Duvelisib (IPI-145), a PI3K-δ,γ Inhibitor, is Clinically Active in Patients with Relapsed/ Refractory Chronic Lymphocytic Leukemia

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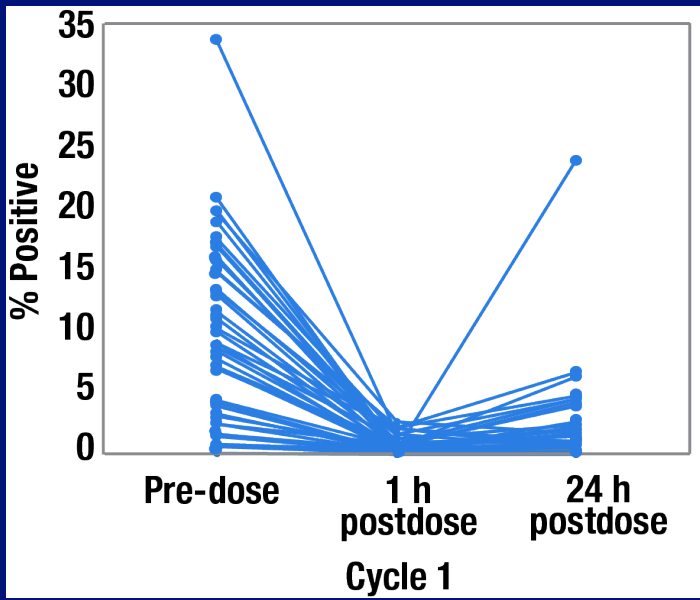
Presented Monday, 07 September 2015
International Workshop of Chronic and Lymphocytic Leukaemia, Sydney, Australia

Study IPI-145-02 Design

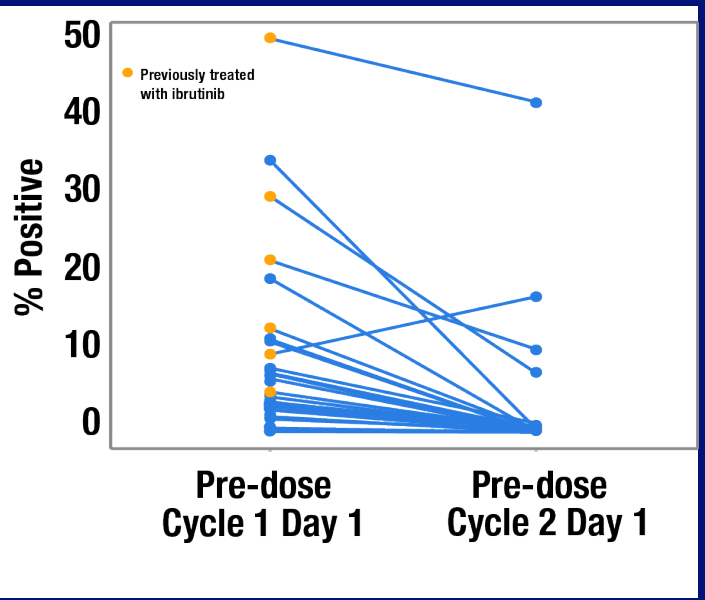
- Objectives – maximum tolerated dose (MTD), pharmacokinetics (PK), pharmacodynamics (PD), safety, and efficacy in patients with advanced hematologic malignancies
- 25 mg BID selected for phase 3 development based on early clinical activity (Flinn et al, ASH 2013)
- 55 R/R CLL/SLL pts received duvelisib BID in 28-day cycles
  - Response criteria per iwCLL 2008
  - AEs per CTCAE v 4.03
  - PD markers: pAKT and Ki67 in CLL cells, serum cytokines & chemokines
  - Prior treatment with a Bruton's tyrosine kinase inhibitor (BTKi) allowed

Pharmacodynamics & Mechanism of Action Studies: pAKT (S473) and Ki67 Measurements in CLL Cells

pAKT (S473) Percent Positive in CLL Cells*(n=41)

