BTK Inhibition as an Anti-Cancer Strategy

Exploring a Model for Modern Targeted Therapy in Hematologic Malignancies and Beyond

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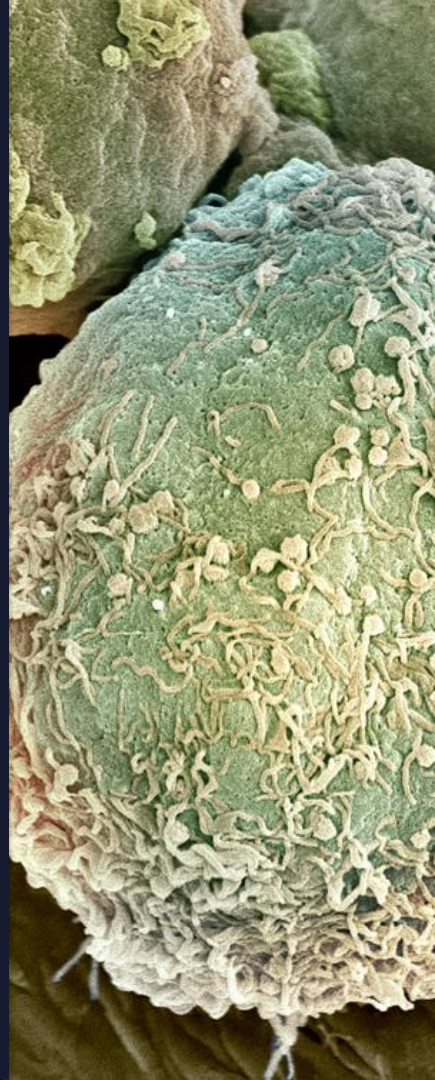

Disclosures

John C. Byrd, MD, has a financial interest/relationship or affiliation in the form of:

Consultant and/or Advisor for Acerta Pharma; AstraZeneca; Jazz Pharmaceuticals, Inc. and Pharmacyclics.

Grant/Research Support from Acerta Pharma; AstraZeneca; and Pharmacyclics.

John C. Byrd, MD, does intend to discuss either non–FDA-approved or investigational use for the following products/devices: acalabrutinib, zanubrutinib, tirabrutinib, sperbrutinib, and other emerging BTK inhibitors with applications in B-cell cancers.

Krish Patel, MD, has a financial interest/relationship or affiliation in the form of:

Consultant and/or Advisor for AstraZeneca; Sunesis Pharmaceuticals; Celgene Corporation; and Verastem, Inc.

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This CME/CNE activity is jointly provided by Penn State College of Medicine and PVI, PeerView Institute for Medical Education; this activity is also co-provided by Medical Learning Institute, Inc.
This activity is supported by an independent educational grant from AstraZeneca.

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Disclosures

CNE Reviewers

Tracy L. Greene, MSN, RN, FNP-C, Lead Nurse Planner, has no financial interests/relationships or affiliations in relation to this activity.

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Medical Directors

Carmine DeLuca
PVI, PeerView Institute for Medical Education

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Aarati Ranganathan, PhD
PVI, PeerView Institute for Medical Education

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Welcome and Introduction

Assessing the Rapid Development of BTK Inhibition as an Anti-Cancer Strategy

John C. Byrd, MD
The Ohio State University
Comprehensive Cancer Center
Arthur G. James Cancer Hospital
and Richard J. Solove Research Institute
Columbus, Ohio

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Tonight's Agenda

1. **Setting the stage:** a look at why targeting BTK matters and the mechanistic aspects of established and emerging agents

2. **Clinical data & practice forum:** the science that has validated the BTK inhibitor drug class in multiple B-cell cancer settings & case discussion on lessons from the evidence

3. **The future:** thinking about BTK resistance and the potential of BTK-immune combinations

MasterClass 1

Behind the Curtain: A Look at How Targeting BTK Works & Implications for a Range of Cancers

Krish Patel, MD
Swedish Cancer Institute
Center for Blood Disorders and
Stem Cell Transplantation
Seattle, Washington

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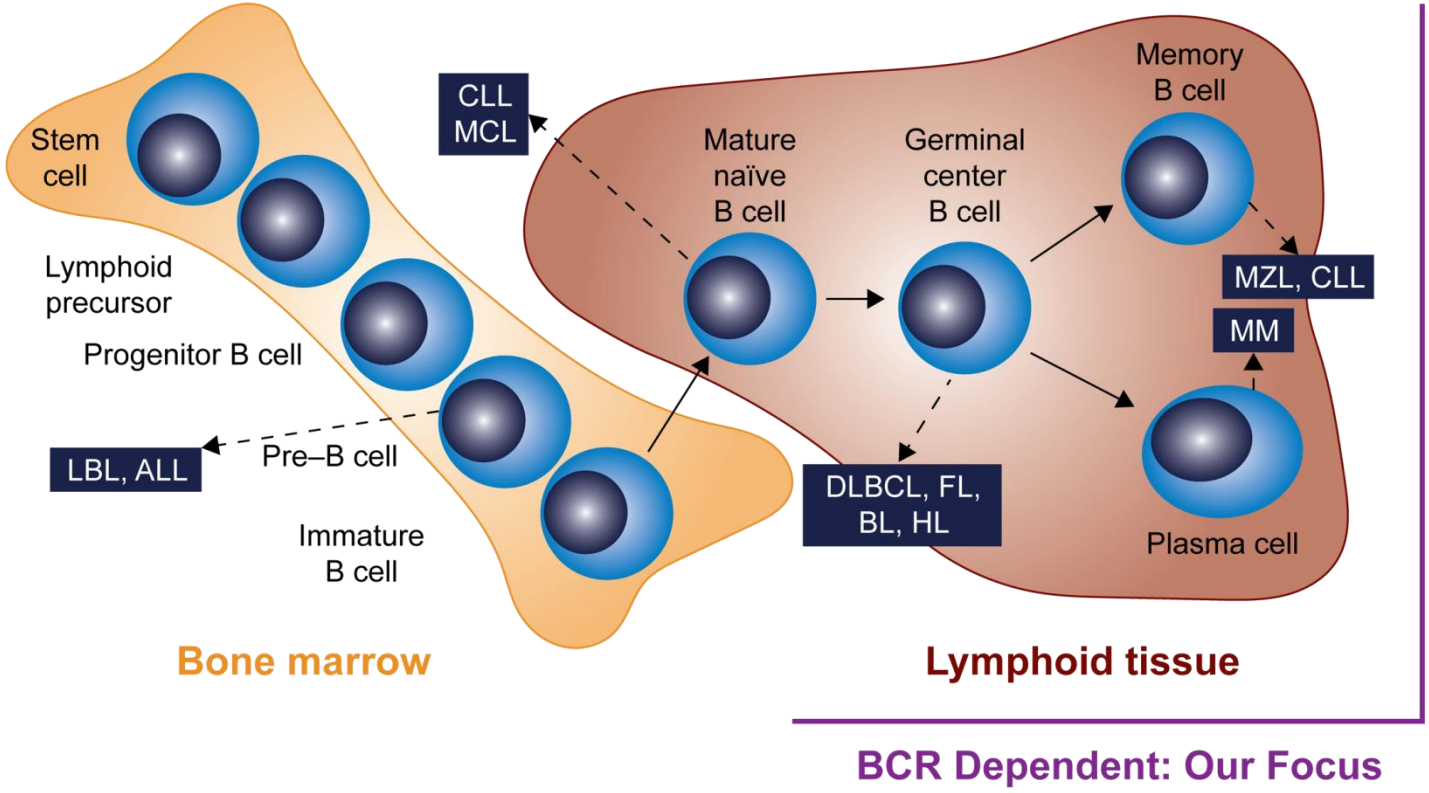
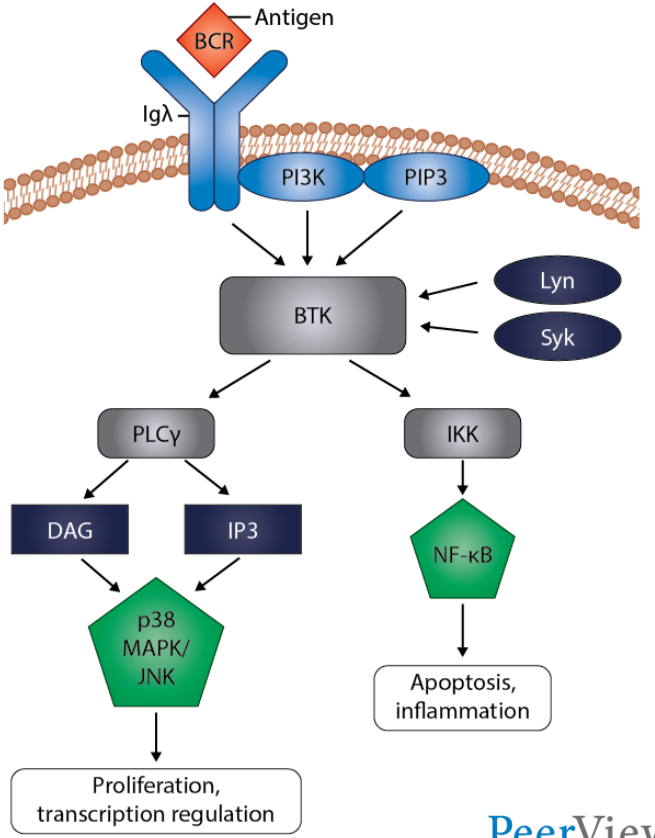
B-Cell Development and Transformation



Targeting BCR Signaling: Where BTK Fits

- Member of the TEC family of kinases
- Roles in signaling (eg, BCR, TLR), as well as transcription
- Leads to activation of PI3K, PLCγ2, MAPK, and NF-κB pathways

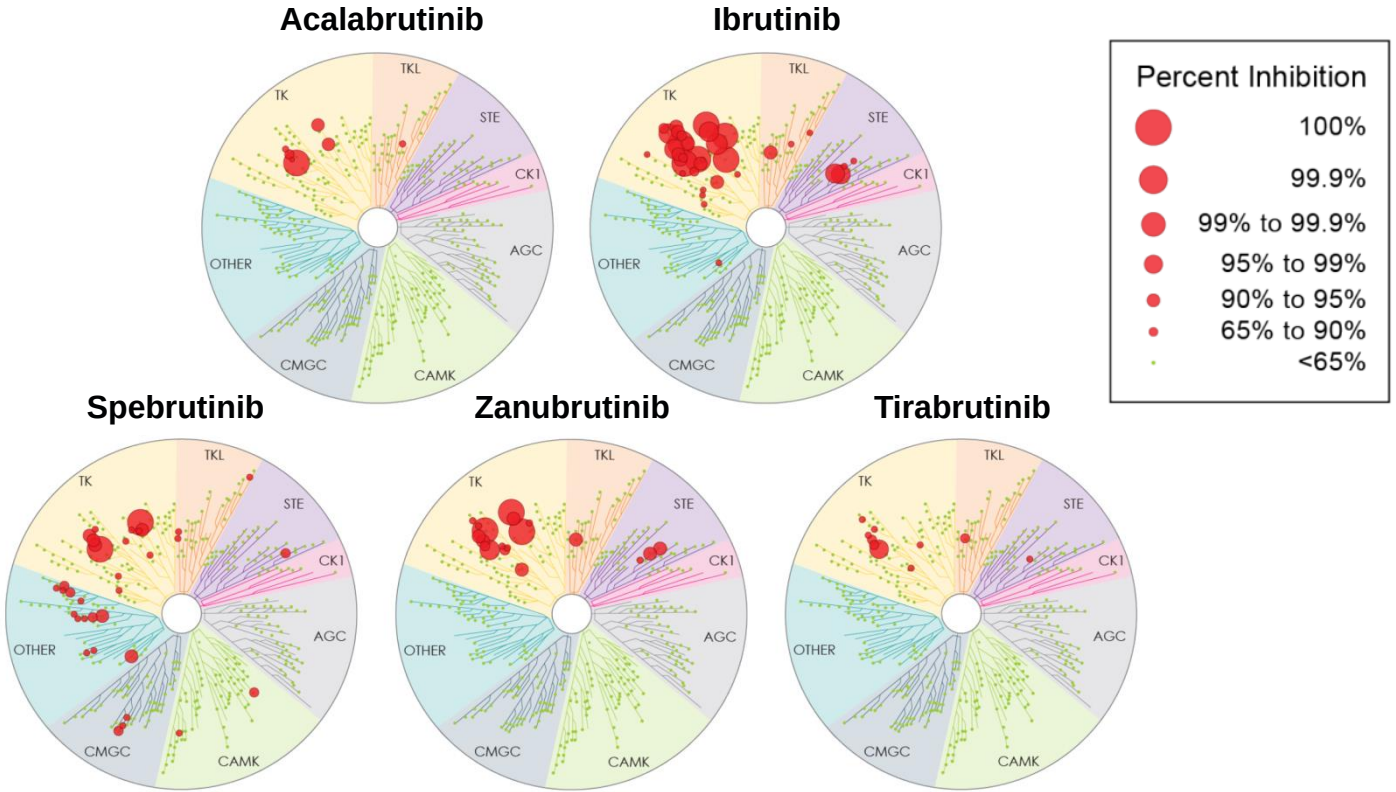


Targeting BCR Signaling: Where BTK Fits (Cont'd)

- BTK-deficient models predominantly have a B-cell phenotype
  - **XID (*BTK* mutant) mouse:** diminished B cells, B1 lymphocytes, and impaired BCR signaling. Modest effect on other immune effector cells (NK, monocyte, macrophage, dendritic cells) due to redundancy of TEC family members
  - ***BTK* knockout mouse**: more profound B-cell defect due to loss of chaperone and transcriptional function

- BTK mutations in humans give rise to X-linked agammaglobulinaemia, an inherited disorder with decreased IgG and an absence of B cells

Differences in Overall Kinase Selectivity Among BTK inhibitors[1]



1. Kaptein A et al. 60th American Society of Hematology Meeting and Exposition (ASH 2018). Abstract 1871.

Inhibition of Off-Target Kinases With BTK Inhibitors[1]

Adverse events potentially related to off-target inhibition

TEC → *Bleeding, cardiac toxicity?*

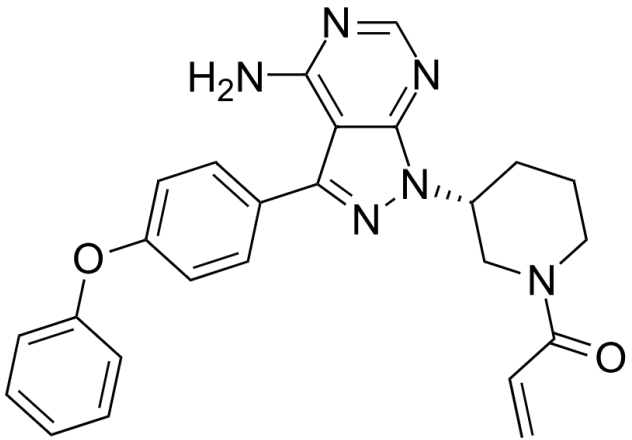
For example, ibrutinib inhibits several off-target kinases, including TEC and EFGR

EGFR → *Rash, diarrhea*

1. Bose P et al. *Expert Opin Drug Metab Toxicol*. 2016;12:1381-1392.

Ibrutinib: First BTK Inhibitor Approved for Use in Hematologic Cancers[1]

