PROPOSAL FOR THE ADDITION OF ZANUBRUTINIB (BRUKINSA®) TO THE WHO MODEL LIST OF ESSENTIAL MEDICINES FOR THE TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA/ SMALL LYMPHOTCYTIC LYMPHOMA

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Abbreviations

AE	Adverse events
BR	Bendamustine–Rituximab
BTKi	Bruton Tyrosine Kinase inhibitor
CI	Confidence Interval
CLL	Chronic Lymphocytic Leukemia
CR	Complete response
CRi	Complete response with incomplete hematologic recovery
DALY	Disability-adjusted life year
DCO	Data cut-off date
HR	Hazard Ratio
OR	Odds ratio
ORR	Overall response rate
OS	Overall Survival
PFS	Progression-free survival
R/R	Relapsed/Refractory
RoB	Risk of Bias
SLL	Small Lymphocytic Lymphoma
T/N	Treatment Naïve

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Section 1: Summary statement of the proposal

This submission advocates for the inclusion of zanubrutinib as an individual medicine in the complementary list of the WHO Model List of Essential Medicines (EML) under the category of targeted therapies of antineoplastics and supportive medicines in the section of Immunomodulators and Antineoplastics. The submission proposes the use of zanubrutinib monotherapy in the treatment adult patients with Chronic Lymphocytic Leukemia (CLL) /Small Lymphocytic Lymphoma (SLL) as follows:

- Zanubrutinib as monotherapy for the treatment of adult patients with CLL/SLL who are treatment naive
- Zanubrutinib as monotherapy for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who are relapsed or refractory to previous treatment

Chronic lymphocytic leukemia (CLL) is a life-threatening blood cancer that affects the white blood cells called B-lymphocytes.[1] CLL is a B-cell malignancy characterized by an accumulation of malignant B cells in the peripheral blood, bone marrow, and secondary lymphoid organs.[2] The terms CLL and SLL are typically used concurrently as they are considered to be different manifestations of the same disease and are managed in the same way.[3] In SLL, the cancerous cells are primarily in the lymph tissue while in CLL the cancerous B-lymphocytes are predominantly circulating in the blood stream.

Globally, CLL-related incidence cases increased significantly (more than doubled) from just over 40,000 in 1990 to over 100,000 in 2019, with age-standardized incidence rate (ASIR) rising from 0.76/100,000 persons in 1990 to 1.34/100,000 persons in 2019.[4] In Western countries, CLL is the most common leukemia in adults with an incidence of 4.92/100,000 people per year.[5] The median age at diagnosis is from 70 to 72 years old, and although it can occur in younger patients,[6,7] the incidence increases to more than 30 per 100,000 people per year at an age of 80 years old and above.[8] The highest increases in age-standardized incidence rate were observed in Western Europe, North America, and Central Europe in 2019.[4]

While China and India have among the highest number of cases because of the large populations in these countries, the incidence rates of CLL in Asian countries, countries of the

Middle East (excluding Israel), Latin America and Africa are low in comparison to North America and Europe. Where the age standardized incidence rate is 4.35 /100,000 in North America and 3.35/100,000 in Europe in 2019, for East Asia, the ASIR is 0.17/100,000; 0.20/100,000 in North Africa and Middle East; Western Sub-Saharan Africa 0.22/100,000; Central Latin America 0.14 per 100,000.[4]

CLL symptoms can include fatigue, nausea/vomiting, pain, dyspnea, sleep disturbance, appetite loss and constipation, although some CLL cases are diagnosed without symptoms.[9,10] CLL often infiltrates the bone marrow and thus disrupts the normal function of hematopoiesis. Patients are often anemic, have thrombocytopenia and neutropenia. Because of the neutropenia associated with both the disease and the therapies used to treat CLL, patients are at increased risk of infections. Patients are also at risk for other secondary cancers which may be due to the disruption of the immune system.[11,12] CLL is a treatable but essentially incurable disease, and the decision to initiate treatment for CLL/SLL is based upon the presence of progressive or active/symptomatic disease such as progressive marrow failure, massive or progressive splenomegaly and/or lymphadenopathy, worsening lymphocytosis with an increase of > 50% over a 2-month period, lymphocyte doubling time of < 6 months, autoimmune complications that respond poorly to corticosteroids or other standard therapies, and/or constitutional symptoms.[13]

Patients often experience mental distress causing depression and anxiety, which has a negative impact on social functioning.[14] CLL is considered an 'indolent' (slow-progressing) disease and so patients may suffer from the symptoms of disease and the side effect of treatment for a long time. A longitudinal study of quality of life (QoL) reported significantly lower QoL scores for people with CLL/SLL compared to people without in almost every domain, particularly regarding physical and cognitive function and being able to undertake daily responsibilities.[10]

All patients diagnosed with CLL/SLL will relapse eventually and median overall survival after diagnosis is about 10 years (though as noted there is wide variation in this estimate). About 20% of patients have a very aggressive presentation with a median OS of only 1.5 to 3 years. Globally, deaths from CLL more than doubled from just over 20,000 in 1990 to almost 45,000 in 2019. This corresponded with a rapid increase in global disability-adjusted life years (DALYs) of CLL from almost 500,000 in 1990 to almost 950,000 in 2019.[15]

As CLL/SLL is diagnosed mainly in older adults, comorbidities are frequently present and therefore the safety profile of the selected treatment is of paramount importance.[16] In a study, almost 90% of CLL/SLL patients had one or more comorbidities, with almost half having at least one major comorbidity (e.g. cardiovascular/cardiopulmonary condition). This, combined with the potential indolent nature of the condition means that it is critical to provide the patient with the most clinically effective therapies that have been carefully weighed against the safety profile of the treatment.[9,17]

Bruton's tyrosine kinase (BTK) inhibitors have changed the therapeutic landscape for patients with CLL/SLL in the last decade.[18,19] A first-generation Bruton tyrosine kinase inhibitor (BTKi), ibrutinib, became the standard treatment option for previously untreated and relapsed/refractory (R/R) CLL/SLL.[20] Ibrutinib was the first BTK inhibitor added into the WHO Essential Medicines List (EML) in 2021 for the treatment of R/R CLL/SLL.

However, since this time, zanubrutinib, (trade name BRUKINSA®), has been developed. Zanubrutinib is a next generation irreversible BTK inhibitor and has been specifically formulated with improved selectivity to BTK to reduce the off-target adverse effects associated with earlier BTK inhibitors. Zanubrutinib has regulatory approval in more than 70 markets globally. Multiple clinical guidelines around the world now recommend the use of zanubrutinib instead of ibrutinib for patients with CLL/SLL who are treatment naïve and R/R (refer to Section 9 for detailed description of Clinical Guideline Recommendations). In countries without access to a BTK inhibitor as a first-line treatment, bendamustine-rituximab (BR) chemotherapy is typically the first-line treatment of choice. However, zanubrutinib demonstrated superiority to BR in PFS in a phase 3 trial in treatment naïve CLL/SLL patients.[21,22]

In patients with treatment naïve (T/N) CLL/SLL, an open-label, multicentre, phase 3 study at 153 academic or community hospitals in 14 countries and regions, with enrolment of 590 patients, showed that zanubrutinib monotherapy significantly prolonged progression free survival (PFS) compared with BR.[21,22] Also, zanubrutinib has demonstrated better safety profile compared to BR, chemotherapy.

In R/R CLL/SLL, a multinational, phase 3, randomized trial, a head-to-head comparison of zanubrutinib with ibrutinib as treatment for R/R CLL/SLL was performed.[23,24] Zanubrutinib monotherapy was shown to significantly improve treatment responses and PFS compared with ibrutinib, regardless of del(17p)/TP53 mutational status, age, sex, disease stage, number of prior therapies, or presence of bulky disease. Zanubrutinib monotherapy was also shown to

have a significantly lower risk of atrial fibrillation or flutter, advantages in overall cardiac safety profile, and fewer treatment discontinuations, compared with ibrutinib.

In the 24th WHO Expert Committee review (2023), it was noted that a lack of survival advantage and safety signals required further data, along with longer follow-up on progression-free survival (PFS), toxicity, and cost-effectiveness. Since then, the evidence base has matured.

Appendix 1 compiles all new evidence generated since the previous submission of zanubrutinib for the 2023 WHO Model List of Essential Medicines. Adding zanubrutinib to the WHO Model List at this stage can help facilitate access to this crucial therapy for patients with CLL/SLL. As the prevalence rates of CLL/SLL grow worldwide due to ageing populations, zanubrutinib can provide a cost-effective treatment option in low- and middle-income countries with demonstrated improvement in efficacy as measured by PFS and ORR. Further, it also has a well-tolerated safety profile; something that is critically important for patients who may have existing comorbidities who require a long-term treatment option for this indolent, but incurable condition.

Section 2: Consultation with WHO technical departments

WHO EML Secretariat (Lorenzo Moja and Bernadette Capello on Thursday 22nd August, follow up on 11th October)

Section 3: Other organization(s) consulted and/or supporting the submission

A letter of support from the Union for International Cancer Control (UICC) is included with this submission. Key points from the letter of support include:

1. *Clinical Importance:* Zanubrutinib is recognized as one of the best-in-class Bruton's tyrosine kinase (BTK) inhibitors.

2. *Alignment with WHO and SDG Goals:* The letter of support aligns with WHO priorities and Sustainable Development Goal 3.4, emphasising the public health value.

3. *Commitment to Access:* ATOM commits to collaborating with BeiGene to establish affordable access pathways.

Additional stakeholders supporting this submission will provide comments as part of the public consultation process in 2025.

Section 4: Key information summary for the proposed medicine(s)

INN	Zanubrutinib		
ATC code	L01EL03		
Indication	First-line: Treatment of adult patients with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) who are **Treatment naïve** (previously untreated) Relapsed/refractory: Treatment of adult patients with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) who are **Relapsed or refractory to previous treatment**		
ICD-11 code	2A82.0 Chronic lymphocytic leukemia or small lymphocytic lymphoma		
Dosage form	**Strength**	**EML**	**EMLc**
Capsule	80 mg	Yes	No

Section 5: Listing as an individual medicine or representative of a pharmacological class / therapeutic group

Zanubrutinib is being proposed for listing as an individual medicine for treatment of adult patients with CLL/SLL who are either treatment naïve and those who are relapsed or refractory to prior treatment.

Ibrutinib, the 1st generation and the only Bruton tyrosine kinase (BTK) inhibitor is currently listed on the WHO EML for adult patients with CLL/SLL that are relapsed or refractory to prior treatment.

However, zanubrutinib is a next-generation BTK inhibitor that has been designed to be a more selective and potent BTK inhibitor that irreversibly binds to and sustainably suppresses BTK activity. In a randomized phase 3 clinical trial, Zanubrutinib was shown to have better

progression-free survival, overall response rate and complete response rate than ibrutinib in R/R CLL/SLL patients.[23,24] Zanubrutinib shows consistently high efficacy in patient subgroups, including difficult-to-treat populations. Zanubrutinib has a differentiated safety and tolerability profile with lower discontinuation rates than ibrutinib in CLL.[24,25] Based on an independent, comprehensive meta-analysis, zanubrutinib had the lowest rate of atrial fibrillation compared with ibrutinib and acalabrutinib.[25] This meta-analysis also demonstrates that zanubrutinib was associated with the lowest rate of infections and other adverse events that limit activities of daily living compared with acalabrutinib and ibrutinib.[25] However, the limitations of network meta-analyses need to be acknowledged, as the included studies had a degree of heterogeneity, including different durations of follow-up. Furthermore, some of the included studies (MABLE, ALLIANCE) were considered to have a high risk of bias and the safety endpoints were originally designated as secondary endpoints in individual clinical trials.[25]

Hence, with more updated evidence in this application, zanubrutinib is proposed to be listed as an individual medicine due to its unique advantages of superior efficacy and safety profile compared to ibrutinib.

Section 6: Information supporting the public health relevance

Globally, during the last 30 years, CLL-related incidence cases increased significantly from 40,537 in 1990 to 103,467 in 2019, with ASIR rising from 0.76/100,000 persons in 1990 to 1.34/100,000 persons in 2019.[4] In the geographical region levels, Western Europe, North America, and Central Europe displayed the highest ASIR in 2019 Global deaths cases of CLL had prompt growth from 21,548 in 1990 to 44,613 in 2019, with age-standardized death rate (ASDR) rising from 0.40/100,000 persons in 1990 to 0.58/100,000 persons in 2019. Global DALY cases of CLL increased rapidly from 492,075 in 1990 to 948,464 in 2019, with age-standardized DALY rate rising from 9.20/100,000 persons in 1990 to 12.26/100,000 persons in 2019. (Figure **1** and Figure 2)

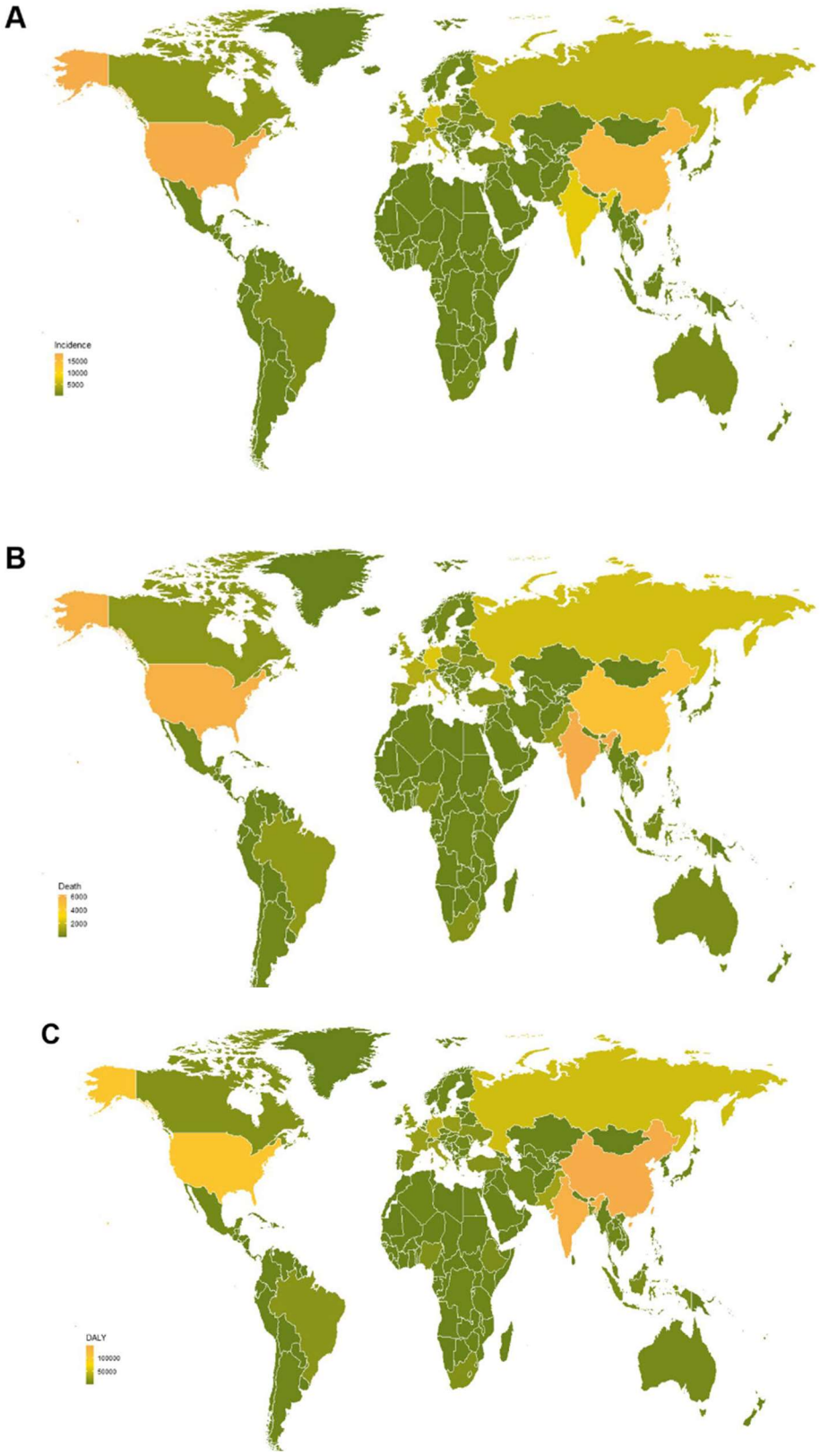


Figure 1. The incidence cases (A), deaths (B), and DALY (C) of CLL in 204 countries or territories in 2019[4]

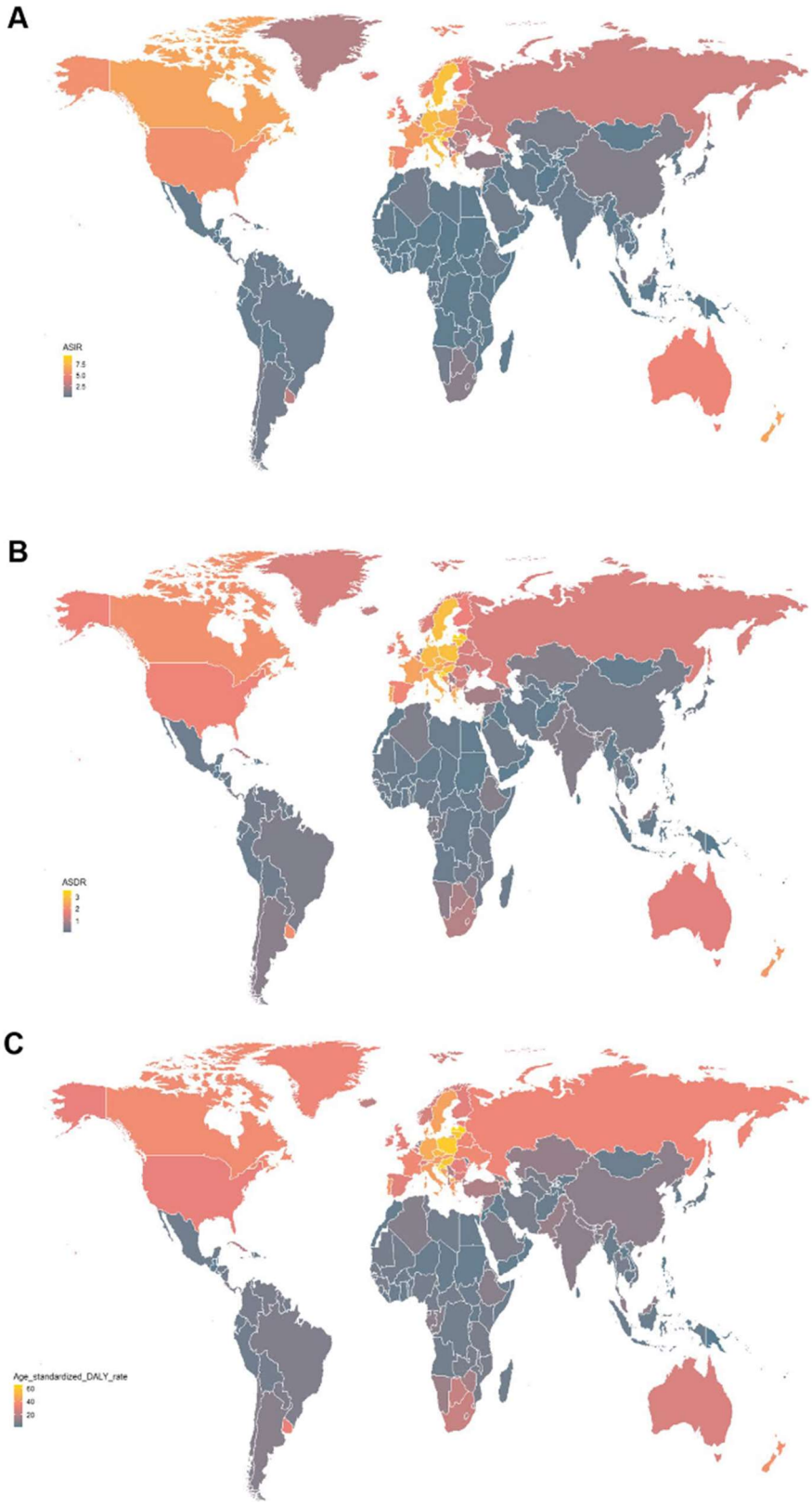


Figure 2. The age-standardized incidence rate (A), the age-standardized death rate (B), and age-standardized DALY rate (C) of CLL in 204 countries or territories in 2019.[4]

CLL/SLL is diagnosed mainly in older adults in whom comorbidities are frequently present and therefore the safety profile of the selected treatment is of paramount importance.[16] At diagnosis, 89% of these patients had one or more comorbidities, and 46% had at least one major comorbidity (cardiopulmonary or vascular diseases, diabetes, secondary tumors, etc.). The number of comorbidities increase continuously with advanced age, which may lead to increased morbidity and mortality.

A longitudinal study investigating the long-term quality of life (QoL) of patients with CLL showed that no differences regarding quality of life (QoL) can be observed between CLL patients who had already received chemotherapy and those who had not.[10] The patients reported lower QoL scores in almost every domain (64.5 vs 70.0, European Organization for Research and Treatment of Cancer (EORTC) QoL Questionnaire), and the difference mainly comes from the influence of the disease on the patients' physical functioning, role functioning and cognitive functioning.

The global CLL/SLL burden continues to rise over the past 30 years. The relocation of medical resource should be considered on a global scale.[4]

Section 7: Treatment details

7.1. Dosage regimen and duration of treatment

7.1.1. Dosage regimen

Zanubrutinib is available in capsule form and can be taken at home by the patient.

The recommended dosage of zanubrutinib is 160 mg taken orally twice daily or 320 mg taken orally once daily until disease progression or unacceptable toxicity.

Zanubrutinib can be taken with or without food. Patients should swallow capsules whole with water. Patients should not open, break, or chew capsules. If a dose of zanubrutinib is missed, it should be taken as soon as possible on the same day with a return to the normal schedule the following day.[26]

7.1.2. Duration of treatment

Zanubrutinib should be taken until disease progression or unacceptable toxicity.

7.2. Requirements to ensure appropriate use of the medicine(s)

7.2.1. Diagnosis of disease

The diagnosis of CLL requires the presence of at least 5 × 10^9/L monoclonal B-lymphocytes in the peripheral blood and the clonality of B cells should be confirmed by flow cytometry (CSLL-1). The diagnosis of SLL requires the presence of lymphadenopathy and/or splenomegaly with less than 5 × 10^9/L monoclonal B lymphocytes in the peripheral blood. B cells with a CLL/SLL phenotype may be found in samples from patients with reactive lymph nodes; however, a diagnosis of SLL should only be made when there is effacement of the lymph node architecture by histology.

More details can be found in the section of “Diagnosis” in NCCN guideline.[27]

7.2.2. Dose modifications

Dose modification for concomitant therapy

Table 1. Recommended dose modifications when co-administered with other medicinal products.[26]

CYP3A	Co-administered medicinal product	Recommended Dose
Inhibition	Strong CYP3A inhibitor (e.g., posaconazole, voriconazole, ketoconazole, itraconazole, clarithromycin, indinavir, lopinavir, ritonavir, telaprevir)	80 mg once daily
	Moderate CYP3A inhibitor (e.g., erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil, aprepitant, imatinib, grapefruit juice, Seville oranges)	80 mg twice daily
Induction	Strong CYP3A inducer (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) Moderate CYP3A inducer (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin)	Avoid concomitant use. Consider alternative agents with less CYP3A induction

Dose modifications for adverse reactions

Table 2. Recommended dose modification for adverse reaction[26]

Adverse reaction	Adverse reaction occurence	Dose modification (Starting Dose: 320 mg once daily or 160 mg twice daily)
≥Grade 3 non-haematological toxicities Grade 3 febrile neutropenia Grade 3 thrombocytopenia with significant bleeding Grade 4 neutropenia (lasting > 10 consecutive days) Grade 4 thrombocytopenia (lasting >10 consecutive days)	First	Interrupt BRUKINSA Once toxicity has resolved to ≤Grade 1 or baseline: Resume at 320 mg once daily or 160 mg twice daily
	Second	Interrupt BRUKINSA Once toxicity has resolved to ≤Grade 1 or baseline: Resume at 160 mg once daily or 80 mg twice daily
	Third	Interrupt BRUKINSA Once toxicity has resolved to ≤Grade 1 or baseline: Resume at 80 mg once daily
	Fourth	Discontinue BRUKINSA

Asymptomatic lymphocytosis should not be regarded as an adverse reaction, and these patients should continue taking BRUKINSA.

7.2.3. Special populations

Elderly

No specific dose adjustment is required for elderly patients (aged ≥65 years).

Renal impairment

No dose modification is recommended in patients with mild to moderate renal impairment (creatinine clearance (CrCl) ≥30 mL/min, estimated by Cockcroft-Gault). There is limited data on patients with severe renal impairment and end-stage renal disease. Patients with severe renal impairment (CrCl <30 mL/min) or on dialysis should be monitored for adverse reactions.

Hepatic impairment

Dose modifications are not needed in patients with mild (Child-Pugh class A) or moderate hepatic impairment (Child-Pugh class B). Patients with mild or moderate hepatic impairment were treated in BRUKINSA clinical studies. The recommended dose of zanubrutinib for patients with severe hepatic impairment (Child-Pugh class C) is 80 mg orally twice daily. The safety of zanubrutinib has not been evaluated in patients with severe hepatic impairment. Monitor these patients closely for adverse events of BRUKINSA.

Paediatric population

The safety and efficacy of BRUKINSA in children and adolescents below 18 years of age has not been established. No data are available.

