2021 WHO Expert Committee on the Selection and Use of Essential Medicines

Application for the Addition of Zanubrutinib on the WHO Model List of Essential Medicines

Submitted by

BeiGene Co., Ltd.

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BeiGene

CONTENTS

General items

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

BeiGene (Beijing) Co., Ltd. (Hereinafter referred to as BeiGene) proposes the inclusion of a new formulation for Zanubrutinib on the complementary list of the WHO Model List of Essential Medicines (EML) under the category of targeted therapies of antineoplastics and supportive medicines.

Zanubrutinib (brand name: Brukinsa®) received accelerated approval after priority review by US Food and Drug Administration (FDA) in 2019 with an identification as orphan drug and breakthrough therapy. It was also granted expedited approval by National Medical Products Administration (NMPA) in China for the treatment of relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with at least one previous treatment.

Zanubrutinib is a next-generation, highly potent, selective, irreversible Bruton tyrosine kinase (BTK) inhibitor, which shows better safety and efficacy than first-generation BTK inhibitor with greater BTK selectivity and less off-target inhibition against alternative kinases. Authoritative guidelines in China has already recommended Zanubrutinib for the treatment of R/R CLL/SLL patients.(1).

2. Relevant WHO technical department and focal point (if applicable)

N/A

3. Name of organization (s) consulted and/or supporting the application

N/A

4. International Nonproprietary Name and Anatomical Therapeutic Chemical code of the medicine

INN：Zanubrutinib

ATC：L01EL03

5. Dose forms (s) and strength (s) proposed for inclusion; including adult and age-appropriate pediatric dose forms/strengths (if appropriate)

Dose forms and strengths: Capsules. Each is 80 mg and size 0, white to off-white opaque capsule

Zanubrutinib was approved by the FDA on November 14, 2019. On June 2, 2020, Zanubrutinib was also approval by the National Medical Products Administration in China for the treatment of adult patients with CLL/SLL who have received at least one prior therapy.

The recommended dose of Zanubrutinib is 160 mg taken orally twice daily or 320 mg taken orally once daily until disease progression or unacceptable toxicity(1).

Safety and effectiveness of Zanubrutinib in pediatric patients have not been established.

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class

Individual medicine

Treatment details, public health relevance and evidence appraisal and synthesis

7. Treatment details (requirements for diagnosis, treatment and monitoring).

7.1 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(2) .

7.2 Recommendation of guidelines

Zanubrutinib has been recommended in the treatment of CLL/SLL in the latest version of lymphoma-related guidelines in China. Guidelines of Chinese Society of Clinical Oncology (CSCO): Lymphoid Malignancies (2020) recommends Zanubrutinib in R/R CLL patients, regardless of whether they have *del (17p) or TP53* mutation [*see Table 7-1*](1).

Table 7-1 Recommendations in Guidelines of CSCO for lymphoid malignancies

Characteristics of CLL/SLL Patients			Grade of Recommendation*
R/R Patients	Prior therapy induces Fludarabine with sustained respond < 3 years, or refractory patients with or not with *del (17P) /TP53* mutation	Generally in good health ; < 65 years old	II
		Generally in poor health or≥ 65 years old	II

7.3 Treatment

Zanubrutinib is indicated for the treatment of adult patients with CLL/SLL who have received at least one prior therapy.

7.3.1 Administration

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.

7.3.2 Dosage

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

7.3.3 Dosage modifications for drug interactions

Zanubrutinib is primarily metabolized by CYP3A in humans. Drug interactions occur when Zanubrutinib is administered in combination with a CYP3A inhibitor or inducer. Recommended dose modifications of Zanubrutinib for drug interactions are illustrated in *Table 7-2*. After discontinuation of a CYP3A inhibitor, previous dose of Zanubrutinib can be resumed.

Table 7-2 Dose Modifications for Use with CYP3A Inhibitors or Inducers

Co-administered Drug	**Recommended ZANUBRUTINIB Dose**
Strong CYP3A inhibitor	80 mg once daily Interrupt dose as recommended for adverse reactions *[see Table 7-3]*.
Moderate CYP3A inhibitor	80 mg twice daily Modify dose as recommended for adverse reactions *[see Table 7-3]*.
Moderate or strong CYP3A inducer	Avoid concomitant use.

Recommended dose modifications of Zanubrutinib for Grade 3 or higher adverse reactions are provided in *Table 7-3.*

Table 7-3 Recommended Dose Modification for Adverse Reaction

Event	**Adverse Reaction Occurrence**	**Dose Modification** (Starting Dose: 160 mg twice daily or 320 mg once daily)
Grade 3 or higher non-hematological toxicities	First	Interrupt Zanubrutinib Once toxicity has resolved to recovery to Grade 1 or lower or baseline: Resume at 160 mg twice daily or 320 mg once daily

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)	Second	Interrupt Zanubrutinib Once toxicity has resolved to recovery 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 recovery to Grade 1 or lower or baseline: Resume at 80 mg once daily
	Fourth	Discontinue Zanubrutinib

7.3.4 Medication for special populations

Hepatic Impairment: Dosage modification of Zanubrutinib is recommended in patients with severe hepatic impairment [*see Table 7-3*]. 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.

Renal Impairment: No dosage modification is recommended in patients with mild to moderate renal impairment (CLcr≥30 mL/min, estimated by Cockcroft-Gault). Monitor for Zanubrutinib adverse reactions in patients with severe renal impairment (CLcr<30 mL/min) or on dialysis is necessary.

