DANA-FARBER CANCER INSTITUTE

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HARVARD MEDICAL SCHOOL

Next Generation BTK Inhibitors: Acalabrutinib

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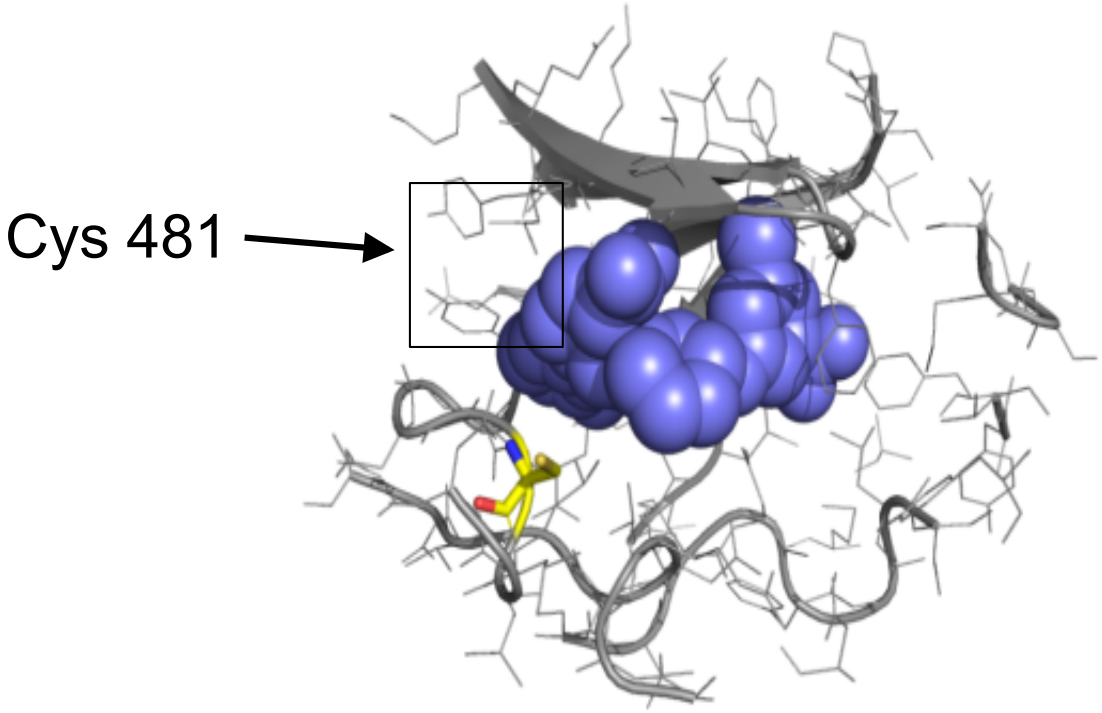
Two Classes of Next Gen BTK Inhibitors

- **Covalent binding to Cys481:**
  - **Acalabrutinib**
  - **BGB-3111**
  - **Tirabrutinib (GS-4059, ONO-4059)**

- **Designed to target the Cys481X resistance mutations:**
  - **SNS-062**
  - **ARQ-531**
  - **LOXO-305 (RXC-005)**

SNS-062 Activity Does Not Require C481

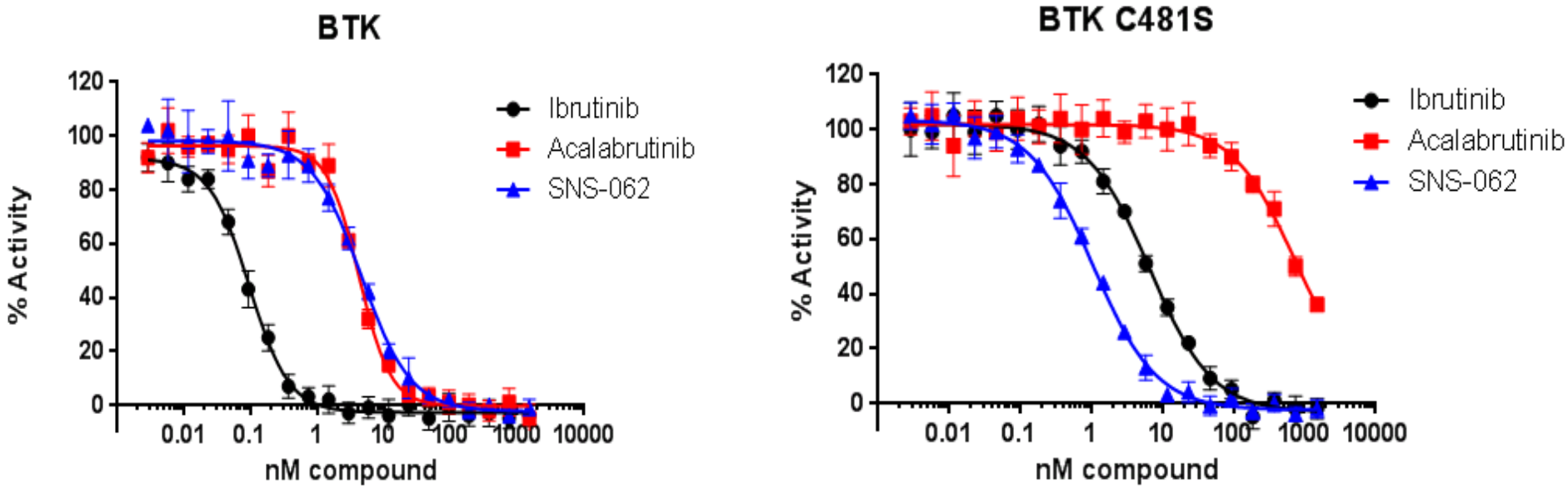
- **Co-crystallization of SNS-062 with the kinase domain of BTK (BTK-KD) shows that SNS-062 binds BTK through non-covalent interactions**



SNS-062 does not bind EGFR, which may translate to lower potential for diarrhea and skin rashes

Sunesis, Whistler Meeting 2016

SNS-062 Activity is Unaffected by C481S Mutation



IC_{50} (nM), [ATP] = 50 mM	WT BTK	C481S BTK	Fold Change
SNS-062	4.6	1.1	0.2
Ibrutinib	0.1	6.6	66
Acalabrutinib	4.2	707	168

Can We Make a Better BTK Inhibitor?

Kinase Inhibition Profile of Ibrutinib

Kinase	IC_{50}, nM	Btk selectivity, fold
BTK	0.5	--
BLK*	0.5	1
BMX*	0.8	1.6
CSK	2.3	4.6
FGR	2.3	4.6
BRK	3.3	6.6
HCK	3.7	7.4
EGFR*	5.6	11.2
YES	6.5	13
ErbB2*	9.4	18.8
ITK*	10.7	21.4
JAK3*	16.1	32.2
FRK	29.2	58.4
LCK	33.2	66.4
RET	36.5	73
FLT3	73	146
TEC*	78	156
ABL	86	172
FYN	96	192
RIPK2	152	304
c-SRC	171	342
LYN	200	400

2nd-Generation Btk Inhibitors: Acalabrutinib (ACP196)

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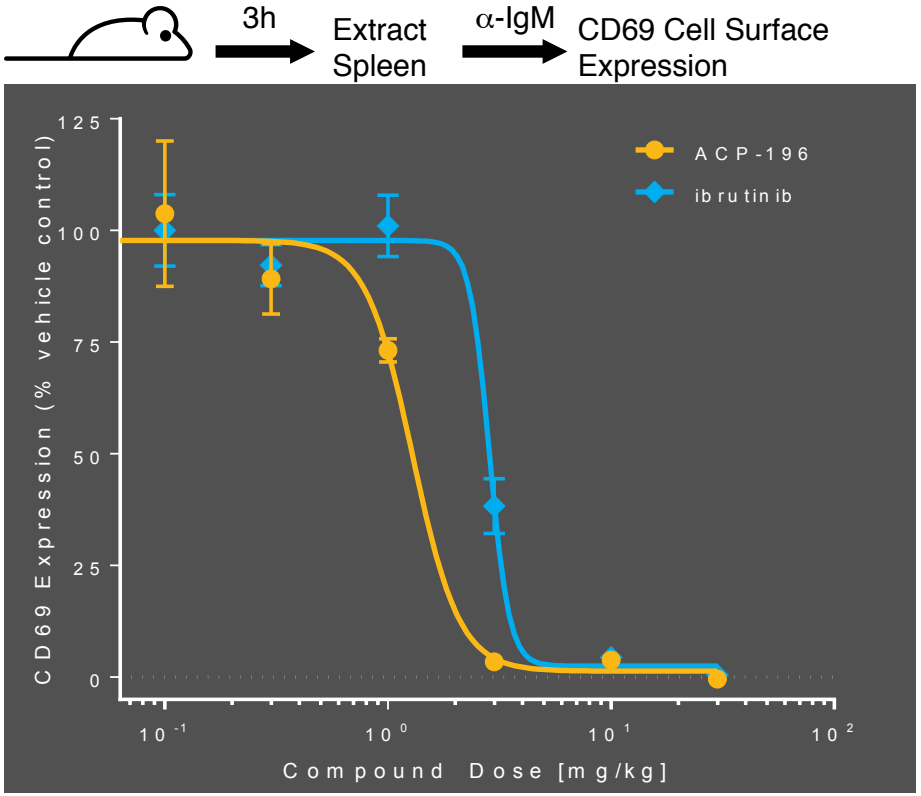
Kinase Inhibition IC_{50} (nM)

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

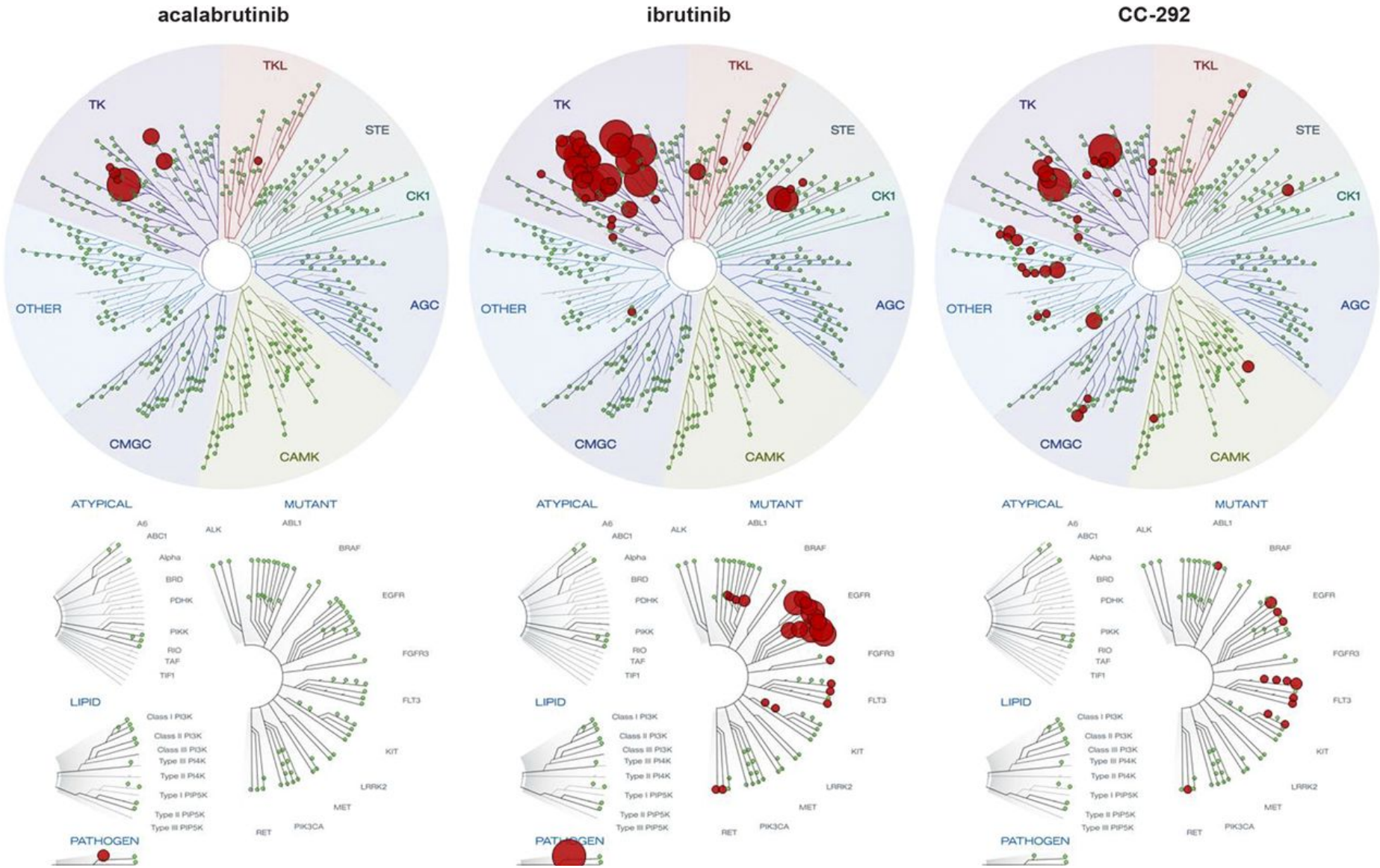
Covey AACR 2015. Abstract 2596.

