Memorial Sloan Kettering Cancer Center

What from the basket of BTK and PI3K inhibitors?

Steven M. Horwitz M.D.
Associate Attending
Lymphoma Service
Memorial Sloan Kettering Cancer Center

Associate Professor of Medicine
Weill Cornell Medical College

Memorial Sloan Kettering Cancer Center

Duvelisib (IPI-145), a Phosphoinositide-3-Kinase-δ,γ Inhibitor, Shows Activity in Patients with Relapsed/Refractory T-Cell Lymphoma

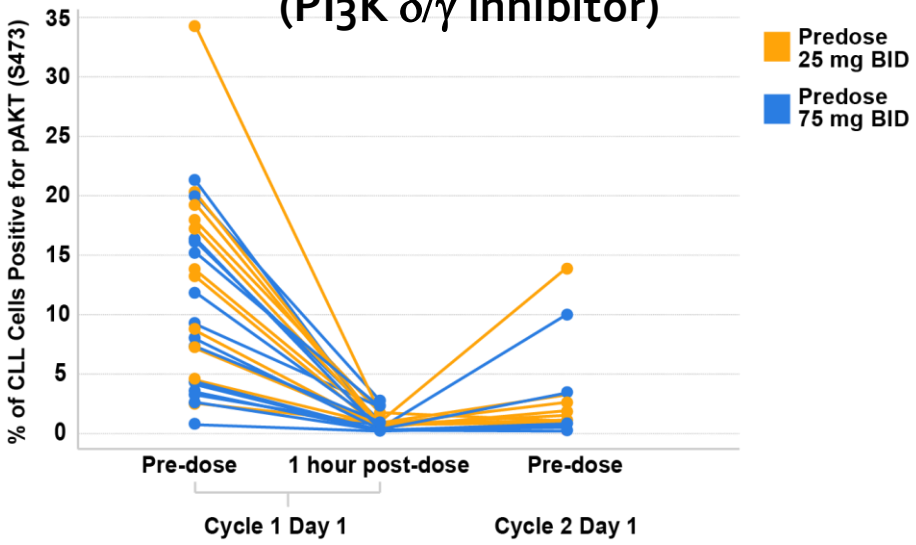
Steven Horwitz[1]; Pierluigi Porcu[2]; Ian Flinn[3]; Brad Kahl[4]; Howard Stern[5]; Mark Douglas[5]; Kerstin Allen[5]; Patrick Kelly[5]; and Francine Foss[6]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]The Ohio State University; [3]Sarah Cannon Research Institute, Nashville, TN, USA; [4]University of Wisconsin, Madison, WI, USA; [5]Infinity Pharmaceuticals, Inc., Cambridge, MA, USA; [6]Yale University Cancer Center, New Haven, CT, USA.

PI3K in B-cell and T-cell Malignancies

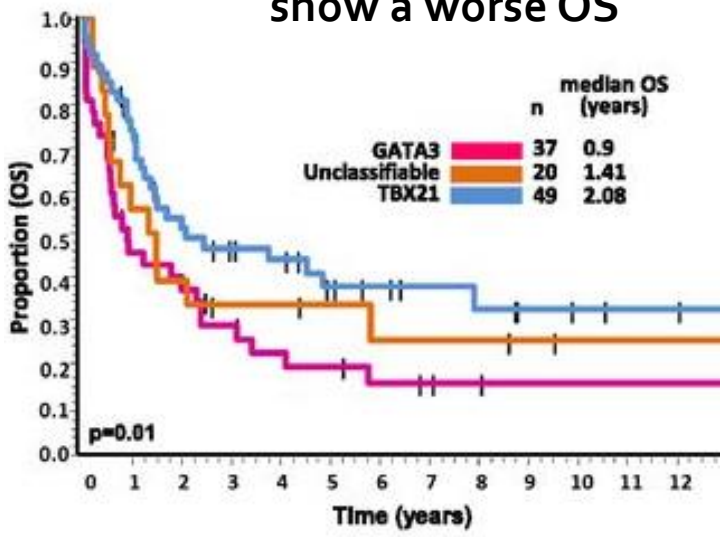
- Antigen receptors, costimulatory molecules, cytokine receptors, and chemokine receptors can all trigger PI3K activation leading to AKT phosphorylation.
- Transcriptional profiling of PTCL-NOS cases identifies distinct subgroups based on high expression of either GATA3 or TBX21 (**t**-bet)
- GATA3-high tumors are enriched for PI3K-induced transcriptional signatures3.

