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Challenging treatment scenarios: How to Manage Potential Adverse and Toxicities of BTKis

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/Salut

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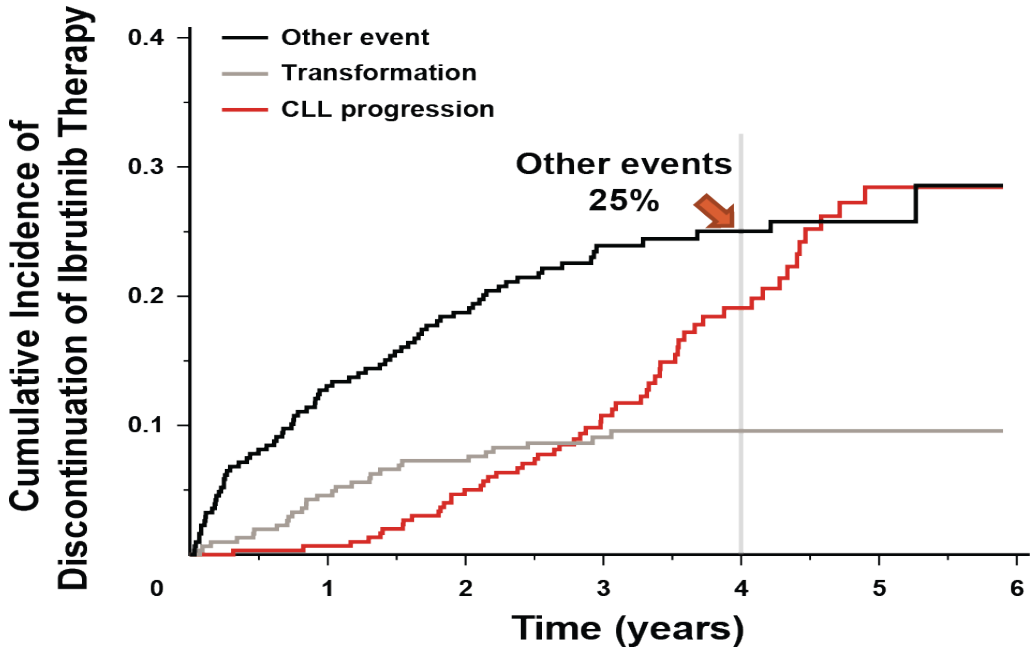
Covalent BTKi Have Improved Outcomes in B-cell Malignancies, but Discontinuation Due to Intolerance Remains a Significant Barrier

Ibrutinib discontinuation from 4 prospective studies[1]



- Ibrutinib discontinuation rates
  - Front line = 57%[2] (median follow-up 7.4 years)
  - Relapsed/refractory = 51%[1] (median follow-up 3.4 years)

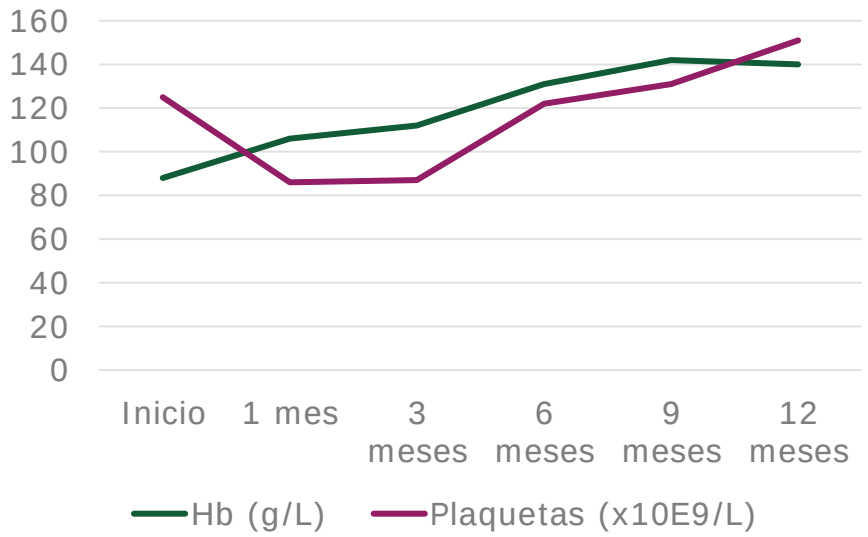
- Discontinuations of cBTKis (e.g., ibrutinib, acalabrutinib, zanubrutinib) commonly occur due to AEs[3]
  - Most common any-grade AEs: anemia, diarrhea, cough, fatigue, headache, hypertension, neutropenia, upper respiratory tract infections[3-5]
  - Most common Grade ≥3 AEs: anemia, atrial fibrillation, hypertension, neutropenia, pneumonia, thrombocytopenia[3,5,6]
- Toxicities may result from BTK off-target inhibition[7,8]
- Later generation cBTKis are more selective than ibrutinib, but the frequencies of cytopenias, upper respiratory infection, and diarrhea have not significantly decreased[4,5]
- Treatment interruptions for toxicity may adversely impact long-term outcomes[9]

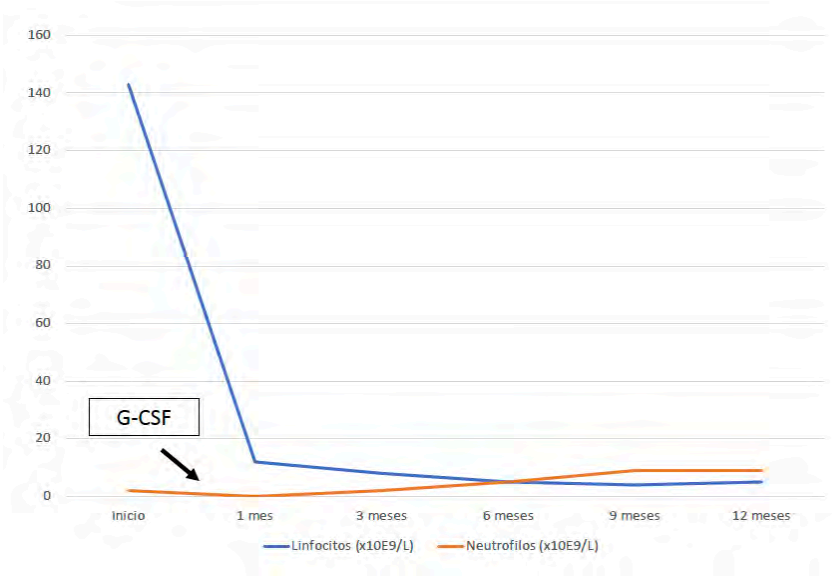
Case Report

- 64 year-old, female from Venezuela, diagnosed of CLL, stage 0, no therapy in July 2013
- In January 2020:
  - Anemia (Hb 88 g/L), thrombocytopenia (125 x 109/L), progressive leukocytosis (143.27 x 109/L)
  - Comorbidities: age 71 yrs, hypertension, type 2 DM, dislipemia, biological aortic valve from 2016
  - Criteria for starting therapy: Rai 3, rapidly increasing lymph nodes, lymphocyte doubling time < 6 mo
  - Prognostic markers: complex chromosome, FISH (+12), unmutated IGHV, unmutated TP53
- In February 2020:
  - Septic shock, pulmonary origin, *P. aeruginosa*, admitted to ICU: severely decreased cardiac function with LVEF of 37% and global hypokinesia – optimization of cardiology treatment

Case Report

- 1st line therapy:
  - Ibrutinib 420 mg po QD from february 2020
  - One single adverse event: neutropenia treated with G-CSF
  - CT at 6 months: marked improvement of the axillary, left supraclavicular, mediastinal, right hiliar and bilateral inguinal lymph nodes





Case Report

- In March 2021, new reevaluation by Cardiology:
  - LVEF without changes but dysfunctional prosthetic valve with cardiac insufficiency
  - Transcatheter aortic valve implantation with partial recovery of the LVEF (56%) at the end of the procedure
  - Increase in peripheral blood lymphocyte count (23 x 109/L) only one week after stopping ibrutinib
- In April 2021:
  - Atrial flutter (120-130 bpm) with cardiac disfunction
  - Antithrombotic therapy with apixaban + 2 beta-blockers
  - Effective cardiac ablation: Return to sinusal rhythm and improvement of LVEF up to 56%
  - Episode of low gastrointestinal bleeding – stopping anticoagulation therapy

Case Report

- In March – April 2022:
  - Asymptomatic atrial fibrilation
  - Worsening cardiac insufficiency with LVEF of 20%, electric cardioversión
  - New episodes of bleeding (hematuria, low tract gastrointestinal bleeding) – Apixaban doce reduction
- In May 2022:
  - Stop ibrutinib and change to acalabrutinib (100 mg po BID)
  - Stop apixaban – Aspirin + clopidogrel
- Excellent response to acalabrutinib
- No side effects
- Patient alive and with adequate control of the underlying disease, last follow up therapy in February/2023

ACE-CL-208 (Acalabrutinib in Ibrutinib-Intolerant Patients With R/R CLL): Study Design

R/R CLL (N=60)

Inclusion Criteria

- ≥1 prior therapy for CLL and not appropriate for treatment/retreatment with purine analog–based therapy
- Intolerant of ibrutinib:
  - Discontinued ibrutinib therapy due to persistent grade 3 or 4 AEs, OR
  - Grade 2 AEs related to ibrutinib that persisted for ≥2 weeks or recurred ≥2 times whether dose was reduced or discontinued
- Disease progression after discontinuing ibrutinib as defined by iwCLL 2008 criteria[2]

Exclusion Criteria

- Ongoing grade 3 or 4 AE attributed to ibrutinib therapy
- Treatment with systemic anticancer therapy for CLL since discontinuation of ibrutinib
- Active Richter transformation or PD while on ibrutinib
- Significant cardiovascular disease[a]
- Previous treatment with BCL-2 inhibitors
- Concomitant use of warfarin or equivalent vitamin K antagonists; alternative anticoagulation was permitted

Acalabrutinib
100 mg BID PO in 28-day cycles until PD or unacceptable toxicity

Primary End Point

- **Investigator-assessed ORR based on the modified iwCLL 2008 criteria**

Secondary End Points

- **DOR**
- **PFS**
- **TTNT**
- **OS**
- **Safety**

[a]Includes symptomatic uncontrolled arrythmias, CHF, or MI within 6 months of screening, any Class 3 or 4 cardiac disease per NYHA Functional Classification, or corrected QT interval >480 ms. Patients with controlled, asymptomatic atrial fibrillation during screening were not excluded.

AE = adverse event; BCL-2 = B-cell lymphoma 2; BID = twice daily; CHF = congestive heart failure; CLL = chronic lymphocytic leukemia; DOR = duration of response; iwCLL, International Workshop on CLL; MI = myocardial infarction; NYHA = New York Heart Association; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PO = orally; R/R = relapsed/refractory; TTNT = time to next treatment.

Rogers K et al. *Haematol*. 2021;106. doi:10.3324/haematol.2020.272500

ACE-CL-208: Patient Demographics[1,2]

Characteristic	N=60
Age, median (range), y	69.5 (43-88)
Male sex, n (%)	38 (63)
ECOG performance status ≤1, n (%)	58 (97)
Bulky lymph nodes ≥5 cm, n (%)	19 (32)
Rai stage III-IV, n (%)	31 (52)
β_2-Microglobulin >3 mg/L, n/N (%)	46/58 (79)
Genetic risk features, n/N (%)	
Unmutated *IGHV*	46/58 (79)
Del(11q)	14/60 (23)
Del(17p)	17/60 (28)
Mutations associated with ibrutinib resistance, n/N (%)	
PLCG2 wild-type	53/55 (96)
BTK wild-type	53/55 (96)

BTK = Bruton tyrosine kinase; ECOG = Eastern Cooperative Oncology Group; *IGHV* = immunoglobulin heavy-chain variable region; *PLCG2* = phospholipase C gamma 2.

Rogers K et al. *Haematol*. 2021;106. doi:10.3324/haematol.2020.272500

ACE-CL-208: Prior Therapies

- The median duration of prior ibrutinib therapy was 5.7 months (<1 to 55.5)
  - **Common AEs (>2 patients) that led to discontinuation of prior ibrutinib therapy were:**
    - **Atrial fibrillation/flutter (26.6%), diarrhea (11.7%), rash (10%), and arthralgia (10%)**
- The median time from the last dose of ibrutinib to starting acalabrutinib was 7.5 months (0.8 to 31.1)

	N=60
No. prior therapies, median (range)	2 (1-10)
Prior therapy, n (%)	
Ibrutinib	60 (100)
Monotherapy	50 (83)
Combination therapy[a]	10 (17)
Anti-CD20[b]	43 (72)
Rituximab	40 (67)
Ofatumumab	9 (15)
Systemic chemotherapy	36 (60)
Alkylator	32 (53)
Nucleoside analog	25 (42)
Alemtuzumab	6 (10)
Lenalidomide	6 (10)
Experimental drug	6 (10)
Idelalisib	2 (3)

[a]Includes ibrutinib + obinutuzumab, ibrutinib + rituximab (n=3), ibrutinib + rituximab + lenalidomide, ibrutinib + ublituximab, rituximab + bendamustine + ibrutinib, monalizumab + ibrutinib, ibrutinib + ofatumumab, and ibrutinib + lenalidomide (n=1 for each). [b]Some patients received both agents.

AE = adverse event; No. = number

Rogers K et al. *Haematol*. 2021;106. doi:10.3324/haematol.2020.272500

ACE-CL-208: Patient Disposition

- At a median follow-up of 34.6 months (1.1 - 47.4), 48% of patients remain on acalabrutinib
  - 75% completed at least one year of acalabrutinib treatment

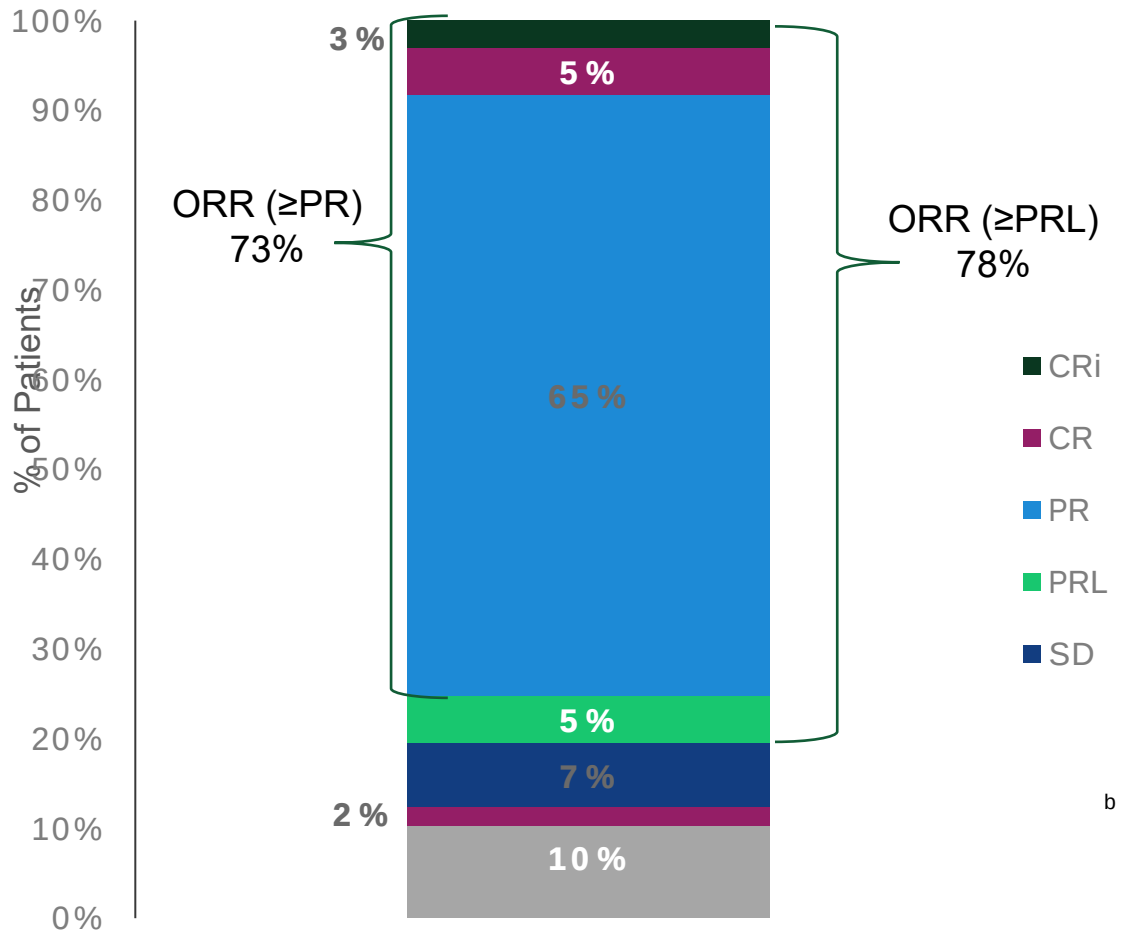
	N=60
Follow-up, median (range), mo	34.6 (1.1-47.4)
On acalabrutinib, n (%)	29 (48)
Discontinued acalabrutinib, n (%)	31 (52)
Disease progression	14 (23)
Adverse event[a]	10 (17)
Patient withdrawal	3 (5)
Physician decision	3 (5)
Other[b]	1 (2)
Deaths on study, n (%)[c]	11 (18)

[a]Adverse events leading to discontinuation were pneumonia (n=2), diarrhea, headache, endometrial cancer, stomatitis, subdural hematoma, cerebrovascular accident. transaminases increase and squamous cell carcinoma of lung (each n=1). Of the 10 patients who discontinued acalabrutinib due to an adverse event, 1 patient discontinued acalabrutinib due to the same AE (diarrhea) that resulted in prior ibrutinib discontinuation. [b]Patient discontinued due to anorexia. [c]Deaths occurred while in follow-up after treatment was discontinued and were due to pneumonia (n=3), Richter transformation (n=3), pulmonary aspergillosis, ventricular fibrillation, multiple organ failure, squamous cell carcinoma of lung, and disease progression (each n=1).

Rogers K et al. *Haematol*. 2021;106. doi:10.3324/haematol.2020.272500

ACE-CL-208: Response to Acalabrutinib[a,b]

- At 34.6 months median follow-up, investigator-assessed ORR (≥PR) was 73% (95% CI: 60, 84), with a 5% CR rate
  - ORR including PRL was 78%
- In the 17 patients with del(17p), ORR (≥PR) was 71% (95% CI: 44, 90)



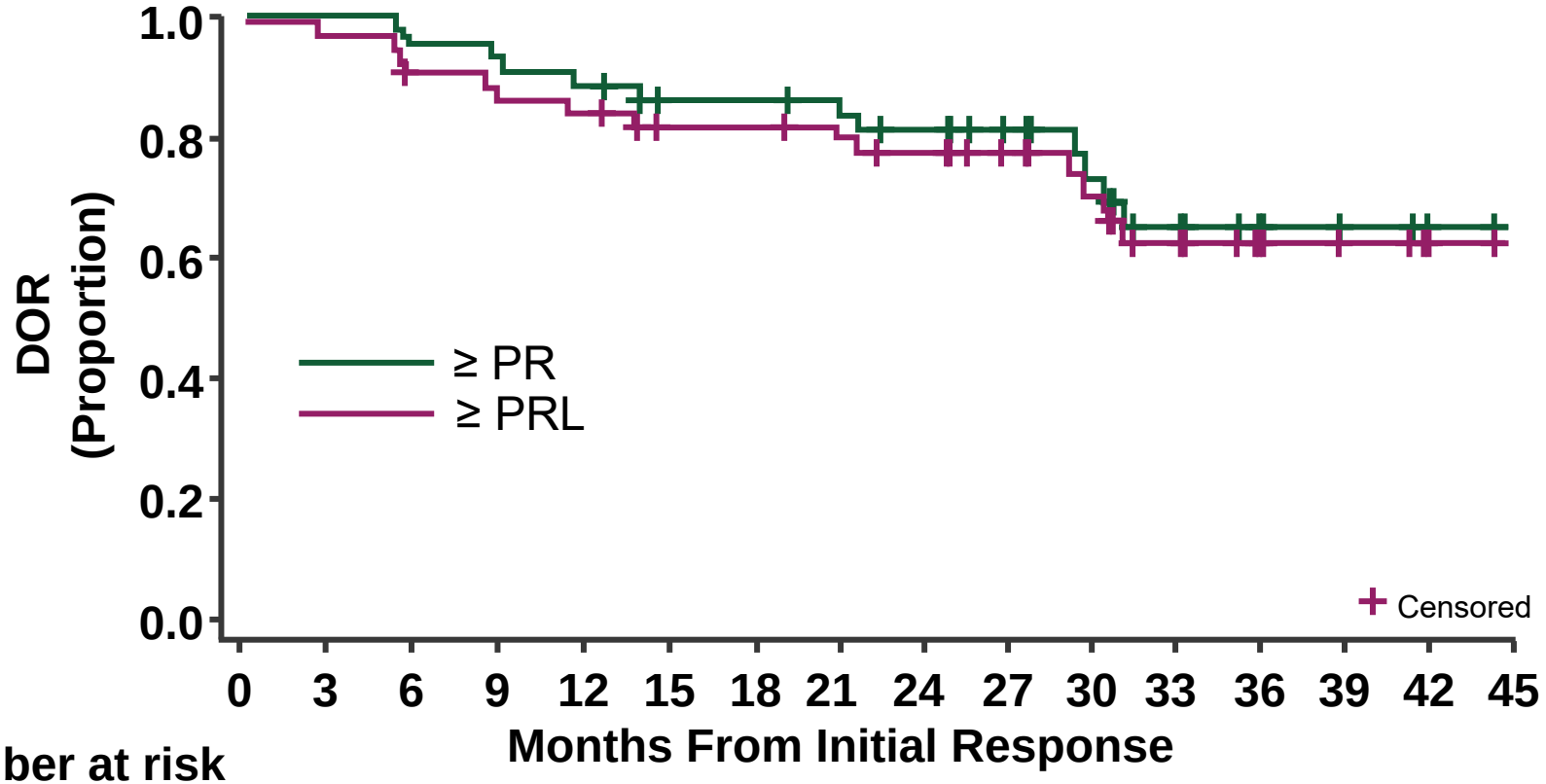
[a]Assessed using iwCLL 2008 criteria. [b]A total of 8 patients were not evaluable (n=6) or not available for response assessment (n=2).