In Vivo Potency



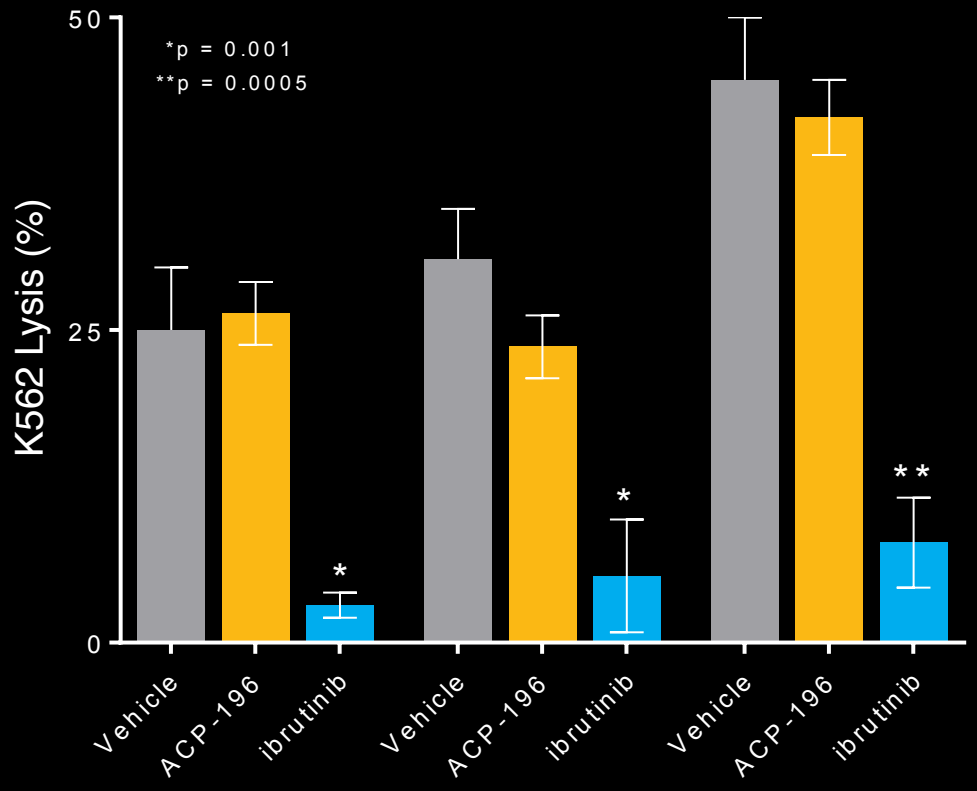
	ACP-196	ibrutinib
ED_{50} (mg/kg)	1.3	2.9

Competitive Binding Assays on Kinases (DiscoverX)

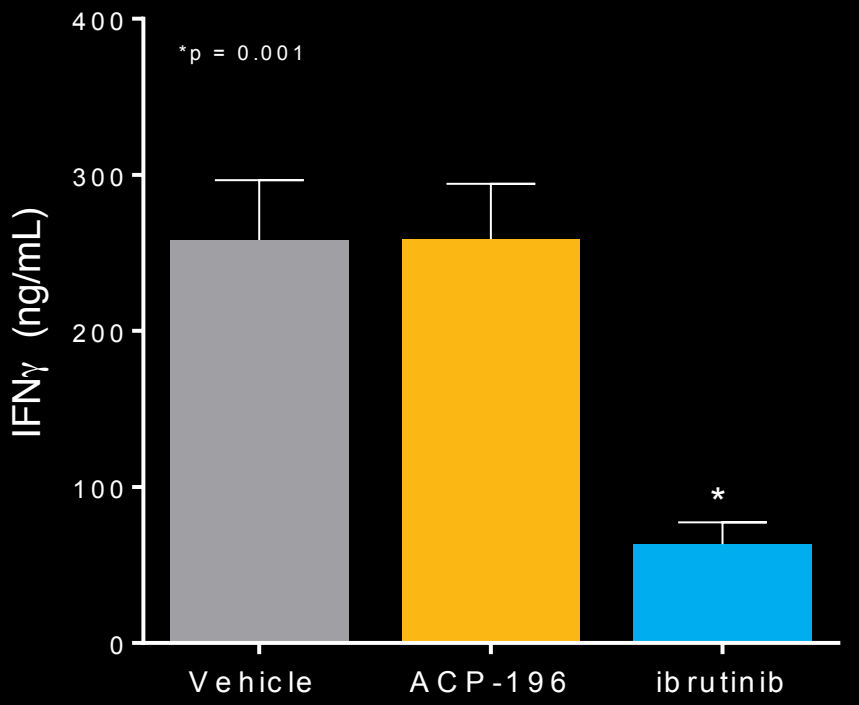


Selectivity Profile: Reduced ITK

Non ADCC-mediated NK cell lysis; CD8+ T cell IFNγ production



ACP-196 does not inhibit NK cell cytolytic activity†



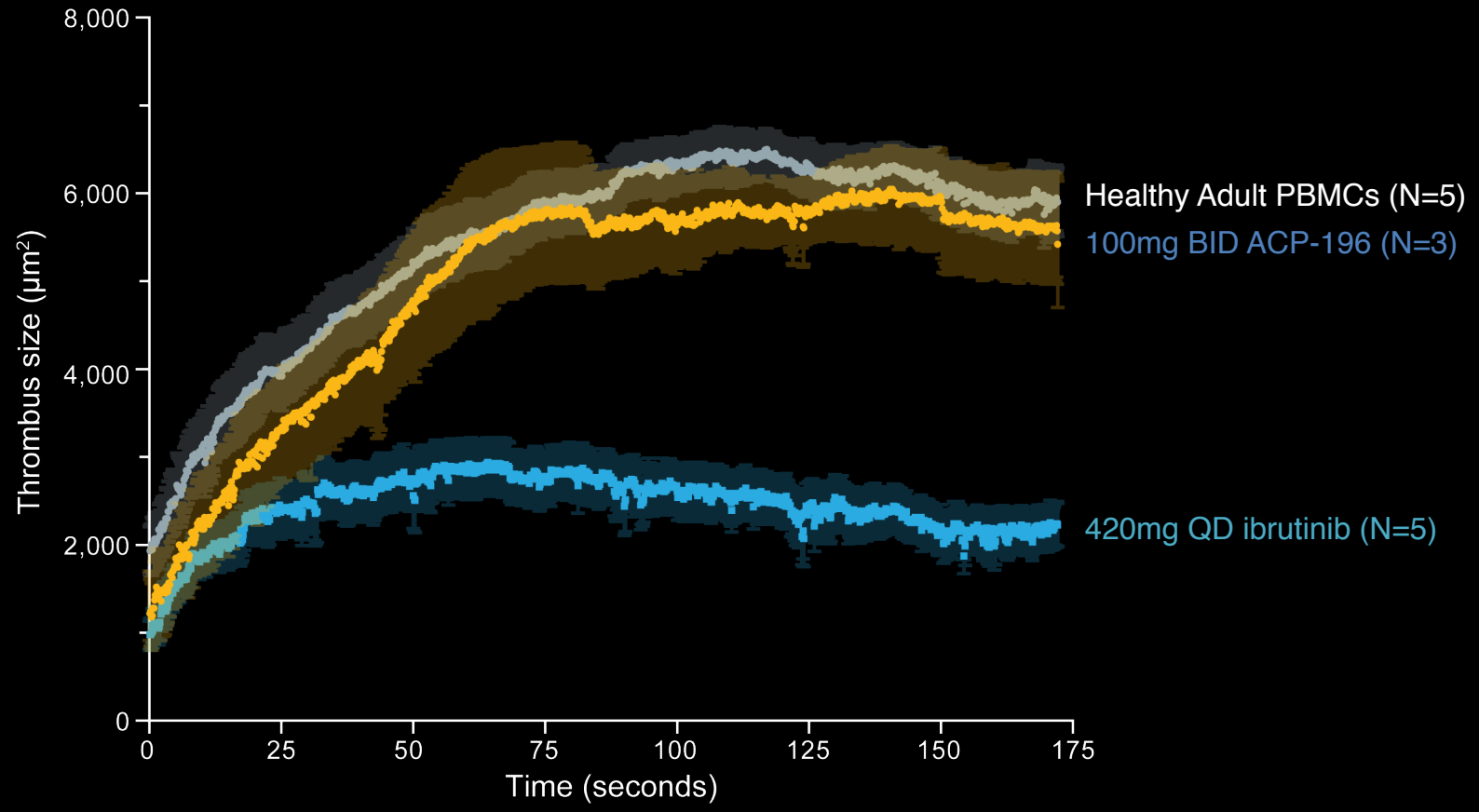
ACP-196 does not inhibit IFNγ CD8+ T cells‡

Lannutti AACR 2015. Abstract 408.
†Cells were preincubated with ACP-196 and ibrutinib (500nM each), then washed before being assayed.

‡Cells were preincubated with ACP-196 and ibrutinib (500nM each), then washed before being assayed.
CD8+ T cells were stimulated with anti-TCR Ab to produce IFNγ.

