The Evolving Role of BTKi's in CLL

June 28, 2022

10 AM PT, 11 AM MT
12 PM CT, 1 PM ET

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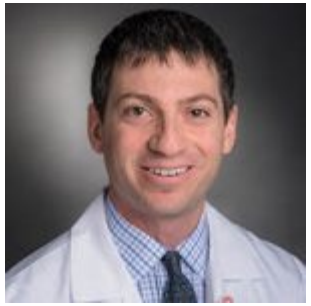
Speakers



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June 28, 2022

Disclosures
Matthew S. Davids, MD, MMSc

I have the following financial relationships to disclose

- **SAB/Consultant/Honoraria:** AbbVie, BMS, Genentech, Janssen, TG Therapeutics, Celgene, AstraZeneca, Eli Lilly, Adaptive Biosciences, BeiGene, Merck, Ascentage Pharma, Research to Practice, Takeda
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Learning Objectives

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- What are BTK inhibitors?
- What is their role in CLL therapy today?
- How do they compare with each other and other treatment options?
- What roles might they play in the future?

Introduction

We Now Have a Diverse Array of Mechanistically Diverse Targeted Therapies for CLL Treatment

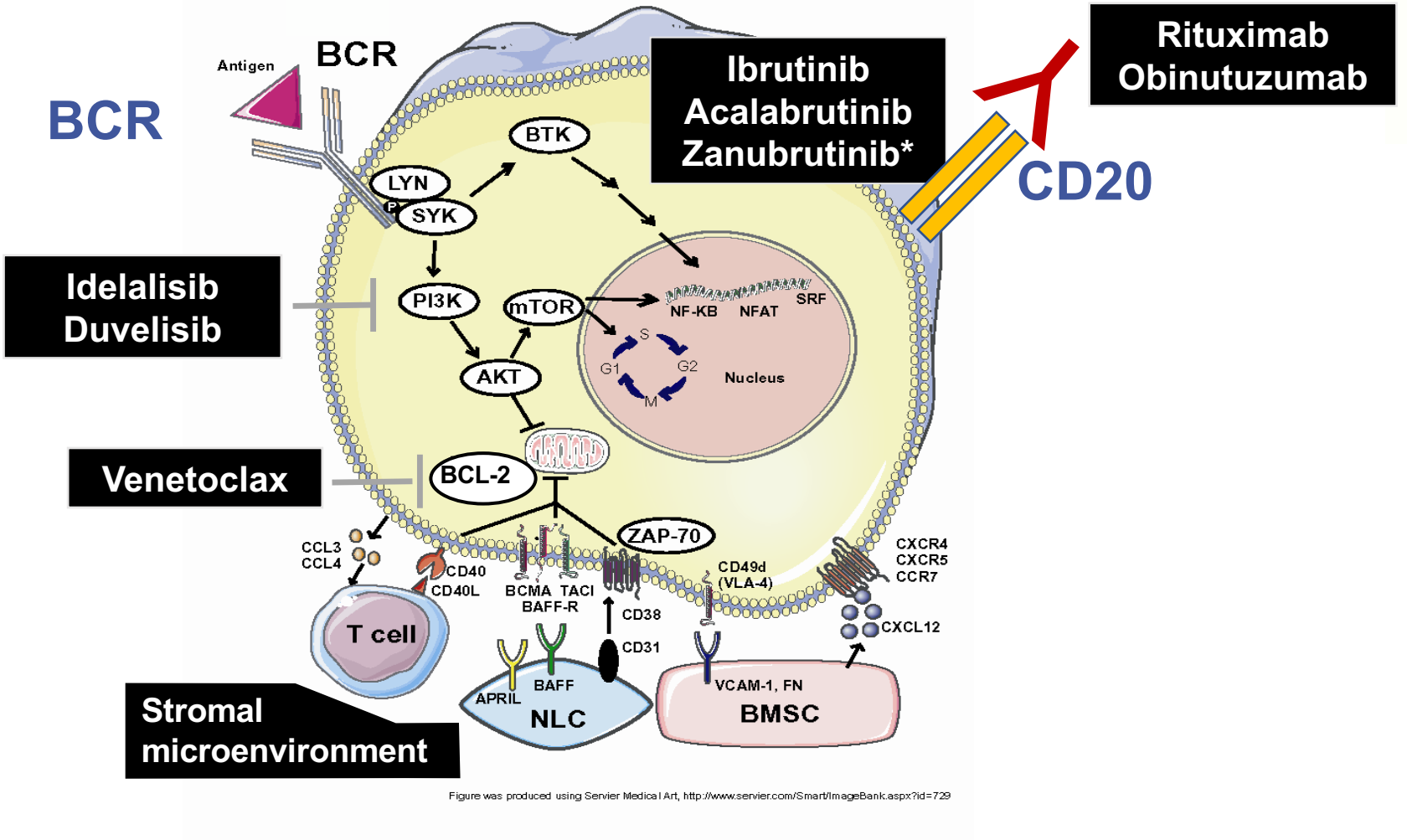
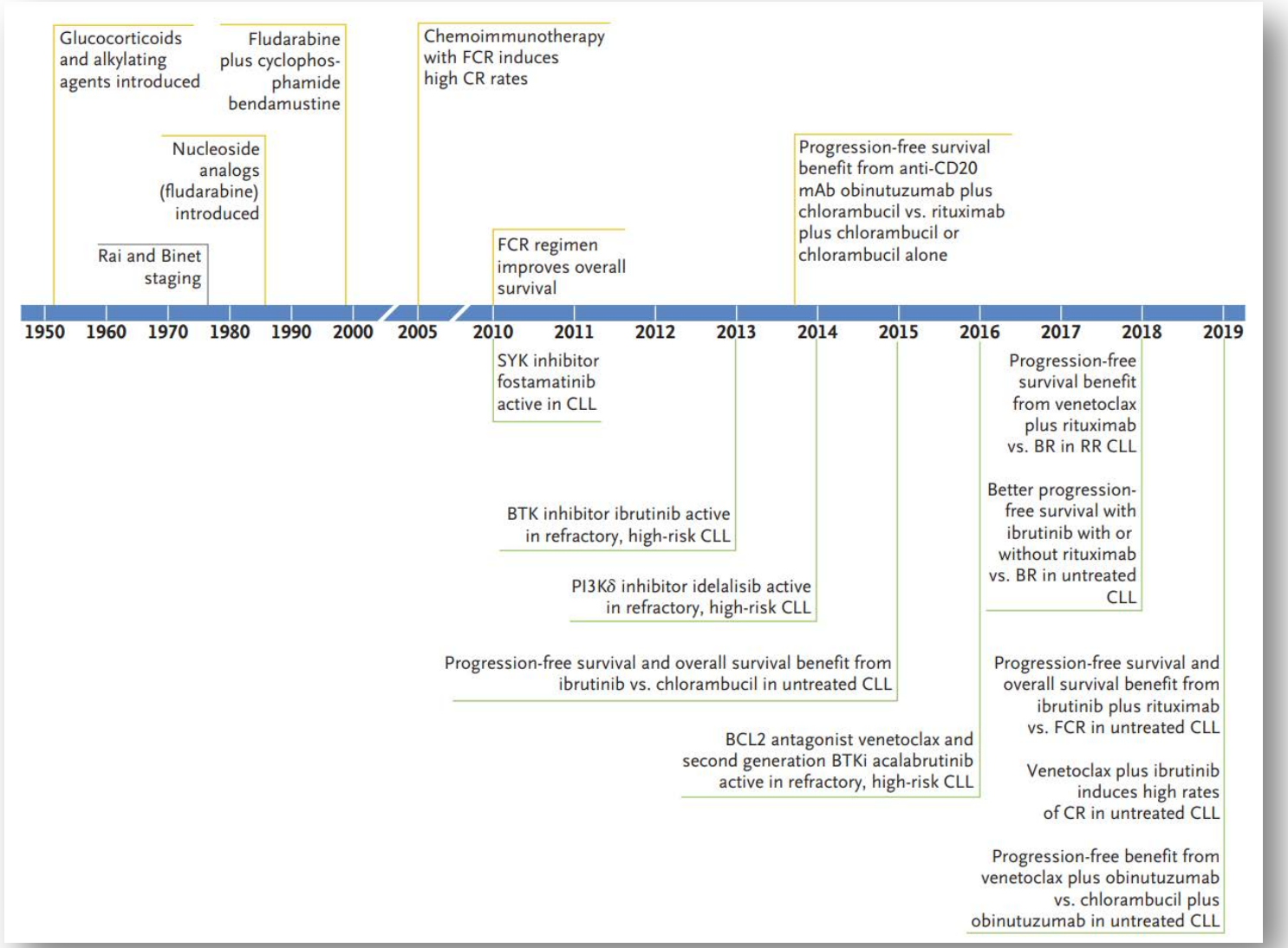


Figure was produced using Servier Medical Art, http://www.servier.com/Smart/ImageBank.aspx?id=729

