DUVELISIB (IPI-145)

Phosphoinositide-3-kinase-δ,γ Inhibitor

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Creating a cancer-free world. One person, one discovery at a time.

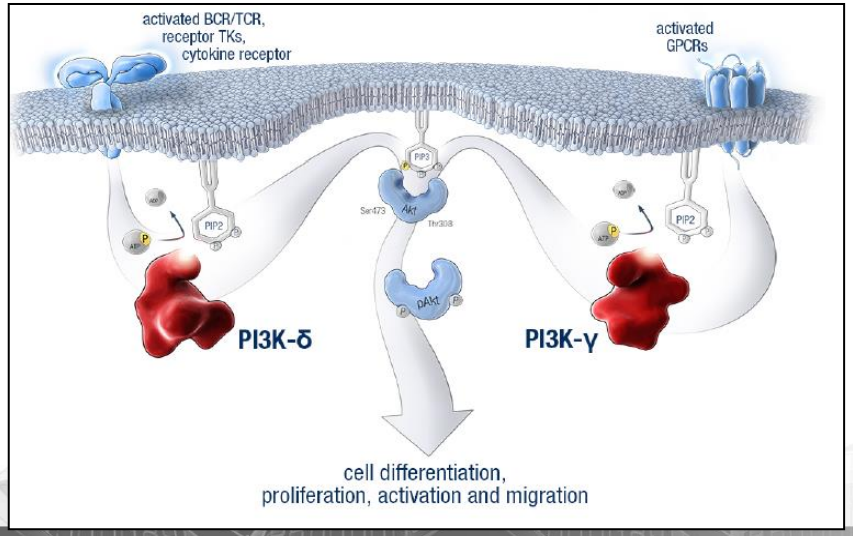


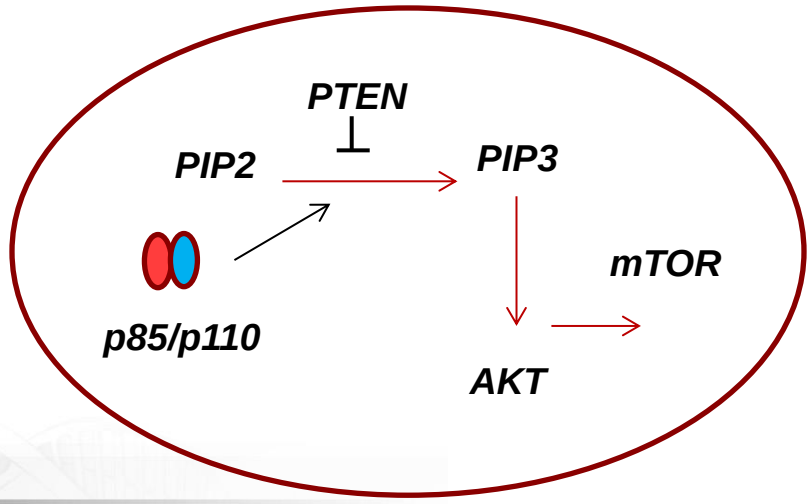

CONFLICTS OF INTEREST

- Current Research Funding from:
  - Innate Pharma
  - Miragen
  - Celgene
  - Kura Oncology
  - Galderma
  - Seattle Genetics
  - Kiowa Kirin

PI3K isoforms composition, expression in B-cells and T-cells, and signaling

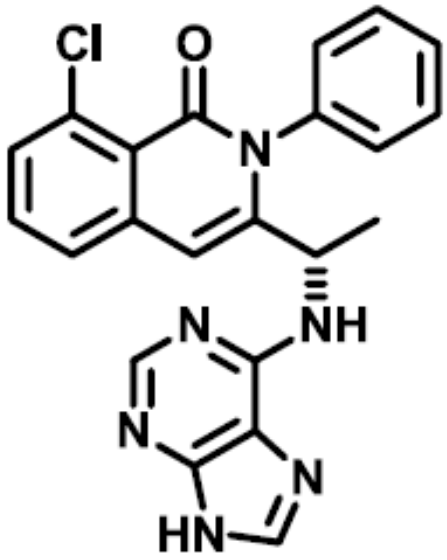
	Catalytic/Regulatory Units			
	p110α/p85	**p110β/p85**	**p110δ/p85**	**p110γ p101**
Expression	Ubiquitous	Ubiquitous	Leukocytes (B-cells)	Leukocytes (T-cells)
Inhibitors			Idelalisib Duvelisib	Duvelisib
Expected Activity			B-cell neoplasms	T-cell and B-cell neoplasms





IPI-145 is a Potent Oral PI-3Kδ,γ Inhibitor

PI3K Isoform	PI3K-δ	PI3K-γ
Expression	Primarily Leukocytes	Primarily Leukocytes
Biochemical Activity (K_D)	23 pM	243 pM
Whole Blood Assay (IC_{50})	96 nM Anti-FcεR1	1028 nM fMLP



