Zanubrutinib for the Treatment of B-cell Malignancies

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Selective Bruton's tyrosine kinase (BTK) inhibition is an important therapeutic approach for B-cell malignancies. Ibrutinib, a first-in-class, oral, irreversible BTK inhibitor, has a toxicity profile attributed to off-target inhibition of kinases structurally related to BTK. A highly potent and selective next-generation BTK inhibitor, zanubrutinib, was designed to address intolerance and toxicity concerns associated with ibrutinib. Zanubrutinib provides complete and sustained BTK occupancy in peripheral blood mononuclear cells and lymph nodes, with reduced toxicity compared with ibrutinib. Zanubrutinib received accelerated approval in the USA for patients with previously treated mantle cell lymphoma (2019) and relapsed/refractory (R/R) marginal zone lymphoma (2021) and was approved for Waldenström's macroglobulinaemia (WM) in 2021. Key clinical trials evaluating the efficacy and safety of zanubrutinib include the ASPEN study in patients with WM (ClinicalTrials.gov identifier: NCT03053440), the ALPINE study in patients with R/R chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL; ClinicalTrials.gov identifier: NCT03734016) and the SEQUOIA study in treatment-naïve patients with CLL/SLL with and without del(17p) mutation (ClinicalTrials.gov identifier: NCT03336333). The more selective BTK binding profile, high potency, favourable pharmacokinetic and pharmacodynamic profile, and minimal cardiovascular toxicity of zanubrutinib compared with ibrutinib suggest that zanubrutinib may be an important treatment option when prescribed in accordance with guidelines.
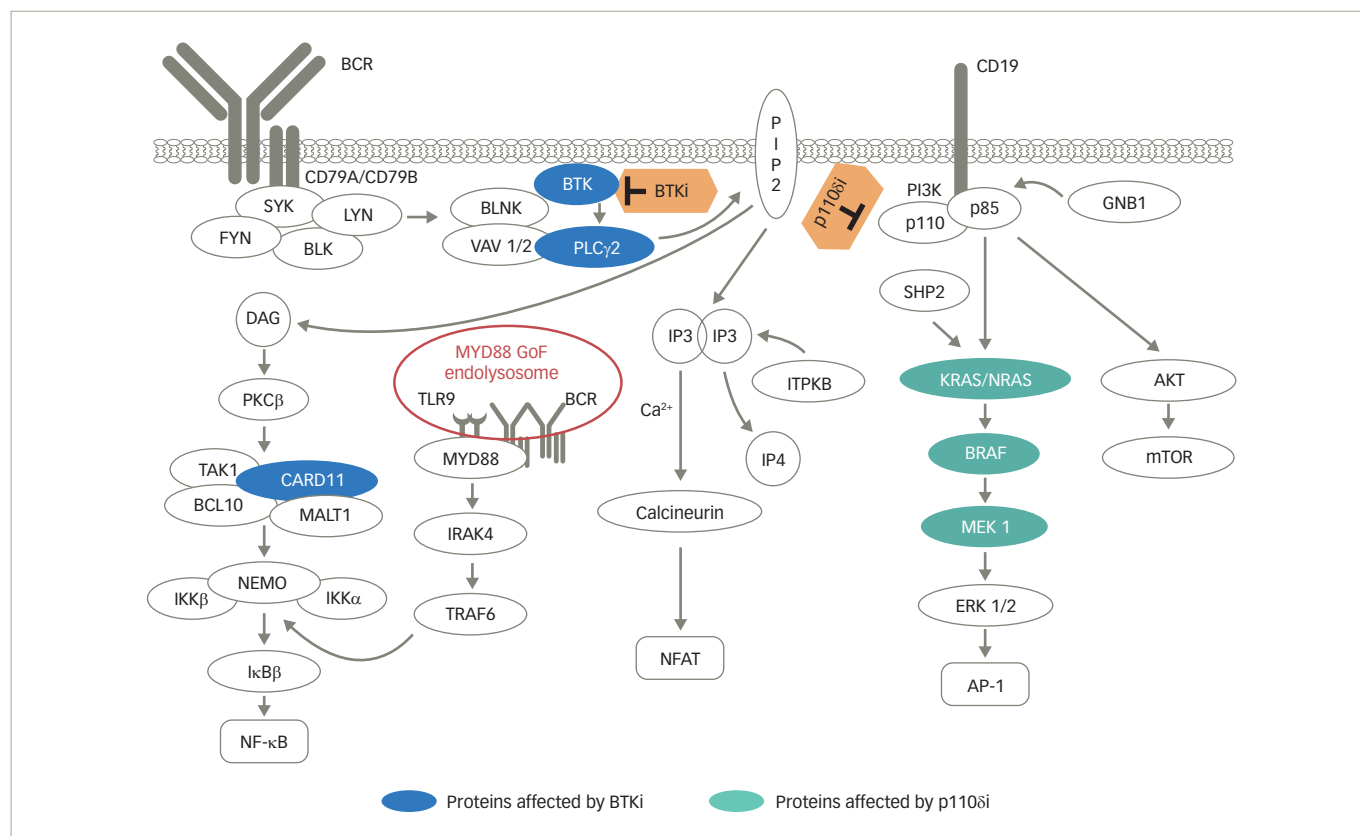
B-cell signalling pathways are critical regulators of B-cell development, expansion, and survival and function via various mediators, including Src family kinases (SFKs), spleen tyrosine kinase, Bruton's tyrosine kinase (BTK) and phosphatidylinositol 3 kinase (PI3K) (*Figure 1*).[1,2] BTK, a member of the Tec protein tyrosine kinase (TEC) family, is overexpressed in many B-cell leukaemias and lymphomas, and regulates survival, proliferation, adhesion and migration of malignant B cells.[3–6] Dysregulated BTK signalling has been implicated in the pathogenesis of chronic lymphocytic leukaemia (CLL),[3] mantle cell lymphoma (MCL),[7] diffuse large B-cell lymphoma (DLBCL),[5,8] Waldenström's macroglobulinaemia (WM)[9] and marginal zone lymphoma (MZL).[6] Currently, selective inhibition of BTK is an important strategy for the chemotherapy-free management of B-cell malignancies.[10]

Ibrutinib therapy for B-cell malignancies: promises and challenges

BTK is a clinically validated target in the treatment of B-cell malignancies, as demonstrated by the efficacy of the first-generation BTK inhibitor (BTKi), ibrutinib.[5] Ibrutinib (PCI-32765) is a first-in-class, oral, irreversible BTKi that binds cysteine 481 in the kinase domain of BTK to block its activity, allowing for chemotherapy-free treatment. Ibrutinib received approval for relapsed/refractory (R/R) MCL in 2013, for R/R CLL/small lymphocytic lymphoma (SLL) in 2014, for WM in 2015 and for R/R MZL in 2017.[10,12] In treatment-naïve patients with CLL/SLL, ibrutinib therapy was approved in 2016, and ibrutinib/rituximab therapy was approved in 2020.[10]

Although ibrutinib therapy is generally well tolerated and has a significant clinical benefit over chemotherapy in CLL/SLL,[13,14] it has a toxicity profile that is attributed to off-target inhibition of kinases structurally related to BTK, including epidermal growth factor receptor (EGFR), TEC, Janus kinase 3 (JAK3) and SFKs.[15–18] Ibrutinib treatment is associated with a significant risk of atrial fibrillation (AF; cumulative incidence rate: 11.2%) and heart failure (3-year risk: 7.7%), possibly due to the off-target inhibition of PI3K-AKT signalling.[19–23] Ibrutinib treatment also has a significant risk of late-onset hypertension, which is associated with a long-term risk