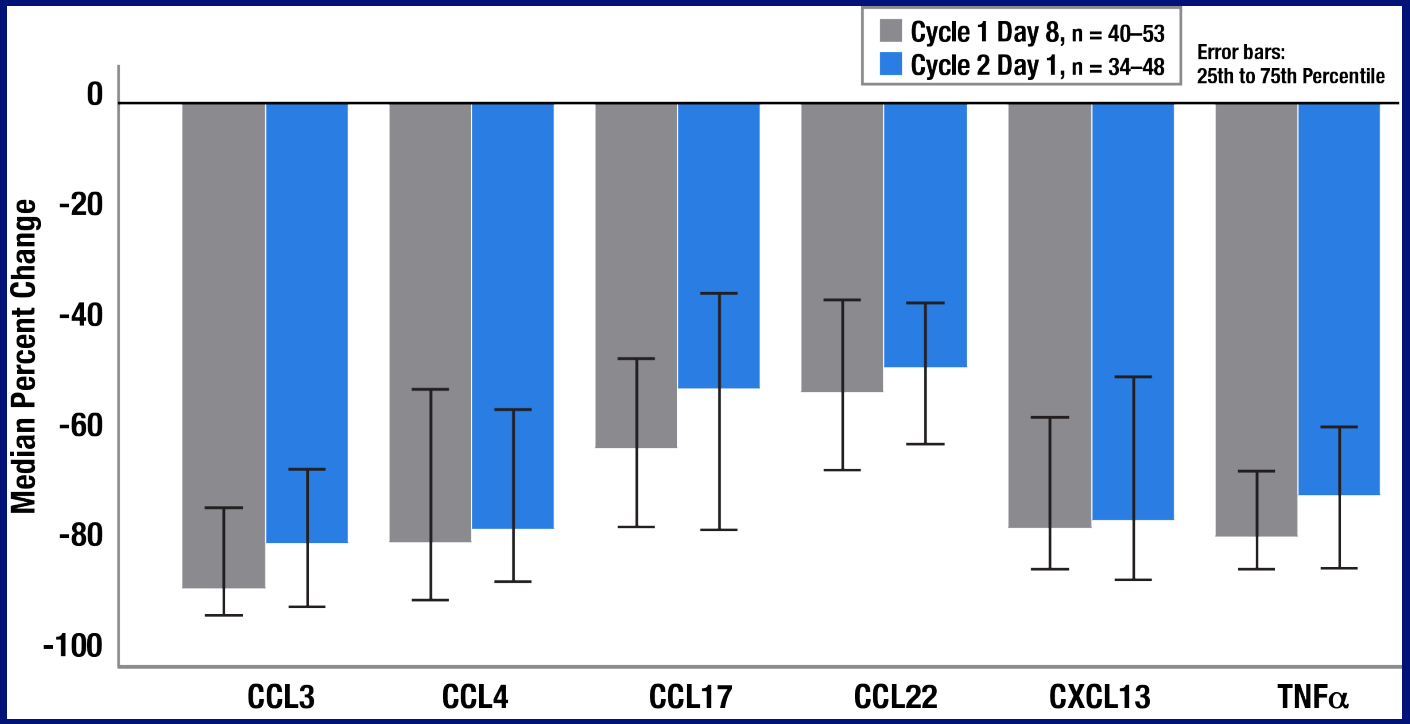


Ki67 Percent Positive in CLL Cells* (n=29)



- Rapid inhibition of pAKT (S473) following duvelisib
- Inhibition of CLL proliferation (Ki67) following 1 cycle of duvelisib, with near complete inhibition in pts not previously treated with BTKi

Change in Key Serum Chemokines and Cytokines



- Evidence of pharmacodynamic modulation of chemokines/cytokines that support the malignant B-cell microenvironment

Study Patients

Demographics	25 mg BID* (N=31)	All Doses (N=55)
Age (years), median (range)	66 (42, 82)	66 (42, 82)
Prior therapies, median (range)	5 (1,11)	4 (1, 11)
Rai Stage ≥ 3, n (%)	18 (64.3)	33 (60.0)
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 $x10^3/\mu L$, median (range)	14 (0.6, 233)	13 (0.6, 280)
Grade 4 cytopenia, n %	3 (9.7)	8 (14.5)
Prior ibrutinib treatment, n %	2 (6)	6 (11)
Risk Factors		
Unmutated *IGHV*, n (%)	20/23 (87)	31/35 (89)
TP53 mutation/17p deletion, n (%)	15/29 (52)	26/50 (52)

* *Includes 1 pt dosed at 8 mg BID, and 2 pts dosed at 15 mg BID*

All TEAEs (> 20% Overall) & Grade 3/4 (N = 55)

