12 October 2023
EMA/CHMP/510757/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Brukinsa

International non-proprietary name: zanubrutinib

Procedure No. EMEA/H/C/004978/II/0014

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
212	Study BGB-3111-212
305	Study BGB-3111-305
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BGB-3111	zanubrutinib
BOR	Best overall response
BTK	Bruton tyrosine kinase
CLL	chronic lymphocytic leukemia
C_{max}	maximum plasma concentration
CO	clinical overview
CR	complete response
CMR	Complete metabolic response
CSR	Clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
EAIR	exposure-adjusted incidence rate
ECOG PS	Eastern Cooperative Oncology Group performance status
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer and Quality of Life Cancer Patients-C30
EQ-5D-5L	European Quality of Life 5-Dimensions 5-Levels
E-R	exposure-response
FDA	Food and Drug Administration
FL	follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index

Abbreviation	Definition
GA101	Study BGB-3111-GA101
G-CSF	granulocyte colony-stimulating factors
GELF	The Groupe d'Etude des Lymphomes Folliculaires
GHS	global health status
ICR	independent central review (same as IRC)
IRC	Independent Review Committee (same as ICR)
ITT	intent-to-treat
LDH	lactate dehydrogenase
LTE	long-term extension
MAH	Market authorization holder
MCL	mantle cell lymphoma
MZL	marginal zone lymphoma
NHL	non-Hodgkin lymphoma
NOS	Not otherwise specified
O	Obinutuzumab (monotherapy)
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
R/R	relapsed/refractory
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SPD	Sum of the products of diameters
SLL	small lymphocytic lymphoma
TTR	Time to response
ULN	upper limit of normal
US	United States
uSCS	Updated summary of clinical safety (08 Aug 2023)

Abbreviation	Definition
WHO	World Health Organization
WM	Waldenström’s macroglobulinemia
ZO	Zanubrutinib + obinutuzumab

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, BeiGene Ireland Ltd submitted to the European Medicines Agency on 7 March 2023 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include in combination with obinutuzumab treatment of adult patients with relapsed or refractory follicular lymphoma who have received at least two prior systemic treatments for BRUKINSA; based on results from studies BGB-3111-212 and BGB-3111-GA101-001. BGB-3111-212 is an ongoing international, Phase 2, open-label, randomized (2:1), active control study of zanubrutinib plus obinutuzumab (Arm A) versus obinutuzumab monotherapy (Arm B) in patients with R/R FL. The primary efficacy endpoint is overall response rate (ORR); while BGB-3111-GA101-001 is 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. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0205/2022 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The MAH sought Scientific Advice at the CHMP.

Scientific advice received [EMEA/H/SA/3376/3/2017/II], 12 October 2017) focused on the design and conduct of Study BGB-3111-212, including endpoints, comparators, duration, stratification factors, and patient population.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Aaron Sosa Mejia Co-Rapporteur: Johanna Lähteenvuo

Timetable	Actual dates
Submission date	7 March 2023
Start of procedure:	25 March 2023
CHMP Co-Rapporteur Assessment Report	1 June 2023
CHMP Rapporteur Assessment Report	23 May 2023
PRAC Rapporteur Assessment Report	25 May 2023
PRAC Outcome	8 June 2023
CHMP members comments	8 June 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	14 June 2023
Request for supplementary information (RSI)	22 June 2023
CHMP Rapporteur Assessment Report	9 September 2023
PRAC Rapporteur Assessment Report	14 September 2023
PRAC members comments	20 September 2023
Updated PRAC Rapporteur Assessment Report	21 September 2023
PRAC Outcome	28 September 2023
CHMP members comments	02 October 2023
Updated CHMP Rapporteur Assessment Report	05 October 2023
Opinion	12 October 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

BRUKINSA in combination with obinutuzumab is indicated for the treatment of adult patients with refractory or relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies.

Epidemiology

FL is the second most common subtype of non-Hodgkin lymphoma (NHL), comprising 20% to 30% of all NHL diagnoses in developed countries (Cerhan 2020). While there is considerable heterogeneity in the clinical course of FL, it is generally an indolent malignancy, with a prolonged but incurable clinical course. The incidence of FL appears to be increasing, with a documented increase of 0.5 cases per million persons per year between 1992 and 2010. In the EU, the annual incidence of this disease has rapidly increased during recent decades and has risen from 2 to 3 per 100,000 persons during the 1950s to 5 per 100,000 recently. The reported median age at diagnosis for FL in EU is 64.9 years (Casulo et al 2015).

Follicular lymphoma is defined as a lymphoma of germinal center B cells, and virtually always demonstrates a growth pattern that is partially follicular.

With modern treatment approaches for FL, median survival exceeds 10 years (Casulo et al 2015). Over the past several decades, the incorporation of novel active agents into treatment practices has resulted in a decline in FL mortality trends (Howlader et al 2016). Yet, FL remains incurable. Its clinical history is typically one of multiple relapses, with successive treatment regimens resulting in progressively shorter disease-control intervals, until fatal, resistant disease emerges. In addition to the morbidity and mortality associated with treatment resistance, cumulative treatment-related toxicity (especially immunosuppression, myelosuppression, and secondary leukaemia related to alkylator exposure) and transformation to diffuse large B-cell lymphoma (DLBCL) remain significant contributors to mortality in patients with FL.

Biologic features, Aetiology and pathogenesis

The molecular pathogenesis of FL is a complex process involving several steps during which a single follicular B cell acquires all of the genetic and epigenetic alterations needed for malignant transformation. The resultant tumour is usually comprised of a mixture of centrocytes (small cleaved germinal center cells) and centroblasts (large noncleaved germinal center cells). Some common steps in this pathway have been described, particularly chromosomal rearrangements involving BCL-2 and certain somatic mutations, some of which are also seen in other non-Hodgkin lymphomas. In most cases, FL is associated with a translocation between the long arm of chromosome 18, the site of the BCL-2 oncogene, and one of the three immunoglobulin (Ig) genes. The most common translocation involves the Ig heavy chain gene resulting in the t(14;18)(q32;q21), found in approximately 85 percent of FL. BCL-2 overexpression in itself is not sufficient for FL development and other genetic lesions or host factors are required. Some of the complementary mutations involve genes that regulate the epigenome (for example histone modifications, chromatin structure). Other important factors involve the local host response and tumour

microenvironment, and modifications in the B cell receptor that may augment B cell receptor signalling. The tumour cells express monotypic immunoglobulin light chain, CD20 (or CD19), CD10,and BCL-6 and are negative for CD5 and CD23

Clinical presentation, diagnosis and stage/prognosis

Initially, patients with FL usually present with painless peripheral adenopathy, often with a long history of waxing and waning lymph node enlargement. Widespread disseminated disease is usually present at baseline, but patients are typically asymptomatic aside from their lymphadenopathy. There are no characteristic laboratory abnormalities and, despite the large tumour burden, the majority has a normal serum lactate dehydrogenase (LDH) level.

After initial therapy, patients are followed at routine intervals to monitor for relapse or complications related to treatment. On suspicion of relapse it is important to rule out transformation to a more aggressive histologic subtype, most commonly diffuse large B cell lymphoma (NOS). Follicular lymphoma grade 3b and transformed FL generally requires a more intensive treatment approach than FL grade 1-3a.

Management

Significant progress has been made with the introduction of newer targeted agents in R/R FL. However, these new treatments are often associated with significant toxicities and none of them provide long-term disease control, particularly in patients who had received multiple lines of therapy and/or who are highly refractory (Dreyling et al 2021).

Rituximab (MabThera) is an anti-CD20 monoclonal antibody, approved in 1998 for the treatment of patients with R/R FL. The efficacy and safety of rituximab monotherapy in patients with R/R FL has been recently evaluated in the CHRONOS-3 trial as a comparator to the copanlisib plus rituximab arm. In this study, 91 patients with R/R FL were randomized in the rituximab plus placebo arm. The overall response rate was 54% (95% CI: 43%, 4%), the complete response rate was 21%, and the median progression-free survival was 18.7 months (95% CI: 5.5, 27.9 months).

Idelalisib (Zydelig), a selective inhibitor of the PI3K-δ isoform, received EU authorization as monotherapy for the treatment of adult patients with FL that is refractory to 2 prior lines of treatment in 2014. The approval was based on complete response and partial response results from a Phase II single arm study on patients with previously treated indolent non-Hodgkin lymphoma (iNHL) (including 72 patients with FL) that was refractory both to rituximab and to alkylating agent-containing chemotherapy. In the pivotal study, 125 patients were enrolled, including 72 with FL. The overall response rate (FL population) was 55.6% and the complete response rate was 16.7% (Gopal et al 2014; Wagner-Johnston et al 2021). The median duration of response was 11.8 months (95% CI: 6.2, 26.9 months) and the median PFS was 11.0 months (95% CI: 8.0, 14.0 months). Common Grade 3 to 4 treatment-emergent adverse events were neutropenia, diarrhea, and pneumonia. There are, however, significant safety concerns associated with the use of idelalisib and the FL indication was voluntarily withdrawn from the US in January 2022 (Gilead statement 2022).

Obinutuzumab (Gazyva; Gazyvaro) is a second-generation anti-CD20 antibody that was engineered to have a higher affinity for the CD20 receptor and to cause enhanced direct target-cell killing compared with rituximab. Obinutuzumab was approved in 2016 in combination with bendamustine followed by monotherapy for the treatment of patients with follicular lymphoma who relapsed after, or are refractory to, a rituximab-containing regimen. The approval is based on the progression-free survival results of a

Phase III study comparing treatment with obinutuzumab in combination with bendamustine, followed by obinutuzumab alone as maintenance therapy, to bendamustine alone in patients with FL not responding to rituximab. The GADOLIN Study was a multicenter, open-label, randomized Phase 3 study of 396 subjects with indolent NHL refractory to rituximab (Sehn et al 2016); 321 had R/R FL and were randomised to receive either bendamustine alone or obinutuzumab plus bendamustine followed by 2 years of maintenance with obinutuzumab. Median progression-free survival was significantly longer in the obinutuzumab-bendamustine arm (25.8 months; 95% CI: 19.5, 41.1 months) than in the bendamustine arm (14.1 months; 95% CI: 12.6, 16.0 months); a treatment benefit was also seen for overall survival (Cheson et al 2018).

Recently, new drugs have been approved for patients with R/R FL, which expands the possibilities of treatment for second-line therapy.

This includes combination of lenalidomide (Revlimid) plus rituximab (Leonard et al 2019) approved in 2019. The combination of lenalidomide plus rituximab is indicated for patients who have relapsed or did not respond to previous treatment (Leonard et al 2019). In this study, 358 patients with R/R FL or R/R MZL were randomly assigned to lenalidomide plus rituximab (n = 178, 147 patients with R/R FL) or placebo plus rituximab (n = 180, 148 patients with R/R FL). The primary endpoint was progression-free survival assessed by an Independent Review Committee (IRC). For the patients with R/R FL, the median progression-free survival assessed by the IRC was 39.4 months (95% CI: 23.1 months, not reached [NR]) with lenalidomide plus rituximab versus 13.9 months (95% CI: 11.2, 16.0 months) with placebo plus rituximab (hazard ratio [HR], 0.40; 95% CI, 0.29, 0.56; $p < 0.0001$). The median progression-free survival assessed by investigators (R/R FL population) was 27.8 months (95% CI: 22.1 months, NR) with lenalidomide plus rituximab. The data with a median follow-up of 28.3 months were not mature to demonstrate overall survival benefit. Neutropenia (including 50% of patients with Grades 3 to 4), gastrointestinal toxicity, cutaneous reactions, and infections were the most common side effects associated with the combination.

