BTK Inhibitors in Indolent NHL

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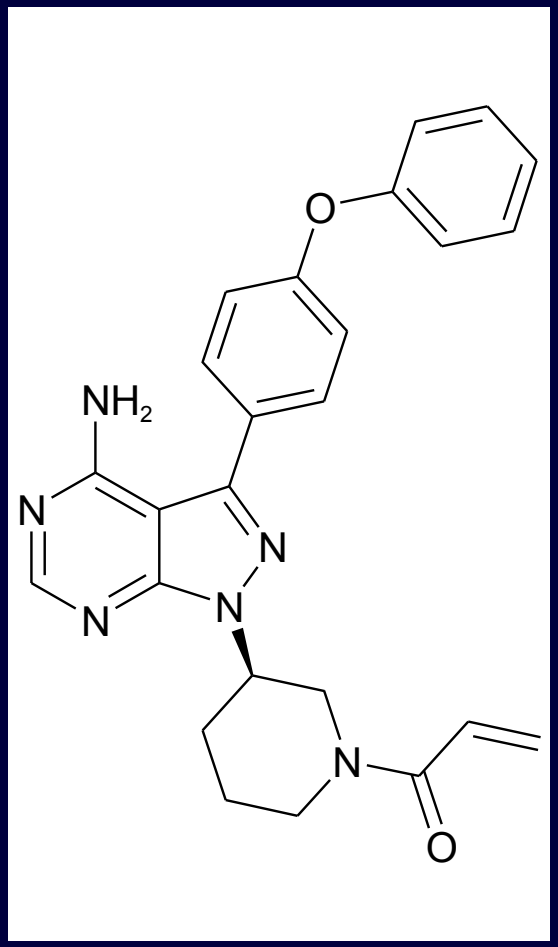
Ibrutinib (PCI-32765), a selective inhibitor of BTK



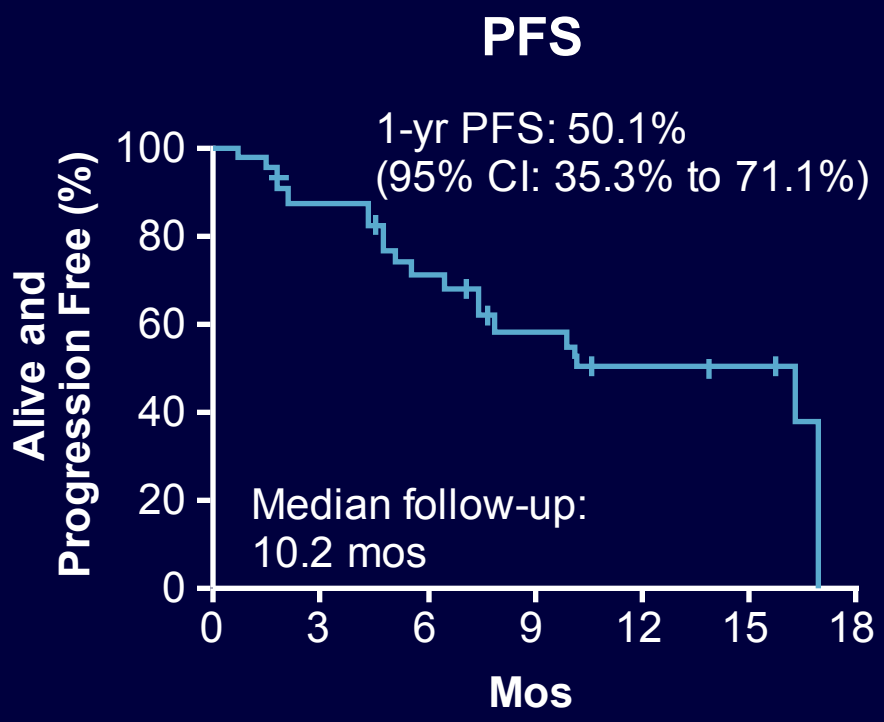
- Forms a specific bond with cysteine-481 in BTK
- Highly potent BTK inhibition at IC50 = 0.5 nM
- Orally administered with once daily dosing resulting in 24-hr target inhibition
- No cytotoxic effect on T-cells or NK-cells
- In CLL cells promotes apoptosis and inhibits CLL cell migration and adhesion
- Phase I/II data of single agent ibrutinib in relapsed/refractory CLL patients demonstrated a high frequency of durable response (O'Brien ASH 2011)

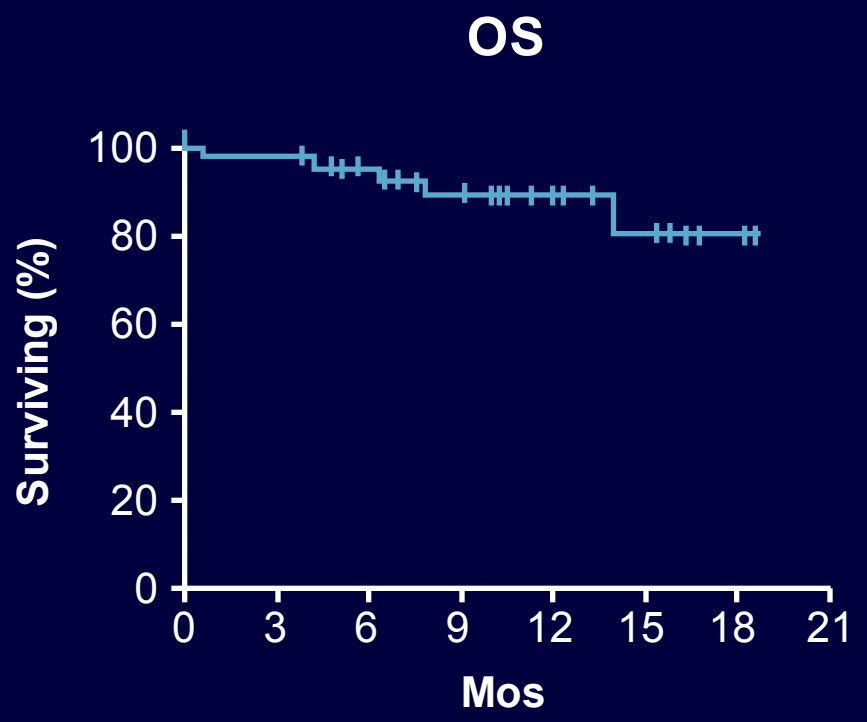
Phase II Consortium: Ibrutinib Monotherapy in Relapsed/Refractory FL

- Single-agent ibrutinib associated with antitumor responses in relapsed/refractory FL
  - ORR: 28%
  - ORR in rituximab-sensitive disease: 42%
  - ORR in rituximab-insensitive disease: 6%
  - 1-yr PFS: 50%

Bartlett NL, et al. ASH 2014. Abstract 800.

Ibrutinib Monotherapy in Relapsed/ Refractory FL: PFS and OS





Bartlett NL, et al. ASH 2014. Abstract 800.

The Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib (PCI-32765) is Active and Tolerated in Relapsed Follicular Lymphoma (FL)

Nathan Fowler MD[1], Ranjana Advani MD[2], Jeff Sharman MD[3], Sonali M. Smith MD[4], Jesse McGreivy MD[5], Lori Kunkel MD[5], Vina Troung[5], Cathy Zhou[5], Thomas Boyd MD[6]

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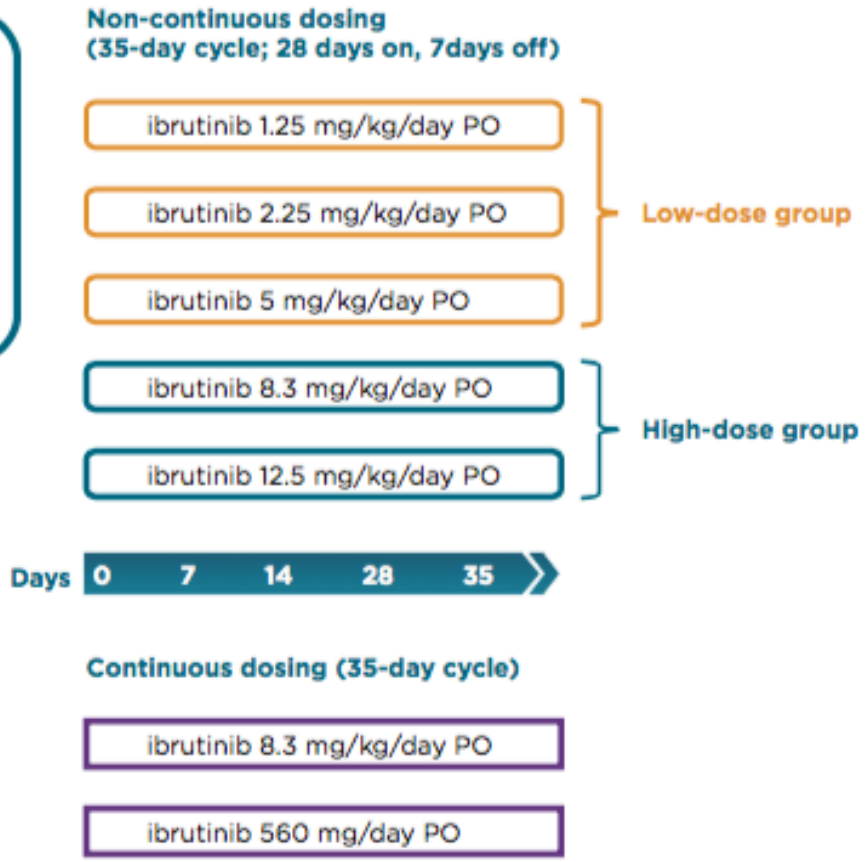
[3]Willamette Valley Center Institute (US Oncology Research), Springfield, OR
[4]Hematology/Oncology, University of Chicago Hospitals, Chicago, IL
[5]Pharmacyclics, Inc., Sunnyvale, CA
[6]North Star Lodge Cancer Center (US Oncology Research), Yakima, WA

Key eligibility criteria

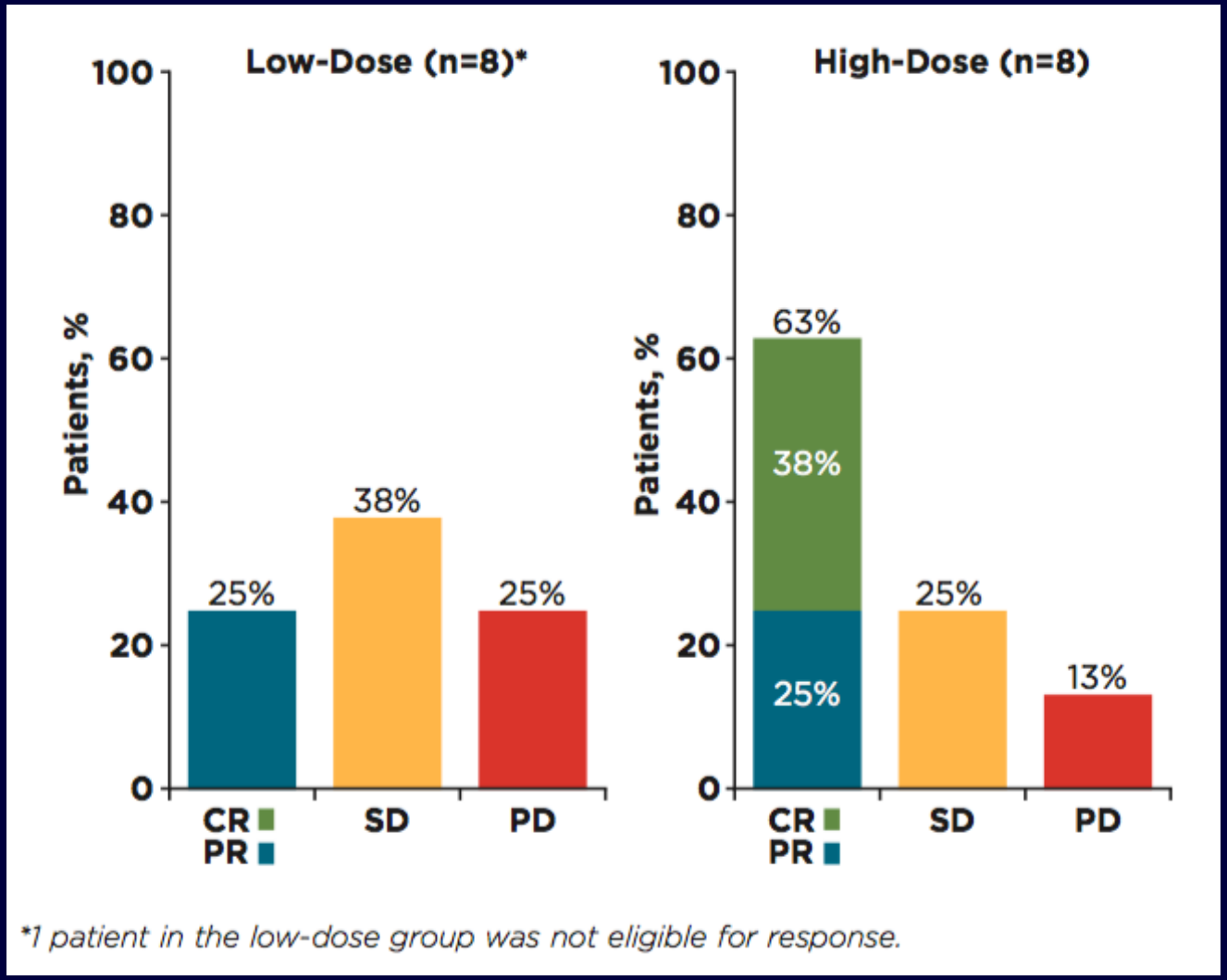
- Patients with refractory, histologically confirmed non-Hodgkin lymphoma, chronic lymphocytic leukemia, or Waldenström macroglobulinemia that failed ≥1 prior therapy



- **Primary endpoints:** dose-limiting toxicities, adverse events (AEs), pharmacokinetic/pharmacodynamic assessments
- **Secondary endpoint:** tumor response