- Adapted from Davids & Brown. *Leuk Lymphoma.* 2012

Milestones in Clinical CLL Research



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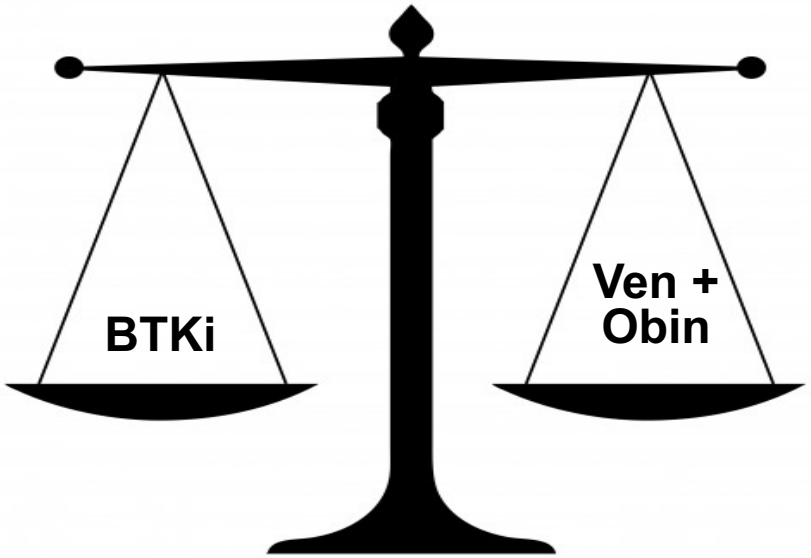
Burger, *NEJM*, 2020

Frontline BTKi vs Venetoclax + Obinutuzumab: Factors to Consider



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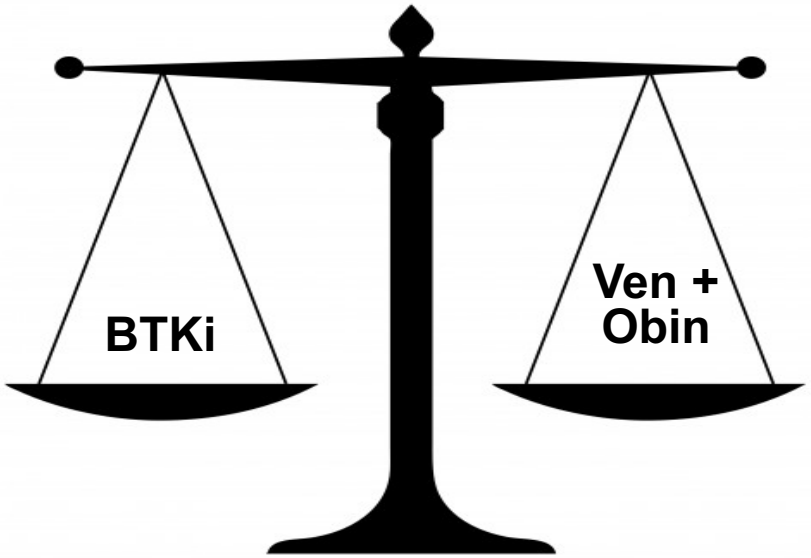
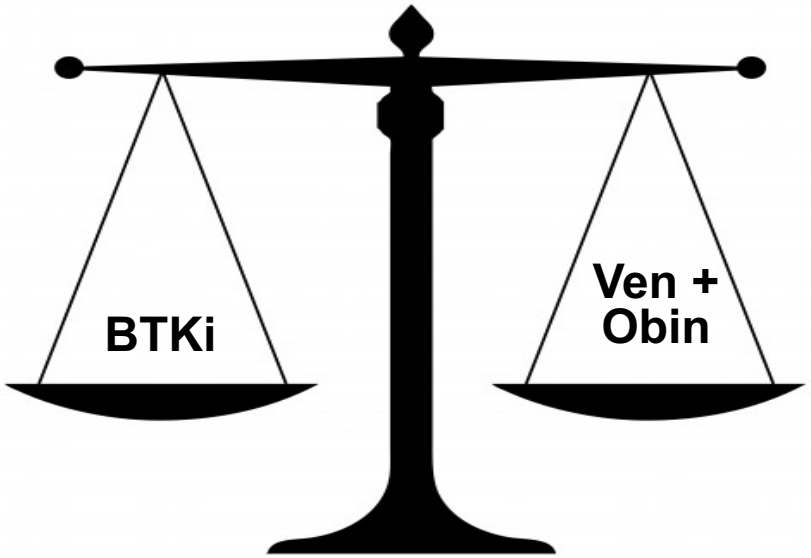
Frontline BTKi vs Venetoclax + Obinutuzumab: Factors to Consider



- Convenience (no infusions, TLS monitoring)
- Long-term efficacy data
- Phase III data compared with FCR and BR
- More data for efficacy of Ven at time of ibrutinib progression

Frontline BTKi vs Venetoclax + Obinutuzumab: Factors to Consider

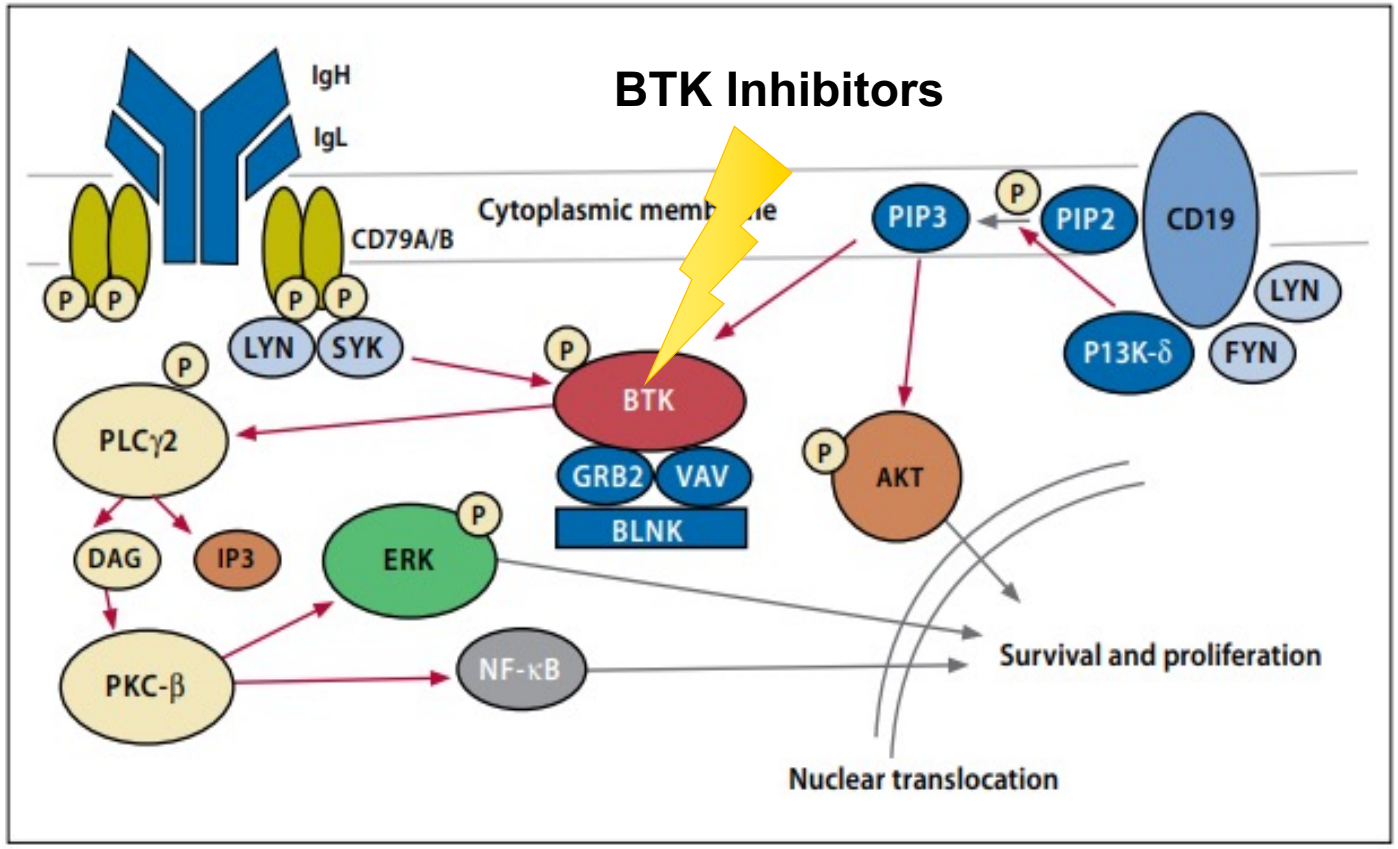


- Convenience (no infusions, TLS monitoring)
- Long-term efficacy data
- Phase III data compared with FCR and BR
- More data for efficacy of Ven at time of ibrutinib progression

- 1-year time-limited therapy
- No known cardiac or bleeding risks
- Less concern for long-term adherence
- Cost-saving

BTK Inhibitors

Mechanism of Action



- Acalabrutinib, Ibrutinib, Zanubrutinib: Form a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity
- Pirtobrutinib, Nemtabrutinib: Noncovalent binding to BTK
- Blocks B-cell receptor signaling and survival, proliferation, and migration of cancerous B cells

- Figure from Bond DA et al. *Clin Advances Hematol Oncol.* 2019;17(4):223-233.