A Potent IRREVERSIBLE BTK Inhibitor

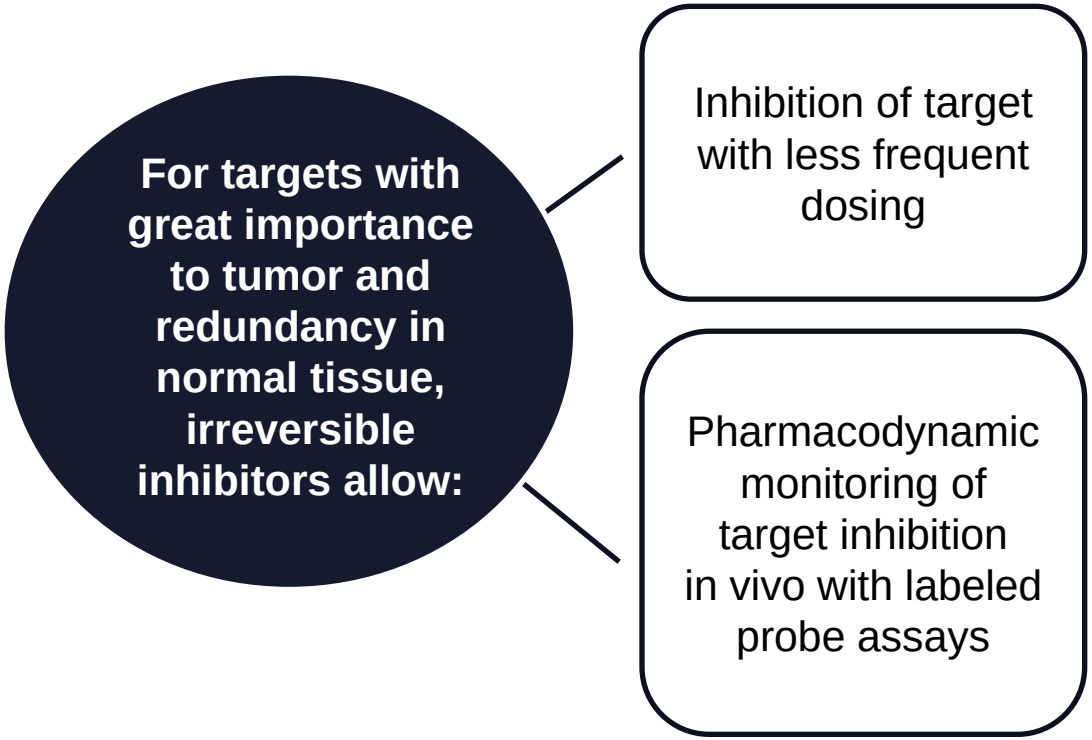


- **Forms a specific and irreversible bond with cysteine-481 in BTK**
- **Potent and irreversible BTK inhibition with IC_{50} = 0.5 nM**
- **Blocks BCR signaling; active in canine model of spontaneous lymphoma**
- **Orally bioavailable with short half-life**
- **Alternative irreversible targets could include EGFR, ERB4, BMX, ITK, TEC, BLK, and JAK3; many reversible targets**

1. Honigberg LA et al. *Proc Natl Acad Sci USA*. 2010;107:13075-13080.

Reversible vs Irreversible BTK Inhibitors

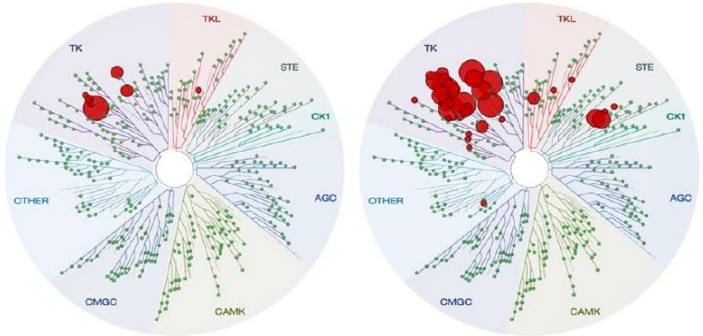
- Before ibrutinib, virtually all drugs developed as kinase inhibitors were reversible due to concerns of:
  - Toxicity if target is ubiquitous
  - Adduct formation as drug bound to protein kinase can be seen by immune system as foreign and may be degraded differently



Acalabrutinib: Next-Generation BTK Inhibitor Approved in MCL, Being Assessed in CLL[1]

Acalabrutinib is more selective for BTK with less off-target kinase inhibition compared with ibrutinib in vitro

Kinase Selectivity Profiling at 1 μM



Larger red circles represent stronger inhibition

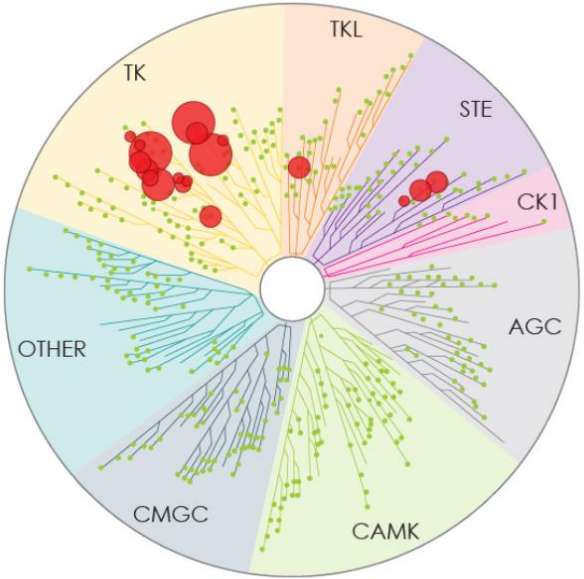
Kinase Inhibition Average IC_{50} (nM)

Kinase	Acalabrutinib	Ibrutinib
BTK	5.1	1.5
TEC	126.0	10
ITK	>1,000	4.9
BMX	46	0.8
TXK	368	2.0
EGFR	>1,000	5.3
ERBB2	~1,000	6.4
ERBB4	16	3.4
BLK	>1,000	0.1
JAK3	>1,000	32

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

Zanubrutinib: The Next Wave of BTK?[1]

Zanubrutinib

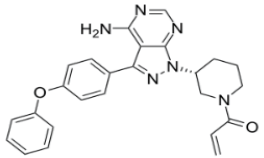


- **Zanubrutinib (BGB-3111) is an investigational second-generation irreversible BTK inhibitor**
- **Lower off-target inhibitory activity on other kinases, including ITK, JAK3, and EGFR[1]**
- **FDA breakthrough therapy designation for the treatment of adult patients with MCL who have previously received ≥1 prior therapy**

1. Li N et al. *Cancer Res*. 2015;75(15 suppl):2597-2597.

What Has This Led To?
BTK Inhibitor FDA Approvals in NHL

Ibrutinib



Full approval

CLL
Initial therapy and for del(17)(p13.1)

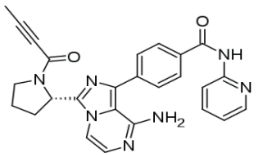
WM
Initial or subsequent therapy

Accelerated, provisional approval

MCL
2nd-line therapy

MZL
Patients needing systemic therapy having received ≥1 prior anti-CD20-based therapy

Acalabrutinib



Accelerated, provisional approval

MCL
2nd-line therapy

Phase 3 testing

CLL
In phase 3 testing

Zanubrutinib: Breakthrough designation in MCL / phase 3 testing

CLL: chronic lymphocytic leukemia; MCL: mantle cell leukemia; MZL: marginal zone lymphoma; WM: Waldenström's macroglobulinemia.

What Has This Led To?
NCCN Recommendations in CLL[1]

Ibrutinib	Acalabrutinib
• Recommended as a single agent as frontline therapy and in patients with relapsed/refractory CLL • Combination therapy with anti-CD20 antibodies also included in recent guidelines • Testing for *BTK* and *PLCγ2* mutations may be useful in patients receiving ibrutinib and suspected of having progression. *BTK* and *PLCγ2* mutation status alone is not an indication to change treatment	• Recommended in relapsed/refractory CLL, except ibrutinib-refractory CLL with BTK C481S mutations • Patients with ibrutinib intolerance have been successfully treated with acalabrutinib without recurrence of these symptoms

1. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 2.2019

What Has This Led To?
NCCN Recommendations in MCL[1]

Ibrutinib	Acalabrutinib
Recommended as a preferred regimen in relapsed/refractory MCL with a short duration of response to prior therapy (± rituximab)	Recommended as a preferred regimen in relapsed/refractory MCL with a short duration of response to prior therapy

1. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. B-Cell Lymphomas. Version 2.2019

What's the Next Generation?
Non-C481 Binding BTK Inhibitors

- **Several reversible BTK inhibitors designed to overcome resistance mutations are in development**

- **These agents do not bind to C481 and include:**
  - Vecabrutinib
  - LOXO-305
  - ARQ531

MasterClass 2

The Clinical Experience With BTK Inhibitors in CLL and MCL

Translating Evidence to Practice

Kerry Rogers, MD
The Ohio State University
Comprehensive Cancer Center
Arthur G. James Cancer Hospital and
Richard J. Solove Research Institute
Columbus, Ohio

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BCR Inhibitors in CLL: From Approved to Emerging Indications

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Ibrutinib in CLL

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Summary of Major Studies With Ibrutinib in CLL

A041202[4]

Randomized phase 3
- Ibrutinib regimens improved PFS vs BR in older patients

E1912[5]

Randomized phase 3
- Ibrutinib + rituximab improved PFS vs FCR in younger patients

RESONATE-2[1]

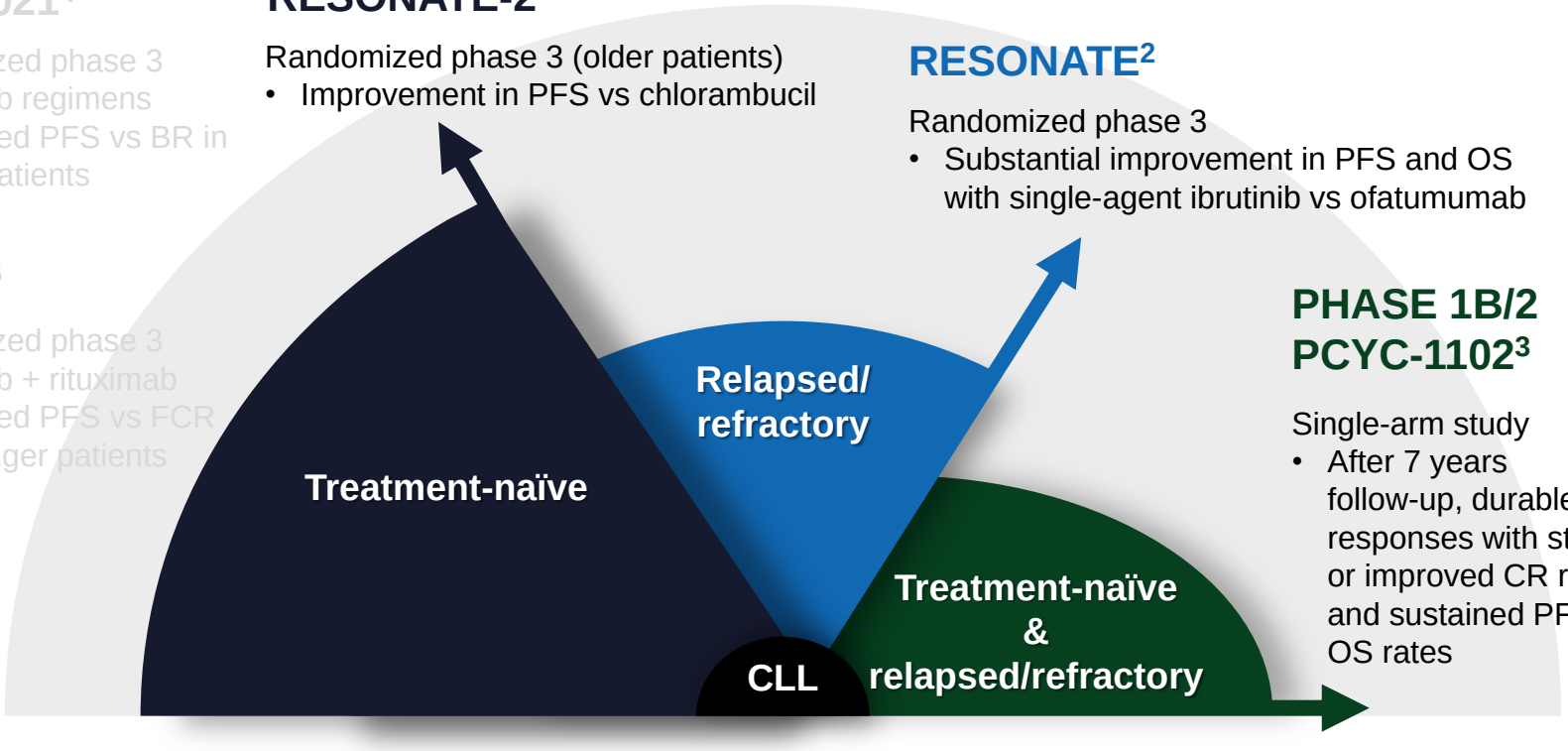
Randomized phase 3 (older patients)
- Improvement in PFS vs chlorambucil

RESONATE[2]

Randomized phase 3
- Substantial improvement in PFS and OS with single-agent ibrutinib vs ofatumumab

PHASE 1B/2 PCYC-1102[3]

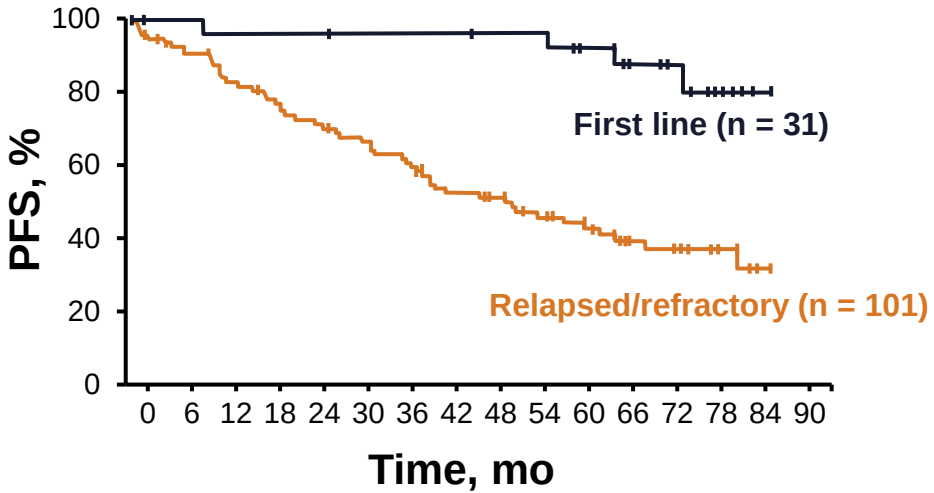
Single-arm study
- After 7 years follow-up, durable responses with stable or improved CR rates, and sustained PFS and OS rates



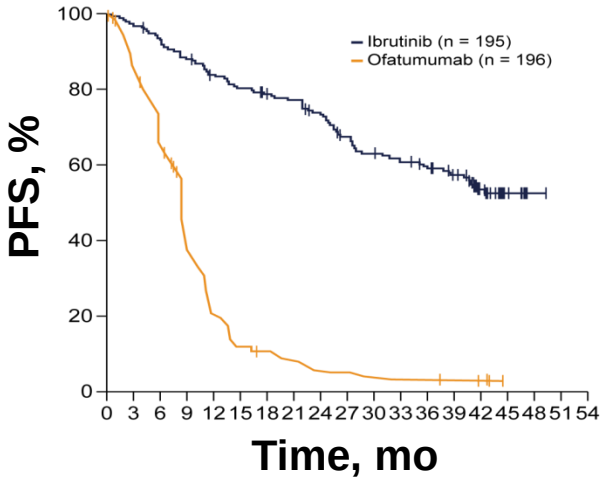
1. Burger JA et al. 23rd Congress of the European Hematology Association (EHA 2018). Abstract PF343. 2. Byrd JC et al. 2017 American Society of Clinical Oncology Annual Meeting (ASCO 2017). Abstract 7510. 3. Byrd J et al. ASH 2018. Abstract 3133.