CI = confidence interval; CR = complete response; CRi= complete remission with incomplete bone marrow recovery; iwCLL = International Workshop on Chronic Lymphocytic Leukemia; NA = not applicable; ORR = overall response rate; PD = progressive disease; PR = partial response; PRL = partial response with lymphocytosis; SD = stable disease.

Rogers K et al. *Haematol*. 2021;106. doi:10.3324/haematol.2020.272500

ACE-CL-208: DOR

- The median DOR was not reached



Number at risk

≥ PR	44	44	42	41	39	35	35	33	31	26	19	14	6	3	1	0
≥ PRL	47	46	43	42	40	36	36	34	32	27	20	15	6	3	1	0

	≥ PR	≥ PRL
Median DOR	**NR**	**NR**
24-m DOR	**81.2%** (95% CI: 65.9, 90.2%)	**78.2%** (95% CI: 63.2, 87.6%)
36-m DOR	**65.3%** (95% CI: 45.6, 79.3%)	**63.6%** (95% CI: 45.1, 77.3%)

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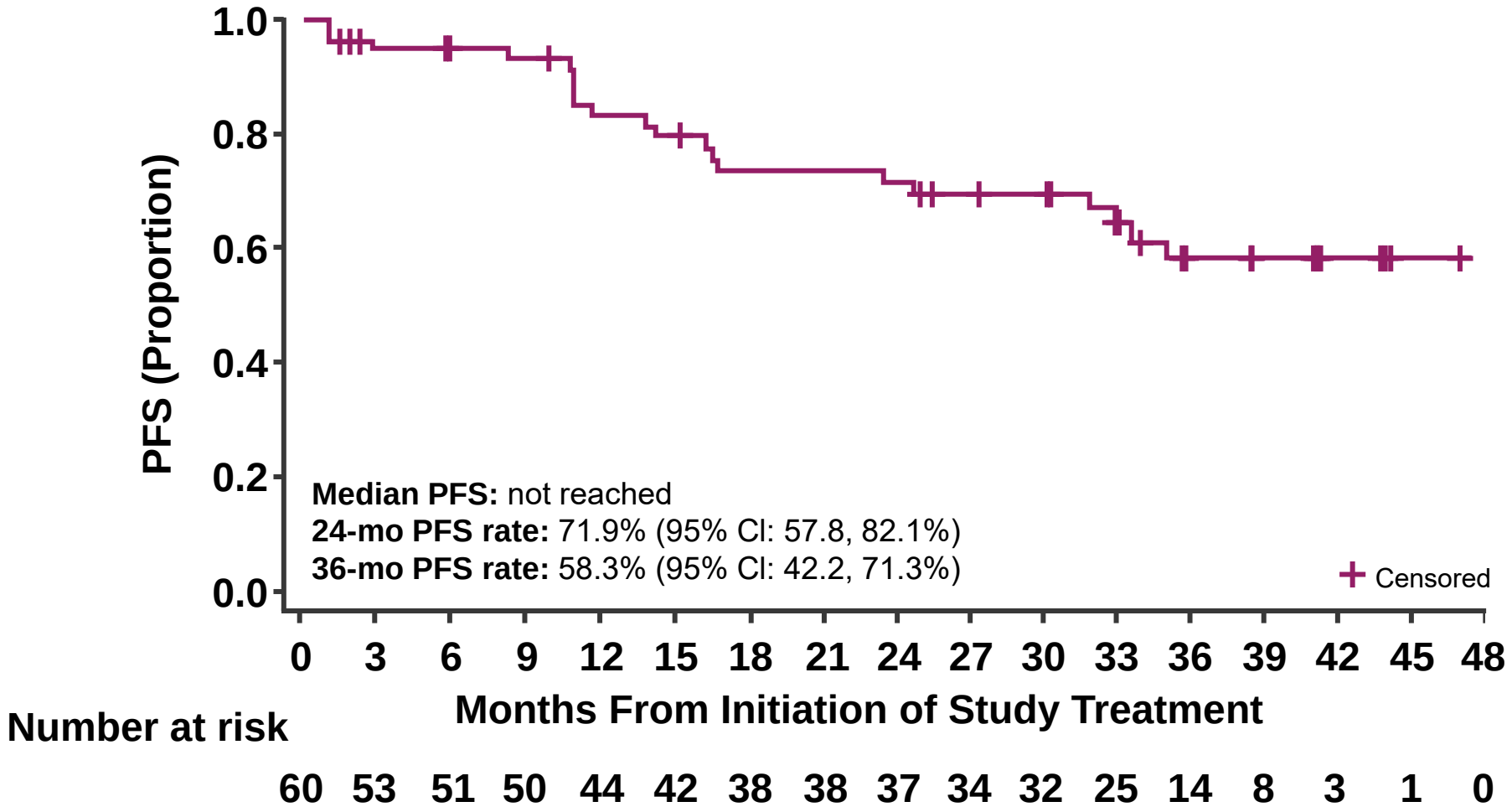
CI = confidence interval; DOR = duration of response; m = month; NR = not reached; PR = partial response; PRL = partial response with lymphocytosis.

Rogers K et al. *Haematol*. 2021;106. doi:10.3324/haematol.2020.272500

ACE-CL-208: PFS

- The median PFS was not reached

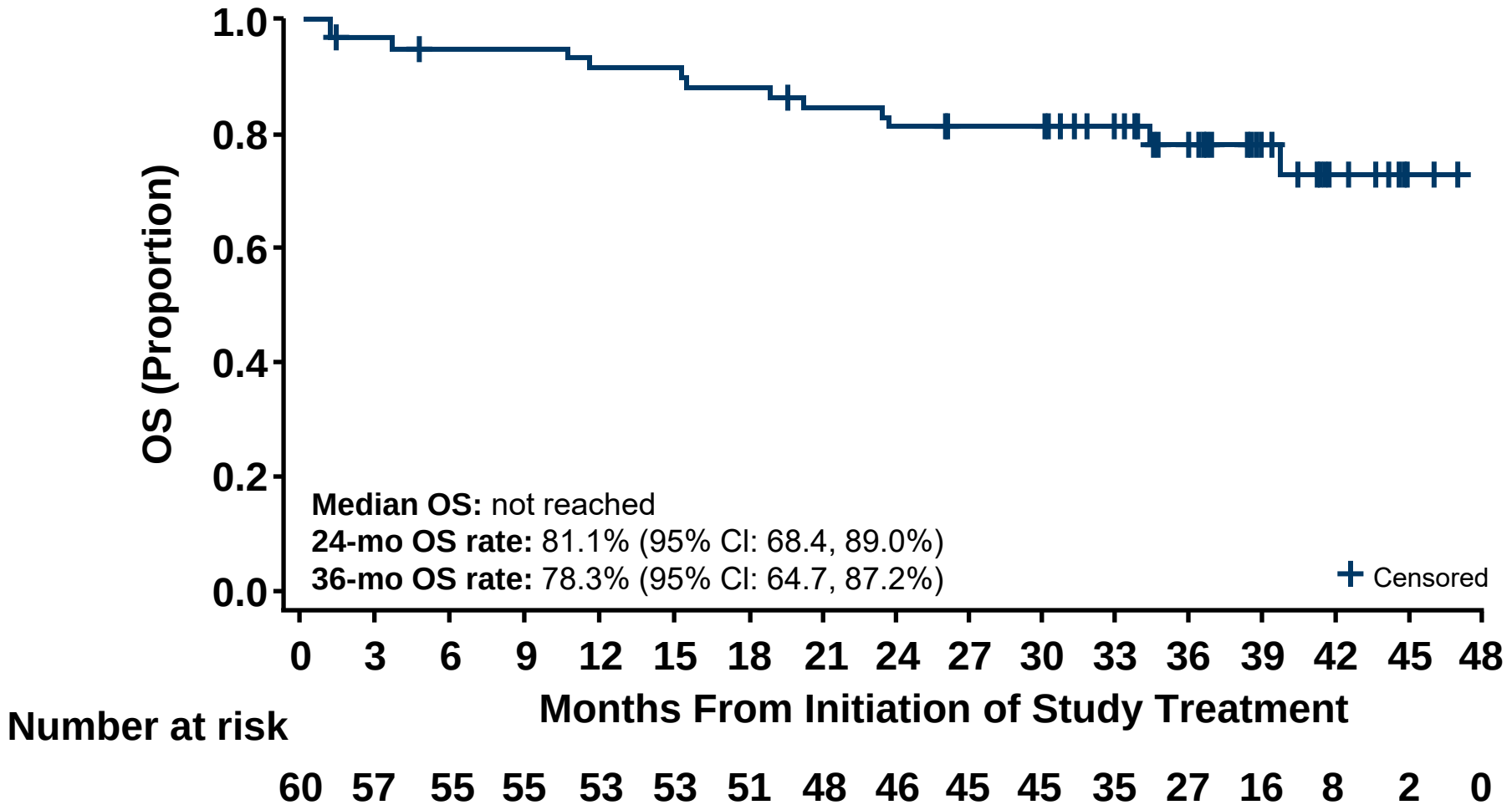


CI = confidence interval; mo = months; PFS = progression-free survival.

Rogers K et al. *Haematol*. 2021;106. doi:10.3324/haematol.2020.272500

ACE-CL-208: OS

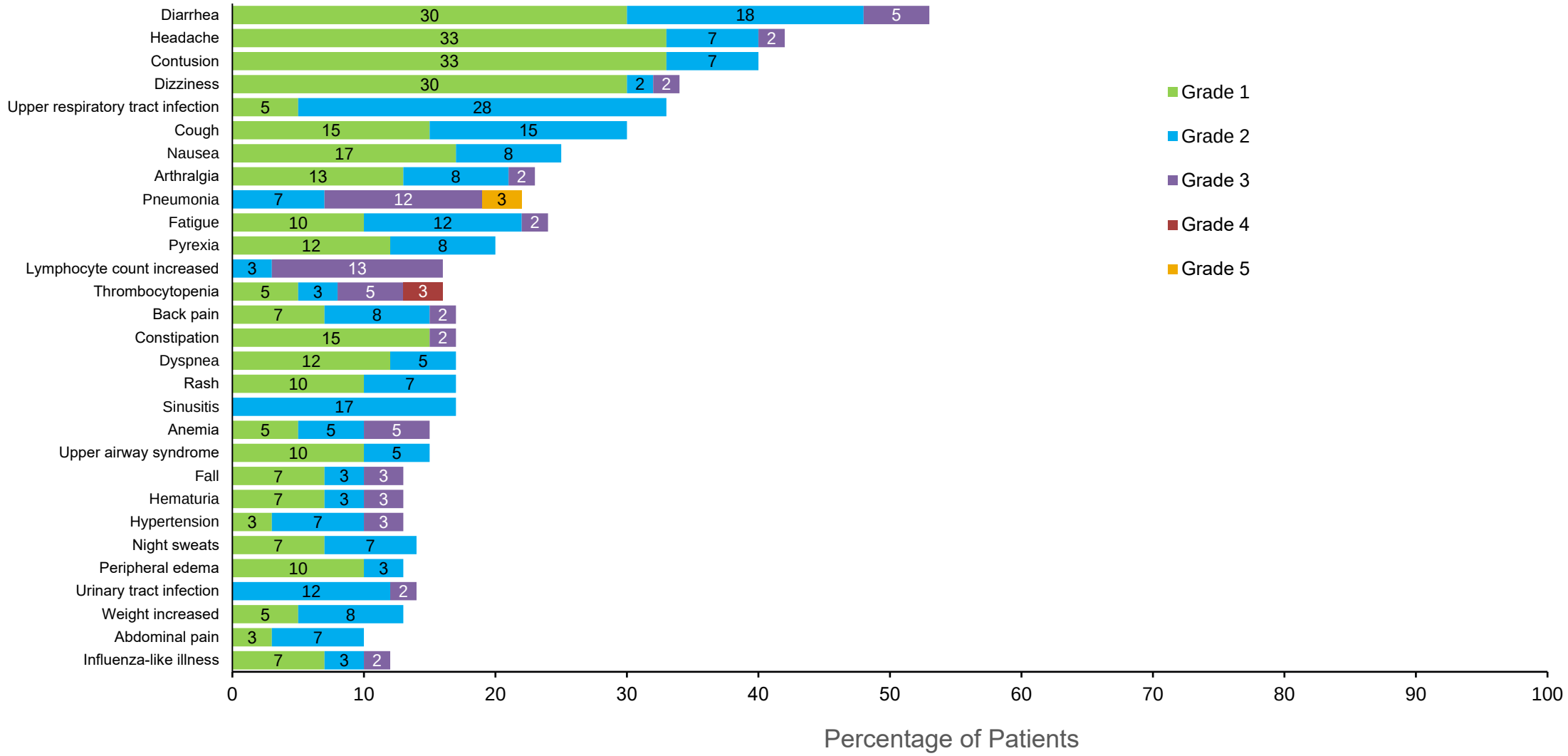
- The median OS was not reached



CI = confidence interval; mo = months; OS = overall survival.

Rogers K et al. *Haematol*. 2021;106. doi:10.3324/haematol.2020.272500

ACE-CL-208: AEs Occurring in >10% of Patients (N=60)[a]



[a]Medical Dictionary for Regulatory Activities preferred terms.
AE = adverse event.
Rogers K et al. *Haematol*. 2021;106. doi:10.3324/haematol.2020.272500

ACE-CL-208: Additional Safety Information

- The most-common grade ≥3 AEs (≥5% of patients) include:
  - Pneumonia (n=9 [15%]), neutropenia (n=7 [12%]), lymphocyte count increased (n=8 [13%]), and thrombocytopenia (n=5 [8%].
- Serious AEs of any grade occurred in 31 patients (52%)
- Ten patients (16.7%) discontinued acalabrutinib due to AEs, which include:
  - Pneumonia (n=2, one G3 and one death), diarrhea (n=1, G2), headache (n=1, G1), endometrial cancer (n=1, G3), stomatitis (n=1, G2), subdural hematoma (n=1, G2), cerebrovascular accident (n=1, G2), transaminases increase (n=1, G4), and squamous cell carcinoma of lung (n=1, G2)

AE = adverse event; G = grade

Rogers K et al. *Haematol*. 2021;106. doi:10.3324/haematol.2020.272500

ACE-CL-208: Recurrence of AEs Commonly Leading to Ibrutinib Discontinuation

- Of the 74 ibrutinib-intolerance AEs in the 60 enrolled patients, 42 (57%) did not recur during acalabrutinib treatment
- Only 24 (40%) patients had recurrence of the same ibrutinib-intolerant AEs (a total of 27 events), yet the majority (67%, n=18/27 events) occurred at a lower grade.
  - 30% (n=8/27 events) of AEs occurred at the same grade.
  - The only AE occurring at higher grade was increased liver function tests (n=1/27 events)

Select AEs that Reoccurred[a]

	Patients Who Discontinued Ibrutinib, n	Median Time to Onset on Ibrutinib (range), days[2]	Acalabrutinib Experience for the Selected AEs			
			Total, n	Lower Grade, n	Same Grade, n	Higher Grade, n
Atrial fibrillation	16	88 (1-1721)	2	2	0	0
Diarrhea	7	26 (2-277)	5	3	2	0
Arthralgia	6	27 (1-956)	2	1	1	0
Rash	6	1 (1-231)	3	3	0	0
Bleeding[b]	6	428 (1-1688)	5	3	2	0
		Total	**17**	**12**	**5**	**0**

Note: Data should be interpreted with caution due to different follow up times and limitations of study design which did not capture all AEs on prior ibrutinib therapy and could have recurred with acalabrutinib.

[a]AE definitions: atrial fibrillation = PT atrial fibrillation + PT atrial flutter; diarrhea = PT diarrhea; arthralgia = PT arthralgia + PT arthritis; rash = any PT containing the word rash; bleeding = all PTs from SMQ hemorrhage terms (excluding laboratory terms). [b]Events categorized as bleeding included ecchymosis, hemorrhage, epistaxis, hematuria, pulmonary hemorrhage, and retinal hemorrhage. All but 1 patient experienced a different type of bleeding event with acalabrutinib compared with ibrutinib.

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SMQ = standardized MedDRA queries.

1. Rogers K et al. *Haematol*. 2021;106. doi:10.3324/haematol.2020.272500 *2*. Rogers K et al. Presented at: ASCO; May 31-June 4, 2019; Chicago, IL. Abs 7530

ACE-CL-208: Summary[2]

- For patients enrolled into ACE-CL-208, the median duration of prior ibrutinib therapy was 5.5 months (range, <1 to 56)
  - Common AEs (>2 patients) that led to discontinuation of prior ibrutinib therapy were atrial fibrillation/flutter, diarrhea, rash, and arthralgia
- Although all patients discontinued prior ibrutinib due to AEs, only 17% discontinued acalabrutinib due to AEs after 35 months of follow-up
- An ORR of 73% was observed in this population of ibrutinib pretreated R/R CLL patients
- Most AEs (64%) causing early discontinuation of ibrutinib did not reoccur while on acalabrutinib treatment with a majority (18/27 events) occurred at a lower grade.
- The most-common grade ≥3 AEs (≥5% of patients) while on acalabrutinib include:
  - Pneumonia (n=9 [15%]), neutropenia (n=7 [12%]), lymphocyte count increased (n=8 [13%]), and thrombocytopenia (n=5 [8%].

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AE = adverse event; CR = complete response; ORR = overall response rate; R/R= relapsed refractory.

Rogers K et al. *Haematol*. 2021;106. doi:10.3324/haematol.2020.272500

CLINICAL TRIALS AND OBSERVATIONS | MAY 14, 2019

Acalabrutinib monotherapy in patients with chronic lymphocytic leukemia who are intolerant to ibrutinib

Clinical Trials & Observations

Farrukh T. Awan, Anna Schuh, Jennifer R. Brown, Richard R. Furman, John M. Pagel, Peter Hillmen, Deborah M. Stephens, Jennifer Woyach, Elena Bibikova, Prista Charuworn, Melanie M. Frigault, Ahmed Hamdy, Raquel Izumi, Bolan Linghu, Priti Patel, Min Hui Wang, John C. Byrd

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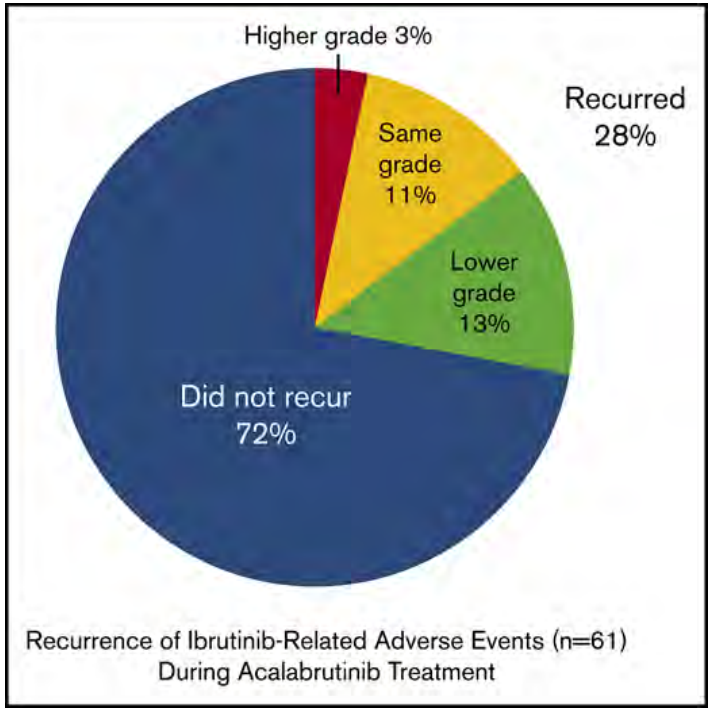
Blood Adv (2019) 3 (9): 1553–1562.