Inhibition of AKT phosphorylation in CLL Cells from patients treated with duvelisib (PI3K δ/γ inhibitor)



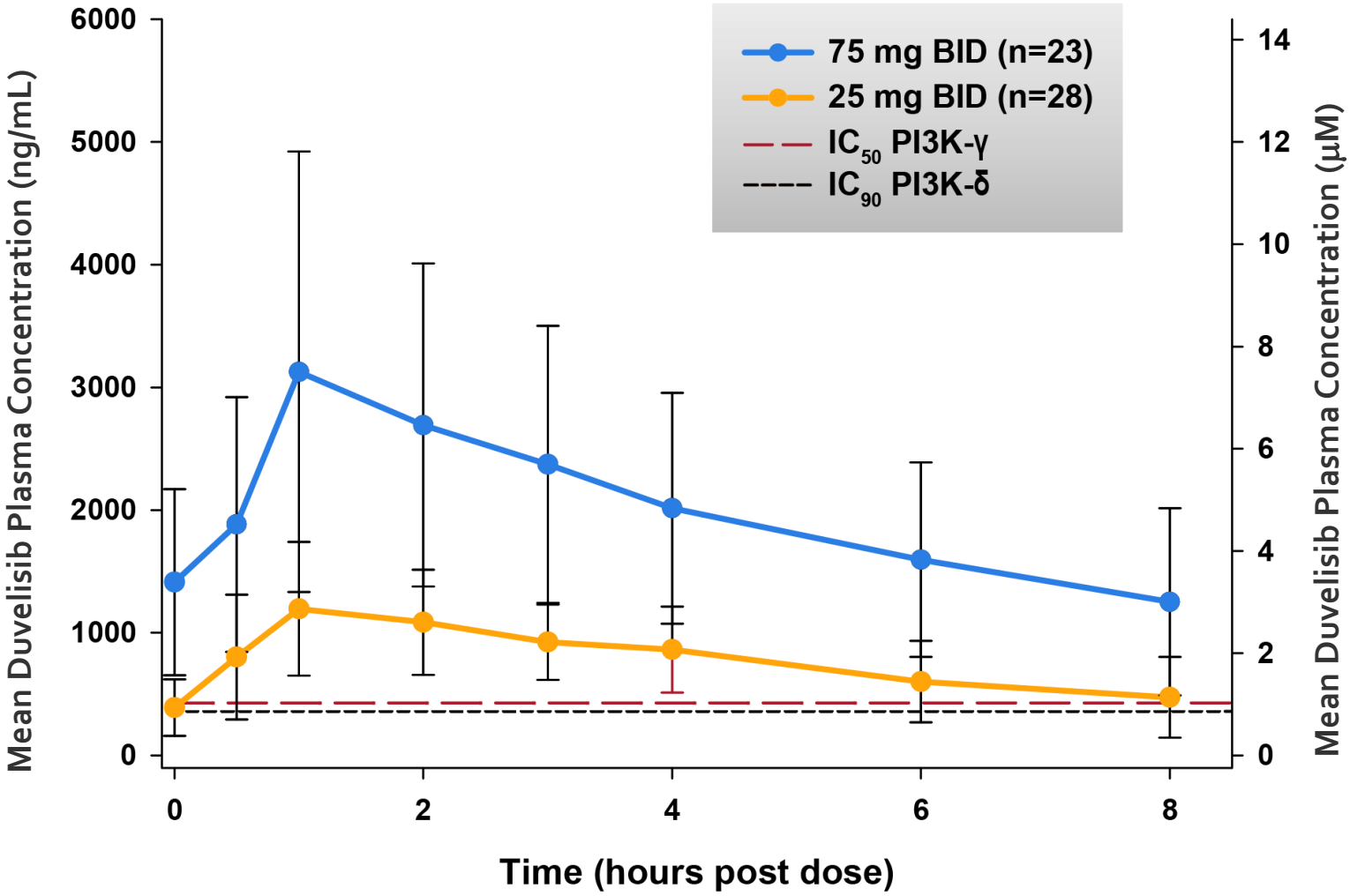
Patel et al., ASCO 2013 & Douglas et al. ASH 2013

PTCL: Gata3 high tumors show a worse OS



Iqbal J et al. Blood 2014;123:2915-2923

Duvelisib (IPI-145) is an Oral PI3K-δ,γ Inhibitor
Coverage of Both PI3K-δ and PI3K-γ at ≥ 25 mg BID