PFS With Ibrutinib in the First-Line and Relapsed/Refractory Setting

PCYC-1102 (7-y follow-up)[1]
PFS With Ibrutinib in Patients With Newly Diagnosed and Relapsed/Refractory CLL

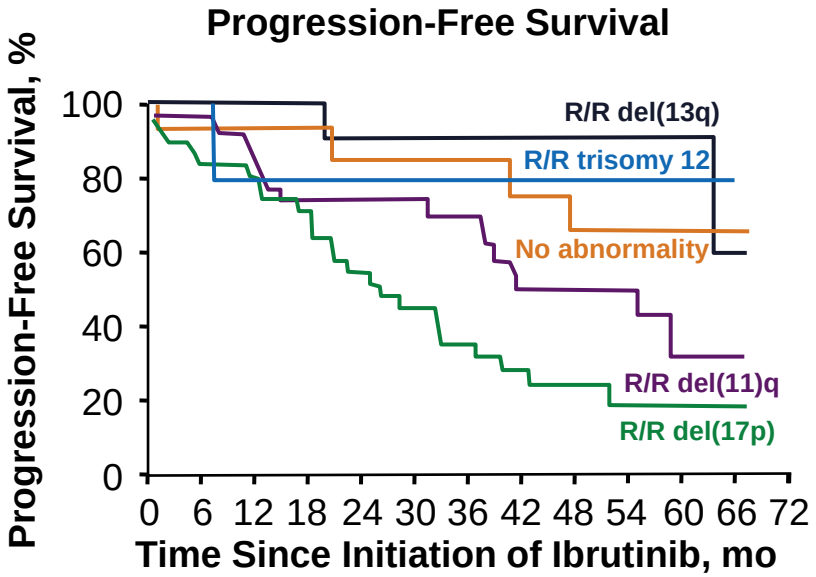


RESONATE[2]
PFS With Ibrutinib vs Ofatumumab in Relapsed/Refractory CLL



1. Byrd J et al. ASH 2018. Abstract 3133. 2. Byrd JC et al. ASCO 2017. Abstract 7510.

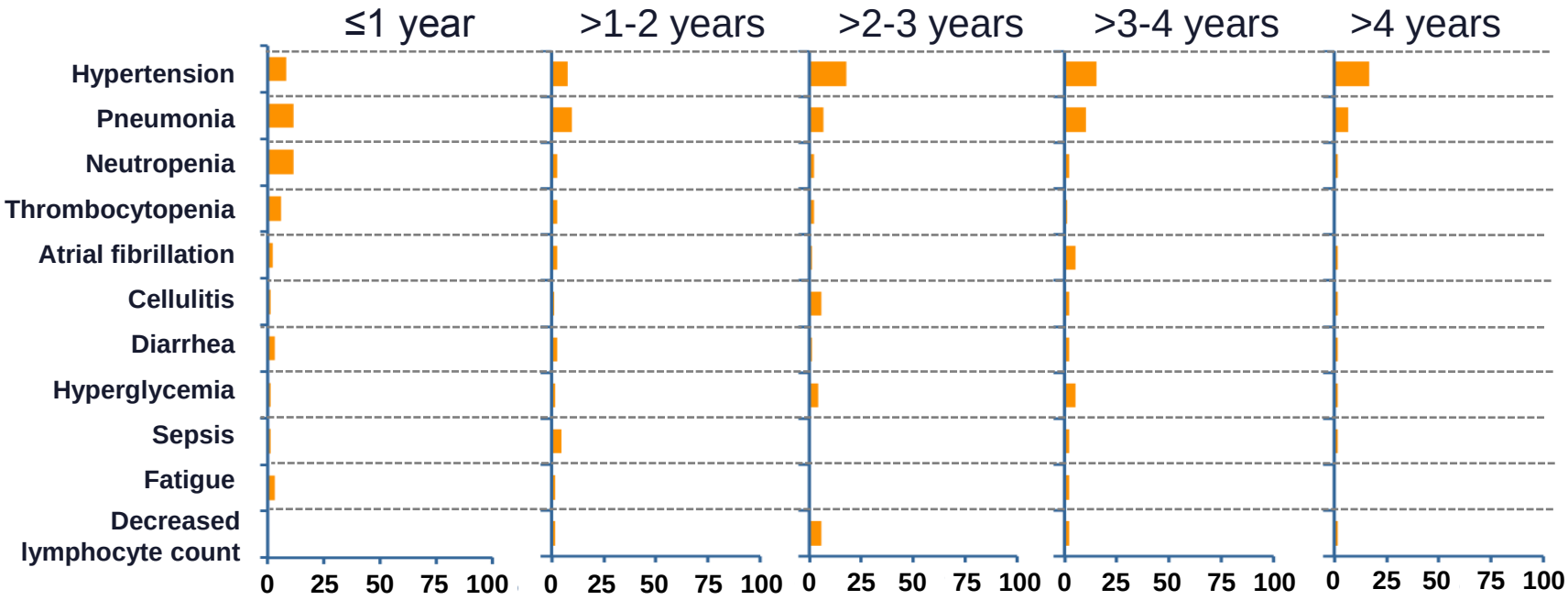
Is BTK Inhibition Effective Across Genetic/Molecular Subgroups in CLL?[1]



	Median PFS	5-y PFS
Del(17p) (n = 34)	26 mo	19%
Del(11q) (n = 28)	55 mo	33%
Trisomy 12 (n = 5)	NR	80%
Del(13q) (n = 13)	NR	91%
No abnormality[a] (n = 16)	NR	66%

1. O'Brien S et al. *Blood*. 2018:131:1910-1919.

Onset of Most Grade ≥3 Adverse Events Decreased Over Time[1]



- Dose reductions and dose discontinuations due to AEs occurred more frequently in R/R patients than in TN patients, and during the first year after treatment versus later

1. O'Brien S et al. *Blood*. 2018:131:1910-1919.

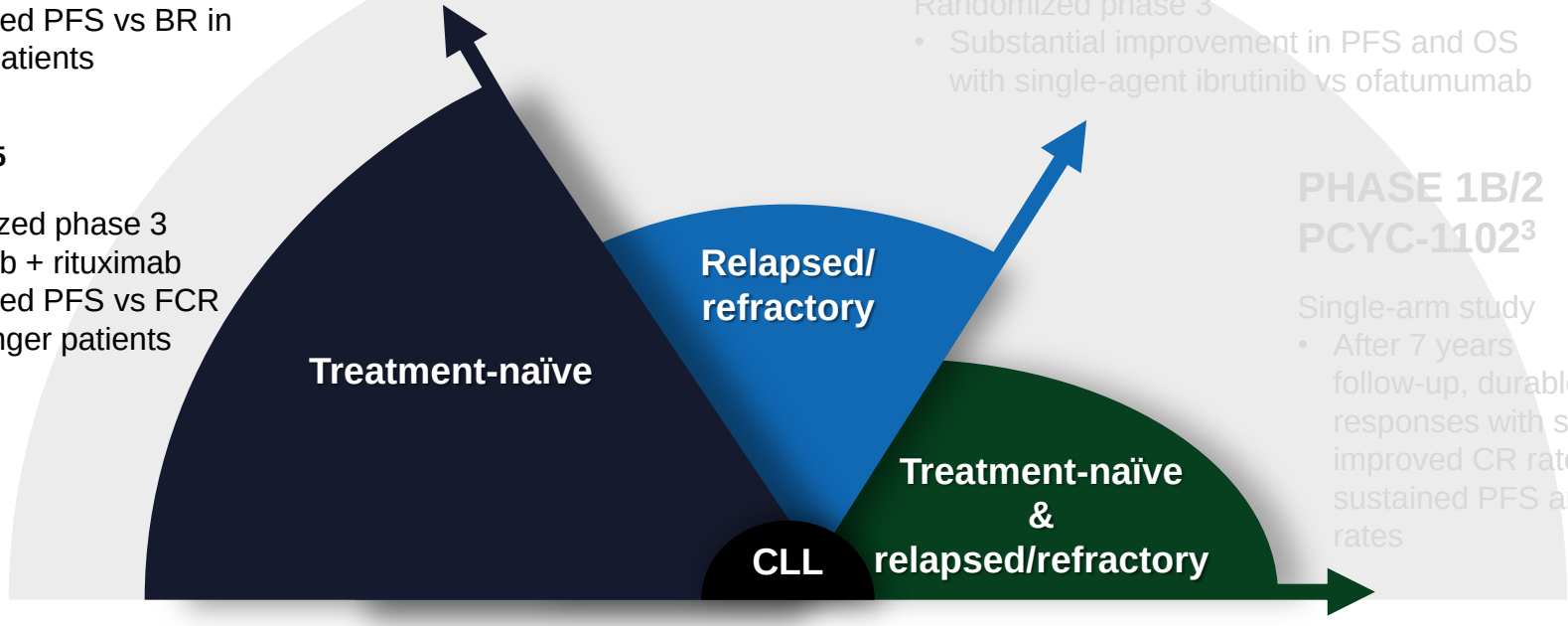
Summary of Major Studies With Ibrutinib in CLL

A0412021[4]

Randomized phase 3
- Ibrutinib regimens improved PFS vs BR in older patients

E1912[5]

Randomized phase 3
- Ibrutinib + rituximab improved PFS vs FCR in younger patients



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Randomized phase 3 (older patients)
- Improvement in PFS vs chlorambucil

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- Substantial improvement in PFS and OS with single-agent ibrutinib vs ofatumumab

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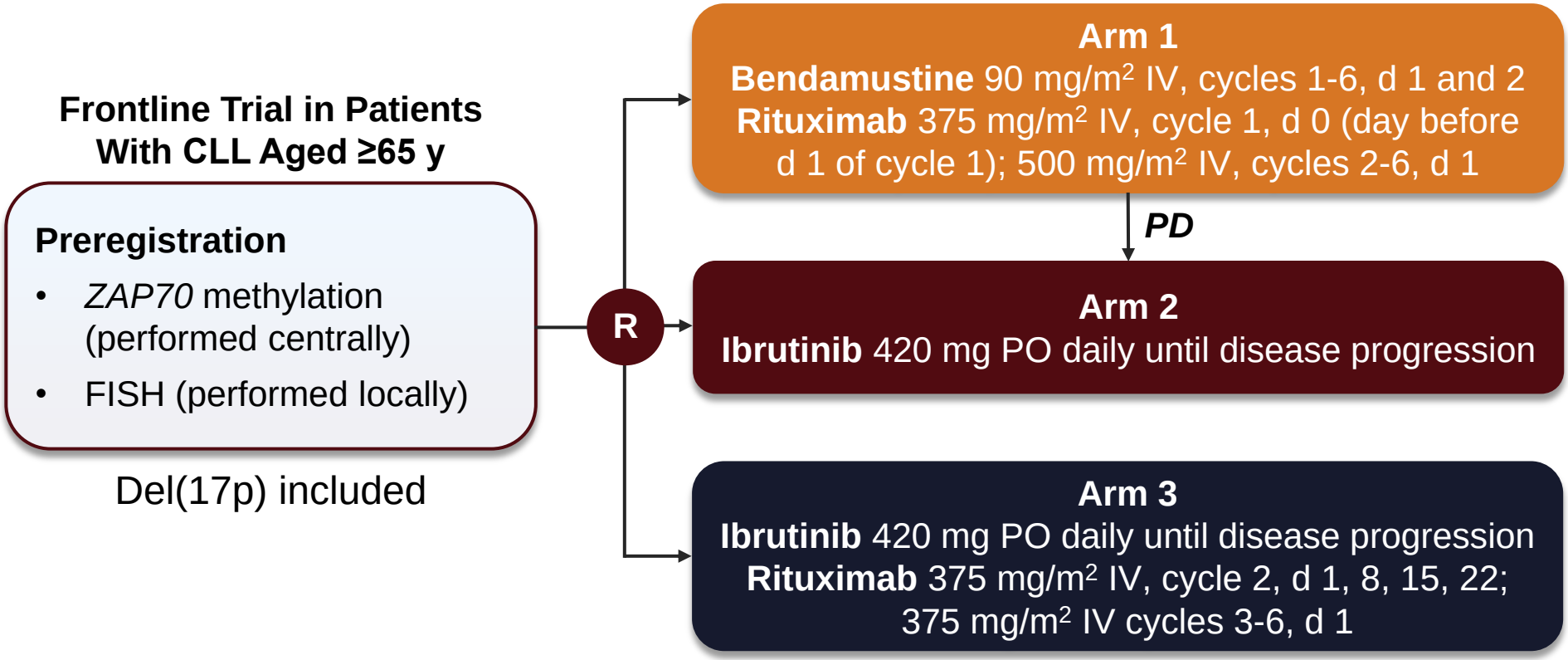
Single-arm study
- After 7 years follow-up, durable responses with stable or improved CR rates, and sustained PFS and OS rates

1. Burger JA et al. EHA 2018. Abstract PF343. 2. Byrd JC et al. ASCO 2017. Abstract 7510. 3. Byrd J et al. ASH 2018. Abstract 3133.
4. Woyach J et al. *N Engl J Med*. 2018;379:2517-2528. 5. Shanafelt TD et al. ASH 2018. Abstract LBA-4.

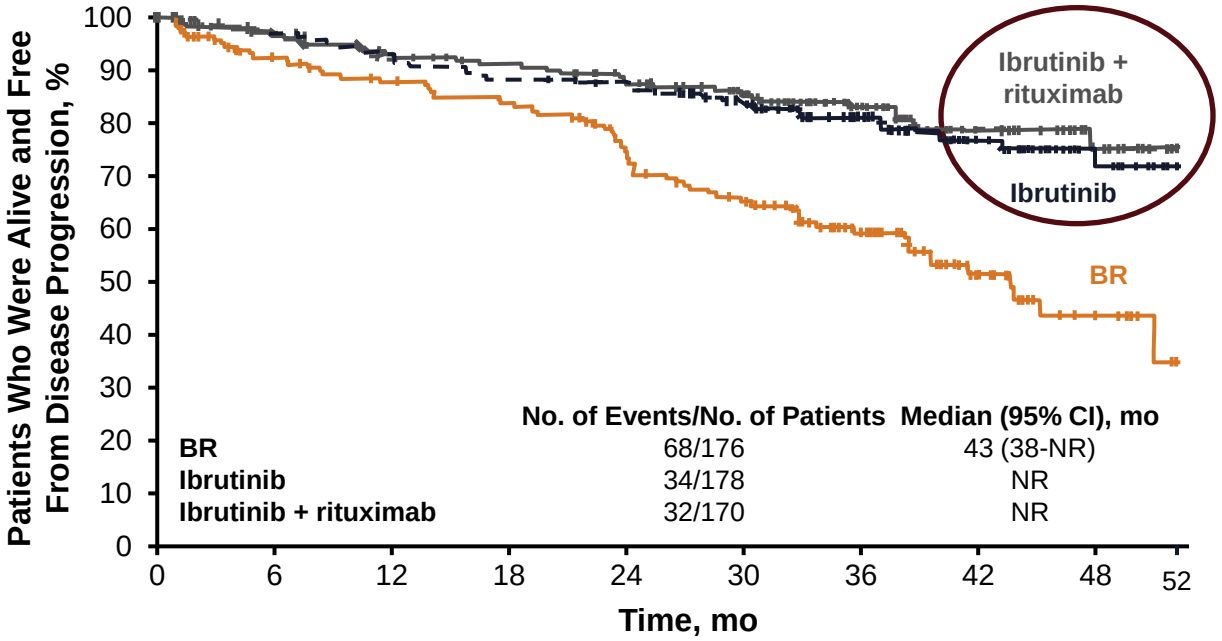
Alliance Study: A0412021[1]



1. https://clinicaltrials.gov/ct2/show/NCT01886872. Accessed March 25, 2019.