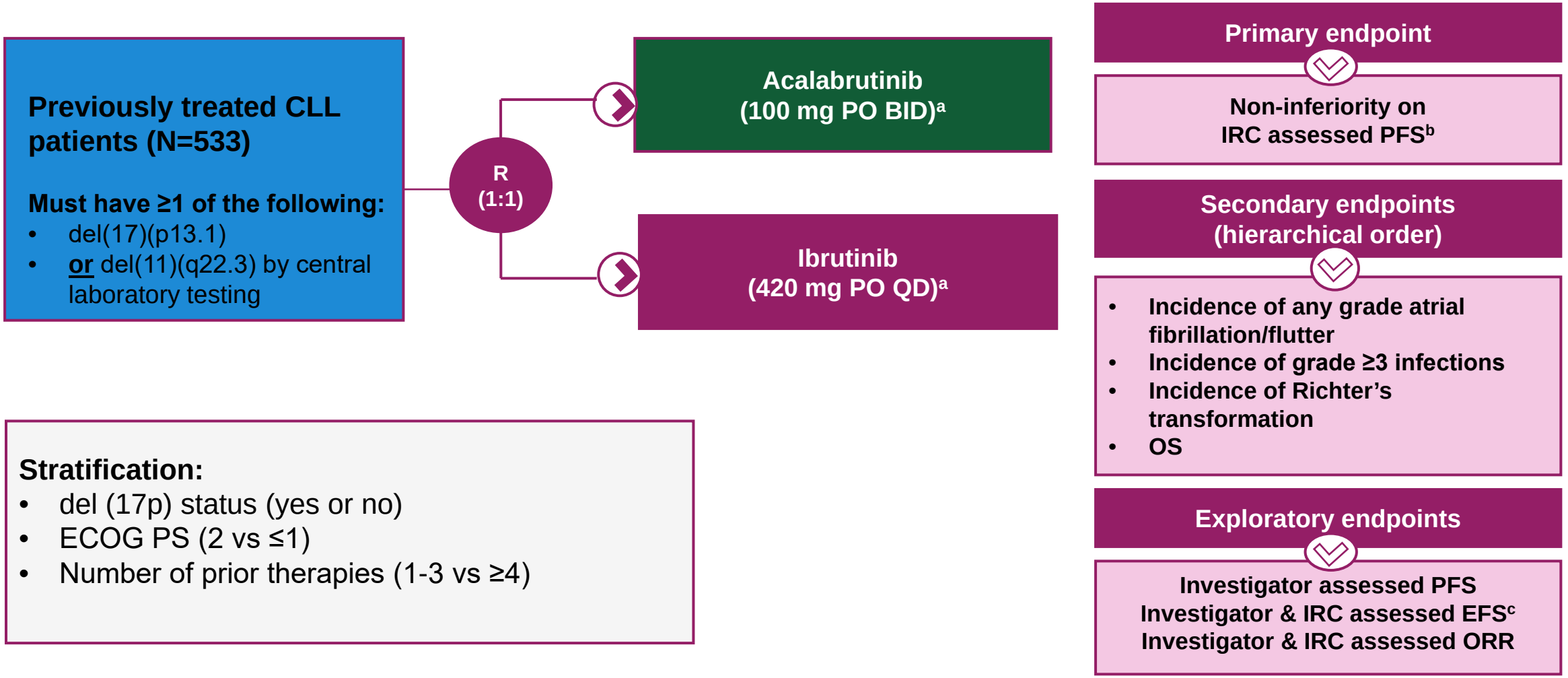
https://doi.org/10.1182/bloodadvances.2018030007

Article history



Recurrence of Ibrutinib-Related Adverse Events (n=61) During Acalabrutinib Treatment

Study Design ELEVATE R/R CLL (ACE-CL-006): Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase



[a]Continued until disease progression or unacceptable toxicity. [b]Conducted after enrollment and accrual of ~250 IRC-assessed PFS events. [c]defined as the time from date of randomization to the date of first disease progression, any-cause death, start of subsequent anticancer therapy, or discontinuation of treatment due to adverse events

BID = twice daily; CLL = chronic lymphocytic leukemia; ECOG PS = eastern cooperative oncology group performance status; EFS = event free survival; IRC = independent review committee; OS = overall survival; PFS = progression-free survival; PO = orally; R = randomization; QD = once daily.

Byrd JC et al. *J. Clin. Oncol.* 2021. https://doi.org/10.1200/JCO.21.01210.

Safety Summary

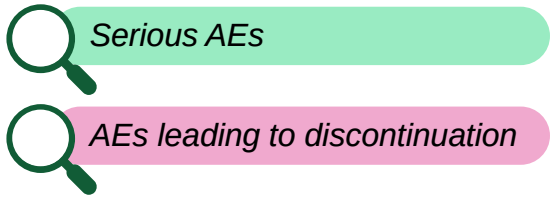
- Treatment discontinuations due to AE's were less frequent with acalabrutinib than ibrutinib
- Duration of treatment exposure was 38.3 (0.3–55.9) for acalabrutinib and 35.5 (0.2–57.7) for ibrutinib

Summary of adverse events n (%)	Acalabrutinib (n=266)			Ibrutinib (n=263)		
	Any grade	Grade 1–2	Grade ≥3	Any grade	Grade 1–2	Grade ≥3
Any	260 (97.7)	77 (28.9)	183 (68.8)	256 (97.3)	59 (22.4)	197 (74.9)
Serious	143 (53.8)	17 (6.4)	126 (47.4)	154 (58.6)	16 (6.1)	138 (52.5)
Led to drug discontinuation (any grade)	39 (14.7)	3 (1.1)	36 (13.5)	56 (21.3)	20 (7.6)	36 (13.7)

Values are reported as n (%) unless stated otherwise.

[a]Includes deaths occurring within 30 days of last dose; deaths occurring after the start of subsequent anticancer therapy were not included in the assessment of deaths within 30 days of last dose, regardless of time after last dose.
AE = adverse event.

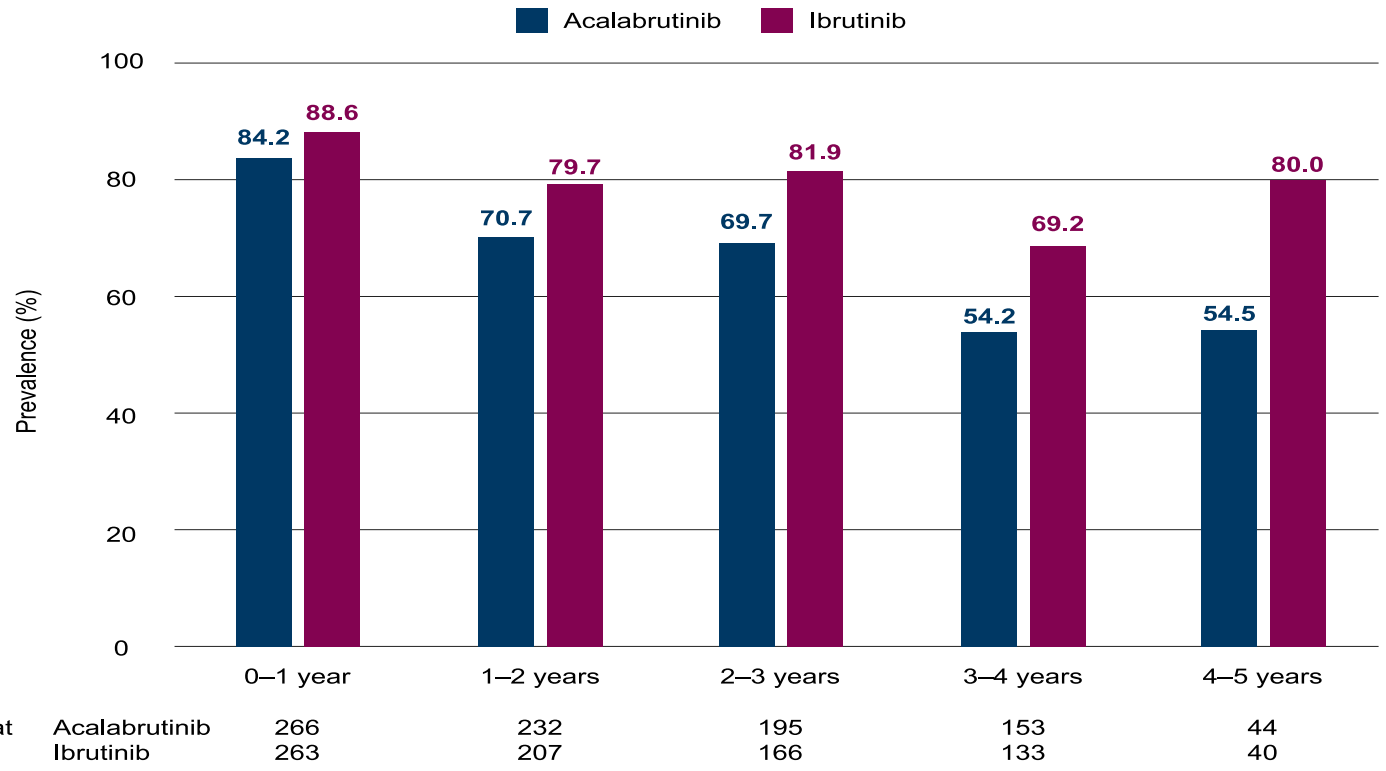
Byrd JC et al. *J. Clin. Oncol.* 2021. https://doi.org/10.1200/JCO.21.01210.



Overall Event of Clinical Interest Prevalence Was Lower With Acalabrutinib Across Most Yearly Intervals

- Overall, the rate of onset of first any grade ECI was lower with acalabrutinib vs ibrutinib (HR 0.81; 95% CI 0.68–0.97)
- Any-grade ECI of atrial fibrillation/flutter, hypertension, interstitial lung disease/pneumonitis and bleeding events were statistically less frequent with acalabrutinib while; the rates for cardiac events, infection and SPMs excluding NMSC were not statistically significant between acalabrutinib and ibrutinib.

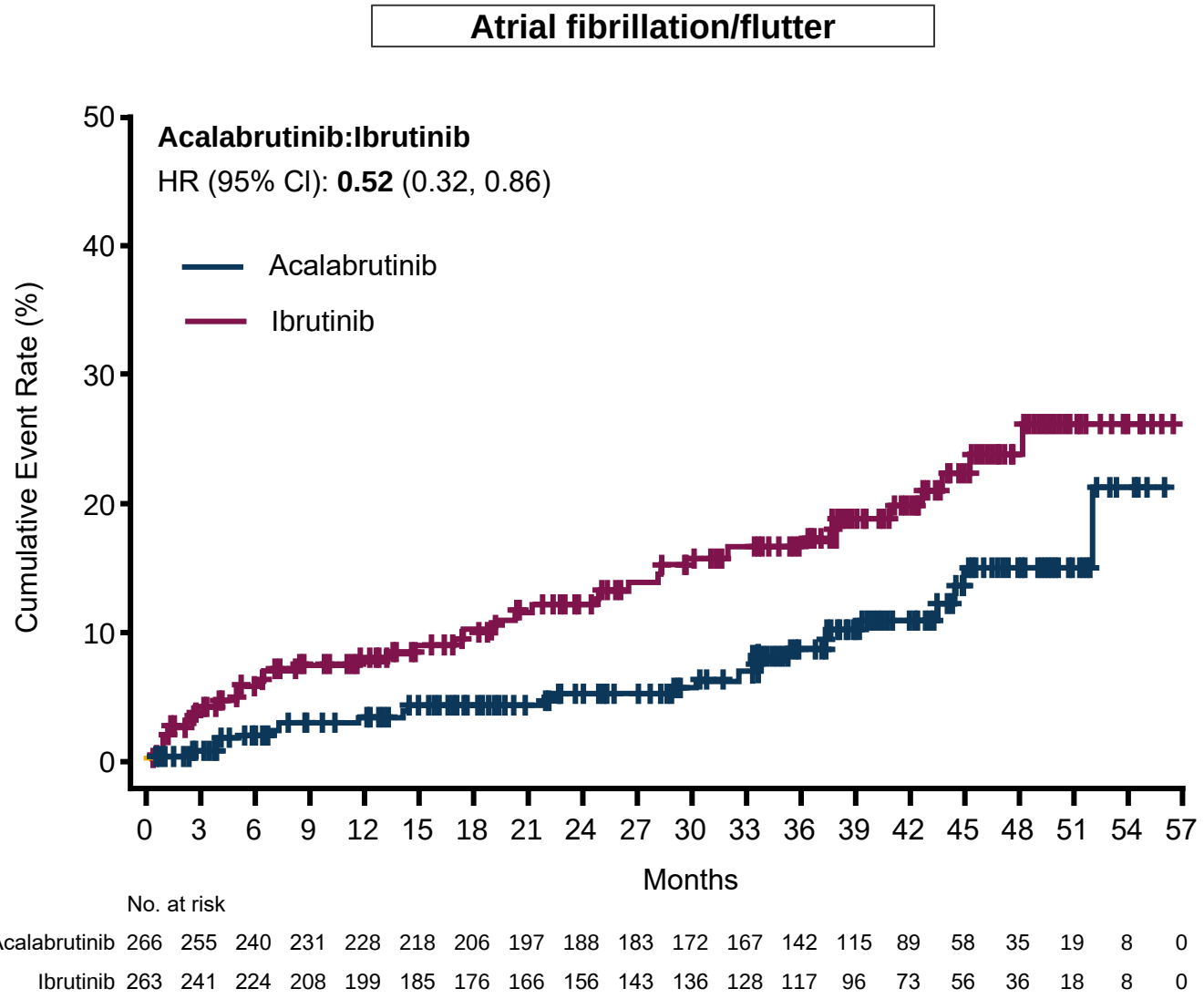
	Acalabrutinib (n=266)	Ibrutinib (n=263)
ECIs (%)	Any Grade	Any Grade
Atrial fibrillation	9.4	16
Hypertension	9.4	23.2
Bleeding events	38	51.3
ILD/pneumonitis	2.6	6.5
Cardiac events	24.1	30
Infections	78.2	81.4
SPMs excluding NMSC	9	7.6



CI = confidence interval; ECI = events of clinical interest; ILD = interstitial lung disease; HR = hazard ratio; NMSC = non-melanoma skin cancer; SPMs = secondary primary malignancies.

Hillmen P et al. Abstract Presented at: iwCLL Virtual Annual Meeting; September 17-20, 2021.

Lower Cumulative Incidences of Any Grade Atrial Fibrillation/Flutter with Acalabrutinib



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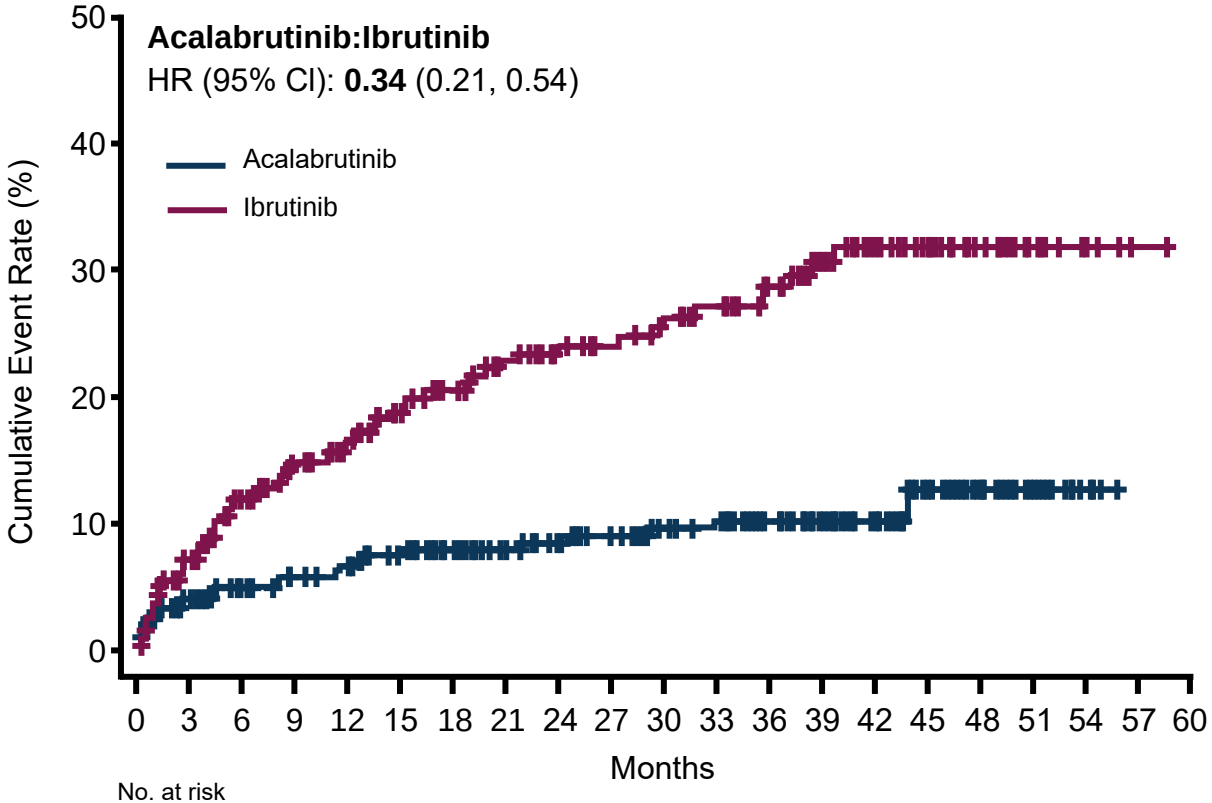
CI = confidence interval; HR = hazard ratio.

Byrd JC et al. *J. Clin. Oncol.* 2021. https://doi.org/10.1200/JCO.21.01210.

Lower Cumulative Incidences of Any Grade Hypertension and Cardiac Events with Acalabrutinib

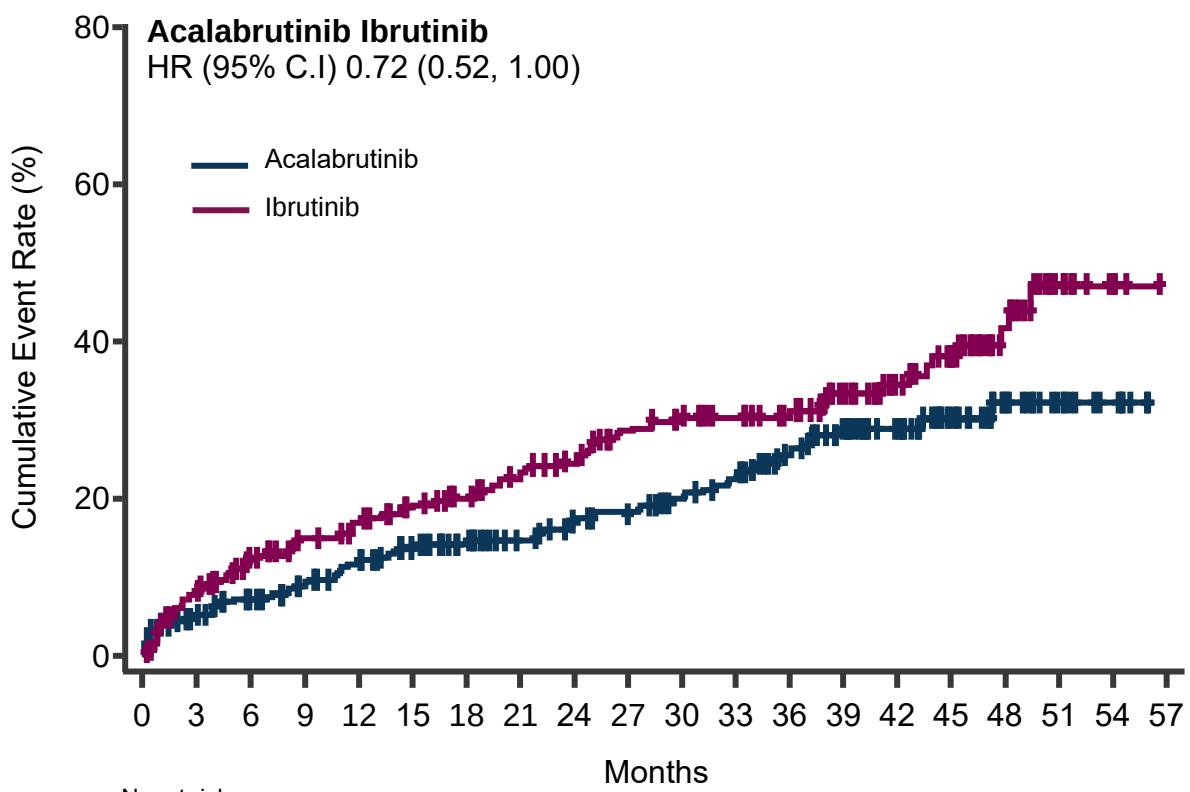
Hypertension



No. at risk

Acalabrutinb	266	246	229	220	216	205	193	184	176	169	157	153	136	114	89	60	34	17	5	0	0
Ibrutinib	263	230	203	183	170	153	141	130	120	111	104	98	85	69	48	40	27	15	7	1	0

