ACP-196 (Acalabrutinib)

in MCL

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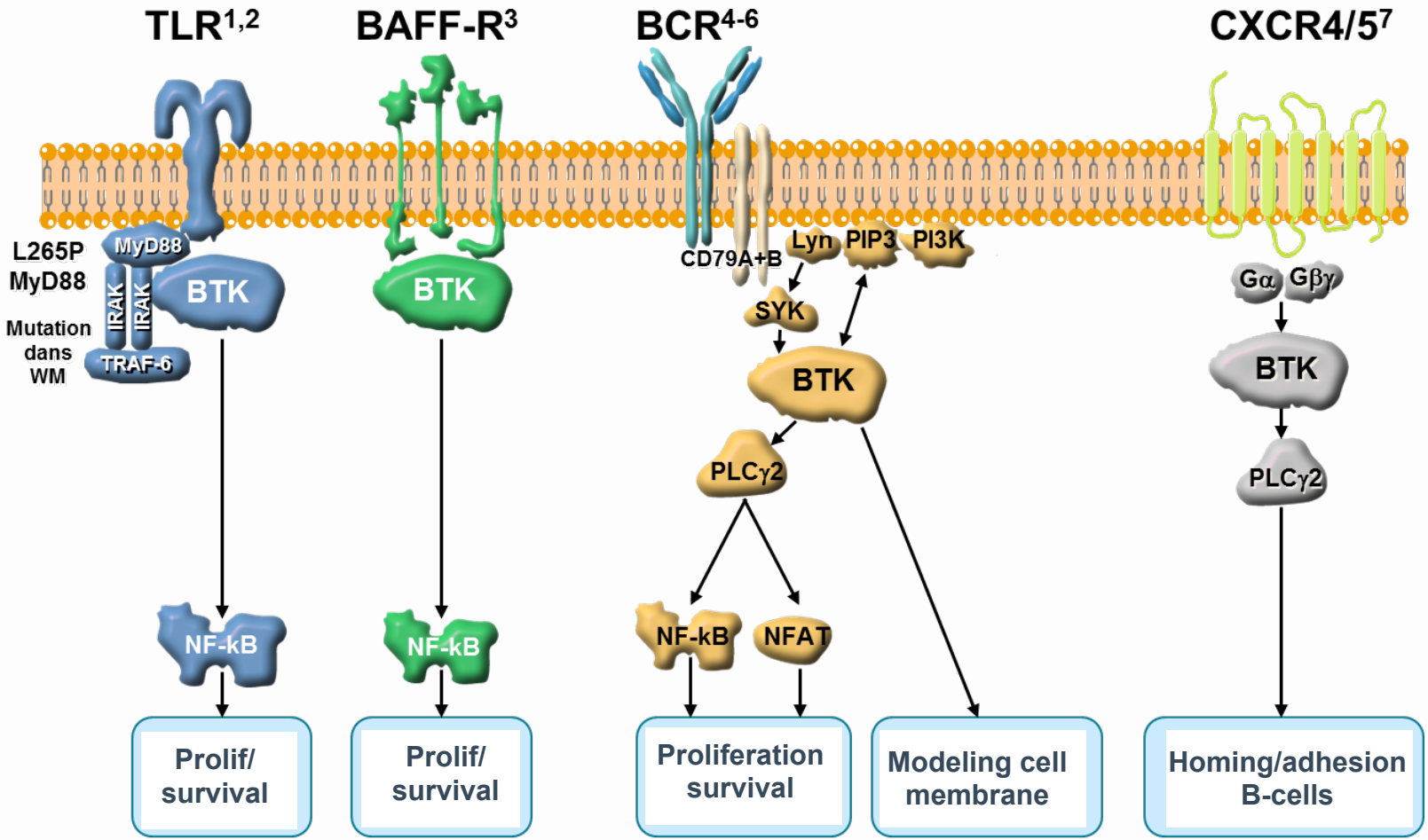
CHU de Nantes, France

Bologna, 2016



1. Liu et al, *Nat Immunol* 2011; 12: 416-425. 2. Treon et al, NEJM 2012; 367: 826-33. 3. Shinners et al, J Immunol 2007; 179: 3872-80.
4. Murphy et al, Janeway's Immuno Biol 7th Ed 2008; 240. 5. Buggy and Elias, Int Rev Immunol 2012; 31: 119-132 . 6. Wiestner, Blood; 120: 4686-4691.
7. de Gorter et al, *Immunity* 2007; 26: 93-104. 8. Pan et al,. ChemMedChem. 2007;2:58-61. 9. Maas et al, Dev Immunol. 2001;8:171-181.