More details can be found in the Product Information posted on the European Medicines Agency website.[26]

Section 8: Review of evidence for benefits and harms

8.1. Systematic literature search

Published systematic reviews, technology assessment reports, and meta-analyses of clinical trials involving zanubrutinib in at least one arm were searched on the database of PubMed, and SCOPUS. The search strategies used are as follows:

Category	Description	Search Terms
Study design	Randomised controlled trials, non-randomised controlled trials, systematic review	Search terms related to RCT design for each bibliographic database
Population	Relapsed/Refractory Chronic Lymphocytic Leukemia Treatment Naive Chronic Lymphocytic Leukemia	Leukemia, Lymphocytic, Chronic, B-Cell, Relaps*, refract*, advanced, recur*; untreated, "treatment naive"; “newly diagnosed"; "first line"
Search 1: Direct trials		
Intervention	zanubrutinib	Zanubrutinib OR Brukinsa
Comparator	Ibrutinib or acalabrutinib or 2nd BTKi	Open search – comparator searched in manual review of results
Search 2: Systematic review and meta-analysis		
Intervention	zanubrutinib	Zanubrutinib OR Brukinsa
Comparator	open	Open search – comparator searched in manual review of results

Search strategy for clinical study in Pubmed:

Date: 9th September 2024

Search number	Query	Search Details
1	"zanubrutinib"[Supplementary Concept]	"zanubrutinib"[Supplementary Concept]
2	"leukemia, lymphocytic, chronic, b cell"[MeSH Terms]	"leukemia, lymphocytic, chronic, b cell"[MeSH Terms]
3	"Clinical Study"[Publication Type]	"Clinical Study"[Publication Type]
4	“Systematic review”[Publication Type]	“Systematic review”[Publication Type]
5	(("zanubrutinib"[Supplementary Concept]) AND ("leukemia, lymphocytic, chronic, b cell"[MeSH Terms])) AND ("Clinical Study"[Publication Type])	"zanubrutinib"[Supplementary Concept] AND "leukemia, lymphocytic, chronic, b cell"[MeSH Terms] AND "Clinical Study"[Publication Type]

Search strategy for clinical study in SCOPUS:

Date: 9th September 2024

Search terms: (TITLE-ABS-KEY (brukinsa) OR TITLE-ABS-KEY (zanubrutinib) AND TITLE-ABS-KEY (chronic AND lymphocytic AND leuk*) AND (TITLE-ABS-KEY (clinical AND trial*) OR TITLE-ABS-KEY (systematic review*)) AND (LIMIT-TO (PUBSTAGE , "final")) AND (LIMIT-TO (LANGUAGE , "English")) AND (EXCLUDE (DOCTYPE , "no") OR EXCLUDE (DOCTYPE , "le"))

Letters, notes, editorials, or commentaries will be excluded.

Citations and abstracts returned were reviewed systematically. Reasons for exclusion were annotated to each citation according to the following schema:

- Incorrect intervention
- Does not include the appropriate disease population (R/R or T/N CLL)
- Not compared with the appropriate comparator

- Not direct comparison
- Does not report relevant outcomes/endpoints
- Exact duplicate record within the literature search result set
- Trial not complete or not reported or superseded by evidence of superior quality

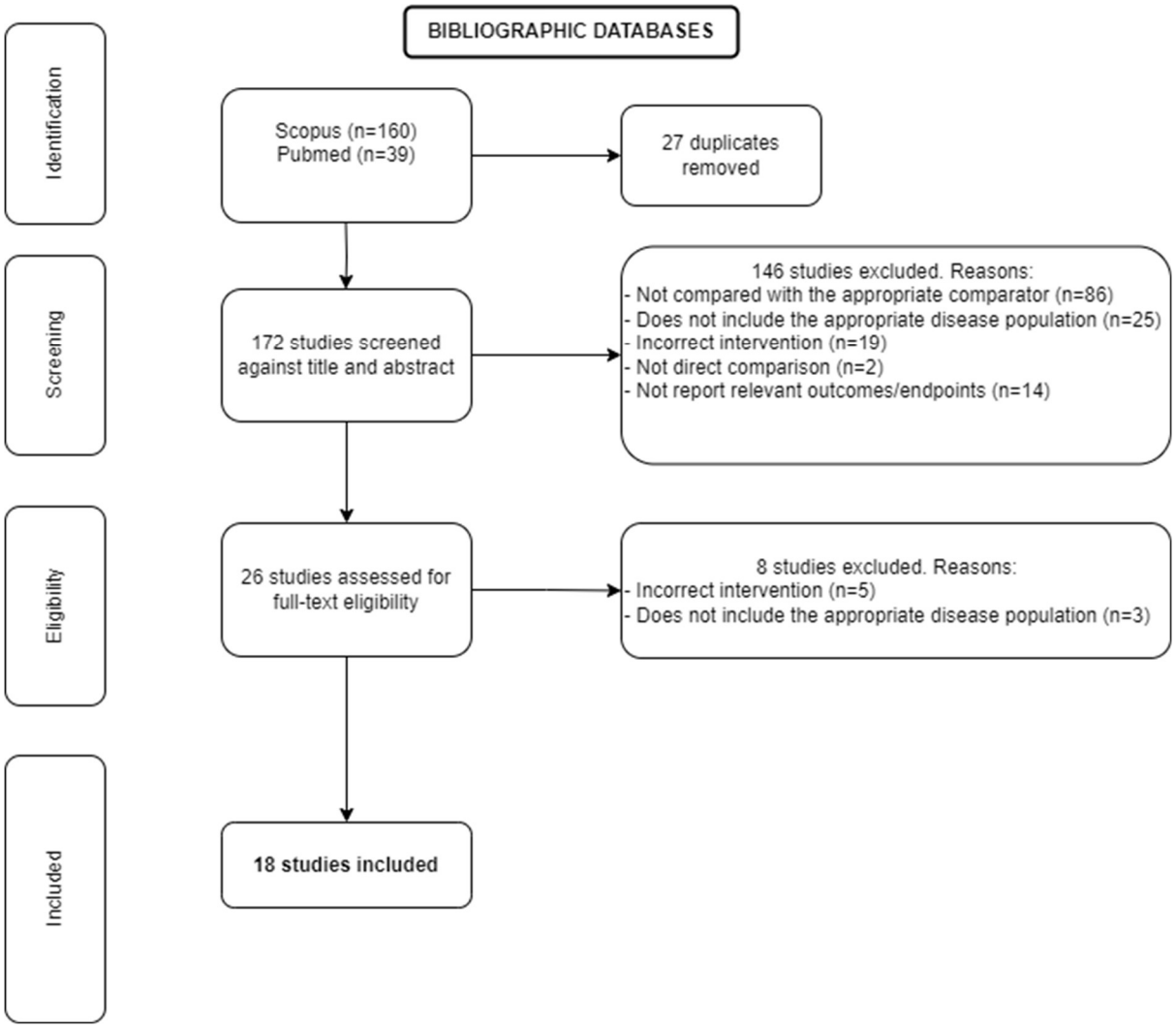


Figure 3. PRISMA flowchart for trial search in R/R and T/N CLL/SLL

Five clinical trials (2 randomised controlled trials and 3 single arm studies) and 3 published systematic literature reviews (SLRs) with meta-analyses were identified.

The ROBIS tool to assess the risk of bias in systematic reviews was applied to each of the included SLRs.[28] The overall level of bias is also included in the summary table; with possible

ratings ranging from high, low, to unclear risk of bias. Two of the SLRs were considered to be at a low risk of bias and one SLR to be at an unclear risk of bias.

A summary and risk of bias assessment of systematic reviews and meta-analyses are included in **Appendix 2**.

8.2. Identified Systematic Literature Reviews and Meta-Analyses

Three systematic literature reviews (SLRs) were identified.

1. Systematic literature review and a Bayesian network meta-analysis (NMA) of *the relative safety profile of first-line targeted therapies in CLL patients with advanced age and/or comorbidities*.[25]

Total studies identified = 10 RCTs including 4,171 patients with naïve CLL requiring therapy with advanced age and/or with comorbidities.

For each analysed endpoint, the overall cumulative ranking of each therapeutic option was estimated using the surface under the cumulative ranking curves (SUCRA). SUCRA can be from 0% to 100%, where the higher value indicates the more preferred therapeutic option.

AEs leading to treatment discontinuation

Ibrutinib+Venetoclax therapy was associated with the highest risk of AEs leading to treatment discontinuation compared with other (evaluated) targeted therapies, i.e., zanubrutinib (16.5 [2.73; 153.68]), acalabrutinib (12.56 [2.58, 102.7]), chlorambucil + Obinutuzumab (6.93 [1.69, 51.72]), acalabrutinib + Obinutuzumab (9.62 [2.02, 78.15]), and Venetoclax + Obinutuzumab (6.67 [1.46, 52.55]), while no significant differences were found between the remaining targeted therapies. Zanubrutinib had the highest probability of being the safest therapeutic option in this area (SUCRA: 86 %).

Grade ≥3 AEs

Grade ≥3 AEs were generally significantly more frequent in groups treated with combined therapies such as venetoclax + Obinutuzumab, acalabrutinib + Obinutuzumab, Ibrutinib + Obinutuzumab, and Ibrutinib+Venetoclax than in monotherapy groups, especially those on

second-generation BTK inhibitors like zanubrutinib or acalabrutinib. Zanubrutinib ranked the highest among the evaluated targeted therapies (SUCRA: 98 %).

Serious AEs

Serious AEs grade 1–5 were significantly less frequent in the case of zanubrutinib therapy as compared with other targeted therapies, such as Ibrutinib (0.35 [0.20, 0.59]), acalabrutinib (0.38 [0.17, 0.85]), ibrutinib + obinutuzumab (0.25 [0.11, 0.57]), ibrutinib + rituximab (0.39 [0.22, 0.67]), ibrutinib + venetoclax (0.28 [0.12, 0.66]), and acalabrutinib + obinutuzumab (0.28 [0.13, 0.62]), but there were no significant differences between zanubrutinib and chlorambucil + obinutuzumab, chlorambucil + ofatumumab or venetoclax + obinutuzumab. Zanubrutinib achieved the highest rank in the SUCRA ranking by 95 %.

Hematological AEs (Anemia)

The most frequently reported hematological AE for targeted therapies was anemia.

Anemia grade 1–5 was significantly less frequent in the case of zanubrutinib therapy than for other treatment options (SUCRA: 92%), such as chlorambucil + obinutuzumab (0.35 [0.12, 0.98]) and acalabrutinib (0.28 [0.08, 0.96]). There were no significant differences between any other individual regimens.

Although there were no significant differences between assessed targeted therapies in terms of anemia grade ≥3, zanubrutinib achieved the highest SUCRA value of 86%.

2. A systematic review and meta-analysis *analyzed and compared treatment-emergent adverse events of ibrutinib, acalabrutinib, and zanubrutinib* reported in clinical trials in different B-cell malignancies including CLL/SLL. A novel Bayesian hierarchical model was developed to jointly estimate the incidence probabilities of different grades of AE and the relative risks (RR) between treatments.[29]

A total of 61 trials were included, involving 6959 patients and 68 treatment arms: ibrutinib (n=31; 46%), ibrutinib plus anti-CD20 mAb (n=15; 22%), acalabrutinib (n=11; 16%), and zanubrutinib (n=11; 16%). Most trials were in CLL/SLL (n=36), MCL (n=9), or WM (n=8). Three trials involved randomized comparison between ibrutinib and either acalabrutinib (ELEVATE-RR) or zanubrutinib (ASPEN, ALPINE). A total of 84 AEs were analyzed.

Results from this meta-analysis show an improved AE profile with acalabrutinib and zanubrutinib compared to ibrutinib. In addition, these data – for the first time – provide a

comprehensive comparison of AE between zanubrutinib and acalabrutinib, which may inform clinicians' choice between these highly effective second-generation BTKi treatments for patients with B-cell malignancies. (

Figure **4**)

Treatment-emergent adverse events of all grades

- Compared with ibrutinib, the average incidence of all grade AE was lower with zanubrutinib (RR=0.83, 95% CrI=0.71-0.93).
- Zanubrutinib and acalabrutinib had similar average incidences of all grade AE (RR=1.12, 95% CrI=0.91-1.37). All grade AE that occurred more frequently with acalabrutinib relative to zanubrutinib included atrial fibrillation (RR=0.51), infections (RR=0.53), pyrexia (RR=0.59), cough (RR=0.71), fatigue (RR=0.61), nausea (RR=0.63), vomiting (RR=0.71), diarrhea (RR=0.52), myalgias (RR=0.49), headaches (RR=0.32), and dizziness (RR=0.63).

Treatment-emergent adverse events of grade ≥3

- Compared with ibrutinib, the average incidence of grade ≥3 AE was also lower with zanubrutinib (RR=0.78, 95% CrI=0.47-1.02).
- Zanubrutinib and acalabrutinib had similar average incidences of grade ≥3 AE (RR=0.90, 95% CrI=0.54-1.37). Grade ≥3 AE that occurred more frequently with acalabrutinib included anemia (RR=0.58), infections (RR=0.76), and rash (RR=0.03).

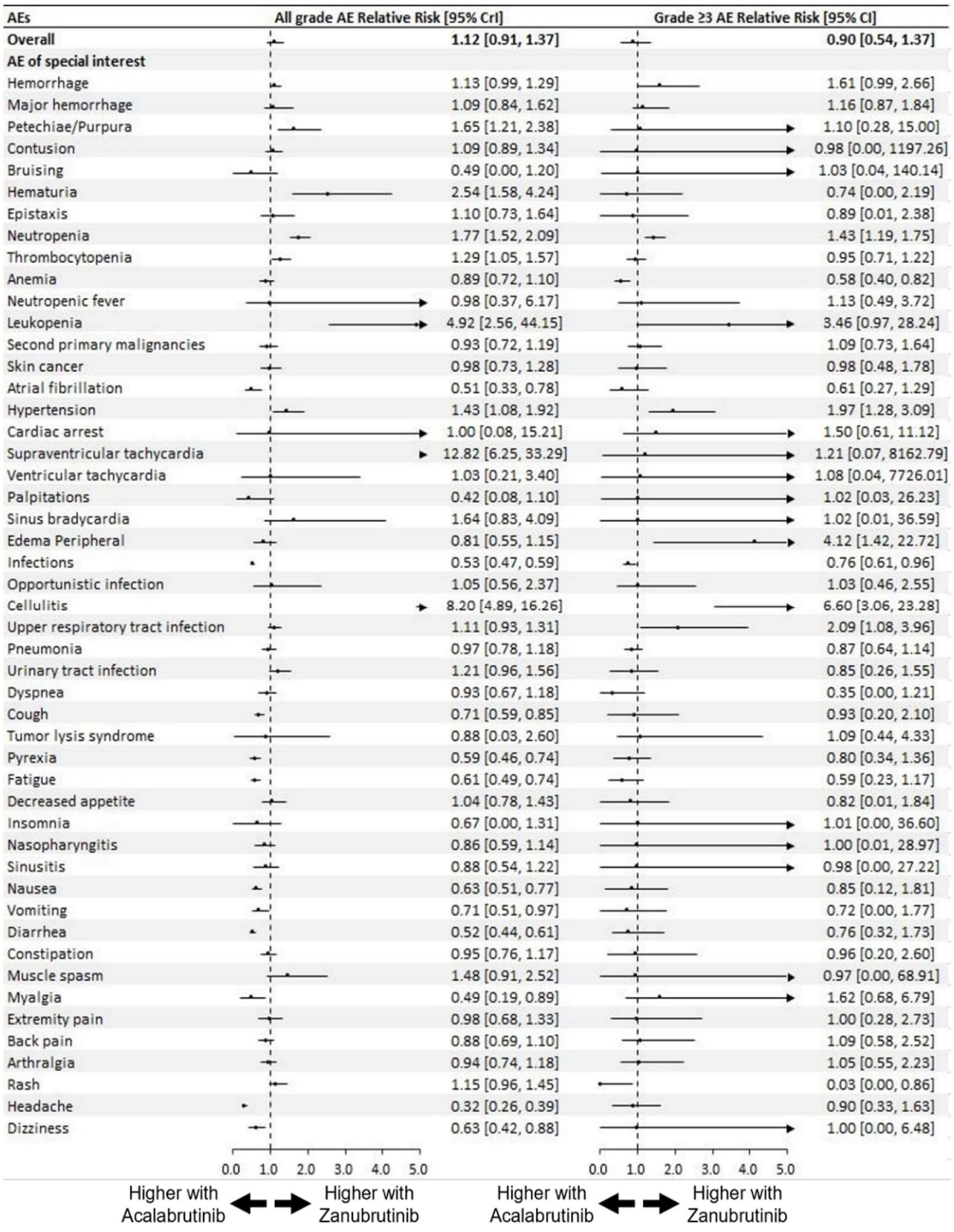


Figure 4. AE profile with acalabrutinib and zanubrutinib compared to ibrutinib.[29]

3. A systematic review and meta-analysis evaluated the *efficacy and safety of new-generation BTKi-based regimens for the treatment of patients with CLL/SLL*.[30]

The meta-analysis included 15 records for a total of 2,066 CLL/SLL patients, across ten single-arm studies and five randomized studies. These studies involving patients treated with new-generation BTKi (acalabrutinib, zanubrutinib, orelabrutinib, or tirabrutinib), both as single-agent therapy and in combination with other agents).

Efficacy: survival

The pooled 24-month OS rate for CLL patients treated with BTKi was 94% (95% CI, 92–97%, I2 = 51.32%, P = 0.06. Sub-group analysis for the acalabrutinib monotherapy and zanubrutinib monotherapy showed a pooled 24-month OS rate of 92% (95% CI, 89–96%, I2 = 0.00%) and 95% (95% CI, 92–96%, I2 = 0.00%, P = 0.72), respectively. Also, sub-group analysis for these two therapies showed a pooled 24-month PFS rate of 83% for acalabrutinib (95% CI, 75–90%, I2 = 57.74%, P = 0.05) and 86% for zanubrutinib (95% CI, 80–91%, I2 = 77.84%, P = 0.00).[30]

Sub-group analysis also showed that the ORR and CR rates from acalabrutinib monotherapy for CLL were 87% and 3%, respectively, while zanubrutinib monotherapy showed OR and CR rates of 93% and 13%, respectively.

Zanubrutinib monotherapy yielded higher efficacy than acalabrutinib monotherapy, indicating that zanubrutinib may be the first choice in monotherapy for CLL compared to acalabrutinib, with more head-to-head RCTs being still in need.

Safety

The pooled rates of grade ≥ 3 neutropenia, anaemia, and thrombocytopenia in acalabrutinib monotherapy were 14%, 7%, and 5%, respectively. The pooled rates of grade ≥ 3 neutropenia, anemia, and thrombocytopenia in zanubrutinib monotherapy were 19%, 2%, and 4%, respectively. Zanubrutinib monotherapy had a similar pooled rate of grade ≥ 3 upper respiratory tract infection (2% vs. 1%), and grade ≥ 3 hypertension (6% vs. 4%) compared to acalabrutinib monotherapy.

8.3. Trials, design, and endpoints

8.3.1. ALPINE: BGB-3111-305 (NCT03734016)

Study name

Study BGB-3111-305 is a randomized, Phase 3 study comparing the efficacy and safety of zanubrutinib versus ibrutinib in patients with R/R CLL/SLL.[23]

Study design

Patients enrolled in BGB-3111-305 at clinical sites in Australia, Belgium, China, Czechia, France, Germany, Italy, Netherlands, New Zealand, Poland, Spain, Sweden, Turkey, the United Kingdom, and the United States. Patients were randomized 1:1 to zanubrutinib 160 mg orally twice daily (n=327) or ibrutinib 420 orally once daily (n=325). Duration of treatment was until disease progression, unacceptable toxicity, treatment consent withdrawal, or end of study.

Endpoints

- **Primary efficacy endpoint:** ORR by investigator was tested for non-inferiority, and superiority (superiority is tested if only non-inferiority had been met in the interim analysis). If the superiority in ORR by investigator at either interim or final analysis is statistically significant, PFS by investigator will be tested for non-inferiority.
- **Key secondary efficacy endpoint:** The single analysis of PFS by investigator was planned and conducted when approximately 205 PFS events have occurred. If non-inferiority has been met, then the superiority will be tested under hierarchical testing.
- **Key secondary safety endpoint:** Incidence of atrial fibrillation/flutter was tested for superiority of zanubrutinib. The endpoint was tested separately from the fixed sequence hierarchical testing that included ORR and PFS and was conditioned on the statistical significance of noninferiority of zanubrutinib to ibrutinib in ORR.

Efficacy

In the Phase 3ALPINE trial, at a median follow-up of 29.6 months, zanubrutinib was found to be superior to ibrutinib with respect to PFS among 652 patients (hazard ratio for disease progression or death, 0.65; 95% confidence interval, [CI], 0.49 to 0.86; P = 0.002), as assessed by the investigators.[23] The results were similar to those as assessed by an independent-review

committee. At 24 months, the investigator-assessed rates of progression-free survival were 78.4% in the zanubrutinib group and 65.9% in the ibrutinib group. (Figure 5A)

Among patients with a 17p deletion, a TP53 mutation, or both, those who received zanubrutinib had longer progression-free survival than those who received ibrutinib (hazard ratio for disease progression or death, 0.53; 95% CI, 0.31 to 0.88) (Figure 5B); progression-free survival across other major subgroups consistently favored zanubrutinib.

As of the data-cutoff date in the final analysis, fewer deaths had been reported in the zanubrutinib group than in the ibrutinib group (48 and 60). In the comparison of zanubrutinib with ibrutinib, the hazard ratio for death was 0.76 (95% CI, 0.51 to 1.11). The median overall survival had not been reached in either treatment group. (Figure 5C)

The percentage of patients with an overall response was higher in the zanubrutinib group than in the ibrutinib group. In the final analysis, the percentage of patients in the intention-to-treat population with an overall response, as assessed by the investigators, was higher in the zanubrutinib group than in the ibrutinib group (83.5% and 74.2%); the percentages of patients with an overall response as assessed by the independent review committee were 86.2% and 75.7%, respectively.

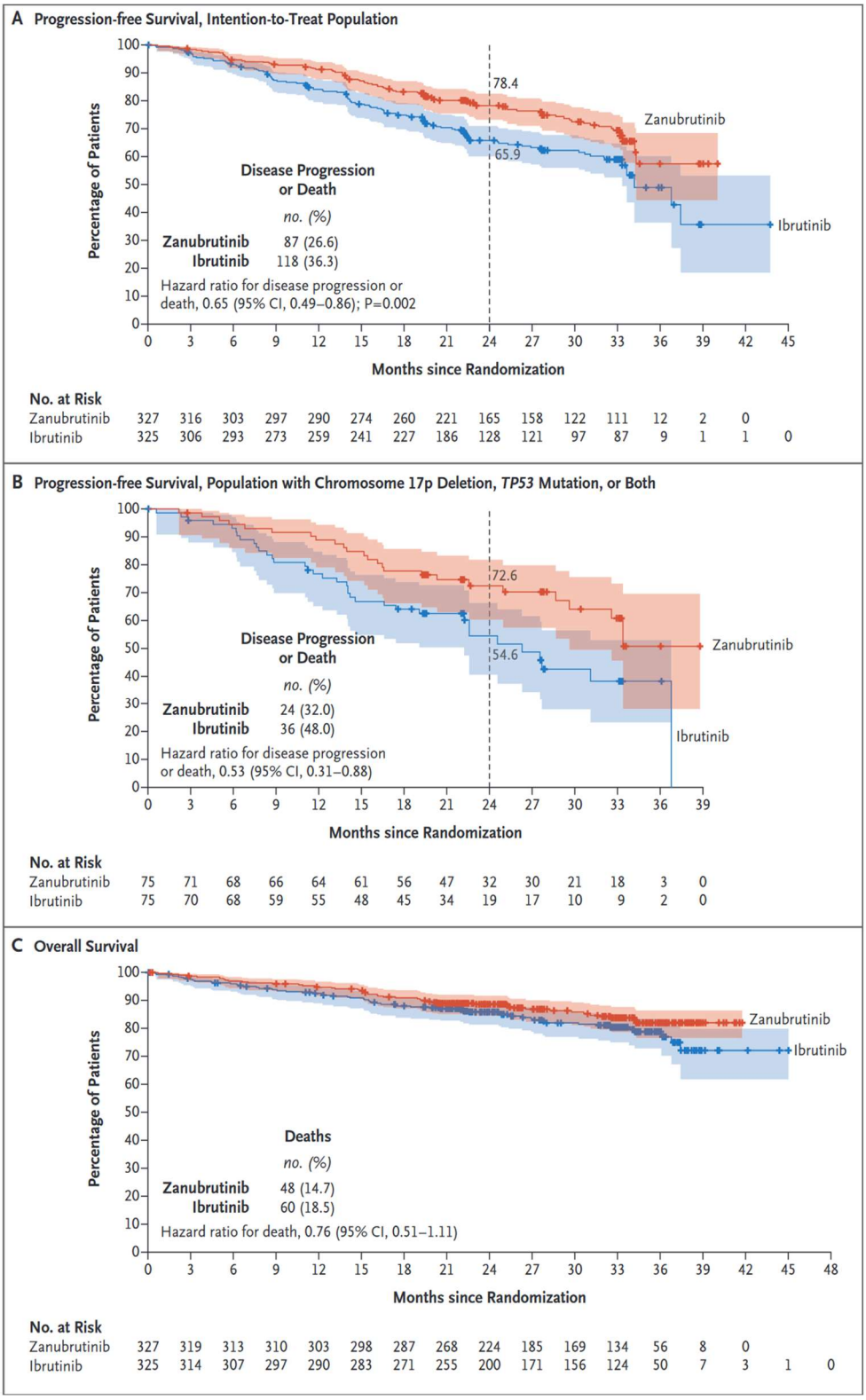
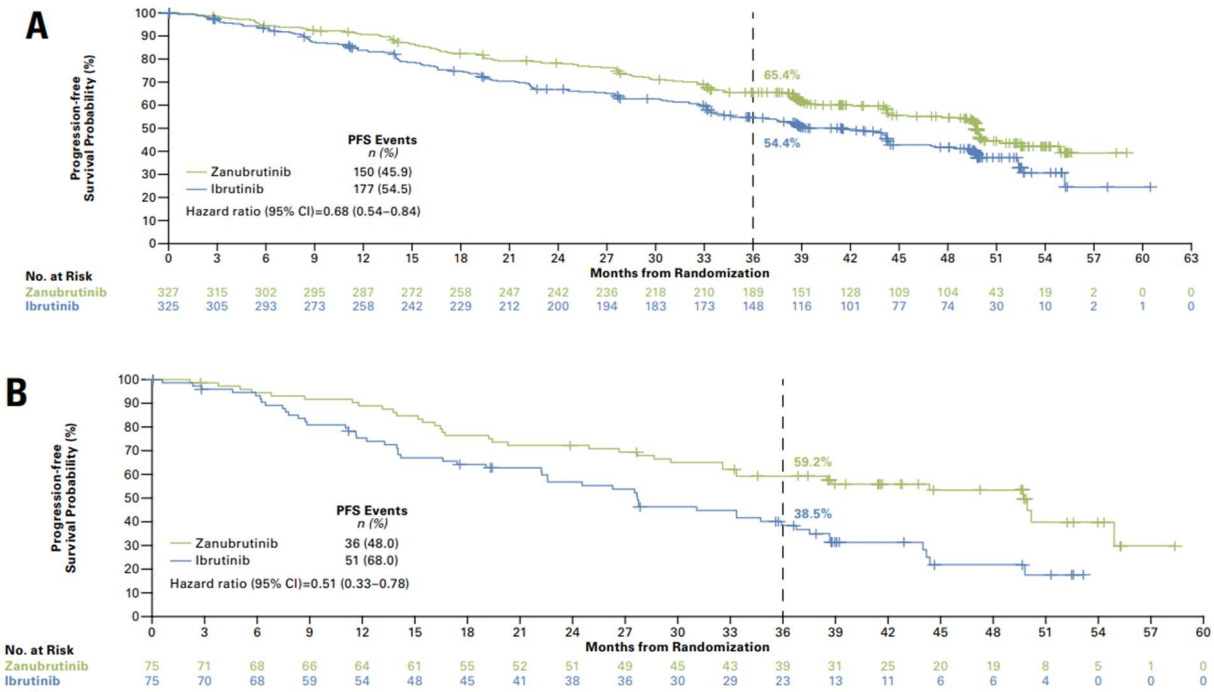


Figure 5. Investigator-assessed PFS (ITT and Population with Chromosome 17p Deletion, *TP53* Mutation, or Both) and Overall Survival between Zanubrutinib and Ibrutinib[23]

With 42.5 months of median follow-up, zanubrutinib PFS benefit was sustained over ibrutinib (HR: 0.68 [95% CI, 0.54-0.84]; Figure 6A); the 36-month PFS rate was 65.4% in the zanubrutinib treatment arm and 54.4% in the ibrutinib treatment arm.[24] Improvement in PFS of zanubrutinib over ibrutinib was sustained in high-risk patients with del(17p)/TP53mut (HR: 0.51 [95% CI, 0.33-0.78]; (Figure 6B) as well as in patients without del(17p)/TP53 mut (HR: 0.79 [95% CI, 0.61-1.02]).

