VIA MEDICA

REVIEW ARTICLE

Acta Haematologica Polonica 2023
Number 2, Volume 54, pages 53–64
DOI: 10.5603/AHP.a2023.0015
ISSN 0001–5814
e-ISSN 2300–7117

Zanubrutinib: novel therapeutic option for treatment of B-cell neoplasms

Alan Majeranowski[1, 2], Filip Lebiedziński[3*], Marcin Okrój[1], Jakub Osowski[4], Andrzej Mital[2]

[1]Department of Cell Biology and Immunology, Intercollegiate Faculty of Biotechnology, University of Gdansk and Medical University of Gdansk, Gdańsk, Poland
[2]Department of Hematology and Transplantology, Medical University of Gdansk, Gdańsk, Poland
[3]Department of Physiopathology, Faculty of Medicine, Medical University of Gdansk, Gdańsk, Poland
[4]Student Scientific Society, Medical University of Gdansk, Gdańsk, Poland

Abstract

Bruton's tyrosine kinase (BTK) is a part of the B-cell receptor (BCR) signaling pathway. Activation of the BCR appears crucial for normal B cells as it regulates proliferation, differentiation, adhesion, survival, and apoptosis. Such signaling is also vital for malignant B cells, since many of them show constitutive activation of the BCR pathway. The development of ibrutinib, a best-in-class BTK inhibitor, has led to a new direction in the treatment of B-cell malignancies. Further studies have enabled the development of more potent and more selective BTK inhibitors, such as zanubrutinib. These novel agents were designed primarily to reduce adverse effects such as diarrhea, atrial fibrillation, rash, or hemorrhagic complications. Compelling data from clinical studies that have verified its efficacy and safety has allowed the approval of zanubrutinib in hematological malignancies such as mantle cell lymphoma, Waldenström's macroglobulinemia, chronic lymphocytic leukemia, and marginal zone lymphoma.

Key words: ibrutinib, zanubrutinib, CLL, non-Hodgkin's lymphoma, Bruton's tyrosine kinase

Acta Haematologica Polonica 2023; 54, 2: 53–64

Introduction

Targeted immunotherapy has been a significant milestone in the treatment of cancer. A boom starting in the 1990s brought innovations also to the field of hematology, especially when rituximab, the first anti-tumor monoclonal antibody (mAb) bondable to CD20 antigen, was approved for clinical use in 1997 [1]. Considered to be the biggest breakthrough in treating B-cell malignancies for over half of a century [2], rituximab became a prototype of new generations of more effective compounds, as many patients are refractory to rituximab [3–5]. Antitumor antibodies bondable to cluster of differentiation (CD) antigens are the most popular so far, but not the only, targeted drugs for B-cell malignancies. Representatives of other classes, including inhibitors of immune checkpoints (nivolumab [6], pembrolizumab [7]), methyltransferase inhibitors (tazemetostat [8]), phosphatidylinositol-3 kinase (PI3K) inhibitors [9], spleen kinase (Syk) inhibitors [10], and some like proteasome inhibitor bortezomib [11], nuclear export inhibitor selinexor [12], and specimens based on chimeric antigenic T-cell receptor (CAR-T) technology [13–16], are undergoing clinical trials or have already been approved in clinics. Into the quickly evolving landscape of anti-B cell therapeutics, a new class of drugs, Bruton's tyrosine kinase (BTK) inhibitors, has emerged as a 'rising star' to

*Address for correspondence: Filip Lebiedziński, Department of Physiopathology, Faculty of Medicine, Medical University of Gdansk, ul. Smoluchowskiego 17, 80–214 Gdańsk, Poland, e-mail: flebiedzinski@gumed.edu.pl

Received: 06.11.2022 Accepted: 26.02.2023 Early publication date: 30.03.2023

be used either alone or in combination with acknowledged immunotherapeutics.

Overexpression or disturbances in the activation of protein kinases involved in cellular proliferation and migration are among the key mechanisms of neoplasia development [17, 18]. Furthermore, hereditary mutations in genes encoding particular protein kinases are associated with the initiation, promotion, progression, and relapse of various neoplasms [19]. Extensive studies into the role of protein kinases in neoplastic diseases have led to the development of drugs that specifically inhibit signals transduced by these enzymes. Such compounds usually have a relatively low molecular weight compared to immunotherapeutics, and some of them can be administered orally. Their introduction is considered to be another milestone in both oncology and hematology [20].

BTK is a non-receptor kinase engaged in signal transduction following the binding of a specific ligand to the B-cell receptor (BCR). Activation of the BCR pathway is critical for normal B-cell maturation, proliferation, differentiation, and migration [21], although downstream events of this cascade also provide anti-apoptotic and proliferative signals for neoplastic cells. BCR signaling in normal and malignant cells, with an emphasis on the role of BTK, was recently reviewed by Efremov et al. [22]. Briefly, binding of antigen to receptor antibody triggers re-organization of the cytoskeleton and assembly of local BCR units into clusters. This rearrangement initiates the pathway, which leads to the formation of a multiprotein complex called the 'BCR signalosome'. Within the signalosome, the lipid kinase PI3Kδ becomes activated and phosphorylates the membrane phospholipid phosphatidylinositol-4,5-bisphosphate (PIP2). Phosphorylated PIP2 (now termed PIP3) forms a docking site for another pool of adaptor molecules and kinases, including BTK. Phosphorylation of BTK by SRC-family kinases and subsequent autophosphorylation turns on the activity of BTK. Downstream effects of BTK activation include dephosphorylation of the transcription factor NFAT, which is then translocated from cytosol to the nucleus and binds promotor regions of genes pivotal for B cell fate [23].

The other, canonical effect of BTK activation is the nuclear translocation of a transcription factor known as NFκB. Besides the canonical signaling through the BCR receptor, many constituents of this pathway are engaged in crosstalk with elements of parallel signaling cascades [24, 25], which often occur in a cell-specific manner and an inducible fashion [26].

Role and status of BCR signaling in B-cell malignancies

The ability to pass the signal through BCR indicates a proper rearrangement of heavy and light chain genes, the assembly of functional receptors, and the appearance of specific antigens demanding a humoral adaptive response, i.e. activation, proliferation, and differentiation of normal B cells. Moreover, downstream elements of the cascade bias cellular mechanisms of self-control into anti-apoptotic scenarios [27]. This is the putative reason why numerous B-cell malignancies, including chronic lymphocytic leukemia (CLL), Burkitt lymphoma, mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and Waldenström's macroglobulinemia (WM), exhibit activated status of the BCR pathway [22].

However, the drivers of the pathway and mutational background/context may be different to those observed in normal B cells. Certain diseases such as CLL are characterized by tumor cells which bear a subset of identical BCRs on their surface [28, 29]. Interestingly, these variants of BCR are rarely identified in normal B cells, and this observation suggests that binding to certain antigens may be supportive of the survival of CLL cells. Indeed, antibodies produced by these CLL clones bind to ubiquitous antigens [22, 30–33]. This ensures continuous, or very frequent, activation of BCR in CLL cells and seems to be crucial for the maintenance of anti-apoptotic proteome [34]. A similar scheme of BCR activation has been reported for DLBCL cells, although they additionally exhibit a mutation in CD79B, which protects from the internalization of BCR by a negative feedback loop [35].

Different mechanisms of BCR activation are characteristic of follicular lymphoma. Somatic mutations of these tumor cells often add glycosylation sites in BCR chains, resulting in the exposure of mannose residues. The chronic activation of BCR is then supported by interactions with macrophages and dendritic cells expressing high levels of mannose-binding lectin DC-SIGN [36]. Constitutive activation of BCR pathway elements is often reported in MCL [37], and the correlation between disease occurrence and bacterial infections putatively resulting in notorious stimulation of BCR by bacterial antigens has been reported in MZL [22].

The abovementioned all point towards a critical role of BCR signaling in B cell-derived lymphatic disorders and posit elements of this cascade, including BTK, as a reliable molecular target.