Second Generation BTK Inhibitors Exhibit Differences in Kinase Selectivity

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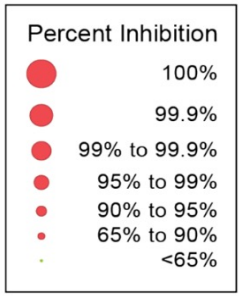
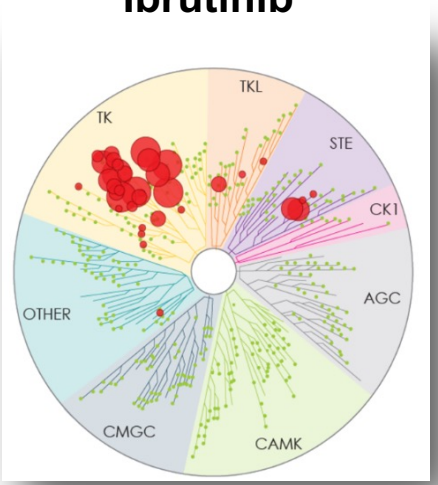
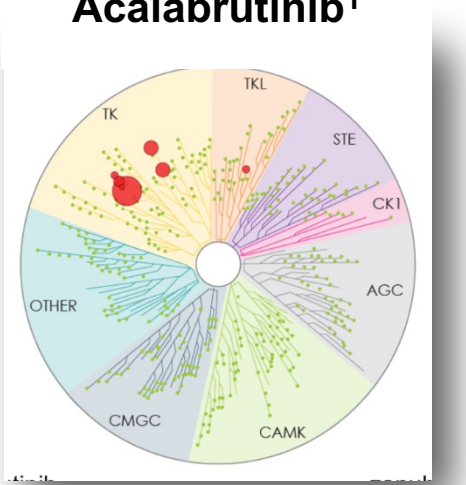


The size of the red circle is proportional to the degree of inhibition.

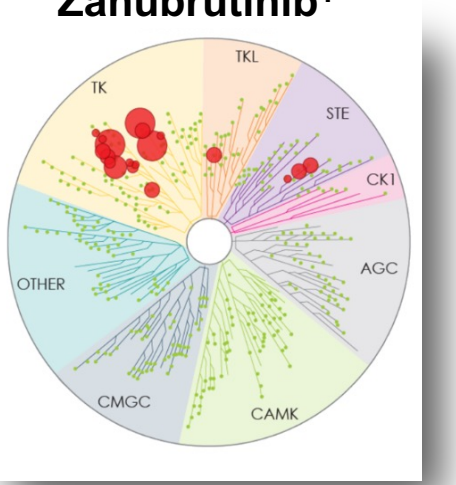
Ibrutinib[1]



Acalabrutinib[1]



Zanubrutinib[1]*



*Not yet FDA approved for the treatment of CLL

This make explain the different "off target" effects.

Kaptein, et al. *Blood*. 2018. 132 (Supplement 1): 1871.

Summary of FDA-Approved BTK Inhibitors

	Ibrutinib	Acalabrutinib	Zanubrutinib
FDA-approved indications	• **CLL (monotherapy or w/ obinutuzumab or rituximab)** • R/R MCL • WM • MZL (after ≥ 1anti-CD20-based therapy) • cGVHD	• **CLL/SLL (monotherapy or with obinutuzumab)** • R/R MCL (monotherapy)	• R/R MCL
Method of administration	• CLL/SLL, WM, and cGVHD: 420 mg taken orally once daily • MCL and MZL: 560 mg taken orally once daily	100 mg every 12 hours orally	Once daily (320 mg) or twice daily (160 mg) orally
Key toxicities	• Bleeding, atrial fibrillation, diarrhea, fatigue, and increased risk for infection	• Headaches, diarrhea, fatigue, infection, anemia	• Diarrhea, infection, fatigue, anemia

Owen, et al. *Curr Oncol.* 2019; 26(2): e233–e240. Agents prescribing information.

How Effective are BTKi's?

8-Year Follow-up of Ibrutinib Monotherapy:

High Rates of OS, ORR and Long-term Tolerability in first-line CLL

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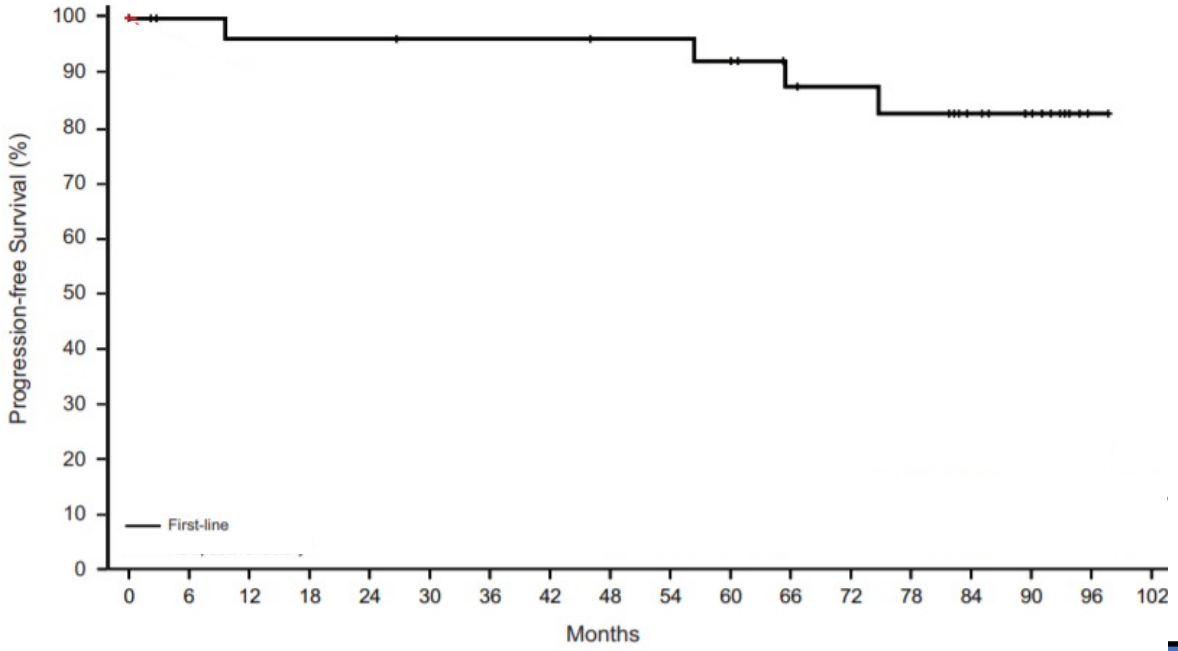
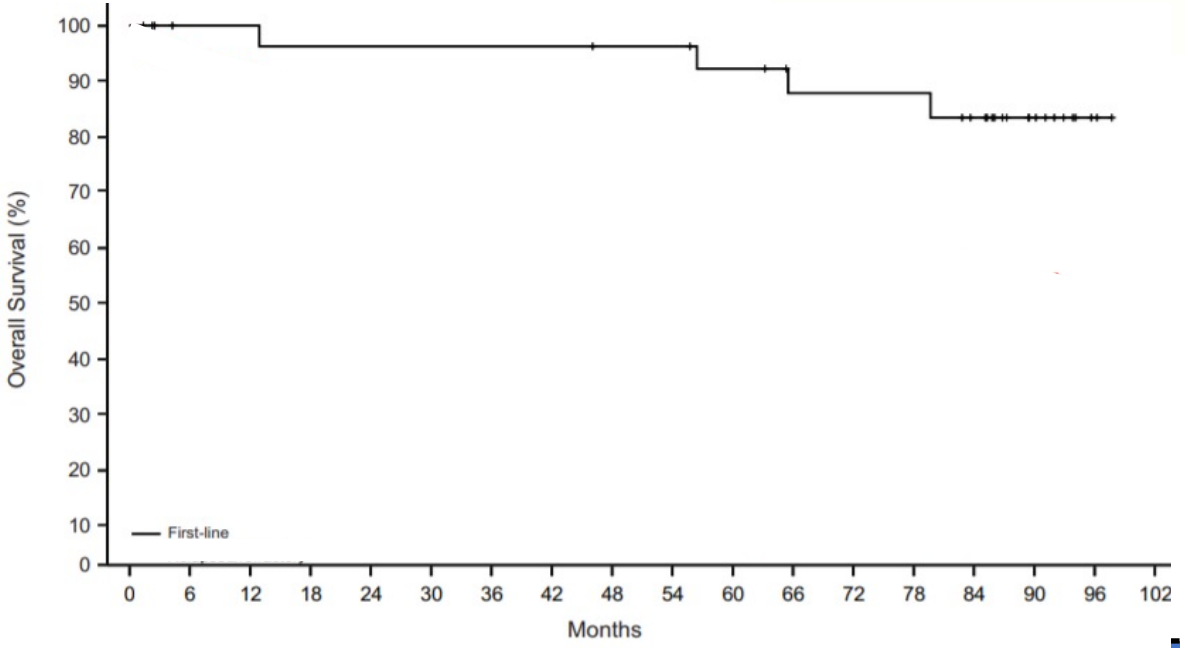
PFS (Progression Free Survival)



	Median, mos (95%CI)	7-year PFS
First-line (n=31)	NR (NE-NE)	83%

OS (Overall Survival)



	Median, mos (95%CI)	7-year OS
First-line (n=31)	NR (NE-NE)	84%

- Byrd, et al. *Clin Cancer Res*. 2020 Mar 24; clincanres.2856.2019.

