Final Results of a Phase 1 Trial with Soquelitinib (SQL), a Selective Interleukin-2-Inducible T Cell Kinase (ITK) Inhibitor for Treatment of Relapsed/Refractory (R/R) T Cell Lymphomas (TCL)

Richard Miller, MD

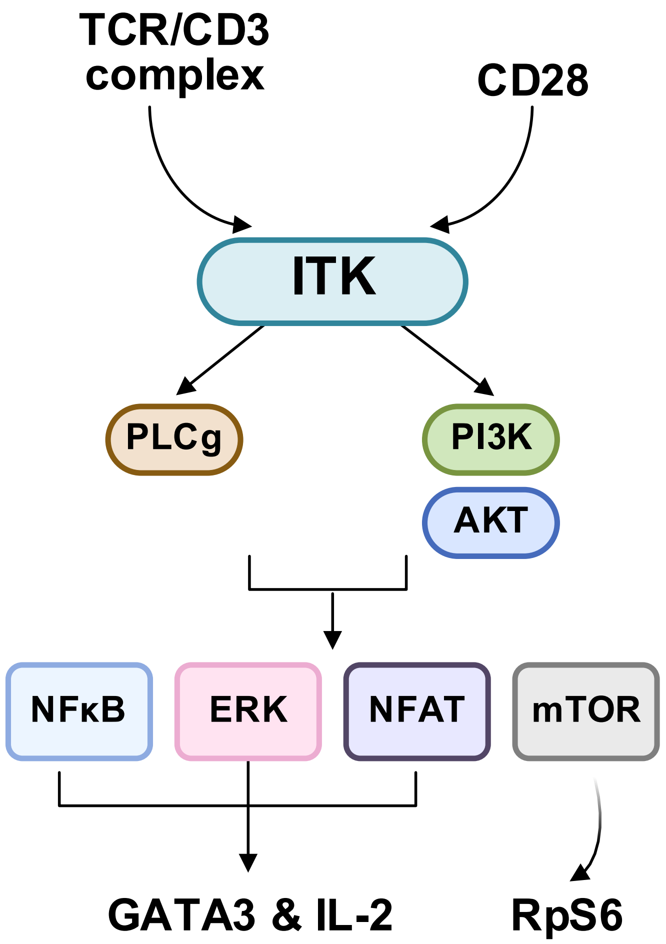
Richard Miller[1], Ryan Wilcox[2], John Reneau[3], Costas K Yannakou[4], Won Seog Kim[5], Tatyana Feldman[6], Youn Kim[7], Michael Khodadoust[7], Dejan Radeski[8], Robin Gasiorowski[9], Dok Hyun Yoon[10], Yuqin Song[11], Andrew Hotson[1], Suresh Mahabhashyam[1]

[1]Corvus Pharmaceuticals Inc, South San Francisco, CA, USA; [2]University of Michigan, Ann Arbor, MI, USA; [3]The Ohio State University and Wexner Medical Center, Columbus, OH, USA; [3]University of Michigan, Ann Arbor, MI, USA; [4]Epworth HealthCare, Melbourne, Victoria, Australia; [5]Samsung Medical Center, Seoul, South Korea; [6]John Theurer Cancer Center at HMH, Hackensack, NJ, USA; [7]Stanford Cancer Institute, Stanford, CA, USA ; [8]Linear Clinical Research, Perth, Western Australia, Australia; [9]Concord Repatriation General Hospital, Sydney, New South Wales, Australia; [10]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [11]Peking University Cancer Hospital & Institute, Beijing, China