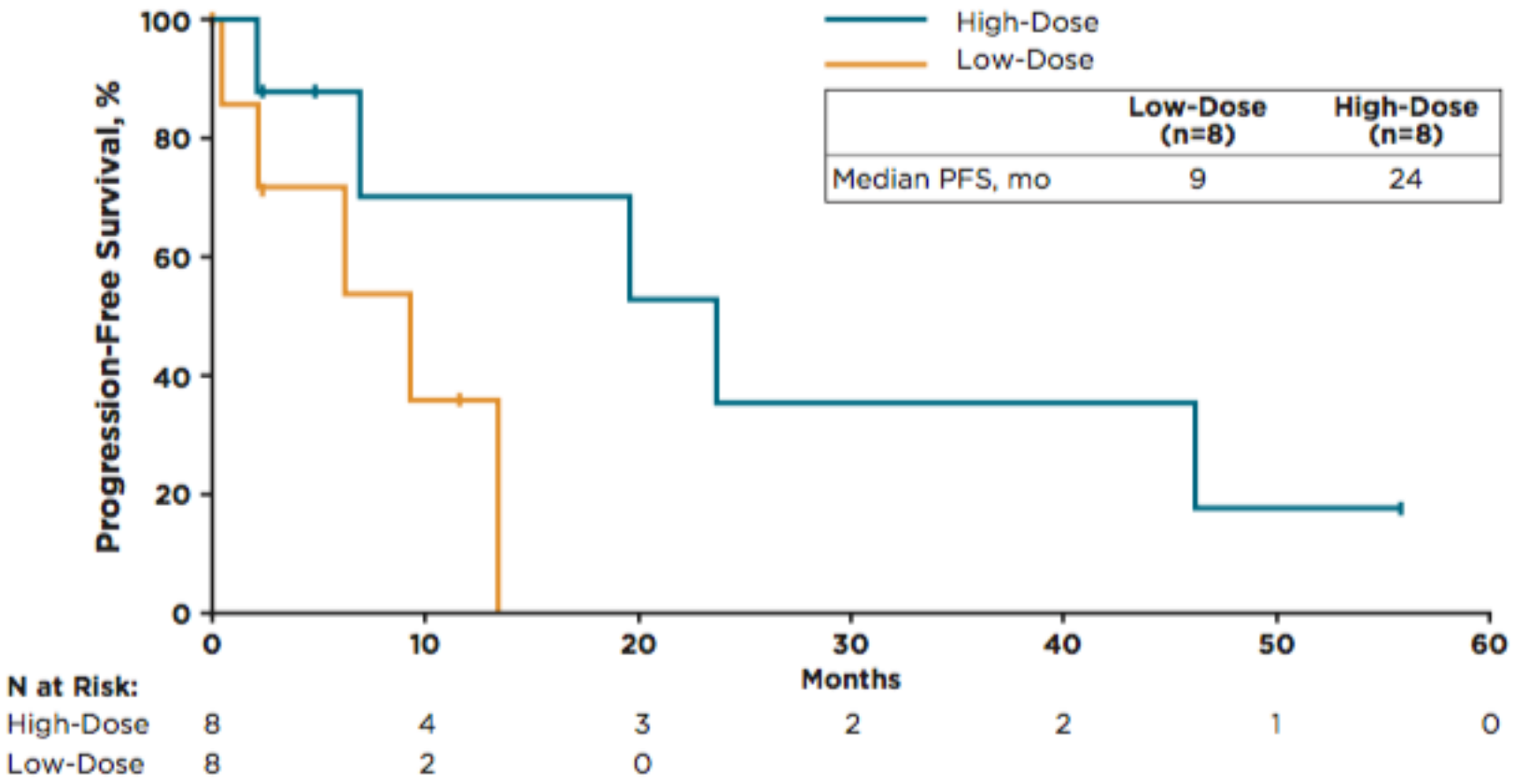
Fowler et al, Proc ASH, abstr 2706, 2015

Response to Ibrutinib in R/R Follicular NHL



Fowler et al, Proc ASH, abstr 2706, 2015

PFS Following Ibrutinib in R/R Follicular NHL



Fowler et al, Proc ASH, abstr 2706, 2015

Grade ≥ 3 Toxicities of Ibrutinib

Adverse Event (Grade ≥3), n	Low-Dose (n=8)	High-Dose (n=8)
Anemia	1	0
Anxiety	0	1
Blood potassium decreased	1	1
Hypersensitivity	0	1
Hypokalemia	0	1
Hypophosphatemia	1	0
Myelodysplastic syndrome	1	0
Neutrophil count decreased	1	0
Noncardiac chest pain	0	1
Pancytopenia	1	0
Pneumonia	1	0
Vomiting	0	1

Fowler et al, Proc ASH, abstr 2706, 2015

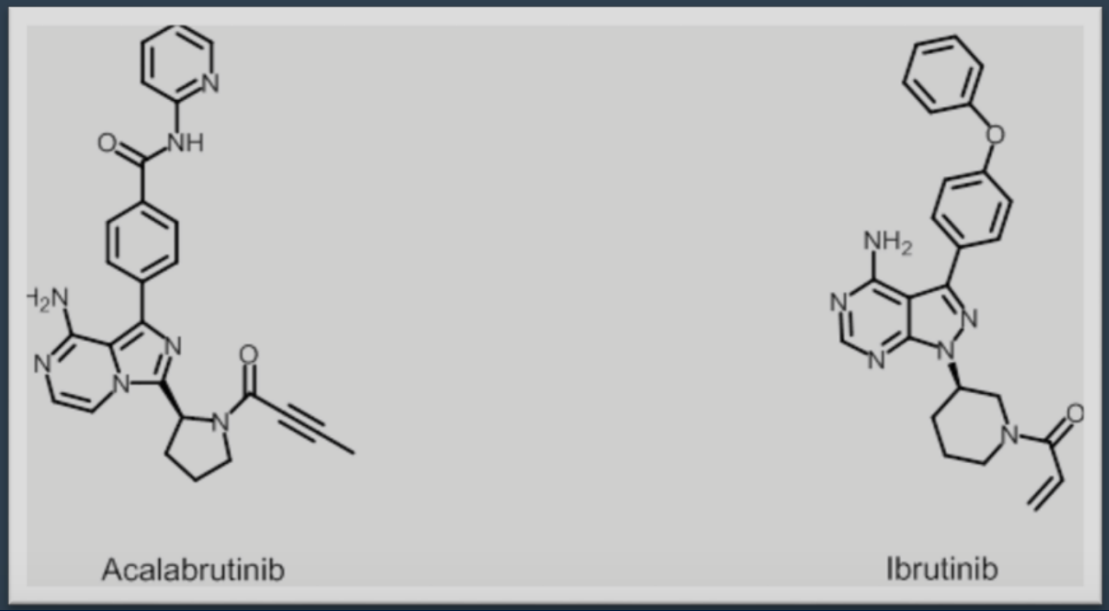
Safety: Atrial Fibrillation and Bleeding-Related Adverse Events

- Atrial fibrillation of any grade, was noted more frequently in patients receiving ibrutinib (n=10) compared with ofatumumab (n=1)
  - Led to discontinuation of ibrutinib in only 1 patient; patients were ≥60 years old (median age 73); most had predisposing risk factors (a prior history of atrial fibrillation or occurrence in the setting of a pulmonary infection)
- Bleeding-related AEs of any grade, most commonly petechiae, and including ecchymoses, were more common with ibrutinib than with ofatumumab (44% vs. 12%)
  - The vast majority of ibrutinib events were grade 1
  - No difference in severe/major bleeding events (reported in 2 patients randomized to ibrutinib and 3 patients receiving ofatumumab, including 1 ibrutinib patient with a subdural hematoma)
  - Only 1 patient discontinued ibrutinib due to a bleeding AE
  - 37% of patients on the ibrutinib arm and 28% of patients on the ofatumumab arm received either concomitant anti-platelets (excluding NSAIDS) or anticoagulants

Byrd et al, NEJM 371:213, 2014

Acalabrutinib: A potent and selective 2nd generation Bruton Tyrosine Kinase (Btk) inhibitor

- **Acalabrutinib was developed to increase the degree of Btk inhibition**
  - Has less avid binding to Btk than first generation Btk inhibitors
  - 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, a second generation Btk inhibitor, appears to improve substantially on the specificity of first generation Btk inhibitors**



Byrd, J,et al. *N Engl J Med* 2016; 374:323-332.
Wilson, WH. N Engl J Med 2016; 374:386-388.

