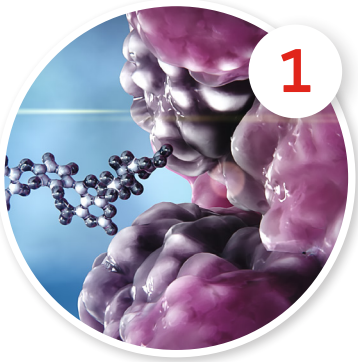
# Importance of Targeting Bruton's Tyrosine Kinase Pathway in Chronic Lymphocytic Leukemia

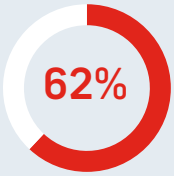
## Inhibition of the BTK protein can suppress downstream BCR signaling and is a key therapeutic target in CLL[1-3]

### 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 C481 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]



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# 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 |
| $IC_{50}$ 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.

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