Across most other major subgroups, PFS improvement with zanubrutinib was also maintained, including by prior lines of therapy.

Zanubrutinib's PFS benefit over ibrutinib remained consistent across multiple sensitivity analyses, including assessment of progression and death events that occurred only while patients remained on active treatment (HR: 0.72 [95% CI, 0.54-0.97]; Figure 6C), and when censoring for deaths attributed to COVID-19 (HR: 0.66 [95% CI, 0.52-0.84]; Figure 6D). The 36-month PFS rates for zanubrutinib and ibrutinib in these sensitivity analyses were 78.7% and 71.5% (active treatment) and 69.4% and 57.8% (COVID-19), respectively.



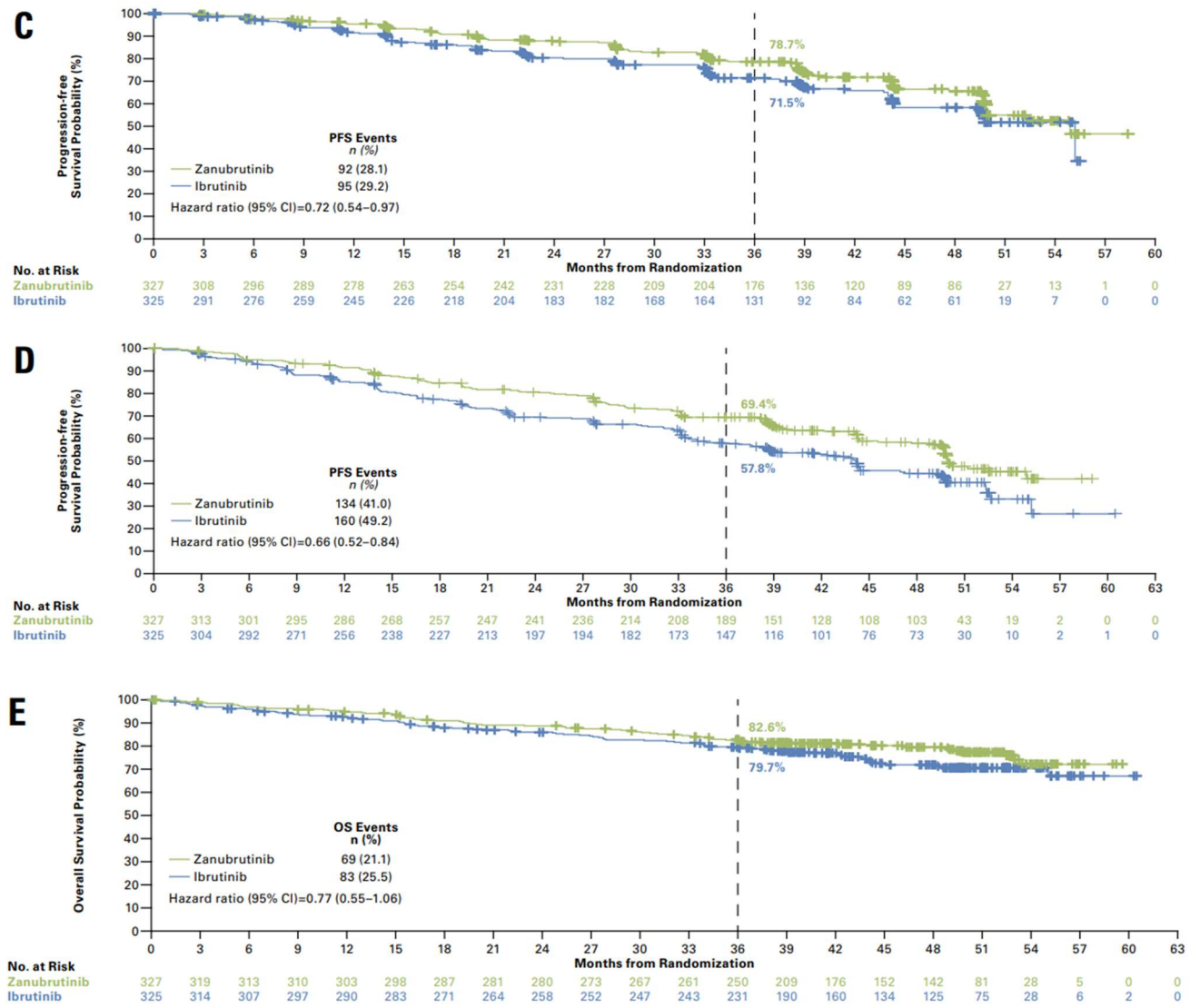


Figure 6. PFS survival probability: zanubrutinib and ibrutinib[24]

At 42.5 months follow-up, ORR remained higher with zanubrutinib compared with ibrutinib (85.6% vs 75.4%; RR: 1.13 [95% CI, 1.05-1.22]); the rate of PR with lymphocytosis or better was 90.2% vs 82.8%, respectively.[24] While clinical responses deepened in both arms over time, zanubrutinib-treated patients reached CR/CRi earlier and more of them achieved CR/CRi than did ibrutinib-treated patients. Median OS had not been reached in either treatment group (Figure 6E). Overall, 69 zanubrutinib- and 83 ibrutinib-treated patients have died (OS HR: 0.77 [95% CI, 0.55-1.06]).

Safety

The phase III ALPINE trial analysis showed that the safety profile of zanubrutinib was better than that of ibrutinib, with fewer adverse events leading to treatment discontinuation and fewer cardiac events, including fewer cardiac events leading to treatment discontinuation or death.[23]

A lower incidence of cardiac disorders was reported in the zanubrutinib group (21.3%) than in the ibrutinib group (29.6%) (Figure 7A); cardiac disorders leading to treatment discontinuation occurred in 1 patient (0.3%) in the zanubrutinib group and 14 patients (4.3%) in the ibrutinib group.

The incidence of **atrial fibrillation or flutter** (a key secondary outcome) of any grade was lower in the zanubrutinib group than in the ibrutinib group (in 17 of 324 patients [5.2%] versus 43 of 324 patients [13.3%]), and the incidence of atrial fibrillation or flutter of grade 3 or higher was also lower in the zanubrutinib group (in 8 of 324 [2.5%] versus in 13 of 324 [4.0%]) (Figure 7B).

Neutropenia of any grade was reported in 29.3% of the patients in the zanubrutinib group and in 24.4% of those in ibrutinib group; the incidences of neutropenia and febrile neutropenia of grade 3 or higher were similar in the two groups (Figure 7C).

Infections of any grade were reported in 71.3% of the patients in the zanubrutinib group and in 73.1% of those in the ibrutinib group, and the incidences of infections of grade 3 or higher were 26.5% and 28.1%, respectively (Figure 7D).

Hypertension of any grade was reported in 23.5% of patients in the zanubrutinib group and in 22.8% of those in the ibrutinib group (Figure 7E), and grade 3 hypertension was reported in 15.1% and 13.6% of the patients, respectively; grade 4 hypertension was not observed in either treatment group.

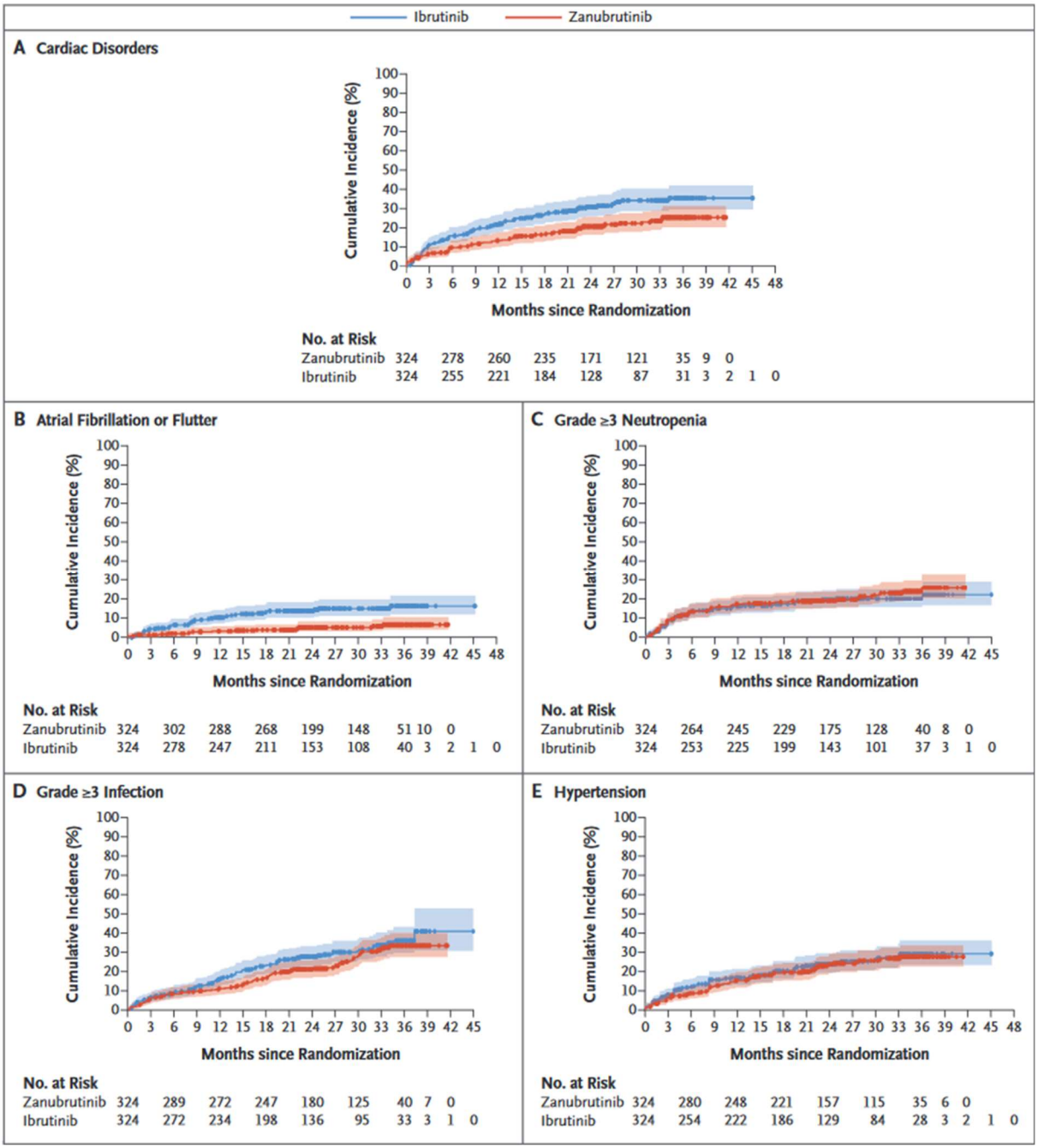


Figure 7. Time to the occurrence of cardiac disorders and adverse events of special interest in the safety population.[23]

At the 42.5 months median follow-up from the ALPINE trial:[24]

- The most common nonhematologic treatment-emergent AEs of any grade with zanubrutinib vs ibrutinib were COVID19-related infections (46.0% vs 33.3%), upper respiratory tract infection (29.3% vs 19.8%), diarrhea (18.8% vs 25.6%), and hypertension (27.2% vs 25.3%). The most commonly reported non-hematologic grade ≥3 AEs were hypertension (17.0% vs 16.0%), COVID-19-related infections (17.9% vs

12.0%), and pneumonia (7.7% vs 10.5%), respectively. Neutropenia was the most common hematologic AE of any grade (31.5% vs 29.6%) and grade ≥3 (22.8% vs 22.8%) with zanubrutinib vs ibrutinib, respectively; febrile neutropenia was low in both arms (n=4, 1.2% each).

- Occurrence of hemolytic anemia (HA), including autoimmune HA, was rare. Two patients receiving ibrutinib experienced HA; one patient treated with zanubrutinib experienced autoimmune HA. The percentage of patients with all-grade and grade ≥3 AEs is presented in Figure 8A-B.

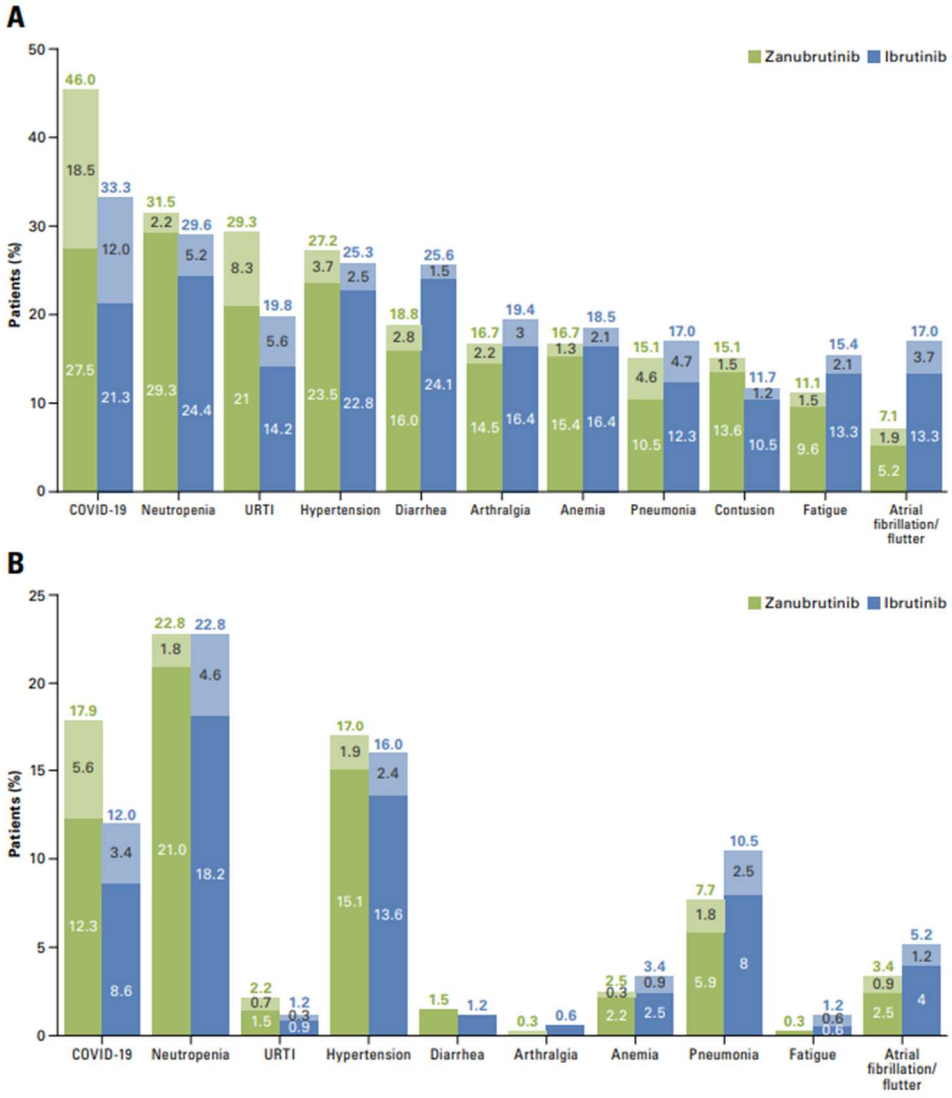


Figure 8. The percentage of patients with all-grade and grade ≥3 AEs[24]

- Although hypertension rates were similar between treatments when evaluated as AEs using MedDRA-coded terms, mean changes from baseline in systolic blood pressure

over time were generally lower in patients treated with zanubrutinib vs ibrutinib; changes in diastolic blood pressure were similar between treatment arms.

- Overall cardiac events remained considerably lower with zanubrutinib compared with ibrutinib (Figure 9A) and the rate of atrial fibrillation/flutter was lower with zanubrutinib vs ibrutinib (7.1% vs 17.0%; Figure 9B) despite similar hypertension rates (Figure 9C). Overall incidence of cardiac events (25.9% vs 35.5%) and discontinuations due to cardiac events (0.9% vs 4.9%) were also lower with zanubrutinib compared with ibrutinib. Six patients treated with ibrutinib died due to cardiac AEs; in the zanubrutinib arm, no deaths due to cardiac AEs occurred.

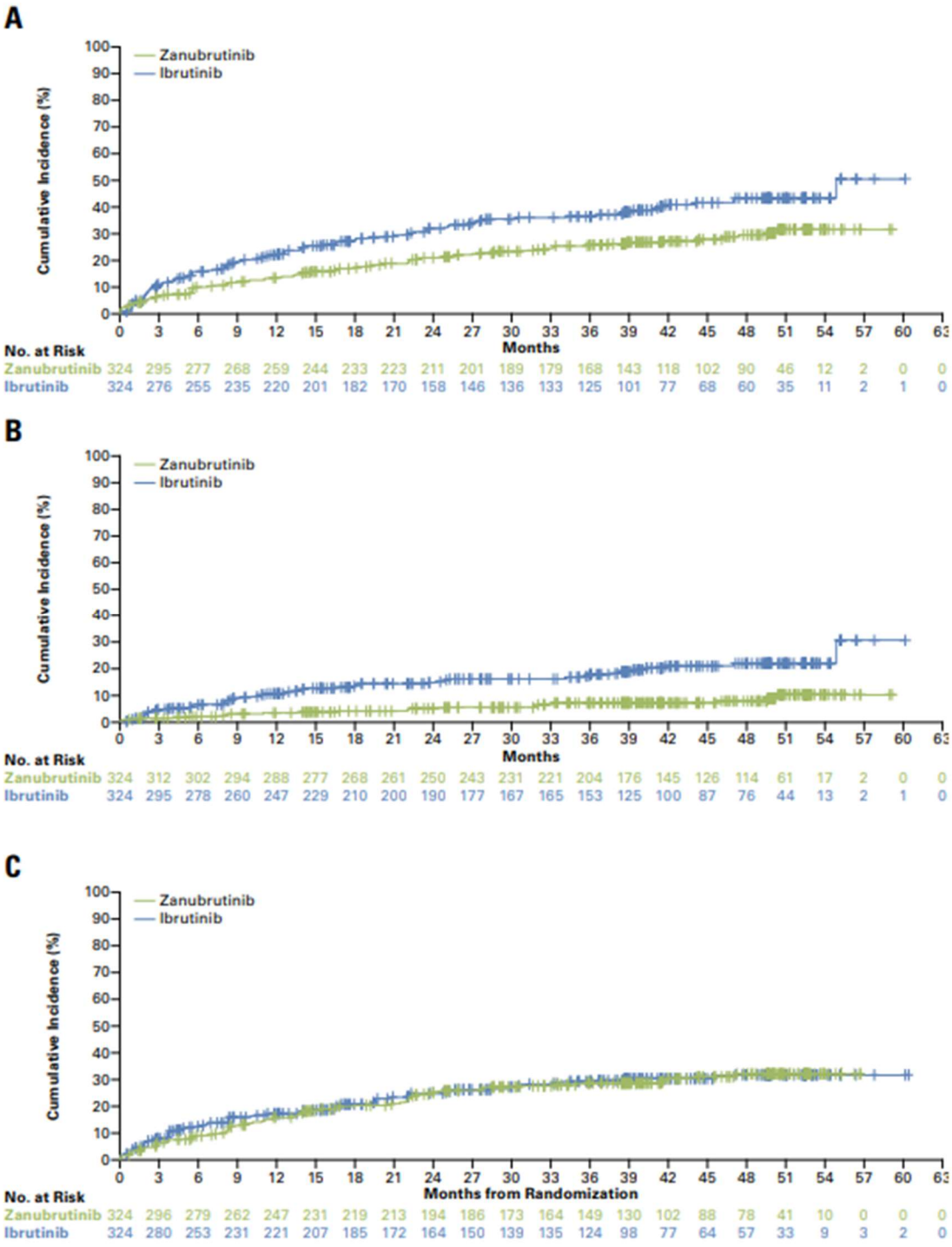


Figure 9. Overall cardiac events, rates of atrial fibrillation/flutter, and hypertension rates[24]

Quality of life

- Patient's QoL was measured by EORTC QLQ-C30 and EQ-5D-5L questionnaires. Presented results are from the latest available analysis of QoL:[31]

- EORTC QLQ-C30: Patients treated with zanubrutinib experienced clinically meaningful improvements in physical and role functioning, as well as pain and fatigue symptoms at both cycles. Patients in the zanubrutinib arm reported lower diarrhea scores. Nausea/vomiting scores were maintained in both arms. (Figure 10)

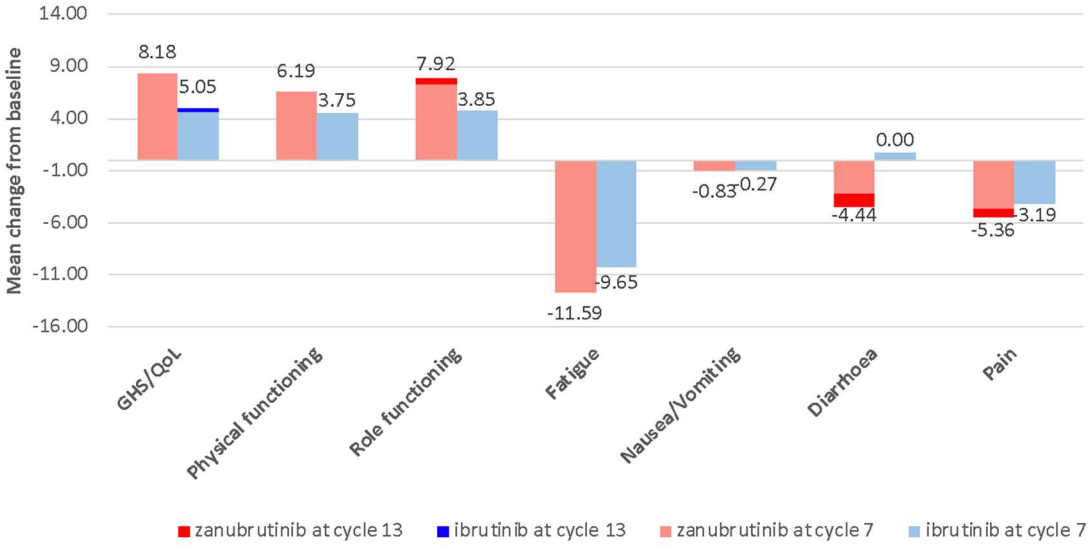


Figure 10. EORTC QLQ-C30 (graph developed based on published data in Tam et al., Curr Med res Opin. 2023)

- EQ-5D-5L: Mean change from baseline in EQ-VAS showed a consistently better improvement in patients in the zanubrutinib arm compared with patients in the ibrutinib arm at both key cycles. The mean change (SD) from baseline in VAS scores were 7.92 (18.245) in the zanubrutinib arm versus 3.44 (16.972) in the ibrutinib arm at Cycle 7; and at Cycle 13, 7.75 (18.806) in the zanubrutinib versus 3.92 (16.778) in the ibrutinib arm.

Quality-adjusted time without symptoms of disease and toxicity (Q-TWiST)

Q-TWiST is a clinical tool to assess overall benefits and risks of cancer therapies by integrating progression, survival, treatment toxicity, and patient QoL into a single metric. Analysis was conducted using individual patient data from the ALPINE trial to enhance comprehensive understanding of the benefits and risks associated with zanubrutinib vs ibrutinib in terms of quality-adjusted survival.[32]

Results showed that in the base case, the mean durations of heath states (zanubrutinib vs ibrutinib) were: 11.54 vs 11.38 months for toxicity; 14.45 vs 11.09 months for time without

symptom of disease and toxicity (TWiST); and 1.70 vs 3.78 months for relapse. (Figure 11) The mean differences for zanubrutinib vs ibrutinib were 0.16 months for the toxicity state, 3.36 months for the TWiST state, and −2.08 months for the relapse state. The mean duration of Q-TWiST was 21.07 months for zanubrutinib vs 18.67 months for ibrutinib. More importantly, the estimated difference in mean Q-TWiST gain was significantly higher for zanubrutinib vs ibrutinib (2.40 months; 95% CI: 1.9, 2.9; P<.001) and the relative Q-TWiST gain was 9.14%.

