The Bruton Tyrosine Kinase (Btk) Inhibitor ACP-196:

Marked Activity in Relapsed/Refractory CLL with a Favorable Safety Profile

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Second-Generation Btk Inhibitor

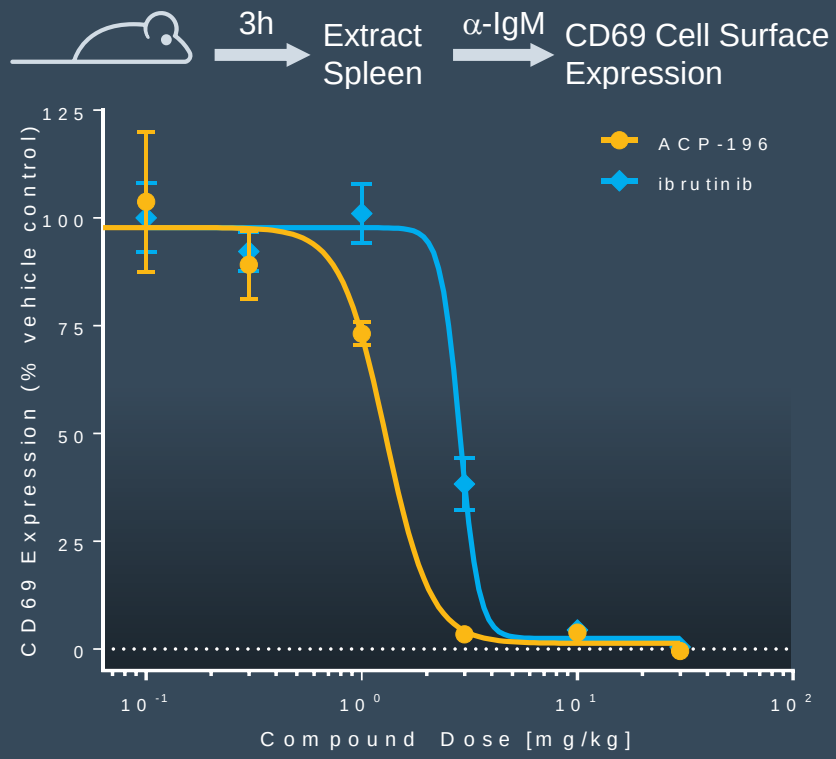
ACP-196 is a potent, selective irreversible Btk inhibitor

Kinase Inhibition IC_{50} (nM)

Kinase	ACP-196	ibrutinib
Btk	5.1	1.5
Tec	93	7.0
BMX	46	0.8
Txk	368	2.0
ERBB2	~1000	6.4
EGFR	>1000	5.3
Itk	>1000	4.9
Jak3	>1000	32
Blk	>1000	0.1

Covey AACR 2015. Abstract 2596.

In Vivo Potency



	ACP-196	ibrutinib
ED_{50} (mg/kg)	1.3	2.9

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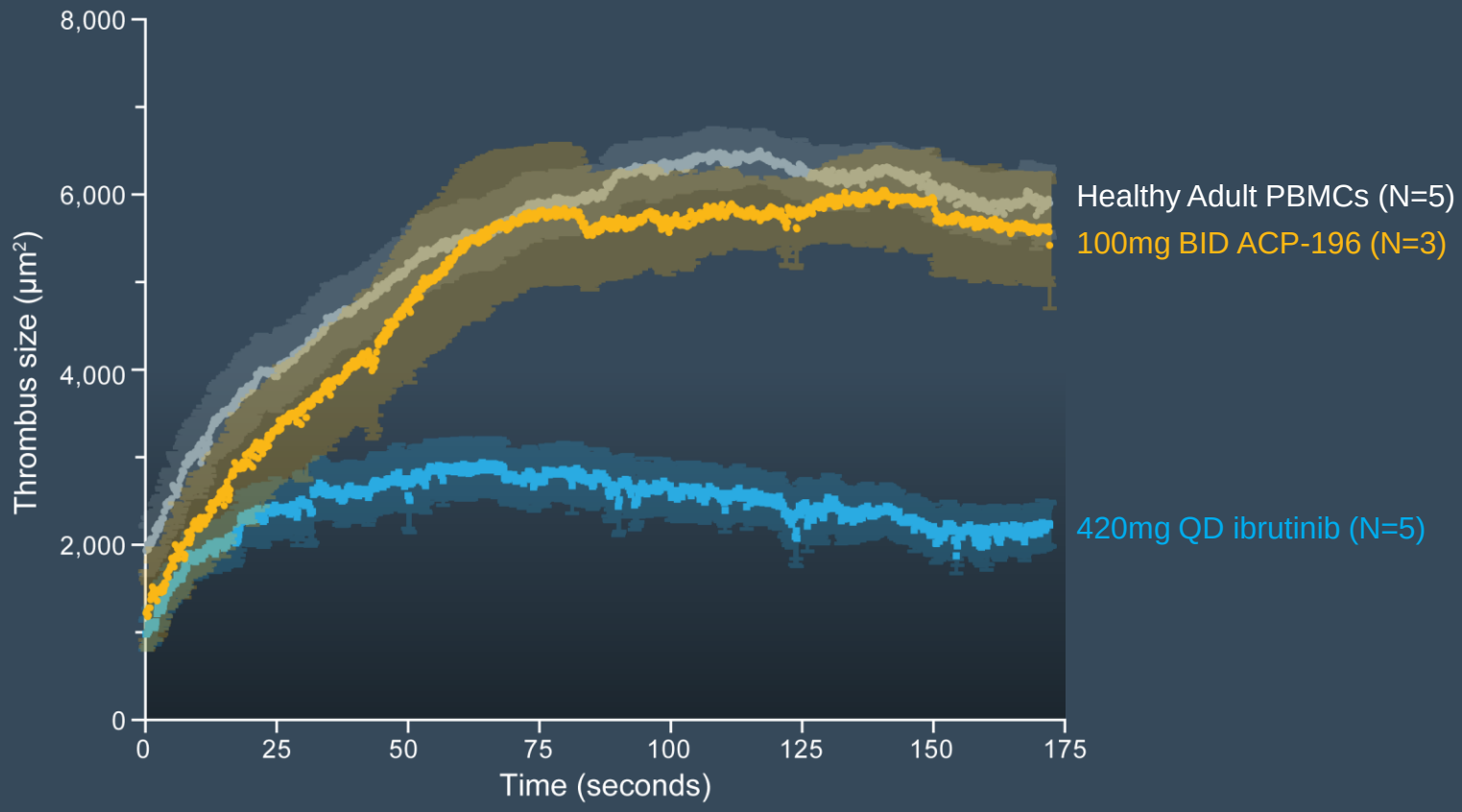
Platelet Aggregation (R/R Patients with CLL)

ACP-196 does not inhibit platelet mediated thrombosis



In vivo murine thrombosis model. Chen, et al. *Blood.* 2014.