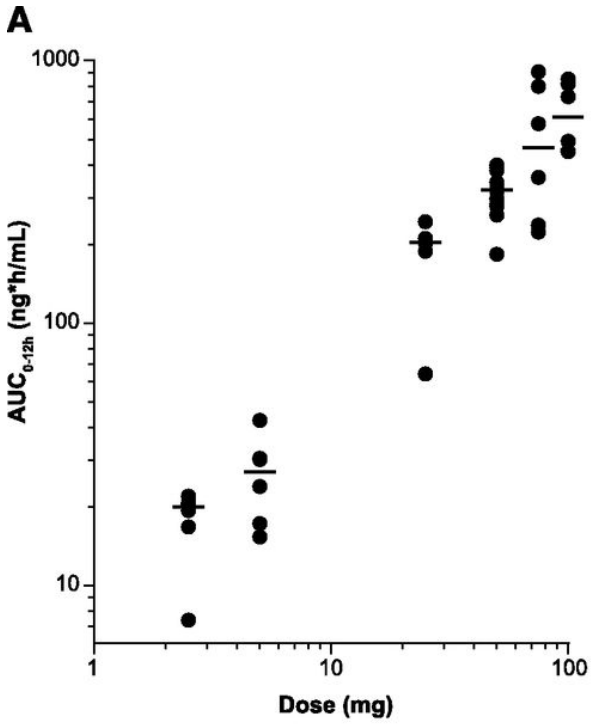
Platelet Aggregation (R/R Pts with CLL)

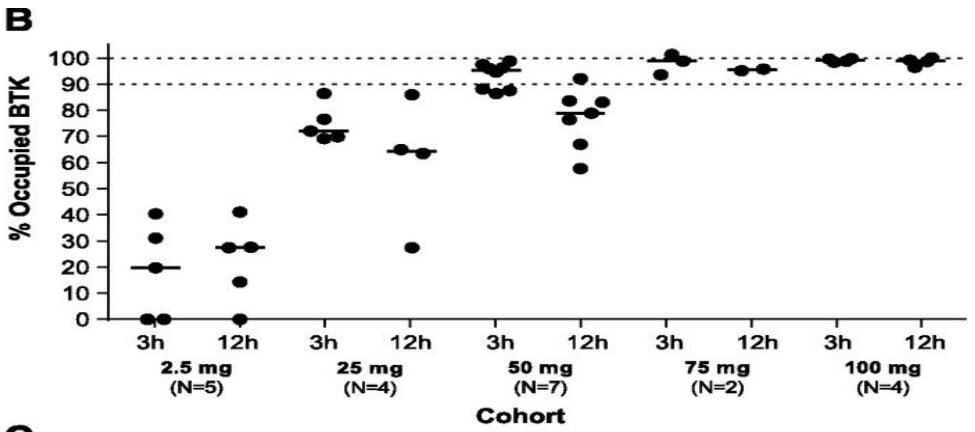
ACP-196 does not inhibit platelet mediated thrombosis

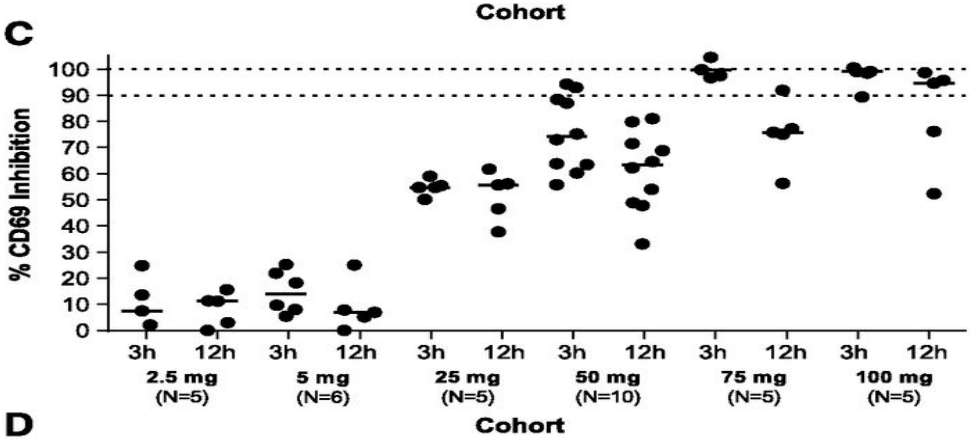


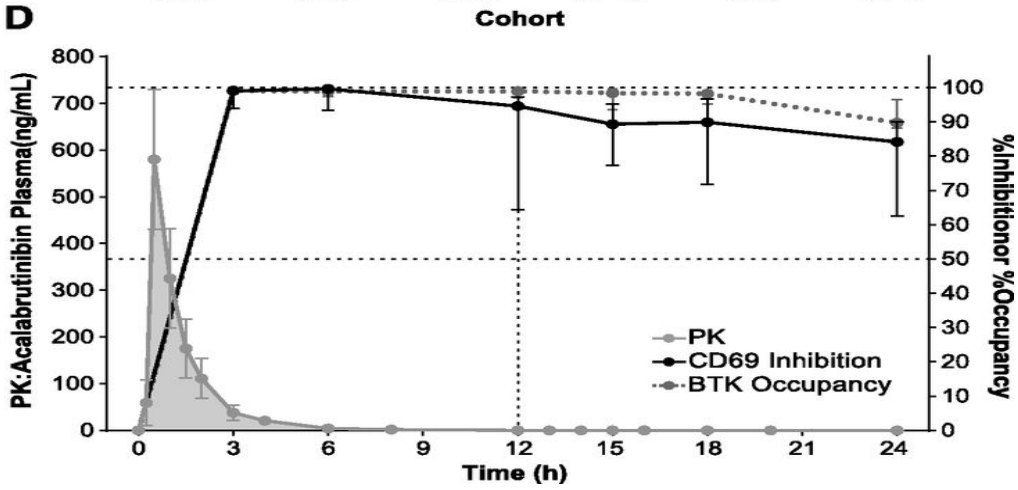
In vivo murine thrombosis model. Chen, et al. *Blood.* 2014.

PK versus PD after Acalabrutinib Dose in Healthy Volunteers



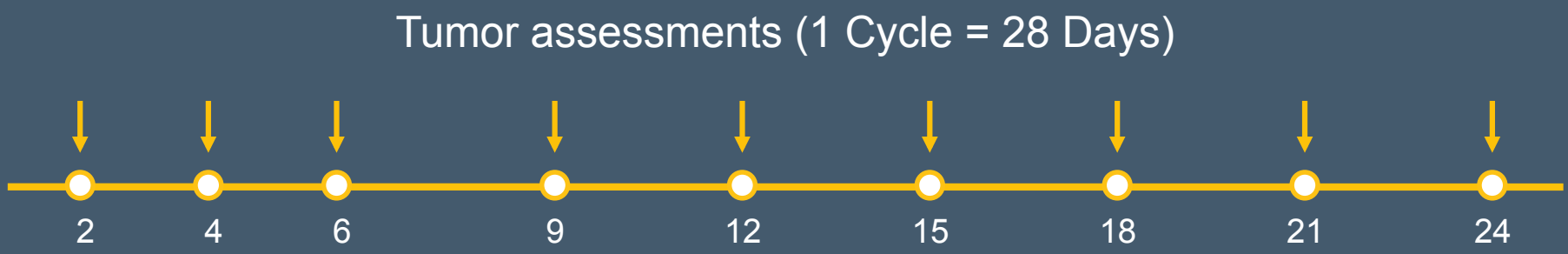






Tjeerd Barf et al. J Pharmacol Exp Ther 2017;363:240-252

ACE-CL-001: Study Design



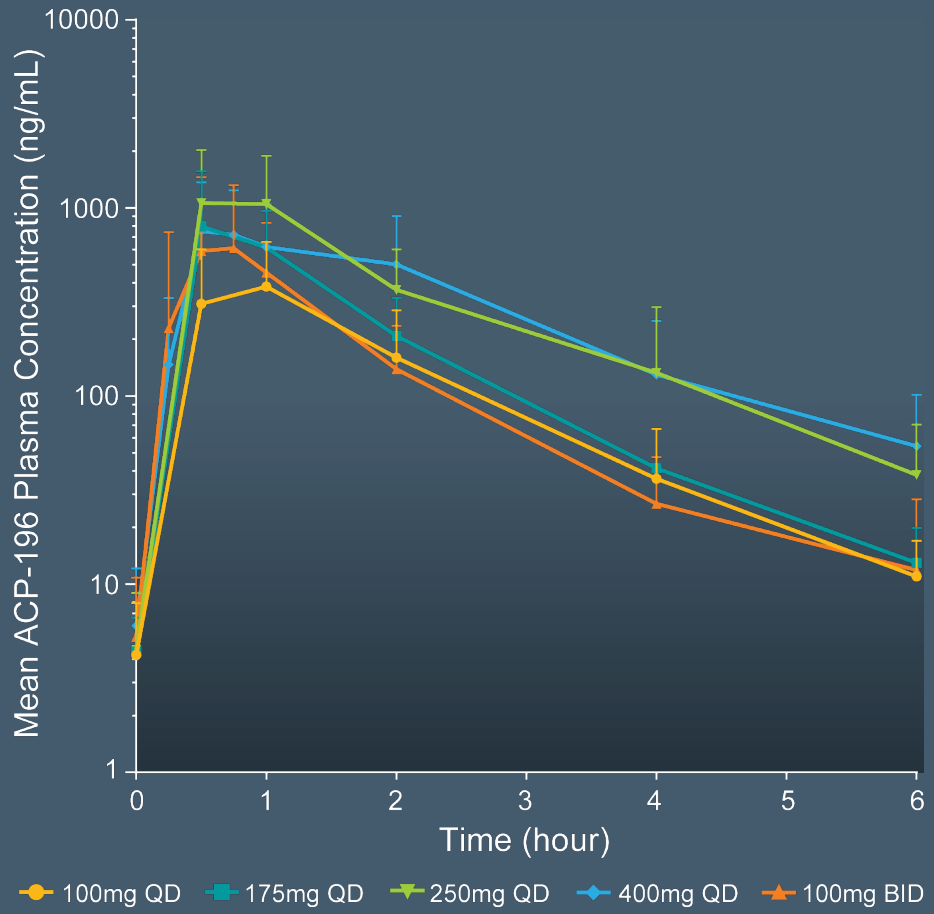
- Relapsed/Refractory CLL
- ECOG PS ≤ 2
- Prior exposure to Btk inhibitors *not* allowed
- Prior exposure to PI3Kδ, BCL-2 inhibitors allowed
- Pancytopenia, prior BMT allowed

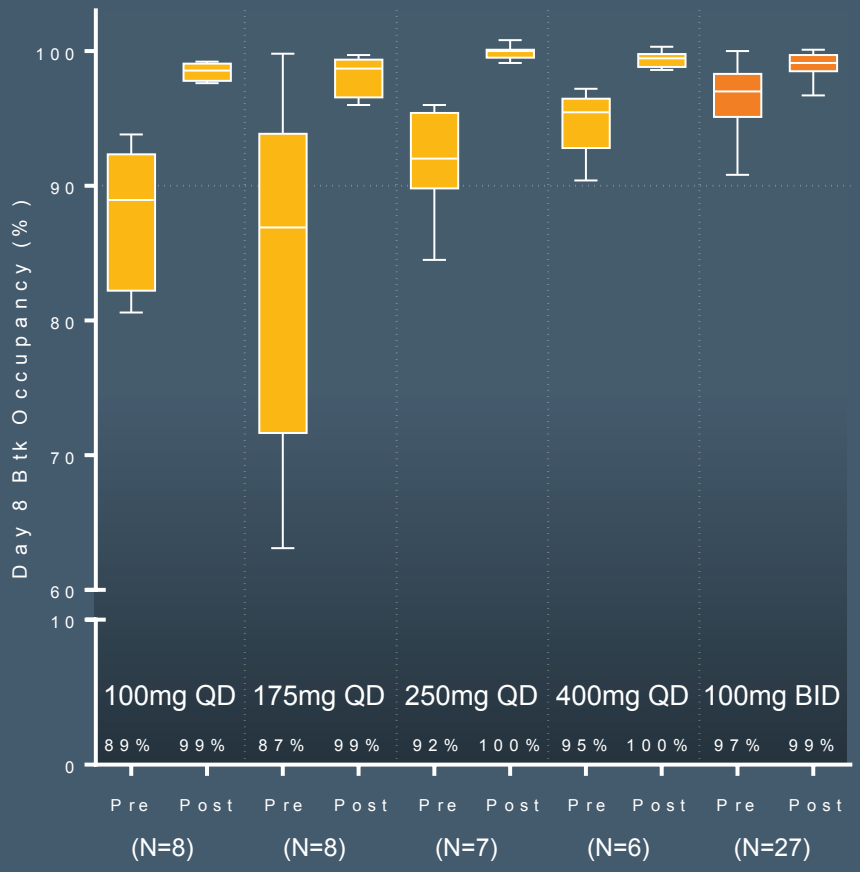
ACP-196 Cohorts	**N=61**
Dose Escalation, 6-8 patients	
100mg QD	9†
175mg QD	8
250mg QD	7
400mg QD	6
Dose Expansion (Phase 2)	
100mg BID	31