ITK Involved in Many T Cell Functions

Plays critical role in TCR signaling

ITK role in TCR signaling pathway



T cell activation

Migration and homing

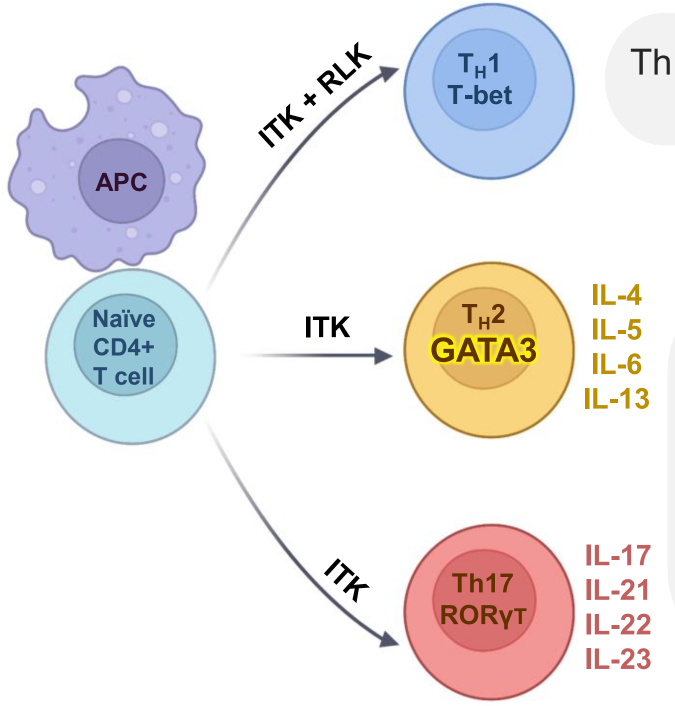
Proliferation

Tonic TCR Signaling
Somatic mutations in TCR pathway drive lymphomagenesis

Soquelitinib Blocks Th2 and Th17 and Induces Th1 Skewing

Modulation of T cell differentiation

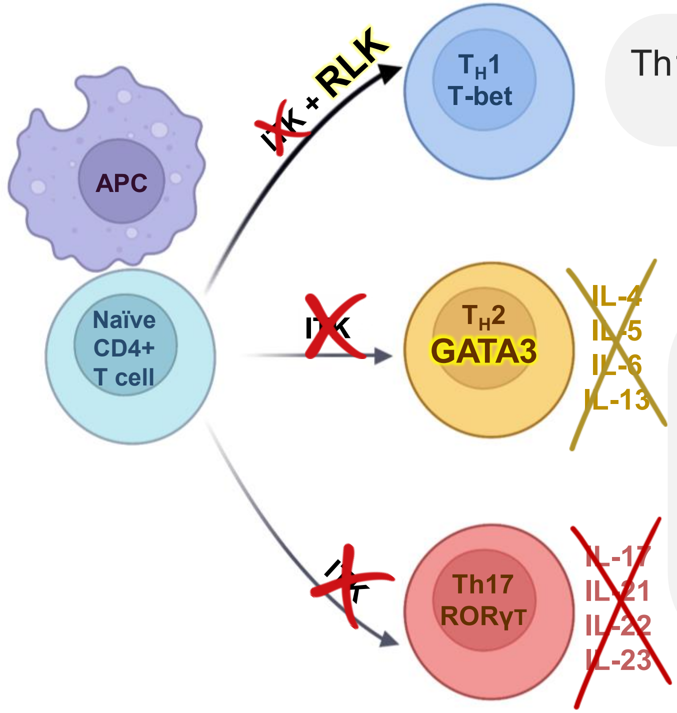
ITK involved in T cell differentiation



Th1 cells play a role in cancer cell and viral elimination

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

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

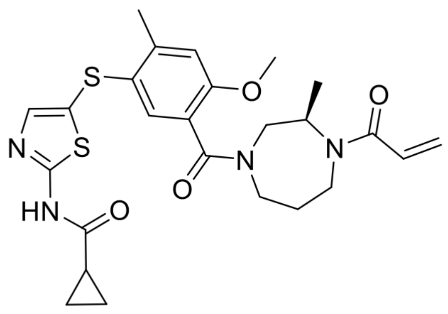


Th1 cells play a role in cancer cell and viral elimination

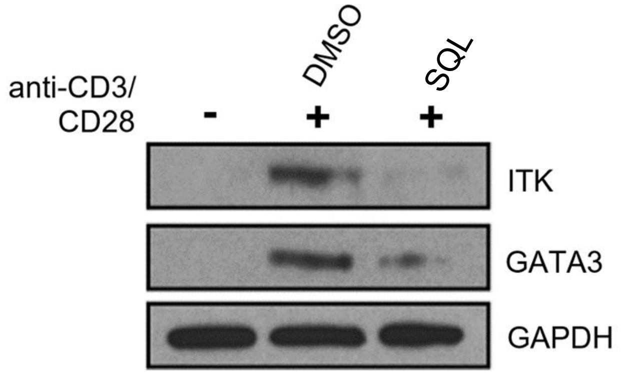
Th2 and Th17 cells are involved in autoimmune, inflammatory, fibrotic and allergic diseases