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Study Objectives

CL-001 FIH study (NCT02029443)

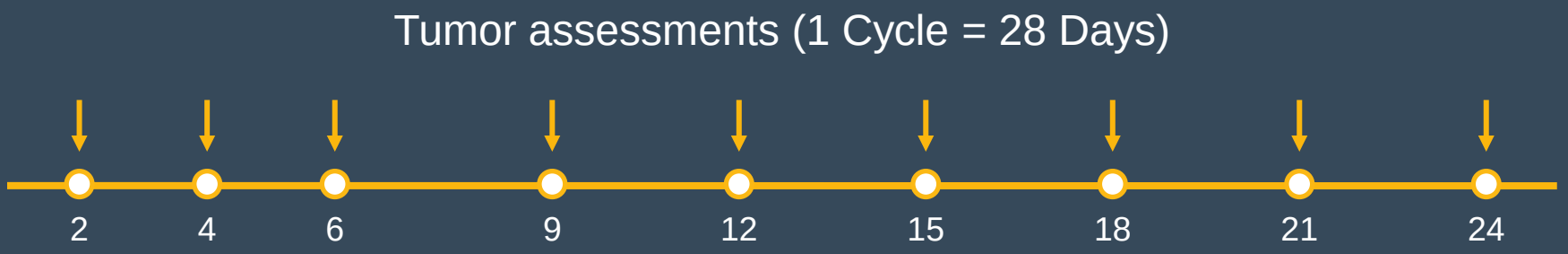
Primary Objective:

- Establish the safety and maximum tolerated dose of ACP-196 monotherapy

Secondary Objectives:

- Pharmacokinetics
- Pharmacodynamics
- Tumor response
- Progression-free survival

Study Eligibility and Design



- Relapsed/Refractory CLL
- ECOG PS ≤ 2
- Prior exposure to Btk inhibitors *not* allowed
- Prior exposure to PI3Kδ, BCL-2 inhibitors allowed
- Pancytopenia, prior BMT allowed

ACP-196 Cohorts	**N=61**
Dose Escalation, 6-8 patients	
100mg QD	9†
175mg QD	8
250mg QD	7
400mg QD	6
Dose Expansion (Phase 2)	
100mg BID	31

†1 patient discontinued prior to the 28 day DLT review.

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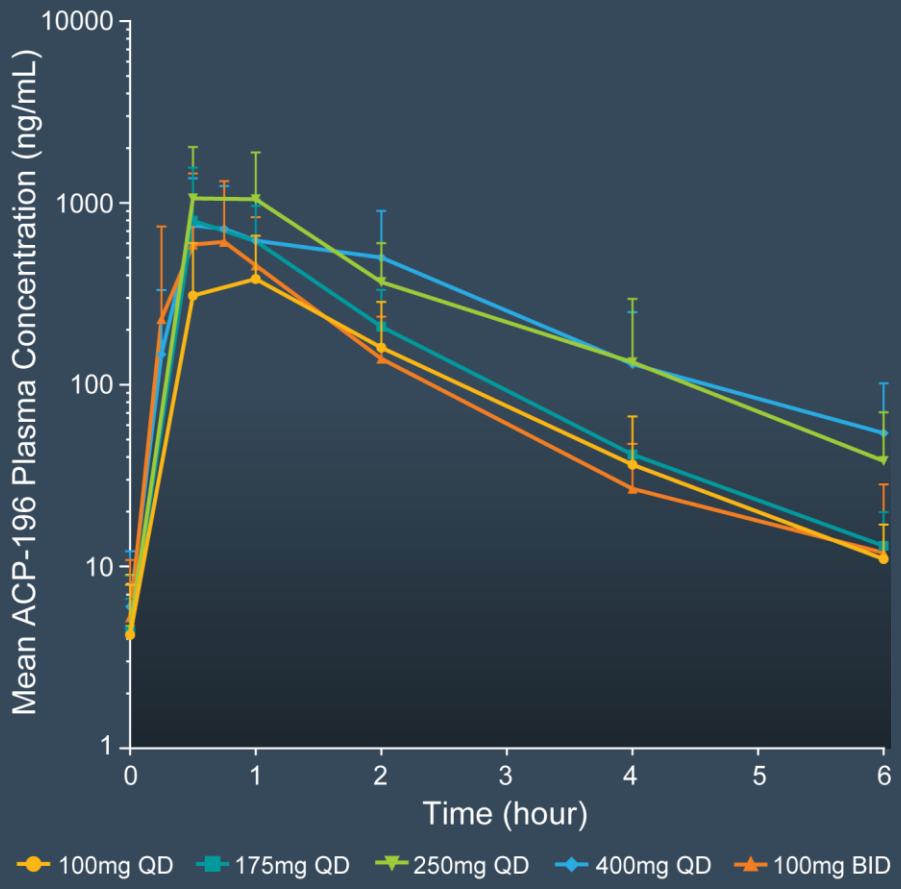
Patient Demographics

