Application to Add Zanubrutinib to WHO Model List of Essential Medicines

As a Medicine for Treatment of Chronic Lymphocytic Leukaemia

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Date: December 16, 2022

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1. Summary statement of the proposal for inclusion, change or deletion

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

Chronic lymphocytic leukaemia is the most common form of leukaemia in western countries(1). Globally, the number of deaths due to chronic lymphocytic leukaemia has increased in 70% from 1990 to 2017. However, the age-adjusted death rates have decreased in high-income regions while increased in Central Sub-Saharan Africa, East Asia, and Southeast Asia(2).

Zanubrutinib (brand name: Brukinsa®) is a small molecule inhibitor of Bruton's tyrosine kinase (BTK) discovered by BeiGene scientists that is currently being evaluated globally in a broad clinical program as a monotherapy and in combination with other therapies to treat various B-cell malignancies. Because new BTK is continuously synthesized, zanubrutinib was specifically designed to deliver complete and sustained inhibition of the BTK protein by optimizing bioavailability, half-life, and selectivity. With differentiated pharmacokinetics compared to other approved BTK inhibitors, zanubrutinib has been demonstrated to inhibit the proliferation of malignant B cells within a number of disease relevant tissues. Zanubrutinib is supported by a broad clinical program which includes more than 4,700+ subjects in 35 trials across 25 markets. To date, zanubrutinib is approved in different indications in 61 countries and regions around the world, including the United States, China, the EU, and Great Britain, Canada, Australia and additional international markets. Currently, more than 40 additional regulatory submissions are in review around the world.

Since Ibrutinib has been added into EML 22nd List (2021) with the indication of relapsed/refractory

(R/R) chronic lymphocytic leukaemia(3), adding zanubrutinib proven to have better efficacy and safety profile in head to head multinational clinical trials with lower cost, to the WHO essential list of medications might help to benefit more patients around the globe(4, 5). And it also might help to promote mechanisms that may enhance its accessibility and affordability.

After joining the WHO essential drug list, zanubrutinib will simultaneously apply for WHO pre-qualification certification, so as to benefit more patients around the world.

2. Consultation with WHO technical departments

N/A

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

N/A

4. Key information for the proposed medicine(s)

4.1 International non-proprietary name (INN) of the proposed medicine(s)

INN：Zanubrutinib.

4.2 Anatomical therapeutic chemical (ATC) code of the proposed medicine(s)

ATC code：L01EL03.

4.3 Dosage forms(s) and strength(s) of the proposed medicine(s)

Dose forms：Capsule.

Strengths: 80 mg.

4.4 Indication(s)

Zanubrutinib is proposed for the indication for the treatment of adult patients with chronic lymphocytic leukemia /small lymphocytic lymphoma.

ICD-11: 2A82.0 Chronic lymphocytic leukaemia or small lymphocytic lymphoma

5. Proposal for an individual medicine or representative of a pharmacological class / Therapeutic group

As individual medicine.

6. Information supporting the public health relevance

6.1 Epidemiological information on disease burden

CLL/SLL is a main non-Hodgkin lymphoma (NHL) subtype which is a disease and mainly occurs in middle-aged and elderly population. CLL and SLL are indolent B cell malignancies that are often considered to be different clinical presentations of one disease, the major difference being whether a patient presents with adenopathy alone or with an elevated lymphocyte count.

In Western countries, CLL is the most common leukemia in adults and accounts for 5%~11% of NHL with an incidence of 4.2/100,000 per year(6). The incidence increases to more than 30:100,000/year at an age of 80 years old above. The median age at diagnosis is 72 years old(7). CLL is much less prevalent in eastern countries. In these countries, CLL accounts for only 1%~3% of NHL in most series and the age-adjusted incidence is about 0.2~0.3/100,000(8). The prevalence of CLL in Europe is about

48.0/100,000(9). During 2010~2016, 5-year relative survival of CLL/SLL patients in the United States was 85.7%, and the relative survival was significantly correlated with age. The 5-year relative survival of CLL/SLL patients aged 0~19, 20~64 years and over 65 years was 93.0%, 92.4% and 81.1%, respectively(10).

Though mostly considered an indolent disease, there is a wide spectrum of clinical presentation and it remains a life-limiting illness. CLL/SLL remains an incurable disease, with all patients who require therapy destined to relapse. The prognosis of different CLL/SLL patients is highly heterogeneous with median overall survival (OS) about 10 years. Some of the patients can survive for years while about 20% of the patients have a very aggressive presentation with median OS 1.5~3 years(11). Besides, treatment options for R/R patients who usually have a very poor prognosis are limited. Besides, CLL/SLL is diagnosed mainly in older adults in whom comorbidities are frequently present. 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 decrease of patient survival period(12, 13).

No differences regarding quality of life (QoL) can be observed between CLL patients who had already received chemotherapy and those who had not. 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(14).

6.2 Target population

The target population for zanubrutinib is adult patients diagnosed with treatment naïve (TN) or R/R chronic lymphocytic leukemia /small lymphocytic lymphoma.

6.3 Alternative medicines currently included on the Model Lists for the proposed indication(s)

Ibrutinib: R/R CLL.

Rituximab: Diffuse large B-cell lymphoma (DLBCL), CLL , Follicular lymphoma (FL).

Bendamustine: CLL , FL(3).

7. Treatment details

7.1 Dosage regimen and duration of treatment

7.1.1 Dosage regimen:

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. Advise patients to swallow capsules whole with water. Advise patients not to open, break, or chew the 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(15).

7.1.2 Duration of treatment:

Zanubrutinib should be taken until disease progression or unacceptable toxicity.

In SEQUOIA, a randomised, controlled, phase 3 trial, which evaluate zanubrutinib versus bendamustine and rituximab (BR) in untreated CLL/SLL,at median follow-up of 26.2 months (IQR 23.7–29.6), median progression-free survival (PFS) per independent review committee (IRC) was not

reached in zanubrutinib group (95% CI not estimable [NE] to NE)(16).

In ALPINE, a randomised, controlled, phase 3 trial, which evaluate zanubrutinib versus ibrutinib in R/R CLL/SLL, in the final analysis, with a median follow-up of 29.6 months, zanubrutinib achieved superior PFS compared with ibrutinib. 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. Median PFS was not reached in the zanubrutinib group and was 34.2 months (95% CI, 33.3 to not estimable) in the ibrutinib group(5).

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

7.2.1 Diagnosis of diseases

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. The diagnosis of SLL requires the presence of lymphadenopathy and/or splenomegaly with less than 5×10^9/L 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 effacement of the lymph node architecture is seen in biopsy samples(1).

More details could be found on the section of “diagnosis” in NCCN guideline(1).

7.2.2 Dose modifications

Dose modifications for use with CYP3A inhibitors or inducers

Recommended dose modifications when co-administered with CYP3A inhibitors or inducers are provided in table. After the discontinuation of a CYP3A inhibitor, resume previous dose of zanubrutinib.

Table 7-1 Dose Modifications for Use with CYP3A Inhibitors or Inducers

Co-administered Drug	**Recommended Dose**
Strong CYP3A inhibitor	80 mg once daily Interrupt dose as recommended for adverse reactions
Moderate CYP3A inhibitor	80 mg twice daily Modify dose as recommended for adverse reactions
Moderate or strong CYP3A Inducer	Avoid concomitant use。

Dose modifications for adverse reactions

Recommended dosage modifications of zanubrutinib for Grade 3 or higher adverse reactions are provided in Table 7-2.

Table 7-2 Recommended Dose Modification for Adverse Reaction

Adverse reactions	**Occurrence**	**Dose modification** (Starting Dose: 160 mg twice daily or 320 mg once daily)
Hematological toxicities		
Grade 3 febrile neutropenia Grade 3 thrombocytopenia with significant bleeding Grade 4 neutropenia (lasting more than 10 consecutive days) Grade 4 thrombocytopenia (lasting more than 10 consecutive days)	First	Interrupt zanubrutinib Once toxicity has resolved to Grade 1 or lower or baseline: Resume at 160 mg twice daily or 320 mg once daily.
	Second	Interrupt zanubrutinib Once toxicity has resolved to Grade 1 or lower or baseline: Resume at 80 mg twice daily or 160 mg once daily.
	Third	Interrupt zanubrutinib Once toxicity has resolved to Grade 1 or lower or baseline: Resume at 80 mg once daily.
	Fourth	Discontinue zanubrutinib
Non-hematological toxicities		
Grade 3 or 4 non-hematological toxicities	First	Interrupt zanubrutinib Once toxicity has resolved to Grade 1 or lower or baseline: Resume at 160 mg twice daily or 320 mg once daily.
	Second	Interrupt zanubrutinib Once toxicity has resolved to Grade 1 or lower or baseline: Resume at 80 mg twice daily or 160 mg once daily.
	Third	Interrupt zanubrutinib Once toxicity has resolved to Grade 1 or lower or baseline: Resume at 80 mg once daily.
	Fourth	Discontinue zanubrutinib

More details could be found on the section of "dose modifications" in FDA approval label(15).

7.2.3 Special populations

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the 847 patients in clinical studies with zanubrutinib, 53% were ≥ 65 years of age, and 20% were ≥ 75 years of age. No overall differences in safety or effectiveness were observed between younger and older patients.