Patel et al., ASCO 2013

IPI-145-02: Phase 1 Study of Duvelisib in Advanced Hematologic Malignancies

- T-cell Lymphoma (TCL) patients completed enrollment in August 2013
  - Duvelisib administered orally BID in 28-day cycles to 35 TCL patients
  - 25 mg (n=1), 50 mg (n=1), 60 mg (n=4), 75 mg (MTD; n=27), 100 mg (n=2)
- Key Study Endpoints
  - Pharmacodynamics: changes in cytokines, chemokines, and matrix metalloproteinases (MMPs) in patient serum, and early PET (Cycle 1 Day 22)
  - Tumor response based on standard disease-specific criteria
    - Systemic/Peripheral TCL (PTCL) = IWG criteria (Cheson et al, 2007)
    - Cutaneous TCL (CTCL) = mSWAT assessment (Olsen et al, 2011)
  - Safety: adverse events (AEs) per CTCAE version 4.03

Patient Characteristics

Characteristics	PTCL N=16	CTCL N=19
Disease subtype	AITCL=3, SPTCL=3, ALCL=2, EATCL=1, NKTCL=1, PTCL NOS=6	MF=9, MF-LCT=4, Sézary=5, pcALCL=1
Age (years), median (range)	70 (34, 86)	64 (48, 81)
Female, n (%)	8 (50)	11 (58)
Prior Systemic Therapies, median (range)	2.5 (1, 7)	6 (2, 11)
Months from Last Therapy to First Dose, median (range)	1.6 (0.4, 24.8)	0.7 (0.2, 2.8)
ECOG Score 0 / 1 / 2 / missing, n	1 / 10 / 4 / 1	4 / 13 / 2 / 0
IPI Score at Screening, n (%)		
0	1 (6)	2/18 (11)
1-2	5 (31)	9/18 (50)
3-5	10 (63)	7/18 (39)

MF = mycosis fungoides; LCT = large-cell transformed; AITCL= angioimmunoblastic TCL; SPTCL= subcutaneous panniculitic TCL; pcALCL= primary cutaneous anaplastic large cell lymphoma; EATCL= enteropathy-associated TCL; NKTCL= natural killer TCL; NOS= not otherwise specified.

Patient Disposition

Disposition	PTCL N=16	CTCL N=19
Time on Treatment (months), median (range)	3.4 (0.4, 17.3)	2.9 (0.5, 13.8)
On Treatment, n (%)	1 (6)	0
Discontinued Treatment, n (%)	15 (94)	19 (100)
Disease Progression	7 (44)	10 (53)
Adverse Event	6 (38)	7 (37)
Death	1 (6)	1 (5)
Subject Withdrawal	0	1 (5)
Other	1 (6)	0