Soquelitinib Selectivity

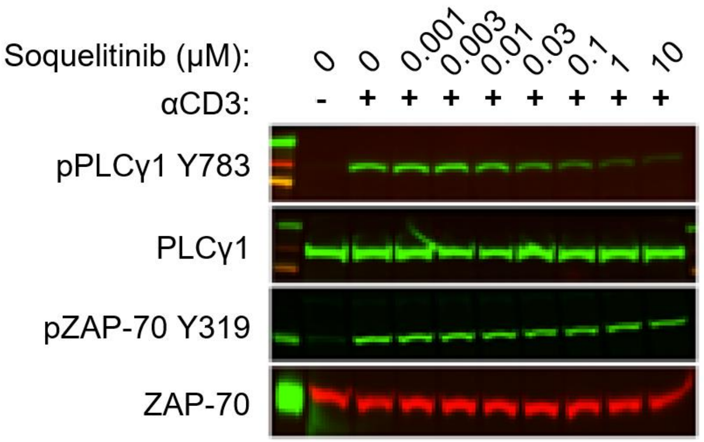
Chemical Structure



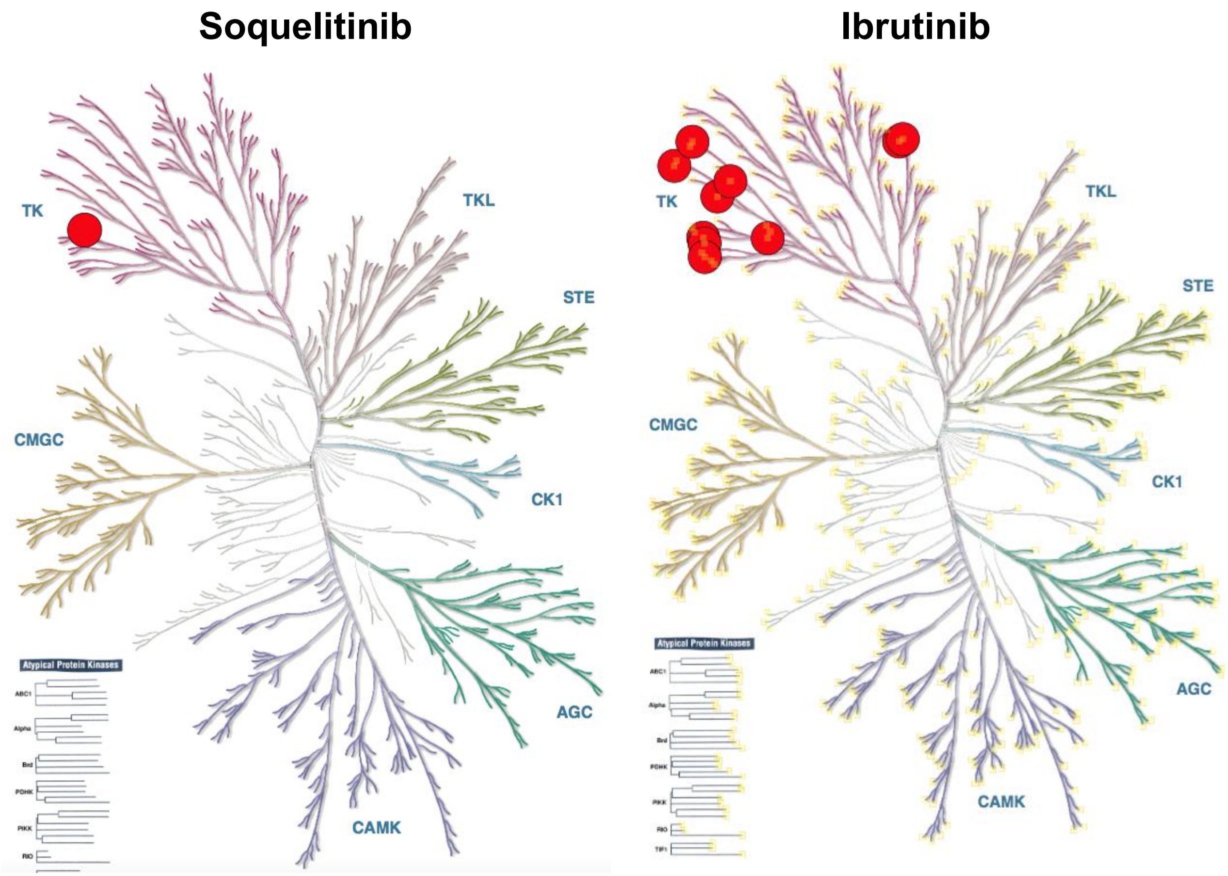
GATA3 Inhibition



Inhibition of PLCγ phosphorylation



Kinase Binding Comparison to Ibrutinib

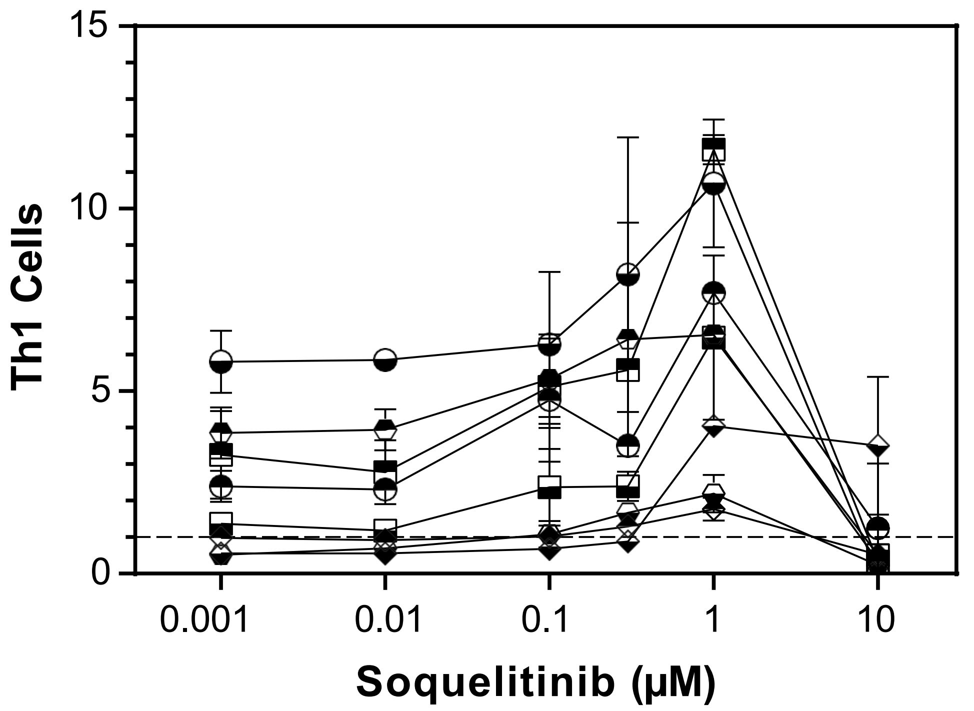


Drug Discovery 2024, 1:2

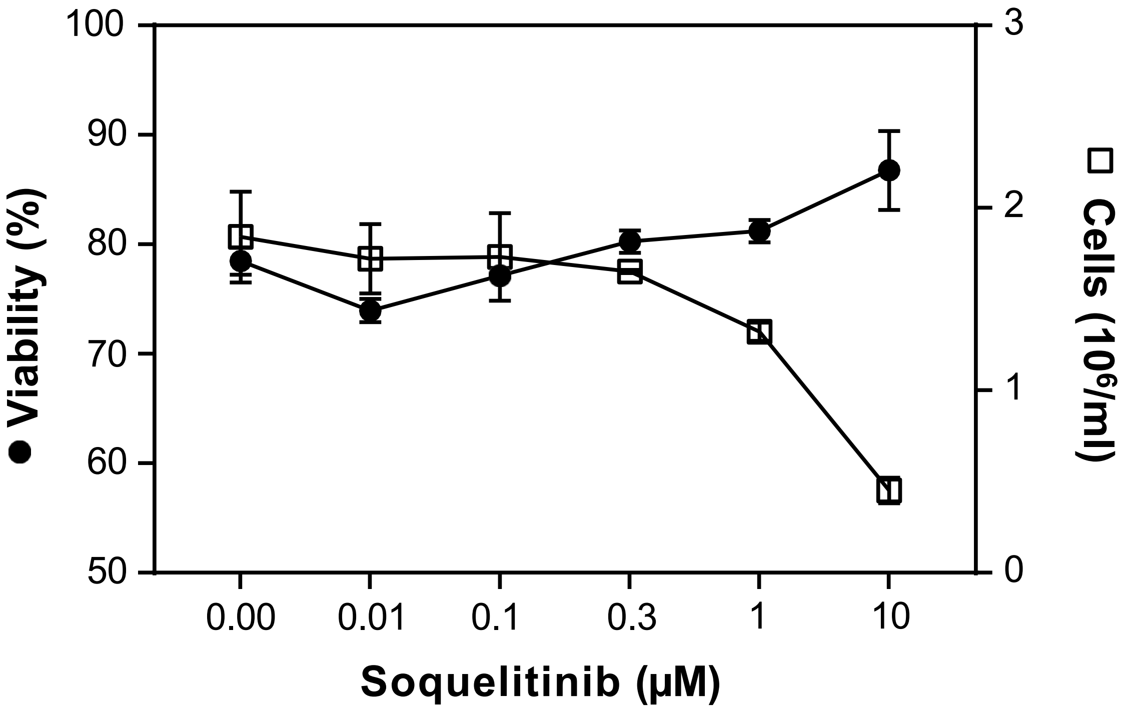
Induces Th1 skewing *in vitro* in Normal T Cells

Concentration dependent effects

Th1 cells (ratio IFNγ:IL-4) dose response effect



High concentrations block T cell proliferation in vitro



Blood T cells from healthy donors were stimulated in vitro with anti-CD3/CD28. Intracellular IFNγ and IL-4 were measured using flow cytometry; Th1 skewing was determined by IFNγ:IL-4 ratio. Effects on cell proliferation and viability were also determined. Concentrations >0.01 and <10 μM induce Th1 skewing with anti-proliferative effects seen ≥1 μM.

Phase I Clinical Trial Design

Objectives

- To evaluate safety
- To determine target occupancy and PK
- To characterize anti-tumor activity

Eligibility

PTCL including:

- **PTCL-NOS**
- **TFHL**
- **NKTCL**
- **CTCL**
- **ALCL (ALK^+)**
- **ATLL**

- Failed >2 lines
- Measurable disease

Dose Escalation

100 mg BID

↓

200 mg BID

↓

400 mg BID

↓

600 mg BID

- Determine PK and occupancy
- DLT
- Tumor response
- Immune markers

Expansion

200 mg BID
in select histologies

Focus on histology and characteristics

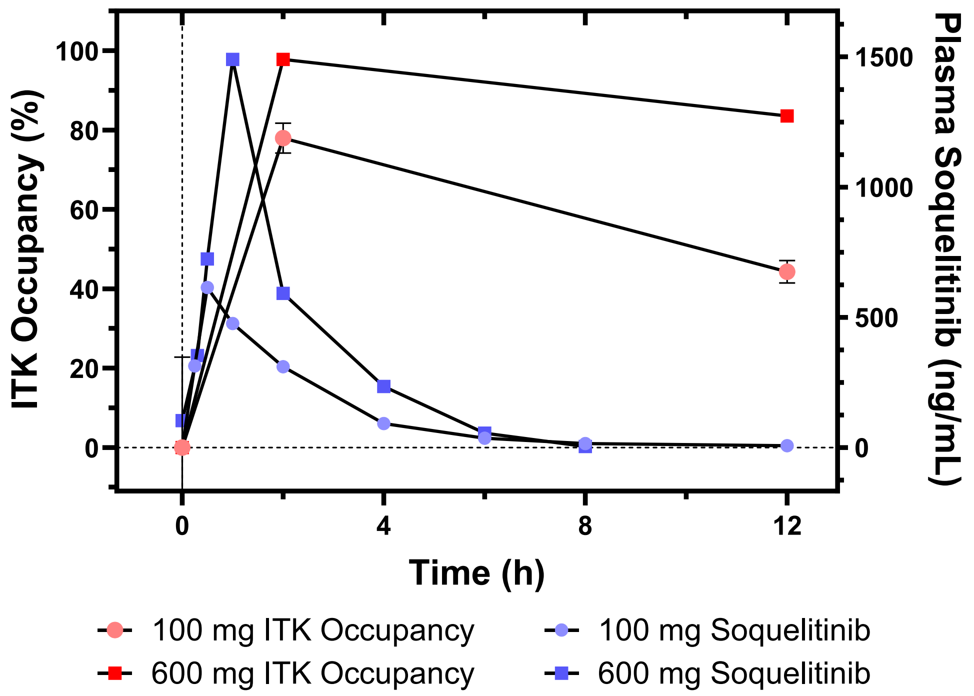
Patient Baseline Characteristics

Patient Characteristics	Dose Escalation (N=27)	Dose Expansion (N=48)	Total (N=75)
Age (yrs.), median (range)	62 (29, 80)	61 (21, 84)	62 (21, 84)
Gender, male N (%)	15 (55.6)	28 (58.3)	43 (57.3)
No. of prior therapies, median (range)	4 (2, 15)	3 (1, 18)	3 (1, 18)
Best response to most recent prior therapy, N (%)			
Objective response (CR or PR)	6 (22.2)	17 (35.4)	23 (30.6)
SD	5 (18.5)	7 (14.6)	12 (16.0)
PD	10 (37.0)	16 (33.3)	26 (34.7)
Not Evaluable/Unknown	6 (22.2)	8 (16.7)	14 (18.7)
Baseline ALC, N (%)			
<900	7 (25.9)	8 (16.7)	15 (20.0)
≥900	20 (74.1)	40 (83.3)	60 (80.0)
Histologies			
PTCL-NOS	11	21	32
AITL	6	6	12
ALCL	2	3	5
CTCL Sezary	5	2	7
CTCL Mycoses	2	10	12
Other	1	6	7

PK and ITK Target Occupancy

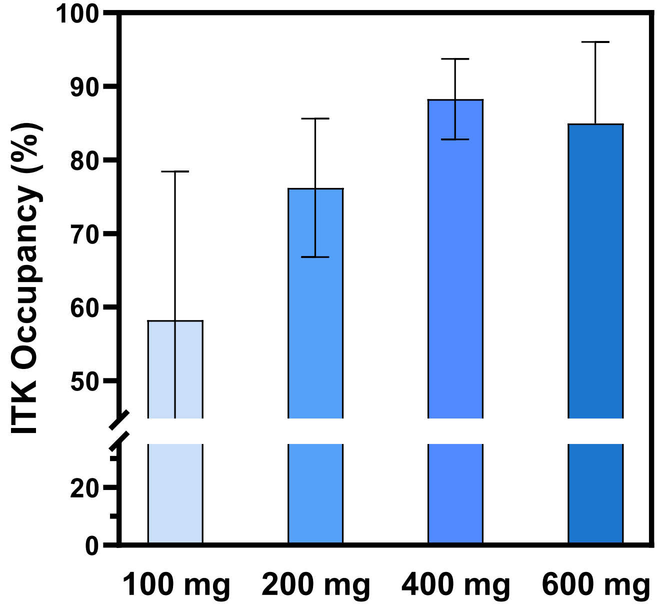
200mg provides durable target occupancy

Plasma Soquelitinib and ITK Occupancy in PBMCs Following a 100 mg or 600 mg QD Dose



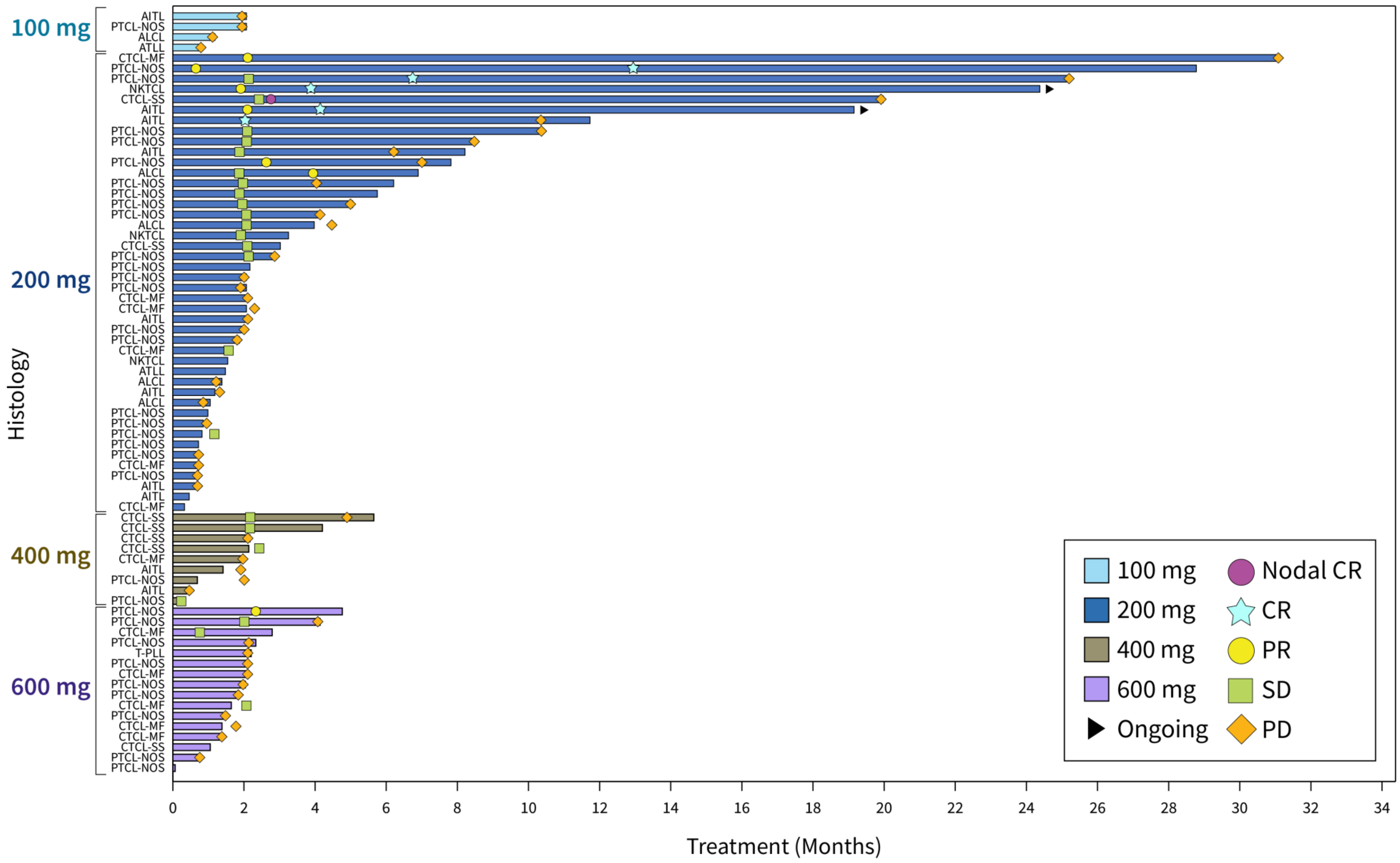
- Plasma PK shows clearance with $t_{1/2}$ = 2–4 hours
- Covalency produces prolonged receptor occupancy