Renal Impairment

No dosage modification is recommended in patients with mild, moderate, or severe renal impairment (CLcr ≥ 15 mL/min, estimated by Cockcroft-Gault). Monitor for zanubrutinib adverse reactions in patients on dialysis.

Hepatic Impairment

The recommended dosage of for patients with severe hepatic impairment is 80 mg

orally twice daily. The safety of zanubrutinib has not been evaluated in patients with severe hepatic impairment. No dosage modification is recommended in patients with mild to moderate hepatic impairment. Monitor for zanubrutinib adverse reactions in patients with hepatic impairment.

Females and Males of Reproductive Potential

Pregnancy Testing：Pregnancy testing is recommended for females of reproductive potential prior to

initiating zanubrutinib therapy.

Females：zanubrutinib can cause embryo-fetal harm when administered to pregnant women [see Use in Specific Populations (8.1)]. Advise female patients of reproductive potential to use effective contraception during treatment with zanubrutinib and for 1 week following the last dose of zanubrutinib. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males：Advise men to avoid fathering a child while receiving zanubrutinib and for 1 week following the last dose of zanubrutinib.

More details could be found on the section of "use in specific populations" in FDA approval label(15).

7.3 Recommendations in existing WHO guidelines

N/A.

7.4 Recommendations in other current clinical guidelines

Guidelines of National Comprehensive Cancer Network (NCCN, v1.2023）, Chinese Society of Clinical Oncology (CSCO) 2022 and the guidelines for diagnosis and treatment of CLL/SLL in China (2022) recommend zanubrutinib in CLL patients for the treatment of first-line and second-line patients, regardless of whether they have *del (17p) or TP53* mutation(1, 17, 18).

It was mentioned in updated version 1.2023 of the NCCN Guidelines：ibrutinib was moved from preferred regimens to other recommended regimens. The panel consensus to list ibrutinib under "other recommended regimens" is based on the toxicity profile. A baseline assessment of cardiac function should be done prior to initiation of ibrutinib. In patients with no intolerance, ibrutinib can be continued until disease progression.

Table 7-3 Recommendations in Guidelines for CLL/SLL

Guidelines	Characteristics of CLL/SLL Patients		Grade of Recommendation	
			Zanubrutinib	Ibrutinib
NCCN v1.2023 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

8. Review of benefits: summary of evidence of comparative effectiveness

Zanubrutinib is the Second generation BTKi, which can maximize BTK occupancy (100% BTK occupancy in PBMCs, PPI/H2RA) and minimize off-target binding with dose flexibility-QD/BID. The global zanubrutinib development program includes more than 4,700 subjects enrolled to-date in more than 25 countries and regions, including the United States, China, the European Union (EU), Great Britain, Canada, Australia, South Korea, Switzerland and additional international markets.

Zanubrutinib has been proved in Multinational head-to-head phase 3 clinical trials to have superior clinical advantage than Ibrutinib/BR in CLL/SLL. A Phase 3 interim data results in TN CLL/SLL demonstrated that zanubrutinib has statistically signficant improvements in PFS vs. BR(16) , and a Phase 3 data in R/R CLL/SLL demonstrated superiority in overall response rate (ORR) vs. ibrutinib(4).

8.1 Systematic literature search

Systematic reviews, technology assessment reports, and meta-analyses of controlled clinical trials involving zanubrutinib in at least one arm were searched on the database of PubMed, EMBASE, Cochrane and public websites. Finally, 6 clinical trials were identified and included in our report, without any published meta-analysis/systematic review. The search strategies are as follows:

Search strategy for clinical study in Pubmed:

Date: Nov 30th, 2022

Search number	Query	Search Details	Results	Time
1	"zanubrutinib"[Supplementary Concept]	"zanubrutinib"[Supplementary Concept]	76	4:13:45
2	"leukemia, lymphocytic, chronic, b cell"[MeSH Terms]	"leukemia, lymphocytic, chronic, b cell"[MeSH Terms]	18,124	4:14:59
3	"Clinical Study"[Publication Type]	"Clinical Study"[Publication Type]	1,095,297	4:16:00
4	(("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]	8	4:16:27

Search strategy for clinical study in EMBASE

Date: Nov 30th, 2022

No.	Query	Results	Date
#1	'zanubrutinib'/de	591	30-Nov-22
#2	'clinical study'/exp	11532225	30-Nov-22
#3	'chronic lymphatic leukemia'/exp	51022	30-Nov-22
#4	'clinical trial'/exp	1740632	30-Nov-22
#5	'observational study'/exp	285422	30-Nov-22

#6	#1 AND #2 AND #3	115	30-Nov-22
#7	#1 AND #3 AND #4	80	30-Nov-22
#8	#1 AND #3 AND #5	3	30-Nov-22
#9	#7 OR #8	83	30-Nov-22

8.2 Summary of available evidence for comparative effectiveness

2 randomized controlled studies showing superior clinical efficacy than ibrutinib and BR, and 4 single arm study are included in our report.

8.2.1 BGB-3111-304 (NCT03336333)

8.2.1.1 Study name

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

8.2.1.2 **Study design**

We conducted an open-label, multicentre, phase 3 study at 153 academic or community hospitals in 14 countries and regions. 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. A central interactive web response system randomly assigned patients without del(17) (p13·1) to zanubrutinib (group A) or bendamustine–rituximab (group B) by sequential block method (permutated blocks with a random block size of four). 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/m² of body surface area on days 1 and 2 for six cycles plus rituximab at 375 mg/m² of body surface area the day before or on day 1 of cycle 1, and 500 mg/m² of body surface area

on day 1 of cycles 2–6, were administered intravenously. The primary endpoint was PFS per IRC in the intention-to-treat (ITT) population in groups A and B. Safety was analysed in all patients who received at least one dose of study treatment(16).

8.2.1.3 Efficacy endpoints

Between Oct 31, 2017, and July 22, 2019, 590 patients were enrolled; patients without del(17)(p13.1) were randomly assigned to zanubrutinib (n=241) or BR (n=238). At median follow-up of 26.2 months (IQR 23.7–29.6), median PFS per IRCwas not reached in either group (group A 95% CI not estimable [NE] to NE; group B 28.1 months to NE). PFS was significantly improved in group A versus group B (HR 0·42 [95% CI 0.28 to 0.63]; two-sided p<0.0001)(16). The key results are summarized as follows:

Cohort 1: Zanubrutinib (group A) vs. B+R(group B) in TN CLL Patients Without del (17p)

- The 24-month PFS rate was 85.5% (95% CI: 80.1, 89.6) in group A, compared to 69.5% (95% CI: 62.4, 75.5) in group B, with a HR of 0.42 (95% CI: 0.27, 0.63), p < 0.0001.

- PFS benefit was consistently observed across key patient subgroups, including patients with del(11q), unmutated IGHV status, Binet stage C, and bulky disease.

- OS results were early, and at 24 months, OS probability was similar between two arms, with 94.3% (95% CI: 90.4, 96.7) in group A and 94.6% (95% CI: 90.6, 96.9) in group B.

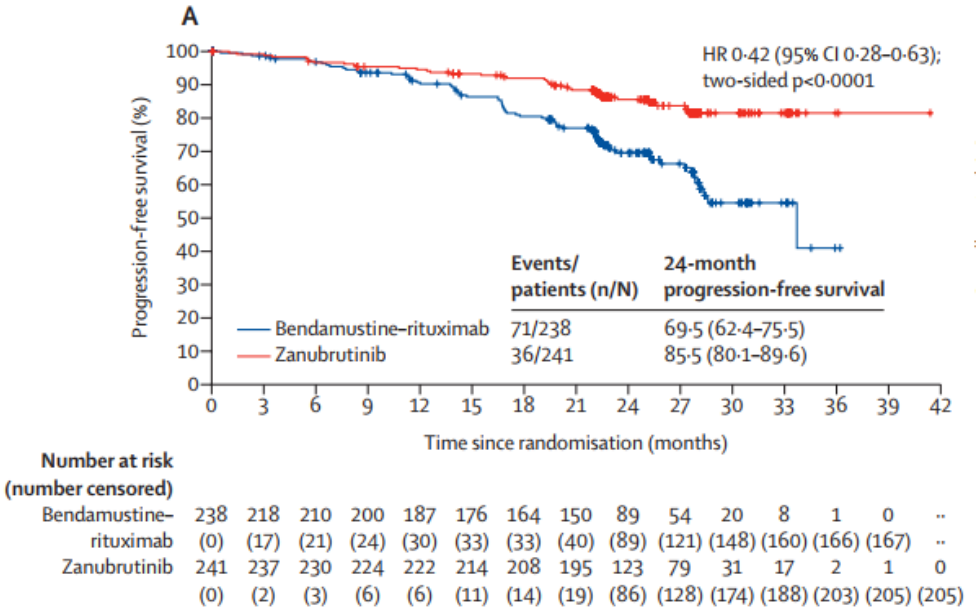

Figure 1: Kaplan-Meier Curve of PFS by IRC in Patients with CLL/SLL without del(17) (p13·1)

Cohort 2 (group C): Zanubrutinib monotherapy in TN Patients with CLL/SLL with del(17p)

- 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.