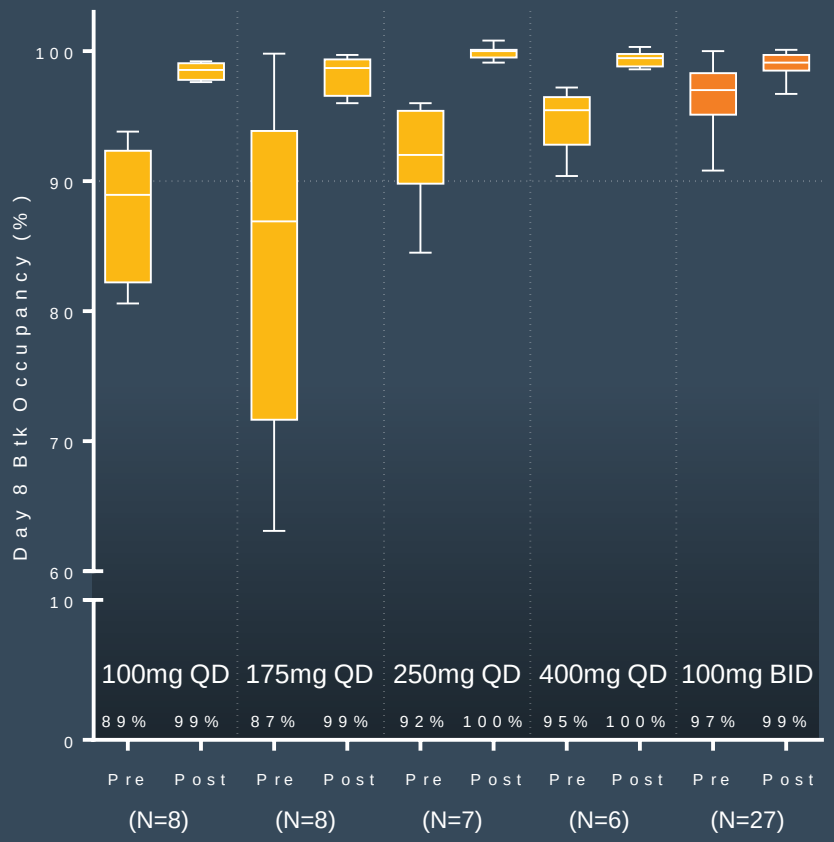
Characteristic	R/R CLL (N=61)
Patient Demographics	
Age (years), median (range)	62 (44-84)
Sex, men (%)	46 (75)
Prior therapies, median (range)	3 (1-13)
≥3 prior therapies, n (%)	32 (52)
Clinical Details	
ECOG performance status ≥1 (%)	39 (64)
Rai stage III/IV	41 (67)
Bulky disease ≥ 5 cm, n (%)	28 (46)
Cytopenia at baseline	44 (72)
Genomic Status	
Chromosome 11q22.3 deletion (del 11q), n (%)	17 (29)†
Chromosome 17p13.1 (del 17p), n (%)	18 (31)†
IGHV status (unmutated), n (%)	38 (75)†

†17/59 patients were evaluated for del(11q); 18/59 patients were evaluated for del(17p); 38/51 patients were evaluated for IGHV status (unmutated).

Pharmacokinetics/Pharmacodynamics

1 hour half-life; Rapid oral absorption; Full Btk occupancy





Pre, predose at 24 hrs; Post, 4 hrs postdose.

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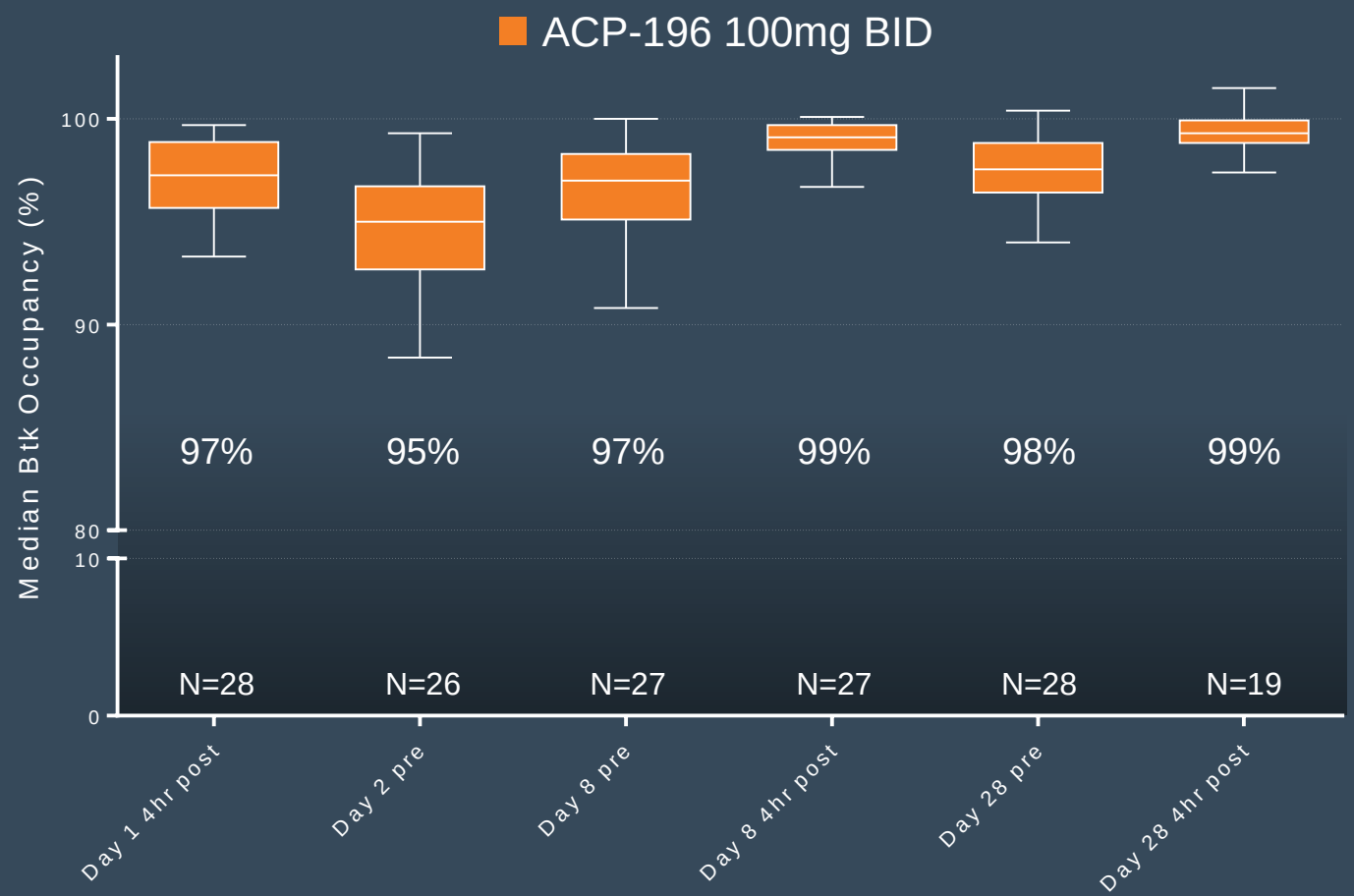
Twice-Daily Dosing (Complete & Continuous Btk Coverage)