Cardiac events



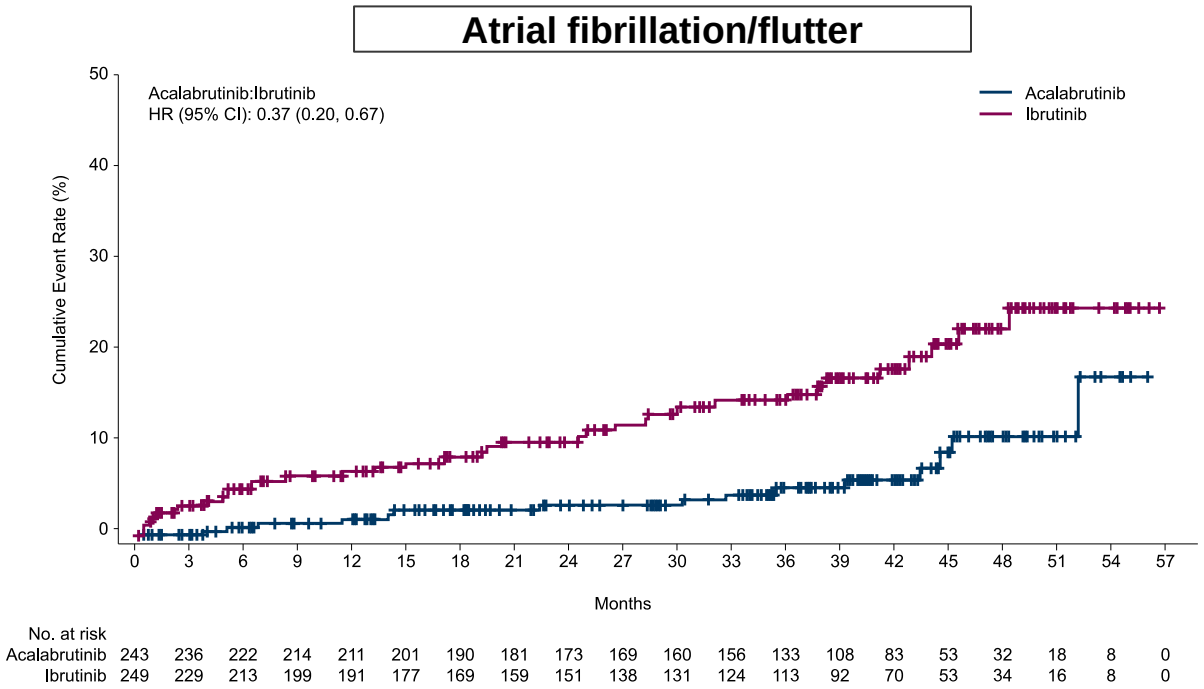
No. at risk

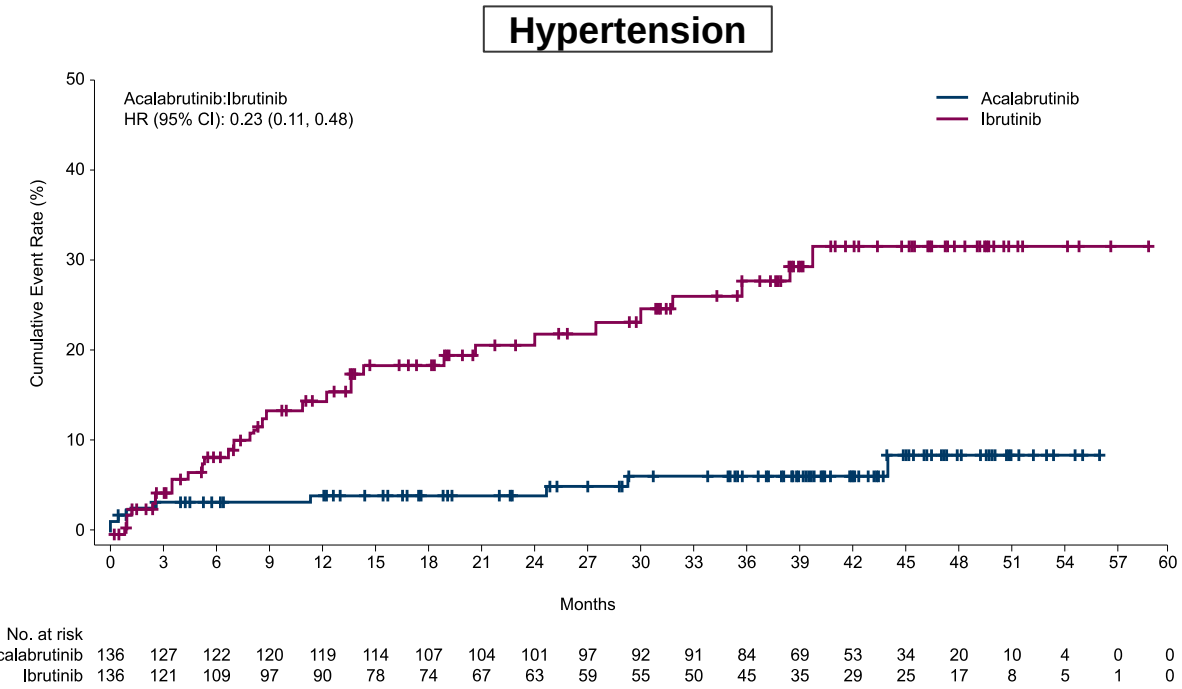
Acalabrutinib	266	245	231	220	210	199	188	178	167	162	150	143	118	94	74	49	28	15	7	0	
Ibrutinib	263	234	212	194	185	170	161	149	138	123	116	109	99	78	59	46	26	10	3	0	

Y axis has been truncated for better visualization
CI = confidence interval; HR = hazard ratio.
Byrd JC et al. *J. Clin. Oncol.* 2021. https://doi.org/10.1200/JCO.21.01210.

Cumulative Incidence of Afib/Flutter and HTN in Patients Without Prior History

- Cox proportional-hazards analysis of new-onset afib/flutter and HTN showed rate reductions of 63% and 77%, respectively, favoring acalabrutinib





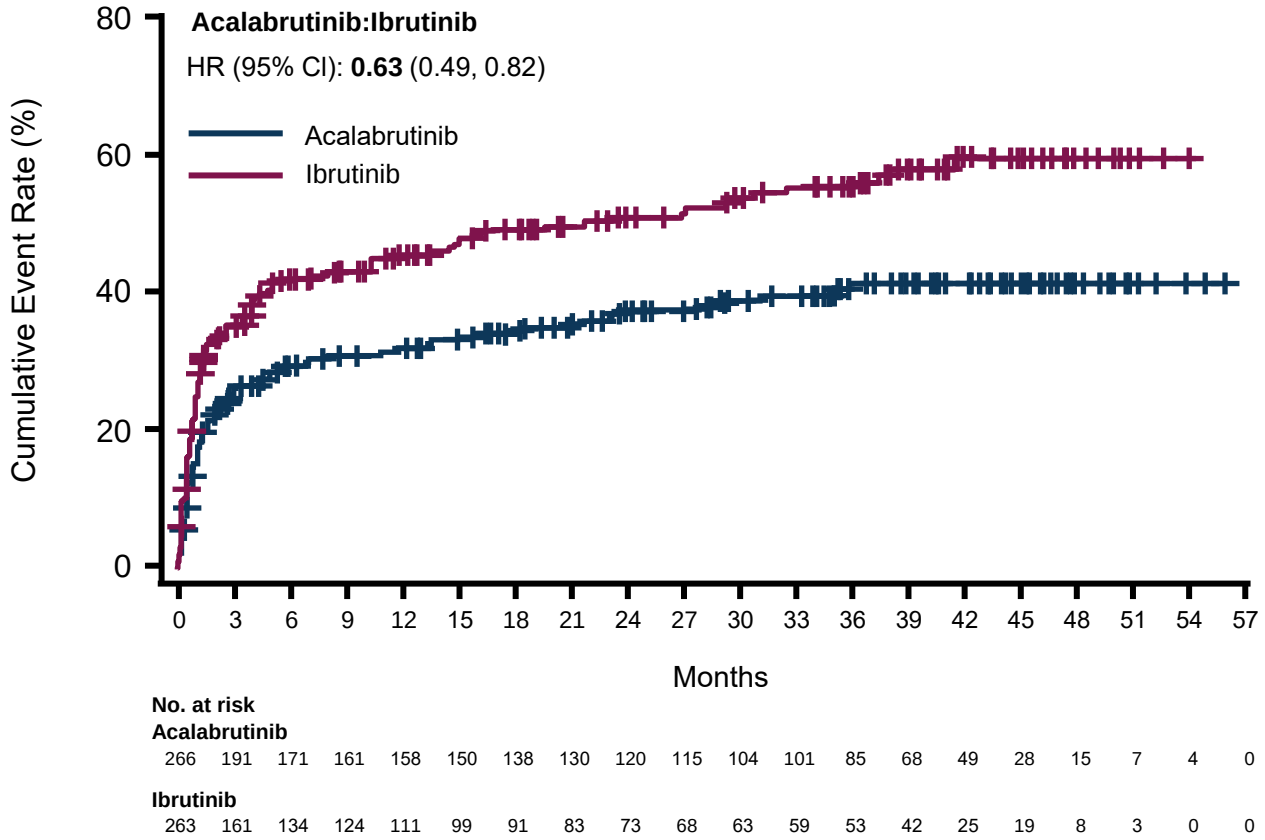
Afib = atrial fibrillation; HTN = hypertension.

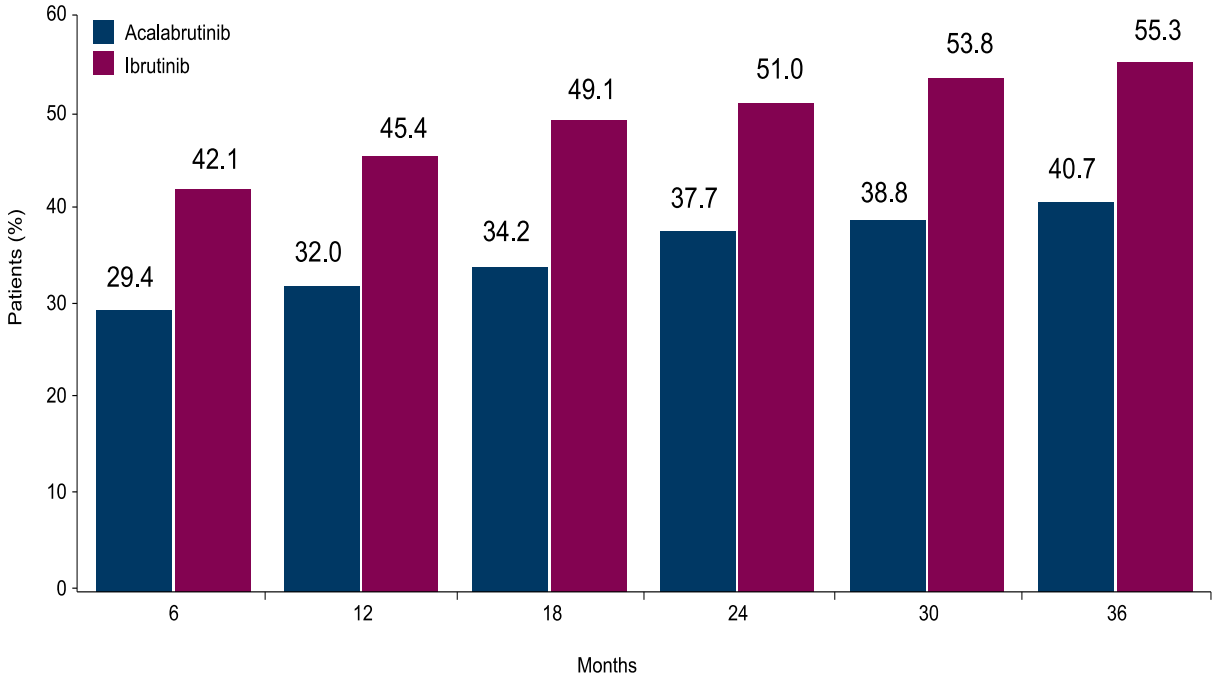
Seymour JF et al. Poster Presented at: ASH; December 11-14, 2021; Atlanta, GA. Abs 3721.

Safety: Cumulative Incidence of Any-Grade Bleeding[1,2]

- Lower cumulative incidences of any grade bleeding with acalabrutinib

Bleeding events





CI = confidence interval; HR = hazard ratio.

1. Byrd JC et al. *J. Clin. Oncol.* 2021. https://doi.org/10.1200/JCO.21.01210. 2. Seymour JF et al. Poster Presented at: ASH; December 11-14, 2021; Atlanta, GA. Abs 3721.

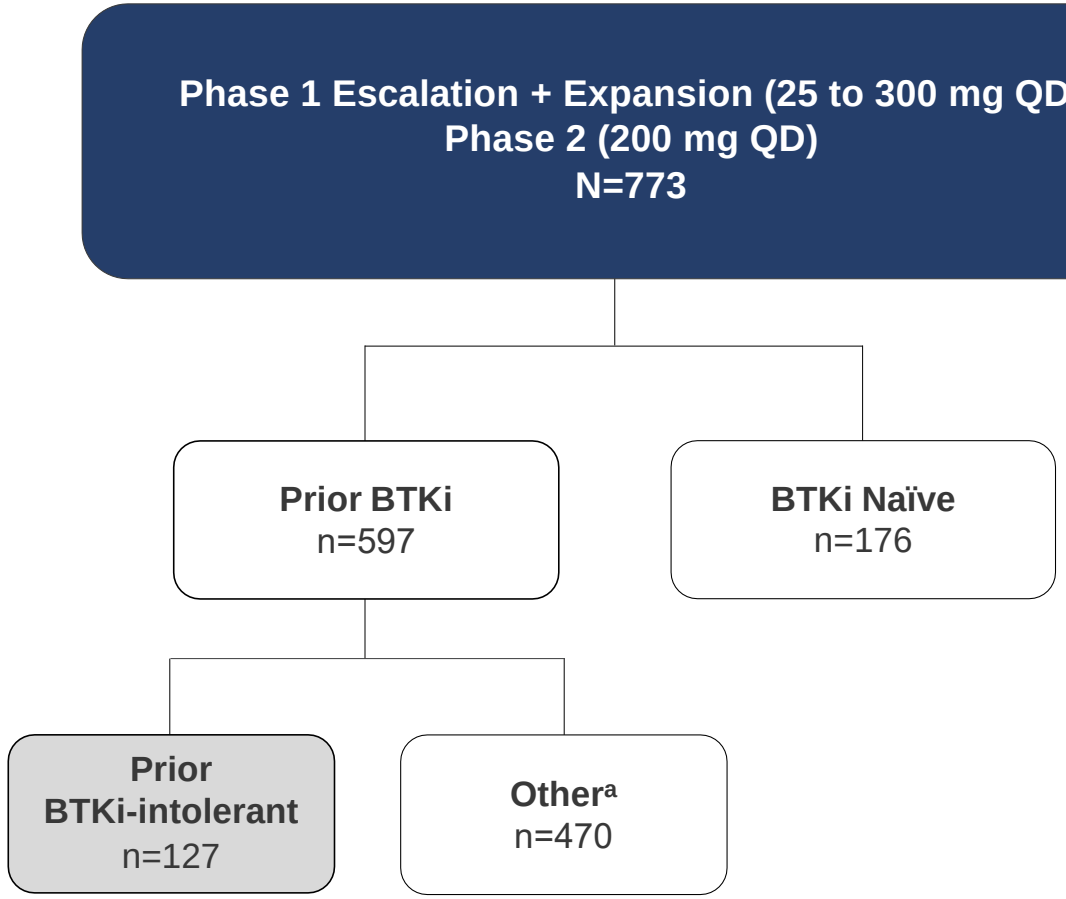
Summary

- At a median follow-up of 40.9 months, acalabrutinib was non-inferior to ibrutinib on the primary endpoint of IRC-assessed PFS (HR: 1.00 [95% CI: 0.79, ¹ ?7])[1]
- Acalabrutinib demonstrated lower frequencies of common AEs, grade ≥3 AEs, SAEs, and lower treatment discontinuations due to AEs overall[1]
  - The incidence of grade ≥3 events were lower with acalabrutinib in high-risk patients with del(17p)[2]
  - Time to treatment discontinuation overall was longer with acalabrutinib[2]
  - Acalabrutinib demonstrated a lower incidence, exposure-adjusted incidence, and exposure-adjusted time with events of CV-related toxicities, such as atrial fibrillation/flutter, hypertension, and bleeding compared with ibrutinib[3]
  - Overall, the total exposure-adjusted time with event for all any-grade AEs was 37% higher with ibrutinib[3]
- Cardiovascular events were less common with acalabrutinib vs ibrutinib[1]
  - Atrial fibrillation/flutter events (any grade) were significantly less frequent with acalabrutinib vs ibrutinib (9.4% vs 16%; p=0.02)
  - Hypertension also was less frequent with acalabrutinib (9.4% vs 23.2%)
  - Cumulative incidences of hypertension and afib/flutter were lower with acalabrutinib in patients without a prior history of these events[3]
- ECIs overall, as well as hypertension and atrial fibrillation/flutter were also less prevalent each year with acalabrutinib[2]
- Among other secondary endpoints:[1]
  - Incidence of grade ≥3 infections and Richter transformation were comparable between arms
  - Median OS was not reached in either arm
- These results demonstrate that acalabrutinib is better tolerated and has similar efficacy to ibrutinib in patients with previously treated CLL

AE = adverse events; CI = confidence interval; HR = hazard ratio; IRC = independent review committee; PFS = progression free survival; OS = overall survival; SAE = severe adverse events; vs = versus.

1. Byrd JC et al. *J. Clin. Oncol.* 2021. https://doi.org/10.1200/JCO.21.01210. 2. Hillmen P et al. Abstract Presented at: iwCLL Virtual Annual Meeting; September 17-20, 2021. 3. Seymour JF et al. Poster Presented at: ASH; December 11-14, 2021; Atlanta, GA. Abs 3721.

Phase 1/2 BRUIN Study. Safety and Efficacy of Pirtobrutinib in Patients with Hematological Malignancies that Have Failed a Prior BTKi



Prior BTKi-intolerant Population

- BTKi intolerance defined as prior BTKi discontinuation due to persistent/recurrent AEs[b]
  - Could have received ≥1 BTKi
- Eligibility permitted with:
  - Cardiac comorbidities including prior atrial fibrillation[c]
  - Ongoing anti-coagulation/anti-platelet treatment[d]

A data cutoff date of 29 July 2022 was used for all analyses. [a]Other includes reasons for discontinuation such as prior BTKi resistance, patient decision, physician decision, or unknown reason. [b]AEs were determined by the investigator. [c]Including due to prior BTKi. [d]Except warfarin.

Patient Characteristics

Characteristics	Prior BTKi-Intolerant (n=127)
Disease types, n (%)	
CLL/SLL	78 (61)
MCL	21 (17)
WM	16 (13)
RT	8 (6)
FL/MZL	4 (3)
Age, median (range), years	70 (42-87)
<50	2 (2)
50-64	36 (28)
65-74	53 (42)
75-84	33 (26)
≥85	3 (2)
Male, n (%)	81 (64)
ECOG PS, n (%)	
0	70 (55)
1	48 (38)
2	9 (7)
Number of prior lines of systemic therapy, median (range)	3 (1-11)
Number of prior lines of BTKi, n (%)	
1	81 (64)
2	34 (27)
≥3	12 (9)
Time since initial diagnosis to first dose of pirtobrutinib, median (range), years	10 (1-29)
Time since end of last prior BTKi discontinued for toxicity to first pirtobrutinib dose, median (range), years	2 (0-8)

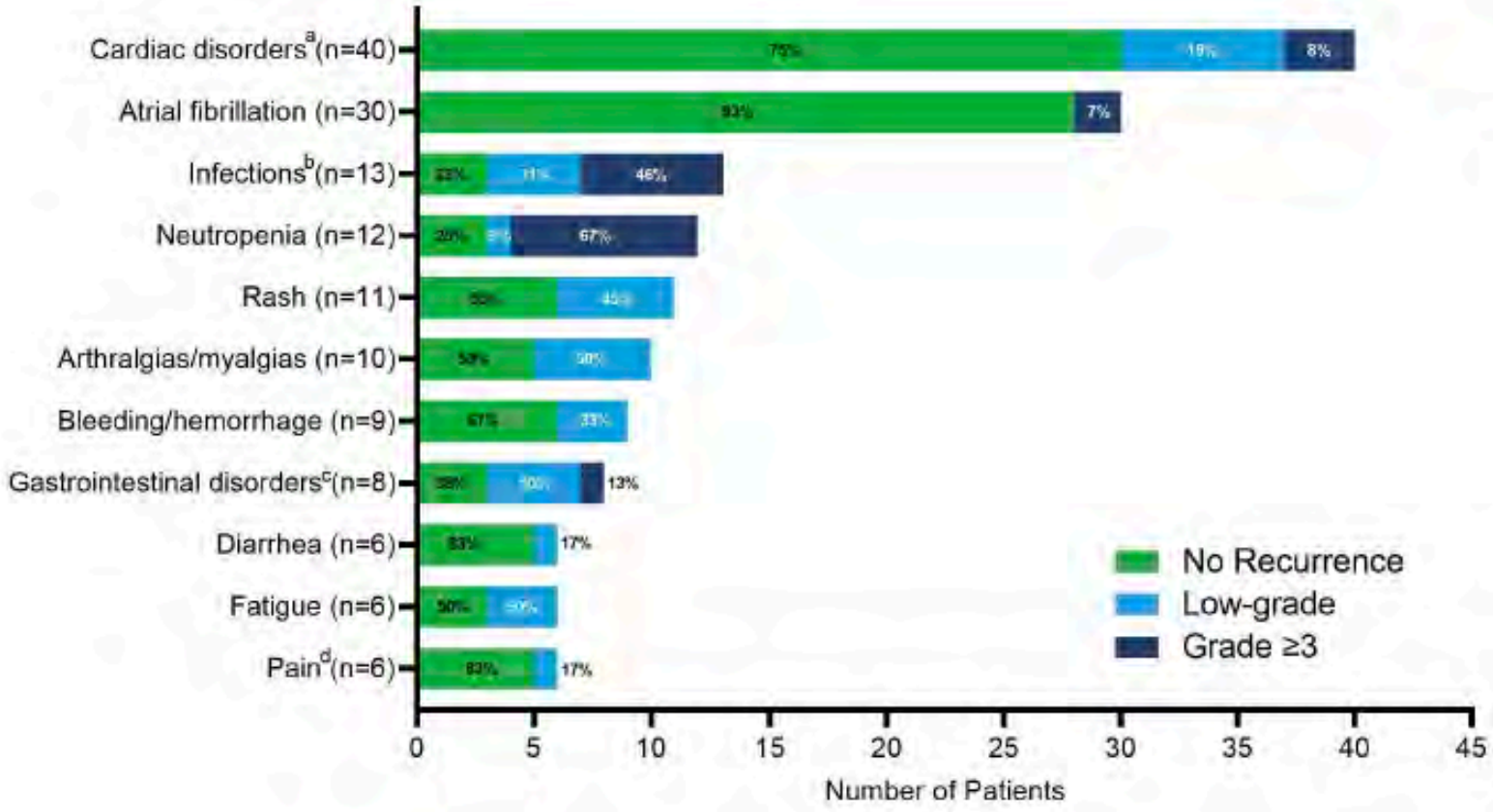
Characteristics	Prior BTKi-Intolerant (n=127)
Prior systemic therapy, n (%)	
BTKi	127 (100)
Anti-CD20 antibody	108 (85)
Chemotherapy	97 (76)
BCL2 inhibitor	34 (27)
PI3K agent	24 (19)
Immunomodulator	13 (10)
Stem cell transplant	9 (7)
Autologous	7 (6)
Allogeneic	2 (2)
CAR-T	9 (7)
Other systemic therapy	35 (28)
Prior BTKi therapy with toxicity as reason for discontinuation, n (%)	
Ibrutinib	120 (95)
Acalabrutinib	9 (7)
Nemtabrutinib	4 (3)
Zanubrutinib	3 (2)
DTRMWXHS-12	1 (1)

AEs Leading to Discotinuation of Prior cBTKIa

AE	Any cBTKi n=127	AEs by Prior cBTKi, n (%) Ibrutinib n=120	Acalabrutinib n=9	Zanubrutinib n=3
Cardiac disorders	40 (32)	39 (33)	1 (11)	-
Atrial fibrillation	30 (24)	30 (25)	-	-
Infection	13 (10)	13 (11)	-	-
Neutropenia[b]	12 (9)	9 (8)	1 (11)	1 (33)
Rash	11 (9)	9 (8)	-	-
Arthralgias/myalgias	10 (8)	9 (8)	2 (22)	-
Bleeding/hemorrhage[c]	9 (7)	8 (7)	1 (11)	-
Gastrointestinal disorders	8 (6)	7 (6)	1 (11)	-
Diarrhea	6 (5)	5 (4)	1 (11)	-
Fatigue	6 (5)	5 (4)	-	1 (33)
Pain	6 (5)	6 (5)	1 (11)	-
Unknown	5 (4)	3 (3)	1 (11)	-
Depression	2 (2)	1 (1)	1 (11)	-
Headache	2 (2)	-	1 (11)	-
Joint effusion	1 (1)	-	-	1 (33)

[a]Most common (≥5% for any one drug) AE categories leading to prior cBTKi discontinuation are shown; an individual patient may be counted in more than one AE category. [b]Neutropenia is an aggregate of neutropenia and neutrophil count decreased in all instances of neutropenia in this display. [c]Included hemorrhage, hematoma, hematuria, and intracranial hemorrhage.