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

Pharmacokinetics/Pharmacodynamics

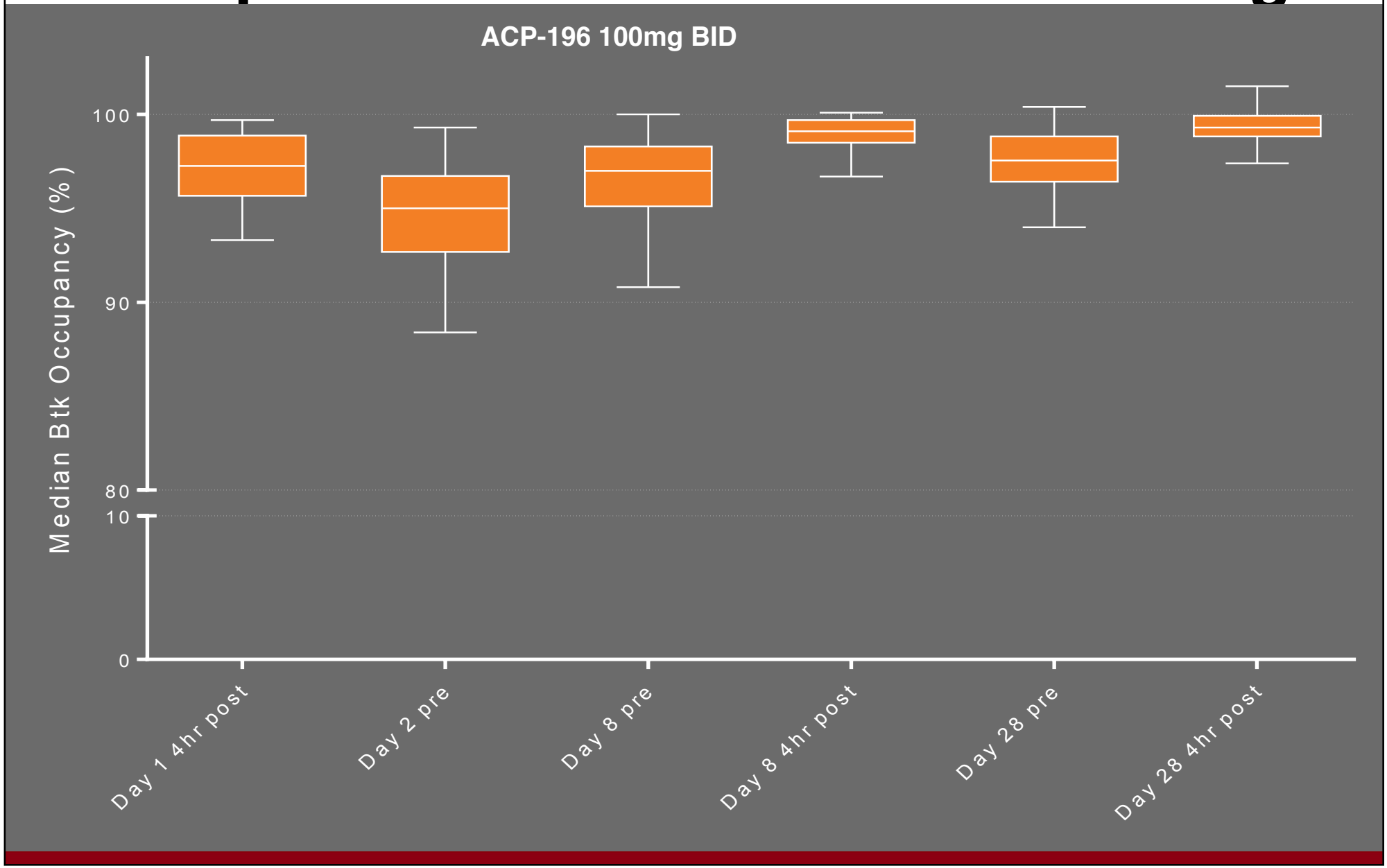
1 hour half-life; Rapid oral absorption; Full Btk occupancy





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

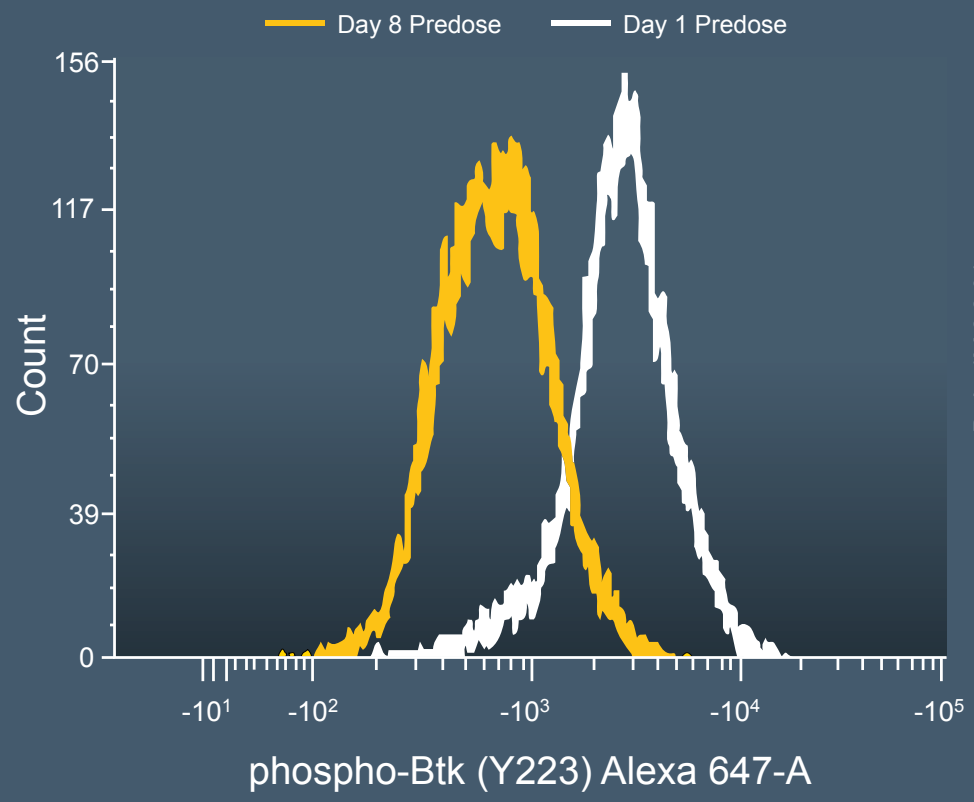
ACP-196 Twice-Daily Dosing: Complete & Continuous Btk Coverage



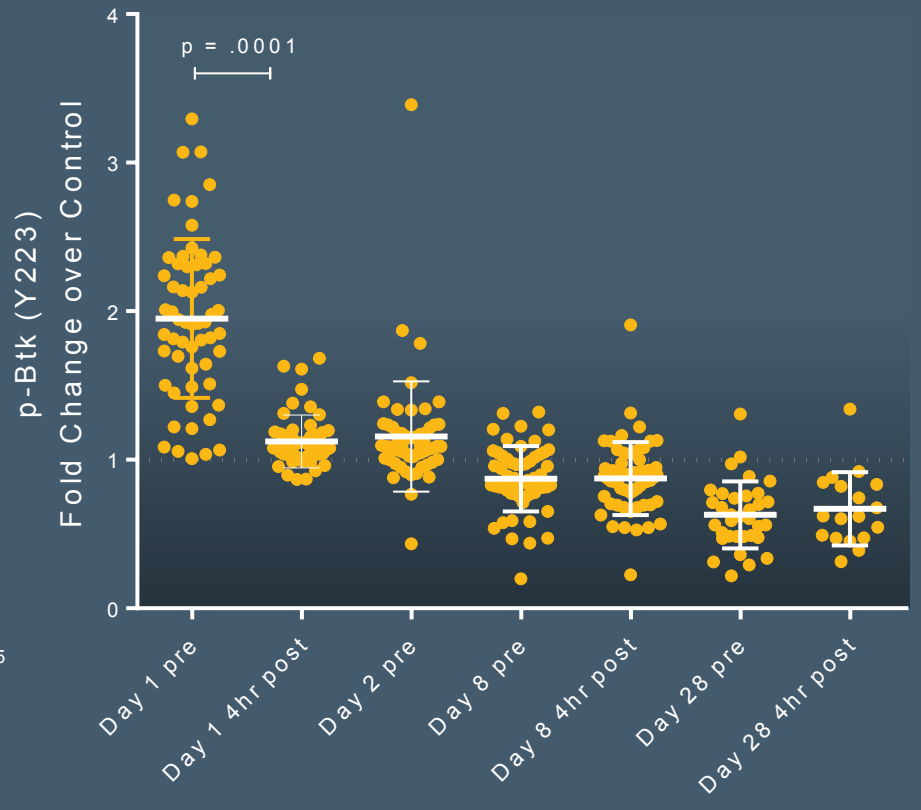
Phospho-Btk Inhibition (R/R Pts with CLL)

Complete inhibition of Btk signaling

Representative CLL Patient



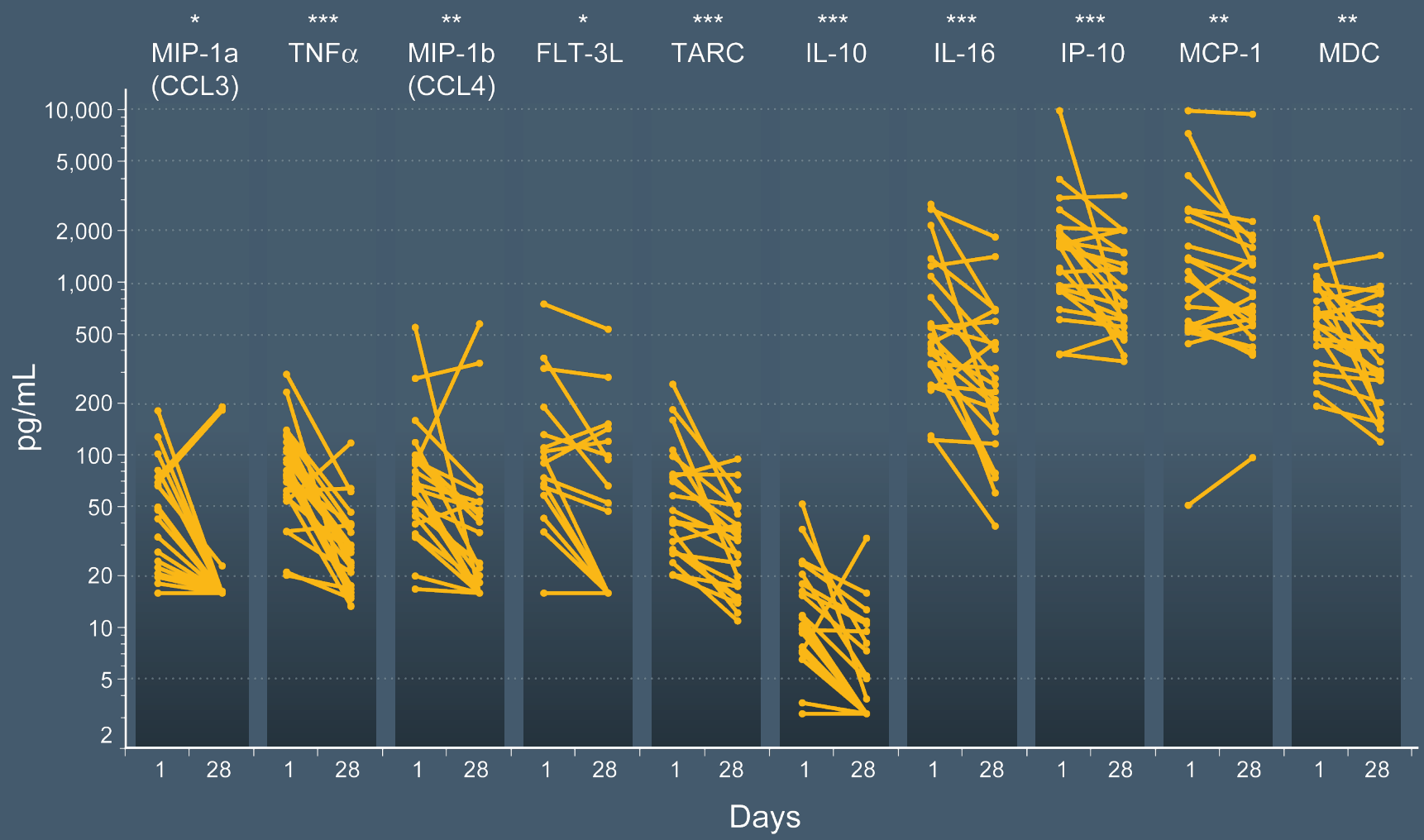
Composite CLL Patients



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

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

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.