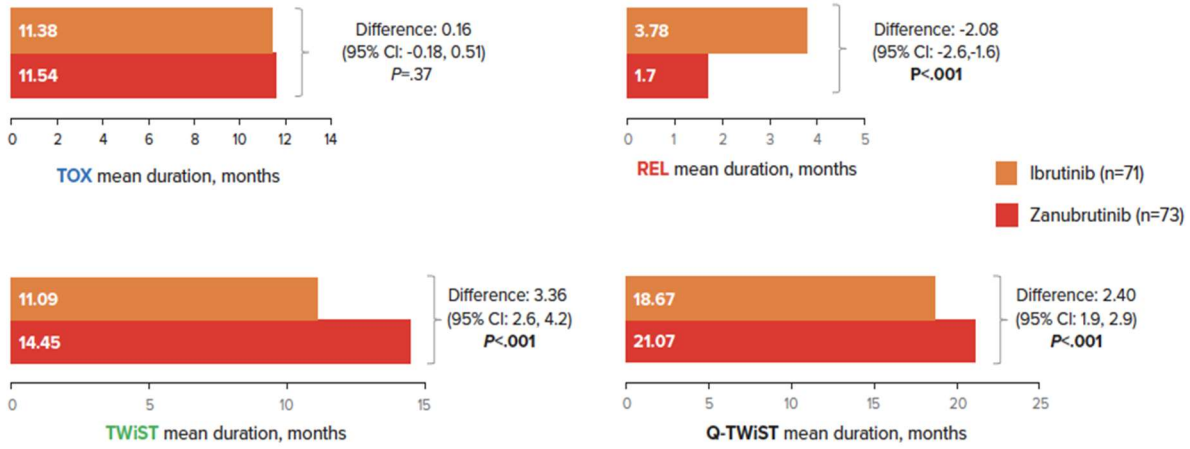


Figure 11. Q-TWiST analysis: Progression, Survival, Treatment toxicity, and QoL[32]

8.3.2. SEQUOIA: BGB-3111-304 (NCT03336333)

Study name

Zanubrutinib versus BR in untreated CLL/SLL (SEQUOIA): a randomised, controlled, phase 3 trial.

Study design

This study conducted an open-label, multicentre, phase 3 study at 153 academic or community hospitals in 14 countries and regions.[21] Patients enrolled in BGB-3111-304 at clinical sites in Australia, Belgium, Czechia, France, Italy, New Zealand, Poland, Russia, Spain, Sweden, China Taiwan, the United Kingdom, and the United States. Eligible patients had untreated CLL or SLL requiring treatment as per International Workshop on CLL criteria; were aged 65 years or older, or 18 years or older and had comorbidities; and had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2.

Randomized pivotal cohort (Cohort 1, Groups A and B): Cohort 1 is a randomized phase 3 trial where patients without del(17) (p13·1) were randomized to zanubrutinib (group A) or bendamustine–rituximab (BR) (group B).

Cohort 2 (Group C): Single-arm, includes patients with del(17)p. Patients with del(17) (p13·1) were enrolled in group C and received zanubrutinib. Zanubrutinib was administered orally at 160 mg twice per day (28-day cycles); bendamustine at 90 mg/m^2 of body surface area on days 1 and 2 for six cycles plus rituximab at 375 mg/m^2 of body surface area the day before or on day 1 of cycle 1, and 500 mg/m^2 of body surface area on day 1 of cycles 2–6, were administered intravenously.

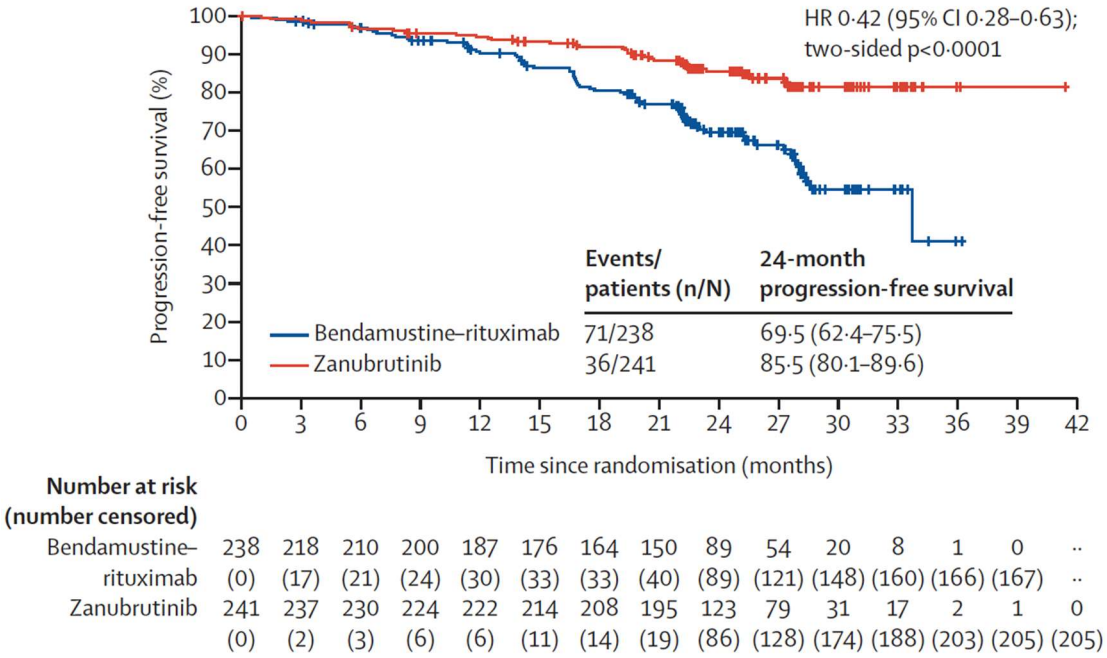
Endpoints

SEQUOIA (Cohort 1)

Zanubrutinib demonstrated PFS superiority to BR in CLL patients without del(17p), including high-risk patient groups. In addition, zanubrutinib's PFS benefit versus BR is maintained with longer study follow-up in patients without del(17p), including high-risk patients. Treatment with zanubrutinib treatment led to a higher disease response compared with BR in patients without del(17p).

Progression-free survival

At the interim analysis of SEQUOIA (Cohort 1), the study met its primary endpoint with zanubrutinib demonstrating superiority to BR in PFS by Independent Review Committee at the interim analysis (DCO: 7th May 2021).[21] With a median follow-up of 26.1 months, zanubrutinib showed a statistically significant reduction in the risk of disease progression (HR=0.42 [95% CI: 0.28, 0.63], 2-sided P<.0001). (Figure 12)



Number at risk (number censored)															
Bendamustine–rituximab	238 (0)	218 (17)	210 (21)	200 (24)	187 (30)	176 (33)	164 (33)	150 (40)	89 (89)	54 (121)	20 (148)	8 (160)	1 (166)	0 (167)	.. ..
Zanubrutinib	241 (0)	237 (2)	230 (3)	224 (6)	222 (6)	214 (11)	208 (14)	195 (19)	123 (86)	79 (128)	31 (174)	17 (188)	2 (203)	1 (205)	0 (205)

Figure 12. Progression-free survival by IRC (Data cut-off: 7th May 2021)[21]

Zanubrutinib had a longer PFS compared to BR in the majority of subgroups, including the difficult-to-treat 11q del: HR=0.21 (95% CI: 0.09, 0.50), and unmutated IGHV: HR=0.24 (95% CI: 0.13, 0.43) (Figure 13)

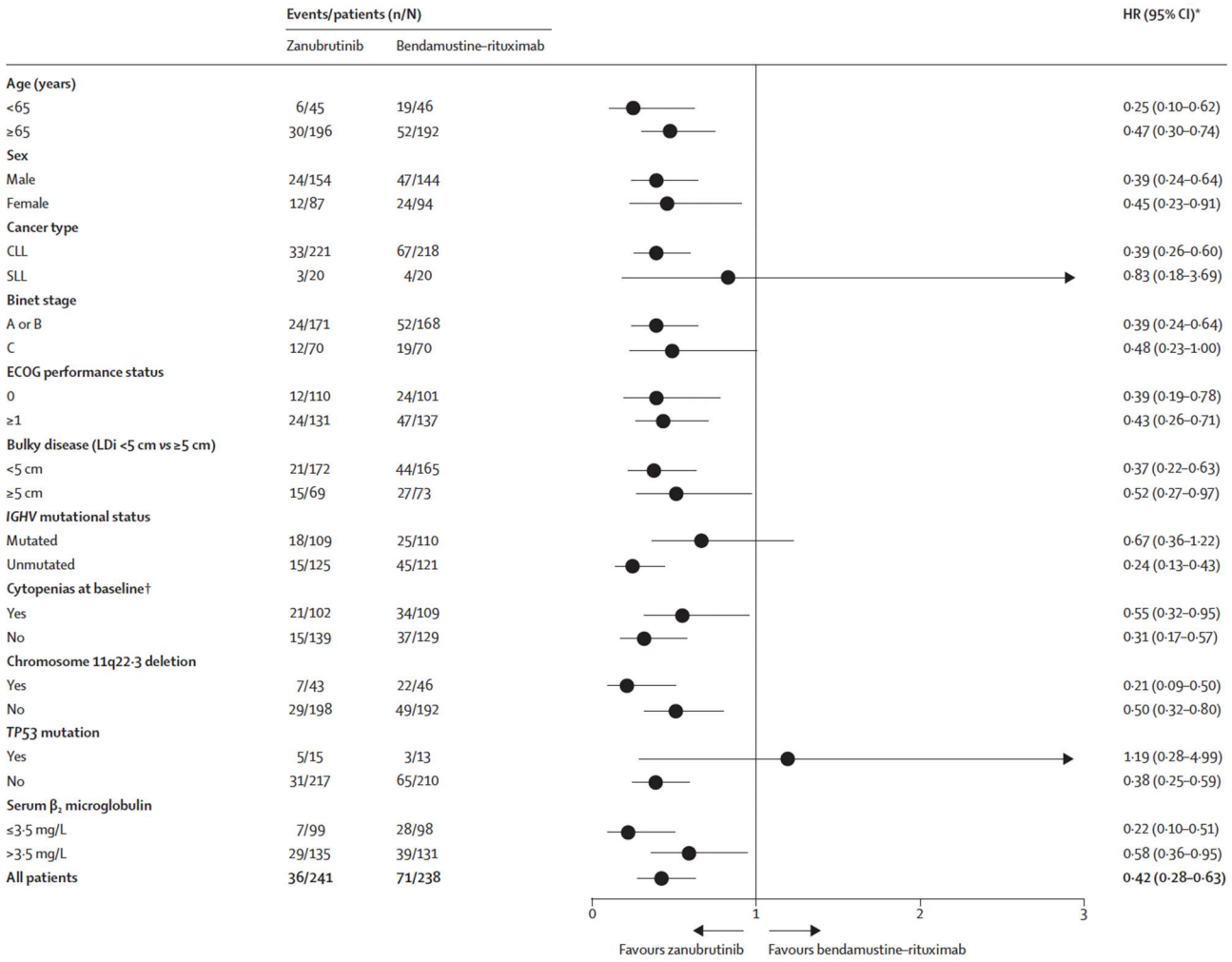


Figure 13. Progression-free survival by IRC: subgroup analysis (DCO: 7th May 2021)[21]

With >3.5 years of median follow-up (extended follow-up), though the median OS was not reached in either zanubrutinib or BR treatment arms, zanubrutinib PFS benefit was sustained over BR (HR: 0.30 [95% CI, 0.21-0.43]; P<.0001).[22] Estimated 42-month PFS rates with zanubrutinib and BR were 82.4% and 50.0%, respectively. (Figure 14)

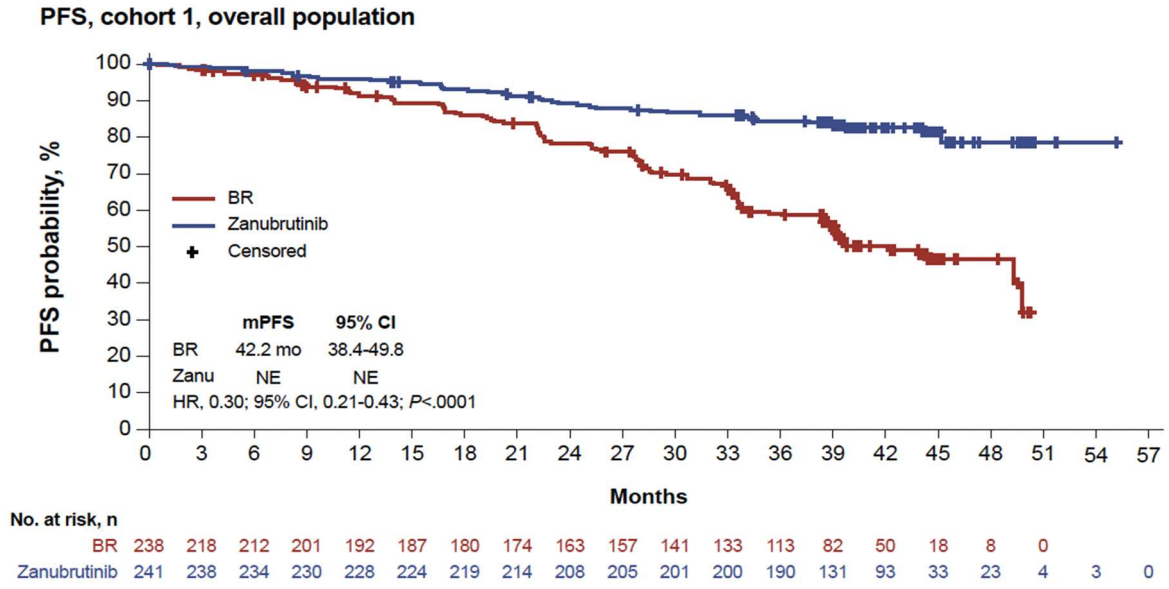


Figure 14. PFS by IRC (DCO: 31st October 2022)[22]

Improvement in PFS of zanubrutinib over BR was sustained regardless of IGHV mutational status. Zanubrutinib showed statistically longer PFS versus BR both in high-risk patients with unmutated IGHV (HR: 0.23 [95% CI, 0.14-0.37]; P<.0001) as well as in patients with mutated IGHV (HR: 0.35 [95% CI, 0.19-0.64]; P<.00033). (Figure 15)

PFS, cohort 1, mutated and unmutated IGHV, overall population

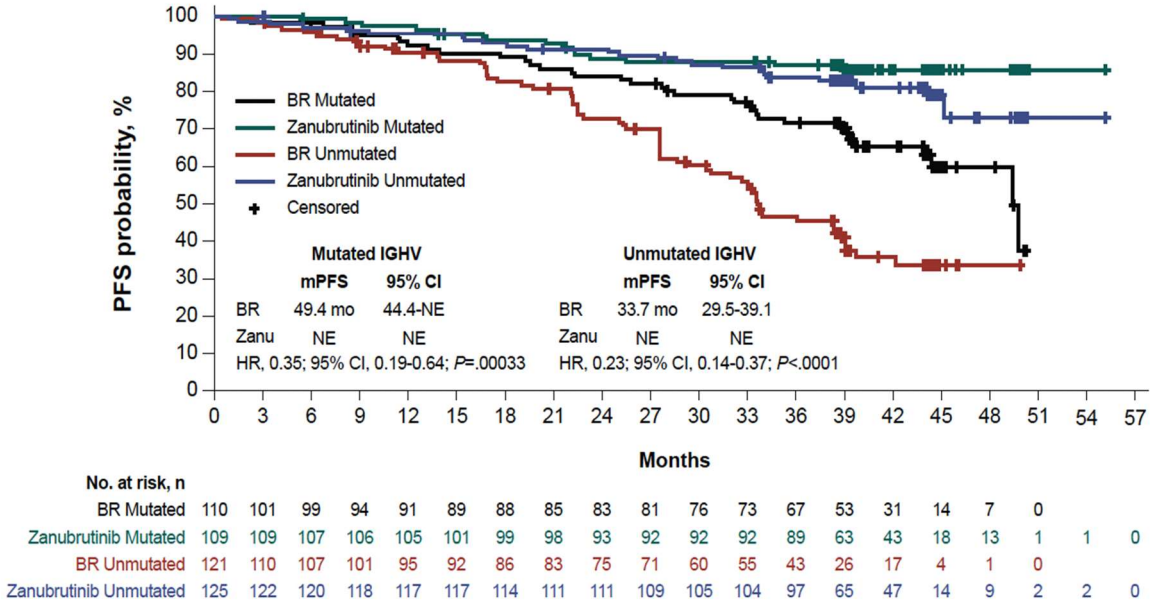


Figure 15. PFS by IRC per IGHV mutational status (DCO: 31st October 2022)[22]

Disease response rates

As of interim analysis (DCO: 7th May 2021):[21]

- The ORR by IRC was higher for patients in the zanubrutinib arm, 94.6%, compared with the BR arm, 85.3%. CR rates were 7% for zanubrutinib and 15% for BR, when assessed by IRC.
- The ORR by investigator was 97.5% for zanubrutinib arm versus 88.7% for BR arm. CR rates were 9% for zanubrutinib and 18% for BR, when assessed by investigator.
- The median duration of response (DOR) by IRC and investigator was not reached for zanubrutinib (for both types of assessment) and for BR was 30·6 months (95% CI: 25.5, NE for IRC and 95% CI: 26.2, NE for investigator assessment).

With >3.5 years of median follow-up (DCO: 31st October 2022), CR/CRi rates were 17.4% for zanubrutinib and 21.8% for BR.[22]

Safety

As of interim analysis (DCO: 7th May 2021),[21] results showed that: (Figure 16)

- Patients treated with zanubrutinib experienced fewer AEs compared to BR:
    - Leading to treatment discontinuations (8% vs. 14%)
    - Serious adverse events (37% vs. 50%)
    - Grade ≥3 (53% vs. 80%)
- Expectedly, two regimens showed distinct safety profiles:
    - Rates of cytopenia were higher in BR arm, as expected for the chemoimmunotherapy regimens
    - Rates of haemorrhage, known AE of BTKi therapy, were higher in zanubrutinib arm.
- Rate of atrial fibrillation of any grade was similar between zanubrutinib and BR

	Group A, zanubrutinib (n=240*)				Group B, bendamustine–rituximab (n=227†)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any	98 (41%)	87 (36%)	28 (12%)	11 (5%)	37 (16%)	88 (39%)	81 (36%)	12 (5%)‡
Serious	16 (7%)	49 (20%)	12 (5%)	11 (5%)	12 (5%)	70 (31%)	19 (8%)	12 (5%)
Common adverse events								
Contusion	46 (19%)	0	0	0	8 (4%)	0	0	0
Upper respiratory tract infection	39 (16%)	2 (1%)	0	0	25 (11%)	2 (1%)	0	0
Diarrhoea	32 (13%)	2 (1%)	0	0	26 (12%)	2 (1%)	0	2 (1%)
Arthralgia	30 (13%)	2 (1%)	0	0	19 (8%)	1 (<1%)	0	0
Neutropenia	10 (4%)	11 (5%)	16 (7%)	0	13 (6%)	50 (22%)	66 (29%)	0
Hypertension	14 (6%)	15 (6%)	0	0	9 (4%)	11 (5%)	0	0
Fatigue	25 (10%)	3 (1%)	0	0	34 (15%)	2 (1%)	0	0
Cough	27 (11%)	0	0	0	23 (10%)	0	0	0
Headache	26 (11%)	0	0	0	17 (7%)	0	0	0
Rash	26 (11%)	0	0	0	38 (17%)	6 (3%)	0	0
Constipation	23 (10%)	1 (<1%)	0	0	43 (19%)	0	0	0
Nausea	24 (10%)	0	0	0	71 (31%)	3 (1%)	0	0
Back pain	21 (9%)	0	0	0	15 (7%)	1 (<1%)	0	0
Pyrexia	17 (7%)	0	0	0	52 (23%)	8 (4%)	0	0
Vomiting	17 (7%)	0	0	0	30 (13%)	3 (1%)	0	0
Pneumonia	8 (3%)	4 (2%)	0	0	9 (4%)	9 (4%)	0	1 (<1%)
Anaemia	10 (4%)	1 (<1%)	0	0	38 (17%)	4 (2%)	0	0
Basal cell carcinoma	10 (4%)	1 (<1%)	0	0	3 (1%)	0	0	0
Thrombocytopenia	5 (2%)	3 (1%)	1 (<1%)	0	14 (6%)	10 (4%)	6 (3%)	0
Infusion-related reaction	1 (<1%)§	0	0	0	37 (16%)	5 (2%)	1 (<1%)	0
All bleeding adverse events¶	99 (41%)	8 (3%)	0	1 (<1%)	21 (9%)	3 (1%)	1 (<1%)	0
All cardiac adverse events¶	24 (10%)	10 (4%)	0	2 (1%)	13 (6%)	9 (4%)	1 (<1%)	1 (<1%)

Figure 16. Treatment and post-treatment AEs (DCO: 7th May 2021)[21]

SEQUOIA (Cohort 2)

With a median follow-up of 30.5 months, the 24-month PFS rate was 88.9% (95% CI: 81.3, 93.6). Estimated 24-month OS was 93.6% (95% CI 87.1–96.9). The ORR was 90.0% (95%CI 82.8–94.9), as assessed by IRC, and 96.4% (95%CI 91.0–99.0), as assessed by investigator.[21]

An extended follow-up of the SEQUOIA study showed that zanubrutinib is also efficacious in the treatment of patients with del(17p) and a safer treatment option for treatment naïve CLL patients compared to BR.[22] Moreover, zanubrutinib showed greater improvement in patients' quality of life compared to BR.

Progression-free survival, overall survival, and disease response rates

With >3.5 years of median follow-up (DCO: 31st October 2022), results showed that: (Figure 17)

- The median PFS was not reached, and the 42-month event-free rate was 79.4%.
- The median OS was not reached, and the 42-month event-free rate was 89.5%.
- The CR/Cri rate was 14.5%.

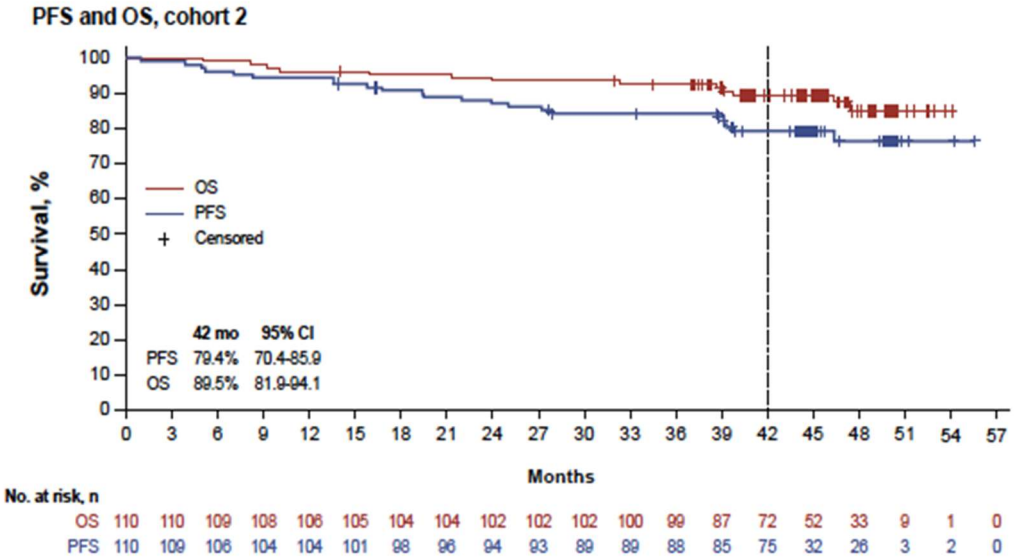


Figure 17. PFS by IRC & OS (DCO: 31st October 2022)[22]

Quality of life

Patient's QoL was measured by EORTC QLQ-C30 and EQ-5D-5L questionnaires. The presented results are from the latest available analysis of QoL (DCO: 7th May 2021).[33] (Figure 18 and Figure 19)

EORTC QLQ-C30

Patients treated with zanubrutinib achieved better improvement in quality of life compared to BR both at week 12 and 24; particularly in global health status, physical and role functions scales, decreased symptoms of fatigue and nausea/vomiting, and diarrhea.