24-hour Btk coverage (95-99%); Relevant to Btk protein resynthesis



Pre, predose at 24 hrs; Post, 4 hrs postdose.

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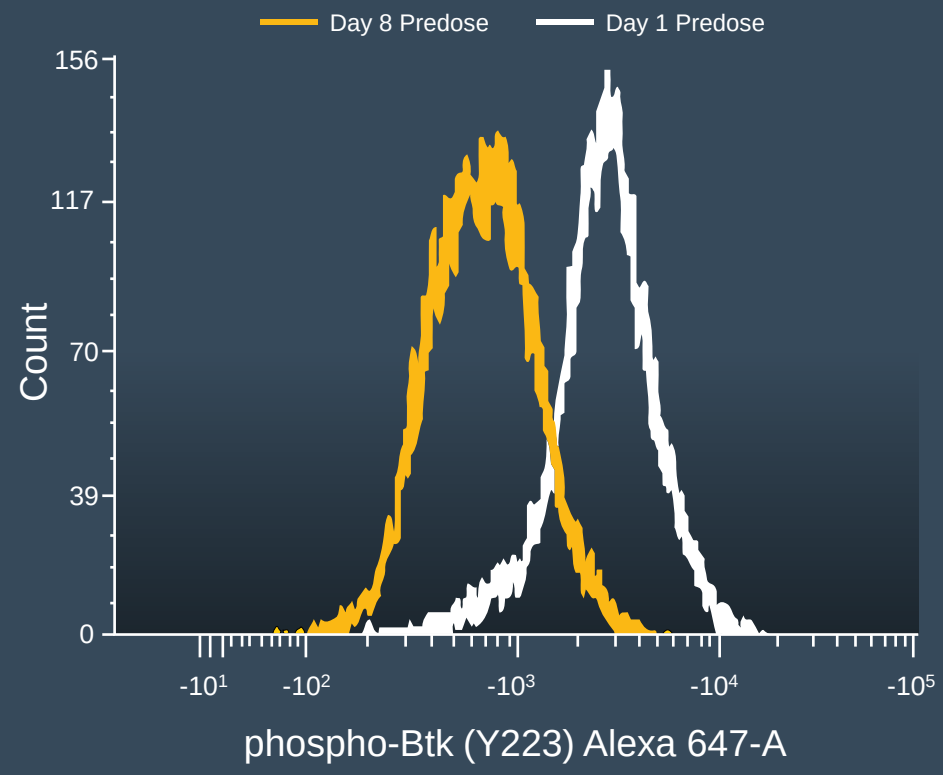
Phospho-Btk Inhibition (R/R Patients with CLL)

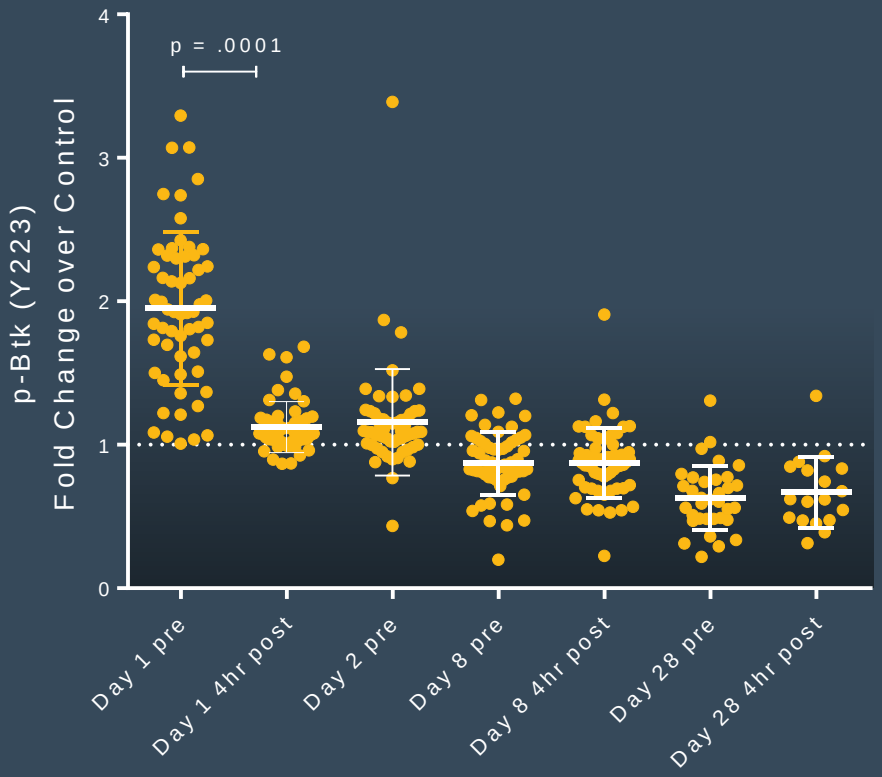
Complete inhibition of Btk signaling

Representative CLL Patient



BCR-Stimulated. Gated on $CD19^+$ $CD5^+$ B-CLL.

Composite CLL Patients



Pre, predose at 24 hrs; Post, 4 hrs postdose.