Pirtobrutinib TEAEs Recurring in the Same Patient as Those Leading to Prior BTKIs Discontinuation



- No patient who discontinued a prior BTKi due to a TEAE had to discontinue pirtobrutinib for the same TEAE
- Of the 62 patients who discontinued pirtobrutinib, the majority did so for progressive disease (55%, n=34)
  - Discontinuations for pirtobrutinib related AEs occurred in 7 patients (1 each) including: COVID-19 pneumonia, myalgia, neutropenia, platelet count decreased, rash maculo-papular, skin necrosis, and staphylococcal sepsis
  - Other reasons for non-PD, non-pirtobrutinib related AE discontinuations included: AEs unrelated to treatment (n=13, including 7 deaths), intercurrent illness (n=1), alternative treatment per investigator (n=2), consent withdrawal (n=4), and other (n=1)
- Median relative dose intensity of pirtobrutinib was 97% (IQR, 92-100)
- 93% of patients received ≥1 pirtobrutinib dose at or above the RP2D of 200 mg daily

Most common TEAE categories that led to discontinuation of prior cBTKi are shown; an individual patient may be counted in more than one category. [a]Cardiac disorders include atrial fibrillation. [b]Prior discontinuation infection types were not specified for most patients, so any infection recurrence was investigated. Eleven grade ≥3 infections in the 6 patients with an infection recurrence included: pneumonia (n=6, including COVID-19 pneumonia, n=2 and fungal pneumonia, n=1), bacteremia, diarrhea, salmonellosis, septic shock, and COVID-19 (n=1 each). [c]Gastrointestinal disorders include diarrhea. [d]1 had recurrence of pain in the same site, 3 had new/different pain, and 2 had no pain; no patient discontinued pirtobrutinib for pain.

Shah NN et al, ASH2022

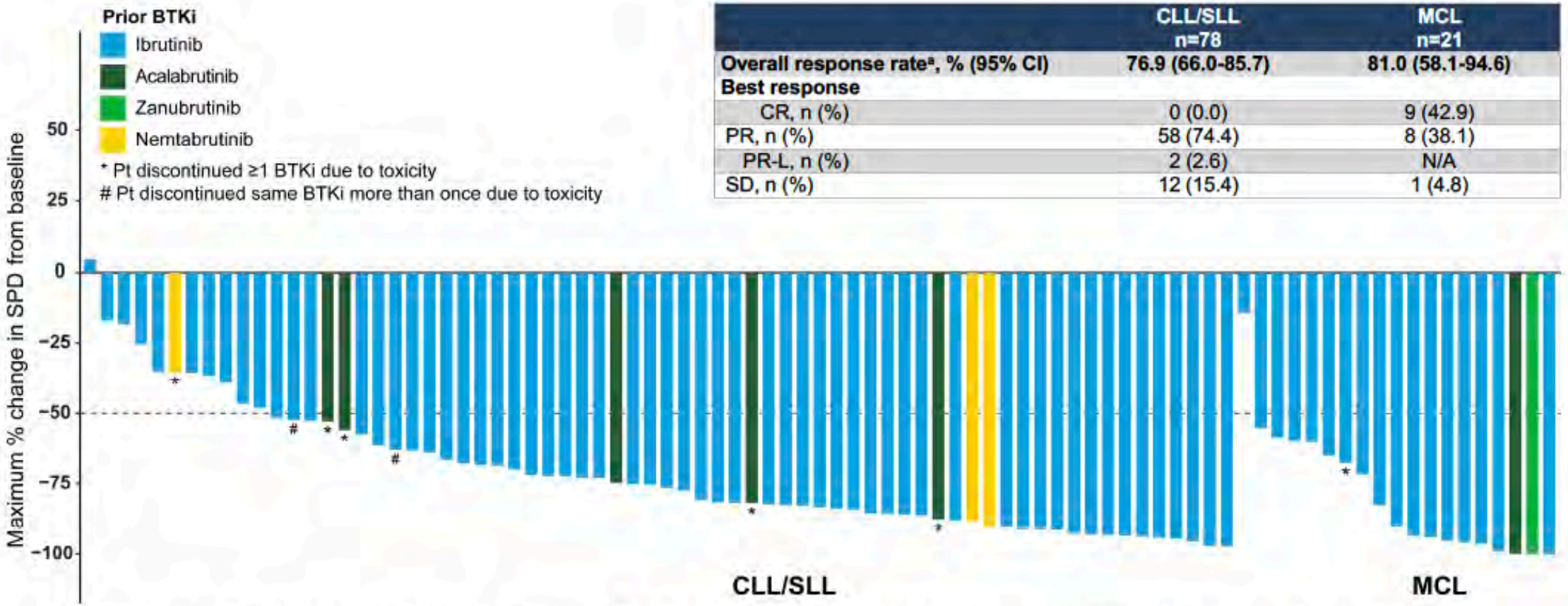
Pirtobrutinib Safety Profile

	Treatment-related AEs, %			
	Any Grade		Grade ≥3	
AE	All Doses and Patients (N=773)	BTKi-Intolerant (n=127)	All Doses and Patients (N=773)	BTKi-Intolerant (n=127)
Fatigue	9.3%	9.4%	0.8%	1.6%
Diarrhea	9.3%	12.6%	0.4%	0.8%
Neutropenia	14.7%	21.3%	11.5%	17.3%
Contusion	12.8%	22.0%	0.0%	0.0%
Cough	2.3%	4.7%	0.0%	0.0%
Covid-19	1.3%	0.0%	0.0%	0.0%
Nausea	4.7%	4.7%	0.1%	0.0%
Dyspnea	3.0%	5.5%	0.1%	0.0%
Anemia	5.2%	6.3%	2.1%	2.4%
AEs of Special Interest[a]	**All Doses and Patients (N=773)**	**BTKi-Intolerant (n=127)**	**All Doses and Patients (N=773)**	**BTKi-Intolerant (n=127)**
Bruising[b]	15.1%	26.8%	0.0%	0.0%
Rash[c]	6.0%	8.7%	0.4%	0.8%
Arthralgia	3.5%	4.7%	0.0%	0.0%
Hemorrhage/hematoma[d]	4.0%	4.7%	0.6%	0.8%
Hypertension	3.4%	3.1%	0.6%	0.0%
Atrial fibrillation/flutter[e,f]	0.8%	0.8%	0.1%	0.0%

- Median time on treatment for the overall population was 10 months and for the BTKi-intolerant population was 15 months
- Discontinuations due to TRAEs occurred in 2.6% (n=20) of overall and 6% (n=7) of BTKi-intolerant patients
- Dose reductions due to TRAEs occurred in 4.5% (n=35) of overall and 9% (n=11) of BTKi-intolerant patients

[a]AEs of special interest are those that were previously associated with cBTKis. [b]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [c]Aggregate of all preferred terms including rash. [d]Aggregate of all preferred terms including hematoma or hemorrhage. [e]Aggregate of atrial fibrillation and atrial flutter. [f]The 1 atrial fibrillation/atrial flutter TRAE in the BTKi-intolerant population occurred in a patient without a prior medical history of atrial fibrillation.

Pirtobrutinib Efficacy in Patients Previously Intolerant to BTKi

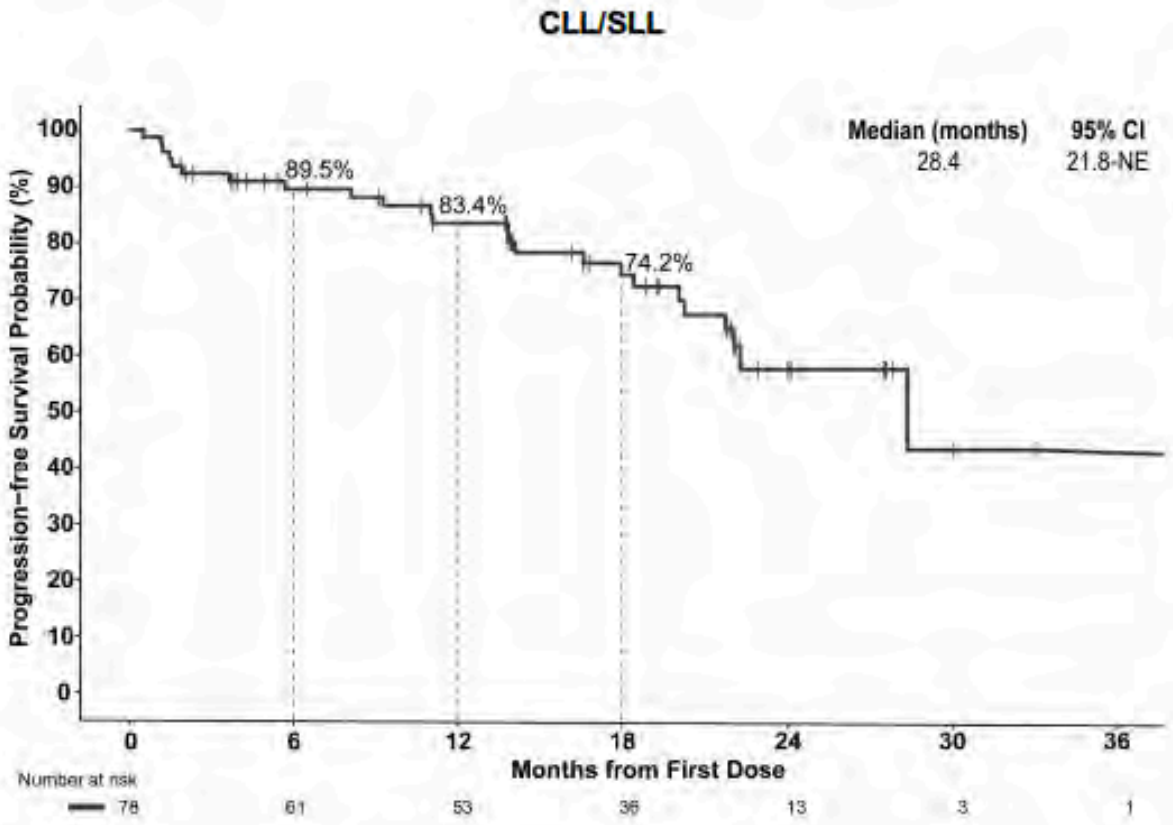


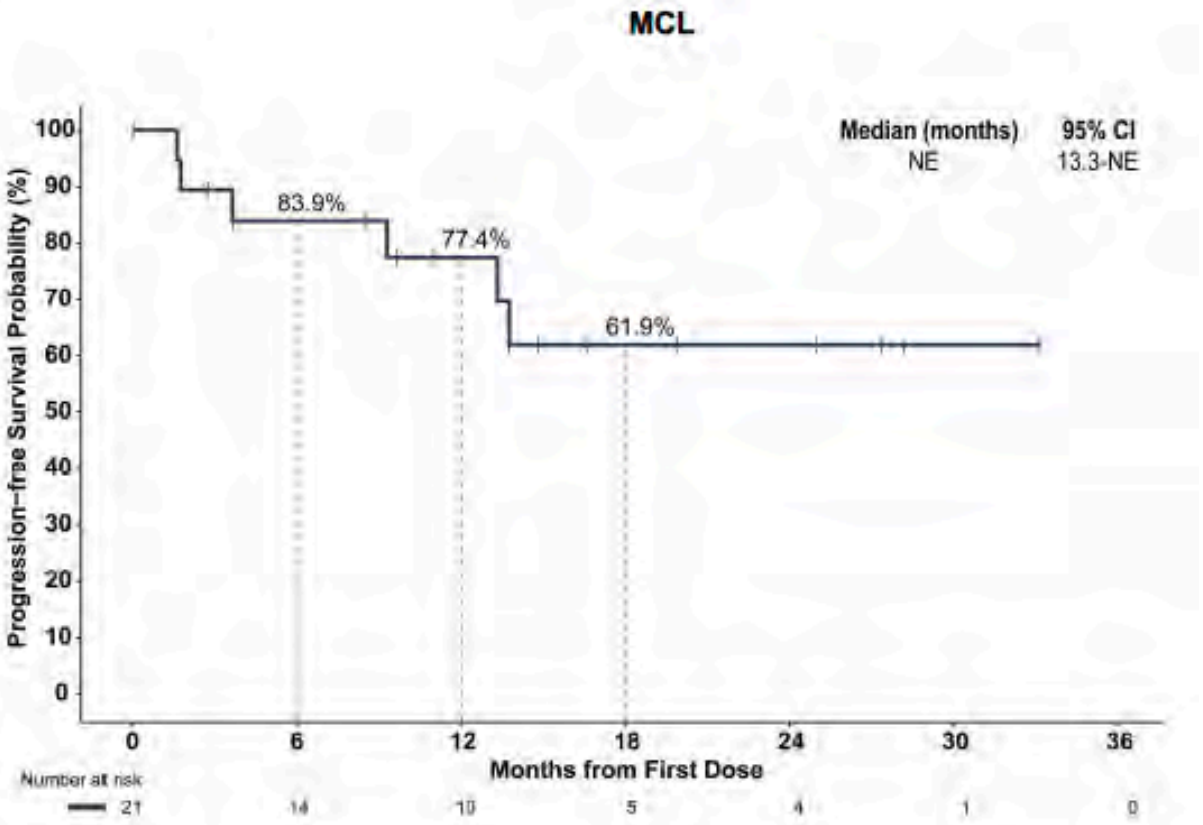
	CLL/SLL n=78	MCL n=21
Overall response rate[a], % (95% CI)	**76.9 (66.0-85.7)**	**81.0 (58.1-94.6)**
Best response		
CR, n (%)	0 (0.0)	9 (42.9)
PR, n (%)	58 (74.4)	8 (38.1)
PR-L, n (%)	2 (2.6)	N/A
SD, n (%)	12 (15.4)	1 (4.8)

- Pirtobrutinib exhibited promising efficacy across B-cell malignancies among patients who experienced intolerance to prior BTKi

[a]Response was assessed by investigator based on iwCLL 2018 or Lugano 2014 criteria for CLL/SLL and MCL, respectively.

Progression Free Survival in Patients Previously Intolerant to BTKi





- Median OS was not estimable for CLL/SLL or MCL
- 18-month OS rate: 84.1% (95% CI, 72.9%-90.9%) for CLL/SLL; 72.4% (95% CI, 45.6%-87.6%) for MCL

Shah NN et al, ASH2022

Conclusions

- Pirtobrutinib monotherapy was safe and well tolerated in patients with B-cell malignancies with documented intolerance to prior BTKi therapy
  - This included patients on anticoagulation and with prior or active atrial fibrillation
- Most patients did not experience high-grade recurrence of AEs that led to discontinuation of prior BTKi
  - Among those who did, none discontinued pirtobrutinib because of this AE
- Pirtobrutinib was effective in patients intolerant to BTKi
- Overall, these data suggest patients who have been intolerant to other BTKi may receive benefit from pirtobrutinib

Thank you!

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Challenging treatment scenarios: resistance to BTK inhibitors

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UNIVERSITY of DEBRECEN

NCCN Guidelines on CLL / SLL

- The NCCN recommendations in CLL, regardless of del(17p) or TP53 mutation status, are acalabrutinib +/- obinutuzumab (meaning obinutuzumab is option) and venetoclax + obintuzumab (obinutuzumab is not optional) and zanubriutinib.

FIRST-LINE THERAPY: CLL/SLL without del(17p)/TP53 mutation

Preferred regimens	Other recommended regimens	Useful in certain circumstances
• Acalabrutinib ± obinutuzumab (category 1) • Venetoclax + obinutuzumab (category 1) • Zanubrutinib (category 1)	• Ibrutinib (category 1) • Bendamustinei + anti-CD20 mAb • Chlorambucil + obinutuzumab • Obinutuzumab • High-dose methylprednisolone (HDMP) + rituximab or obinutuzumab (category 2B; category 3 for patients <65 y without significant comorbidities) • Ibrutinib + obinutuzumab (category 2B) • Ibrutinib + rituximab (category 2B) • Ibrutinib + venetoclax (category 2B)	• (consider for IGHV-mutated CLL in patients age <65 y without significant comorbidities) • FCR (fludarabine, cyclophosphamide, rituximab)

FIRST-LINE THERAPY:CLL/SLL with del(17p)/TP53 mutation (alphabetical by category). CIT is not recommended since del(17p)/TP53 mutation is associated with low response rates

Preferred regimens	Other recommended regimens
• Acalabrutinib ± obinutuzumab • Venetoclax + obinutuzumab • Zanubrutinib	• Alemtuzumab ± rituximab • HDMP + rituximab • Ibrutinib • Obinutuzumab • Ibrutinib + venetoclax (category 2B)

William G. Wierda; Jennifer Brown; Jeremy S. Abramson; *et al*. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma. Version 2.2023. *NCCN*. January 25, 2023(https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf).

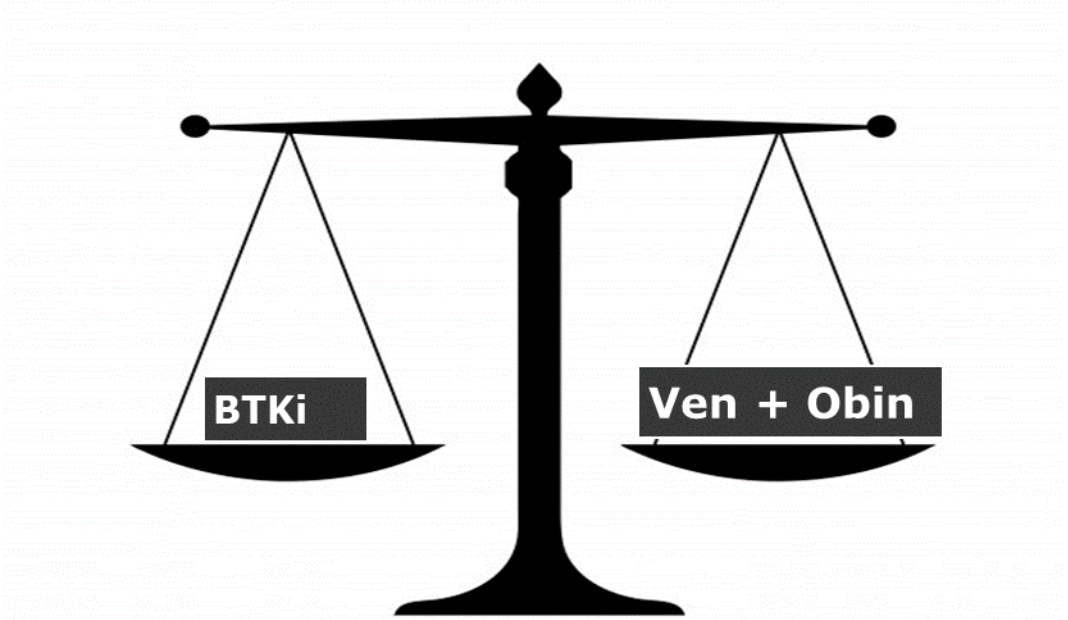
Frontline BTKi versus venetoclax + obinutuzumab

BTK inhibitors:

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

BCL-2 inhibitors:

- Potential for 1 year time-limited therapy
- No known cardiac or bleeding risks
- Less concern for long term adherence
- Potential for cost-saving if 1 year of therapy is durable



Elizabeth A. Brem, Susan O'Brien. Is a BTKi or BCL2i preferable for first "novel" therapy in CLL? The case for BTKis. *Blood Adv* 2022; 6 (4): 1361–1364. DOI: https://doi.org/10.1182/bloodadvances.2019001204

NCCN Guidelines on WALDENSTRM MACROGLOBULINEMIA/ LYMPHOPLASMACYTIC LYMPHOMA (WM/LPL)

- In WM for most patients, rituximab plus chemotherapy is preferred. However, continuous therapy with a BTK inhibitor is also an appropriate alternative.
- Some people prefer to reserve BTK inhibitors for the treatment of relapsed or refractory WM.