Clinical Activity in TCL

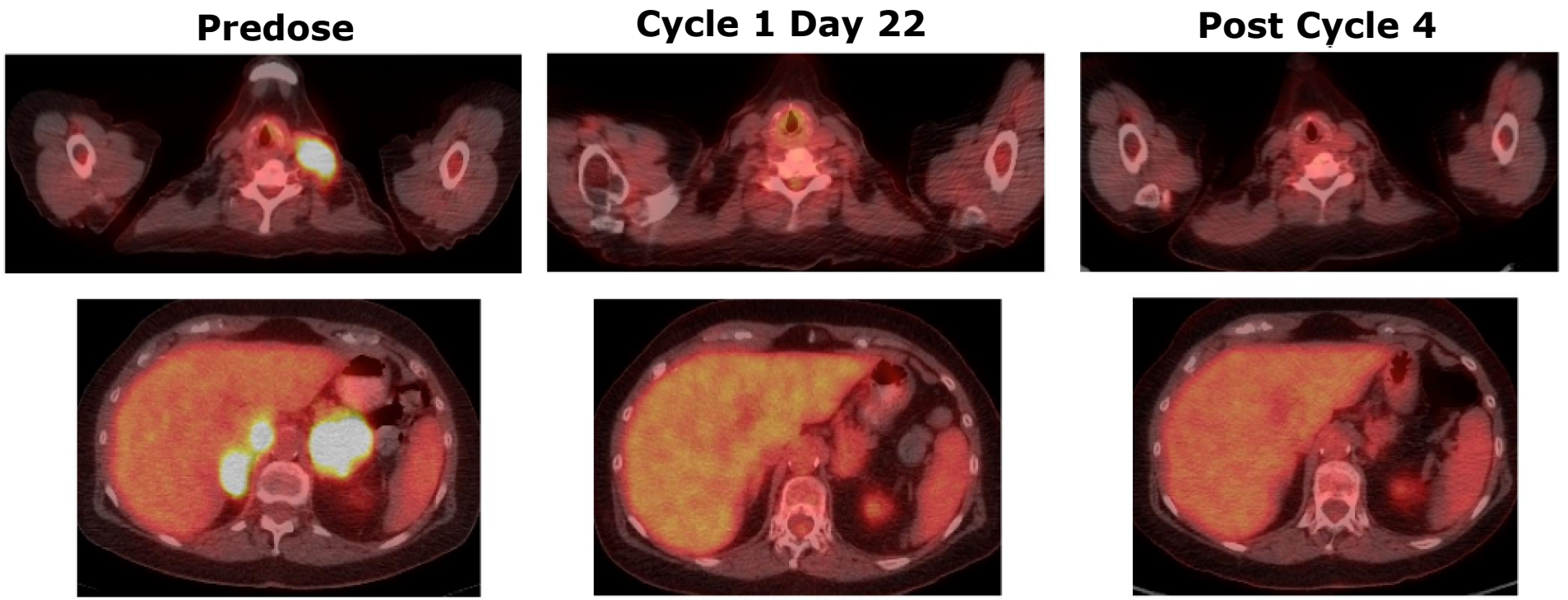
Population		Best Response, n (%)					Median Time to Response, months (Range)
	n	CR	PR	SD	PD	ORR	
All TCL	33	2 (6)	12 (36)	7 (21)	12 (36)	**14 (42)**	1.9 (1.5, 3.8)
PTCL	15	2 (13)	6 (40)	1 (7)	6 (40)	**8 (53)**	1.9 (1.5, 3.5)
CTCL	18	0	6 (33)	6 (33)	6 (33)	**6 (33)**	2.4 (1.6, 3.8)

Includes evaluable patients = at least 1 on-treatment response assessment or PD without assessment
CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease
ORR = CR + PR

- Clinical activity observed across PTCL and CTCL subtypes
  - PTCL: CRs in 1 EATCL and 1 PTCL NOS
    PRs in 2 AITCL, 2 SPTCL, 1 PTCL NOS, 1 ALCL (ALK-negative)
  - CTCL: PRs in 4 MF, 1 Sézary syndrome, and 1 MF-LCT

