Targeted Therapeutics in CLL and MCL

Applying Emerging BTK Inhibitor Therapy Data to Practice

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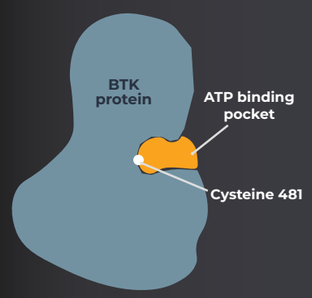
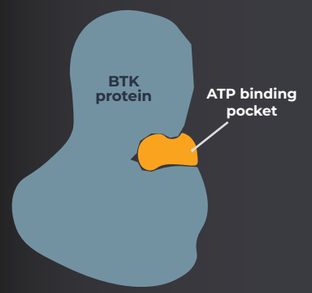
MoA for Approved BTK Inhibitors[1–3]

Covalent BTKi



Ibrutinib, acalabrutinib and zanubrutinib are covalent BTKi that bind to the ATP binding site to form an irreversible, covalent bond with C481.[3]

Non-covalent BTKi



Pirtobrutinib is a non-covalent BTKi that binds reversibly to the BTK protein in the ATP binding pocket. It does not depend on C481, and pirtobrutinib can bind to wild-type and C481^{mut} BTK.[1]

Drug Interactions

Avoid grapefruit juice

COVID-19 considerations: nirmatrelvir/ritonavir is a strong CYP3A4 inhibitor that interacts with all BTKi

Consider holding BTKi for duration of 5-day nirmatrelvir/ritonavir course

	Ibrutinib[4]	Acalabrutinib[5]	Zanubrutinib[6]	Pirtobrutinib[7]
CYP3A4 inhibitors (moderate)	**Decrease** to 280 mg once daily	**Decrease** to 100 mg once daily	**Decrease** to 80 mg twice daily	N/A
CYP3A4 inhibitors (strong)	**Avoid or hold** ibrutinib if CYP3A4i used ≤7 days Decrease to 140 mg or 70 mg once daily for concomitant use with voriconazole or posaconazole, depending on CYP3A4i dosing schedule	**Avoid or hold** acalabrutinib for ≥24 hours after last dose of CYP3A4i if used ≤7 days	**Decrease** to 80 mg once daily Interrupt dose as recommended for any AEs	**Avoid**; if unavoidable, decrease dose by 50 mg. After 5 half-lives of CYP3A4, resume at previous dose
CYP3A4 inducers	**Avoid**; may consider monitoring for reduced efficacy with moderate inducers	**Avoid**; if unavoidable, increase dose to 200 mg orally twice daily	**Avoid**; if moderate inducers unavoidable, increase dose to 320 mg twice daily	**Avoid**; if moderate inducers unavoidable, increase dose to 300 mg once daily if current dose is 200 mg once daily, or increase by 50 mg for other doses
Anticoagulants	⚠ Consider risk versus benefit and monitor for increased risk of bleeding ⚠			
Antiplatelets	⚠ Consider risk versus benefit and monitor for increased risk of bleeding ⚠			

New tablet formulation for acalabrutinib no longer has a restriction for gastric acid-reducing agents

Dose Modifications

STARTING DOSE → 1 → 2 → 3 → 4

Ibrutinib Dose Modifications[4]

Grade 2 cardiac failure, Grade 3/4 non-haematologic AEs, Grade 3/4 neutropenia with infection/fever, Grade 4 haematologic AEs

420 mg daily for CLL/SLL → 1st occurrence: ***INTERRUPT*** and reduce by 140 mg once AE resolves to Grade 1 → 2nd occurrence: ***INTERRUPT*** and reduce by 140 mg once AE resolves to Grade 1 → 3rd occurrence: ***DISCONTINUE***

Grade 3 cardiac arrhythmias

420 mg daily for CLL/SLL → 1st occurrence: ***INTERRUPT*** and reduce by 140 mg once AE resolves to Grade 1 → 2nd occurrence: ***DISCONTINUE***

Grade 3 cardiac failure or Grade 4 cardiac arrhythmias

420 mg daily for CLL/SLL → 1st occurrence: ***DISCONTINUE***

Acalabrutinib Dose Modifications[5]

For Grade ≥3 non-haematologic AEs, Grade 3 thrombocytopenia with bleeding, Grade 4 thrombocytopenia, or Grade 4 neutropenia lasting >7 days

100 mg BID → 1st occurrence: ***INTERRUPT*** and resume at current dose once AE resolves to Grade 1 → 2nd occurrence: ***INTERRUPT*** and resume at current dose once AE resolves to Grade 1 → 3rd occurrence: ***INTERRUPT*** and resume at 100 mg QD once AE resolves to Grade 1 → 4th occurrence: ***DISCONTINUE***

Grade 3 cardiac arrhythmias

Zanubrutinib Dose Modifications[6]