Ibrutinib: first generation BTK inhibitor

Ibrutinib was the first BTK inhibitor approved by the US Food and Drug Administration (FDA) in 2013 for treating relapsed-refractory (R/R) MCL [38]. MCL affects mostly older men, and it is usually diagnosed at stages III or IV, which significantly limits the number of available therapeutic options. Ibrutinib's approval was granted after publishing the results of the clinical trial PCYC-1104 [39]. Patients involved in this study received a median of three prior therapies followed by a daily oral dose of 560 mg ibrutinib. 75 of

111 patients (68%) responded to the therapy, including 21% complete response (CR) and 47% partial response (PR). Secondary end-points, namely duration of response (DOR) and progression-free survival (PFS), were 15.3 months and 13.9 months, respectively (medians). Median overall survival (OS) was not reached, and that estimated at 18 months was 58% [39]. Two further studies on ibrutinib as a single agent for treating R/R MCL (the SPARK phase II study, n = 120 and the RAY phase III study, n = 139 in the ibrutinib arm), revealed similar outcomes: overall response rates (ORR) were 63% and 72%, median PFS was 10.5 and 14.6 months, and OS at 18 months was 58% and 61%, respectively [40].

Other clinical trials have assessed the efficacy of ibrutinib's combination with approved immunotherapeutics (reviewed in [41]). ORR as high as 88% (including 44% CR) was reported for R/R MCL patients treated with ibrutinib + rituximab [42]. Even more encouraging results, such as 94% ORR (76% CR), were achieved when a combination of ibrutinib + rituximab + bendamustine was used [43]. Notably, equally promising data has been preliminarily reported for combinations of ibrutinib + rituximab (98% ORR, 60% CR) [44], ibrutinib + obinutuzumab + venetoclax (100% ORR, 47% CR) [45], and ibrutinib + rituximab followed by short-course R-HCVAD (rituximab plus hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone)/methotrexate (MTX) (100% ORR, 90% CR) [46], when used as a frontline MCL therapy. Further clinical studies have led to ibrutinib's approval for CLL [47], WM [48], and MZL [49]. Promising results were also obtained in a trial testing ibrutinib's combination with lenalidomide and rituximab for the treatment of R/R DLBCL [50].

The clinical approval of ibrutinib was a breakthrough, not only due to its efficacy against lymphoproliferative diseases, but also to the decreased risk of side effects. Previous treatment regimens applied in B-cell malignancies contained chemotherapeutic components like chlorambucil, fludarabine and cyclophosphamide, which rendered patients subjected to such treatment to a high risk of early bone marrow suppression and of late onset myelodysplasia. The introduction of BTK inhibitors in monotherapy, or combined with other agents, brings nearer the prospect of chemo-free therapies.

Why are next generation BTK inhibitors necessary?

Despite the clinical success of ibrutinib, some patients experience adverse effects (AEs) which can eventually enforce discontinuation of therapy. Typical AEs associated with ibrutinib are different than those observed in acknowledged chemotherapy regimens and are therefore considered to be class-specific ones [51]. Rates of discontinuation due to AE vary between trials/diagnoses. In MZL, such discontinuation accounts for 17% of patients, whereas serious AEs of any grade occurred in 44% of patients. Pneumonia grade ≥3 was the most common severe side effect, reported in 8% of the cohort [49]. Serious AEs occurred in 42% of CLL patients receiving single-agent ibrutinib, becoming the reason for discontinuation in 4% of patients, and fatal in another 4% [47]. In this study, out of 81 cases of serious AE, 46 accounted for infections and 13 for cardiac disorders, including atrial fibrillation.

A separate study analyzed the prevalence of atrial fibrillation in a retrospective follow-up analysis of CLL patients receiving ibrutinib. Atrial fibrillation was found in 6.1% of individuals without a prior history of this disorder [52]. Other AEs of grade ≥3 reported in the CLL clinical trial were pyrexia, diarrhea, fatigue, nausea, anemia, neutropenia, thrombocytopenia, arthralgia, dyspnea, stomatitis, and sinusitis. Another clinical study on ibrutinib in R/R CLL and small lymphocytic lymphoma (SLL) patients of the high risk associated with del(17p) showed a discontinuation rate due to AEs of 15% (22 of 144 patients) and fatality in two patients, although an extended analysis reported death due to AEs in 18 patients [53]. In the R/R MCL study, 7% of patients discontinued ibrutinib and 3% died from AEs, whereas diarrhea, neutropenia, thrombocytopenia, fatigue and dyspnea, but not upper respiratory tract infection, were the most common AEs of grade ≥3 [39]. The occurrence of thrombocytopenia but also direct activity on the signaling pathway in platelets predisposes to bleeding and hemorrhage, which is especially noticeable in head-to-head clinical trials comparing the effect of ibrutinib and chemo plus immunotherapeutics (reviewed in [54]). Some of these AEs, including diarrhea, bleeding, and atrial fibrillation, are attributed to off-target effects [55]. Ibrutinib covalently and irreversibly binds cysteine 481 in the ATP-binding pocket of BTK [38]. However, many other kinases share a similar molecular architecture of this functional site as that of BTK, e.g. interleukin-2-inducible T-cell kinase (ITK), Tec protein tyrosine kinase (TEC), bone marrow tyrosine kinase gene in chromosome X (BMX), and epidermal growth factor receptor (EGFR) (reviewed in [54, 56]). Kaptein et al. [57] assessed the specificity of ibrutinib in terms of kinase inhibition (excluding BTK) and, by the application of KinomeScan technology, found that the activity of 9.4% of human wild-type kinases was inhibited by more than 65% at a 1 μM concentration. They also provided IC_{50} values from biochemical assays showing non-specific inhibition of particular kinases. The IC_{50} value for BTK was 1.5 nM, whereas those for TEC, ITK, BMX, and EGFR were 10 nM, 4.9 nM, 0.8 nM, and 5.3 nM, respectively. Importantly, functional impairment of these kinases is thought to be associated with diarrhea, dysfunction of antibody-dependent cellular cytotoxicity (ADCC) mechanism, dysfunction of platelets, and the risk of bleeding [38, 58, 59].

Next generation irreversible BTK inhibitors

Selective BTK inhibitors were developed mainly with the aim of reducing significant AEs occurring during ibrutinib therapy while maintaining high efficacy in the treatment of B-cell malignancies. Apart from zanubrutinib, other selective irreversible BTK inhibitors have been approved or are under investigation. The first approved second-generation agent was acalabrutinib (approved for MCL in 2017 [60], which due to increased selectivity compared to ibrutinib, e.g. lack of TEC, ITK and HER 2 inhibition, presented fewer or no AEs such as bleeding or atrial fibrillation [61].

Although there is limited data regarding a direct comparison between acalabrutinib and zanubrutinib in terms of efficacy and safety, recent findings from the ongoing BGB-3111-215 trial (NCT04116437) showed that zanubrutinib could prove beneficial to many patients with B-cell neoplasms who had to discontinue acalabrutinib because of AEs. In patients intolerant to acalabrutinib who received zanubrutinib, 75% of acalabrutinib AEs of any grade did not occur during zanubrutinib therapy, and no acalabrutinib AEs recurred at a high severity [62].

Other important irreversible BTK inhibitors already approved for B-cell malignancies are tirabrutinib (CNS lymphoma, WM, CLL) and orelabrutinib EGFR, BMX, TEC (MCL, CLL, SLL). Studies on these molecules have also shown improved selectivity against potential off-target enzymes, e.g. BMX, EGFR, TEC, and ITK [63, 64]. Clinical trials have led to the approval of these drugs for treating various hematological malignancies, including CNS lymphoma (in the case of tirabrutinib) [65].

Many irreversible BTK inhibitors, such as evobrutinib, spebrutinib, remibrutinib, tolebrutinib and olmutinib, are currently under pre-clinical and clinical investigation. So far, the results are promising and support the continued investigation of these molecules, which may, in the future, contribute to approval for the treatment of autoimmune disorders (e.g. SLE, arthritis, Sjogren's syndrome) and cancers, such as non-small cell lung cancer [65].

Reversible BTK inhibitors

Another important issue is resistance to BTK inhibitors, whose mechanism of action relies on covalent and irreversible binding to cysteine 481. Substitution of cysteine with serine, despite being conservative in terms of amino acid homology, precludes effective inhibition of BTK by either ibrutinib or zanubrutinib. Such C481S mutation is often manifested in CLL patients receiving prolonged treatment, and is believed to stem from the selection and expansion of rare clones of tumor cells already present in patients before treatment initiation [66].