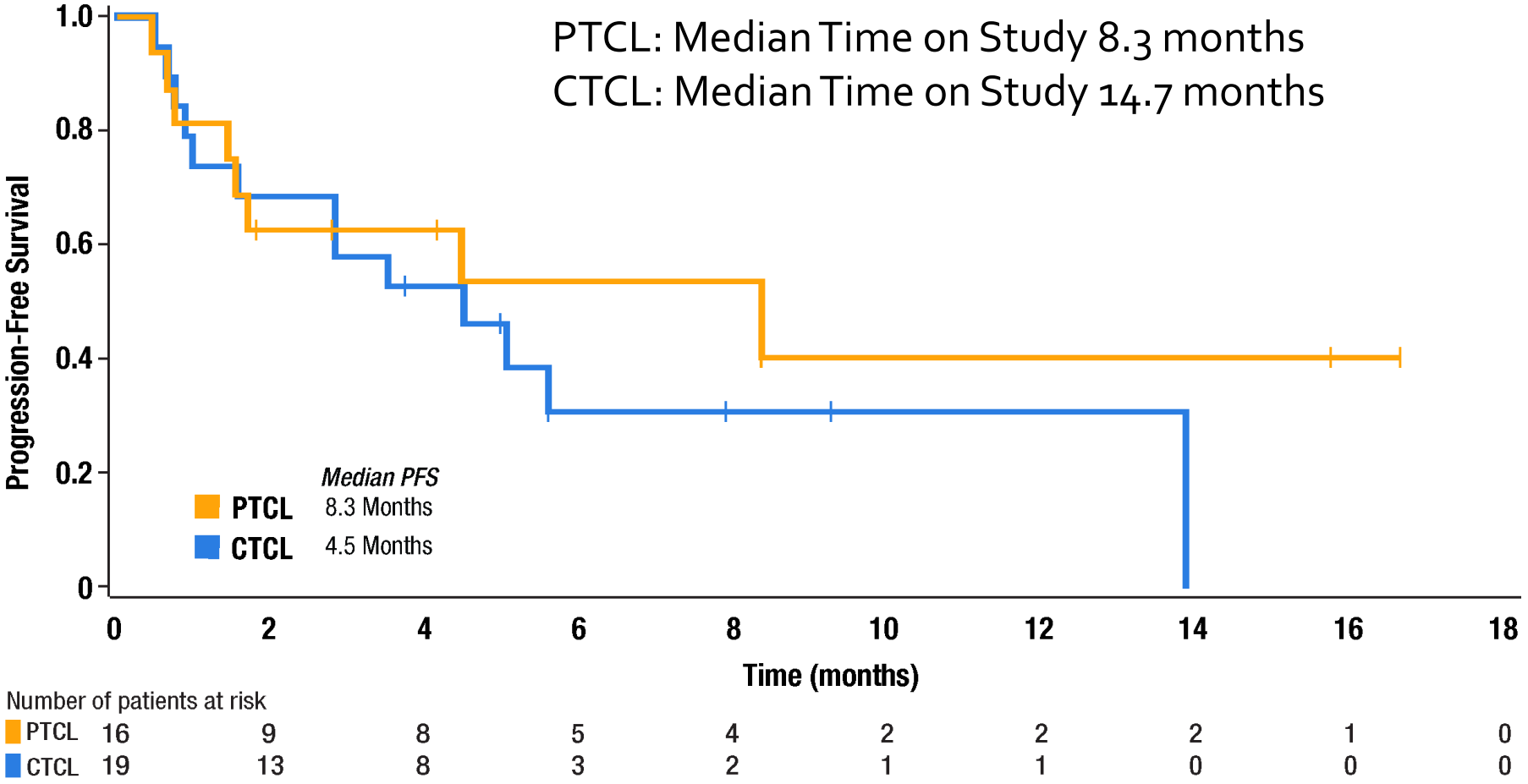
Early Pharmacodynamic Response in PET Avid Disease May Predict Best Clinical Response

- Below: PET/CT scans from a 75 year-old woman with relapsed AITCL. Prior therapies: rituximab (ITP), CHOP, pralatrexate, vorinostat, brentuximab vedotin