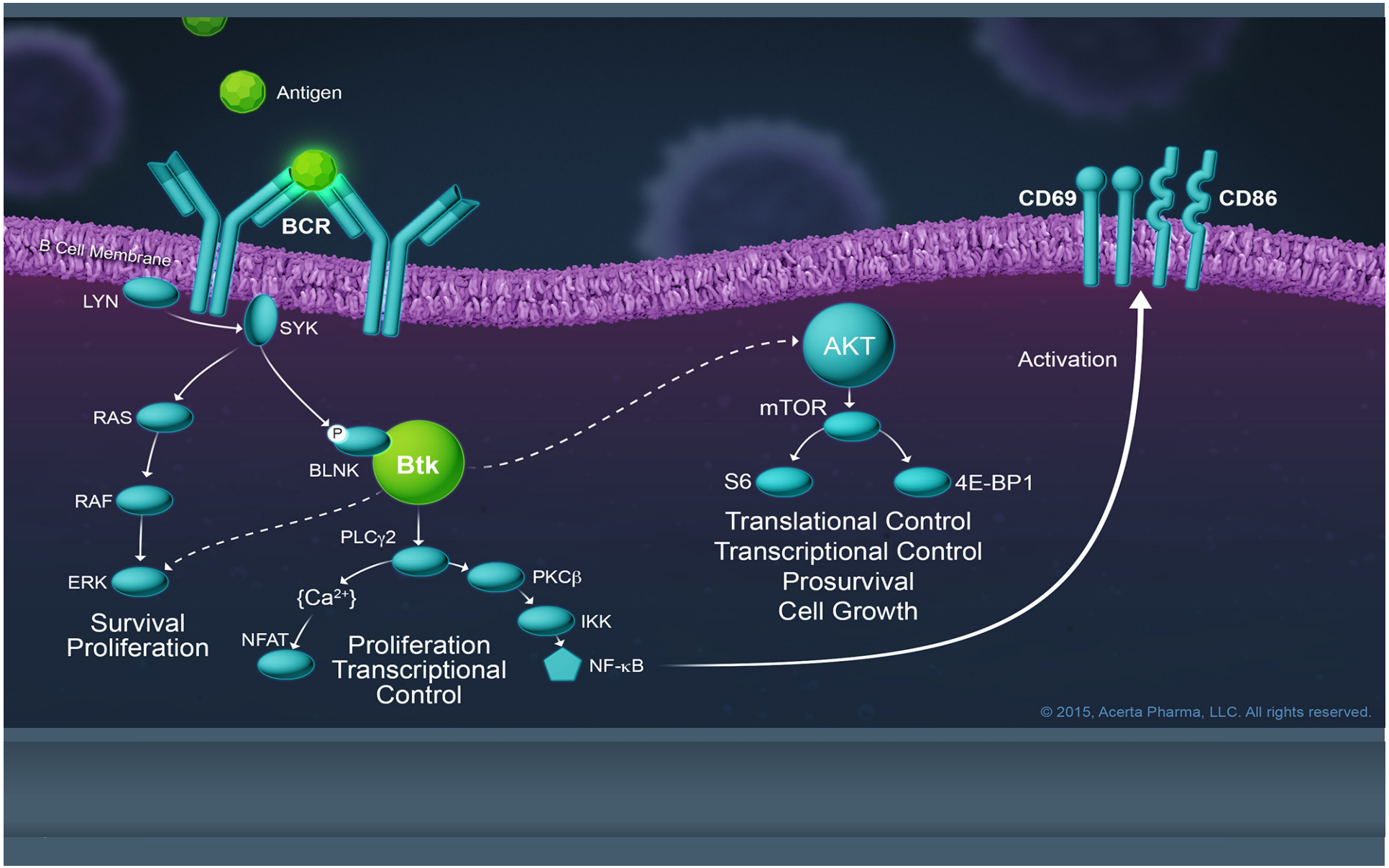
Ibrutinib: first in class but not alone in the class

