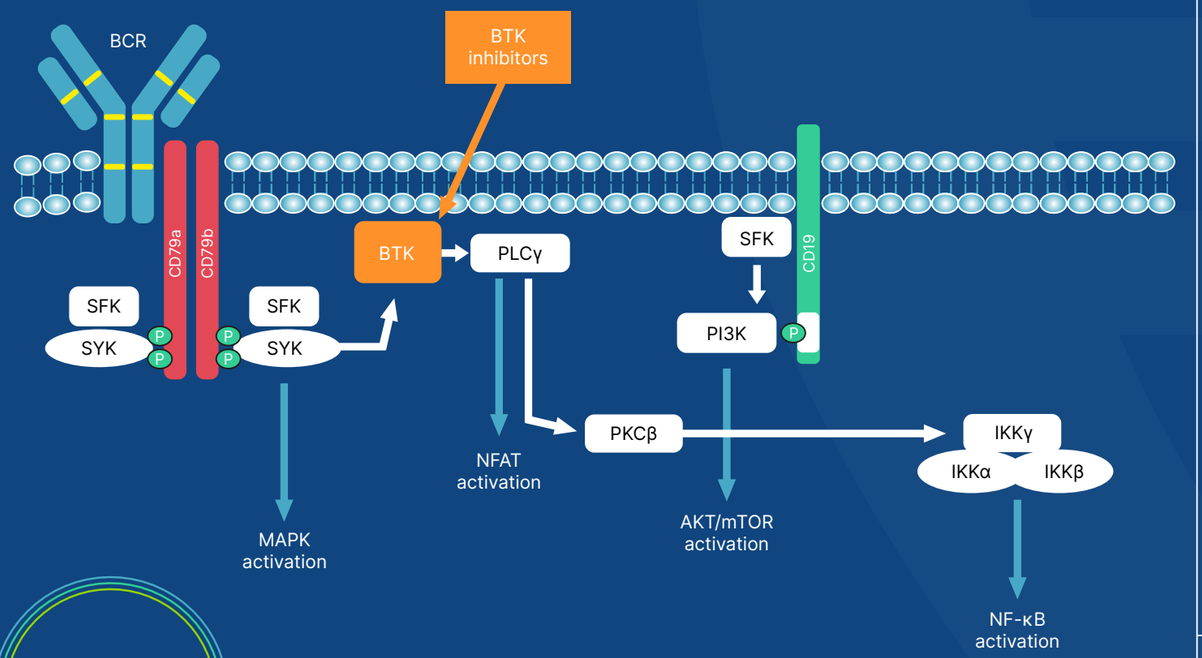
DIFFERENCES IN MECHANISM OF ACTION AND SELECTIVITY OF COVALENT AND NON-COVALENT BTK INHIBITORS

Provided by Clinical Care Options, LLC. Supported by an educational grant from Lilly.

The BCR Pathway and BTK's Role in B-Cell Malignancies[1]



BCR & BTK

The BCR pathway plays a role in the growth, proliferation, and survival of normal and malignant B-cells

BTK is an essential enzyme in the BCR signalling pathway

Inhibition of BTK leads to downstream mitigation of cell growth, proliferation, adhesion, migration, and survival of malignant B-cells

Three covalent BTK inhibitors are approved in multiple lymphoma settings including CLL, MCL and MZL, and Waldenström macroglobulinaemia.

These inhibitors form irreversible covalent bonds with a cysteine (C481) in the BTK kinase domain.

Kinase Selectivity of Covalent and Non-Covalent BTK Inhibitors in Vitro[2]

Covalent

Kinase	IC_{50} (nM) Ibrutinib	Acalabrutinib	Zanubrutinib
BTK	1.5	5.1	0.3
TEC	10	126	2
ITK	4.9	≥1000	56
BMX ETK	0.8	46	0.62
EGFR	5.3	≥1000	2.6
HER2	6.4	~1000	530
HER4	3.4	16	1.58
JAK3	32	≥1000	580
BLK	0.1	≥1000	1.13
RLK TXK	2.0	368	2.5

Non-covalent

Kinase	IC_{50} (nM) Pirtobruinib	Nemtabrutinib	Fenebrutinib
BTK	3.15	0.85	2.3
TEC	1234	5.8	1000
ITK	>5000	>10000	1000
BMX ETK	1155	5.2	351
EGFR	>1000	--	1000
HER2	--	--	1000
HER4	13.3	--	1000
JAK3	--	--	1000
BLK	4100	9.7	1000
RLK TXK	209	36	1000

Select Adverse Events of Special Interest of Covalent Versus Non-Covalent BTKis

Ibrutinib[4]
- Arthralgia/myalgia: **11%**
- Bleeding: **23%**
- Hypertension: up to **19%**
- Incidence of atrial fibrillation: **11% in MCL**

Acalabrutinib[5]
- Arthralgia/myalgia: **up to 29%**
- Bleeding: **22%**
- Hypertension: **up to 5%**
- Incidence of atrial fibrillation: **None in MCL (8% other cardiac dysfunction)**