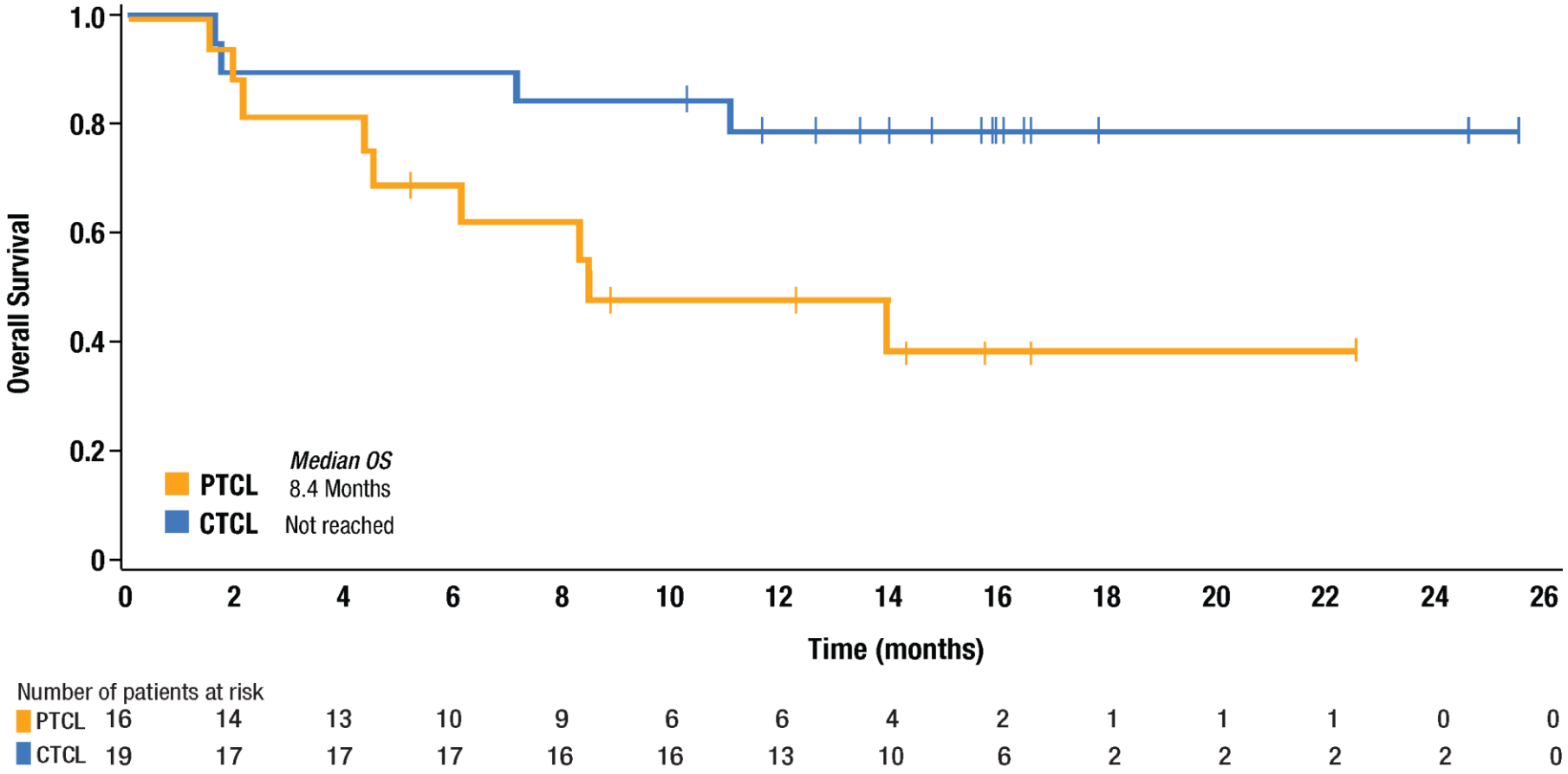
- 10 patients evaluated with PET (PET-CT) at Cycle 1 Day 22, 6 with a reduction in SUV, 4 with an increase in SUV
- 83% (5/6) with PET response had a subsequent clinical response (CR or PR)
- 100% (4/4) without PET response had disease progression

Progression-Free Survival



- PTCL: Median PFS 8.3 months, Median DOR -NR
- CTCL: Median PFS 4.5 months, Median DOR-8.1 months

Overall Survival



- Median OS for PTCL 8.4 months
- Median OS for CTCL not reached
  - 79 % survival at 24 months

Safety: AEs ≥ 20% All TCL Patients (N=35)

AE (regardless of relationship)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
ALT or AST increased	19 (54)	11 (31)	2 (6)
Pyrexia	13 (37)	0	0
Fatigue	12 (34)	3 (9)	0
Cough	11 (31)	0	0
Diarrhea	11 (31)	1 (3)	0
Rash (combined terms)	10 (29)	6 (17)	0
Headache	8 (23)	0	0
Weight decreased	8 (23)	0	0
Pneumonia (combined terms)	8 (23)	5 (14)	1 (3)
Nausea	7 (20)	0	0

Pneumonia (combined) = all preferred terms of pulmonary inflammation due to infectious or noninfectious etiologies
Rash (combined) = all preferred terms associated with rash within Skin & Subcutaneous Tissue Disorders SOC

- Most AEs were Grade 1 or 2
- Most common ≥ Grade 3 AEs: ALT/AST increased, rash, and pneumonia

SAEs and AEs Leading to Discontinuation

SAEs > 1 Patient

	Overall TCL N=35 n (%)
Pneumonia (combined)	8 (23)
Diarrhea	3 (9)
Pyrexia	3 (9)
Colitis	2 (6)
Dehydration	2 (6)
Vomiting	2 (6)
Acute renal failure	2 (6)

Pneumonia combined = all preferred terms of pulmonary inflammation due to infectious and non-infectious etiologies

AEs Leading to Discontinuation

	Overall TCL N=35 n (%)
ALT/AST	5 (14)
Blood alkaline phosphatase	1 (3)
C. difficile positive	1 (3)
Colitis	1 (3)
Cough	1 (3)
Diarrhea	1 (3)
Neutropenia	1 (3)
Rhinovirus infection	1 (3)
Staphylococcal sepsis	1 (3)

- SAEs were reported in 18 (51%) of TCL patients
- There were 3 deaths on treatment (< 30 days from last dose)
  - 1 disease progression, 1 declined supportive therapy, and 1 HSV pneumonia