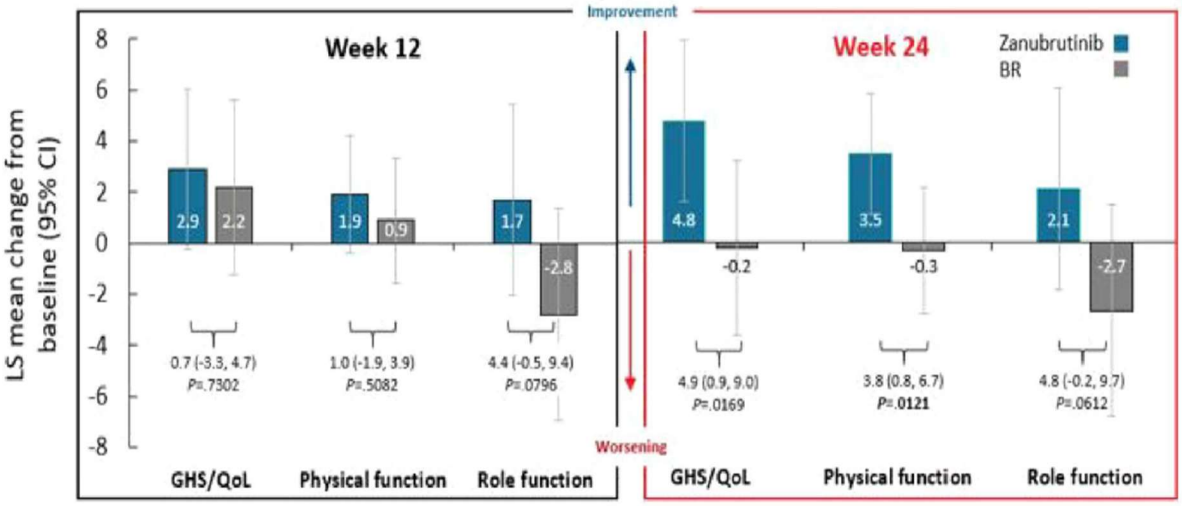


Figure 18. GHS/QoL and Functional Scales. EORTC QLQ-C30 (DCO: 7th May 2021)[33]

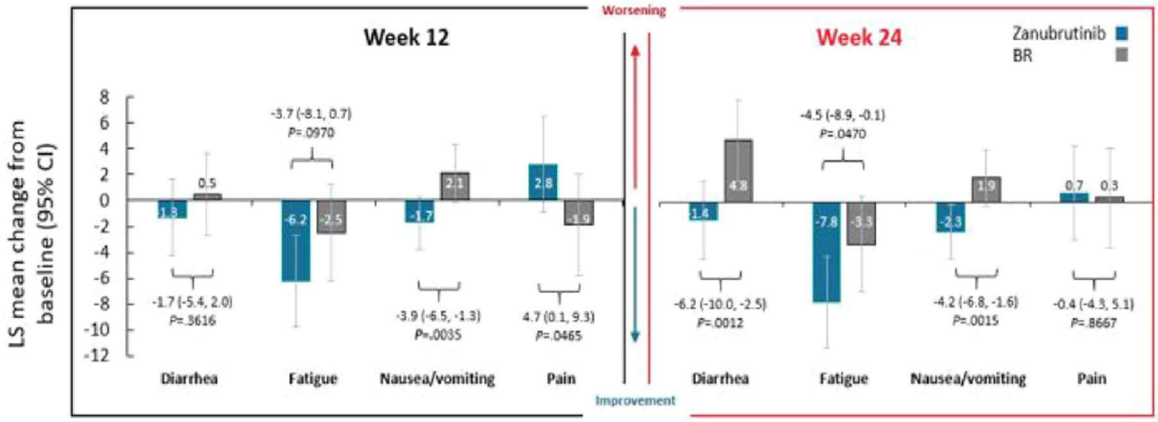


Figure 19. Symptom Scales - EORTC QLQ-C30 (DCO: 7th May 2021)[33]

EQ-5D-5L

Comparable improvement in the EQ-5D-5L VAS scale was observed in the zanubrutinib and BR arms at weeks 12 and 24.

Results from BGB-3111-18-427 (NCT03824483) showed that the most common AEs of any grade were thrombocytopenia (59%), fatigue (54%), neutropenia (51%), bruising (51%), diarrhea (46%), infusion-related reactions (44%), anaemia (41%), cough (36%), rash (33%), and nausea (31%).[3] Grade ≥3 AEs occurring in ≥5% of patients were neutropenia (18%), thrombocytopenia (8%), rash (8%), lung infection (8%), and infusion-related reactions (5%). Nine patients required G-CSF for neutropenia (4 Grade 2 and 5 Grade 3-4). Dose reductions of zanubrutinib were

required in 3 patients due to AEs. Two deaths were reported during the study; 1 was on day 1 of cycle 1 due to intracranial haemorrhage, and the other was on day 25 of cycle 1 due to metastatic adenocarcinoma.

Additional efficacy and safety results were reported after a median of >26 months of study follow-up (range, 4.5-30.5+), with 95% (35/37) of patients having achieved uMRD-FC4 in peripheral blood. Among these patients, 94% (n=33) also achieved MRD by immunosequencing (sensitivity ≤10^{-5}), which was evaluated every 3 months from the end of treatment for median of 12 months (range, 3-18). The most common AEs of any grade were neutropenia (51%), thrombocytopenia (44%), diarrhea (44%), infusion-related reactions (41%), and bruising (41%). The most common Grade ≥3 AE was neutropenia (15%).

8.3.3. BGB-3111-205 (NCT03206918)

A single-arm, open-label, multicentre phase 2 study to evaluate safety and efficacy of zanubrutinib, a BTK inhibitor in R/R CLL or SLL. [34] Secondary objectives were to evaluate the efficacy of zanubrutinib at a dose of 160 mg orally twice daily in patients with R/R CLL or SLL measured by IRC-assessed PFS, duration of response (DOR), time to response, investigator-assessed ORR and to evaluate the safety of zanubrutinib at a dose of 160 mg orally twice daily. Of the 91 evaluable patients, 77 (84.6%) achieved a response, with three (3.3%), 54 (59.3%), and 20 (22%) patients achieving a complete response, partial response, and partial response with lymphocytosis, respectively, after a median follow-up of 15.1 months. The estimated 12-month event-free rate for duration of response was 92.9%. The most commonly reported grade ≥ 3 adverse events (AEs) were neutropenia (44%), thrombocytopenia (15.4%), lung infection/pneumonia (13.2%), upper respiratory tract infection (9.9%), and anemia (8.8%). The 12month overall survival rate was 96%. Eight (9.0%) patients discontinued zanubrutinib due to AEs, and seven (8.0%) patients required at least one dose reduction.

A study reported the final results after extended follow-up and provided an update on the resistance study and exploratory correlative analysis of lymphocytosis on prognostic factors of CLL/SLL. [35] With a median follow-up of 34 months:

Efficacy

- The primary endpoint was overall response rate (ORR; 87.9%, 95% confidence interval [CI] 79.4–93.8%) assessed by an independent review committee (IRC) and defined as the proportion of patients achieving a complete response (CR; 6.6%). A CR with incomplete bone marrow recovery (0%), a partial response (PR; 69.2%), or a PR with lymphocytosis (PRL; 12.1%). The median duration of response assessed by IRC was not reached. The ORR as assessed by the investigator was 92.3%, with 13.2% of patients achieving a CR. The response to treatment increased and deepened over time. (Figure 20A)
- The ORR was generally consistent across all subgroups analyzed, including those with unfavorable prognostic factors. Patients with del(17p) or TP53 mutation and those with IGHV unmutated status achieved high response rates: 90.9% (95% CI 70.8–98.9%) and 88.2% (95% CI 76.195.6%), respectively. All patients harboring del(11q) achieved a response (ORR 100%, 95% CI 83.2–100%) (Figure 20B).
- The median progression-free survival (PFS) assessed by IRC was not reached. The estimated PFS event-free rates by IRC at 24, 30 and 36 months were 80.5% (95% CI 70.5 87.4%), 75.7% (95% CI 65.2 - 83.4%), and 68.1% (95% CI 56.6 - 77.2%), respectively. The PFS curves were comparable among patients carrying unfavorable chromosomal abnormalities versus wild types, including del(17p) or TP53 mutation, del(13q), and del(11q). IGHV unmutated status remained a prognostic factor for patients treated with zanubrutinib (hazard ratio for unmutated versus mutated, 4.63 [95% CI 1.33–29.16]; p ¼ 0.0238 from log-rank test; Figure 20C).
- Median overall survival was not reached. Estimated survival rates at 24, 30 and 36 months were 89.8% (95% CI 81.3 - 94.6%), 88.6% (95% CI 79.8 - 93.7%) and 86.5% (95% CI 76.6 - 92.4%), respectively.

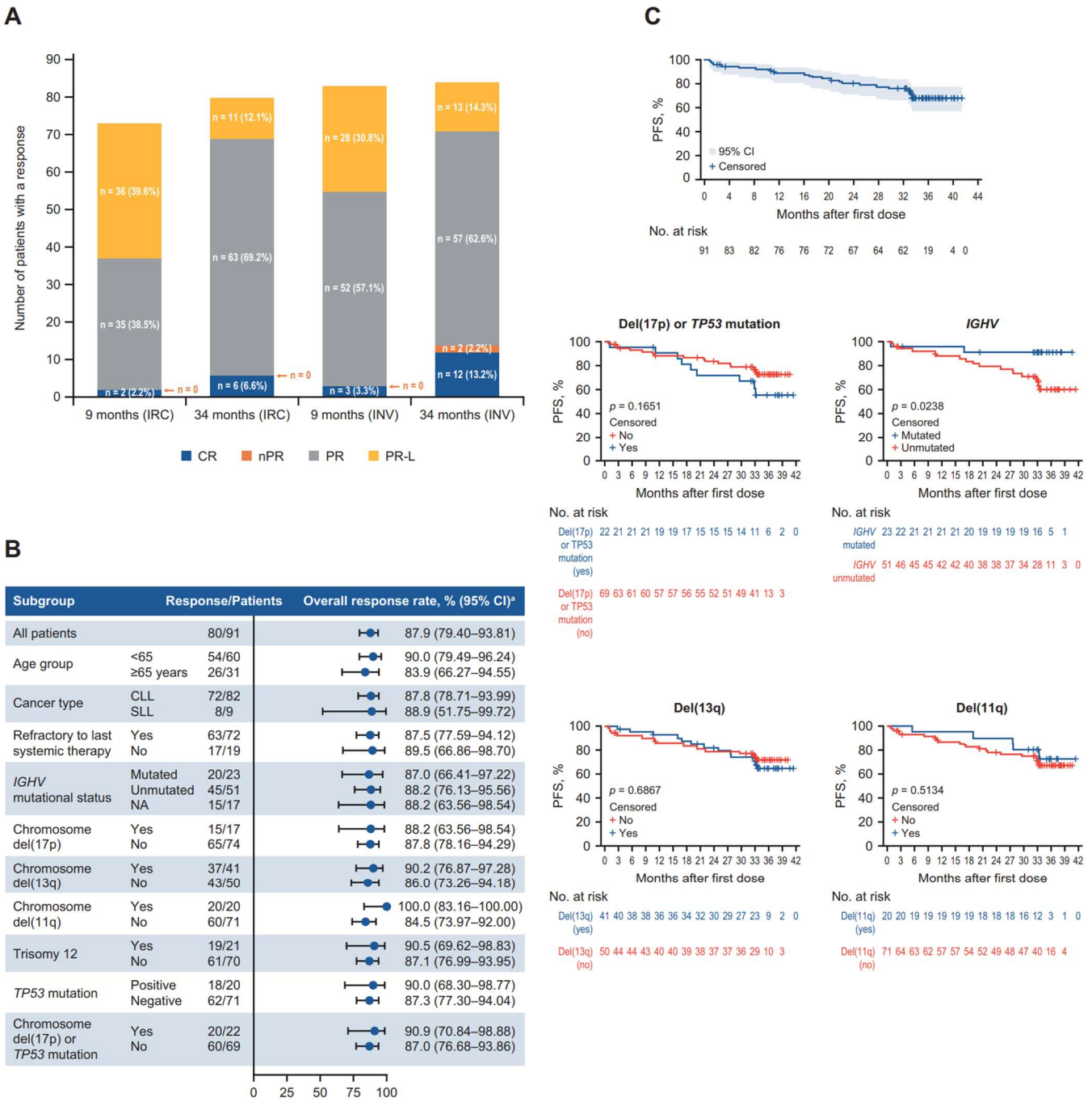
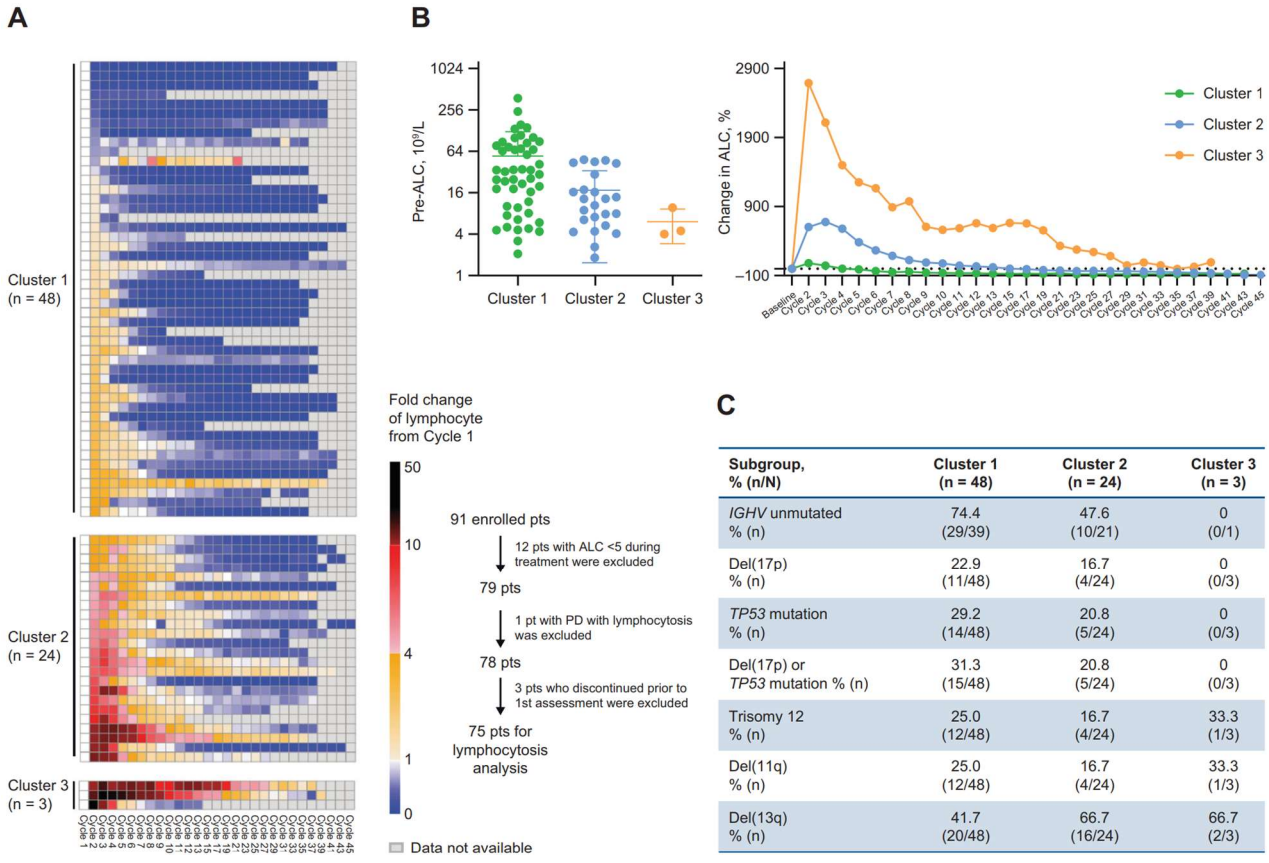


Figure 20. Clinical efficacy outcomes of patients treated with zanubrutinib[35]

(A) Overall response rate assessed by IRC and INV over time. (B) Forest plot of ORR by a predefined subgroup analysis. (C) Kaplan–Meier curves of progression-free survival for the safety population and patients with selected chromosomal abnormalities. For IGHV mutation status, 17 patients were excluded due to the following reasons: three patients with IGHV gene rearrangement undetected, 13 patients with multiclonal IGHV gene rearrangement detected, and one patient with test failed. [a]Two-sided Clopper–Pearson 95% CIs. CI: confidence interval; CLL: chronic lymphocytic leukemia; CR: complete response; IGHV: immunoglobulin heavy chain variable region gene; INV: investigator; IRC: independent review committee; NA: not applicable; nPR: nodular partial response; ORR: overall response rate; PFS: progression-free survival; PR: partial response; PR-L: partial response with lymphocytosis; SLL: small lymphocytic lymphoma.

Toxicity profile

- 75 of 91 (82.4%) patients with absolute lymphocyte count (ALC) ≥5 x 10^9/L during treatment were selected to explore zanubrutinib-induced lymphocytosis patterns using unsupervised cluster analysis and to explore their association with baseline risk factors.
- Three lymphocytosis patterns were identified (Figure 21A). Cluster 1 had higher baseline ALC counts, smaller ALC increases and faster ALC resolution after treatment compared to Clusters 2 and 3 (Figure 21B). Clusters 2 and 3 were characterized by persistent lymphocytosis, tended to have less unfavorable prognostic factors such as IGHV unmutated status, TP53 mutation, and del(17p) (Figure 21C); and did not show inferior PFS compared with Cluster 1



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Subgroup, % (n/N)	Cluster 1 (n = 48)	Cluster 2 (n = 24)	Cluster 3 (n = 3)
IGHV unmutated % (n)	74.4 (29/39)	47.6 (10/21)	0 (0/1)
Del(17p) % (n)	22.9 (11/48)	16.7 (4/24)	0 (0/3)
TP53 mutation % (n)	29.2 (14/48)	20.8 (5/24)	0 (0/3)
Del(17p) or *TP53* mutation % (n)	31.3 (15/48)	20.8 (5/24)	0 (0/3)
Trisomy 12 % (n)	25.0 (12/48)	16.7 (4/24)	33.3 (1/3)
Del(11q) % (n)	25.0 (12/48)	16.7 (4/24)	33.3 (1/3)
Del(13q) % (n)	41.7 (20/48)	66.7 (16/24)	66.7 (2/3)

Figure 21. Zanubrutinib-induced lymphocytosis and association with prognostic factors[35]
(A) Identification of three different lymphocytosis patterns by unsupervised cluster analysis using ALC fold change from baseline. (B) Baseline ALC comparison among three lymphocytosis patterns plotted in mean ± SD (left); and percentage change in ALC over different treatment time periods shown in mean value (right). (C) Comparison of baseline prognostic factors among three lymphocytosis patterns. ALC: absolute lymphocyte count; CLL: chronic lymphocytic leukemia; IGHV: immunoglobulin heavy chain variable region gene; PD: progressive disease; pts: patients; SD: standard deviation; SLL: small lymphocytic lymphoma

- 83.5% of patients had at least one Grade ≥ 3 AE, and 51.6% reported at least one serious AE. Grade ≥ 3 AEs reported in ≥5% of patients included neutrophil count decreased (49.5%); pneumonia (24.2%); upper respiratory tract infection (12.1%); anemia (11.0%); platelet count decreased (8.8%); neutrophil percentage decreased, thrombocytopenia, white blood cell counts decreased and hypokalemia (7.7% each); and hyponatremia (5.5%).
- Second primary malignancies were reported in five patients (two gastric adenocarcinomas; and one each of colon cancer, breast cancer, and rectal cancer). One patient experienced atrial fibrillation (Grade 2). Hypertension was reported in 11 patients (12.1%), including 3.3% Grade 3 events. While minor mucocutaneous bleeding events were relatively common (72.5%), other bleeding AEs observed were all Grade 1 or 2 events. Fourteen (15.4%) patients experienced AEs that led to discontinuation of study drug, most commonly due to pneumonia (n ¼ 4) and hepatitis B (n ¼ 2). Six (6.6%) patients experienced an AE leading to death.

Results with longer follow-up continued to show a high response rate for zanubrutinib. Deep and durable responses were achieved in all patient subgroups, including patients with high-risk prognostic factors and those with prolonged lymphocytosis. Data support the tolerability of long-term zanubrutinib treatment in R/R CLL/SLL patients, with no new safety signals identified. Zanubrutinib may represent an important treatment option for these patients.

8.3.4. BGB-3111-AU-003 (NCT023443120)

A phase I/II, open-label, multiple-dose, dose escalation and expansion study to investigate the safety and pharmacokinetics of the BTK Inhibitor zanubrutinib in patients with B-cell lymphoid malignancies, including TN and R/R CLL/SLL.[36]

The phase I/II AU-003 study in patients with TN/RR CLL/SLL demonstrated that zanubrutinib therapy results in clinically meaningful and durable responses with acceptable safety and tolerability. Updated safety and efficacy data for 123 patients with a median follow-up of 47.2 months were reported. Patients received zanubrutinib 160 mg twice daily (n=81), 320 mg once daily (n=40), or 160 mg once daily (n=2). Discontinuations due to AEs or disease progression were uncommon. The ORR was 95.9% (TN, 100%; R/R, 95%) with 18.7% achieving CR. Ongoing response at 3 years was reported in 85.7% of patients. The ORR in patients with del(17p)/tumour protein p53 mutation was 87.5% (CR 16.7%). The 2- and 3-year PFS estimates were 90% (TN, 90%; R/R, 91%) and 83% (TN, 81%; R/R, 83%) respectively. (Table 3)

Table 3. BGB-3111-AU-003: Efficacy Endpoints in Patients with CLL/SLL

Assessment	TN CLL/SLL N = 22	R/R CLL/SLL N = 101
Overall response, no. (%)	22 (100)	96 (95.0)
Best overall response, no. (%)		
Complete response	5 (22.7)	16 (15.8)
Complete response with incomplete bone marrow recovery	0	2 (2.0)
Partial response	17 (77.3)	72 (71.3)
Partial response with lymphocytosis	0	4 (4.0)
Stable disease	0	4 (4.0)
Discontinued before first assessment, no. (%)	0	1 (1.0)
Event rate remaining in response at 12 months, % (95% CI)	95.2 (70.7-99.3)	97.8 (91.6-99.5)

8.3.5. BGB-3111-215 (NCT04116437)

Safety and tolerability of zanubrutinib can be supported by an ongoing Phase II BGB-3111-215 study in patients with previously treated B-cell malignancies who have become intolerant to ibrutinib or acalabrutinib.[37] 67 patients who were intolerant to ibrutinib (Cohort 1, n=57; CLL, n=38 [67%]; SLL, n=6 [11%]) or to acalabrutinib or acalabrutinib and ibrutinib (Cohort 2, n=10; CLL, n=5 [50%]; SLL, n=1 [10%]) were enrolled and received ≥1 dose of zanubrutinib. The median follow-up was 12 months. (Table 4)

- 70% of ibrutinib- and 83% of acalabrutinib-intolerant AEs did not recur on zanubrutinib.
- 79% of the ibrutinib-intolerant AEs and 33% of acalabrutinib-intolerant AEs that reoccurred on zanubrutinib were of lower severity.

- Among the 64 efficacy-evaluable patients, 60 (93·8%; 95% CI 84·8–98·3) had disease control and 41 (64·1%; 51·1–75·7) had an overall response: 19 (30%) of 64 patients had a best overall response of stable disease and two (3%) patients had a best overall response of progressive disease.

Table 4. Adverse events leading to intolerance, recurrence and severity change of recurrence on zanubrutinib

Previous therapy (N)	Adverse events leading to intolerance, N	Recurrence on zanubrutinib, n (%)		Severity changes of recurrence on zanubrutinib, n (%)	
		No	Yes	Recurred at lower severity	Recurred at same severity
Ibrutinib (57)	115	81 (70)	34 (30)	27 (79)	7 (21)
Acalabrutinib or Acalabrutinib + Ibrutinib (10)	18	15 (83)	2 (22.2)	1 (33)	2 (67)

Note: Adverse events and previous adverse events for ibrutinib and acalabrutinib were evaluated and graded according to the Common Terminology Criteria for Adverse Events version 5.0. In patients with CLL, treatment-emergent cytopenia were graded per IWCLL criteria. Previous ibrutinib-intolerant and acalabrutinib-intolerant AEs were recorded at study entry. An intolerant adverse event was considered to have recurred if the same Medical Dictionary for Regulatory Activities preferred term, independent of grade, occurred while on zanubrutinib therapy.

8.4. Real-world evidence

Treatment switching and sequencing

A study evaluated real-world switching and sequencing to next line of therapy in patients initiating BTKis as first-line (1L) or second-line (2L) CLL/SLL treatment.[38] Using IntegraConnect PrecisionQ to identify adult patients with ≥1 diagnosis for CLL/SLL initiating zanubrutinib, acalabrutinib, or ibrutinib in 1L or 2L between 1/1/2020-2/28/2023 (index period), the study found that a total of 2,816 and 1,253 patients initiated a 1L or 2L BTKi during the period respectively. In 1L, ibrutinib (50.5%) was the most common BTKi followed by acalabrutinib (44.0%) and zanubrutinib (5.6%). In 2L, acalabrutinib (53.6%) was the most commonly utilized BTKi followed by ibrutinib (37.8%) and zanubrutinib (8.54%).

The study showed that median follow-up in 1L was 123 days for zanubrutinib, 406 days for acalabrutinib, and 637 days for ibrutinib. Zanubrutinib patients had significantly lower switching

rate within 90 days and lower proportion of patients receiving next line of therapy at 180 days when compared with acalabrutinib and ibrutinib in 1L and 2L.

Regardless of line of therapy, switching rate at ≤60 days and 61-89 days was statistically significantly lower for patients receiving zanubrutinib vs acalabrutinib and ibrutinib (P<0.0001, both 1L and 2L). (Figure 22) In 1L, the percentage of patients switching before 90 days was lowest for zanubrutinib (10.2%) compared to acalabrutinib (20.5%) and ibrutinib (15.6%). Zanubrutinib also had the lowest switch rate before 90 days (7.5%) compared to 13.2% for acalabrutinib and 21.1% for ibrutinib among 2L patients.

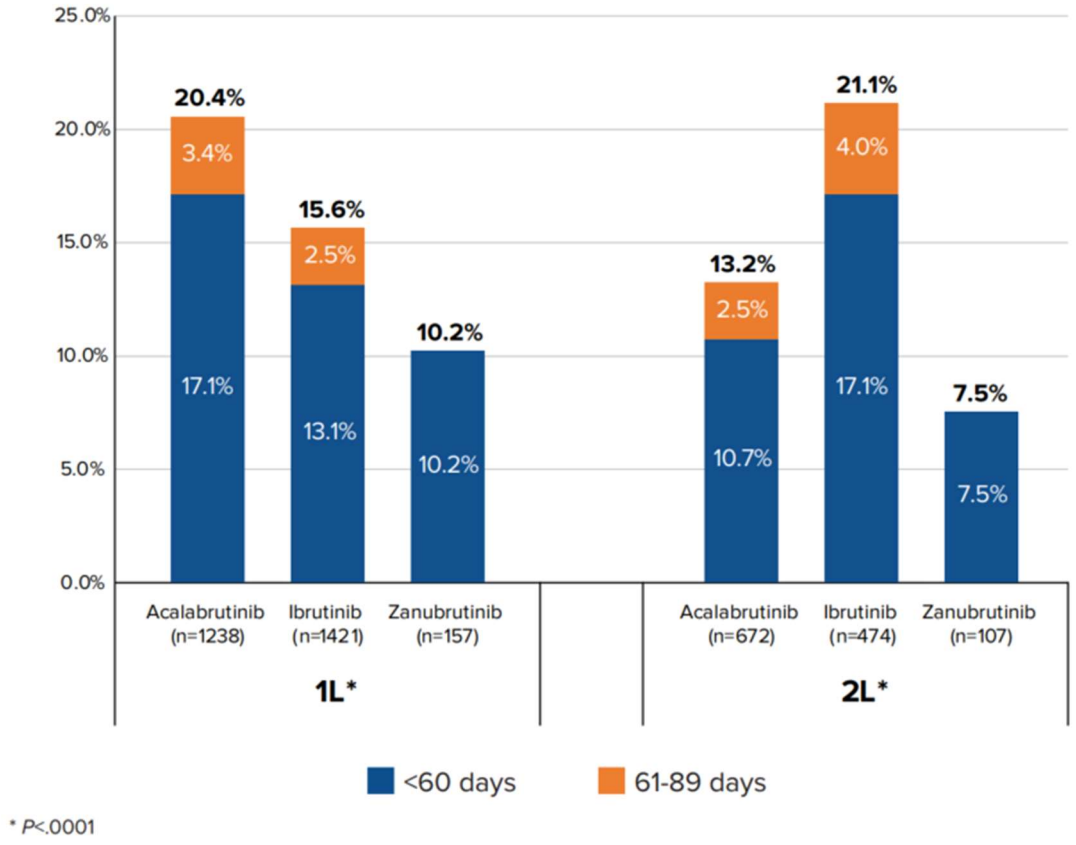

Figure 22. Treatment switching for patients initiating a BTKi in 1L or 2L[38]

The proportion of patients receiving next line of therapy at 180 days was lower for zanubrutinib vs acalabrutinib and ibrutinib (1L *P*=.2958; 2L *P*<.0001). (Figure 23). Among 1L patients, the proportion of receiving the next line of therapy at 180 days was 13.9% for zanubrutinib compared to 24.5% for acalabrutinib and 21.1% for ibrutinib. In 2L, the proportion at 180 days of receiving the next line of therapy was 9.1% for zanubrutinib compared to 18.6% for acalabrutinib and 29.2% for ibrutinib.