IPI-145

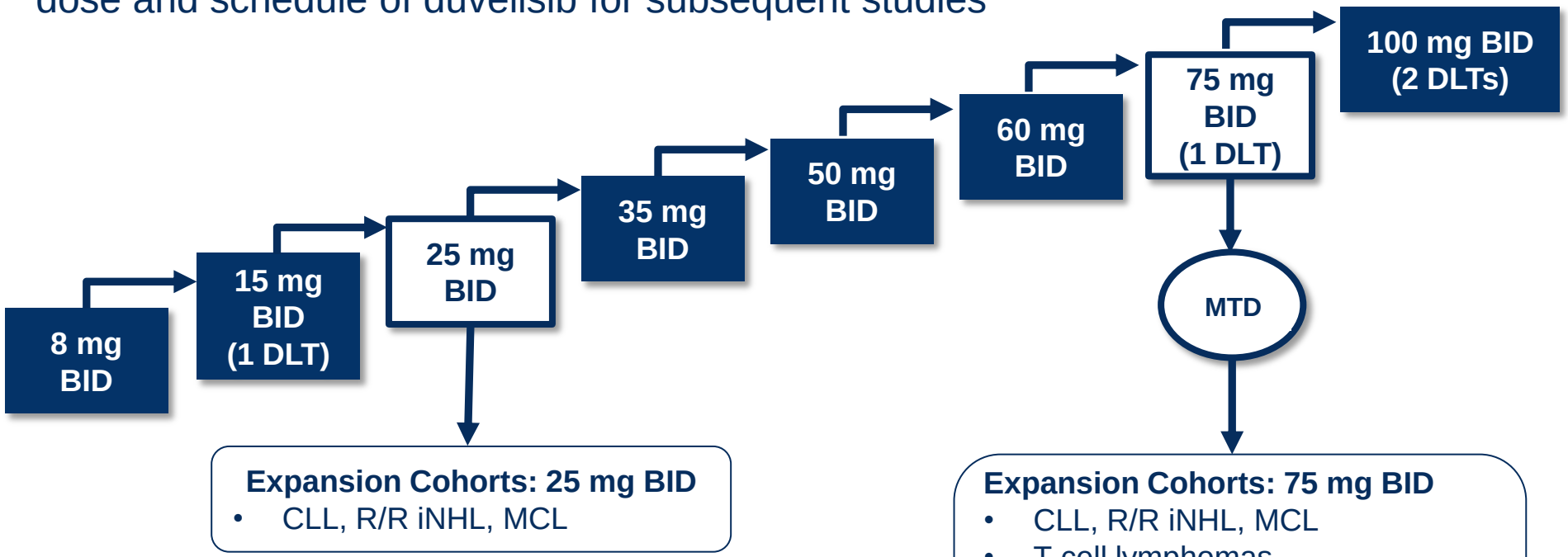
- Selective for PI3Ks over other protein and lipid kinases
- Inhibits malignant B- and T-cell survival
  - direct effects on tumor cells
  - disrupting tumor cell interactions within the microenvironment

IPI-145-02:

Phase I study Duvelisib in Hematologic Malignancies

ENROLLMENT COMPLETE

Primary Objective: To determine the safety and MTD of duvelisib; recommend a dose and schedule of duvelisib for subsequent studies



Primary Endpoints:

• Incidence of reported AEs, abnormal lab test results, including dose-limiting toxicities (DLTs).

Secondary endpoints :

• Plasma concentrations of IPI-145 and, if applicable, its metabolite(s).

• Disease-specific responses CR/PR

Duvelisib is an investigational agent available for clinical trial use only.
Safety and efficacy have not been established.

Infinity PHARMACEUTICALS

IPI-145-02:
R/R CLL Study Patients

Demographics	25 mg BID (N=31)	All Doses (N=55)
Age (years), median (range)	66 (42-82)	66 (42-82)
Male, n (%)	27 (87)	42 (76)
White, n (%)	27 (87)	49 (89)
Baseline Disease Status		
ECOG score, 0 / 1 / 2 / missing, n	8 / 20 / 2 / 2	12 / 38 / 3 / 2
Bulky lymphadenopathy (> 5 cm lesion), n (%)	13/31 (42)	24/51 (47)
Organomegaly, n (%)	8/26 (31)	13/48 (42)
ALC x103/µL, median (range)	14 (0.6, 233)	13 (0.6, 280)
Prior Therapies		
≥ 3 prior systemic therapies, n (%)	25 (81)	44 (80)
Number of prior therapies, median (range)	5 (1,11)	4 (1, 11)
Months from last therapy, median (range)	5 (0.3, 39)	2.5 (0.3, 39)
< 6 months from last therapy, n (%)	16 (52)	35 (65)
Prior ibrutinib treatment, n (%)	2 (6)	6 (11)
Baseline Disease Status		
Unmutated *IGHV*, n (%)	20/23 (87)	31/35 (89)
*TP53*mut/del(17p), n (%)	15/29 (52)	26/50 (52)