Trough ITK Occupancy for Cycle 1 with BID Dosing of Soquelitinib

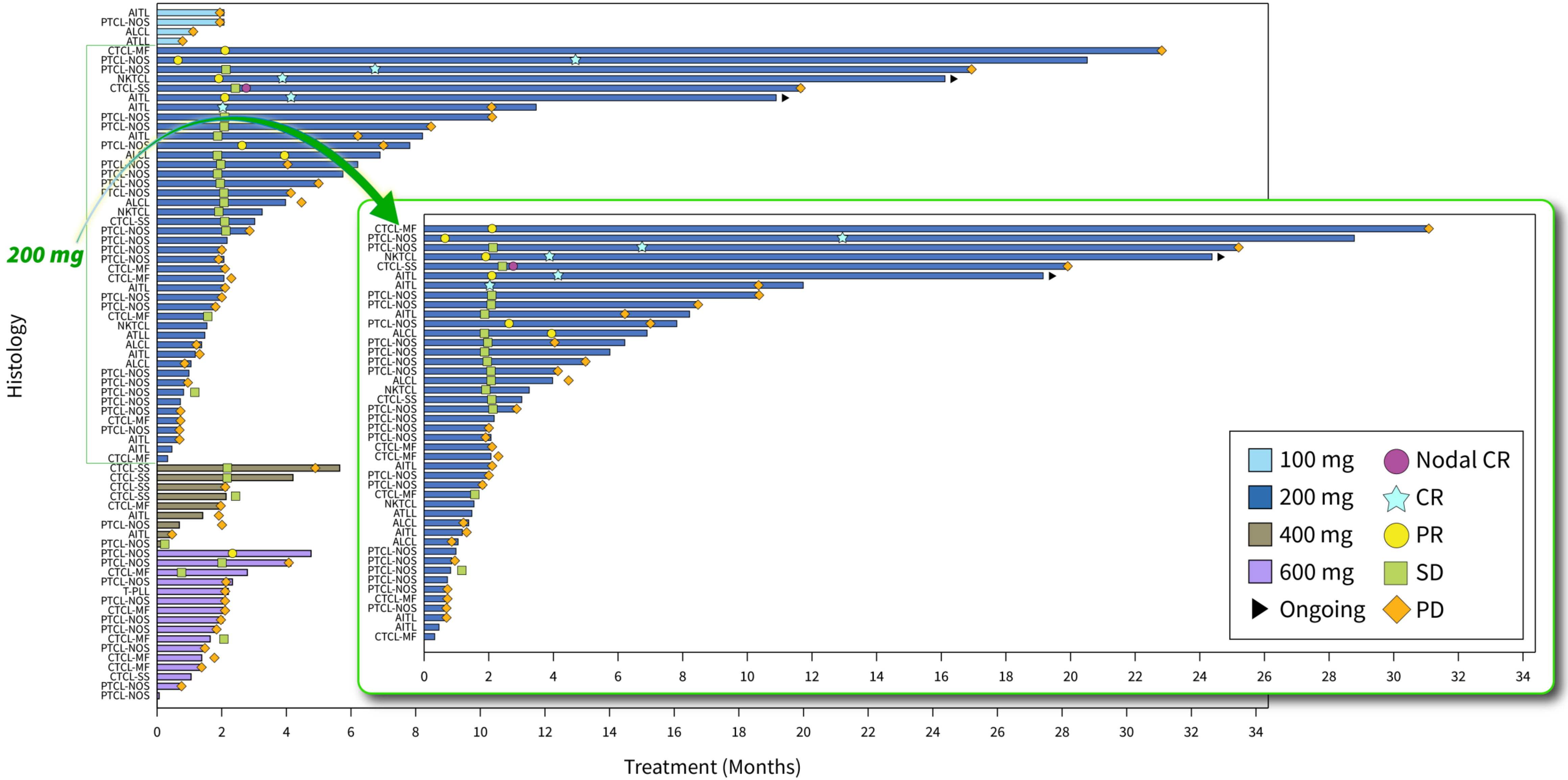


- ≥200 mg single dose achieves near complete trough occupancy