The novel, reversible inhibitors of BTK, such as vecabrutinib (SNS-062) [67], pirtobrutinib (LOXO-305) [68], and nemtabrutinib (ARQ-531, MK-1026) [69] have been shown to effectively diminish the activity of the C481S variant in preclinical testing. Their selectivity, safety, tolerability, pharmacokinetics, and efficacy are now being assessed in clinical trials [70]. At this stage, the evidence suggests that these novel agents may provide clinical benefit for patients with CLL or MCL who are resistant to ibrutinib [71, 72].

Advantages of zanubrutinib over ibrutinib in biochemical and mechanistic context

Zanubrutinib is a novel irreversible BTK inhibitor developed as a therapeutic agent dedicated to the treatment of B-cell lymphoproliferative diseases. Initial studies have shown potent on-target activity against BTK comparable to that of ibrutinib, but with higher selectivity and an excellent pharmacodynamic profile *in vivo* [73]. KinomeScan analyses have revealed a halving in the percentage of non-BTK kinase inhibition by zanubriutinib compared to ibrutinib (4.3% vs. 9.4%, respectively) [57]. Importantly, off-target effects of zanubrutinib toward vital tyrosine kinases such as EGFR, human epidermal growth factor receptor (2HER2), HER4, ITK, Janus kinase 3 (JAK3), and TEC are considerably lower than ibrutinib [55, 57]. The effective inhibitory concentrations depended on the assay, and the average IC_{50} values reported for EGRF, ITK, JAK3, HER2, and TEC were respectively 8, 26, 51, 70, and 2.4-fold higher for zanubrutinib than for ibrutinib. Such characteristics may result in more favorable pharmacodynamics, as well as limited AEs, such as diarrhea, rash, atrial fibrillation, bleeding, and fatigue. Dobue et al. analyzed the effect of BTK inhibitors on thrombus formation, and found that pretreatment of mice with ibrutinib, but not zanubrutinib, resulted in either *in vitro* reduction of platelets' adhesion to immobilized type I collagen, von Willebrand factor (vWF), and fibrinogen, or thrombus formation *in vivo* [74]. The same conclusions were drawn from experiments performed on platelets collected from ibrutinib-treated CLL patients, who formed smaller thrombi than those collected from zanubrutinib-treated patients or healthy controls. Such results show a lower incidence of zanubrutinib-related bleeding and underline zanubrutinib's advantage over ibrutinib in patients receiving anticoagulants [75].

The relative sparing of ITK by zanubrutinib could result in less interference with the tumor-clearing mechanism of anti-CD20 antibody-induced antibody-dependent cytotoxicity (ADCC), resulting in enhanced efficacy when combined with obinutuzumab [76]. Another advantage of zanubrutinib includes favorable drug-drug interaction characteristics that allow co-administration with azole antifungals, proton pump inhibitors, and vitamin K antagonists [76, 77]. Moreover, according to preclinical trials, zanubrutinib has better bioavailability when administered orally [55].

Better selectivity and bioavailability of zanubrutinib should be mirrored in fewer AEs in patients and comparable on-target activity should make it as effective as the parental molecule. Such a thesis is being verified in clinical trials, which assess safety and efficacy, as well as a head-to-head comparison with ibrutinib.

Clinical trials of zanubrutinib

Ongoing and completed clinical trials of zanubrutinib in B-cell malignancies are set out in Table I [78–86]. Here, we provide a more detailed description of studies concerning MCL, CLL/SLL, and WM.

Mantle cell lymphoma

In the clinical trial NCT02343120, 62 individuals with a variety of non-Hodgkin lymphoma (NHL) types were assessed. ORR was 58.1% among all patients, 60.9% among 46 patients with aggressive NHLs — DLBCL or MCL, and 50% among 16 patients with indolent lymphomas (FL or MZL). CR ratios were 12.9%, 15.2%, and 6.3% respectively and PR ratios were 45.2%, 45.7%, and 43.8% respectively [87]. In the BGB-3111-AU-003 study among 37 previously treated patients with MCL, ORR was 86.5%, CR was 29.7% and PR was 56.8%. The median duration of response was 17.1 months [79]. In the single-arm, open, phase II trial NCT03206970, zanubrutinib was effective in patients with MCL who had been given at least one prior line of treatment, particularly CHOP/CHOP-R (cyclophosphamide, doxorubicin, oncovin, prednisone, and rituximab). Among 86 patients evaluated, ORR was 84%, CR was 59%, and PR was 24%. The median duration of treatment was 19.5 months, whereas the median PFS was 16.7 months [78]. Independent review committee (IRC) evaluated the response, based on the Lugano 2014 classification [88]. Compelling results of zanubrutinib clinical trials in patients previously treated for MCL led to FDA approval in November 2019. Zanubritinib is currently indicated for the treatment of adult patients with MCL who have received at least one prior therapy. The recommended dosage in this indication is 160 mg twice daily, or 320 mg once daily, until the progression of the disease or unacceptable toxicity.

Chronic lymphocytic leukemia/ /small lymphocytic lymphoma

In the non-randomized arm of the international, open, phase III clinical trial SEQUOIA, comparing zanubrutinib to bendamustine plus rituximab among 90 previously untreated patients with CLL/SLL and del(17p) present, ORR was 92.2% [80]. In another cohort trial, NCT02343120, ORR was 96.7% among all 120 patients with CLL/SLL and 93.8% in patients with del(17p) at median follow-up (MFU) of 26.4 months. ORR was comparable in both previously untreated patients and those with relapsed/refractory

Table I. List of clinical trials of zanubrutinib in B-cell malignancies

Disease	Trial	Phase	N (population tested)	ORR [%]	CR [%]	PR [%]	PR-L [%]	DOR [median in months]	PFS [median in months]	MFU [months]	VGPR [%]	VGPR or CR [%]	MR [%]	2y PFS [%]
MCL	NCT03206970 [78]	II	86	83.7	68,6			19.5	22.1	18.4				
	NCT02343120 [79]	I/II	37	86.5	29,7	56.8				17.1				
CLL/SLL	NCT03336333 (SEQUOIA) [80]	III	90	92.2	0	75.6	16.7			7				
	NCT03734016 (ALPINE) [81, 82]	III	66 — TN = 16	94	6									
			R/R = 50		2									
	NCT02343120 [83]	I/II	120	96.7 (all) 93.8 [del(17p)]						26.4				
WM	NCT02343120 [84]	I/II	73 — TN = 24	100	0	54.2				23.5	33.3	33.3	12.5	91.5
			R/R = 49	93.9	2	28.6				35.8	49	51	14.3	76.2
	BGB-3111-302 (ASPEN) [85]	III	102 — TN = 19	95	0	47		NE	NE	19.4	26	26	74	
			R/R = 83	94	0	49		NE	NE		29	29	78	
MZL	BGB-3111–214; NCT03846427 (MAGNOLIA) [86]	II	68	68.2	17	28		NE	NE	15.7				

ORR — overall response rate; CR — complete response; PR — partial response; PR-L — partial response with lymphocytosis; DOR — duration of response; PFS — progression-free survival; MFU — median follow-up; VGPR — very good partial response; MR — minimal response; MCL — mantle cell lymphoma; CLL/SLL — chronic lymphocytic leukemia/small lymphocytic lymphoma; TN — treatment-naive; R/R — relapsed/refractory; WM — Waldenström's macroglobulinemia; NE — not estimable; MZL — marginal zone lymphoma

disease (RR CLL/SLL) [83]. Long-term follow-up of zanubrutinib monotherapy in treatment-naïve CLL/SLL patients with del(17p) proved the durability of responses in this high-risk cohort, with an estimated 18-month PFS of 88.6% and an estimated 18-month OS of 95.1%. Zanubrutinib was generally well tolerated, with low rates of discontinuation due to AEs. These findings support the potential utility of zanubrutinib in the frontline management of patients with the high-risk [del(17p) positive] disease [89].

