ACALABRUTINIB IN MCL

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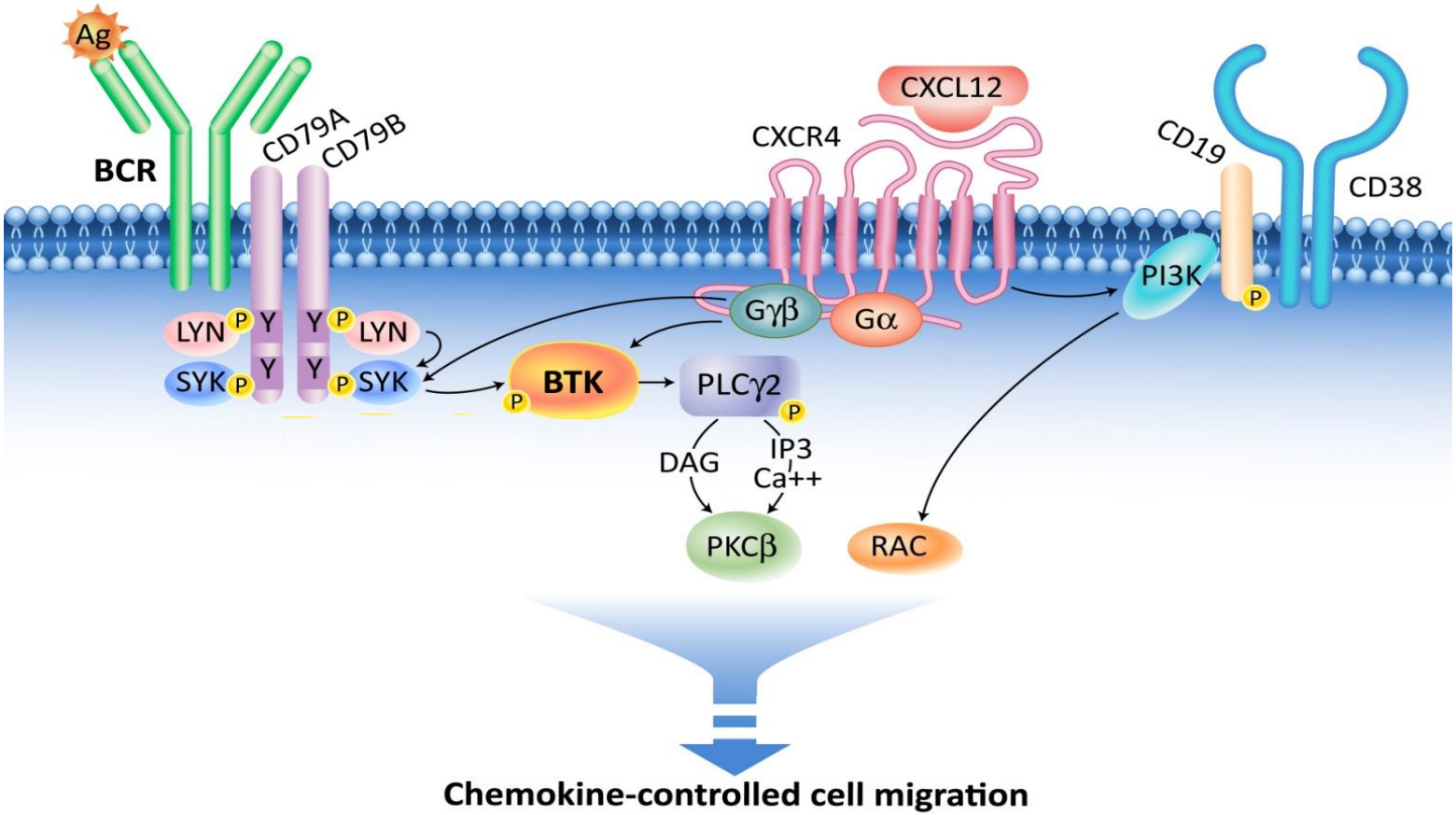
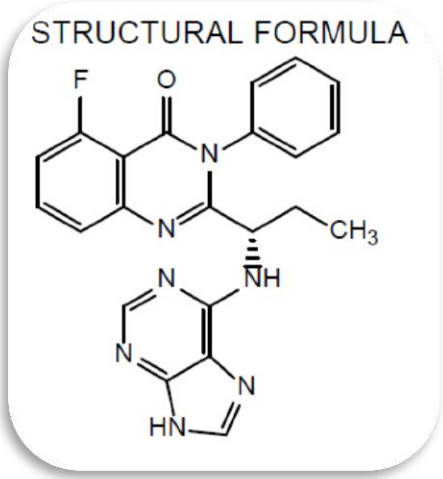
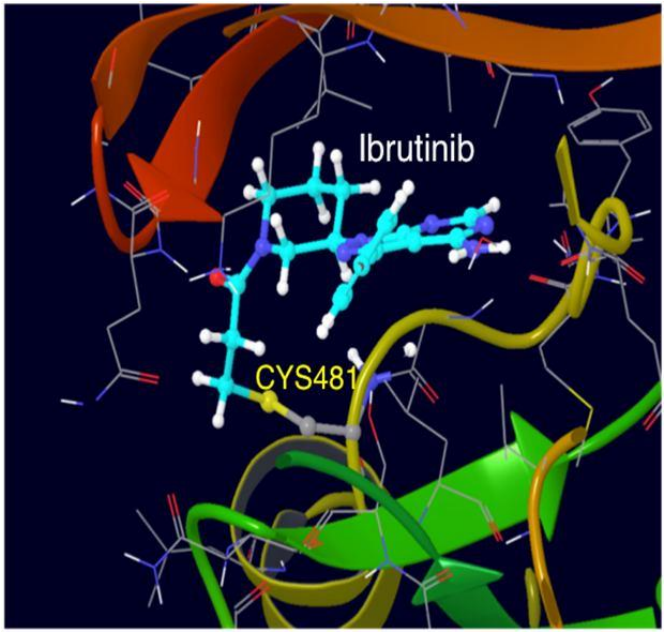
BRUTON'S TYROSINE KINASE (BTK): A CRITICAL KINASE FOR LYMPHOMA CELL SURVIVAL AND PROLIFERATION



- Bruton's tyrosine kinase (BTK) is an essential element of the BCR signaling pathway (Niiro, NRI 2002)
- Inhibitors of BTK block BCR signaling and induce apoptosis
- BTK also acts downstream of certain chemokine receptors impacting integrin molecules that help in promoting egression from the lymph node environment