Geriatric Use: No dosage modification is recommended in older patients.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Pregnancy: Women should be advised to avoid pregnancy while taking Zanubrutinib. If Zanubrutinib is used during pregnancy, or if the patient becomes pregnant while taking Zanubrutinib, the patient should be apprised of the potential hazard to the fetus.

Lactation: Advise lactating women not to breastfeed during treatment with Zanubrutinib and for at least two weeks following the last dose.

Females and Males of Reproductive Potential: Pregnancy testing is recommended for females of reproductive potential prior to initiating Zanubrutinib therapy. Advise female patients of reproductive potential to use effective contraception during treatment with Zanubrutinib and for at least 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. Advise men to avoid fathering a child while receiving Zanubrutinib and for at least 1 week following the last dose of Zanubrutinib.

8. Information supporting the public health relevance

Zanubrutinib is indicated for the treatment of adult patients with CLL/SLL who have received at least one prior therapy.

8.1 Epidemiological information on disease burden

CLL/SLL is a main non-Hodgkin lymphoma 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(3) with an incidence of 4.2:100,000/year. 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(4). CLL is much less prevalent in eastern countries. In these countries, CLL accounts for only 1%~3% of NHL in most series(3) and the age-adjusted incidence is about 0.2~0.3/100,000(5). The prevalence of CLL in Europe is about 48.0/100,000(6). 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(7).

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 (8). 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 (9, 10).

No differences regarding QoL can be observed between CLL patients who had already received chemotherapy and those who had not. The patients reported lower quality of life scores in almost every domain (64.5 vs 70.0, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire), and the difference mainly comes from the influence of the disease on the patients' physical functioning, role functioning and cognitive functioning (11).

8.2 Assessment of current use

Courses of CLL may be indolent and require no treatment, but may also be aggressive and progress rapidly(12). To date, treatments for CLL/SLL varies depending on the exact diagnosis and progression(13). The standard treatment of patients with early disease is a watch-and-wait strategy(2). Treatment should be initiated when there is marked evidence of bone-marrow suppression or disease-related symptoms such as B symptoms or fatigue.

Patients with CLL/SLL had limited benefit and poor tolerance from Chemoimmunotherapy (CIT). Treatment landscape of CLL has changed since 2014 after the introduction of inhibitors of B-cell receptor signaling pathway(14). According to the latest guidelines from National Comprehensive Cancer Network (NCCN) and CSCO, Ibrutinib is included as preferred options for patients with R/R disease, regardless of patient’s age and comorbidities(2). In addition, an Allogeneic Hematopoietic Stem Cell Transplantation (AHCT) may be considered in relapsing patients with *TP53 or del (17p)* mutations, or patients that are refractory to inhibitor therapy, which is the only curative regimen for CLL/SLL(2). However, this regimen represents a high price and risk, and it also unfits for older patients(1). Ibrutinib is a first in class irreversible BTK inhibitor, and it is well established as both a frontline and salvage therapy for CLL/SLL due to its excellent efficacy in CLL/SLL patients(15).

Despite its efficacy and widespread use, Ibrutinib monotherapy of CLL/SLL patients comes with some essential drawbacks: an increased financial burden, relatively high rates of cardiac arrhythmias because of the off-target effects, as well as resistance mutations and rapid relapses after discontinuation of the drug in some cases(16). In comparison to ibrutinib, Zanubrutinib, a second-generation irreversible BTK inhibitor, displays greater selectivity for BTK relative to interleukin-2-inducible T cell kinase resulting in less inhibition of antigen-dependent cell mediated cytotoxicity in vitro(15). Thus, Zanubrutinib appears as a new alternative to be well tolerated and has limited off-target effects which makes it a better choice for R/R CLL/SLL patients(17).

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

The B-cell receptor signaling pathway is not only essential for normal B-cell development but is also implicated in the survival and proliferation of malignant B cells. Inhibition of B-cell receptor signaling has recently been established as an effective approach for management of B-cell malignancies. BTK is a key component of the B-cell receptor signaling pathway. Zanubrutinib is a highly specific next-generation BTK inhibitor (18).

9.1 Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

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 Clinical Trials, PubMed, and Cochrane. However, no meta-analysis including Zanubrutinib trials was reported.

Geethakumari *et al* (2020) provided a brief overview of the BTK signaling pathway as well as available, approved BTK inhibitors for CLL/SLL(17). In addition, they review pre-clinical and clinical data related to Zanubrutinib and its use and CLL/SLL and other lymphoid malignancies(17). It concluded that Zanubrutinib provides an option to utilize a specific BTK inhibitor with potentially limited toxicities and it is an attractive option to combine with other targeted agents as a selective BTK inhibitor in CLL/SLL.

9.2 Summary of available data (appraisal of quality, outcome measures, summary of results)

The following studies describe the clinical development of Zanubrutinib for B-cell malignancies:

BGB-3111-AU-003 (NCT023443120) was an international first-in-human phase I clinical trial of Zanubrutinib comprising a total of 144 patients with various B-cell malignancies. This multicenter study of Zanubrutinib in patients with B-cell malignancies comprises 2 parts: dose escalation (Part 1) and cohort expansion (part 2). Part 1 evaluated the safety, pharmacokinetics (PK), and pharmacodynamics (BTK occupancy in peripheral blood mononuclear cells [PBMCs]) in patients with relapsed/refractory B-cell malignancies who had received at least 1 prior therapy, with no therapy of higher priority available in the assessment of the investigator. Part 2 characterized the safety and preliminary efficacy of Zanubrutinib in multiple cohorts of patients with B-cell malignancies. The 160 mg twice-daily dose was selected as the recommended phase II dose(18).