Second-Generation Btk Inhibitor

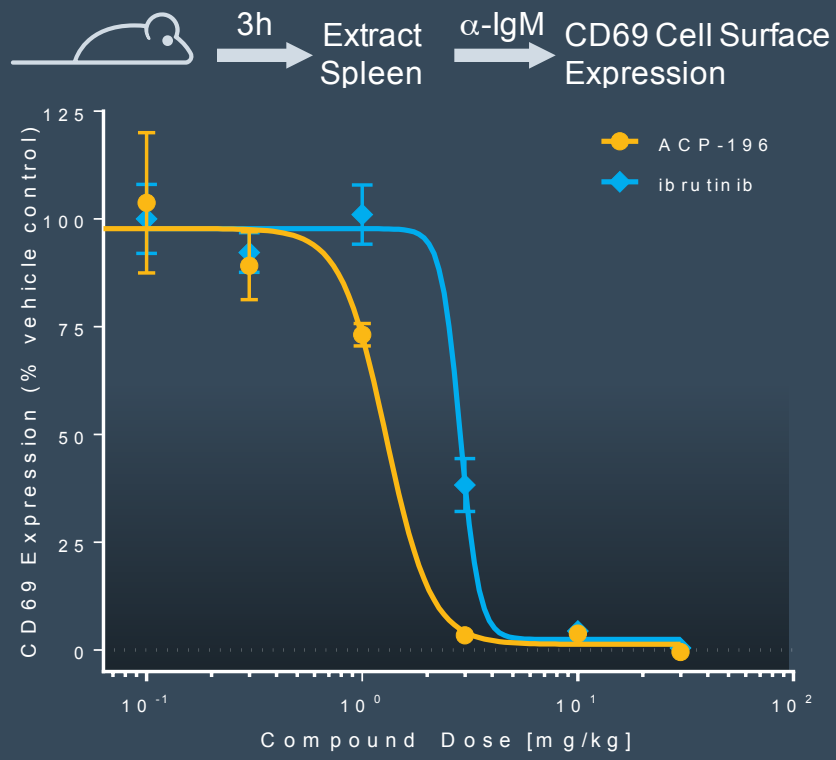
ACP-196 is a potent, selective irreversible Btk inhibitor

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.

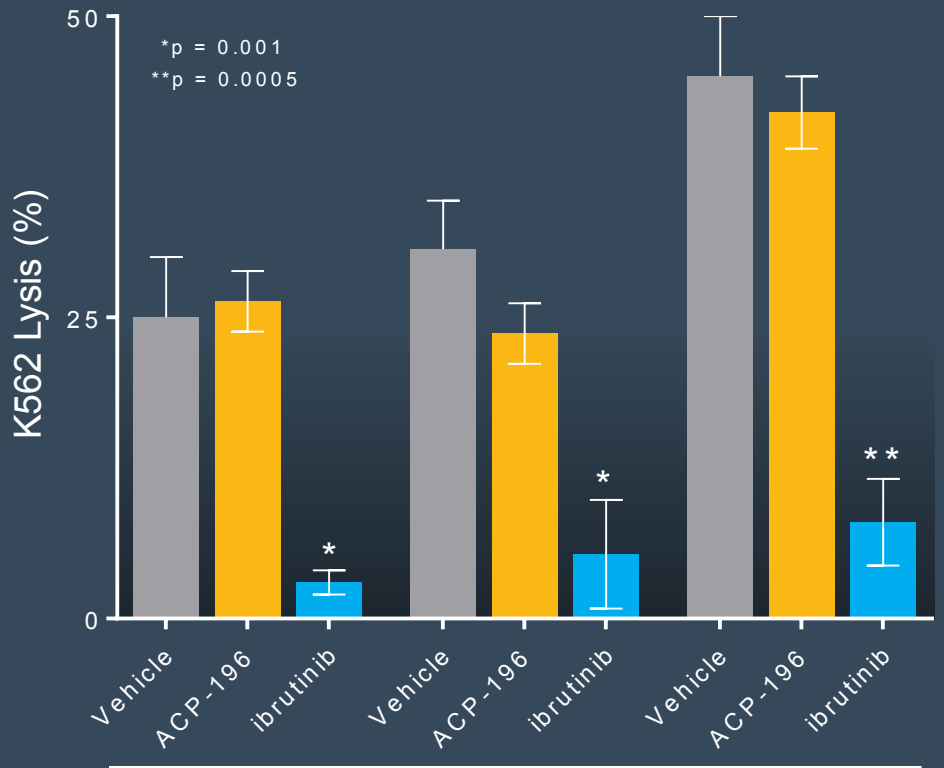
In Vivo Potency



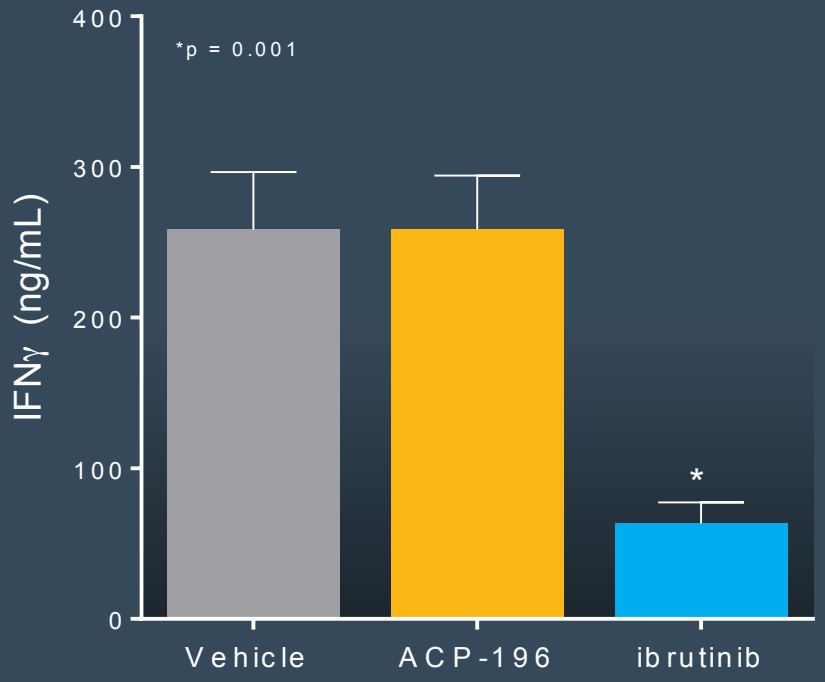
	ACP-196	ibrutinib
ED_{50} (mg/kg)	1.3	2.9

Selectivity Profile (Preclinical)

