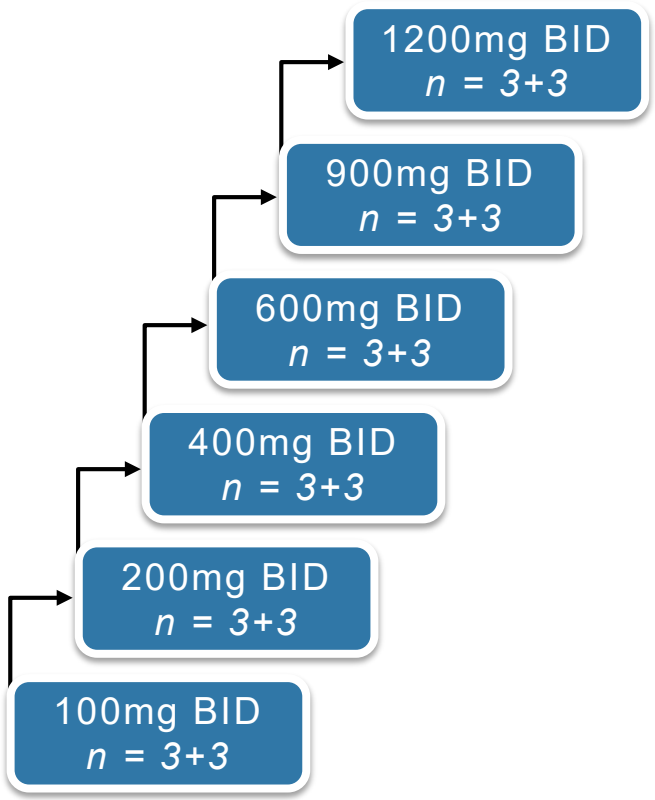






CPI-818-001 Phase 1/1b Clinical Trial Design
Dose escalation

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

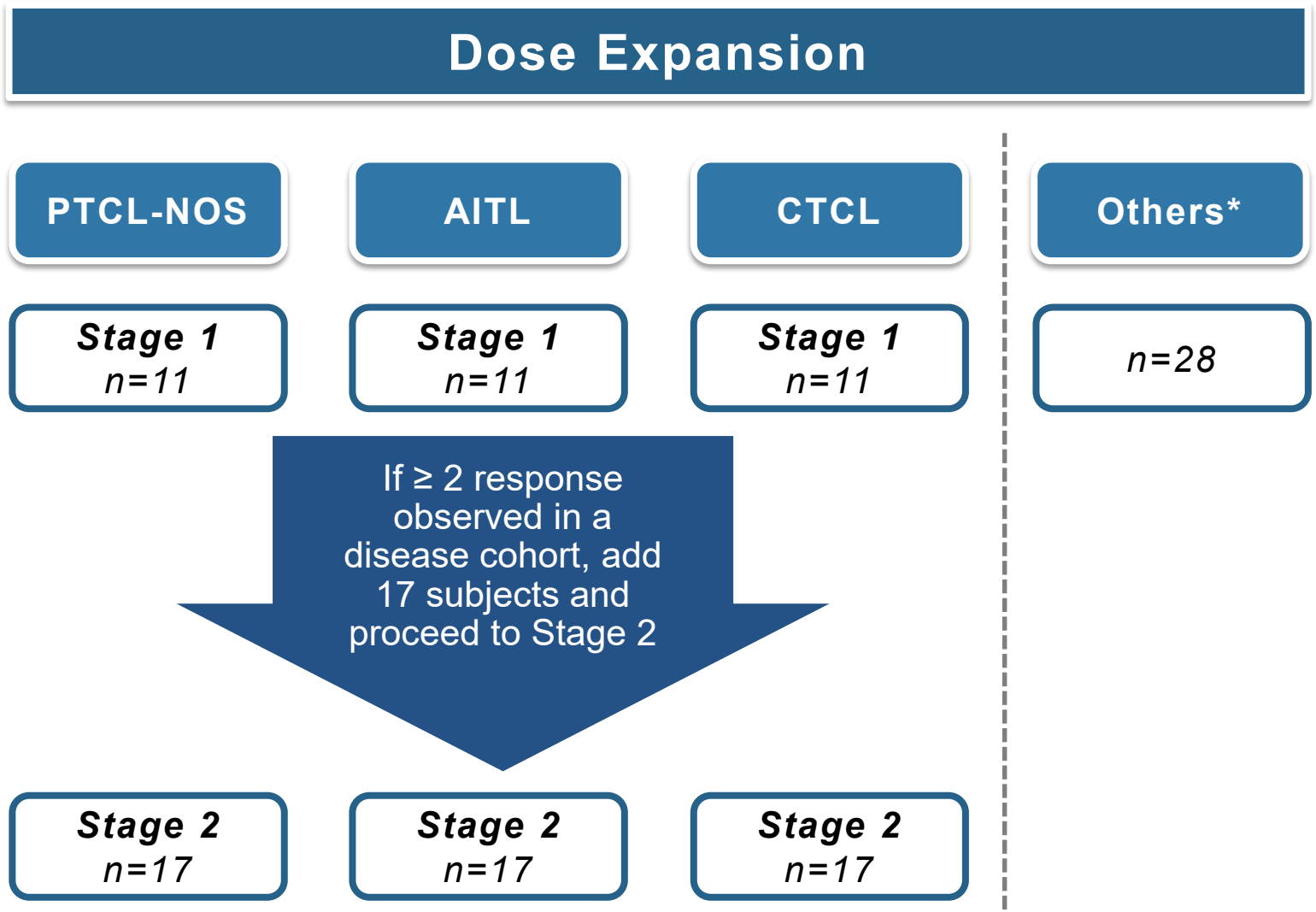
Objectives

- 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



* *Other types include NKTCL, ALCL, ATLL, etc*

CPI-818-001 Study
Patient Characteristics

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

*Data cut off date: 27Jan2020

All Adverse Events
No grade 3/4 AEs

Adverse Events N (%)	100mg (N=4)	200mg (N=3)	400mg (N=5)	Total (N=12)
Patients with any TEAE	4 (100%)	3 (100%)	3 (60%)	10 (83.3%)
Abdominal distension	1 (25.0%)	0	0	1 (8.3%)
Diarrhea	1 (25.0%)	0	0	1 (8.3%)
Nausea	1 (25.0%)	0	1 (20%)	2 (16.7%)