BTK	Pharma	disease	Clinical
IBRUTINIB	Parmacyclics/Janssen-Cilag	CLL and MCL	approved for clinical used
ONO-4059	ONO Pharmaceutical/ Gilead	NHLs, CLL	Phase I
CC-292 (AVL 292)	Celgene	B-cell malignancies	Phase I
HM 71224	Hanmi	rheumatoid arthritis	FIH, healthy volonteers
ACP-196	Acerta	B-cell malignancies	FIH, phase I
BGB-3111	Beigene	B-cell malignancies	Phase I
CNX-774	Avila Therapeutics	?	preclinical
RN 486	F. Hoffmann-La Roche	autoimmune diseases	preclinical
GDC-0834	Genentech/Gilead	rheumatoid arthritis	preclinical
CGI 1746	CGI Pharmaceuticals	rheumatoid arthritis	preclinical
CGI 560	CGI Pharmaceuticals	rheumatoid arthritis	preclinical
LFM-A13	?	?	?

- Pharma Dislosures: member of Acerta Pharma advisory board

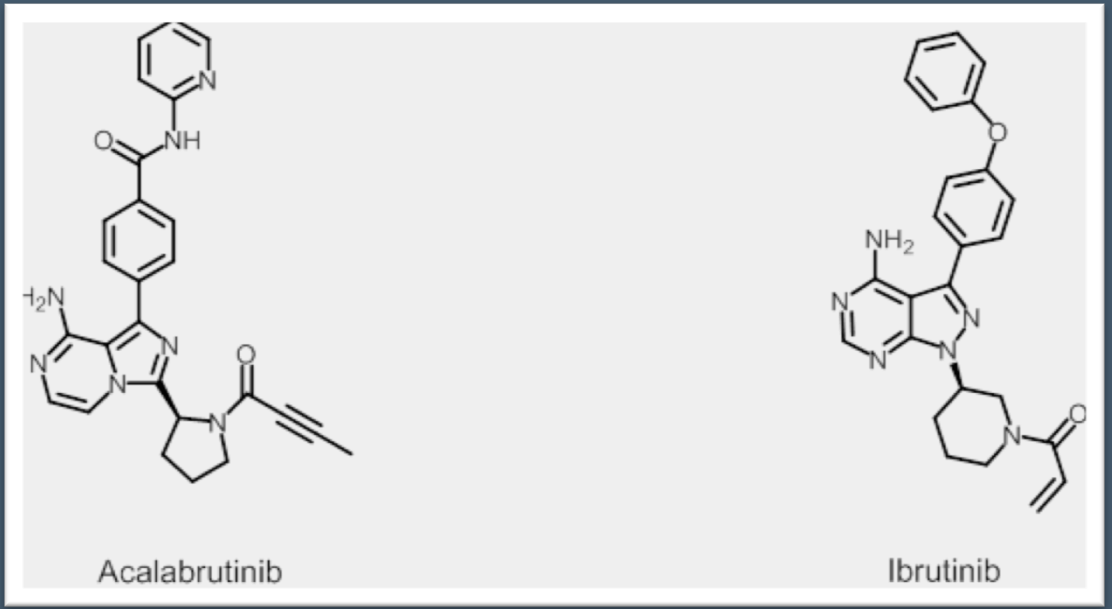
- Following slides provided by Acerta Pharma