In 2021, duvelisib (Copiktra), another PI3K inhibitor was approved for patients with FL not responding to two previous treatments. The pivotal study in FL is a Phase 2, open-label, single arm efficacy and safety study of duvelisib monotherapy administered orally to subjects with R/R indolent NHL, including the subtypes of FL (n = 83), SLL (n = 28), and MZL (n = 18) for a total of 129 subjects. This study was designed to evaluate the effect of duvelisib 25 mg twice daily monotherapy in subjects with indolent NHL refractory to rituximab and to either chemotherapy or radioimmunotherapy. The overall response rate was 42.2% (FL patients); median duration of response (all population) was 10 months (95% CI: 6.5, 10.5 months). The R/R FL indication was voluntarily withdrawn from the US market in December 2021 (US FDA Notification 2022).

In 2022, mosunetuzumab (Lunsumio), a CD20 x CD3 T-cell bispecific antibody (Budde et al 2022) received conditional marketing authorization in EU for R/R FL. The pivotal study enrolled 90 patients with R/R FL, and the median study follow-up was 18.3 months. Overall response rate by IRC assessment was 80.0% (95% CI: 70.3%, 87.7%), and the complete response rate was 60.0%. Median duration of response was 22.8 months (95% CI: 9.7 months, NR) and median progression-free survival was 17.9 months (95% CI: 10.1 months, NR).

Finally, other recently approved treatments for R/R FL are two CD19 CAR-T cell products, axicabtagene ciloleulel, and tisagenlecleucel (Fowler et al 2021; Jacobson et al 2022).

Currently approved therapies in EU for R/R FL are summarized below.

Table 1: Current Treatment Options for R/R FL in the EU

Product	Class	Approved Line of FL Treatment	Major Concerns
Rituximab (MabThera)	anti-CD20 monoclonal antibody	R/R FL	High rates of rituximab resistance Limited duration of response as monotherapy
Idelalisib (Zydelig)	PI3K-δ inhibitor	R/R FL	Serious infections including opportunistic infections, neutropenia, hepatotoxicity, diarrhoea/colitis, pneumonitis and organizing pneumonia, severe cutaneous reactions. Survival detriment in three randomized trials
Duvelisib (Copiktra)	PI3K inhibitor	R/R FL	Pneumonitis, infections, intestinal toxicity including colitis, severe cutaneous reaction, neutropenia, potential survival detriment
Obinutuzumab (Gazyva; Gazyvaro)	second-generation anti-CD20 antibody	R/R FL in combination with bendamustine, followed by maintenance	Infusion reactions, infections, neutropenia, thrombocytopenia. Unknown efficacy in patients previously treated with bendamustine
Lenalidomide (Revlimid)	Modulator of the immune system	R/R FL in combination with Rituximab	Neutropenia, leucopenia, intestinal toxicity, thromboembolism, rash, secondary primary malignancy
Mosunetuzumab (Lunsumio)	CD20-CD3 bispecific antibody	R/R FL (CMA) After at least two prior systemic therapies.	Cytokine release syndrome, serious infections, tumor flare, tumor lysis syndrome, pneumonia, neurotoxicity Hospitalization required, need appropriate medical support
Axicabtagene ciloleulel (Yescarta)	CD19 CAR-T cells	R/R FL	Cytokine release syndrome, encephalopathy, febrile neutropenia, and infections, prolonged

Product	Class	Approved Line of FL Treatment	Major Concerns
		after three or more lines of systemic therapy	cytopenia, hypogammaglobulinemia. Administration in a qualified medical setting.
Tisagenlecleucel (Kymriah)	CD19 CAR-T cells	R/R FL after two or more lines of systemic therapy	Cytokine release syndrome, encephalopathy, febrile neutropenia, and infections, prolonged cytopenia, hypogammaglobulinemia. Administration in a qualified medical setting.

Abbreviations: CMA, conditional marketing authorization; EU, European Union; FL, follicular lymphoma; R/R, relapsed/refractory.

In summary, with each relapse of FL, the duration of remission tends to be shorter (Batlevi et al 2020). Acceptable options for patients with R/R FL remain somewhat limited and may not be useful for many patients, whether because of advanced patient age (precluding use of stem cell transplantation, chemotherapy, or cellular therapy) or limited bone marrow reserve following prior therapies (radioimmunotherapy) (Dreyling et al 2021 ESMO). Thus, treatments capable of inducing high rates of durable responses with favorable safety and tolerability profiles are still needed in the high-risk population of patients with R/R FL, especially in second or greater relapse.

BTK inhibitors as monotherapy have been shown to be very effective in the treatment of B-cell malignancies such as CLL. Unfortunately, in FL, the first generation BTK inhibitor, ibrutinib, has been disappointing due to low response rates (Bartlett et al 2018; Gopal et al 2018). In contrast, the second generation BTK inhibitor, zanubrutinib, showed initial efficacy as monotherapy in early studies enrolling a variety of B-cell lymphomas, including those with R/R FL. Results of Study BGB-3111-212, which provide pivotal study data for this application in FL, showed that the efficacy of zanubrutinib as monotherapy can be markedly enhanced by the addition of obinutuzumab. This combination was shown to be efficacious in high-risk patient populations, and the safety profile is such that it can be administered to patients who are not chemotherapy candidates. As a consequence, the combination of zanubrutinib plus obinutuzumab could expand treatment options and further address the substantial unmet need of the R/R FL population.

2.1.2. About the product

Brukinsa (zanubrutinib) is a BTK inhibitor, which is a member of the tyrosine kinase expressed in hepatocellular carcinoma (TEC) family of kinases, many of which are abundantly expressed in hematopoietic tissues and play key roles in the growth and differentiation processes of hematopoietic cells. BTK plays a critical role in B-cell receptor signalling, which mediates B-cell growth, proliferation, migration, and adhesion. Constitutive activation of B-cell receptor signalling is critical for cell survival and clonal expansion in B-cell malignancies, and BTK has been validated as a therapeutic target in a variety of B-cell malignancies. FL harbours recurrent cell-intrinsic genetic changes, including mutations

in genes involved in the B-cell receptor signalling pathway (Singh et al 2018) including BTK (Krysiak et al 2017). This supports a role in lymphomagenesis and, therefore, a role for BTK inhibition for patients with R/R FL.

Given these features, inhibition of BTK with zanubrutinib is an attractive approach for patients with R/R FL, particularly when used in combination with anti-CD20 monoclonal antibodies.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Key points from the Scientific advice EMEA/H/SA/3376/3/2017/II) (EMA/CHMP/SAWP/669794/2017) include:

- Determination of ORR by independent central review using the Lugano Classification for NHL (Cheson 2014) is acceptable. Of note, patients with no response to obinutuzumab after 12 months will receive BGB-311 in addition to obinutuzumab. The benefit of this approach is largely hypothetical and such an option will confound longer-term assessment of endpoints. The CHMP does not recommend cross-over. During the discussion meeting the Applicant discussed the option of offering cross-over at progression. This would at least preserve assessment of PFS.
- Proposed size and design in the relevant population would not automatically establish a compelling clinical benefit.

The scientific advice has been overall adhered to, except for advice given regarding crossover in the study 212.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The MAH has provided the variation report from the EMEA/H/C/004978/II/0010 procedure in which the full environmental risk assessment for zanubrutinib for the treatment of lymphoplasmacytic lymphoma was updated including $PEC_{SURFACEWATER}$.

Table 2 Results on persistence of TP-1 and TP-3

<table>
<tr><th colspan="4">Phase II Physical-chemical properties and fate</th></tr>
<tr><th>Study type</th><th>Test protocol</th><th>Results</th><th>Remarks</th></tr>
<tr><td>Aerobic and Anaerobic Transformation in Aquatic Sediment systems</td><td>OECD 308</td><td><table><tr><td>Compartment</td><td>DT50, 20 °C [d]</td></tr><tr><td>SW total System</td><td>15</td></tr><tr><td>SW water</td><td>5.8</td></tr><tr><td>SW sediment</td><td>18</td></tr><tr><td>EV total System</td><td>35</td></tr><tr><td>EV water</td><td>4.6</td></tr><tr><td>EV sediment</td><td>26</td></tr></table>% shifting to sediment = 92-100% on day 101</td><td>Phase II Tier B assessment for sediment is triggered.

Two major transformation products TP-1 and TP-3 > 10% found in sediment. DT_{50} for TP-1 and TP-3 are not estimable, however TP-1 concentration shows a steady increase until test end, TP-3 concentration</td></tr>
</table>

		(1) Schoonrewoerdse Wiel (SW) sediment, (2) = Van Esschenven (EV) sediment % CO2 = 1.3% (1), 2.1% (2) at test end % NER = 49.2% (1), 67.2% (2) at test end Transformation products >10% = YES, TP-1 = 37.3% TP-3 = 10.3% DT_{50} not available	seems stable until test end. Hence, both transformation products have to be considered persistent. Proposed molecular formula: TP-1:$C_{27}H_{29}N_5O_3$ Exact Mass of Transformation Product TP-1: 474.2500 ([M+H]+) TP-3: $C_{27}H_{25}N_5O_3$ Exact Mass of Transformation Product TP-3: 468.2030 ([M+H]+)

2.2.2. Discussion on non-clinical aspects

Based on the given DT50 values for the parent, zanubrutinib itself is considered not persistent, however the transformation products TP-1 and TP-3 have to be considered persistent as both remain stable or even increase over the test period, respectively.

2.2.3. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of zanubrutinib.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 3

Table 2: Key Design Features of Clinical Studies Contributing Efficacy and/or Safety Data in the Submission

Study Location	Study Design	Population	Zanubrutinib Starting Dose	Number of Treated Patients			First Patient First Dose/ Data Cutoff Date/ Study Status
				Zanubrutinib		Comparator	
				FL	All		
Pivotal study							
BGB-3111-212 (AU, BG, BY, CA, CN, CZ, DE, ES, FR, GB, IT, KR, NZ, PO, RU, TW, US)	Phase 2, randomized, open-label, multicenter study	Patients with R/R FL	160 mg BID	143 (in combination with obinutuzumab)	143	Obinutuzumab 71	14 November 2017/ 25 June 2022/ Ongoing
Supportive studies							
BGB-3111_GA101 (AU, KR, US)	Phase 1b, open-label, multicenter study	Patients with B-cell malignancies	160 mg BID or 320 mg QD	36 (in combination with obinutuzumab)	119	N/A	13 January 2016/ 02 September 2020/ Closed
BGB-3111-AU-003 (AU, IT, KR, NZ, UK, US)	Phase 1/2, single-arm, dose escalation and cohort expansion	Patients with R/R or TN CLL/SLL, DLBCL, FL, HCL, MALT, MCL, MZL, NHL, RT, or WM	40 mg QD starting dose up to 160 mg BID or 320 mg QD	33	373 (patients who received 160 mg BID or 320 mg QD)	N/A	16 September 2014/ 31 March 2021/ Closed
BGB-3111-1002 (China)	Phase 1, single-arm	Patients with R/R CLL/SLL, MCL, WM/LPL, FL, MZL, HCL or nGCB DLBCL	160 mg BID or 320 mg QD	26	44	N/A	05 July 2016/ 30 August 2020/ Closed

2.3.2. Pharmacokinetics

This is a summary of the updated clinical pharmacology results since the initial MAA including:

- Non-compartmental analysis based on intensive pharmacokinetic (PK) data from study BGB-3111-GA101 (Day 1, N=12; steady state, N=111) to assess zanubrutinib PK after administration of 160 mg twice daily and 320 mg once daily in combination with obinutuzumab (CSR).