Retching	1 (25.0%)	0	0	1 (8.3%)
Vomiting	1 (25.0%)	0	0	1 (8.3%)
Chills	1 (25.0%)	0	0	1 (8.3%)
Fatigue	0	1 (33.3%)	0	1 (8.3%)
Pyrexia	0	1 (33.3%)	0	1 (8.3%)
Skin wound (trauma)	0	1 (33.3%)	0	1 (8.3%)
Decreased weight	1 (25.0%)	0	0	1 (8.3%)
Decreased appetite	1 (25.0%)	0	0	1 (8.3%)
Hypercalcaemia	1 (25.0%)	0	0	1 (8.3%)
Hyperuricaemia	1 (25.0%)	0	0	1 (8.3%)
Hypomagnesaemia	1 (25.0%)	0	0	1 (8.3%)
Musculoskeletal pain	0	0	1 (20%)	1 (8.3%)
Headache	0	1 (33.3%)	0	1 (8.3%)
Anxiety	1 (25.0%)	0	0	1 (8.3%)
Cough	0	1 (33.3%)	0	1 (8.3%)
Rash erythematous	0	1 (33.3%)	0	1 (8.3%)
Hyperhidrosis	1 (25.0%)	0	0	1 (8.3%)
Skin Pain	1 (25.0%)	0	0	1 (8.3%)
Pruritus	1 (25.0%)	1 (33.3%)	0	2 (16.7%)
Rash	0	1 (33.3%)	1 (20%)	2 (16.7%)