Conclusions

Efficacy

- Clinical activity observed in relapsed/refractory TCL
  - ORR: PTCL = 53%, CTCL= 33%
  - PFS and OS suggests potential for therapeutic benefit in this high-risk TCL population

Safety

- AEs were generally grade 1-2, reversible, and clinically manageable

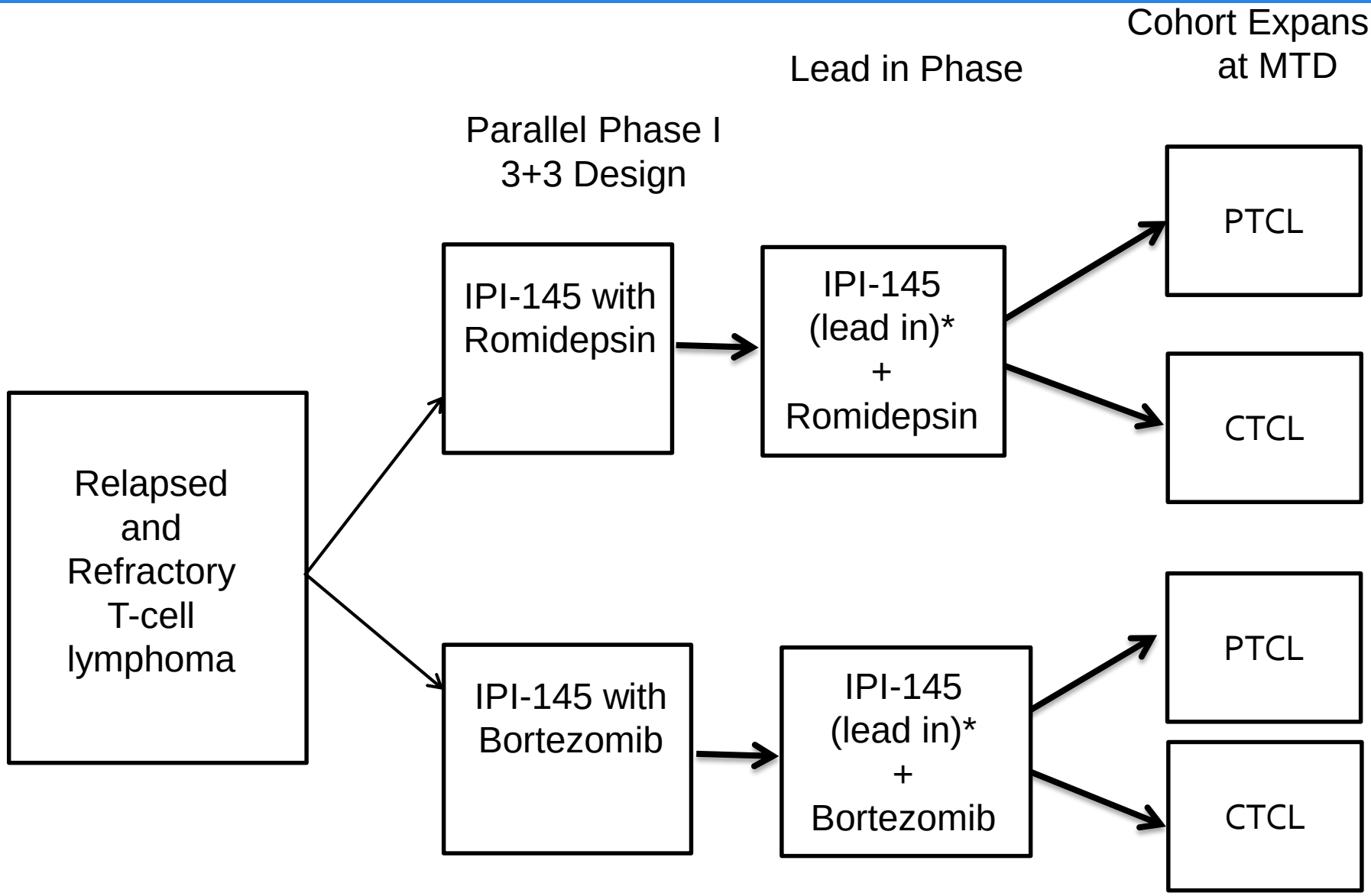
Pharmacodynamics

- Pharmacodynamic response by PET at Cycle 1 Day 22 may predict clinical response