What Is the Benefit of Adding Anti-CD20 Antibodies to BTK Inhibitors?

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Trial	ORR (Overall Response Rate)	PFS
Ibrutinib vs ibrutinib + rituximab[1] **MD Anderson R/R or 1L high risk**	92% vs 92%	86% vs 86.9%
Ibrutinib vs ibrutinib + rituximab[2] **Alliance Study 1L CLL**	93% vs 94%	NR vs NR
Acalabrutinib vs acalabrutinib + obinutuzumab[3] **ELEVATE-TN**	85% vs 94%	82% vs 90% (30-mo PFS)

1L, first line; BTK, Bruton tyrosine kinase; ORR, overall response rate; PFS, progression-free survival; R/R, relapsed/refractory.

1. Burger JA, et al. *Blood*. 2019;133:1011-1019. 2. Woyach JA, et al. *N Engl J Med*. 2018;379:2517-2528. 3. Sharman JP, et al. ASH. 2019. Abstract #31. 4. Sharman JP, et al. ASCO 2020. Abstract #8022.

4-Year Follow-Up of ELEVATE-TN

Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in TN (Treatment Naïve) CLL

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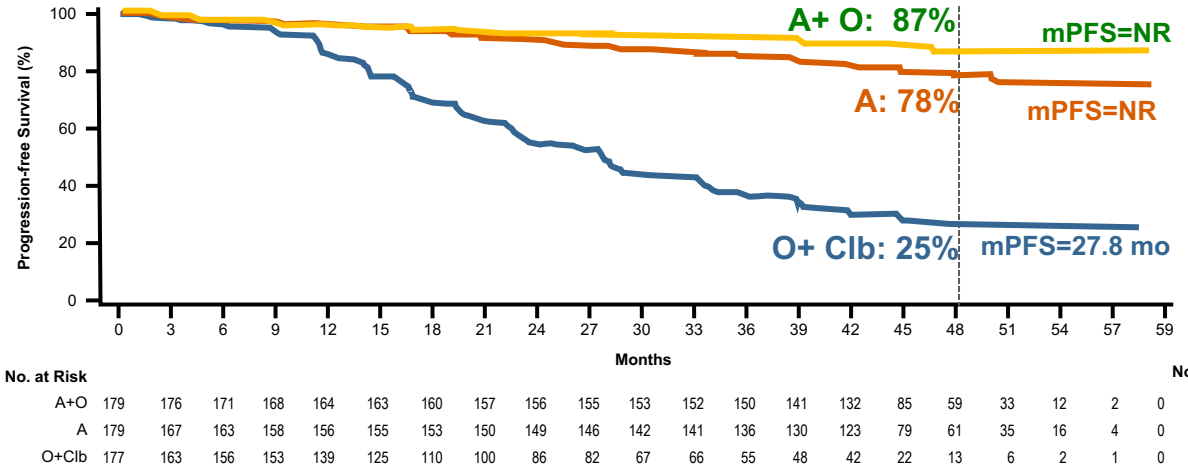
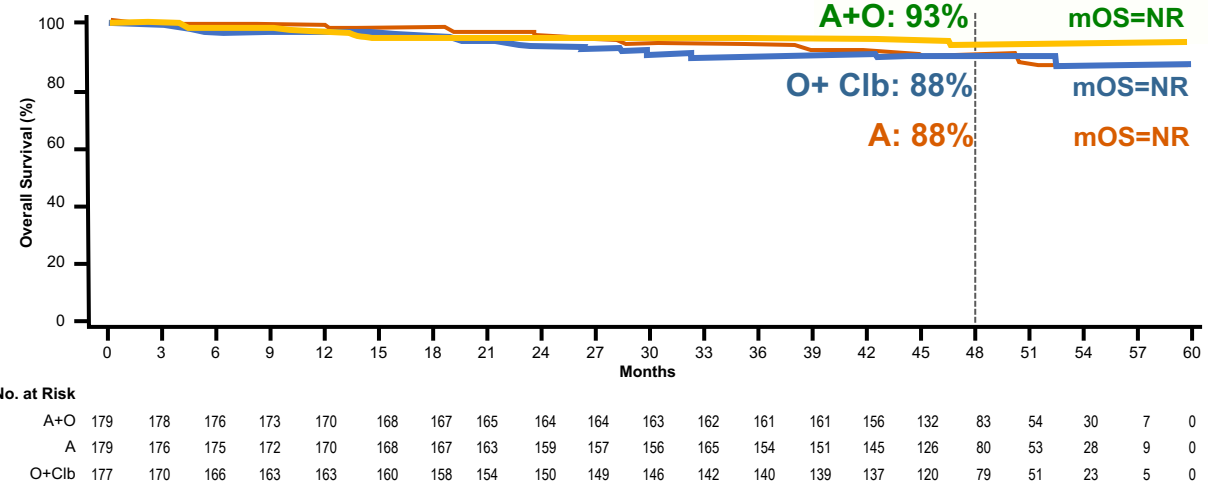
Investigator-Assessed PFS Overall



Overall Survival



	HR (95% CI)	*P*
A+O vs O+Clb	0.10 (0.07, 0.17)	< 0.0001
A vs O+Clb	0.19 (0.13, 0.28)	< 0.0001
A+O vs A	0.56 (0.32, 0.95)	< 0.0001

	HR (95% CI)	*P*
A+O vs O+Clb	0.50 (0.25, 1.02)	0.0604
A vs O+Clb	0.95 (0.52, 1.74)	0.9164

Acalabrutinib + Obinutuzumab (A+O), Acalabrutinib Monotherapy (A), Obinutuzumab + Chlorambucil (O+Clb)

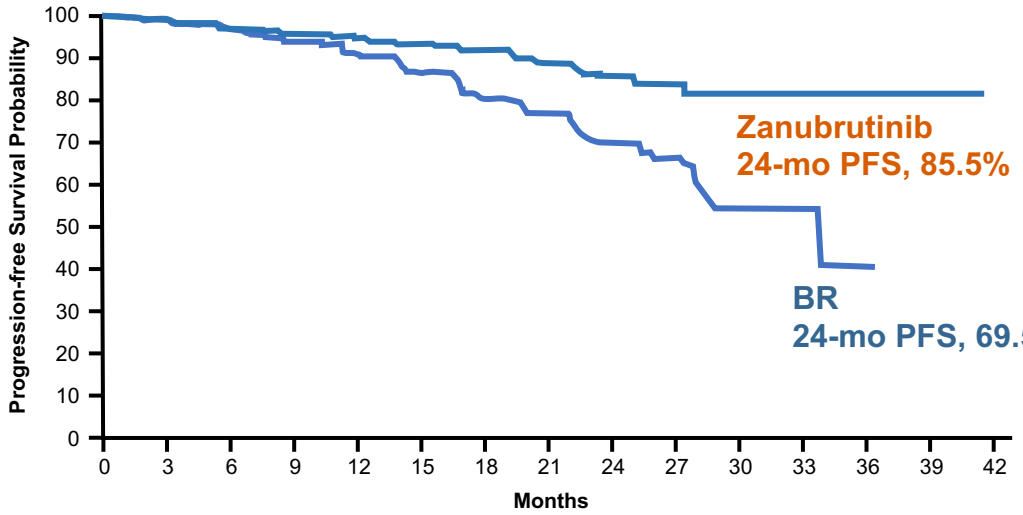
Sharman JP, et al. EHA 2021. Abstract S148. Sharman JP, et al. [published online ahead of print, 2022 Jan 1]. *Leukemia*. 2022;10.1038/s41375-021-01485-x.