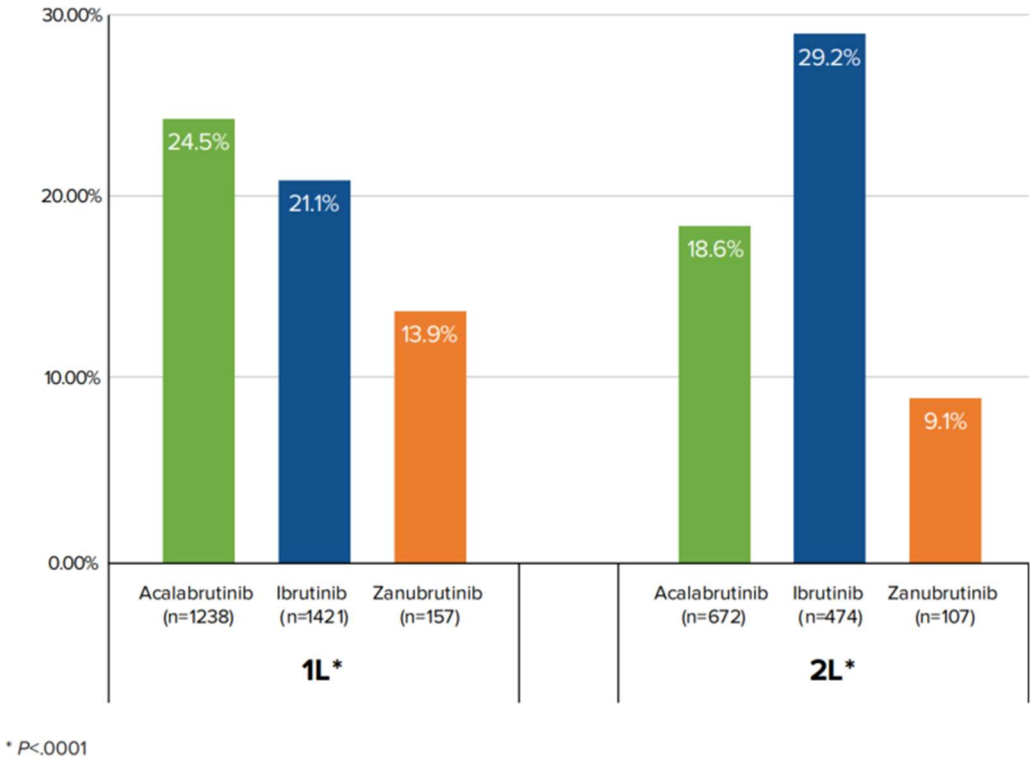

Figure 23. Proportion of Patients Receiving Next Line of Therapy at 180 Days 1L or 2L BTKi[38]

Treatment patterns and outcomes

A study investigated real-world treatment patterns based on a formulary change from ibrutinib to zanubrutinib in patients with CLL/SLL in an integrated community oncology practice.[39] The authors retrospectively analysed CLL/SLL patients 18 years and older who received at least 3 months of zanubrutinib from October 1, 2018, to September 15, 2023 at Kaiser Permanente Northern California. Treatment patterns, treatment-emergent adverse events (TEAEs: AEs reported during BTKi use), treatment-limiting adverse events (TLAEs: AEs leading to BTKi discontinuation), and mortality were reported. Results showed that median follow-up time after initiation of first BTKi was longer in the ibru-zanubrutinib group. (Table 5) Similar TEAE rates were seen with use of both BTKi therapies, with lower TLAE rates with zanubrutinib. Most common TLAE were atrial fibrillation and fatigue for ibrutinib, and cytopenia and rash/bruising for zanubrutinib. Cardiac TLAE and non-TLAE rates overall were higher with ibrutinib than zanubrutinib, and the rates decreased while on zanubrutinib after switching from ibrutinib (Table). In the real-world setting post-formulary change, zanubrutinib is effective and safe in patients with or without prior ibrutinib use. Zanubrutinib use had lower cardiotoxicity and TLAE rates than ibrutinib though data was limited by a difference in follow-up time. Similar results

were seen in zanubrutinib-only patients despite being older and having more comorbidities, with discontinuation most often due to grade <3 AEs.

Table 5. Outcomes from treatment patterns

Outcomes	While on Ibru (n=190)	While on Zanu (n=281)	After IbruZanu Switch (n=190)	After Initiating Zanu Only (n=91)
Median Follow Up, mos. (range)	46(15,115)	23.7(3.3,26)	24.4(5.5,26)	8.2(3.3,25)
Median treatment duration, mos.	20.8(0.2,89)	20.5(3,25)	22.8(3,25)	6.6(3,25)
TEAE, n (%)	69 (36.3)	88 (31.3)	56 (29.5)	32 (35.2)
TLAE, n (%)	21 (11.1)	22 (7.8)	14 (7.4)	8 (8.8)
Cardiotoxicity, n (%)				
TEAE	18 (9.5)	6 (2.1)	5 (2.6)	1 (1.1)
TLAE	8 (4.2)	2 (0.7)	2 (1.1)	0 (0)
CTCAE grade of TLAE ≥3, n (%)	7 (3.6)	4 (1.4)	3 (1.6)	1 (1.1)

Another study exploring the clinical characteristics, treatment patterns, and AEs among BTKi-treated patients with CLL/SLL demonstrated better real-world CLL/SLL safety and effectiveness outcomes for acalabrutinib and zanubrutinib vs ibrutinib.[40] Patient population included adults with CLL/SLL who initiated BTKi treatment between January 1, 2020 – July 31, 2023, with follow-up through October 31, 2023 and patients had ≥5 CLL/SLL visits or more CLL/SLL visits than non-CLL/SLL visits with all patients having ≥2 evaluation and management visits. Outcomes included Cardiovascular AEs, Time-to-next-treatment (TTNT): time from line of therapy (LOT) initiation to initiation of next LOT or death, and Time-to-treatment discontinuation (TTD) or death: time between treatment initiation and treatment discontinuation or death.

7,875 patients initiated 1L, including 2,815 in BTKi and 4,060 in non-BTKi (with 249 initiating BTKi in later lines). More patients experienced cardiovascular AEs when treated with ibrutinib than acalabrutinib or zanubrutinib. The proportions of patients continuing treatment and the median TTNT was longer for patients who received zanubrutinib. Of patients within the first 3 months of follow-up post-BTKi initiation, the rate of cardiac AEs was highest in patients who initiated ibrutinib (8.7%), followed by zanubrutinib (7.4%). (Figure 24) Significantly more patients experienced cardiovascular AEs among those who received 1L ibrutinib vs acalabrutinib or zanubrutinib at month 6 (12.1%, 7.6%, and 7.3%, respectively; $P<.05$) and at month 9 (14.6%, 9.4%, and 8.5%, respectively; $P<.05$).

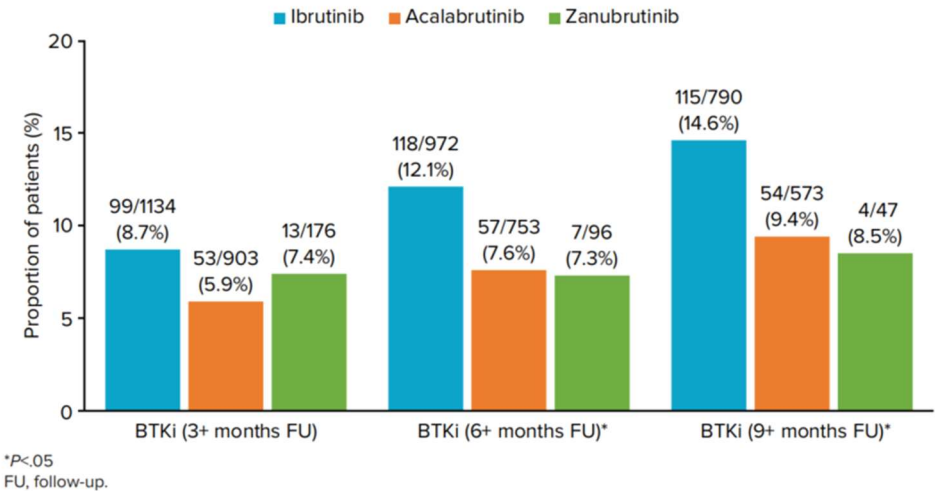

Figure 24. Cardiovascular AEs in the 1L setting[40]

Of patients treated with 1L ibrutinib, 12.7% discontinued ibrutinib and switched to a second-generation BTKi. The median TTD in 1L was shorter for ibrutinib than acalabrutinib and zanubrutinib (the median TTD (95% CI) in the 1L setting was 13.7 (12.2, 16.0) months for ibrutinib, 19.2 (15.1, 25.3) months for acalabrutinib, and 19.3 (14.1, NR) months for zanubrutinib. The associated probability of continuing treatment and not having new treatment were higher with zanubrutinib vs ibrutinib or acalabrutinib at month 6. (Figure 25)

	Overall (n=2815)	Ibrutinib (n=1389)	Acalabrutinib (n=1223)	Zanubrutinib (n=203)
Median duration of follow-up from BTKi initiation, mo	-	20.5 (0.4, 46.0)	14.2 (0.1, 46.0)	6 (1.1, 26.6)
Discontinued/ death, n (%)	1376 (48.9)	775 (55.8)	556 (45.5)	45 (22.2)
Censored, n (%)	1439 (51.1)	614 (44.2)	667 (54.5)	158 (77.8)
Median TTD (95% CI), mo	16.2 (14.4, 19.1)	13.7 (12.2, 16.0)	19.2 (15.1, 25.3)	19.3 (14.1, NR)
Probability of Continuing Same Treatment (95% CI), %				
6 mo	65.9 (64.1, 67.7)	64.8 (62.2, 67.3)	64.8 (62.0, 67.4)	81.6 (75.1, 86.6)
12 mo	56.1 (54.1, 58)	53.3 (50.5, 56.0)	57.7 (54.7, 60.6)	64.1 (51.0, 74.6)
18 mo	49.1 (47, 51.2)	46.2 (43.3, 49.0)	51.2 (48.0, 54.4)	51 (30.5, 68.4)
24 mo	44 (41.7, 46.2)	40.9 (37.9, 43.8)	46.9 (43.3, 50.4)	42.5 (20.6, 62.9)
30 mo	39.8 (37.4, 42.3)	36.5 (33.5, 39.6)	43.9 (39.9, 47.8)	-
36 mo	34.6 (31.6, 37.6)	32.0 (28.6, 35.4)	37.0 (30.6, 43.3)	-
42 mo	32.6 (29.2, 36)	29.8 (26, 33.6)	37.0 (30.6, 43.3)	-

CI, confidence interval; NR, not reached.

Figure 25. Time to treatment discontinuation or death in 1L BTKi[40]

The median TTNT (95% CI) was not reached (16.7, NR) for those who received zanubrutinib in the 1L setting, while it was 35.8 (29.8, NR) months for acalabrutinib and 30.2 (26.2, 35.5) months for ibrutinib. (Figure 26)

	Overall (n=2815)	Ibrutinib (n=1389)	Acalabrutinib (n=1223)	Zanubrutinib (n=203)
Next treatment/ death, n (%)	1111 (39.5)	617 (44.4)	457 (37.4)	37 (18.2)
Median TTNT (95% CI), mo	32.3 (29.1, 36.0)	30.2 (26.2, 35.5)	35.8 (29.8, NR)	NR (16.7, NR)
Probability of No Next Treatment (95% CI), %				
6 mo	74.3 (72.6, 75.9)	75.4 (73, 77.6)	71.3 (68.7, 73.8)	85.3 (79.2, 89.8)
12 mo	67.4 (65.6, 69.2)	67.3 (64.6, 69.7)	66.3 (63.4, 69.0)	75 (64.3, 82.9)
18 mo	60.9 (58.8, 62.8)	60.5 (57.7, 63.2)	60.3 (57.1, 63.3)	63.3 (46.1, 76.3)
24 mo	55.6 (53.4, 57.8)	54.9 (51.9, 57.7)	56.1 (52.6, 59.4)	57 (37.2, 72.6)
30 mo	51.4 (49, 53.8)	50.0 (46.9, 53.1)	53.9 (49.9, 57.6)	-
36 mo	47.1 (44.2, 49.9)	45.8 (42.3, 49.2)	49.2 (43.5, 54.7)	-
42 mo	42 (38.3, 45.5)	39.9 (35.7, 44)	49.2 (43.5, 54.7)	-

1L, first-line; BTKi, Bruton tyrosine kinase inhibitor; CI, confidence interval; NR, not reached; TTNT, time-to-next treatment.

Figure 26. Time to next treatment or death in 1L BTKi[40]

Section 9: Summary of recommendations in current clinical guidelines

The recommended use of zanubrutinib in first-line treatment over other treatments has become more common in international guideline reviews in recent years.

They are Guidelines of the Chinese Society of Clinical Oncology (CSCO) (2022)[41], the guidelines for diagnosis and treatment of CLL/SLL in China (2022)[42], National Comprehensive Cancer Network (NCCN, v1.2025)[43], and European Society for Medical Oncology (ESMO) interim update on new targeted therapies in the first line and at relapse of chronic lymphocytic leukemia (2024)[44] (Table 6).

Table 6. Recommendations in Guidelines for CLL/SLL

Guidelines	Characteristics of CLL/SLL Patients				Grade of Recommendation	
					Zanubrutinib	Ibrutinib
NCCN v1.2025 CLL/SLL	First-line therapy	without del(17p)/TP53 mutation			Preferred	Other recommend*
		with del(17p)/TP53 mutation			Preferred	Other recommend*
	Second-line and subsequent therapy	without del(17p)/TP53 mutation			Preferred	Other recommend*
		with del(17p)/TP53 mutation			Preferred	Other recommend*
CSCO 2022	First-line therapy	without del(17p)/TP53 mutation			Level 1	Level 1
		with del(17p)/TP53 mutation			Level 1	Level 1
	Second-line and subsequent therapy	without del(17p)/TP53 mutation			Level 1	Level 1
		with del(17p)/TP53 mutation			Level 1	Level 1
The guidelines for diagnosis and treatment of CLL/SLL in China (2022)	First-line therapy	without del(17p)/TP53 mutation			Priority	Priority
		with del(17p)/TP53 mutation			Priority	Priority
	Second-line and subsequent therapy	without del(17p)/TP53 mutation			Priority	Priority
		with del(17p)/TP53 mutation			Priority	Priority
ESMO Clinical Practice	First-line therapy	IGHV-mutated	without del(17p)/TP53 mutation	Fit or younger patients	III, A	I, A

Guidelines	Characteristics of CLL/SLL Patients			Grade of Recommendation	
				Zanubrutinib	Ibrutinib
Guideline (2024)			Unfit or older patients	I, A	I, A**
		IGHV-unmutated	without del(17p)/TP53 mutation	Fit or younger patients	III, A	I, A
				Unfit or older patients	I, A	I, A**
		with del(17p)/TP53 mutation			III, A	I, A**
	Second-line and subsequent therapy	Relapse after CIT or late relapse (≥36 months) after venetoclax-based, time-limited Tx and no TP53 mutation or del(17p)			I, A	I, B**
		Early relapse (<36 months) after venetoclax-based, time-limited TX			II, B	II, B**
		Progression on a BTKi			III, A	III, A
		TP53 mutation or del(17p)			I, A	I, A**

* Includes Ibrutinib + Venetoclax as category 2B (other recommended regiments)

** Ibrutinib should be considered carefully in older patients with cardiac comorbidities. See **Appendix 3** for explanation of the classification system.

Section 10: Summary of available data on comparative cost and cost-effectiveness

10.1. Medicine prices in different markets

BeiGene is committed to expanding access to its innovative medicines globally, striving to reach patients in diverse settings with affordable, impactful treatments. We actively develop long-term strategies to support sustainable access and are open to collaborations with organizations like the WHO and other global health leaders to ensure more patients, especially those in underserved regions, can benefit from our therapies.

10.2. Economic evaluation studies

Search strategies

Pubmed

Date: 9th September 2024

Search number	Query	Search Details
1	"zanubrutinib"[Supplementary Concept]	"zanubrutinib"[Supplementary Concept]
2	"leukemia, lymphocytic, chronic, b cell"[MeSH Terms]	"leukemia, lymphocytic, chronic, b cell"[MeSH Terms]
3	"Costs and Cost Analysis"[Mesh]	"Costs and Cost Analysis"[MeSH Terms]
4	"Cost-Benefit Analysis"[Mesh]	"Cost-Benefit Analysis"[MeSH Terms]
5	"cost effectiveness analysis"[MeSH Terms]	“cost-effectiveness[MeSH Terms]”
6	(("zanubrutinib"[Supplementary Concept]) AND ("leukemia, lymphocytic, chronic, b cell"[MeSH Terms])) AND ("Costs and Cost Analysis"[Mesh])	"zanubrutinib"[Supplementary Concept] AND "leukemia, lymphocytic, chronic, b cell"[MeSH Terms] AND "Costs and Cost Analysis"[MeSH Terms]
7	(("zanubrutinib"[Supplementary Concept]) AND ("leukemia, lymphocytic, chronic, b cell"[MeSH Terms])) AND	"zanubrutinib"[Supplementary Concept] AND "leukemia, lymphocytic, chronic, b cell"[MeSH Terms] AND "Cost-Benefit Analysis"[MeSH Terms]

Search number	Query	Search Details
	("Cost-Benefit Analysis"[Mesh]) - Schema: all	
8	((zanubrutinib[Supplementary Concept]) AND (leukemia, lymphocytic, chronic, b cell[MeSH Terms])) AND (cost-effectiveness[MeSH Terms])	"zanubrutinib"[Supplementary Concept] AND "leukemia, lymphocytic, chronic, b cell"[MeSH Terms] AND "cost effectiveness analysis"[MeSH Terms]

Scopus

Date: 9th September 2024

Search terms: (TITLE-ABS-KEY (zanubrutinib) AND TITLE-ABS-KEY (cost*) OR TITLE-ABS-KEY (budget) OR TITLE-ABS-KEY (economic AND evaluation))

Included studies

There are six studies in total, including 1 cost-utility analysis, 1 cost-minimisation analysis, and 1 cost-effectiveness analysis, 1 number needed to treat and cost saving analysis. (A summary of these results is presented in **Appendix 4**). Two budget impact analyses were also included.

A cost-utility analysis (CUA) was developed based on a partitioned survival model (PSM) with 3 mutually exclusive health-states (progression-free, progressive disease and death) to assess the cost effectiveness of zanubrutinib versus ibrutinib for the treatment of R/R CLL from the commercial US payer perspective in the horizon of 10-years.[45] The model was developed based on survival curves from the phase III ALPINE trial.

Zanubrutinib is likely to be cost effective versus ibrutinib in relapsed or refractory chronic lymphocytic leukemia in the USA. Zanubrutinib is associated with a gain of 0.528 life-years and of 0.399 quality-adjusted life-years versus ibrutinib. (Table 7) Over a 10-year analysis period, the incremental cost-effectiveness ratio of zanubrutinib versus ibrutinib was $91,260 per life-year gained and $120,634 per quality-adjusted life-year gained, making it cost effective within a

threshold of $150,000 per quality-adjusted life-year gained. The incremental cost-effectiveness ratio was most sensitive to drug acquisition costs and progression-free survival distributions, and the probability of zanubrutinib being cost effective was approximately 52.8%, with a 30.0% likelihood of dominance.

Table 7. Cost-effectiveness results of zanubrutinib vs ibrutinib[45]

	Zanubrutinib	Ibrutinib	Difference
Total LYs	6.605	6.077	0.528
LYs in progression-free	3.360	2.773	0.587
LYs in progressed	3.245	3.305	− 0.060
Total QALYs	4.389	3.990	0.399
QALYs in progression-free	2.442	2.007	0.435
QALYs in progressed	1.947	1.983	− 0.036
Total costs ($)	1,012,752	964,581	48,171
Drug acquisition costs	707,879	671,915	35,963
Pre-progression costs	102,443	84,534	17,909
Post-progression costs	187,266	190,704	− 3438
Adverse event costs	5381	5560	− 179
Terminal care costs	9784	11,868	− 2084
Incremental cost per LY gained ($/LY)	91,260		
Incremental cost per QALY gained ($/QALY)	120,634		

LY life-year, *QALY* quality-adjusted life-year

A cost-minimisation analysis was conducted to characterize the costs associated with BTKi monotherapies (zanubrutinib, acalabrutinib, and ibrutinib) for the treatment of adults with R/R CLL.[46] The CMA was performed using a 3- health-state (progression free, progressive disease, death) partitioned survival model with a United Kingdom National Health Service payer perspective in the horizon of 30-years. The model was developed based on the assumption of equal efficacy of zanubrutinib to ibrutinib and acalabrutinib.

Over a lifetime horizon, treatment with zanubrutinib in adults with R/R CLL was associated with cost savings of £7,802 per person versus acalabrutinib and an incremental cost of £19,677 per person versus ibrutinib. (Table 8) Treatment with acalabrutinib was associated with an incremental cost of £27,478 per person versus ibrutinib. Difference in treatment acquisition costs was the key reason for the cost differential between treatments. Zanubrutinib was associated with fewer AE management costs compared with acalabrutinib and ibrutinib, due to an improved safety profile. Under this CMA approach, zanubrutinib was less costly than another second-generation BTKi, acalabrutinib. Zanubrutinib was slightly more costly than the first-generation BTKi, ibrutinib.

Table 8. Cost-minimisation results of Zanubrutinib, ibrutinib, and acalabrutinib

Input, £	Zanubrutinib	Ibrutinib	Acalabrutinib
Deterministic results			
Drug acquisition	294,529	274,830	302,319
AE management	286	309	298
Total costs	294,815	275,139	302,617
Incremental costs	–	19,677	−7,802
Probabilistic results			
Incremental costs, mean (95% CI)	–	19,868 (14,162 to 26,661)	−7876 (−10,603 to −5630)

A Markov model-based cost-effectiveness analysis compared the cost-effectiveness of zanubrutinib and ibrutinib for managing relapsed and refractory chronic lymphocytic leukemia in China and the US. It used Markov models to compare the drugs based on cost, quality-adjusted life years, and the incremental cost-effectiveness ratio.[47]

For Chinese payers, zanubrutinib exhibited superior cost-effectiveness compared to ibrutinib. Zanubrutinib also proved to be a more affordable option for US payers when considering the payment threshold. The zanubrutinib group incurred an incremental cost per patient of $-24,586.53 compared to the ibrutinib group. (Table 9) The zanubrutinib group exhibited an incremental utility per capita of 0.28 quality-adjusted life years, resulting in an incremental cost-effectiveness ratio of $-88,068.16 per quality-adjusted life year, which is lower than the payment threshold in China. The willingness-to-pay value in China for 2022 was three times the country's gross domestic product per capita. *In the US*, patients in the zanubrutinib group experienced per capita incremental costs of $-79,421.56, per capita incremental utility of 0.28 quality-adjusted life years, and an incremental cost-effectiveness ratio of $-284,485.45 per quality-adjusted life year.

Table 9. Results of Markov models

	China		US	
	Zanubrutinib	**Ibrutinib**	**Zanubrutinib**	**Ibrutinib**
Cost per capita/$	208,500.15	233,086.68	1,794,023.64	1,873,445.20
Incremental cost per capita/$	-24,586.53	–	−79,421.56	–
Per capita utility/QALY	4.47	4.19	4.47	4.19
Incremental utility per capita/QALYs	0.28	–	0.28	–
ICER/($/QALY)	-88,068.16	–	−284,485.45	–

A study compared zanubrutinib versus ibrutinib in R/R CLL by calculating the number needed to treat (NNT) to avoid one progression or death and associated incremental costs.[48] The base-case results from the NNT model showed that for every 8 patients treated with zanubrutinib, 1 event of progression or death would be avoided compared to using ibrutinib. The total costs per patient treated with zanubrutinib and ibrutinib are $370,558 and $430,150, respectively, with a cost savings of $59,593 associated with using zanubrutinib (Table 10). The NNT model suggests that using zanubrutinib to treat R/R CLL patients, compared to ibrutinib, will result in more favourable clinical and economic outcomes in the US.