BTK Mechanism of Action



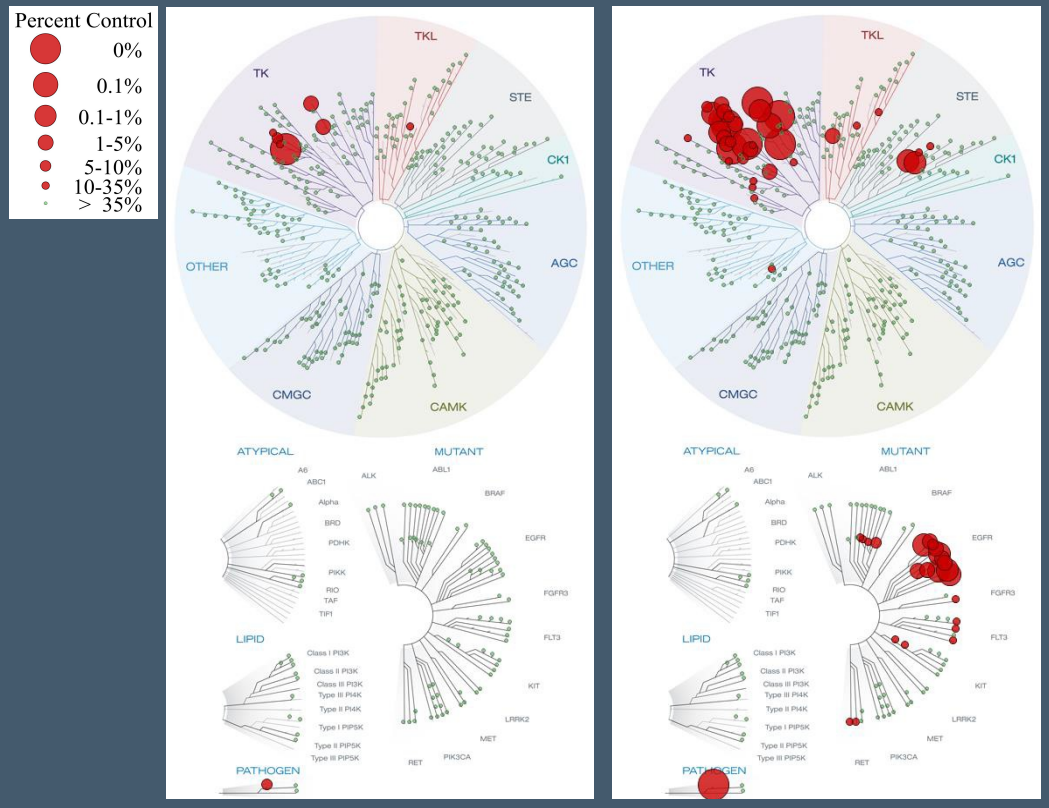
Acalabrutinib: A highly selective, potent Bruton Tyrosine Kinase (BTK) inhibitor

- 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



Byrd JC, Harrington B, O'Brien S, et al. *N Engl J Med* 2016;374:323-32. Supplement.
DOI: 10.1056/NEJMoa1509981.
Wilson, WH. *N Engl J Med* 2016; 374:386-388.

Acalabrutinib: A highly selective, potent BTK inhibitor



KinomeScan Competitive Binding Assay (DiscoverX)
456 human kinase panel tested at 1uM drug.

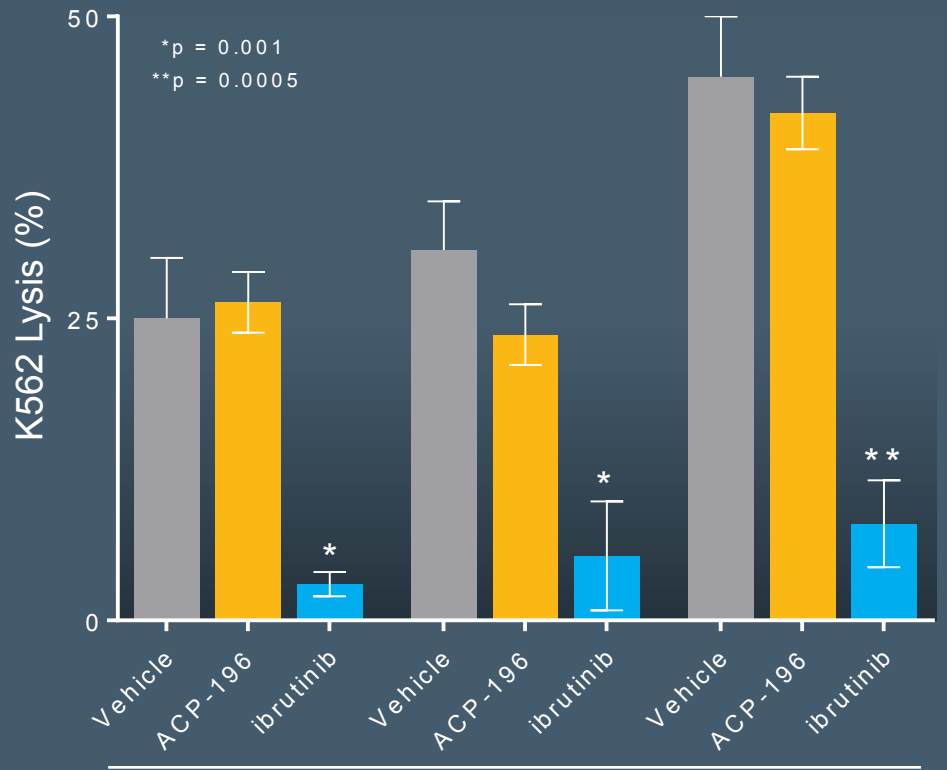
Kinase Inhibition IC_{50} (nM)

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

Covey, et al. *Cancer Res*. 2015; 2596.
Byrd JC, Harrington B, O'Brien S, et al. *N Engl J Med* 2016;374:323-32. Supplement. DOI: 10.1056/NEJMoa1509981.

