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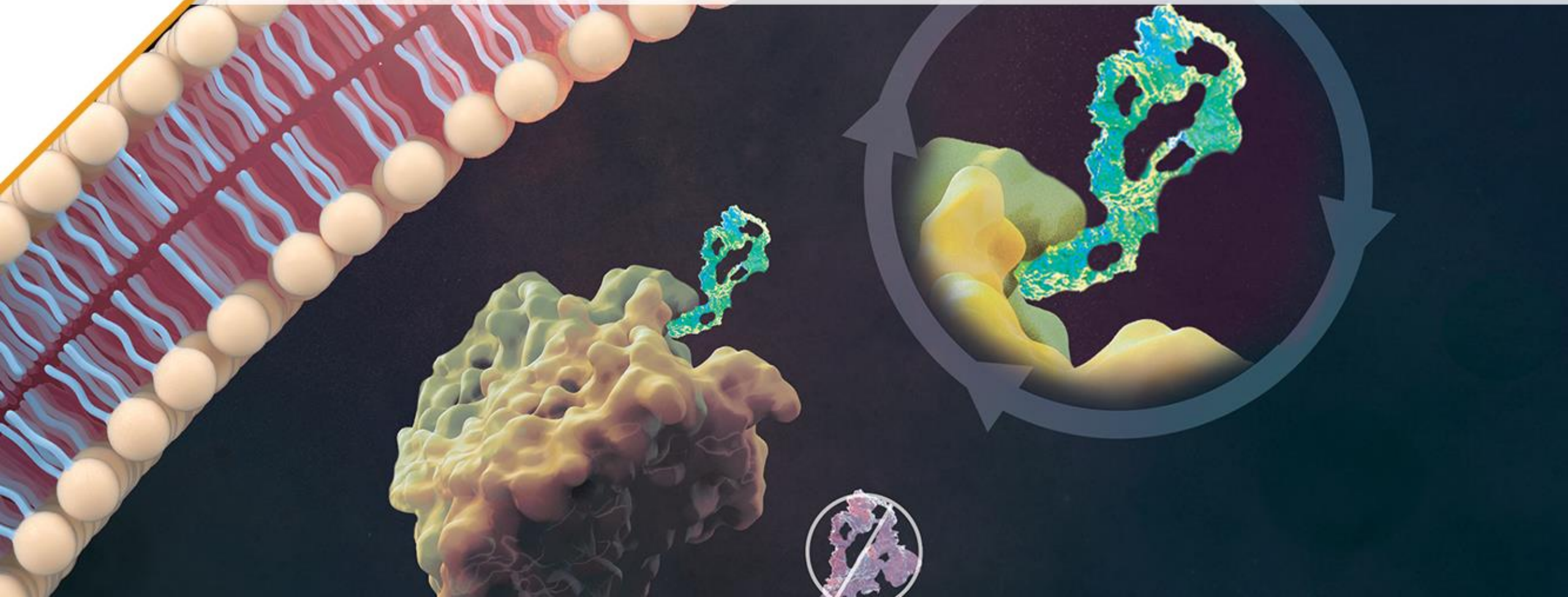
Practice-Changing Strategies in Community Care Settings for Patients with CLL/SLL and MCL



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Learning Objectives

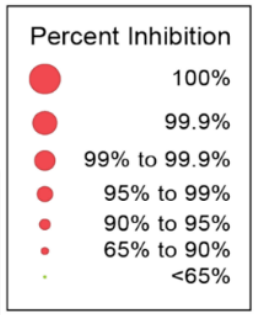
Upon completion of this activity, participants should be better able to:

1. Compare the novel MOA and the selectivity of reversible, noncovalent BTK inhibitors to that of irreversible, covalent BTK inhibitors
2. Apply real-world clinical evidence and clinical trial data on the efficacy and tolerability of reversible, noncovalent BTK inhibitors to incorporate them into evidence-driven treatment sequencing for patients with CLL/SLL or MCL
3. Integrate monitoring and management strategies for adverse events related to the use of reversible, noncovalent BTK inhibitors

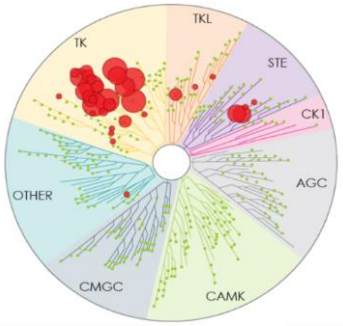
Mechanisms and Advantages of BTK Inhibitors

Covalent and Non-Covalent BTK Inhibitors Differ in Specificity, MOA, and Potential for Off-Target Effects

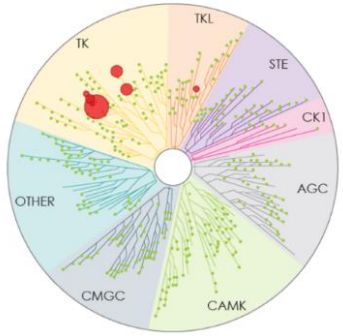
Covalent/ Irreversible



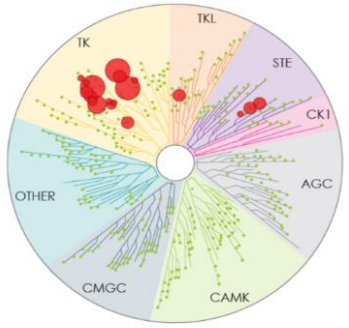
Ibrutinib



Acalabrutinib

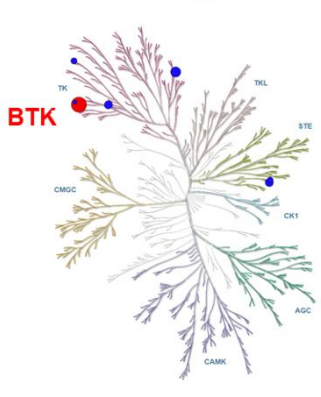


Zanubrutinib

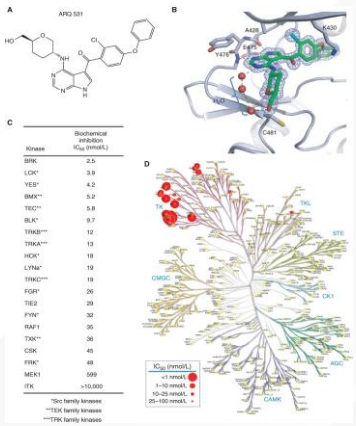


Noncovalent/ Reversible

Pirtobrutinib/LOXO-305



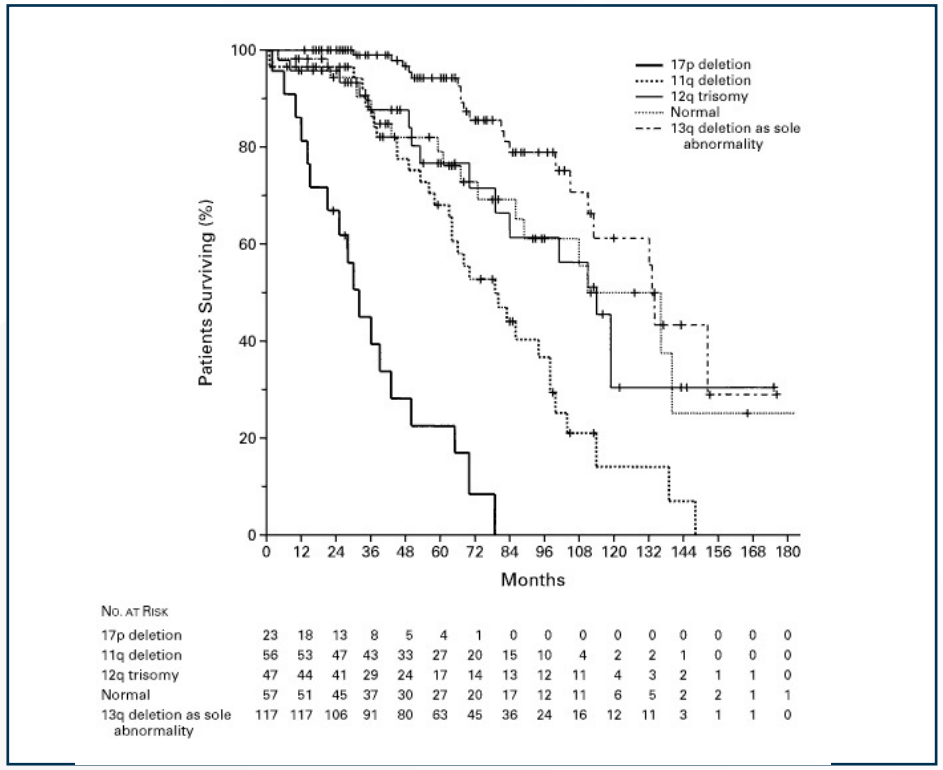
Nemtabrutinib/ARQ-531



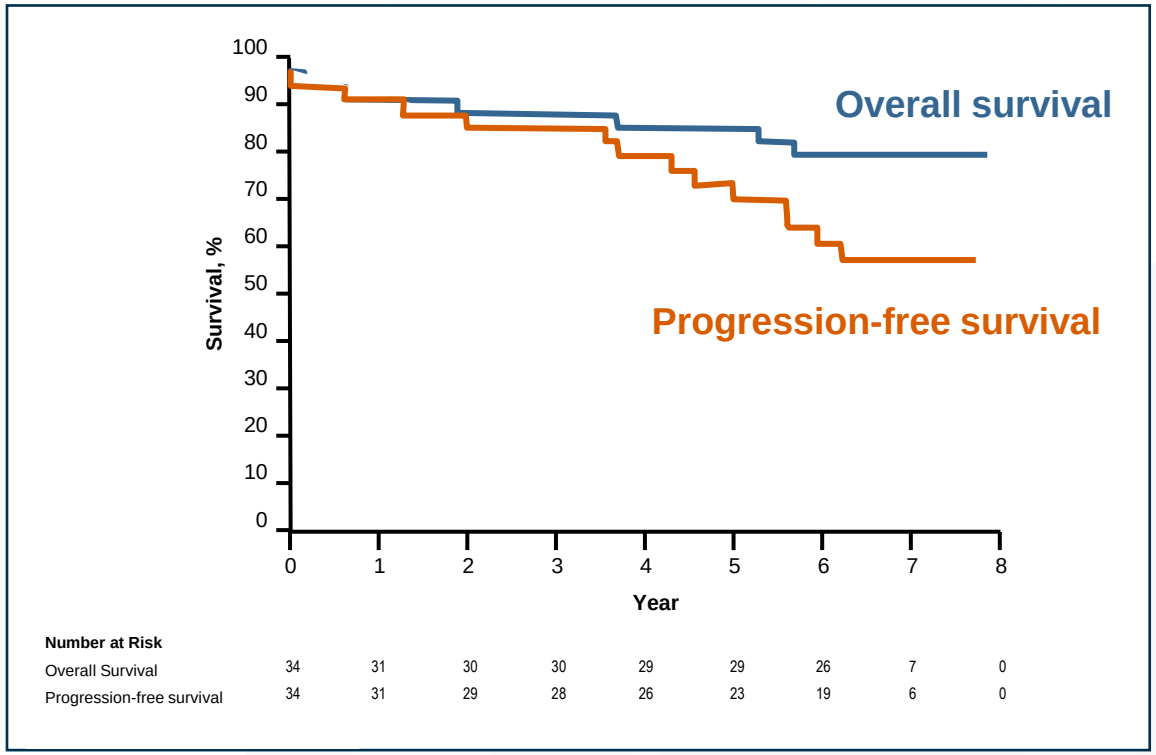
Kaptein A, et al. *Blood*. 2018;132(suppl 1):1871.
BTKi, Bruton's tyrosine kinase inhibitor; MOA, mechanism of action.

Covalent BTK Inhibitors Have Revolutionized the Treatment of CLL

Chemotherapy



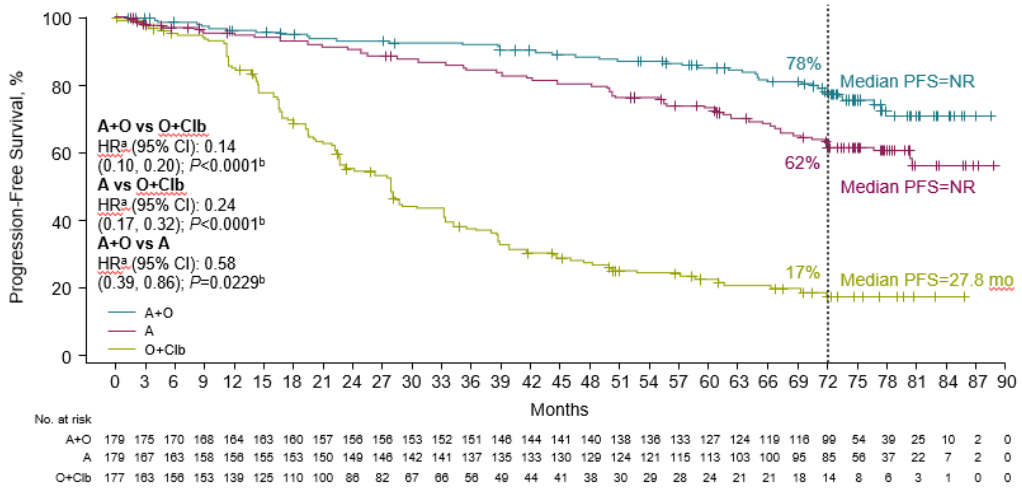
Ibrutinib



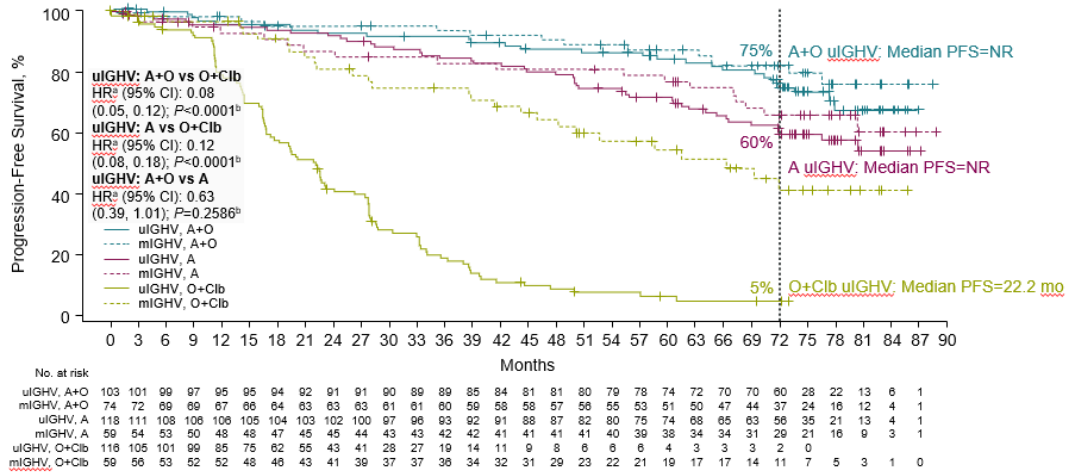
Döhner H, et al. *N Engl J Med*. 2000;343(26):1910-1916. Ahn IE, et al. *N Engl J Med*. 2020;383(5):498-500. Itsara A, et al. ASH 2023. Abstract 201.
BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; OS, overall survival.

Acalabrutinib ± Obinutuzumab vs Chlorambucil + Obinutuzumab in Treatment-Naive CLL: 6-Year Follow-Up from ELEVATE-TN Trial

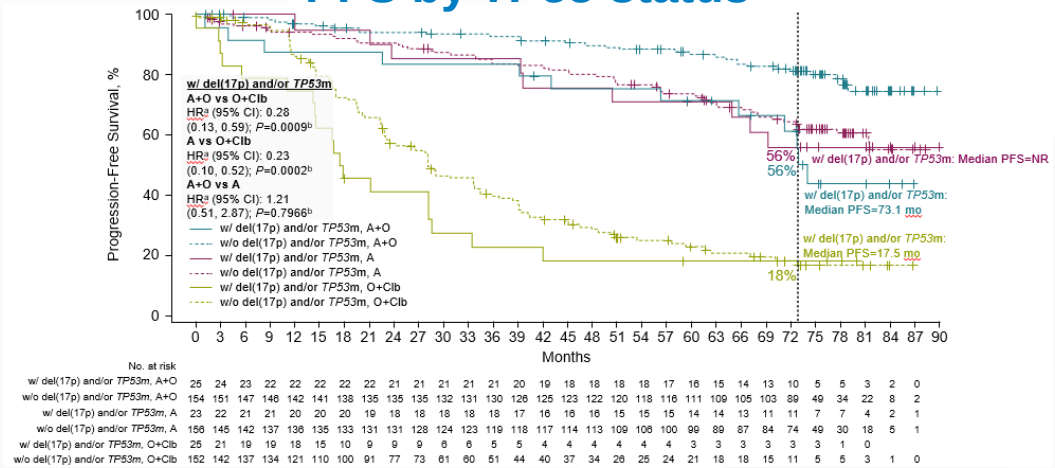
PFS for Overall Population



PFS by IGHV status



PFS by *TP53* status

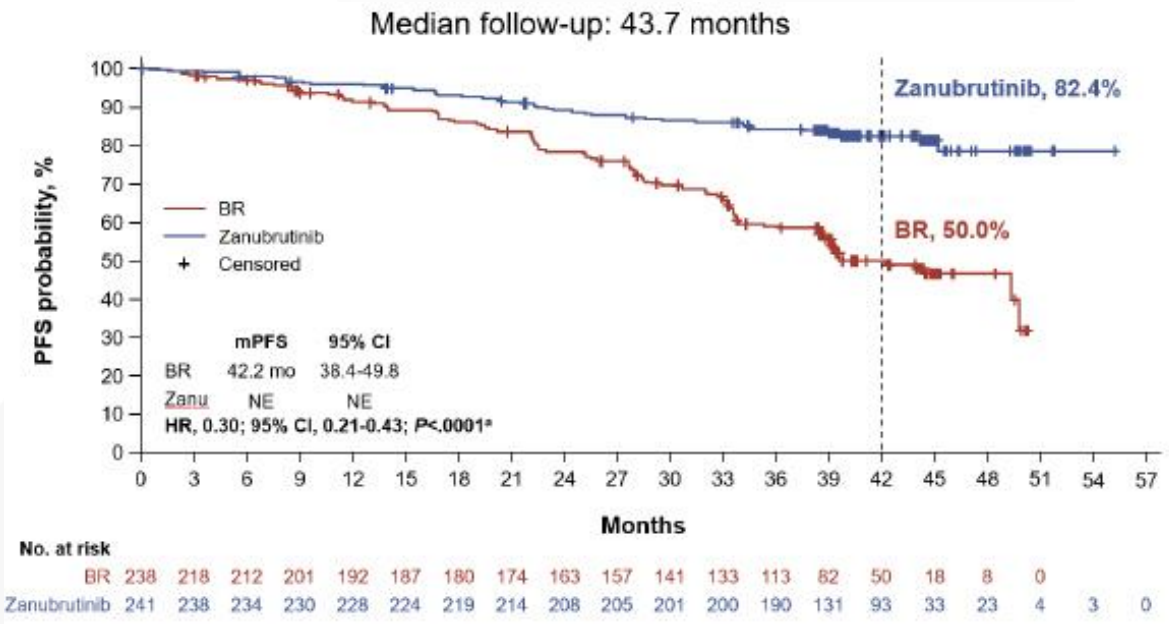


Sharman, et al. ASH 2023. Abstract 636.

CLL, chronic lymphocytic leukemia; IGHV, immunoglobulin heavy-chain variable region gene; PFS, progression-free survival; TN, treatment-naive.

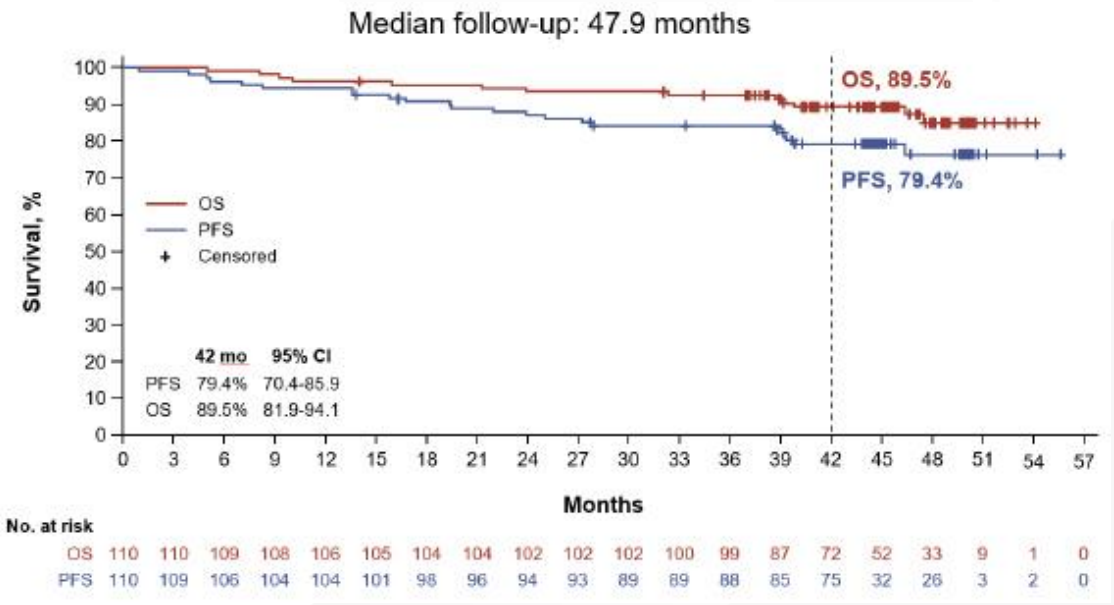
Efficacy Data from Phase 3 Open-Label SEQUOIA Study of Zanubrutinib vs. BR in Treatment-Naive CLL/SLL

PFS in non-del(17p)



CR/Cri rates: Zanubrutinib, 17.4%; BR, 21.8%

PFS in del(17p)



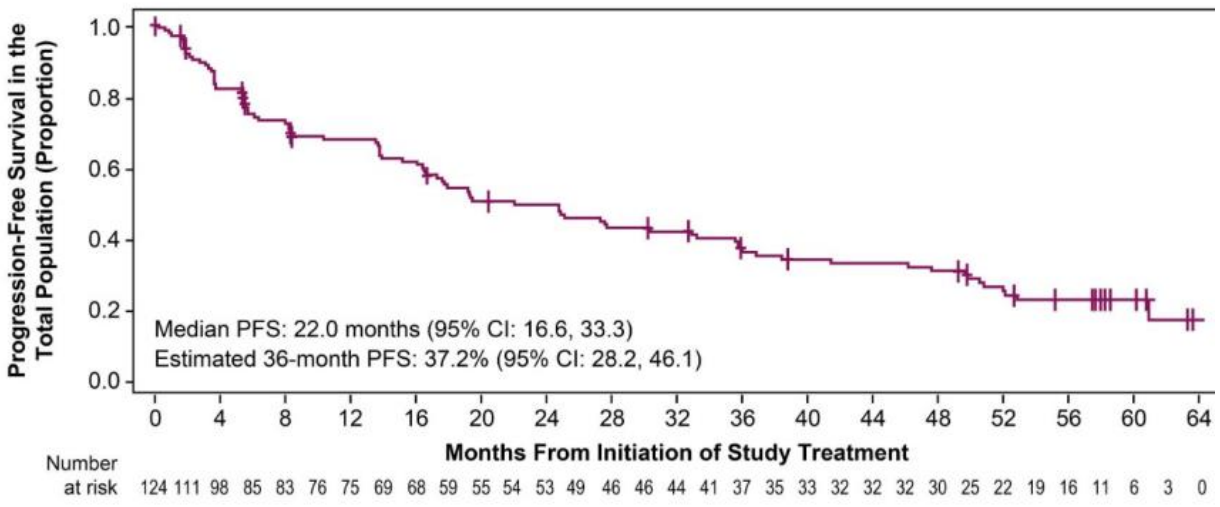
CR/Cri rate,14.5%

Tam CS, et al. *Lancet Oncol.* 2022;23(8):1031-1043. Shadman M, et al. ICML 2023. Abstract 154.