8.2.1.4 Health-Related Quality of Life

An interim analysis of health-related quality of life (HRQoL) outcomes was assessed using patient reported outcomes (PROs) using EORTC QLQ-C30 and EQ-5D-5L VAS. Patients who were treated

with zanubrutinib showed greater improvements with HRQoL at weeks 12 and 24 compared to their BR treated counterparts. At 24 weeks, these differences were significantly higher for zanubrutinib in global health status, physical functioning, role functioning, and reduction in diarrhea, fatigue, and nausea/vomiting(19).

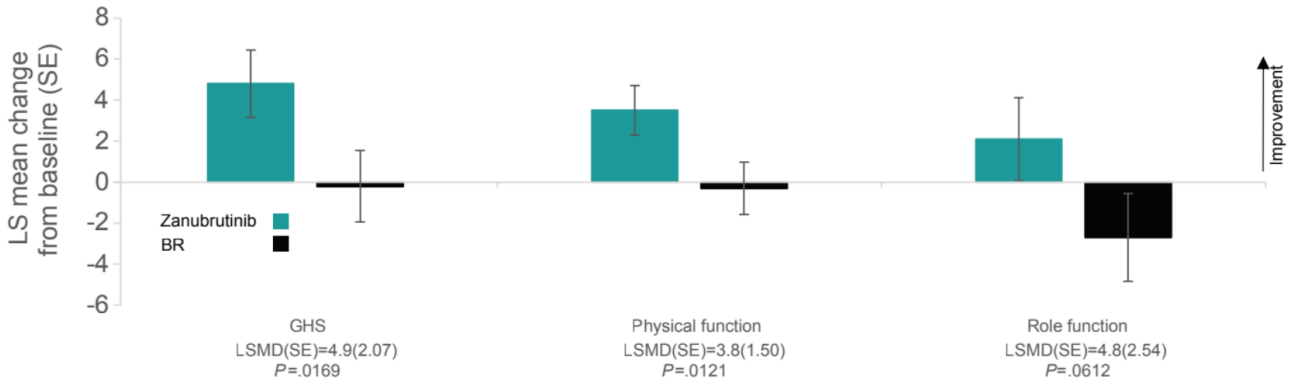

Figure 2: EORTC QLQ-C30 LS Mean Change From Baseline in GHS and Functioning Scales at Week 24

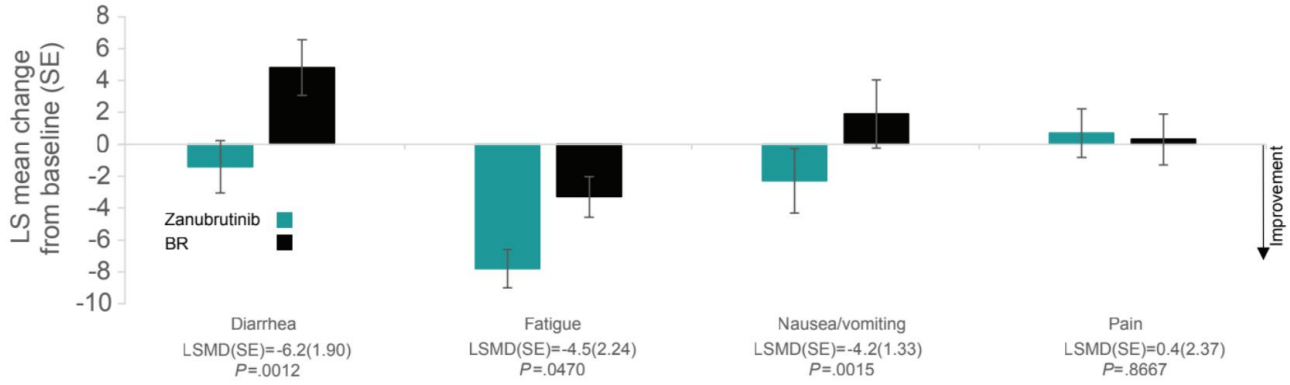

Figure 3: EORTC QLQ-C30 LS Mean Change From Baseline in Symptom Scales at Week 24

8.2.2 BGB-3111-305(NCT03734016)

8.2.2.1 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.

8.2.2.2 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(5).

8.2.2.3 Efficacy Endpoints

Zanubrutinib demonstrates superior both PFS and ORR compared with ibrutinib for treatment of R/R CLL/SLL: results from final analysis of ALPINE randomized phase 3 study(5).

- At a median follow-up of 29.6 months, zanubrutinib was found to be superior to ibrutinib with respect to progression-free survival 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; 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. Median PFS was not reached in the zanubrutinib group and was 34.2 months (95% CI, 33.3 to not estimable) in the ibrutinib group. 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); progression-free survival across other major subgroups consistently favored zanubrutinib.

- Compared with ibrutinib, zanubrutinib had a higher ORR_{IRC} (86.2 vs 75.7%, nominal 2-sided P=0.0007), with a rate of PR-L or better of 91.7% vs 83.1% (nominal 2-sided P=.001).