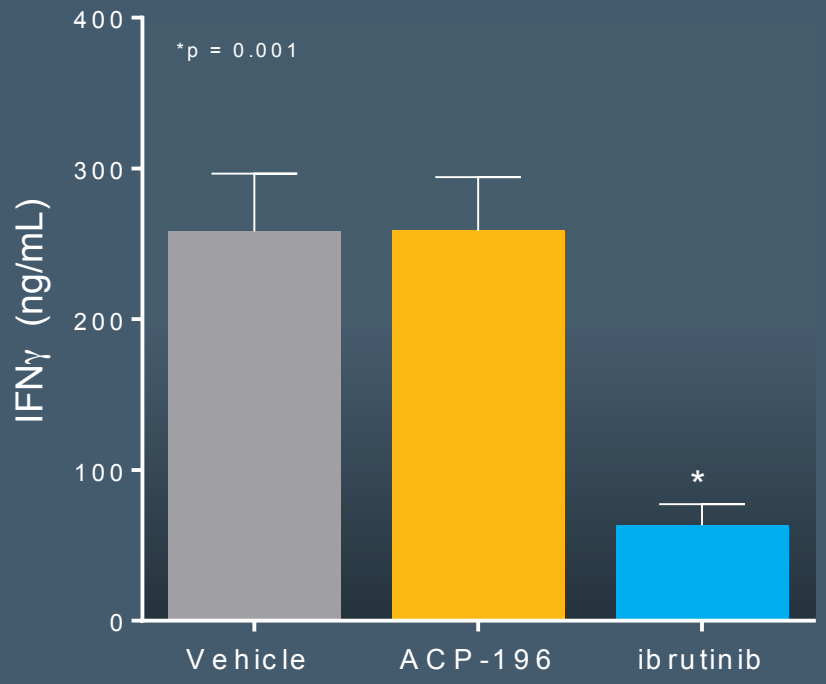
Selectivity Profile (Preclinical)

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



ACP-196 does not inhibit NK cell cytolytic activity†

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



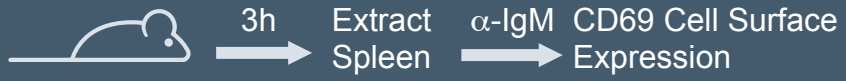
ACP-196 does not inhibit IFNγ CD8+ T cells‡

‡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.

Lannutti, et al. *Cancer Res*, 2015; 408.
Byrd JC, Harrington B, O'Brien S, et al. *N Engl J Med* 2016;374:323-32. Supplement. DOI: 10.1056/NEJMoa1509981

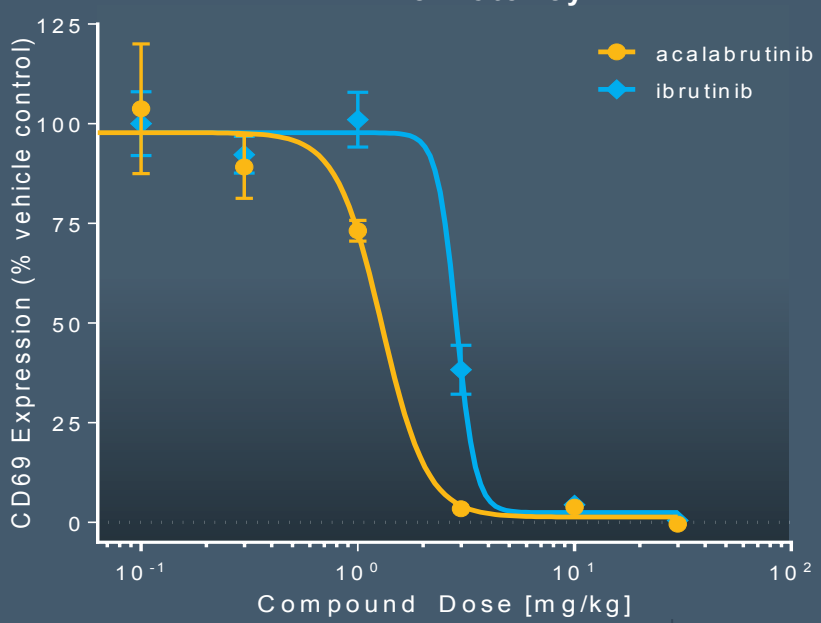
Acalabrutinib: Potency in Mouse Splenocyte Model