Adverse Events (Median 14.3 Mos F/U)

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)

Serious Adverse Events

Reported in all patients

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

Reported in ≥2 patients

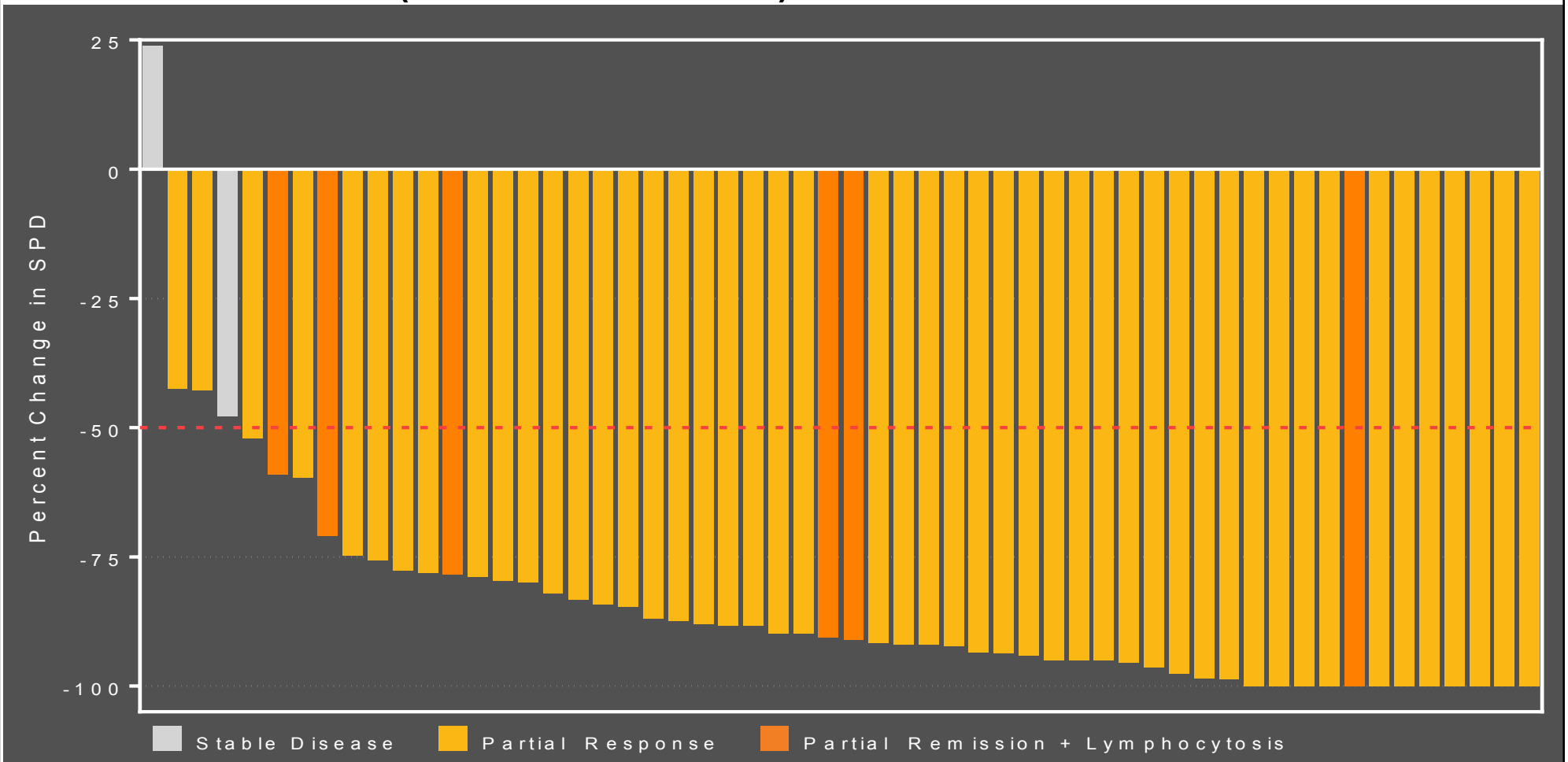
Serious Adverse Events (Treatment-Emergent), n (%)	Grade	N=61
Pneumonia	3-4-5[†]	6 (10)
Autoimmune hemolytic anemia	3	2 (3)
Pyrexia	2-3	2 (3)

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

No atrial fibrillation or major bleeding events

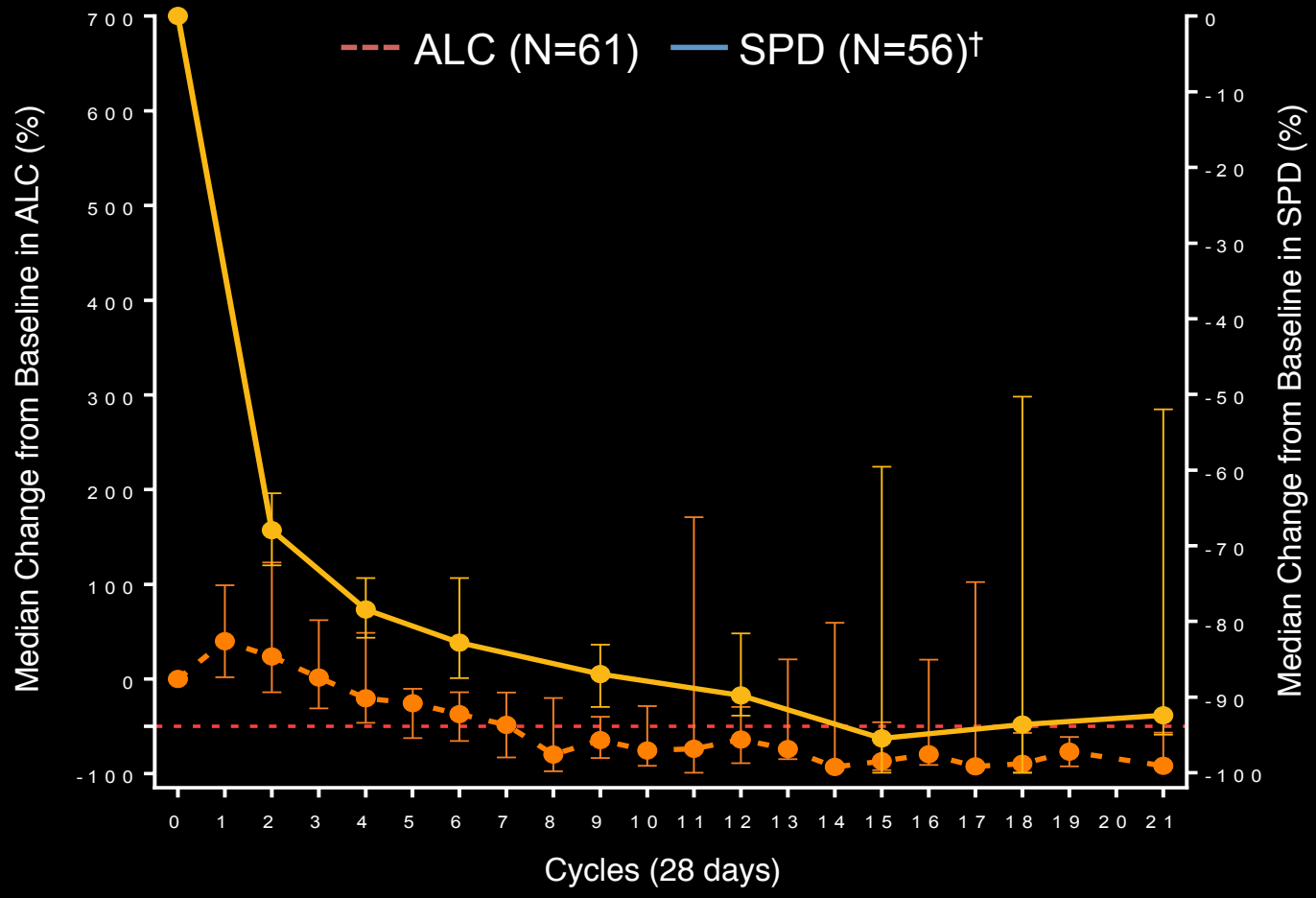
Acalabrutinib Nodal Response (CT Scan)

ORR 95% (85% PR + 10% PR-L) at 14.3 mo F/U



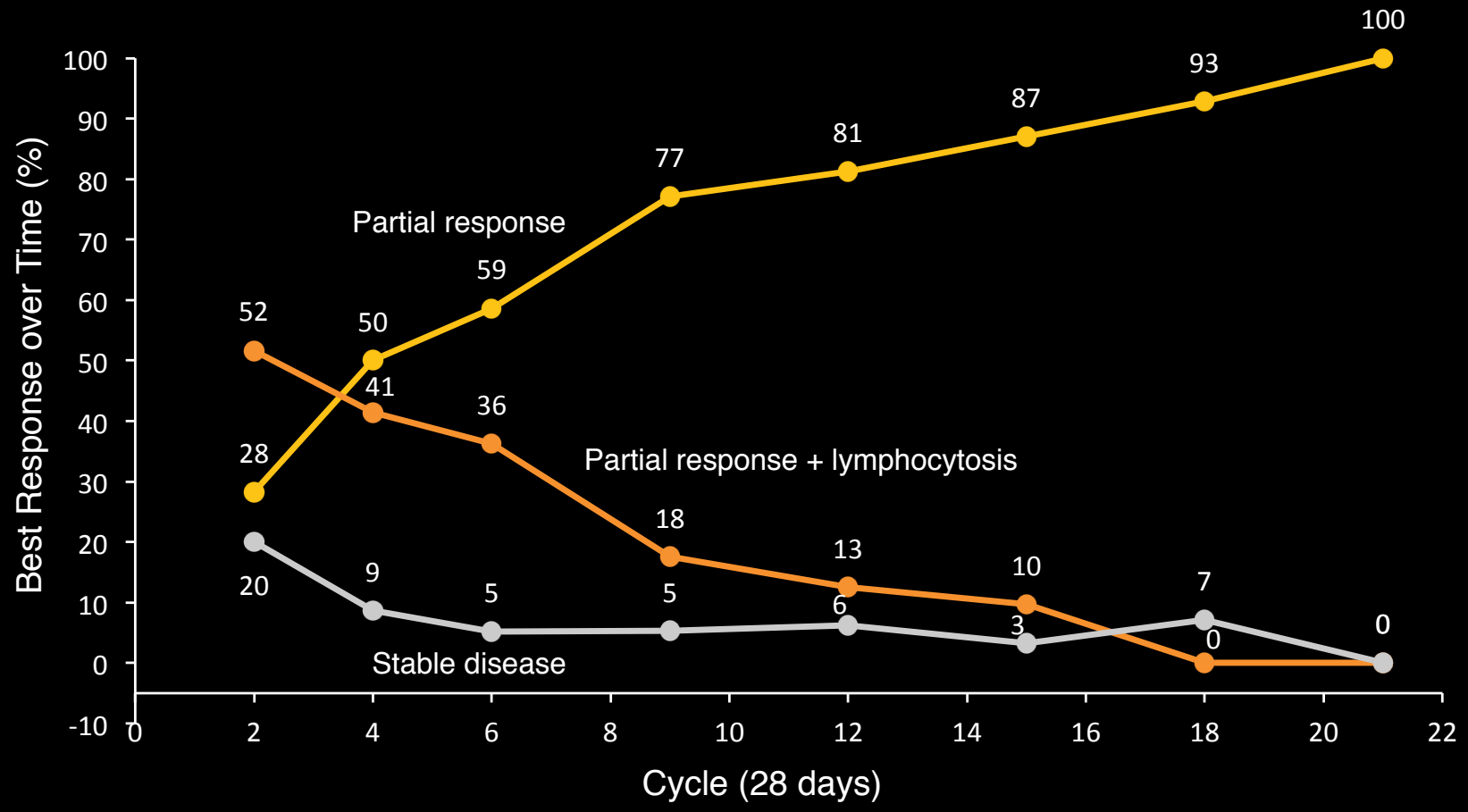
01Oct2015; R/R CLL patients; Median 14.3 months of follow-up.
4/61 patients had no baseline lymphadenopathy;
1 patient discontinued prior to first assessment.