O'Brien et al., ASH 2014

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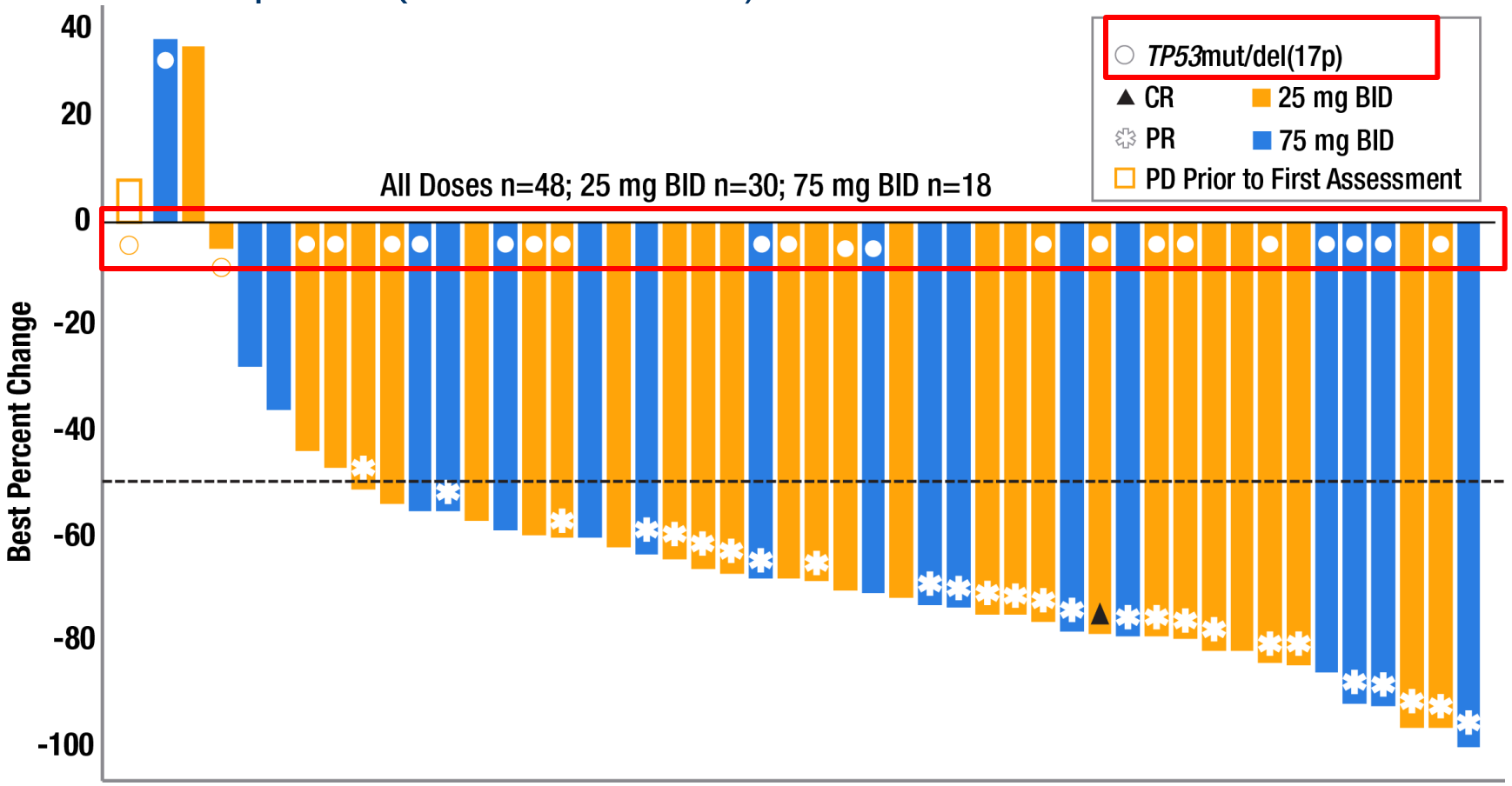
IPI-145-02: R/R CLL (Phase I)

Maximum change in adenopathy

- 83% (25/30) of CLL patients at 25 mg BID with baseline CT scan had a nodal response (reduction ≥ 50%)



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IPI-145-02: R/R CLL (Phase I)
Overall Response Rate (iwCLL)