Figure 1: B cell receptor signalling pathway

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AKT = protein kinase B; AP-1 = activator protein 1; BCL10 = B-cell lymphoma/leukaemia; BCR = B cell receptor; BLK = B-lymphocyte kinase; BLNK = B-cell linker protein; BRAF = B-Raf proto-oncogene serine/threonine kinase; BTK = Bruton's tyrosine kinase; BTKi = Bruton's tyrosine kinase inhibitor; CARD11 = caspase recruitment domain family member 11; DAG = diacylglycerol; ERK = extracellular signal-regulated kinase; FYN = FYN proto-oncogene, Src family tyrosine kinase; GNB1 = guanine nucleotide-binding protein subunit beta-1; GoF = gain-of-function; IκBα = nuclear factor of κ light polypeptide gene enhancer in B-cells inhibitor, α; IKK = inhibitor of nuclear factor κ-B kinase; IP3 = inositol trisphosphate; IP4 = inositol tetrakisphosphate; IRAK4 = interleukin 1 receptor-associated kinase 4; ITPKB = IP 3-kinase B; KRAS = Kirsten ras oncogene homologue; LYN = LYN proto-oncogene, Src family tyrosine kinase; MALT1 = mucosa-associated lymphoid tissue lymphoma translocation protein 1; MEKc1 = mitogen-activated protein kinase kinase 1; mTOR = mammalian target of rapamycin; MYD88 = myeloid differentiation primary response protein 88; NEMO = NF-κ-B essential modulator; NFAT = nuclear factor of activated T cells; NF-κB = nuclear factor κ-light-chain-enhancer of activated B cells; NRAS = neuroblastoma ras viral oncogene homologue; p110δ = PI3Kδ isoform inhibitor; PI3K = phosphoinositide 3-kinase; PIP2 = phosphatidylinositol 4,5-bisphosphate; PKCβ = protein kinase C β type; PLCγ2 = phospholipase C γ 2; SHP2 = Src homology region 2-containing protein tyrosine phosphatase 2; SYK = spleen tyrosine kinase; TAK1 = transforming growth factor β-activated kinase 1; TLR9 = toll-like receptor 9; TRAF6 = tumour necrosis factor receptor-associated factor 6; VAV 1/2 = vav guanine nucleotide exchange factors 1 and 2.
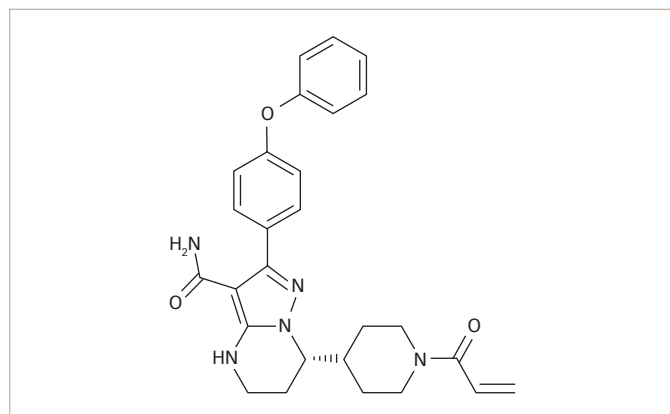
of developing other major cardiac events.[20,24] The BTK–TEC pathway mediates platelet function, and ibrutinib use was shown to be associated with an increased risk of bleeding, especially in older patients and in those receiving antithrombotic treatment.[22,25–27] Gastrointestinal and skin toxicities associated with ibrutinib therapy may be the result of the off-target inhibition of EGFR signalling.[28–31] Ibrutinib intolerance and disease progression are the main factors dictating treatment discontinuation.[32–35] BTKis with a better selectivity profile could benefit patients who become intolerant to ibrutinib.[36]

Acalabrutinib and zanubrutinib (first approved in 2017 and 2019, respectively) are next-generation BTKis that were developed to reduce the off-target effects associated with ibrutinib.[10,18,37,38] Acalabrutinib (ACP 196) is an irreversible BTKi that was rationally designed to have higher target selectivity than ibrutinib.[17,39] The efficacy and safety of acalabrutinib were shown in trials for R/R MCL, CLL and WM.[17,39–41] Zanubrutinib (BGB-3111) is a highly potent and selective next-generation BTKi designed to provide complete and sustained BTK occupancy for efficacy across disease-relevant tissues, with theoretically fewer off-target adverse events compared with ibrutinib.[18,42] Other orally available BTKis currently in clinical development include the following: 1) orelabrutinib, a highly selective irreversible BTKi that showed efficacy in R/R CLL, MCL and R/R WM;[43,44] 2) pirtobrutinib (LOXO-305), a highly selective, third-generation, reversible

BTKi that showed efficacy in heavily pretreated patients with CLL, MCL or WM who were intolerant/resistant to previous BTKi treatment;[32] and 3) nemtabrutinib (MK-1026 or ARQ-531), a non-covalent, reversible BTKi undergoing late-stage clinical development for B-cell malignancies.[45]

Zanubrutinib: United States Food and Drug Administration approval and mechanism of action

Based on data from two key phase II studies in MCL[46] and MZL,[47] zanubrutinib received accelerated approval by the United States Food and Drug Administration in 2019 for the treatment of MCL in adults who have received ≥1 prior therapy, and in 2021 for patients with R/R MZL who have received ≥1 anti-CD20-based regimen. Other studies evaluating the efficacy and safety of zanubrutinib include a phase II study in R/R MZL,[48] a phase III study in WM,[16] a phase II study in DLBCL,[49] a phase III study in R/R CLL/SLL,[50] a phase III study in treatment-naïve patients with CLL/SLL with and without del(17p)[51] and phase II study in patients with previously treated B-cell lymphoma that was ibrutinib and/or acalabrutinib intolerant.[52] Zanubrutinib was approved for WM in the USA and EU in 2021;[38,53] for R/R CLL and R/R MCL in 2020 and R/R WM in 2021 in China;[54–56] for R/R MCL and WM in Canada in 2021;[57] for R/R WM in the UK in 2021; for R/R MCL and R/R WM in Australia in 2021; for R/R WM in Estonia, Iceland, Ireland, Netherlands and Norway

Figure 2: Zanubrutinib molecular structure[38]

in 2021; for R/R MCL in Ecuador, Chile, United Arab Emirates, Saudi Arabia and Israel in 2021; and for R/R MCL and R/R WM in Taiwan in 2021. Zanubrutinib has a molecular weight of 471.55 Da. The molecular structure is depicted in *Figure 2*.

Zanubrutinib covalently binds with high specificity to the BTK adenosine triphosphate binding pocket at cysteine 481 to deliver irreversible, sustained kinase inhibition.[18,42] In a phase I study of patients with B-cell malignancies, median BTK occupancy in peripheral blood mononuclear cells (PBMCs) was >95% at all doses tested; in lymph-node tissue, a higher proportion of patients achieved >95% BTK occupancy at trough with the 160 mg twice daily (BID) dosing regimen compared with the 320 mg once daily (QD) regimen (89% versus 50%, respectively).[48] The high, sustained BTK inhibition in both PBMCs and lymph nodes maximizes the chances for deep and sustained remission.[18,48,50]

Compared with ibrutinib, zanubrutinib binds with minimal affinity to EGFR (3.5× less), JAK3 (58× less), human EGFR2 (28× less), interleukin (IL)-2-inducible T-cell kinase (19× less) and TEC protein tyrosine kinase (3.5× less).[18] Zanubrutinib has similar or increased potency compared with other BTKis (concentration for 50% inhibition [IC_{50}] values for zanubrutinib, ibrutinib and acalabrutinib are 0.5 nM, 1.5 nM and 5.1 nM, respectively).[58] The unbound fraction of zanubrutinib in plasma is approximately twice that of ibrutinib or acalabrutinib (~6% versus ~3%; *Table 1*).[58]

Pharmacokinetics and pharmacodynamics of zanubrutinib

Based on the pharmacokinetic (PK) profile of zanubrutinib after its single- and multiple-dose administration in patients with B-cell malignancies (ClinicalTrials identifier: NCT02343120),[48] the recommended dosing of zanubrutinib is 160 mg orally BID or 320 mg orally QD.[48,58] Orally administered zanubrutinib was rapidly absorbed (peak plasma concentration [C_{max}] 2 hours after dosing). The mean terminal elimination half-life ($t_{1/2}$) was ~2–4 hours; the median time to peak plasma concentration (T_{max}) was ~2 hours. Systemic accumulation was limited after repeated dosing.[58] The C_{trough}/IC_{50} ratios were 7 and 2 for zanubrutinib doses at 160 mg BID and 320 mg QD, respectively. Therefore, zanubrutinib plasma concentration was consistently above the IC_{50} during the 24-hour dosing schedule for both dosing regimens. The C_{trough}/IC_{50} ratio for zanubrutinib was higher than that of ibrutinib and acalabrutinib (*Figure 3*).[58]

Zanubrutinib can be administered with or without food,[58] and there were no clinically significant differences in area under the curve (AUC) or C_{max} following a high-fat meal in healthy subjects (ClinicalTrials.gov identifier: NCT04163523).[38,58] The absorption of zanubrutinib was not affected

Table 1: Approved dose regimens in the USA and key clinical pharmacology properties of zanubrutinib relative to those of ibrutinib and acalabrutinib