Next Steps

- Results support further evaluation of duvelisib in TCL to determine the optimal dose and to evaluate the potential of combinations to optimize efficacy

Phase I Combination of Duvelisib + Romidepsin or Bortezomib (Proposed collab w/MSKCC, DFCI, Stanford,BCCA)



Preliminary Phase II Results of Copanlisib (Bay 80-6946) in R/R NHL/CLL: Study Schema

Copanlisib (BAY 80-6946): Potent and reversible class I PI3K-δ,α inhibitor

Key eligibility criteria
- R/R indolent or aggressive NHL/CLL
- ≥ 2 prior treatments

→ BAY 80-6946
Starting dose 0.8 mg/kg (max 65 mg) 1h IV infusion, d1, 8, 15; q28d until PD or toxicity

→ Responses assessed every 2 cycles (IWG 1999/ IWCLL 2008)

	FL (n = 16)	CLL (n = 14)	DLBCL (n = 15)	MCL (n = 7)	Transformed (n = 6)	T-cell (n = 4)
ORR	40%	43%	13%	71%	17%	50%
CR/CRu	1	–	2	1	–	1
PR	5	6	–	4	1	1
SD	9	6	3	–	–	–
PD	–	1	10	2	5	2
N/A	1	1	–	–	–	–

Dreyling et al. ASH 2013, Abstract 87.

What about BTK inhibition?
Why Ibrutinib in T-cell Lymphoma?

- Ibrutinib is an irreversible inhibitor of Interleukin-2-Inducible T-cell kinase (ITK)
- ITK-Role in T-cell proliferation, differentiation (Th2 vs. Th1), and activation

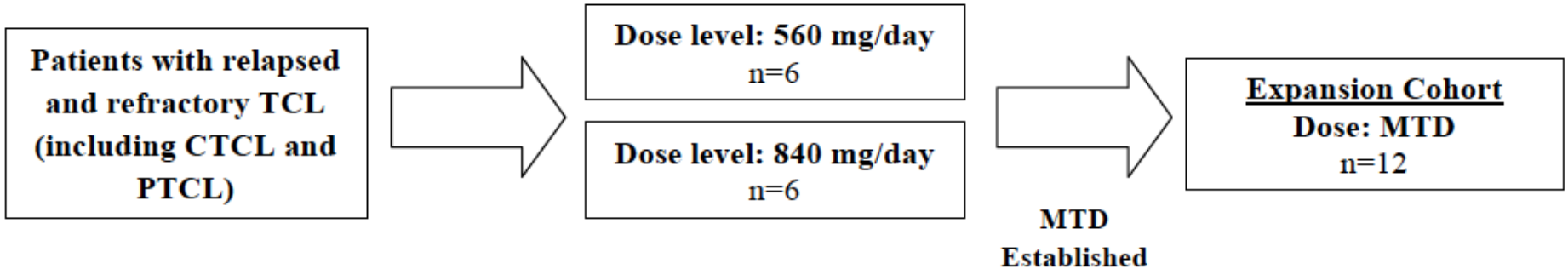
Hypothesis:

- Downregulate pro-survival signaling through the TCR pathway
- Augment immune surveillance of malignant T-cells with increased cytotoxic Th1 versus Th2 CD_4 effector T-cells

Schwartzberg *et al.* Nat Rev Immunol 5:284-95, 2005.
Dubovsky JA *et al*. Blood 2013; 122(15): 2539-2549

Phase I trial of Ibrutinib in T-cell Lymphoma

- Dose-escalation study to evaluate MTD/Prelim efficacy
- Multi-center: MSKCC (PI: A. Kumar) and Ohio State (P.Porcu)



Correlates

- Effect of ibrutinib on helper T-cell polarization (Th1 vs. Th2)
  - Serum cytokine levels
  - Gene-expression profiling using NanoString technology
  - GATA3 and TBX21 protein expression by IHC
- Effect of ibrutinib therapy on ITK signaling pathway
  - Assess phosphorylation of PLC-γ using phosphoflow

What from the basket of BTK and PI3K inhibitors? Conclusions

- PI3K inhibitors
  - Active in TCL (preliminary ORR ~50%)
  - Define role
    - Most responsive subsets
    - Predictive biomarkers
  - Partner in combination studies-strong rationale
  - Better regimens for relapse, maintenance
  - ? Upfront
- BTK (ITK) inhibition
  - We will see-I'll let you know, hopefully soon