- An updated population PK analysis (N=248) incorporating PK data from studies BGB-3111-GA101 and BGB-3111-212 based on the population PK model previously developed (N=1291). The external model validation approach was used to evaluate the PK characteristics of zanubrutinib in combination with obinutuzumab compared to that in patients with zanubrutinib monotherapy in patients of B-cell malignancies.

- Exposure-efficacy analysis using data from study BGB-3111-212 to understand the relationship between exposure and efficacy endpoints in patients with FL following concomitant use of zanubrutinib and obinutuzumab (N=137).

Exposure-safety analysis using pooled data from studies BGB-3111-GA101 and BGB-3111-212 to understand the relationship between zanubrutinib exposure and safety endpoints in patients with FL and other B-cell malignancies following concomitant use of zanubrutinib and obinutuzumab (N=248).

Studies BGB-3111-GA101 and BGB-3111-212

Title of Studies

Study BGB-3111-GA101: 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.

Study BGB-3111-212: An International, Phase 2, Open-Label, Randomized Study of BGB-3111 Combined With Obinutuzumab Compared With Obinutuzumab Monotherapy in Relapsed/Refractory Follicular Lymphoma.

Study GA101 was a 2-part, uncontrolled phase 1b study, in which zanubrutinib in combination with obinutuzumab was investigated patients with B-cell lymphoid malignancies including FL. Study GA101 included a safety evaluation (Part 1) for selecting recommended phase 2 doses in subsequent indication-specific expansion cohorts (Part 2). The pivotal phase 2 study 212 enrolled only patients with relapsed-refractory FL, who were randomized in a 2:1 manner to zanubrutinib + obinutizumab (Arm A) or obinutuzumab monotherapy (Arm B). (See Clinical efficacy section).

Study drug administration

Study GA101:

Zanubrutinib was administered orally either 320 mg once daily or 160 mg twice daily. Obinutuzumab was administered intravenously at a final concentration of 0.4 to 4 mg/mL for up to 6 cycles at doses consistent with the US prescribing information:

Part 1:

- Day 2 Cycle 1: 100 mg obinutuzumab
- Day 3 Cycle 1: 900 mg obinutuzumab
- Day 9 and Day 16 Cycle 1: 1000 mg obinutuzumab
- Day 1 Cycles 2 to 6: 1000 mg obinutuzumab

Part 2:

- Day 1 Cycle 1: 100 mg obinutuzumab
- Day 2 Cycle 1: 900 mg obinutuzumab
- Day 8 and Day 15 Cycle 1: 1000 mg Obinutuzumab
- Day 1 Cycles 2 to 6: 1000 mg obinutuzumab

In Part 1, Cycle 1 was 29 days and Cycle 2 and each cycle thereafter was 28 days. In Part 2, all cycles were 28 days.

Study 212:

Zanubrutinib was administered 160 mg twice daily with or without food. Obinutuzumab (1000 mg) was administered intravenously on Days 1, 8, and 15 of Cycle 1; on Day 1 of Cycles 2 to 6; and then every 8 weeks. At the discretion of the investigator, obinutuzumab may have been administered intravenously on Day 1 (100 mg) and on Day 2 (900 mg) of Cycle 1 instead of 1000 mg on Day 1 of Cycle 1. Responding patients may have continued to receive maintenance obinutuzumab every 8 weeks for an additional 24

months (eg, maximum total duration of obinutuzumab of approximately 30 months [maximum of 20 doses]).

Sampling

Study GA101:

Blood samples were collected to evaluate the PK profiles of zanubrutinib and obinutuzumab. For intensive PK profiling, blood samples for zanubrutinib were collected from up to 15 patients on Cycle 1 Day 1 (Part 1 only) at predose and at 1, 2, 4, and 7 hours postdose; on Cycle 1 Day 2 (Part 1 only) at predose; and on Cycle 2 Day 1 at predose and at 1, 2, 4, and 7 hours postdose.

The PK profile for obinutuzumab in Part 1 was determined by serum concentrations on Cycle 1 Day 2, Cycle 1 Day 3, Cycle 1 Day 9, Cycle 1 Day 16, and Day 1 on Cycles 2, 4, and 6 measured before the start of the infusion and at 4 hours (end of infusion). In Part 2, the obinutuzumab serum concentrations were measured on Day 1 of Cycles 4 and 6 before the start of the infusion and at 4 hours (end of infusion).

Study 212:

Blood samples were collected from patients in Arm A (zanubrutinib + obinutuzumab) to assess plasma zanubrutinib concentrations. Sparse PK samples were collected at the following timepoints: predose (within 30 min prior to zanubrutinib dose), and 2 hours (± 30 min) post-zanubrutinib dose on Cycle 1 Day 1 and Cycle 2 Day 1.

Bioanalytical methods and analyses

All bioanalytical methods for zanubrutinib PK analyses were based on high-performance liquid chromatography–tandem mass spectrometry (LC-MS/MS). These methods were fully validated.

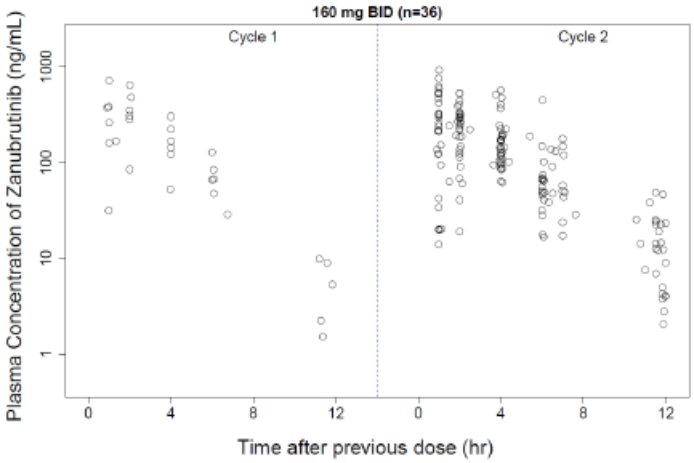
Pop PK analyses

Assembly of the PK dataset as performed using SAS or R software by Shanghai Qiangshi Information Technology Co., Ltd. (SHQS) as Microsoft Excel format (.csv) for input into NONMEM. Model parameter estimation and model evaluation were implemented with NONMEM 7, version 7.4.3; PopPK estimation was performed using the FOCEI method in NONMEM.

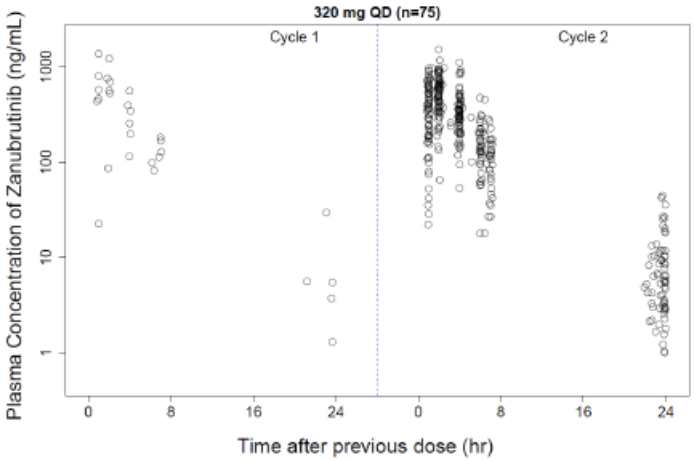
Figure 1

Figure 1. Zanubrutinib concentration versus time

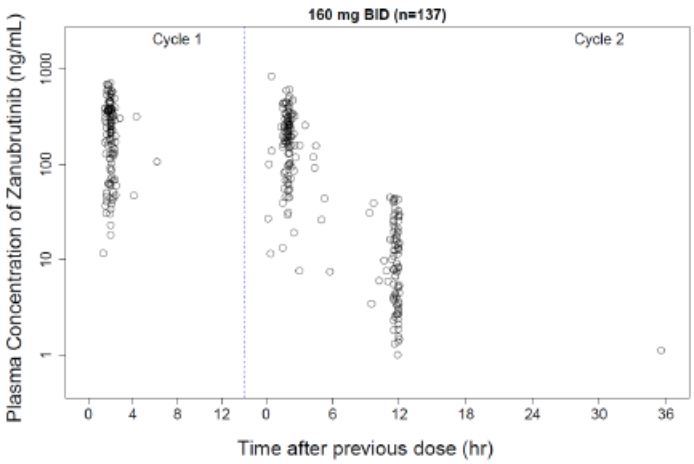
BGB-3111-GA101



BGB-3111-GA101



BGB-3111-212



A population pharmacokinetic (PopPK) model for zanubrutinib has been previously developed based on data from 11 zanubrutinib monotherapy studies in healthy volunteers and patients with B-cell malignancies. The previous model was structured with two-compartments, with sequential zero-order

and first-order absorption as well as first-order elimination from the central compartment and redistribution from the peripheral compartment. The previous final zanubrutinib PopPK model was used to obtain empirical Bayes estimates of individual PK parameters of all zanubrutinib treated subjects from studies BGB-3111-GA101 and BGB-3111-212 by external validation. Study GA101 included rich and sparse data from patients with various B-cell lymphoma (N=119 patients enrolled of which 36 had FL), and two dose regimens of zanubrutinib (320 mg once daily and 160 mg twice daily) in combination with obinutuzumab were evaluated. Study 212 included sparse data from patients with FL (N=145 patients enrolled). BLQ observations were omitted (n=205). Outliers (n=27) and switched peak/trough samples (n=10) were also removed. A total of 94 (10.3%) data points were excluded from calculation of bias. The final external model validation dataset was comprised of 248 subjects with B-cell lymphoma that included 171 FL patients with 910 zanubrutinib concentration-time data points.