BR, bendamustine and rituximab; CLL, chronic lymphocytic leukemia; CR, complete response; CRi, complete response with incomplete blood recovery; PFS, progression-free survival; SLL, small lymphocytic lymphoma; TN, treatment-naive.

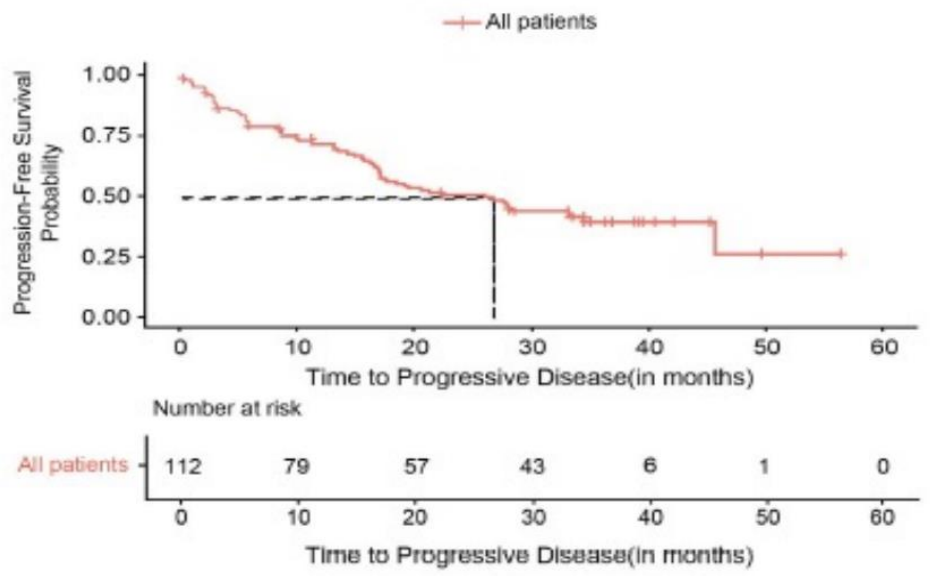
Second-Generation BTK Inhibitors a Preferred Option for 2nd Line MCL Treatment

Acalabrutinib



Median Follow-up 38.1 months

Zanubrutinib



Le Gouill S, et al. *Haematologica*. 2024;109(1):343-350.
Song Y, et al. *Cancer Med.* 2023;12(18):18643-18653.

BTK, Bruton's tyrosine kinase; MCL, mantle cell lymphoma.

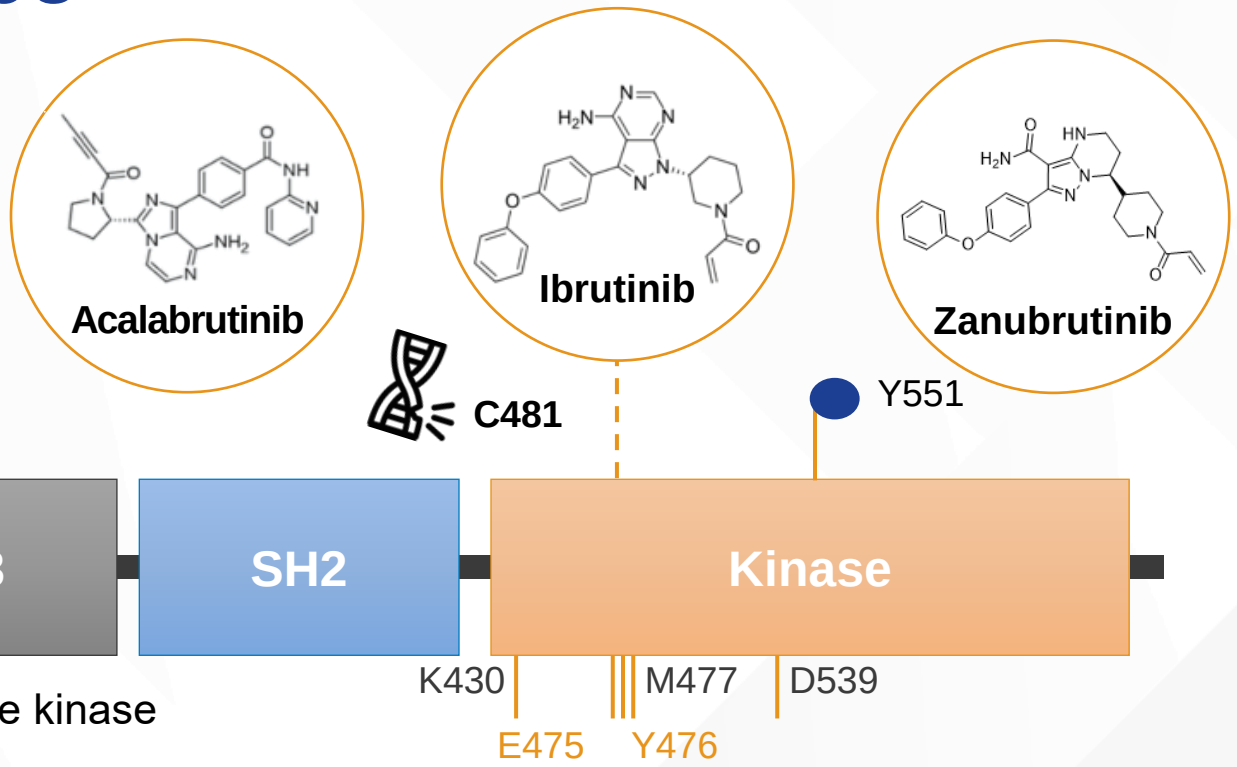
Covalent BTK Inhibitors in CLL in Frontline Setting

Ibrutinib	Acalabrutinib	Zanubrutinib
• As monotherapy • + rituximab • + obinutuzumab	• As monotherapy • + obinutuzumab	• As monotherapy

NCCN Guidelines for CLL/SLL. Version 2.2023.
BTK, Bruton's tyrosine kinase.

Application in the Community-Based Setting: Resistance/Intolerance

BTK C481 mutations confer resistance to the covalent BTK inhibitors ibrutinib, acalabrutinib, and zanubrutinib



Structure of the Bruton's tyrosine kinase

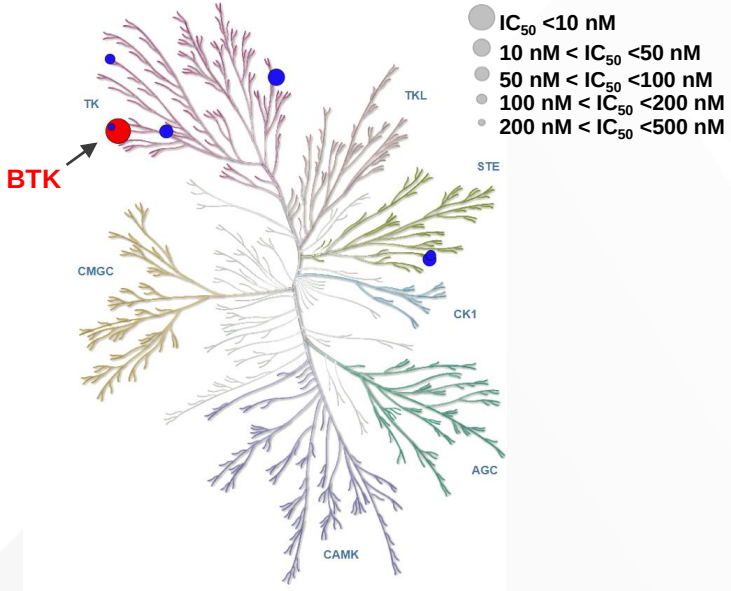
BTK resistance contributes to disease progression and diminishes the efficacy of **all covalent BTK** inhibitors in CLL; resistance mechanisms less well understood in MCL[1-8]

1. Woyach JA, et al. *J Clin Oncol*. 2017;35(13);1437-1443. 2. Lampson BL, Brown JR. *Expert Rev Hematol*. 2018;11(3):185-194. 3. Burger JA, et al. *Leukemia*. 2020;34(3):787-798. 4. Byrd JC, et al. *N Engl J Med*. 2016;374(4):323-332. 5. Hershkovitz-Rokah O, et al. *Br J Haematol.* 2018;181(3):306-319. 6. Woyach JA, et al. *N Engl J Med*. 2014;370(24):2286-2294. 7. Woyach JA, et al. *Blood*. 2019;134(suppl 1):504. 8. Xu L, et al. *Blood*. 2017;129:2519-2525.

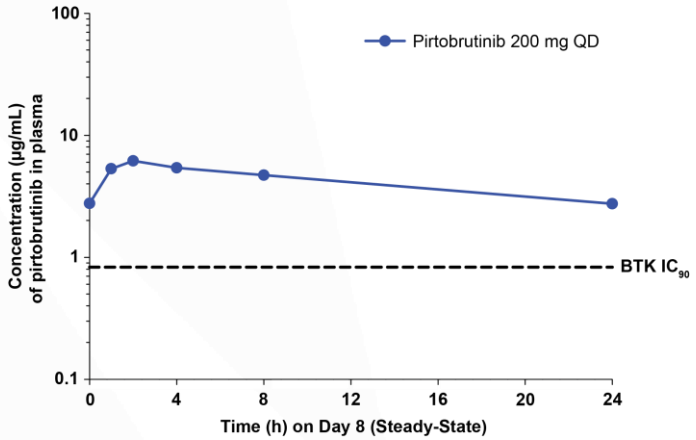
BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; PH, pleckstrin homology domain; TH, TEC homology domain; SH, SRC homology domain.

Pirtobrutinib is a Highly Selective, **Noncovalent** (Reversible) BTK Inhibitor

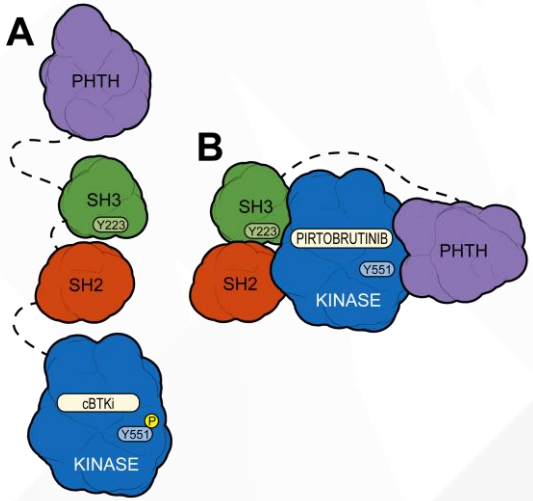
Highly selective for BTK[1,2]



Plasma exposures exceeded BTK IC_{90} throughout dosing interval



Pirtobrutinib may stabilize/maintain BTK in a closed inactive conformation[3]



- Inhibits both WT and C481-mutant BTK with equal low nM potency[3]
- Steady state plasma exposure corresponding to 96% BTK target inhibition and a half-life of about 20 hours[3]
- In contrast to covalent BTK inhibitors, pirtobrutinib appears to stabilize BTK in a closed, inactive conformation, blocking access to upstream kinases and phosphorylation of Y551, thus inhibiting scaffolding interactions that support kinase-independent BTK signaling[3]

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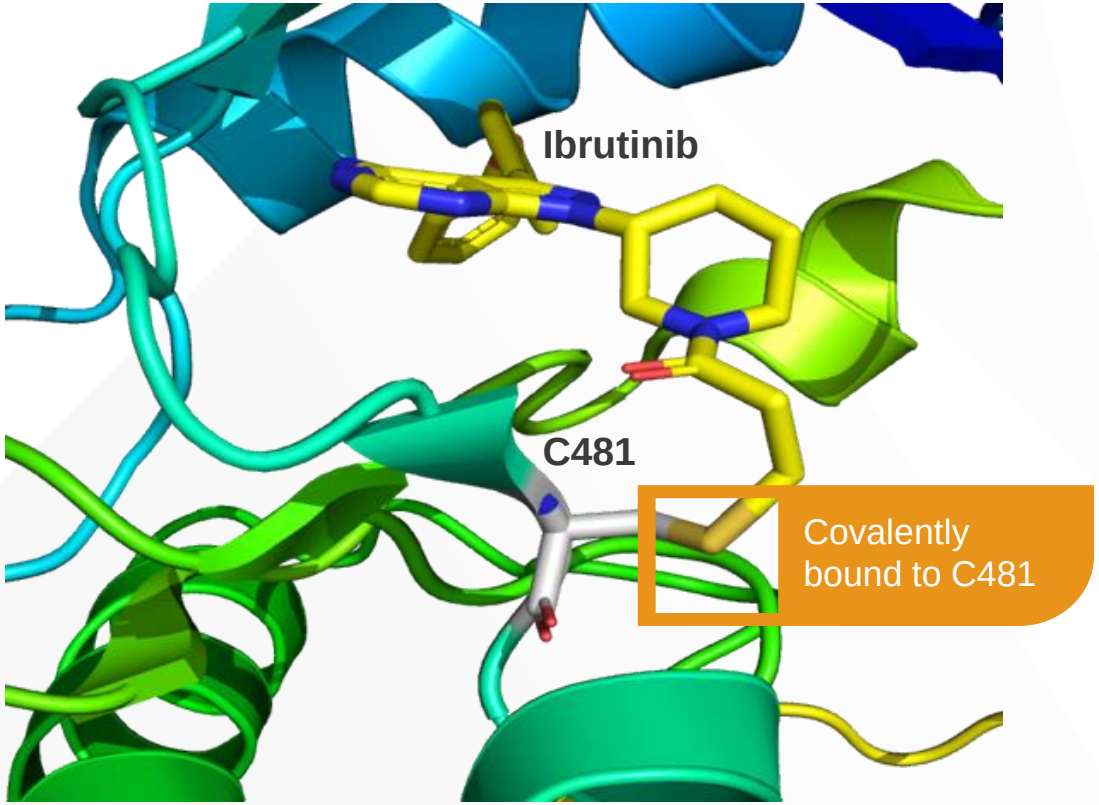
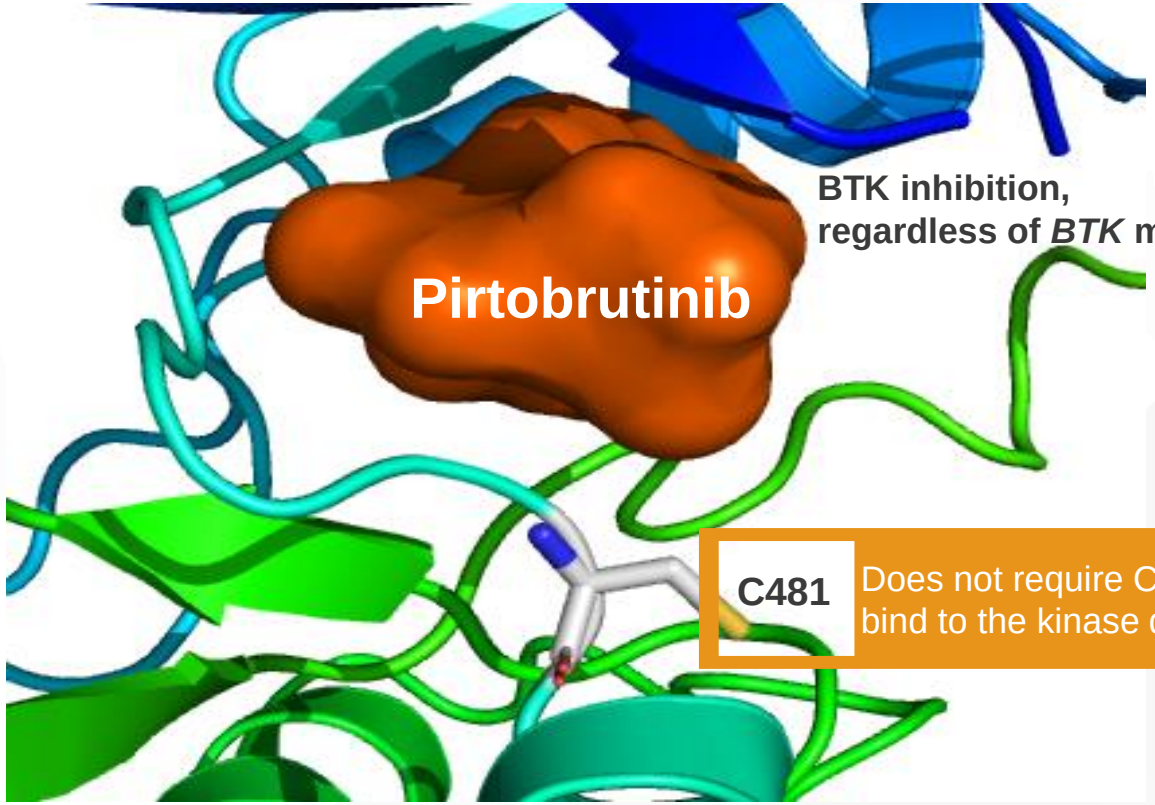
1. Mato AR, et al. *Lancet.* 2021;397(10277):892-901. 2. Brandhuber B, et al. *Clin Lymphoma Myeloma Leuk*. 2018;18(suppl 1):S216. 3. Gomez EB, et al. *Blood*. 2023;142(1):62-72.
cBTKi, covalent Bruton's tyrosine kinase inhibitor; IC, inhibitory concentration; nM, nanomolar; WT, wild type.

How Noncovalent BTK Inhibitors Overcome Resistance

Covalent BTK Inhibitors (Ibrutinib, Acalabrutinib, and Zanubrutinib) Require WT *BTK* for Activity[1]



Pirtobrutinib Is a Noncovalent BTK Inhibitor That Is Potent Against Both WT and C481-Mutated *BTK*[2]



1. Wang E, et al. *N Engl J Med*. 2022;386(8):735-743. 2. Aslan B, et al. *Blood Cancer J*. 2022;12(5):80.
BTK, Bruton's tyrosine kinase; WT, wild type.

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BTK Inhibitors Overview

BTK Inhibitor	Ibrutinib	Acalabrutinib	Zanubrutinib	Pirtobrutinib	Nemtabrutinib
Generation	First	Second	Second	Third	Third
FDA approval (Earliest FDA approval)	(2014) CLL/SLL, WM, cGVHD	(2018) CLL/SLL, R/R MCL	(2019) CLL/SLL, R/R MCL, WM, R/R MZL	(2023) R/R MCL after 2+ lines of tx including BTKi (2023) CLL/SLL after 2+ lines of tx including BTKi and BCL-2i	In clinical trials
Mechanism of action	Covalent	Covalent	Covalent	Noncovalent	Noncovalent
Dosing	420 mg daily	100 mg twice daily	160 mg twice daily or 320 mg daily	200 mg daily	65 mg daily (Phase II dosing)

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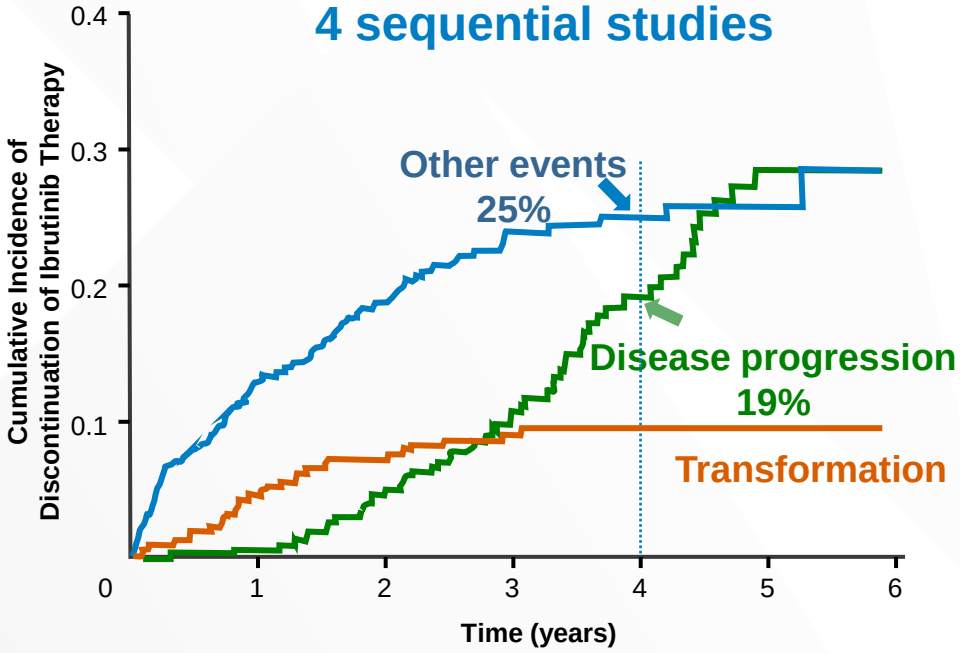
IMBRUVICA® (ibrutinib). Prescribing information. Janssen Biotech; 2022. CALQUENCE® (acalabrutinib). Prescribing information. AstraZeneca Pharmaceuticals; 2022. BRUKINSA® (zanubrutinib). Prescribing information. BeiGene USA; 2023. JAYPIRCA (pirtobrutinib). Prescribing information. Eli Lilly; 2023. Montoya S, Thompson MC. *Cancers (Basel).* 2023;15(14):3648. FDA.gov. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pirtobrutinib-chronic-lymphocytic-leukemia-and-small-lymphocytic

BCL-2, B-cell leukemia/lymphoma 2 protein; BTKi, Bruton's tyrosine kinase inhibitor; cGVHD, chronic graft versus host disease; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; tx, treatment; WM, Waldenström's macroglobulinemia.