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



ACP-196 does not inhibit NK cell cytolytic activity†

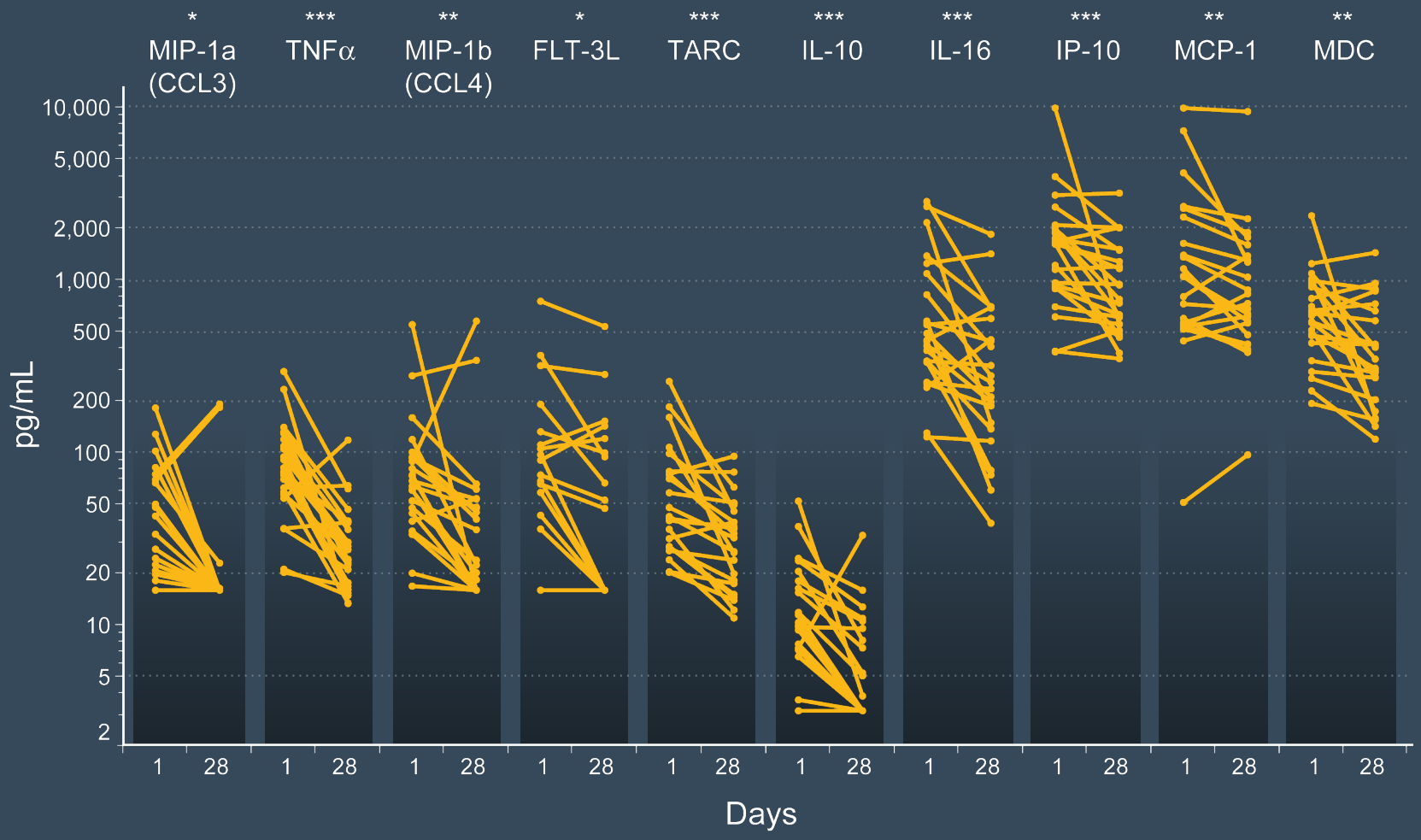


ACP-196 does not inhibit IFNγ CD8+ T cells‡

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

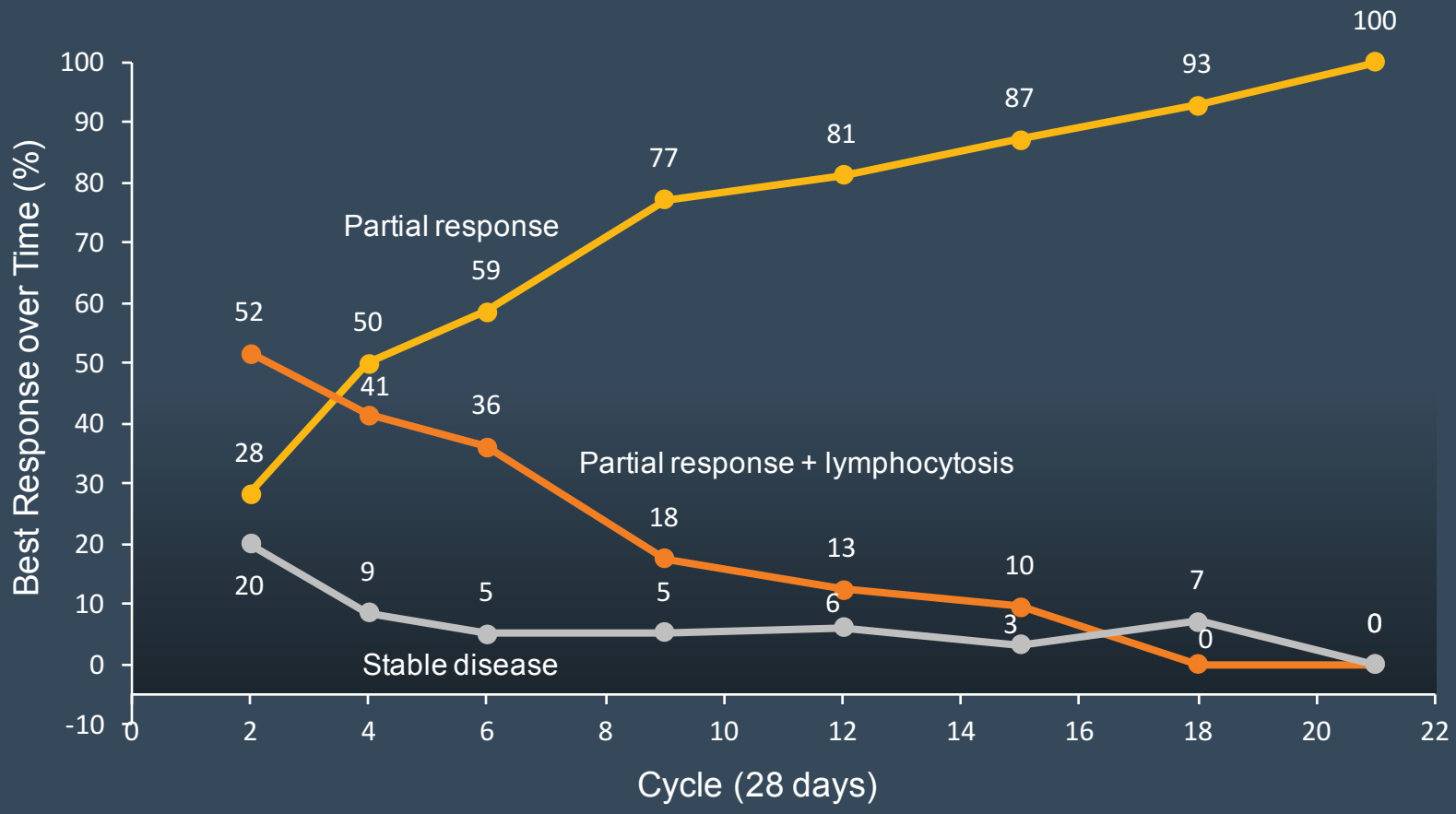
‡Cells were preincubated with ACP-196 and ibrutinib (500nM each), then washed before being assayed.
CD8+ T cells were stimulated with anti-TCR Ab to produce IFNγ.

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.

Best Response Over Time



Patients	60	58	58	57	48	31	14	3

01Oct2015; R/R CLL patients.

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)