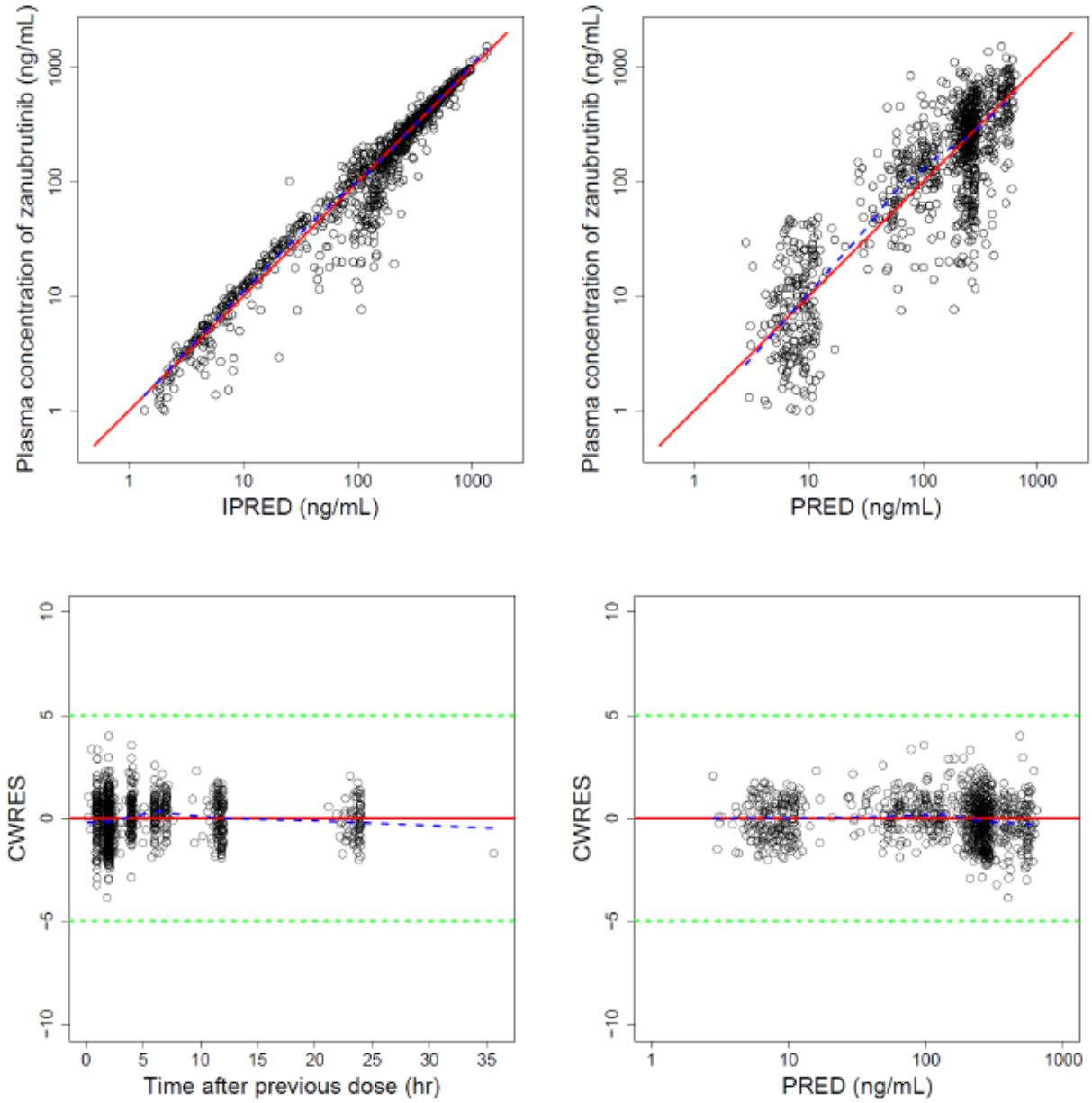
Table 4 Summary of final population PK parameters

Parameter	Parameter Description		Population Estimate (%RSE)	Median (95% CI) from bootstrapping	Shrinkage (%)
$exp(\theta_1+\theta_{10})$	Apparent oral clearance, CL/F (L/hr)	Patient	155 (19.5 %)	157 (124, 199)	—
$exp(\theta_1)$		HV	96.4 (19.5%)	95.8 (84.5, 107)	—
θ_{11}	Influence of ALT on CL/F		-0.123 (1.34%)	-0.130 (-0.189, -0.0769)	—
θ_{12}	Influence of age on CL/F		-0.463 (0.302%)	-0.455 (-0.608, -0.300)	—
$exp(\theta_2)$	Apparent central volume, V_c/F (L)		73.6 (0.819%)	71.3 (58.7, 85.2)	—
θ_{13}	Influence of age on Vc/F		-0.788 (0.0482%)	-0.762 (-0.963, -0.455)	—
$exp(\theta_3)$	Apparent inter-compartmental clearance, Q/F (L/hr)		15.5 (2.67%)	15.6 (13.6, 18.3)	—
$exp(\theta_4)$	Apparent peripheral volume, V_p/F (L)		472 (9.48%)	487 (410, 585)	—
$exp(\theta_5)$	Absorption rate constant, k_a (hr^{-1})		0.477 (1.59%)	0.480 (0.462, 0.501)	—
$exp(\theta_6)$	Duration, D_1 (hr)		1.26 (1.32%)	1.27 (1.16, 1.38)	—
$\omega^2_{CL,Vc}$	Covariance (CL/F,Vc/F)		0.147 (31.7%)	0.142 (0.0681, 0.200)	—
θ_9	Additive residual error (ng/mL, TFDS<5 hr)		72.4 (0.659%)	72.4 (65.1, 80.0)	—

Parameter	Parameter Description	Population Estimate (%RSE)	Median (95% CI) from bootstrapping	Shrinkage (%)
θ_7	Additive residual error (ng/mL, TFDS≥5 hr)	0.730 (2.33%)	0.719 (0.411, 1.10)	—
θ_8	Proportional residual error (%)	45.6 (0.664%)	45.2 (42.7, 47.2)	20.9
IIV (%RSE)	CL/F	37.0 (10.5%)	37.0 (33.8, 40.1)	29.2
	Vc/F	55.1 (26.5%)	55.1 (36.1, 76.6)	44.1
	Q/F	123 (27.9%)	125 (114, 138)	36.5
	Vp/F	70.0 (3.32%)	70.3 (58.9, 85.7)	73.7
	D1	55.2 (2.18%)	55.4 (48.3, 61.5)	56.7
IOV (%RSE)	CL/F	33.7 (13.2%)	34.0 (30.8, 37.6)	44.3
	Vc/F	61.7 (0.490%)	63.3 (51.4, 79.2)	71.2

The model fit was evaluated by GoF plots, NPC and pcVPCs. Figures 2, 4, 5 and 7 show a selection of the diagnostic plots.

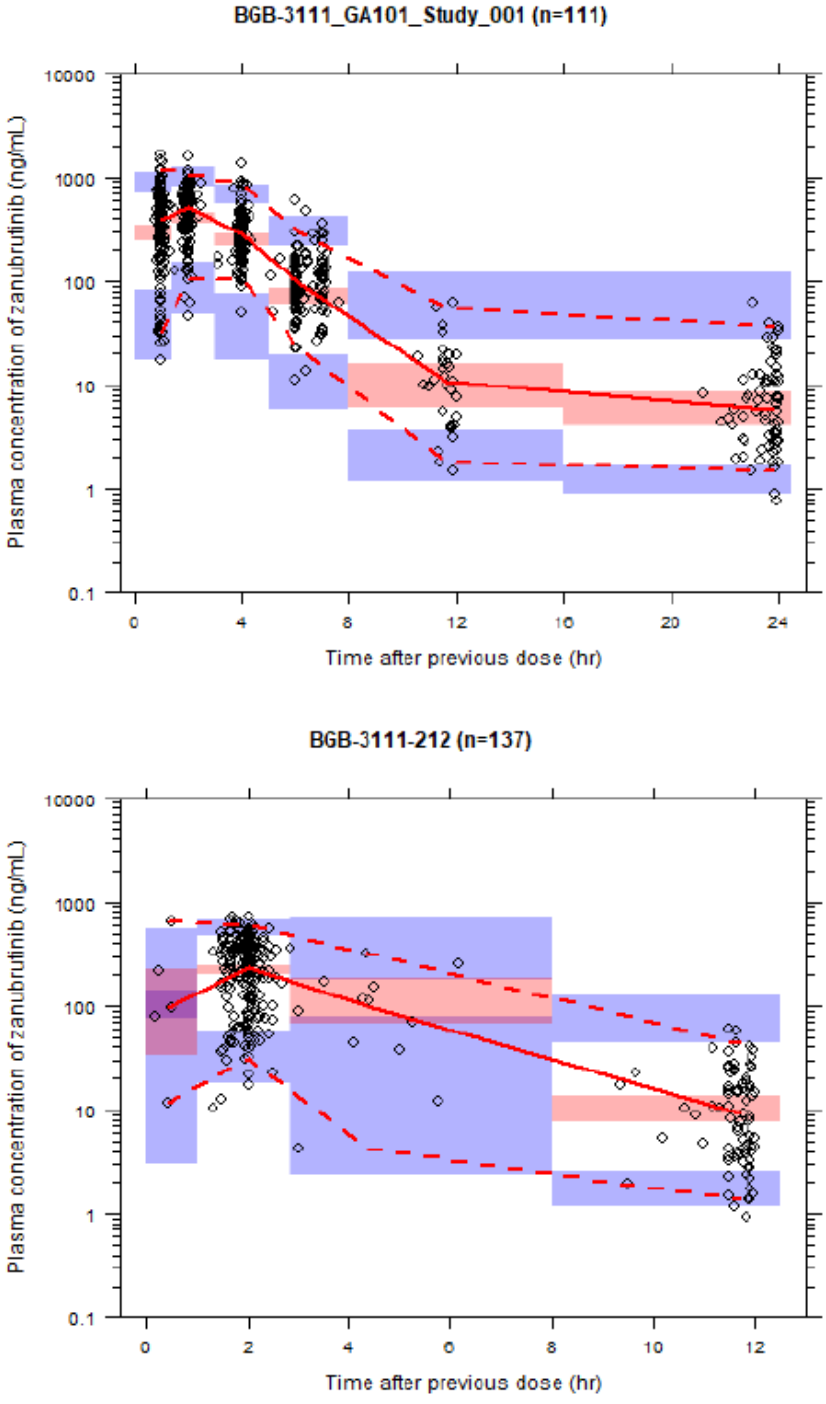
Figure 2 General goodness – of -fit plots for all zanubrutinib validation subjects



Top: individual predicted plasma zanubrutinib concentrations (IPRED) versus observed zanubrutinib concentrations (left) and population predicted plasma zanubrutinib concentrations (PRED) versus observed plasma zanubrutinib concentrations (right). Bottom: conditional weighted residuals (CWRES) versus time after previous dose (left) and PRED (right). Points are individual data. Red solid lines represent the unit diagonal (top) or line at zero (bottom). Green dashed lines represent |CWRES| of 5. Blue dashed lines represent the lowess smooth curves.