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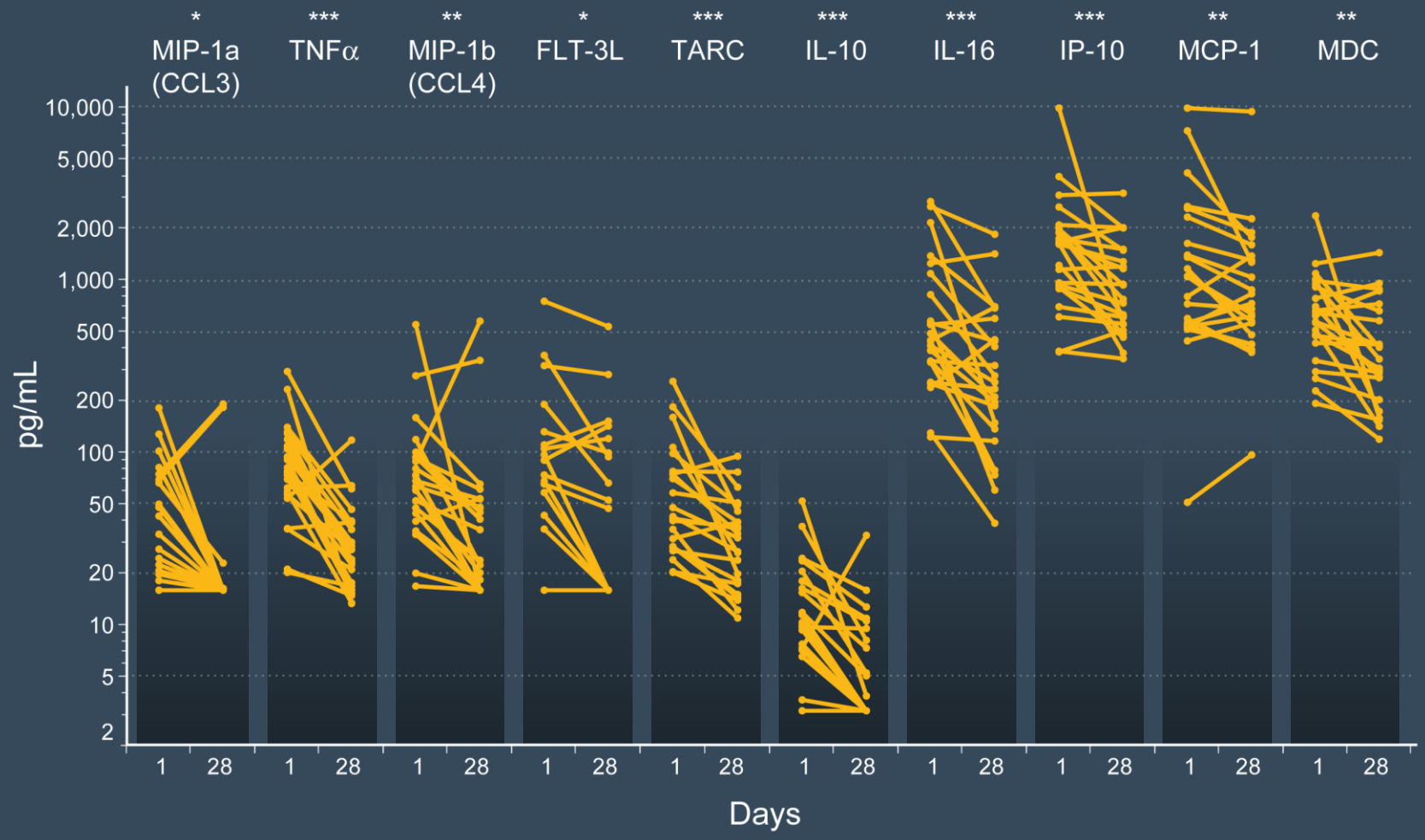
Cytokines Relevant to BCR Signaling & Tumor Homing Significantly Decrease



*P<0.05; **P<0.01, ***P<0.001. P-values based on Wilcoxon Signed-Rank test; n = 23.

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Status of All Patients (Median 14.3 Months of Follow-up)

- Number of patients enrolled on study, N=61
- Patients who have discontinued study, n=8
- Reasons for study discontinuation included:
  - Investigator or patient decision (n=2)
  - Active autoimmune hemolytic anemia that required additional therapy (n=1)
  - Diarrhea, gastritis and dyspnea (n=1, each)
  - Fatal pneumonia (n=1)
  - CLL progression (n=1)

Adverse Events (Median 14.3 Months of Follow-up)

Reported in ≥5% patients

Adverse Events (Treatment-Related), n (%)	Grade 1-2	Grade 3	N=61
Headache	12 (20)	–	12 (20)
Increased tendency to bruise	7 (12)	–	7 (12)
Petechiae	7 (12)	–	7 (12)
Diarrhea	6 (10)	–	6 (10)
Ecchymosis	5 (8)	–	5 (8)

Reported in ≥20% patients

Adverse Events (Treatment-Emergent), n (%)	Grade 1-2	Grade 3	N=61
Headache	26 (43)	–	26 (43)
Diarrhea	23 (38)	1 (2)	24 (39)
Increased weight	15 (25)	1 (2)	16 (26)
Pyrexia	12 (20)	2 (3)	14 (23)
Upper respiratory tract infection	14 (23)	–	14 (23)
Fatigue	11 (18)	2 (3)	13 (21)
Peripheral edema	13 (21)	–	13 (21)

01Oct2015; R/R CLL patients.

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Serious Adverse Events (Median 14.3 Months of Follow-up)

Reported in all patients

Serious Adverse Events (Treatment-Related), n (%)	Grade	N=61
Febrile neutropenia	4	1 (2)

Reported in ≥2 patients

Serious Adverse Events (Treatment-Emergent), n (%)	Grade	N=61
Pneumonia	3-4-5†	6 (10)
Autoimmune hemolytic anemia	3	2 (3)
Pyrexia	2-3	2 (3)

01Oct2015; R/R CLL patients.
†1 fatal pneumonia, unrelated.