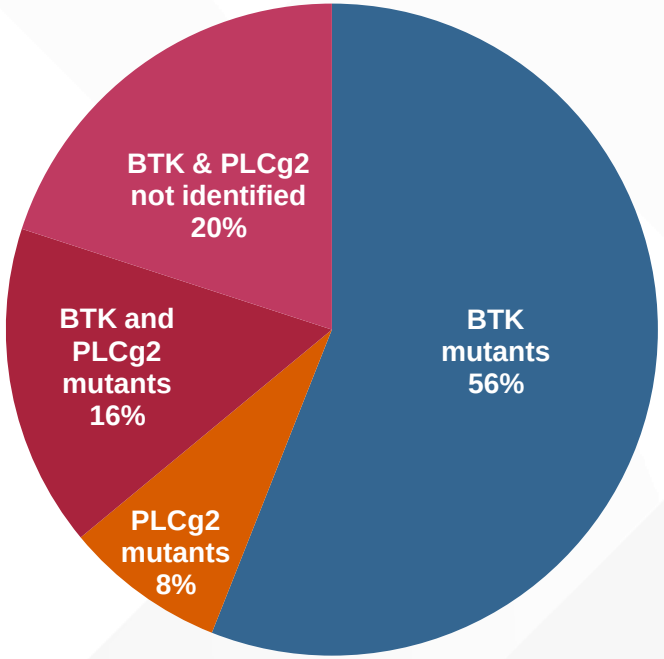
Clinical Efficacy and Safety Profiles of BTK Inhibitors

Resistance and Intolerance to Covalent BTK Inhibitors Affect Outcomes in CLL

Ibrutinib discontinuation from 4 sequential studies



Ibrutinib acquired resistance in patients with progressive CLL



- Front-line: Ibrutinib discontinuation rate at 5 years = 41%
- Relapse/refractory: Predicted ibrutinib discontinuation rate at 5 years + 53.7% (4 sequential studies)
- The appearance of BTK C481 mutations is the dominant reason for progressive CLL after covalent BTK inhibitors
- BTK C481 mutations prevent covalent BTK inhibitors from effective target inhibition

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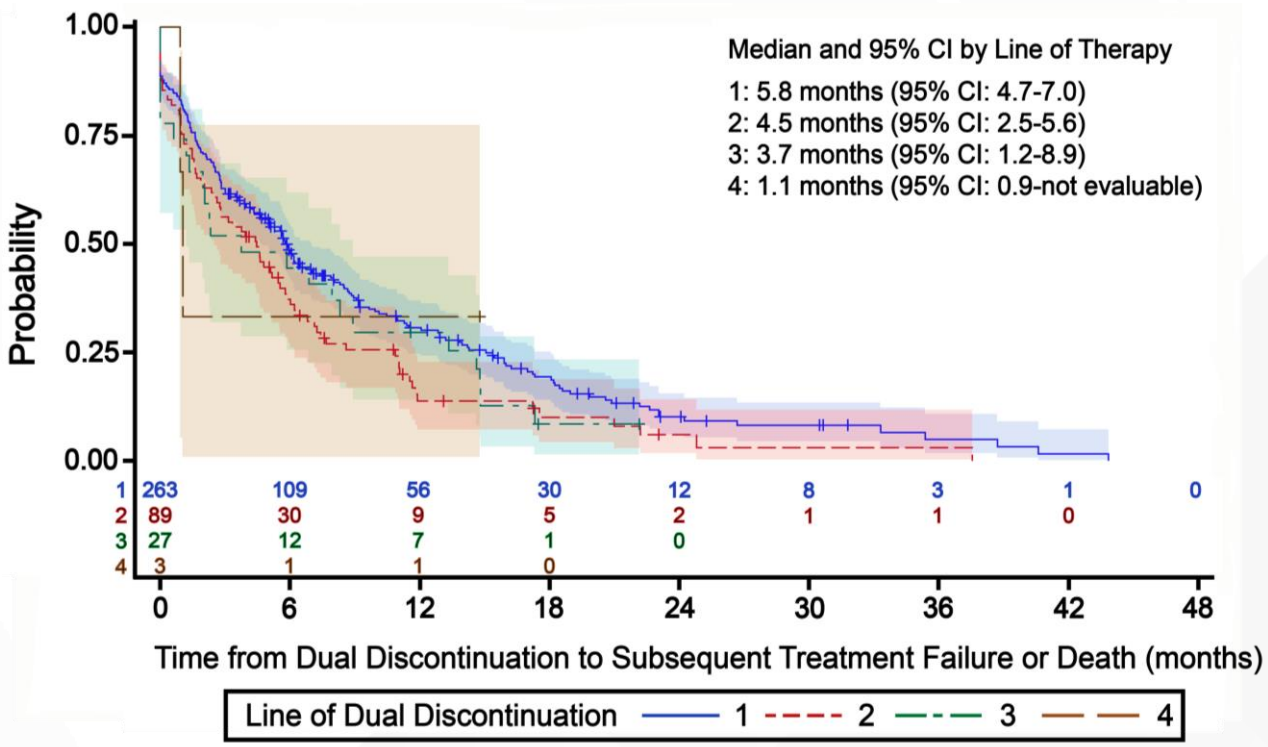
1. Woyach JA, et al. *J Clin Oncol*. 2017;35(13):1437-1343. 2. Lampson BL, et al. *Expert Rev Hematol*. 2018;11(3):185-194. 3. Woyach JA, et al. *N Engl J Med*. 2014;370(24):2286-2294. 4. Byrd JC, et al. *N Engl J Med*. 2016;374(4):323-332. 5. Xu L, et al. *Blood*. 2017;129(18):2519-2525. 6. Hershkovitz-Rokah, et al. *Br J Haematol*. 2018;181(3):306-319. 7. Burger JA. *Leukemia*. 2020;34(3):787-798, 8. Woyach J, et al. ASH 2019. Abstract 504.
BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia.

Limited Therapeutic Options and Poor Outcomes after Covalent BTK Inhibitor Treatment Represent a Major Unmet Medical Need in CLL/SLL

- The vast majority of patients discontinue cBTKi for either progression or intolerance[1-3]
- Limited prospective data and treatment options in the post-cBTKi setting currently exist
- Venetoclax (BCL2i) based regimens have often been a next treatment option after cBTKi for patients with CLL/SLL
- An increasing number of patients who have discontinued cBTKi have also discontinued venetoclax
  - Outcomes are poor and there is a need for additional treatment options[4]

Time from cBTKi/BCL2i Discontinuation to Subsequent Treatment Failure or Death[4]

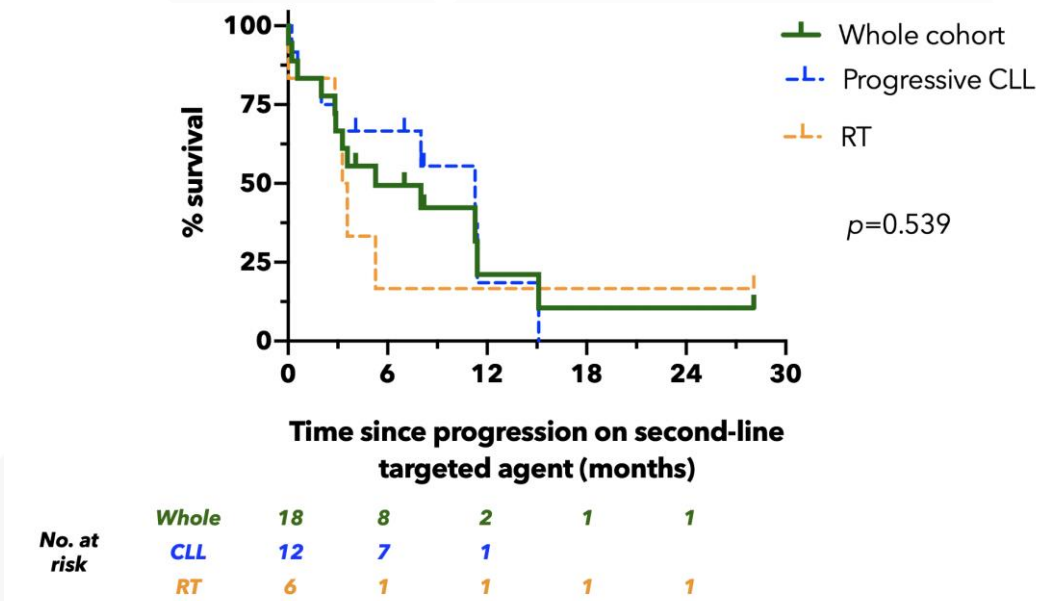


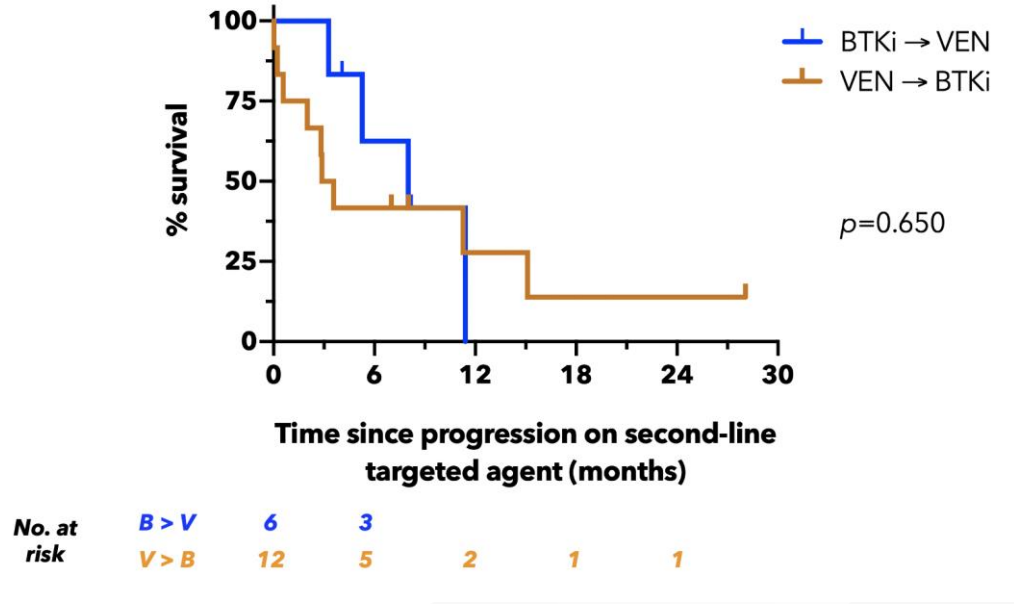
1. Woyach JA, et al. *J Clin Oncol*. 2017;35(13):1437-1443. 2. Barr PM, et al. *Blood Adv*. 2022;6(11):3440-3450. 3. Byrd JC, et al. ASH 2022. Abstract 4431. 4. Mato AR, et al. *Clin Lymphoma Myeloma Leuk*. 2023;23(1):57-67.

BCL2i, B-cell lymphoma 2 inhibitor; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.

Outcomes for “Double Class Resistant” CLL Are Poor

2011 to 2020: 165 pts treated with Ven or BTKi → 42 double exposed → 18 double refractory



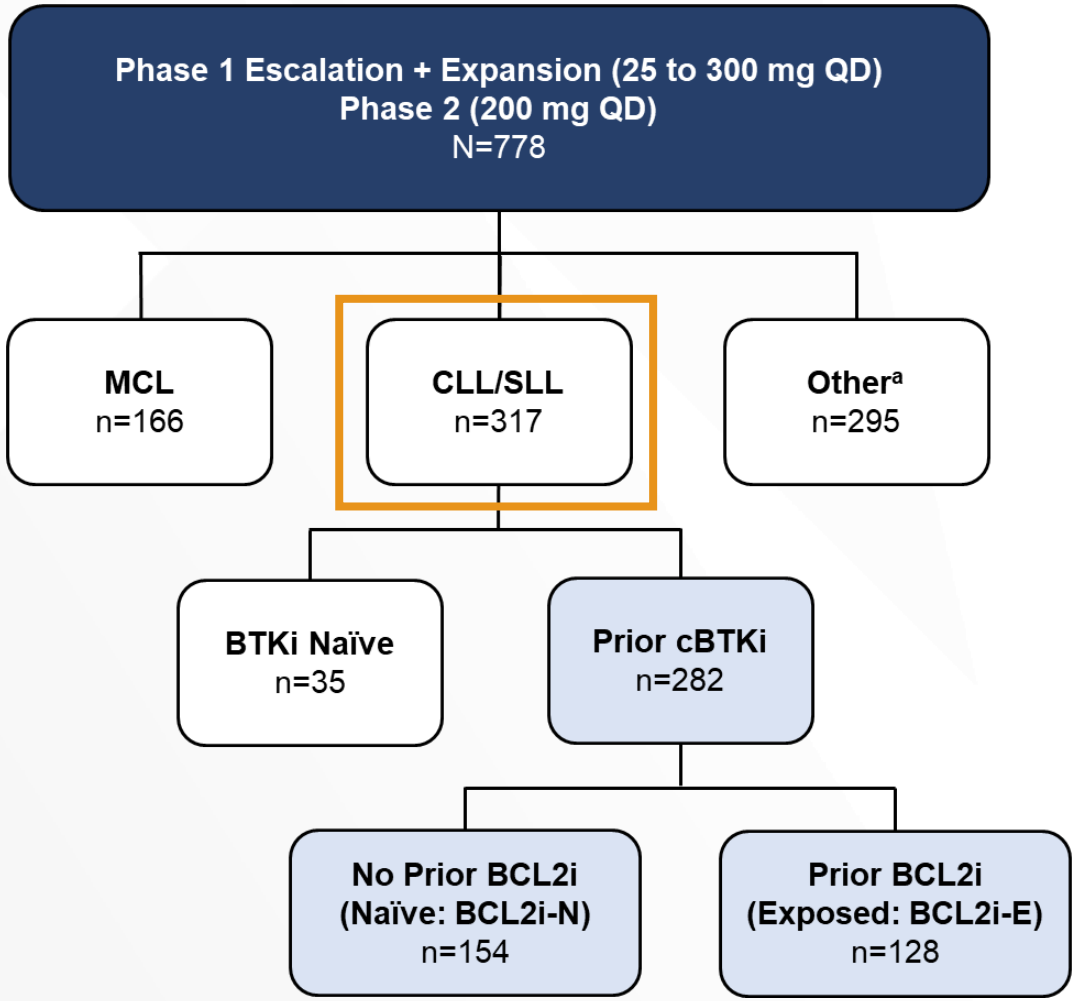


- Whole cohort median OS: 5.3 months
- No difference in OS between progressive CLL (11.3 months) and RT (3.4 months)

- No difference in OS between BTKi → VEN (8 months) and VEN → BTKi (3.2 months)

Lew TE, et al. *Blood Adv.* 2021;5(20):4054-4058.
BTKi, Bruton’s tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; OS, overall survival; RT, Richter transformation; VEN, venetoclax.

Pirtobrutinib in CLL/SLL Phase 1/2 BRUIN Study: Design, Eligibility and Enrollment



Phase 1 3+3 design

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

Eligibility

- Age ≥18
- ECOG PS 0-2
- Active disease and in need of treatment
- Previously treated

Key endpoints

- Safety/tolerability
- Determine MTD and RP2D
- Pharmacokinetics
- Efficacy (ORR according to iwCLL 2018 criteria, DoR, PFS, and OS)

Woyach JA, et al. ASH 2023. Abstract 325.

Data cutoff of 05 May 2023 (NCT03740529). aOther includes DLBCL, WM, FL, MZL, Richter transformation, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformation.

BCL2i, B-cell lymphoma 2 inhibitor; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; OS, overall survival; ORR, overall response rate; PFS, progression-free survival; RP2D, recommended phase II dose; QD, once a day; SLL, small lymphocytic lymphoma.

BRUIN Study: Baseline Characteristics of Patients with CLL/SLL who Received Prior Covalent BTK Inhibitor

Characteristics	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Median age, years (range)	69 (36-88)	69 (36-87)	68 (41-88)
Male, n (%)	192 (68)	106 (69)	86 (67)
Rai staging, n (%)			
0-II	147 (52)	94 (61)	53 (41)
III-IV	120 (43)	58 (38)	62 (48)
Missing	15 (5)	2 (1)	13 (10)
Bulky Lymphadenopathy ≥5 cm, n (%)	88 (31)	42 (27)	46 (36)
ECOG PS, n (%)			
0	144 (51)	89 (58)	55 (43)
1	118 (42)	56 (36)	62 (48)
2	20 (7)	9 (6)	11 (9)
Median number of prior lines of systemic therapy, (range)	4 (1-11)	3 (1-9)	5 (1-11)
Prior therapy, n (%)			
BTK inhibitor	282 (100)	154 (100)	128 (100)
Anti-CD20 antibody	251 (89)	127 (83)	124 (97)
Chemotherapy	228 (81)	114 (74)	114 (89)
BCL2 inhibitor	128 (45)	0 (0)	128 (100)
PI3K inhibitor	71 (25)	17 (11)	54 (42)
CAR T	17 (6)	2 (1)	15 (12)
Allogeneic stem cell transplant	7 (3)	1 (1)	6 (5)

Characteristics	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Median time from diagnosis to first dose, years (IQR)	11 (8-15)	11 (7-15)	12 (8-15)
Reason for any prior BTKi discontinuation[a], n (%)			
Progressive disease	217 (77)	110 (71)	107 (84)
Toxicity/Other	64 (23)	43 (28)	21 (16)

Baseline Molecular Characteristics[b]	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Mutation status, n/n available (%)			
BCL2 mutated	19/246 (8)	0/133 (0)	19/113 (17)
BTK C481-mutant	96/245 (39)	57/138 (41)	39/107 (36)
PLCG2-mutant	18/245 (7)	10/138 (7)	8/107 (8)
High Risk Molecular Features, n/n available (%)			
17p deletion and/or TP53 mutation	104/217 (48)	57/123 (46)	47/94 (50)
IGHV unmutated	193/225 (86)	100/125 (80)	93/100 (93)
Complex Karyotype	33/73 (45)	17/41 (42)	16/32 (50)
11q deletion	47/202 (23)	28/115 (24)	19/87 (22)

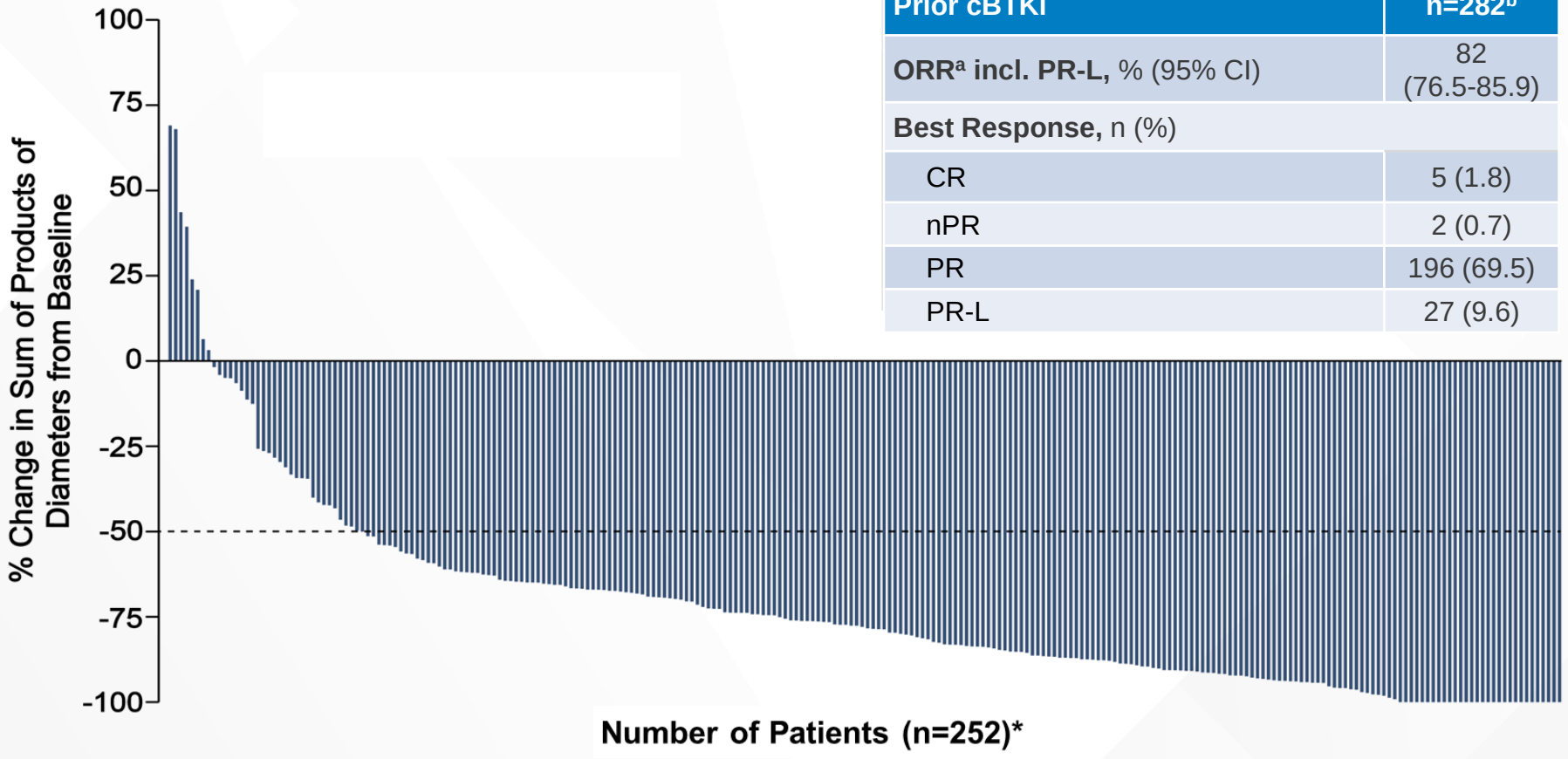
[a]In the event more than one reason was noted for discontinuation, disease progression took priority. [b]Molecular characteristics were determined centrally and are presented based on data availability, in those patients with sufficient sample to pass assay quality control.

Woyach JA, et al. ASH 2023. Abstract 325.

BCL2i, B-cell lymphoma 2 inhibitor; CAR T, chimeric antigen receptor T-cell therapy; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IGHV, immunoglobulin heavy-chain variable region gene; IQR, interquartile range; N, naïve; E, experienced; PI3K, Phosphoinositide 3-kinases; PLCG2, Phospholipase C Gamma 2.