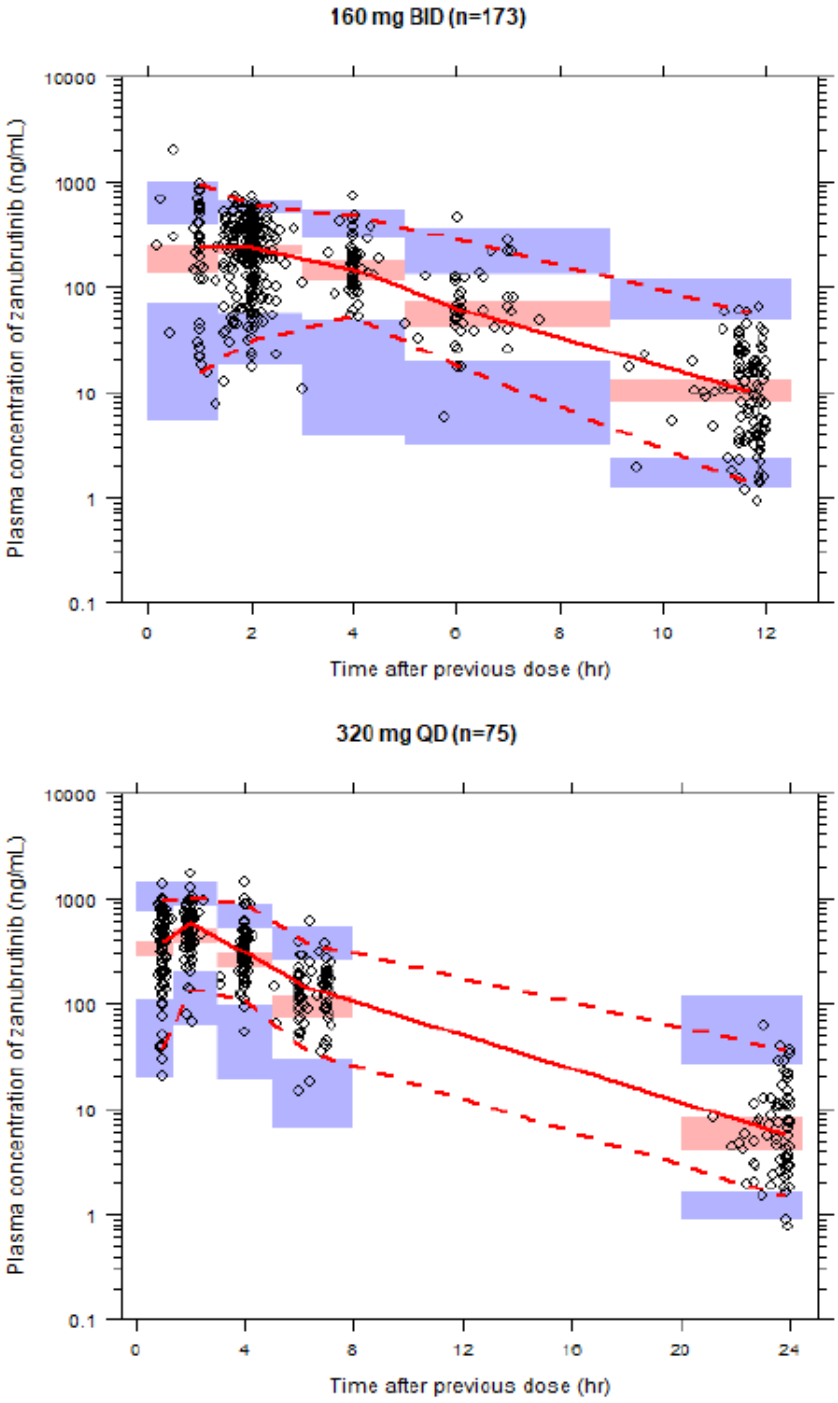
Figure 3

Figure 6. pcVPC of zanubrutinib concentration-time profiles stratified by study for zanubrutinib validation subjects



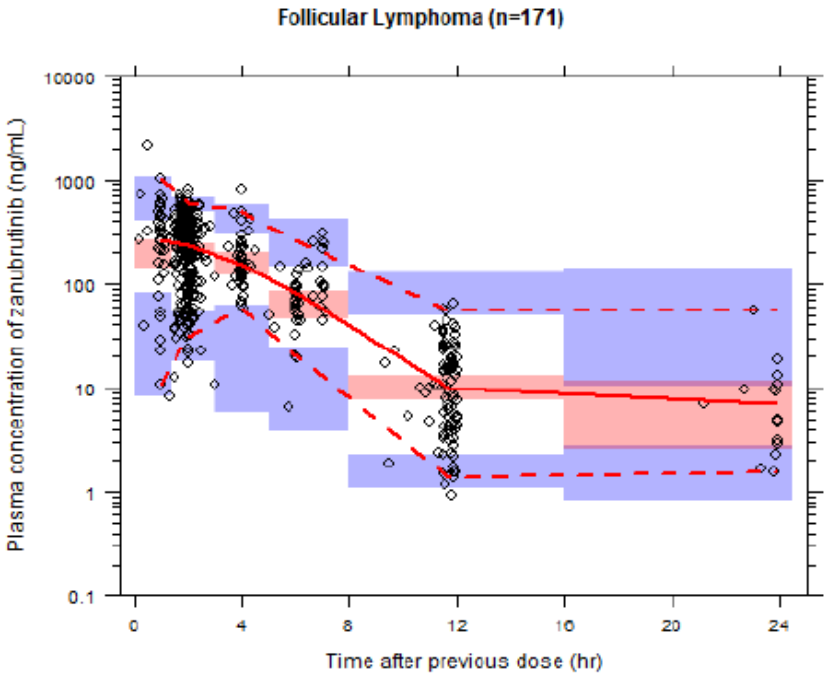
Circles are observed zanubrutinib plasma concentrations, solid red lines represent the median observed value, and dashed red lines represent 2.5 percentile and 97.5 percentile of the observed values. Pink shaded areas represent the 95% CI of the predicted median concentrations, and the blue shaded areas represent the 95% CI of the 2.5 percentile and 97.5 percentile of the predicted concentrations.

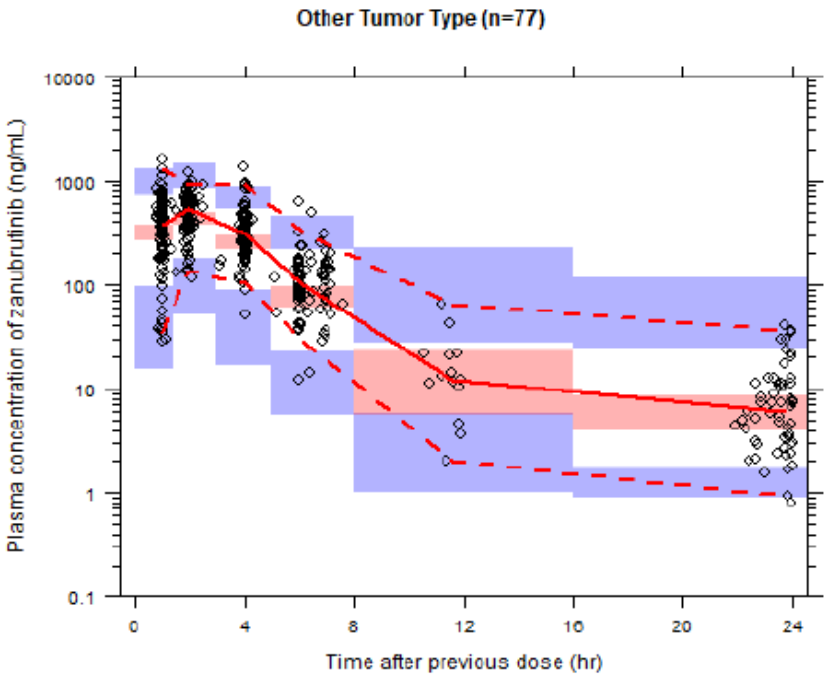
Figure 4 pc VPC of zanubrutinib concentration – time profiles stratified by regimen



Circles are observed zanubrutinib plasma concentrations, solid red lines represent the median observed value, and dashed red lines represent 2.5 percentile and 97.5 percentile of the observed values. Pink shaded areas represent the 95% CI of the predicted median concentrations, and the blue shaded areas represent the 95% CI of the 2.5 percentile and 97.5 percentile of the predicted concentrations.

Figure 5 pcVPC of zanubrutinib concentration – time profiles stratified by tumour type



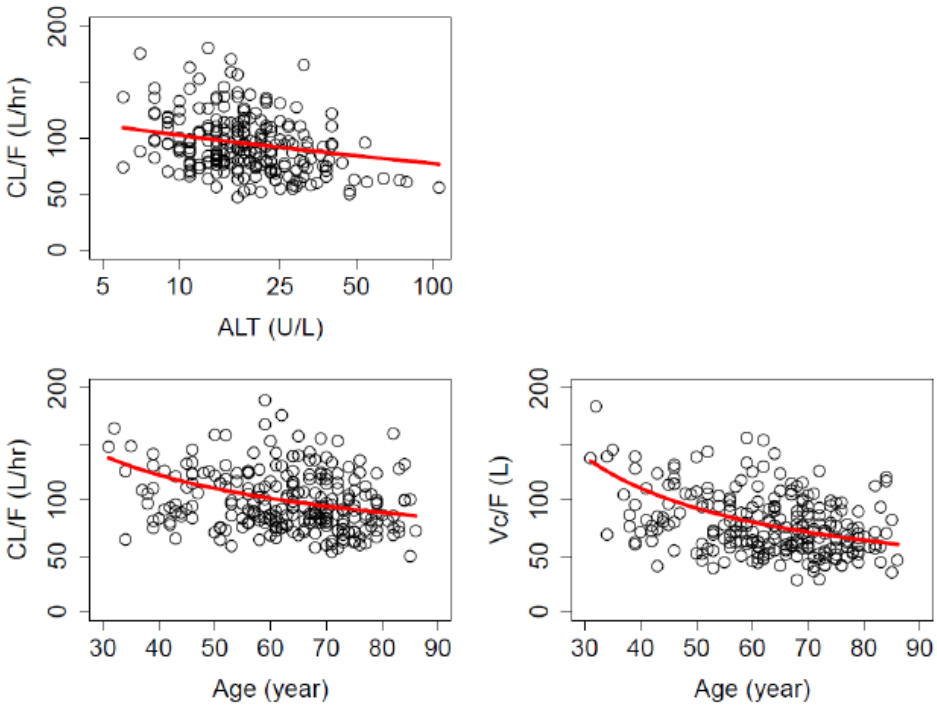


Circles are observed zanubrutinib plasma concentrations, solid red lines represent the median observed value, and dashed red lines represent 2.5 percentile and 97.5 percentile of the observed values. Pink shaded areas represent the 95% CI of the predicted median concentrations, and the blue shaded areas represent the 95% CI of the 2.5 percentile and 97.5 percentile of the predicted concentrations.

The final model was used to generate zanubrutinib exposure metrics (AUC0-24,ss, Cmax,ss, and Cmin,ss) for studies BGB-3111-GA101 and BGB-3111-212. Predicted drug plasma concentrations for all subjects in the validation dataset were obtained by fixing the parameters in the structural and variance model to the parameter estimates in the final model using post-hoc Bayesian forecasting with NONMEM 7.

Impact of covariates

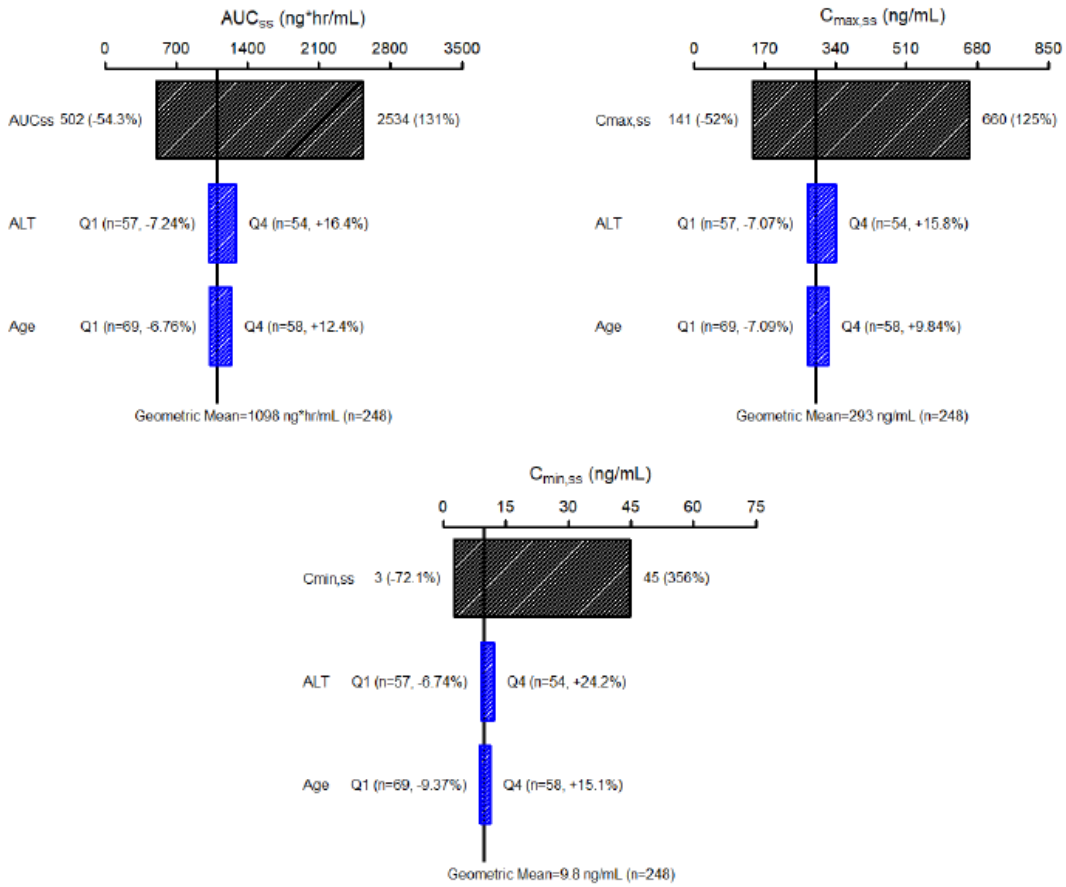
Figure 6 PK parameter -covariate relationships for validation subjects



Points are the individual parameter estimates after correcting for other covariates. Red line represents the typical (population) predicted covariate relationship.