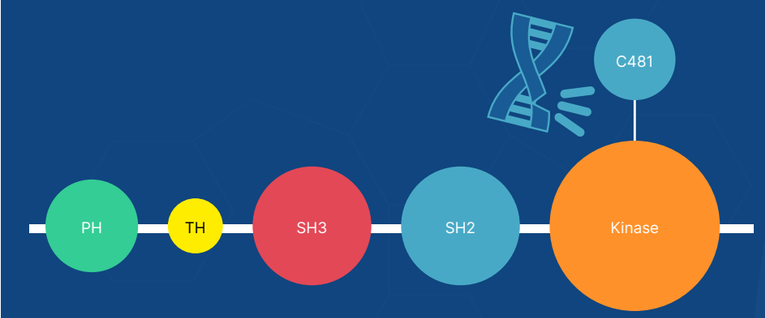
Zanubrutinib[6]
- Arthralgia/myalgia: **up to 14%**
- Bleeding: **50%**
- Hypertension: **12%**
- Incidence of atrial fibrillation/flutter: **2% in MCL**

Pirtobrutinib[7]
- Arthralgia/myalgia: **up to 11%**
- Bleeding: **8%**
- Hypertension: **7%**
- Incidence of atrial fibrillation: **2% across different hematologic cancers including MCL**

Nemtabrutinib[8]
- Arthralgia/myalgia: **20%**
- Bleeding: **none reported**
- Hypertension: **23%**
- Incidence of atrial fibrillation: **None reported across different B-cell malignancies**

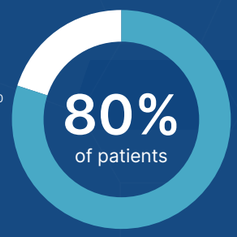
Acquired Resistance to Covalent BTK Inhibitors[9]

Acquired resistance to covalent BTK inhibitors is generally driven by mutations in *BTK* at the C481 site



BTK C481 mutations, most of which are C481S mutations, have been found in patients with CLL and MCL after treatment with a covalent BTK inhibitor

For example, in one study[10]



with CLL who experienced relapse after ibrutinib harboured a C481 mutation

Acquired resistance to covalent BTK inhibitors contributes to disease progression. Noncovalent reversible BTK inhibitors do not require C481 for binding.

Relative Binding Affinities of BTK Inhibitors to Different *BTK* Mutations[3]

Non-covalent Covalent

	Pirtobrutinib	Nemtabrutinib	Vecabrutinib	Fenebrutinib	Ibrutinib	Acalabrutinib	Zanubrutinib
Wild type	Normal	Normal	Normal	Normal	Normal	Normal	Normal
A428D	None	Decreased	None	None	None	None	None
M437R	Decreased	Normal	Decreased	Decreased	Normal	Decreased	Normal
T474I	Decreased	Decreased	Decreased	Normal	Normal	Decreased	Decreased
L528W	None	None	Decreased	Normal	None	Decreased	None
C481S	Normal	Normal	Normal	Normal	Decreased	Decreased	Decreased

BCR: B-cell receptor; BTK: Bruton's tyrosine kinase; CLL: chronic lymphocytic leukaemia; IC_{50}: half-maximal inhibitory concentration; MCL: mantle-cell lymphoma; MZL: marginal zone lymphoma

References 1. Young RM, Staudt LM. Targeting pathological B cell receptor signalling in lymphoid malignancies. Nat Rev Drug Discov. 2013;12(3):229-43. 2. Estupiñán HY, Berglöf A. Comparative analysis of BTK inhibitors and mechanisms underlying adverse effects. Front Cell Dev Biol. 2021;9:630942. 3. Wang E et al. Mechanisms of resistance to noncovalent Bruton's tyrosine kinase inhibitors. N Engl J Med. 2022;386:735-43. 4. Imbruvica. Highlights of prescribing information. 2022. Available at: https://www.imbruvica.com/files/prescribing-information.pdf. Last accessed: 19 October 2022. 5. Calquence. Highlights of prescribing information. 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/210259s000lbl.pdf. Last accessed: 19 October 2022. 6. Brukinsa. Highlights of prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213217s000lbl.pdf. Last accessed: 19 October 2022. 7. Wang M et al. Pirtobrutinib, a next generation, highly selective, non-covalent BTK inhibitor in previously treated mantle cell lymphoma: updated results from the phase 1/2 BRUIN study. Blood. 2021;DOI:10.1182/blood-2021-149138. 8. Woyach J et al. Nemtabrutinib (MK-1026), a non-covalent inhibitor of wild-type and C481S mutated bruton tyrosine kinase for B-cell malignancies: efficacy and safety of the phase 2 dose-expansion BELLWAVE-001 study. Hemasphere. 2022;6:578-9. 9. Gu. J, Tang H. Targeting Bruton tyrosine kinase using non-covalent inhibitors in B cell malignancies. J Hematol Oncol. 2021;14(1):40. 10. Woyach JA, Ruppert AS. BTKC481S-mediated resistance to ibrutinib in chronic lymphocytic leukemia. J Clin Oncol. 2017;35(13):1437-1443.