	Zanubrutinib	Ibrutinib	Acalabrutinib
Approved indications	MCL, MZL and WM	MCL, CLL, WM, MZL and chronic graft versus host disease*	MCL, CLL
FDA-approved dose	160 mg BID or 320 mg QD	420 mg or 560 mg QD	100 mg BID
IC_{50} against BTK, nM[59]	0.5	1.5	5.1
Potency of major active metabolite against BTK	N/A	~15-fold less potent than parent molecule[60]	~2-fold less potent than parent molecule[59]
Half-life	~2–4	~4–6	~0.6–2.8
Plasma protein binding, %	~94	97.3–97.7[60]	97.4–97.5[61]
AUC_{0-24} (CV%), ng.h/mL	160 mg BID: 2,295 (37) 320 mg QD: 2,180 (41)	420 mg QD: 707–1,159 (50–72) 560 mg QD: 865–978 (69–82)	100 mg BID: 1,843–1,850 (38–72)[62]
fu.AUC_{0-24}, nM.h	160 mg BID: 278 320 mg QD: 267	420 mg QD: 37–60 560 mg QD: 46–51	100 mg BID: 103
Plasma exposure of major active metabolite	N/A	1- to 2.8-fold higher than parent AUC[60]	2- to 3-fold higher than parent AUC[61]
Median BTK occupancy in PBMC at trough, %	160 mg BID: 100 320 mg QD: 100	420–820 mg QD: >90[14,63]	100 mg BID: ≥95[64]
Median BTK occupancy in lymph node at trough, %	160 mg BID: 100 320 mg QD: 94	420 mg QD: >90[65]	200 mg BID: 90[66] 100 mg BID: 95.8
P-gp and brain penetration	Weak P-gp substrate Brain penetration data in patients available	Not a P-gp substrate Brain penetration data in patients available	P-gp substrate Likely limited brain penetration[58]
Major enzyme involved	CYP3A	CYP3A	CYP3A

If not noted, data were taken from respective US Prescribing Information for zanubrutinib,[38] ibrutinib[67] and acalabrutinib.[37]
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*Ibrutinib was approved for R/R chronic graft versus host disease in 2017.
AUC_{0-24} = area under the plasma concentration–time curve from time 0 to 24 h; BID = twice daily; BTK = Bruton's tyrosine kinase; CLL = chronic lymphocytic leukaemia; CYP3A = cytochrome P450 3A; FDA = US Food and Drug Administration; fu = fraction of unbound drug in plasma; IC_{50} = concentration for 50% inhibition, MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; PBMC = peripheral blood mononuclear cell; P-gp = P-glycoprotein; QD = once daily; R/R = relapsed/refractory; WM = Waldenström's macroglobulinaemia.

by gastric-acid-reducing agents, and it can be taken concomitantly with proton-pump inhibitors and acid-reducing agents without dose adjustment.[58] The PK of zanubrutinib was not significantly affected by race (Asian versus non-Asian)[68] or by mild/moderate hepatic impairment.[69]

Zanubrutinib undergoes extensive metabolism via a cytochrome P450 3A (CYP3A) pathway and has no active metabolites in circulation; in contrast, ibrutinib and acalabrutinib both have major active metabolites in circulation.[58,68,70] Co-administration with moderate or strong CYP3A inhibitors (e.g. azole antifungals) increased zanubrutinib AUC and C_{max},

Figure 3: Free-drug concentration–time profiles relative to IC_{50} for zanubrutinib, ibrutinib and acalabrutinib

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Acala = acalabrutinib; ACP = active metabolite of acala; BID = twice daily; BTK = Bruton's tyrosine kinase; C_{trough} = trough concentration; Ibr = ibrutinib; IC_{50} = concentration for 50% inhibition; QD = once daily;
Zanu = zanubrutinib.

thereby increasing the risk of zanubrutinib toxicity. Co-administration with CYP3A inducers (e.g. rifampin) decreased zanubrutinib AUC and C_{max}. Dose reduction is therefore recommended when zanubrutinib is administered with moderate-to-strong CYP3A inhibitors, but not with weak CYP3A inhibitors/inducers.[70]

The pharmacodynamic assessment of zanubrutinib-mediated BTK inhibition in pre- and on-treatment lymph nodes and in PBMCs showed complete and sustained BTK inhibition at 160 mg BID (100% median steady-state BTK occupancy in both lymph nodes and PBMCs) and at 320 mg QD (94% median steady-state BTK occupancy in lymph nodes and 100% occupancy in PBMCs; *Table 1*).[48] BTK occupancy was comparable or higher than that for acalabrutinib and ibrutinib.[58] Zanubrutinib was also shown to have no clinically relevant effects on cardiac repolarization at therapeutic as well as supratherapeutic doses.[71,72]

Based on the low susceptibility of zanubrutinib to PK modulation by intrinsic and extrinsic factors (e.g. hepatic impairment, food effects) leading to consistent, sustained therapeutic exposures, and its ability to be prescribed concomitantly with proton-pump inhibitors and moderate/strong CYP3A4 inhibitors (with reduced dose), zanubrutinib is considered a safe and effective treatment option when prescribed according to its approved label.

Evaluation of the efficacy and safety of zanubrutinib

Key studies evaluating the efficacy and safety of zanubrutinib include the following: ASPEN, a randomized, open-label, phase III study, which was the first head-to-head comparison of zanubrutinib versus ibrutinib in patients with myeloid differentiation primary response 88 (MYD88)-mutant WM and in patients with wild-type MYD88;[16,73] ALPINE, an on-going, head-to-head, phase III, randomized, open-label study comparing the efficacy and safety of zanubrutinib versus ibrutinib in patients with R/R CLL/SLL;[50] and SEQUOIA, an on-going, global, open-label, randomized, phase III study comparing the efficacy of zanubrutinib versus bendamustine plus rituximab (BR) in treatment-naïve patients with CLL/SLL with or without del(17p).[51]

The ASPEN trial recruited patients with MYD88[L265P] WM who were either R/R (>1 prior line of treatment) or treatment naïve and unsuitable for standard immunochemotherapy. Prior BTKi treatment was exclusionary.[16] Patients in Cohort 1 were randomized to receive either 160 mg zanubrutinib BID (Arm A, n=102) or 420 mg ibrutinib QD (Arm B, n=99). In Cohort 2, patients with MYD88[WT] WM received 160 mg zanubrutinib BID (Arm C). The primary endpoint was the proportion of patients achieving a complete response (CR) or very good partial response (VGPR) by independent review. Key secondary endpoints included major response rate, progression-free survival (PFS), duration of response (DOR), disease burden and safety.[16] At a median follow-up of 19.4 months, no patient achieved CR. Although the study did not meet its statistical primary endpoint for superiority, there was a trend towards better disease control for zanubrutinib versus ibrutinib; independent review committee (IRC)-assessed VGPR was higher in the zanubrutinib arm compared with the ibrutinib arm (28% versus 19%, respectively, two-sided p=0.09). PFS rates at 18 months were 84% with ibrutinib and 85% with zanubrutinib, while estimated overall survival (OS) rates at 18 months were 93% with ibrutinib and 97% with zanubrutinib.[16]

The ASPEN study reported that neutropenia, upper respiratory tract infections and diarrhoea were the most common all-grade AEs among zanubrutinib-treated patients (n=101), whereas diarrhoea, upper respiratory tract infections, contusion and muscle spasms were the most common all-grade AEs among ibrutinib-treated patients (n=98).[16] Ibrutinib-treated patients had a ≥10% higher incidence of AF, diarrhoea, contusion, muscle spasms, peripheral oedema and pneumonia compared with zanubrutinib-treated patients, whereas the incidence of neutropenia was ≥10% higher among zanubrutinib-treated patients (grade ≥3 neutropenia was ≥5% higher). Nonetheless, grade ≥3 infection rates were comparable in both arms (1.2 and 1.1 events per 100 person-months for ibrutinib and zanubrutinib, respectively).[16] Ibrutinib-treated patients had a ≥5% higher incidence of grade ≥3 hypertension and pneumonia compared with zanubrutinib-treated patients. More patients treated with ibrutinib than zanubrutinib required dose reductions due to AEs (23% versus 14%, respectively).[16] The zanubrutinib group showed a greater improvement versus ibrutinib in most quality-of-life measures.[16]

A sub-study (Cohort 2) of the ASPEN trial reported that zanubrutinib also induced high-quality responses in patients with MYD88[WT] WM; 27% of MYD88[WT] patients had VGPRs or better, but there were no CRs. Although cross-study comparisons are not reliable, these rates were comparable to rates in zanubrutinib-treated patients with R/R and treatment-naïve MYD88[MUT] disease and identical to VGPRs in patients with MYD88[WT] disease treated with ibrutinib plus rituximab.[16,74,75] The safety profiles were similar in zanubrutinib-treated MYD88[WT] patients and those with MYD88[MUT] disease.[75]