BGB-3111-104 (NCT03301181) was an open-label, parallel-group, fixed-sequence study in healthy male and female subjects conducted in two parts, Part A and Part B. Part A investigated the effect of CYP3A induction by steady-state Rifampin on the single-dose PK of 320 mg Zanubrutinib, and Part B investigated the effect of CYP3A inhibition by steady-state Itraconazole on the single-dose PK of 20 mg Zanubrutinib(19).

BGB-3111-205 (NCT03206918) was a single-arm, open-label, multi-center phase II study in participants with histologically documented CLL/SLL who have relapsed after or refractory to at least 1 prior treatment regimen (s). The study is composed of an initial screening phase, a single-arm treatment phase, and a follow-up phase. The primary endpoint is ORR assessed by IRC (per IWCLL 2008); secondary endpoints include duration of reaction (DOR), time to reaction (TTR), progression free survival (PFS) and safety(20).

9.2.1 Pharmacokinetics

Zanubrutinib is rapidly absorbed after oral administration with maximal plasma concentration (C_{max}) observed about 2 hours after dosing [*see Figure 9-1*]. The C_{max} and area under the concentration-time curve increased in a nearly dose-proportional manner from 40 to 320 mg after initial dose. Mean C_{max} was 346 and 658 ng/mL after a single dose of 160 and 320 mg, respectively. The mean half-life of

Zanubrutinib administered either as 160 mg twice daily or 320 mg once daily was about 4 hours with minimal accumulation observed after repeated dosing(18).

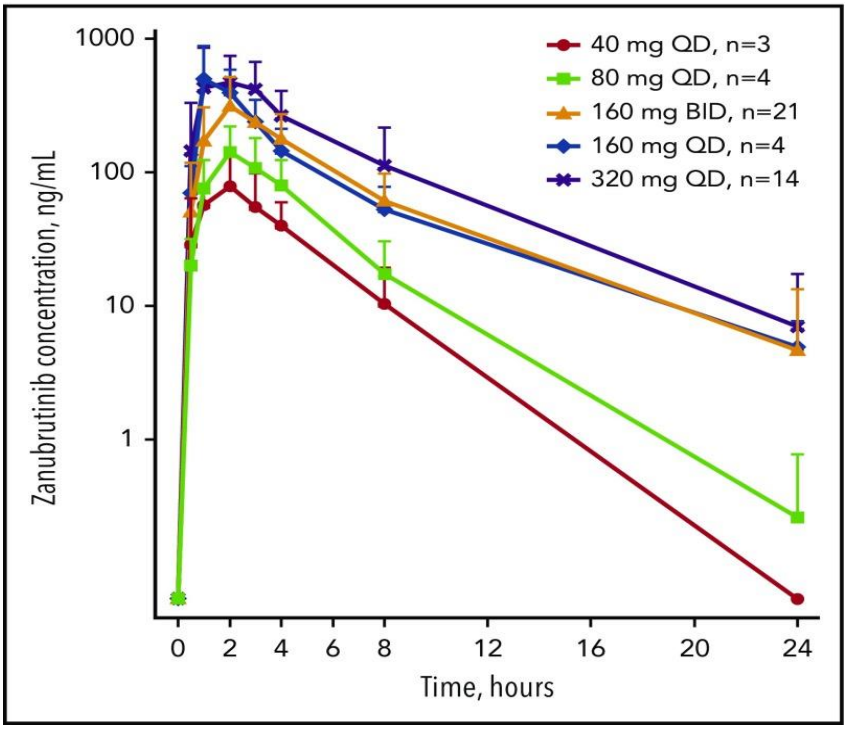

Figure 9-1. Plasma concentration-time profile of Zanubrutinib after initial doses of 40, 80, 160, and 320 mg once daily and 160 mg twice daily

9.2.2 Pharmacodynamics

In PBMCs, complete or near complete (>95%) BTK occupancy was achieved starting at doses of 40 mg per day; BTK occupancy >95% was observed 4 hours after the drug administration in almost all patients across all doses [*see Figure 9-2A*]. No significant differences were observed across dose groups. These results indicate that BTK remains fully occupied by Zanubrutinib well after achieving peak plasma levels. Median (range) BTK occupancy on day 3 of week 1 (Predose) in the 30 pairs of nodal tissue was 94% in the 320-mg once-daily group and 100% in the 160-mg twice-daily group. Nodal BTK occupancy was >95% in 50% of patients receiving 320 mg once daily and in 89% of patients receiving 160 mg twice daily [*see Figure 9-2B*]. Based on the higher proportion of patients who achieved >95% sustained BTK occupancy in lymph nodes at trough concentrations of Zanubrutinib, the 160-mg twice-daily regimen was determined to be the recommended phase 2 dose (RP2D) (18).