The impact of existing covariates of ALT and age on model predicted steady state exposures (AUCss, Cmax,ss, and Cmin,ss) was further quantified by calculating the difference in geometric mean of exposures at the lowest or highest quartile of covariate distribution from that of the overall population. The impact of baseline ALT and age on zanubrutinib exposure was relatively small (-7.24% to 24.2% for ALT and -9.37% to +15.1% for age).

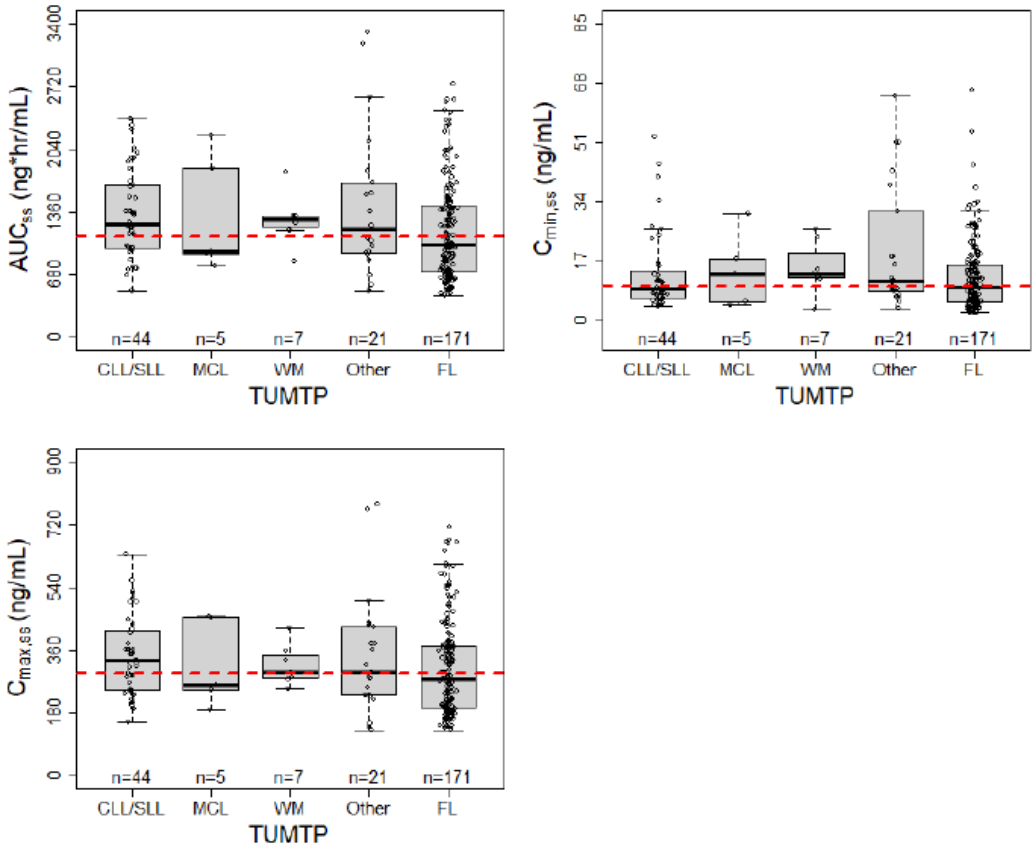
Figure 7 the effect of covariates on zanubrutinib exposures (AUSss, Cmax,ss and Cmin,ss)



The black shaded bar shows 2.5th to 97.5th percentile AUC_{ss} (top left), $C_{max,ss}$ (top right) and $C_{min,ss}$ (bottom) across the entire population. Blue shaded bar represents the influence of covariates on AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$. The label at left end of the bar represents the covariate being evaluated. The two ends of blue shaded bar represent the geometric mean exposure values at values at lowest or highest quartile of the covariate distribution. The number of subjects within the subgroup and the percent change in the geometric mean values within the subgroup from that of the overall population (black vertical line) are shown in parenthesis.

Post-hoc estimated exposures by tumor type (AUCss, Cmax,ss and Cmin,ss) for validation patients indicated the geometric mean simulated exposures (AUCss, Cmax,ss and Cmin,ss) in FL patients were up to 6.85% lower compared with those of the overall patient population (p values were 0.241, 0.509, and 0.310 for AUCss, Cmax,ss, and Cmin,ss, respectively by t-test).

Figure 8 Simulated steady state exposures of zanubrutinib by tumour type



The median is represented by the horizontal line in the middle of each box. The top and bottom ends of the box plot represent the 25th and 75th percentile (the lower and upper quartiles, respectively). The bars extending from the ends of the box to the outermost data represent 1.5 × (the upper or lower interquartile range). The dashed red horizontal line represents overall geometric mean of post hoc estimates in validation subjects.

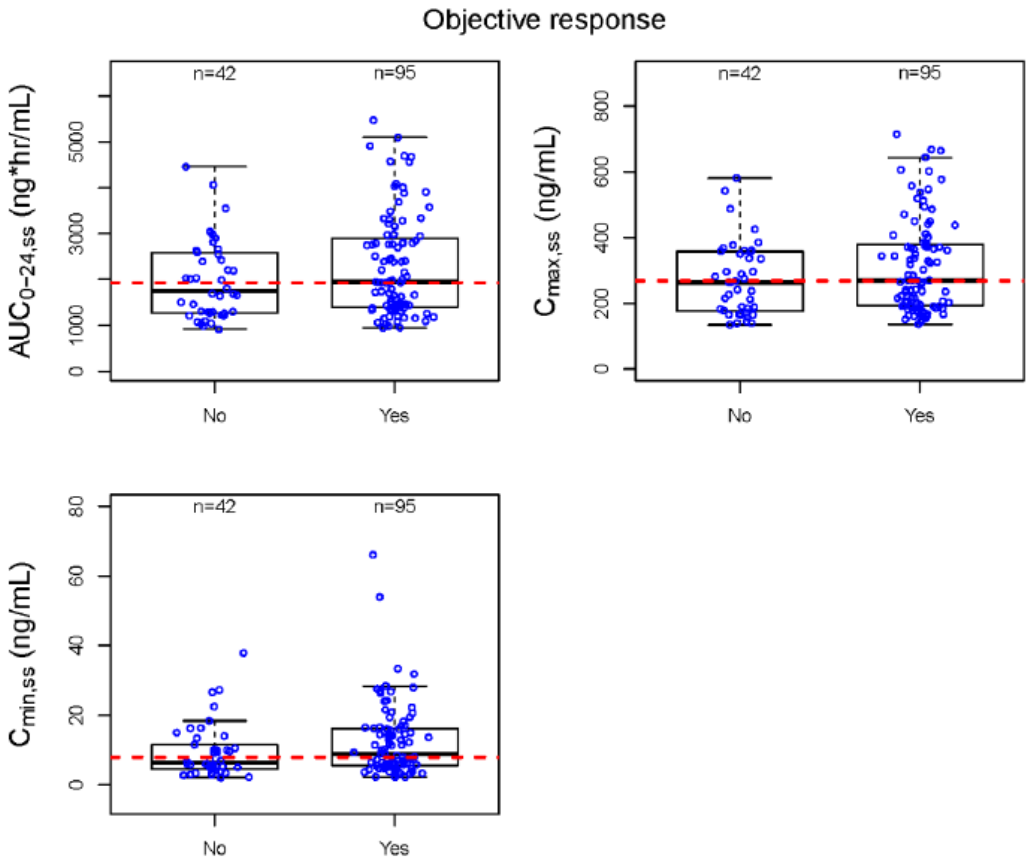
Parameter	Parameter Description	Population Estimate (%RSE)	Median (95% CI) from bootstrapping	Shrinkage (%)
θ_7	Additive residual error (ng/mL, TFDS≥5 hr)	0.730 (2.33%)	0.719 (0.411, 1.10)	—
θ_8	Proportional residual error (%)	45.6 (0.664%)	45.2 (42.7, 47.2)	20.9
IIV (%RSE)	CL/F	37.0 (10.5%)	37.0 (33.8, 40.1)	29.2
	V_c/F	55.1 (26.5%)	55.1 (36.1, 76.6)	44.1
	Q/F	123 (27.9%)	125 (114, 138)	36.5
	V_p/F	70.0 (3.32%)	70.3 (58.9, 85.7)	73.7
	D_1	55.2 (2.18%)	55.4 (48.3, 61.5)	56.7
IOV (%RSE)	CL/F	33.7 (13.2%)	34.0 (30.8, 37.6)	44.3
	V_c/F	61.7 (0.490%)	63.3 (51.4, 79.2)	71.2

Exposure-response analyses

Assembly of the efficacy and safety dataset was performed using R software by SHQS. For binary response variables, boxplots of exposures stratified by responses were generated. The probability of response was calculated and plotted versus exposure metrics (AUC0-24,ss, Cmax,ss and Cmin,ss) or covariates of interest, after binning patients according to quantiles of exposure metrics or covariate values. If an E-R trend was observed, further analysis with linear logistic regression models were performed.

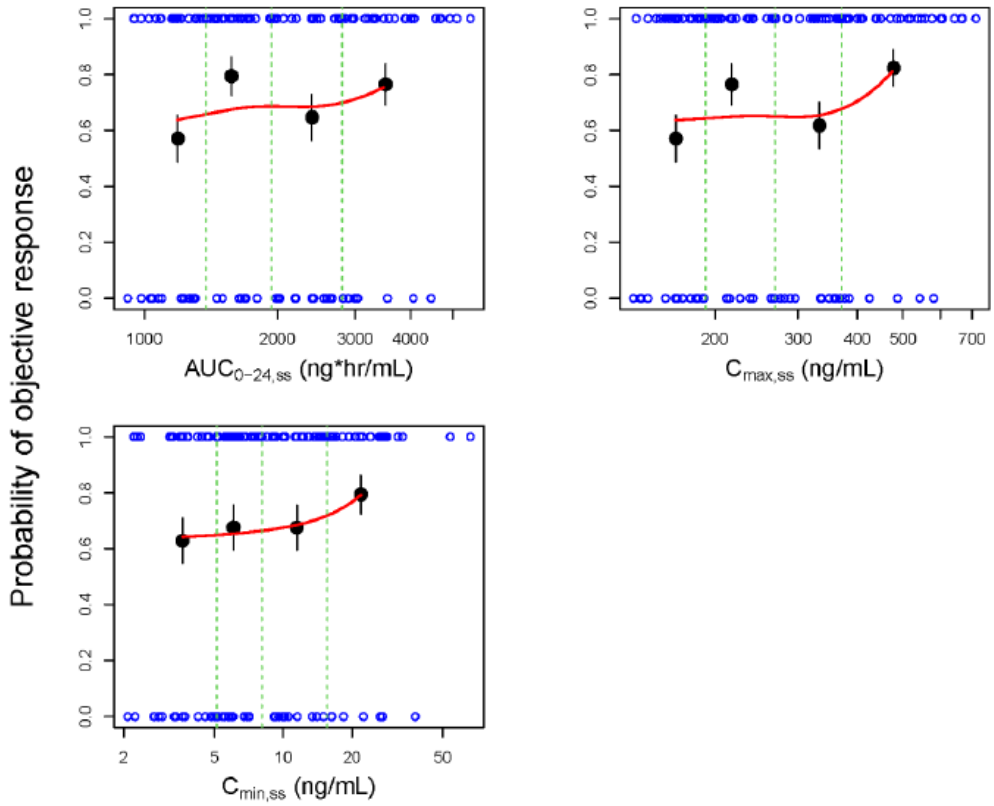
Data collected of the primary endpoint ORR by IRC in patients with FL from study BGB-3111-212 were used in the exposure-efficacy analysis (N=137).