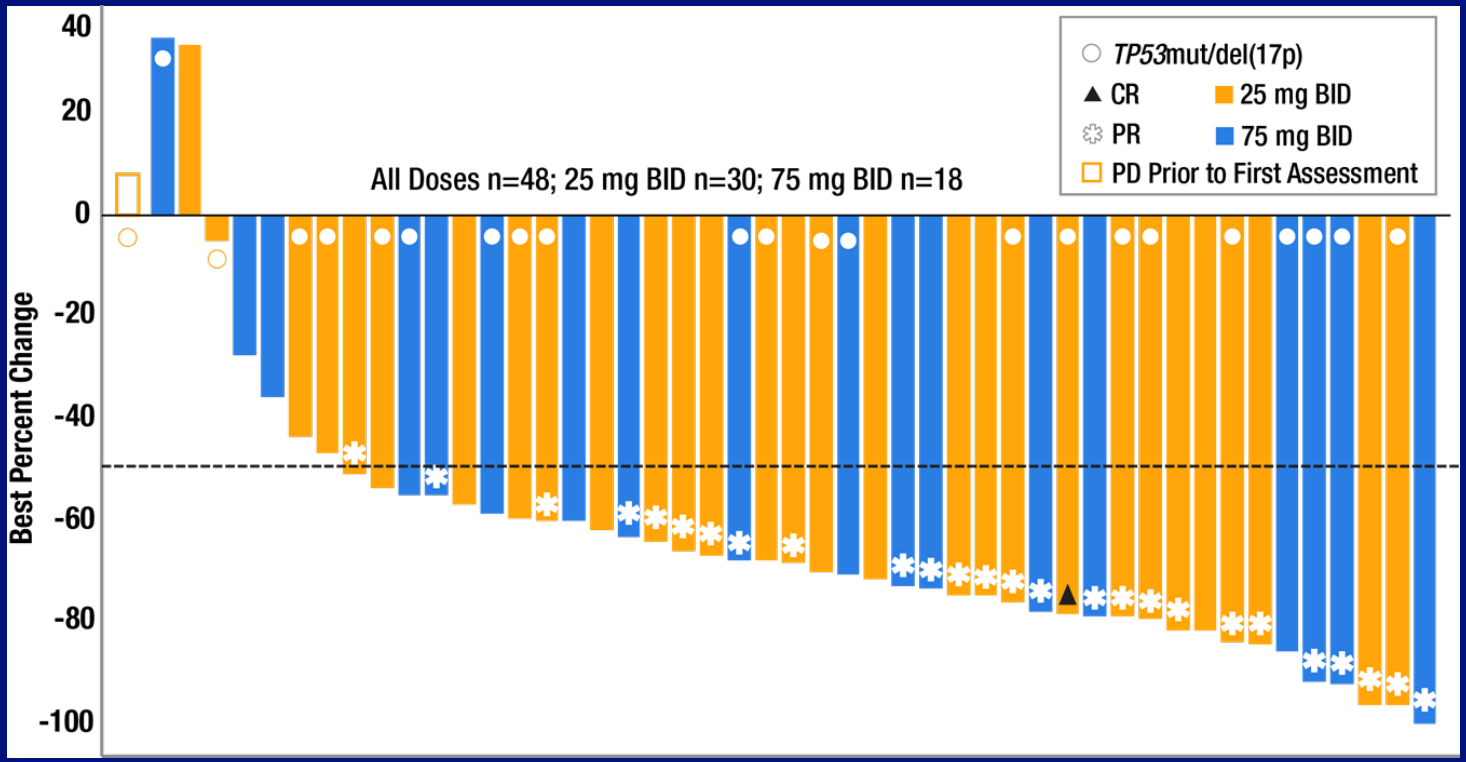
AE (preferred term)	Overall n (%)	Grade 3 n (%)	Grade 4 n (%)
Neutropenia	29 (53)	10 (18)	13 (24)
Rash (combined)	25 (46)	1 (2)	1 (2)
Diarrhea	24 (44)	5 (9)	0
Cough	21 (38)	0	0
Fatigue	21 (38)	4 (7)	1 (2)
Pneumonia (combined)	20 (36)	13 (24)	1 (2)
ALT/AST increase	16 (29)	4(7)	1 (2)
Anemia	16 (29)	9 (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

TEAEs Leading to Treatment Discontinuation

AE (Preferred term)	n
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

Maximum Lymph Node Reduction



- 25/30 (83%) pts at 25 mg BID with baseline CT scan achieved a nodal response (≥ 50% reduction in measurable area of disease)

