

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.

Version date: -November 24th 2020



BeiGene

CONTENTS

General items	1
1. Summary statement of the proposal for inclusion, change or deletion	1
2. Relevant WHO technical department and focal point (if applicable)	1
3. Name of organization (s) consulted and/or supporting the application.....	1
4. International Nonproprietary Name and Anatomical Therapeutic Chemical code of the medicine	2
5. Dose forms (s) and strength (s) proposed for inclusion; including adult and age- appropriate pediatric dose forms/strengths (if appropriate).....	2
6. Whether listing is requested as an individual medicine or as representative of a pharmacological class	2
Treatment details, public health relevance and evidence appraisal and synthesis	3
7. Treatment details (requirements for diagnosis, treatment and monitoring).	3
8. Information supporting the public health relevance.....	6
9. Review of benefits: summary of evidence of comparative effectiveness	9
10. Review of harms and toxicity: summary of evidence of safety	15
11. Summary of available data on comparative cost and cost-effectiveness of the medicine 19	
12. Summary of regulatory status and market availability of the medicine.....	20
13. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopoeia)	21
References	21

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 for the treatment of adult patients with mantle cell lymphoma (MCL) with an identification as orphan drug and breakthrough therapy. It was also granted expedited approval by National Medical Products Administration (NMPA) for the treatment of relapsed/refractory (R/R) MCL 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 the US and China recommended Zanubrutinib as the second line therapy for for the treatment of R/R MCL patients soon (1, 2).

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 for the treatment of adult patients with MCL who had received at least one prior therapy. On June 2, 2020, Zanubrutinib was also approved by the National Medical Products Administration for the treatment of adult patients with MCL 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, 2).

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

7.1.1 Diagnostic criteria of MCL

Diagnosis is based on lymph node, bone marrow, or tissue morphology of centrocytic lymphocytes, small cell type, or blastoid variant cells. A chromosomal translocation t(11:14) is the molecular hallmark of MCL, resulting in the overexpression of cyclin D1. Cyclin D1 is detected by immunohistochemistry in 98% of cases. The absence of SOX-11 or a low Ki-67 may correlate with a more indolent form of MCL. The differential diagnosis of MCL includes small lymphocytic lymphoma, marginal zone lymphoma, and follicular lymphoma (3).

7.2 Recommendation of guidelines

Zanubrutinib has been recommended in the treatment of MCL in the latest version of lymphoma-related guidelines. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: B-Cell Lymphomas (2020, Version 2) suggests Zanubrutinib as the preferred treatment regimen in the second line therapy for patients with MCL who have short or extended response duration to prior chemoimmunotherapy (the desired median progression-free survival time is bound value) (1). Guidelines of Chinese Society of Clinical Oncology (CSCO): Lymphoid Malignancies (2020) recommends Zanubrutinib in patients with R/R MCL (grade I recommendation) (2).

7.3 Treatment

Zanubrutinib is indicated for the treatment of adult patients with MCL 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 7-1](#). After discontinuation of a CYP3A inhibitor, previous dose of Zanubrutinib can be resumed.

Table 7-1 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 7-2].
Moderate CYP3A inhibitor	80 mg twice daily Modify dose as recommended for adverse reactions [see Table 7-2].
Moderate or strong CYP3A inducer	Avoid concomitant use.

Recommended dose modifications of Zanubrutinib for Grade 3 or higher adverse reactions are provided in [Table 7-2](#).

Table 7-2 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 Grade 3 febrile neutropenia	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 thrombocytopenia with significant bleeding Grade 4 neutropenia (lasting	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

more than 10 consecutive days) Grade 4 thrombocytopenia (lasting more than 10 consecutive days)	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 7-2]. 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 ($\text{CL}_{\text{Cr}} \geq 30 \text{ mL/min}$, estimated by Cockcroft-Gault). Monitor for Zanubrutinib adverse reactions in patients with severe renal impairment ($\text{CL}_{\text{Cr}} < 30 \text{ mL/min}$) 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 mantle cell lymphoma (MCL) who have received at least one prior therapy.

8.1 Epidemiological information on disease burden

MCL is an uncommon subtype of non-Hodgkin lymphoma (NHL) (3). According to national standards for the identification of rare diseases(4), MCL is officially recognized as a rare disease in the United States(5), the European Union(6), Japan(7, 8) and Australia(7, 9). MCL cases represent between 2~10% of all NHL. In Europe and the US, average incidence rates of approximately 0.5 cases per 100,000 person-years were reported, with a male-to-female ratio of 2.3~5:1, and a median age at diagnosis of close to 70 years(6). The global incidence of NHL was 6.7 per 100,000 (7), and MCL accounted for 7.8% of NHL in developed regions while 3.8% in developing regions (10). MCL is an aggressive disease, with poor prognosis and a limited survival (5) [see Figure 8-1]. During 2010~2016, 5-year relative survival of MCL patients in the United States was 61.9%, and the relative survival was significantly correlated with age. The 5-year relative survival of MCL patients aged 20-64 years and over 65 years was 71.2% and 54.9%, respectively(5).