Figure 9 Relationship between exposure metrics and ORR



Symbols are the model predicted exposure matrices. The median is represented by the horizontal black line in the middle of each box. The lower and upper ends of the box plot represent the 25th and 75th percentile (the lower and upper quartiles, respectively). The bars extend to the most extreme data point which is no more than 1.5×IQR from the box. The dashed red horizontal line represents the median value of exposures for those 2 "Yes" and "No" groups.

Figure 10 Probability of ORR vs exposure metrics in BGB 3112-212



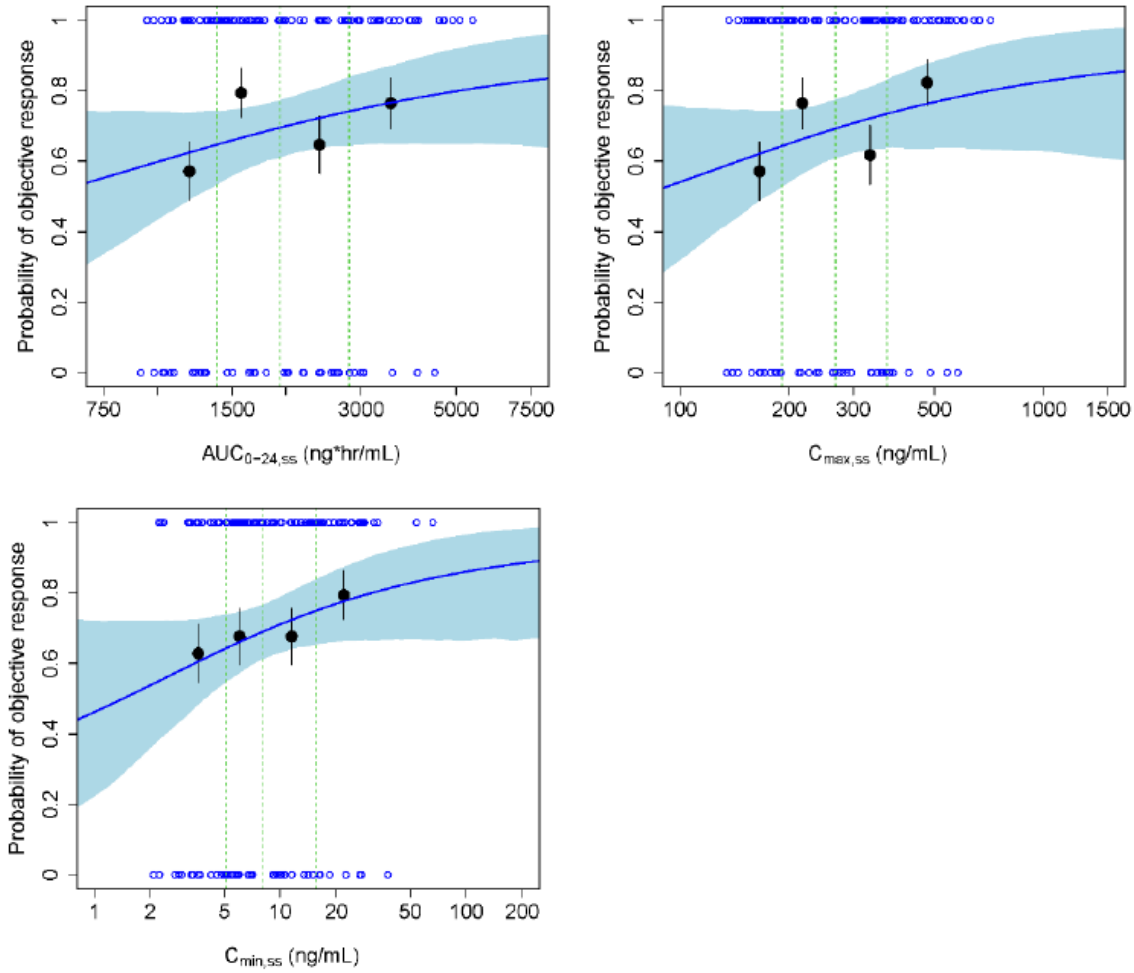
The blue open circles reflect the observed events in zanubrutinib treated patients. The black solid circles are the observed probability of endpoints and the error bars are the standard errors (calculated as sqrt (P*(1-P)/N), where P is probability of endpoint and N is the number of patients in each quantile bin) for quantiles (at $100x(1/n)^{th}$ percentiles, green vertical dotted lines) of exposures (plotted at the median value within each quantile). The red lines are smooth curves to show the relationship between two variables.

The logistic regression model results suggested that AUC0-24,ss, Cmax,ss, and Cmin,ss were not associated with the probability of ORR in zanubrutinib treated patients with FL (p value > 0.05).

Table 5 Summary of model parameters for ORR

Run	Exposure Metrics	Logistic Regression Model	Parameter	Estimates (SE)	p-value
1	$AUC_{0\text{-}24,ss}$	$logit(P(Y_i = 1)) = \beta_0 + \beta_1 \cdot \log(AUC_{0-24,ss})$	β_0	-3.93 (3.22)	0.222
			β_1	0.627 (0.426)	0.141
2	$C_{max,ss}$	$logit(P(Y_i = 1)) = \beta_0 + \beta_1 \cdot \log(C_{max,ss})$	β_0	-2.88 (2.53)	0.256
			β_1	0.661 (0.454)	0.146
3	$C_{min,ss}$	$logit(P(Y_i = 1)) = \beta_0 + \beta_1 \cdot \log(C_{min,ss})$	β_0	-0.158 (0.57)	0.782
			β_1	0.461 (0.261)	0.0771

Figure 11 Logistic regression of probability of ORR vs exposure



The open blue circles reflect the observed events. The filled black symbols are the observed probability of events and the error bars are SE [sqrt (P*(1-P)/N)] for quantiles (at 100x(1/4)th percentiles, green vertical dotted lines) of exposures (plotted at the median value within each quantile). The blue line and light blue shaded area are the median and 95% prediction interval based on the 1000 bootstrap samples of the model

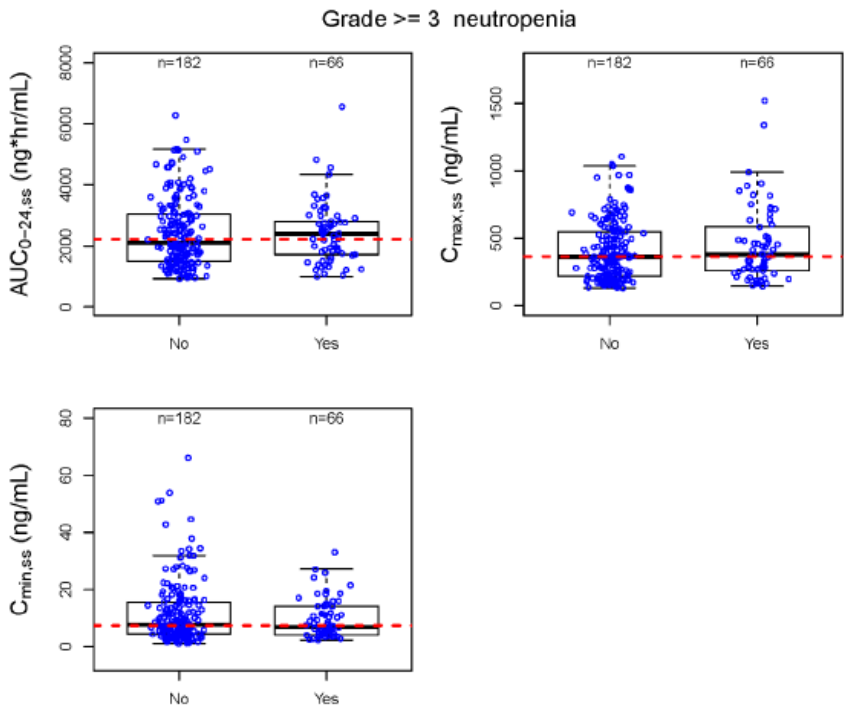
The safety endpoints were grade ≥3 neutropenia, grade ≥ 3 thrombocytopenia, grade ≥ 3 anemia, grade ≥ 3 infections/infestations, all events of secondary primary malignancies, all events of atrial fibrillation and flutter, major bleeding events, and AE leading to treatment discontinuation. These endpoints were characterized by incidence only, and pooled data collected from studies BGB-3111-GA101 and BGB-3111-212 were used in the analysis (N=248).

The summary of the safety endpoints is shown below -by study.

Table 6 Summary of safety endpoints in the exposure safety analysis dataset (by study)

Safety Endpoints	The percentage of patients having AE [%(Yes/No)]		
	BGB-3111-212 (N=137)	BGB-3111-GA101 (N=111)	Total (N=248)
Grade≥3 neutropenia	26.3% (36/101)	27% (30/81)	26.6% (66/182)
Grade≥3 thrombocytopenia	15.3% (21/116)	9.01% (10/101)	12.5% (31/217)
Grade≥3 anemia	5.11% (7/130)	1.8% (2/109)	3.63% (9/239)
Grade≥3 infections/infestations	27% (37/100)	33.3% (37/74)	29.8% (74/174)
All events of secondary primary malignancies	6.57% (9/128)	22.5% (25/86)	13.7% (34/214)
All events of atrial fibrillation and flutter	2.92% (4/133)	0% (0/111)	1.61% (4/244)
Major bleeding events	0.73% (1/136)	7.21% (8/103)	3.63% (9/239)
AE leading to treatment discontinuation	13.1% (18/119)	9.0% (10/101)	11.3% (28/220)

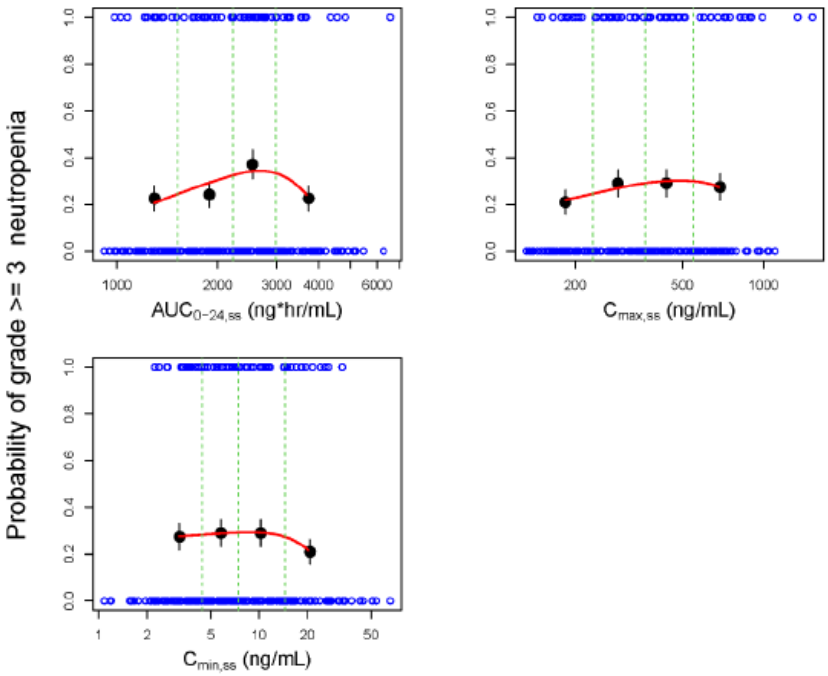
Figure 12 Relationship between exposure metrics and grade ≥ 3 neutropenia



Symbols are the model predicted exposure matrices. The median is represented by the horizontal black line in the middle of each box. The lower and upper ends of the box plot represent the 25th and 75th percentile (the lower and upper quartiles, respectively). The bars extend to the most extreme data point which is no more than 1.5×IQR from the box. The dashed red horizontal line represents the median value of exposures for those 2 "Yes" and "No" groups.