The on-going ALPINE trial, which is currently the only comparative BTKi study that includes zanubrutinib, compares the efficacy and safety of zanubrutinib versus ibrutinib in ~600 patients with R/R CLL/SLL who have received one or more prior systemic therapies.[50] Prior BTKi therapy is exclusionary. The primary endpoint of the ALPINE study is the overall response rate (ORR: partial response [PR] + CR) by investigator assessment. The first interim analysis included 207 patients who were randomized to zanubrutinib (Arm A: 160 mg BID) and 208 patients who were randomized to ibrutinib (Arm B: 420 mg QD). Median follow-up was 15.3 months for Arm A and 15.4 months for Arm B. ORR was significantly higher in Arm A than in Arm B (78.3% versus 62.5%, respectively; p=0.0006).[76] Arm A had higher ORR than Arm B in patients with del(17p) (83% versus 54%, respectively) and in key subgroups including age (<65 years versus ≥65 years, respectively), sex, disease stage, number of lines of prior therapy (1–3 versus >3, respectively), baseline del(17p)/TP53 mutation status (80% for Arm A versus 50% for Arm B) and bulky disease (80% for Arm A versus 64% for Arm B).[76] Arm A had higher 12-month PFS rates (94.9% versus 84.0%; hazard ratio [HR] 0.40; 95% confidence interval [CI] 0.23–0.69; p=0.0007) and a trend towards higher 12-month OS rates (97.0% versus 92.7%; HR 0.54; 95% CI 0.25–1.16; p=0.1081) compared with Arm B.[76]

At the first interim analysis, the ALPINE study reported that 55.9% of patients in Arm A had grade ≥3 AEs compared with 51.2% in Arm B. AEs leading to treatment discontinuation occurred in 7.8% and 13% of patients in Arm A and Arm B, respectively.[76] Neutropenia (any grade) occurred in 28.4% and 21.7% of Arm A and Arm B, respectively, whereas grade ≥3 neutropenia was seen in 18.6% and 15.0% of patients, respectively. The higher rate of neutropenia did not translate into a higher rate of infections; any-grade infections occurred in 59.8% and 63.3% of patients, respectively, and grade ≥3 infections occurred in 12.7% and 17.9% of patients, respectively.[76] The rates of hypertension were similar in the two treatment arms (16.7% versus 16.4% for any grade, and 10.8% versus 10.6% for grade ≥3, respectively).[76] Major haemorrhage (any grade) occurred in 2.9% and 3.9% of patients in the two arms, respectively.[76] The rate of AF and atrial flutter (any grade) was significantly lower in Arm A compared with Arm B (2.5% versus 10.1%, respectively, two-sided p=0.0014). AF and flutter (grade ≥3) occurred in 1% and 1.9% of patients in the two arms, respectively. Treatment was discontinued due to cardiac disorders in seven patients in the ibrutinib arm.[76] The superior response rate, improved PFS and lower rate of AF/flutter compared with ibrutinib supported the potential use of zanubrutinib for R/R CLL/SLL. The ALPINE study limitations include the relatively short follow-up time to date, the use of lymphoma response criteria rather than the revised criteria including PR-L, and the unblinded nature of the study with investigator-assessed ORR primary endpoint.[76]

The on-going SEQUOIA trial was designed to compare the efficacy of zanubrutinib versus a combination of BR in treatment-naïve patients with CLL/SLL. Patients with CLL and del(17p) mutation show marked resistance to genotoxic chemotherapies, which cannot be overcome by incorporating anti-CD20 antibodies.[77] Additionally, most patients with del(17p) lack wild-type TP53, leading to genomic instability and poor responsiveness to chemotherapy.[77] Therefore, Cohort 1 included participants without del(17p), whereas participants with del(17p) were enrolled in Cohorts 2 and 3.[51] Participants in Cohort 1 were randomized 1:1 to zanubrutinib (Arm A, n=241) or six cycles of BR (Arm B, n=238). Randomization was stratified by age, Binet stage, immunoglobulin variable region heavy chain (IGHV) mutational status and geographical region. The primary endpoint for Cohort 1 was PFS by IRC, and key secondary endpoints were PFS by investigator assessment, ORR (per IRC and investigator assessment), OS and safety.[78] The median age was 70 years in both arms; 29.0% and 29.4% of patients in the zanubrutinib and BR arms had Binet Stage C disease, respectively; unmutated IGHV occurred in 53.4% of patients in the zanubrutinib arm versus 52.4% of patients in the BR arm.
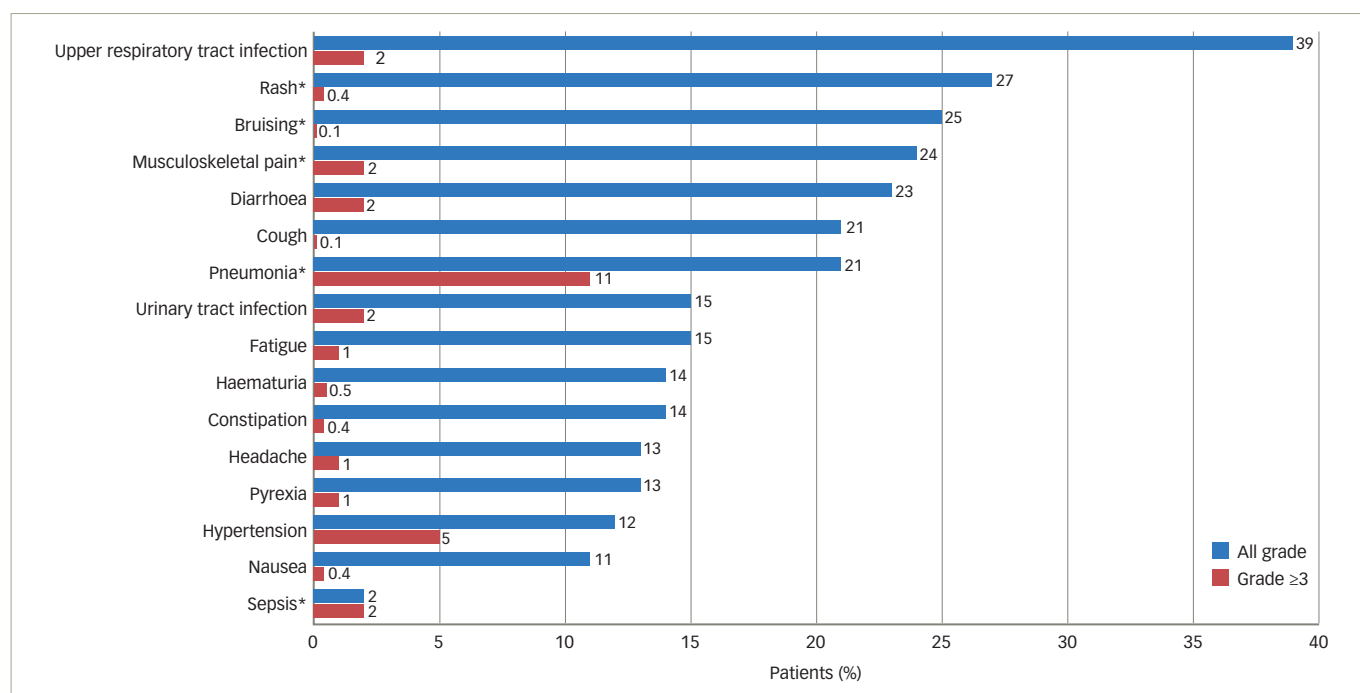
The 24-month PFS rates per IRC assessment were 85.5% and 69.5% in the zanubrutinib and BR arms, respectively (HR 0.42; 95% CI 0.27–0.63; p<0.0001).[78] PFS rates by IRC were also higher in the zanubrutinib arm compared with the BR arm in key subgroups, including age (<65 versus ≥65 years, respectively), sex, Binet stage (A or B versus C, respectively), bulky disease (<5 cm versus ≥5 cm, respectively), cytopenia at baseline, chromosome 11q deletion and IGHV mutational status (mutated versus unmutated).[78]

The SEQUOIA study reported 11 deaths each in the zanubrutinib and the BR arms at a median follow-up of 26.4 and 25.9 months, respectively.[78] Grade ≥3 AEs were recorded in 52.5% and 79.7% of patients in the zanubrutinib and BR arms, respectively.[78] AEs leading to dose reduction were recorded in 7.5% and 37.4% of patients in the zanubrutinib and BR arms, respectively. AEs leading to dose interruption or delay were recorded in 46.3% and 67.8% of patients in the two arms, respectively, and AEs leading to discontinuation of treatment were recorded in 8.3% and 13.7% of patients in the two arms, respectively.[78] In the zanubrutinib and BR arms, 11.7% and 51.1% of patients had grade ≥3 neutropenia; 2.1% and 7.9% had grade ≥3 thrombocytopenia; 0.4% and 1.3% had grade ≥3 AF; 3.8% and 1.8% had grade ≥3 major bleeding; and 6.3% and 4.8% had grade ≥3 hypertension, respectively.[78]

Cohort 2 of the SEQUOIA trial included 110 patients with del(17p) who received zanubrutinib (160 mg BID; Arm C).[51,78] With a median follow-up of 30.5 months, the 24-month PFS was 88.9%.[78] Data from Cohorts 1 and 2 of the SEQUOIA trial showed that zanubrutinib was well tolerated, was associated with low AF rates and demonstrated superiority in PFS over the BR regimen per IRC assessment, including in high-risk subgroups (e.g. unmutated IGHV, del[11q]).