There is a wide variation in outcomes of the treatment with MCL patients. Some patients had a very aggressive presentation and succumbing to their disease less than 6 months, while other patients (8%) at the opposite end of the spectrum had a very indolent clinical course with survival more than 10 years(11). The majority (>90%) of patients present with advanced stage disease (Stage III~IV), and need immediate medical attention. (12).

Compared with the general population, MCL patients had lower quality of life (QoL) and well-being, and the score of QoL decreased significantly with the increase of disease recurrence frequency. Utilities of MCL patients in different health states are provided in Table 8-1. The utility of MCL patients under progression-free survival (PFS) from first-line treatment is 0.764. With the progression of the disease, the QoL of MCL patients becomes worse and worse. When the patient had a second relapse, the health

utility will decrease to 0.45 (13).

Table 8-1 Utilities of MCL patients in different health states

Health state	Utility*
Progression-free survival from first-line treatment	0.764
Progressed from first-line treatment	0.693
Progression-free survival from second-line treatment	0.764
Progressed from second-line treatment	0.45

* Utility scores ranging from 0 to 1, with 0 representing death and 1 representing perfect health, defined the quality of life of patients.

8.2 Assessment of current use

Mantle cell lymphoma (MCL) is a heterogeneous non-Hodgkin lymphoma subtype with a wide range in clinical and biological behavior resulting in treatment approaches at diagnosis varying from initial observation in select patients to aggressive chemoimmunotherapy (CIT) and consolidation with autologous stem cell transplantation (ASCT) in others(14-16).

Given the unfavorable prognosis and the fact that standard therapy does not appear to cure patients with MCL, a “watch and wait” strategy for patients with asymptomatic, low MCL international prognostic index or elderly MCL patients should be considered(3). If treatment is required, recommendations for classical MCL apply. Currently, first therapy for MCL is divided into modalities based on the age of the patient. Younger patients may be eligible for ASCT while older patients may be unfit for such an aggressive approach. In both types of upfront MCL therapy, two crucial agents are used, and one of them is Rituximab. For several decades, the gold standard of upfront treatment was the CHOP regimen (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone), which has been used more recently in combination with anti-CD20 monoclonal antibody (mAb), Rituximab (R-CHOP regimen). Younger patients were treated with more aggressive CIT, implementing high doses of cyclophosphamide as part of a hyper-CVAD regimen (Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone). High-doses of Cytarabine were also considered incorporated into other regimens for clinically fit MCL patients under 60~65 years old. Maintenance treatment with Rituximab was shown

to prolong response duration after Rituximab-containing chemotherapy. Additionally, allogeneic hematopoietic stem cell transplantation (AHCT) may be also an option for treatment of R/R MCL patients (1, 2, 15, 16). Although standard CIT is associated with high ORR, no proven curative treatment exists for MCL patients. The majority of patients experience relapsed after initial response, with some patients being primarily resistant to first-line treatment. In these situations, the use of novel drugs may provide an opportunity to control the disease(14, 15).

Although a response to therapy was initially observed in the majority of patients, the rate of complete response (CR) was less than 50%, and the time of remission is short (up to 3 years) with median overall survival (OS) 3~4 years (15, 17). There is no standard therapeutic approach at relapse. Excluding transplant-eligible patients, median survival after first relapse of MCL was 1~2 years(12). Although response rates to frontline CIT are generally high, relapse occurs in nearly all patients and chemoresistance generally increases with increasing prior lines of treatment. The median age at diagnosis of MCL was 67 years old, resulting in many patients not being candidates for intensive treatment approaches such as AHCT consolidation due to age and comorbid illness.(18).Currently, the treatment of MCL is at a turning point from aggressive CIT to no-chemotherapy regimen. Among the newly licensed agents for R/R MCL, BTK inhibitors are the most effective(1, 19, 20) , which combine with Rituximab can further extend PFS[see Figure 8-2].