No atrial fibrillation or major bleeding events

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Investigator-Assessed Response (Median 14.3 Months of Follow-up)

n (%)	All Cohorts (N=60)†	100mg QD (N=8)	175mg QD (N=8)	250mg QD (N=7)	400mg QD (N=6)	100mg BID (N=31)‡
PR	51 (85)	8 (100)	6 (75)	7 (100)	6 (100)	24 (77)
PR+L	6 (10)	0 (0)	2 (25)	0 (0)	0 (0)	4 (13)
SD	3 (5)	0 (0)	0 (0)	0 (0)	0 (0)	3 (10)
PD	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Median (range) Months of Patient Follow-up†

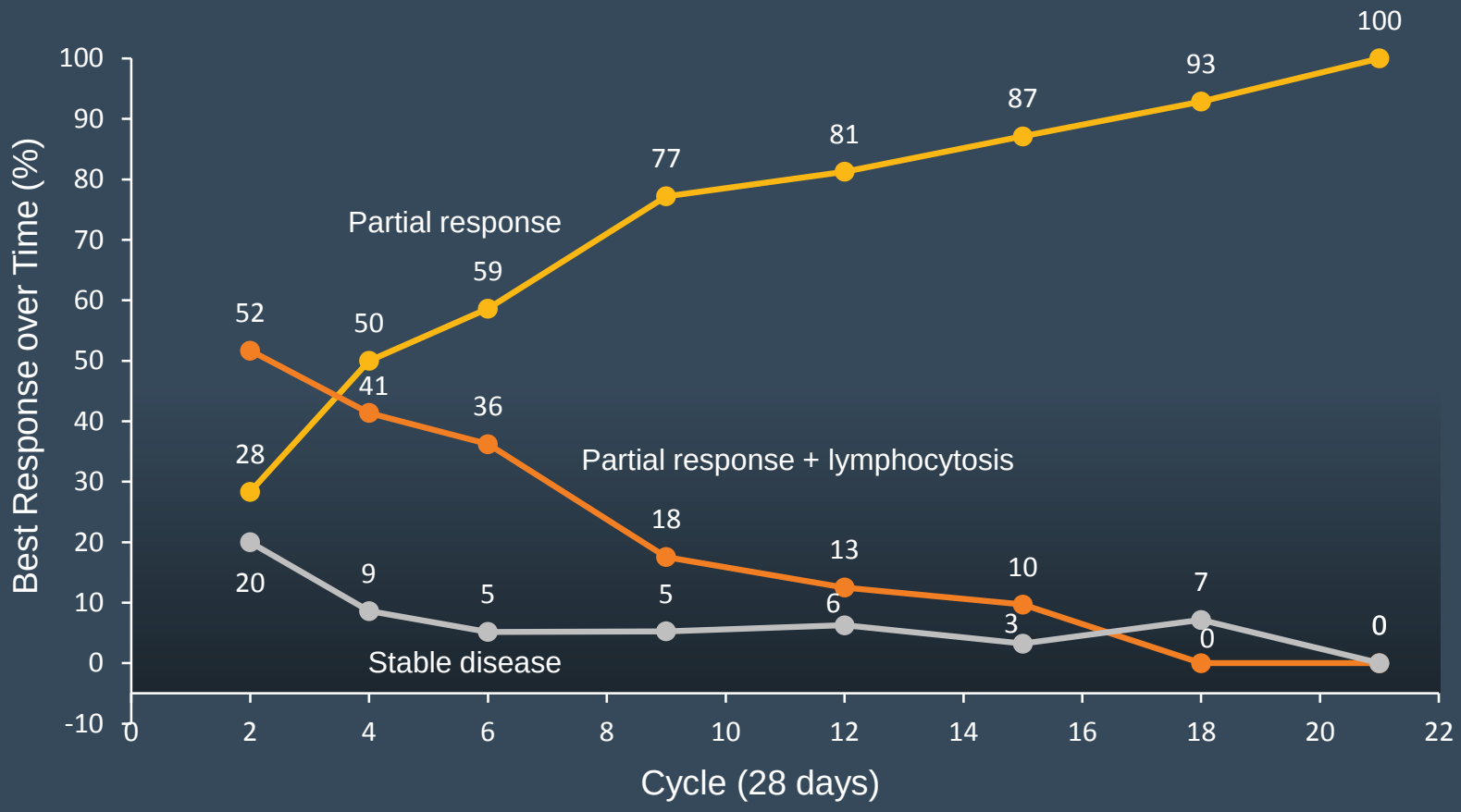
All Cohorts	100mg QD	175mg QD	250mg QD	400mg QD	100mg BID
14.3 (2.4-19.9)	19.2 (16.3-19.9)	17.8 (4.0-18.2)	16.4 (12.7-16.7)	14.6 (14.3-15.0)	11.8 (2.4-15.0)

PR, partial response; PR+L, partial response with lymphocytosis; SD, stable disease; PD, progressive disease.
†01Oct2015; R/R CLL patients; Based on modified IWCLL Halleck 2008; Best overall response assessment.
‡Includes 2 SD patients (100mg BID) with all nodes <1.5 cm at baseline CT.
*ORR, overall response rate (PR, PR+L); Del(17p) patients n = 18.

ORR* = 95% (57/60)

Del(17p) ORR* = 100% (89% PR, 11% PR+L)

Best Response Over Time



01Oct2015; R/R CLL patients.