Population	n	CR n (%)	PR n (%)	SD* n (%)	PD n (%)	ORR n (%)
All Doses	52	1 (2)	29 (56)	21 (40)	1 (2)	30 (58)
25 mg BID	30	1 (3)	16 (53)	12 (40)	1 (3)	17 (57)
Unmutated *IGHV*	20	1 (5)	11 (55)	8 (40)	0	12 (60)
*TP53*mut/del(17p)	15	1 (7)	6 (40)	7 (48)	1 (7)	7 (48)

Includes efficacy evaluable patients only = at least one response assessment or PD without a response assessment
** Stable disease includes patients with PR + lymphocytosis*

- 57% ORR by iwCLL at 25 mg BID, including 1 CR
  - Median time to iwCLL response 1.9 months

O'Brien et al., ASH 2014

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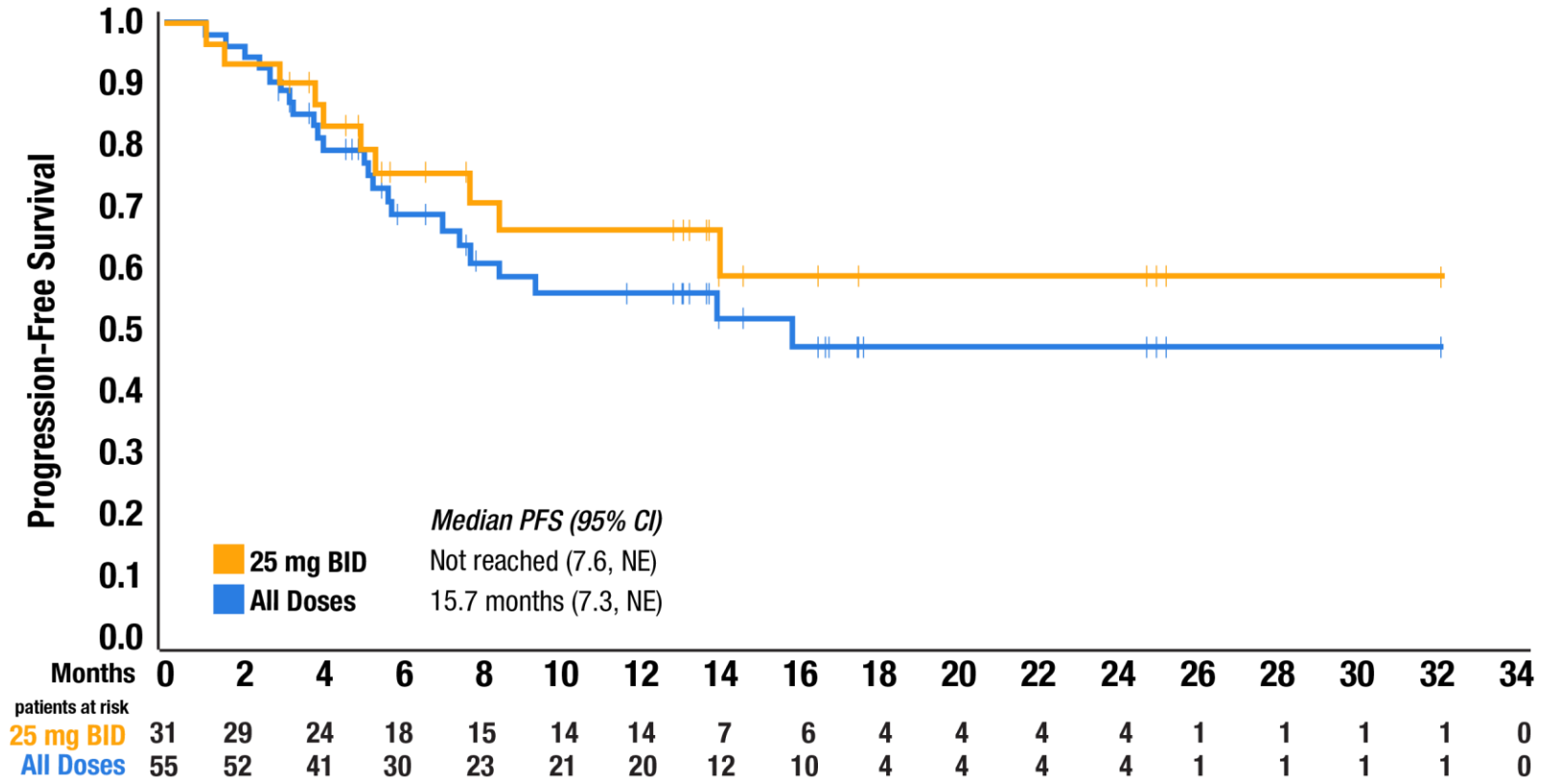
IPI-145-02: R/R CLL (Phase I)

Progression-Free Survival, All doses and 25 mg BID



- Median PFS at 25 mg BID not reached
  - 66% progression-free at 12 months
  - 59% progression-free at 24 months