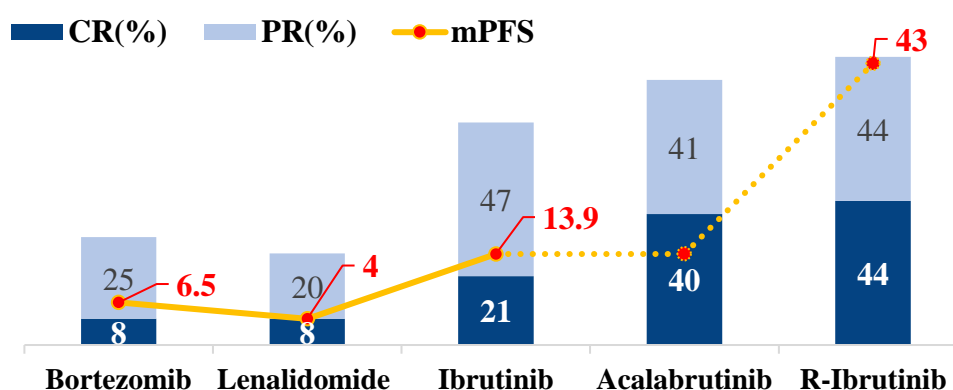


Figure 8-2 Efficacy of novel drugs for R/R MCL

Three BTK inhibitors are currently approved by the US Food and Drug Administration in relapsed/refractory MCL: ibrutinib, acalabrutinib, and Zanubrutinib. Despite the relative clinical

success of first-generation BTK inhibitors (Ibrutinib) in the management of MCL, it is not curative, and CR are relatively uncommon with single-agent therapy. Toxicities, some likely related to off-target effects, are relatively frequent causes for Ibrutinib discontinuation both in clinical trial and clinical practice settings(21). The second-generation BTK inhibitors, such as Zanubrutinib, were designed to have less off-target inhibition than Ibrutinib and an enhanced safety profile. Beyond safety, the improved selectivity of the second-generation BTK inhibitors might impact their efficacy and potential for combination therapy(22), which may improve QoL of patients and reduce the loss of social productivity.

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 (23).

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.

Sawalha *et al* (2020) summarized data from clinical trials of currently FDA-approved BTK inhibitors in MCL with a focus on Zanubrutinib in a review article (22). The review 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 MCL.

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(23).

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(24).

BGB-3111-206 (NCT03206970) was a single-arm, open-label, multicenter phase II study to evaluate efficacy and safety of Zanubrutinib in subjects with R/R MCL. The objective of this study is to evaluate the efficacy and safety of Zanubrutinib in participants with centrally confirmed R/R MCL. The primary endpoint is overall response rate (ORR) assessed by an independent review committee (IRC, per Lugano 2014 classification); secondary endpoints include duration of response (DOR), time to response (TTR), PFS and safety(25).

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(23).

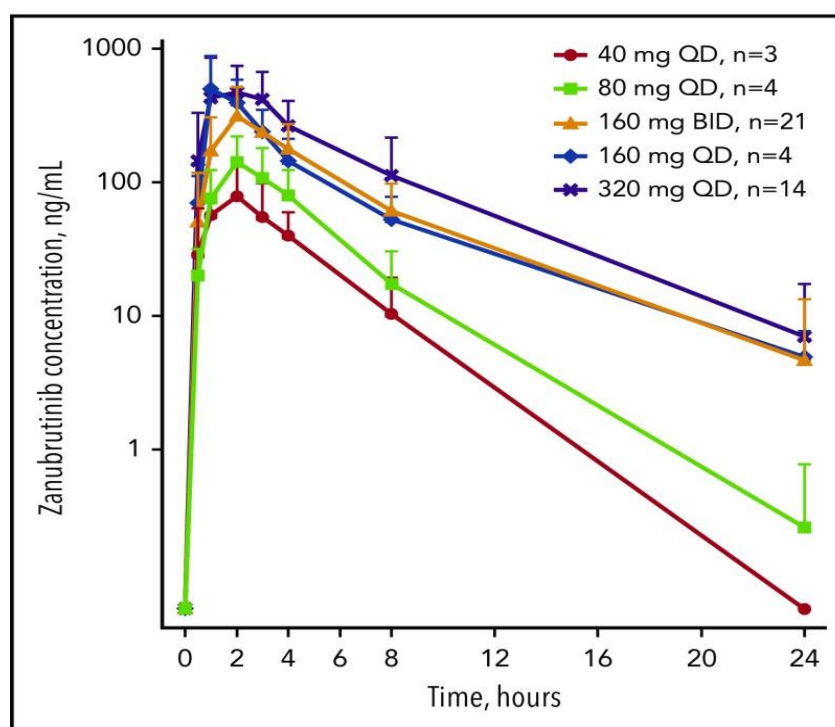


Figure 9-1. Plasma concentration-time profile of Zanubrutinib after initial doses of 40, 80, 160, and 320 mg once daily and 160 mg twice daily

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 postdose 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) (24).