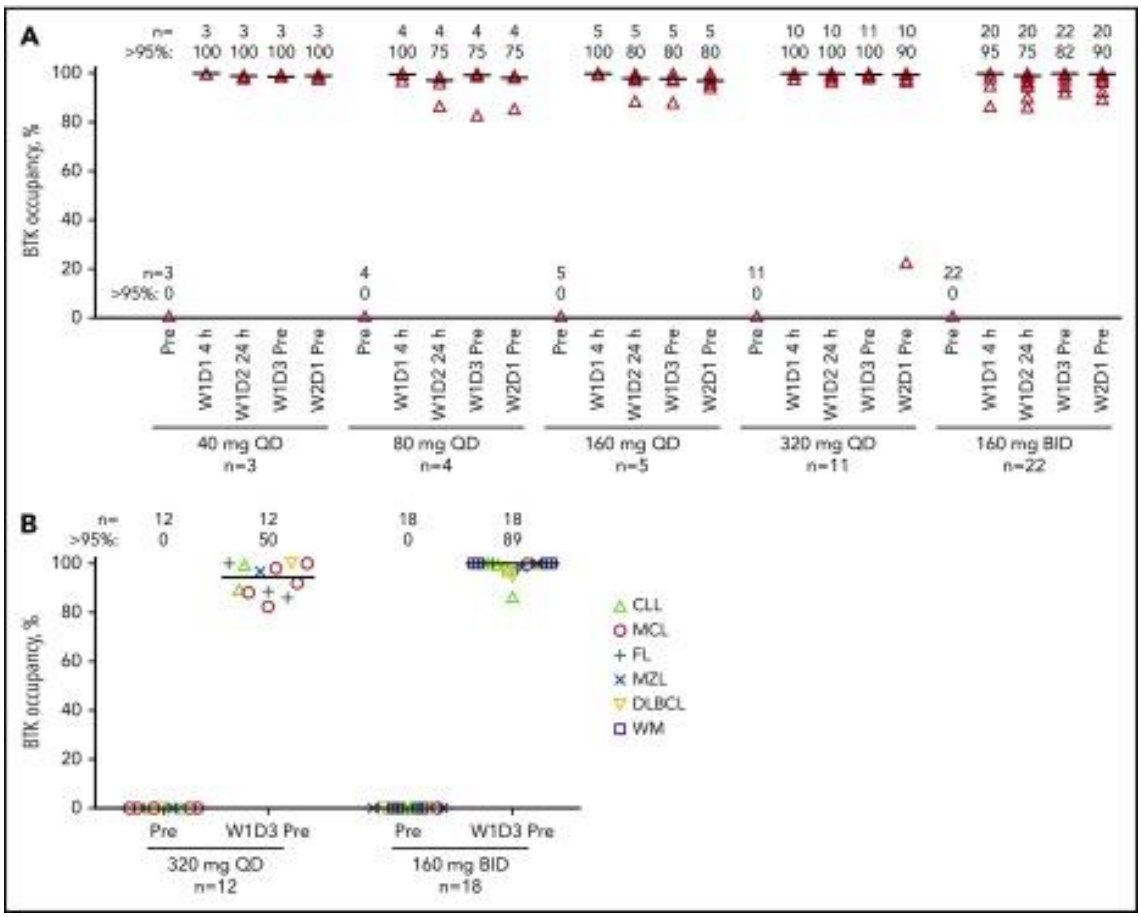

Figure 9-2 BTK occupancy (A: PBMSs; B: nodal tissue)

9.2.3 Efficacy

Result from part 2 of BGB-3111-AU-003 showed that the ORR in evaluable CLL/SLL patients with 160 mg twice daily (n=78) was 96.2%, including 2 patients (2.6%) who achieved a CR, 63 (80.8%) with partial response (PR), and 10 (12.8%) PR with lymphocytosis (PR-L) at a median follow-up of 13.7 months [*see Table 9-1*]. Early redistribution lymphocytosis was observed with return to baseline within 12 weeks in most patients. All efficacy-evaluable patients with *del (17p) or TP53* mutation responded (n= 16; ORR = 100%). Response rates were comparable in treatment-naive patients and those with relapsed/refractory disease (ORR, 100% and 94.6%; CR rates, 4.5% and 1.8%, respectively [*see Table 9-1*].). Likewise, reductions in lymph node disease burden observed in treatment-naive patients and patients with relapsed/refractory disease were similar. There has been no incidence of Richter transformation. Median progression-free survival has not been reached and 12-month estimated progression-free survival is 100%; 2 patients have progressed at 15.3 and 16.4 months(18).

Table 9-1 Response rates in evaluable patients with CLL/SLL in part 2 of BGB-3111-AU-003

Best response per investigator	Treatment-naive, n = 22	Relapsed or refractory, n = 56	Total, N = 78
ORR, n (%) [95% CI]	22 (100) [84.56-100]	53 (94.6) [85.13-98.88]	75 (96.2) [89.17-99.2]
CR, n (%)	1 (4.5)	1 (1.8)	2 (2.6)
PR, n (%)	18 (81.8)	45 (80.4)	63 (80.8)
PR-L, n (%)	3 (13.6)	7 (12.5)	10 (12.8)
Stable disease, n (%)	0	2 (3.6)	2 (2.6)
Progressive disease, n (%)	0	0	0
Missing/not evaluable, n (%)	0	1 (1.8)	1 (1.3)

Results from BGB-3111-205 showed that, 77 (84.6%, 95% CI, 75.5–91.3)out of the 91 evaluable R/R CLL/SLL patients who received Zanubrutinib 160 mg twice daily in 28-day cycles until disease progression or intolerance achieved a response, with 3 (3.3%), 54 (59.3%), and 20 (22%) patients achieving a CR, PR, and PR-L, respectively, after a median follow-up of 15.1 months [*see Table 9-2*]. Subgroup analysis of ORR revealed results generally consistent with the overall study population, including in subgroups with poor prognostic features (e.g., IGHV unmutated status [82%], del (17p)/TP53 mutation [86%], and refractory disease [83%]). After median follow-up of 12.9 months (range, 0.8–20.4 months) for PFS, an estimated 87.2% of patients had neither progressed nor died at 12 months; the median PFS has not been reached [*see Table 9-2, Figure 9-3*](20).