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

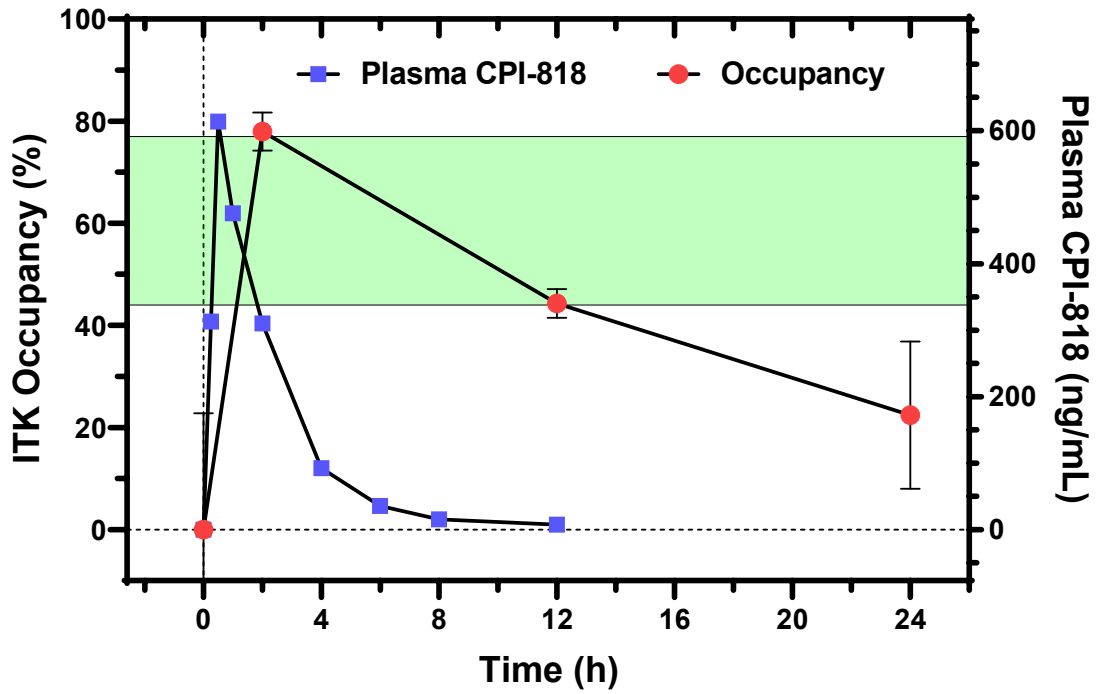
Safety
No DLTs

- **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

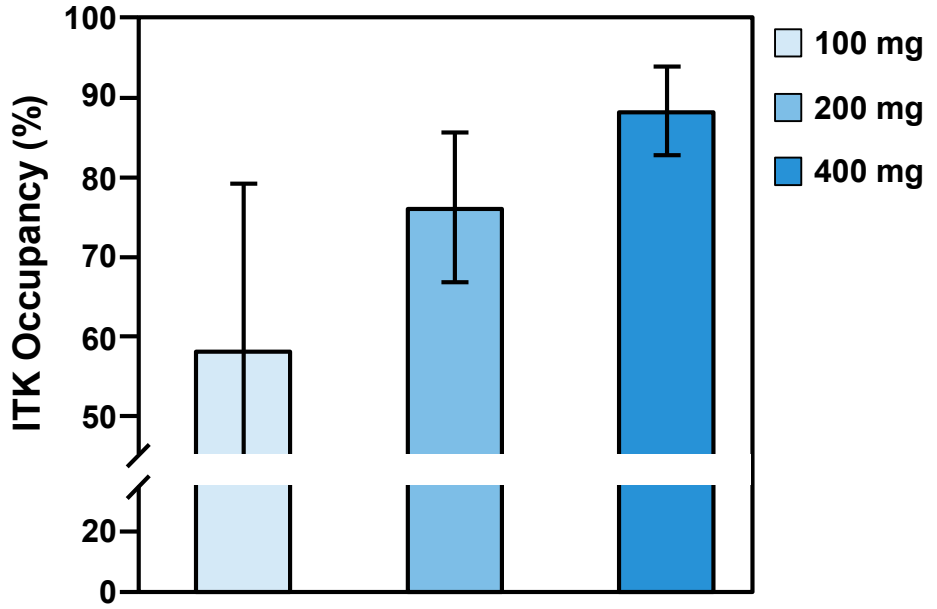
Occupancy is increasing as a function of dose, BID Dosing Required