O'Brien et al., ASH 2014

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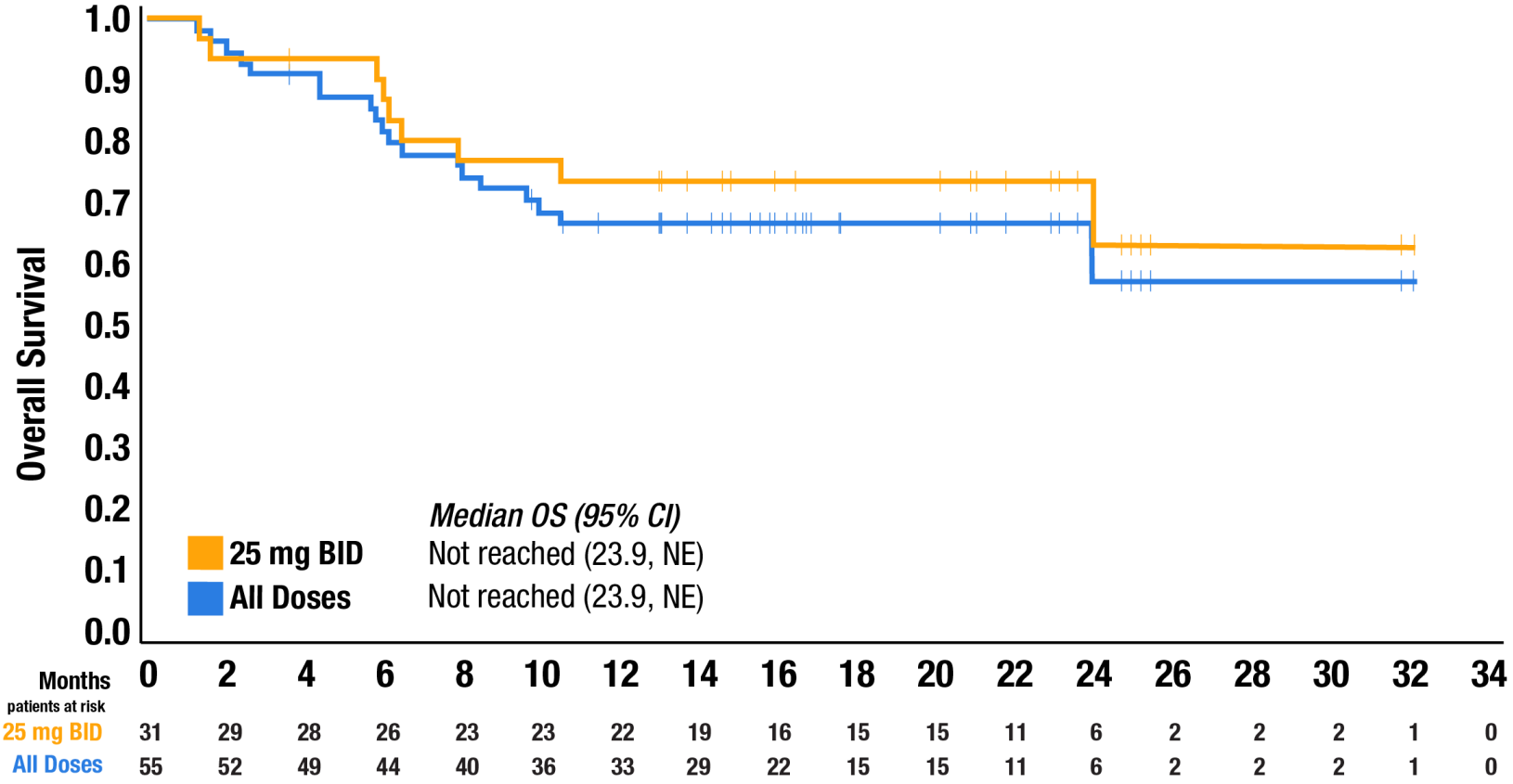
IPI-145-02: R/R CLL (Phase I)

Overall Survival, all doses and 25 mg BID



- Median OS at 25 mg BID not reached, with a minimum of 10 months observation
  - 74% survival at 12 months
  - 63% survival at 24 months