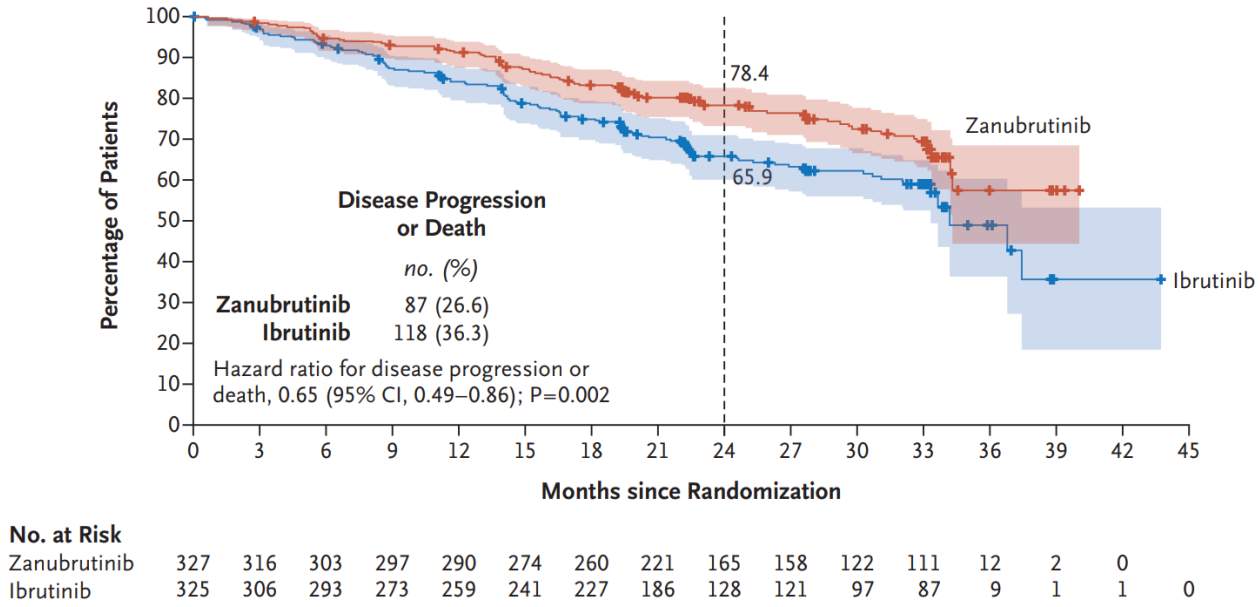

Figure 4: IRC-Assessed PFS （ITT Population）

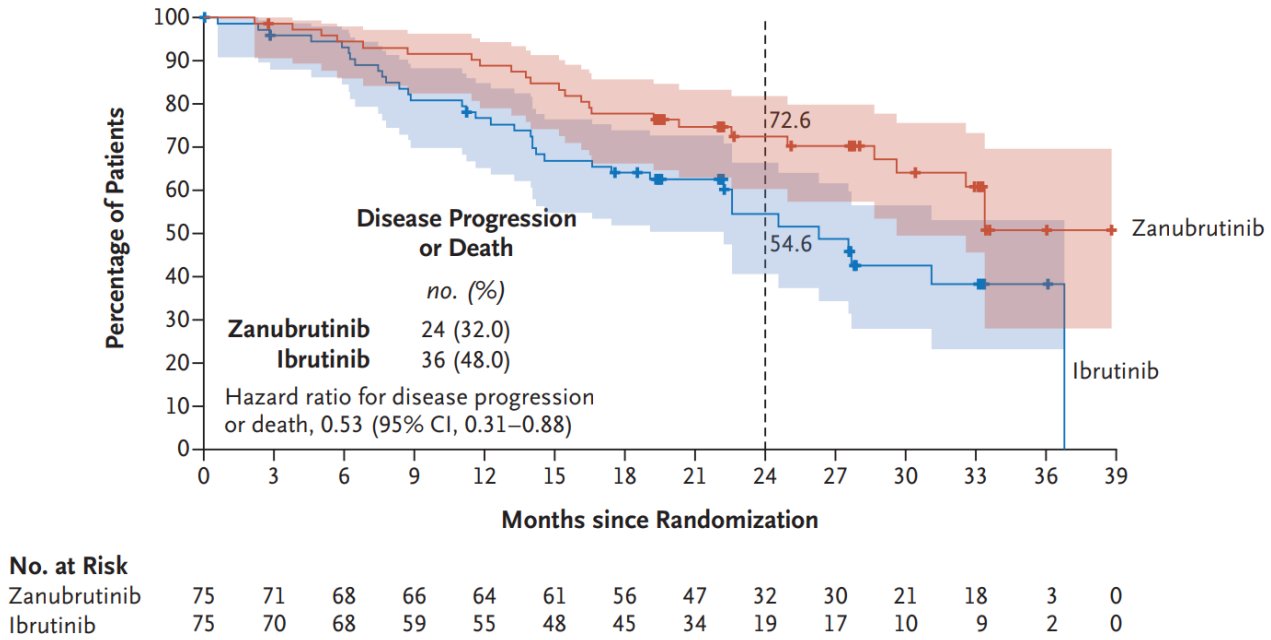

Figure 5: IRC-Assessed PFS in Patients with del(17p)/TP53 mutation

8.2.2.4 Health-Related Quality of Life

An interim analysis of HRQoL outcomes was assessed using PROs using EORTC QLQ-C30 and EQ-5D-5L VAS. Compared with baseline, the positive improvements in HRQoL, as assessed by disease-related symptoms and treatment-related effects and functioning, were more profound in cycle 7 (6 months after the initiation of therapy), which suggests that treatment with zanubrutinib could potentially alleviate disease burden earlier than ibrutinib in this patient population.The HRQoL results align with results from the interim analysis of ALPINE showing that rates of adverse events (AEs) such as atrial fibrillation, major bleeding, and AEs leading to discontinuation or death were lower in patients treated with zanubrutinib vs ibrutinib(20).

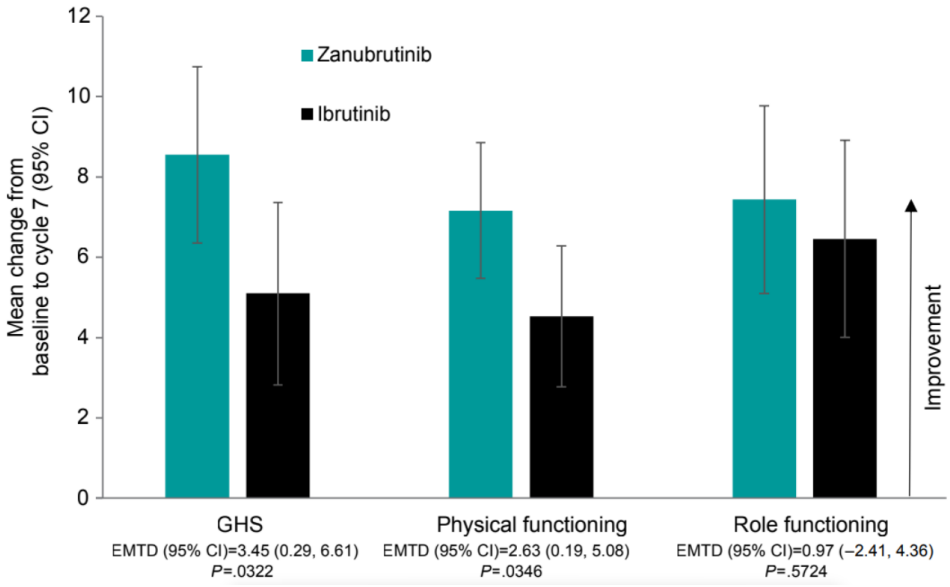

Figure 6: EORTC QLQ-C30 Mean Change From Baseline in GHS and Functioning Scales at Cycle 7 (6 Months) by treatment (ITT)

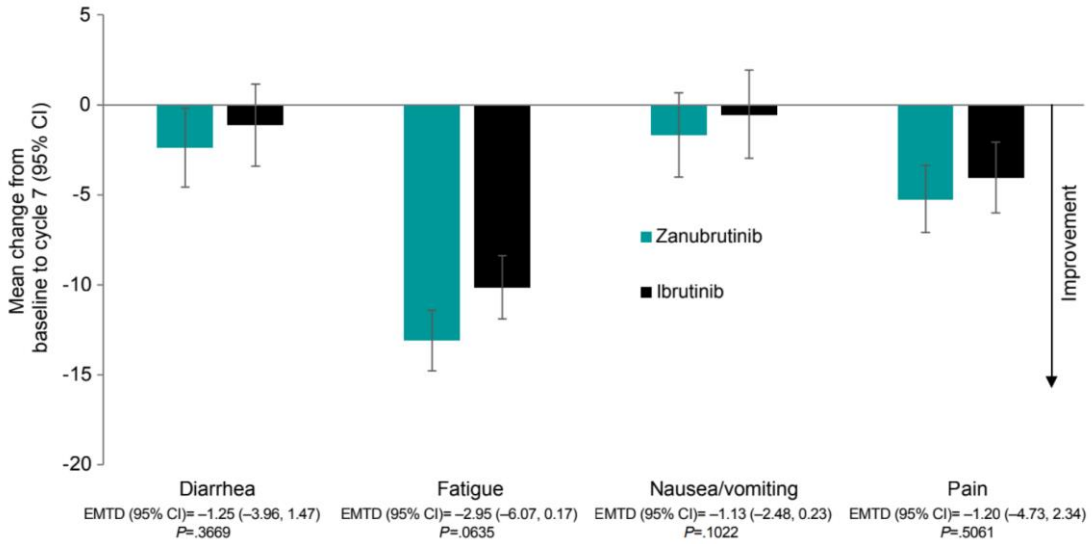

Figure 7: EORTC QLQ-C30 Mean Change From Baseline in Symptom Scales at Cycle 7 (6 Months) by Treatment(ITT)

8.2.3 Other trials

8.2.3.1 BGB-3111-205 (NCT03206918)

A single-arm, open-label, multicenter phase 2 study to evaluate safety and efficacy of zanubrutinib, a BTK inhibitor in R/R CLL or SLL. 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(21).

The ORR was 87.9% with 6.6% of patients achieving a complete response (CR), 69.2% achieving a partial response (PR), and 12.1% achieving a PR with lymphocytosis.

ORR was generally consistent across all subgroups analyzed, including patients with high-risk cytogenetics. Patients with del (17p) and/or TP53 mutation and del (11q)achieved high response rates of 91% (95% CI, 70.8%-98.9%) and 100% (95% CI, 83.2%-100%), respectively(22).

Table 8-1 BGB-3111-205: IRC-Assessed Primary and Secondary Endpoints Assessed

Response by IRC	**Patients with R/R CLL/SLL N =91**
Efficacy	
Overall response, % (95% CI)	87.9 (79.4-93.8)
Median, TTR, months (range)	2.79 (2.6-16.8)
Best overall response, no. (%)	
Complete response	6 (6.6)
Partial response	63 (69.2)
Partial response with lymphocytosis	11 (12.1)
Stable disease	3 (3.3)
Partial disease	3 (3.3)
Not evaluable, no. (%)	2 (2.2)
Discontinued prior to first postbaseline assessment, no.(%)	3 (3.3)

8.2.3.2 BGB-3111-AU-003 (NCT023443120)

A phase 1/2, 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.

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. We report

updated safety and efficacy data for 123 patients with a median follow-up of 47.2 months. 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%. 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(23).

Table 8-2 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 12mo, % (95% CI)	95.2 (70.7-99.3)	97.8 (91.6-99.5)

8.2.3.3 BGB-3111_GA101_Study_001 (NCT02569476)

A phase 1b study to assess safety, tolerability and antitumor activity of the combination of BGB 3111 with obinutuzumab in subjects with B-cell lymphoid malignancies.

The primary objective was to evaluate the efficacy of combination zanubrutinib and obinutuzumab as measured by ORR and DOR assessed by an IRC in patients with treatment-naïve or R/R CLL or SLL

as well as R/R FL.

Secondary objectives were to evaluate the safety of combination zanubrutinib and obinutuzumab in patients with treatment-naïve or R/R CLL or SLL. Exploratory endpoints included assessment of MRD in patients with treatment-naïve or R/R CLL or SLL.

In R/R patients, the ORR was 92% (n=23) with 28% (n=7) CRs and 64% (n=16) PRs; an additional 8% of patients (n=2) achieved stable disease (SD). In patients with treatment-naïve disease,the ORR was 100% (n=20) with 30% (n=6) CRs and 70% (n=14) PRs. The median PFS and median DOR were not reached. The estimated event-free DOR rate at 24 months was 90.4% (95% CI, 76.5%-96.3%)(24).

Table 8-3 BGB-3111_GA101_Study_001: Primary Endpoint

Outcome[a]	**TN CLL/SLL N = 20**	**R/R CLL/SLL N = 25**
Overall response, no. (%)	20 (100)	23 (92.0)
Best overall response, no. (%)		
Complete response[b]	6 (30.0)	7 (28.0)
Partial response	14 (70.0)	16 (64.0)
Stable disease	0	2 (8.0)
Progressive disease	0	0
Overall response in molecular subtypes, no./N (%)		
Del(17p)/TP53 mutation	6/6 (100)	8/10 (80.0)

8.2.3.4 BGB-3111-18-427 BOVen (NCT03824483)

Phase 2 Study of zanubrutinib, Obinutuzumab, and Venetoclax in Previously Untreated Patients With CLL or SLL and Mantle Cell Lymphoma (MCL).The purpose of this study is to determine the rate of minimum residual disease (MRD) negative response (i.e. the rate of no evidence of disease) of the study drugs, zanubrutinib, obinutuzumab, and venetoclax, given in combination as a treatment for CLL/SLL

and previously untreated TP53 mutated MCL.