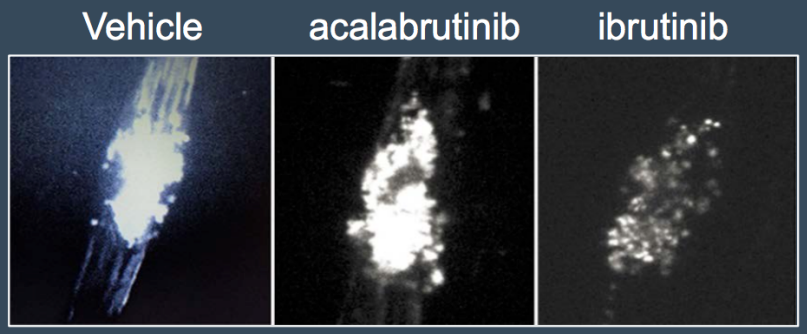
Reported in ≥20% patients

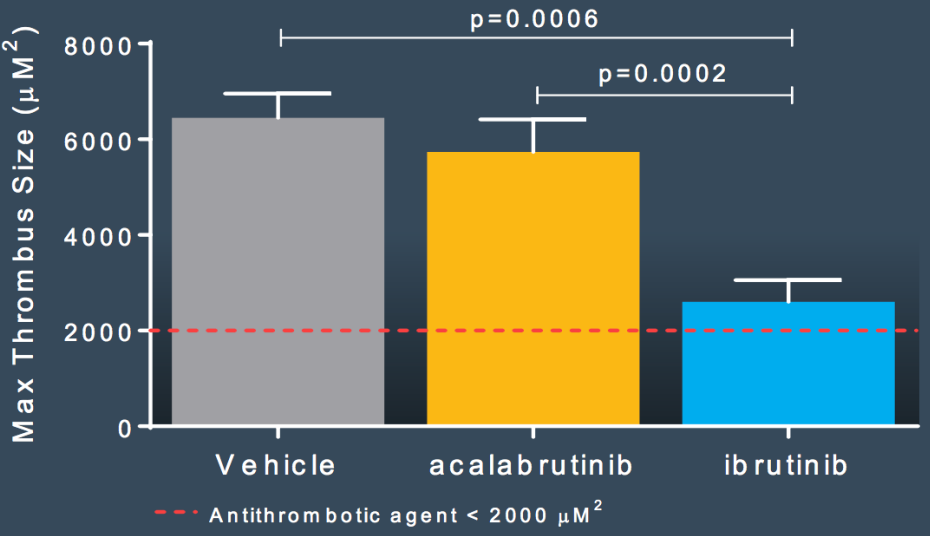
Adverse Events (Treatment-Emergent), n (%)	Grade 1-2	Grade 3	N=61
Headache	26 (43)	–	26 (43)
Diarrhea	23 (38)	1 (2)	24 (39)
Increased weight	15 (25)	1 (2)	16 (26)
Pyrexia	12 (20)	2 (3)	14 (23)
Upper respiratory tract infection	14 (23)	–	14 (23)
Fatigue	11 (18)	2 (3)	13 (21)
Peripheral edema	13 (21)	–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

01Oct2015; R/R CLL patients.

Acalabrutinib Does Not Impair Thrombus Formation *In Vivo*

- A side effect of Tec kinase inhibition is bleeding due to impaired platelet aggregation
- Acalabrutinib does not inhibit Tec which results in no impairment of thrombus formation
- METHODS:
  - Fluorescently labelled human platelets were pre-incubated with vehicle, acalabrutinib or ibrutinib.
  - The platelets were then administered to mice.
  - A laser was used to induce vascular injury





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

ONO/GS-4059 Project Status

- Licensed from ONO on Dec. 19, 2014[1]
  - Development and Commercialization
  - Gilead responsible for development in Gilead Territory (all countries except ONO territory [Asia*])
- Clinical Data
  - Phase 1 monotherapy, conducted in the EU in approximately 90 subjects; demonstrated promising efficacy and safety in CLL, MCL, and DLBCL[2,3]
- IND for use in hematologic malignancies filed on March 26, 2015
  - Safe to proceed granted April 24, 2015
  - Initial development focused on combination with idelalisib
- Planned Studies
  - GS-US-401-1757 is a planned Phase 1b clinical study to evaluate GS-4059 in combination with idelalisib in patients with relapsed/refractory B-cell malignancies
    - Study began enrolling patients in 2Q 2015

* Japan, South Korea, Taiwan, China, Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand and Vietnam

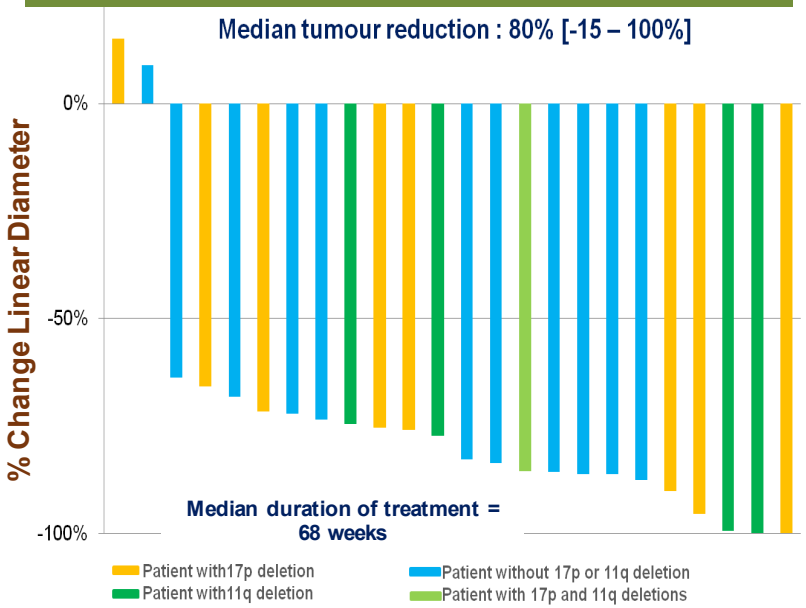
1. Gilead Sciences Inc.19-December-2014 [Press Release]
2. Fegan C, et al. Abstract #3328. ASH, 2014
3. Rule S, et al. Abstract #P462. EHA 2014

Study ONO-4059POE001 (Phase 1b)

ONO/GS-4059 has completed a single agent Phase 1 dose escalation study in CLL and NHL

Data is investigator reported and has not been audited or corroborated by Gilead

CLL Response[1]



NHL Response[2,3]

Disease	Best ORR % (n)
Mantle cell	60% (10)
Non-GCB DLBCL	47% (15)
Waldenstrom's	33% (3)
GCB-DLBCL	0% (2)
Follicular	0% (5)
Marginal zone	0% (1)

- Best Overall Response (BOR):
  - All patients: 21/25 (89%)
  - 17p deletion: 8/9 (89%)
  - Refractory disease: 13/15 (87%)

- Responses in non-GCB DLBCL, MCL, and WM

1. Fegan C, et al. Abstract #3328. ASH, 2014
2. Rule S, et al. Abstract #P461. EHA, 2014
3. Data on File

ONO/GS-4059 Common AEs in CLL and iNHL

- Safety:
  - Wide range of effective and tolerable doses: 40-480 mg QD[1,2]
  - Reported AEs mainly Grade 1-2 in severity[1,2]
  - Most common AEs:[1,2]
    - Infections, hematological abnormalities, skin disorders, and gastrointestinal disorders
      - No Grade 3-4 diarrhea reported[3]
- Planned Studies
  - GS-US-401-1757 is a planned Phase 1b clinical study to evaluate GS-4059 in combination with idelalisib in patients with relapsed/refractory B-cell malignancies
    - This study is scheduled to begin enrolling patients in 2Q 2015

1. Fegan C, et al. Abstract #3328. ASH, 2014
2. Rule S, et al. Abstract #P461. EHA, 2014
3. Data on File

Phase 2 Study of Ibrutinib Plus Rituximab in Treatment-Naïve FL: Study Design

Key eligibility criteria

- Treatment-naïve, histologically confirmed FL
- Stage II, III, or IV disease
- Age ≥18 years
- ≥1 measurable lesion ≥2 cm by CT scan
- ECOG PS ≤2

Arm 1: Main Study (N = 60)
Ibrutinib + Rituximab
Ibrutinib 560 mg PO QD
Rituximab 375 mg/m^2 QW for 4 weeks

Arm 2: Exploratory Arm (N = 20)
Ibrutinib + Rituximab
Ibrutinib 560 mg PO QD with 2-month lead-in
Rituximab 375 mg/m^2 QW for 4 weeks

Until PD or unacceptable toxicity

Primary endpoint: ORR (2007 IWG criteria)
Secondary endpoints: DOR, PFS, OS, and safety

Fowler et al. ASH 2015. Abstract 470.

Phase 2 Study of Ibrutinib Plus Rituximab in Treatment-Naïve FL: Efficacy

Efficacy Outcomes*		Arm 1: Ibrutinib-R (N=60)
ORR, %		82%
CR		30%
PR		52%
SD		18%
Median time to best response, months (range)		2.7 (1.1-13.6)
PFS	Median, months (range)	NR (0.92-16.6)
	12-month rate (95% CI)	86% (72.8, 93.1)
OS	Median, months (range)	NR (5.8-19.3)
	12-month rate (95% CI)	98% (88.6, 99.8)
Median DOR, months (range)		NR (0.03-11.9)
Median duration of ibrutinib treatment, months (range)		12.55 (0.8-19.6)

*Median follow-up 13.8 months [range, 5.8-19.3].