The ongoing ALPINE study has been comparing zanubrutinib to ibrutinib in relapsed/refractory CLL/SLL. This is the first head-to-head comparison of the efficacy and safety of these two compounds in a randomized trial [81, 82]. Thus far, zanubrutinib has been shown to be superior to ibrutinib with respect to PFS and OS. Zanubrutinib has also caused fewer AEs leading to discontinuation or death than ibrutinib. Also, the risk of atrial fibrillation or grade 3 infection was lower with zanubrutinib. The risk of cardiovascular AEs, such as hypertension, was very similar between the zanubrutinib (16.7%) and ibrutinib arms (16.4%). Overall, zanubrutinib in the ALPINE trial seems to have a favorable benefit-risk profile compared to ibrutinib in patients with R/R CLL/SLL [86, 90]. In a phase I trial (NCT02343120) zanubrutinib has demonstrated encouraging activity in CLL/SLL patients, with a low incidence of major toxicities. Among 78 efficacy-evaluable CLL/SLL patients, the overall response rate was 96.2% (95% confidence interval, 89.2–99.2). The estimated progression-free survival at 12 months was 100% [55]. Grade 3/4 AEs reported included neutropenia (6.4% of patients), anemia (2.1%), pneumonia (2.1%), and hypertension (2.1%). One patient had febrile neutropenia (grade 3), and one patient had disseminated herpes zoster infection (grade 3). Atrial fibrillation (grade 2) occurred in one patient with a history of hypertension and hyperlipidemia. Only one patient with CLL/SLL (receiving concomitant aspirin) experienced major hemorrhage (grade 3 subcutaneous hemorrhage). Concomitant antiplatelets (aspirin, clopidogrel, or nonsteroidal anti-inflammatory drugs) and anticoagulants (unfractionated or low-molecular-weight heparin, direct thrombin inhibitors, or warfarin) were used by 16.0% and 8.5% of patients, respectively. The exposure-adjusted incidence rate for grade 3 petechiae/purpura/contusions was 0.086 per 100 person-months. There were no deaths in the CLL/SLL cohort [55].

A 4-year follow-up of the phase I/II AU-003 study evaluated long-term tolerability and efficacy of zanubrutinib in CLL/SLL patients. In treatment-naïve patients, ORR was 100%, and in R/R CLL/SLL it was 95%. Complete response was observed in 18.7% of patients. At three years, 85.7% of patients had ongoing response. AEs leading to discontinuation of therapy were uncommon, and the incidence of AF, major hemorrhage or grade ≥3 infection decreased. This study showed that, with durable efficacy and acceptable tolerability, zanubrutinib can provide long-term clinical benefits for patients with CLL/SLL.

Waldenström's macroglobulinemia

Clinical trial NCT02343120 evaluated the safety, tolerability, pharmacokinetic profile, and effectiveness of zanubrutinib. Among 73 individuals with WM (24 previously untreated, and 49 with relapsing/refractory disease), long-term zanubrutinib treatment resulted in an overall response rate of 96% and a very good partial response (VGPR)/CR rate of 45%, which increased over time: 20.5% at six months, 32.9% at 12 months, and 43.8% at 24 months. The estimated 3-year progression-free survival rate was 80.5%, and the overall survival rate was 84.8% [84]. In the ASPEN study, a randomized phase III trial, zanubrutinib was head-to-head compared with ibrutinib in symptomatic WM [85]. Zanubrutinib was associated with fewer major hemorrhages than ibrutinib (0.3 vs. 0.6 events/100 person-months). Ibrutinib patients experienced a ~10-fold higher incidence of atrial fibrillation/flutter (1.0 vs. 0.1 events/100 person-months) and an approximately doubled frequency of hypertension on an exposure-adjusted basis (1.2 vs. 0.7 events/100 person-months). The frequency of diarrhea among zanubrutinib patients in the study was half that reported among ibrutinib patients (1.3 and 2.6 events per 100 person-months, respectively), probably explained by the less potent inhibition of epidermal growth factor receptor by zanubrutinib. Grade 3 neutropenia was more common among zanubrutinib patients (29% vs. 13%). Both agents inhibit BTK in neutrophil precursors by similar mechanisms, so higher rates of severe neutropenia among zanubrutinib patients may be a function of its greater bioavailability. However, the higher incidence of neutropenia did not result in a higher infection incidence compared to that of ibrutinib. Paradoxically, the incidence of some respiratory tract infections (mostly pneumonia) was higher among ibrutinib recipients. More ibrutinib than zanubrutinib patients required dose reductions for AEs (23% vs. 14%, respectively. Treatment with zanubrutinib was associated with fewer discontinuations than treatment with ibrutinib (4% vs. 9%, respectively), and fewer deaths were attributed to AEs (1% vs. 4%). A lower proportion of zanubrutinib-treated patients experienced an AE that led to dose reductions (13.9% vs. 23.5%) or doses being withheld (46.5% vs. 56.1%) [85]. Data from real-life studies of zanubrutinib in WM is still limited. However, results provided by Itchaki et al. [91] from their retrospective multi-center study seem to be consistent with clinical studies, with an 83% ORR and a 23% rate of grade ≥3 AEs.

Recent case studies indicate that zanubrutinib is effective in the treatment of Bing-Neel syndrome, an extremely rare complication of WM characterized by infiltration of the central nervous system by clonal lymphoplasmocytes, sometimes accompanied by hyperglobulinemia in the cerebrospinal fluid [92].

Marginal zone lymphoma

The phase II MAGNOLIA trial (BGB-3111–214; NCT03846427), conducted in 2020 in nine countries, evaluated the efficacy and safety profiles of zanubrutinib in patients with relapsed/refractory marginal zone lymphoma. The study included 68 R/R MZL patients who had previously received at least one line of therapy with a CD20-directed agent. After a median follow-up of 15.7 months, ORR was 68.2% and CR was 25.8%. The estimated DOR rate at 12 months after the first response was 93%. At a median follow-up, 40 (89%) of the 45 patients who responded were free from progression or death. The response to treatment varied between MZL subtypes (nodal, extranodal, splenic, unknown). Zanubrutinib in R/R MCL patients was generally well tolerated. Most AEs that occurred were in grades 1 or 2. The most common AEs were infections (45.6%), diarrhea (22.1%), contusion (20.6%), constipation (14.7%), and pyrexia (13.2%). A total of four patients developed COVID pneumonia during the investigations, being fatal in two cases. However, these cases were assessed to not have been related to zanubrutinib. Bleeding occurred in 36.6% of subjects, but no patient experienced a major hemorrhage [93].

In September 2021, due to its high efficacy and a favorable safety profile, zanubrutinib was approved by the FDA for adult patients with relapsed or refractory marginal zone lymphoma who had received at least one anti-CD20-based regimen [94].

Current position of BTK inhibitors and zanubrutinib in treatment of B-cell malignancies

The position of BTK inhibitors in the treatment of B-cell malignancies is not yet completely established. However, in CLL, BTK inhibitors have emerged as the most successful therapeutic approach inhibiting signals transmission from the B-cell receptor into the cell. The critical role of the B-cell receptor for CLL cells has been one of the major discoveries of the last two decades, improving outcomes in CLL patients, including those with unmutated immunoglobulin heavy-chain variable region gene and with p53 deletion/mutation. This explains the expansion of FDA approval of ibrutinib to the frontline treatment of all adult patients with CLL in April 2020 based on the results of the E1912 trial [95], and acalabrutinib in November 2019 based on the results of two phase III randomized trials — ELEVATE-TN and ASCEND [96, 97]. Also, early administration of zanubrutinib has led to higher overall response rates and greater durability of therapeutic benefit [98].

In our opinion, BTK inhibitors are also changing the treatment paradigm for MCL [70], which remains incurable, and patients will ultimately relapse with shortened remission durations with each successive therapy. As yet, BTK inhibitors are only approved for second-line MCL: ibrutinib in 2013, acalabrutinib in 2017 and zanubrutinib in 2019, but clinical trials in untreated MCL patients are ongoing with very promising results [99]. BTK inhibition has changed the treatment landscape of WM. Ibrutinib has resulted in deep and durable responses both as an upfront and as a salvage treatment, whereas zanubrutinib has resulted in similar antitumor activity, including deep and durable responses, but with a low discontinuation rate due to treatment-related toxicity [85].

Considering the similar efficacy of different BTK inhibitors, the choice between them mainly depends on their toxicities. Acalabrutinib and zanubrutinib, recently approved in China for patients with relapsed/refractory CLL, appear to have a more favorable toxicity profile compared to ibrutinib, especially cardiovascular, making them particularly interesting agents in the current treatment of patients with CLL. In our opinion, they have become the BTK inhibitors of choice for CLL and MCL treatment.