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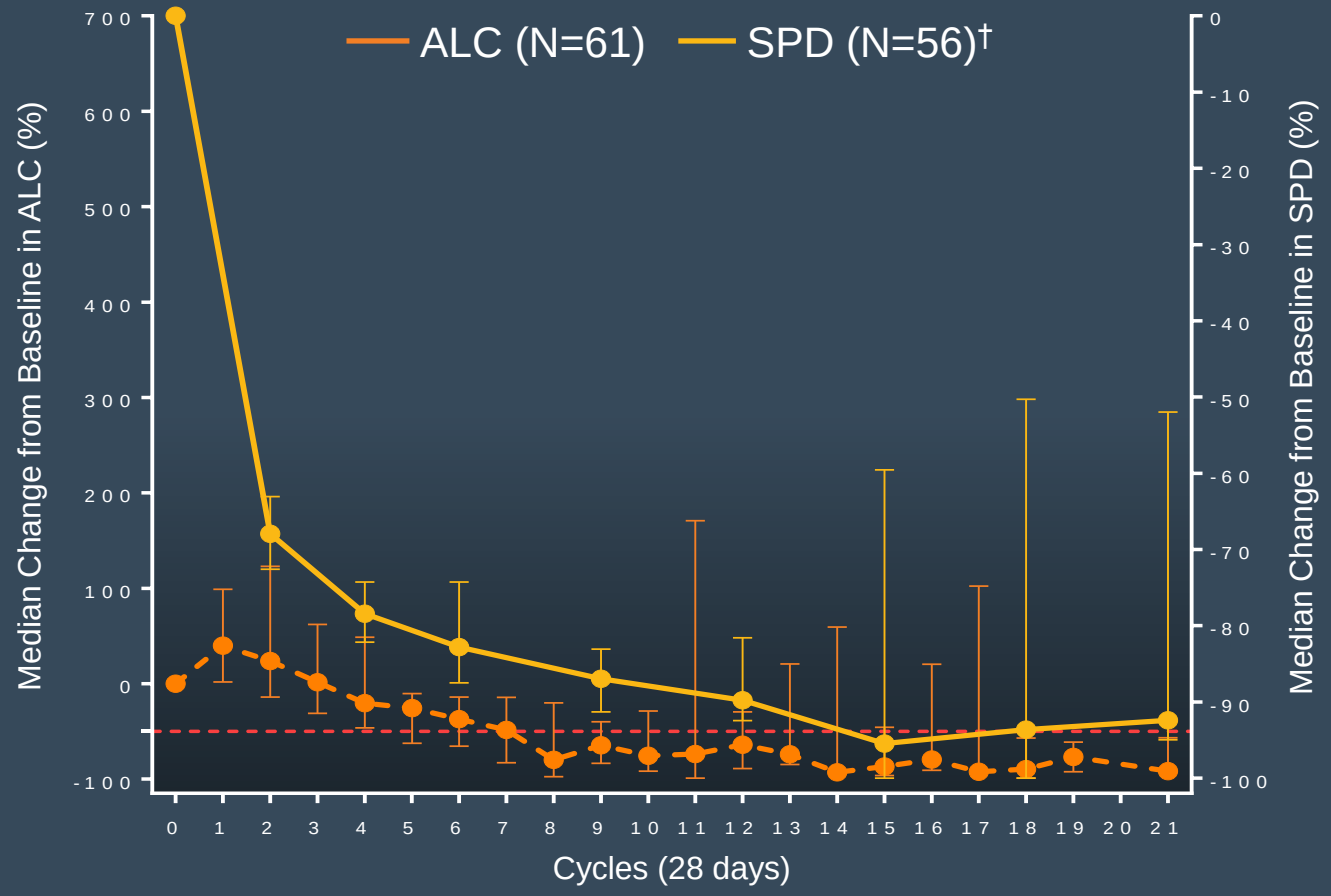
Change in ALC/SPD Over Time



01Oct2015; R/R CLL patients.
†4/61 patients had no baseline lymphadenopathy;
1 patient discontinued prior to first assessment.

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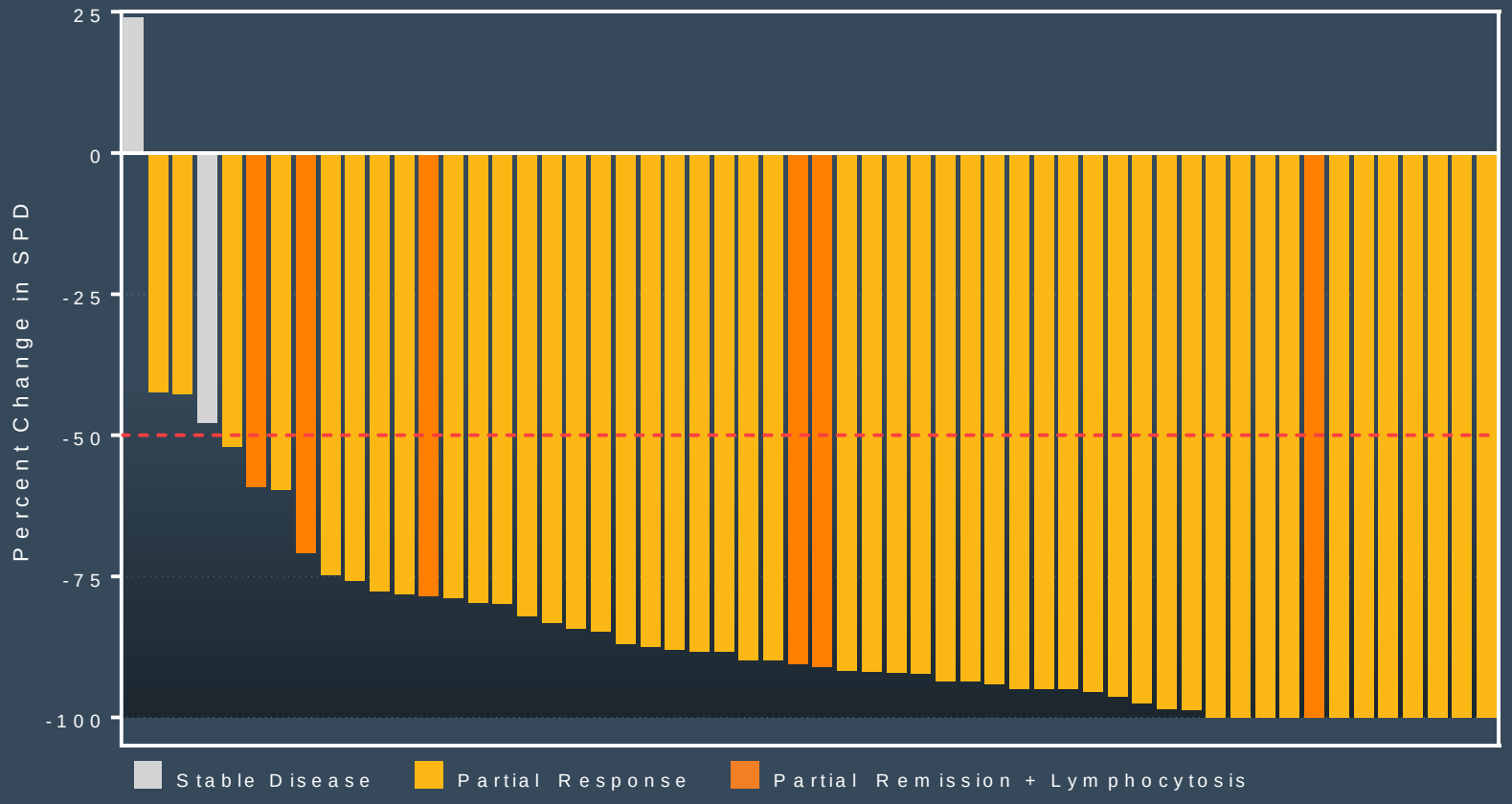
Change in Lymphadenopathy (CT Scan)