Ibrutinib-Based Therapy Improves PFS vs Bendamustine + Rituximab in Older CLL Patients[1]

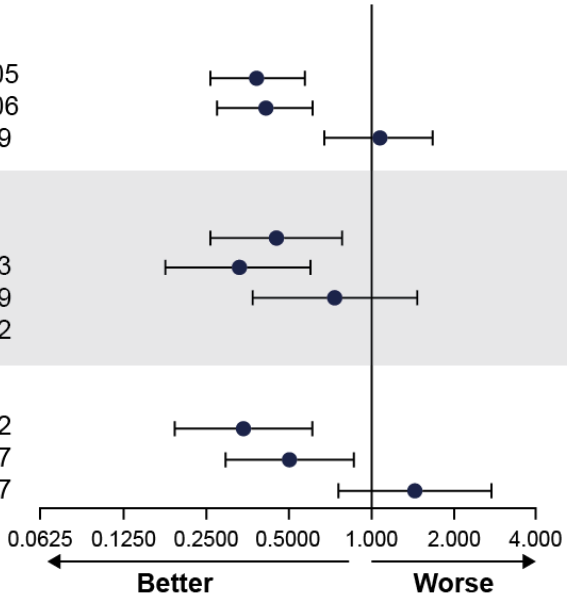
- Improved PFS with ibrutinib regimens vs BR
  - HR for PFS, 0.39 (ibrutinib alone); 0.38 (IR)
- No difference in PFS between ibrutinib arms
- No differences in OS noted at this time



1. Woyach J et al. *N Engl J Med*. 2018;379:2517-2528.

A041202 Study: Subgroup Analysis[1]

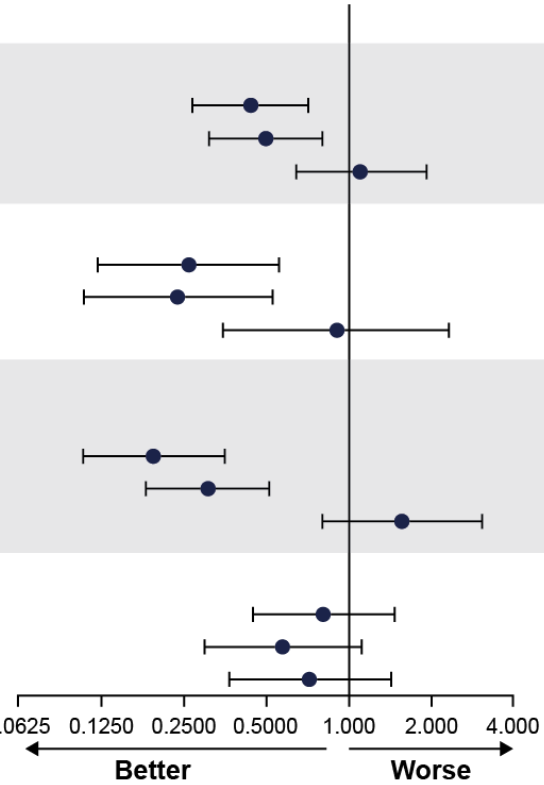
Subgroup	No. of Patients	No. of Events	HR for Disease Progression or Death (95% CI)
All patients			
Ibrutinib vs bendamustine + rituximab	365	105	0.37 (0.25-0.56)
Ibrutinib + rituximab vs bendamustine + rituximab	365	106	0.40 (0.27-0.60)
Ibrutinib + rituximab vs ibrutinib	364	69	1.06 (0.66-1.70)
Risk category according to modified Rai stage			
Intermediate			
Ibrutinib vs bendamustine + rituximab	167	53	0.44 (0.25-0.78)
Ibrutinib + rituximab vs bendamustine + rituximab	168	49	0.32 (0.17-0.59)
Ibrutinib + rituximab vs ibrutinib	167	32	0.73 (0.36-1.46)
High			
Ibrutinib vs bendamustine + rituximab	198	52	0.33 (0.18-0.60)
Ibrutinib + rituximab vs bendamustine + rituximab	197	57	0.50 (0.29-0.85)
Ibrutinib + rituximab vs ibrutinib	197	37	1.44 (0.75-2.76)



1. Woyach J et al. *N Engl J Med*. 2018;379:2517-2528.

A041202 Study: Subgroup Analysis[1] (Cont'd)

Subgroup Status with regard to del(17p13.1) or del(11q22.3)	No. of Patients	No. of Events	HR for Disease Progression or Death (95% CI)
Absent			
Ibrutinib vs bendamustine + rituximab	263	70	0.44 (0.27-0.72)
Ibrutinib + rituximab vs bendamustine + rituximab	265	72	0.50 (0.31-0.80)
Ibrutinib + rituximab vs ibrutinib	266	52	1.11 (0.65-1.92)
Present			
Ibrutinib vs bendamustine + rituximab	102	35	0.26 (0.12-0.56)
Ibrutinib + rituximab vs bendamustine + rituximab	100	34	0.24 (0.11-0.53)
Ibrutinib + rituximab vs ibrutinib	98	17	0.90 (0.35-2.32)
ZAP70 methylation status			
Unmethylated			
Ibrutinib vs bendamustine + rituximab	191	61	0.19 (0.11-0.35)
Ibrutinib + rituximab vs bendamustine + rituximab	191	68	0.31 (0.18-0.51)
Ibrutinib + rituximab vs ibrutinib	192	35	1.57 (0.80-3.09)
Methylated			
Ibrutinib vs bendamustine + rituximab	173	43	0.81 (0.45-1.48)
Ibrutinib + rituximab vs bendamustine + rituximab	173	37	0.58 (0.30-1.12)
Ibrutinib + rituximab vs ibrutinib	172	34	0.72 (0.36-1.43)



1. Woyach J et al. *N Engl J Med*. 2018;379:2517-2528.

E1912: FCR vs Ibrutinib + Rituximab as Frontline Therapy in Patients Aged 18-70 Years[1]

Stratification

- Age <60 y vs ≥60 y
- PS 0, 1 vs 2
- Stage 3/4 vs 1/2
- Del 11q22.3 (ATM) vs other
- Del(17p) excluded
- Planned N = 519

Primary endpoint: PFS

R

2:1

Arm A

Ibrutinib 420 mg PO daily, d 1-28, cycles 1-7
Rituximab 50 mg/m^2 IV, d 1, cycle 2,
then 325 mg/m^2 IV, day 2, cycle 2
Rituximab 500 mg/m^2 IV, d 1, cycles 3-7
Subsequent cycles: Ibrutinib 420 mg PO daily,
d 1-28 until disease progression

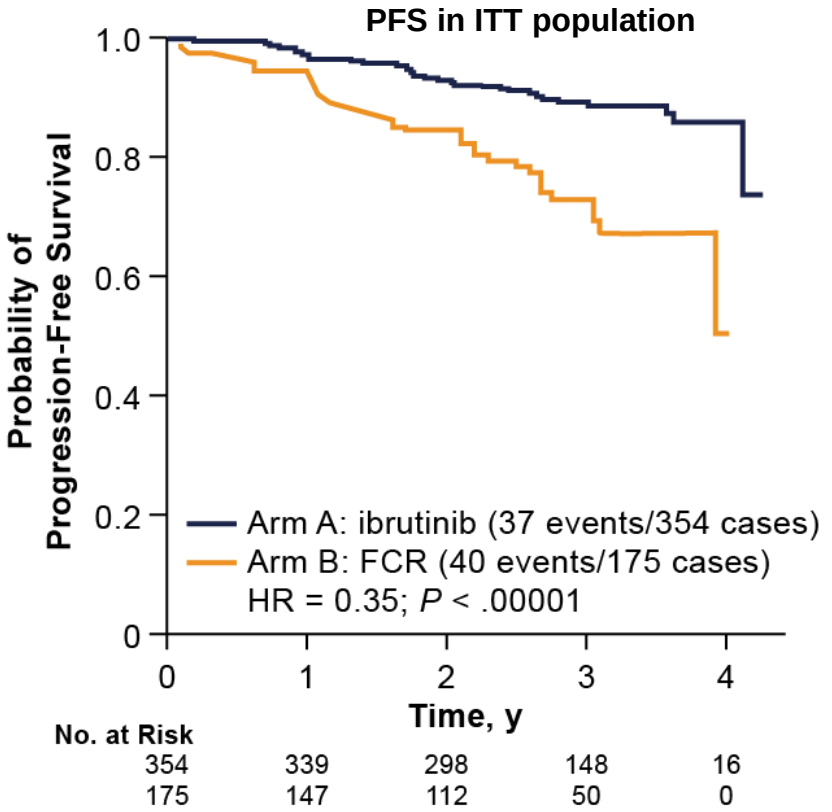
Arm B

Rituximab 50 mg/m^2 IV, d 1, cycle 1; 325 mg/m^2 IV,
d 2, cycle 1; 500 mg/m^2 IV, d 1, cycles 2-6
Fludarabine 25 mg/m^2 IV, d 1, 2, and 3 for 6 cycles
Cyclophosphamide 250 mg/m^2, IV, d 1, 2, 3

1. https://clinicaltrials.gov/ct2/show/NCT02048813. Accessed March 25, 2019.

Ibrutinib + Rituximab Improves PFS and OS in Younger Patients With CLL vs FCR[1]

	ITT Population		Eligible Population	
	Ibrutinib + R	FCR	Ibrutinib + R	FCR
PFS outcomes				
Events/ cases (n)	37/354	40/175	33/332	39/166
HR 1-sided *P*	0.35 (0.22-0.50) < .00001		0.32 (0.20-0.51) < .00001	
OS outcomes				
Events/ cases (n)	4/354	10/175	3/332	10/166
HR 1-sided *P*	0.17 (0.05-0.54) < .00003		0.13 (0.03-0.46) < .00001	



1. Shanafelt TD et al. ASH 2018. Abstract LBA-4.

E1912: PFS by *IGHV* Status[1]

	Unmutated *IGHV*		Mutated *IGHV*	
	Ibrutinib + R	FCR	Ibrutinib + R	FCR
Events/cases (n)	20/210	21/71	8/70	6/44
HR	0.26 (0.14-0.50)		0.44 (0.14-1.36)	
1-sided *P*	< .00001		.07	

1. Shanafelt TD et al. ASH 2018. Abstract LBA-4.

Characterizing Adverse Events With Ibrutinib From Recent Frontline Phase 3 Studies

- **E1912 trial:** With ibrutinib + R vs FCR, significantly higher rates of AF, HTN (both $P < .05$); significantly lower rates of grade ≥3 AEs, myelosuppression, any infection, neutropenic fever (all $P \leq .004$)[1]

Grade 3-5 TRAEs in E1912 and Alliance 041202 Trials[1,2]

Grade 3-5 TRAE	E1912: Ibrutinib + R[3] (n = 352)	A041202: Ibrutinib + R[1,2] (n = 181)
Median age, y (range)	57 (31-70)	71 (65-86)
Infection, %	5	20
Atrial fibrillation, %	3	6
Bleeding, %	1	3
Hypertension, %	7	34
Deaths during active treatment + 30 d %	1	7

1. Shanafelt TD et al. ASH 2018. Abstract LBA-4. 2. Woyach J et al. *N Engl J Med*. 2018;379:2517-2528.

Discontinuation of Ibrutinib for Intolerance (10%-20%)

Reasons

- Atrial fibrillation
- Bleeding
- Arthralgias/myalgias
- Diarrhea
- Recurrent erythema nodosa
- Panniculitis

WHAT TO DO?

BTK is a great target that when inhibited promotes durable remissions

Second-Generation Agents: Acalabrutinib in CLL

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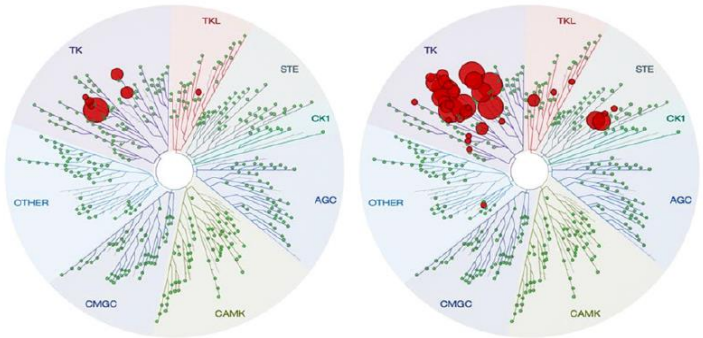
Acalabrutinib (ACP-196)[1]

Acalabrutinib is more selective for BTK with less off-target kinase inhibition compared with ibrutinib in vitro

Kinase Selectivity Profiling at 1 μM



Larger red circles represent stronger inhibition

Kinase Inhibition Average IC_{50} (nM)

Kinase	Acalabrutinib	Ibrutinib
BTK	5.1	1.5
TEC	126.0	10
ITK	>1,000	4.9
BMX	46	0.8
TXK	368	2.0
EGFR	>1,000	5.3
ERBB2	~1,000	6.4
ERBB4	16	3.4
BLK	>1,000	0.1
JAK3	>1,000	32

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

ACE-CL-001: Acalabrutinib Phase 1/2 Study in CLL (R/R Cohort)[1]

- **Multiple cohorts explored; all levels >90% BTK occupancy, but 100 mg BID chosen to get 98% to 99% 24-h occupancy**
  - 134 pts with R/R CLL enrolled with median of 3 prior therapies; 67% Rai advanced disease, 31% del(17p)

- **Well tolerated with good safety profile (no atrial fibrillation) and diminished toxicity**

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

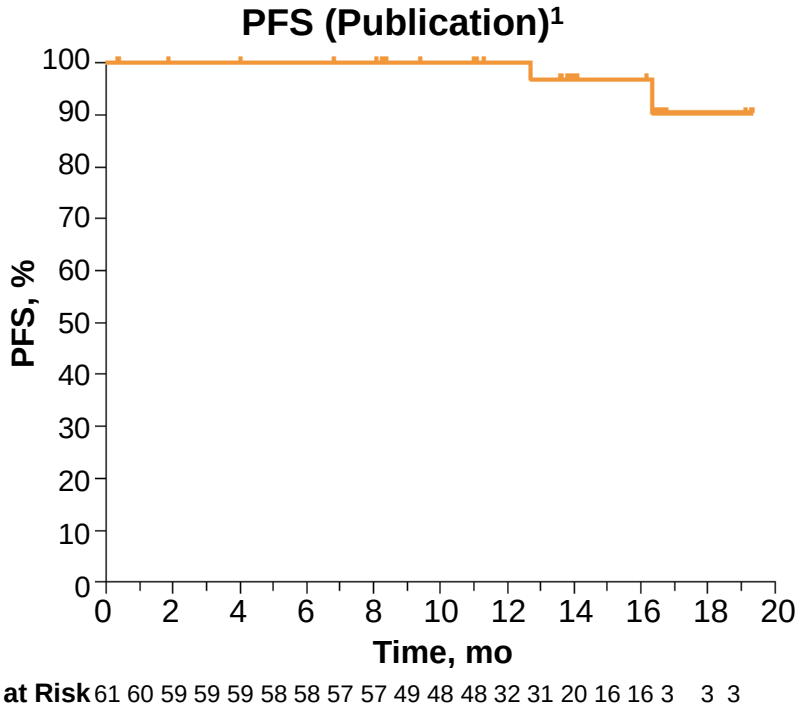
ACE-CL-001: Safety[1]

Adverse Event[a]	All Grades[b]	Grades 1-2, n (%)	Grades 3-4, n (%)
Headache	26 (43)	26 (43)	0
Diarrhea	24 (39)	23 (38)	1 (2)
Increased weight	16 (26)	15 (25)	1 (2)
Pyrexia	14 (23)	12 (20)	2 (3)
Upper respiratory tract infection	14 (23)	14 (23)	0
Fatigue	13 (21)	11 (18)	2 (3)
Peripheral edema	13 (21)	13 (21)	0
Hypertension	12 (20)	8 (13)	4 (7)
Nausea	12 (20)	12 (20)	0
Contusion	11 (18)	11 (18)	0
Arthralgia	10 (16)	9 (15)	1 (2)
Petechiae	10 (16)	10 (16)	0
Decreased weight	10 (16)	10 (16)	0

[a] Listed are AEs that were reported in ≥15% of the 61 patients, on or before the data cutoff date of October 1, 2015, regardless of the cause. [b] One grade 5 event of pneumonia was reported.