BRUIN Study: Pirtobrutinib Efficacy in All Patients With CLL/SLL Who Received Prior Covalent BTK Inhibitor

Prior cBTKi	n=282[b]
ORR[a] incl. PR-L, % (95% CI)	82 (76.5-85.9)
Best Response, n (%)	
CR	5 (1.8)
nPR	2 (0.7)
PR	196 (69.5)
PR-L	27 (9.6)



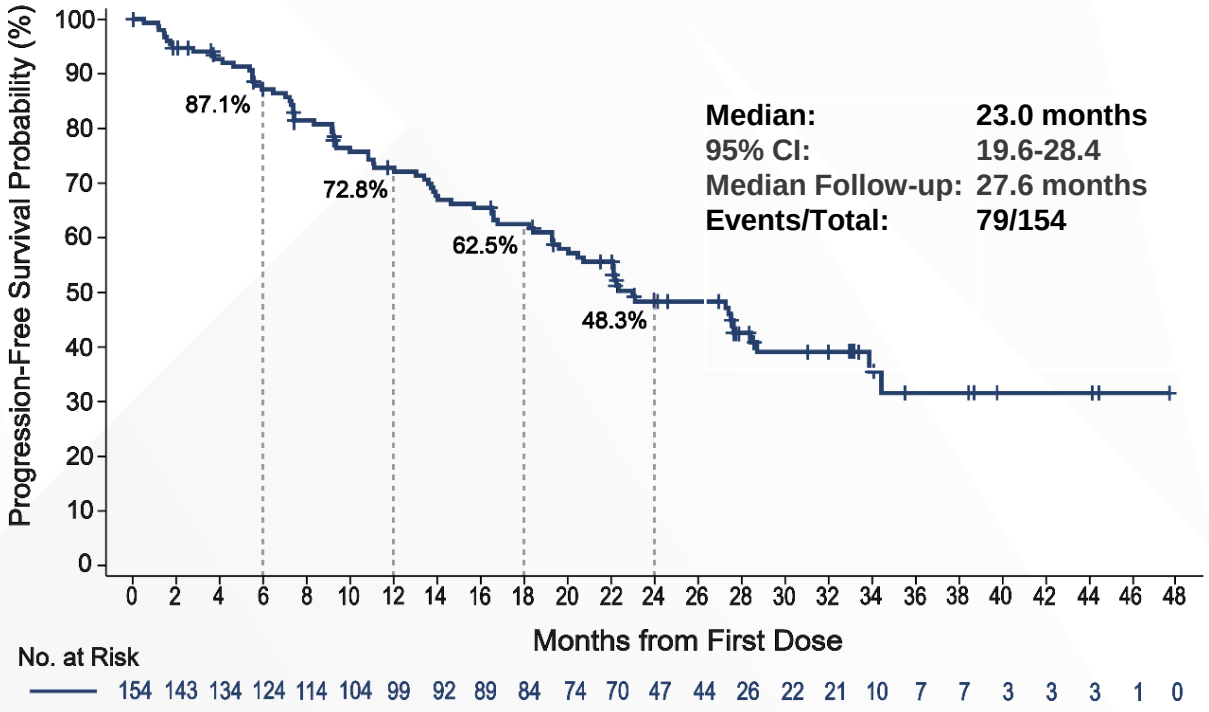
Data of patients with baseline and at least one evaluable post baseline tumor measurement. *Data for 30/282 patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. [a]ORR including PR-L is the number of patients with best response of PR-L or better divided by the total number of patients; 14 patients with a best response of not evaluable (NE) are included in the denominator. [b]Post-cBTKi patients included a subgroup of 19 patients with one prior line of cBTKi-containing therapy and second line therapy of pirtobrutinib, who had an ORR including PR-L of 89.5% (95% CI: 66.9-98.7). Response status per iwCLL 2018 based on IRC assessment.

Woyach JA, et al. ASH 2023. Abstract 325.

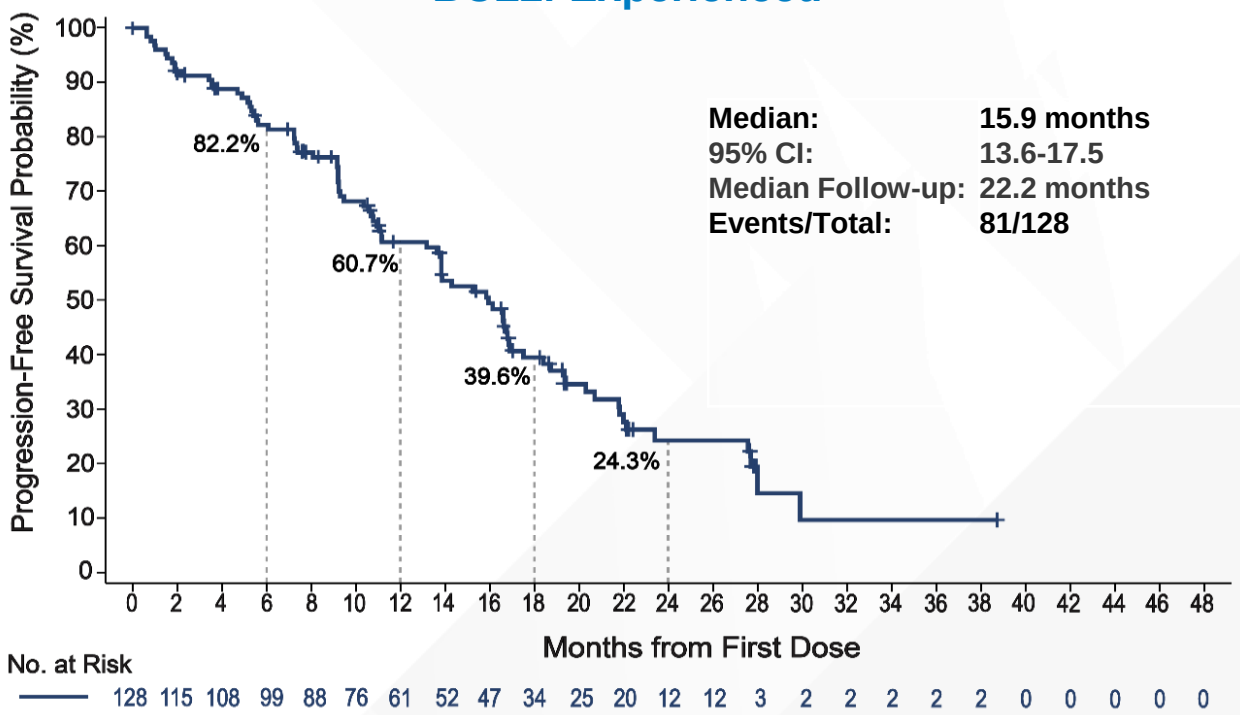
cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CR, complete response; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; nPR, nodular partial response; ORR, overall response rate; PI3k, PR, partial response; PR-L, partial response with lymphocytosis; SLL, small lymphocytic lymphoma.

BRUIN Study: Pirtobrutinib Progression-Free Survival With Prior Covalent BTK Inhibitor, With or Without Prior BCL2 Inhibitor

BCL2i-Naive



BCL2i-Experienced



Median PFS for entire study population: 19.4 months

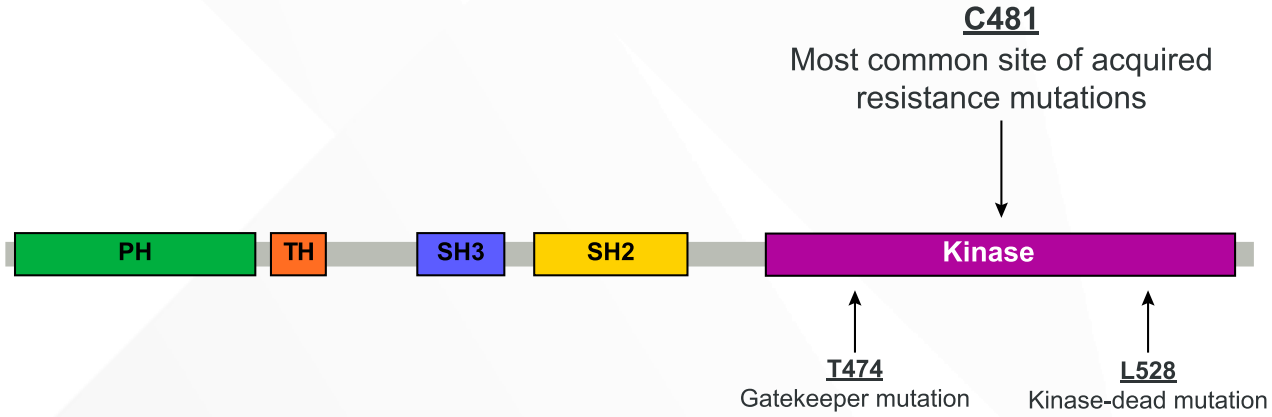
Medical Education

Woyach JA, et al. ASH 2023. Abstract 325.

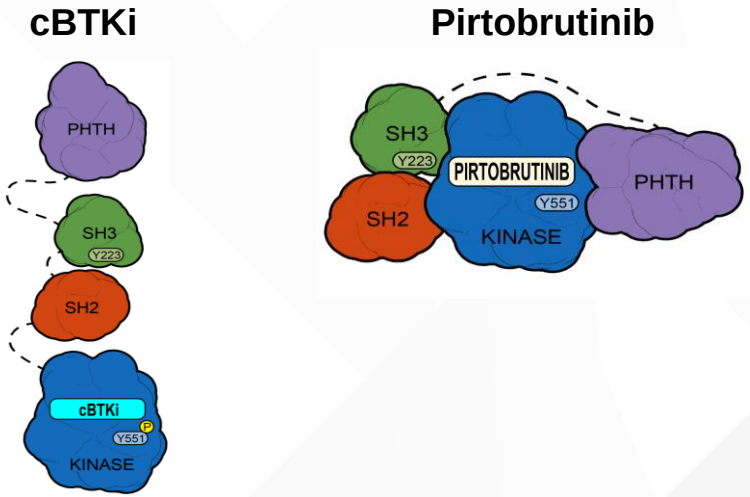
BCL2i, B-cell lymphoma 2 inhibitor; cBTKi, covalent Bruton's tyrosine kinase inhibitor; PFS, progression-free survival.

Pirtobrutinib Noncovalent Binding Inhibits Both WT and C481-Mutated BTK

BTK sites with known cBTKi resistance mutations



Pirtobrutinib may stabilize BTK in a closed inactive conformation[9]



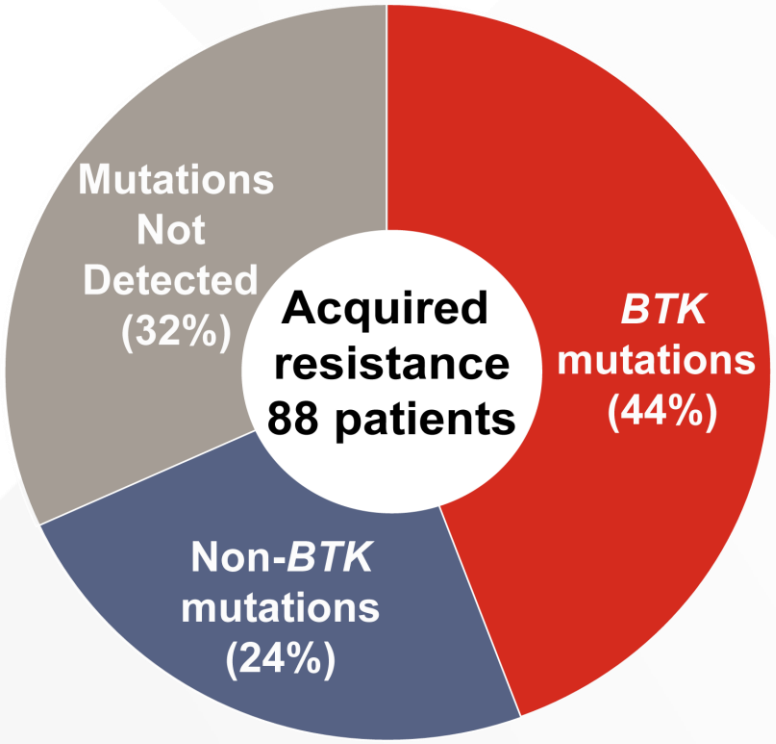
- The majority of patients discontinue covalent BTK inhibitors (cBTKi) due to intolerance or progression [1,2,3]
- BTK C481 substitutions are the most common resistance mechanism to cBTKi [4,5,6]
- Acquired mutations have been identified in a limited number of patients treated with pirtobrutinib [7,8]

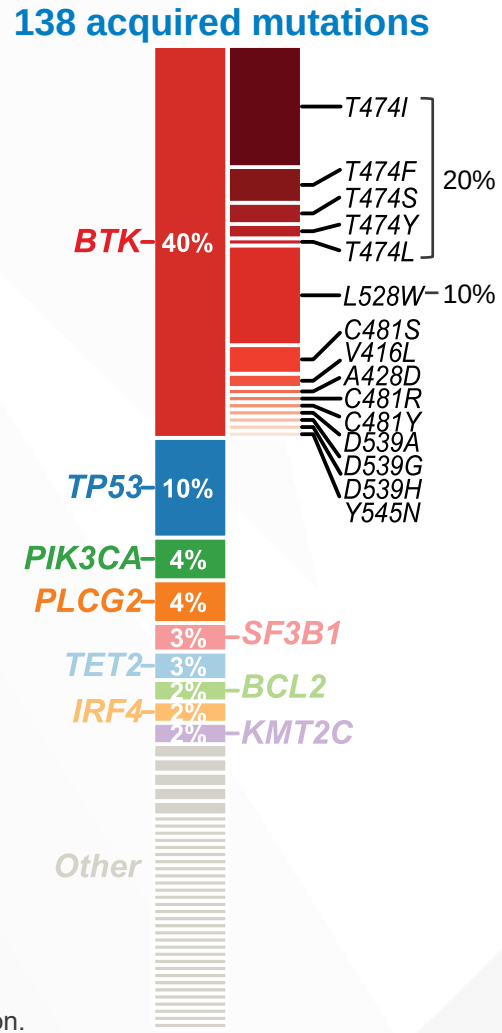
- Inactive conformation of BTK by pirtobrutinib:
  - blocks access to upstream kinases and phosphorylation of Y551
  - inhibits both WT and C481-mutant BTK with equal low nM potency [7,9]
  - may inhibit kinase-independent BTK signaling [9]

Brown JR, et al. ASH 2023. Abstract 326.
1. Woyach JA, et al. *J Clin Oncol*. 2017;35(13):1437-1443. 2. Barr PM, et al. *Blood Adv*. 2022;6(11):3440-3450. 3. Byrd JC, et al. ASH 2022. Abstract 4431. 4. Estupiñán HY, et al. *Leukemia.* 2021;35(5):1317-1329. 5. Handunnetti, et al. ASH 2019. Abstract 756. 6. Blombery P, et al. *Blood Adv.* 2022;6(20):5589-5592. 7. Wang E, et al. *N Engl J Med.* 2022;386(8):735-743. 8. Naeem A, et al. *Blood Adv*. 2023;7(9):1929-1943. 9. Gomez EB, et al. *Blood*. 2023;142(1):62-72.

cBTKi, covalent Bruton's tyrosine kinase inhibitor; nM, nanomolar; WT, wild type.

Acquired Mutations Were Detected at PD in 68% of Patients

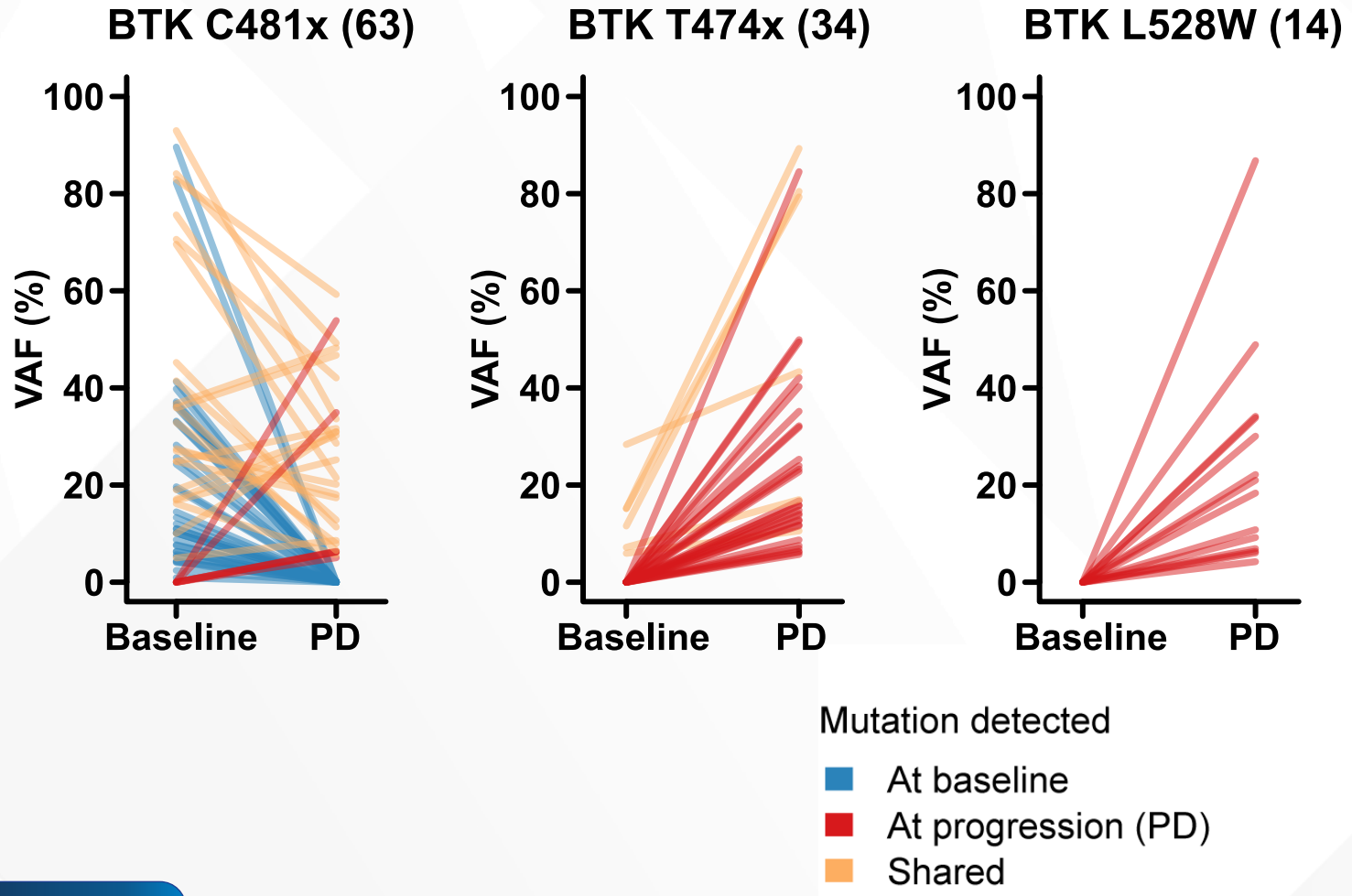




- 68% (60/88) acquired mutations at PD
  - 44% (39/88) had at least one acquired BTK mutation at PD
    - > 64% (25/39) who acquired a BTK mutation had a BTK mutation at baseline
- 56% (49/88) did not acquire a BTK mutation
  - The most frequently acquired non-BTK mutation was TP53
- 32% (28/88) had no acquired mutations detected at PD

Brown JR, et al. ASH 2023. Abstract 326.
BTK, Bruton's tyrosine kinase; PD, disease progression.

The Majority of BTK Acquired Mutations Were T474x and L528W



- Decrease/clearance of C481x[a] clones observed at progression in 84% (36/43) patients (clearance = 23/43, 53%)
- *BTK* C481S/Y/R, T474x[a], L528W, other kinase mutations arose at/near progression (55 mutations in 39 patients, VAF range 3-86%)
- ORR was similar across groups regardless of the acquired BTK mutation (T474x, 22/23, 96%; L528W; 11/14, 79%)

[a]Any amino acid substitutions.
Brown JR, et al. ASH 2023. Abstract 326.
BTK, Bruton's tyrosine kinase; ORR, overall response rate; PD, disease progression; VAF, variant allele frequency.

Pirtobrutinib FDA Approval in CLL/SLL

- December 2023: the Food and Drug Administration granted accelerated approval to pirtobrutinib for adults with CLL/SLL who have received at least two prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor
- BRUIN Trial (NCT03740529)
  - ORR: 72%
  - Median DoR: 12.2 months
- ASH 2023 updated data:
  - Prior BTK inhibitor (n=282)
    - > ORR: 81.6%
    - > mPFS: 19.4 months
  - Prior covalent BTK inhibitor and BCL-2 inhibitor (n=128)
    - > ORR: 79.7%
    - > mPFS: 15.9 months

AXIS Medical Education

FDA.gov. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pirtobrutinib-chronic-lymphocytic-leukemia-and-small-lymphocytic.
Woyach JA, et al. ASH 2023. Abstract 325.
BCL2, B-cell lymphoma 2; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; DoR, duration of response; mPFS, median progression-free survival; ORR, overall response rate; SLL, small lymphocytic lymphoma.