Fowler et al. ASH 2015. Abstract 470.

Alliance 051103: Phase I Study of Rituximab, Lenalidomide, and Ibrutinib in Previously Untreated Follicular Lymphoma

CS Ujjani[1], SH Jung[2], B Pitcher[2], P Martin[3], SI Park[4], KA Blum[5], SM Smith[6], MS Czuczman[7], MS Davids[8], JP Leonard[3], BD Cheson[1]

[1]Georgetown University, [2]Alliance Statistics and Data Center, Duke University, [3]Weill Cornell Medical College, [4]University of North Carolina, [5]Ohio State University, [6]University of Chicago, [7]Celgene Corporation, [8]Dana-Farber Cancer Institute

American Society of Hematology, December 7, 2015

Response

	Overall (n = 22)	DL 0 (n = 3)	DL 1 (n = 3)	DL 2 (n = 16)
ORR	**95%**	100%	100%	94%
CR*	63%	67%	33%	69%
PR	32%	33%	67%	25%
SD	5%	0	0	6%

- Median time to first response: 2.3 months (1.9-11.1)
- Median time to best response: 5.5 months (1.9-20.2)

* 8 patients who achieved a negative PET/CT did not undergo confirmatory bone marrow biopsy

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Safety and Activity of the Chemotherapy-free Triplet of Ublituximab, TGR-1202, and Ibrutinib in Relapsed B-cell Malignancies

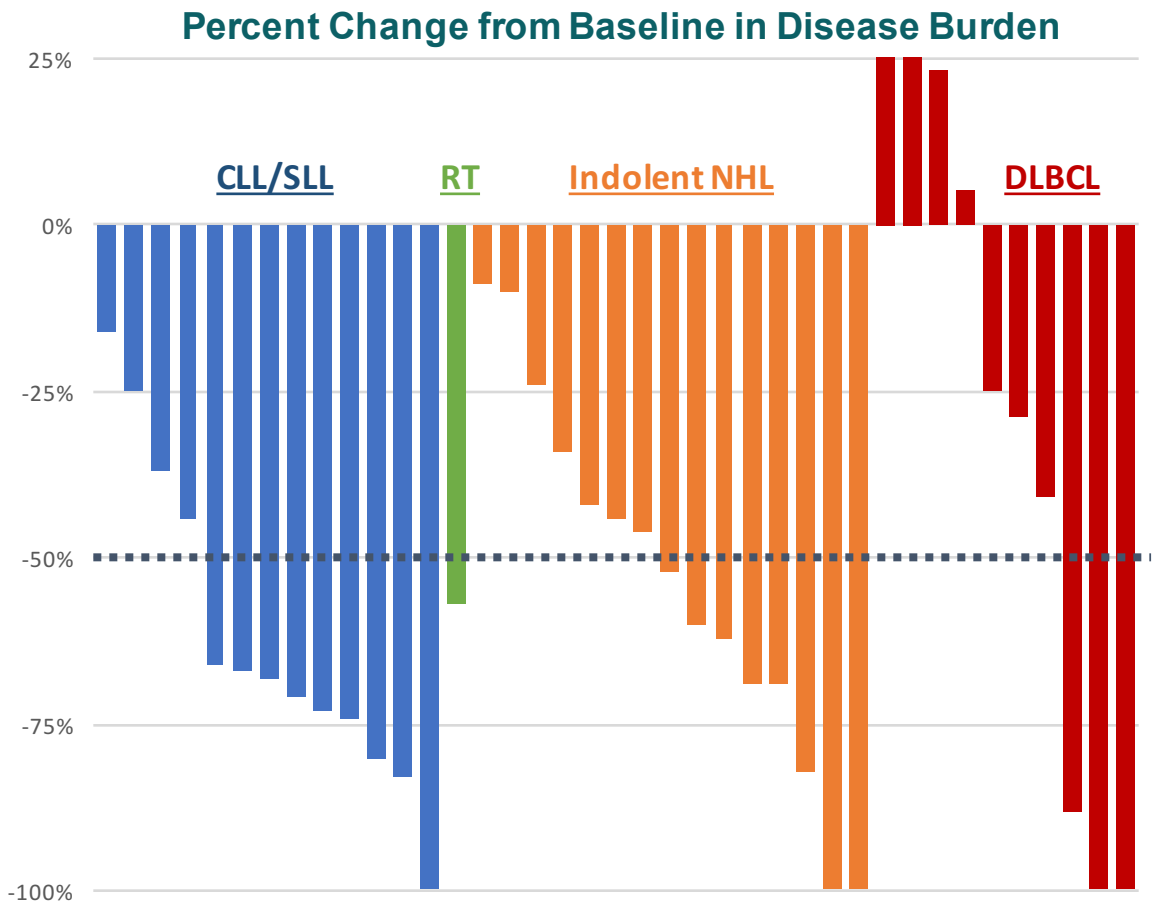
Nathan Fowler, MD[1], Loretta Nastoupil, MD[1], Matthew Lunning, DO[2], Julie Vose, MD[2], Tanya Siddiqi, MD[3], Christopher Flowers, MD[4], Jonathon Cohen, MD[4], Jan Burger, MD, PhD[1], Marshall T. Schreeder, MD[5],
Myra Miguel, RN[1], Susan Blumel, RN, BSN[2], Brianna Phye, BS[3], Emily K. Pauli, PharmD[5], Kathy Cutter, RN[5], Peter Sportelli[6], Hari P. Miskin, MS[6], Michael S. Weiss[6], Swaroop Vakkalanka, PhD[7], Srikant Viswanadha, PhD[8] and Susan O'Brien, MD[9]

[1]MD Anderson Cancer Center, Houston, TX; [2]University of Nebraska Medical Center, Omaha, NE; [3]City of Hope National Medical Center, Duarte, CA; [4]Emory University/Winship Cancer Institute, Atlanta, GA; [5]Clearview Cancer Institute, Huntsville, AL; [6]TG Therapeutics, Inc., New York, NY; [7]Rhizen Pharmaceuticals S.A, La Chaux-de-Fonds, Switzerland; [8]Incozen Therapeutics, Hyderabad, India; [9]University of California Irvine Cancer Center, Orange, CA.

PRESENTED AT: ASCO Annual '15 Meeting

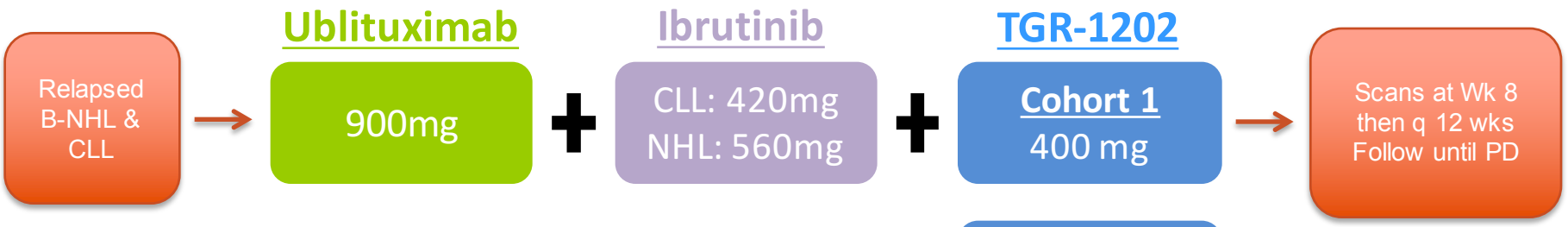
TGR-1202 + Ublituximab Doublet

- 55 patients treated to date
  - 60% ≥3 prior therapies
  - 51% refractory to prior therapy
- Combination well tolerated
  - Minimal Gr. 3/4 AE's
- Clinical activity demonstrated in CLL, indolent NHL, and aggressive NHL