01Oct2015; R/R CLL patients; Median 14.3 months of follow-up.
4/61 patients had no baseline lymphadenopathy;
1 patient discontinued prior to first assessment.

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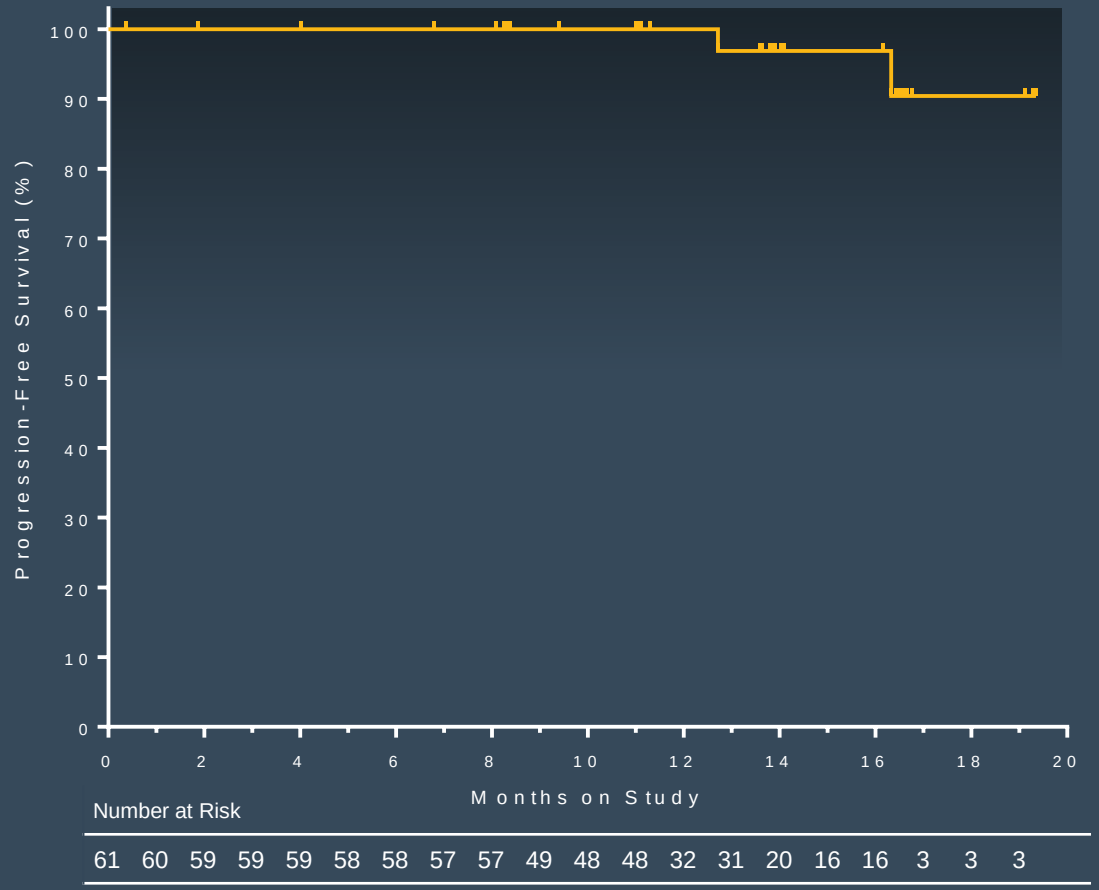
Change in B Symptoms/Cytopenia

Parameter, n (%)	N=61
B symptoms at study entry	16 (26)
No B symptoms (Cycle 3)	14/16 (88)
No B symptoms (Cycle 9)	15/15 (100)
Hemoglobin	
Pre-treatment ≤ 11 g/dL	21 (34)
On ACP-196 > 11 g/dL	16/21 (76)
ANC	
Pre-treatment ≤ 1,500/µL	15 (25)
On ACP-196 >1,500/µL	12/15 (80)
Platelet Count	
Pre-treatment ≤ 100,000/µL	32 (52)
On ACP-196 >100,000/µL	20/32 (63)

01Oct2015; R/R CLL patients.

Progression-Free Survival

2 reported K-M events†



01Oct2015; R/R CLL patients; N = 61. Median 14.3 months of follow-up.
†1 fatal pneumonia; 1 CLL Progression.

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Summary of Safety & Efficacy

- ACP-196 is a second-generation, selective Btk inhibitor with favorable biochemical and pharmacokinetic properties.
- ACP-196 has a promising safety profile in this pretreated group of CLL patients; no episodes of atrial fibrillation or major bleeding observed at this time.
- Early onset treatment-related lymphocytosis was not as significant or persistent as reported with other BCR antagonists.
- ACP-196 demonstrated a high response rate (95%) and durable remissions, irrespective of del(17p) status.
- Despite median follow-up beyond 1 year, no cases of Richter's transformation have been observed.

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Comparative Phase 3 Study

Based on these data, a global phase 3 study of ACP-196 compared with ibrutinib has commenced in patients with high-risk, relapsed CLL (NCT02477696).

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