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



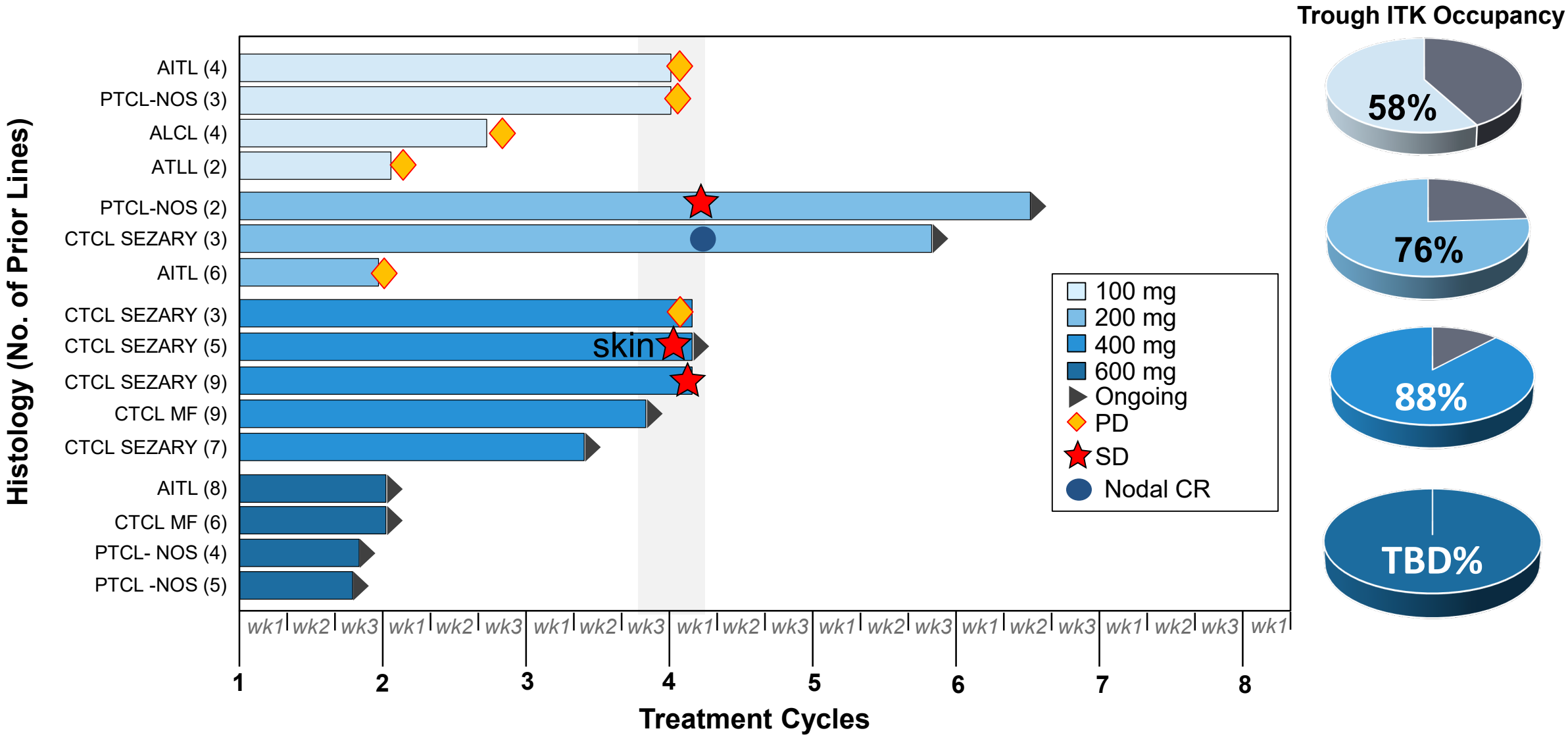
Rapid absorption and clearance drives
- ~ 80% ITK occupancy near Cmax
- ~ 50% occupancy at 12hr