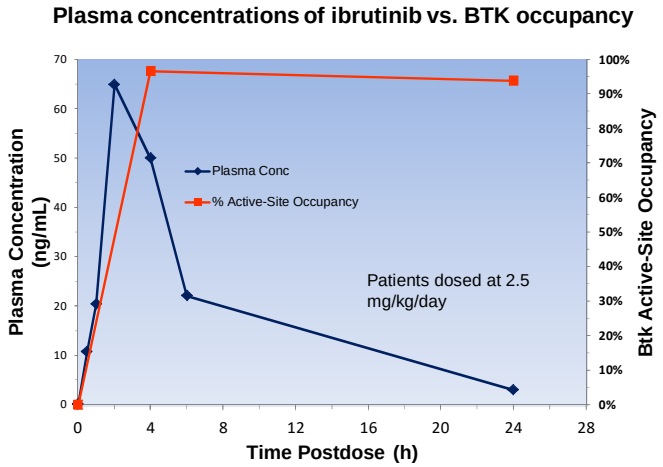
Ibrutinib: A potent BTK inhibitor





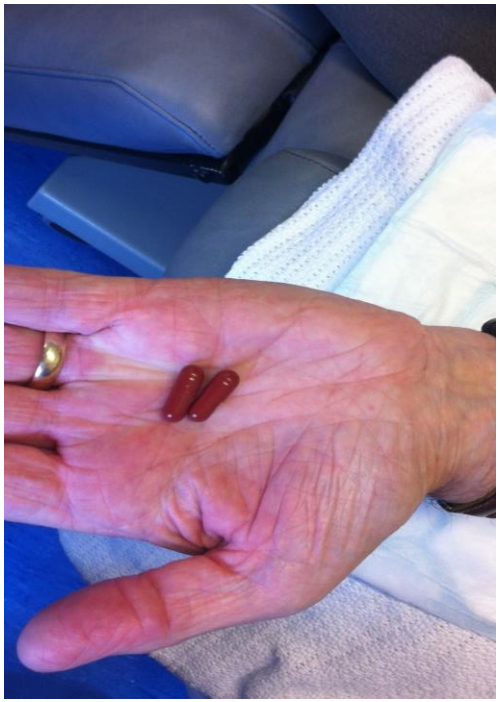
- Ibrutinib (PCI-32765) forms a bond with cysteine-481 in BTK
- Highly potent BTK inhibition at IC_{50} = 0.5 nM
- High degree of specificity for hematopoietic cells
- Orally administered once daily dosing until PD or no longer tolerated by patient

Durable Btk inhibition, despite rapid drug elimination



Advani et al. J Clin Oncol 28:15s, 2010 (suppl; abstr 8012)

NEXT GENERATION BTKI'S



ONO 4059

ACP 196

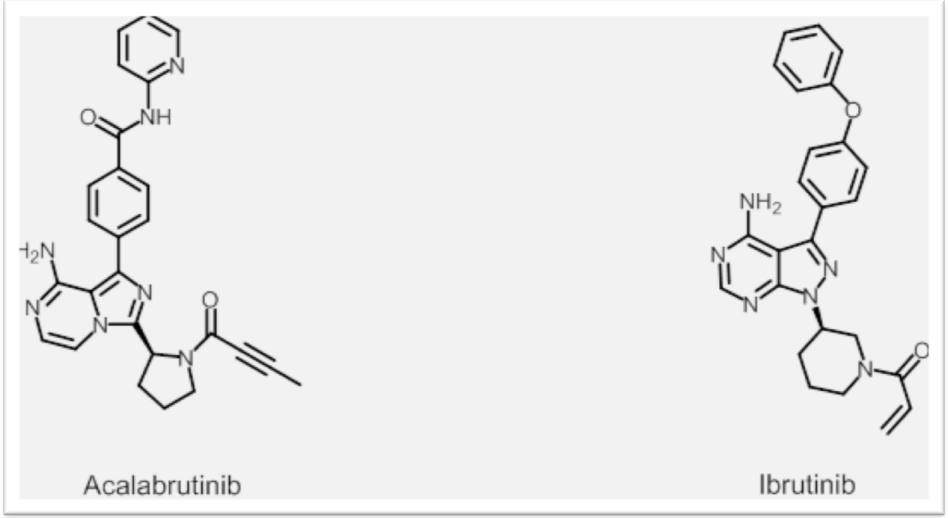
M 7583

ACALABRUTINIB: A HIGHLY SELECTIVE, POTENT BRUTON TYROSINE KINASE (BTK) INHIBITOR

Acalabrutinib was developed to increase the degree of BTK inhibition

- Very low binding to interleukin-2 inducible T-cell kinase (ITK), TEC protein tyrosine kinase (TEC), and epidermal growth factor receptor (EGFR)

- Acalabrutinib selectively binds with a short half-life allowing twice-daily dosing and near total BTK inhibition
  - Potentially reducing drug resistance
- Acalabrutinib appears to improve substantially on the specificity of first generation BTK inhibitors

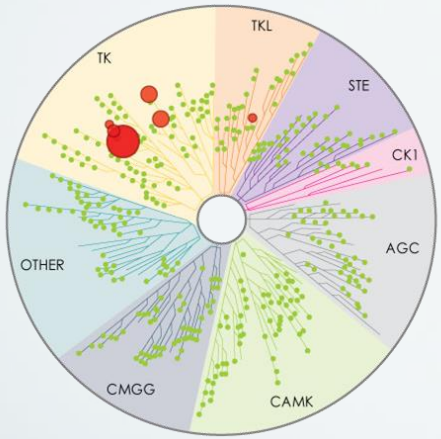


ACALABRUTINIB (ACP-196)

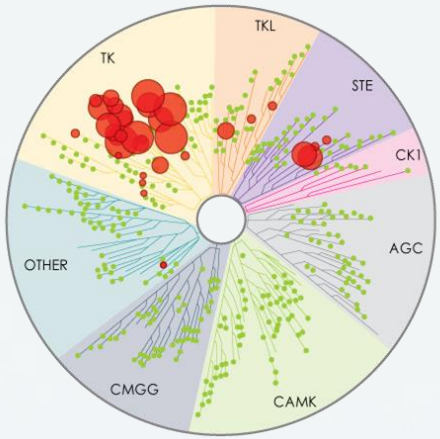
- Acalabrutinib is a highly selective, potent BTK inhibitor
- Minimal off-target effects on TEC, EGFR, or ITK signaling in vitro

Kinase Selectivity Profiling at 1 μmol/L[1]

Acalabrutinib



Ibrutinib



Larger red circles represent stronger inhibition

Kinase Inhibition IC_{50} (nmol/L)[1]