Dose Response (po)



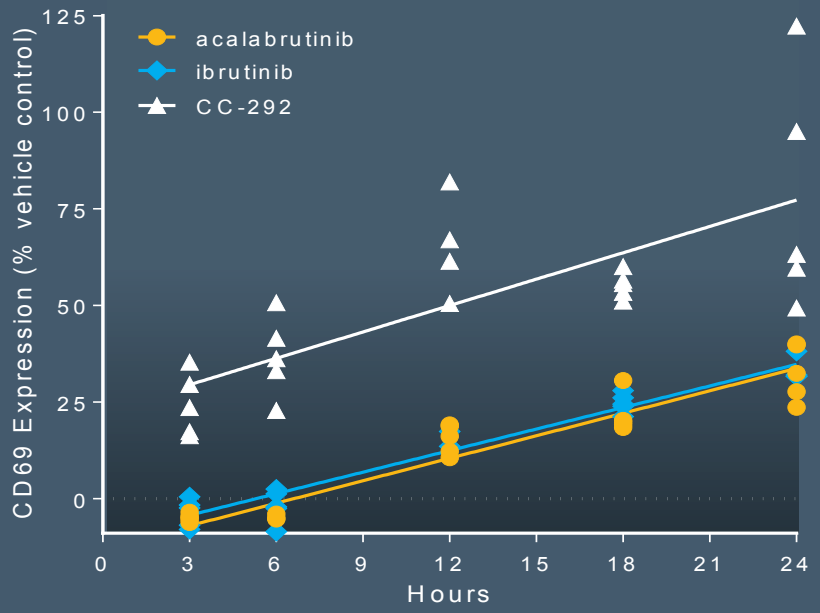
Single Dose (25 mg/kg, po)

***In Vivo* Potency**



	acalabrutinib	ibrutinib
ED_{50} (mg/kg)	1.3	2.9

Return of B Cell Function



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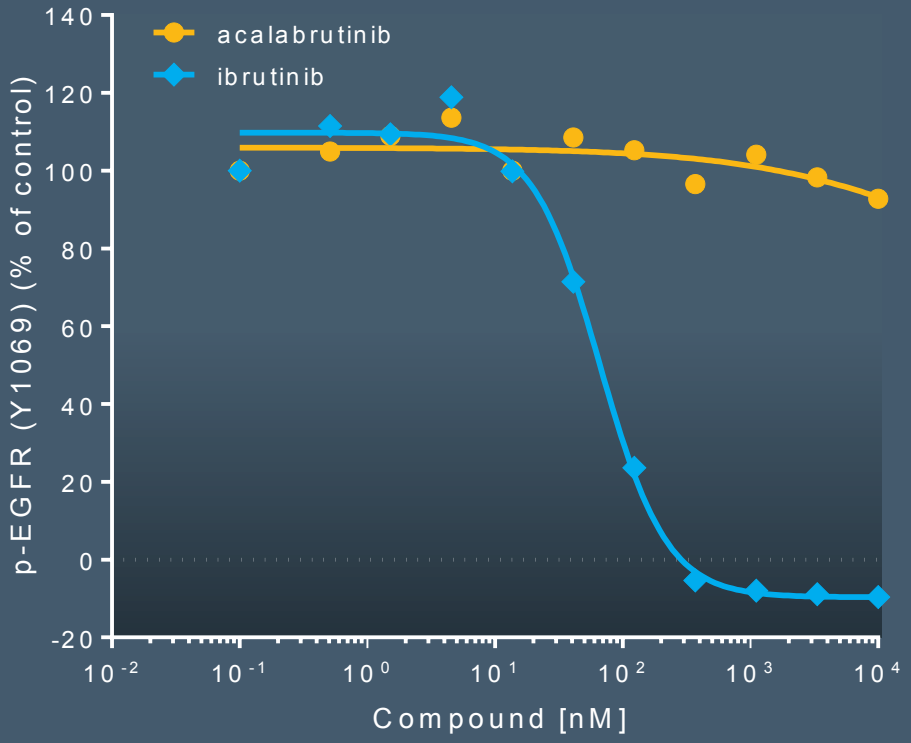
Acalabrutinib: Highly selective with no EGF Receptor Phosphorylation *in Vitro*