SEQUOIA (BGB-3111-304)

Arm A & B: Zanubrutinib vs Bendamustine+Rituximab in TN CLL

Progression-Free Survival per IRC Assessment

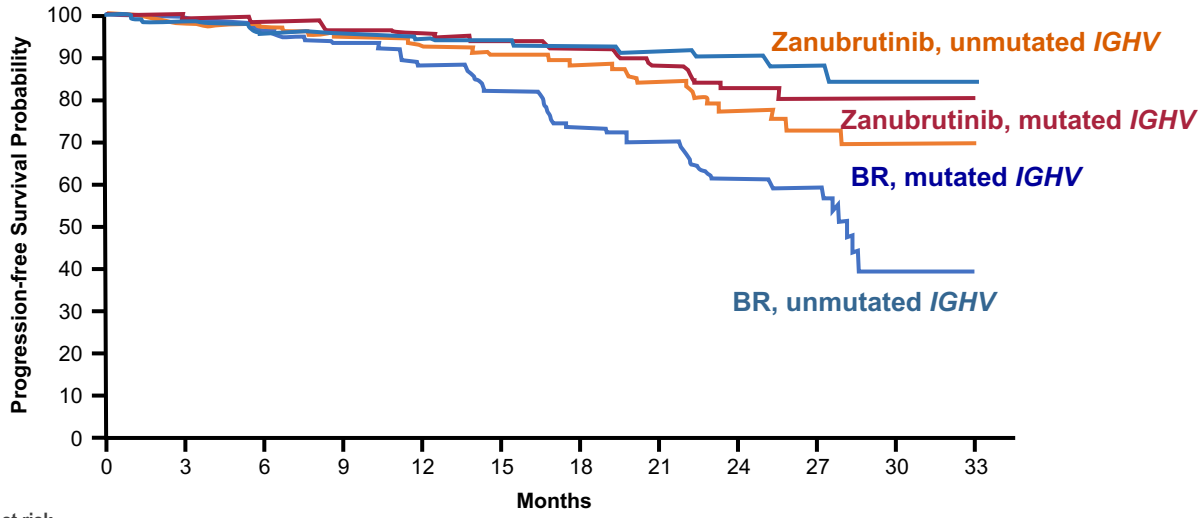
HR, 0.42 (95%CI, 0.27-0.63); *P* < .0001



No. of patients at risk														
Zanubrutinib	241	237	230	224	222	214	208	195	123	79	31	17	2	1	0
BR	238	218	210	200	187	176	164	150	89	54	20	8	1	0	

Zanubrutinib, unmutated *IGHV* vs BR, unmutated *IGHV*
HR, 0.24 (95% CI, 0.13–0.43); *P* < 0.001

Zanubrutinib, mutated *IGHV* vs BR, mutated *IGHV*
HR, 0.67 (95% CI, 0.36–1.22); 2-sided *P* = 0.186

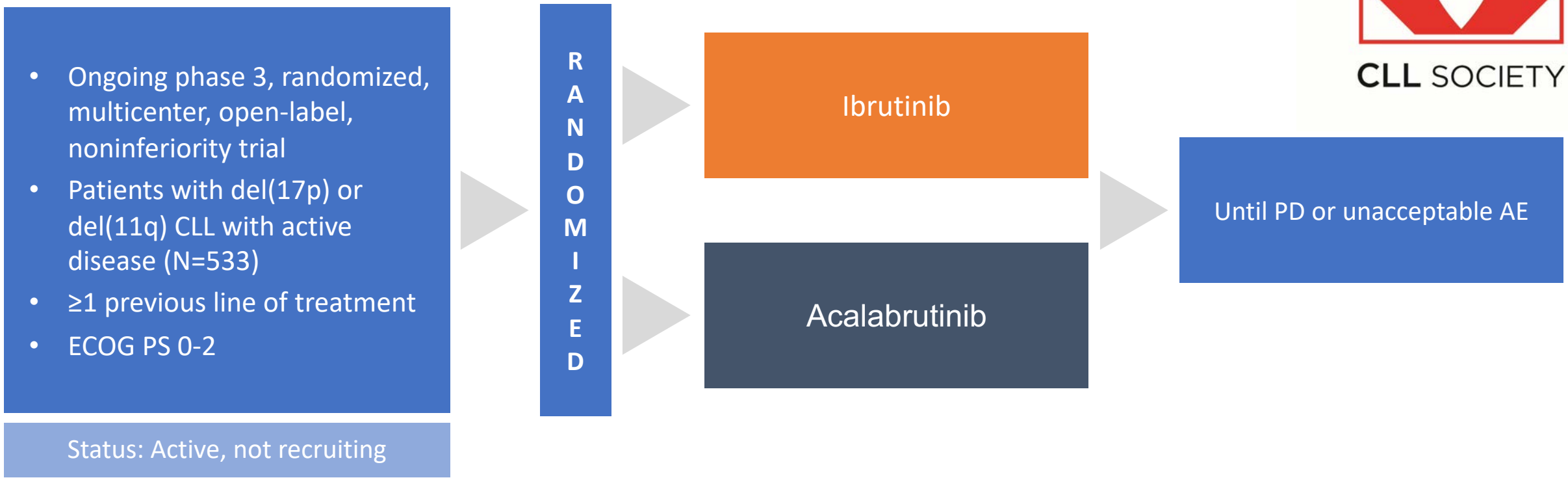


No. of patients at risk												
Zanubrutinib - Unmutated	125	121	117	114	113	112	109	104	68	44	14	6
BR – Unmutated	121	110	106	100	90	82	73	65	39	25	6	1
Zanubrutinib – Mutated	109	109	106	104	103	97	94	88	53	33	15	10
BR - Mutated	110	101	98	94	91	88	86	80	47	27	14	7

BR, bendamustine + rituximab; IRC, independent review committee; PFS, progression-free survival.

Tam, et al. *Blood*. Abstract 396, 2021.

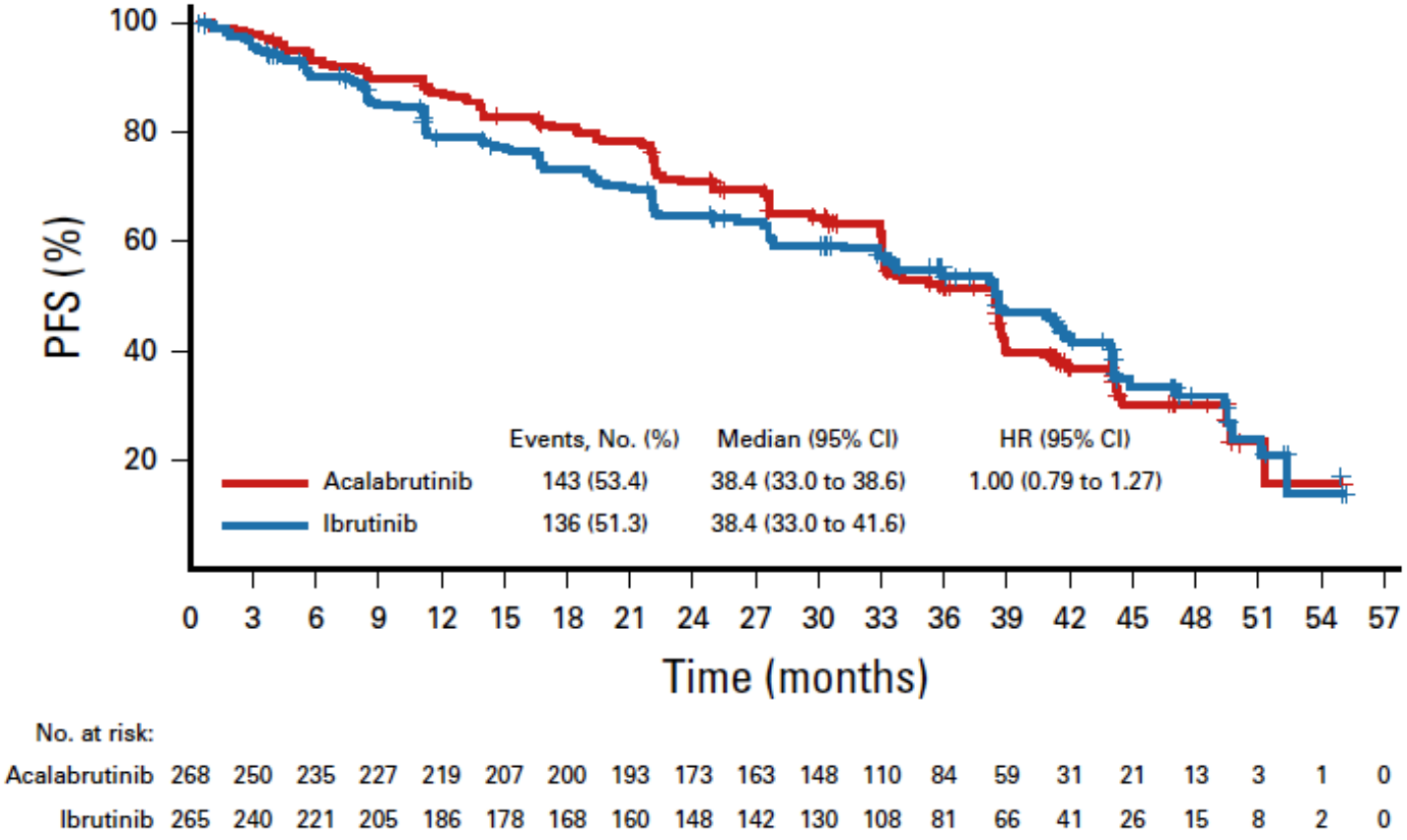
ELEVATE-RR Trial: Ibrutinib vs Acalabrutinib in Patients With High-Risk R/R (Relapsed/Refractory) CLL



AE, adverse event; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; PD, progressive disease;
PFS, progression-free survival; R/R, relapsed/refractory

Clinicaltrials.gov. NCT02477696.