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

Time-to-Event Outcomes With Acalabrutinib in Relapsed/Refractory CLL



ACE-CL-001 (Updated Results)[2]	N = 134
Median PFS, mo (95% CI)	NR (35.7-NR)
del(17p)	NR (21.4-NR)
del(11q)	NR (NR-NR)
Complex karyotype	27.9 (18.4-NR)
No complex karyotype	NR (35.7-NR)
18-mo PFS, % (95% CI)	90 (83-94)
del(17p)	80 (59-91)
del(11q)	100 (100-100)
No complex karyotype	95 (81-99)

- Median PFS in the overall population NR
- Median TTR (≥PR) was 5.3 mo (95% CI, 1.7-22.4), and median DOR was NR

1. Byrd JC et al. *N Engl J Med*. 2016;374:323-332. 2. Byrd JC et al. ASH 2017. Abstract 498.

ACE-CL-001: Acalabrutinib Phase 1/2 Study in CLL
Treatment-Naïve Cohort[1]

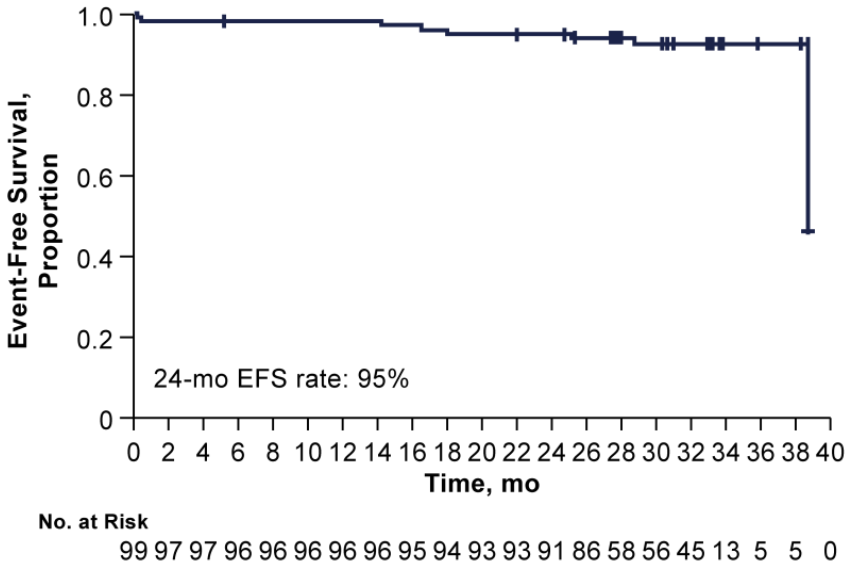
Safety profile consistent with prior acalabrutinib experience

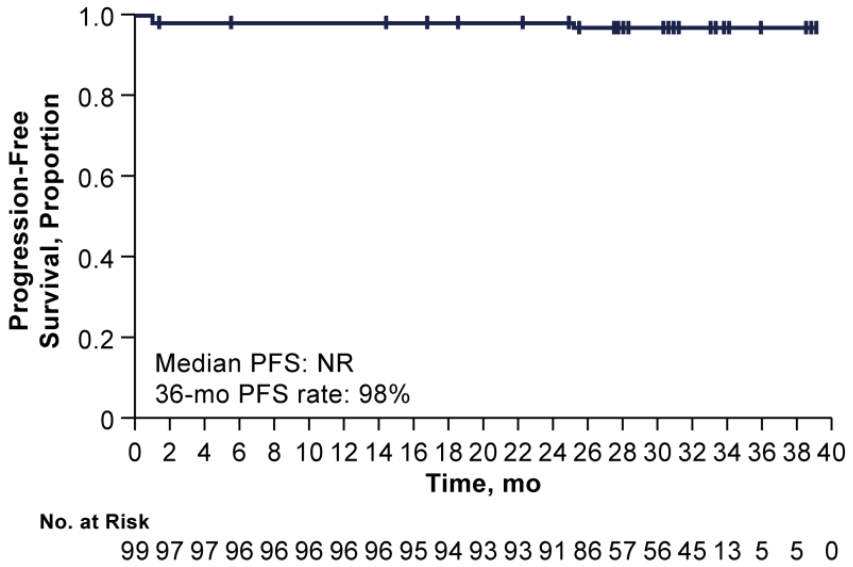
- Grade 3/4 AEs 49% (49/99) of patients; grade 3/4 atrial fibrillation, 1%; grade 3 hypertension, 3%; grade 3 bleeding events, 2% (hematuria, upper GI hemorrhage)
- Serious AEs (all grades): infection (pneumonia, influenza, and sinusitis)

n (%)	N = 99
ORR (CR + PR)	96 (97)
CR	5 (5)
PR	91 (92)
• Median TTR: 3.7 mo	
• Median time to CR: 28 mo	
• Median DOR: NR	

1. Byrd JC et al. ASH 2018. Abstract 692.

ACE-CL-001: Acalabrutinib Phase 1/2 Study in CLL
Treatment-Naïve Cohort[1] (Cont'd)





1. Byrd JC et al. ASH 2018. Abstract 692.

Acalabrutinib for Ibrutinib-Intolerant CLL Patients[1]

- 33-patient cohort enrolled

Safety	Other Outcomes
• 21 patients (64%) did not experience a recurrence of ibrutinib-related AEs during treatment with acalabrutinib • 12 patients (36%) had a persistent AE – 47% decreased in severity – 41% remained stable – 12% worsened (fatigue and ecchymosis)	• 79% response; 81% had response lasting ≥12 mo • Higher frequency of development of C481S mutation long term, possibly due to on-and-off exposure to ibrutinib (next study will examine pre-C481S mutation clones)

- Registration follow-up study based upon these data

1. Awan FT et al. ASH 2016. Abstract 638.

Ongoing Phase 3 Studies With Acalabrutinib in R/R CLL

Elevate CLL R/R[1]

- N = 500 (anticipated)
- Patients with previously treated high-risk CLL (del[17p] or del[11q])

R

- Acalabrutinib
- Ibrutinib

Primary endpoint: PFS

ACE-CL-309[2]

- ECOG PS 0-2
- Received ≥1 prior systemic therapy for CLL
- N = 306

R

- Acalabrutinib
- Bendamustine + Rituximab (or) Idelalisib + Rituximab

Primary endpoint: PFS

1. https://clinicaltrials.gov/ct2/show/NCT02475681. Accessed March 25, 2019. 2. https://clinicaltrials.gov/ct2/show/NCT02970318. Accessed March 25, 2019.

Acalabrutinib Studies in Frontline CLL

Phase 3 Elevate CLL TN[1]

- N = 535 (anticipated)
- Patients with newly diagnosed CLL

R

- **Obinutuzumab + Chlorambucil**
- **Acalabrutinib + Obinutuzumab**
- **Acalabrutinib Monotherapy**

Primary endpoint: PFS

Phase 2 AVO[2]

- CLL or SLL by IWCLL 2018 criteria
- ECOG PS 0-2
- N = 37

Acalabrutinib 100 mg PO BID

Venetoclax dose ramp-up from 20 to 400 mg PO QD

Obinutuzumab 100 mg on cycle 1, d 1; 900 mg on cycle 1, d 2; and then 1,000 mg on cycle 1, d 8, 15, and 1 of cycles 2-6 for 6 mo

Primary endpoint: rate of BM MRD-negative complete response

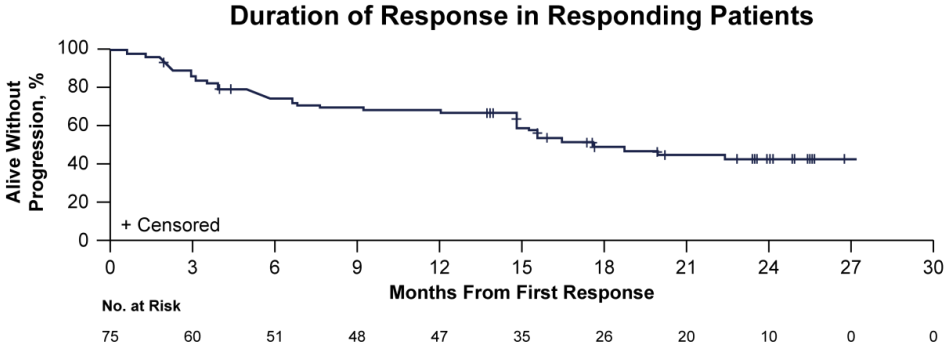
1. https://clinicaltrials.gov/show/NCT02477696. Accessed March 25, 2019. 2. https://clinicaltrials.gov/ct2/show/NCT03580928. Accessed March 25, 2019.

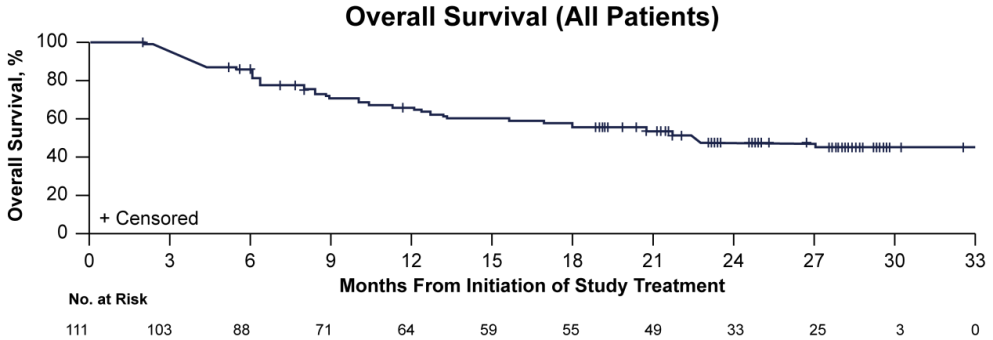
Targeting BTK in MCL and Other Lymphoid Cancers
A Look at the Evidence

PeerView
Live

Pivotal Study of Ibrutinib in Relapsed MCL[1,2]

- 111 pts with R/R MCL received ibrutinib **560 mg/d**
- Most common AEs: diarrhea, fatigue, and nausea, with grade 3 heme toxicity uncommon (<20%)
- ORR was 67%
  - 23% CR by Cheson criteria
- At a median follow-up of 26.7 mo, median PFS was 13 mo and median OS was 22.5 mo





1. Wang ML et al. *Blood*. 2015;126:739-745. 2. Wang ML et al. *N Engl J Med*. 2013;369:507-516.

Acalabrutinib in R/R MCL: ACE-LY-004 Pivotal Phase 2 Study[1]

- N = 124 patients; median age: 68 y; 2 prior therapies
- Acalabrutinib 100 mg BID until progression
- Median time on study: 26.3 mo

Efficacy

- **ORR was 81%**
  - **43% attained CR**
- Median DOR: 25.7 mo

Safety Summary
Treatment discontinuation: 44% due to PD and 8% from AEs
Common AEs (all grade): headache (38%), diarrhea (36%), fatigue (28%), cough (22%), and myalgia (21%)
Common grade ≥3 AEs: neutropenia (10%), anemia (10%), infections (15%), and pneumonia (6%)
Cardiac AEs: 13 patients (4 grade 3/4), with no cases of atrial fibrillation

1. Wang M et al. ASH 2018. Abstract 2876.

Ibrutinib Combinations in MCL

Rituximab: Higher response rate; long-term benefit in low proliferative rate disease[1]

Lenalidomide/rituximab: High response rate in relapsed MCL, justifying phase 3 trial[2]

BR: Can be safely combined, and multicenter phase 3 trial **(SHINE)** completed enrollment with final results pending[3]

Venetoclax: High CR rate (42%) in relatively high-risk pts, but short follow-up[4]

Tam et al. 2018: Ibrutinib + Venetoclax in MCL[4]

Response at 16 wk, %	Without PET (n = 24)	With PET (n = 24)
CR	42	62
CRu	17	–
PR	17	8
SD	8	4
MRD negative	67 (14/18 pts)	15 (2/13 pts)

- **Best CR = 67% without PET, 71% with PET**
- **Best MRD negative: 16/19 pts (84%) without PET; 9/16 pts (56%) with PET**

Phase 3 study of ibrutinib + venetoclax in MCL (SYMPATICO) is underway[5]

1. Jain P et al. *Br J Haematol*. 2018;182:404-411. 2. Jerkeman M et al. *Lancet Haematol*. 2018;5:e109-e116. 3. https://clinicaltrials.gov/ct2/show/NCT01776840. Accessed March 25, 2019. 4. Tam CS et al. *N Engl J Med*. 2018;378:1211-1223. 5. https://clinicaltrials.gov/ct2/show/NCT03112174. Accessed March 25, 2019.

Phase 1b: Acalabrutinib + BR in Newly Diagnosed and R/R MCL[1]

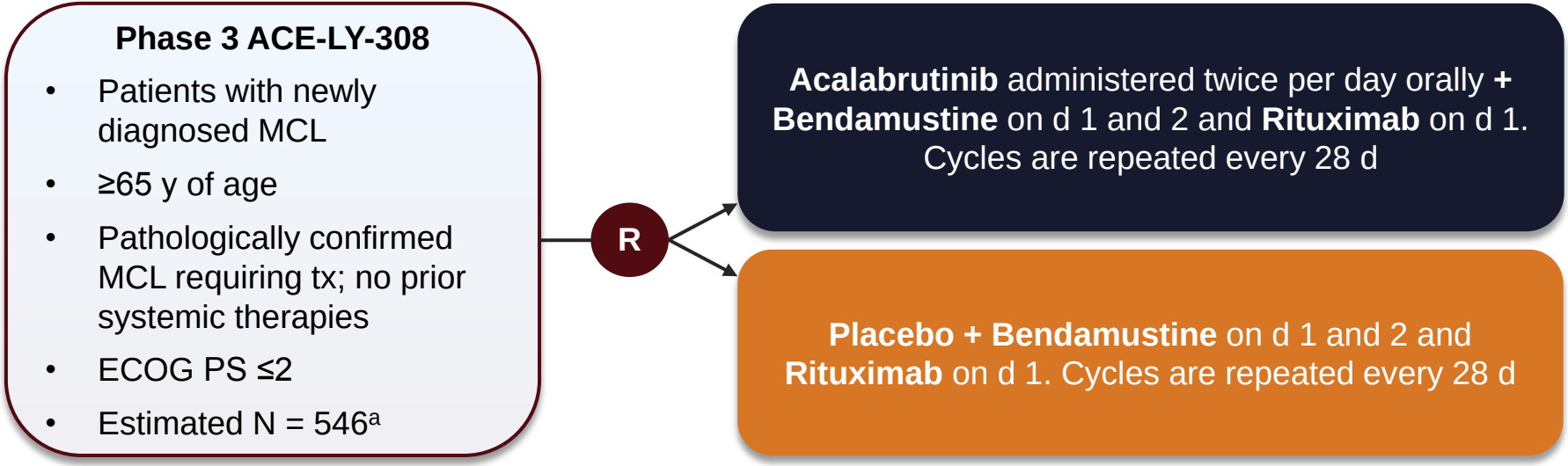
	TN (n = 18), n (%)	R/R (n = 20), n (%)
ORR	17 (94)	16 (80)
CR	13 (72)	13 (65)
PR	4 (22)	3 (15)

- Median time on study
  - 17.6 mo for TN
  - 14.2 mo for R/R
- No DLTs
- No patients had cytomegalovirus infection, pneumocystis jiroveci pneumonia, or atrial fibrillation

AEs in ≥30% of Patients in Any Cohort		
AE, n (%)	**TN (n = 18)**	**R/R**
Nausea	14 (78)	8 (40)
Fatigue	13 (72)	7 (35)
Vomiting	10 (56)	5 (25)
Constipation	9 (50)	5 (25)
Headache	9 (50)	4 (20)
Diarrhea	8 (44)	8 (40)
Cough	7 (39)	7 (35)
Dizziness	7 (39)	4 (20)
Upper respiratory tract infection	7 (39)	7 (35)
Neutropenia	6 (33)	11 (55)
Pyrexia	6 (33)	2 (10)
Infusion-related reaction	3 (17)	6 (30)

1. Phillips TJ et al. ASH 2018. Abstract 4144.

Phase 3 ACE-LY-308 Study: Acalabrutinib + BR in Newly Diagnosed MCL[1]



Primary endpoint: PFS per the Lugano classification for NHL in arm 1 vs arm 2

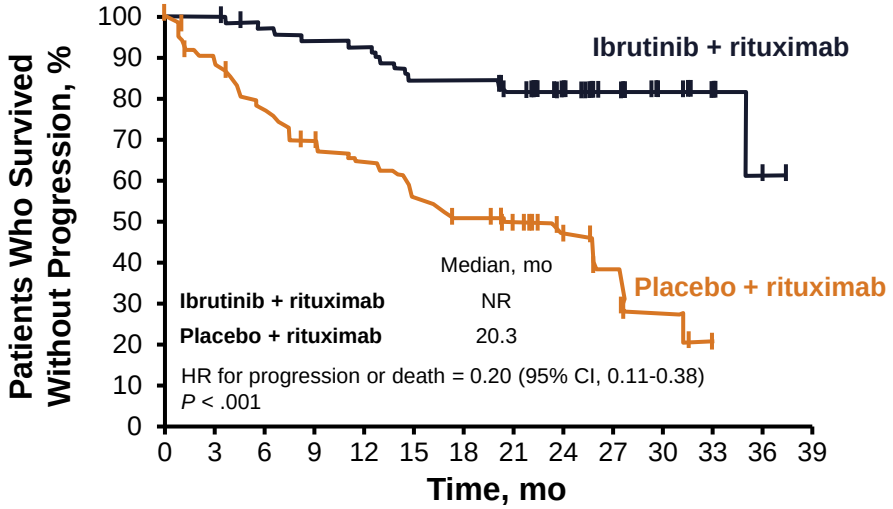
[a] Agreement to use highly effective forms of contraception during the study and 90 days after the last dose of acalabrutinib, 6 months after the last dose of bendamustine, or 12 months after the last dose of rituximab, whichever is longest.