O'Brien et al., ASH 2014

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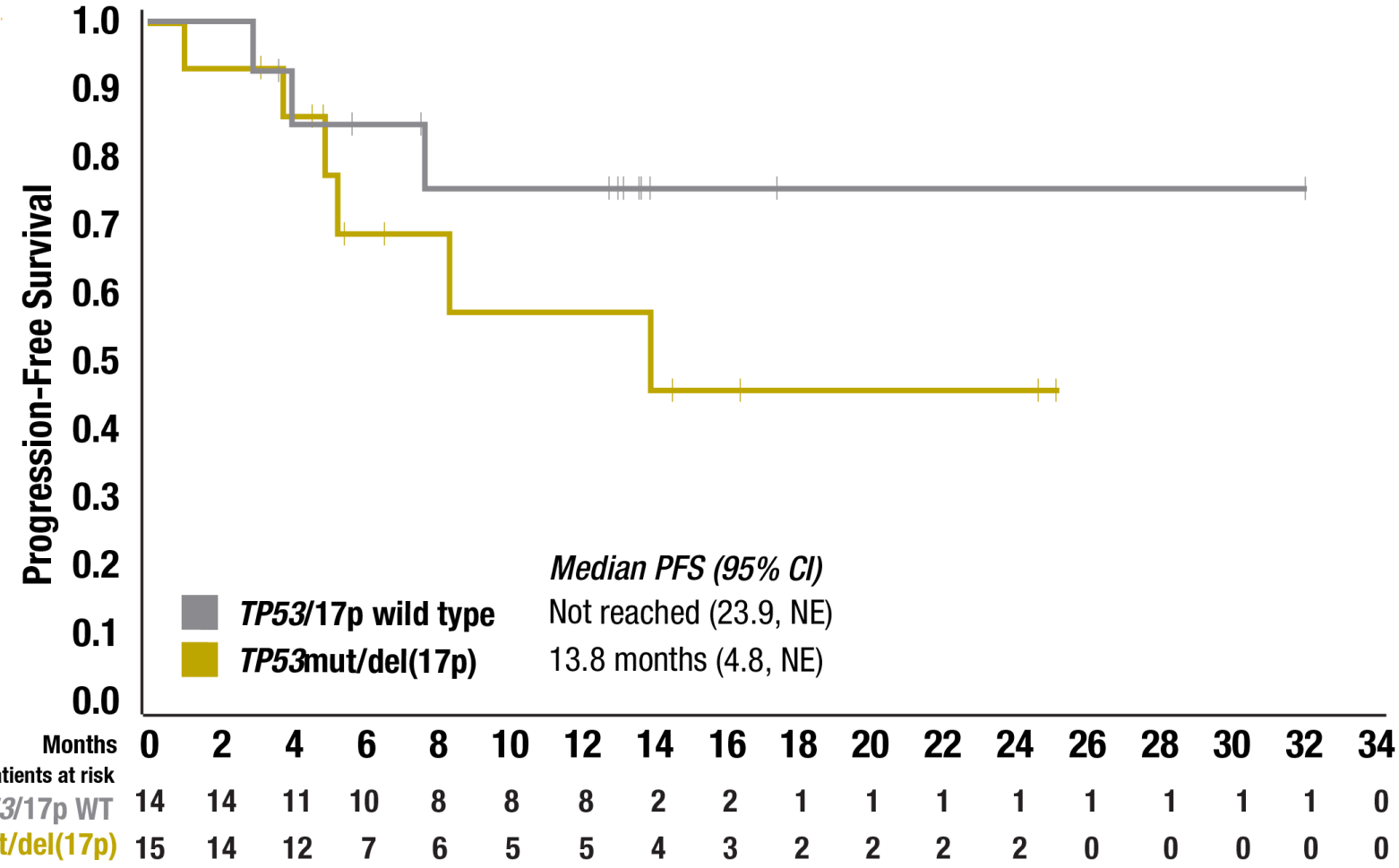
IPI-145-02: R/R CLL (Phase I)

Progression-Free Survival at 25 mg BID by TP53/17p mutation status



O'Brien et al., ASH 2014

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IPI-145-02: R/R CLL (Phase I)
Safety

All causality AEs (>20% Overall) and Grade 3 / 4, All Doses (N=55)			
AE (preferred term)	**Overall n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Neutropenia	29 (53)	10 (18)	13 (24)
Rash (combined)	25 (46)	1 (2)	1 (2)
Diarrhea	24 (44)	5 (9)	0
Cough	21 (38)	0	0
Fatigue	21 (38)	4 (7)	1 (2)
Pneumonia (combined)	20 (36)	13 (24)	1 (2)
ALT/AST increase	16 (29)	4(7)	1 (2)
Anemia	16 (29)	9 (16)	1 (2)
Pyrexia	15 (27)	2 (4)	0
Nausea	14 (26)	1 (2)	0
Decreased Appetite	13 (24)	1 (2)	0
Thrombocytopenia	12 (22)	2 (4)	8 (15)

Rash (combined) = any preferred terms associated with rash within Skin and Subcutaneous Tissue Disorders SOC
Pneumonia (combined) = all preferred terms of lung inflammation due to infectious or non-infectious etiologies

- 9 patients died while on study treatment or within 30 days of last dose: progressive disease (4), pneumonia (2), metabolic acidosis (1), respiratory failure/cardiac arrest (1), and sepsis (1)