Lunning et al, ASCO 2015

Trial Design: TGR-1202 + Ublituximab + Ibrutinib



- 3 + 3 dose escalation design (CLL and NHL)
- No limit on prior # of therapies
- ECOG Performance Status ≤ 2
- ANC > 500 / Plts > 30,000
- Patients with Richter's Transformation, or refractory to prior PI3Kδ inhibitors or prior BTK inhibitors are eligible
- All 3 agents started on Day 1

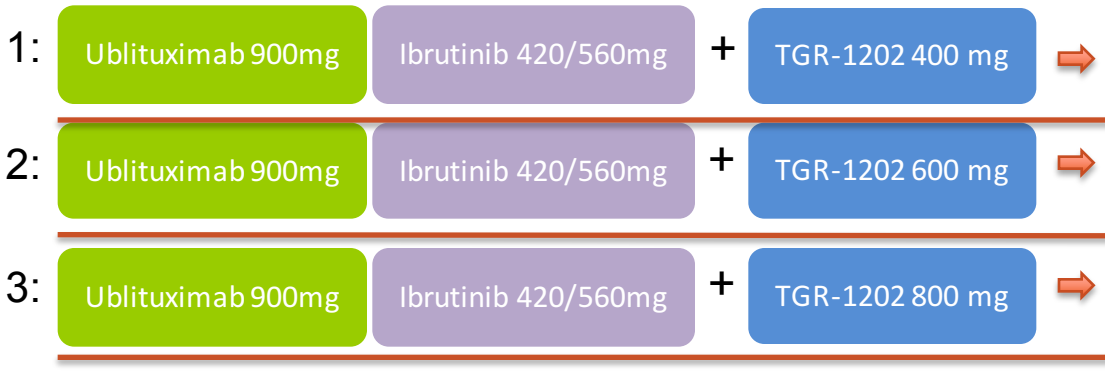
Endpoints:

- Primary: Safety
- Secondary: ORR, DOR, PFS

Safety: TGR-1202 + Ublituximab + Ibrutinib

Cohort Summary

- CLL and NHL cohorts evaluated separately



NHL Pts	# DLT	CLL Pts	# DLT
3	0	5	1*
4	0	0	0
4	0	0	0

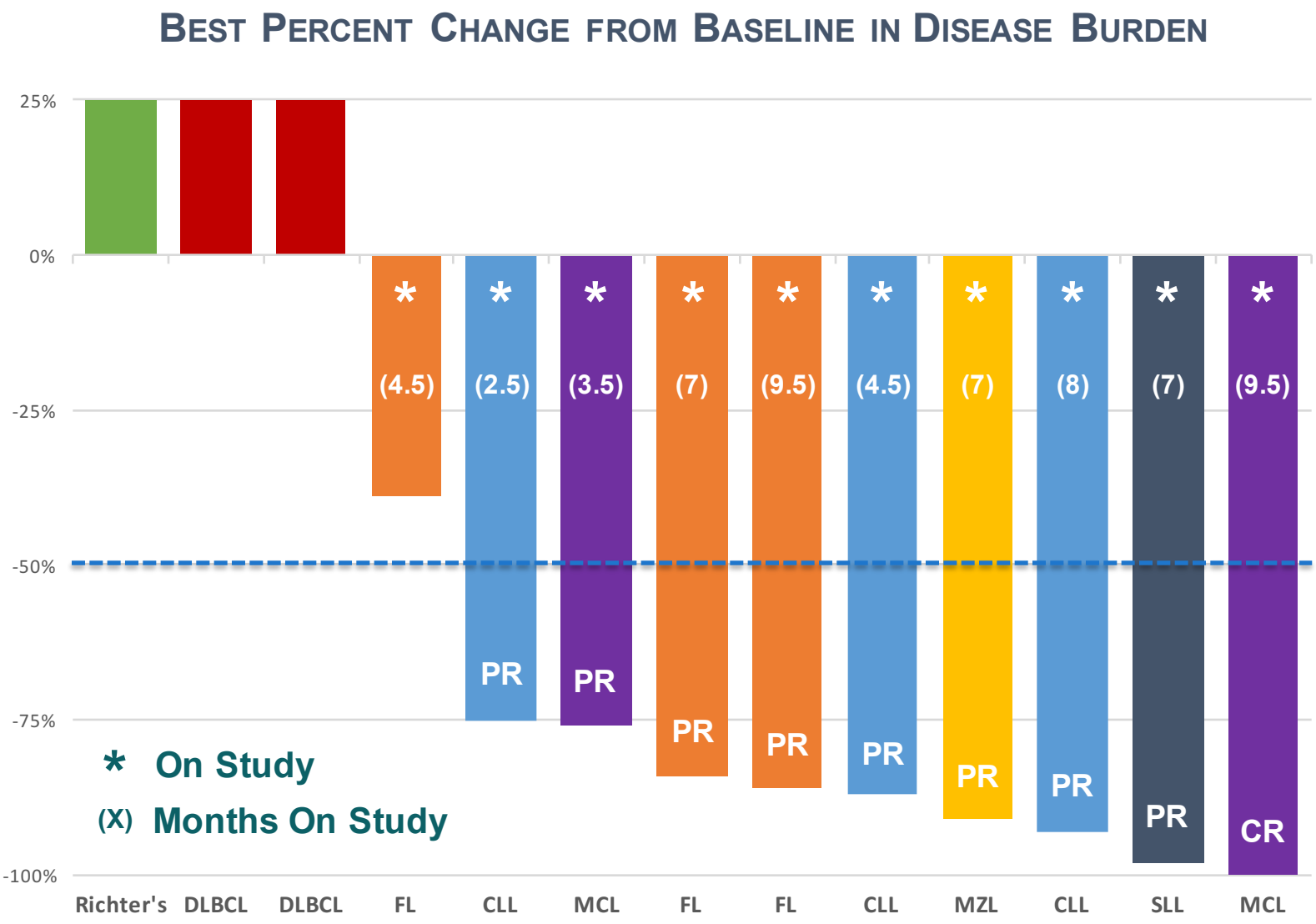
**DLT of reactivated varicella zoster – no additional DLT's to date in CLL cohort*

- Median time on study = 4 mos (range 1 – 9 mos)
- DLT in CLL 400 mg cohort
- 800 mg TGR-1202 cohort cleared in NHL

Safety: TGR-1202 + Ublituximab + Ibrutinib

AE's (at least possibly related) in > 1 Patient N=16		
Adverse Event	**All Grades** n (%)	**Grade 3/4** n (%)
Infusion reaction	4 (25%)	-
Diarrhea	3 (19%)	-
Nausea	3 (19%)	-
Fatigue	3 (19%)	-
Rash	3 (19%)	-
Anemia	2 (13%)	-
Neutropenia	2 (13%)	1 (6%)
Leukopenia	2 (13%)	1 (6%)
Insomnia	2 (13%)	-

Activity in NHL: TGR-1202 + Ublituximab + Ibrutinib



Ongoing Trials With Btk Inhibitors in FL

Drugs	Disease Status	Sponsor
Acalabrutinib (ACP-196)+pembrolizumab	R/R	Acerta
Acalabrutinib+ACP-319	R/R	Acerta
Acalabrutinib+rituximab	R/R	Acerta
Ono/GS-4059+idelalisib	R/R	Gilead
Ibrutinib+Venetoclax	R/R	Georgetown
Ublituximab+ibrutinib	R/R	TG Therapeutics
Ublituxumab+TGR-1202+ibrutinib	Front-line	TG Therapeutics

Conclusions

- Btk inhibitors are promising agents in B-NHL
- As single agents less active in NHL than CLL
- Combinations with other targeted agents are in development
- Further research would be facilitated by availability of new biomarkers
- Potential to improve patient outcome