1. https://clinicaltrials.gov/ct2/show/NCT02972840. Accessed March 25, 2019.

BTK Inhibitors in Other Settings: WM

- **Ibrutinib in Waldenström's macroglobulinemia:** ORR of 90% in phase 3 iNNOVATE trial in R/R WM confirmed results of phase 2 testing[1,2]

Phase 3 study of ibrutinib + rituximab vs rituximab in newly diagnosed WM[3]: significant improvement in PFS



1. Treon SP et al. *N Engl J Med*. 2015;372:1430-1440. 2. Dimopoulos MA et al. *Lancet Oncol*. 2017;18:241-250.
3. Dimopoulos MA et al. *N Engl J Med*. 2018; 378:2399-2410.

ACE-WM-001: Acalabrutinib Efficacy and Safety[1,2]

Characteristic	6th IWWM Criteria[1]		Modified 3rd IWWM Criteria[2]	
	TN (n = 14)	R/R (n = 92)	TN (n = 14)	R/R (n = 92)
ORR (≥MR), n (%) 95% CI	13 (93) 66-100	86 (93) 86-98	13 (93) 66-100	86 (93) 86-98

Survival

24-mo Rate	TN, %	R/R, %
DOR	90	82
PFS	90	82
OS	92	89

Grade ≥3 AEs

Preferred Term	All Patients (N = 106)	
	Any Grade, n (%)	Grade 3/4, n (%)
Neutropenia	18 (17)	17 (16)
Lower respiratory tract infection	18 (17)	5 (5)
Anemia	10 (9)	5 (5)
Pneumonia	10 (9)	7 (7)

1. Owen R et al. *J Clin Oncol.* 2018;36(suppl):Abstract 7501. 2. Owen R et al. Society of Hematologic Oncology Sixth Annual Meeting (SOHO 2018). Abstract NHL-224.

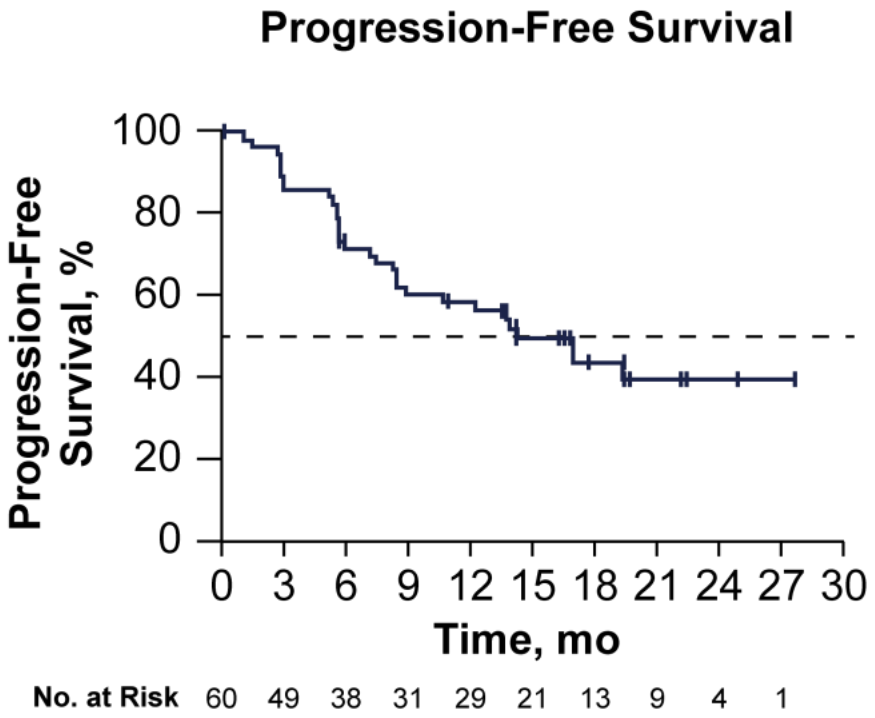
Ibrutinib in Marginal Zone Lymphoma[1]

Phase 2 study

- N = 63 patients with R/R (1 treatment or more including rituximab) MZL
- 560 mg/d until progression/intolerance

Results

- ORR = 48%, with 3% attaining CR
- 11% with treatment-related lymphocytosis; median TTR: ~5 mo
- Grade 3 SAEs: infections (19%), anemia (14%), pneumonia (8%), fatigue (6%), and atrial fibrillation (6%)



1. Noy A et al. *Blood*. 2017;129:2224-2232.

Newer BTK Inhibitors Under Clinical Investigation

PeerView Live

Zanubrutinib (BGB 3111): Early Outcomes in NHL

Phase 1b trial in R/R or TN NHL (MCL, DLBCL, FL, MZL)[1]

- Evaluable N = 84
- **ORR: 60%**

Phase 1 trial in WM[2]

- Evaluable N = 51
- **ORR: 92%**
- **12-mo PFS: 91%**

Phase 1 trial in CLL/SLL[3]

- TN (n = 16) and R/R (n = 50)
- **ORR: 94%** (100% TN, 92% R/R)
- Zanubrutinib induced deep and sustained responses

Zanubrutinib is in phase 3 testing in WM and CLL

1. Tam CS et al. ASH 2017. Abstract 152. 2. Trotman J et al. EHA 2018. Abstract PS1186. 3. Seymour JF et al. 14th International Conference on Malignant Lymphoma (ICML 2017). Abstract 237.

Other BTK Inhibitors in R/R B-Cell NHL

M7583: Phase 1[1]

- N = 14
- AEs
  - 1 grade 4 neutropenia
  - No DLTs
- Response
  - 12/14 pts (1 CR, 6 PR, 2 MR, 3 SD)
- Trial ongoing

Tirabrutinib (ONO/GS-4059): Phase 1[2]

- N = 90
- AEs
  - 1 hematoma
- Response in evaluable pts
  - CLL: 24/25 pts (96%)
  - MCL: 11/12 pts (92%)
  - DLBCL: 11/31 (35%)
- Long-term extension study: 28 pts with CLL[3]
  - Response: 24/28 pts (86%)
  - Median PFS: 38.5 mo
  - Median OS: 44.9 mo
- Combination with PI3K and BCL-2 inhibitors ongoing

1. Jurczak W et al. *Ann Oncol*. 2018;29:Abstract 1014PD. 2. Walter HS et al. *Blood*. 2016;127:411-419. 3. Walter HS et al. *Blood*. 2017;129:2808-2810.

Clinical Practice Forum

Applying the Evidence on BTK Inhibitors in B-Cell Cancer

PeerView Live

An Older Patient With Relapsed High-Risk CLL After Prior Chemoimmunotherapy

David, a 75-year-old man with CLL treated with BRx6 3 years ago

- Fit with active lifestyle
- Retired banker
- Continues to jog 3x a week and perform yard work

Presents features of symptomatic relapsed CLL

- Bulky nodes in neck, axilla
- WBC: 88,000 (90% lymphocytes)
- Hb: 11.1 g/dL
- Plt: 104,000

Results of further testing

- FISH has del17p
- Complex karyotype
- *IGHV* is unmutated

Treatment Pathway

Given this patient's features and current evidence …

→ **Use of ibrutinib 420 mg daily recommended**

Response achieved with rapid resolution of symptoms

Relapse after 2 years of therapy with testing showing a BTK C481S mutation

→ **Evidence supports use of venetoclax in this instance**

Do NOT stop ibrutinib until venetoclax started:
weekly ramp-up 20 → 400mg

Considerations in High-Risk Patients

If this high-risk patient had been in poorer health, frail, had CV disease (atrial fibrillation), or needed anticoagulation, potential options could include

→ **Acalabrutinib (off-label) or Venetoclax ± rituximab**

In high-risk patients, next option after venetoclax should be planned

→ **CAR-T cells (investigational)**
Allogeneic transplant (fit)
Clinical trial with novel agents

A Younger Patient With Symptomatic CLL

Alex, a 58-year old man with asymptomatic CLL

- Diagnosed with routine blood work
- Followed for 2 years, then developed fatigue that limited his work as a farmer

Work-up

- Extensive LAD; Hb: 8; plt: 85; WBC: 285 (95% lymphocytes)
- Bone marrow: 98% CLL
- FISH del13q
- *IGHV* mutated (4.3%)

Treatment Pathway & Sequencing

After discussing FCR vs ibrutinib with his doctor, Alex starts therapy with ibrutinib

Achieves a response and tolerates therapy well for 6 months

However, after a year of therapy Alex struggles to tolerate therapy due to panniculitis and mouth ulceration

Next steps to consider

- ✓ **Second-generation agent: acalabrutinib**
- ✓ **Change agent class: venetoclax**

Alternative Pathways for First Treatment

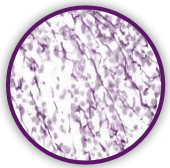
If this patient had been older, in poorer health, frail, had CV disease (atrial fibrillation), or needed anticoagulation, potential options could include

→

Acalabrutinib (off-label)

Obinutuzumab

Venetoclax (off-label)



A Patient With MCL Relapsing After Upfront Immunochemotherapy and ASCT

66-year-old male with MCL s/p intensive CIT plus ASCT in 2009

- Induction chemoimmunotherapy was maxi-R-CHOP + cytarabine/etoposide
- Patient is a recovered alcoholic, but no other medical comorbidities

Presents now with anemia and fatigue

- Patient has iron-deficiency anemia
- Colonoscopy shows scattered ulcerated nodules
- Biopsy with recurrent classic MCL; Ki67: 25%; FISH with t(11;14)

Results of further testing

- Marrow has 30% involvement by MCL
- PET/CT with diffuse adenopathy, largest lesion 3 cm

Treatment Pathway

Given this patient's features and current evidence, options available for treatment include …

Chemoimmunotherapy

Ibrutinib ± rituximab

Acalabrutinib

Lenalidomide + rituximab

Patient starts ibrutinib monotherapy 560 mg daily

PET/CT scan after 3 months shows complete metabolic response

An Alternate Pathway

Alternatively, if this patient had been frail/elderly and with history of uncontrolled atrial fibrillation or history of subdural hematoma, potential options could include ...

Venetoclax

Lenalidomide + rituximab

Acalabrutinib

Need to monitor for TLS with venetoclax

Need to consider prophylaxis for VTE with lenalidomide

Clinical Take-Homes: How I Sequence BTK Inhibitors Into Therapy

CLL

- Untreated *IGHV* mutated: Ibrutinib or FCR—choice based on patient factors
- Untreated *IGHV* unmutated: Ibrutinib
- R/R, NO prior BTK inhibitor: Ibrutinib or acalabrutinib vs venetoclax if comorbidities
- R/R prior BTK inhibitor: Venetoclax

MCL

- Acalabrutinib, ibrutinib can be considered as second-line therapy in many MCL cases
- Patients in ibrutinib study more heavily pretreated (3 vs 2 prior tx)
- Weigh differing AE profiles, patient characteristics (eg, history of cardiac events), and prior treatment when deciding on therapy

WM

- Ibrutinib as first-line therapy, unless contraindicated due to anticoagulation or significant CV disease

MZL

- Ibrutinib as third-line or higher therapy after rituximab, and also idelalisib

Clinical Take Homes: What I Do NOT Do With BTK Inhibitors

- X Administer with rituximab or other therapeutic directed outside of a trial—*Phase 3 data do NOT support this; NOT YET a standard of care*
- X Administer together with warfarin—*Studies excluded these patients, although other anticoagulants may have similar risks*
- X Administer with anticoagulation in all patients with atrial fibrillation—*Risk of bleeding is increased and anticoagulation may not be needed*
- X Administer in patients with prolonged history of corticosteroid therapy—*Higher risk of invasive fungal infections*
- X Stop BTK inhibitors when I suspect progression—*Results in disease flare; stop when new therapy has been started and disease controlled*

MasterClass 3

Looking to the Future: New Developments and Next Steps With BTK Inhibitors in Cancer

John C. Byrd, MD
The Ohio State University
Comprehensive Cancer Center
Arthur G. James Cancer Hospital
and Richard J. Solove Research Institute
Columbus, Ohio

PeerView
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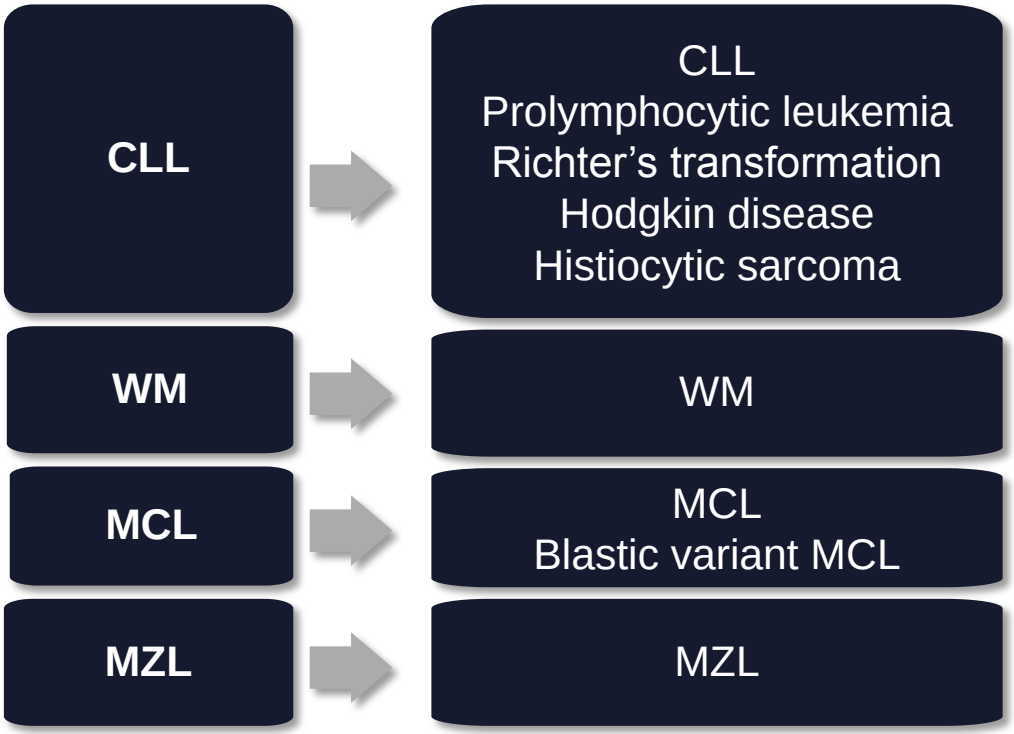
Characterizing & Overcoming Resistance to BTK Inhibitors