ELEVATE-RR Trial: Ibrutinib vs Acalabrutinib in Patients With High-Risk R/R CLL



CLL, chronic lymphocytic leukemia; PFS, progression-free survival; R/R, relapsed/refractory.

Byrd J. et al. *J Clin Oncol. 2021;39:3441-3452.*

ELEVATE-RR: AEs (Adverse Events) of Clinical Interest

- Most common grade ≥3 infections: pneumonia (acalabrutinib vs ibrutinib, 10.5% vs 8.7%), sepsis (1.5% vs 2.7%), and urinary tract infections (1.1% vs 2.3%)

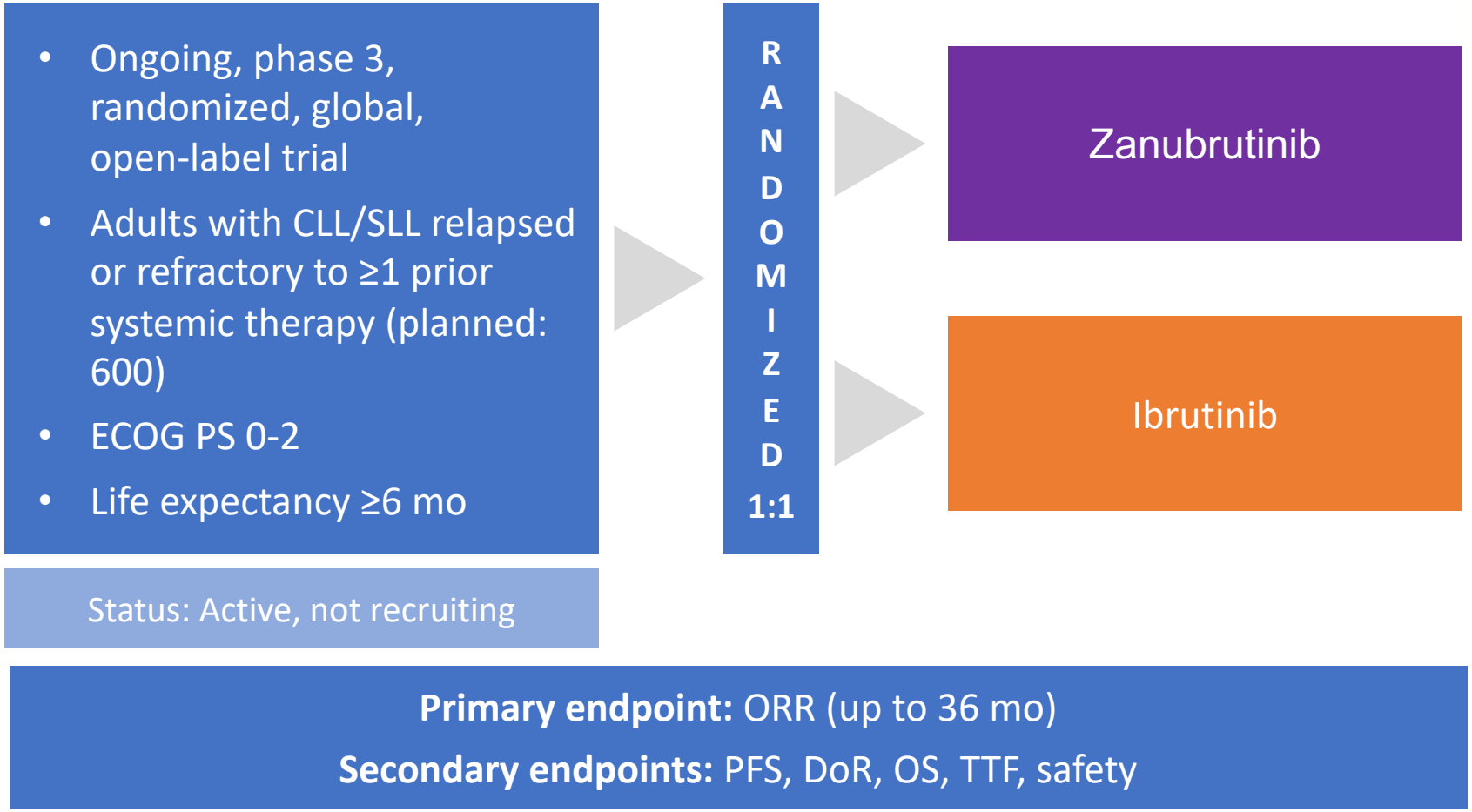
AE, n (%)	Acalabrutinib (n=266)		Ibrutinib (n=263)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac events	64 (24.1)	23 (8.6)	79 (30.0)	25 (9.5)
• Atrial fibrillation/flutter	**25 (9.4)**	13 (4.9)	**42 (16.0)[a]**	10 (3.8)
• Ventricular arrhythmias	0	0	3 (1.1)	1 (0.4)
Bleeding events	**101 (38.0)**	10 (3.8)	**135 (51.3)**	12 (4.6)
• Major bleeding events	12 (4.5)	10 (3.8)	14 (5.3)	12 (4.6)
Hypertension	**25 (9.4)**	**11 (4.1)**	**61 (23.2)**	**24 (9.1)**
Infections	208 (78.2)	82 (30.8)	214 (81.4)	79 (30.0)
ILD/pneumonitis	**7 (2.6)**	1 (0.4)	**17 (6.5)**	2 (0.8)
SPMs, excluding NMSC	24 (9.0)	16 (6.0)	20 (7.6)	14 (5.3)

AE, adverse event; ILD, interstitial lung disease; NMSC, nonmelanoma skin cancer; SPMs, second primary malignancies.

[a] Bolded numbers statistically significantly higher vs the comparator ($P<0.05$).

Byrd. ASCO 2021. Abstract #7500.

ALPINE Trial: Zanubrutinib vs Ibrutinib in R/R CLL/SLL



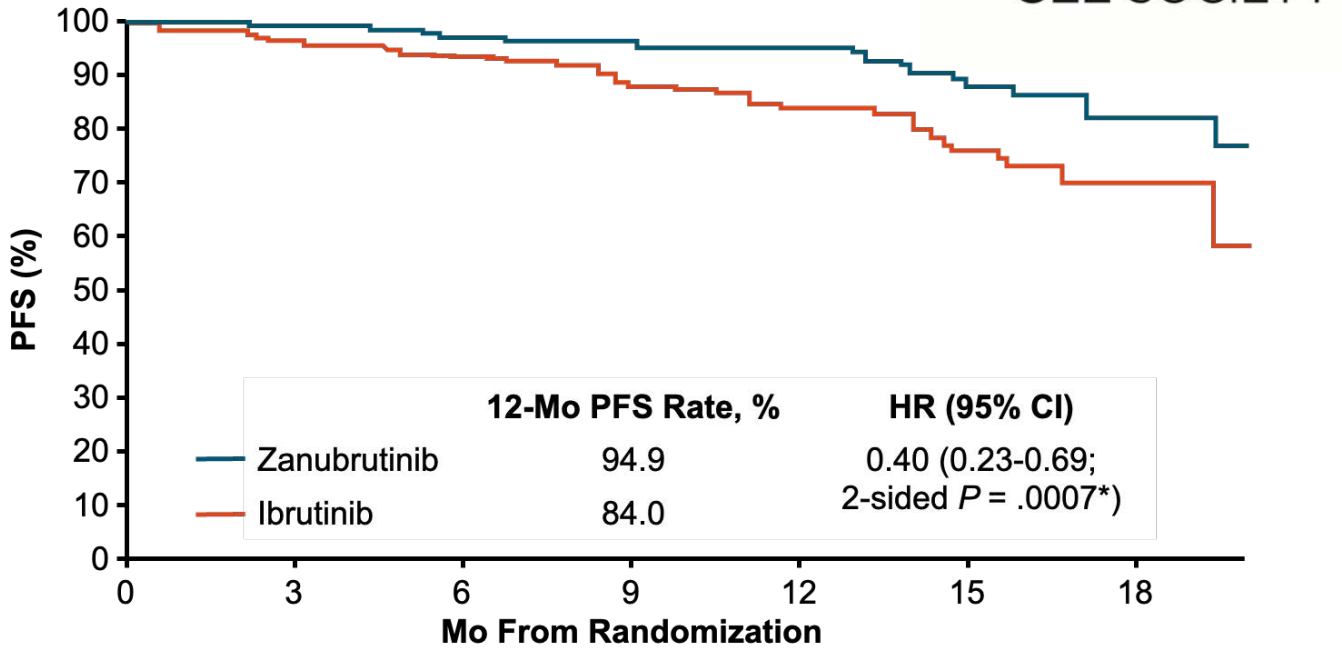
CLL, chronic lymphocytic leukemia; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group performance status; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; TTF, time-to-treatment failure.

Clinicaltrials.gov. NCT03734016.

ALPINE Trial: Zanubrutinib vs Ibrutinib in R/R CLL/SLL

ORR	Zanubrutinib	Ibrutinib
Overall	78.3%	62.5%
del(11q)	83.6%	69.1%
del(17p)	83.3%	53.8%

PFS by Investigator Assessment



*Comparison is not from a prespecified analysis. Formal PFS analysis to be performed on all patients once target number of events attained.