Cohort 3 of the SEQUOIA trial included patients with a del(17p)/TP53 mutation, who received zanubrutinib plus venetoclax (Arm D).[51,78] The key endpoints included safety, ORR, PFS, DOR and undetectable minimal residual disease (uMRD).[79] The del(17p)/TP53 mutation safety population included 49 patients who received zanubrutinib (160 mg BID for ~≥27 cycles). Tumour lysis syndrome (TLS) was assessed between baseline and the end of cycle 3 of zanubrutinib. Venetoclax ramp-up was initiated after the 3-cycle lead-in of zanubrutinib; then, venetoclax (400 mg QD) was administered for 12–24 cycles.[79] The post-baseline efficacy assessment included 36 patients, and the combination treatment included 34 patients.[79] The median age of the study population was 65 years; 93.9% and 91.9% of patients were positive for del(17p) and TP53 mutation, respectively, and IGHV was unmutated in 87.8% of patients.[79] There were no reports of clinical

Figure 4: Non-haematological treatment-emergent adverse events of all grades reported in ≥10% of patients or grade ≥3 reported in ≥2% of patients in the pooled analysis of single-agent zanubrutinib treatment (N=779)

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Includes multiple preferred terms within the Medical Dictionary for Regulatory Activities (MedDRA).

TLS, and the 3-cycle zanubrutinib lead-in decreased the risk of TLS.[79] With a median follow-up of 12 months, 36% of patients who received combination therapy achieved CR/CRi (CR with incomplete bone marrow recovery). Although four additional patients met the criteria for CR/CRi, bone marrow assessment was not performed to confirm CR/CRi.[79] No AEs led to dose reduction, 29.4% of AEs led to dose interruption and no AEs led to discontinuation. There were no fatal AEs.[79] Data from Cohort 3 (Arm D) of the SEQUOIA trial showed that zanubrutinib plus venetoclax combination treatment resulted in a high response rate in the high-risk del(17p)/*TP53* mutation subgroup of patients with CLL/SLL. Responses were deeper with longer durations of treatment, as evidenced by the achievement of CR/CRi and uMRD. The combination was well tolerated.[79]

Zanubrutinib safety, tolerability and adverse event management

A pooled safety analysis of six studies (N=779 patients with B cell malignancies treated with zanubrutinib) was conducted to understand treatment-emergent AEs and treatment-limiting toxicities of zanubrutinib monotherapy.[80] The studies included A Phase I/II, Open-Label, Multiple-Dose, Dose Escalation and Expansion Study to Investigate the Safety and Pharmacokinetics of the BTK Inhibitor BGB-3111 in Subjects With B-Cell Lymphoid Malignancies (ClinicalTrials.gov identifier: NCT02343120; B-cell malignancies, n=385);[48] A Phase I Clinical Study to Investigate the Safety, Tolerability, and Pharmacokinetics/Pharmacodynamics of BTK Inhibitor BGB-3111 in Chinese Patients With B-cell Lymphoma (ClinicalTrials.gov identifier: NCT03189524; B-cell lymphomas, n=44);[81] A Single-Arm, Open-Label, Multicenter Phase 2 Study to Evaluate Safety and Efficacy of BGB-3111, a Bruton's Tyrosine Kinase (BTK) Inhibitor in Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) (ClinicalTrials.gov identifier: NCT03206918; CLL/SLL, n=91);[82] A Single-Arm, Open-Label, Multicenter Phase 2 Study to Evaluate Efficacy and

Safety of BGB-3111, a Bruton's Tyrosine Kinase (BTK) Inhibitor, in Subjects With Relapsed or Refractory Mantle Cell Lymphoma (MCL) (ClinicalTrials.gov identifier: NCT03206970; MCL, n=86);[46] A Phase 2, Single-Arm, Open-Label, Multicenter Study of Bruton's Tyrosine Kinase (BTK) Inhibitor BGB-3111 in Chinese Subjects With Relapsed/Refractory Waldenström's Macroglobulinemia (WM) (ClinicalTrials.gov identifier: NCT03332173; WM, n=44);[83] and A Phase 3, Randomized, Open-Label, Multicenter Study Comparing the Efficacy and Safety of the Bruton's Tyrosine Kinase (BTK) Inhibitors BGB-3111 and Ibrutinib in Subjects With Waldenström's Macroglobulinemia (WM) (ClinicalTrials.gov identifier: NCT03053440; WM, n=129).[73] The most common non-haematological toxicities reported were upper respiratory tract infection (39%), rash (27%), bruising (25%), musculoskeletal pain (24%), diarrhoea (23%), cough/pneumonia (21% each), urinary tract infection/fatigue (15% each), haematuria/constipation (14% each), headache/pyrexia (13% each), hypertension (12%) and nausea (11%).[80] Grade ≥3 non-haematological treatment-emergent AEs included pneumonia (11%), hypertension (5%), upper respiratory tract infection, urinary tract infection, sepsis, diarrhoea and musculoskeletal pain (2% each) (*Figure 4*). Bleeding or bruising events were reported in 55% of patients, although most were grade 1 or 2.[80] Zanubrutinib had consistently low rates of AEs of interest commonly associated with the BTKi class.[80]

Additionally, in zanubrutinib-treated patients with R/R B-cell malignancies who were intolerant to prior BTKis, 70% of ibrutinib intolerance events and 83% of acalabrutinib intolerance events did not recur on zanubrutinib, and no events occurred at a higher severity.[84] These data support the use of zanubrutinib after intolerance to other BTKis.

Dosage modifications are recommended for AEs based on recommendations from the US prescribing information (*Table 2*).[38] Dose interruption is recommended after the first, second and third

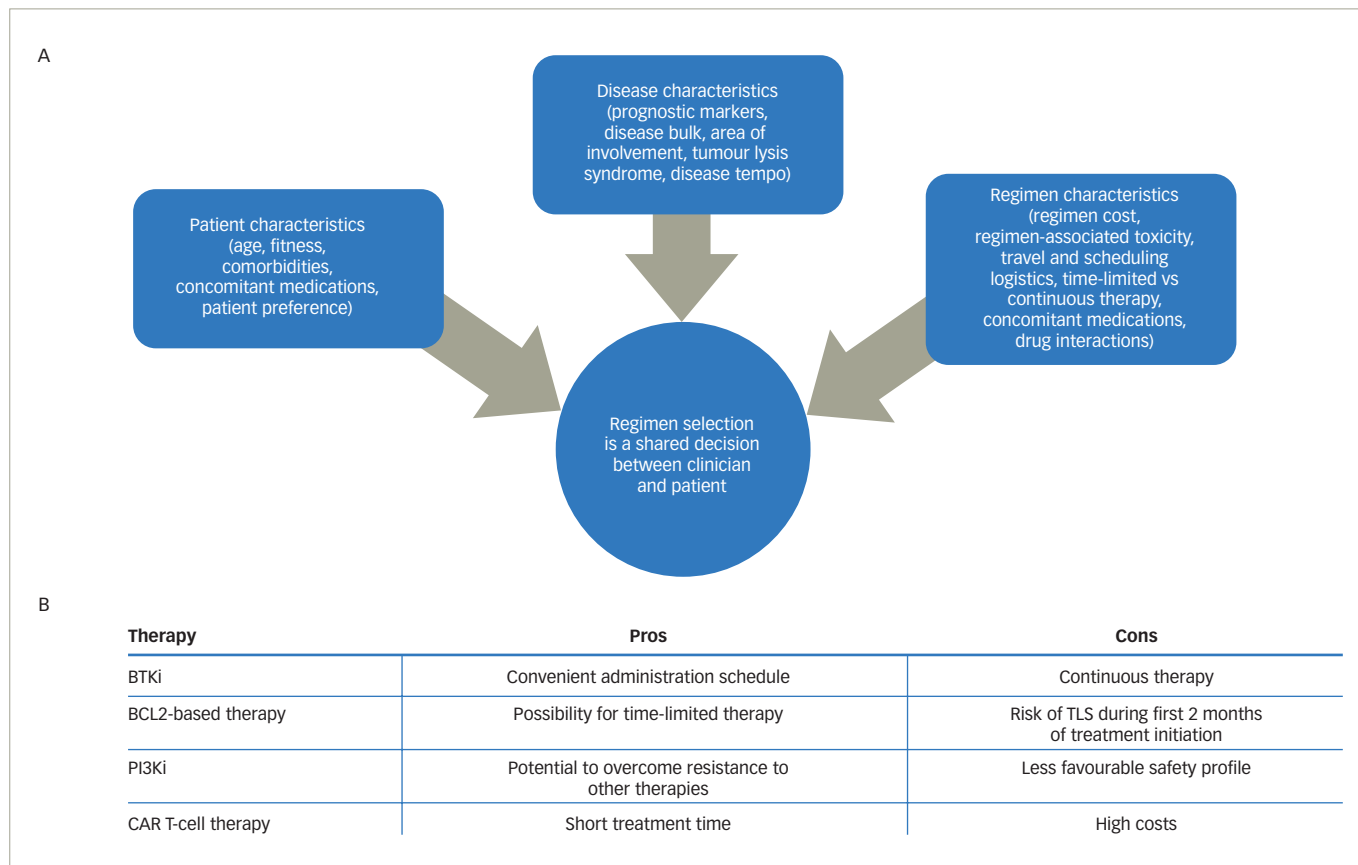## Table 2: Recommended dose modifications for adverse reactions