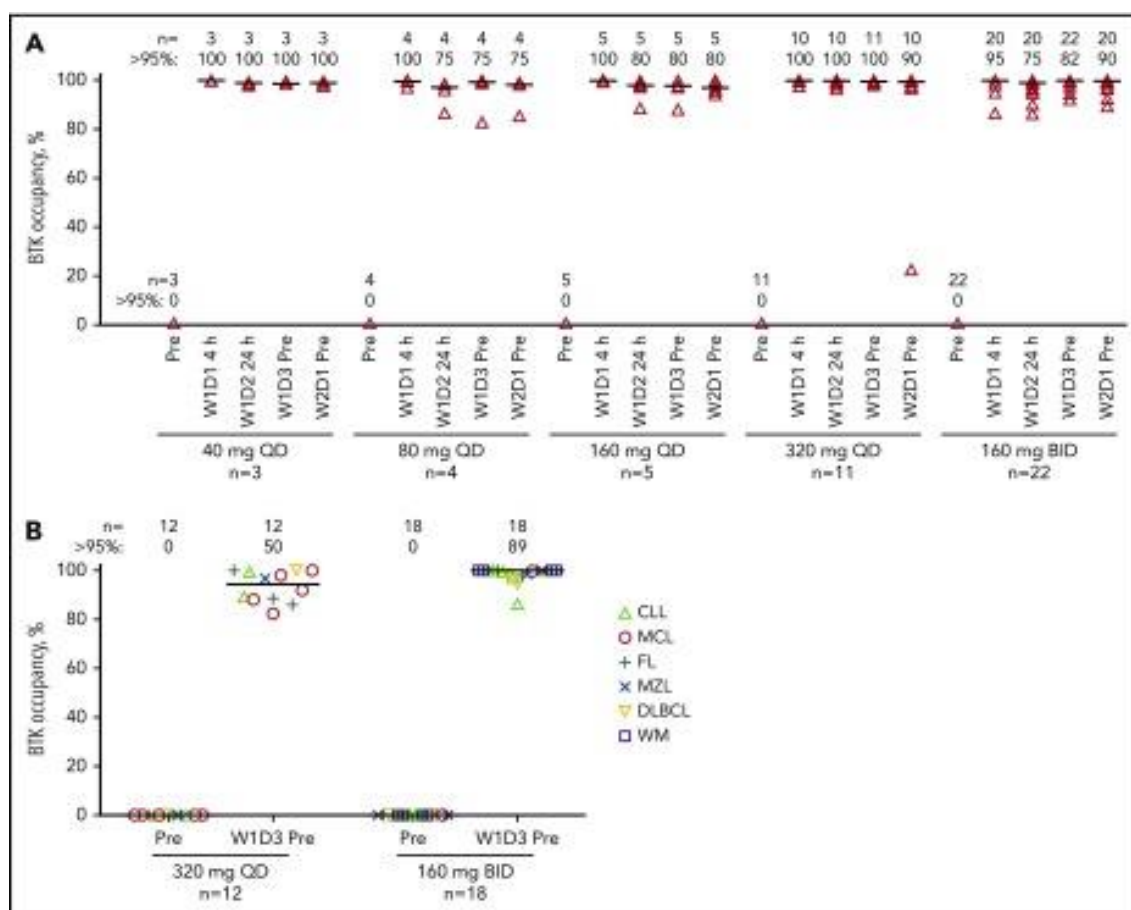


Figure 9-2 BTK occupancy (A: PBMSs; B: nodal tissue)

9.2.3 Efficacy

Result from part 2 of BGB-3111-AU-003 showed that median follow-up for efficacy evaluable MCL patients with 160 mg twice daily was 16.0 months. Twenty-six patients discontinued treatment (16 due to progressive disease (PD); 10 due to treatment emergent adverse events (TEAEs). ORR for treatment-naïve (TN), R/R and overall was 87.5% (7/8), 86.5% (32/37) and 86.7% (39/45) respectively [see Table 9-2]. Median progression-free survival was 15.4 months [see Table 9-2](26).

Table 9-2 Response rates in evaluable patients with MCL in part 2 of BGB-3111-AU-003

Best response per investigator (n)	TN (n=8)	R/R (n=37)	Overall (n=45)
ORR, n (%); 95% CI	7 (87.5); [47.3, 99.7]	32 (86.5); [71.2, 95.5]	39 (86.7); [73.2, 94.9]
CR, n (%)	3 (37.5)	11 (29.7)	14 (31.1)
PR, n (%)	4 (50.0)	21 (56.8)	25 (55.6)
Stable disease, n (%)	0 (0.0)	2 (5.4)	2 (4.4)
Progressive disease, n (%)	1 (12.5)	3 (8.1)	4 (8.9)

Results from BGB-3111-206 showed that, 72 (84%, 95% CI: 74.2–90.8) of the 86 evaluable R/R MCL patients who received Zanubrutinib 160 mg twice daily in a 28-day cycle until disease progression or intolerance achieved a response, with 59 (68.6%) patients achieving a CR after a median follow-up of 18.4 months [see [Table 9-3](#)]. Subgroup analysis revealed that overall response rates were generally high across all subgroups analyzed. After a median follow-up of 16.4 months from initial response, the estimated median DOR was 19.5 months [see [Figure 9-3A](#)]. Responders were alive and progression-free. After a median follow-up of 19.2 months, the estimated median PFS was 22.1 months with an estimated 76% of patients alive and without disease progression at 12 months[see [Figure 9-3B](#)](25).