Anti-tumor Activity in Various Dosing Cohorts

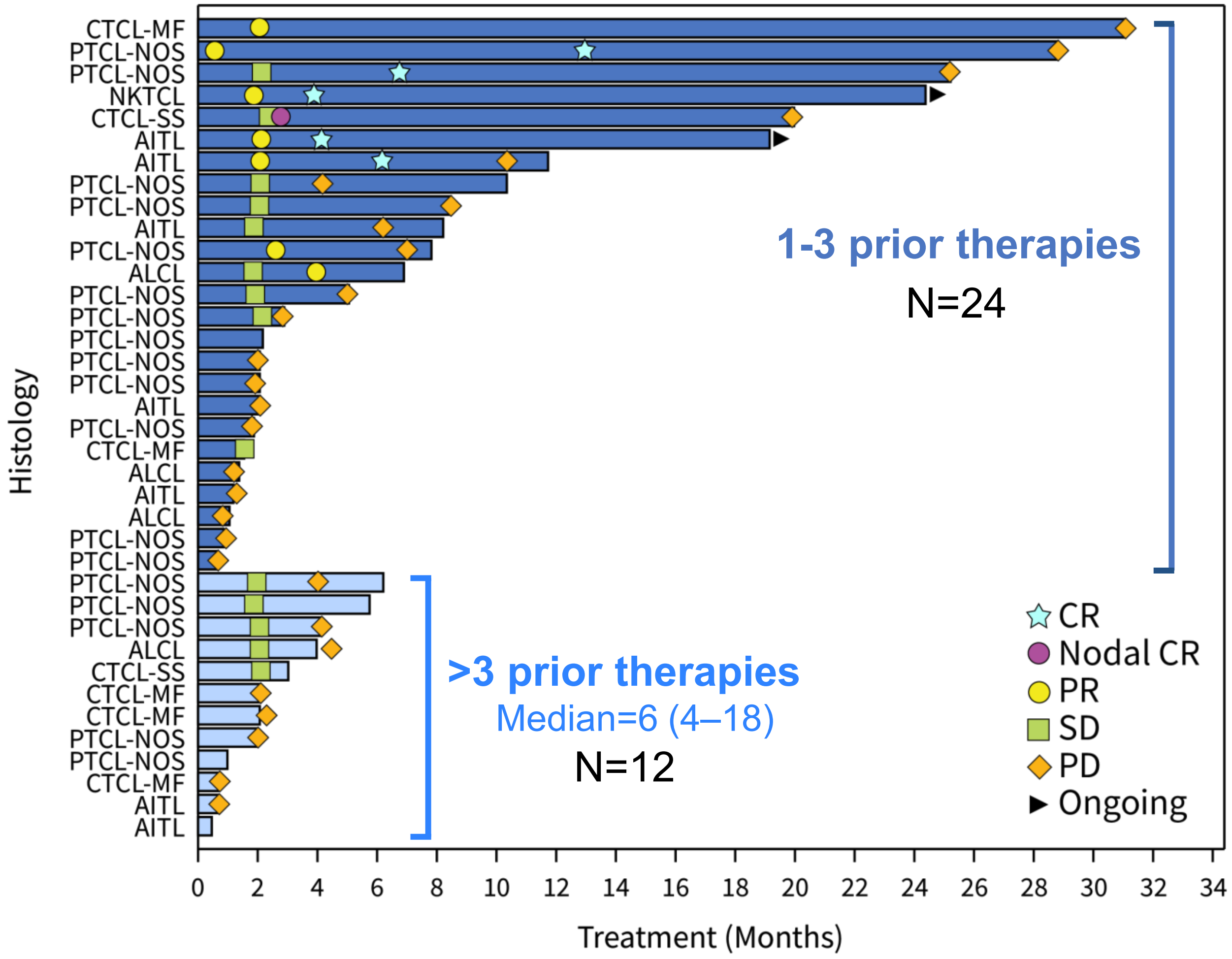


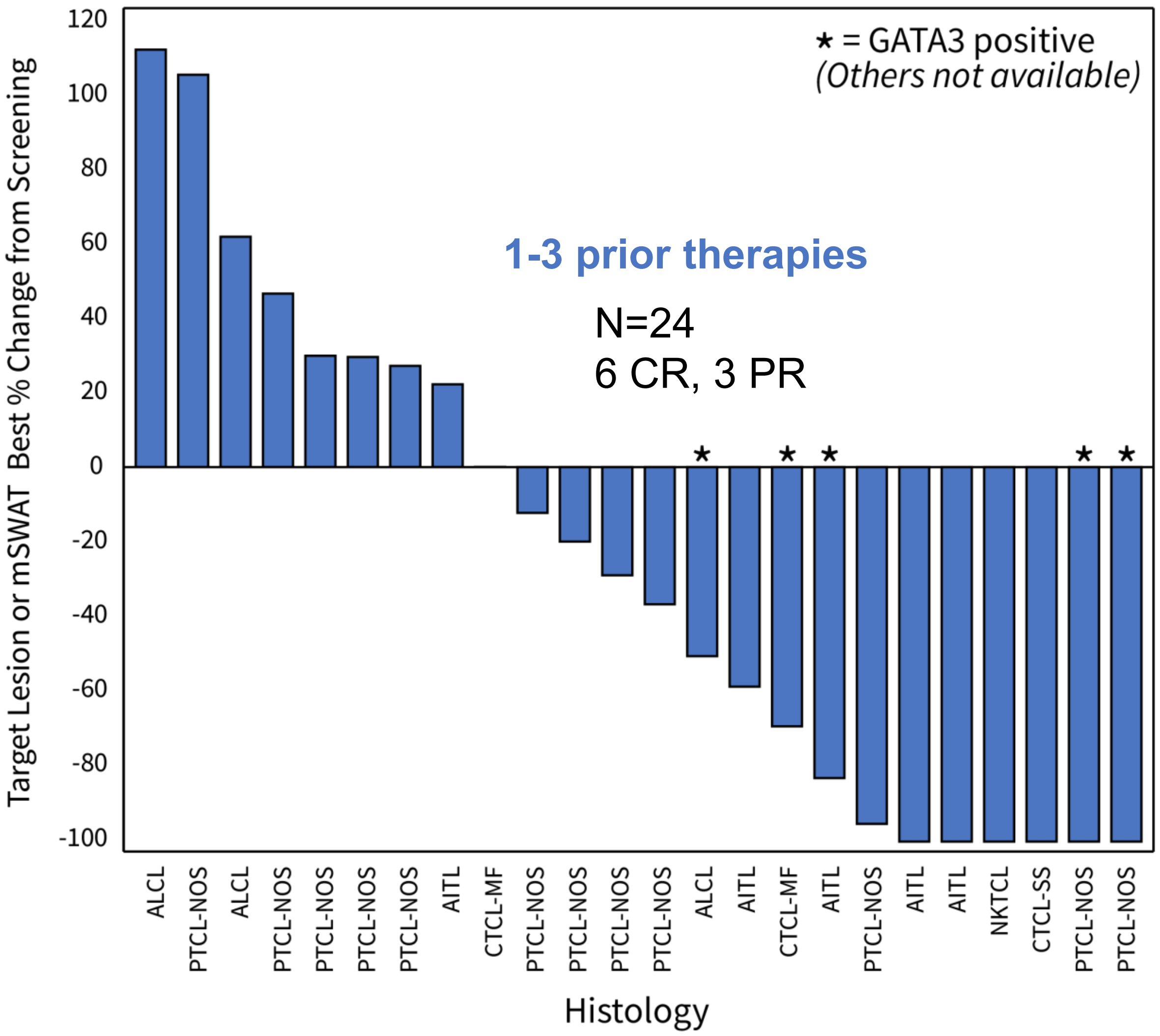
Anti-tumor Activity in 200 mg BID Cohort