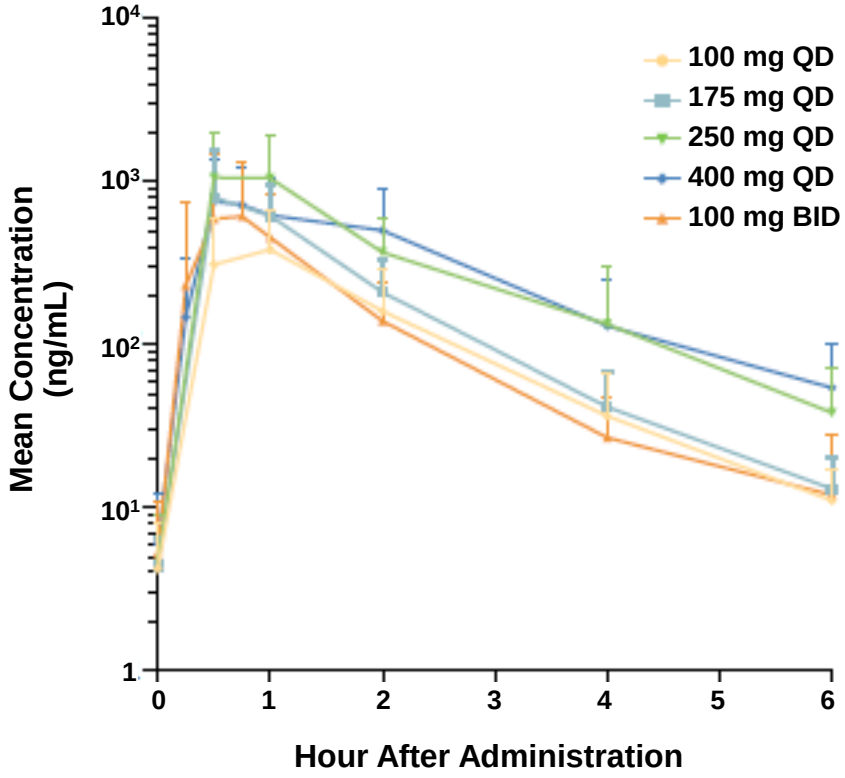
Kinase	Acalabrutinib	Ibrutinib
BTK	5.1	1.5
TEC	93	7.0
BMX	46	0.8
TXK	368	2.0
ERBB2	~1000	6.4
EGFR	>1000	5.3
ITK	>1000	4.9
JAK3	>1000	32
BLK	>1000	0.1

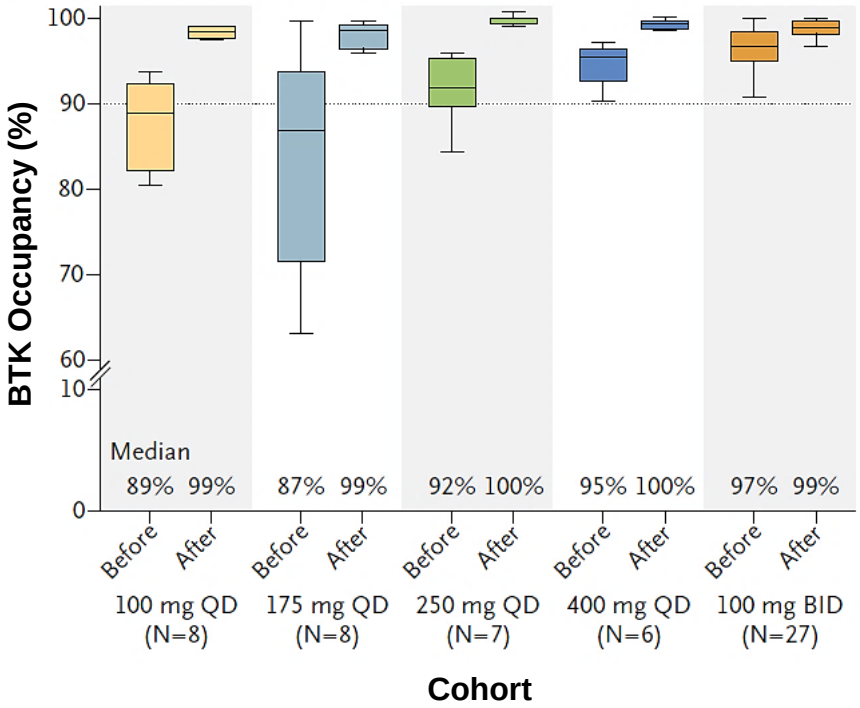
[1]Covey AACR 2015. Abstract 2596.

Byrd JC et al. *N Engl J Med*. 2016;374(4):323-332.