The median time to achievement of bone marrow uMRD-FC4 was 8 months (interquartile range, 6-10), representing 6 months of treatment with the BOVen triplet regimen. The ORR was 100% (n=37), the CR/CRi rate was 57% (n=21), and the PR rate was 45% (n=15). MedianPFS was not reached. Of the 33 patients who met criteria for uMRD and discontinued therapy, 31 (94%) had ongoing uMRD-FC4 in the peripheral blood following a median of 15.8 months (interquartile range, 13-18.6). Three patients with persistent detectable MRD in bone marrow discontinued therapyafter 24 cycles (25).

8.2.4 Assessment of applicability of the available evidence across diverse populations and settings

Consistent efficacy results were shown in all trials including ALPINE. In prespecified subgroup analyses of PFS by independent review committee, PFS was consistently longer with zanubrutinib than with BR independent of age, sex, or high-risk disease status, including Binet stage C, bulky disease, or presence of unmutated IGHV gene, or del(11) (q22·3) .

9. Review of harms and toxicity: summary of evidence of comparative safety

9.1 Estimates of total patient exposure to date

As of Nov 30th, 2022, zanubrutinib is supported by a broad clinical program which includes more than 4,700 subjects in 35 trials in more than 25 countries and regions,including the United States, China, EU, Great Britain, Canada, Australia, South Korea, Switzerland and additional international markets.

9.2 Information on the identification of clinical evidence using a systematic literature search

Systematic reviews, technology assessment reports, and meta-analyses of controlled clinical trials involving zanubrutinib in at least one arm were searched on the database of PubMed, EMBASE, Cochrane and public websites. Finally, 6 clinical trials were identified and included in our report, without any published meta-analysis/systematic review. The search strategies are as follows:

Search strategy for clinical study in Pubmed:

Date: Nov 30th, 2022

Search number	Query	Search Details	Results	Time
1	"zanubrutinib"[Supplementary Concept]	"zanubrutinib"[Supplementary Concept]	76	4:13:45
2	"leukemia, lymphocytic, chronic, b cell"[MeSH Terms]	"leukemia, lymphocytic, chronic, b cell"[MeSH Terms]	18,124	4:14:59
3	"Clinical Study"[Publication Type]	"Clinical Study"[Publication Type]	1,095,297	4:16:00
4	(("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]	8	4:16:27

Search strategy for clinical study in EMBASE

Date: Nov 30th, 2022

No.	Query	Results	Date
#1	'zanubrutinib'/de	591	30-Nov-22
#2	'clinical study'/exp	11532225	30-Nov-22
#3	'chronic lymphatic leukemia'/exp	51022	30-Nov-22
#4	'clinical trial'/exp	1740632	30-Nov-22
#5	'observational study'/exp	285422	30-Nov-22
#6	#1 AND #2 AND #3	115	30-Nov-22
#7	#1 AND #3 AND #4	80	30-Nov-22
#8	#1 AND #3 AND #5	3	30-Nov-22
#9	#7 OR #8	83	30-Nov-22

9.3 Descriptions of adverse effects of the proposed medicine(s) and estimates of their frequency and grading of severity

9.3.1 BGB-3111-304 (NCT03336333)

Safety was assessed in patients who received at least 1 dose of treatment; 1 patient in group a and 11 patients in group b did not received treatment. AEs were reported until disease progression for both arms(16).

Table 9-1 Safety Summary of Patients in SEQUOIA Cohort 1

AE, n %	Zanubrutinib n=240	BR n=227
Any AE	224 (93.3)	218 (96.0)
Any grade ≥3 AEs	126 (52.5)	181 (79.7)
Serious AEs	88 (36.7)	113 (49.8)
Grade 5 AEs	11 (4.6)	11 (4.8)
Leading to dose reduction	18 (7.5)	84 (37.4)
Leading to dose interruption/delay	111 (46.3)	154 (67.8)
Leading to treatment discontinuation	20 (8.3)	31 (13.7)

Table 9-2 AEs of Interest in SEQUOIA Cohort 1

AE, n %	Zanubrutinib n=240		BR n=227	
	Any Grade	Grade ⩾3	Any Grade	Grade ⩾3
Anemia	11 (4.6)	1 (0.4)	44 (19.4)	4 (1.8)
Neutropenia	38 (15.8)	28 (11.7)	129 (56.8)	116 (51.1)
Thrombocytopenia	11 (4.6)	5 (2.1)	40 (17.6)	18 (7.9)
Arthralgia	32 (13.3)	2 (0.8)	20 (8.8)	1 (0.4)
Atrial Fibrillation	8 (3.3)	1 (0.4)	6 (2.6)	3 (1.3)

Bleeding Major Bleeding	108 (45) 12 (5)	9 (3.8) 9 (3.8)	25 (11) 4 (1.8)	4 (1.8) 4 (1.8)
Diarrhea	33 (13.8)	2 (0.8)	31 (13.7)	5 (2.2)
Hypertension	34 (14.2)	15 (6.3)	24 (10.6)	11 (4.8)
Infections	149 (62.1)	39 (16.3)	127 (55.9)	43 (18.9)
Myalgias	9 (3.8)	0 (0)	3 (1.3)	0 (0)
Other cancers Dermatologic: other cancers	31 (12.9) 16 (6.7)	17 (7.1) 2 (0.8)	20 (8.8) 10 (4.4)	7 (3.1) 2 (0.9)

9.3.2 BGB-3111-305 (NCT03734016)

Treatment discontinuation rate was lower with zanubrutinib (26.3%) vs ibrutinib (41.2%) with most due to AEs (16.2 vs 22.8%) or progressive disease (7.3 vs 12.9%); discontinuation rates due to cardiac disorders were 0.3% vs 4.3%. Rates of grade ⩾3 AEs (67.3 vs 70.4%), serious AEs (42.0% vs 50.0%), dose interruption (50.0% vs 56.8%), and dose reduction (12.3 vs 17.0%) were also lower with zanubrutinib vs ibrutinib. Rate of atrial fibrillation/flutter was lower with zanubrutinib compared with ibrutinib (5.2% vs 13.3%); rates of other AEs of special interest were similar between treatments. There were no grade 5 AEs due to cardiac disorders with zanubrutinib vs 6 (1.9%) with ibrutinib(5).

Zanubrutinib had a favorable safety profile compared with ibrutinib, with a lower rate of treatment discontinuation and fewer cardiac disorder events, including fewer cardiac events leading to death.

9.3.3 BGB-3111-302 (NCT03053440)

The ASPEN Trial is a pivotal Phase 3 randomized, open-label, multicenter study evaluating zanubrutinib compared to ibrutinib in patients with R/R or TN Waldenström's macroglobulinemia (WM).ASPEN was the first randomized Phase 3 study comparing two BTK inhibitors in any indication and is the largest prospective randomized Phase 3 study in WM. The ASPEN trial is a randomized Phase 3 trial in 229 patients with WM conducted in 61 centers in Europe, Australia, and the United States. The study includes two cohorts, a randomized cohort (cohort 1) consisting of 201 patients with a MYD88 mutation and a non-randomized cohort (cohort 2) in which 28 patients with MYD88 wild-type (MYD88WT) received zanubrutinib because they have historically responded poorly to ibrutinib

therapy(26).

In the long-term follow-up results of ASPEN, Zanubrutinib when compared with ibrutinib had fewer AEs leading to death, treatment discontinuation, and dose reduction. The prevalence of atrial fibrillation, hypertension, and bleeding were lower in the zanubrutinib arm at all time intervals(27).

Table 9-3 Safety Summary of Patients in ASPEN

AE, n %	Cohort 1		Cohort 2
	Zanubrutinib (n=101)	Ibrutinib (n=98)	Zanubrutinib (n=28)
Patients with ⩾1 AE	100 (99.0)	98 (100.0)	26 (92.9)
Grade ⩾3	75 (74.3)	71 (72.4)	20 (71.4)
Serious	57 (56.4)	49 (50.0)	14 (50.0)
AE leading to death	3 (3.0)	5 (5.1)	3 (10.7)
AE leading to treatment discontinuation	9 (8.9)	20 (20.4)	6 (21.4)
AE leading to dose reduction	16 (15.8)	26 (26.5)	2 (7.1)
AE leading to dose held	63 (62.4)	62 (63.3)	18 (64.3)
COVID-19-related AE	4 (4.0)	4 (4.1)	2 (7.1)