PRIMARY THERAPY FOR WALDENSTRM MACROGLOBULINEMIA/ LYMPHOPLASMACYTIC LYMPHOMA. Order of regimens is alphabetical and does not indicate preference

Preferred regimens	Other recommended regimens
• Bendamustine/rituximab • Bortezomib/dexamethasone/ rituximab • Ibrutinib ± rituximab (category 1) • Zanubrutinib (category 1)	• Bendamustine • Carfilzomib/rituximab/ dexamethasone • Ixazomib/rituximab/ dexamethasone • Rituximab • Rituximab/cyclophosphamide/ dexamethasone • Rituximab/cyclophosphamide/ prednisone

Shaji K. Kumar; Natalie S. Callander; Kehinde Adekola; *et al*. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma. Version 1.2023. *NCCN*. July 6, 2022 (https://www.nccn.org/professionals/physician_gls/pdf/waldenstroms.pdf).

Current Treatment Landscape in Mantle Cell Lymphoma

Induction Therapy

- **Candidate for HDT/ASCT**
  - Consider aggressive regimens
- **Ineligible for HDT/ASCT**
  - Consider less-aggressive regimens

Second-line + Subsequent Therapy

Preferred Regimens

- BTKi
  - Acalabrutinib
  - Ibrutinib ± rituximab
  - Zanubrutinib
- Lenalidomide + rituximab (if BTKi is contraindicated)

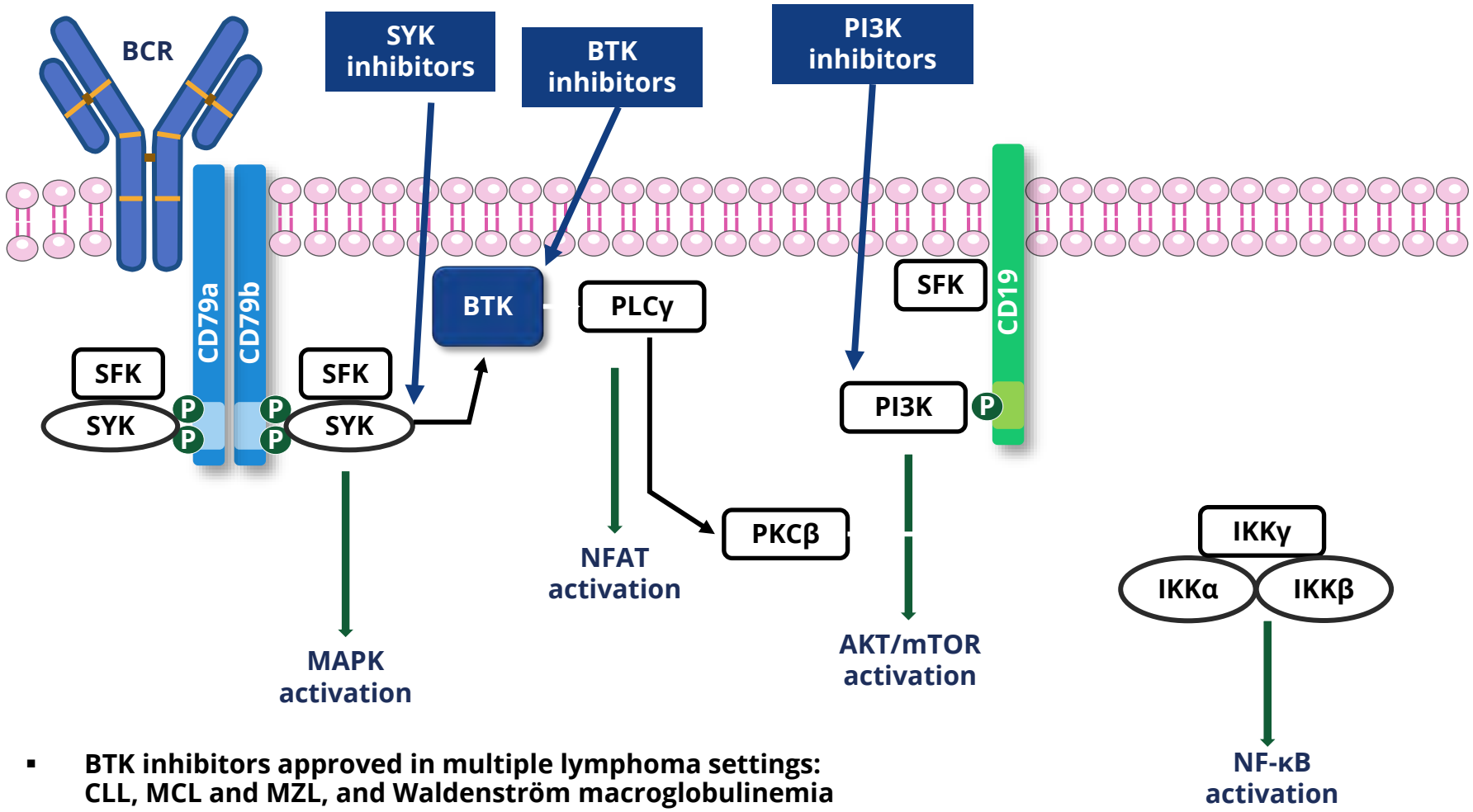
Third-line Therapy

- **CAR T-Cell Therapy**
  - Brexu-cel

Andrew D. Zelenetz, Jeremy S. Abramson, Leo I. Gordon, *et al*. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): B-Cell Lymphomas. Version 2.2023. *NCCN*. February 8, 2023 (https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf).

BTK in B-Cell Malignancies

- BCR pathway plays role in growth, proliferation, and survival of normal and malignant B-cells
- BTK is essential enzyme in BCR signaling pathway
- Inhibition of BTK leads to downstream mitigation of cell growth, proliferation, adhesion, migration, and survival of malignant B-cells



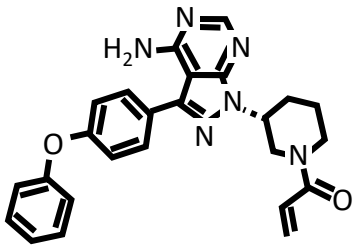
- **BTK inhibitors approved in multiple lymphoma settings: CLL, MCL and MZL, and Waldenström macroglobulinemia**

Young RM, Staudt LM. Targeting pathological B cell receptor signalling in lymphoid malignancies. *Nat Rev Drug Discov*. 2013 Mar;12(3):229-43. DOI: 10.1038/nrd3937. PMID: 23449308; PMCID: PMC7595252.

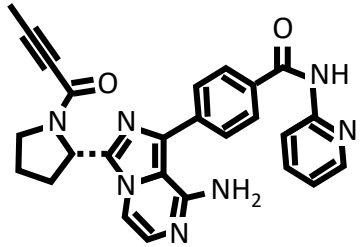
Covalent vs Noncovalent BTK Inhibitors

Irreversible Covalent BTK Inhibitors

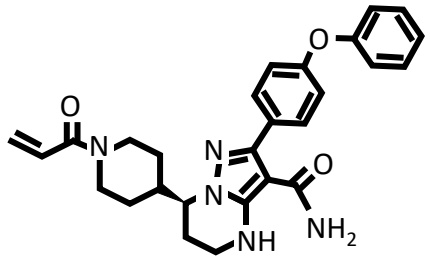
Ibrutinib



Acalabrutinib

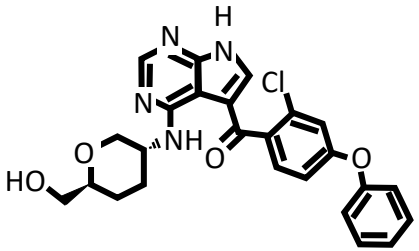


Zanubrutinib

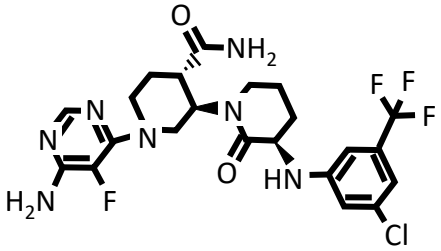


Reversible Noncovalent BTK Inhibitors

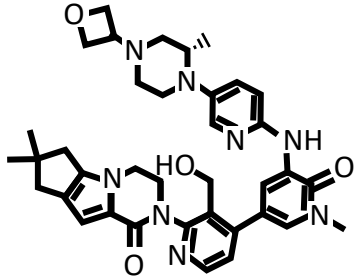
Nemtabrutinib (ARQ-531)



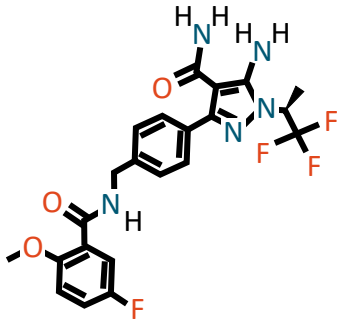
Vecabrutinib



Fenebrutinib



Pirtobrutinib (LOXO-305)



WILEY Fansheng Ran, Yun Liu, Chen Wang, et al. Review of the development of BTK inhibitors in overcoming the clinical limitations of ibrutinib. *European Journal of Medicinal Chemistry*. Vol 229;2022:114009. DOI: https://doi.org/10.1016/j.ejmech.2021.114009.

BTK Inhibitors for CLL/SLL and MCL: Regulatory Status

Agent	MOA	CLL/SLL		MCL	
		EU	US	EU	US
Ibrutinib1	Covalent	Approved	Approved	Approved (2L)	Approved (2L)
Acalabrutinib2	Covalent	Approved	Approved	Phase III	Approved (2L)
Zanubrutinib3	Covalent	Approved	Phase III	Phase III	Approved (2L)
Pirtobrutinib	Noncovalent	Phase III BRUIN CLL-313 (NCT05023980) Phase III BRUIN CLL-314 (NCT05254743) Phase III BRUIN CLL-321 (NCT04666038) Phase III BRUIN CLL-322 (NCT04965493)		Phase III	Approved
Nemtabrutinib	Noncovalent	Phase II (NCT04728893)			

1. European Medicines Agency (EMA). Ibrutinib. *EMA.* 18/11/2022 (https://www.ema.europa.eu/en/medicines/human/EPAR/imbruvica)
2. European Medicines Agency (EMA). Calquence. *EMA.* 06/03/2023 (https://www.ema.europa.eu/en/medicines/human/EPAR/calquence)
3. European Medicines Agency (EMA). Brukinsa. *EMA.* 13/02/2023 (https://www.ema.europa.eu/en/medicines/human/EPAR/brukinsa)

Patient Case Study: 1

- 77 yo man
- 2016: fever, loss of weight, DVT (iliacal vein), rapid progression of leukocytosis (WBC: 160 G/L) + lymphadenomegaly
- Periferal flow cytometry: B-CLL (zap70+, CD38+)
- FISH: del13q & TP53 mutation
- LMWH
- Referal for ibrutinib to the National Health Insurance Fund -> refused (??)
- 2x **rituximab-bendamustin** – resistance, WBC increased again after temporary reduction
- 1x fludarabin, cyclophophamide, rituximab (**FCR**) - resistance, WBC increased again

Case is a courtesy of Dr. R. Szász

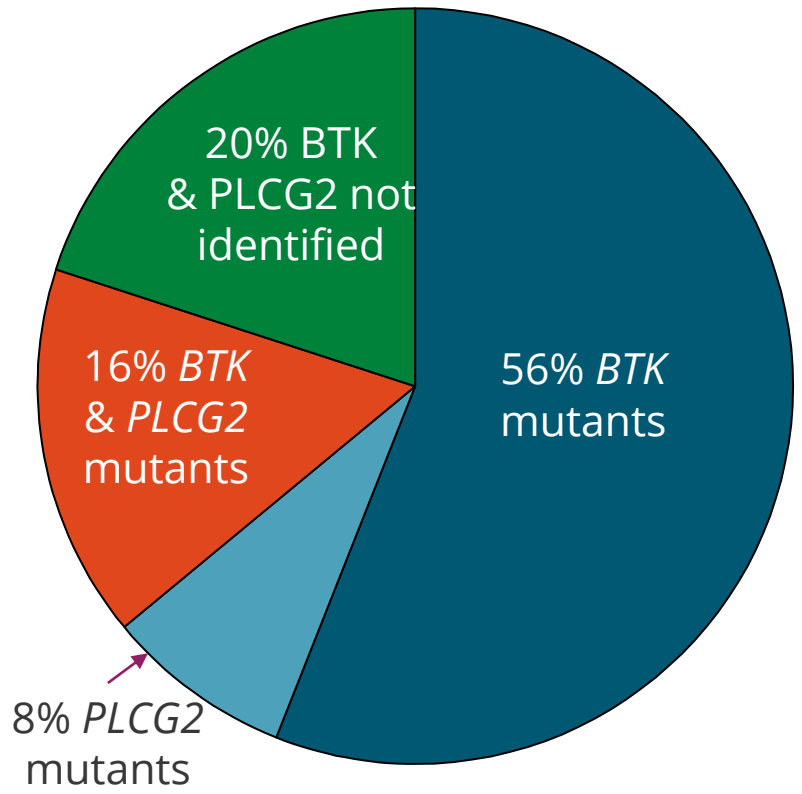
Patient Case Study: 1 (continued)

- September 2016: initiation of **ibrutinib** 420mg (control arm of a clinical trial)
  - WBC: 79 G/L, Hgb: 106 g/L, Plt: 169 G/L
  - CT: hepato-splenomegaly, supra-, infradiaphragmatic lymphadenomegaly
- June 2017: CR
  - WBC: 8 G/L, Hgb: 130 g/L, Plt: 135 G/L
  - CT: lymph nodes regressed
- November 2020: BTK C481S mutation positive VAF 74%
- Slow progression (blood count, WBC: 16 G/L)
- COVID 2nd wave…
- May 2021: initation of **rituximab – venetoclax** (WBC: 65 G/L)
- February 2023: CR
  - WBC: 4.52 G/L, Hgb: 131 g/L, Plt: 116 G/l

Case is a courtesy of Dr. R. Szász

Resistance and Intolerance Limit: Covalent BTKi Outcomes

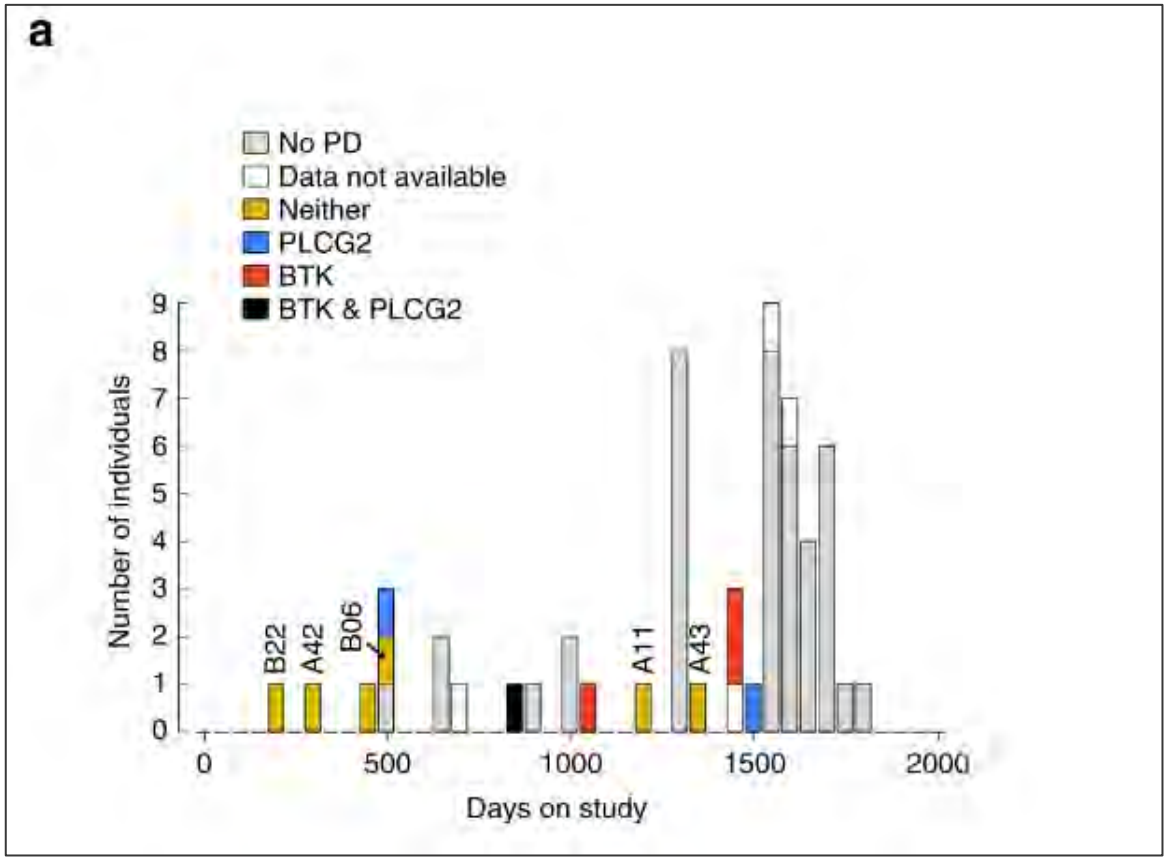
Ibrutinib Acquired Resistance in Patients With Progressive CLL[1]

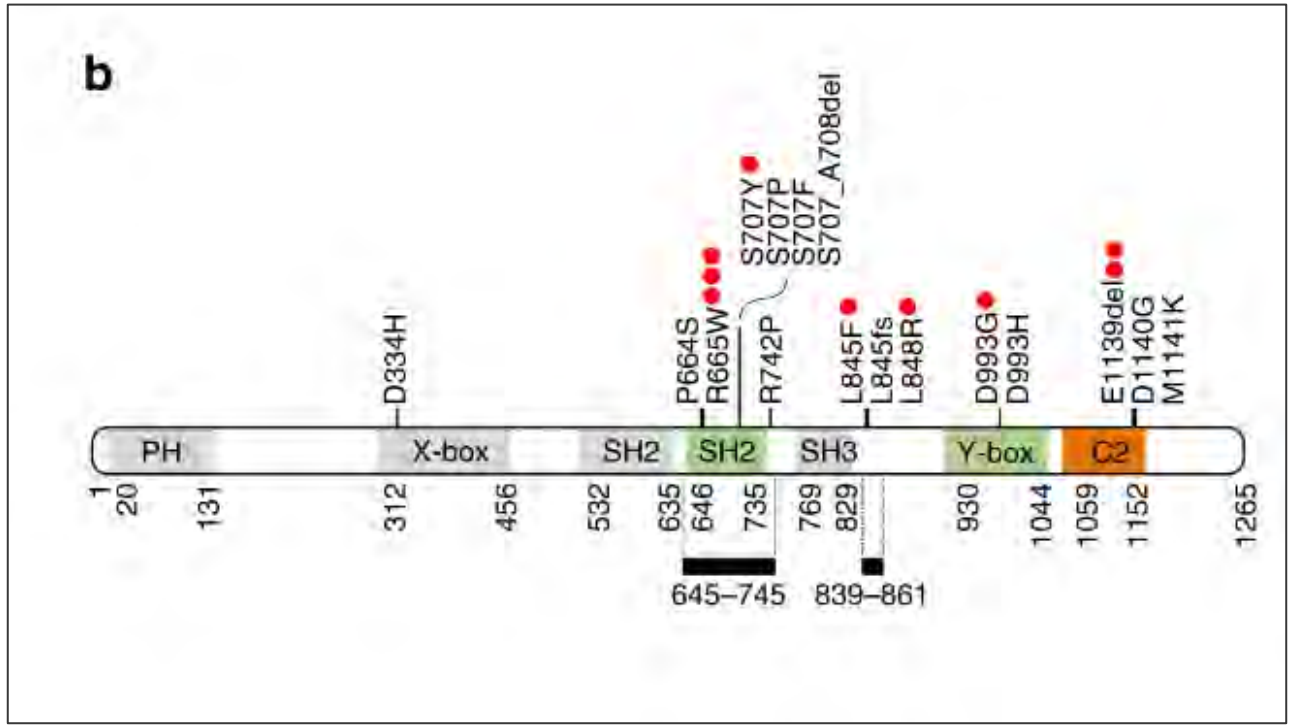


- Ibrutinib discontinuation rate at 5 yr
  - Frontline: 41%[2]
  - R/R: 53.7%[6]
- Appearance of *BTK* C481 mutations dominant reason for progressive CLL after covalent BTKi[1-6]
- *BTK* C481 mutations prevent covalent BTKi from effective target inhibition[1-6]