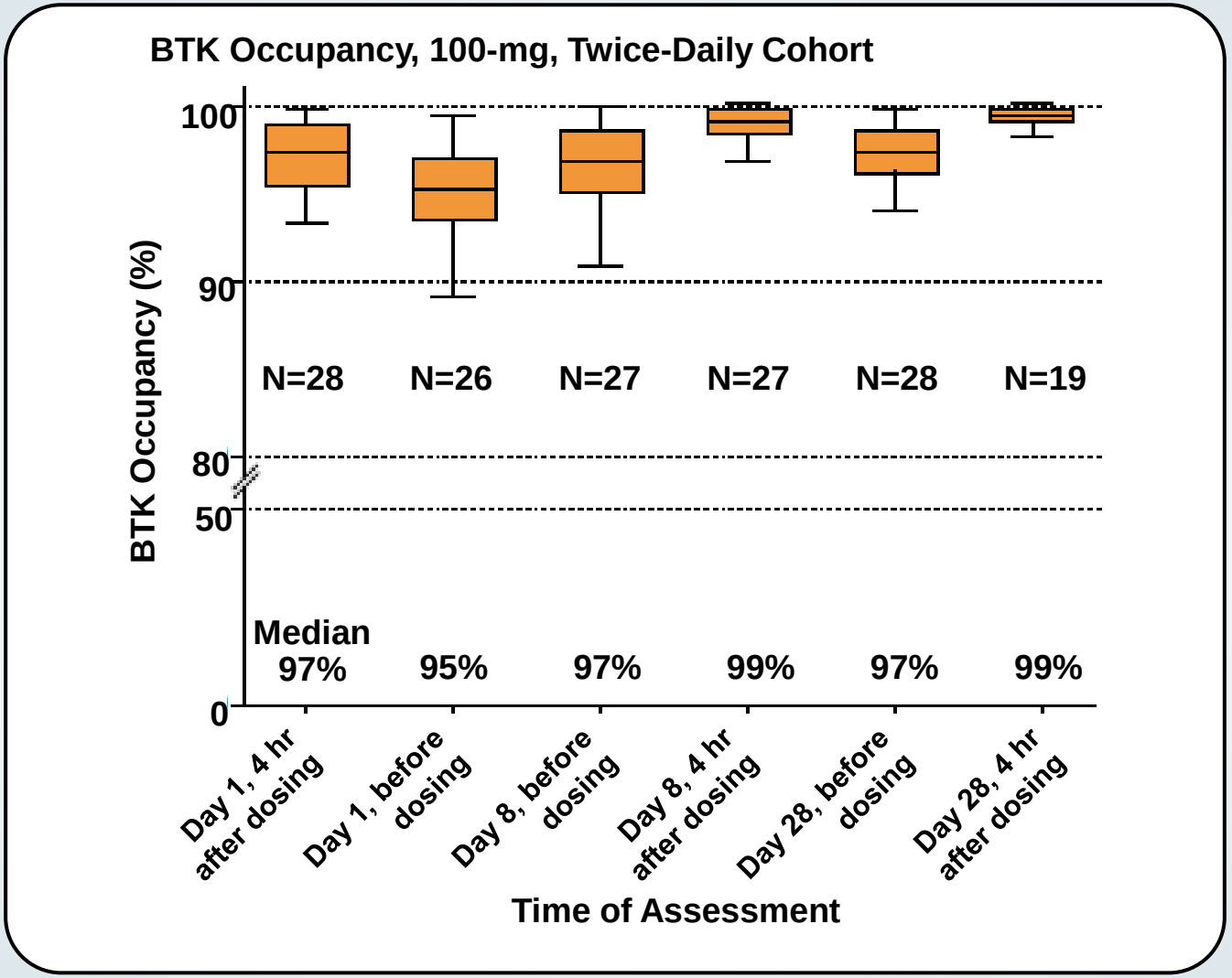
PHARMACOKINETICS/PHARMACODYNAMICS

1-hour half-life; rapid oral absorption; complete BTK occupancy



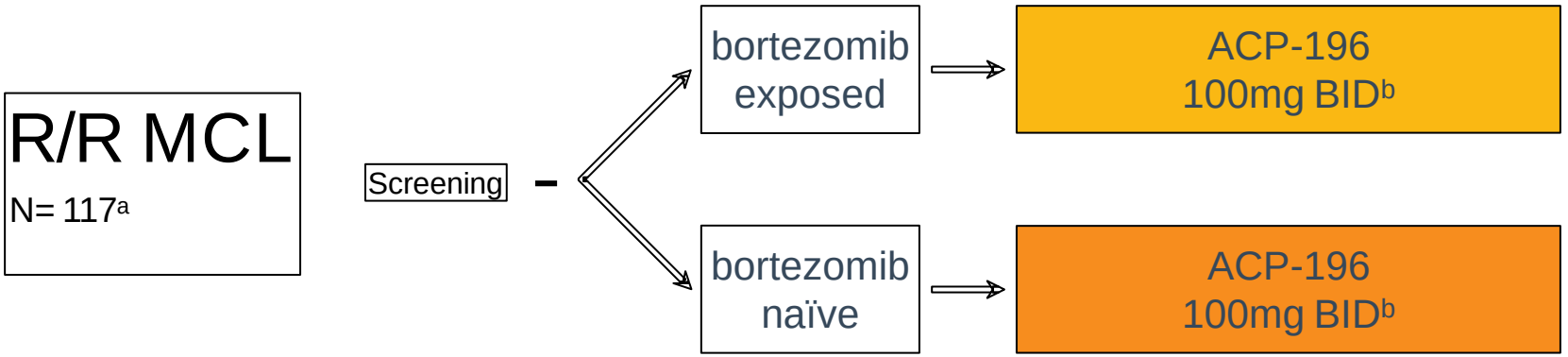


ACALABRUTINIB TWICE-DAILY DOSING (COMPLETE AND CONTINUOUS BTK COVERAGE)



ACE-LY-004: AN OPEN-LABEL, GLOBAL PHASE 2 STUDY OF ACP-196 IN SUBJECTS WITH MANTLE CELL LYMPHOMA (MCL)

- **ACP-196 is an investigational oral Bruton tyrosine kinase (Btk) inhibitor**
- **ACP-196 is a second-generation, potent, selective, covalent inhibitor of Btk**

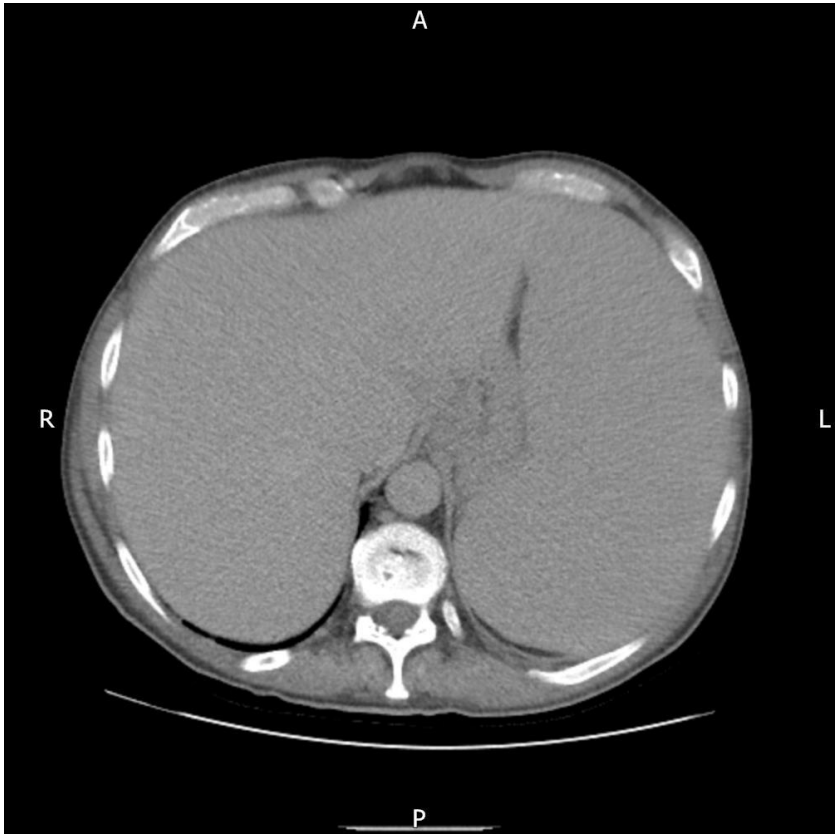


[b]Subjects will be followed every 28 days ***or*** until progression of disease ***or*** start of another anti-cancer treatment for at least 1 year