Table 9-4 Most Common AEs in ASPEN Cohort 1

AE, n (%)	All grades (⩾20%)		Grade ⩾3 (⩾5%)	
	Zanubrutinib (n=101)	Ibrutinib (n=98)	Zanubrutinib (n=101)	Ibrutinib (n=98)
Diarrhea	23 (22.8)	34 (34.7)	3 (3.0)	2 (2.0)
Upper respiratory tract infection	33 (32.7)	32 (32.7)	0	1 (1.0)
Muscle spasms	12 (11.9)	28 (28.6)	0	1 (1.0)
Contusion	19 (18.8)	27 (27.6)	0	0
Arthralgia	24 (23.8)	24 (24.5)	3 (3.0)	0
Hypertension	15 (14.9)	24 (24.5)	10 (9.9)	19 (19.4)
Peripheral edema	18 (17.8)	21 (21.4)	0	0
Epistaxis	17 (16.8)	21 (21.4)	1 (1.0)	0
Atrial fibrillation	7 (6.9)	21 (21.4)	2 (2.0)	6 (6.1)
Cough	19 (18.8)	20 (20.4)	0	0
Fatigue	26 (25.7)	19 (19.4)	1 (1.0)	1 (1.0)
Pneumonia	5 (5.0)	18 (18.4)	1 (1.0)	10 (10.2)
Syncope	5 (5.0)	8 (8.2)	5 (5.0)	6 (6.1)

Table 9-5 AEs of Interest in ASPEN Cohort 1

AE, n (%)	All grades		Grade ⩾3	
	Zanubrutinib (n=101)	Ibrutinib (n=98)	Zanubrutinib (n=101)	Ibrutinib (n=98)
Infection	80 (79.2)	78 (79.6)	22 (21.8)	27 (27.6)
Bleeding	56 (55.4)	61 (62.2)	9 (8.9)	10 (10.2)
Diarrhea	23 (22.8)	34 (34.7)	3 (3.0)	2 (2.0)
Hypertension	15 (14.9)	25 (25.5)	10 (9.9)	20 (20.4)
Atrial fibrillation/flutter	8 (7.9)	23 (23.5)	2 (2.0)	8 (8.2)
Anemia	18 (17.8)	22 (22.4)	12 (11.9)	6 (6.1)
Neutropenia	35 (34.7)	20 (20.4)	24 (23.8)	10 (10.2)
Thrombocytopenia	17 (16.8)	17 (17.3)	11 (10.9)	6 (6.1)
Second primary malignancy/nonskin cancers	17 (16.8) / 6 (5.9)	17 (17.3) / 6 (6.1)	6 (5.9) / 4 (4.0)	3 (3.1) / 3 (3.1)

9.3.4 Other trials

9.3.4.1 BGB-3111-205 (NCT03206918)

Safety data is included from an earlier publication (median follow-up of 15.1 months) with a comprehensive set of safety results. One-third of patients experienced an SAE, with 58 (63.7%) experiencing an AE of grade 3 or higher and 8 (8.8%) experiencing a grade 4 AE. Seven patients (7.7%) reported AEs leading to dose reductions, and 8 patients(9.0%) reported AEs leading to discontinuation of zanubrutinib therapy. Three patients experienced AEs leading to death (lung infection, cardiopulmonary failure, and multiorgan system failure)(22).

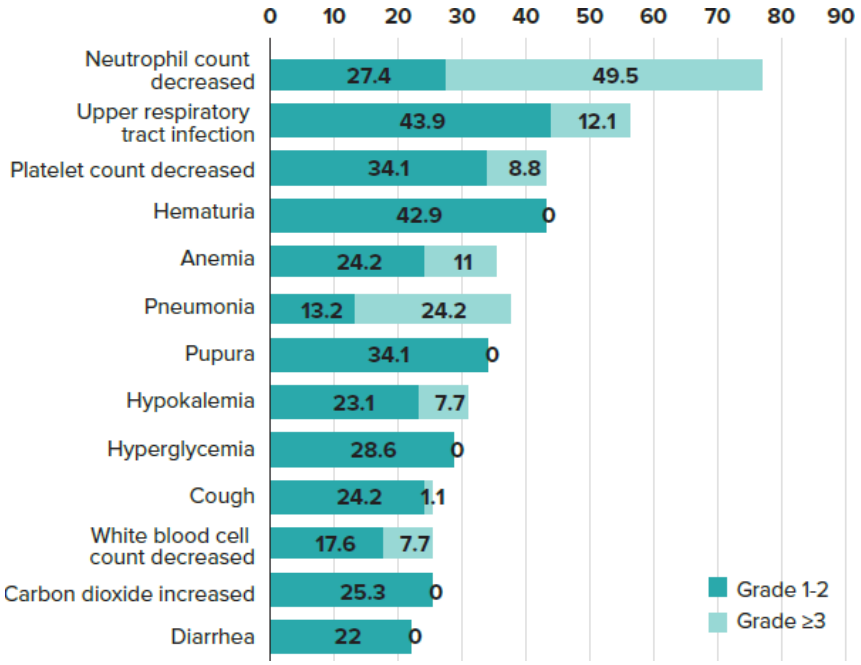

Figure 8. BGB-3111-205: Treatment Emergent AEs in ≥20% of Patients with CLL or SLL Regardless of Causality Error! Bookmark not defined.

9.3.4.2 BGB-3111-AU-003 (NCT023443120)

Seventy-six patients (61.8%) experienced at least one grade 3 or higher AE. Five patients(4.1%) discontinued zanubrutinib therapy due to an AE; 3 were deemed unrelated and 2 related to zanubrutinib therapy. One person experienced an AE leading to death, deemed unrelated by investigators(23).

Table 9-6 BGB-3111-AU-003: Summary of AEs Reported in Patients with CLL or SLL Safety Analysis Set

Event	**CLL/SLL, No. % N = 123**
Patients with any AE	123 (100)
Grade ≥3 AEs	76 (61.8)
Serious AEs	58 (47.2)
AEs leading to treatment discontinuation	5 (4.1)
AEs leading to death	1 (0.8)

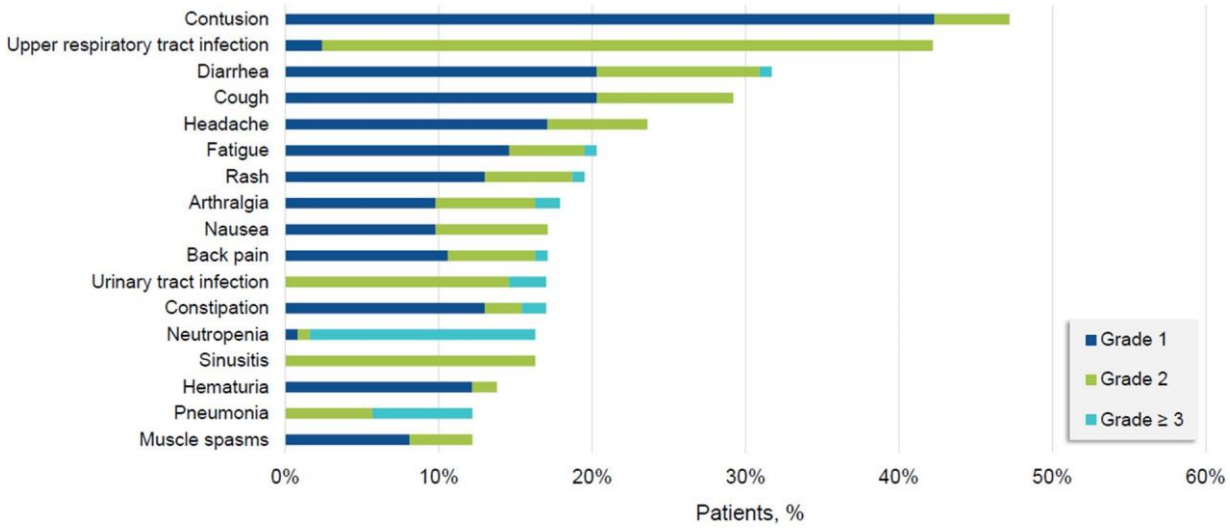

Figure 9. BGB-3111-AU-003: AEs in ≥ 10% of Patients with CLL or SLL Regardless of Causality

9.3.4.3 BGB-3111_GA101_Study_001 (NCT02569476)

The most common AEs of any grade (≥20% of patients with CLL/SLL) during the dose-expansion phase were upper respiratory tract infection (51.1%), neutropenia (44.4%), contusion (33.3%), cough (26.7%), fatigue (26.7%), diarrhea (26.7%), and pyrexia (22.2%). Additional AEs of interest that occurred included all-grade infections (87%), infusion-related reactions (24%), and hypertension (9%). Grade ≥3 AEs included infections (38%), neutropenia (31.1%), pneumonia (8.9%), thrombocytopenia (6.7%), hypertension (7%), back pain (4.4%), fatigue (2.2%), and infusion-related reactions (2.2%). Thirty-three patients (73.3%) experienced at least one grade 3 or higher AE. Four patients (8.9%) discontinued therapy due to an AE(24).

9.3.4.4 BGB-3111-18-427 BOVen (NCT03824483)

The most common AEs of any grade were thrombocytopenia (59%), fatigue (54%), neutropenia (51%), bruising (51%), diarrhea (46%), infusion-related reactions (44%), anemia (41%), cough (36%), rash (33%), and nausea (31%). 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 hemorrhage, and the other was on day 25 of cycle 1 due to metastatic adenocarcinoma(25).

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 $\leq 10^{-5}$), 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%)(25).

9.4 A summary of comparative safety versus relevant comparators

Please refer to the safety comparison results of two head-to-head studies (see 9.3.1 and 9.3.2 for details).