1. Lampson BL, Brown JR. Are BTK and PLCG2 mutations necessary and sufficient for ibrutinib resistance in chronic lymphocytic leukemia? *Expert Rev Hematol*. 2018 Mar;11(3):185-194. doi: 10.1080/17474086.2018.1435268.
2. Woyach JA, Ruppert AS, Guinn D, *et al*. BTKC481S-Mediated Resistance to Ibrutinib in Chronic Lymphocytic Leukemia. *J Clin Oncol*. 2017 May 1;35(13):1437-1443. doi: 10.1200/JCO.2016.70.2282.
3. Xu L, Tsakmaklis N, Yang G, *et al.* Acquired mutations associated with ibrutinib resistance in Waldenström macroglobulinemia. *Blood*. 2017 May 4;129(18):2519-2525. doi: 10.1182/blood-2017-01-761726.
4. Hershkovitz-Rokah O, Pulver D, Lenz G, Shpilberg O. Ibrutinib resistance in mantle cell lymphoma: clinical, molecular and treatment aspects. *Br J Haematol*. 2018 May;181(3):306-319. doi: 10.1111/bjh.15108.
5. Burger JA, Barr PM, Robak T, *et al*. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. *Leukemia*. 2020 Mar;34(3):787-798. doi: 10.1038/s41375-019-0602-x.
6. Jennifer Woyach, Ying Huang, Kerry Rogers, *et al*. Resistance to Acalabrutinib in CLL Is Mediated Primarily By BTK Mutations. *Blood* 2019; 134 (Supplement_1): 504. doi: https://doi.org/10.1182/blood-2019-127674

Resistance due to BTK and PLCG2 mutations

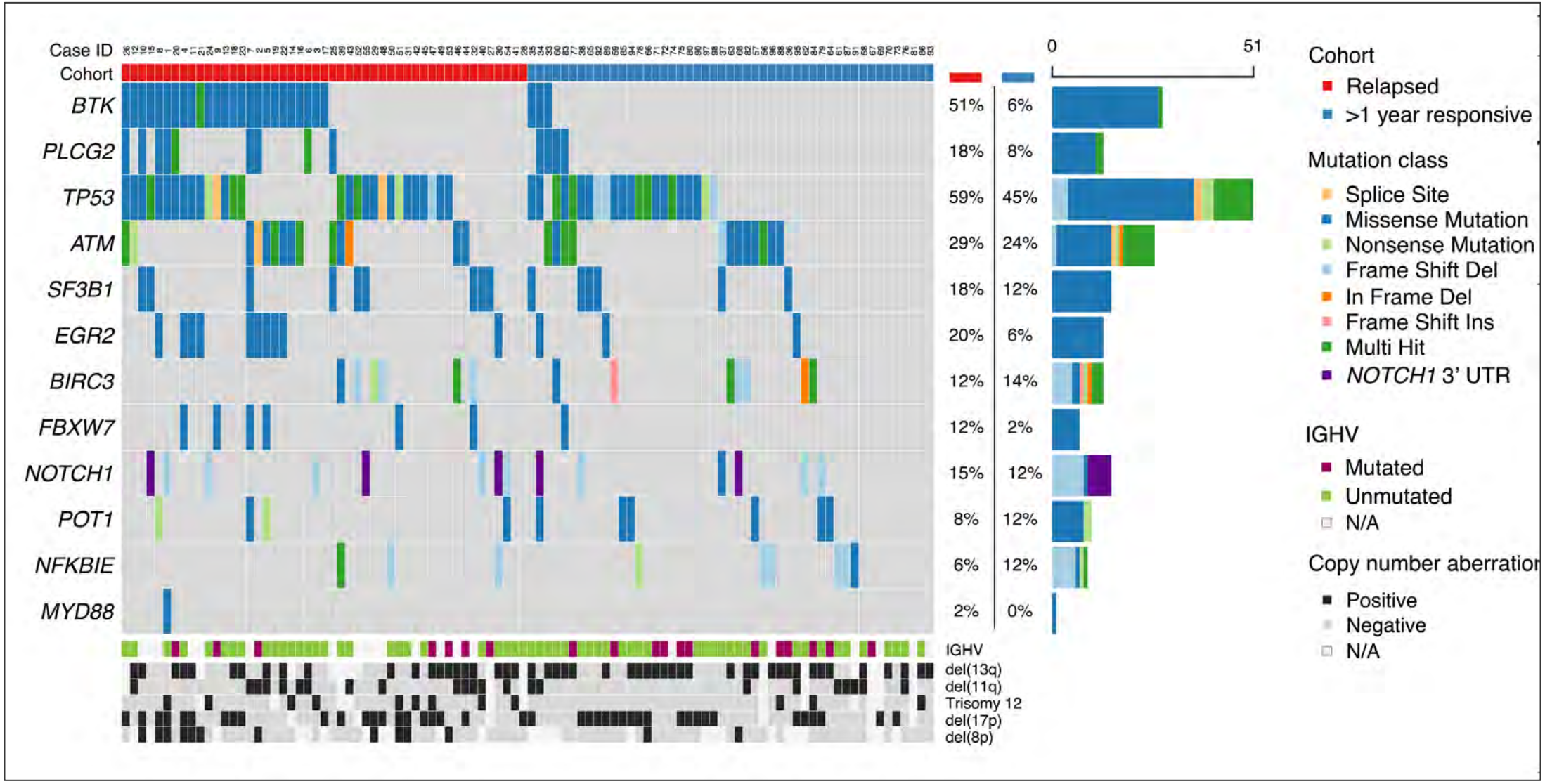




WILEY

Landau DA; Sun C; Rosebrock D; *et al*. The evolutionary landscape of chronic lymphocytic leukemia treated with ibrutinib targeted therapy. *Nat Commun* 8, 2185 (2017).
DOI: https://doi.org/10.1038/s41467-017-02329-y

BTK and PLCG2 remain unmutated in one-third of patients with CLL relapsing on ibrutinib



WILEY

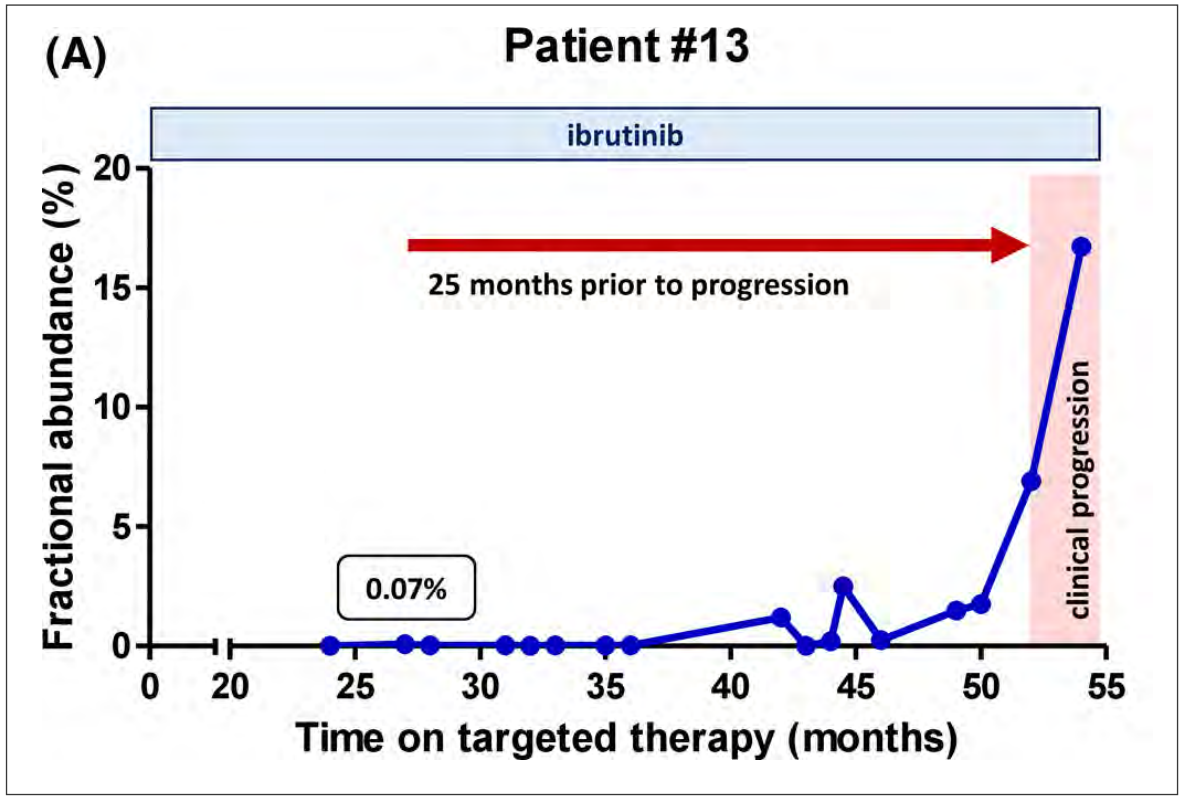
Bonfiglio S, Sutton LA, Ljungström V, *et al*. BTK and PLCG2 remain unmutated in one third of patients with CLL relapsing on ibrutinib. *Blood Adv*. 2023 Jan 25:bloodadvances.2022008821. DOI: 10.1182/bloodadvances.2022008821.

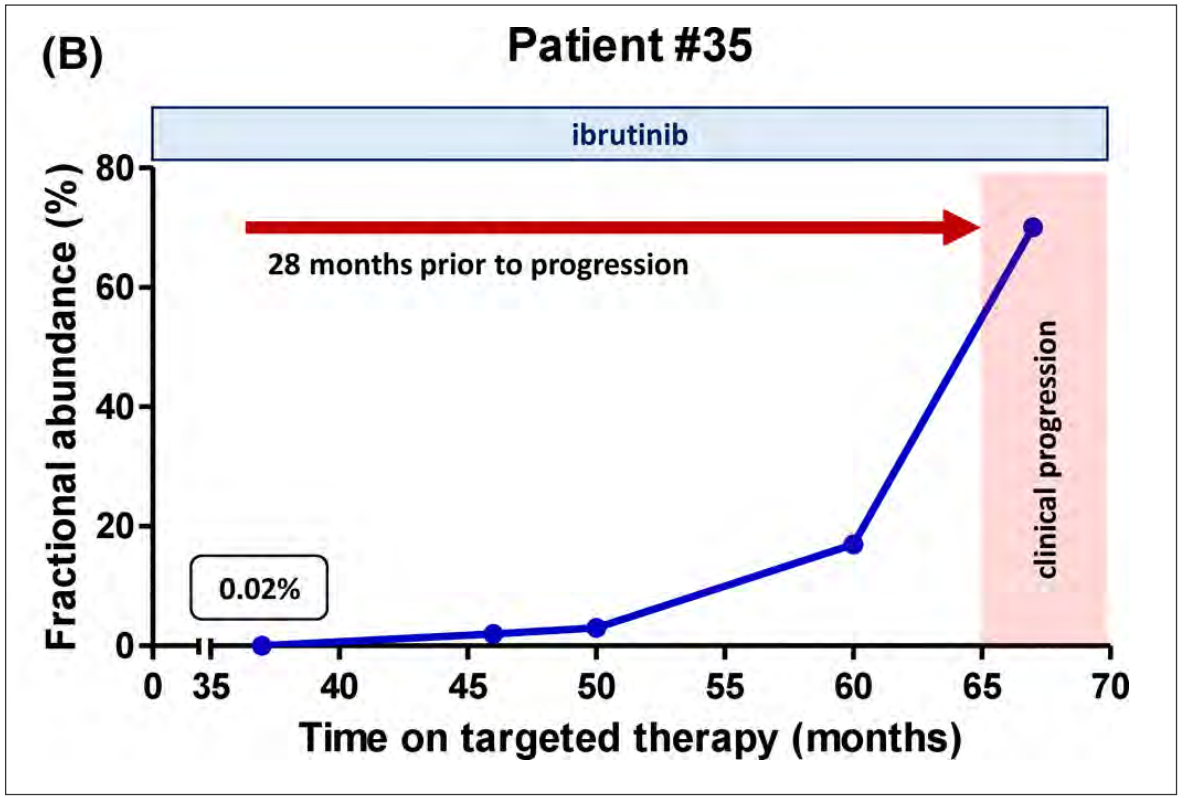
Patient Case Study: 2

- 67 yo woman
- 2004: B-CLL, 5x FC (stopped side effects)
- 2017: progression (lymphadenomegaly) 4x rituximab-bendamustin (stopped due to patient's decision)
- March 2019: Rai IV progression, ibrutinib 420mg (WBC: 171 G/L, Hgb 95 g/L, Plt: 78 G/L)
- Best response CR
- April 2021: BTK C481 mutation VAF 0.08%
- December 2021: BTK C481 mutation VAF 6%
- December 2022: BTK C481 mutation VAF 25%
- WBC: 15 G/L, Hgb: 131 g/L, Plt: 153 G/L
- Still no need for therapy change

Case is a courtesy of Dr. R. Szász

Temporal dynamics of the BTK C481S resistance mutation in CLL patients treated with ibrutinib





WILEY

Bödör, C., Kotmayer, L., László, T., *et al*. (2021), Screening and monitoring of the BTKC481S mutation in a real-world cohort of patients with relapsed/refractory chronic lymphocytic leukaemia during ibrutinib therapy. *Br. J. Haematol.*, 194: 355-364. https://doi.org/10.1111/bjh.17502

Absence of BTK, BCL2, and PLCG2 mutations in relapsing CLL after first-line treatment with fixed-duration ibrutinib plus venetoclax (CAPTIVATE trial)

- After frontline treatment with a fixed-duration of ibrutinib plus venetoclax, no resistance-associated mutations in *BTK*, *PLCG2*, or *BCL2* were identified in patients with CLL who had progressive disease according to findings from the phase 2 CAPTIVATE study presented at the EHA 2022 Congress.
- The patient samples in this study were assessed for resistance mutations by targeted next-generation sequencing with a customized panel for *BTK*, *PLCG2*, or *BCL2* variants, no significant differences were seen between the PD and non-PD group.

Baseline mutations and high-risk disease features

		PD (n=30)	Non PD (n=160)
Pts with mutations in genes of interest, n/N (%)	*ATM*	11/30 (37)	43/160 (27)
	BIRC3	0/30 (0)	11/160 (7)
	BRAF	2/30 (7)	10/160 (6)
	CHD2	3/30 (10)	11/160 (7)
	EZH2	0/30 (0)	0/160 (0)
	FBXW7	1/30 (3)	8/160 (5)
	MYD88	2/30 (7)	10/160 (6)
	NOTCH1	8/30 (27)	34/160 (21)
	POT1	2/30 (7)	22/160 (14)
	RPS15	0/30 (0)	11/160 (7)
	SF3B1	8/30 (27)	29/160 (18)
	XPO1	2/30 (7)	10/160 (6)
Pts with genomic rish features, n/N (%)	Unmutated IGHV	23/30 (77)	89/156 (57)
	Complex karyotype	8/27 (30)	26/136 (19)
	del(17p)	5/30 (17)	16/157 (10)
	del(11q)	9/30 (30)	27/159 (17)
	Trisomy 12	7/30 (23)	26/157 (17)
	del(13q)	15/30 (50)	92/160 (57)
	TP53 mutated (ERIC)*	4/30 (13)	11/160 (7)

*Mutations with variant allele frequency ≥10% are reported per European Research Initiative on CLL (ERIC) recommendations

Croner LJ, Allan JN, Jain N, *et al*. P670: ABSENCE OF BTK, BCL2, AND PLCG2 MUTATIONS IN RELAPSING CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) AFTER FIRST-LINE TREATMENT WITH FIXED-DURATION IBRUTINIB (I) PLUS VENETOCLAX (V). *HemaSphere* 6():p 568-569, June 2022. | DOI: 10.1097/01.HS9.0000845564.15449.7d

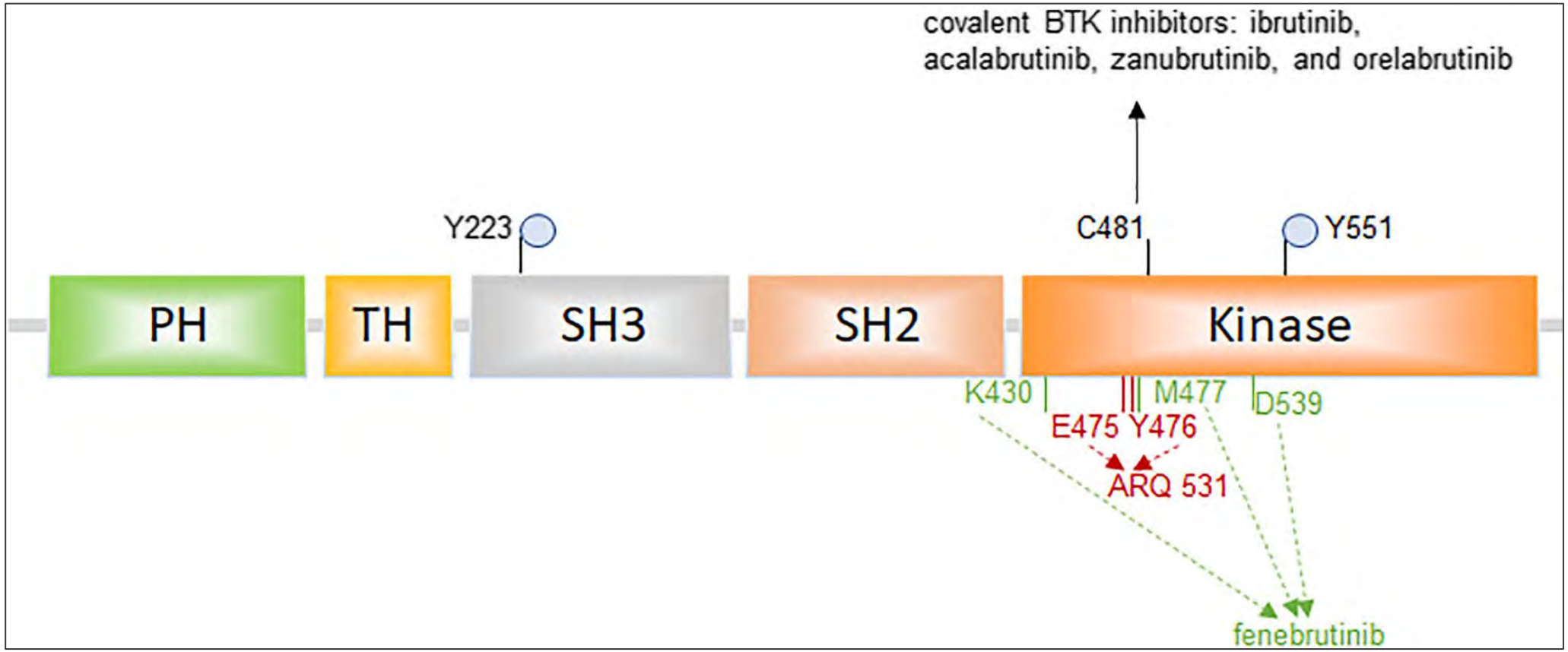
Primary and secondary resistance mechanisms to BTK inhibitors in B cell malignancies

B cell malignancy subtype	Covalent BTK inhibitors	Mechanisms underlying resistance
Primary resistance		
MCL	Ibrutinib	• Mutations involving NF-κB pathway: A20 mutations, TRAF2 mutations, BIRC3 mutations or BIRC2 mutations, RELA E39Q mutation, and others • Sustained PI3K/AKT/mTOR activation • Tumor microenvironment • Metabolic reprogramming toward oxidative phosphorylation and glutaminolysis • CCND1 mutation
WM	Ibrutinib	• CXCR4 WHIM-like mutations
DLBCL	Ibrutinib	• PIM1 mutation • PI3K/AKT activation • MAPK activation • Aberrations activating NF-κB pathway: CARD11 mutation, A20 aberrations • High expression of PDGFD
Acquired resistance		
CLL/SLL	Ibrutinib	• BTK C481 and T474 mutations • PLCG2 mutations (R665W, S707, L845F, and others) • del(8p)
CLL/SLL	Acalabrutinib	• BTK C481 mutations and T474I mutation, PLCG2 mutations
CLL/SLL	Zanubrutinib	• BTK Leu528Trp mutation and C481 mutation
MCL	Ibrutinib	• BTK C481S mutation • PLCG2 mutations • CARD11 mutation • Tumor microenvironment
WM	Ibrutinib	• BTK C481 mutations • PLCG2 Tyr495His mutation
MZL	Ibrutinib	• BTK C481S mutation • PLCG2 R665W
DLBCL	Ibrutinib	• BTK C481S mutation

Key: BTK Bruton tyrosine kinase, MCL mantle cell lymphoma, WM Waldenstrom's macroglobulinemia, DLBCL diffuse large B cell lymphoma, CLL/SLL chronic lymphocytic leukemia/small lymphocytic lymphoma, MZL marginal zone lymphoma

WILEY Gu, D., Tang, H., Wu, J. et al. Targeting Bruton tyrosine kinase using non-covalent inhibitors in B cell malignancies. J Hematol Oncol 14, 40 (2021).
DOI: https://doi.org/10.1186/s13045-021-01049-7

Acquired Resistance to Covalent BTK Inhibitors Is Generally Driven by Mutations in BTK at C481 Site