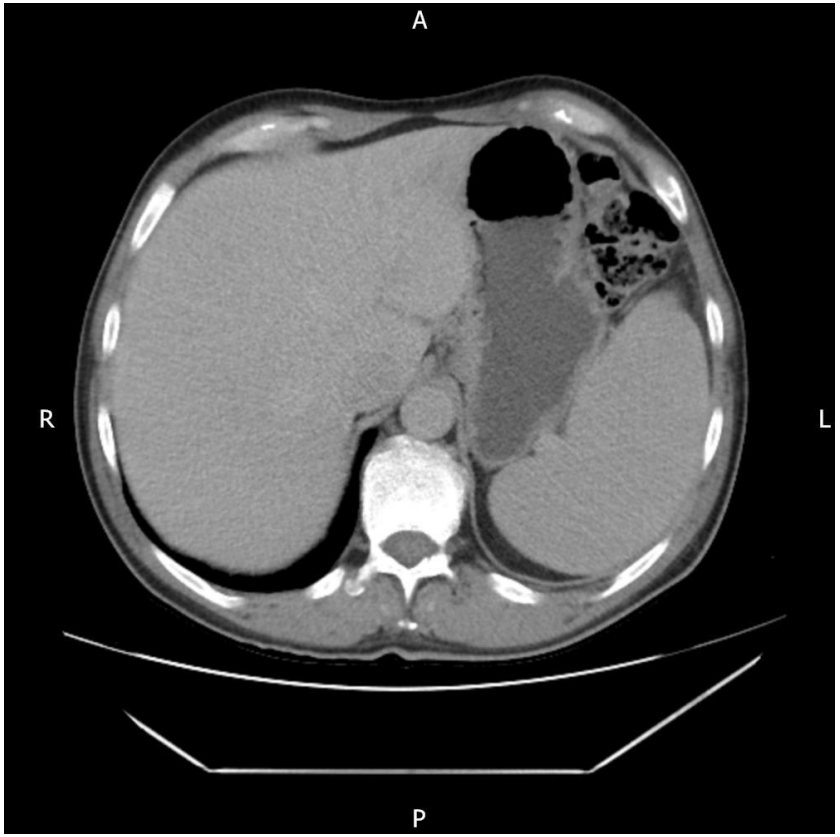
CLINICAL EFFICACY IN MCL

MR

CT Pre ACP

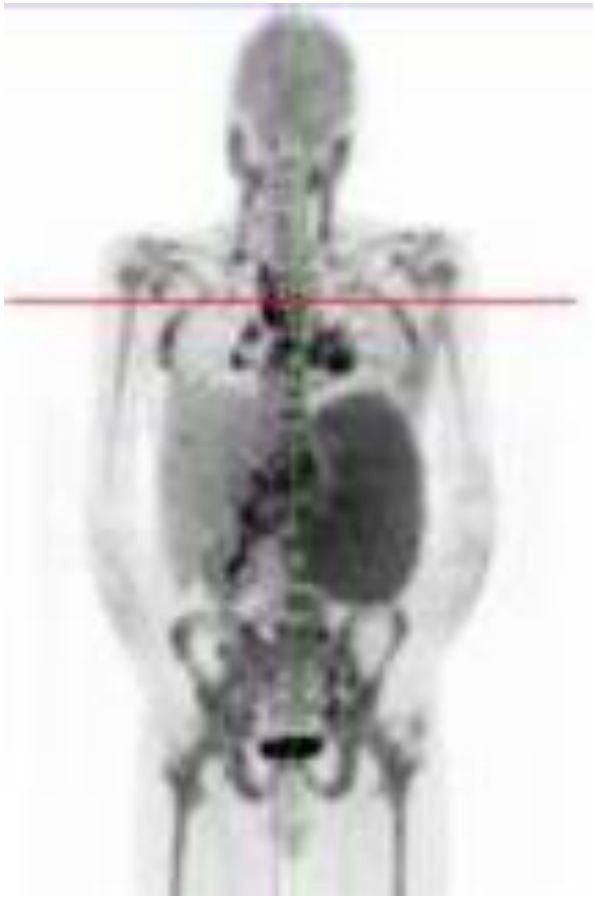


CT C2D28

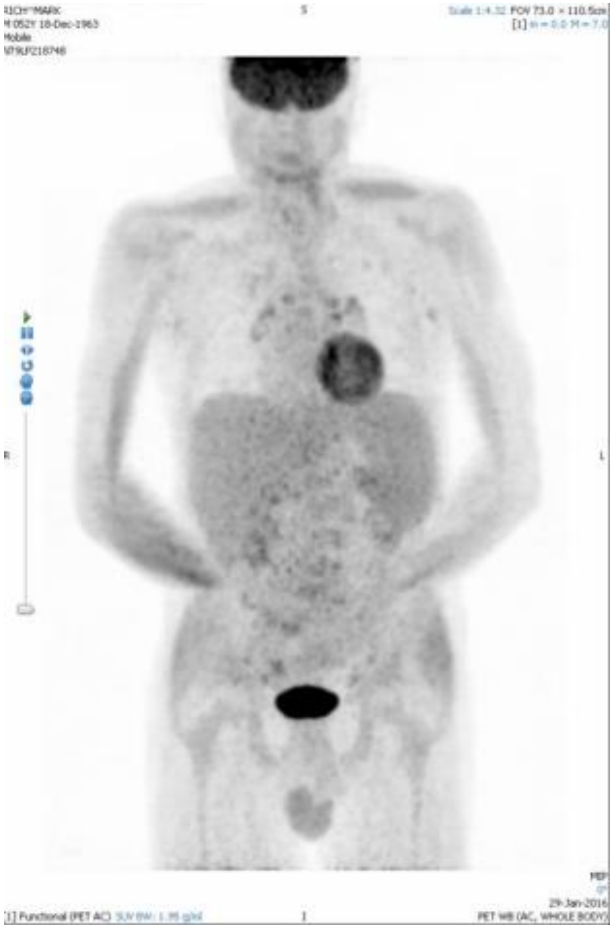


MR

PET Pre

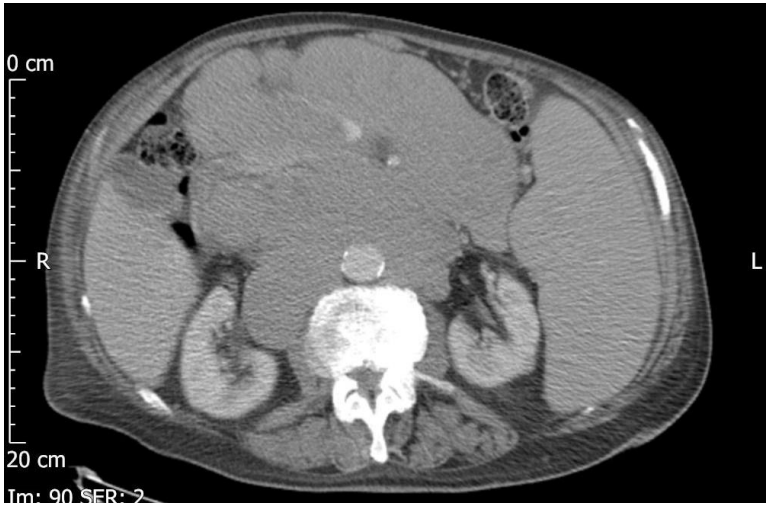


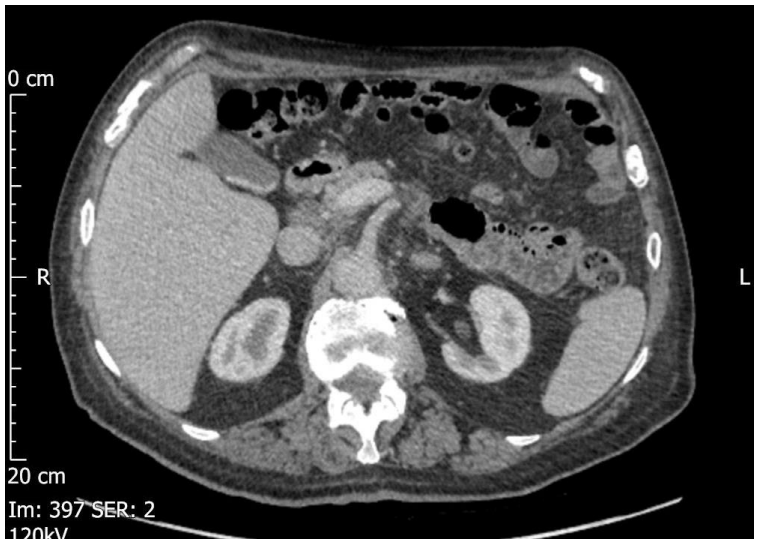
PET C2D28



91 YEAR OLD MALE WITH MANTLE CELL LYMPHOMA

- Presents with B-symptoms, leukocytosis and bulky lymphadenopathy – Jan 2015
- Commenced Rituximab-chlorambucil
- Fails to respond after 2 cycles with significant cytopenias.
- Commenced ACP-196 (June ‘15)
- Partial remission with leukocytosis within 1 month – excellent clinical response.
- Significant bruising – aspirin stopped
- PET negative PR on imaging with residual marrow involvement at 9 months.
- Very good partial remission at 12 months