9.5 Consideration of the potential for and consequences of inappropriate use or use outside the proposed indication

By reviewing cases of off-label use of zanubrutinib, we did not find safety findings or any associated patterns of use.

9.6 Information on any variation in safety that may relate to health systems or patient factors.

There is no evidence of disparities in the safety of zanubrutinib across ethnic groups and populations.

9.7 Information on any warning or safety issues identified by regulatory authorities (e.g., black box warning, drug safety alerts etc).

Since the first launch of zanubrutinib in USA in 2019, it has not received any safety warning, black box warning, withdrawal from the market and other information issued by any national drug regulatory authorities.

10. Summary of available data on comparative cost and cost-effectiveness

10.1 Medicine prices in different markets

Aiming to benefit more patients around the world, the global average price of zanubrutinib is much lower than ibrutinib in most countries. The percentage of price cut is 0.3%~24% in average due to different indications. Price data from Navlin database(https://data.navlin.com/).

Table 10-1 Medicine prices in different markets as of Nov 30th, 2022

Country	Currency	Source	Zanubrutinib Capsules 80mg		Ibrutinib Capsules/Tablets 140mg			Price cut comparing to Ibrutinib	
			Costs/Unit	Costs/Day (All Indications)	Costs/Unit	Costs/Day (CLL/SLL, WM)	Costs/Day (MCL/MZL)	Costs/Day (CLL/SLL, WM)	Costs/Day (MCL/MZL)
Australia	AUD	PPI[1]	73	293	98	293	391	0.0%	-25.0%
Belgium[3]	EUR	MNF[2]	48	191	64	191	255	0.0%	-25.0%
Brazil	BRL	PPI	529	2,117	706	2,117	2,823	0.0%	-25.0%
Canada	CAD	MNF	68	272	100	300	399	-9.2%	-31.9%
China	CNY	PPI	99	396	169	507	676	-21.9%	-41.4%
Denmark[3]	DKK	PPI	484	1,935	642	1,926	2,568	0.5%	-24.6%
Germany[3]	EUR	PPI	55	219	71	213	284	2.6%	-23.0%
Ireland	EUR	PPI	49	197	66	198	264	-0.7%	-25.5%
Italy	EUR	PPI	83	334	111	334	445	0.0%	-25.0%
Liechtenstein[3]	CHF	PPI	45	179	63	189	251	-5.3%	-29.0%
Netherlands[3]	EUR	PPI	48	192	63	188	251	2.2%	-23.3%
Norway	NOK	PPI	524	2,095	698	2,095	2,793	0.0%	-25.0%
Oman	OMR	PPI	29	117	33	99	131	18.7%	-11.0%
Qatar	QAR	PPI	278	1,111	371	1,114	1,485	-0.2%	-25.2%
Saudi Arabia	SAR	PPI	238	950	267	801	1,068	18.7%	-11.0%
Spain	EUR	PPI	58	230	77	230	306	0.2%	-24.8%
Switzerland[3]	CHF	PPI	45	179	63	189	251	-5.3%	-29.0%

United Kingdom	GBP	MNF	41	164	51	153	204	7.2%	-19.6%
United States[3]	USD	MNF	117	467	534	534	534	-12.7%	-12.7%
Average								-0.3%	-24.1%

1 PPI (Public Price Including VAT): Price from the pharmacy to the patient with VAT.

2 MNF (Manufacture Price): Price from the manufacturer to the wholesaler.

3 The dosage form of ibrutinib in these countries is tablet.

10.2 Cost-effectiveness and cost-utility analyses

Direct comparative data on Pharmacoeconomics containing zanubrutinib on R/R CLL/SLL are still lacking. Results from cost-effectiveness analyses showed that BTK inhibitor (ibrutinib) versus CIT for the treatment of R/R CLL showed that ibrutinib is more cost-effective for R/R CLL patients with at least one prior treatment(28-30).As a next-generation of BTK inhibitor, zanubrutinib has more advantages on efficacy and safety, which can not only improve quality adjusted life years (QALYs) in patients, but also further saves the cost of follow-up treatment caused by poor prognosis and AEs.

The Search strategy for economic evaluations are as follows:

Pubmed

Date: Nov 30th, 2022

Search number	Query	Search Details	Results	Time
1	"zanubrutinib"[Supplementary Concept]	"zanubrutinib"[Supplementary Concept]	76	4:13:45
2	"leukemia, lymphocytic, chronic, b cell"[MeSH Terms]	"leukemia, lymphocytic, chronic, b cell"[MeSH Terms]	18,124	4:14:59
3	"Costs and Cost Analysis"[Mesh]	"Costs and Cost Analysis"[MeSH Terms]	259,653	4:36:32
4	"Cost-Benefit Analysis"[Mesh]	"Cost-Benefit Analysis"[MeSH Terms]	90,441	4:37:44
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]	0	4:38:06
7	(("zanubrutinib"[Supplementary Concept]) AND ("leukemia, lymphocytic, chronic, b cell"[MeSH Terms])) AND ("Cost-Benefit Analysis"[Mesh]) - Schema: all	"zanubrutinib"[Supplementary Concept] AND "leukemia, lymphocytic, chronic, b cell"[MeSH Terms] AND "Cost-Benefit Analysis"[MeSH Terms]	0	4:38:38

8	(("zanubrutinib"[Supplementary Concept]) AND ("leukemia, lymphocytic, chronic, b cell"[MeSH Terms])) AND ("Cost-Benefit Analysis"[Mesh])	"zanubrutinib"[Supplementary Concept] AND "leukemia, lymphocytic, chronic, b cell"[MeSH Terms] AND "Cost-Benefit Analysis"[MeSH Terms]	0	4:38:38

EMBASE

Date: Nov 30th, 2022

No.	Query	Results	Date
#1	'zanubrutinib'/de	591	30-Nov-22
#2	'chronic lymphatic leukemia'/exp	51022	30-Nov-22
#3	'cost effectiveness analysis'/exp	170752	30-Nov-22
#4	'cost utility analysis'/exp	11302	30-Nov-22
#5	'economic evaluation'/exp	338181	30-Nov-22
#6	'health economics'/exp	993260	30-Nov-22
#7	'budget impact analysis'/exp	119	30-Nov-22
#8	#1 AND #2 AND #6	22	30-Nov-22
#9	#1 AND #2 AND #5	3	30-Nov-22
#10	#1 AND #2 AND #4	0	30-Nov-22
#11	#1 AND #2 AND #3	1	30-Nov-22
#12	#1 AND #7	0	30-Nov-22
#13	#10 OR #11 OR #12	1	30-Nov-22

10.3 Budget impact

As zanubrutinib has better clinical advantage and much cheaper price than ibrutinib, uptaking zanubrutinib to substitute ibrutinib will save lots of financial funds considering large number of CLL/SLL patients across the globe. According to Global Cancer Statistic Data from International

Agency For Research On Cancer (IARC) in 2020, the estimated number of NHL cases with 5 years in worldwide is 1544,488(31), 6.1-7.0% of which are CLL/SLL patients(32). Based on the data, the estimated number of NHL cases with 5 years in worldwide is 94,214-108,114. According to a real world study(33), the proportion of each current treatment for CLL/SLL (either first-line therapy or second-line therapy) was listed below: BR (32%), FCR (14%), Rituximab (24%), and Ibrutinib (15%). There are no more than 16,217 people taking zanubrutinib in worldwide.

11. Regulatory status, market availability and pharmacopoieal standards

11.1 Regulatory status of the proposed medicine(s)

As of Nov 30th, 2022, zanubrutinib was approved in 61 markets including the U.S., China, EU, Great Britain, Canada, Australia, South Korea and Switzerland in selected indications and under development for additional approvals globally. Currently, more than 40 additional regulatory submissions are in review around the world. R/R CLL/CLL has been approved in China, TN/RR CLL/SLL has been approved in EU and formally accepted in regulatory authorities of FDA/NMPA/Health Canada and is estimated to be approved very soon.