PeerView
Live

Resistance to BTK Inhibitor Therapy



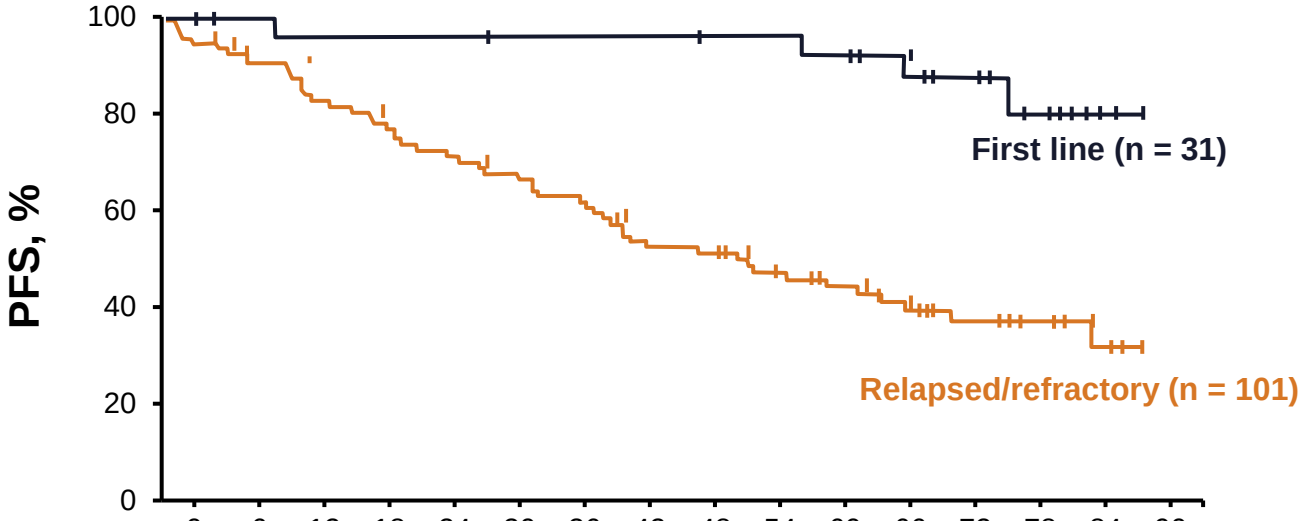
Patient-Related Resistance Data

- CLL/PLL: Well characterized
  Others: Minimally characterized
- Partially characterized
- Minimally characterized
- Very minimally characterized

Types of Resistance to BTK Inhibitor Therapy

	Initial Treatment	Salvage Treatment
CLL	1° resistance: Nonexistent 2° resistance: Very rare	1° resistance: Very rare 2° resistance: Common
WM	Not well characterized	1° resistance: Occurs 2° resistance: Common
MCL	Not well characterized	1° resistance: Common 2° resistance: Very common
MZL	Unknown	1° resistance: Common 2° resistance: Very common

PFS: Ibrutinib (7 y)[1]

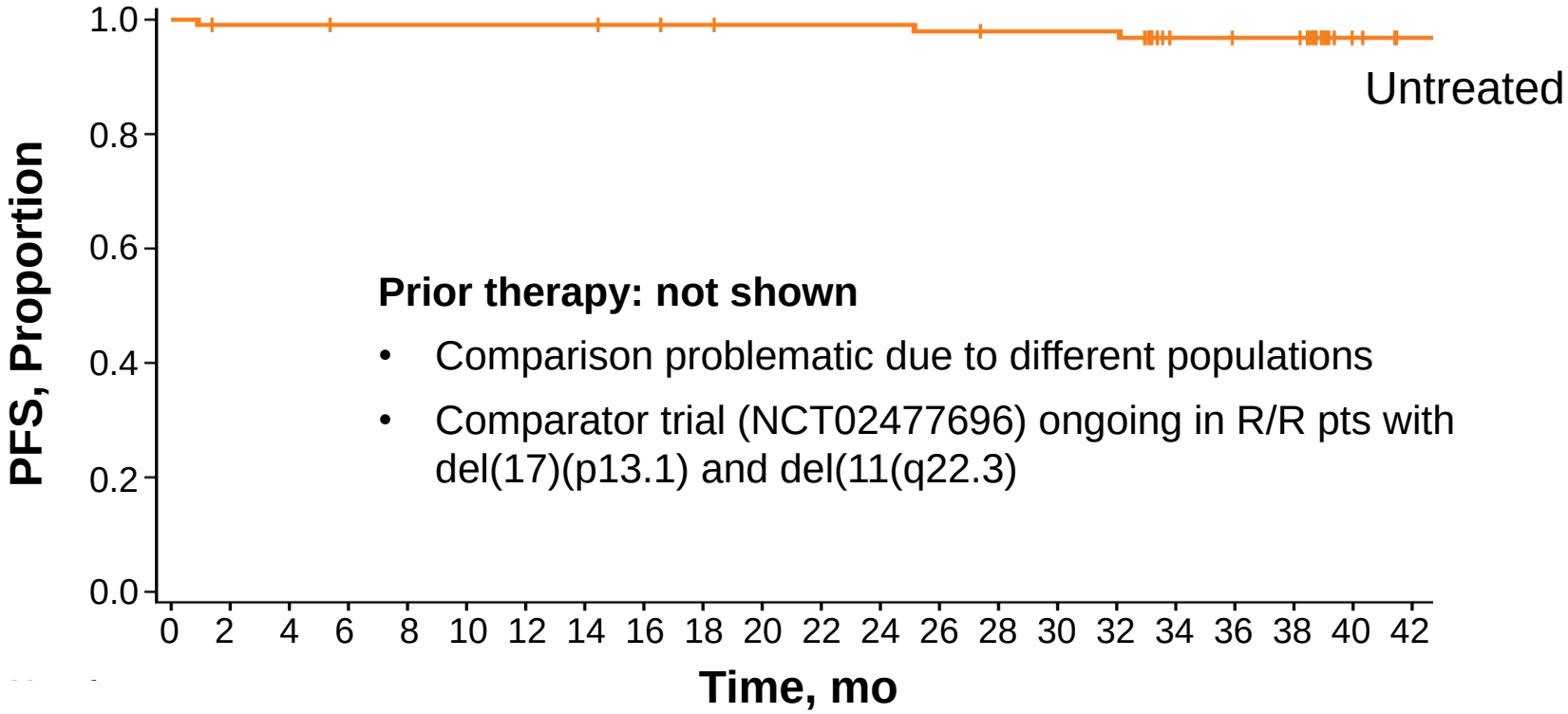


First line	31	27	26	26	26	25	25	25	24	24	23	19	18	17	13	9
Relapsed/refractory	101	86	78	71	63	58	54	44	41	34	29	24	22	19	15	8

	Median, mo (95% CI)	7-y PFS
First-line (n = 31)	NR (NE-NE)	83%
R/R (n = 101)	51 (37-70)	36%

1. Byrd J et al. ASH 2018. Abstract 3133.

PFS: Acalabrutinib (3.5 y)[1]



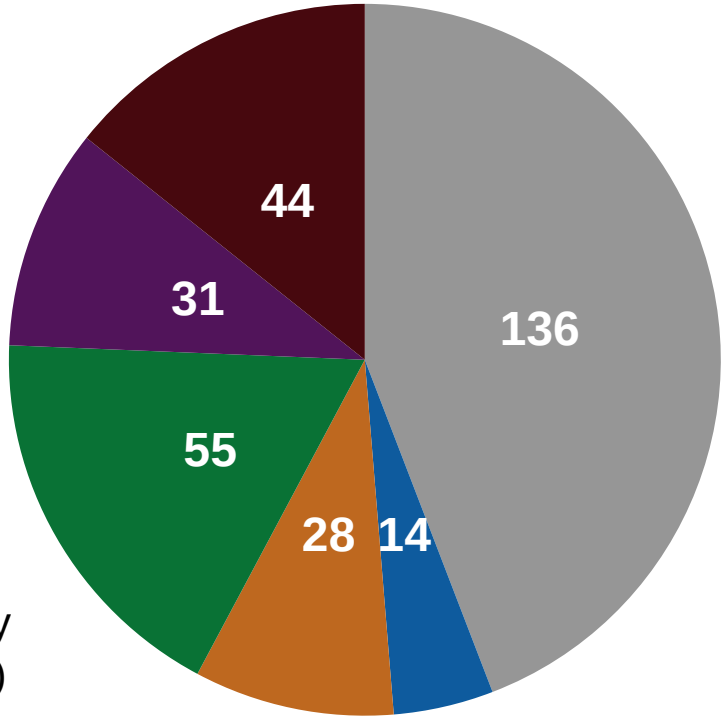
Prior therapy: not shown

- Comparison problematic due to different populations
- Comparator trial (NCT02477696) ongoing in R/R pts with del(17)(p13.1) and del(11(q22.3)

1. Byrd J, Furman R. ASH 2018.

Reasons for Discontinuation of Ibrutinib at OSU[1]

N = 308

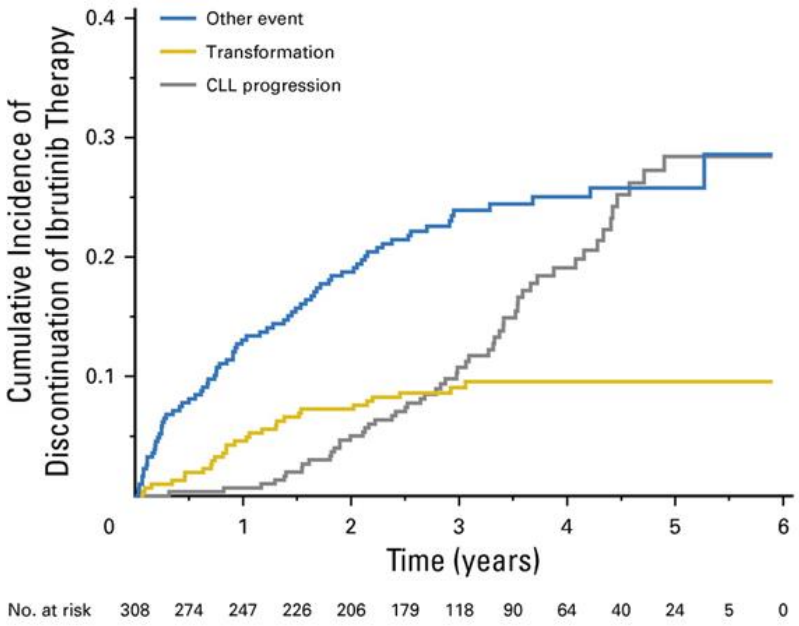


- Remaining on study
- Transplant/therapy elsewhere
- Transformation
- CLL progression
- Infection
- Other AE

Median follow-up: 3.4 y (range, 0.3-59)

1. Woyach JA et al. *J Clin Oncol*. 2017;35:1437-1443.

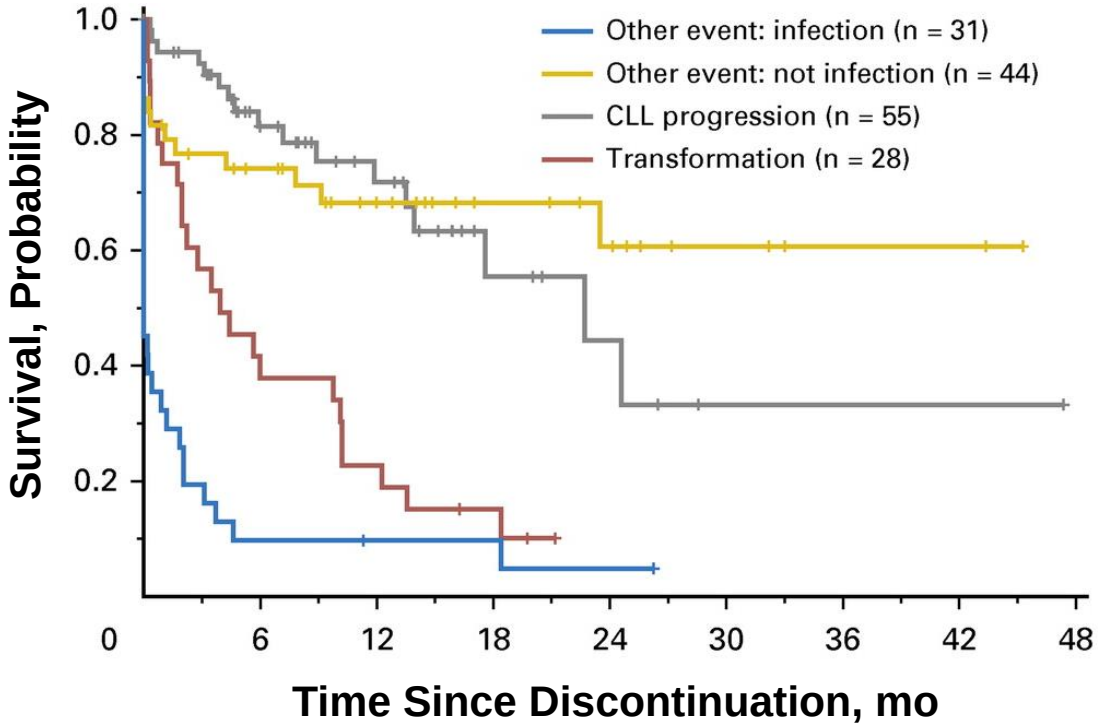
Timeline and Cause of Ibrutinib Discontinuation[1]



Cumulative Incidence Estimate (95% CI)	At 2 y	At 3 y	At 4 y
CLL progression	5.0% (2.5% to 7.5%)	10.8% (7.1% to 14.4%)	19.1% (13.9% to 24.3%)
Transformation	7.3% (4.3% to 10.2%)	9.1% (5.8% to 12.4%)	9.6% (6.2% to 13.0%)
Other event	18.7% (14.3% to 23.1%)	23.9% (19.0% to 28.8%)	25.0% (20.0% to 30.1%)

1. Woyach JA et al. *J Clin Oncol*. 2017;35:1437-1443.

Survival After Ibrutinib Impacted by Cause of Discontinuation[1]



1. Woyach JA et al. *J Clin Oncol*. 2017;35:1437-1443.

Multivariate Analysis for Discontinuation Type[1]

Variable	Transformation		Progressive CLL[a]	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Complex karyotype (yes vs no)	5.00 (1.51 to 16.52)	.008	2.81 (1.34 to 5.88)	.006
MYC abnormality (yes vs no)	2.15 (1.00 to 4.65)	.051	—	—
Del(17)(p13.1) present on FISH (yes vs no)	—	—	2.14 (1.15 to 3.96)	.016
Age (≥ vs <65 y)	—	—	0.49 (0.27 to 0.91)	.023
Prior therapies >3 (yes vs no)	—	—	—	—

[a] Landmark analysis at 1 year.