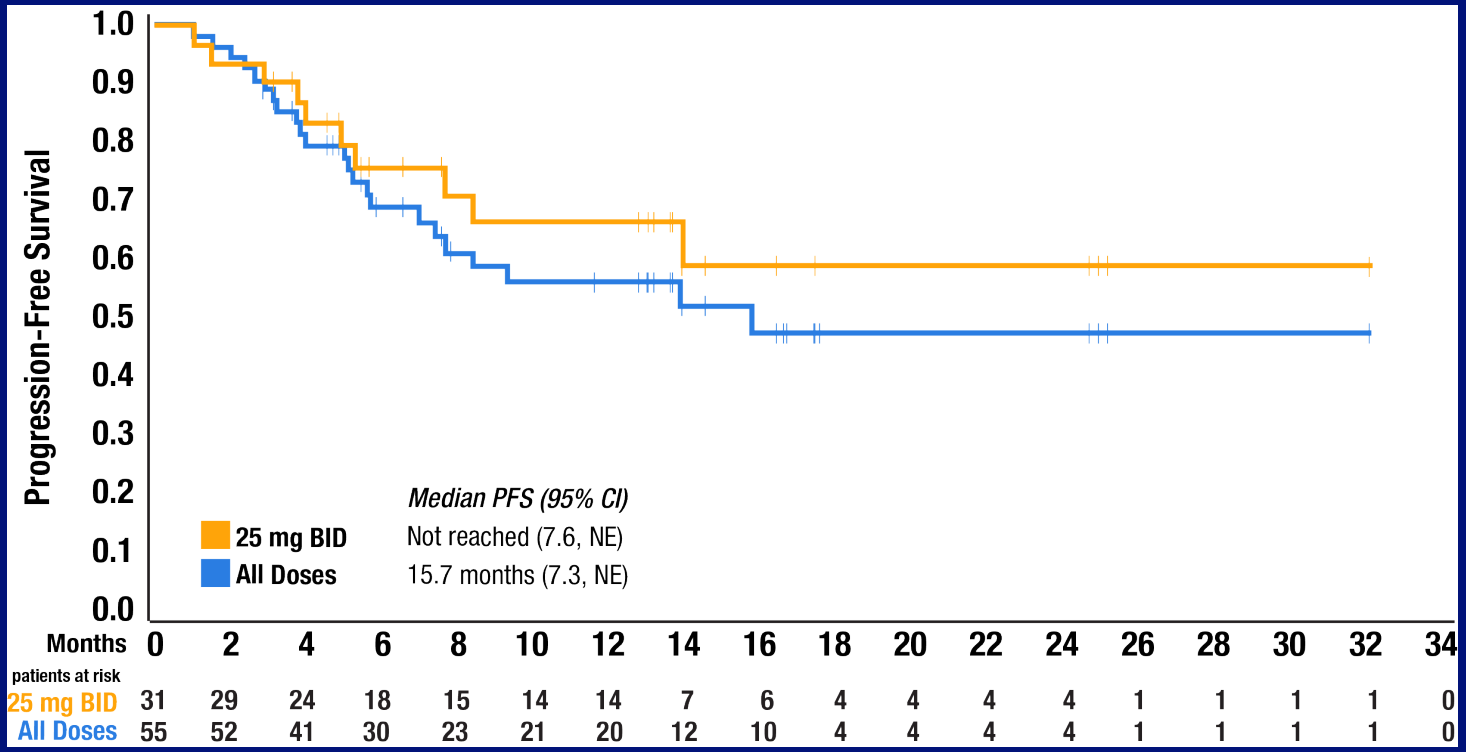
Best Overall Response (ORR) per iwCLL

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)
Previous BTKi	6	0	1 (17)	5 (83)	0	1 (17)

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

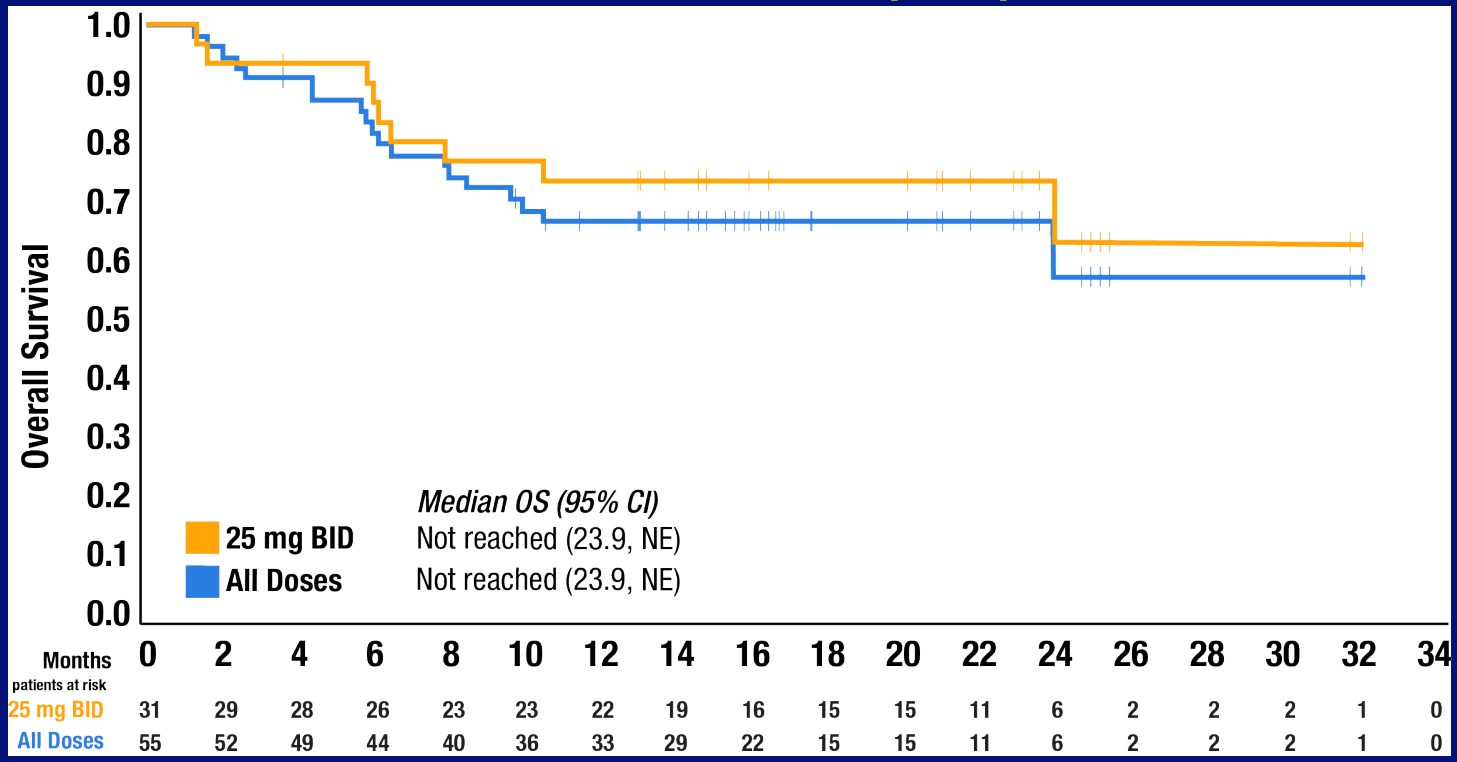
- **57% ORR by iwCLL at 25 mg BID, including 1 CR**
- **Median time to iwCLL response = 1.9 months**