For Grade ≥3 non-haematologic AEs, Grade 3/4 febrile neutropenia, platelet count decreased to 25,000–50,000/mm³ with significant bleeding, neutrophil count decreased to <500/mm³ (lasting >10 consecutive days), platelet count decreased to <25,000/mm³ (lasting >10 consecutive days)

320 mg once daily or 160 mg BID → 1st occurrence: ***INTERRUPT*** and resume at current dose once AE resolves to Grade 1 → 2nd occurrence: ***INTERRUPT*** and resume at 160 mg QD (or 80 mg BID) once AE resolves to Grade 1 → 3rd occurrence: ***INTERRUPT*** and resume at 80 mg QD once AE resolves to Grade 1 → 4th occurrence: ***DISCONTINUE***

Grade 3 cardiac arrhythmias

Pirtobrutinib Dose Modifications[7]

For Grade 3/4 non-haematologic AEs, absolute neutrophil count <1–0.5x10⁹/L with fever and/or infection, absolute neutrophil count <0.5x10⁹/L lasting ≥7 days, platelet count <50–25x10⁹/L with bleeding, platelet count <25x10⁹/L

200 mg once daily → 1st occurrence: ***INTERRUPT*** and restart at the same dose once AE resolves to Grade 1 → 2nd occurrence: ***INTERRUPT*** and reduce to 100 mg daily once AE resolves to Grade 1 → 3rd occurrence: ***INTERRUPT*** and reduce to 50 mg daily once AE resolves to Grade 1 → 4th occurrence: ***DISCONTINUE***

No dose adjustments or discontinuations required for Grade 1/2 AEs*

Dosing and Administration

	Ibrutinib[4]	Acalabrutinib[5] NEW FORMULATION	Zanubrutinib[6]	Pirtobrutinib[7]
	Capsules: 70 mg, 140 mg Tablets: 140 mg, 280 mg, 420 mg	100 mg tablet formulation can be co-administered with gastric acid–reducing agents*	80 mg capsules	50 mg, 100 mg tablets
	420 mg once daily for adult patients	100 mg orally twice daily	160 mg twice daily or 320 mg once daily	200 mg once daily
	Capsules should be swallowed whole with water	Tablet should be swallowed whole with water, with or without food	Tablet should be swallowed whole with water, with or without food	Tablet should be swallowed whole with water, with or without food
	For missed doses: Take as soon as possible on same day and return to normal schedule on the next day	**For missed doses:** If dose is >3 hours past normal time, skip and resume at the next scheduled time	**For missed doses:** Take as soon as possible on same day and return to normal schedule on the next day	**For missed doses:** >12 hours past normal time: skip and resume at next scheduled time

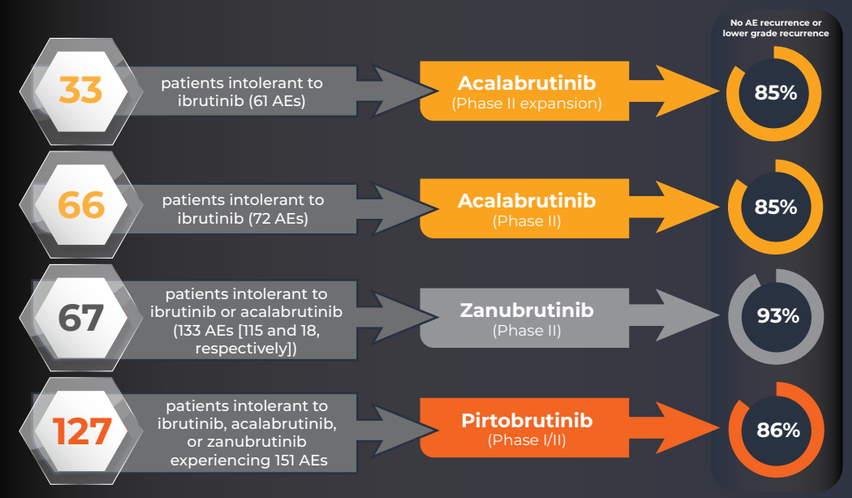
*Acalabrutinib exposures were comparable for tablet versus capsule formulations (AUC_{inf} 567.8 ng h/mL [36.9] versus 572.2 ng h/mL [38.2]; C_{max} 537.2 ng/mL [42.6] versus 535.7 ng/mL [58.4], respectively) and tablet can be co-administered with PPIs, food, or via NG tube without affecting the PKs or PDs.
†Non-covalent, reversible BTKi