Table 9-3 IRC-assessed efficacy outcomes of BGB-3111-206

Efficacy variable	N = 91
OR, n (%)	72 (83.7) [95% CI: 74.2–90.8]
CR, n (%)	59 (68.6)
PR, n (%)	13 (15.1)
Median TTR (months)	14 (16.3)
DOR (months)	
Median DOR	19.5 [95% CI:16.6-NE]
Event-free rates at 12 months (%)	78.3 [95% CI: 67-86]
PFS (months)	
Median PFS	22.1 [95% CI:17.4-NE]
Event-free rates at 12 months (%)	75.5 [95% CI: 65-83]

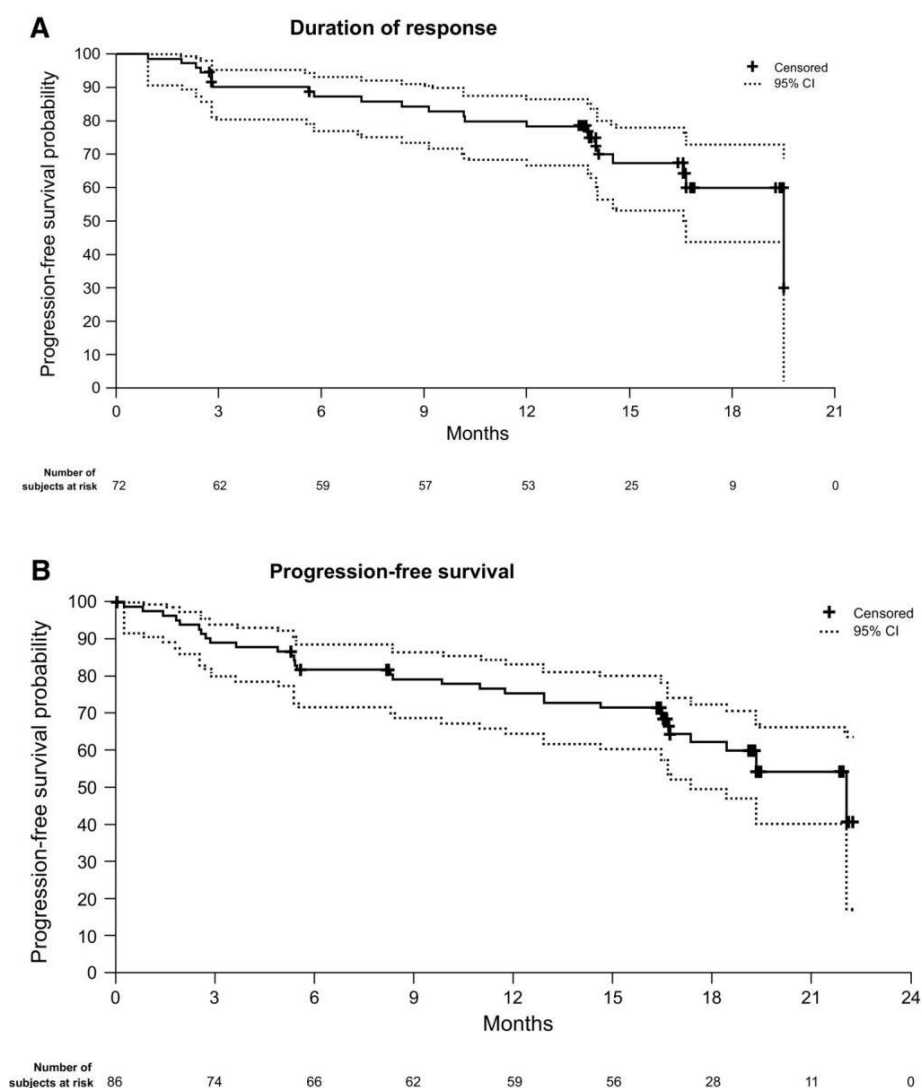


Figure 9-4 DOR and PFS outcomes of BGB-3111-206

9.3 Summary of available estimates of comparative effectiveness

Direct comparative data are still lacking. [Table 9-5](#) lists the data of efficacy for R/R MCL reported with Ibrutinib, Acalabrutinib, and Zanubrutinib. According to the data, IRC-assessed ORR of Zanubrutinib (83.7%(25)) was higher than Acalabrutinib (80%(19)) and Ibrutinib (72%(27)). Besides, Zanubrutinib (68.6%(25)), represent a higher CR than Acalabrutinib and Ibrutinib (39.5%(19), 19.0%(27), respectively).