CLL, chronic lymphocytic leukemia; KM, Kaplan-Meier; ORR, overall response rate; PFS, progression-free survival; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

Hillmen P. Presented at EHA 2021. Abstract #LB1900.

ALPINE Trial: Zanubrutinib vs Ibrutinib in R/R CLL/SLL

- Cardiac disorders leading to treatment discontinuation: zanubrutinib, n=0; ibrutinib, n=7 (3.4%)

AE of Special Interest in Safety Analysis Population, n (%)	Zanubrutinib (n=204)		Ibrutinib (n=207)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac disorders	**28 (13.7)**	5 (2.5)	**52 (25.1)**	14 (6.8)
Atrial fibrillation and flutter	**5 (2.5)**	2 (1.0)	**21 (10.1)**	4 (1.9)
Hemorrhage • Major hemorrhage[a]	73 (35.8) 6 (2.9)	6 (2.9) 6 (2.9)	75 (36.2) 8 (3.9)	6 (2.9) 6 (2.9)
Hypertension	34 (16.7)	22 (10.8)	34 (16.4)	22 (10.6)
Infections	122 (59.8)	26 (12.7)	131 (63.3)	37 (17.9)
Neutropenia (low neutrophils)	**58 (28.4)**	38 (18.6)	b	31 (15.0)
Thrombocytopenia (low platelets)	19 (9.3)	7 (3.4)	26 (12.6)	7 (3.4)
Secondary primary malignancies • Skin cancers	17 (8.3) 7 (3.4)	10 (4.9) 3 (1.5)	13 (6.3) 10 (4.8)	4 (1.9) 2 (1.0)

AE, adverse event; CLL, chronic lymphocytic leukemia; CNS, central nervous system; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

[a] Includes serious or grade ≥3 hemorrhage or any-grade CNS hemorrhage.

Select Ongoing Phase 3 Clinical Trials of BTK Inhibitors in CLL

Clinical Trial	Study Design	Population	Estimated Enrollment	Treatment Arms
UK FLAIR Trial	Phase 3, randomized	Newly diagnosed, aged 18-75 years	1516	Ibrutinib vs ibrutinib + rituximab vs ibrutinib + venetoclax vs FCR
CLL13 (NCT02950051)	Phase 3, randomized	Newly diagnosed	926	FCR or BR vs venetoclax + rituximab vs venetoclax + obinutuzumab vs venetoclax + ibrutinib + obinutuzumab
EA9161 (NCT03701282)	Phase 3, randomized, open label	Aged 18-69 years	720	Ibrutinib + obinutuzumab vs ibrutinib + obinutuzumab + venetoclax
A041702 (NCT03737981)	Phase 3, randomized, open label	Untreated, aged ≥70 years	454	Ibrutinib + obinutuzumab vs ibrutinib + obinutuzumab + venetoclax
CLL17	Phase 3, randomized	Newly diagnosed, aged ≥18 years	897	Ibrutinib vs ibrutinib + venetoclax vs obinutuzumab + venetoclax
ACE-CL-311 (NCT03836261)	Phase 3, randomized, global, open label	Aged ≥18 years	780	Acalabrutinib + venetoclax vs acalabrutinib + venetoclax + obinutuzumab vs standard chemotherapy
MAJIC	Phase 3, randomized, global, open label	Newly diagnosed, aged ≥18 years	600	MRD-guided acalabrutinib + venetoclax vs MRD-guided venetoclax + obinutuzumab

BR, bendamustine/rituximab; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; FCR, fludarabine, cyclophosphamide, and rituximab; MRD, minimal residual disease. Reference: ClinicalTrials.gov.

Pirtobrutinib (LOXO-305): Selective Noncovalent BTK Inhibitor

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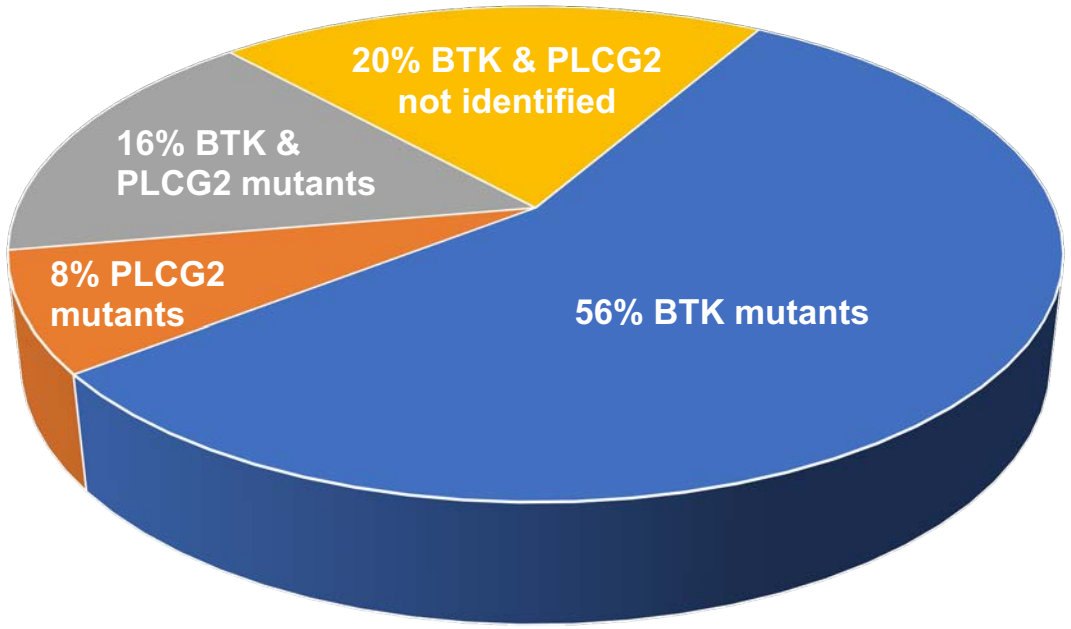
Acquired Resistance to Ibrutinib in Patients With Progressive CLL[1]

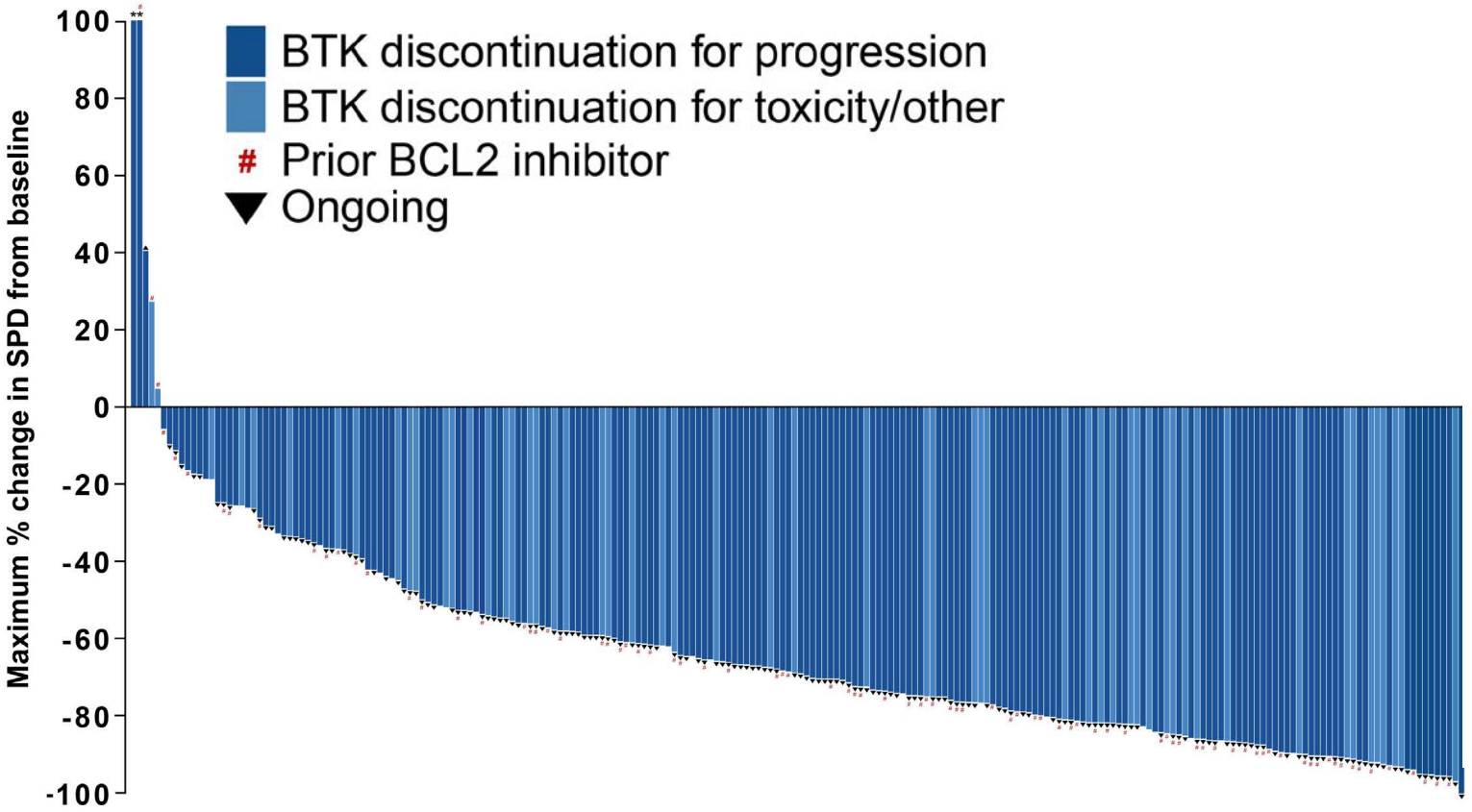


- BTK C481 mutations are the principal reason for progressive CLL after treatment with covalent BTK inhibitors[2]
- BTK C481 mutations impair target inhibition by covalent BTK inhibitors[2]
- BTK C481 is where the covalent (irreversible) BTKi bind

BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; PLCG2, phospholipase C gamma 2.