BELLWAVE-001: Nemtabrutinib Demonstrated Robust and Durable Clinical Responses in Pretreated CLL[1,2]

Nemtabrutinib: Noncovalent, Reversible Inhibitor of Both WT and Ibrutinib-Resistant C481S-Mutated *BTK*

n (%) [95% CI]	CLL/SLL 65 mg QD n = 57	CLL/SLL Cohort A[a] n = 25	CLL/SLL Cohort B[b] n = 10
ORR	**30 (53) [39-66]**	**15 (60) [39-79]**	**4 (40) [12-74]**
CR	2 (4) [0.4-12]	0 (0) [0-14]	1 (10) [0.3-45]
PR	15 (25) [15-40]	5 (20) [7-41]	2 (20) [3-56]
PR-L	13 (23) [13-36]	10 (40) [21-61]	1 (10) [0.3-45]
SD	17 (30) [18-43]	8 (32) [15-54]	3 (30) [7-65]
PD	2 (4) [0.4-12]	0 (0) [0-14]	2 (20) [3-56]
No assessment	8 (14) [6-26]	2 (8) [1-26]	1 (10) [0.3-45]

AXIS Medical Education

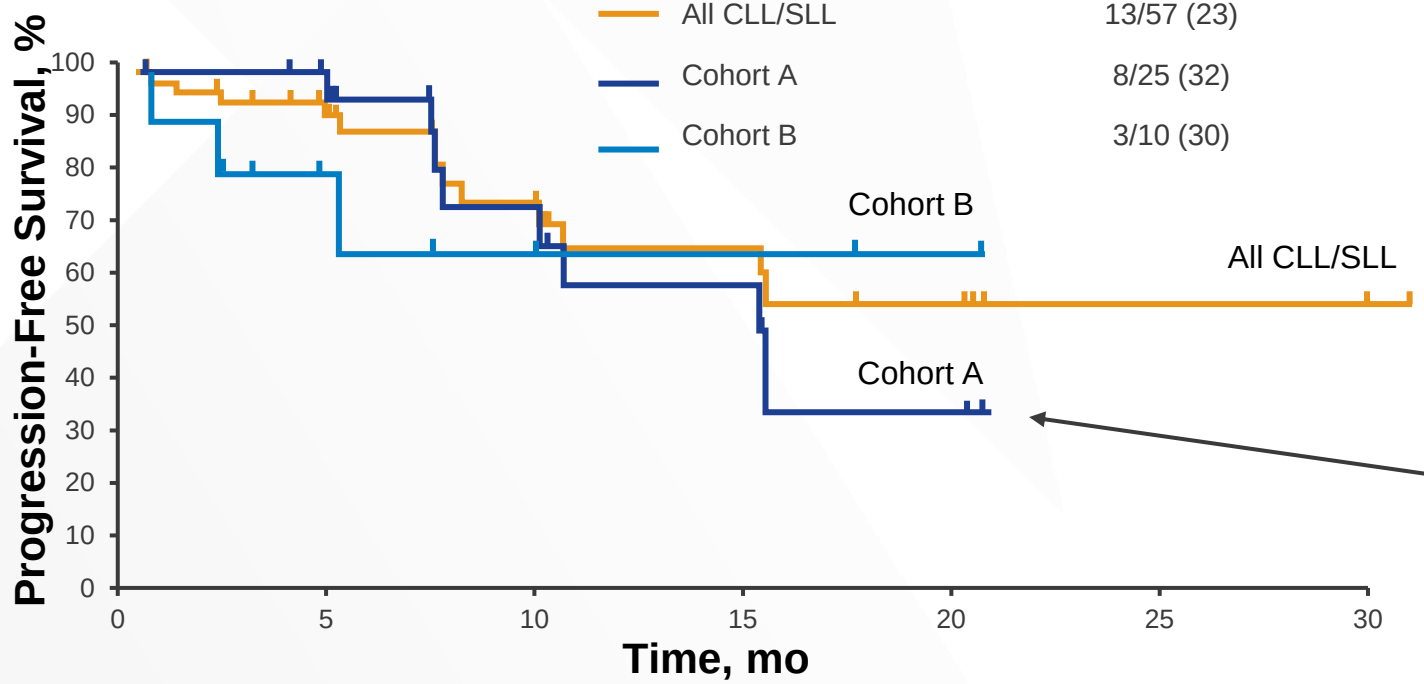
[a]Cohort A comprises patients with mCLL/SLL who received ≥2 prior therapies, including covalent BTKi and who have C481S mutation. [b]Cohort B comprises patients with mCLL/SLL who received ≥2 prior therapies, are intolerant to BTKi, and who have no C481S mutation.

1. Woyach J, et al. EHA 2022. Abstract P682. 2. ClinicalTrials.gov identifier: NCT03162536.

BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; CR, complete response; ORR, overall response rate; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease; PD, disease progression; QD, once daily; SLL, small lymphocytic lymphoma; WT, wild type.

BELLWAVE-001: Nemtabrutinib Is Effective Against *BTK* Resistance Mutations[1]

	PFS Events, n/N, %	PFS Median (95% CI), mo
All CLL/SLL	13/57 (23)	NE (10.6-NE)
Cohort A	8/25 (32)	15.7 (7.6-NE)
Cohort B	3/10 (30)	NE (5.0-NE)



No. at Risk						
All	57	28	19	14	7	2
Cohort A	25	15	10	7	2	0
Cohort B	10	4	2	2	1	0

Cohort A: patients with R/R CLL/SLL who received ≥2 prior therapies, including covalent BTKi, and who have a C481S mutation

1. Woyach J, et al. EHA 2022. Abstract P682.

BTK, Bruton's tyrosine kinase; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; NE, not evaluable; PFS, progression-free survival; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

Ongoing Phase 3 Trials With Noncovalent BTK Inhibitors in CLL

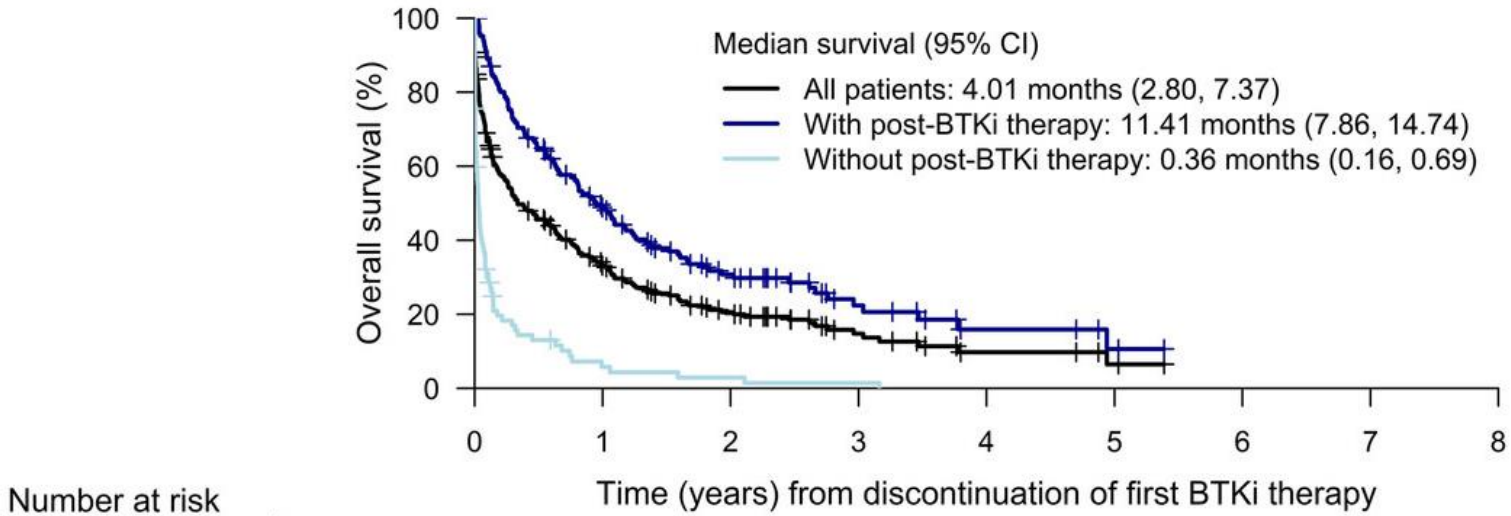
Noncovalent BTKi	Phase 3 Trial	Study Arms	Population
Pirtobrutinib	BRUIN CLL-321 (NCT04666038)	pirtobrutinib vs idelalisib + R or BR	Prior BTKi required
	BRUIN CLL-322 (NCT04965493)	pirtobrutinib + venetoclax + R vs venetoclax + R	Prior BTKi allowed
	BRUIN CLL-313 (NCT05023980)	pirtobrutinib vs BR	Treatment-naive patients
	BRUIN CLL-314 (NCT05254743)	pirtobrutinib vs ibrutinib	BTKi-naive patients
Nemtabrutinib	BELLWAVE-008 (NCT05624554)	nemtabrutinib vs FCR or BR	Previously untreated CLL; no TP53 mutation/del(17p)
	BELLWAVE-010 (NCT05947851)	nemtabrutinib + venetoclax vs venetoclax + R	Following at least 1 prior therapy

AXIS Medical Education

BR, bendamustine, rituximab; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; FCR, fludarabine, cyclophosphamide, rituximab; R, rituximab.

Covalent BTK Inhibitor Resistance is Common and Not Well Understood in MCL

- Most patients will ultimately experience disease progression
- Post-progression outcomes historically poor (OS <1 year)
- Mechanisms less well understood compared to CLL
- Options:
  - Noncovalent BTKi
  - CAR T
  - Trials



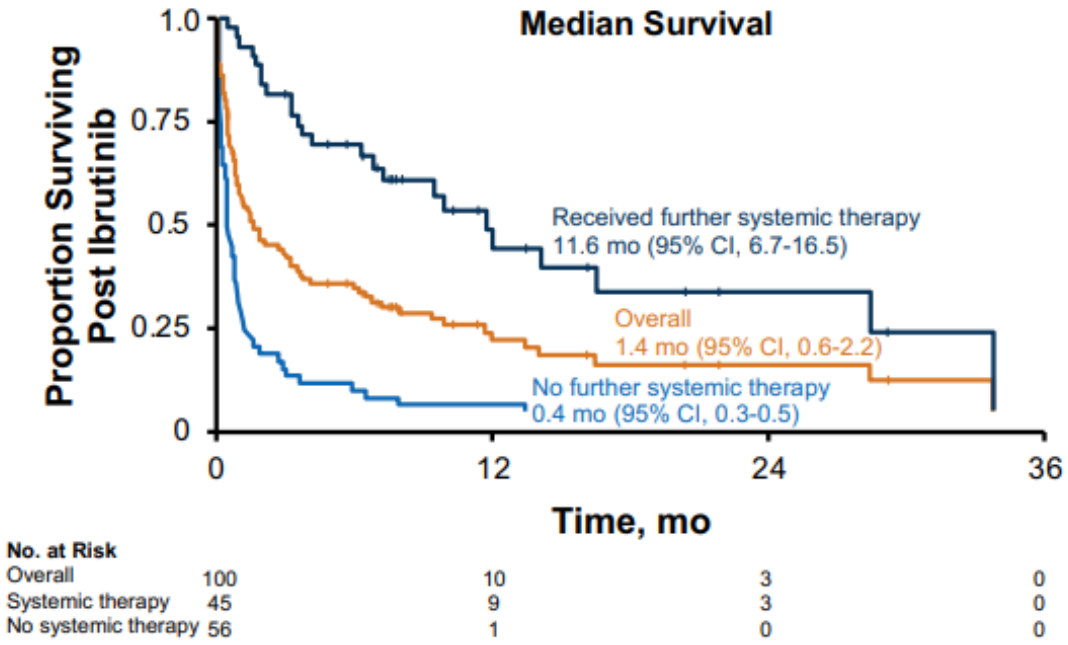
Hess, G et al. *Br J Haematol.* 2023;202(4):749-759.

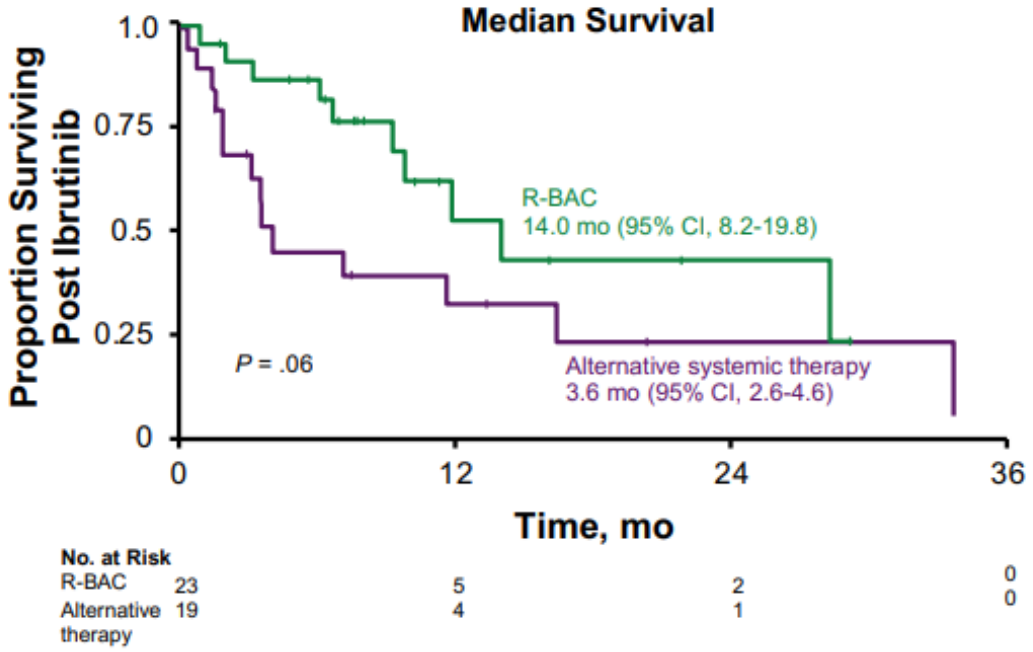
CAR T, chimeric antigen receptor T-cell therapy; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; OS, overall survival.

In MCL, Real-World Data Confirm That Outcomes Are Poor After Progression on Covalent BTK Inhibitor Therapy

- Post-ibrutinib OS for patients progressing on ibrutinib and receiving additional treatment versus no further treatment

- Progression on BTKi likely involves therapeutic resistance
- **Overall post-ibutinib OS was 1.4 months**
- 0.4 months for patients receiving no further therapy



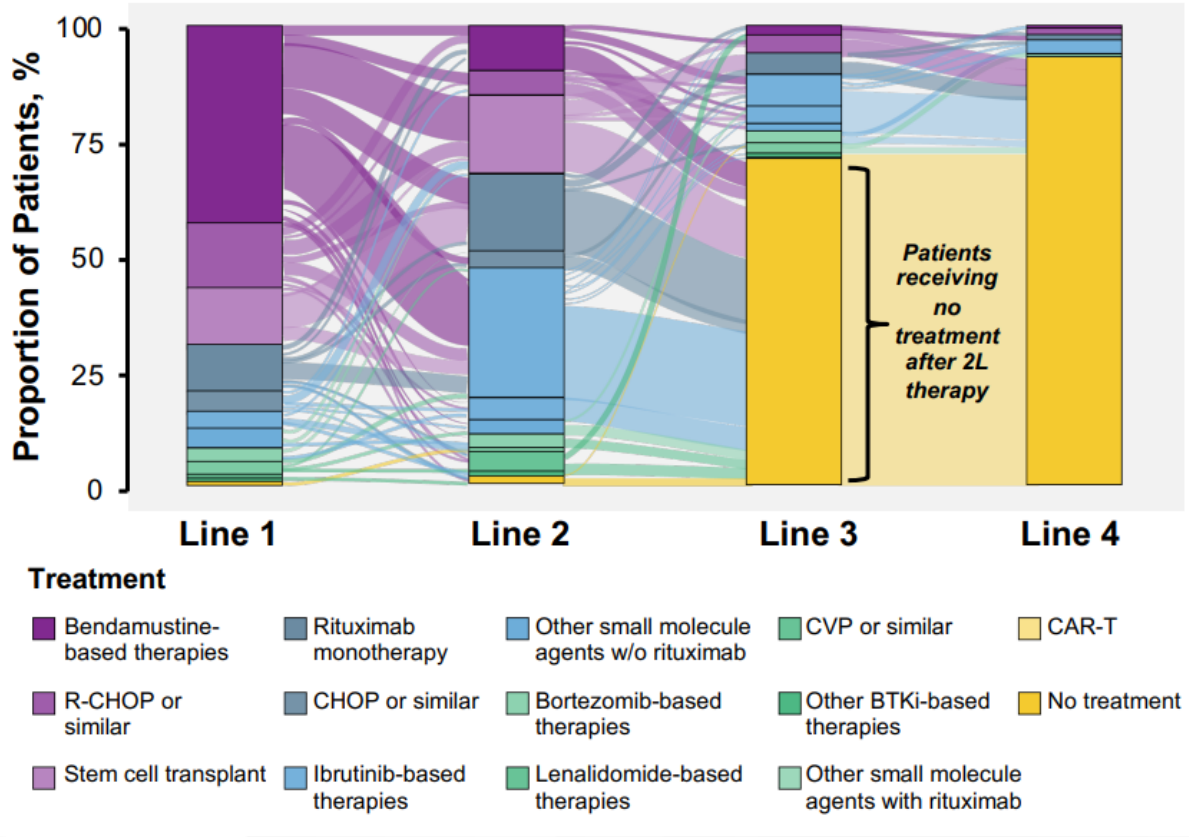


McCulloch R, et al. *Br J Haematol.* 2021;193:290-298.

BTKi, Bruton's tyrosine kinase inhibitor; MCL, mantle cell lymphoma; OS, overall survival; R-BAC, rituximab, bendamustine, cytarabine.

Although BTK Inhibitors Are a Step Forward in MCL, More Needs to Be Done in Later-Line Care

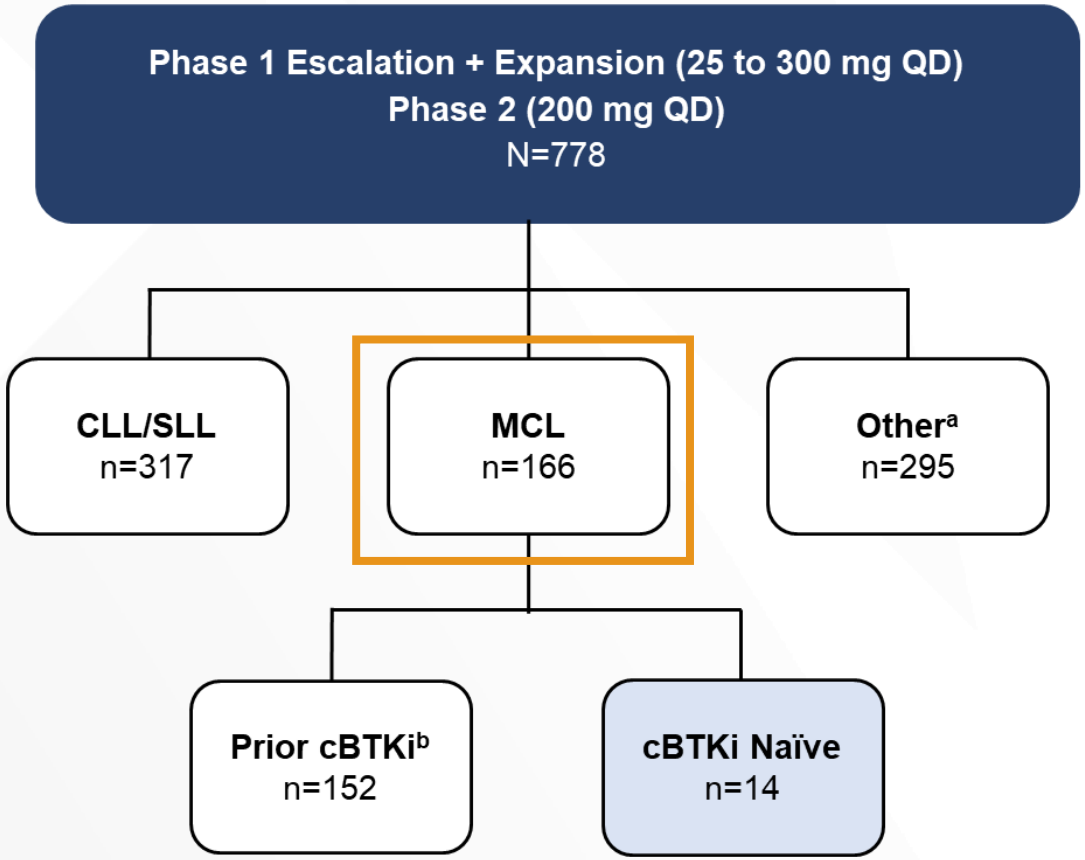
- Based on retrospective claims data from the United States between 2015 and 2021 (N = 696)
- Majority of patients received no treatment in the 3L setting
- Data demonstrate clear unmet needs for 3L care in MCL



Garg M, et al. ASH 2022. Abstract 3534.

2L, second-line; 3L, third-line; BTK, Bruton's tyrosine kinase; CVP, cyclophosphamide, vincristine, prednisone; MCL, mantle cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; CAR-T, chimeric antigen receptor T-cell therapy.

Pirtobrutinib in MCL Phase 1/2 BRUIN Study: Design, Eligibility and Enrollment



Phase 1 3+3 design

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

Eligibility

- Age ≥18
- ECOG 0-2
- Active disease and in need of treatment
- Previously treated

Key endpoints

- Safety/tolerability
- Determine MTD and RP2D
- Pharmacokinetics
- Efficacy (ORR according to Lugano criteria, DoR, PFS, and OS)

Medical Education

Data cutoff of 05 May 2023 (NCT03740529). [a]Other includes DLBCL, WM, FL, MZL, Richter transformation, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformations. [b]Prior cBTKi includes Primary Analysis Set (PAS) n=90 and Supplemental Cohort n=62. The PAS comprised the first 90 patients enrolled and served as the primary efficacy population for regulatory interactions and met the following criteria:; had measurable disease, had received a prior cBTKi containing regimen, had no known central nervous system involvement. Updated data from the PAS90 population can be found in supplemental via QR code.

Cohen JB, et al. ASH 2023. Abstract 981.

cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QD, once a day; RP2D, recommended phase II dose; SLL, small lymphocytic lymphoma.