Progression-Free Survival



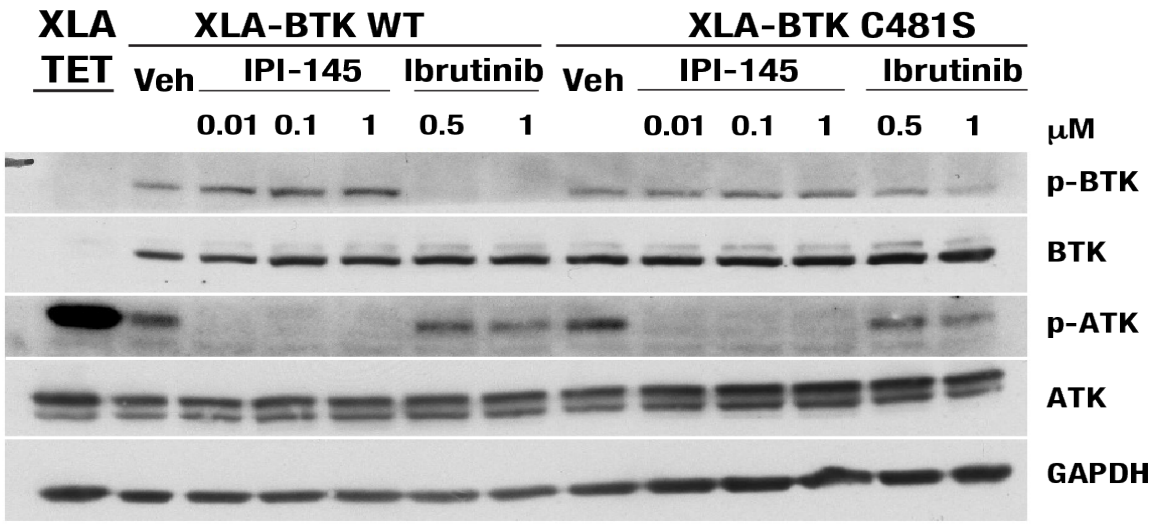
- Median PFS at 25 mg BID not reached
  - 66% progression-free at 12 months
  - 59% progression-free at 24 months

Overall Survival (OS)



- Median OS at 25 mg BID not reached
  - 74% survival at 12 months
  - 63% survival at 24 months

Duvelisib Inhibits the PI3K Pathway in the Setting of Ibrutinib Resistance in Vitro (cont)



- In an XLA cell transfection assay, ibrutinib is unable to inhibit phosphorylation of mutant BTK to the same extent as wild type BTK12
- Duvelisib robustly inhibits AKT phosphorylation regardless of BTK mutation status12

Demographics and Baseline Disease Characteristics of Patients Treated with Ibrutinib Prior to Study Entry

Characteristic	CLL (N=6)	aNHL(N=7)
Duvelisib 25 mg BID	2	0
Duvelisib 75 mg BID	4	7
Age (years), median (range)	58 (42, 79)	60 (36, 81)
Male, n (%)	4 (67)	5 (71)
White, n (%)	5 (83)	5 (71)
ECOG score, 0 / 1 / 2 / missing, n	0 / 4 / 1 / 1	1 / 5 / 1 / 0
Stage IV disease, n (%)	3 (50)	4/6 (67)
Bulky lymphadenopathy (> 5 cm lesion), n (%)	2/5 (40)	3/5 (60)
Organomegaly, n (%)	1/6 (17)	N/A
ALC x10^3/μL, median (range)	27 (2.2, 74)	1.1 (0.4, 56)