Event	Adverse reaction occurrence	Dosage modification Starting dose: 160 mg BID or 320 mg QD
Haematological toxicities		
Grade 3 febrile neutropenia Grade 3 thrombocytopenia with significant bleeding Grade 4 neutropenia (lasting more than 10 consecutive days) Grade 4 thrombocytopenia (lasting more than 10 consecutive days)	First	Interrupt zanubrutinib Once toxicity has resolved to grade 1 or lower or baseline: resume at 160 mg BID or 320 mg QD
	Second	Interrupt zanubrutinib Once toxicity has resolved to grade 1 or lower or baseline: resume at 80 mg BID or 160 mg QD
	Third	Interrupt zanubrutinib Once toxicity has resolved to grade 1 or lower or baseline: resume at 80 mg QD
	Fourth	Discontinue zanubrutinib
Non-haematological toxicities		
Grade 3 or 4 non-haematological toxicities	First	Interrupt zanubrutinib Once toxicity has resolved to grade 1 or lower or baseline: resume at 160 mg BID or 320 mg QD*
	Second	Interrupt zanubrutinib Once toxicity has resolved to grade 1 or lower or baseline: resume at 80 mg BID or 160 mg QD
	Third	Interrupt zanubrutinib Once toxicity has resolved to grade 1 or lower or baseline: resume at 80 mg QD
	Fourth	Discontinue zanubrutinib

Adapted from Zanubrutinib package insert.[38]
*Evaluate the benefit–risk before resuming treatment at the same dose for a grade 4 non-haematological toxicity.
BID = twice daily; QD = once daily.

Figure 5: Treatment diagram for B-cell malignancies with pros and cons of using Bruton's tyrosine kinase inhibitors, B-cell lymphoma 2 inhibitors phosphatidyl inositol 3 kinase inhibitors and chimeric antigen receptor T-cell therapy

Therapy	Pros	Cons
BTKi	Convenient administration schedule	Continuous therapy
BCL2-based therapy	Possibility for time-limited therapy	Risk of TLS during first 2 months of treatment initiation
PI3Ki	Potential to overcome resistance to other therapies	Less favourable safety profile
CAR T-cell therapy	Short treatment time	High costs

A: Selection of an appropriate treatment regimen is a decision shared by the clinician and patient, and it is dependent on multiple factors; B: Pros and cons of various regimens for chronic lymphocytic leukaemia.
BCL2 = B-cell lymphoma 2; BTKi = Bruton's tyrosine kinase inhibitor; CAR = chimeric antigen receptor; CLL = chronic lymphocytic leukaemia; PI3Ki = phosphatidylinositol 3 kinase inhibitor; TLS = tumour lysis syndrome.

occurrences of any of the following: grade 3 febrile neutropenia, grade 3 thrombocytopenia with significant bleeding, grade 4 neutropenia (lasting >10 consecutive days) and grade 4 thrombocytopenia (lasting >10 consecutive days). Zanubrutinib should be discontinued upon the fourth occurrence of these events and after the fourth occurrence of grade 3 or higher non-haematological toxicities.

Precautions recommended for zanubrutinib therapy include the following: 1) discontinuation of treatment upon any signs of intracranial bleeding and for 3–7 days pre- and post-surgery if there is a risk of bleeding; 2) dosage modification or termination in the case of grade 3 or 4 cytopenias; 3) careful monitoring and appropriate therapy for grade 3 or higher infections (most commonly pneumonia), which occur in more than a quarter of patients treated with zanubrutinib; 4) use of sun protection and regular monitoring for second primary malignancies, as non-melanoma skin cancer was the most common non-primary malignancy in zanubrutinib-treated patients; 5) monitoring for AF and atrial flutter. Patients who take zanubrutinib while pregnant should be informed about potential embryo-fetal toxicity.[38]

Impact of zanubrutinib on future clinical practice for B-cell malignancies

The emergence of therapeutic modalities such as BTKis, B-cell lymphoma 2 (BCL2)-based therapies, PI3K inhibitor-based therapies and chimeric antigen receptor (CAR) T-cell therapies has altered the treatment landscape for B-cell malignancies. Selection of an appropriate therapeutic regimen is a decision that is shared between the clinician and patient and is dependent on various factors, including 1) patient characteristics (age, fitness, comorbidities and concomitant medications), 2) disease characteristics (presence of prognostic markers, disease bulk, area of involvement, risk of TLS), and 3) regimen characteristics (cost, toxicity and convenience) (*Figure 5a*). Other parameters include genetic risk and response to prior lines of treatment.[77]

Although targeted therapies such as the BTKis are rapidly replacing chemoimmunotherapeutic regimens for CLL, head-to-head comparisons are lacking among the more recently developed strategies such as BTKis, BCL2-based therapies, PI3Ki-based therapies and CAR T-cell therapies. Some of the advantages and disadvantages of selected therapeutic regimens for CLL are listed in *Figure 5b*. BTKis require continuous treatment, which can be associated with financial burden, drug toxicity and development of resistance. In contrast, BCL2-based therapies have been developed as 1-year or 2-year fixed-term regimens. Although the time-limited strategy of BCL2-based therapies such as venetoclax may not be suitable for subgroups of patients with specific genetic abnormalities, BCL2-based therapies are associated with the achievement of uMRD.[85] PI3Kis such as idelalisib and umbralisib have demonstrated activity in ibrutinib-resistant patients but are often associated with serious toxicities and are only recommended for patients who progress on prior lines of therapy.[86] Although CAR T-cell therapy shows promise in R/R CLL, the long-term durability of response is not clear, and logistical considerations may impact therapeutic decisions.[87]

Conclusions

Selective inhibition of BTK activity is an important modality in targeted precision therapy to treat B-cell malignancies. The first-generation BTKi, ibrutinib, has well-described off-target effects that contribute to its toxicity profile, notably an increased risk for cardiovascular toxicities, including AF, hypertension and haemorrhage. Zanubrutinib is a potent and highly selective next-generation BTKi designed to provide complete and sustained BTK occupancy for efficacy across disease-relevant tissues, with lower rates of certain off-target AEs compared with ibrutinib. Its safety features include minimal cardiovascular toxicity.[16] The development of new classes of therapeutic agents (e.g. BTKis, BCL2-based agents, PI3Kis and CAR T-cell therapy) makes it important to study and optimize sequencing strategies carefully and to determine the potential benefits of combination therapies (e.g. BTKi plus venetoclax) in selected high-risk patients.[88] ❏