BRUIN Study: Baseline Characteristics of Patients With MCL

Characteristics	Prior cBTKi n=152	cBTKi Naïve n=14
Median age, years (range)	70 (46-88)	67 (60-86)
Male, n (%)	120 (79)	10 (71)
Histology, n (%)		
Classic/leukemic	120 (79)	11 (79)
Pleomorphic/Blastoid	32 (21)	3 (21)
ECOG PS, n (%)		
0	93 (61)	5 (36)
1	56 (37)	8 (57)
2	3 (2)	1 (7)
sMIPI score, n (%)		
Low risk (0-3)	30 (20)	3 (21)
Intermediate risk (4-5)	79 (52)	5 (36)
High risk (6-11)	43 (28)	6 (43)
Bulky Lymphadenopathy (cm), n (%)		
<5	94 (62)	8 (57)
≥5	36 (24)	5 (36)
No Measurable Lymph Node	22 (15)	1 (7)
Bone marrow involvement, n (%)		
Yes	81 (53)	4 (29)
No	71 (47)	10 (71)
Median number of prior lines of systemic therapy, n (range)	3 (1-9)	2 (1-3)

Characteristics	Prior cBTKi n=152	cBTKi Naïve n=14
Prior therapy, n (%)		
BTK inhibitor	152 (100)	0 (0)
Anti-CD20 antibody	147 (97)	14 (100)
Chemotherapy	137 (90)	14 (100)
Immunomodulator	26 (17)	1 (7)
Stem cell transplant	33 (22)	7 (50)
Autologous	30 (20)	7 (50)
Allogeneic	7 (5)	0 (0)
BCL2 inhibitor	24 (16)	0 (0)
CAR T	13 (9)	0 (0)
PI3K inhibitor	6 (4)	1 (7)
Reason discontinued any prior BTKi[a], n (%)		
Progressive disease	128 (84)	-
Toxicity / Other	21 (14)	-
Unknown	3 (2)	-
TP53 Mutation status, n (%)		
Yes	30 (20)	3 (21)
No	30 (20)	4 (29)
Missing	92 (61)	7 (50)
Ki-67 index, n (%)		
<30%	18 (12)	2 (14)
≥30%	45 (30)	6 (43)
Missing	89 (59)	6 (43)

AXIS Medical Education

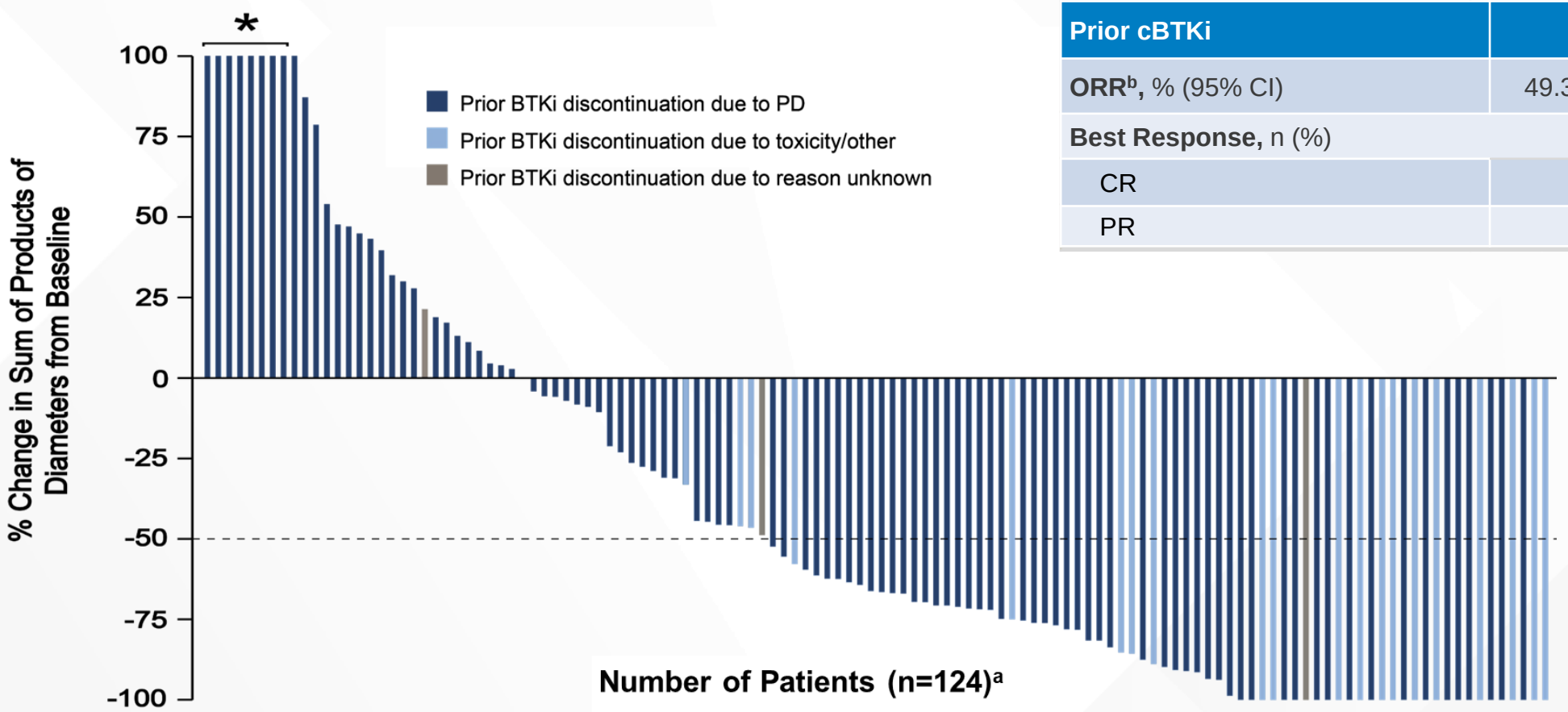
[a]In the event more than one reason was noted for discontinuation, disease progression took priority. Total percentages may not sum to 100% due to rounding.

Cohen JB, et al. ASH 2023. Abstract 981.

BCL2, B-cell lymphoma 2; BTK, Bruton's tyrosine kinase; CAR T, chimeric antigen receptor T-cell therapy; cBTKi, covalent Bruton's tyrosine kinase inhibitor; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MCL, mantle cell lymphoma; PI3K, phosphoinositide 3-kinases; sMIPI, Simplified Mantle Cell Lymphoma International Prognostic Index.

BRUIN Study: Pirtobrutinib Efficacy in Patients With MCL Who Received Prior Covalent BTK Inhibitor

Prior cBTKi	n=152
ORR[b], % (95% CI)	49.3 (41.1-57.6)
Best Response, n (%)	
CR	24 (15.8)
PR	51 (33.6)



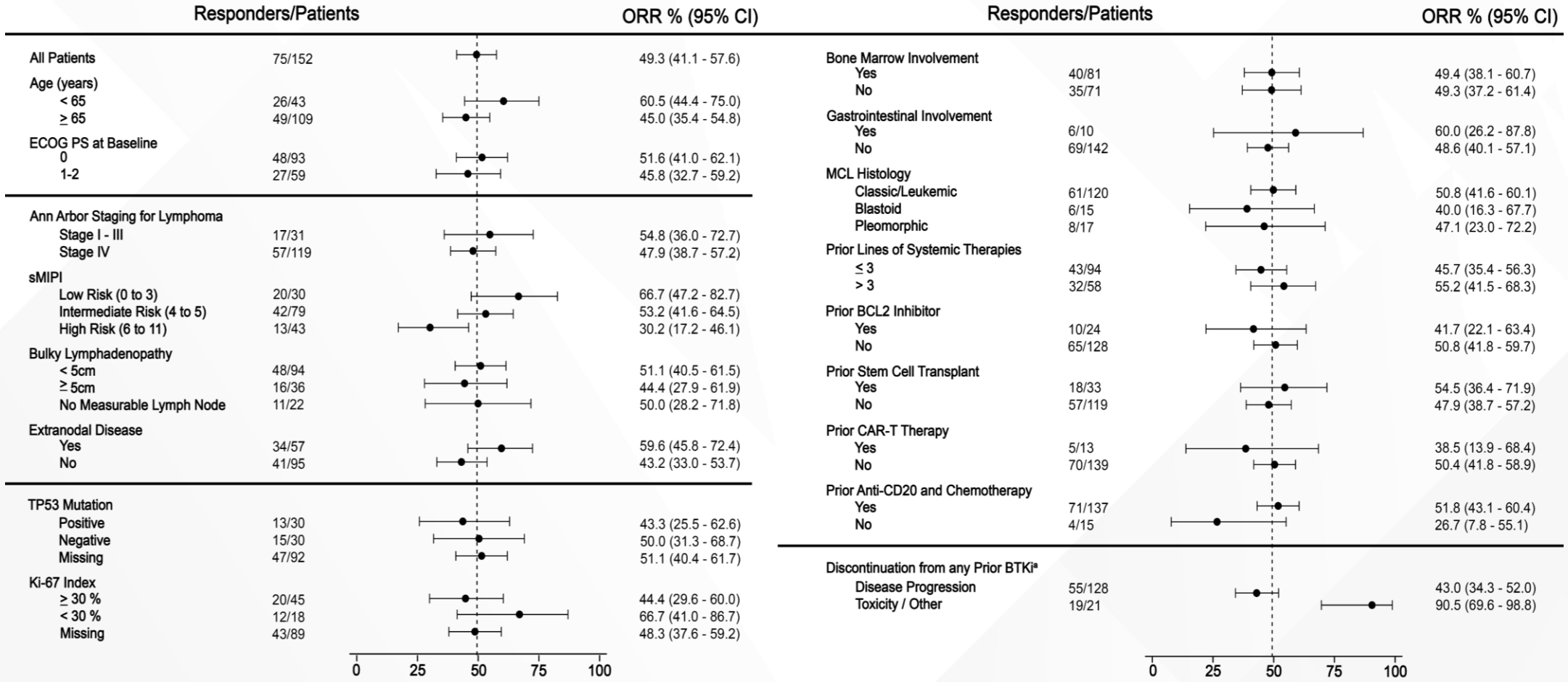
Median Time to First Response was 1.8 months (range: 0.8-13.8)

Data of patients with baseline and at least one evaluable post baseline tumor measurement. *Patients with >100% increase in SPD. [a]Data for 28/152 patients who received prior cBTKi 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. [b]ORR is the number of patients with best response of CR or PR divided by the total number of patients; 13 patients with a best response of not evaluable (NE) are included in the denominator. Response status per Lugano 2014 criteria based on IRC assessment.

Cohen JB, et al. ASH 2023. Abstract 981.

cBTKi, covalent Bruton's tyrosine kinase inhibitor; CR, complete response; MCL, mantle cell lymphoma; ORR, overall response rate; PD, disease progression; PR, partial response.

BRUIN Study: Overall Response Rate in Prior Covalent BTK Inhibitor Patients With MCL, Including High-Risk Subgroups



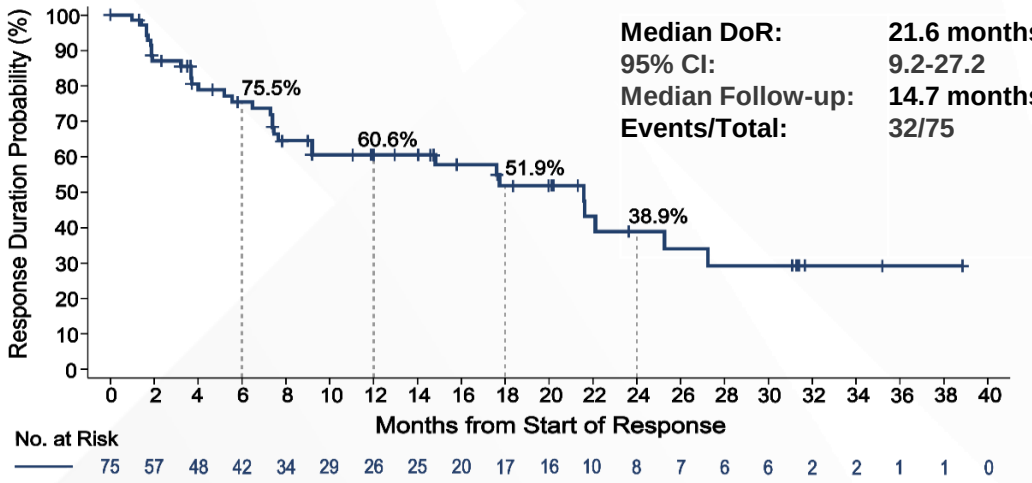
Data reported in the forest plot is overall response rate by prespecified patient characteristic subgroups. Two-sided 95% CI were calculated using the exact binomial distribution. [a]In the event more than one reason was noted for discontinuation, disease progression took priority. Response status per Lugano 2014 criteria based on IRC assessment.

Cohen JB, et al. ASH 2023. Abstract 981.

BCL2, B-cell lymphoma 2; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CAR T, chimeric antigen receptor T-cell therapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MCL, mantle cell lymphoma; ORR, overall response rate; sMIPI, Simplified Mantle Cell Lymphoma International Prognostic Index.

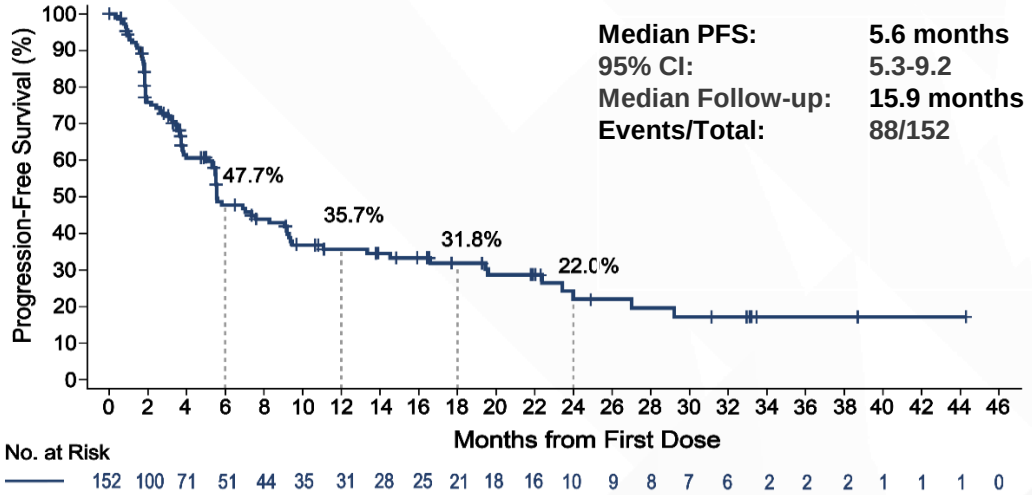
BRUIN Study: Pirtobrutinib Outcomes in Prior Covalent BTK Inhibitor Patients With MCL

Duration of Response



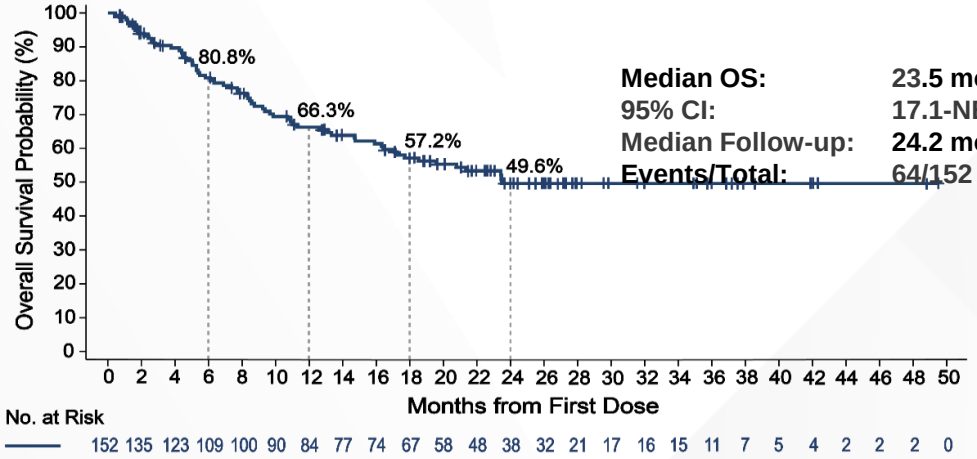
Median DoR: 21.6 months
95% CI: 9.2-27.2
Median Follow-up: 14.7 months
Events/Total: 32/75

Progression-Free Survival



Median PFS: 5.6 months
95% CI: 5.3-9.2
Median Follow-up: 15.9 months
Events/Total: 88/152

Overall Survival



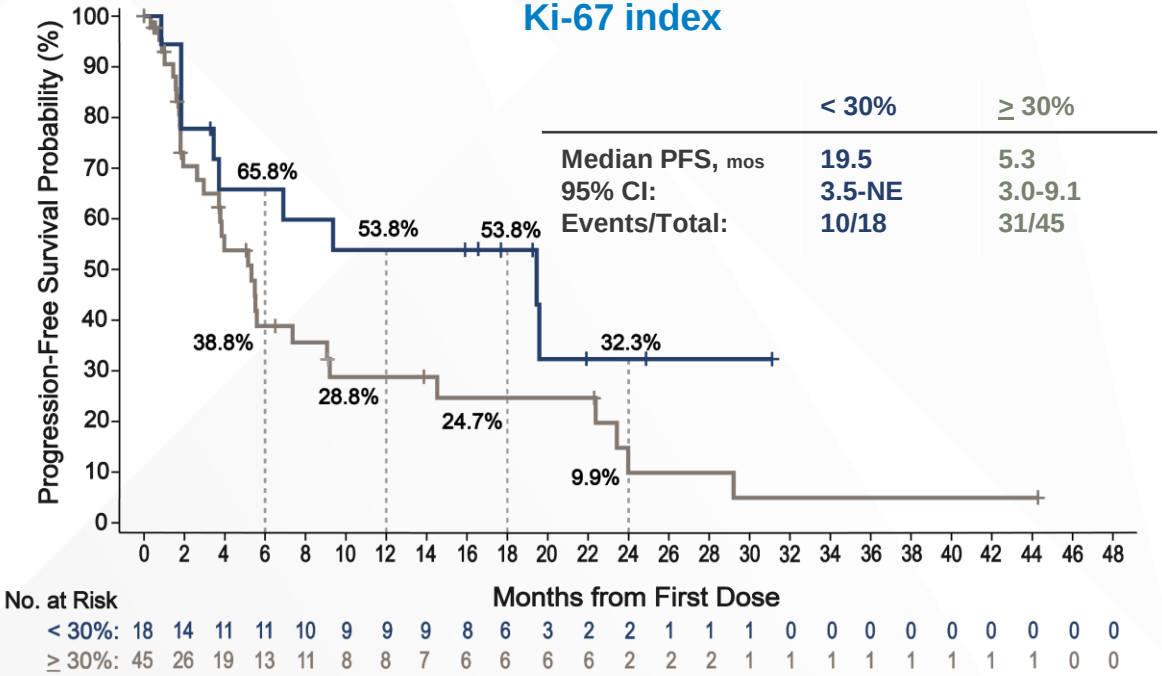
Median OS: 23.5 months
95% CI: 17.1-NE
Median Follow-up: 24.2 months
Events/Total: 64/152

Cohen JB, et al. ASH 2023. Abstract 981.

cBTKi, covalent Bruton's tyrosine kinase inhibitor; DoR, duration of response; MCL, mantle cell lymphoma; NE, not evaluable; OS, overall survival; PFS, progression-free survival.

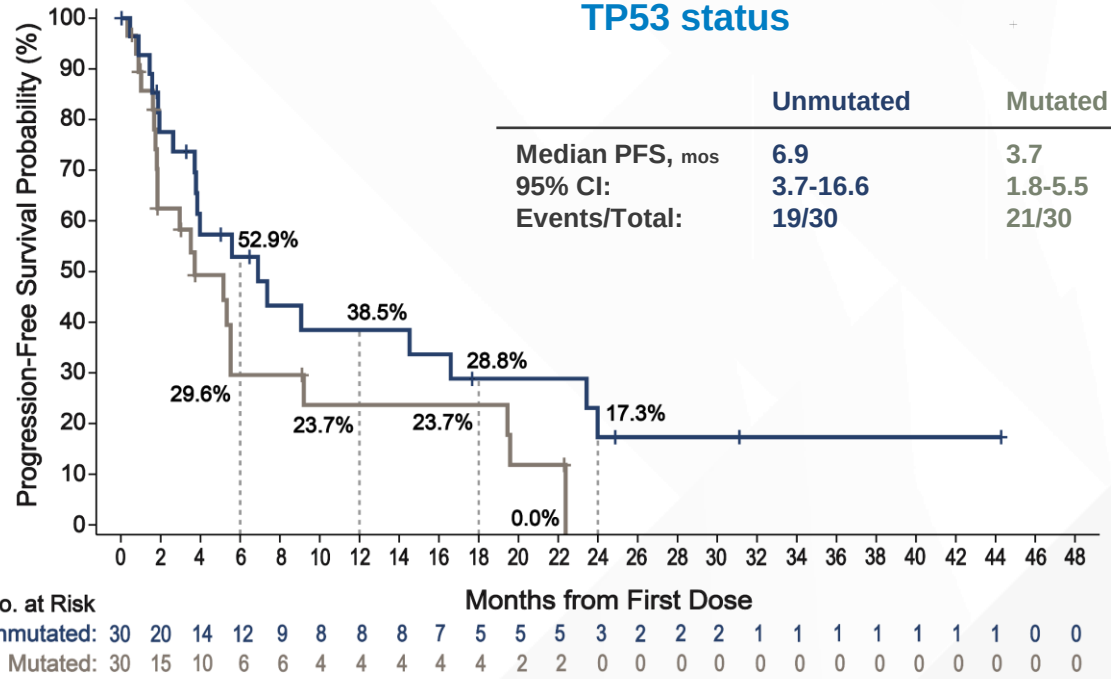
BRUIN Study: Pirtobrutinib Outcomes in Prior Covalent BTK Inhibitor Patients With MCL by High-Risk Subgroups

Ki-67 index



	< 30%	≥ 30%
Median PFS, mos	19.5	5.3
95% CI:	3.5-NE	3.0-9.1
Events/Total:	10/18	31/45

TP53 status



	Unmutated	Mutated
Median PFS, mos	6.9	3.7
95% CI:	3.7-16.6	1.8-5.5
Events/Total:	19/30	21/30

	Median DoR (95% CI)	Median OS (95% CI)
Ki-67		
< 30%	17.7 (1.9-N.E.)	NE (9.4-NE)
≥ 30%	21.6 (5.6-27.2)	23.4 (13.1-NE)

	Median DoR (95% CI)	Median OS (95% CI)
TP53		
Unmutated	14.8 (1.9-NE)	NE (10.7-NE)
Mutated	17.6 (1.7-NE)	15.9 (7.8-NE)

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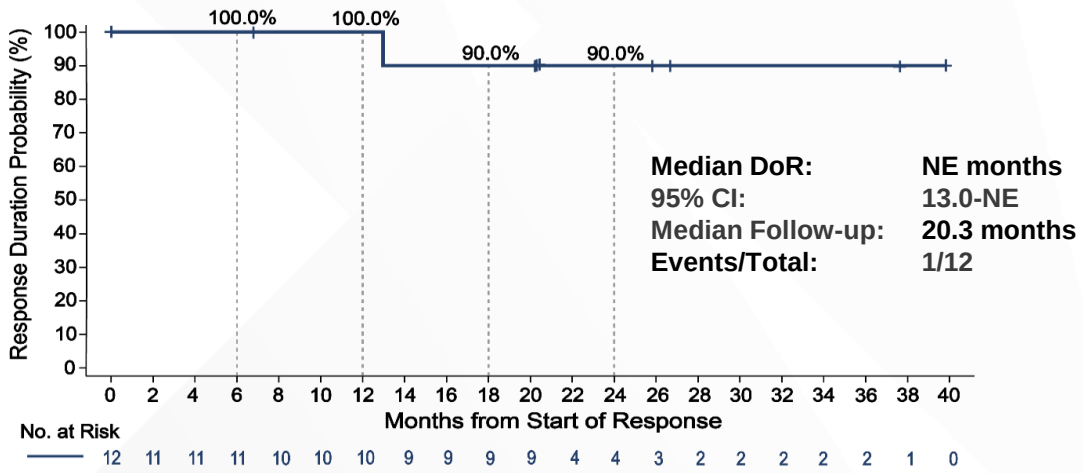
Cohen JB, et al. ASH 2023. Abstract 981.

cBTKi, covalent Bruton's tyrosine kinase inhibitor; DoR, duration of response; MCL, mantle cell lymphoma; NE, not evaluable; OS, overall survival; PFS, progression-free survival.