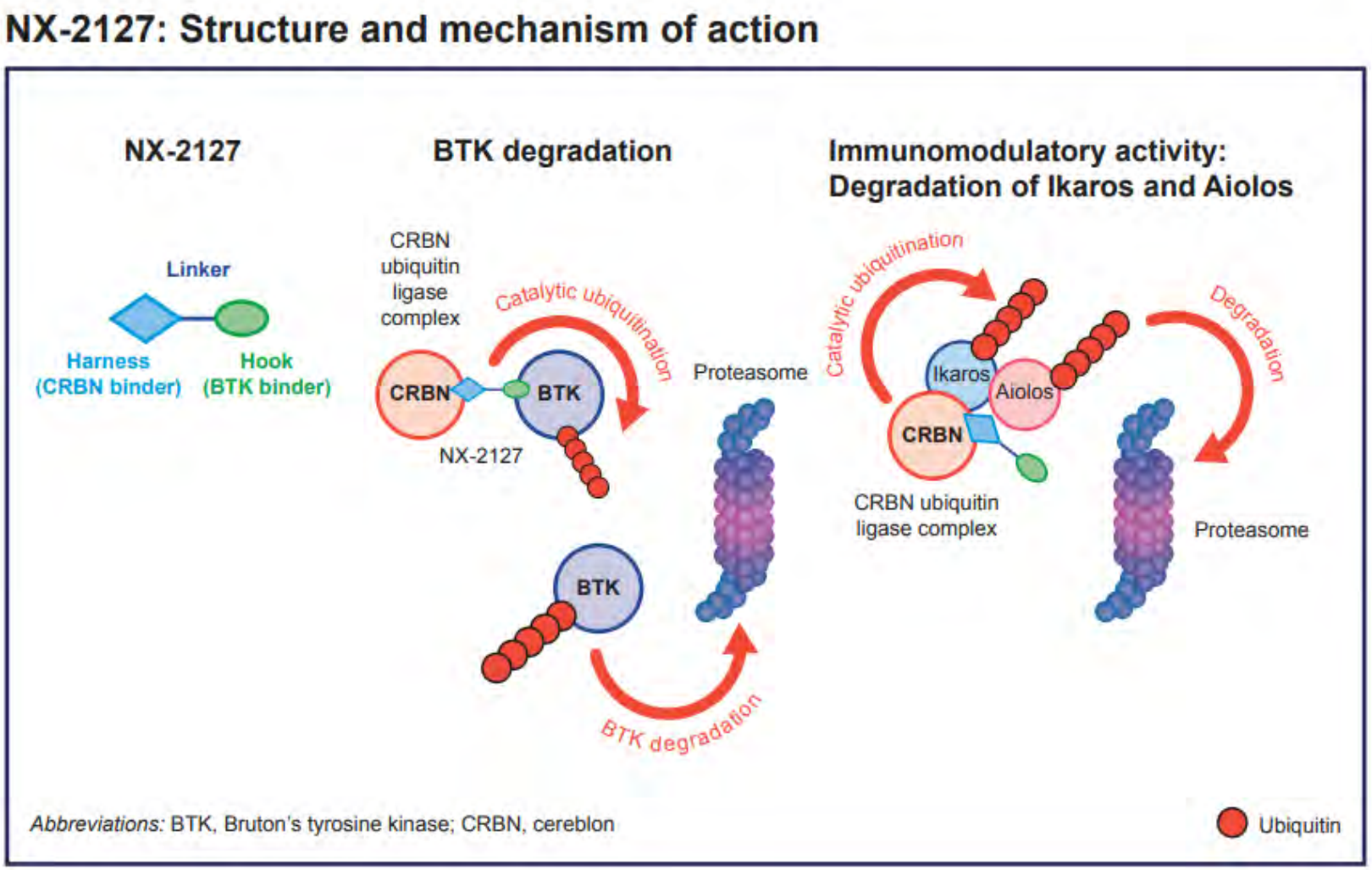
The structural diagram of Bruton tyrosine kinase (BTK). The BTK protein is a 77 kDa protein of 659 amino acids, which contains five different protein interaction domains. There are two critical tyrosine phosphorylation sites, Y223 in the SH3 domain and Y551 in the kinase domain. BTK inhibitors bind to the BTK kinase domain and blocks the catalytic activity of BTK. Currently available covalent BTK inhibitors, including ibrutinib, acalabrutinib, zanubrutinib, and orelabrutinib, selectively bind to C481 residue in the allosteric inhibitory segment of the BTK kinase domain. The non-covalent BTK inhibitors do not bind to C481. For example, ARQ 531 binds to BTK by forming hydrogen bonds with E475 and Y476 residues. Fenebrutinib forms hydrogen bonds with K430, M477, and D539 residues

WILEY Gu, D., Tang, H., Wu, J. et al. Targeting Bruton tyrosine kinase using non-covalent inhibitors in B cell malignancies. J Hematol Oncol 14, 40 (2021).
DOI: https://doi.org/10.1186/s13045-021-01049-7

Noncovalent BTK Inhibitors Are Active Against BTK C481 Mutations

Feature	Ibrutinib	Nemtabrutinib (ARQ-531)	Pirtobrutinib (LOXO-305)
Target	BTK	BTK	BTK
Bond type	Irreversible covalent	Reversible noncovalent	Reversible noncovalent
Requires C481 residue?	Yes	No	No
Active in C481 mutations?	No	Yes	Yes

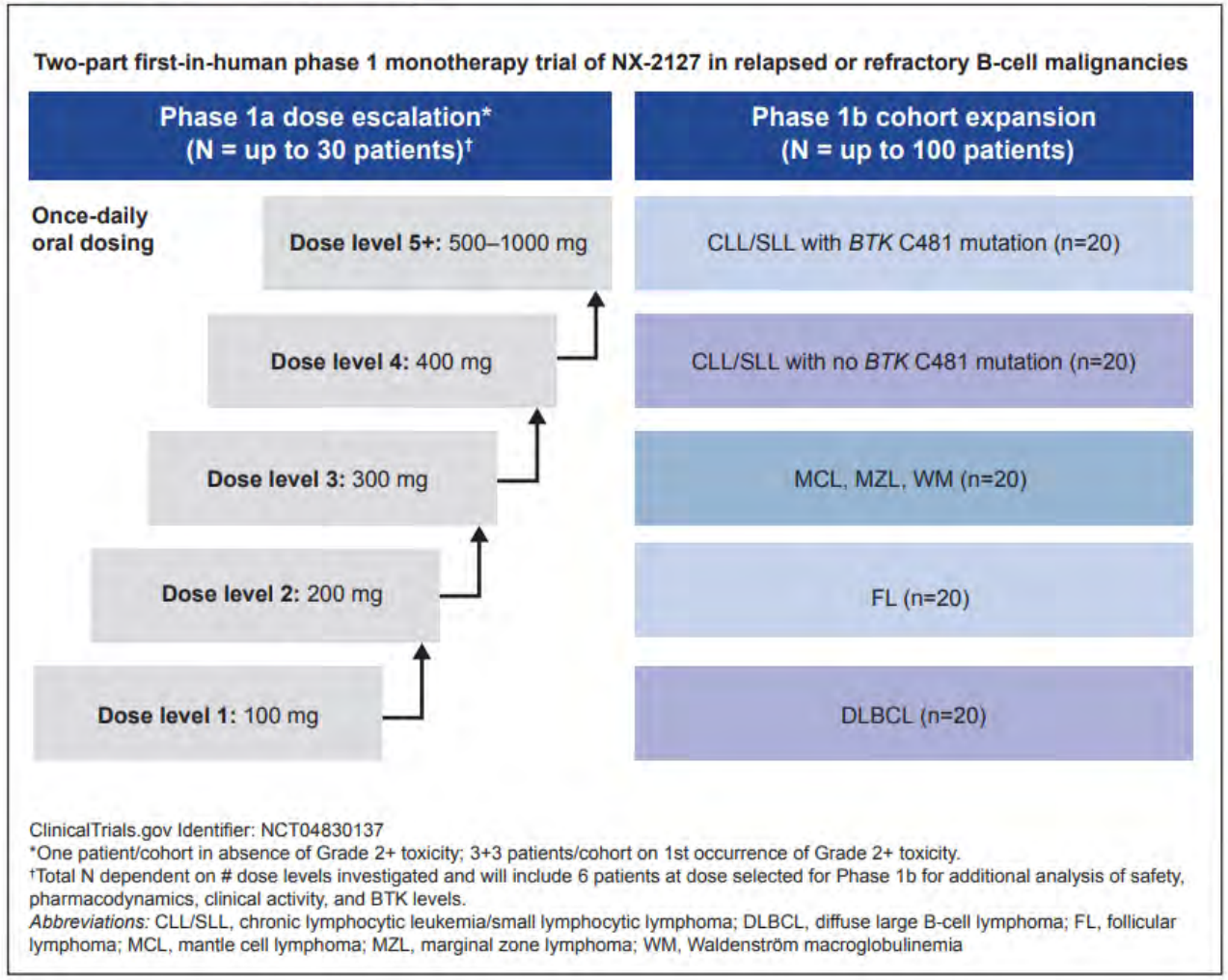
BTK Degradation



Mato ASH 2022 Abstr 965.

BTK Degradation

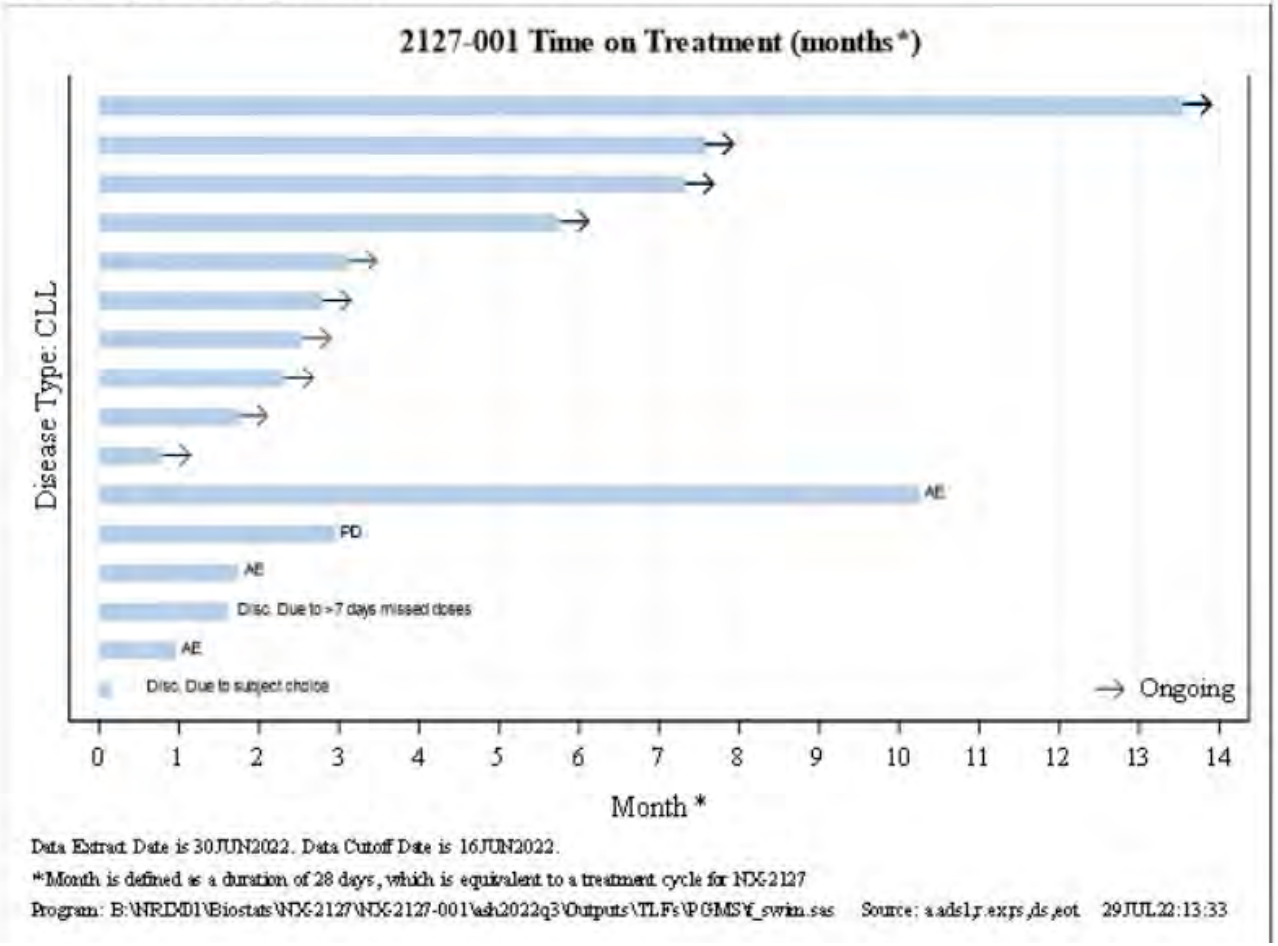
NX-2127-001: Study design



Mato ASH 2022 Abstr 965.

NX-2127: Targeted BTK and IKZF3 Degrader

Figure 1. CLL patient disposition



- Mean 86% BTK degradation observed
- ORR 33% but increasing with more follow-up
- Responses seen in BTK/BCL-2 double refractory and ncBTK inhibitor progressors

Mato ASH 2022 Abstr 965.

BRUIN: Pirtobrutinib (LOXO-305) for Previously Treated CLL/SLL

- Primary endpoints: MTD and recommended phase II dose (phase I), ORR (phase II). Secondary endpoints: safety, PK, ORR by investigator, DoR, PFS, OS
- Noncovalent, reversible BTK inhibitors were developed to improve and overcome mutations against BTK C481.
- The phase 1–2 study of pirtobrutinib showed promising efficacy for patients with B-cell malignancies, who had previously been treated with covalent BTK inhibitors including patients with or without BTK C481 mutations.
- The phase 1 portion was a standard dose-escalation study, while in the phase 2 dose-expansion cohort, patients were treated with pirtobrutinib at the recommended phase 2 dose of 200 mg once daily.
- The BRUIN study included two previous lines of therapy, which was later amended to one previous line of therapy if it included a covalent BTK inhibitor.

Phase I/II study with dose escalation and expansion in phase I

Patients ≥18 yr of age with CLL/SLL* or B-cell non-Hodgkin lymphoma; ≥2 prior therapies including BTK inhibitor; ECOG PS 0-2 (N = 618)

Pirtobrutinib
Phase I: 25-300 mg QD
Phase II: 200 mg QD

*Safety population: n = 296; efficacy population: n = 252 (all previously treated with BTK inhibitor).

R. Mato A. PIRTOBRUTINIB, A HIGHLY SELECTIVE, NON-COVALENT (REVERSIBLE) BTK INHIBITOR IN PREVIOUSLY TREATED CLL/SLL: UPDATED RESULTS FROM THE PHASE 1/2 BRUIN STUDY. Abstract release date: 05/12/22. *EHA Library*. 06/12/2022; 357011; S147

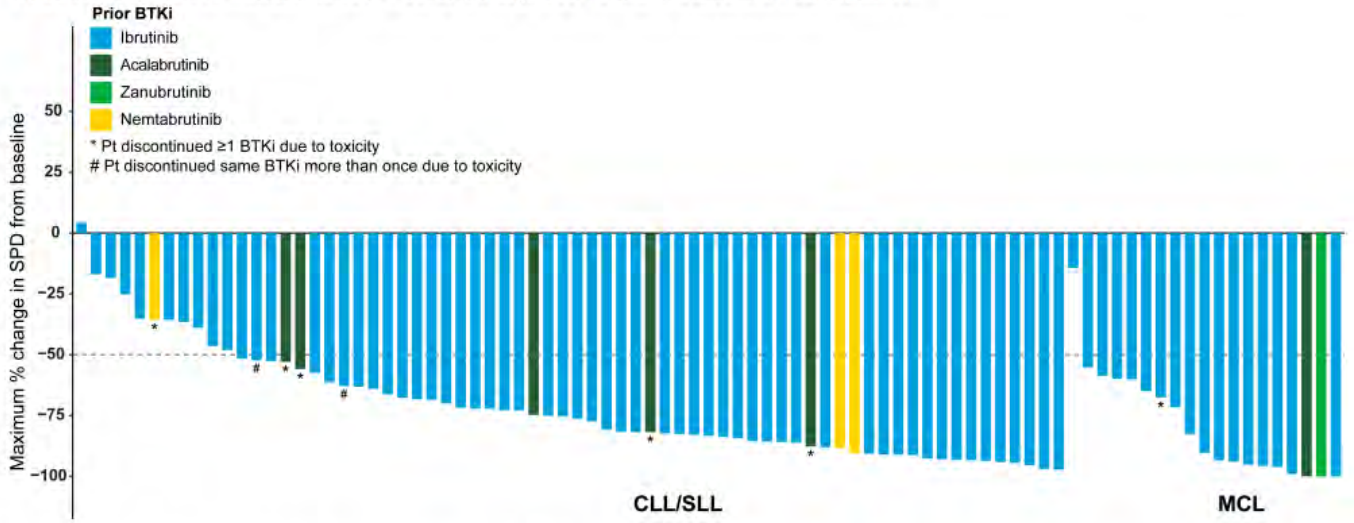
BRUIN: Responses in Patients With MCL or CLL/SLL Previously Intolerant to Covalent BTK Inhibitor

Pirtobrutinib demonstrated promsising efficacy in both CLL and MCL patients after being on therapy with ibrutinib, acalbrutinib, zanubritinib and nemtabrutinib.

Pirtobrutinib Efficacy in Patients Intolerant to Prior BTKi

	CLL/SLL n=78	MCL n=21
Overall response rate[a], % (95% CI)	**76.9 (66.0-85.7)**	**81.0 (58.1-94.6)**
Best response		
CR, n (%)	0 (0.0)	9 (42.9)
PR, n (%)	58 (74.4)	8 (38.1)
PR-L, n (%)	2 (2.6)	N/A
SD, n (%)	12 (15.4)	1 (4.8)

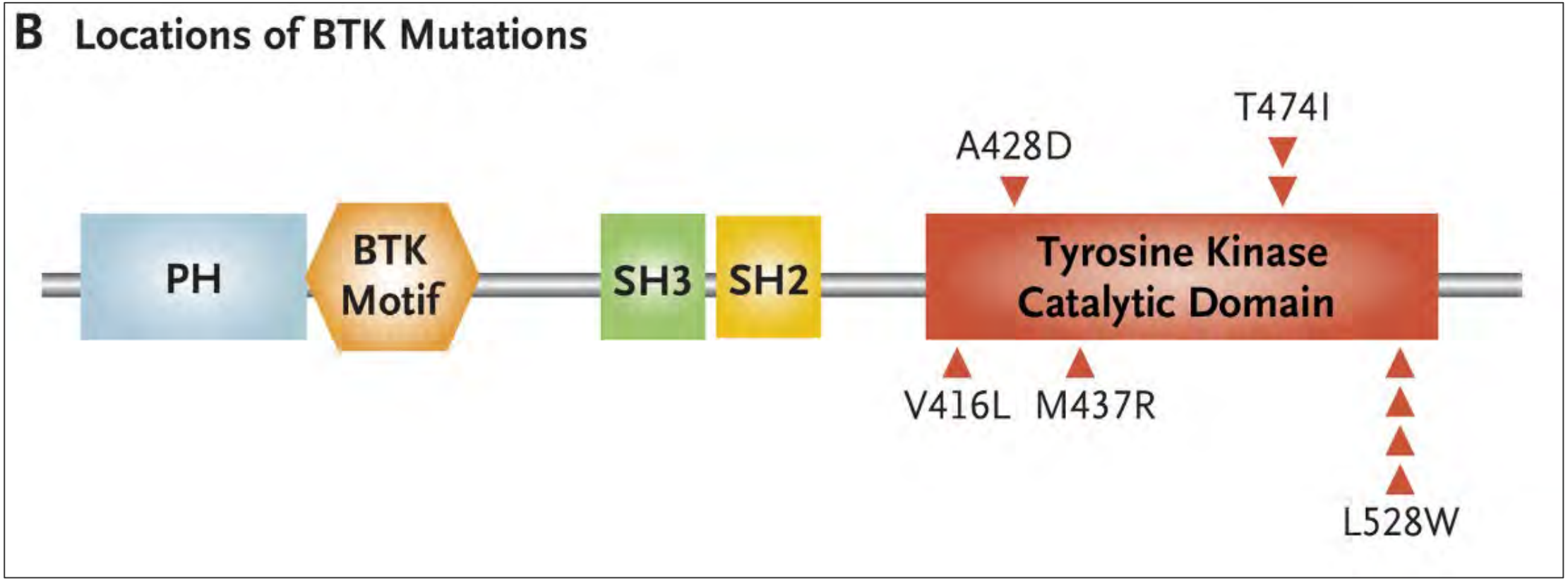
[a]Response was assessed by investigator based on iwCLL 2018 or Lugano 2014 criteria for CLL/SLL and MCL, respectively.



- Pirtobrutinib exhibited promising efficacy across B-cell malignancies among patients who experienced intolerance to prior BTKi

Nirav N Shah, Michael L. Wang, Jennifer R. Brown, *et al.* 1797 Safety and Tolerability of Pirtobrutinib Monotherapy in Patients with B-Cell Malignancies Who Were Previously Intolerant to a Covalent BTK Inhibitor: Results from the Phase 1/2 BRUIN Study. *64th ASH 2022*. Session: 642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological: Poster. December 10, 2022.

BTK Mutations in Patients with Chronic Lymphocytic Leukemia with Acquired Resistance to Noncovalent BTK Inhibitor pirtobrutinib



- Samples were obtained before treatment and at the time of disease progression from patients with CLL who had been treated with the noncovalent BTK inhibitor pirtobrutinib.
- 9 patients were identified with relapsed or refractory CLL and acquired mechanisms of genetic resistance to pirtobrutinib. Mutations V416L, A428D, M437R, T474I, and L528W were clustered in the kinase domain of BTK.

WILEY Eric Wang, Xiaoli Mi, Meghan C. Thompson, *et al*. Mechanisms of Resistance to Noncovalent Bruton's Tyrosine Kinase Inhibitors. *N Engl J Med* 2022; 386:735-743.
DOI: 10.1056/NEJMoa2114110

Thank you!