Trough ITK Occupancy for Cycle 1 with BID Dosing of CPI-818



Preliminary Patient Status in Dose Escalation

CPI-818-001 Study

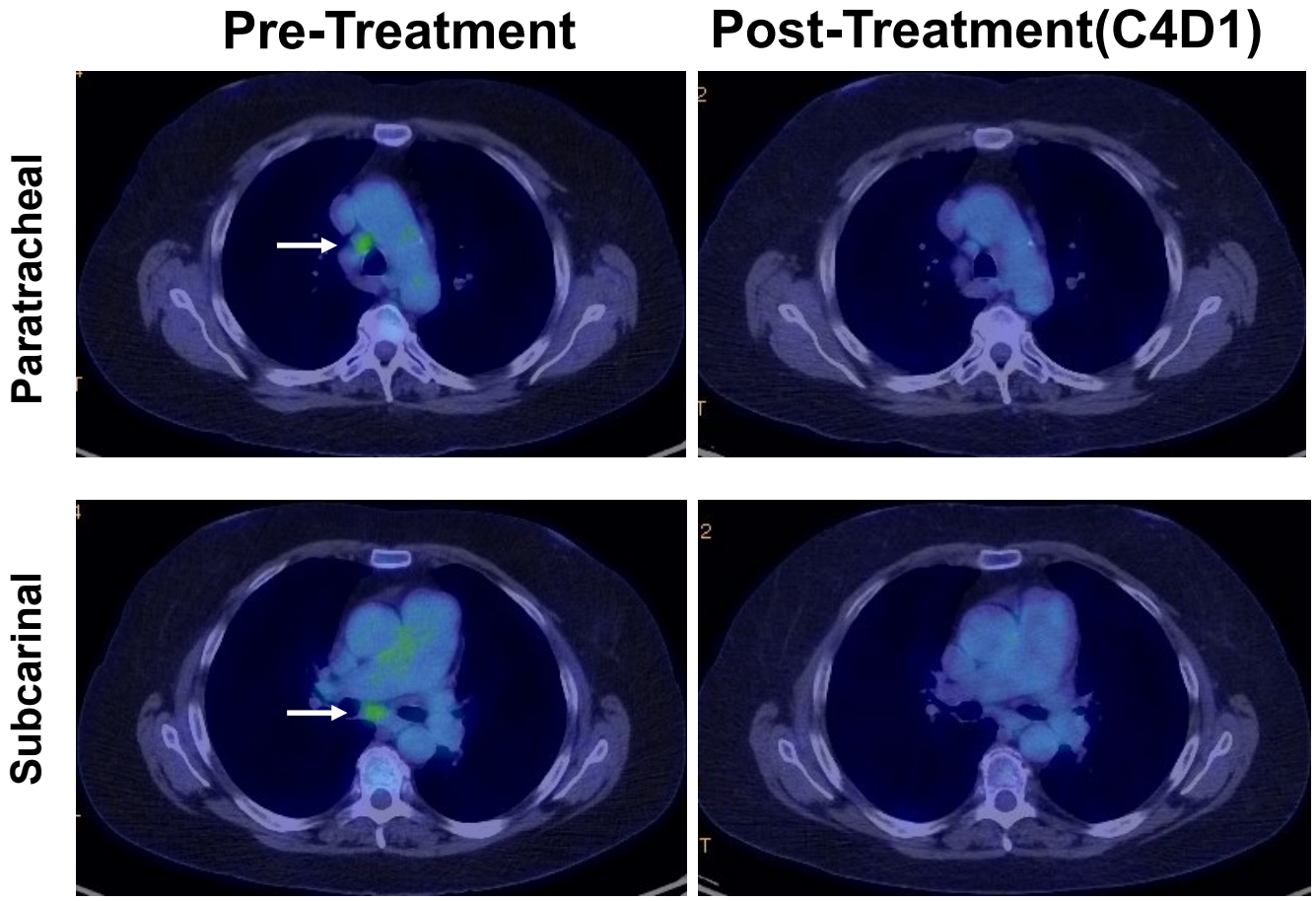


median time on treatment to 55 days

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

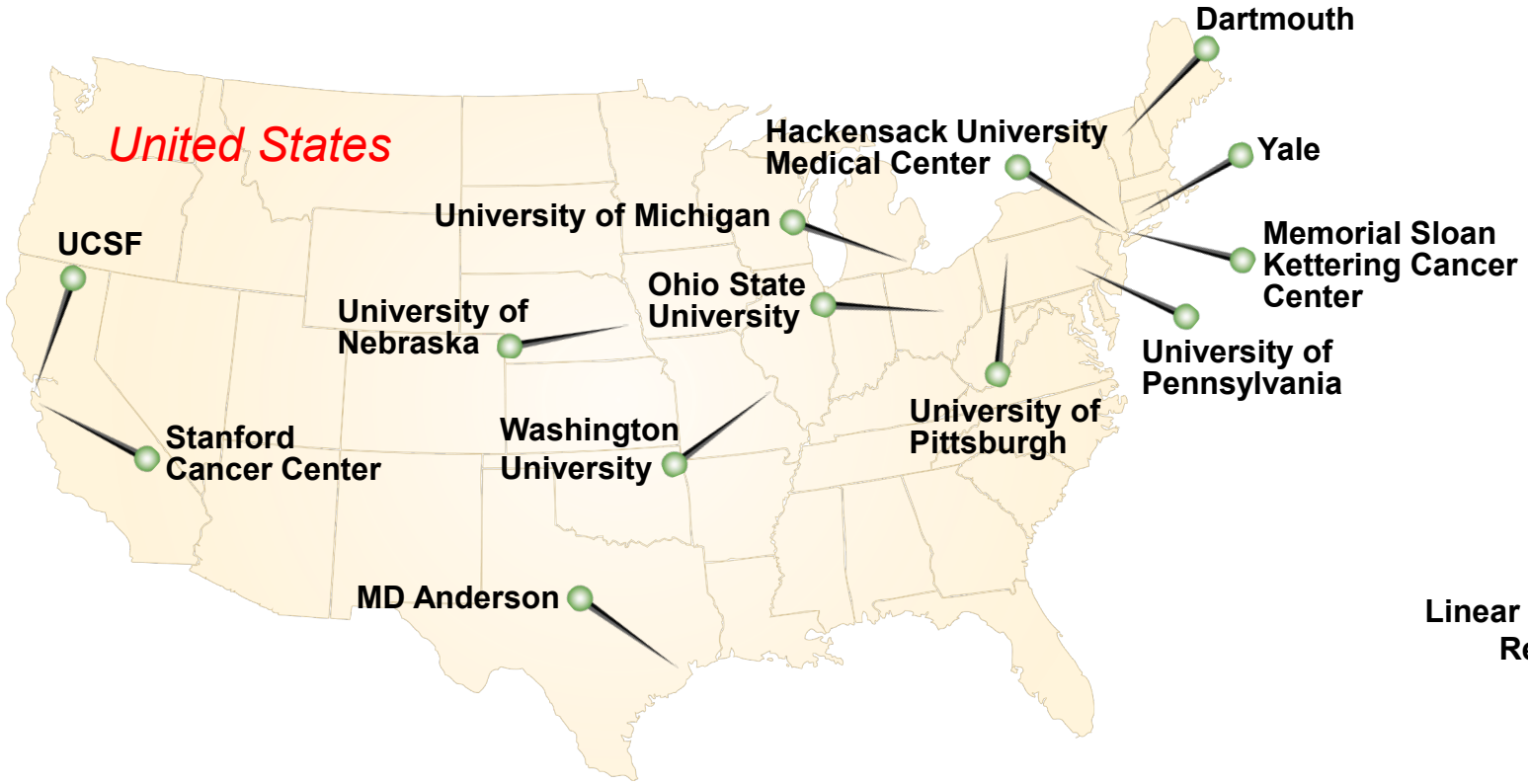
- 80 year old Caucasian male CTCL (Sézary Syndrome)
- Started C1D1 on 400mg BID cohort on 25-Nov-2019
- Screening: no visceral disease or target lesions on CT, absolute Sézary count $5.6x10^9/L$
- Patient reported decreased skin redness with start of treatment after treatment
- C4D1 response assessment: There has been a clinical improvement **(mSWAT 92->71)**
- Lymphocytosis stable