1. Lampson BL. *Expert Rev Hematol*. 2018;11(3):185-194. 2. Mato AR. Lancet. 2021;397(10277):892-901.
Mato. ASH 2020. Abstract #542.

BRUIN: Efficacy in BTK Pretreated Patients



Efficacy evaluable BTK pre-treated CLL/SLL Patients[a]	n = 252
Overall Response Rate, % (95% CI)[b]	**68 (62 – 74)**
Best response	
CR, n (%)	2 (1)
PR, n (%)	137 (54)
PR-L, n (%)	32 (13)
SD, n (%)	62 (25)

Data cutoff date of 16 July 2021. *Patients with >100% increase in SPD. Data for 30 patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. [a]Efficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment. [b]ORR includes patients with a best response of CR, PR, and PR-L. Response status per iwCLL 2018 according to investigator assessment. Total % may be different than the sum of the individual components due to rounding.

BCL2, B-cell lymphoma-2; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CR, complete response; CT, computed tomography; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; ORR, overall response rate; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease; SLL, small lymphocytic lymphoma; SPD, sum of the products of lymph node diameters.

Mato AR, et al. ASH 2021. Abstract #391.

BRUIN: Safety

	All doses and patients (n=618)						
	Treatment-emergent AEs, (≥15%), %					Treatment-related AEs, %	
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grades 3/4	Any Grade
Fatigue	13%	8%	1%	-	23%	1%	9%
Diarrhea	15%	4%	<1%	<1%	19%	<1%	8%
Neutropenia[a]	1%	2%	8%	6%	18%	8%	10%
Contusion	15%	2%	-	-	17%	-	12%
AEs of special interest[b]							
Bruising[c]	20%	2%	-	-	22%	-	15%
Rash[d]	9%	2%	<1%	-	11%	<1%	5%
Arthralgia	8%	3%	<1%	-	11%	-	3%
Hemorrhage[e]	5%	2%	1%[g]	-	8%	<1%	2%
Hypertension	1%	4%	2%	-	7%	<1%	2%
Atrial fibrillation/flutter[f]	-	1%	<1%	<1%	2%[h]	-	<1%

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No DLTs reported and MTD not reached

96% of patients received ≥ 1 pirtobrutinib dose at or above RP2D of 200 mg daily

1% (n=6) of patients permanently discontinued due to treatment-related AEs

Data cutoff date of 16 July 2021. Total % may be different than the sum of the individual components due to rounding. [a]Aggregate of neutropenia and neutrophil count decreased. [b]AEs of special interest are those that were previously associated with covalent BTK inhibitors. [c]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [d]Aggregate of all preferred terms including rash. [e]Aggregate of all preferred terms including hematoma or hemorrhage. [f]Aggregate of atrial fibrillation and atrial flutter. [g]Represents 6 events (all grade 3), including 2 cases of post-operative bleeding, 1 case each of GI hemorrhage in the setting of sepsis, NSAID use, chronic peptic ulcer disease, and one case of subarachnoid hemorrhage in setting of traumatic bike accident. [h]Of 10 total afib/aflutter TEAEs, 3 occurred in patients with a prior medical history of atrial fibrillation, 2 in patients presenting with concurrent systemic infection, and 2 in patients with both.

AE, adverse event; BTK, Bruton tyrosine kinase; DLT; dose-limiting toxicities; GI, gastrointestinal; MTD, maximum tolerated dose; NSAID, nonsteroidal anti-inflammatory drug; RP2D, recommended phase 2 dose; TEAE; treatment-emergent adverse event.

Mato AR, et al. ASH 2021. Abstract #391.

What kind of side effects are seen with BTKi's?

CLL12: CLL Patients Commonly Have Symptoms and Complications

	Ibrutinib n=158	Placebo n=155
Any grade AEs (%)	150 (94.9)	148 (95.5)
AEs ≥ grade 3 (%)	80 (50.6)	67 (43.2)
AEs leading to interruption (%)	77 (41.6)	38 (21.3)
Arrhythmias	18	0
Bleeding	8	1
Diarrhea	4	3
Neoplasia (cancer)	4	3
Infection	3	4
Myocardial infarction	1	3
Other	39	24

Langerbeins et al., *iwCLL*, 2019

Recent US Cooperative Group Studies Suggest Gr 3/4 Ibrutinib Toxicities May Be Less in Younger Patients

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Adverse event	IR Arm Alliance n=181	IR Arm E1912 N=352
Median Age Age range	71 yrs 65 – 86	57 yrs 31 - 70
Infection	19%	5%
Atrial fibrillation	6%	3%
Bleeding	4%	1%
Hypertension	34%	7%
Deaths during active treatment +30 days	**7%**	**1%**

Adapted from Shanafelt et al., ASH, 2018

BTKi: Side Effect Management

- **Higher bleeding risk with lack of data with platelets < 30K**
  - **Hold for procedures**
    - General guideline: Cataracts (1/1), Colonoscopy (3/3), Cholecystectomy (7/7)
    - Consider platelet transfusion for emergent surgery
- **Cardiac disease**
  - Difficult to control hypertension
  - Atrial fibrillation
- **Active infection**
  - Usually hold drug to control infection
- **Active autoimmunity can flare before achieving longer term control**

BTKi: What to Watch Out For

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- **Anticoagulants: Avoid if possible. If necessary, use DOACs (Direct oral anticoagulants) instead of warfarin (Coumadin)**
- **Avoid dual antiplatelet therapy**
- **Strong/moderate CYP3A inhibitors (i.e. grapefruit, erythromycin, verapamil, goldenseal): Generally avoid, but can reduce dose if needed**

General Considerations

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- In the setting of active infection it is generally best to hold drug at least until seeing signs of clinical improvement
- For most toxicities requiring drug hold, it is preferable to either rechallenge with full dose or to start back at dose reduction but then get back to full dose
- In general, I am more hesitant to hold drug soon after starting a BTKi or in a patient who is progressing on a novel agent
- I am less concerned about stopping drug in patients who have been on BTKi for at least a few months and are in a good clinical response

General Considerations

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- **BTKi are infrequently the cause of cytopenias (low blood counts)**
- **It is generally safe to give growth factor support concomitantly with novel agents**
- **Patients who have to permanently discontinue a novel agent due to toxicity do not necessarily need to immediately start on a new therapy**

General Considerations

Optimizing Adherence to Oral Therapy

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- Shared responsibility between clinician and patient[1]
  - Prescriptions will be filled
  - Patient will administer correct dosage at correct time of day
  - Patient will alert clinician of AEs
- Effect of ibrutinib dose adherence on patients' outcomes evaluated in the RESONATE trial[2]
  - Patients missing ≥8 consecutive days had shorter median PFS
  - Patients with higher DI (dose intensity) demonstrated improved PFS, higher ORR, and trend toward improved OS

AE, adverse event; DI, dose intensity; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

1. Weingart SN, et al. *J Natl Compr Canc Netw*. 2008;6(suppl 3):S1-S14. 2. Barr PM, et al. *Blood*. 2017;129:2612-2615.

Dana-Farber Cancer Institute

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Key Takeaways on BTKi Therapy in CLL in 2022

- BTK inhibitors are now a mainstay of therapy in CLL
- Up to 20% of patients discontinue ibrutinib due to side effects
- Next-generation BTKi have similar efficacy as ibrutinib
- These newer agents are associated with reduction in cardiovascular complications (especially afib) and also other side effects
- Reversible BTK inhibitors in development may help overcome resistance mutations
- BTKi have some common side effects but these are manageable for most patients
- With the rapid evolution in this field, active participation in clinical trials remains critical

Q & A

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This program was made possible by grant support from

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Please take a moment to complete our **post-event survey**, your feedback is important to us

If you're question was not answered, please feel free to email asktheexpert@cllsociety.org

Join us on July 7th for our new **Facebook Live event**, July 23rd for our inaugural, **virtual 5K Walk/Run event**, and August 2nd for our webinar on **CAR-T Therapy**

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