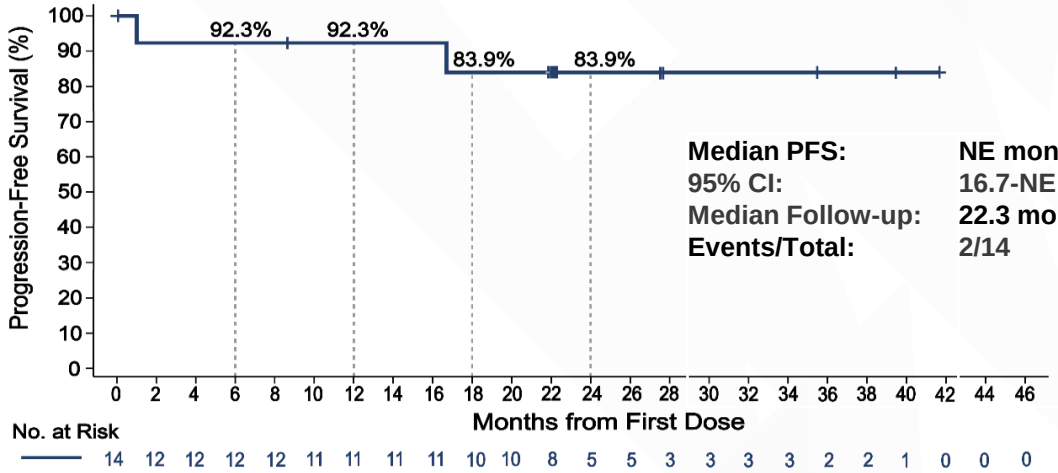
BRUIN Study: Pirtobrutinib Outcomes in Covalent BTK Inhibitor-Naïve Patients With MCL

Duration of Response



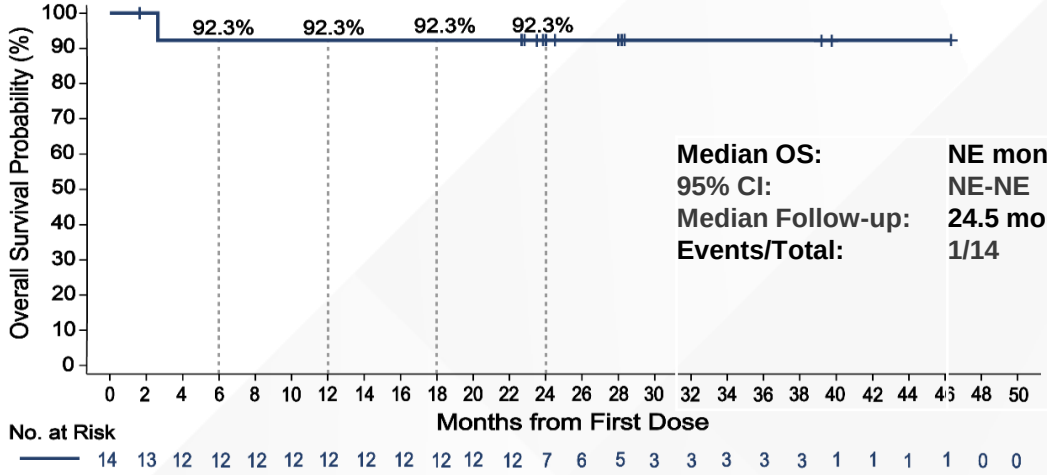
Median DoR:	**NE months**
95% CI:	13.0-NE
Median Follow-up:	**20.3 months**
Events/Total:	1/12

Progression-Free Survival



Median PFS:	**NE months**
95% CI:	16.7-NE
Median Follow-up:	**22.3 months**
Events/Total:	2/14

Overall Survival



Median OS:	**NE months**
95% CI:	NE-NE
Median Follow-up:	**24.5 months**
Events/Total:	1/14

cBTKi Naive Cohort:

- The ORR was 85.7% (95% CI: 57.2-98.2)
  - 6 CR (42.9%) and 6 PR (42.9%)

[a]1 cBTKi-naïve patient was not evaluable. Response status per Lugano 2014 criteria based on IRC assessment.
Cohen JB, et al. ASH 2023. Abstract 981.
cBTKi, covalent Bruton's tyrosine kinase inhibitor; CR, complete response; DoR, duration of response; MCL, mantle cell lymphoma; NE, not evaluable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

Pirtobrutinib FDA Approval in MCL

- January 2023: the Food and Drug Administration granted accelerated approval to pirtobrutinib for relapsed or refractory MCL after at least two lines of systemic therapy, including a BTK inhibitor
- BRUIN Trial (NCT03740529)
  - ORR: 50%
    - CR: 13%
  - DOR: 8.3 months
- ASH 2023 updated data:
  - Prior covalent BTK inhibitor (n=152)
  - ORR of 49.3%
    - CR: 15.8%
    - PR: 33.6%
  - Median DoR: 21.6 months
  - Median PFS: 5.6 months
  - Median OS: 23.5 months

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FDA.gov. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pirtobrutinib-relapsed-or-refractory-mantle-cell-lymphoma.
Cohen JB, et al. ASH 2023. Abstract 981.

ASH, American Society of Hematology; BTK, Bruton's tyrosine kinase; CR, complete response; DoR, duration of response; MCL, mantle cell lymphoma; ORR, overall response rate; PFS, progression-free survival; PR, partial response.

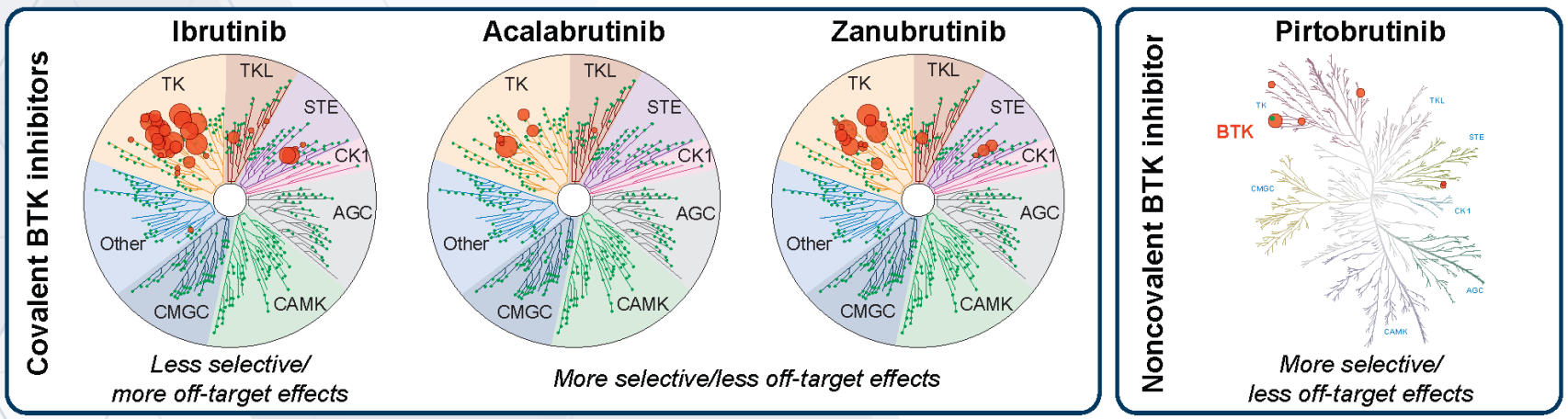
Ongoing Phase 3 Trials With Noncovalent BTK Inhibitors in MCL

Noncovalent BTKi	Phase 3 Trial	Study Arms	Population
Pirtobrutinib	BRUIN MCL-321 (NCT04662255)	pirtobrutinib vs investigator's choice of BTKi (ibrutinib, acalabrutinib, or zanubrutinib)	Previously treated and BTKi-naïve

Wang M, et al. *J Clin Oncol.* 2023;41(16_suppl):TPS7587.
BTKi, Bruton's tyrosine kinase inhibitor; MCL, mantle cell lymphoma.

Management Strategies for Adverse Events

What Are the Implications of Covalent and Noncovalent BTKi Selectivity for Off-Target Effects?



Less selective BTK inhibitors (eg, ibrutinib) have more off-target effects, which contribute to more toxicity compared with more selective agents

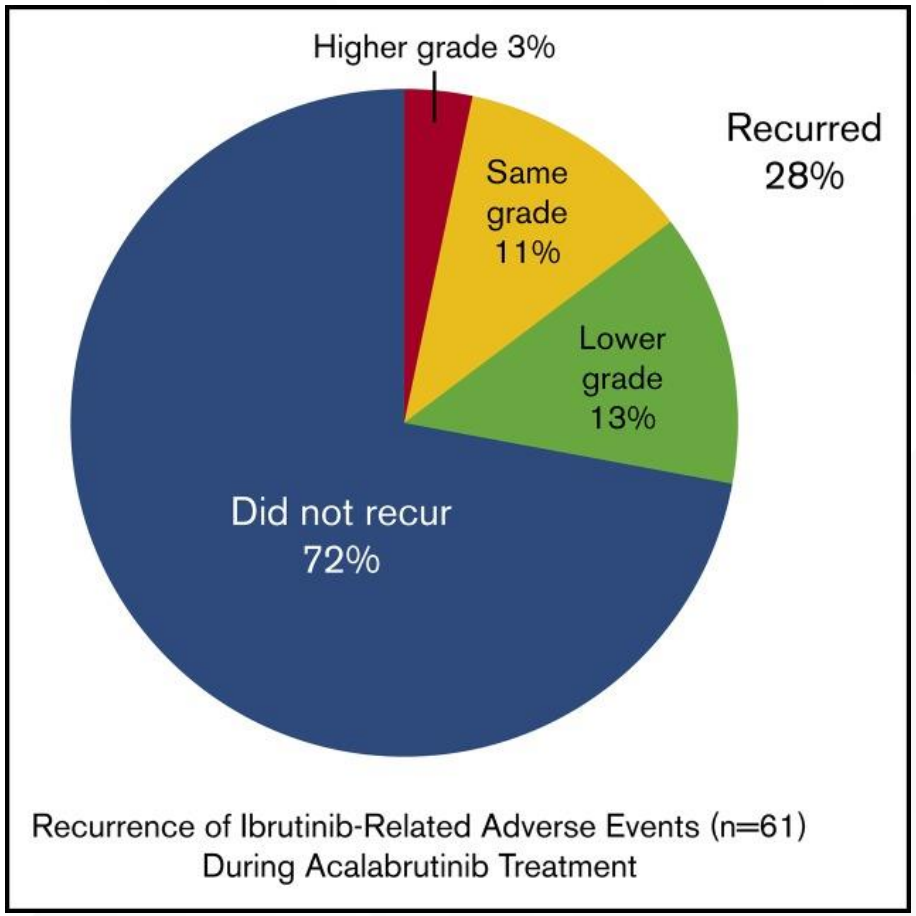
Potential off-target effects include:

Kaptein A, et al. *Blood.* 2018;132(suppl 1):1871.

AGC, containing PKA, PKG, PKC families; BTK, Bruton's tyrosine kinase; BTKi, Bruton's tyrosine kinase inhibitor; CAMK, calcium/calmodulin-dependent protein kinase; CK1, casein kinase 1; CMGC, containing CDK, MAPK, GSK3, CLK families; EGFR, epidermal growth factor receptor; STE, homologs of yeast Sterile 7, Sterile 11, Sterile 20 kinases; TEC, tyrosine kinase expressed in hepatocellular carcinoma; TK, tyrosine kinase; TKL, tyrosine kinase-like.

Phase I/II ACE-CL-001 Trial: Acalabrutinib in Ibrutinib-Intolerant Cohort

- Among 33 patients who could not tolerate ibrutinib, 23 remained on acalabrutinib
- No acalabrutinib dose reductions occurred
- Of 61 ibrutinib-related AEs, 72% did not recur and 13% recurred at a lower grade with acalabrutinib
- ORR: 76%
- Median PFS: not reached
- 1-yr PFS: 83.4%



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

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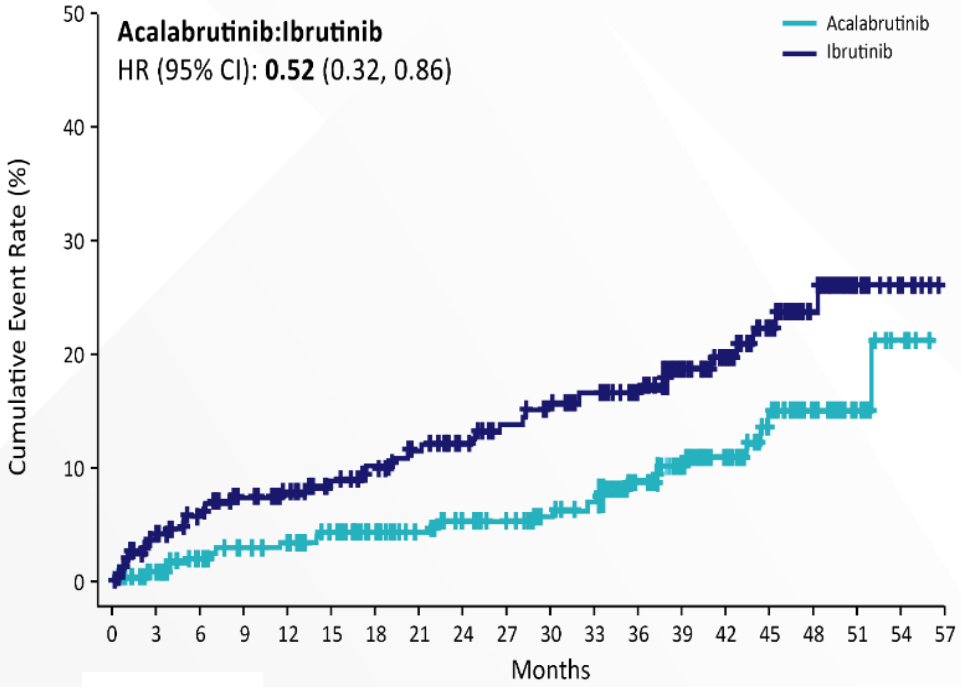
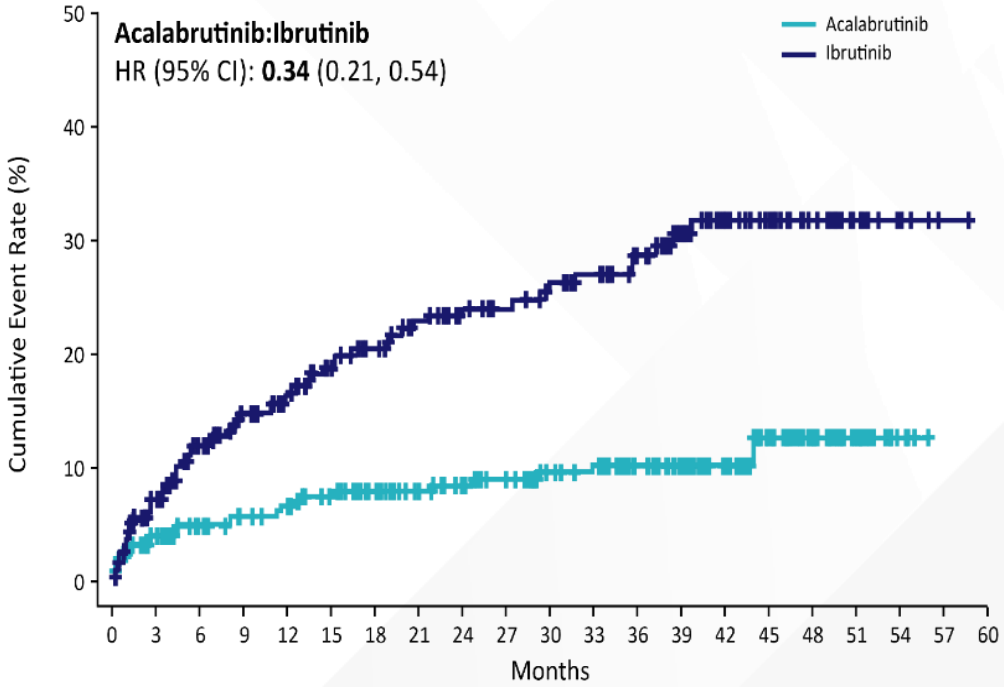
Awan FT, et al. *Blood Adv*. 2019;3(9):1553-1562.
AE, adverse event; PFS, progression-free survival; ORR, overall response rate.

ELEVATE RR Trial: Lower Cumulative Incidence of Atrial Fibrillation and Hypertension With Acalabrutinib

Afib/Flutter, Any Grade



Hypertension, Any Grade



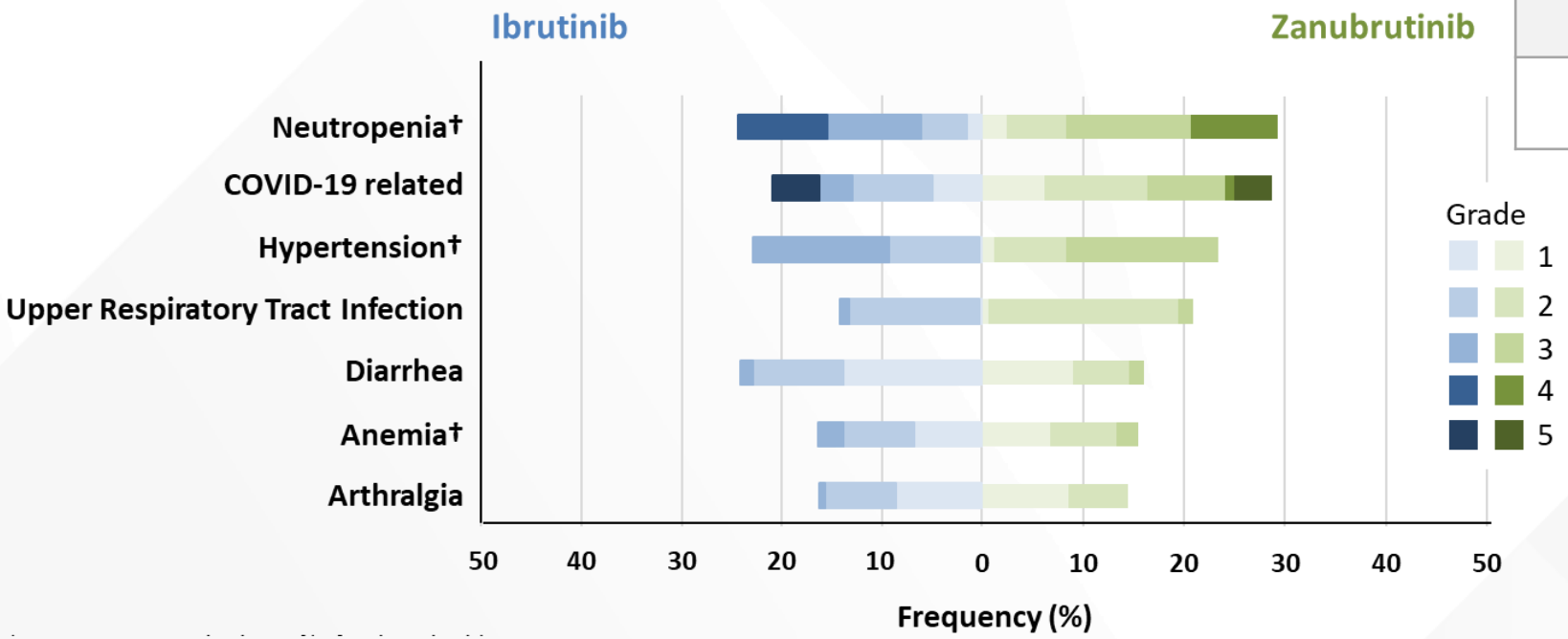
Overall, AEs led to treatment discontinuation in 14.7% of acalabrutinib-treated pts vs 21.3% of ibrutinib-treated pts

Byrd JC, et al. *J Clin Oncol*. 2021;39(31):3441-3452.
AE, adverse event.

AXIS Medical Education

ALPINE Trial: Ibrutinib vs. Zanubrutinib in R/R CLL Most Common Adverse Events*

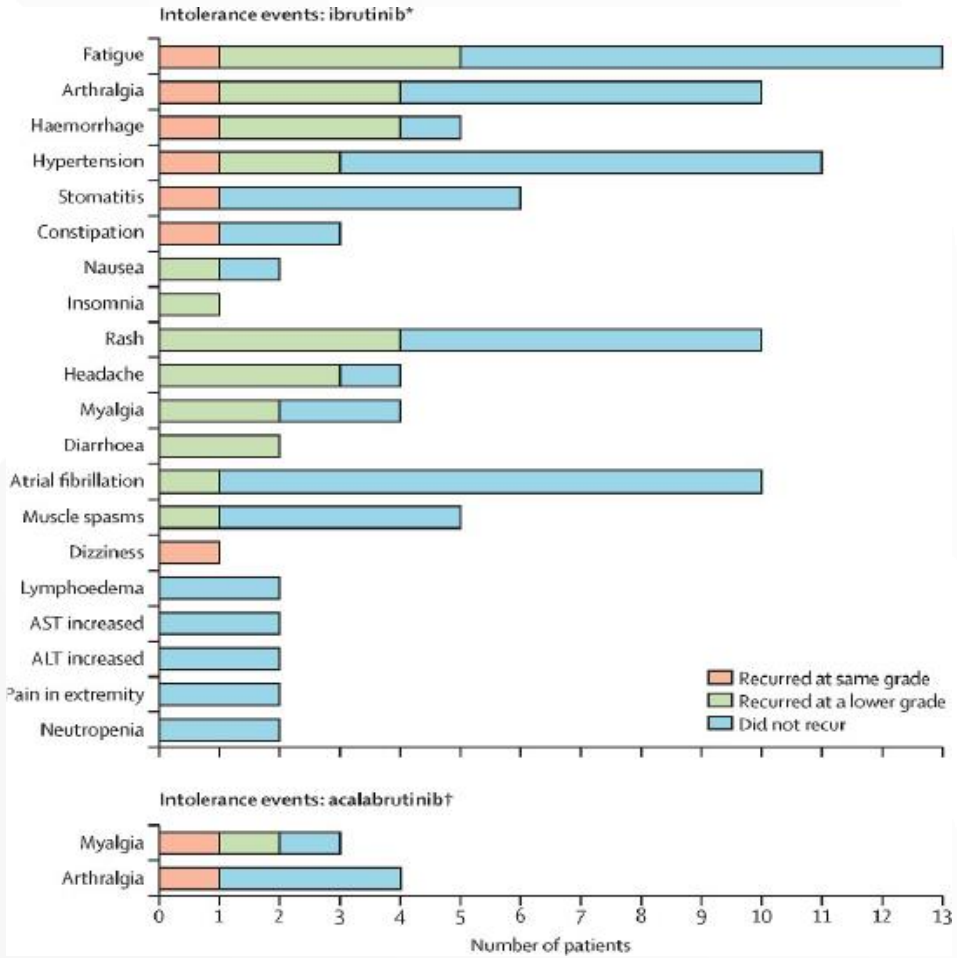
Adverse Events Leading to	Zanubrutinib (N=324)	Ibrutinib (N=324)
Dose reduction	40 (12.3)	55 (17.0)
Dose interruption	162 (50.0)	184 (56.8)
Treatment discontinuation	50 (15.4)	72 (22.2)



*Adverse events occurring in ≥15% of patients in either arm.
†Pooled terms.
Brown JR, et al. *N Engl J Med*. 2023;388(4):319-332.
CLL, chronic lymphocytic leukemia; R/R relapsed/refractory.