Prior Anticancer Therapy and Mutation Status

Characteristic	CLL (N=6)	aNHL(N=7)
≥ 3 prior systemic therapies, n (%)	6 (100)	4 (57)
Number of prior therapies, median (range)	5.5 (3, 11)	3 (1, 7)
Months from last therapy, median (range)	0.4 (0.3, 1,6)	0.8 (0.2, 3.7)
Months from last ibrutinib dose, median (range)	0.4 (0,3, 9.2)	2.1 (0.2, 13.2)
BTK mutation, n	C481S = 2, C481F = 1	0
PLCG2 mutation, n	S707F = 1	0
*TP53*mut/del(17p), n (%)	2 (33)	4 (57)

- **Most patients were heavily pretreated with a short duration from prior regimen**
  - **100% CLL and 57% aNHL had ≥ 3 prior anticancer therapies**
  - **Median months from last therapy: 0.4 months CLL, 0.8 months aNHL**

Overall Response

Population	n	CR	PR	SD	PD	ORR
CLL	6	0	1 (17)	5 (83)	0	1 (17)
aNHL	5	0	2 (40)	1 (20)	2 (40)	2 (40)

Includes efficacy evaluable patients = at least 1 post-baseline disease response assessment while on treatment or PD without assessment: 2/7 aNHL patients not evaluable

- **Tumor cells in the CLL partial responder did not have a mutation in BTK or PLCG2**
- **One CLL patient (SD, BTK C481F mutation) remains on treatment after 14 months**

Study IPI-145-02 Design

»TN CLL Expansion Cohort (n=18)

- Duvelisib 25 mg BID in 28-day cycles
- TN CLL pts enriched for high-risk status:
  - TP53mutation/17p-deletion; *and/or*
  - ≥ 65 years old
  - Response criteria per iwCLL 2008

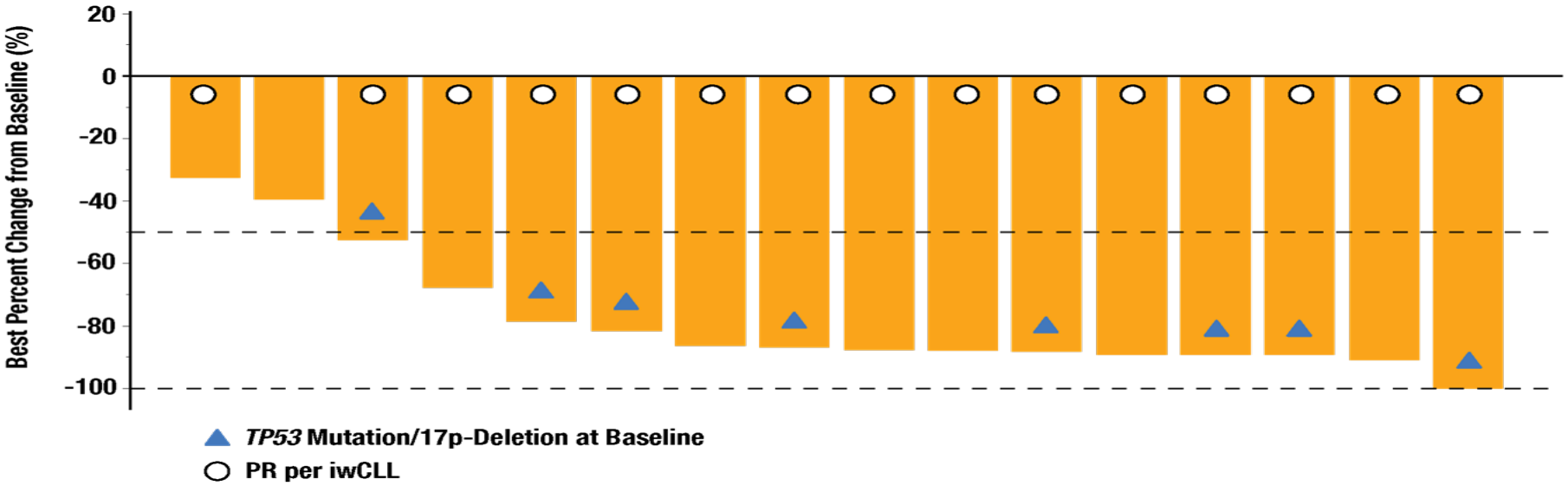
Study Patients

Demographics	TN CLL (N = 18)
Age (years), median (range)	74 (49, 83)
Years from initial diagnosis, median (range)	3 (0, 9)
Rai Stage ≥3, n (%)	8 (47)*
ECOG Score, 0 / 1, n	8 / 10
Bulky lymphadenopathy (> 5 cm lesion), n (%)	1 (6)
Splenomegaly, n (%)	8 (44)
Hepatomegaly, n (%)	1 (6)
Grade 4 cytopenia, n (%)	2 (11)
ALC X 10^3/μL, median (range)	54 (2, 204)
Risk Factors	
≥ 65 years, n (%)	15 (83)
TP53 mutation/17p deletion, n (%)	10 (56)