SAEs > 1 Patient, All Doses (N=55)	
AE (preferred term)	n
Pneumonia (combined)	15
Febrile neutropenia	8
Diarrhea	3
Fatigue	3
Constipation	2
Hypercalcemia	2
Pyrexia	2
Stomatitis	2

AEs Leading to Discontinuation, All Doses (N=55)	
Pneumonia (combined)	7
Diarrhea	2
Stomatitis	2
ALT/AST	1
Cold-type hemolytic anemia	1
Colitis	1
Metabolic acidosis	1
Hand-foot syndrome	1
Polyarthritis	1
Pruritis	1
Squamous cell carcinoma	1

O'Brien et al., ASH 2014

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Key safety insights from phase I study to optimize patient management in CLL studies

Adverse events	Management in phase III study
Cytopenias	• Transient growth factors allowed • Drug interruption for febrile neutropenia

Respiratory	• Early intervention (drug interruption for ≥ Gr 2);
	  • Pneumonia
	  • Pneumonitis

Infections	• Dose interruption while active, antibiotics as indicated • Prophylaxis required at study entry for HSV/VZV, PJP
Diarrhea	• Dose interruption until resolution; retreat with same dose • Can occur late in treatment, monitor for potential colitis • Steroids allowed
↑ ALT/AST	• Dose interruption until resolution; retreat with same dose • More common in lymphoma vs. CLL

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PHASE 3 STUDY OF DUVELISIB VS. OFATUMUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

ENROLLMENT COMPLETE

DUO™

Study design
Rel or Ref CLL patients
N ~319
Randomized 1:1

Treatment arm 1
Duvelisib
25 mg BID orally, continuously

Treatment arm 2
Ofatumumab*
Dosage and administration consistent with approved prescribing information*

Study end points
- **Primary:**
  - Progression-free survival (PFS)
- **Secondary:**
  - Overall response rate (ORR)
  - Lymph node response rate
  - Overall survival (OS)
  - Hematologic improvement rate
  - Duration of response (DOR)
  - Safety
  - Pharmacokinetics (PK)

***8 weekly infusions, starting with an initial IV dose of 300 mg ofatumumab on Day 1 followed by 7 weekly doses of 2,000 mg. Thereafter, 2,000 mg ofatumumab monthly for 4 months..**

Selected inclusion criteria
- Relapsed or refractory CLL/SLL after ≥1 previous therapy
- Not appropriate for treatment with a purine-based analogue regimen
- ECOG PS 0-2

PHASE 1B STUDY OF DUVELISIB IN COMBINATION WITH OBINUTUZUMAB IN CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

PATIENTS PREVIOUSLY TREATED WITH A BTK INHIBITOR (BTKi)

SYNCHRONY

Study design
- Open-label
- Safety lead-in
- N ~46

Safety lead-in
Tolerability of combination based on dose limiting toxicities (DLTs) occurring during cycle 1

Duvelisib: 25 mg BID orally, continuously

Obinutuzumab: Administered per label on day 1, 2, 8, and 15 of cycle† 1; monthly on day 1 of cycles 2 through 6

Expansion
Expansion cohort to further evaluate tolerability and preliminary clinical activity
(N ~ 40)

† 1 Cycle = 28 days

Selected inclusion criteria
- CLL/SLL
- BTKi progression or BTKi intolerance
- At least measurable lesion (lymph node or tumor mass >1.5 cm)
- ECOG PS 0-2

Study end points
- **Primary:**
  - Dose limiting toxicities (DLTs)
  - Treatment-emergent adverse events (TEAEs) and lab safety values
- **Secondary:**
  - Overall response rate (ORR)
  - Duration of response (DOR)
  - Progression-free survival (PFS)
  - Overall survival (OS)
  - BTK mutation status
  - Pharmacokinetics (PK)

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IPI-145-18 NCT02292225

Duvelisib in T-cell lymphoma

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Study Population and Clinical Activity of IPI-145 in *T-cell malignancies* – Phase I (IPI-145-02)

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)

AITCL= angioimmunoblastic TCL; EATCL= enteropathy-associated TCL; ECOG = Eastern Cooperative Oncology Group performance status; IPI = International Prognostic Index; LCT = large-cell transformed; MF = mycosis fungoides; NKTCL= natural killer TCL; NOS= not otherwise specified; pcALCL= primary cutaneous anaplastic large cell lymphoma; SPTCL= subcutaneous panniculitic 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; PD = progressive disease ; PR = partial response; SD = stable disease. Overall response rate (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