AXIS Medical Education

BGB-3111-215 (BTKi Intolerance Trial): Low Recurrence of BTK Inhibitor Intolerance on Zanubrutinib



- Intolerable AEs experienced on ibrutinib or acalabrutinib were unlikely to recur with zanubrutinib
  - 75% of ibrutinib and acalabrutinib intolerance events did not recur with zanubrutinib
  - <10% recurrence of a prior intolerance event led to zanubrutinib discontinuation
- Zanubrutinib was effective; 90% of patients' disease was controlled or responded to therapy

Shadman M, et al. *Lancet Haematol*. 2023;10(1):e35-e45.
AE, adverse event; ALT, alanine transaminase; AST, aspartate transferase; BTKi, Bruton's tyrosine kinase inhibitor.

BRUIN Trial: Pirtobrutinib Safety Profile of CLL Patients Who Received Prior Covalent BTK Inhibitor

	Treatment-Emergent AEs in Patients with CLL/SLL (n=282)			
	All Cause AEs, (≥25%), %		Treatment-Related AEs, %	
Adverse Event	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Fatigue	36.9	1.8	3.5	0.0
Neutropenia[b,c]	34.4	28.4	19.5	15.2
Diarrhea	28.4	0.4	7.8	0.0
Cough	27.3	0.0	1.8	0.0
Contusion	26.2	0.0	17.4	0.0
Covid-19	25.9	4.6	0.7	0.0
AEs of Interest[a]	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infections[d]	74.1	30.9	12.8	4.3
Bruising[e]	30.1	0.0	19.1	0.0
Rash[f]	24.5	1.1	5.7	0.4
Arthralgia	22.7	1.4	4.3	0.0
Hemorrhage[g]	13.5	2.1	4.6	1.1
Hypertension	14.2	4.3	3.5	0.4
Atrial Fibrillation/Flutter[h,i]	4.6	1.8	1.4	0.7

Median time on treatment was 18.7 months (prior cBTKi), 24.3 months (BCL2i-N) and 15.3 months (BCL2i-E)

11 (3.9%; 9 BCL2i-N, 2 BCL2i-E) patients had Treatment-Related AEs leading to pirtobrutinib dose reduction

7 (2.5%; 4 BCL2i-N, 3 BCL2i-E) patients had Treatment-Related AEs leading to pirtobrutinib discontinuation

Safety profiles of BCL2i-N and BCL2i-E subgroups were similar and are described via the QR code

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[a]AEs of interest are those that were previously associated with covalent BTK inhibitors. [b]Neutropenia at baseline for prior BTKi (n=282) was 18.4, BCL2i-N (n=154) was 11.0 and BCL2i-E (n=128) was 27.3. [c]Aggregate of neutropenia and neutrophil count decreased. [d]Aggregate of all preferred terms including infection and COVID-19. [e]Aggregate of contusion, ecchymosis, increased tendency to bruise and oral contusion. [f]Aggregate of all preferred terms including rash. [g]Aggregate of all preferred terms including hemorrhage or hematoma. [h]Aggregate of atrial fibrillation and atrial flutter. [i]Of the 13 total afib/aflutter TEAEs in the prior BTKi safety population (n=282), 6 occurred in patients with a prior medical history of atrial fibrillation.

Woyach JA, et al. ASH 2023. Abstract 325.

AE, adverse event; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; N, naice; E, experienced.

BRUIN Trial: Pirtobrutinib and Venetoclax Safety Profile

- No DLTs were observed
- Pirtobrutinib dose was reduced in 1 patient who experienced treatment-related diarrhea and thrombocytopenia
- Two cases of clinical TLS related to venetoclax dose escalation
  - Grade 3 case resolved spontaneously after 24 hours
  - Grade 4 case resolved after short-term IV fluids and dialysis
  - Both patients completed all 24 cycles of combination therapy

	Treatment-emergent AEs in Patients Treated with PV (n=15)			
	All-cause AEs (≥25%) , %		Treatment-related AEs, %	
Adverse Event (AE)	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Neutropenia[a]	7 (46.7)	7 (46.7)	7 (46.7)	7 (46.7)
Nausea	9 (60.0)	0 (0.0)	7 (46.7)	0 (0.0)
Fatigue	8 (53.3)	0 (0.0)	5 (33.3)	0 (0.0)
Diarrhea	7 (46.7)	2 (13.3)	4 (26.7)	2 (13.3)
Hypophosphatemia	5 (33.3)	0 (0.0)	2 (13.3)	0 (0.0)
Constipation	4 (26.7)	0 (0.0)	3 (20.0)	0 (0.0)
Cough	4 (26.7)	0 (0.0)	1 (6.7)	0 (0.0)
Platelet Count Decreased	4 (26.7)	1 (6.7)	4 (26.7)	1 (6.7)
Vomiting	4 (26.7)	0 (0.0)	2 (13.3)	0 (0.0)
Anemia	3 (20.0)	3 (20.0)	2 (13.3)	2 (13.3)
Tumor Lysis Syndrome	2 (13.3)	2 (13.3)	2 (13.3)	2 (13.3)
Pyrexia	3 (20.0)	1 (6.7)	1 (6.7)	1 (6.7)
AEs of Interest[b]	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infections[c]	12 (80.0)	4 (26.7)	7 (46.7)	3 (20.0)
Bruising[d]	3 (20.0)	0 (0.0)	3 (20.0)	0 (0.0)
Rash[e]	1 (6.7)	0 (0.0)	1 (6.7)	0 (0.0)
Arthralgia	4 (26.7)	0 (0.0)	2 (13.3)	0 (0.0)
Hemorrhage[f]	1 (6.7)	0 (0.0)	1 (6.7)	0 (0.0)
Hypertension	3 (20.0)	1 (6.7)	2 (13.3)	0 (0.0)
Atrial Fibrillation/Flutter[g]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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[a]Aggregate of neutropenia and neutrophil count decreased. [b]AEs of interest are those that were previously associated with covalent BTK inhibitors regardless of occurrence rate. [c]Aggregate of all preferred terms including infection and COVID-19. [d]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [e]Aggregate of all preferred terms including rash. [f]Aggregate of all preferred terms including hemorrhage or hematoma. [g]Aggregate of atrial fibrillation and atrial flutter.

Roeker LE, et al. ASH 2023. Abstract 3269.

AE, adverse event; DLT, dose-limiting toxicity; PV, pirtobrutinib and venetoclax; TLS, tumor lysis syndrome.

BRUIN Trial: Pirtobrutinib and Venetoclax Plus Rituximab Safety Profile

- No DLTs were observed
- Treatment-related pirtobrutinib and venetoclax dose reductions occurred in 2 patients
  - 1 patient with thrombocytopenia
  - 1 patient with neutropenia
- Treatment-related discontinuations occurred in 2 patients
  - 1 patient with neutropenia
  - 1 patient with a UTI

	Treatment-emergent AEs in Patients Treated with PVR (n=10)			
	All-cause AEs (≥25%) , %		Treatment-related AEs, %	
Adverse Event (AE)	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Neutropenia[a]	7 (70.0)	6 (60.0)	7 (70.0)	6 (60.0)
Diarrhea	6 (60.0)	0 (0.0)	6 (60.0)	0 (0.0)
Fatigue	5 (50.0)	1 (10.0)	2 (20.0)	0 (0.0)
Nausea	4 (40.0)	0 (0.0)	4 (40.0)	0 (0.0)
Constipation	4 (40.0)	0 (0.0)	1 (10.0)	0 (0.0)
Infusion Related Reaction	4 (40.0)	2 (20.0)	4 (40.0)	2 (20.0)
Anemia	3 (30.0)	1 (10.0)	2 (20.0)	1 (10.0)
Back Pain	3 (30.0)	1 (10.0)	1 (10.0)	0 (0.0)
Chills	3 (30.0)	0 (0.0)	3 (30.0)	0 (0.0)
Dry Mouth	3 (30.0)	0 (0.0)	1 (10.0)	0 (0.0)
Platelet Count Decreased	2 (20.0)	1 (10.0)	2 (20.0)	1 (10.0)
Hypertension Urgency	1 (10.0)	1 (10.0)	1 (10.0)	1 (10.0)
AEs of Interest[b]	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infections[c]	9 (90.0)	4 (40.0)	2 (20.0)	1 (10.0)
Bruising[d]	2 (20.0)	0 (0.0)	2 (20.0)	0 (0.0)
Rash[e]	3 (30.0)	0 (0.0)	1 (10.0)	0 (0.0)
Arthralgia	4 (40.0)	0 (0.0)	1 (10.0)	0 (0.0)
Hemorrhage[f]	2 (20.0)	1 (10.0)	1 (10.0)	1 (10.0)
Hypertension	1 (10.0)	1 (10.0)	0 (0.0)	0 (0.0)
Atrial Fibrillation/Flutter[g]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a]Aggregate of neutropenia and neutrophil count decreased. [b]AEs of interest are those that were previously associated with covalent BTK inhibitors regardless of occurrence rate. [c]Aggregate of all preferred terms including infection and COVID-19. [d]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [e]Aggregate of all preferred terms including rash. [f]Aggregate of all preferred terms including hemorrhage or hematoma. [g]Aggregate of atrial fibrillation and atrial flutter.

Roeker LE, et al. ASH 2023. Abstract 3269.

AE, adverse event; DLT, dose-limiting toxicity; PVR, pirtobrutinib, venetoclax, and rituximab; UTI, urinary tract infection.

BELLWAVE-001 Trial: Nemtabrutinib Safety Profile

Treatment-related Adverse Events, n (%)	All Patients at 65 mg QD N=112	
	All	Grade ≥3
Any treatment-related AEs	82 (73)	45 (40)
Treatment-related AEs ≥ 5%		
Dysgeusia	23 (21)	0 (0)
Neutropenia	22 (20)	19 (17)
Fatigue	14 (13)	2 (2)
Thrombocytopenia	13 (12)	5 (4)
Nausea	13 (12)	0 (0)
Hypertension	11 (10)	4 (4)
Diarrhea	11 (10)	2 (2)

Woyach J, et al. ASH 2022. Abstract 3114.
AE, adverse event; QD, once daily.

BRUIN Trial: Pirtobrutinib Safety Profile in R/R MCL Patients

	Treatment-Emergent AEs in Patients with MCL (n=166)			
	All Cause AEs, (≥15%), %		Treatment-Related AEs, %	
Adverse Event	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Fatigue	31.9	3.0	21.1	2.4
Diarrhea	22.3	0.0	12.7	0.0
Dyspnea	17.5	1.2	9.0	0.6
Anemia	16.9	7.8	7.2	2.4
Thrombocytopenia	15.1	7.8	7.8	3.0
AEs of Interest[a]	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infections[b]	42.8	19.9	15.7	3.6
Bruising[c]	16.3	0.0	11.4	0.0
Rash[d]	14.5	0.6	9.0	0.0
Arthralgia	9.0	1.2	2.4	0.0
Hemorrhage[e]	10.2	2.4	4.2	0.6
Hypertension	4.2	0.6	1.8	0.0
Atrial Fibrillation/Flutter[f,g]	3.6	1.8	0.6	0.0

Median time on treatment was 5.5 months for the MCL cohort

Discontinuations due to TRAEs occurred in 3% (n=5) of patients with MCL

Dose reductions due to TRAEs occurred in 5% (n=8) of patients with MCL

[a]AEs of interest are those that were previously associated with covalent BTK inhibitors. [b]Aggregate of all preferred terms including infection and COVID-19. [c]Aggregate of contusion, bone contusion, ecchymosis, and increased tendency to bruise. [d]Aggregate of all preferred terms including rash. [e]Aggregate of all preferred terms including hemorrhage or hematoma. [f]Aggregate of atrial fibrillation and atrial flutter. [g]Of 6 total atrial fibrillation and atrial flutter TEAEs, 3 occurred in patients with a prior medical history of atrial fibrillation. In the MCL cohort, treatment-related AEs leading to discontinuation included weight decrease/alopecia/fatigue (1), neutropenia (1), platelet count decreased (1), pneumonitis (1), and cholecystitis (1).

Cohen JB, et al. ASH 2023. Abstract 981.

AE, adverse event; MCL, mantle cell lymphoma; R/R, relapsed/refractory; TRAE, treatment-related adverse event.

Pirtobrutinib Adverse Event Summary

Infections	Monitor for signs and symptoms of infection, evaluate promptly, and treat appropriately
	Based on severity, reduce dose, temporarily withhold, or permanently discontinue
	Consider prophylaxis, including vaccinations and antimicrobial prophylaxis, in patients who are at increased risk for infections, including opportunistic infections
Hemorrhage	Monitor for bleeding and manage appropriately
	Based on severity of bleeding, reduce dose, temporarily withhold, or permanently discontinue
Cytopenias	Monitor complete blood counts during treatment
	Based on severity, reduce dose, temporarily withhold, or permanently discontinue
Cardiac Arrhythmias	Monitor for symptoms of arrhythmias (eg, palpitations, dizziness, syncope, dyspnea) and manage appropriately
	Based on severity, reduce dose, temporarily withhold, or permanently discontinue
Second Primary Malignancies	Monitor and advise patients to use sun protection
Embryo-Fetal Toxicity	Advise females of potential risk to a fetus and recommend use of effective contraception
Most common adverse reactions (≥20%)	Fatigue, musculoskeletal pain, diarrhea, COVID-19, bruising, and cough
Grade 3 or 4 laboratory abnormalities (≥10%)	Neutropenia, thrombocytopenia, anemia, and lymphopenia

JAYPIRCA (pirtobrutinib). Prescribing information. Eli Lilly and Company; 2023.

Managing BTK Inhibitor Common and Serious AEs

Rash

- Topical steroids[1]
- Oral antihistamines

Hair/Nail Changes

- Biotin supplementation[1]
- Application of nail oil[1]

Diarrhea

- Loperamide[1]
- Hydration[1]
- Bedtime dosing[1]

Nausea

- Bedtime dosing[2]
- Antiemetics

Arthralgia/Myalgia

- Exercise
- Avoid frequent NSAIDs[1]
- Alternative supplements/treatments[2]

Headache

- Caffeine[1]
- Acetaminophen[1]
- Avoid NSAIDs/aspirin-containing products[1]

Infection

- No standard recommendations for routine screening or prophylaxis; practices differ across institutions[1]
- Monitor closely[1]
- Be aware of drug-drug interactions with antifungal agents[1]
- May consider holding BTKi for severe infection[1]

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1. Lipsky A, et al. *Hematology Am Soc Hematol Educ Program.* 2020;2020:336-345. 2. Brown JR. *Blood.* 2018;131(4):379-386.
AE, adverse event; BTKi, Burton's tyrosine kinase inhibitor; NSAID, non-steroidal anti-inflammatory drug.

Additional Considerations for Optimizing BTK Inhibitor Therapy in CLL and MCL

- Interprofessional collaboration is key for optimizing safety
  - Assessment and monitoring (leveraging expertise of APPs, nursing, pharmacists)
  - Management protocols (toxicity management pathways/algorithms either within a group or through online resources)
- Incorporating patient goals/preferences
  - Patient-reported outcomes data on quality of life are lacking
  - Individualized discussion is key, taking into account logistics and specific co-morbidities of particularly patients

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APP, advanced practice provider; TKi, Burton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma.

Case-Based Learning Lab

Relapsed/Refractory CLL Case

- A 59-year-old man with hypertension but no other medical conditions is diagnosed with Rai stage 1 CLL
- Prognostic markers show normal FISH, unmutated IGHV, *TP53* wild type
- Over the next 3 years he gradually develops cytopenias and palpable lymphadenopathy up to 4-5 cm
- Now at age 62 years, he needs frontline therapy for CLL
- **He achieves a PR on ibrutinib and stays in remission for about 8 years, but now at age 70 develops progressive bulky lymphadenopathy and repeat genetic testing reveals a *TP53* mutation**

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CLL, chronic lymphocytic leukemia; FISH, fluorescence in situ hybridization; IGHV, immunoglobulin heavy-chain variable region gene; PR, partial response.

Relapsed/Refractory CLL Clinical Course

- A 59-year-old man with hypertension but no other medical conditions is diagnosed with Rai stage 1 CLL
- Prognostic markers show normal FISH, unmutated IGHV, *TP53* wild type
- Over the next 3 years he gradually develops cytopenias and palpable lymphadenopathy up to 4-5 cm
- Now at age 62 years, he needs frontline therapy for CLL
- He achieves a PR on ibrutinib and stays in remission for about 8 years, but now at age 70 develops progressive bulky lymphadenopathy and repeat genetic testing reveals a *TP53* mutation
- **He starts venetoclax and achieves a PR with undetectable MRD and small residual lymphadenopathy**
- **After 18 months on venetoclax, he develops steadily progressive lymph nodes which are now bulky**

AXIS Medical Education

CLL, chronic lymphocytic leukemia; FISH, fluorescence in situ hybridization; IGHV, immunoglobulin heavy-chain variable region gene; MRD, minimal residual disease; PR, partial response.

Relapsed/Refractory CLL
Case Study Audience Question

What would you recommend for this patient as the next line of therapy?

a) Zanubrutinib
b) BR
c) Pirtobrutinib
d) Acalabrutinib + Obinutuzumab
e) Unsure

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Relapsed/Refractory CLL
Case Study Rationale for Best Answer

What would you recommend for this patient as the next line of therapy?

a) Zanubrutinib
b) BR
c) Pirtobrutinib
d) Acalabrutinib + Obinutuzumab
e) Unsure

Correct answer: C) Pirtobrutinib would be expected to have about an 80% ORR with a median PFS of 15.9 months based on the phase ½ BRUIN study (Woyach et al., ASH, 2023). Chemoimmunotherapy with BR would not be expected to be effective in this double-refractory population, and since cBTKi have similar resistance mechanisms, going back to either zanu- or acala-based therapy would be unlikely to be effective either.

Relapsed/Refractory CLL Case Study Conclusion

- Patients with double-refractory CLL are difficult to treat, particularly in the community setting, where access to clinical trials can be more limited
- Rechallenging with cBTKi in a patient already refractory to a different cBTKi is unlikely to be effective and carries a risk of side effects
- A ncBTKi such as pirtobrutinib can provide effective disease control with excellent tolerability in double-refractory CLL

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cBTKi/ncBTKi, covalent/noncovalent Burton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia.

Relapsed/Refractory MCL Case

- A 59-year-old woman with no major co-morbidities presents with a 25 lb. unintentional weight loss over the last 6 months, and CT scans revealed widespread lymphadenopathy
- Biopsy reveals stage IV MCL with Ki-67 45% and no *TP53* mutation
- She is treated with frontline BR and achieves a CR, then receives autoSCT followed by 3 years of rituximab maintenance
- One year after transplant, she develops drenching night sweats with a rising LDH and recurrent lymphadenopathy, and she is started on acalabrutinib

AXIS Medical Education

autoSCT, autologous stem cell transplantation; BR, bendamustine and rituximab; CR, complete response; CT, computed tomography; LDH, lactate dehydrogenase; MCL, mantle cell lymphoma.

Relapsed/Refractory MCL Clinical Course

- A 59-year-old woman with no major co-morbidities presents with a 25 lb. unintentional weight loss over the last 6 months, and CT scans revealed widespread lymphadenopathy
- Biopsy reveals stage IV MCL with Ki-67 45% and no *TP53* mutation
- She is treated with frontline BR and achieves a CR, then receives autoSCT followed by 3 years of rituximab maintenance
- One year after transplant, she develops drenching night sweats with a rising LDH and recurrent lymphadenopathy, and she is started on acalabrutinib
- **She achieves PR on acalabrutinib which lasts for about 2 years, but then redevelops progressive lymphadenopathy**

AXIS Medical Education

autoSCT, autologous stem cell transplantation; BR, bendamustine and rituximab; CR, complete response; CT, computed tomography; LDH, lactate dehydrogenase; MCL, mantle cell lymphoma; PR, partial response.

Relapsed/Refractory MCL
Case Study Audience Question

How would you treat this patient now?

a) Zanubrutinib
b) Pirtobrutinib
c) Bortezomib
d) BR
e) Unsure

AXIS Medical Education

Relapsed/Refractory MCL
Case Study Rationale for Best Answer

How would you treat this patient now?

a) Zanubrutinib

b) Pirtobrutinib

c) Bortezomib

d) BR

e) Unsure

Correct answer is B) Pirtobrutinib. A patient like this would have about a 50% chance of achieving response to pirtobrutinib, and although the median PFS is just under 6 months, the median OS is close to 2 years, suggesting that the drug can potentially bridge patients to other therapies. Zanubrutinib would not be expected to have efficacy post-acalabrutinib due to likely common resistance mechanisms, although BR is effective frontline, additional courses of treatment are not effective, and although bortezomib is approved in this setting, it is beneficial only for a small number of patients.

Relapsed/Refractory MCL Case Study Conclusion

- For MCL patients who progress after CIT/autoSCT and covalent BTKi, noncovalent BTKi such as pirtobrutinib are able to achieve response in about half of patients and are a well-tolerated treatment option
- For fit patients in this setting, CAR T-cell therapy with brexu-cel should also be considered
- Noncovalent BTKi monotherapy is unlikely to achieve long term remission, and therefore could be used as a bridge to CAR T in those who are candidates or to a clinical trial in those who are not

AXIS Medical Education

autoSCT, autologous stem cell transplantation; BTKi, Burton's tyrosine kinase inhibitor; CAR, chimeric antigen receptor; CIT, chemoimmunotherapy; MCL, mantle cell lymphoma.

Key Takeaways

- ncBTKi may provide benefit for patients with progression on cBTKi
- The safety profiles for these agents are generally favorable
- Consider patient comorbidities and disease status when determining appropriate treatment
- Consider expectations of therapy and patient preference
- With many questions still unanswered, active participation in clinical trials remains crucial to further improve outcomes

AXIS Medical Education

cBTKi/ncBTKi, covalent/noncovalent Burton's tyrosine kinase inhibitor.

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Practice-Changing Strategies in Community Care Settings for Patients with CLL/SLL and MCL