Patient Disposition

	TN CLL (N = 18)
Time on Treatment (months), median (range)	14 (1, 20)
Discontinued Treatment, n (%)	8 (44)
Adverse Event	6 (33)
Subject Withdrawal	1 (6)
Other	1 (6)

Maximum Lymph Node Reduction



- 14/16 (88%) pts with baseline CT scan achieved a nodal response (≥ 50% reduction in measurable area of disease), all had a PR per iwCLL

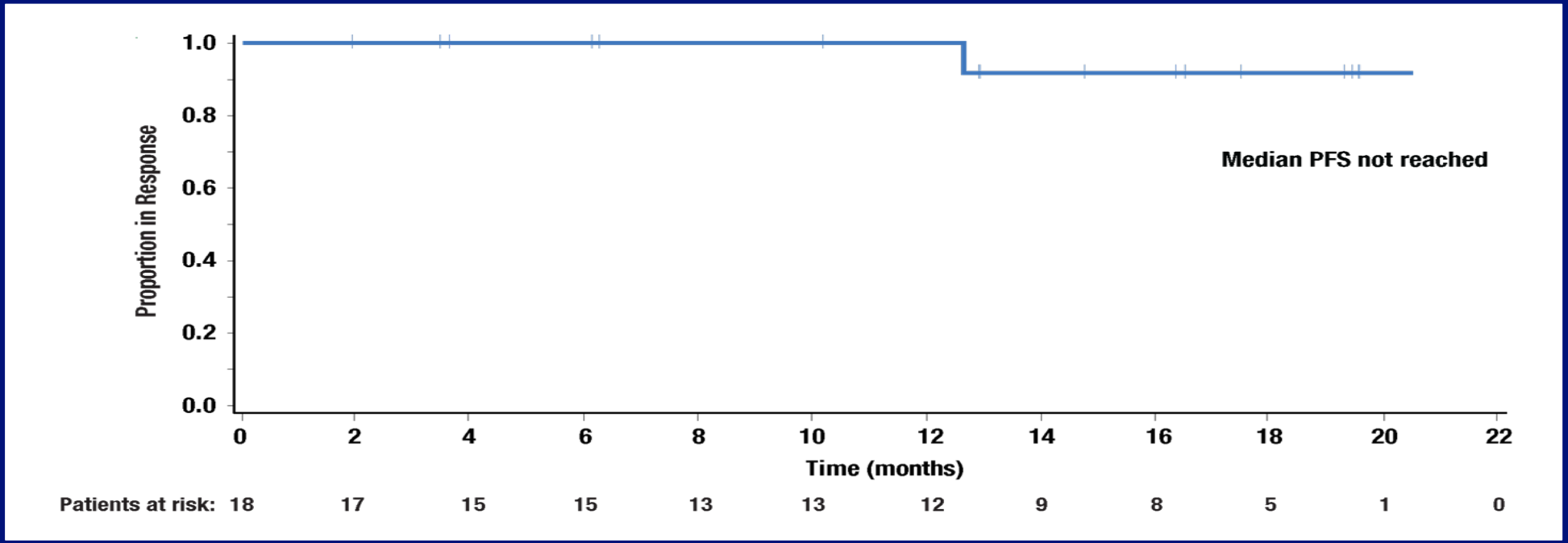
Best Overall Response (ORR) per iwCLL

Population *	n	CR n (%)	PR n (%)	SD n (%)	PD n (%)	ORR n (%)
TN CLL	17	0	15 (88)	2 (12)	0	15 (88)
P53 mutation/17p(del)	9	0	8 (89)	1 (11)	0	8 (89)

* 1 pt with TP53 mutation/17p-deletion withdrew consent prior to the first efficacy assessment (C3D1), and was not in the efficacy evaluable population