Table 10. Number needed to treat to avoid one progression or death and cost difference in a 24-months' time horizon (base-case results)

	24-Month PFS	Total Cost per Treated Patient
zanubrutinib	79.5%	$370,558
ibrutinib	67.3%	$430,150
Results	**Number Needed to Treat with zanubrutinib**	**Cost Savings with zanubrutinib**
	8 patients	$59,593

10.3. Budget impact analysis

A budget impact analysis (BIA) was conducted to estimate the incremental costs associated with using zanubrutinib in R/R CLL/SLL patients from the US payer perspective.[49] Results from the economic analysis suggested that providing access to zanubrutinib for patients with R/R CLL/SLL is associated with cost savings to a US health plan. The model analysis compared a reference scenario with the "current market mix" (i.e., before the introduction of zanubrutinib) and an alternative scenario with a "revised market mix" where the uptake of zanubrutinib was included (i.e., after zanubrutinib entry). The base-case analysis of a hypothetical one-million-member health plan in which two patients were estimated to have R/R CLL/SLL and initiated treatment showed that total healthcare costs were $412K with zanubrutinib and $414K without, suggesting that adding zanubrutinib is associated with a cost-saving of $2,031 over 1 year (Per-member-per-month PMPM <-$0.001; Per-treated-member-per-month: -$88). One-way sensitivity analysis results showed that the budget impact on healthcare costs over a one-year time horizon were most sensitive to zanubrutinib wholesale acquisition cost.

Another BIA was developed to estimate the incremental costs associated with using zanubrutinib in the population from the US commercial and Medicare perspectives, for patients with T/N CLL/SLL.[50] The budget impact analysis suggests that providing access to zanubrutinib for patients with TN CLL/SLL is associated with cost savings in a US health plan. In a hypothetical health plan with 1,000,000 members, 31 patients were estimated to receive active treatment each year for TN CLL/SLL. Over a three-year time-horizon, the overall budget impact was a reduction of $82,437, representing a 0.22% cost-saving with the use of zanubrutinib. Total healthcare costs were $37.75m with zanubrutinib and $37.83m without. The expected average per-member-per-month budget reduction was $0.002. Deterministic sensitivity analysis indicated that drug costs, payer perspective and treatment duration had the greatest impact on the financial budget of healthcare costs estimated over a three-year time horizon.

Section 11: Regulatory status, market availability and pharmacopoeial standards

11.1. Regulatory status of the proposed medicine(s)

As of September 18th, 2024, zanubrutinib was approved in more than 70 markets. Currently, around 40 health authorities representing 40 countries/jurisdictions have approved the use of zanubrutinib for R/R and T/N CLL/CLL across the world. (Table 11 – filtered by year and income

group) Majority of these jurisdictions are from high-income settings, followed by upper-middle income and lower-income settings.

Table 11. List of countries/jurisdictions approving BRUKINSA for CLL/SLL treatment by income group

No.	Approval year	Country/Jurisdiction	Income group by World Bank	Indication (both = R/R and T/N)	Health Authority
1	2024	Bahrain	High income	both	NHRA
2	2024	New Zealand	High income	both	Medsafe
3	2024	Panama	High income	both	N/A
4	2024	Saudi Arabia	High income	both	MoH
5	2024	Egypt	Lower-middle income	both	EDA
6	2024	Nicaragua	Lower-middle income	both	ANRS
7	2024	Brazil	Upper-middle income	both	ANVISA
8	2024	Dominican Republic	Upper-middle income	both	DIGEMAPS
9	2024	Guatemala	Upper-middle income	both	MSPAS
10	2024	Serbia	Upper-middle income	both	ALIMS
11	2024	South Africa	Upper-middle income	both	SAHPRA
12	2024	Thailand	Upper-middle income	both	Thai FDA
13	2023	Australia	High income	both	TGA
14	2023	Canada	High income	both	Health Canada
15	2023	Chile	High income	both	ISP
16	2023	Great Britain	High income	both	MHRA
17	2023	Hong Kong	High income	both	DoH
18	2023	Israel	High income	both	Ministry of Health of Israel
19	2023	Kuwait	High income	both	Ministry of Health
20	2023	Liechtenstein	High income	R/R	National Administration, Office of Public Health
21	2023	Macao	High income	both	ISAF
22	2023	Oman	High income	both	Ministry of Health Sultanate of Oman
23	2023	Qatar	High income	both	Ministry of public health Qatar
24	2023	Singapore	High income	both	HSA

No.	Approval year	Country/Jurisdiction	Income group by World Bank	Indication (both = R/R and T/N)	Health Authority
25	2023	South Korea	High income	both	MFDS
26	2023	Switzerland	High income	R/R	Swissmedic
27	2023	Taiwan	High income	both	Taiwan FDA
28	2023	UAE	High income	both	Health Authority Abu Dhabi
29	2023	United States	High income	both	FDA
30	2023	Uruguay	High income	both	MSP
31	2023	Honduras	Lower-middle income	both	Health Regulatory Agency
32	2023	Argentina	Upper-middle income	both	ANMAT
33	2023	Ecuador	Upper-middle income	both	ARCSA
34	2023	El Salvador	Upper-middle income	both	Superintendence of Health Regulation
35	2023	Mexico	Upper-middle income	both	COFEPRIS
36	2023	Peru	Upper-middle income	both	DIGEMID
37	2022	European Union*	High income	both	EMA
38	2022	Iceland	High income	both	Icelandic medicines Agency
39	2022	Norway	High income	both	Norway Medicines Agency
40	2020	China	Upper-middle income	both	NMPA

*Applicable for Denmark, Ireland, Belgium, Italy, Netherlands, Spain, Germany

11.2. Market availability of the proposed medicine(s):

BeiGene's vision is to transform the biotechnology industry by creating impactful medicines that are affordable and accessible to far more cancer patients around the world. Our mission is to build the first next-generation oncology company—one that expands the highest quality therapies to more people globally through courage, persistent innovation, and challenging the status quo. With a geographically diverse, state-of-the-art supply chain and manufacturing facilities operating under GMP standards from the U.S. FDA, China's NMPA, and Europe's EMA, BeiGene is positioned to achieve these ambitious goals.

Our global clinical trials span diverse geographies and patient populations, employing advanced technologies and strategic operations to increase access in previously underserved regions.

BeiGene's commitment to affordability means our medicines are competitively priced, with considerations for middle- and low-income countries, ensuring that more patients worldwide benefit from our high-quality, life-changing treatments.

Patent information

World Intellectual Property Organization (WIPO): Valid

United States Patent: Valid

European Patent: Valid

Japanese Patent: Valid

Chinese Patent: Valid

WHO List of Prequalified Finished Pharmaceutical Products: No

11.3. Pharmacopoieal standards

International Pharmacopoeia: No

British Pharmacopoeia: No

European Pharmacopoeia: No

United States Pharmacopoeia: No

Appendix

Appendix 1. Summary of new evidence since the 2023 WHO EML submission for zanubrutinib

In the 24th WHO Expert Committee review (2023), it was noted that a lack of survival advantage and safety signals required further data, along with longer follow-up on OS, PFS, toxicity, and cost-effectiveness. Since then, the evidence base has matured. Appendix 1 compiles all new evidence generated since the previous submission of zanubrutinib for the 2023 WHO Model List of Essential Medicines.

Note: While median overall survival has not been reached in new studies, it is worth noting that relatively indolent conditions such as CLL are characterized by a very long median PFS or OS, as indicated in the ESMO-Magnitude of Clinical Benefit Scale for haematological malignancies.[51]

Article Title (year)	New Evidence
	EVIDENCE FOR BENEFITS AND HARMS
Systematic reviews	

Safety profile of first-line targeted therapies in elderly and/or comorbid chronic lymphocytic leukemia patients (unfit subpopulation). A systematic review and network meta-analysis[25] (2024)	Systematic literature review and a Bayesian network meta-analysis (NMA) of the relative safety profile of first-line targeted therapies in CLL patients with advanced age and/or comorbidities. **AEs leading to treatment discontinuation** Ibrutinib+Venetoclax therapy was associated with the highest risk of AEs leading to treatment discontinuation compared with other (evaluated) targeted therapies, i.e., zanubrutinib (16.5 [2.73; 153.68]), acalabrutinib (12.56 [2.58, 102.7]), chlorambucil + Obinutuzumab (6.93 [1.69, 51.72]), acalabrutinib + Obinutuzumab (9.62 [2.02, 78.15]), and Venetoclax + Obinutuzumab (6.67 [1.46, 52.55]), while no significant differences were found between the remaining targeted therapies. Zanubrutinib had the highest probability of being the safest therapeutic option in this area (SUCRA: 86 %). **Grade ≥3 AEs** Grade ≥3 AEs were generally significantly more frequent in groups treated with combined therapies such as venetoclax + Obinutuzumab, acalabrutinib + Obinutuzumab, Ibrutinib + Obinutuzumab, and Ibrutinib+Venetoclax than in monotherapy groups, especially those on second-generation BTK inhibitors like zanubrutinib or acalabrutinib. Zanubrutinib ranked the highest among the evaluated targeted therapies (SUCRA: 98 %). **Serious AEs** Serious AEs grade 1–5 were significantly less frequent in the case of zanubrutinib therapy as compared with other targeted therapies, such as Ibrutinib (0.35 [0.20, 0.59]), acalabrutinib (0.38 [0.17, 0.85]), ibrutinib + obinutuzumab (0.25 [0.11, 0.57]), ibrutinib +

Article Title (year)	New Evidence
	rituximab (0.39 [0.22, 0.67]), ibrutinib + venetoclax (0.28 [0.12, 0.66]), and acalabrutinib + obinutuzumab (0.28 [0.13, 0.62]), but there were no significant differences between zanubrutinib and chlorambucil + obinutuzumab, chlorambucil + ofatumumab or venetoclax + obinutuzumab. Zanubrutinib achieved the highest rank in the SUCRA ranking by 95 %. **Hematological AEs (Anemia)** The most frequently reported hematological AEs for targeted therapies were anemia. Anemia grade 1–5 was significantly less frequent in the case of zanubrutinib therapy than for other treatment options (SUCRA: 92%), such as chlorambucil + obinutuzumab (0.35 [0.12, 0.98]) and acalabrutinib (0.28 [0.08, 0.96]). There were no significant differences between any other individual regimens. Although there were no significant differences between assessed targeted therapies in terms of anemia grade ≥3, zanubrutinib achieved the highest SUCRA value of 86%.
Comparison of treatment-emergent adverse events of acalabrutinib and zanubrutinib in clinical trials in B-cell malignancies: a systematic review and meta-analysis[29] (2023)	A systematic review and meta-analysis analyzed and compared treatment-emergent adverse events of ibrutinib, acalabrutinib, and zanubrutinib reported in clinical trials in different B-cell malignancies including CLL/SLL. A novel Bayesian hierarchical model was developed to jointly estimate the incidence probabilities of different grades of AE and the relative risks (RR) between treatments. Results from this meta-analysis show an improved AE profile with acalabrutinib and zanubrutinib compared to ibrutinib. In addition, these data – for the first time – provide a comprehensive comparison of AE between zanubrutinib and acalabrutinib, which will

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	inform clinicians' choice between these highly effective second-generation BTKi treatments for patients with B-cell malignancies. **Treatment-emergent adverse events of all grades** • Compared with ibrutinib, the average incidence of all grade AE was lower with zanubrutinib (RR=0.83, 95% CrI=0.71-0.93). • Zanubrutinib and acalabrutinib had similar average incidences of all grade AE (RR=1.12, 95% CrI=0.91-1.37). All grade AE that occurred more frequently with acalabrutinib relative to zanubrutinib included atrial fibrillation (RR=0.51), infections (RR=0.53), pyrexia (RR=0.59), cough (RR=0.71), fatigue (RR=0.61), nausea (RR=0.63), vomiting (RR=0.71), diarrhea (RR=0.52), myalgias (RR=0.49), headaches (RR=0.32), and dizziness (RR=0.63). **Treatment-emergent adverse events of grade ≥3** • Compared with ibrutinib, the average incidence of grade ≥3 AE was also lower with zanubrutinib (RR=0.78, 95% CrI=0.47-1.02). • Zanubrutinib and acalabrutinib had similar average incidences of grade ≥3 AE (RR=0.90, 95% CrI=0.54-1.37). Grade ≥3 AE that occurred more frequently with acalabrutinib included anemia (RR=0.58), infections (RR=0.76), and rash (RR=0.03).

Article Title (year)	New Evidence
Efficacy and safety of new-generation Bruton tyrosine kinase inhibitors in chronic lymphocytic leukemia/small lymphocytic lymphoma: a systematic review and meta-analysis[30] (2024)	A systematic review and meta-analysis evaluated the efficacy and safety of new-generation BTKi-based regimens for the treatment of patients with CLL/SLL. The meta-analysis included 15 records for a total of 2,066 CLL/SLL patients, across ten single-arm studies and five randomized studies. These studies involving patients treated with new-generation BTKi (acalabrutinib, zanubrutinib, orelabrutinib, or tirabrutinib), both as single-agent therapy and in combination with other agents). **1. Efficacy: survival** The pooled 24-month **OS rate** for CLL patients treated with BTKi was 94% (95% CI, 92–97%, I2 = 51.32%, P = 0.06. Sub-group analysis for the acalabrutinib monotherapy and zanubrutinib monotherapy showed a pooled 24-month OS rate of 92% (95% CI, 89–96%, I2 = 0.00%) and 95% (95% CI, 92–96%, I2 = 0.00%, P = 0.72), respectively. Also, sub-group analysis for these two therapies showed a pooled 24-month PFS rate of 83% for acalabrutinib (95% CI, 75–90%, I2 = 57.74%, P = 0.05) and 86% for zanubrutinib (95% CI, 80–91%, I2 = 77.84%, P = 0.00).[30] Sub-group analysis also showed that the **ORR and CR rates** from acalabrutinib monotherapy for CLL were 87% and 3%, respectively, while zanubrutinib monotherapy showed OR and CR rates of 93% and 13%, respectively. Zanubrutinib monotherapy yielded higher efficacy than acalabrutinib monotherapy, indicating that zanubrutinib may be the first choice in monotherapy for CLL compared to acalabrutinib, with more head-to-head RCTs being still in need. **2. Safety**

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	The pooled rates of grade ≥ 3 neutropenia, anaemia, and thrombocytopenia in acalabrutinib monotherapy were 14%, 7%, and 5%, respectively. The pooled rates of grade ≥ 3 neutropenia, anemia, and thrombocytopenia in zanubrutinib monotherapy were 19%, 2%, and 4%, respectively. Zanubrutinib monotherapy had a similar pooled rate of grade ≥ 3 upper respiratory tract infection (2% vs. 1%), and grade ≥ 3 hypertension (6% vs. 4%) compared to acalabrutinib monotherapy.
Randomised Controlled Trials	
ALPINE: BGB-3111-305 (NCT03734016) Sustained Benefit of Zanubrutinib vs Ibrutinib in Patients With R/R CLL/SLL: Final Comparative Analysis of ALPINE[24] (2024) Toxicity, Progression-Free Survival, and Quality of Life of Patients Treated with Zanubrutinib Versus Ibrutinib: A Q-TWiST Analysis from the ALPINE Study in Relapsed or Refractory Chronic Lymphocytic Leukemia[32] (2023)	**1. Efficacy** With 42.5 months of median follow-up:[24] • Zanubrutinib **PFS** benefit was sustained over ibrutinib (HR: 0.68 [95% CI, 0.54-0.84]; Figure 6A); the 36-month PFS rate was 65.4% in the zanubrutinib treatment arm and 54.4% in the ibrutinib treatment arm. • Improvement in **PFS** of zanubrutinib over ibrutinib was sustained in high-risk patients with del(17p)/TP53mut (HR: 0.51 [95% CI, 0.33-0.78]; as well as in patients without del(17p)/TP53 mut (HR: 0.79 [95% CI, 0.61-1.02]). • Across most other major subgroups, **PFS** improvement with zanubrutinib was also maintained, including by prior lines of therapy. • Zanubrutinib's **PFS** benefit over ibrutinib remained consistent across multiple sensitivity analyses, including assessment of progression and death events that occurred only while patients remained on active treatment (HR: 0.72 [95% CI, 0.54-

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	0.97]), and when censoring for deaths attributed to COVID-19 (HR: 0.66 [95% CI, 0.52-0.84]). The 36-month PFS rates for zanubrutinib and ibrutinib in these sensitivity analyses were 78.7% and 71.5% (active treatment) and 69.4% and 57.8% (COVID-19), respectively. • **ORR** remained higher with zanubrutinib compared with ibrutinib (85.6% vs 75.4%; RR: 1.13 [95% CI, 1.05-1.22]); the rate of PR with lymphocytosis or better was 90.2% vs 82.8%, respectively.[24] While clinical responses deepened in both arms over time, zanubrutinib-treated patients reached **CR/CRi** earlier and more of them achieved CR/CRi than did ibrutinib-treated patients. • **Median OS** had not been reached in either treatment group. Overall, 69 zanubrutinib- and 83 ibrutinib-treated patients have died (OS HR: 0.77 [95% CI, 0.55-1.06]). **2. Safety** At the 42.5 months median follow-up from the ALPINE trial:[24] ● The most common **nonhematologic treatment-emergent AEs** of any grade with zanubrutinib vs ibrutinib were COVID19-related infections (46.0% vs 33.3%), upper respiratory tract infection (29.3% vs 19.8%), diarrhea (18.8% vs 25.6%), and hypertension (27.2% vs 25.3%). The most commonly reported non-hematologic grade ≥3 AEs were hypertension (17.0% vs 16.0%), COVID-19-related infections (17.9% vs 12.0%), and pneumonia (7.7% vs 10.5%), respectively. Neutropenia was

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	the most common hematologic AE of any grade (31.5% vs 29.6%) and grade ≥3 (22.8% vs 22.8%) with zanubrutinib vs ibrutinib, respectively; febrile neutropenia was low in both arms (n=4, 1.2% each). ● Occurrence of **hemolytic anemia (HA)**, including autoimmune HA, was rare. Two patients receiving ibrutinib experienced HA; one patient treated with zanubrutinib experienced autoimmune HA. ● **Overall cardiac events** remained considerably lower with zanubrutinib compared with ibrutinib and the rate of atrial fibrillation/flutter was lower with zanubrutinib vs ibrutinib (7.1% vs 17.0%) despite similar hypertension rates (Figure 9C). Overall incidence of cardiac events (25.9% vs 35.5%) and discontinuations due to cardiac events (0.9% vs 4.9%) were also lower with zanubrutinib compared with ibrutinib. Six patients treated with ibrutinib died due to cardiac AEs; in the zanubrutinib arm, no deaths due to cardiac AEs occurred. **3. Quality-adjusted time without symptoms of disease and toxicity (Q-TWiST)** Analysis was conducted using individual patient data from the ALPINE trial to enhance comprehensive understanding of the benefits and risks associated with zanubrutinib vs ibrutinib in terms of quality-adjusted survival.[32] Results showed that in the base case, the mean durations of heath states (zanubrutinib vs ibrutinib) were: 11.54 vs 11.38 months for toxicity; 14.45 vs 11.09 months for time without symptom of disease and toxicity (TWiST); and 1.70 vs 3.78 months for relapse. The mean

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	differences for zanubrutinib vs ibrutinib were 0.16 months for the toxicity state, 3.36 months for the TWiST state, and −2.08 months for the relapse state. The mean duration of Q-TWiST was 21.07 months for zanubrutinib vs 18.67 months for ibrutinib. More importantly, the estimated difference in mean Q-TWiST gain was significantly higher for zanubrutinib vs ibrutinib (2.40 months; 95% CI: 1.9, 2.9; P<.001) and the relative Q-TWiST gain was 9.14%.
SEQUOIA: BGB-3111-304 (NCT03336333) Zanubrutinib (ZANU) vs Bendamustine + Rituximab (BR) in patients with treatment-naive chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL): Extended follow-up of the SEQUOIA study[22] (2023) Health-related quality-of-life in treatment-naive CLL/SLL patients treated with zanubrutinib versus bendamustine plus rituximab[33] (2023)	**SEQUOIA (Cohort 1)** **1. Efficacy:** With >3.5 years of median follow-up (extended follow-up):[22] • Though the median OS was not reached in either zanubrutinib or BR treatment arms, zanubrutinib **PFS** benefit was sustained over BR (HR: 0.30 [95% CI, 0.21-0.43]; P<.0001). Estimated 42-month PFS rates with zanubrutinib and BR were 82.4% and 50.0%, respectively. • Improvement in **PFS** of zanubrutinib over BR was sustained regardless of IGHV mutational status. Zanubrutinib showed statistically longer PFS versus BR both in high-risk patients with unmutated IGHV (HR: 0.23 [95% CI, 0.14-0.37]; P<.0001) as well as in patients with mutated IGHV (HR: 0.35 [95% CI, 0.19-0.64]; P<.00033). • **CR/CRi** rates were 17.4% for zanubrutinib and 21.8% for BR.[22] **2. Safety:** As of interim analysis (DCO: 7th May 2021),[21] results showed that:

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	● Patients treated with zanubrutinib experienced fewer AEs compared to BR: ○ Leading to treatment discontinuations (8% vs. 14%) ○ Serious adverse events (37% 50%) ○ Grade ≥3 (53% vs. 80%) ● Expectedly, two regimens showed distinct safety profiles: ○ Rates of cytopenia were higher in BR arm, as expected for the chemoimmunotherapy regimens ○ Rates of haemorrhage, known AE of BTKi therapy, were higher in zanubrutinib arm. Rate of atrial fibrillation of any grade was similar between zanubrutinib and BR. **SEQUOIA (Cohort 2)** **1. Efficacy:** An extended follow-up of the SEQUOIA study showed that zanubrutinib is also efficacious in the treatment of patients with del(17p) and a safer treatment option for treatment naïve CLL patients compared to BR.[22] Moreover, zanubrutinib showed greater improvement in patients' quality of life compared to BR. With >3.5 years of median follow-up (DCO: 31st October 2022), results showed that: ● The median **PFS** was not reached, and the 42-month event-free rate was 79.4%. ● The median **OS** was not reached, and the 42-month event-free rate was 89.5%.

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	● The **CR/Cri** rate was 14.5%. **2. Quality of life** Patient's QoL is measured by EORTC QLQ-C30 and EQ-5D-5L questionnaires. The presented results are from the latest available analysis of QoL (DCO: 7th May 2021).[33] **EORTC QLQ-C30** Patients treated with zanubrutinib achieved better improvement in quality of life compared to BR both at week 12 and 24; particularly in global health status, physical and role functions scales, decreased symptoms of fatigue and nausea/vomiting, and diarrhea. **EQ-5D-5L** Comparable improvement in the EQ-5D-5L VAS scale was observed in the zanubrutinib and BR arms at weeks 12 and 24. Results from BGB-3111-18-427-BOVen (NCT03824483) showed that the most common AEs of any grade were thrombocytopenia (59%), fatigue (54%), neutropenia (51%), bruising (51%), diarrhea (46%), infusion-related reactions (44%), anaemia (41%), cough (36%), rash (33%), and nausea (31%).[3] Grade ≥3 AEs occurring in ≥5% of patients were neutropenia (18%), thrombocytopenia (8%), rash (8%), lung infection (8%), and infusion-related reactions (5%). Nine patients required G-CSF for neutropenia (4 Grade 2 and 5 Grade 3-4). Dose reductions of zanubrutinib were required in 3 patients due to AEs. Two deaths were reported during the study; 1 was on day 1 of cycle 1 due to intracranial haemorrhage, and the other was on day 25 of cycle 1 due to metastatic adenocarcinoma.

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	Additional efficacy and safety results were reported after a median of >26 months of study follow-up (range, 4.5-30.5+), with 95% (35/37) of patients having achieved uMRD-FC4 in peripheral blood. Among these patients, 94% (n=33) also achieved MRD by immunosequencing (sensitivity ≤10^{-5}), which was evaluated every 3 months from the end of treatment for median of 12 months (range, 3-18). The most common AEs of any grade were neutropenia (51%), thrombocytopenia (44%), diarrhea (44%), infusion-related reactions (41%), and bruising (41%). The most common Grade ≥3 AE was neutropenia (15%).
Other studies (non-RCTs, real-world evidence)	
BGB-3111-215 (NCT04116437) Safety and tolerability of zanubrutinib can be supported by an ongoing Phase II BGB-3111-215 study in patients with previously treated B-cell malignancies who have become intolerant to ibrutinib or acalabrutinib[37] (2023)	67 patients who were intolerant to ibrutinib (Cohort 1, n=57; CLL, n=38 [67%]; SLL, n=6 [11%]) or to acalabrutinib or acalabrutinib and ibrutinib (Cohort 2, n=10; CLL, n=5 [50%]; SLL, n=1 [10%]) were enrolled and received ≥1 dose of zanubrutinib. The median follow-up was 12 months. ● 70% of ibrutinib- and 83% of acalabrutinib-intolerant AEs did not recur on zanubrutinib. ● 79% of the ibrutinib-intolerant AEs and 33% of acalabrutinib-intolerant AEs that reoccurred on zanubrutinib were of lower severity. ● Among the 64 efficacy-evaluable patients, 60 (93·8%; 95% CI 84·8–98·3) had disease control and 41 (64·1%; 51·1–75·7) had an overall response: 19 (30%) of 64

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	patients had a best overall response of stable disease and two (3%) patients had a best overall response of progressive disease.
Real-world treatment switching and sequencing to next line of therapy of zanubrutinib, acalabrutinib, and ibrutinib in CLL/SLL[38] (2024)	The study evaluated **real-world switching and sequencing** to next line of therapy in patients initiating BTKis as first-line (1L) or second-line (2L) CLL/SLL treatment.[38] Using IntegraConnect PrecisionQ to identify adult patients with ≥1 diagnosis for CLL/SLL initiating zanubrutinib, acalabrutinib, or ibrutinib in 1L or 2L between 1/1/2020-2/28/2023 (index period), the study found that a total of 2,816 and 1,253 patients initiated a 1L or 2L BTKi during the period respectively. In 1L, ibrutinib (50.5%) was the most common BTKi followed by acalabrutinib (44.0%) and zanubrutinib (5.6%). In 2L, acalabrutinib (53.6%) was the most commonly utilized BTKi followed by ibrutinib (37.8%) and zanubrutinib (8.54%). The study showed that median follow-up in 1L was 123 days for zanubrutinib, 406 days for acalabrutinib, and 637 days for ibrutinib. Zanubrutinib patients had significantly lower switching rate within 90 days and lower proportion of patients receiving next line of therapy at 180 days when compared with acalabrutinib and ibrutinib in 1L and 2L. Regardless of line of therapy, switching rate at ≤60 days and 61-89 days was statistically significantly lower for patients receiving zanubrutinib vs acalabrutinib and ibrutinib ($P<0.0001$, both 1L and 2L). In 1L, the percentage of patients switching before 90 days was lowest for zanubrutinib (10.2%) compared to acalabrutinib (20.5%) and ibrutinib (15.6%).