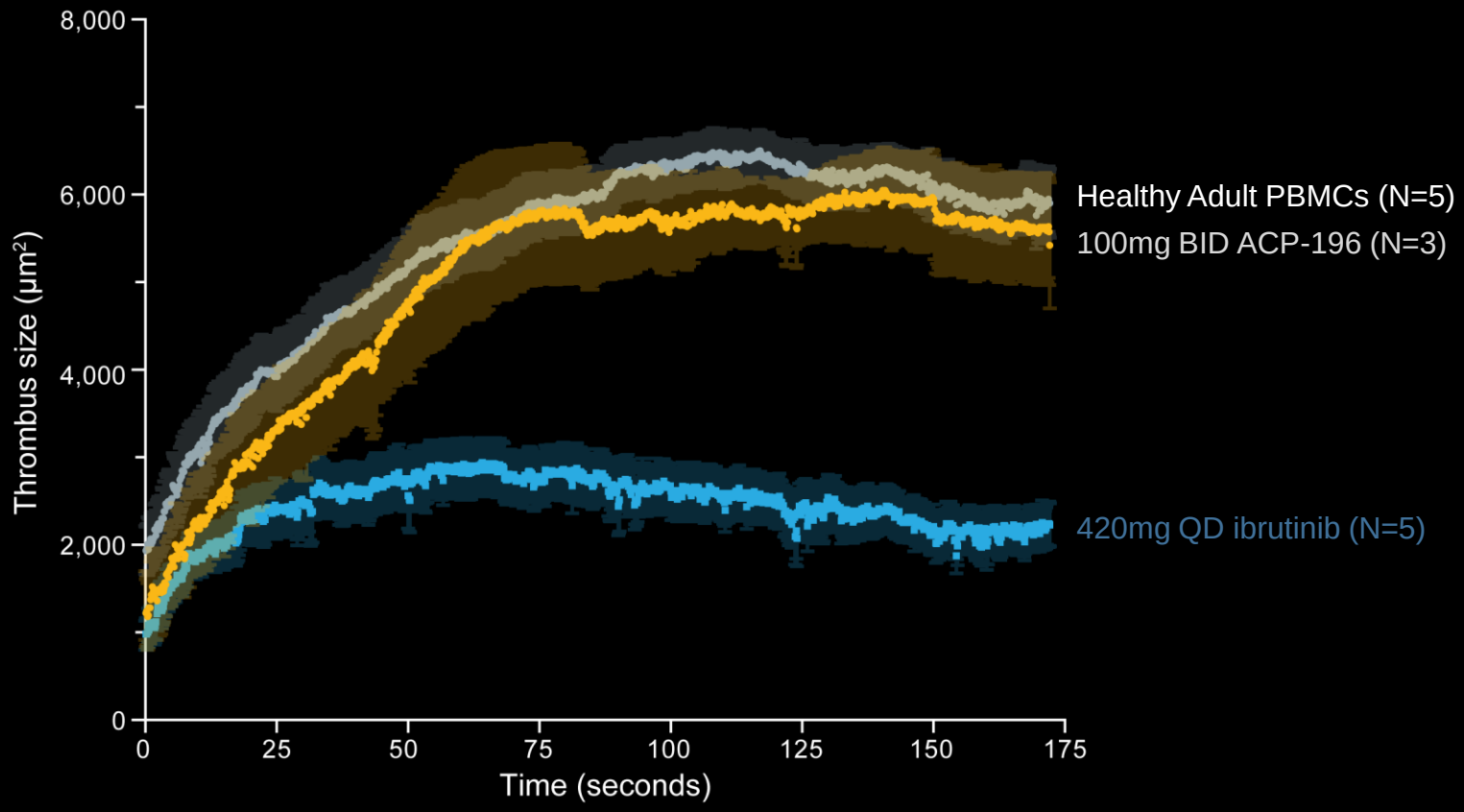




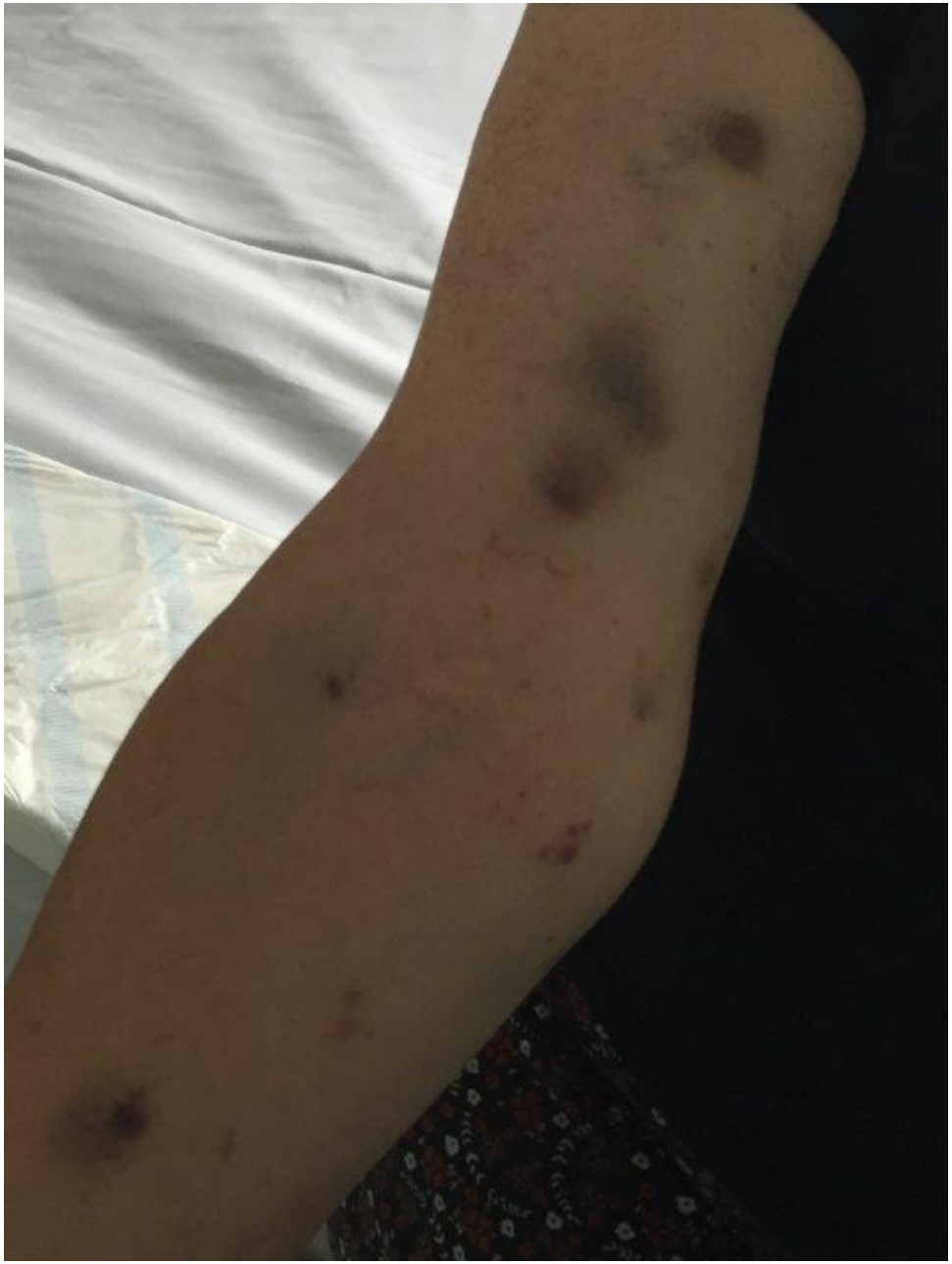
SIDE EFFECTS

PLATELET AGGREGATION (R/R PATIENTS WITH CLL)

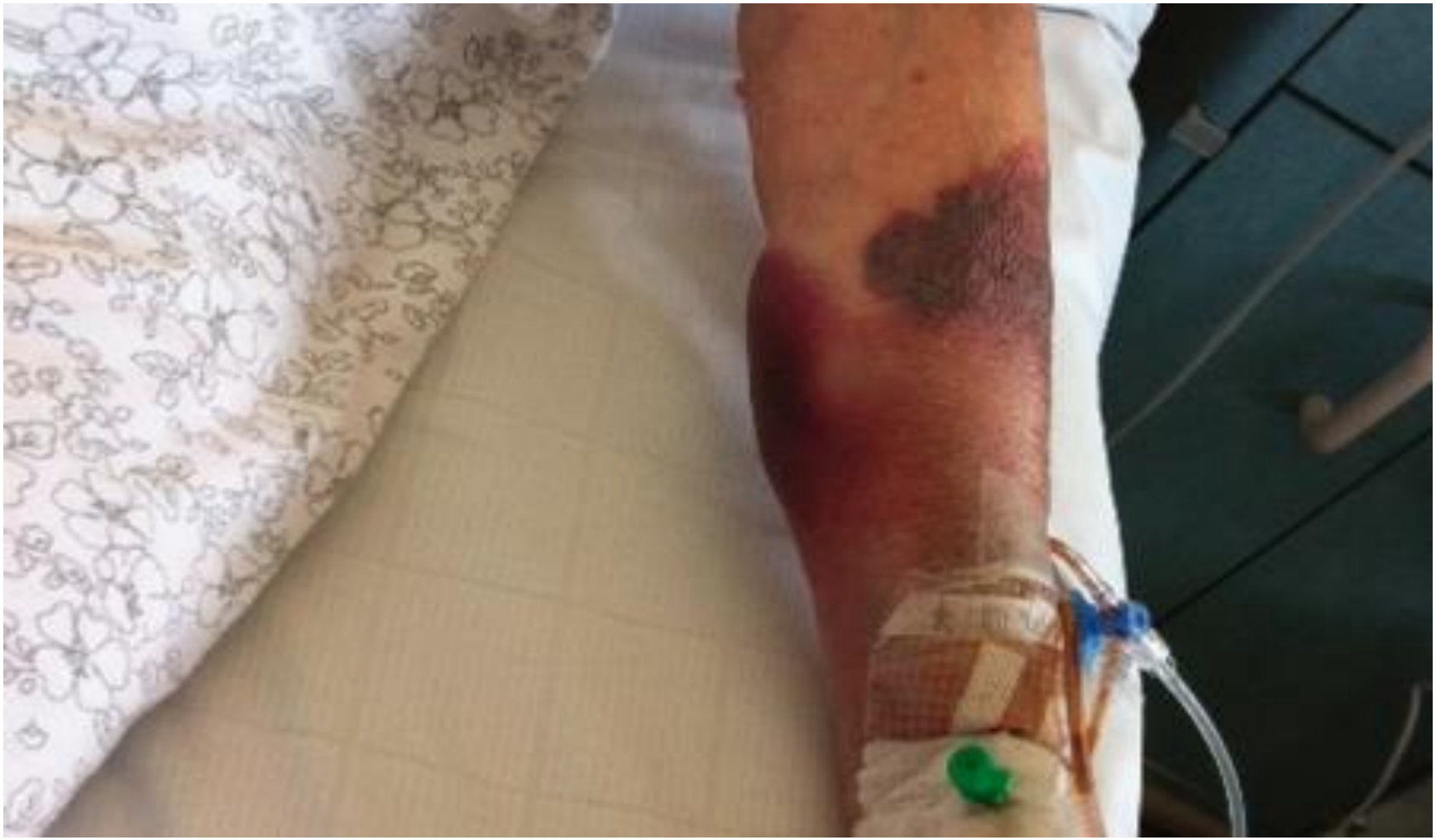
ACP-196 does not inhibit platelet mediated thrombosis



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



BLEEDING WITH PROCEDURES



Acalabrutinib Monotherapy in Patients With Richter Transformation From the Phase 1/2 ACE-CL-001 Clinical Study

