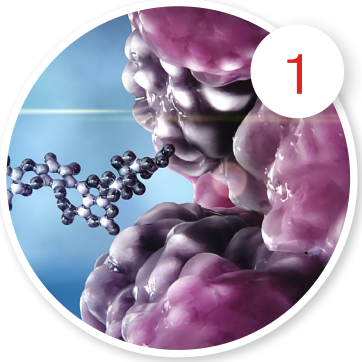
Importance of Targeting Bruton's Tyrosine Kinase Pathway in Chronic Lymphocytic Leukemia

Inhibition of the BTK protein can suppress downstream BCR signaling and is a key therapeutic target in CLL[1-3]

The BTK protein can be inhibited by 2 different types of binding[1,2,4-7]

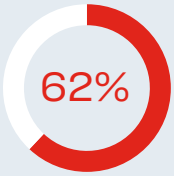


COVALENT (irreversible)

Mutations in the C481 residue of the BTK ATP binding site can diminish covalent inhibition of BTK[2,8]

NON-COVALENT (reversible)

Non-covalent binding can overcome the effects of C481S mutations to allow continued BTK inhibition[2,5,9]



of patients with CLL treated with a covalent BTK inhibitor were found to have C481 mutations at the time of disease progression or Richter transformation[10]

Additional mechanisms of acquired resistance to newer BTK inhibitors, both covalent and non-covalent, are still being investigated[9]

More data are needed to better inform appropriate treatment sequencing and understand patterns of potential cross resistance[9]

In patients with CLL who have developed resistance to prior covalent BTK inhibition

- A binding mechanism that avoids dependence on C481 could provide an alternative option for CLL treatment with the potential to reestablish BTK inhibition and restore blockade of B cell signaling[2,7,9]
- The different effects of C481 mutations on covalent and non-covalent BTK inhibition can help inform optimal sequencing of CLL treatments[7,9]

Lilly

Covalent BTK Inhibitors

BTK C481S mutations lead to acquired resistance[2,8,10]

	Acalabrutinib[4,11-13]	Ibrutinib[4,12-14]	Zanubrutinib[4,12, 13, 15,16]
Oral bioavailability	25%	2.9%	15%
Half-life (mean, hours)	1.4	4-6	2-4
Plasma exposure (BTK occupancy)	Median steady state ≥95% in peripheral blood maintained over 12 hours	>90% occupancy in peripheral blood observed up to 24 hours	Median steady state maintained at 100% over 24 hours
SELECTIVITY FOR BTK: IC_{50} for BTK (nM)	5.1	0.5	0.22
SELECTIVITY FOR BTK: Off-target kinases meaningfully inhibited at physiological concentrations	TEC, BMX/ETK, ERBB4/HER4	ITK, TEC, EGFR, BMX/ETK, ERBB2/HER2, ERBB4/HER4, JAK3, RLK/TXK, Src kinases (SRC, LYN, FYN, YES, BLK)	ITK, TEC, BLK, EGFR, BMX/ETK, ERBB4/HER4, RLK/TXK

These data derive from separate studies; cross-study comparisons cannot be drawn.

What pharmacological properties should be considered to extend BTK inhibition in R/R CLL?

Oral bioavailability
Low oral bioavailability may reduce drug exposure and limit therapeutic drug levels[8]

Half-life
CLL has high rates of BTK resynthesis. Longer half-life enables the continued inhibition of newly synthesized BTK protein[6,7]

Plasma exposure
High exposure throughout the dosing interval correlates with BTK active site occupancy[6]

Selectivity for BTK
High selectivity for BTK may reduce off-target effects and influence tolerability[7]

Non-covalent BTK Inhibitor

BTK inhibition is independent of C481S mutations[2,5,9]

	Pirtobrutinib[12,17,18]
Oral bioavailability	86%
Half-life (mean, hours)	≈19
Plasma exposure (BTK occupancy)	Trough concentrations >BTK IC_{96}
IC_{50} for BTK (nM)	3.2
Off-target kinases meaningfully inhibited at physiological concentrations	ERBB4/HER4, BRK, MEK2, MEK1, YES/YES1, TXK

This presentation was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific and educational purposes.

ATP, adenosine triphosphate; BCR, B cell receptor; BTK, Bruton's tyrosine kinase; C481, cysteine 481; C481S, cysteine 481 to serine mutation; CLL, chronic lymphocytic leukemia; R/R, relapsed/refractory.

1. Pal Singh S, et al. Mol Cancer. 2018;17(1):57. 2. Gu D, et al. J Hematol Oncol. 2021;14(1):40. 3. Hendriks RW, et al. Nat Rev Cancer. 2014;14(4):219-232. 4. Estupiñán HY, et al. Front Cell Dev Biol. 2021;9:630942. 5. Tasso B, et al. Molecules. 2021;26(23):7411. 6. Sun C, et al. Blood. 2020;136(1):93-105. 7. Tambaro FP, et al. J Exp Pharmacol. 2021;13:923-935. 8. Brullo C, et al. Int J Mol Sci. 2021;22(14):7641. 9. Mato AR, et al. N Engl J Med. 2023;389:33-44. 10. Kangal-Shamanna R, et al. Cancer. 2019;125(4):559-574. 11. Calquence. Prescribing information. AstraZeneca; 2022. 12. Lipsky A, Lamanna N. Hematology Am Soc Hematol Educ Program. 2020(1):336-345. 13. von Hundelshausen P, Siess W. Cancers (Basel). 2021;13(5):1103. 14. Imbruvica. Prescribing information. Pharmacyclics; 2024. 15. Brukinsa. Prescribing information. BeiGene; 2024. 16. Tam CS, et al. Expert Rev Clin Pharmacol. 2021;14(11):1329-1344. 17. Gomez EB, et al. Blood. 2023;142(1):62-72. 18. Jaypirca. Prescribing information. Eli Lilly and Company; 2023.

BRUKINSA® (zanubrutinib) prescribing information: https://d1e94vsyskgtht.cloudfront.net/brukinsa/pdfs/brukinsa-prescribing-information.pdf

CALQUENCE® (acalabrutinib) prescribing information: https://den8dhaj6zs0e.cloudfront.net/50fd68b9-106b-4550-b5d0-12b045f8b184/e2a005a7-65a0-4388-a671-dc887815a938/e2a005a7-65a0-4388-a671-dc887815a938_viewable_rendition__v.pdf

IMBRUVICA® (ibrutinib) prescribing information: https://www.rxabbvie.com/pdf/imbruvica_pi.pdf

Jaypirca® (Pirtobrutinib) prescribing information: https://uspl.lilly.com/jaypirca/jaypirca.html?s=pi