- US Food and Drug Administration (FDA)
    - Approved on 14.11.2019 for MCL (first approval for zanubrutinib)
    - Approved on 31.8.2021 for WM
    - Approved on 14.9.2021 for marginal zone lymphoma (MZL)
    - Received acceptance for sNDA for CLL/SLL which has a PDUFA target action date of January 2023
- China National Medical Products Administration (NMPA)

  - Approved on 2.6.2020 for MCL
  - Approved on 2.6.2020 for R/R CLL/SLL
  - Approved on 16.6.2021 for WM
  - Received acceptance for sNDA for TN CLL/SLL

- European Medicines Agency (EMA)
  - Approved on 22.11.2021 for WM
  - Approved on 2.11.2022 for MZL
  - Approved on 17.11.2022 for TN/RR CLL/SLL

- Health Canada
  - Approved on 1.3.2021 for WM
  - Approved on 22.7.2021 for MCL
  - Approved on 18.2.2022 for MZL
  - Received acceptance for sNDS for CLL;

- Australian Therapeutic Goods Administration (TGA)
  - Approved on 7.10.2021 for WM
  - Approved on 8.10.2021 for MCL

- Singapore Health Sciences Authority (HSA)
  - Approved on 1.10.2021 for MCL

- UK Medicines and Healthcare products Regulatory Agency Medicines and Healthcare products Regulatory Agency (MHRA)
  - Approved on 6.12.2021 for WM

- Switzerland Swissmedic

- Approved on 8.2.2022 for WM

11.2 Market availability of the proposed medicine(s)

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

12. Appendix

ADR	adverse drug reaction
AE	adverse event

B	bendamustine
BR	bendamustine + rituximab
BTK	bruton's tyrosine kinase
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete response/remission
CRi	complete recovery with incomplete count recovery
DLBCL	diffuse large b-cell lymphoma
DOR	duration of response
ECOG	eastern cooperative oncology group
EFS	event free survival
EORTC	european organization for research and treatment of cancer
EU	european union
F	fludarabine
FCR	fludarabine + cyclophosphamide + rituximab
FDA	food and drug administration
FL	follicular lymphoma
HR	hazard ratio
HRQoL	health-related quality of life
IARC	international agency for research on cancer
IQR	interquartile range
IRC	independent review committee
ITT	intention-to-treat
MCL	mantle cell lymphoma
MRD	minimum residual disease
MZL	marginal zone lymphoma
NCCN	national comprehensive cancer network

NHL	non-hodgkin's lymphoma
NMA	network meta-analysis
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression free survival
PR	partial response
PRO	patient reported outcome
QALY	quality adjusted life year
QoL	quality of life
R	rituximab
R/R	relapsed or refractory
RR	relative risk/ risk ratio
SAE	serious AEs
SD	stable disease
SLL	small lymphocytic lymphoma
TE	treatment emergent
TEAE	treatment-emergent AE
TN	treatment naïve
WIPO	world intellectual property organization
WM	waldenström macroglobulinemia

13. References

1. Wierda W, Brown J, Abramson J. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 1. 2023, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2022.

2. Miranda-Filho A, Piñeros M, Ferlay J, Soerjomataram I, Monnereau A, Bray F. Epidemiological patterns of leukaemia in 184 countries: a population-based study. Lancet Haematol. 2018;5(1):e14-e24.

3. World Health Organization Model List of Essential Medicines 22nd List（2021）. WHO. 2021:1-62.

4. Hillmen P, Eichhorst B, Brown JR, Lamanna N, O'Brien SM, Tam CS, et al. Zanubrutinib Versus Ibrutinib in Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma: Interim Analysis of a Randomized Phase III Trial. J Clin Oncol. 2022:Jco2200510.

5. Brown JR, Eichhorst B, Hillmen P, Jurczak W, Kaźmierczak M, Lamanna N, et al. Zanubrutinib or Ibrutinib in Relapsed or Refractory Chronic Lymphocytic Leukemia. New England Journal of Medicine. 2022.

6. Wu SJ, Huang SY, Lin CT, Lin YJ, Chang CJ, Tien HF. The incidence of chronic lymphocytic leukemia in Taiwan, 1986-2005: a distinct increasing trend with birth-cohort effect. Blood. 2010;116(22):4430-5.

7. Eichhorst B, Robak T, Montserrat E, Ghia P, Hillmen P, Hallek M, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 Suppl 5:v78-84.

8. Yang SM, Li JY, Gale RP, Huang XJ. The mystery of chronic lymphocytic leukemia (CLL): Why is it absent in Asians and what does this tell us about etiology, pathogenesis and biology? Blood Rev. 2015;29(3):205-13.

9. R D. Orphanet Report Series-Prevalence of rare diseases : Bibliographic data. Methodology. 2008;1(1):1-29.

10. Howlader N, Noone A, Krapcho M, Miller D, Brest A, Yu M. SEER Cancer Statistics Review, 1975-2017. National Cancer Institute. 2020.

11.Smolewski P, Robak T. Current Treatment of Refractory/Relapsed Chronic Lymphocytic Leukemia:

A Focus on Novel Drugs. Acta Haematol. 2021;144(4):365-79.

12. Goede V, Cramer P, Busch R, Bergmann M, Stauch M, Hopfinger G, et al. Interactions between comorbidity and treatment of chronic lymphocytic leukemia: results of German Chronic Lymphocytic Leukemia Study Group trials. Haematologica. 2014;99(6):1095-100.

13. Thurmes P, Call T, Slager S, Zent C, Jenkins G, Schwager S, et al. Comorbid conditions and survival in unselected, newly diagnosed patients with chronic lymphocytic leukemia. Leuk Lymphoma. 2008;49(1):49-56.

14. Holzner B, Kemmler G, Kopp M, Nguyen-Van-Tam D, Sperner-Unterweger B, Greil R. Quality of life of patients with chronic lymphocytic leukemia: results of a longitudinal investigation over 1 yr. Eur J Haematol. 2004;72(6):381-9.

15. FDA. BRUKINSA® (zanubrutinib) capsules approval label. US Food and Drug Administration. 2021.

16. Tam CS, Brown JR, Kahl BS, Ghia P, Giannopoulos K, Jurczak W, et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. The Lancet Oncology. 2022;23(8):1031-43.

17. Ma J, Zhu J, Shen Z. Guidelines of Chinese Society of Clinical Oncology (CSCO): Lymphoid Malignancies (2022). . Beijing: People's Medical Publishing House. 2022.

18. The guidelines for diagnosis and treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma in China(2022). Chin J Hematol. 2022;43(5):353-8.

19. Ghia P, Barnes G, Yang K, Tam C. Patient-Reported Outcomes From a Phase 3 Randomized Study of Zanubrutinib vs Bendamustine Plus Rituximab (BR) in Patients With Treatment-Naive (TN) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL). Poster presented at: European Hematology Association 2022 Virtual 2022.

20. Hillmen P, Brown J, Lamanna N. Health-Related Quality of Life Outcomes Associated With Zanubrutinib vs Ibrutinib Monotherapy in Patients With Relapsed/Refractory (RR) CLL/SLL: Results From the Randomized Phase 3 ALPINE Trial. Poster presented at: European Hematology Association 2022 Virtual. 2022.

21. Xu W, Yang S, Zhou K, Pan L, Li Z, Zhou J, et al. Treatment of relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma with the BTK inhibitor zanubrutinib: phase 2,

single-arm, multicenter study. J Hematol Oncol. 2020;13(1):48.

22. Xu W, Yang S, Zhou K. Zanubrutinib monotherapy in patients with relapsed or refractory chronic lymphocytic leukemia: 34-month follow-up results. Poster presented at: European Hematology Association 2021 Virtual. 2021.

23. Cull G, Burger JA, Opat S, Gottlieb D, Verner E, Trotman J, et al. Zanubrutinib for treatment-naive and relapsed/refractory chronic lymphocytic leukaemia: long-term follow-up of the phase I/II AU-003 study. Br J Haematol. 2022;196(5):1209-18.

24. Tam CS, Quach H, Nicol A, Badoux X, Rose H, Prince HM, et al. Zanubrutinib (BGB-3111) plus obinutuzumab in patients with chronic lymphocytic leukemia and follicular lymphoma. Blood Adv. 2020;4(19):4802-11.

25. Soumerai JD, Mato AR, Dogan A, Seshan VE, Joffe E, Flaherty K, et al. Zanubrutinib, obinutuzumab, and venetoclax with minimal residual disease-driven discontinuation in previously untreated patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: a multicentre, single-arm, phase 2 trial. The Lancet Haematology. 2021;8(12):e879-e90.

26. Tam CS, Opat S, D'Sa S, Jurczak W, Lee HP, Cull G, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. Blood. 2020;136(18):2038-50.

27. Dimopoulos M, Opat S, D'Sa S. ASPEN: Long-Term Follow-Up Results of a Phase 3 Randomized Trial of Zanubrutinib Versus Ibrutinib in Patients With Waldenström Macroglobulinemia. European Hematology Association 2022 Virtual. 2022.

28. Welten H, Ignacio TJ, Verheggen BG. COST-EFFECTIVENESS OF IBRUTINIB IN ADULT PATIENTS WITH RELAPSED CHRONIC LYMPHOCYTIC LEUKAEMIA IN THE NETHERLANDS. Value in Health. 2016;19(7):A737-A.

29. Costa S, Connors J, Cromwell I. A COST-EFFECTIVENESS EVALUATION OF IBRUTINIB FOR PATIENTS WITH RELAPSED CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) IN BRITISH COLUMBIA, CANADA. Oral Presentation at：Society for Medical Decision Making. 2016.

30. Sorensen S, Peng S, Dorman E. The Cost-Effectiveness of Ibrutinib in Treatment of Relapsed or Refractory Chronic Lymphocytic Leukemia. Health Econ Outcome Res. 2016;2(4).

31. IACR. Estimated number of prevalent cases in 2020, worldwide, both sexes, all ages. The Global Cancer Observatory 2020. 2020.

32. Perry AM, Diebold J, Nathwani BN, MacLennan KA, Muller-Hermelink HK, Bast M, et al. Non-Hodgkin lymphoma in the developing world: review of 4539 cases from the International Non-Hodgkin Lymphoma Classification Project. Haematologica. 2016;101(10):1244-50.

33. Kabadi SM, Goyal RK, Nagar SP, Kaye JA, Davis KL. Treatment patterns, adverse events, and economic burden in a privately insured population of patients with chronic lymphocytic leukemia in the United States. Cancer Med. 2019;8(8):3803-10.