Approximate Rates of Select AEs

	Ibrutininb[4,8,9]	Acalabrutinib[5,8]	Zanubrutinib[6,9]	Pirtobrutinib[7,10]
Atrial Fibrillation	Any Grade: 13-16% Grade ≥3: 3-4%	Any Grade: 9% Grade ≥3: 5%	Any Grade: 5% Grade ≥3: 2.5%	Any Grade: 2.8% Grade ≥3: 1.2%
Hypertension	Any Grade: 20-22% Grade ≥3: 9-14%	Any Grade: 9% Grade ≥3: 4%	Any Grade: 23% Grade ≥3: 15%	Any Grade: 9% Grade ≥3: 2%
Bruising or Bleeding	Any Grade: 41-51% Grade ≥3: 4-5%	Any Grade: 38% Grade ≥3: 4%	Any Grade: 42% Grade ≥3: 3%	Any Grade: 35% Grade ≥3: 0%
Infection	Any Grade: 73-81% Grade ≥3: 28-30%	Any Grade: 78% Grade ≥3: 31%	Any Grade: 71% Grade ≥3: 27%	Any Grade: NR Grade ≥3: 17%*
Cytopenias	Any Grade: 43% Anemia: 19% Neutropenia: 26% Thrombocytopenia: 14% Grade ≥3: 36%	Any Grade: 41% Anemia: 22% Neutropenia: 23% Thrombocytopenia: 16% Grade ≥3: 29%	Any Grade: NR Anemia: 15% Neutropenia: 39% Thrombocytopenia: 13% Grade ≥3: NR	Any Grade: NR Anemia: 7% Neutropenia: 13% Thrombocytopenia: NR Grade ≥3: NR
Arthralgia	Any Grade: 16-23% Grade ≥3: 1%	Any Grade: 16% Grade ≥3: 0%	Any Grade: 15% Grade ≥3: NR	Any Grade: 14% Grade ≥3: <1%

*Data only reported in PI.

Consider Switching BTKi due to AE Intolerance[11-14]



Abbreviations: AE: adverse events; AUC_{inf}: total drug exposure across time; BID: twice daily; BTK: Bruton tyrosine kinase; BTKi: Bruton tyrosine kinase inhibitor; CLL: chronic lymphocytic leukaemia; C_{max}: peak concentration; MCL: mantle cell lymphoma; MoA: mechanism of action; NG tube: nasogastric tube; PD: pharmacodynamic; P-gp: P-glycoprotein; PK: pharmacokinetic; PPI: proton pump inhibitors; QD: once daily; SLL: small lymphocytic lymphoma.

1. Woyach JA et al. BTKC481S-mediated resistance to ibrutinib in chronic lymphocytic leukemia. J Clin Oncol. 2017;35:1437-43. 2. Brandhuber BJGE et al. LOXO-305, a next generation reversible BTK inhibitor, for overcoming acquired resistance to irreversible BTK inhibitors. Clin Lymphoma Myeloma Leuk. 2018;18:S216. 3. Mato AR et al. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. Lancet. 2021;397(10277):892-901. 4. AbbVie. Imbruvica highlights of prescribing information. 2022. Available at: https://www.rxabbvie.com/pdf/imbruvica_pi.pdf?utm_source=google&utm_medium=cpc&utm_campaign=GO-USA-ENG-PS-Imbruvica-BC-EX-RN-DTC_Generic&utm_content=Package+Insert&utm_term=ibrutinib+pi&gclid=CjwKCAjwkLCkBhA9EiwAka9QRu05PnCcWFqPpDzYQAtWxoWwWIjgFrUCjn3yMfMlg2Tda5-ROq0ThoCtFIQAvD_BwE&gclsrc=aw.ds. Last accessed: 19 June 2023. 5. Calquence highlights of prescribing information. 2022. Available at: https://den8dhaj6zs0e.cloudfront.net/50fd68b9-106b-4550-b5d0-12b045f8b184/e2a005a7-65a0-4388-a671-dc887815a938/e2a005a7-65a0-4388-a671-dc887815a938_viewable_rendition__v.pdf. Last accessed: 19 June 2023. 6. Brukinsa. Brukinsa (zanbrutinib) highlights of prescribing information. 2023. Available at: https://www.brukinsa.com/prescribing-information.pdf. Last accessed: 19 June 2023. 7. Eli Lilly and Company. Jaypirca highlights of prescribing information. 2023. Available at: https://uspl.lilly.com/jaypirca/jaypirca.html#pi. Last accessed: 19 June 2023. 8. Byrd JC et al. Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: results of the first randomized phase III trial. J Clin Oncol. 2021;39(31):3441-52. 9. Brown JR et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med. 2023;388(4):319-32. 10. Coombs CC et al. Long-term safety with ≥12 months of pirtobrutinib in relapsed/refractory (R/R) B-cell malignancies. ASCO 2023. Abstr 7513. 11. Awan FT et al. Acalabrutinib monotherapy in patients with chronic lymphocytic leukemia who are intolerant to ibrutinib. Blood Adv. 2019;3(9):1353-62. 12. Rogers KA et al. Phase II study of acalabrutinib in ibrutinib-intolerant patients with relapsed/refractory chronic lymphocytic leukemia. Haematologica. 2021;106(9):2364-73. 13. Shadman M et al. Zanubrutinib in patients with previously treated B-cell malignancies intolerant of previous Bruton tyrosine kinase inhibitors in the USA: a phase 2, open-label, single-arm study. Lancet Haematol. 2023;10:e35 14. Shah NN et al. 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. Blood. 2022;140(Suppl 1): 4127-32.

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