Table 9-2 IRC-assessed efficacy outcomes of BGB-3111-205

Efficacy variable	*N* = 91
ORR, *n* (%, [95% CI])	77 (84.6, [75.5-91.3])
CR, *n* (%)	3 (3.3)
PR, *n* (%)	54 (59.3)
PR-L, *n* (%)	20 (22.0)
Median TTR (months)	2.8
DOR (months)	
Median DOR	Not estimable
Event-free rates at 12 months (%) [95%CI]	92.9 [83.6-97.0]
PFS (months)	
Median PFS	Not estimable
Event-free rates at 12 months (%) [95%CI]	87.2 [78.0-92.7]

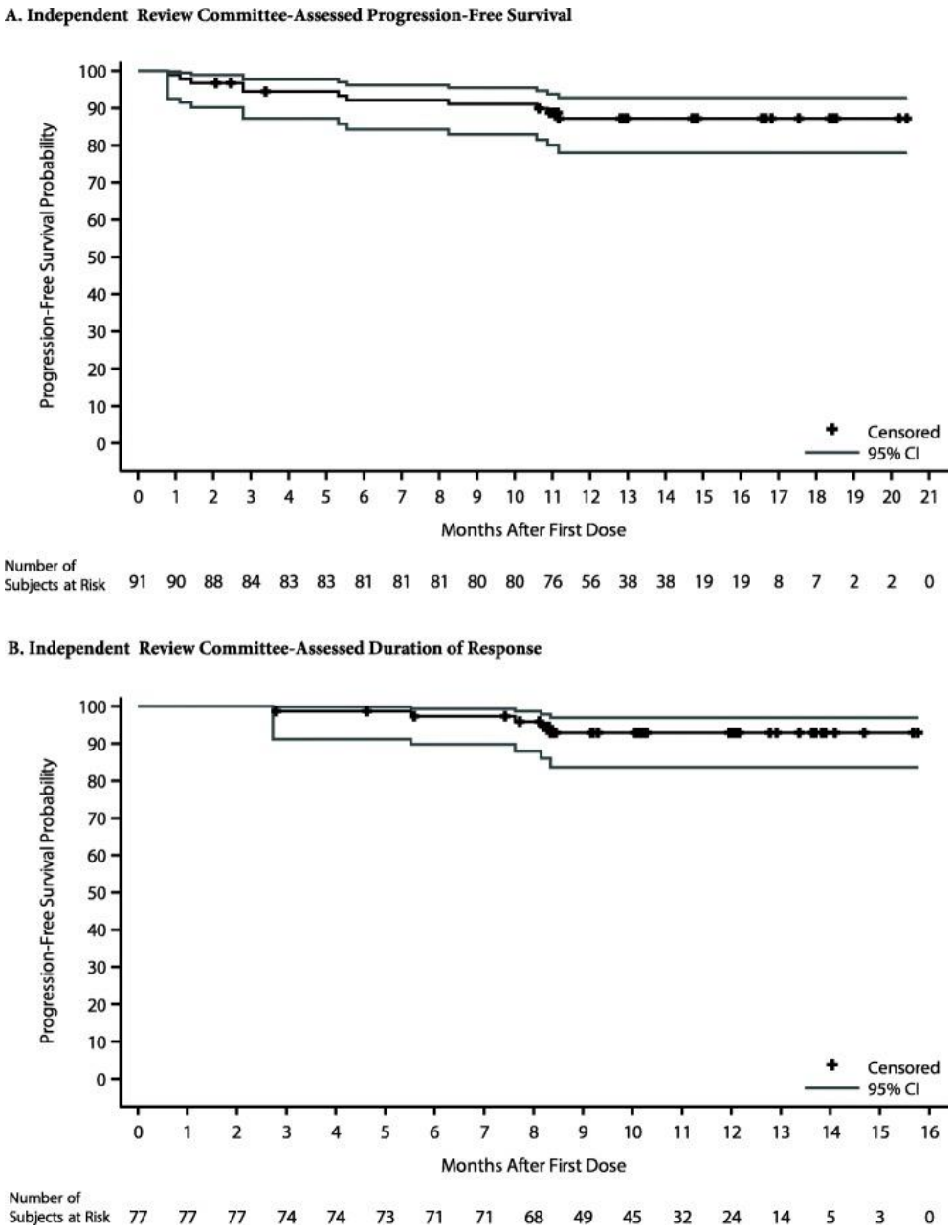

Figure 9-3 DOR and PFS outcomes of BGB-3111-205

9.3 Summary of available estimates of comparative effectiveness

BTK inhibitors are the preferred treatment option for patients with relapsed/refractory CLL/SLL. Direct comparative data are still lacking. *Table 9-3* lists the data of efficacy for R/R CLL/SLL reported with Ibrutinib and Zanubrutinib. According to the data, IRC-assessed ORR of Zanubrutinib (91.2%(20)) was higher than Ibrutinib (67.9%(21)). Besides, Zanubrutinib (92.2%, 87.2%, respectively(20)) resulted in higher PFS rates at 6 months and 12months than Ibrutinib (86.0%, 61.0%, respectively(21)).