Table 9-5 Data of efficacy for R/R MCL reported with different BTK inhibitors

Drug Clinical Trial	Phase	N	Median Age	Inter-vention	Median follow-up (Month)	ORR	CR	PFS
Zanubrutinib BGB-3111-206 NCT03206970 (25)	II	86	60.5	160mg b.i.d	8.2 18.4	IRC- assessed: 83.7% [95% CI: 74.2–90.8]	68.6%	PFS rates at 12 months: 75.5% [95% CI: 65- 83]
Acalabrutinib (19) LY-004 NCT02213926	II	124	68	100mg b.i.d	15.2	IRC- assessed: 80.0%[95% CI: 72-87]	39.5% [95% CI: 31- 49]	PFS rates at 12 months: 67% [95% CI: 62-80]
Ibrutinib PCYC-1104-CA NCT01236391 (28)	II	111	68	560mg q.d	15.3	Researcher- assessed: 68.0%	21.0%	Median PFS: 13.9 months [95% CI: 7.0 -NE]
Ibrutinib MCL3001 NCT01646021 (27)	III	139	67	560mg q.d	20.0	IRC- assessed: 72.0%	19.0%	Median PFS: 14.6months [95% CI: 10.4 -NE]

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, 134 of which are MCL patients (25, 26).

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 \geq 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; supplemental Table 6). 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(23).

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 (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(24).

10.2.3 Safety results from BGB-3111-206

Almost all patients (96.5%) experienced at least one AE, with the majority being grade 1 or 2 in severity; Grade ≥ 3 AEs were reported in 41.9% of patients. The most common (all grade) hematologic AEs were neutropenia (48.8%), leukopenia (34.9%), and thrombocytopenia (32.6%). And the most common nonhematologic AEs were upper respiratory infection (34.9%) and rash (33.7%). The most common grade ≥ 3 AEs were neutropenia (19.8%) and lung infection/pneumonia (9.3%) [see *Figure 10-1*](25).

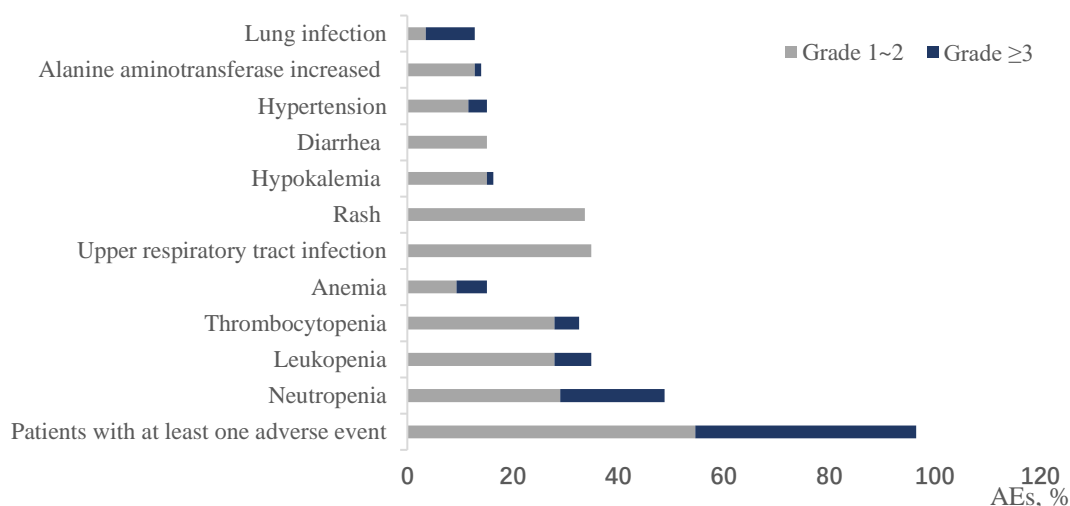


Figure 10-1 Adverse Events (≥10%) in MCL Patients in BGB-3111-206

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 (25).

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

The very common AEs (occurred $\geq 10\%$) associated with Zanubrutinib included: neutropenia, hemocytopenia, rash, leukopenia, and petechiae (29).

The common AEs associated with Zanubrutinib ($5\% \leq$ occurred $< 10\%$) included: anemia, purpura, hematuria, lung infection, upper respiratory tract infection, diarrhea and bleeding (29).

10.4 Summary of comparative safety against comparators

Compared with ibrutinib, Zanubrutinib for the treatment of R/R MCL resulted in a lower rate of SAEs such as atrial fibrillation [see Table 10-1] and treatment discontinuation rates due to AEs were lower (9.3% vs 11%).