The second important issue is to establish whether BTK inhibitors should be used in monotherapy or alongside anti-CD20 monoclonal antibodies or bcl-2 inhibitors. The bcl-2 inhibitor venetoclax, given for a fixed period of time together with an anti-CD20 antibody, is a valid option for CLL patients. Among patients with untreated CLL and coexisting conditions, venetoclax + obinutuzumab has been associated with longer progression-free survival than chlorambucil + obinutuzumab [100]. Several clinical trials [101–103] are now reviewing ways to incorporate venetoclax into the treatment with BTK inhibitors, but it remains an unanswered question as to within which setting this strategy would work best. In MCL, BTK inhibitors should be combined with other agents to improve treatment outcomes. The combination of obinutuzumab, ibrutinib, and venetoclax provides high response rates, including at the molecular level, in relapsed and untreated MCL patients [99]. In WM, it is unclear whether BTK inhibitors should be combined with other agents [104].

The third unresolved issue is how to sequence BTK and bcl-2 inhibitors. In CLL, there is no randomized trial comparing BTK inhibitors given continuously to bcl-2 inhibitors given for a limited time, so it is very difficult to decide which is the better approach. Obviously, limited-time treatment has some advantages over continuous treatment. It should be stressed however, that the greatest benefit from venetoclax is for patients who achieve MRD negativity, whereas MRD in continuous treatment with BTK inhibitors, in our opinion, is not the treatment goal. We also think that patients with 17p deletion seem to-have better outcomes on BTK inhibitors than bcl-2 inhibitors. Most of the patients who come off the BTK inhibitor move to venetoclax. It is unclear whether a patient could be successfully transferred from venetoclax to a BTK inhibitor. There is no prospective data in that setting, but in our experience, and looking at data from retrospective studies, it seems that

most patients who are treated with venetoclax in any line of therapy, who then relapse either on or after venetoclax, can be successfully rescued with a BTK inhibitor. Patients with CLL who are resistant to BTK-inhibitors and venetoclax should be referred to novel treatments such as CAR-T cell therapy. Interestingly, BTK inhibitors can improve the efficacy of CAR-T cells [105]. In MCL, we believe that combined therapy of BTK inhibitors with bcl-2 inhibitors and anti-CD20 antibodies will soon become a standard first--line treatment. Relapsing patients should be referred for CAR-T cell therapy, which has recently been reported to induce durable remissions in most patients with relapsed or refractory MCL [16].

Conclusions

Bruton's tyrosine kinase inhibitors have already become an acknowledged element of the treatment for lymphoproliferative neoplasms. Ibrutinib, the best-in-class BTK inhibitor, has so far been the most evaluated and has been most widely used in numerous indications. Its efficacy and relatively good safety profile are well-proven. However, the incidence of serious AEs such as atrial fibrillation and hemorrhagic complications has led to the development of novel agents with reduced off-target effects.

Zanubrutinib, a second-generation BTK inhibitor, exhibits higher selectivity against BTK than ibrutinib, and appears to have a more favorable toxicity profile, especially regarding cardiovascular AEs, primarily atrial fibrillation. Clinical studies have already led to the approval of zanubrutinib in WM, MZL and CLL/SLL.

Nonetheless, further studies of zanubrutinib, both in monotherapy and in combination with other agents, are necessary to extend the scope of potential indications and evaluate its long-term safety profile. Longer follow-ups, more clinical experience, and comparative trials should help answer the question as to whether zanubrutinib could become the first-line treatment for a variety of lymphoproliferative neoplasms.

Authors' contributions

All authors were engaged in the preparation and writing of the manuscript, and all agreed on the final version.

Conflict of interest

The authors declare no conflict of interest.

Financial support

The authors did not receive support from any organization for the submitted work.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

References

1. Maloney DG, Grillo-López AJ, White CA, et al. IDEC-C2B8 (rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low--grade non-Hodgkin's lymphoma. Blood. 1997; 90(6): 2188–2195, doi: 10.1182/blood.v90.6.2188.2188_2188_2195.
2. Murawski N, Pfreundschuh M. New drugs for aggressive B-cell and T-cell lymphomas. Lancet Oncol. 2010; 11(11): 1074–1085, doi: 10.1016/s1470-2045(10)70210-2.
3. Czuczman MS, Fayad L, Delwail V, et al. Ofatumumab monotherapy in rituximab-refractory follicular lymphoma: results from a multicenter study. Blood. 2012; 119(16): 3698–3704, doi: 10.1182/blood-2011-09-378323.
4. Marcus R, Davies A, Ando K, et al. Obinutuzumab for the first-line treatment of follicular lymphoma. N Engl J Med. 2017; 377(14): 1331–1344, doi: 10.1056/NEJMoa1614598, indexed in Pubmed: 28976863.
5. Okroj M, Österborg A, Blom AM. Effector mechanisms of anti-CD20 monoclonal antibodies in B cell malignancies. Cancer Treat Rev. 2013; 39(6): 632–639, doi: 10.1016/j.ctrv.2012.10.008, indexed in Pubmed: 23219151.
6. Ansell SM, Minnema MC, Johnson P, et al. Nivolumab for relapsed/ /refractory diffuse large B-cell lymphoma in patients ineligible for or having failed autologous transplantation: a single-arm, phase II study. J Clin Oncol. 2019; 37(6): 481–489, doi: 10.1200/JCO.18.00766, indexed in Pubmed: 30620669.
7. Armand P, Shipp MA, Ribrag V, et al. Programmed death-1 blockade with pembrolizumab in patients with classical Hodgkin lymphoma after brentuximab vedotin failure. J Clin Oncol. 2016; 34(31): 3733–3739, doi: 10.1200/JCO.2016.67.3467, indexed in Pubmed: 27354476.
8. Morschhauser F, Tilly H, Chaidos A, et al. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. Lancet Oncol. 2020; 21(11): 1433–1442, doi: 10.1016/S1470-2045(20)30441-1, indexed in Pubmed: 33035457.
9. Lenz G, Hawkes E, Verhoef G, et al. Single-agent activity of phosphatidylinositol 3-kinase inhibition with copanlisib in patients with molecularly defined relapsed or refractory diffuse large B-cell lymphoma. Leukemia. 2020; 34(8): 2184–2197, doi: 10.1038/s41375-020-0743-y, indexed in Pubmed: 32060403.
10. Liu D, Mamorska-Dyga A. Syk inhibitors in clinical development for hematological malignancies. J Hematol Oncol. 2017; 10(1): 145, doi: 10.1186/s13045-017-0512-1, indexed in Pubmed: 28754125.
11. Hambley B, Caimi PF, William BM. Bortezomib for the treatment of mantle cell lymphoma: an update. Ther Adv Hematol. 2016; 7(4): 196–208, doi: 10.1177/2040620716648566, indexed in Pubmed: 27493710.
12. Kalakonda N, Maerevoet M, Cavallo F, et al. Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, phase 2 trial. Lancet Haematol. 2020; 7(7): e511–e522, doi: 10.1016/S2352-3026(20)30120-4, indexed in Pubmed: 32589977.