Table 9-3 Data of efficacy for R/R CLL/SLL reported with different BTK inhibitors

Drug Clinical Trial	Phase	*N*	Median Age	Intervention	Median follow-up (Month)	ORR [95%CI]	CR	PFS [95%CI]
Zanubrutinib BGB-3111-205 NCT03206918 (20)	II	91	61	160mg b.i.d	15.1	IRC-assessed: 84.6%[75.5%-91.3%] Researcher-assessed: 91.2%	IRC-assessed: 3.3%	PFS rates at 6 months: 92.2%; PFS rates at 12 months: 87.2%[78.0-92.7];
Ibrutinib PCYC-1102-CA NCT01105247 (22)	Ib-II	85	66	420mg q.d	24	Researcher-assessed: 71%[60%-80%]	Researcher-assessed: 2.4%	PFS rates at 26 months: 75.0%
Ibrutinib PCYC-1112-CA NCT01578707 (23)	III	195	67	420mg q.d	12	IRC-assessed: 63.0% Researcher-assessed: 83.0%	IRC-assessed: 0.0% Researcher-assessed: 2.0%	PFS rates at 6 months: 88.0% PFS rates at 12 months: 67.0%
Ibrutinib NCT01973387 (21)	III	106	65	420mg q.d	16.4	Researcher-assessed: 67.9%	Researcher-assessed: 3.8%	PFS rates at 6 months: 86.0% PFS rates at 12 months: 61.0%

10. Review of harms and toxicity: summary of evidence of safety

10.1 Estimate of total patient exposure to date

As of June 15, 2020, the estimated cumulative clinical trial exposure to Zanubrutinib is 2,700 patients, 235 of which are CLL/SLL patients (data from the publication)(18, 20).

10.2 Description of the adverse events/reactions and estimates of their frequency

The following section details the undesirable effects of Zanubrutinib.

10.2.1 Safety results from BGB-3111-AU-003

The most common adverse events (AEs) in the dose-finding set were upper respiratory tract infection

(n = 22; 39.3%), contusion (n = 20; 35.7%), and cough and diarrhea (n = 15; 26.8% each). Grade ⩾ 3 AEs reported in >2 patients were anemia (n = 7), pneumonia and pyrexia (n = 4 each), and acute kidney injury and neutropenia (n = 3 each). At the cutoff date, 32 patients (57.1%) in the dose-finding set had discontinued study treatment. 20 patients discontinued because of disease progression and 8 patients discontinued due to AEs. No significant differences in AE profiles were observed between the 320 mg daily and 160 mg twice daily treatment schedules(18).

10.2.2 Safety results from BGB-3111-104

Zanubrutinib was well tolerated in this study. The overall incidence of TEAEs was low–less than 30% in both Part A and Part B. Single doses of 320 mg and 20 mg Zanubrutinib administered alone or co-administered with 600 mg rifampin and 200 mg itraconazole, respectively, were well tolerated in healthy subjects. In both parts, no subject reported a TEAE higher than Grade 2 or a serious adverse events (SAE), and no subject discontinued due to a TEAE. The majority of TEAEs were considered not related to the study drugs, which were Grade 1 in severity, and resolved without treatment. No clinically significant changes or findings were noted in clinical laboratory evaluations, vital signs, physical examinations, or body weight in this study (19).

Totally, 14 (16.3%) patients died during the study, seven within 30 days of the last study treatment (six due to complications of AEs and one due to disease progression). AEs leading to death included one case each of traffic accident, left occipital lobe hemorrhage (as previously described), pneumonia, and three due to unknown causes. 7 deaths that occurred more than 30 days after the last dose of study drug, 5 were due to progressive disease, one was due to complications of fungal pneumonia, and one was due to unknown cause after receiving 3 additional lines of therapy (24).

Result from BGB-3111-104 showed that coadministration with Rifampin decreased $AUC_{0-\infty}$ of Zanubrutinib by 13.5-fold and C_{max} by 12.6-fold. Coadministration with Itraconazole increased the $AUC_{0-\infty}$ of Zanubrutinib by 3.8-fold and C_{max} by 2.6-fold. The PK of Zanubrutinib was consistent between Asian and non-Asian subjects, and Zanubrutinib was well tolerated in this study(19).