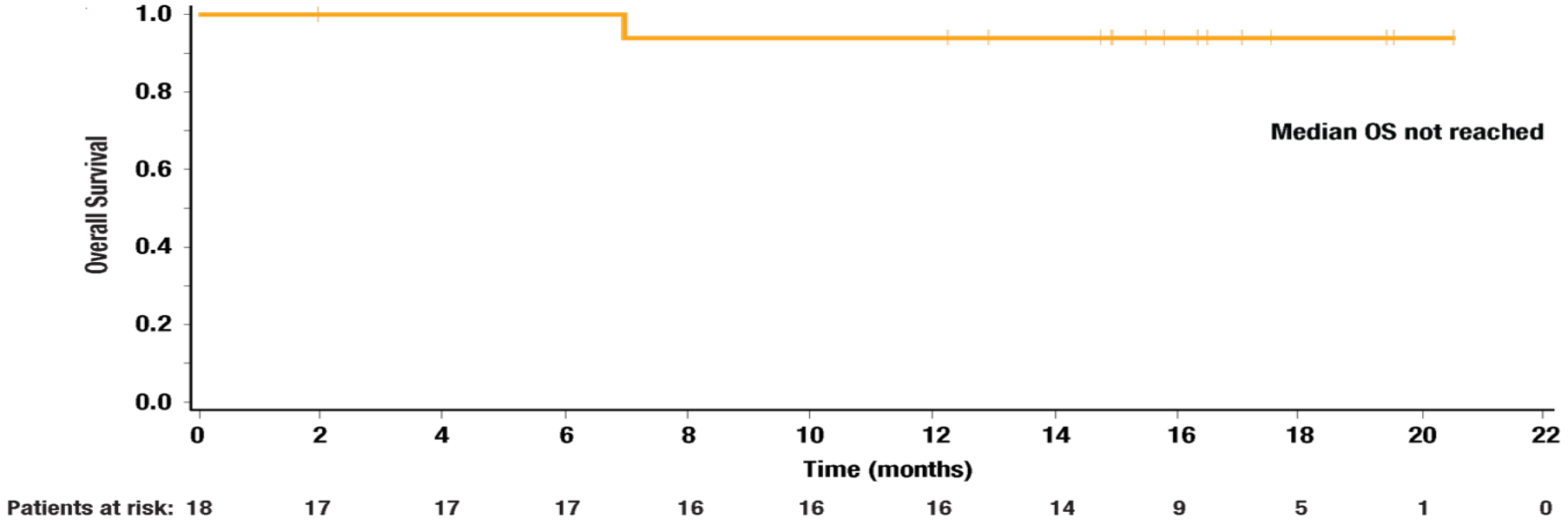
- Median time to iwCLL response = 3.7 months
- 7 of 15 (47%) responses occurred by the first assessment (Cycle 3 Day 1)

Progression-Free Survival



- Median PFS not reached
  - PFS rate 100% at 12 months and 92% at 18 months
- 1 pt progressed at Cycle 13

Overall Survival (OS)



- Median OS not reached
  - 94% survival at 12 months and 18 months
  - 1 pt died (PD) during survival follow-up, ≈ 5 months after last dose

All AEs (>25% Overall) and Grade 3/4 (N = 18)

AE (preferred term)*	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Diarrhea	14 (78)	4 (22)	0
Rash (combined)**	9 (50)	2 (11)	0
Cough	8 (44)	0	0
Neutropenia/Neutrophil count decreased	8 (44)	1 (6)	5 (28)
Peripheral edema	8 (44)	0	0
Fatigue	7 (39)	1 (6)	0
Nausea	7 (39)	1 (6)	0
Pyrexia	6 (33)	0	0
ALT/AST increased	5 (28)	3 (17)	0
Anemia/Hemoglobin decreased	5 (28)	1 (6)	0
Dizziness	5 (28)	0	0

* >1 AE may have occurred in a single pt.
** Rash (combined) = any PT associated w/ rash w/in Skin and Subcutaneous Tissue Disorders SOC

SAEs and AEs Leading to Treatment Discontinuation

SAEs in > 1 Patient

SAE (preferred term)*	n
Diarrhea	3
Colitis	2
Dehydration	2
Pneumonia	2
Pneumonitis	2

- 13 pts with an SAE(s)
  - 9 pts remained on duvelisib
- No SAEs resulted in death

AEs Leading to Treatment Discontinuation

Pt	AE (Grade)	Week *
1	ALT/AST increased (G3); dehydration (G3); spinal stenosis (G3)	9
2	Arthritis (G2)	11
3	Pneumonitis (G3)	20
4	Colitis (G3)	36
5	Diarrhea (G1)	47
6	Colitis (G1) and stomatitis (G3)	53

* Date of pt discontinuation from study drug

DUO™: a positive Phase 3 study of Duvelisib in relapsed/refractory Chronic lymphocytic leukemia

DUO™

Relapsed or Refractory CLL/SLL patients
(N = 319) (Randomized 1:1)

Treatment arm 1
Duvelisib 25 mg BID

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)
  - Overall survival (OS)
  - Duration of response (DOR)
  - Safety

✓ First Phase 3 trial showing PI3K inhibitor monotherapy efficacy in CLL/SLL

* 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.

POSITIVE PHASE 3 STUDY, TOP LINE DATA ANNOUNCED SEPTEMBER 2017

DUO™ met its primary endpoint of PFS by IRC in both the ITT and del(17p) subpopulation

DUO™ TOP LINE DATA

	Duvelisib	Ofatumumab
PRIMARY ENDPOINT: PROGRESSION-FREE SURVIVAL (PFS) BY IRC		
ITT population, median	13.3 months	9.9 months
	HR = 0.52; p < 0.0001	
del(17p) subset, median	12.7 months	9.0 months
	HR = 0.41; p = 0.0011	

Duvelisib monotherapy had a manageable safety profile, with results from this study consistent with the well-characterized safety profile of duvelisib monotherapy observed to date in patients with advanced hematologic malignancies.

Detailed results to be presented at ASH 2017 on Sunday, December 10th at 4:30pm ET

IRC: Independent Review Committee; ITT: Intent-to-Treat

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