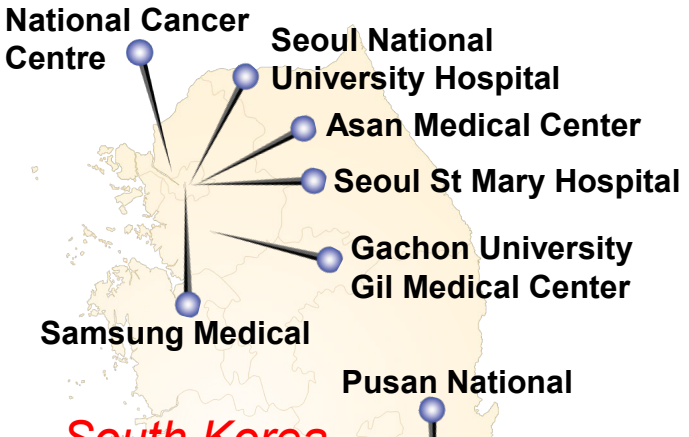
Conclusion

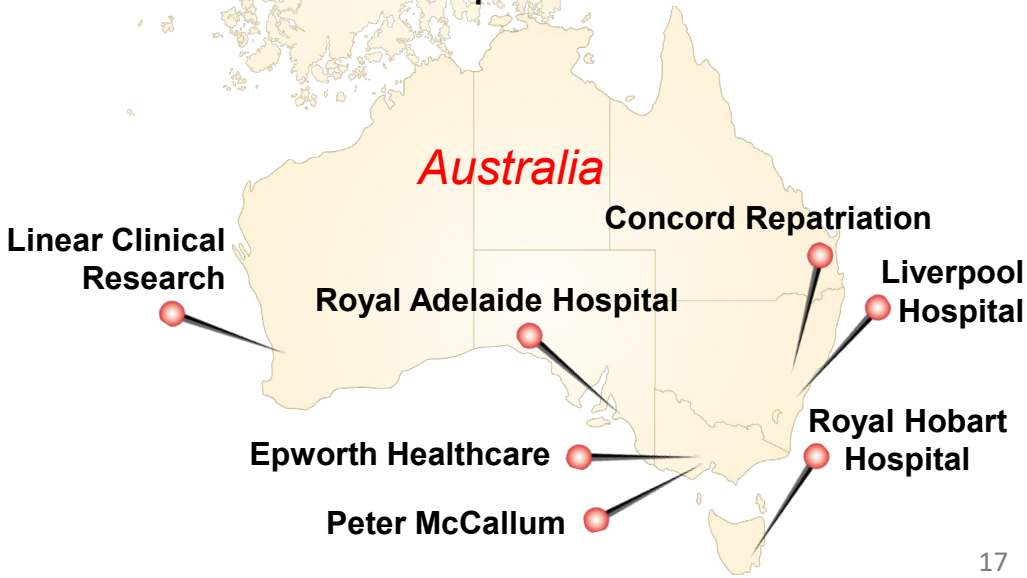
- CPI-818 is a selective, covalent inhibitor of ITK (sparing RLK and BTK)
- Blocks signal transduction in endpoints downstream of T-cell activation
- Inhibits lymphoproliferative disease in MRL mouse model
- Preferentially inhibits the proliferation of malignant cells sparing normal T cells in blood 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**:







- **The patients and their families**
- **Colleagues at Corvus**