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.

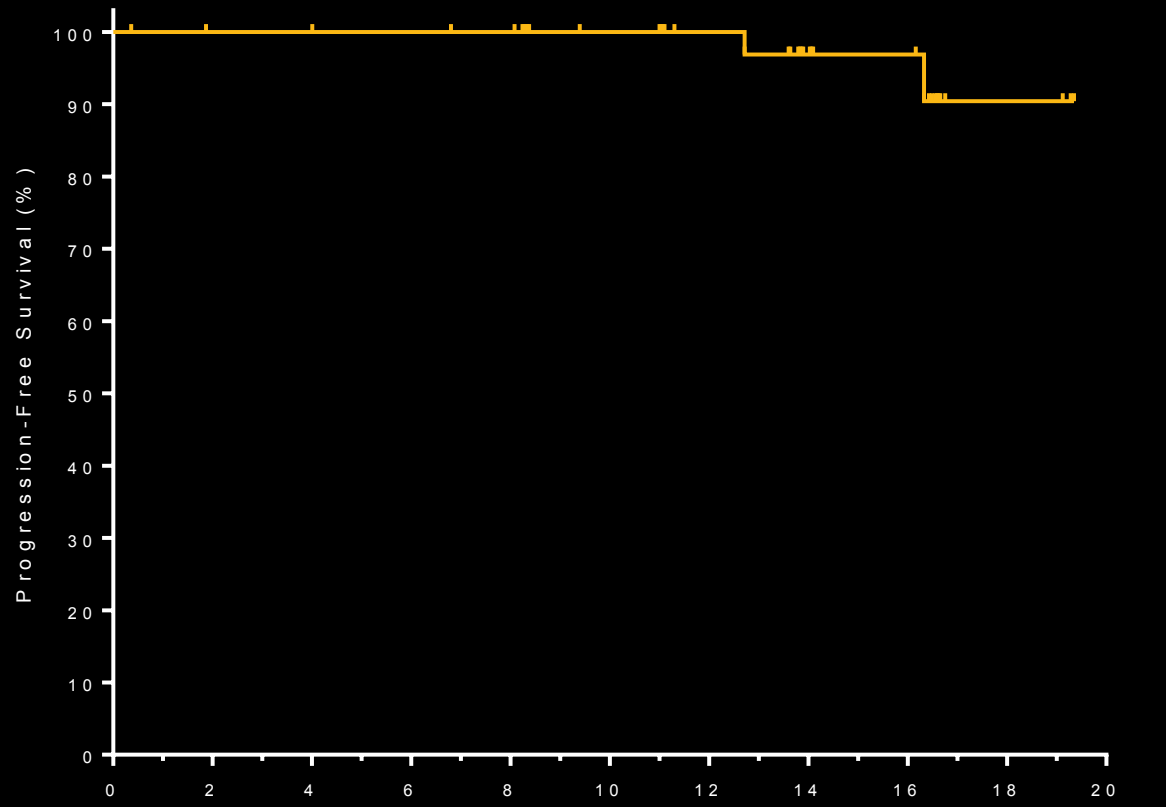
Best Response Over Time



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.

ACE-CL-001: ASH Update

Efficacy: ORR 85%, +PR-L, 93%

18 mo PFS: 88%, 17p 78%

81% remain on therapy

Safety: N=610, median 1 prior regimen, median 14.2 mos on therapy

Atrial fibrillation 2.3%

Major hemorrhage 2.5% (5 GI, 3 CNS)

Gr3+ infections, 16.2% (PJP, 2 aspergillus, 1 crypto)

ACE-CL-001: Acalabrutinib Ibrutinib Intolerant Cohort

Ibrutinib-Intolerant CLL Cohort (N = 33)[a]

Inclusion criteria

- Confirmed CLL and intolerance to ibrutinib as determined by the investigator[b]
- Age ≥18 years
- ECOG PS ≤2

Exclusion criteria

- Central nervous system involvement of lymphoma
- Significant cardiovascular disease[c]

Primary objective

- Safety, including frequency, severity, and attribution of AEs

Secondary objectives

- ORR, duration of response, PFS

Awan F, et al. ASH 2016

Baseline Patient Characteristics

Characteristic	N = 33
Median age, y (range)	64 (50-82)
Rai stage III-IV[a], n (%)	17 (52)
Bulky disease ≥5 cm, n/N (%)	10/32 (31)
Median no. of prior therapies (range)	4 (2-13)
Ibrutinib as last prior therapy, n (%)	30 (91)
Median duration of prior ibrutinib treatment, mo (range)	11.5 (1-62)
Median time from ibrutinib end to acalabrutinib start, d (range)	47 (3-331)
Baseline Cytopenias	
ANC ≤1500/µL	4 (12)
Hemoglobin ≤11.0 g/dL	9 (27)
Platelets ≤100,000/µL	13 (39)
Genomic Status	
Del11q	10/32 (31)
Del17p	12/32 (38)
Unmutated *IGHV*	25/31 (81)

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Patient Disposition

Disposition, n (%)	
Treated	33 (100)
Discontinued treatment	9 (27)
Progressive disease	3 (9)
Adverse event[a]	3 (9)
Physician decision[b]	1 (3)
Other[c]	2 (6)
On treatment	24 (73)

[a]Stroke (hemorrhagic) and fungal infection led to death (n = 1 patient each); metastatic endometrial cancer (n = 1).
[b]Concurrent hemophilia.
[c]Increase in BTK C481S mutation frequency in peripheral blood and central nervous system involvement (n = 1 patient each).

- Median time on treatment: 12.2 months (range, 0.2-23.6 months)

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AEs on Ibrutinib (≥2 Patients) (Investigator Assessed; N=33)

Adverse Event, n (%)	Grade 1	Grade 2	Grade 3	Unknown	Total
Rash	3 (9)	1 (3)	2 (6)	0	7 (21)
Arthralgia	1 (3)	2 (9)	2 (6)	0	6 (18)
Diarrhea	1 (3)	1 (3)	2 (6)	1 (3)	5 (15)
Fatigue	2 (6)	1 (3)	1 (3)	0	4 (12)
Hemorrhage	2 (6)	0	1 (3)	1 (3)	4 (12)
Myalgia	1 (3)	1 (3)	1 (3)	0	3 (9)
Atrial fibrillation	0	2 (6)	0	0	2 (6)
Erythema nodosum	0	2 (6)	0	0	2 (6)
Hematoma	1 (3)	1 (3)	0	0	2 (6)

Multiple occurrences of the same AE for a given patient were counted once for each Preferred Term.
Patients may have experienced ≥1 AE.
Resolution of ibrutinib-related AEs was not required prior to study entry.

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Recurrence of Prior Ibrutinib-Related AEs

	Grade Change in Severity on Acalabrutinib vs on Ibrutinib		
Adverse Event	**Increased**	**Decreased**	**Unchanged**
Arthralgia (n = 1)		2 → 1	
Atrial fibrillation (n = 1)			2 → 2
Contusion (n = 1)	1 → 2[a]		
Diarrhea (n = 2)		2 → 1 3 → 1	
Ecchymosis (n = 1)		2 → 1[a]	
Fatigue (n = 3)	1 → 2[a]	2 → 1	1 → 1
Muscle spasms (n = 1)			1 → 1
Myalgia (n = 1)			1 → 1
Peripheral edema (n = 1)			1 → 1
Panniculitis (n = 1)		3 → 2[a]	
Rash (n = 3)		3 → 1*	1 → 1 1 → 1[a]

[a]Determined by investigator as related to acalabrutinib.

- A total of 12 of 33 (36%) patients experienced a recurrent AE.
  - 14 of 16 events either decreased or were unchanged in severity with acalabrutinib
- No patients discontinued acalabrutinib because of a prior ibrutinib-related AE.

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Additional Safety Outcomes

- **Grade ≥3 AEs in ≥2 patients:**
  - **Thrombocytopenia (n = 3; 9%)**
  - **Anemia, neutropenia, pneumonia and hypertension, and parasthesia (n = 2; 6%)**
- **SAEs occurred in 11 patients (33%)**
  - **One SAE occurred in ≥2 patients: pneumonia (n = 2, 6%)**
- **2 atrial fibrillation events were reported**
  - **The grade 2 event was a recurrence of previous atrial fibrillation on ibrutinib**
  - **The grade 3 event occurred in setting of pseudomonal infection and pleural effusion and resolved after 2 days**
- **2 grade 5 events: stroke and disseminated systemic fungal infection (both deemed unrelated to study drug).**

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Investigator-Assessed Responses in Evaluable Patients[a]

Best Response[b], n (%)	N = 29[c]
CR	1 (3.4)
PR	15 (51.7)
PRL	7 (24.1)
SD	6 (20.7)
ORR (CR + PR), n (%)	16 (55.2)
95% CI	35.7-73.6
ORR (CR + PR + PRL), n (%)	23 (79.3)
95% CI	60.3-92.0

[a]Efficacy-evaluable patients had at least 1 response assessment after first dose of study drug and had measurable disease at baseline; 2 patients discontinued study before response assessment; 2 patients did not have measurable disease at baseline.

[c]Includes 200 mg QD (n = 2) and 100 mg BID (n = 27)

- All evaluable patients achieved at least SD
- Median time to PRL or better: 1.9 months (95% CI, 1.9-2.0).
- 81% of responding patients have a duration of response (PRL or better) ≥12 months.
- Median PFS has not been reached.

Awan F, et al. ASH 2016

ACE-CL-001: Acalabrutinib for Richter's

- ACE-CL-001 is an ongoing, multinational, phase 1/2 study designed to evaluate acalabrutinib monotherapy in patients with CLL/SLL.
- Multiple disease cohorts were enrolled: relapsed/refractory, treatment-naïve, ibrutinib-intolerant, and RT/prolymphocytic leukemia.
- Previously reported ORR with acalabrutinib monotherapy (100 mg BID):
  - R/R: 95% (85% PR, 10% PRL; n = 60)[1]
  - TN: 97% (87.5% PR; 10% PRL; n = 72)[2]
- Data are presented for 29 patients with RT or other transformations for safety and 21 evaluable patients with RT for efficacy.
  - All patients were treated with acalabrutinib 200 mg BID.
  - Data cutoff: 01 September 2016

[1]Byrd JC, et al. *N Engl J Med*. 2016;374(4):323-332. [2]Byrd JC, et al. ASCO 2016 [poster presentation].