Anti-tumor Activity in 200 mg BID Cohort

Role of baseline immunocompetence based on prior therapies



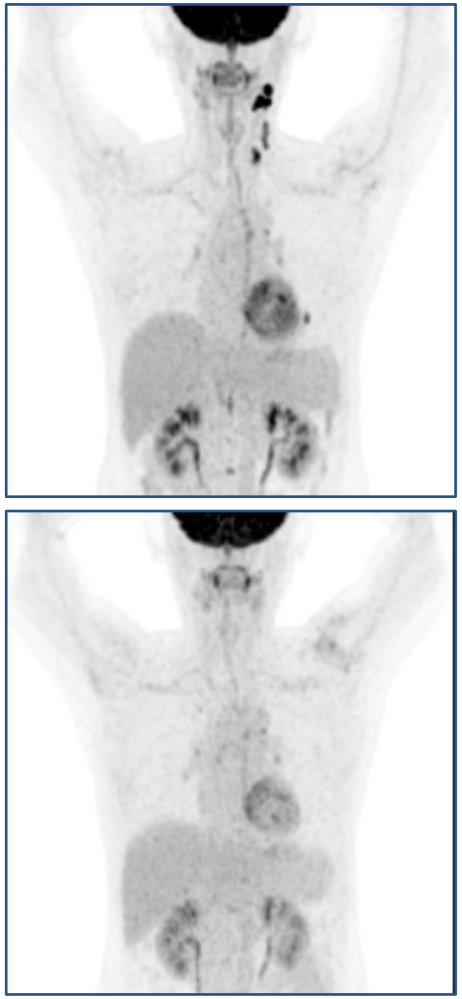


Anti-tumor Activity in Refractory PTCL, CTCL

PTCL-NOS

Failed CHOP, HDACi

PTCL-NOS



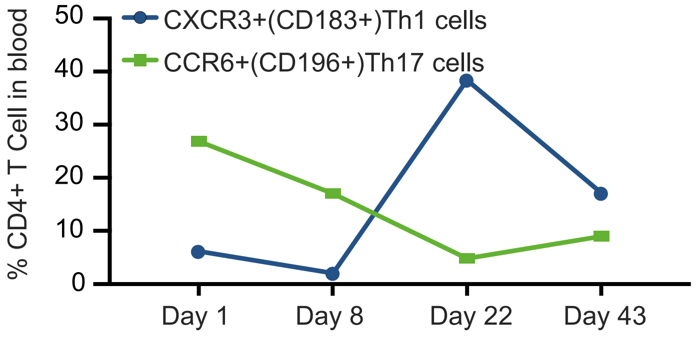
Failed CHOP and auto-BMT

CTCL-MF

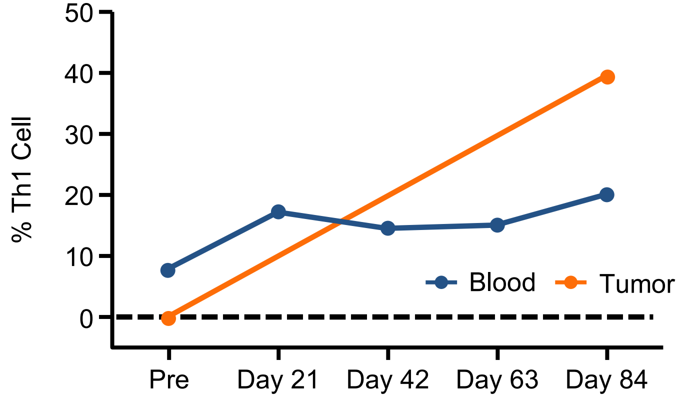
Transformed large cell

Soquelitinib Treatment Effects on Th1, Th2, Th17

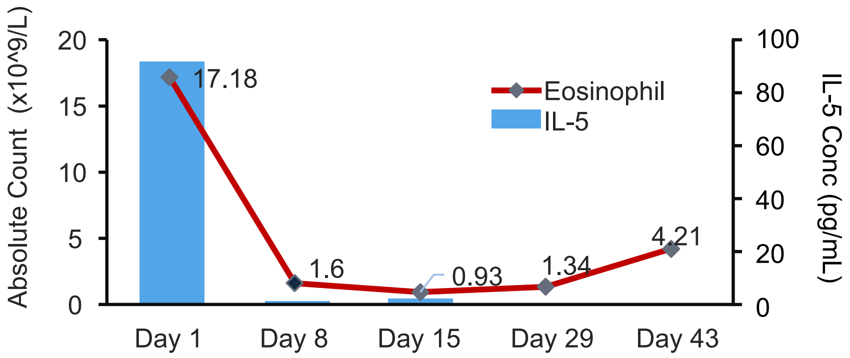
Frequency of Th1 & Th17 CD4 cells in Blood



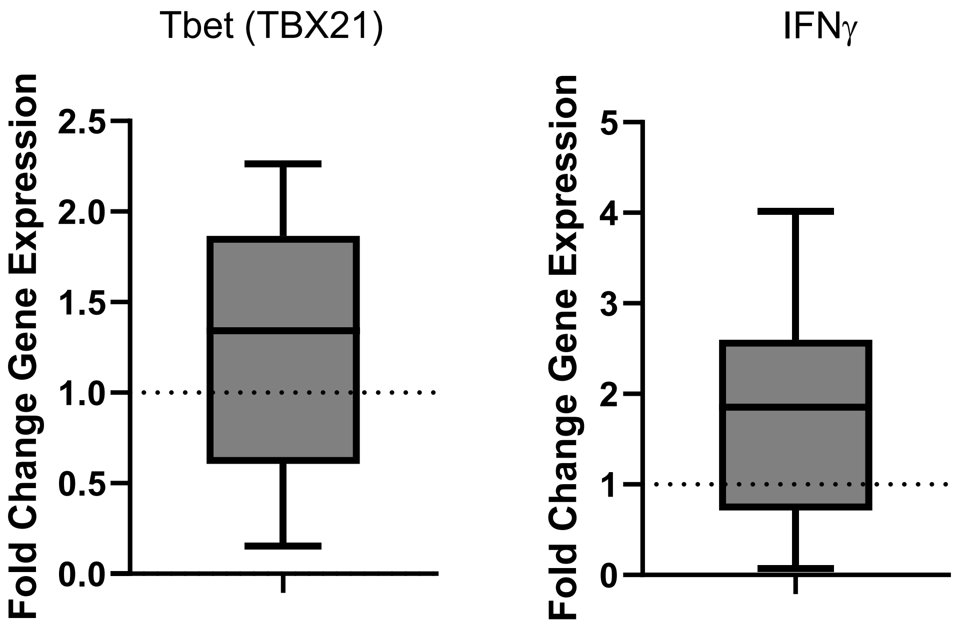
Th1 Effector Cells in Blood and Tumor During Soquelitinib Treatment