13. Chavez JC, Bachmeier C, Kharfan-Dabaja MA. CAR T-cell therapy for B-cell lymphomas: clinical trial results of available products. Ther Adv Hematol. 2019; 10: 2040620719841581, doi: 10.1177/2040620719841581, indexed in Pubmed: 31019670.
14. Schuster SJ, Bishop MR, Tam CS, et al. JULIET Investigators. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019; 380(1): 45–56, doi: 10.1056/NEJMoa1804980, indexed in Pubmed: 30501490.
15. Neelapu SS, Jacobson CA, Ghobadi A, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017; 377(26): 2531–2544, doi: 10.1056/NEJMoa1707447, indexed in Pubmed: 29226797.
16. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2020; 382(14): 1331–1342, doi: 10.1056/NEJMoa1914347, indexed in Pubmed: 32242358.
17. Maurer G, Tarkowski B, Baccarini M. Raf kinases in cancer-roles and therapeutic opportunities. Oncogene. 2011; 30(32): 3477–3488, doi: 10.1038/onc.2011.160, indexed in Pubmed: 21577205.
18. Torkamani A, Schork NJ. Prediction of cancer driver mutations in protein kinases. Cancer Res. 2008; 68(6): 1675–1682, doi: 10.1158/0008-5472.CAN-07-5283, indexed in Pubmed: 18339846.
19. Bhullar KS, Lagarón NO, McGowan EM, et al. Kinase-targeted cancer therapies: progress, challenges and future directions. Mol Cancer. 2018; 17(1): 48, doi: 10.1186/s12943-018-0804-2, indexed in Pubmed: 29455673.
20. Cuellar S, Vozniak M, Rhodes J, et al. BCR-ABL1 tyrosine kinase inhibitors for the treatment of chronic myeloid leukemia. J Oncol Pharm Pract. 2018; 24(6): 433–452, doi: 10.1177/1078155217710553, indexed in Pubmed: 28580869.
21. Wu J, Liu C, Tsui ST, et al. Second-generation inhibitors of Bruton tyrosine kinase. J Hematol Oncol. 2016; 9(1): 80, doi: 10.1186/s13045-016-0313-y, indexed in Pubmed: 27590878.
22. Efremov DG, Turkalj S, Laurenti L. Mechanisms of B cell receptor activation and responses to B cell receptor inhibitors in B cell malignancies. Cancers (Basel). 2020; 12(6), doi: 10.3390/cancers12061396, indexed in Pubmed: 32481736.
23. Maguire O, Tornatore KM, O'Loughlin KL, et al. Nuclear translocation of nuclear factor of activated T cells (NFAT) as a quantitative pharmacodynamic parameter for tacrolimus. Cytometry A. 2013; 83(12): 1096–1104, doi: 10.1002/cyto.a.22401, indexed in Pubmed: 24136923.
24. Erdmann T, Klener P, Lynch JT, et al. Sensitivity to PI3K and AKT inhibitors is mediated by divergent molecular mechanisms in subtypes of DLBCL. Blood. 2017; 130(3): 310–322, doi: 10.1182/blood-2016-12-758599, indexed in Pubmed: 28202458.
25. Suthers AN, Sarantopoulos S. TLR7/TLR9- and B cell receptor-signaling crosstalk: promotion of potentially dangerous B cells. Front Immunol. 2017; 8: 775, doi: 10.3389/fimmu.2017.00775, indexed in Pubmed: 28751890.
26. Lindvall J, Islam TC. Interaction of Btk and Akt in B cell signaling. Biochem Biophys Res Commun. 2002; 293(5): 1319–1326, doi: 10.1016/S0006-291X(02)00382-0, indexed in Pubmed: 12054657.
27. Berry CT, Liu X, Myles A, et al. BCR-induced Ca signals dynamically tune survival, metabolic reprogramming, and proliferation of naive B cells. Cell Rep. 2020; 31(2): 107474, doi: 10.1016/j.celrep.2020.03.038, indexed in Pubmed: 32294437.
28. Tobin G, Thunberg U, Karlsson K, et al. Subsets with restricted immunoglobulin gene rearrangement features indicate a role for antigen selection in the development of chronic lymphocytic leukemia. Blood. 2004; 104(9): 2879–2885, doi: 10.1182/blood-2004-01-0132, indexed in Pubmed: 15217826.
29. Agathangelidis A, Darzentas N, Hadzidimitriou A, et al. Stereotyped B-cell receptors in one-third of chronic lymphocytic leukemia: a molecular classification with implications for targeted therapies. Blood. 2012; 119(19): 4467–4475, doi: 10.1182/blood-2011-11-393694, indexed in Pubmed: 22415752.
30. Chu CC, Catera R, Hatzi K, et al. Chronic lymphocytic leukemia antibodies with a common stereotypic rearrangement recognize nonmuscle myosin heavy chain IIA. Blood. 2008; 112(13): 5122–5129, doi: 10.1182/blood-2008-06-162024, indexed in Pubmed: 18812466.
31. Hoogeboom R, van Kessel KPM, Hochstenbach F, et al. A mutated B cell chronic lymphocytic leukemia subset that recognizes and responds to fungi. J Exp Med. 2013; 210(1): 59–70, doi: 10.1084/jem.20121801, indexed in Pubmed: 23296468.
32. Lanemo Myhrinder A, Hellqvist E, Sidorova E, et al. A new perspective: molecular motifs on oxidized LDL, apoptotic cells, and bacteria are targets for chronic lymphocytic leukemia antibodies. Blood. 2008; 111(7): 3838–3848, doi: 10.1182/blood-2007-11-125450, indexed in Pubmed: 18223168.
33. Steininger C, Widhopf GF, Ghia EM, et al. Recombinant antibodies encoded by IGHV1-69 react with pUL32, a phosphoprotein of cytomegalovirus and B-cell superantigen. Blood. 2012; 119(10): 2293–2301, doi: 10.1182/blood-2011-08-374058, indexed in Pubmed: 22234695.
34. Gobessi S, Laurenti L, Longo PG, et al. Inhibition of constitutive and BCR-induced Syk activation downregulates Mcl-1 and induces apoptosis in chronic lymphocytic leukemia B cells. Leukemia. 2009; 23(4): 686–697, doi: 10.1038/leu.2008.346, indexed in Pubmed: 19092849.
35. Young RM, Wu T, Schmitz R, et al. Survival of human lymphoma cells requires B-cell receptor engagement by self-antigens. Proc Natl Acad Sci USA. 2015; 112(44): 13447–13454, doi: 10.1073/pnas.1514944112, indexed in Pubmed: 26483459.
36. Amin R, Mourcin F, Uhel F, et al. DC-SIGN-expressing macrophages trigger activation of mannosylated IgM B-cell receptor in follicular lymphoma. Blood. 2015; 126(16): 1911–1920, doi: 10.1182/blood-2015-04-640912, indexed in Pubmed: 26272216.
37. Pighi C, Gu TL, Dalai I, et al. Phospho-proteomic analysis of mantle cell lymphoma cells suggests a pro-survival role of B-cell receptor signaling. Cell Oncol (Dordr). 2011; 34(2): 141–153, doi: 10.1007/s13402-011-0019-7, indexed in Pubmed: 21394647.
38. Wen T, Wang J, Shi Y, et al. Inhibitors targeting Bruton's tyrosine kinase in cancers: drug development advances. Leukemia. 2020; 35(2): 312–332, doi: 10.1038/s41375-020-01072-6.
39. Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2013; 369(6): 507–516, doi: 10.1056/NEJMoa1306220, indexed in Pubmed: 23782157.
40. Rule S, Dreyling M, Goy A, et al. Outcomes in 370 patients with mantle cell lymphoma treated with ibrutinib: a pooled analysis from three open-label studies. Br J Haematol. 2017; 179(3): 430–438, doi: 10.1111/bjh.14870, indexed in Pubmed: 28832957.
41. Ruan J, Yamshon S, van Besien K, et al. An update on options of therapy for aggressive mantle cell lymphoma. Leuk Lymphoma. 2020; 61(9): 2036–2049, doi: 10.1080/10428194.2020.1755860, indexed in Pubmed: 32336184.