Response in RT

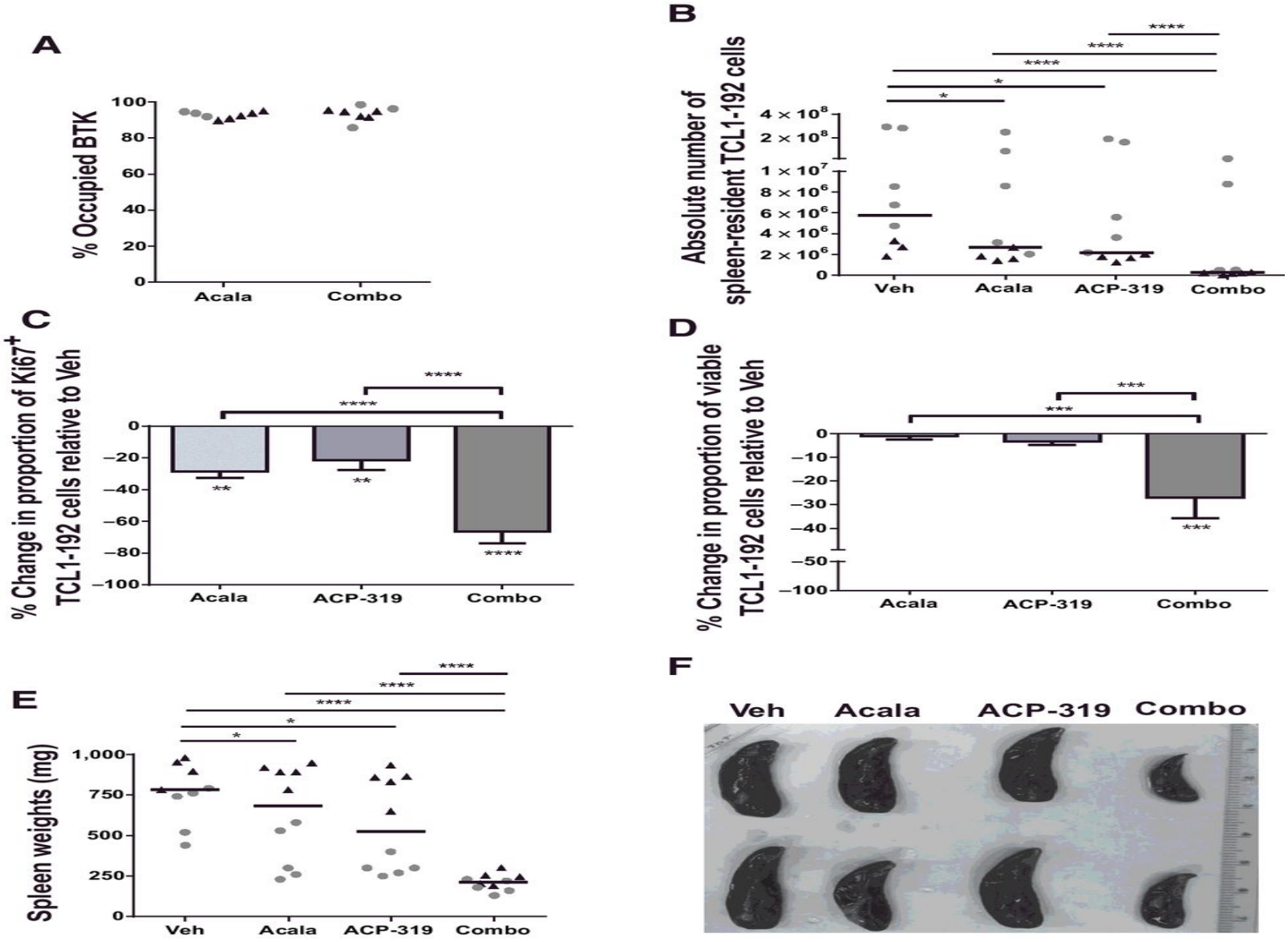
- ORR 38.1% (n=8; 95% CI 18.1-61.6)
- Median time on treatment 3.4 months (range, 1.7-12.0 mos)
- Median DOR: 5.2 months (range, 0.3 - 6.5+ months)
  - 3 of 8 responders remain on treatment (DOR: 3.9+, 5.1+[a], and 6.5+ months)
  - DOR in 3 responders with prior ibrutinib: 0.6+[a], 1.5, and 1.8 months
- Median PFS: 2.1 months (range, 0.03+-8.3+ months)

[a]Censored at date of transplant.

Summary: Acalabrutinib

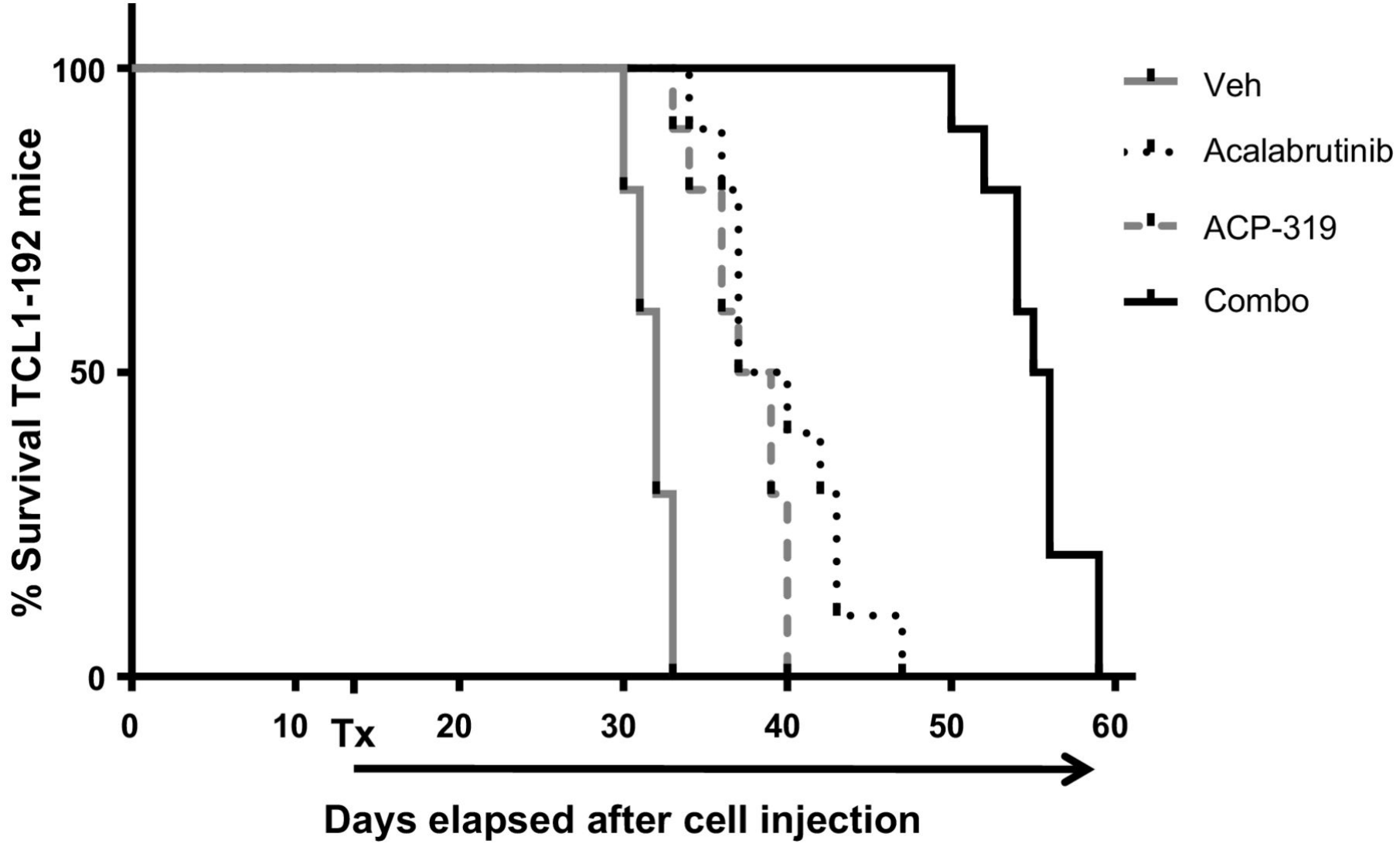
- Potent and more specific BTK inhibitor that binds covalently to Cys481, does not inhibit ITK or EGFR, and has less activity against TEK
- Clinical data demonstrate very high BTK occupancy at 100 mg BID, with 95% ORR. PFS to be updated at ASH, 88% at 18 mos
- Evidence for similar, possibly fewer toxicities than ibrutinib
- ORR 38.4% in RT, but median DOR 5 mos

Impact of Acalabrutinib, ACP-319, or Their Combination on Tissue-Resident TCL1-192 Cells



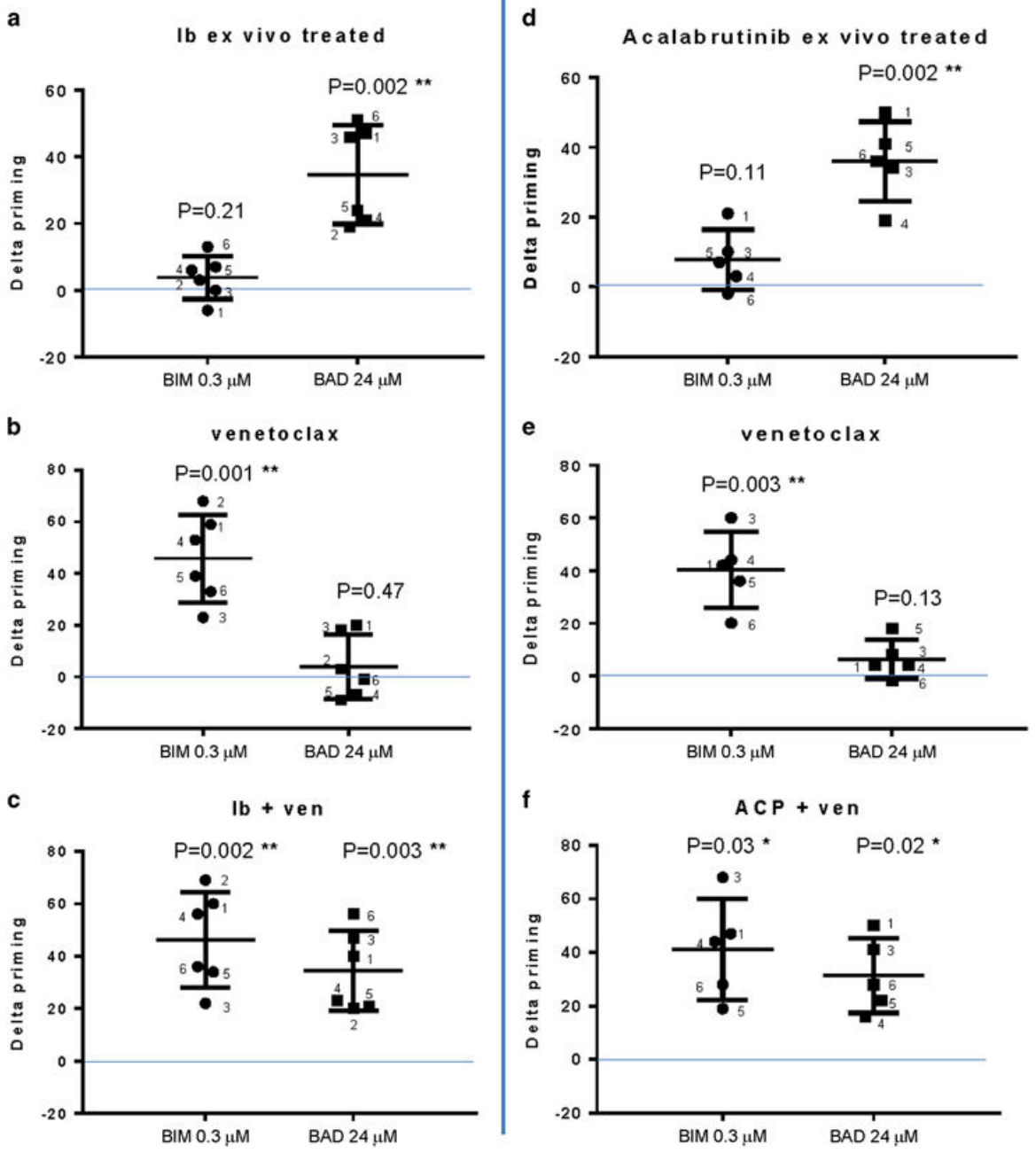
Carsten U. Niemann et al. Clin Cancer Res 2017;23:5814-5823