10.2.3 Safety results from BGB-3111-205

All patients reported at least one AEs. 58 (63.7%) patients reported at least 1 grade 3 AEs, 8 (8.8%) patients reported grade 4 AEs, and 3 (3.3%) had grade 5 AEs (one in the setting of PD). The most frequently reported AEs of any grade were neutropenia (69.2%), upper respiratory tract infection (45.1%), thrombocytopenia (41.8%), petechiae/purpura/contusion (35.2%), anemia and hematuria (each 29.7%), hypokalemia (25.3%), cough (24.2%), and increased carbon dioxide and hyperglycemia (each 20.9%). The most common grade 3 AEs were neutropenia (37.4%), thrombocytopenia (14.3%), lung infection/pneumonia (12.1%), upper respiratory tract infection (9.9%), and anemia (8.8%) [see *Figure 10-1*]. 6 patients reported grade 4 neutropenia, 1 reported grade 4 thrombocytopenia, and 1 reported grade 4 hyperuricemia, the latter without other laboratory or clinical manifestations of tumor lysis syndrome. One third of the patients reported at least one serious AE, the most common being lung infection (n = 7), pneumonia (n = 3), upper respiratory infection (n = 3), and bronchitis (n = 2). 3 patients had grade 5 (fatal) AEs: lung infection accompanied by cardiac and respiratory failure on study day 24 in a 66-year-old male with one prior regimen for CLL, who received 6 days of study drug; cardiopulmonary failure on study day 43 in a 67-year-old male with three prior regimens for CLL in the setting of high tumor burden and chronic obstructive pulmonary disease; and multiorgan system failure in the setting of PD on study day 46 in a 52-year-old male with nine prior regimens for CLL. 8 (9%) patients discontinued Zanubrutinib due to AEs, and seven (8.0%) patients required at least one dose reduction. (20)

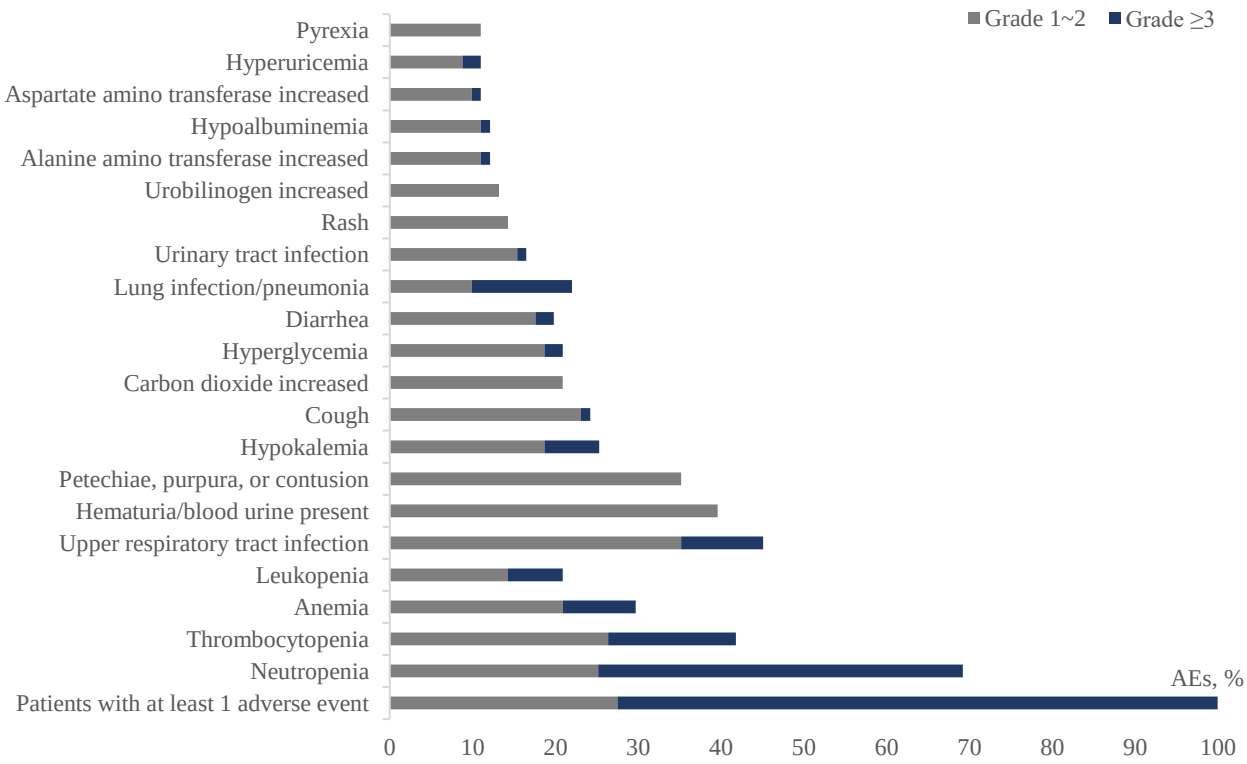

Figure 10-1 Adverse events (≥10%) in CLL/SLL Patients in BGB-3111-205

10.3 Summary of available data (appraisal of quality, summary of results)

The very common AEs (occurred ⩾ 10%) associated with Zanubrutinib included: neutropenia, hemocytopenia, rash, leukopenia, and petechiae (25).

The common AEs associated with Zanubrutinib (5% ⩽ occurred < 10%) included: anemia, purpura, hematuria, lung infection, upper respiratory tract infection, diarrhea and bleeding(25).

10.4 Summary of comparative safety against comparators

Compared with ibrutinib, Zanubrutinib for the treatment of R/R CLL/SLL resulted in a lower rate of AEs such as severe bleeding, atrial fibrillation and a lower discontinuation rates due to AEs [*see Table 10-1*].