42. Wang ML, Lee H, Chuang H, et al. Ibrutinib in combination with rituximab in relapsed or refractory mantle cell lymphoma: a single-centre, open-label, phase 2 trial. Lancet Oncol. 2016; 17(1): 48–56, doi: 10.1016/S1470-2045(15)00438-6, indexed in Pubmed: 26640039.
43. Maddocks K, Christian B, Jaglowski S, et al. A phase 1/1b study of rituximab, bendamustine, and ibrutinib in patients with untreated and relapsed/refractory non-Hodgkin lymphoma. Blood. 2015; 125(2): 242–248, doi: 10.1182/blood-2014-08-597914, indexed in Pubmed: 25355819.
44. Jain P, Lee H, Steiner R, et al. Frontline treatment with ibrutinib with rituximab (IR) combination is highly effective in elderly (≥65 years) patients with mantle cell lymphoma (MCL) — results from a phase II trial. Blood. 2019; 134(Suppl_1): 3988–3988, doi: 10.1182/blood-2019-125800.
45. Le Gouill S, Morschhauser F, Bouabdallah K, et al. Ibrutinib, venetoclax plus obinutuzumab in newly diagnosed mantle cell lymphoma patients. Blood. 2019; 134(Suppl_1): 1530–1530, doi: 10.1182/blood-2019-125681.
46. Wang ML, Jain P, Lee HJu, et al. Frontline treatment with ibrutinib plus rituximab (IR) followed by short course R-HyperCVAD/MTX is extremely potent and safe in patients (age ≤ 65 years) with mantle cell lymphoma (MCL) — results of phase-II WINDOW-1 clinical trial. Blood. 2019; 134(Supplement_1): 3987–3987, doi: 10.1182/blood-2019-126044.
47. Byrd JC, Brown JR, O'Brien S, et al. RESONATE Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014; 371(3): 213–223, doi: 10.1056/NEJMoa1400376, indexed in Pubmed: 24881631.
48. Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenström's macroglobulinemia. N Engl J Med. 2015; 372(15): 1430–1440, doi: 10.1056/NEJMoa1501548, indexed in Pubmed: 25853747.
49. Noy A, de Vos S, Thieblemont C, et al. Targeting Bruton tyrosine kinase with ibrutinib in relapsed/refractory marginal zone lymphoma. Blood. 2017; 129(16): 2224–2232, doi: 10.1182/blood-2016-10-747345, indexed in Pubmed: 28167659.
50. Goy A, Ramchandren R, Ghosh N, et al. Ibrutinib plus lenalidomide and rituximab has promising activity in relapsed/refractory non-germinal center B-cell-like DLBCL. Blood. 2019; 134(13): 1024–1036, doi: 10.1182/blood.2018891598, indexed in Pubmed: 31331917.
51. 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(5): 874–879, doi: 10.3324/haematol.2017.182907, indexed in Pubmed: 29419429.
52. Shanafelt TD, Parikh SA, Noseworthy PA, et al. Atrial fibrillation in patients with chronic lymphocytic leukemia (CLL). Leuk Lymphoma. 2017; 58(7): 1630–1639, doi: 10.1080/10428194.2016.1257795 , indexed in Pubmed: 27885886.
53. O'Brien S, Jones JA, Coutre SE, et al. Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study. Lancet Oncol. 2016; 17(10): 1409–1418, doi: 10.1016/S1470-2045(16)30212-1, indexed in Pubmed: 27637985.
54. Shatzel JJ, Olson SR, Tao DL, et al. Ibrutinib-associated bleeding: pathogenesis, management and risk reduction strategies. J Thromb Haemost. 2017; 15(5): 835–847, doi: 10.1111/jth.13651, indexed in Pubmed: 28182323.
55. 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(11): 851–859, doi: 10.1182/blood.2019001160, indexed in Pubmed: 31340982.
56. Paydas S. Management of adverse effects/toxicity of ibrutinib. Crit Rev Oncol Hematol. 2019; 136: 56–63, doi: 10.1016/j.critrevonc.2019.02.001, indexed in Pubmed: 30878129.
57. Kaptein A, Bruin Gde, Hoek MEv, et al. Potency and selectivity of BTK inhibitors in clinical development for B-cell malignancies. Blood. 2018; 132(Suppl 1): 1871–1871, doi: 10.1182/blood-2018-99-109973.
58. Lynch TJ, Kim EdS, Eaby B, et al. Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: an evolving paradigm in clinical management. Oncologist. 2007; 12(5): 610–621, doi: 10.1634/theoncologist.12-5-610, indexed in Pubmed: 17522250.
59. 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 USA. 2010; 107(29): 13075–13080, doi: 10.1073/pnas.1004594107, indexed in Pubmed: 20615965.
60. Markham A, Dhillon S. Acalabrutinib: first global approval. Drugs. 2018; 78(1): 139–145, doi: 10.1007/s40265-017-0852-8, indexed in Pubmed: 29209955.
61. Estupiñán HY, Berglöf A, Zain R, et al. Comparative analysis of BTK inhibitors and mechanisms underlying adverse effects. Front Cell Dev Biol. 2021; 9: 630942, doi: 10.3389/fcell.2021.630942, indexed in Pubmed: 33777941.
62. Shadman M, Flinn I, Kingsley E, et al. Zanubrutinib in acalabrutinib-intolerant patients (pts) with B-cell malignancies. Blood. 2022; 140(Suppl 1): 3655–3657, doi: 10.1182/blood-2022-159726.
63. Liclican A, Serafini L, Xing W, et al. Biochemical characterization of tirabrutinib and other irreversible inhibitors of Bruton's tyrosine kinase reveals differences in on — and off — target inhibition. Biochim Biophys Acta Gen Subj. 2020; 1864(4): 129531, doi: 10.1016/j.bbagen.2020.129531, indexed in Pubmed: 31953125.
64. Zhang B, Zhao R, Liang R, et al. Abstract CT132: Orelabrutinib, a potent and selective Bruton's tyrosine kinase inhibitor with superior safety profile and excellent PK/PD properties. Cancer Res. 2020; 80(16_Suppl): CT132–CT132, doi: 10.1158/1538-7445.am2020-ct132.
65. Tasso B, Spallarossa A, Russo E, et al. The development of BTK inhibitors: a five-year update. Molecules. 2021; 26(23), doi: 10.3390/molecules26237411, indexed in Pubmed: 34885993.
66. Burger JA, Landau DA, Taylor-Weiner A, et al. Clonal evolution in patients with chronic lymphocytic leukaemia developing resistance to BTK inhibition. Nat Commun. 2016; 7: 11589, doi: 10.1038/ncomms11589, indexed in Pubmed: 27199251.
67. Fabian CA, Reiff SD, Guinn D, et al. Abstract 1207: SNS-062 demonstrates efficacy in chronic lymphocytic leukemia in vitro and inhibits C481S mutated Bruton tyrosine kinase. Cancer Res. 2017; 77(13_Suppl): 1207–1207, doi: 10.1158/1538-7445.am2017-1207.
68. Naeem AS, Nguy WI, Tyekucheva S, et al. LOXO-305: targeting C481S Bruton tyrosine kinase in patients with ibrutinib-resistant CLL. Blood. 2019; 134(Suppl_1): 478–478, doi: 10.1182/blood-2019-124362.
69. Reiff SD, Mantel R, Smith LL, et al. The BTK inhibitor ARQ 531 targets ibrutinib-resistant CLL and Richter transformation. Cancer Discov. 2018; 8(10): 1300–1315, doi: 10.1158/2159-8290.CD-17-1409, indexed in Pubmed: 30093506.