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

	Zanubrutinib (25)	Ibrutinib(30)
≥Grade 3 Lung pneumonia	2.3%	8%
≥Grade 3 Diarrhea	0%	5%
Bleeding	2.3%	6%
Atrial fibrillation	0%	6%
Discontinuation due to AEs	9.3%	11%

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 (29).

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 (29).

10.5.3 Embryo-fetal toxicity

Based on findings in animals, Zanubrutinib can cause fetal harm when administered to a pregnant

woman(29). 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 (31).

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(29).

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(29).

10.5.6 Pediatric use

Safety and effectiveness in pediatric patients have not been established(29).

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(29).

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 MCL

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 22,600 RMB. Comparatively, the first-generation BTK inhibitor (Ibrutinib) is listed in China priced at 22,680 RMB per month for MCL patients.

11.2.2 Data on comparative cost-effectiveness

Direct comparative data on pharmacoeconomics containing Zanubrutinib on R/R CLL/SLL are still lacking.

A Pharmacoeconomics evaluation assessed the cost effectiveness of a BTK inhibitor (ibrutinib) versus CIT (Rituximab plus chemotherapy) for the treatment of R/R MCL from the perspective of the National Health Service (NHS) and Personal Social Services over a lifetime horizon. Results showed that Ibrutinib is more cost-effective for R/R MCL patients with at least one prior treatment (the incremental cost-effectiveness ratio (ICER)=£62,650/ quality-adjusted life-year (QALY)(32).

11.2.3 Budget impact

MCL 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(7), 3.6% of which are MCL patients(10). Based on the data, the estimated number of NHL cases with 5 years in China is 8,196. The estimated number of NHL cases with 5 years in the US is 225,032 in 2018(7), 7.8% of which are MCL patients(10). Based on the data, the estimated number of NHL cases with 5 years in the US is 17,552. According to a real world study(33), the proportion of each current treatment for MCL (either first-line therapy or second-line therapy) was listed below: BR (41.1%), RCHOP (26.7%), Rituximab (20.4%) and Ibrutinib (14.2%). Based on Ibrutinib's market share (14.2%), there are no more than 1,163 people taking Zanubrutinib in China and 2,593 in the US.

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

Zanubrutinib was approved by the FDA on November 14, 2019 for the treatment of patients with MCL

who had received at least one prior therapy, priced at 12,935 USD per bottle with 120 capsules.

On June 2, 2020, Zanubrutinib was also approved by NMPA for the treatment of patients with MCL who have received at least one prior therapy, priced at 11,300 RMB per bottle with 64 capsules.

Zanubrutinib is under regulatory review in Israel for the treatment of patients with MCL who had received at least one prior therapy. In addition, the new drug application of Zanubrutinib has also been submitted to medicines agency in Australia, Canada and Europe.

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

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

References

1. NCCN. NCCN Clinical Practice Guidelines in Oncology: B-Cell Lymphomas, Version 2.2020.
2. He J, Li J. Guideline of Chinese Society of Clinical Oncology (CSCO): Lymphoid Malignancies (2020). Beijing: People's Medical Publishing House. 2020.
3. Vose JM. Mantle cell lymphoma: 2017 update on diagnosis, risk-stratification, and clinical management. *AM J HEMATOL*. 2017;92(8):806-13.
4. Rufang H, Wenbin S. China Rare Disease Drug Accessibility Report: 2019, Department/Division; 2019.
5. Howlader N, Noone A, Krapcho M, Miller D, Brest A, Yu M. SEER Cancer Statistics Review, 1975-2017, National Cancer Institute. 2020.
6. Smedby KE, Henrik H. Epidemiology and etiology of mantle cell lymphoma and other non-Hodgkin lymphoma subtypes. 2011;21(5):293-8.
7. IAFC. The Global Cancer Observatory. 2020.