Peter Hillmen,[1] Anna Schuh,[2] Toby A. Eyre,[3] John M. Pagel,[4] Jennifer R. Brown,[5] Paolo Ghia,[6] John N. Allan,[7] William Wierda,[8] Ahmed Hamdy,[9] Raquel Izumi,[9] Priti Patel,[9] Min Hui Wang,[9] John C. Byrd[10]

[1]St. James's University Hospital, Leeds, UK; [2]Department of Oncology, University of Oxford, Oxford, UK; [3]Department of Haematology, Churchill Hospital Cancer Centre, Oxford, UK; [4]Swedish Medical Center, Seattle, WA; [5]Dana-Farber Cancer Institute, Boston, MA; [6]Università Vita-Salute San Raffaele and IRCCS Istituto Scientifico San Raffaele, Milano, Italy; [7]Weill Cornell Medical College, New York Presbyterian Hospital, New York, NY; [8]The University of Texas MD Anderson Cancer Center, Houston, TX; [9]Acerta Pharma, Redwood City, CA; [10]The Ohio State University Comprehensive Cancer Center, Columbus, OH

MOST COMMON AES (≥15%) FOR ALL PATIENTS (N = 29)

	All AEs		Treatment-Related AEs	
AE, n (%)	**All Grades**	**Grade ≥3**	**All Grades**	**Grade ≥3**
Headache	12 (41)	0	10 (35)	0
Diarrhea	10 (35)	0	6 (21)	0
Anemia	9 (31)	4 (14)	4 (14)	1 (3)
Fatigue	7 (24)	2 (7)	0	0
Arthralgia	5 (17)	1 (3)	2 (7)	0
Back pain	5 (17)	3 (10)	0	0

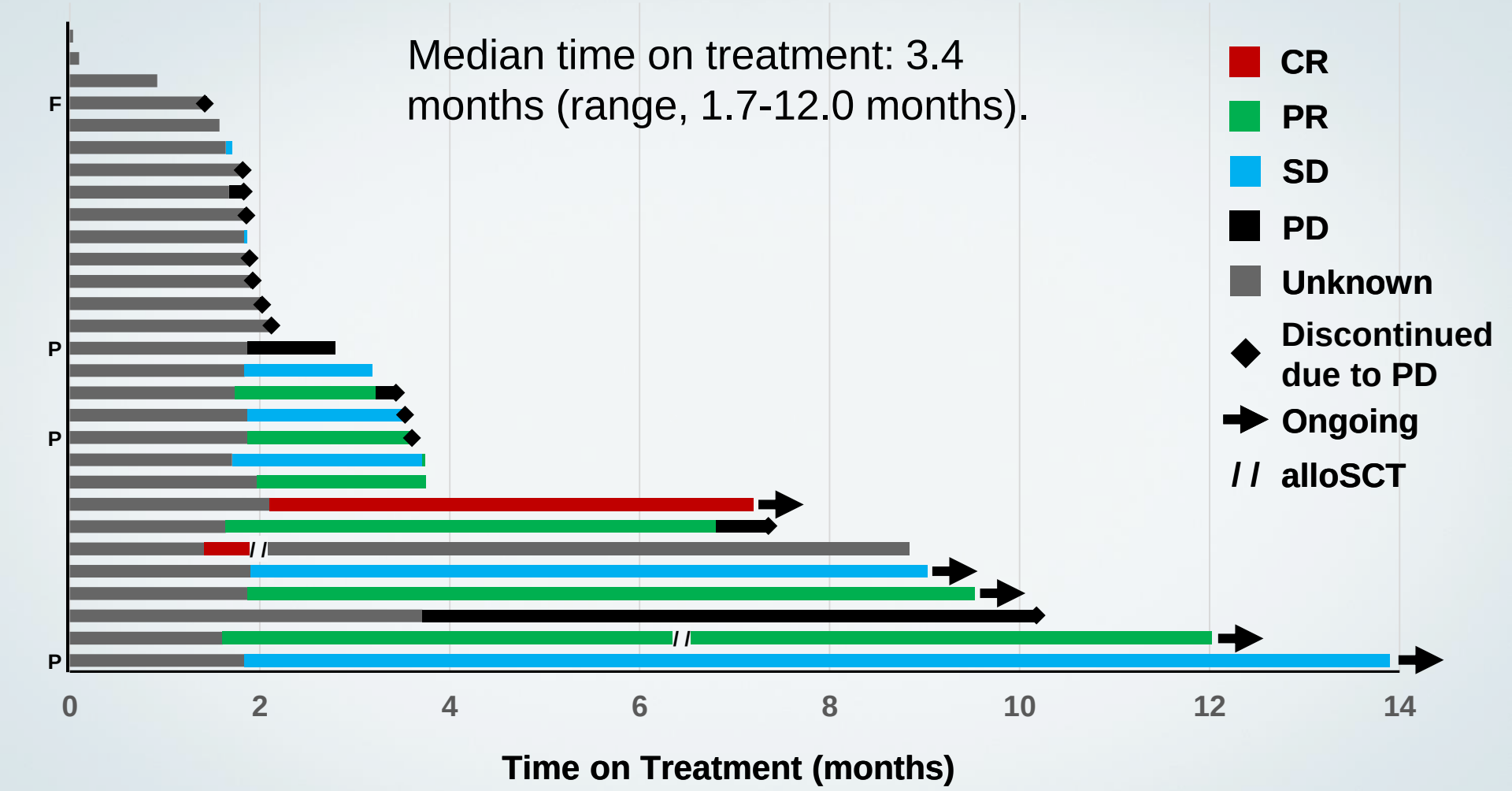
Multiple occurrences of the same event for a given patient were counted once for each Preferred Term.

- Grade ≥3 AEs occurred in 18 patients (62%).
- 2 patients experienced grade 5 AEs: cerebellar abscess and sepsis.
  - These events were deemed unrelated to study drug by the investigator.

SAFETY

- Grade ≥3 AEs that occurred in ≥2 patients were anemia and neutropenia (n = 4; 14% each), hypercalcemia, back pain (n = 3; 10% each), fatigue, asthenia, and acute kidney injury (n = 2; 7% each).
- SAEs occurred in 16 patients (55%).
  - SAEs in ≥2 patients were hypercalcemia (n = 3; 10%), fatigue and acute kidney injury (n = 2; 7% each).
- No patients discontinued because of AEs.

TIME ON TREATMENT



F, FL; P, PLL.

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.

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

CONCLUSION

ACP-196 is a second-generation, selective Btk inhibitor with favorable biochemical and pharmacokinetic properties.
ACP-196 has a promising safety profile
In CLL patients; no episodes of atrial fibrillation or major bleeding observed at this time.
Head to head trial v ibrutinib on-going in CLL
Early onset treatment-related lymphocytosis was not as significant or persistent as reported with other BCR antagonists.
In MCL data awaited!