70. Bond DA, Woyach JA. Targeting BTK in CLL: beyond ibrutinib. Curr Hematol Malig Rep. 2019; 14(3): 197–205, doi: 10.1007/s11899-019-00512-0, indexed in Pubmed: 31028669.
71. Alu A, Lei H, Han X, et al. BTK inhibitors in the treatment of hematological malignancies and inflammatory diseases: mechanisms and clinical studies. J Hematol Oncol. 2022; 15(1): 138, doi: 10.1186/s13045-022-01353-w, indexed in Pubmed: 36183125.
72. Gu D, Tang H, Wu J, et al. Targeting Bruton tyrosine kinase using non-covalent inhibitors in B cell malignancies. J Hematol Oncol. 2021; 14(1): 40, doi: 10.1186/s13045-021-01049-7, indexed in Pubmed: 33676527.
73. Guo Y, Liu Ye, 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(17): 7923–7940, doi: 10.1021/acs.jmedchem.9b00687, indexed in Pubmed: 31381333.
74. Dobie G, Kuriri FA, Omar MMA, et al. Ibrutinib, but not zanubrutinib, induces platelet receptor shedding of GPIb-IX-V complex and integrin αIIbβ3 in mice and humans. Blood Adv. 2019; 3(24): 4298–4311, doi: 10.1182/bloodadvances.2019000640, indexed in Pubmed: 31869418.
75. Lipsky AH, Farooqui MZH, Tian X, et al. Incidence and risk factors of bleeding-related adverse events in patients with chronic lymphocytic leukemia treated with ibrutinib. Haematologica. 2015; 100(12): 1571–1578, doi: 10.3324/haematol.2015.126672, indexed in Pubmed: 26430171.
76. Tam CS, Quach H, Nicol A, et al. Zanubrutinib (BGB-3111) plus obinutuzumab in patients with chronic lymphocytic leukemia and follicular lymphoma. Blood Adv. 2020; 4(19): 4802–4811, doi: 10.1182/bloodadvances.2020002183, indexed in Pubmed: 33022066.
77. 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(2): 391–399, doi: 10.1007/s00280-019-04015-w, indexed in Pubmed: 31875923.
78. 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(16): 4216–4224, doi: 10.1158/1078-0432.CCR-19-3703, indexed in Pubmed: 32461234.
79. Tam CS, Wang M, Simpson D, et al. Updated safety and efficacy data in the phase 1 trial of the patients with mantle cell lymphoma (MCL) treated with the Bruton Tyrosine Kinase (BTK) inhibitor zanubrutinib (BGB-3111). Hematological Oncology. 2019; 37(Suppl 2): 245–247, doi: 10.1002/hon.55_2630.
80. Tam CS, Robak T, Ghia P, et al. Efficacy and safety of zanubrutinib in patients with treatment-naive chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) with del(17p): initial results from arm C of the SEQUOIA (BGB-3111-304) trial. Blood. 2019; 134(Suppl_1): 499–499, doi: 10.1182/blood-2019-125394.
81. Hillmen P, Brown J, Byrd J, et al. ALPINE: phase III zanubrutinib (BGB-3111) versus ibrutinib in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). J Clin Oncol. 2019; 37(15_Suppl): TPS7572–TPS7572, doi: 10.1200/jco.2019.37.15_suppl.tps7572.
82. Hillmen P, Brown J, Byrd J, et al. ALPINE: phase 3 trial of zanubrutinib (BGB-3111) vs ibrutinib in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Blood. 2019; 134(Suppl_1): 4307–4307, doi: 10.1182/blood-2019-124213.
83. Cull G, Simpson D, Opat S, et al. Treatment with the Bruton tyrosine kinase inhibitor zanubrutinib (BGB-3111) demonstrates high overall response rate and durable responses in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): updated results from a phase 1/2 trial. Blood. 2019; 134(Suppl_1): 500–500, doi: 10.1182/blood-2019-125483.
84. Trotman J, Opat S, Gottlieb D, et al. Zanubrutinib for the treatment of patients with Waldenström macroglobulinemia: 3 years of follow-up. Blood. 2020; 136(18): 2027–2037, doi: 10.1182/blood.2020006449, indexed in Pubmed: 32698195.
85. Tam CS, Opat S, D'Sa S, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. Blood. 2020; 136(18): 2038–2050, doi: 10.1182/blood.2020006844, indexed in Pubmed: 32731259.
86. Hillmen P, Eichhorst B, Brown JR, et al. Zanubrutinib versus ibrutinib in relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma: interim analysis of a randomized phase III trial. J Clin Oncol. 2023; 41(5): 1035–1045, doi: 10.1200/JCO.22.00510, indexed in Pubmed: 36395435.
87. Tam CS, Simpson D, Opat S, et al. Safety and activity of the highly specific BTK inhibitor BGB-3111 in patients with indolent and aggressive non Hodgkin's lymphoma. Blood. 2017; 130: 152, doi: 10.1182/blood.V130.Suppl_1.152.152.
88. Cheson BD, Fisher RI, Barrington SF, et al. Alliance, Australasian Leukaemia and Lymphoma Group, Eastern Cooperative Oncology Group, European Mantle Cell Lymphoma Consortium, Italian Lymphoma Foundation, European Organisation for Research, Treatment of Cancer/Dutch Hemato-Oncology Group, Grupo Español de Médula Ósea, German High-Grade Lymphoma Study Group, German Hodgkin's Study Group, Japanese Lymphorra Study Group, Lymphoma Study Association, NCIC Clinical Trials Group, Nordic Lymphoma Study Group, Southwest Oncology Group, United Kingdom National Cancer Research Institute. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014; 32(27): 3059–3068, doi: 10.1200/JCO.2013.54.8800, indexed in Pubmed: 25113753.
89. Brown JR, Robak T, Ghia P, et al. Efficacy and safety of zanubrutinib in patients with treatment-naïve (TN) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) with del(17p): follow-up results from arm C of the SEQUOIA (BGB-3111-304) Trial. Blood. 2020; 136(Suppl 1): 11–12, doi: 10.1182/blood-2020-134280.
90. Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med. 2023; 388(4): 319–332, doi: 10.1056/nejmoa2211582.
91. Itchaki G, Benjamini O, Levi M, et al. "Real-life" data of zanubrutinib in patients with Waldenström macroglobulinemia — a multi-center retrospective study. Blood. 2022; 140(Suppl 1): 11981–11982, doi: 10.1182/blood-2022-163009.
92. Wong J, Cher L, Griffiths J, et al. Efficacy of canubrutinib in the treatment of Bing-Neel syndrome. Hemasphere. 2018; 2(6): e155, doi: 10.1097/HS9.0000000000000155, indexed in Pubmed: 31723793.
93. Opat S, Tedeschi A, Linton K, et al. The MAGNOLIA trial: zanubrutinib, a next-generation Bruton tyrosine kinase inhibitor, demonstrates safety and efficacy in relapsed/refractory marginal zone lymphoma. Clin Cancer Res. 2021; 27(23): 6323–6332, doi: 10.1158/1078-0432.CCR-21-1704, indexed in Pubmed: 34526366.
94. Opat S, Tedeschi A, Hu B, et al. Long-term efficacy and safety of zanubrutinib in patients with relapsed/refractory (R/R) marginal

zone lymphoma (MZL): final analysis of the MAGNOLIA (BGB-3111-214) trial. Blood. 2022; 140(Suppl 1): 573–576, doi: 10.1182/blood-2022-163371.
95. Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. N Engl J Med. 2019; 381(5): 432–443, doi: 10.1056/NEJMoa1817073, indexed in Pubmed: 31365801.
96. Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. Lancet. 2020; 395(10232): 1278–1291, doi: 10.1016/S0140-6736(20)30262-2, indexed in Pubmed: 32305093.
97. Ghia P, Pluta A, Wach M, et al. ASCEND: phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia. J Clin Oncol. 2020; 38(25): 2849–2861, doi: 10.1200/JCO.19.03355, indexed in Pubmed: 32459600.
98. Xu W, Yang S, Tam C, et al. Earlier use of zanubrutinib monotherapy in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma is associated with greater efficacy: a pooled analysis from 3 studies. Blood. 2020; 136(Suppl 1): 36–37, doi: 10.1182/blood-2020-136236.
99. Le Gouill S, Morschhauser F, Chiron D, et al. Ibrutinib, obinutuzumab, and venetoclax in relapsed and untreated patients with mantle cell lymphoma: a phase 1/2 trial. Blood. 2021; 137(7): 877–887, doi: 10.1182/blood.2020008727, indexed in Pubmed: 33181832.
100. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. N Engl J Med. 2019; 380(23): 2225–2236, doi: 10.1056/NEJMoa1815281, indexed in Pubmed: 31166681.
101. Woyach JA, Blachly JS, Rogers KA, et al. Acalabrutinib in combination with venetoclax and obinutuzumab or rituximab in patients with treatment-naïve or relapsed/refractory chroniclymphocytic leukemia. Blood. 2020; 136(Suppl 1): 16–18, doi: 10.1182/blood-2020-136317.
102. Davids MS, Lampson BL, Tyekucheva S, et al. Updated safety and efficacy results from a phase 2 study of acalabrutinib, venetoclax and obinutuzumab (AVO) for frontline treatment of chronic lymphocytic leukemia (CLL). Blood. 2020; 136(Suppl 1): 20–21, doi: 10.1182/blood-2020-139864.
103. Tam CS, Flinn IW, Tedeschi A, et al. Zanubrutinib in combination with venetoclax for patients with treatment-naïve chronic lymphocytic leukemia or small lymphocytic lymphoma and del(17p): arm D of the SEQUOIA (BGB-3111-304) trial. Blood. 2020; 136(Supplement 1): 24–25, doi: 10.1182/blood-2020-134179.
104. Ntanasis-Stathopoulos I, Gavriatopoulou M, Fotiou D, et al. Current and novel BTK inhibitors in Waldenström's macroglobulinemia. Ther Adv Hematol. 2021; 12: 2040620721989586, doi: 10.1177/2040620721989586, indexed in Pubmed: 33613931.
105. Wierda WG, Dorritie KA, Munoz J, et al. Transcend CLL 004: phase 1 cohort of lisocabtagene maraleucel (liso-cel) in combination with ibrutinib for patients with relapsed/refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Blood. 2020; 136(Suppl 1): 39–40, doi: 10.1182/blood-2020-140622.