The ability of acalabrutinib or ibrutinib to inhibit the phosphorylation of EGFR was measured: acalabrutinib does not inhibit EGFR phosphorylation

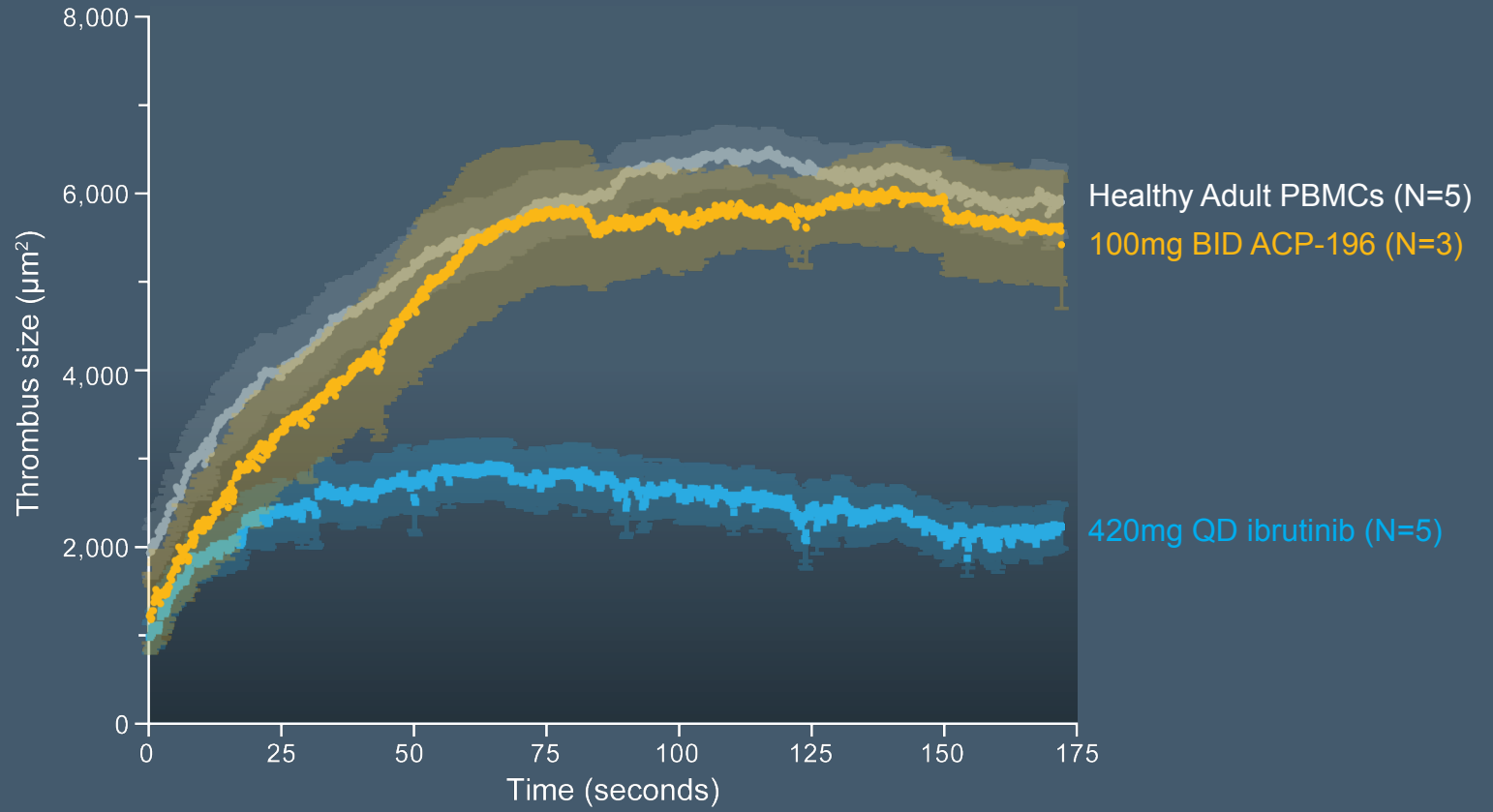


	acalabrutinib	ibrutinib
EGF-induced pEGFR	7% inhibition at 10 μM	EC_{50} = 66 nM

Covey, et al. *Cancer Res*. 2015; 2596.