1. Fowler N, Davis E. Targeting B-cell receptor signaling: Changing the paradigm. *Hematology Am Soc Hematol Educ Program*. 2013;2013:553–60.
2. Honigberg LA, Smith AM, Sirisawad M, et al. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. *Proc Natl Acad Sci U S A*. 2010;107:13075–80.
3. Herman SE, Gordon AL, Hertlein E, et al. Bruton tyrosine kinase represents a promising therapeutic target for treatment of chronic lymphocytic leukemia and is effectively targeted by PCI-32765. *Blood*. 2011;117:6287–96.
4. Niemann CU, Wiestner A. B-cell receptor signaling as a driver of lymphoma development and evolution. *Semin Cancer Biol*. 2013;23:410–21.
5. Hendriks RW, Yuvaraj S, Kil LP. Targeting Bruton's tyrosine kinase in B cell malignancies. *Nat Rev Cancer*. 2014;14:219–32.
6. Noy A, de Vos S, Thieblemont C, et al. Targeting Bruton tyrosine kinase with ibrutinib in relapsed/refractory marginal zone lymphoma. *Blood*. 2017;129:2224–32.
7. Saba NS, Liu D, Herman SE, et al. Pathogenic role of B-cell receptor signalling and canonical NF-kappaB activation in mantle cell lymphoma. *Blood*. 2016;128:82–92.
8. Davis RE, Ngo VN, Lenz G, et al. Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma. *Nature*. 2010;463:88–92.
9. Hunter ZR, Yang G, Xu L, et al. Genomics, signaling, and treatment of Waldenstrom macroglobulinemia. *J Clin Oncol*. 2017;35:994–1001.
10. Wen T, Wang J, Shi Y, et al. Inhibitors targeting Bruton's tyrosine kinase in cancers: drug development advances. *Leukemia*. 2021;35:312–32.
11. Smith CIE, Burger JA. Resistance mutations to BTK inhibitors originate from the NF-κB but not from the PI3K-RAS-MAPK arm of the B cell receptor signaling pathway. *Front Immunol*. 2021;12:689472.
12. Berglof A, Hamasy A, Meinke S, et al. Targets for ibrutinib beyond B cell malignancies. *Scand J Immunol*. 2015;82:208–17.
13. Burger JA, Barr PM, Robak T, et al. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. *Leukemia*. 2020;34:787–98.
14. Advani RH, Buggy JJ, Sharman JP, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. *J Clin Oncol*. 2013;31:88–94.
15. Munir T, Brown JR, O'Brien S, et al. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *Am J Hematol*. 2019;94:1353–63.
16. Tam CS, Opat S, D'Sa S, et al. A randomized phase 3 trial of zanubrutinib versus ibrutinib in symptomatic Waldenstrom macroglobulinemia: The ASPEN study. *Blood*. 2020;136:2038–50.
17. Byrd JC, Hillmen P, Ghia P, et al. Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: Results of the first randomized phase III trial. *J Clin Oncol*. 2021;39:3441–52.
18. Guo Y, Liu Y, Hu N, et al. Discovery of zanubrutinib (BGB-3111), a novel, potent, and selective covalent inhibitor of Bruton's tyrosine kinase. *J Med Chem*. 2019;62:7923–40.
19. Brown JR, Moslehi J, O'Brien S, et al. Characterization of atrial fibrillation adverse events reported in ibrutinib randomized controlled registration trials. *Haematologica*. 2017;102:1796–805.
20. Caldeira D, Alves D, Costa J, et al. Ibrutinib increases the risk of hypertension and atrial fibrillation: Systematic review and meta-analysis. *PLoS One*. 2019;14:e0211228.
21. McMullen JR, Boey EJ, Ooi JY, et al. Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling. *Blood*. 2014;124:3829–30.
22. Abdel-Qadir H, Sabrie N, Leong D, et al. Cardiovascular risk associated with ibrutinib use in chronic lymphocytic leukemia: A population-based cohort study. *J Clin Oncol*. 2021;39:3453–62.
23. Zhu J, Bian SY. Late-chronic cardiotoxicity and heart failure caused by ibrutinib: A case report and literature review. *J Geriatr Cardiol*. 2021;18:307–11.
24. Dickerson T, Wiczer T, Waller A, et al. Hypertension and incident cardiovascular events following ibrutinib initiation. *Blood*. 2019;134:1919–28.
25. Mock J, Kunk PR, Palkimas S, et al. Risk of major bleeding with ibrutinib. *Clin Lymphoma Myeloma Leuk*. 2018;18:755–61.
26. Caron F, Leong DP, Hillis C, et al. Current understanding of bleeding with ibrutinib use: A systematic review and meta-analysis. *Blood Adv*. 2017;1:772–8.
27. Pellegrini L, Novak U, Andres M, et al. Risk of bleeding complications and atrial fibrillation associated with ibrutinib treatment: A systematic review and meta-analysis. *Crit Rev Oncol Hematol*. 2021;159:103238.
28. Hirsh V, Blais N, Burkes R, et al. Management of diarrhea induced by epidermal growth factor receptor tyrosine kinase inhibitors. *Curr Oncol*. 2014;21:329–36.
29. Perez-Soler R, Delord JP, Halpern A, et al. HER1/EGFR inhibitor-associated rash: Future directions for management and investigation outcomes from the HER1/EGFR inhibitor rash management forum. *Oncologist*. 2005;10:345–56.
30. Stephens DM, Byrd JC. How I manage ibrutinib intolerance and complications in patients with chronic lymphocytic leukemia. *Blood*. 2019;133:1298–307.
31. Paydas S. Management of adverse effects/toxicity of ibrutinib. *Crit Rev Oncol Hematol*. 2019;136:56–63.
32. Mato AR, Shah NN, Jurczak W, et al. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): A phase 1/2 study. *Lancet*. 2021;397:892–901.
33. Jain P, Thompson PA, Keating M, et al. Long-term outcomes for patients with chronic lymphocytic leukemia who discontinue ibrutinib. *Cancer*. 2017;123:2268–73.
34. Jain P, Kanagal-Shamanna R, Zhang S, et al. Long-term outcomes and mutation profiling of patients with mantle cell lymphoma (MCL) who discontinued ibrutinib. *Br J Haematol*. 2018;183:578–87.
35. Mato AR, Nabhan C, Thompson MC, et al. Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: A real-world analysis. *Haematologica*. 2018;103:874–9.
36. Khountham S, Shindiapina P, Mo X, et al. Natural history of noninfectious, ibrutinib-attributable adverse events in patients with chronic lymphocytic leukemia. *Leuk Lymphoma*. 2021;62:716–21.
37. AstraZeneca. Calquence® [package insert]. Gaithersburg, MD: AstraZeneca. November 2019.
38. BeiGene Co. Ltd. Brukinsa® [package insert]. Beijing, China: BeiGene Co. Ltd. November 2019.
39. Wu J, Zhang M, Liu D. Acalabrutinib (ACP-196): A selective second-generation BTK inhibitor. *J Hematol Oncol*. 2016;9:21.
40. Wang M, Rule S, Zinzani PL, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): A single-arm, multicentre, phase 2 trial. *Lancet*. 2018;391:659–67.
41. Owen RG, McCarthy H, Rule S, et al. Acalabrutinib monotherapy in patients with Waldenstrom macroglobulinemia: A single-arm, multicentre, phase 2 study. *Lancet Haematol*. 2020;7:e112–21.
42. Ou YC, Liu L, Tariq B, et al. Population pharmacokinetic analysis of the BTK inhibitor zanubrutinib in healthy volunteers and patients with B-cell malignancies. *Clin Transl Sci*. 2021;14:764–72.
43. Dhillon S. Orelabrutinib: First approval. *Drugs*. 2021;81:503–7.
44. Zhou D, Jin J, Fu ZZ, et al. Efficacy and safety of orelabrutinib in relapsed/refractory Waldenstrom's macroglobulinemia patients. *Blood*. 2021;138(Suppl. 1):46.
45. Shirley M. Bruton tyrosine kinase inhibitors in B-cell malignancies: Their use and differential features. *Target Oncol*. 2022;17:69–84.
46. Song Y, Zhou K, Zou D, et al. Treatment of patients with relapsed

or refractory mantle-cell lymphoma with zanubrutinib, a selective inhibitor of Bruton's tyrosine kinase. *Clin Cancer Res.* 2020;26:4216–24.

47. Opat S, Marcus R, Portell CA, et al. Phase-2 study of zanubrutinib (BGB-3111) in patients with relapsed/refractory marginal zone lymphoma. *Blood.* 2019;134(Suppl. 1):5256.

48. Tam CS, Trotman J, Opat S, et al. Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL. *Blood.* 2019;134:851–9.

49. ClinicalTrials.gov. Study of BTK Inhibitor Zanubrutinib in Participants with Relapsed/Refractory Non-GCB Type Diffuse Large B Cell Lymphoma. ClinicalTrials.gov Identifier: NCT03145064. Available at: https://clinicaltrials.gov/ct2/show/NCT03145064 (accessed 22 February 2022).

50. Hillmen P, Brown JR, Eichhorst BF, et al. ALPINE: Zanubrutinib versus ibrutinib in relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma. *Future Oncol.* 2020;16:517–23.

51. ClinicalTrials.gov. A study comparing zanubrutinib with bendamustine plus rituximab in participants with previously untreated CLL or SLL (SEQUOIA). ClinicalTrials.gov Identifier: NCT03336333. Available at: https://www.clinicaltrials.gov/ct2/show/NCT03336333 (accessed 22 February 2022).

52. ClinicalTrials.gov. Zanubrutinib (BGB-3111) in Participants with Previously Treated B-cell Lymphoma Intolerant of Prior Bruton Tyrosine Kinase Inhibitor (BTKi) Treatment. ClinicalTrials.gov Identifier: NCT04116437. Available at: https://clinicaltrials.gov/ct2/show/NCT04116437 (accessed 22 February 2022).