Effects on Eosinophils and Serum IL-5

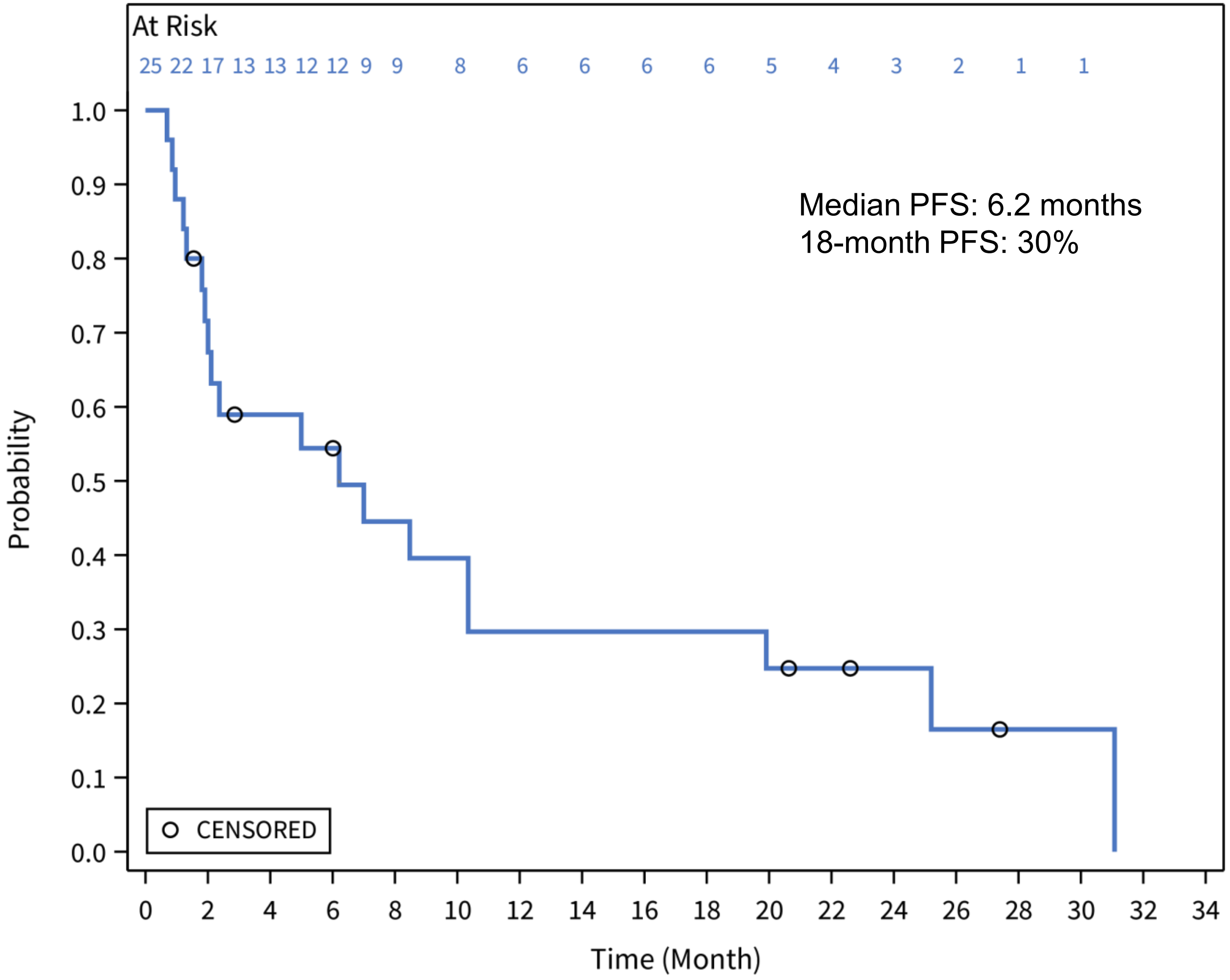


Increase in Th1 Gene Expression RNA seq of paired tumor biopsies (N=6, day 0 vs 8)

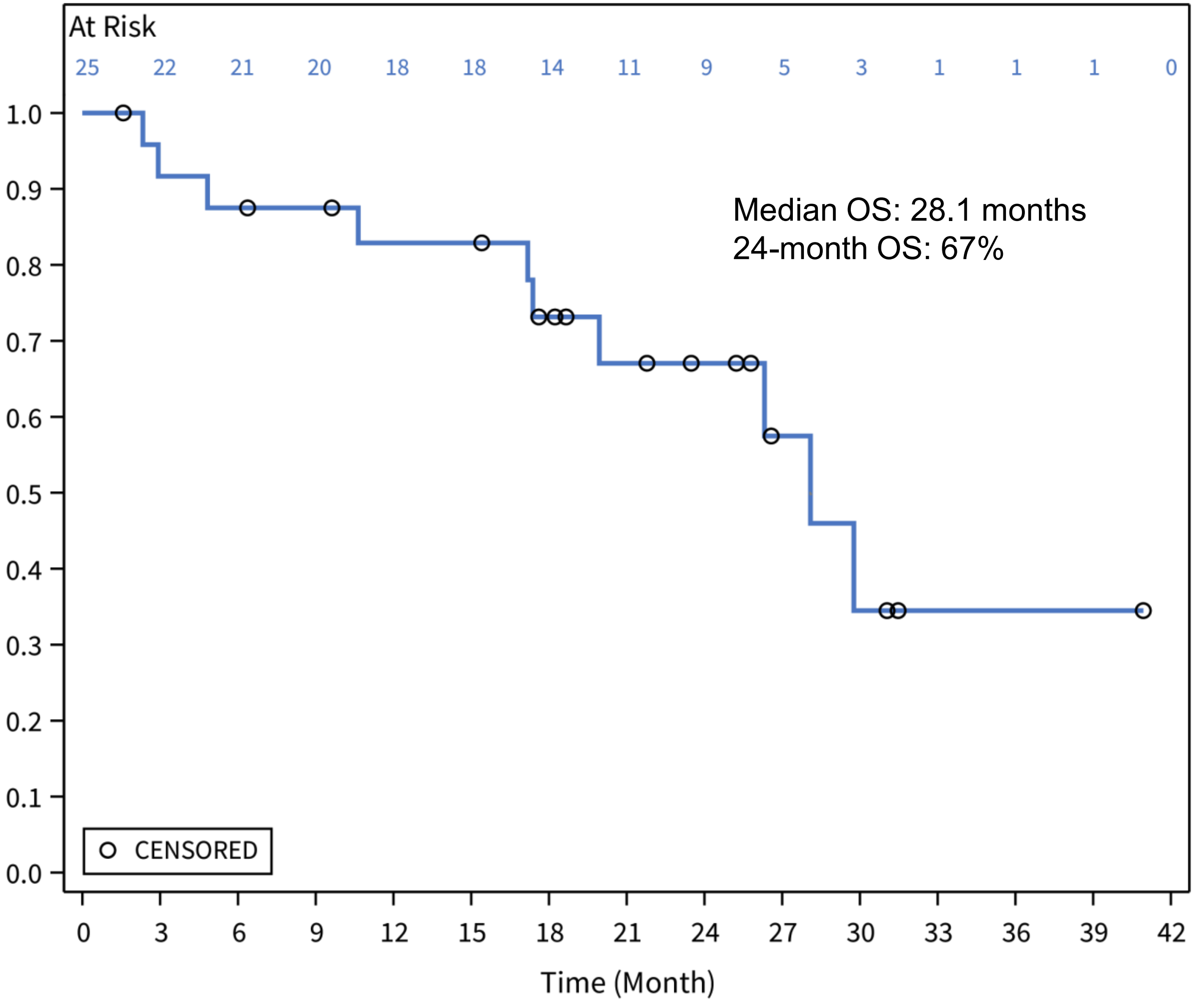


PFS & OS in 200 mg Cohort with 1-3 Prior Therapies

Progression-free Survival



Overall Survival



Adverse Event Summary

All causality grade ≥3 adverse events

Preferred Term	100 mg (N =4) n (%)	200 mg (N=46) n (%)	400 mg (N=9) n (%)	600 mg (N=16) n (%)	Total (N=75) n (%)
Subjects with any Grade ≥3 AE	**1 (25.0)**	**12 (26.1)**	**3 (33.3)**	**6 (37.5)**	**22 (29.3)**
Pruritus	0 (0.0)	2 (4.3)	1 (11.1)	1 (6.3)	4 (5.3)
Anemia	0 (0.0)	2 (4.3)	0 (0.0)	1 (6.3)	3 (4.0)
Neutropenia	0 (0.0)	3 (6.5)	0 (0.0)	0 (0.0)	3 (4.0)
Pyrexia	0 (0.0)	0 (0.0)	1 (2.2)	1 (6.3)	2 (2.7)
Hepatic failure	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (1.3)
Cardiac failure congestive	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (1.3)
Diarrhea	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (1.3)
Corona virus infection	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (1.3)
Infection	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (1.3)
Ophthalmic herpes simplex	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.3)
Sepsis	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.3)
White blood cell count decreased	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (1.3)
Hyponatremia	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (1.3)
Headache	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (1.3)
Status epilepticus	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (1.3)
Pneumonitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.3)
Cutaneous vasculitis	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (1.3)
Pain of skin	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Rash erythematous	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (1.3)
Urticaria	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (1.3)
Deep vein thrombosis	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (1.3)
Hypotension	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (1.3)

Summary

- Soquelitinib is an oral selective ITK inhibitor
- MOA appears based on induction of host anti-tumor response or possibly other effects on tumor microenvironment
- Potential direct effect on tumor cells
- Doses up to 600 mg BID well tolerated with no DLTs observed
- Durable objective responses seen in PTCL, TFHL, NKTCL, ALCL and CTCL patients with adequate baseline immunocompetence
- Randomized control phase 3 comparing soquelitinib to either belinostat or pralatrexate is enrolling
- Other trials in immune/inflammatory diseases ongoing