Horwitz S, Porcu P., et al. T-cell Lymphoma Forum, San Francisco, 2015

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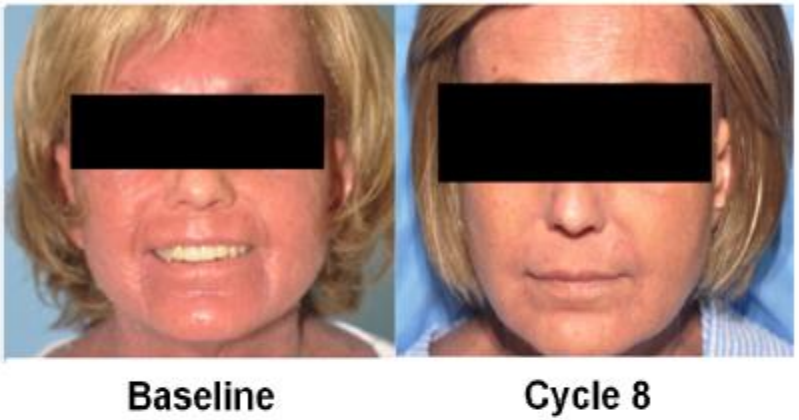
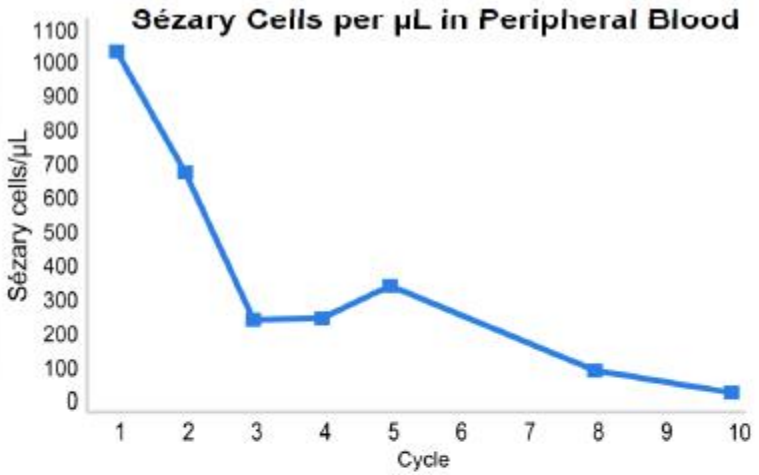
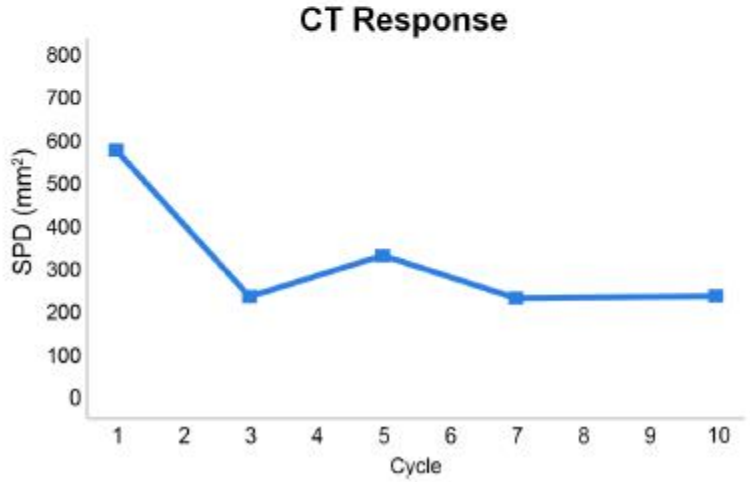
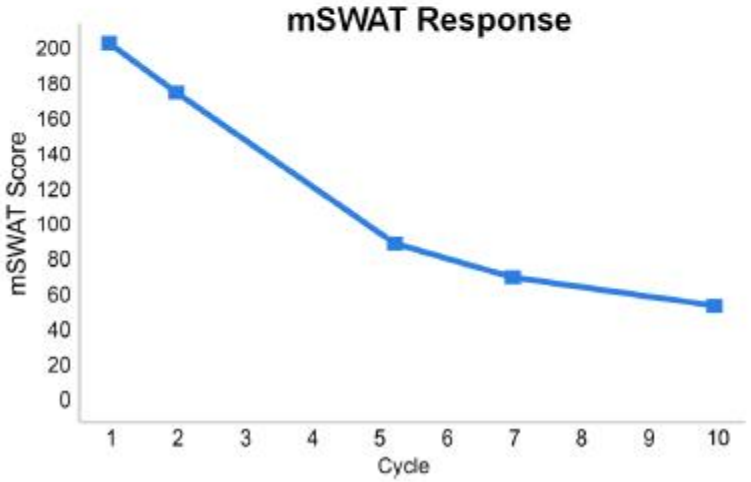
Clinical Activity of IPI-145 in Sezary Syndrome: response in skin, blood, and lymph nodes









Horwitz S. et al. ASCO 2015

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