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	Zanubrutinib also had the lowest switch rate before 90 days (7.5%) compared to 13.2% for acalabrutinib and 21.1% for ibrutinib among 2L patients. The proportion of patients receiving next line of therapy at 180 days was lower for zanubrutinib vs acalabrutinib and ibrutinib (1L *P*=.2958; 2L *P*<.0001). Among 1L patients, the proportion of receiving the next line of therapy at 180 days was 13.9% for zanubrutinib compared to 24.5% for acalabrutinib and 21.1% for ibrutinib. In 2L, the proportion at 180 days of receiving the next line of therapy was 9.1% for zanubrutinib compared to 18.6% for acalabrutinib and 29.2% for ibrutinib.
Real-world treatment patterns and outcomes of zanubrutinib in chronic lymphocytic leukemia and small lymphocytic leukemia (CLL/SLL)[39] (2024)	The study investigated **real-world treatment patterns** based on a formulary change from ibrutinib to zanubrutinib in patients with CLL/SLL in an integrated community oncology practice.[39] The authors retrospectively analysed CLL/SLL patients 18 years and older who received at least 3 months of zanubrutinib from October 1, 2018, to September 15, 2023 at Kaiser Permanente Northern California. Treatment patterns, treatment-emergent adverse events (TEAEs: AEs reported during BTKi use), treatment-limiting adverse events (TLAEs: AEs leading to BTKi discontinuation), and mortality were reported. Results showed that median follow-up time after initiation of first BTKi was longer in the ibru-zanubrutinib group. (Table 5) Similar TEAE rates were seen with use of both BTKi therapies, with lower TLAE rates with zanubrutinib. Most common TLAE were atrial fibrillation and fatigue for ibrutinib, and cytopenia and rash/bruising for zanubrutinib. Cardiac TLAE and non-TLAE rates overall were higher with ibrutinib than zanubrutinib, and the rates decreased while on

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	zanubrutinib after switching from ibrutinib (Table). In the real-world setting post-formulary change, zanubrutinib is effective and safe in patients with or without prior ibrutinib use. Zanubrutinib use had lower cardiotoxicity and TLAE rates than ibrutinib though data was limited by a difference in follow-up time. Similar results were seen in zanubrutinib-only patients despite being older and having more comorbidities, with discontinuation most often due to grade <3 AEs.
Real-world Bruton tyrosine kinase inhibitor (BTKi) treatment patterns and outcomes among patients with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) in US community oncology practices[40] (2024)	The study exploring the **clinical characteristics, treatment patterns, and AEs among BTKi-treated patients with CLL/SLL** demonstrated better real-world CLL/SLL safety and effectiveness outcomes for acalabrutinib and zanubrutinib vs ibrutinib.[40] Patient population included adults with CLL/SLL who initiated BTKi treatment between January 1, 2020 – July 31, 2023, with follow-up through October 31, 2023 and patients had ≥5 CLL/SLL visits or more CLL/SLL visits than non-CLL/SLL visits with all patients having ≥2 evaluation and management visits. Outcomes included Cardiovascular AEs, Time-to-next-treatment (TTNT): time from line of therapy (LOT) initiation to initiation of next LOT or death, and Time-to-treatment discontinuation (TTD) or death: time between treatment initiation and treatment discontinuation or death. 7,875 patients inititated 1L, including 2,815 in BTKi and 4,060 in non-BTKi (with 249 initiating BTKi in later lines). More patients experienced cardiovascular AEs when treated with ibrutinib than acalabrutinib or zanubrutinib. The proportions of patients continuing treatment and the median TTNT was longer for patients who received zanubrutinib. Of

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	patients within the first 3 months of follow-up post-BTKi initiation, the rate of cardiac AEs was highest in patients who initiated ibrutinib (8.7%), followed by zanubrutinib (Figure 24[OBJ]) Significantly more patients experienced cardiovascular AEs among those who received 1L ibrutinib vs acalabrutinib or zanubrutinib at month 6 (12.1%, 7.6%, and 7.3%, respectively; *P*<.05) and at month 9 (14.6%, 9.4%, and 8.5%, respectively; *P*<.05). Of patients treated with 1L ibrutinib, 12.7% discontinued ibrutinib and switched to a second-generation BTKi. The median TTD in 1L was shorter for ibrutinib than acalabrutinib and zanubrutinib (the median TTD (95% CI) in the 1L setting was 13.7 (12.2, 16.0) months for ibrutinib, 19.2 (15.1, 25.3) months for acalabrutinib, and 19.3 (14.1, NR) months for zanubrutinib. The associated probability of continuing treatment and not having new treatment were higher with zanubrutinib vs ibrutinib or acalabrutinib at month 6. The median TTNT (95% CI) was not reached (16.7, NR) for those who received zanubrutinib in the 1L setting, while it was 35.8 (29.8, NR) months for acalabrutinib and 30.2 (26.2, 35.5) months for ibrutinib.
EVIDENCE FOR COMPARATIVE COST/COST-EFFECTIVENESS AND BUDGET IMPACT STUDIES	
Cost Effectiveness of Zanubrutinib Versus Ibrutinib in Relapsed or Refractory Chronic Lymphocytic Leukemia[45] (2024)	The model was developed based on survival curves from the **phase III ALPINE trial**. The cost-utility analysis (CUA) was developed based on a partitioned survival model (PSM) with 3 mutually exclusive health-states (progression-free, progressive disease and death) to assess the cost effectiveness of zanubrutinib versus ibrutinib for the treatment of R/R CLL from the commercial US payer perspective in the horizon of 10-years.[45]

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	Zanubrutinib is likely to be cost effective versus ibrutinib in relapsed or refractory chronic lymphocytic leukemia in the USA. Zanubrutinib is associated with a gain of 0.528 life-years and of 0.399 quality-adjusted life-years versus ibrutinib. Over a 10-year analysis period, the incremental cost-effectiveness ratio of zanubrutinib versus ibrutinib was $91,260 per life-year gained and $120,634 per quality-adjusted life-year gained, making it cost effective within a threshold of $150,000 per quality-adjusted life-year gained. The incremental cost-effectiveness ratio was most sensitive to drug acquisition costs and progression-free survival distributions, and the probability of zanubrutinib being cost effective was approximately 52.8%, with a 30.0% likelihood of dominance.
Cost-Minimization Analysis (CMA) of Bruton Tyrosine Kinase Inhibitors (BTKi) in Adults with Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia (CLL)[46] (2023)	A cost-minimisation analysis was conducted to characterize the costs associated with BTKi monotherapies (zanubrutinib, acalabrutinib, and ibrutinib) for the treatment of adults with R/R CLL.[46] The CMA was performed using a 3- health-state (progression free, progressive disease, death) partitioned survival model with a United Kingdom National Health Service payer perspective in the horizon of 30-years. The model was developed based on the assumption of equal efficacy of zanubrutinib to ibrutinib and acalabrutinib. Over a lifetime horizon, treatment with zanubrutinib in adults with R/R CLL was associated with cost savings of £7,802 per person versus acalabrutinib and an incremental cost of £19,677 per person versus ibrutinib. Treatment with acalabrutinib was associated with an incremental cost of £27,478 per person versus ibrutinib. Difference in treatment acquisition costs was the key reason for the cost differential between treatments. Zanubrutinib was associated with fewer AE management costs compared with

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	acalabrutinib and ibrutinib, due to an improved safety profile. Under this CMA approach, zanubrutinib was less costly than another second-generation BTKi, acalabrutinib. Zanubrutinib was slightly more costly than the first-generation BTKi, ibrutinib.
A Markov model-based cost-effectiveness analysis comparing zanubrutinib to ibrutinib for treating relapsed and refractory chronic lymphocytic leukemia[47] (2023)	**A Markov model-based cost-effectiveness analysis** compared the cost-effectiveness of zanubrutinib and ibrutinib for managing R/R CLL in China and the US. It used Markov models to compare the drugs based on cost, quality-adjusted life years, and the incremental cost-effectiveness ratio.[47] *For Chinese payers*, zanubrutinib exhibited superior cost-effectiveness compared to ibrutinib. Zanubrutinib also proved to be a more affordable option for US payers when considering the payment threshold. The zanubrutinib group incurred an incremental cost per patient of $-24,586.53 compared to the ibrutinib group. The zanubrutinib group exhibited an incremental utility per capita of 0.28 quality-adjusted life years, resulting in an incremental cost-effectiveness ratio of $-88,068.16 per quality-adjusted life year, which is lower than the payment threshold in China. The willingness-to-pay value in China for 2022 was three times the country's gross domestic product per capita. *In the US*, patients in the zanubrutinib group experienced per capita incremental costs of $-79,421.56, per capita incremental utility of 0.28 quality-adjusted life years, and an incremental cost-effectiveness ratio of $-284,485.45 per quality-adjusted life year.
Number Needed to Treat Analyses of Zanubrutinib in Relapsed/Refractory Chronic Lymphocytic Leukemia[48] (2023)	A study compared zanubrutinib versus ibrutinib in R/R CLL by calculating the number needed to treat (NNT) to avoid one progression or death and associated incremental

Article Title (year)	New Evidence
	costs.[48] The base-case results from the NNT model showed that for every 8 patients treated with zanubrutinib, 1 event of progression or death would be avoided compared to using ibrutinib. The total costs per patient treated with zanubrutinib and ibrutinib are $370,558 and $430,150, respectively, with a cost savings of $59,593 associated with using zanubrutinib (Table 10). The NNT model suggests that using zanubrutinib to treat R/R CLL patients, compared to ibrutinib, will result in more favourable clinical and economic outcomes in the US.
Budget Impact of Zanubrutinib for Treatment of Relapsed or Refractory Chronic Lymphocytic Leukemia in the United States[49] (2022)	A budget impact analysis (BIA) was conducted to estimate the incremental costs associated with using zanubrutinib in R/R CLL/SLL patients from the US payer perspective.[49] Results from the economic analysis suggested that providing access to zanubrutinib for patients with R/R CLL/SLL is associated with cost savings to a US health plan. The model analysis compared a reference scenario with the "current market mix" (i.e., before the introduction of zanubrutinib) and an alternative scenario with a "revised market mix" where the uptake of zanubrutinib was included (i.e., after zanubrutinib entry). The base-case analysis of a hypothetical one-million-member health plan in which two patients were estimated to have R/R CLL/SLL and initiated treatment showed that total healthcare costs were $412K with zanubrutinib and $414K without, suggesting that adding zanubrutinib is associated with a cost-saving of $2,031 over 1 year (Per-member-per-month PMPM <-$0.001; Per-treated-member-per-month: -$88). One-way sensitivity

Article Title (year)	New Evidence
	analysis results showed that the budget impact on healthcare costs over a one-year time horizon were most sensitive to zanubrutinib wholesale acquisition cost.
Budget Impact Analysis of Zanubrutinib for Patients With Treatment-Naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma in the United States[50] (2022)	Another BIA was developed to estimate the incremental costs associated with using zanubrutinib in the population from the US commercial and Medicare perspectives, for patients with T/N CLL/SLL.[50] The budget impact analysis suggests that providing access to zanubrutinib for patients with TN CLL/SLL is associated with cost savings in a US health plan. In a hypothetical health plan with 1,000,000 members, 31 patients were estimated to receive active treatment each year for TN CLL/SLL. Over a three-year time-horizon, the overall budget impact was a reduction of $82,437, representing a 0.22% cost-saving with the use of zanubrutinib. Total healthcare costs were $37.75m with zanubrutinib and $37.83m without. The expected average per-member-per-month budget reduction was $0.002. Deterministic sensitivity analysis indicated that drug costs, payer perspective and treatment duration had the greatest impact on the financial budget of healthcare costs estimated over a three-year time horizon.

Appendix 2. Summary and risk of bias assessment of systematic reviews and meta-analyses

Article Title (year)	**Relevant technologies included (n=sample size)**	**RoB**	**Outcomes**
Safety profile of first-line targeted therapies in elderly and/or comorbid chronic lymphocytic leukemia patients (unfit subpopulation). A systematic review and network meta-analysis.[24] (2024) **Total studies identified = 10 RCTs including 4,171 patients** with naïve CLL requiring therapy with advanced age and/or with comorbidities.	- Zanubrutinib (n=241) as monotherapy in 1 study - Ibrutinib (n=318) as monotherapy in 2 studies - Acalabrutinib (n=179) as monotherapy in 1 study	Low	**AEs leading to treatment discontinuation** - Zanubrutinib had the highest probability of being the safest therapeutic option in this area (SUCRA: 86 %). Ibrutinib+Venetoclax therapy was associated with the highest risk compared with other (evaluated) targeted therapies, i.e., zanubrutinib (16.5 [2.73; 153.68]), acalabrutinib (12.56 [2.58, 102.7]), chlorambucil + Obinutuzumab (6.93 [1.69, 51.72]), acalabrutinib + Obinutuzumab (9.62 [2.02, 78.15]), and Venetoclax + Obinutuzumab (6.67 [1.46, 52.55]) **Grade ≥3 AEs** - Zanubrutinib ranked the highest among the evaluated targeted therapies (SUCRA: 98 %). Grade ≥3 AEs were generally significantly more frequent in groups treated with combined therapies such as venetoclax +

Article Title (year)	Relevant technologies included (n=sample size)	RoB	Outcomes
			Obinutuzumab, acalabrutinib + Obinutuzumab, Ibrutinib + Obinutuzumab, and Ibrutinib+Venetoclax than in monotherapy groups **Serious AEs** - Zanubrutinib achieved the highest rank in the SUCRA ranking by 95 %. Serious AEs grade 1–5 were significantly less frequent in the case of zanubrutinib therapy as compared with other targeted therapies, such as Ibrutinib (0.35 [0.20, 0.59]), acalabrutinib (0.38 [0.17, 0.85]), ibrutinib + obinutuzumab (0.25 [0.11, 0.57]), ibrutinib + rituximab (0.39 [0.22, 0.67]), ibrutinib + venetoclax (0.28 [0.12, 0.66]), and acalabrutinib + obinutuzumab (0.28 [0.13, 0.62]) **Hematological AEs (Anemia)** - Anemia grade 1–5 was significantly less frequent in the case of zanubrutinib therapy than for other treatment options (SUCRA: 92%), such as

Article Title (year)	Relevant technologies included (n=sample size)	RoB	Outcomes
			chlorambucil + obinutuzumab (0.35 [0.12, 0.98]) and acalabrutinib (0.28 [0.08, 0.96]) - Although there were no significant differences between assessed targeted therapies in terms of anemia grade ≥3, zanubrutinib achieved the highest SUCRA value of 86%.
Efficacy and safety of new-generation Bruton tyrosine kinase inhibitors in chronic lymphocytic leukemia/small lymphocytic lymphoma: a systematic review and meta-analysis.[30] (2024) **Total studies identified = ten single arm studies + five randomized studies, including 2,066 CLL/SLL patients**	- Zanubrutinib (n=932) as monotherapy in 7 studies - Acalabrutinib (n=844) as monotherapy in 8 studies	Low	**Survival** - Pooled 24-month OS rate: 95% for zanubrutinib monotherapy (95% CI, 92–96%, I2 = 0.00%, P = 0.72) and 92% for acalabrutinib monotherapy (95% CI, 89–96%, I2 = 0.00%). - Pooled 24-month PFS rate: 86% for zanubrutinib (95% CI, 80–91%, I2 = 77.84%, P = 0.00) and 83% for acalabrutinib (95% CI, 75–90%, I2 = 57.74%, P = 0.05)

Article Title (year)	Relevant technologies included (n=sample size)	RoB	Outcomes
			- Pooled ORR and CR rate for zanubrutinib monotherapy: 93% (95% CI, 89–97%, I2 = 79.48%, P = 0.00) and 13% (95% CI, 6–22%, I2 = 90.36%, P = 0.00) respectively. - Pooled ORR and CR rate for acalabrutinib monotherapy: 87% (95% CI, 81–93%, I2 = 82.23%, P = 0.00) and 3% (95% CI, 1–6%, I 2 = 61.78%, P = 0.00) respectively. **Toxicity** - Pooled rates of grade ≥ 3 neutropenia, anemia, and thrombocytopenia in zanubrutinib monotherapy were 19%, 2%, and 4% respectively. - Pooled rates of grade ≥ 3 neutropenia, anaemia, and thrombocytopenia in acalabrutinib monotherapy were 14%, 7%, and 5% respectively. - Zanubrutinib monotherapy had a similar pooled rate of grade ≥ 3 upper respiratory tract infection (2% vs.

Article Title (year)	Relevant technologies included (n=sample size)	RoB	Outcomes
			1%), and grade ≥ 3 hypertension (6% vs. 4%) compared to acalabrutinib monotherapy. Compared to acalabrutinib, Zanubrutinib may be the preferred monotherapy for CLL.
Comparison of treatment-emergent adverse events of acalabrutinib and zanubrutinib in clinical trials in B-cell malignancies: a systematic review and meta-analysis.[29] (2023) A total of 61 trials were included, involving 6959 patients and 68 treatment arms: ibrutinib (n=31; 46%), ibrutinib plus anti-CD20 mAb (n=15; 22%), acalabrutinib (n=11; 16%), and zanubrutinib (n=11; 16%). Most trials were in CLL/SLL (n=36), MCL (n=9), or	Ibrutinib, acalabrutinib, zanubrutinib	Unclear	Results from this meta-analysis show an improved AE profile with acalabrutinib and zanubrutinib compared to ibrutinib. In addition, these data – for the first time – provide a comprehensive comparison of AE between zanubrutinib and acalabrutinib, which will inform clinicians' choice between these highly effective second-generation BTKi treatments for patients with B-cell malignancies. **Treatment-emergent adverse events of all grades**

Article Title (year)	Relevant technologies included (n=sample size)	RoB	Outcomes
WM (n=8). Three trials involved randomized comparison between ibrutinib and either acalabrutinib (ELEVATE-RR) or zanubrutinib (ASPEN, ALPINE). A total of 84 AE was analyzed.			• Compared with ibrutinib, the average incidence of all grade AE was lower with zanubrutinib (RR=0.83, 95% CrI=0.71-0.93). • Zanubrutinib and acalabrutinib had similar average incidences of all grade AE (RR=1.12, 95% CrI=0.91-1.37). All grade AE that occurred more frequently with acalabrutinib relative to zanubrutinib included atrial fibrillation (RR=0.51), infections (RR=0.53), pyrexia (RR=0.59), cough (RR=0.71), fatigue (RR=0.61), nausea (RR=0.63), vomiting (RR=0.71), diarrhea (RR=0.52), myalgias (RR=0.49), headaches (RR=0.32), and dizziness (RR=0.63). **Treatment-emergent adverse events of grade ≥3** • Compared with ibrutinib, the average incidence of grade ≥3 AE was also lower with zanubrutinib (RR=0.78, 95% CrI=0.47-1.02).

Article Title (year)	Relevant technologies included (n=sample size)	RoB	Outcomes
			• Zanubrutinib and acalabrutinib had similar average incidences of grade ≥3 AE (RR=0.90, 95% CrI=0.54-1.37). Grade ≥3 AE that occurred more frequently with acalabrutinib included anemia (RR=0.58), infections (RR=0.76), and rash (RR=0.03).

Appendix 3. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society Of America-United States Public Health Service Grading System)

Levels of evidence

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinions

Grades of recommendation

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited

	clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Appendix 4. Summary of economic evaluation studies

Title (year)	Interventions	Results
Cost Effectiveness of Zanubrutinib Versus Ibrutinib in Relapsed or Refractory Chronic Lymphocytic Leukemia (2024)	Zanubrutinib Ibrutinib	Zanubrutinib is associated with a gain of 0.528 life-years and of 0.399 quality-adjusted life-years versus ibrutinib. ICER (zanubrutinib vs ibrutinib) = $91,260 per life-year gained and = $120,634 per quality-adjusted life-year gained, making it cost effective within a threshold of $150,000 per quality-adjusted life-year gained. ICER was most sensitive to drug acquisition costs and progression-free survival distributions, and the probability of zanubrutinib being cost effective was approximately 52.8%, with a 30.0% likelihood of dominance. **Zanubrutinib is likely to be cost effective versus ibrutinib in relapsed or refractory chronic lymphocytic leukemia.**
Cost-Minimization Analysis (CMA) of Bruton Tyrosine Kinase Inhibitors (BTKi) in Adults with Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia (CLL) (2023)	Zanubrutinib Acalabrutinib Ibrutinib	Treatment with zanubrutinib in adults with R/R CLL was associated with cost savings of £7,802 per person versus acalabrutinib and an incremental cost of £19,677 per person versus ibrutinib. **Zanubrutinib was less costly than another second-generation BTKi, acalabrutinib. Zanubrutinib was slightly more costly than the first-generation BTKi, ibrutinib.**
A Markov model-based cost-effectiveness analysis comparing zanubrutinib to ibrutinib for treating	Zanubrutinib Ibrutinib	The study compared the cost-effectiveness of zanubrutinib and ibrutinib for managing relapsed and refractory chronic lymphocytic leukemia in China and the US.

Title (year)	Interventions	Results
relapsed and refractory chronic lymphocytic leukemia (2023)		For Chinese payers, zanubrutinib exhibited superior cost-effectiveness compared to ibrutinib. **Zanubrutinib also proved to be a more affordable option for US payers when considering the payment threshold.**
Number Needed to Treat (NNT) Analyses of Zanubrutinib in Relapsed/Refractory Chronic Lymphocytic Leukemia (2023)	Zanubrutinib Ibrutinib	The base-case results from the NNT model showed that for every 8 patients treated with zanubrutinib, 1 event of progression or death would be avoided compared to using ibrutinib. The total costs per patient treated with zanubrutinib and ibrutinib are $370,558 and $430,150, respectively, with a cost savings of $59,593 associated with using zanubrutinib. **The NNT model suggests that using zanubrutinib to treat R/R CLL patients, compared to ibrutinib, will result in more favourable clinical and economic outcomes.**

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28 October 2024

The Secretary

Expert Committee on the Selection and Use of Essential Medicines

Medicines Selection, IP and Affordability (MIA)

Department of Health Products Policy and Standards (HPS)

20 Avenue Appia

CH-1211 Geneva 27

Dear Secretary and Expert Committee Members,

RE: Application to add zanubrutinib to the WHO Model List of Essential Medicines

The Access to Oncology Medicines Coalition (ATOM) of the Union for International Cancer Control (UICC) submits this letter to support the application for the addition of zanubrutinib to the 24th WHO Model List of Essential Medicines (WHO EML)

UICC together with a number of partners have established a global initiative, the ATOM Coalition to improve access to essential cancer medicines and diagnostics in low-and lower middle-income countries (LLMICs) and to increase the capacity to use these medicines effectively. The Coalition was launched on 22May, 2022 at the side-lines of the World Health Assembly in Geneva and brings together close to 40 partners from civil society as well as the public and private sectors with expertise in implementing cancer-focused access programmes. The Coalition will focus on increasing access to medicines which are already included on the WHO EML and medicines which are likely candidates to be included in future revisions. One of the objectives of the Coalition is to support the inclusion of essential medicines on to the WHO EML and EMLc, as a crucial first step to increase access and availability.

Zanubrutinib is currently recognized as one of the best-in-class Bruton's tyrosine kinase (BTK) inhibitors. However, unless the price is addressed, it will not be very cost-effective. Therefore, it is crucial to develop strategies to make this medicine available and accessible to as many patients as possible.

The submission proposes the use of zanubrutinib monotherapy for the treatment of adult patients with Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL). This includes:

- Treatment for patients who are treatment-naive.
- Treatment for patients who are relapsed or refractory to previous treatment.

Globally, the incidence of CLL-related cases has more than doubled from just over 40,000 in 1990 to over 100,000 in 2019. As mentioned in the application, given the potential indolent nature of the condition, it is critical to provide patients with the most clinically effective therapies that have been carefully weighed against the safety profile of the treatment.

BTK inhibitors have revolutionized the therapeutic landscape for patients with CLL/SLL over the last decade. Ibrutinib, a first-generation BTK inhibitor, became the standard treatment option for previously untreated and relapsed/refractory CLL/SLL and was the first BTK inhibitor added to the WHO Essential Medicines List (EML) in 2021 for the treatment of R/R CLL/SLL. However, zanubrutinib, is a next-generation irreversible BTK inhibitor, with improved selectivity to BTK and reduced adverse effects associated with earlier BTK inhibitors. Many clinical guidelines now recommend the use of zanubrutinib instead of ibrutinib for treatment-naive patients with CLL/SLL.

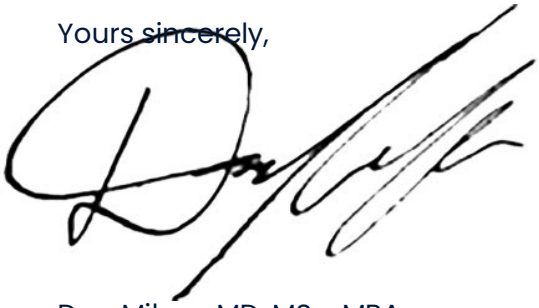
As the WHO EML serves to help countries prioritise their medicines procurement and is an important tool to ensure access, inclusion of zanubrutinib on the list will help towards its increased availability (through inclusion on National Essential Medicines Lists and procurement lists). The addition of zanubrutinib to the WHO EML will play a role in the much-needed progress towards achieving sustainable development goal (SDG) 3.4, addressing premature mortality from non-communicable diseases through prevention and treatment. Zanubrutinib is widely available in high-income countries and should be available in resource-constrained settings also, where the burden of cancer is the highest.

Expanding access to essential cancer treatments in underserved regions and creating a sustainable pathway for affordable care is a priority for the ATOM coalition and its partners, including BeiGene. In this regard, the Coalition will be happy to explore the establishment of a robust and comprehensive access

pathway with BeiGene to ensure broad, affordable access to zanubrutinib in low- and middle-income countries (LMICs).

We respectfully submit that the addition of zanubrutinib to the WHO EML will support the objective of the WHO EML to identify priority medicines that meet the most important and urgent health needs for populations globally.

Yours sincerely,



Dan Milner, MD, MSc, MBA

Executive Director,

The ATOM Coalition