Acalabrutinib + ACP-319 Improves Survival of Mice Injected with TCL1-192

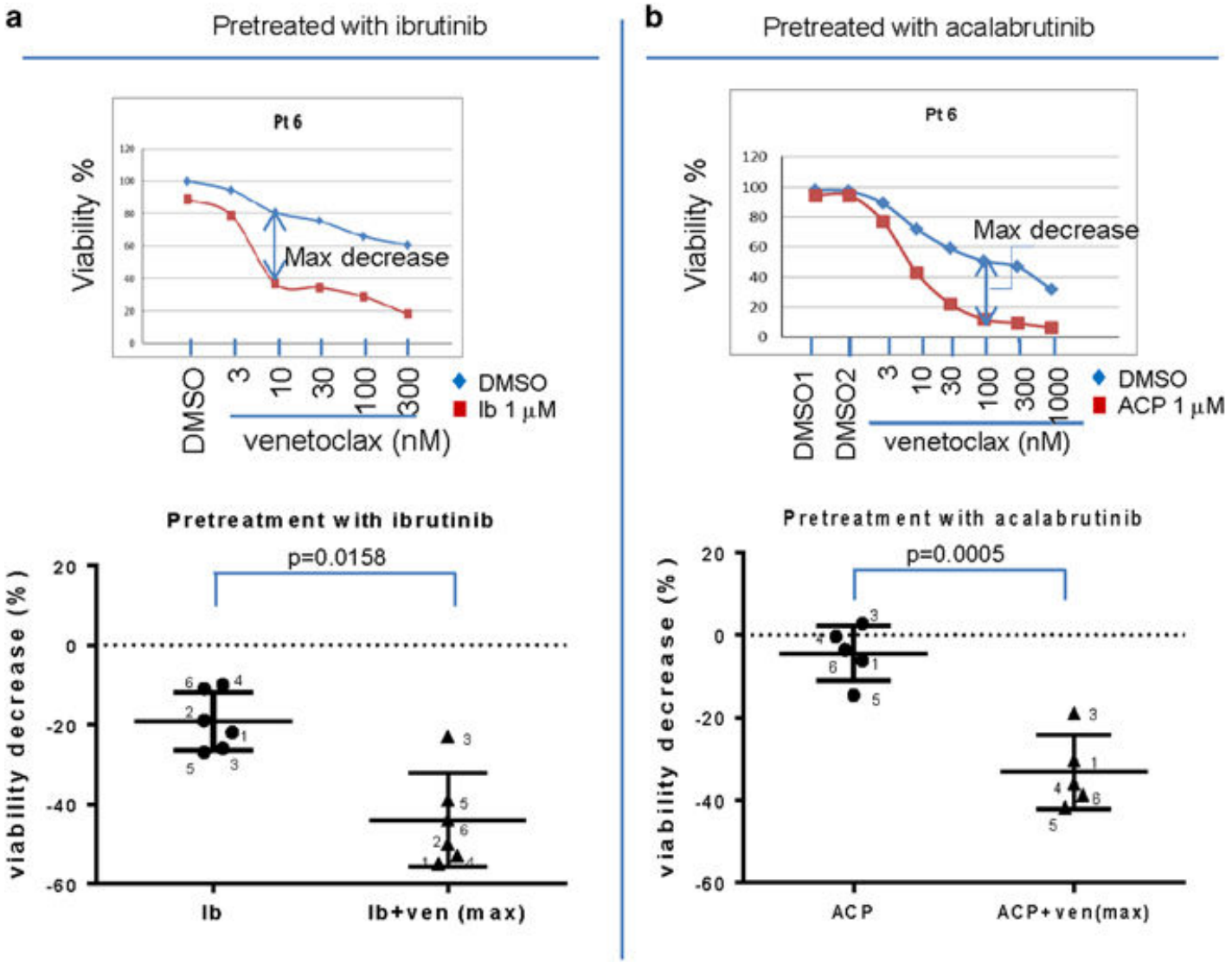


Carsten U. Niemann et al. Clin Cancer Res 2017;23:5814-5823

Similar Ex Vivo Effects with Ibrut vs Acala



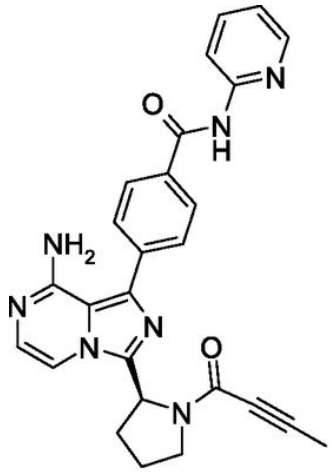
Similar Effects on Viability Together with Venetoclax



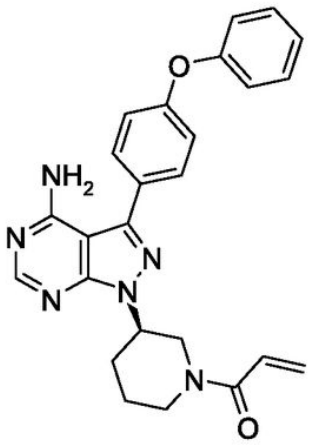
CLL Registration Trials

- **Untreated older patients:**
  - **Acala vs acala-obin vs obin- chl**
- **Relapsed refractory with del 17p or 11q:**
  - **Acala vs ibrutinib**

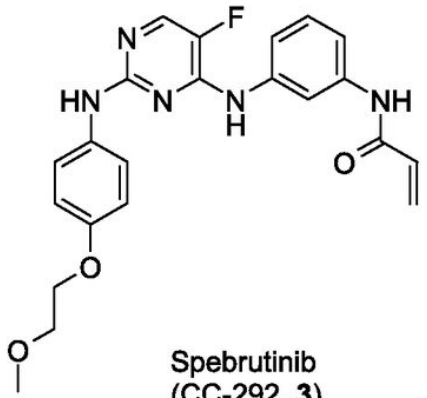
(Left) Chemical structures of clinical irreversible binding BTK inhibitors.



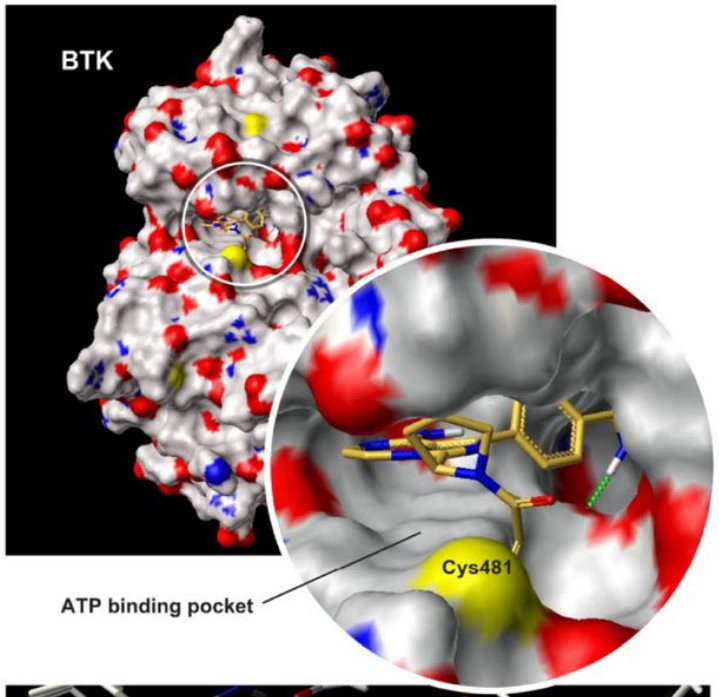
Acalabrutinib
(ACP-196, **1**)

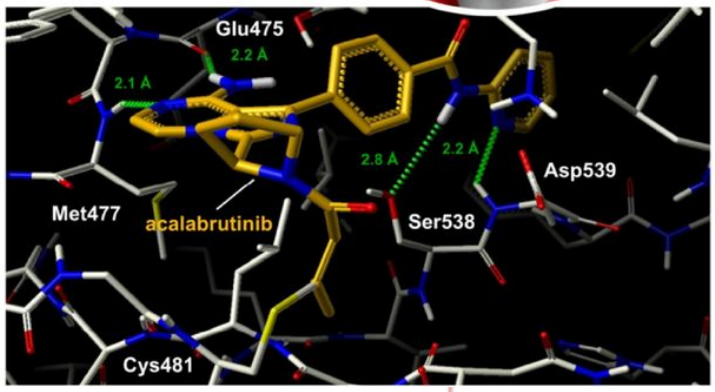


Ibrutinib
(PCI-32765, **2**)



Spebrutinib
(CC-292, **3**)





Tjeerd Barf et al. J Pharmacol Exp Ther 2017;363:240-252

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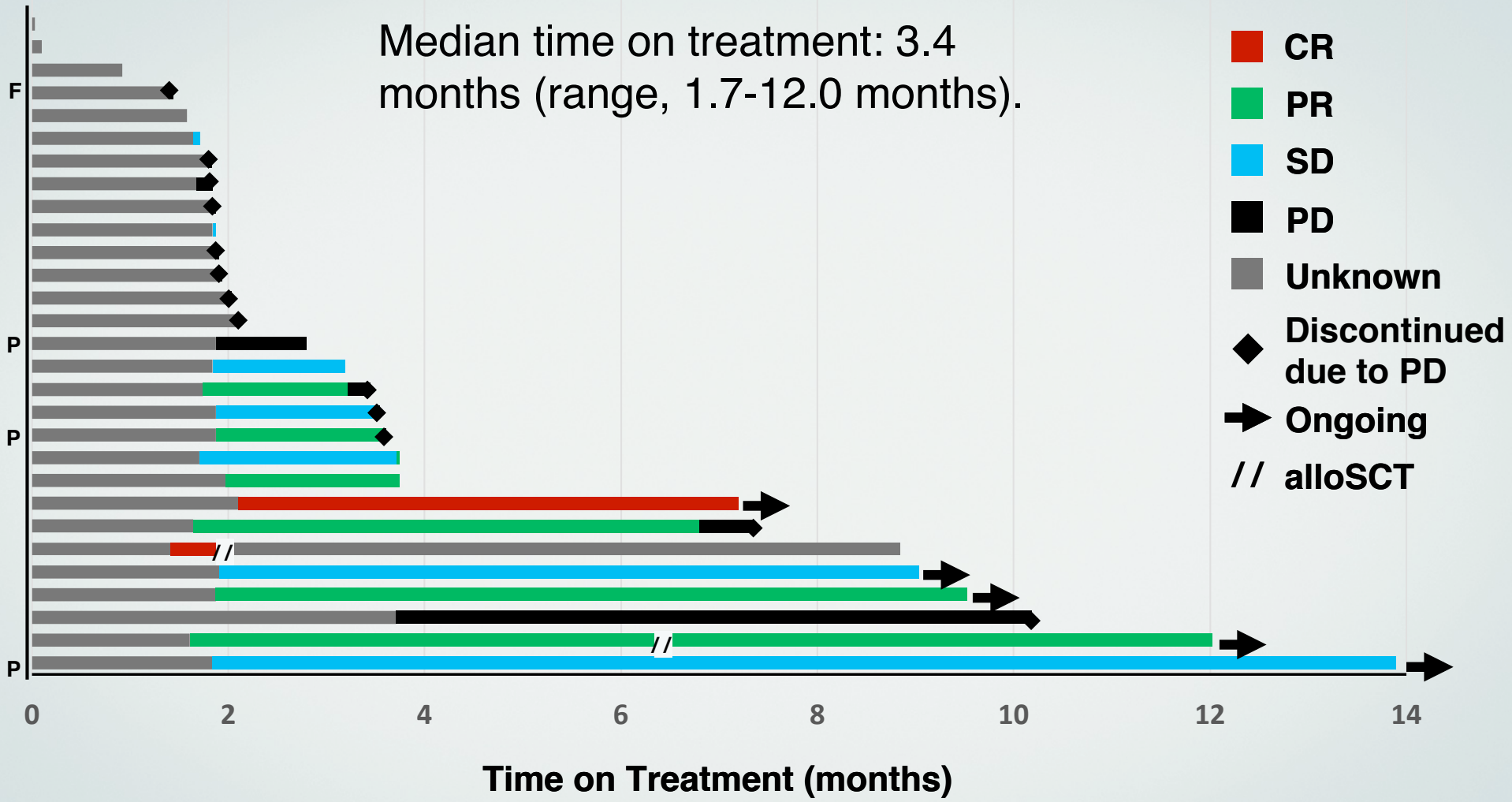
RT: Time on Treatment



F, FL; P, PLL.