8. Miyoshi H, Ohshima K. Epidemiology of malignant lymphoma and recent progress in research on adult T-cell leukemia/lymphoma in Japan. *INT J HEMATOL*. 2018;107(4):420-7.
9. van Leeuwen MT, Turner JJ, Joske DJ, Falster MO, Srasuebkul P, Meagher NS, et al. Lymphoid neoplasm incidence by WHO subtype in Australia 1982-2006. *INT J CANCER*. 2014;135(9):2146-56.
10. Perry AM, Diebold J, Nathwani BN, MacLennan KA, Müller-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 2016-10-01;101(10):1244-50.
11. Cortelazzo S, Ponzoni M, Ferreri AJ, Dreyling M. Mantle cell lymphoma. *Crit Rev Oncol Hematol*. 2012;82(1):78-101.
12. McKay P, Leach M, Jackson B, Robinson S, Rule S. Guideline for the management of mantle cell lymphoma. *Br J Haematol*. 2018;182(1):46-62.
13. Van Keep M, Gairy K, Seshagiri D, Thilakarathne P, Lee D. Cost-effectiveness analysis of bortezomib in combination with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (VR-CAP) in patients with previously untreated mantle cell lymphoma. *BMC CANCER*. 2016;16(1):598.
14. Bond DA, Maddocks KJ. Current Role and Emerging Evidence for Bruton Tyrosine Kinase Inhibitors in the Treatment of Mantle Cell Lymphoma. *Hematol Oncol Clin North Am*. 2020;34(5):903-21.
15. Smolewski P, Witkowska M, Robak T. Treatment options for mantle cell lymphoma. *Expert Opin Pharmacother*. 2015;16(16):2497-507.
16. Dreyling M, Ghielmini M, Rule S, Salles G, Ladetto M. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *ANN ONCOL*. 2017;28(12):v62-71.
17. Kluin-Nelemans JC, Doorduijn JK. What is the optimal initial management of the older MCL patient? *Best Pract Res Clin Haematol*. 2018;31(1):99-104.
18. Steiner RE, Romaguera J, Wang M. Current trials for frontline therapy of mantle cell lymphoma. *J HEMATOL ONCOL*. 2018;11(1):13.
19. Wang M, Rule S, Zinzani PL, Goy A, Casasnovas O, Smith SD, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. *LANCET*. 2018:659-67.

20. Wang ML, Lee H, Chuang H, Wagner-Bartak N, Zhang L. Ibrutinib in combination with rituximab in relapsed or refractory mantle cell lymphoma: a single-centre, open-label, phase 2 trial. *LANCET ONCOL*. 2016;17(1):48-56.
21. McMullen JR, Boey EJH, Ooi JYY, Seymour JF, Tam CS. Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling. *BLOOD*. 2014;124(25):3829-30.
22. Sawalha Y, Bond DA, Alinari L. Evaluating the Therapeutic Potential of Zanubrutinib in the Treatment of Relapsed/Refractory Mantle Cell Lymphoma: Evidence to Date. *Onco Targets Ther*. 2020;13:6573-81.
23. Tam CS, Trotman J, Opat S, Burger JA, Cull G, Gottlieb D, et al. Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL. *BLOOD*. 2019;134(11):851-9.
24. Mu S, Tang Z, Novotny W, Tawashi M, Li TK, Ou Y, et al. Effect of rifampin and itraconazole on the pharmacokinetics of zanubrutinib (a Bruton's tyrosine kinase inhibitor) in Asian and non-Asian healthy subjects. *Cancer Chemother Pharmacol*. 2020 2020-02-01;85(2):391-9.
25. Song Y, Zhou K, Zou D, Zhou J, Hu J, Yang H, et al. Treatment of Patients with Relapsed or Refractory Mantle-Cell Lymphoma with Zanubrutinib, a Selective Inhibitor of Bruton's Tyrosine Kinase. *CLIN CANCER RES*. 2020;26(16):4216-24.
26. Tam CS, Wang M, Simpson D, Opat S, Cull G, Munoz J, et al. UPDATED SAFETY AND EFFICACY DATA IN THE PHASE 1 TRIAL OF PATIENTS WITH MANTLE CELL LYMPHOMA (MCL) TREATED WITH BRUTON TYROSINE KINASE (BTK) INHIBITOR ZANUBRUTINIB (BGB-3111). *HEMATOL ONCOL*. 2019;S2(37):245-7.
27. Dreyling M, Jurczak W, Jerkeman M, Silva RS, Rule S. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. *LANCET*. 2016;387(10020):770-8.
28. Wang ML, Rule S, Martin P, Goy A, Auer R, Kahl BS, et al. Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma. *NEW ENGL J MED*. 2013.
29. BeiGene. Package Insert of Zanubrutinib Capsules. 2020.
30. Wang ML, Blum KA, Martin P, Goy A, Auer R, Kahl BS, et al. Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results. *BLOOD*. 2015;126(6):739-45.

31. Zhang C, Tian B. Nonclinical Safety Assessment of Zanubrutinib: A Novel Irreversible BTK Inhibitor. *INT J TOXICOL*. 2020;39(3):232-40.
32. Paul, Tappenden, Emma, Simpson, Jean, Hamilton, et al. Ibrutinib for Treating Relapsed or Refractory Mantle Cell Lymphoma: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. *Pharmacoeconomics*. 2018;37(3):333-43.
33. Goyal RK, Nagar SP, Kabadi SM, Kaye JA, Seal B, Mato AR. Adverse events, resource use, and economic burden associated with mantle cell lymphoma: a real-world assessment of privately insured patients in the United States. *LEUKEMIA LYMPHOMA*. 2018;60:1-9.