Table 10-1 Safety of Zanubrutinib versus ibrutinib for R/R CLL/SLL patients

	Zanubrutinib (20)	Ibrutinib (21)
⩾Grade 3 Lung pneumonia	9.9%	16.3%

⩾Grade 3 Diarrhea	2.2%	3.8%
Bleeding	2.2%	2.9%
Atrial fibrillation	0%	5.8%
Discontinuation due to AEs	8.8%	12.5%

10.5 Identification of variation in safety that may relate to health systems and patient factors

10.5.1 Hemorrhage

Fatal and serious hemorrhagic events have occurred in patients with hematological malignancies treated with Zanubrutinib monotherapy. Grade 3 or higher bleeding events including intracranial and gastrointestinal hemorrhage, hematuria, and hemothorax have been reported in 2% of patients treated with Zanubrutinib monotherapy. Bleeding events of any grade, including purpura and petechiae, occurred in 50% of patients treated with Zanubrutinib monotherapy.

Bleeding events have occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Co-administration of Zanubrutinib and antiplatelet or anticoagulant medications may further increase the risk of hemorrhage (25).

10.5.2 Infections

Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematological malignancies treated with Zanubrutinib monotherapy. Grade 3 or higher infections occurred in 23% of patients treated with Zanubrutinib monotherapy. The most common Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation have also occurred (25).

10.5.3 Embryo-fetal toxicity

Based on findings in animals, Zanubrutinib can cause fetal harm when administered to a pregnant woman(25). Administration of Zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity, including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily (26).

10.5.4 Second primary malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 9% of patients treated with Zanubrutinib monotherapy. The most frequent second primary malignancy was skin cancer (basal cell carcinoma and squamous cell carcinoma of skin), reported in 6% of patients. Advise patients to use sun protection(25).

10.5.5 Cardiac arrhythmias

Atrial fibrillation and atrial flutter have occurred in 2% of patients treated with Zanubrutinib monotherapy. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher events were reported in 0.6% of patients treated with Zanubrutinib monotherapy. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate(25).

10.5.6 Pediatric use

Safety and effectiveness in pediatric patients have not been established(25).

10.5.7 Geriatric use

Among the 641 patients in clinical studies with Zanubrutinib, 49% were older than 65 years of age, while 16% were older than 75 years of age. No overall differences in safety or effectiveness were observed between younger and older patients(25).

11. Summary of available data on comparative cost and cost-effectiveness of the medicine

11.1 Medicine prices

Zanubrutinib is listed in the US priced at 12,935 USD per bottle with 120 capsules.

Zanubrutinib is listed in China priced at 11,300 RMB per bottle with 64 capsules.

11.2 Data on the economics of treating CLL/SLL

11.2.1 Data on comparative cost

Zanubrutinib is listed in China priced at 11,300 RMB per bottle with 64 capsules, of which monthly treatment cost is 21,188 RMB. Comparatively, the first-generation BTK inhibitor (Ibrutinib) is listed

in China priced at 17,010 RMB per month for CLL/SLL patients.

11.2.2 Data on comparative cost-effectiveness

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 [*see Table 11-1*,(27-29)].As a next-generation of BTK inhibitor, Zanubrutinib has more advantages on efficacy and safety, which can not only improve QALYs in patients, but also further saves the cost of follow-up treatment caused by poor prognosis and AEs.

Table 11-1 Data on comparative cost-effectiveness

Subjects	Country	Intervention	Result
R/R CLL (27)	Sweden	Ibrutinib vs Ofatumumab vs Idelalisib + Ofatumumab	QALYs: 4.69 vs 1.94 vs 2.64 ICER: 546,904 SEK/QALY vs 556,976 SEK/QALY
R/R CLL; R/R CLL with del (17p) mutations (28)	Canada	Ibrutinib vs CIT	ICER (dep17p): 122,038 USD/QALY ICER (R/R CLL): 126,089 USD/QALY < WTP* (150,000 USD)
R/R CLL (29)	Netherlands	Ibrutinib vs Ofatumumab	ICER: 54,264EUR/QALY< WTP (78,000 EUR)

**WTP, the threshold of willingness to pay*

11.2.3 Budget impact

CLL/SLL is a rare disease so that incorporating Zanubrutinib in national reimbursement drug list will not impact on the health care fund heavily. According to *Global Cancer Statistic Data* from International Agency For Research On Cancer (IARC) in 2018, the estimated number of NHL cases with 5 years in China is 227,661 (30), 2.7% of which are CLL/SLL patients(31). Based on the data, the estimated number of NHL cases with 5 years in China is 6,147. The estimated number of NHL cases with 5 years in the US is 225,032(30), 7.0% of which are CLL/SLL patients(31). Based on the data, the estimated number of NHL cases with 5 years in the US is 15,752. According to a real world

study (32), the proportion of each current treatment for MCL (either first-line therapy or second-line therapy) was listed below: BR (32%), FCR (14%), Rituximab (24%), and Ibrutinib (15%). Based on Ibrutinib's market share (14.2%), there are no more than 993 people taking Zanubrutinib in China and 2,363 in the US.

12. Summary of regulatory status and market availability of the medicine

On June 2, 2020, Zanubrutinib was also approved by NMPA in China for the treatment of patients with CLL/SLL who have received at least one prior therapy, priced at 11,300 RMB per bottle with 64 capsules (80mg).

The new drug application of Zanubrutinib has also been submitted to medicines agency in Australia, Canada, Europe and Israel.

13. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia)

Zanubrutinib is not included in at least one of the following Pharmacopeia: *British Pharmacopoeia*, *International Pharmacopoeia*, *United States Pharmacopoeia* and *European Pharmacopoeia.*

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