Platelet Aggregation (R/R Patients with CLL)

ACP-196 does not inhibit platelet mediated thrombosis



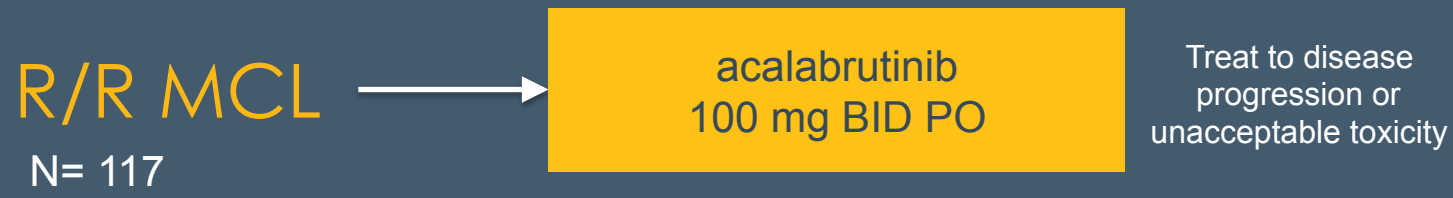
In vivo murine thrombosis model. Chen, et al. *Blood.* 2014.

Covey, et al. *Cancer Res*. 2015; 2596.
Byrd JC, Harrington B, O'Brien S, et al. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. *N Engl J Med* 2016;374:323-32. Supplement. DOI: 10.1056/NEJMoa1509981.

Acalabrutinib in MCL

Acalabrutinib in Subjects with Relapsed/Refractory MCL

Open label, phase 2 study of acalabrutinib in subjects with MCL
NCT02213926
(*Fully enrolled*)



Key inclusion criteria:

- Pathologically confirmed MCL with monoclonal B cells that have translocation t(11;14) (q13;q32) and/or overexpression of cyclin D1
- Have relapsed after ≥ 1 (but not > 5) prior treatment regimens
- ECOG PS ≤ 2

Primary endpoint: ORR*

*IRC review per Lugano Classification for NHL

Acalabrutinib in MCL

Phase 1b open-label study of acalabrutinib in combination with bendamustine and rituximab (BR) in subjects with MCL
NCT02717624
(*Enrolling*)

MCL
N= 48

→ acalabrutinib[§] + bendamustine[±] rituximab[±*]

Key eligiblity criteria

- Pathologically confirmed MCL with monoclonal B cells that have translocation t(11;14)(q13;q32) and/or overexpression of cyclin D1
- MCL requiring treatment
- Radiographically measurable LAD or extranodal lymphoid malignancy
- ECOG PS ≤ 2
- Prior exposure to a BCR inhibitor or BCL-2 inhibitor are excluded

- **Primary endpoint:** To characterize the safety profile of acalabrutinib in combination with BR in subjects with newly diagnosed and relapsed/refractory MCL

[§] acalabrutinib given until disease progression or unacceptable toxicity
[±] bendamustine, rituximab given for a maximum of 6 cycles
*rituximab maintenance in newly diagnosed MCL cohort

- From clinical.gouv

An Open-label, Phase 2 Study of ACP 196 in Subjects With Mantle Cell Lymphoma

This study is ongoing, but not recruiting participants.
Sponsor: Acerta Pharma BV
ClinicalTrials.gov Identifier: NCT02213926
First received: August 5, 2014Last updated: February 5, 2016Last verified: February 2016

A Study of ACP-196 in Combination With Bendamustine and Rituximab in Subjects With Mantle Cell Lymphoma

This study is currently recruiting participants.
Sponsor:Acerta Pharma
ClinicalTrials.gov Identifier:NCT02717624
First received: February 24, 2016Last updated: March 23, 2016

A Study of Acalabrutinib in Combination With Rituximab Versus Ibrutinib Versus Acalabrutinib in Subjects With Relapsed or Refractory Mantle Cell Lymphoma

This study is not yet open for participant recruitment.
Sponsor: Acerta Pharma
ClinicalTrials.gov Identifier:NCT02735876
First received: April 8, 2016Last updated: April 12, 2016Last verified: April 2016

CONCLUSION

- No published clinical results regarding ACP-196 in MCL
- Trials in MCL are ongoing: result expected 2016 ?
- No clinical data regarding ACP-196 vs Ibrutinib in MLC
- ACP-196 were designed to be highly selective for BTK inhibition: better or not ?
- Side effects in MCL ?