53. BeiGene Ireland, Ltd. Brukinsa® [summary of product characteristics]. Dublin, Ireland: BeiGene Ireland. Ltd. November 2021.

54. Li G, Liu X, Chen X. Simultaneous development of zanubrutinib in the USA and China. *Nat Rev Clin Oncol.* 2020;17:589–90.

55. BeiGene. Press release. BeiGene Announces the Approval of BRUKINSA™ (Zanubrutinib) in China for Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma and Relapsed/Refractory Mantle Cell Lymphoma. 3 June 2020. Available at: https://ir.beigene.com/news-details/?id=069a2fc1-be44-46c0-aa8f-ebd60dd8a65c (accessed 22 February 2022).

56. Xu W, Yang S, Zhou K, et al. Treatment of relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma with the BTK inhibitor zanubrutinib: Phase 2, single-arm, multicenter study. *J Hematol Oncol.* 2020;13:48.

57. BeiGene. Press release. Zanubrutinib (BRUKINSA®) (Zanubrutinib) for the Treatment of Waldenstrom's Macroglobulinemia. 2 March 2021. Available at: https://ir.beigene.com/news-details/?id=2dcdbaf1-b5cb-4d9e-8de9-dc8959b1f2dc (accessed 22 February 2022).

58. Tam CS, Ou YC, Trotman J, Opat S. Clinical pharmacology and PK/PD translation of the second-generation Bruton's tyrosine kinase inhibitor, zanubrutinib. *Expert Rev Clin Pharmacol.* 2021;14:1329–44.

59. Kaptein A, de Bruin G, Emmelot-van Hoek M, et al. Potency and selectivity of BTK inhibitors in clinical development for B-cell malignancies. *Blood.* 2018;132(Suppl. 1):1871.

60. Center For Drug Evaluation and Research U.F.a.D.A.C.f.D.E.a. *Application Number 20552Orig2s000.* 2013. Available

at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205552Orig2s000ClinPharmR.pdf (accessed 15 December 2021).

61. Zhou D, Podoll T, Xu Y, et al. Evaluation of the drug-drug interaction potential of acalabrutinib and its active metabolite, ACP-5862, using a physiologically-based pharmacokinetic modeling approach. *CPT Pharmacometrics Syst Pharmacol.* 2019;8:489–99.

62. Byrd JC, Harrington B, O'Brien S, et al. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. *N Engl J Med.* 2016;374:323–32.

63. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N Engl J Med.* 2013;369:32–42.

64. Alsadhan A, Cheung J, Gulrajani M, et al. Pharmacodynamic analysis of BTK inhibition in patients with chronic lymphocytic leukemia treated with acalabrutinib. *Clin Cancer Res.* 2020;26:2800–9.

65. Herman SE, Mustafa RZ, Gyamfi JA, et al. Ibrutinib inhibits BCR and NF-kappaB signaling and reduces tumor proliferation in tissue-resident cells of patients with CLL. *Blood.* 2014;123:3286–95.

66. Sun C, Nierman P, Kendall EK, et al. Clinical and biological implications of target occupancy in CLL treated with the BTK inhibitor acalabrutinib. *Blood.* 2020;136:93–105.

67. Pharmacyclics. Imbruvica® (ibrutinib) [package insert]. Sunnyvale, CA: Pharmacyclics, LLC. 2015.

68. Mu S, Tang Z, Novotny W, et al. Effect of rifampin and itraconazole on the pharmacokinetics of zanubrutinib (a Bruton's tyrosine kinase inhibitor) in Asian and non-Asian healthy subjects. *Cancer Chemother Pharmacol.* 2020;85:391–9.

69. Ou YC, Preston RA, Marbury TC, et al. A phase 1, open-label, single-dose study of the pharmacokinetics of zanubrutinib in subjects with varying degrees of hepatic impairment. *Leuk Lymphoma.* 2020;61:1355–63.

70. Wang K, Yao X, Zhang M, et al. Comprehensive PBPK model to predict drug interaction potential of zanubrutinib as a victim or perpetrator. *CPT Pharmacometrics Syst Pharmacol.* 2021;10:441–54.

71. Mu S, Darpo B, Tang Z, et al. No QTc prolongation with zanubrutinib: Results of concentration-QTc analysis from a thorough QT study in healthy subjects. *Clin Transl Sci.* 2020;13:923–31.

72. ClinicalTrials.gov. A Two-Part Phase 1 Study to Investigate the Safety and Tolerability of Supratherapeutic Dose of Zanubrutinib and Effect of Zanubrutinib on Cardiac Repolarization in Healthy Subjects. ClinicalTrials.gov Identifier: NCT03432884. Available at: https://clinicaltrials.gov/ct2/show/NCT03432884 (accessed 22 February 2022).

73. ClinicalTrials.gov. A Study Comparing BGB-3111 and Ibrutinib in Participants with Waldenström's Macroglobulinemia (WM) (ASPEN). ClinicalTrials.gov Identifer: NCT03053440. Available at: https://clinicaltrials.gov/ct2/show/NCT03053440 (accessed 22 February 2022).

74. Dimopoulos MA, Tedeschi A, Trotman J, et al. Phase 3 trial of ibrutinib plus rituximab in Waldenstrom's macroglobulinemia. *N Engl J Med.* 2018;378:2399–410.

75. Dimopoulos M, Sanz RG, Lee HP, et al. Zanubrutinib

for the treatment of MYD88 wild-type Waldenstrom macroglobulinemia: A substudy of the phase 3 ASPEN trial. *Blood Adv.* 2020;4:6009–18.

76. Hillmen P, Eichhorst B, Brown JR, et al. First interim analysis of ALPINE study: Results of a phase 3 randomized study of zanubrutinib vs ibrutinib in patients with relapsed/refractory chronic lymphocytic leukemia/ small lymphocytic lymphoma. Presented at: European Hematology Association Virtual Congress, 11 June 2021. Abstract LB1900.

77. Hallek M. Chronic lymphocytic leukemia: 2020 update on diagnosis, risk stratification and treatment. *Am J Hematol.* 2019;94:1266–87.

78. Tam CS, Giannopoulos K, Jurczak W, et al. SEQUOIA: Results of a phase 3 randomized study of zanubrutinib versus bendamustine + rituximab in patients with treatment-naive chronic lymphocytic leukemia/small lymphocytic lymphoma. *Blood.* 2021;138(Suppl. 1):396.

79. Tedeschi A, Ferrant E, Flinn IW, et al. Zanubrutinib in combination with venetoclax for patients with treatment-naive chronic lymphocytic leukemia or small lymphocytic lymphoma with del(17p): Early results from arm D of the SEQUOIA (BGB-3111-304) triaL. *Blood.* 2021;138(Suppl. 1):67.

80. Tam CS, Dimopoulos MA, Garcia-Sanz R, et al. Pooled safety analysis of zanubrutinib monotherapy in patients with B-cell malignancies. *Blood Adv.* 2022;6:1296–308.

81. ClinicalTrials.gov. A Study to Investigate Zanubrutinib in Chinese Participants with B-cell Lymphoma. ClinicalTrials.gov Identifier: NCT03189524. Available at: https://clinicaltrials.gov/ct2/show/NCT03189524 (accessed 22 February 2022).

82. ClinicalTrials.gov. Efficacy and Safety of Zanubrutinib in Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. ClinicalTrials.gov Identifer: NCT03206918. Available at: https://clinicaltrials.gov/ct2/show/NCT03206918 (accessed 22 February 2022).

83. ClinicalTrials.gov. Study of BTK Inhibitor BGB-3111 in Chinese Participants with Relapsed/Refractory Waldenström's Macroglobulinemia (WM). ClinicalTrials.gov Identifier: NCT03332173. Available at: https://clinicaltrials.gov/ct2/show/NCT03332173 (accessed 22 February 2022).

84. Shadman M FI, Moshe Y. Levy M.Y, Porter R, et al. Phase 2 study of zanubrutinib in BTK inhibitor-intolerant patients with relapsed/refractory B-cell malignancies. *Blood.* 2021;138(Suppl. 1):1410.

85. Molica S. Venetoclax: A real game changer in treatment of chronic lymphocytic leukemia. *Int J Hematol Oncol.* 2020;9:IJH31.

86. Ondrisova L, Mraz M. Genetic and non-genetic mechanisms of resistance to BCR signaling inhibitors in B cell malignancies. *Front Oncol.* 2020;10:591577.

87. Porter DL, Hwang WT, Frey NV, et al. Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia. *Sci Transl Med.* 2015;7:303ra139.

88. Mato AR, Hill BT, Lamanna N, et al. Optimal sequencing of ibrutinib, idelalisib, and venetoclax in chronic lymphocytic leukemia: Results from a multicenter study of 683 patients. *Ann Oncol.* 2017;28:1050–6.