1. Woyach JA et al. *J Clin Oncol*. 2017;35:1437-1443.

Ibrutinib Resistance (What We Know)[1,2]

- **Acquired resistance to ibrutinib occurs via**
  - Mutations in BTK at C481 site, which changes ibrutinib to reversible inhibitor with decreased binding efficiency and increases BTK enzymatic activity
  - Mutations in PLCγ2 at multiple hotspots, including R665, L845, and S707, which promotes gain of function in the setting of BCR activation

- **Early intrinsic resistance to ibrutinib is rare and often manifests as Richter's transformation**
  - Pathophysiology uncertain (clonal or epigenetic evolution?)
  - Acquired mutations in BTK C481S or PLCG2 are rare in Richter's and often present in CLL blood clone

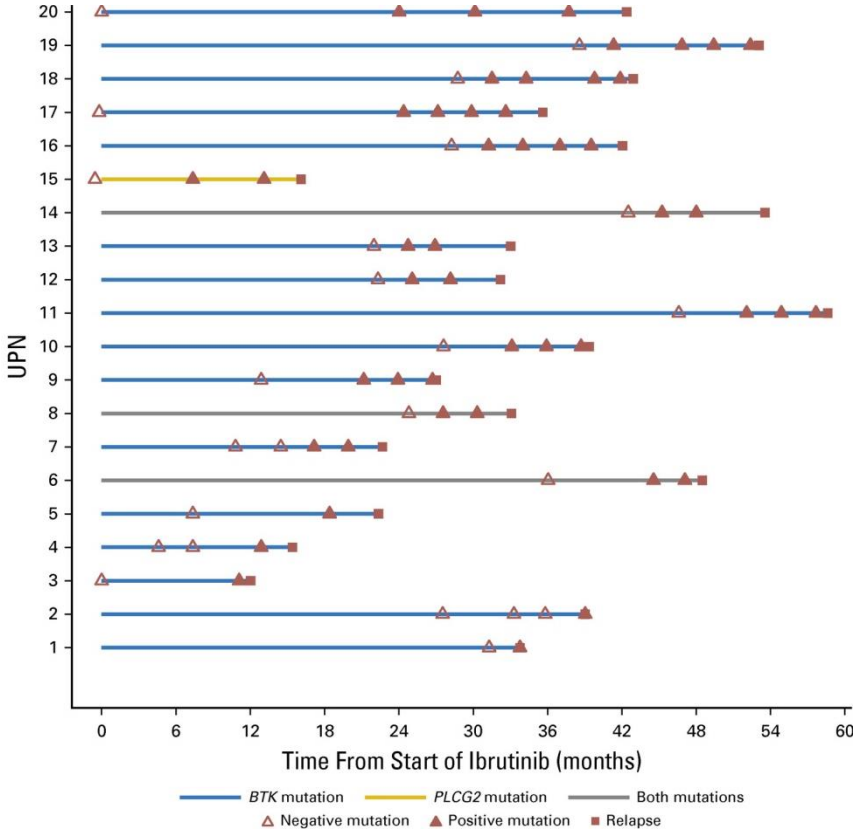
1. Woyach JA et al. *J Clin Oncol*. 2017;35:1437-1443. 2. Furman RR et al. *N Engl J Med*. 2014;370:2352-2354.

Association of CLL Progression With BTK and PLCγ2 Mutations[1]

- Deep sequencing Ion Torrent Assay for BTK and PLCγ2 performed on blood or marrow on 46 patients
- 87% have mutations in BTK or PLCγ2 acquired at relapse
  - 31 had BTK C481 as sole mutations
  - 3 had PLCγ2 hotspot mutations only
  - 6 had both BTK C481S and PLCγ2 hotspot mutations
  - 6 had neither mutation

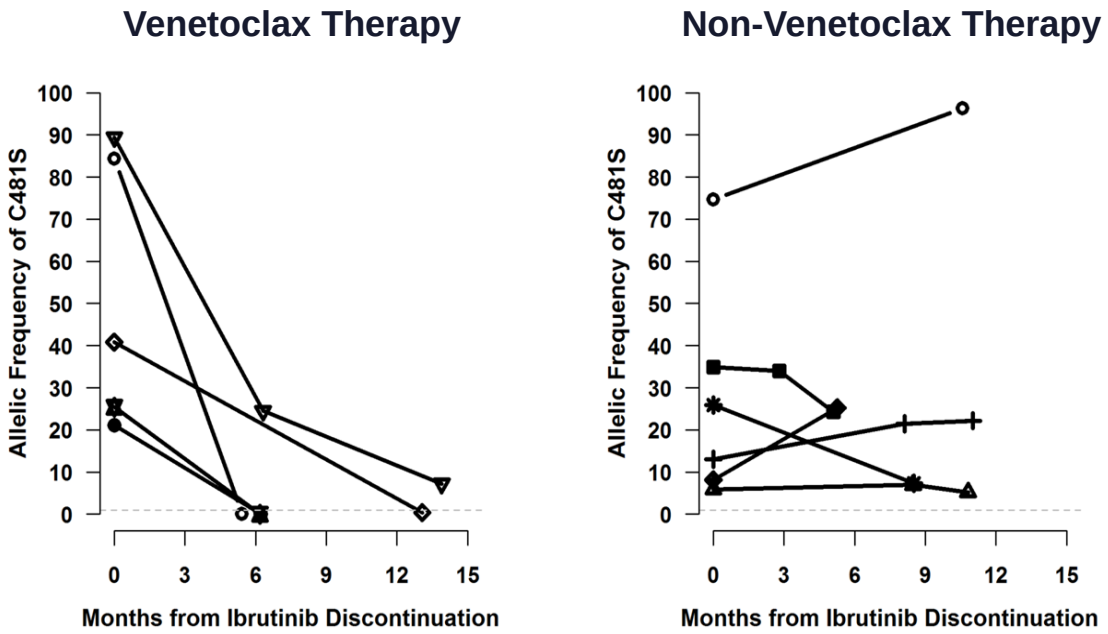
1. Woyach JA et al. *J Clin Oncol*. 2017;35:1437-1443.

Resistance Mutations Appear Over Time[1]



1. Woyach JA et al. *J Clin Oncol*. 2017;35:1437-1443.

Resistance Mutations Persist After Salvage Therapy[1]



1. Woyach JA et al. *J Clin Oncol*. 2017;35:1437-1443.

Targeting BTK With Reversible BTKi

- **GDC-0853:**[1] development ceased due to business reasons
- **ARQ531:**[2] potent BTK inhibitor with favorable PK; improved activity in preclinical models of CLL and Richter's currently in phase 1 clinical trials
- **SNS-062:**[3] potent reversible BTK in phase 1 clinical trial
- **LOXO305:**[4] potent BTK inhibitor in phase 1 clinical trial

1. Reiff SD et al. ASCO 2016. Abstract 7530. 2. Reiff SD et al. ASH 2016. Abstract 3232. 3. Binnerts ME et al. 2015 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics. Abstract C186. 4. Brandhuber B et al. SOHO 2018. Abstract CLL-200.

ARQ 531: A Broad Inhibitor of TEC and SRC Family Kinases[1]

- SAR to be as effective against C481S mutant
- Orally bioavailable
- Long half-life in vivo in multiple species with uM levels of drug
- Favorable in vivo toxicity profile

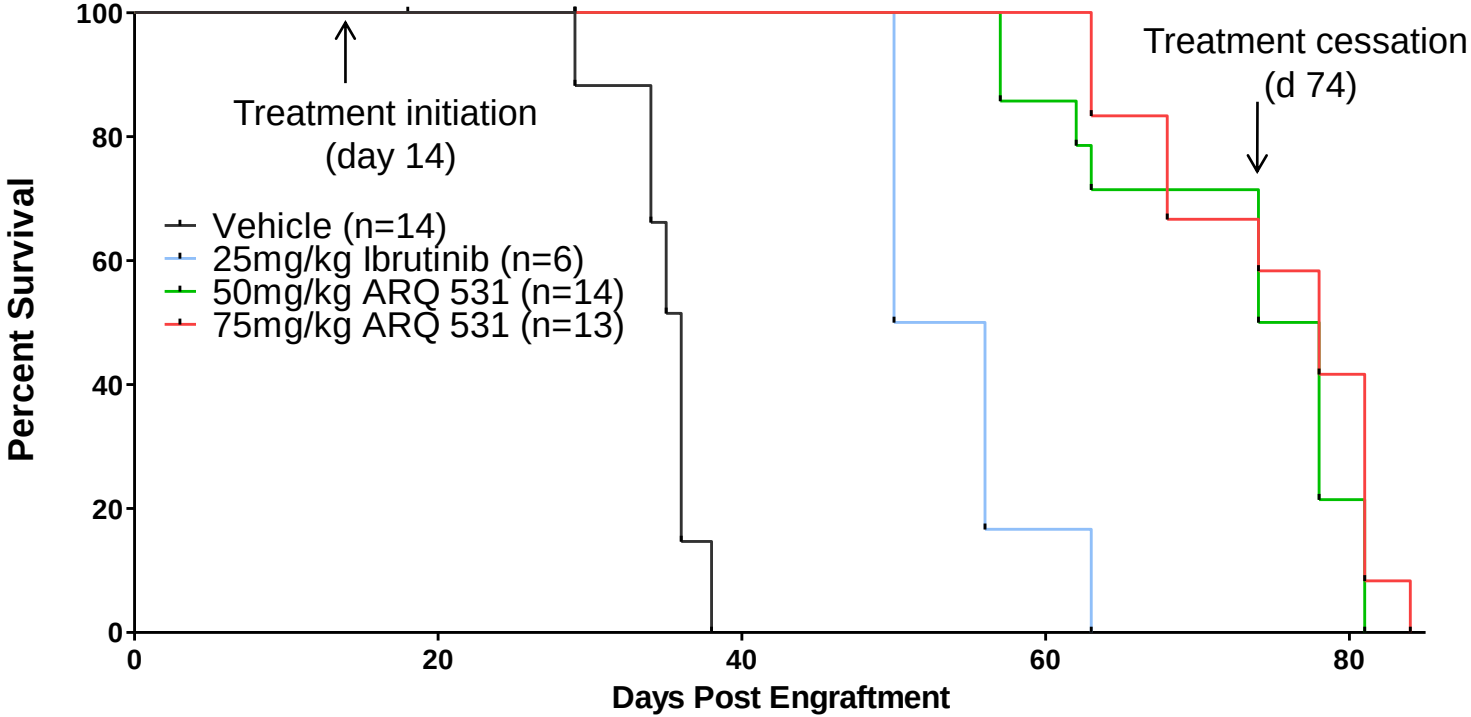
Kinase	ARQ 531 IC50 (nM)	Ibrutinib IC_{50} (nM)
Lck	0.298	5.5
Yes	0.301	3
TEC	0.57	0.35
Hck	0.641	12
BTK	0.65	0.15
Blk	0.95	0.4
BMX	0.99	0.36
LYN	1.09	15
Fyn	1.46	16
RET	3.8	101
Src	4.17	58
Raf	16.2	431
MEK1	292	3000
ITK	344	61

SRC kinases

TEC kinases

1. Reif SD et al. *Cancer Discov*. 2018;8:1300-1315.

ARQ 531 Demonstrates Superior In Vivo Activity to Ibrutinib in TCL1 Transplant Model[1]



1. Reif SD et al. *Cancer Discov*. 2018;8:1300-1315.

Other Strategies for Resistance in CLL

- **Preventing acquired ibrutinib resistance**
  - Sequencing of therapies to optimize cellular and innate immune response
  - Utilizing agents in combination that have alternative mechanisms of action

- **Treating emerging clones of resistance by adding to ibrutinib before clinical relapse occurs (different paradigm for cancer)**
  - VAY736, venetoclax, and CAR-T cells

- **Preventing Richter's transformation**
  - Alternative Rx approach for high-risk patients using PLX2853 (BRD4 inhibitor with ibrutinib)

Ibrutinib in Waldenstrom's Macroglobulinemia[1]

- Phase 2 study treated 63 pts with ibrutinib (420 mg/d) until progression or intolerance
  - Demographics: median age of 63 y; 2 prior treatments
- ORR of 90%, with major response of 73%; difference in response by genomic feature
  - MYD88(L265P)CXCR4(WT): 100% ORR and 91% major response
  - MYD88(L265P)CXCR4(WHIM): 85% ORR and 61% major response
  - MYD88(WT)CXCR4(WT): 71% ORR and 28% major response
- Common grade 3 or higher SAEs included neutropenia (14%), thrombocytopenia (13%), bleeding (6%), atrial fibrillation (5%)
- Estimated 2-y PFS was 69% and OS was 95%

1. Treon SP et al. *N Engl J Med*. 2015;372:1430-1440.

Resistance in Waldenstrom's

- C481S BTK mutations are common and subclonal as in CLL with secondary CARD11 and PLCG2 mutations noted
- C481S BTK mutations can be identified prospectively in asymptomatic patients who relapse
- Majority of patients with C481 BTK mutations had baseline CXCR4 mutations
- BTK mutations have increased ERK1 signaling and downstream paracrine-mediated resistance via IL-6 and IL-10

Resistance to Ibrutinib in MCL[1,2]

Primary/secondary resistance more common in MCL

- Primary resistance associated with cell cycle, *TRAF2, BIRC2,* and other mutations that activate NF-κB, ERB4, and PIM
- Secondary resistance to ibrutinib complicated, but includes uncommon mutations in C481S, PLCγ2 mutations, CARD11

Driving mechanisms may represent signal reprogramming

- PI3K, AKT, mTOR signaling
- CXCR4/α4β1 integrin activation (via BAFF signaling)

1. Woyach JA et al. *N Engl J Med*. 2014;370:2286-2294. 2. Woyach JA et al. *J Clin Oncol*. 2017;35:1437-1443.

Closing Points on Resistance to BTKi

Diseases where ibrutinib (and acalabrutinib) work best are ones where they target multiple targets <u>essential</u> to tumor

- BCR signaling and downstream NF-κB signaling
- Integrin signaling/cell adhesion in microenvironment
- TLR9 signaling
- Immune recovery and surveillance

Hypothesis

Primary or secondary resistance develops when one or more are not important to tumor survival and growth or mutation/epigenetic modification develops to mediate this

Abbreviations

AICD: activation-induced cell death

ALL: acute lymphocytic leukemia

ASCT: autologous stem cell transplant

BCR: B-cell receptor

BID: twice a day

BM: bone marrow

BR: bendamustine plus rituximab

BTK: Bruton's tyrosine kinase

BTKi: BTK inhibitor

CAR: chimeric antigen receptor

CD: cluster of differentiation

CI: confidence interval

CIT: chemoimmunotherapy

CLL: chronic lymphocytic leukemia

CR: complete response

CXCR: C-X-C chemokine receptor

DAG: diacylglycerol

DLBCL: diffuse large B-cell lymphoma

DLT: dose-limiting toxicity

DOR: duration of response

ECOG PS: Eastern Cooperative Oncology Group Performance Status

EFS: event-free survival

FCR: fludarabine, cyclophosphamide, and rituximab

FISH: fluorescence in situ hybridization

FL: follicular lymphoma

Abbreviations (Cont'd)

HL: Hodgkin lymphoma

HLA-G: major histocompatibility complex, class I, G

HR: hazard ratio

HTN: hypertension

IC_{50}: half maximal inhibitory concentration

IgG: immunoglobulin G

IGHV: immunoglobulin heavy-chain gene

IKK: IκB kinase

IL: interleukin

IP3: inositol trisphosphate

IR: intermediate risk

irAE: immune-related adverse event

ITK: IL-2 inducible T-cell kinase

IWCLL: International Workshop on Chronic Lymphocytic Leukemia

JAK3: Janus kinase 3

JNK: c-Jun N-terminal protein kinase

K_I: inhibitor concentration at half of the maximal rate

K_{inact}: maximal rate of kinase inactivation

LAD: leukocyte adhesions deficiency

LBL: lymphoblastic lymphoma

MAPK: mitogen-activated protein kinase

MCL: mantle cell leukemia

MM: multiple myeloma

MR: major response

Abbreviations (Cont'd)

MRD: minimal residual disease

mTOR: mechanistic target of rapamycin

MZL: marginal zone lymphoma

NE: not evaluable

NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells

NHL: non-Hodgkin lymphoma

NK: natural killer

NR: not reached

ORR: overall response rate

PD: progressive disease

PI3K: phosphatidylinositol 3′ kinase

PIP3: phosphatidylinositol (3,4,5)-trisphosphate

PK: pharmacokinetics

PLCγ: phospholipase C gamma 1

PLL: prolymphocytic leukemia

Plt: platelet

PR: partial response

PS: performance status

QD: every day

R/R: relapsed/refractory

R: rituximab

R-CHOP: rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone

s/p: status post

SAE: serious adverse event

Abbreviations (Cont'd)

SAE: serious adverse event

SAR: structure-activity relationship

SD: stable disease

SLL: small lymphocytic lymphoma

TET2: tet methylcytosine dioxygenase 2

TLR: Toll-like receptor

TLS: tumor lysis syndrome

TN: treatment naïve

TRAE: treatment-related adverse event

TRAF2: TNF receptor–associated factor 2

TTR: time to response

WM: Waldenström's macroglobulinemia

ZAP70: zeta chain of T-cell receptor–associated protein kinase 70

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