The boxplots show the distribution of steady state exposures in zanubrutinib treated patients with or without grade ≥ 3 neutropenia. The probability of grade ≥ 3 neutropenia by quantiles of steady state zanubrutinib exposure are shown below.

Figure 13 Probability of grade ≥ 3 neutropenia vs exposure metrics



The blue open circles reflect the observed events in zanubrutinib treated patients. The black solid circles are the observed probability of endpoints, and the error bars are the standard errors (calculated as sqrt (P*(1-P)/N), where P is probability of endpoint and N is the number of patients in each quantile bin) for quantiles (at 100x(1/N)th percentiles, green vertical dotted lines) of exposures (plotted at the median value within each quantile). The red lines are smooth curves to show the relationship between two variables.

No apparent E-R relationship was observed for grade ≥ 3 neutropenia based on zanubrutinib treated patients in studies BGB-3111-GA101 and BGB-3111-212.

The probability of grade ≥ 3 neutropenia in the highest and the lowest AUC0-24,ss groups are 0.242 and 0.226, respectively. The corresponding AUC0-24,ss are 1890 and 1294 ng*hr/mL. The probability of grade ≥ 3 neutropenia in the highest and the lowest Cmax,ss groups are 0.290 and 0.210, respectively. The corresponding Cmax,ss are 288.1 and 183.8 ng/mL.

ADME characteristics

Based on the previous final model, the estimated CL/F was 155 L/hr, Vc/F was 73.6 L, Q/F was 15.5 L/hr, Vp/F was 472 L, ka was 0.477 hr-1, and D1 was 1.26 hr, and geometric mean elimination half-life was 2.52 hours with a CV of 47.6%.

Non-compartmental PK analysis – Study GA101

In Part 1, 12 patients were included in the PK Analysis Set. In Part 2, 112 patients were included in the PK Analysis Set.

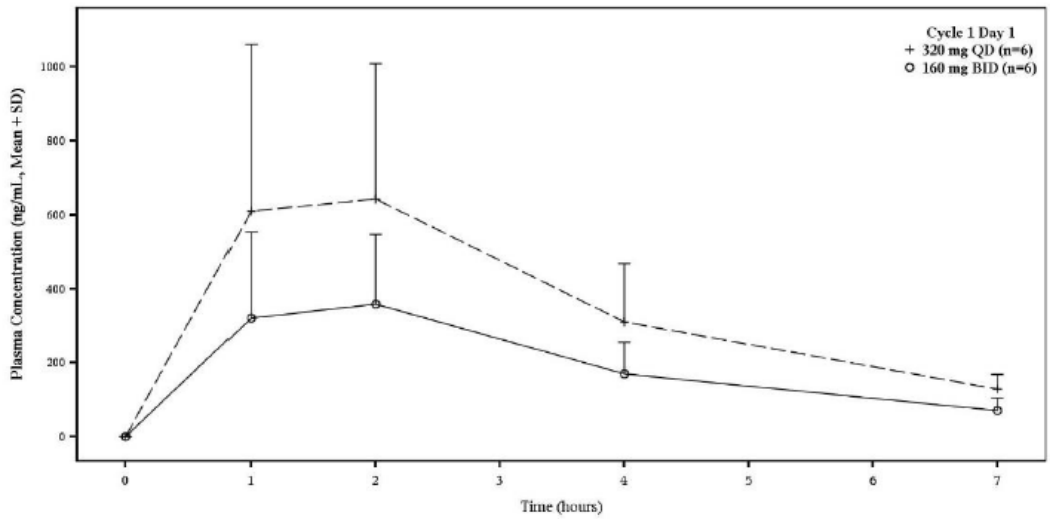
Plots of mean plasma zanubrutinib concentration-time profiles on Cycle 1 Day 1 and Cycle 2 Day 1 are presented. Zanubrutinib was rapidly absorbed after oral administration and reached the geometric mean of maximum observed plasma concentration (C_{max}) (coefficient of variation of geometric mean [%GCV]) at 360.4 (90.4%) ng/mL and 589.4 (79.9%) ng/mL after the administration of single doses of 160 and 320 mg, respectively. The median time to reach C_{max} (t_{max}) was 2.0 and 1.4 hours in the 160 mg and

320 mg dose groups, respectively. The estimated area under the plasma concentration time curve from 0 to last measurable concentration ($AUC_{0\text{-last}}$) was 1123.6 (71.5%) ng•h/mL and 2179.5 (70.2%) ng•h/mL after the administration of single 160 and 320 mg doses, respectively. The estimated geometric mean of steady state $AUC_{0\text{-last}}$ was 1074.1 (42.1%) ng•h/mL and 2003.9 (42.6%) ng•h/mL after the administration of multiple 160 and 320 mg doses, respectively, in the presence of obinutuzumab.

The interpatient variability (measured as % GCV) was 79.9% to 90.4% for C_{max} and 70.2% to 71.5% for $AUC_{0\text{-last}}$ after a single dose. The variability dropped at steady state after multiple doses as the sample size increased. The % GCV was 42.6% to 52.3% for steady state C_{max} and 42.1% to 42.6% for steady state $AUC_{0\text{-last}}$. Considering the variability, zanubrutinib single-dose exposure was consistent with the exposure observed in other studies (Study BGB-3111-AU-003, BGB-3111-CP-006 PK Report: single-dose $AUC_{0\text{-last}}$ was 1132 [61.1%] ng•h/mL for 160 mg [N = 76] and 2281 [60.5%] ng•h/mL for 320 mg (N = 19). The steady state plasma exposures of zanubrutinib after the admini-stration of 160 mg twice daily and 320 mg once daily were also consistent with those in other studies of zanubrutinib monotherapy (Study BGB-3111-AU-003 CSR, BGB-3111-CP-006 PK Report: multiple-dose $AUC_{0\text{-last}}$ was 994.4 [43.6%] ng•h/mL for 160 mg [N = 60] and 1706 [54.2%] ng•h/mL for 320 mg [N = 28]). The results indicated that obinutuzumab had minimal impact on zanubrutinib exposure.

Figure 14

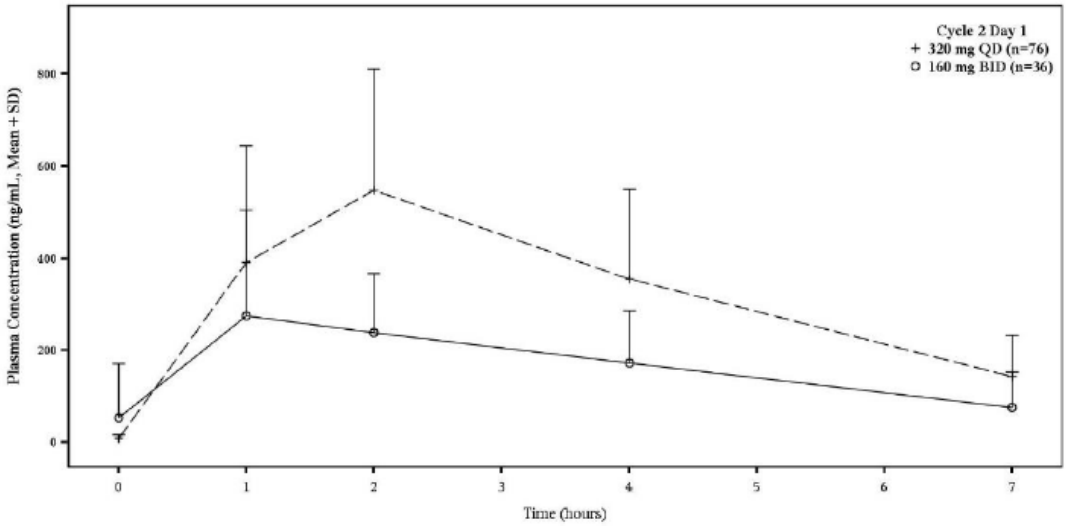
Figure 1: Mean (± SD) Plasma Concentrations of Zanubrutinib versus Time Profiles after a Single Oral Dose on Cycle 1 Day 1 in BGB-3111-GA101



Source: BGB-3111_GA101_Study_001 CSR Figure 19; Figure 14.3.6.1. Database lock date: 27 Nov 2020.
Abbreviations: BID, twice daily; QD, once daily; SD, standard deviation.
Note: Samples for single-dose PK were collected from patients from Part 1 (N = 12).

Figure 15

Figure 2: Mean (± SD) Steady State Plasma Concentrations of Zanubrutinib After Multiple Oral Doses on Cycle 2 Day 1 in BGB-3111-GA101



Source: BGB-3111_GA101_Study_001 CSR Figure 20; Figure 14.3.6.2. Database lock date: 27 Nov 2020.
Abbreviations: BID, twice daily; QD, once daily; SD, standard deviation.
Note: Samples for multiple-dose PK were collected from patients from Part 1 and Part 2 (N = 112).

Table 7

Table 1: Summary of PK Parameters of Zanubrutinib After a Single Oral Dose of Zanubrutinib on Cycle 1 Day 1 in BGB-3111-GA101

Dose	Summary	$AUC_{0\text{-last}}$ (ng•h/mL)	$AUC_{0\text{-inf}}$ (ng•h/mL)	C_{max} (ng/mL)	t_{max} (hour)	$t_{1/2}$ (hour)
160 mg	n	6	6	6	6	6
	GM	1123.6	1324.6	360.4	1.6	1.9
	GCV (%)	71.5	61.0	90.4	38.3	29.5
	AM[a]	1280.2 ± 556.3	1470.5 ± 594.9	434.7 ± 230.1	2.0 (1.0-2.1)	2.0 ± 0.6
	ACV (%)	43.5	40.5	52.9	31.9	31.1
320 mg	n	6	5	6	6	5
	GM	2179.5	3052.5	589.4	1.7	1.8
	GCV (%)	70.2	33.7	79.9	88.7	19.9
	AM[a]	2514.3 ± 1348.0	3201.6 ± 1223.6	699.0 ± 397.8	1.4 (1.0-7.0)	1.8 ± 0.4
	ACV (%)	53.6	38.2	56.9	101.2	20.4

Source: BGB-3111_GA101_Study_001 CSR Table 19; Table 14.3.6.2; Table 14.3.6.2.1. Database lock date: 27 Nov 2020.

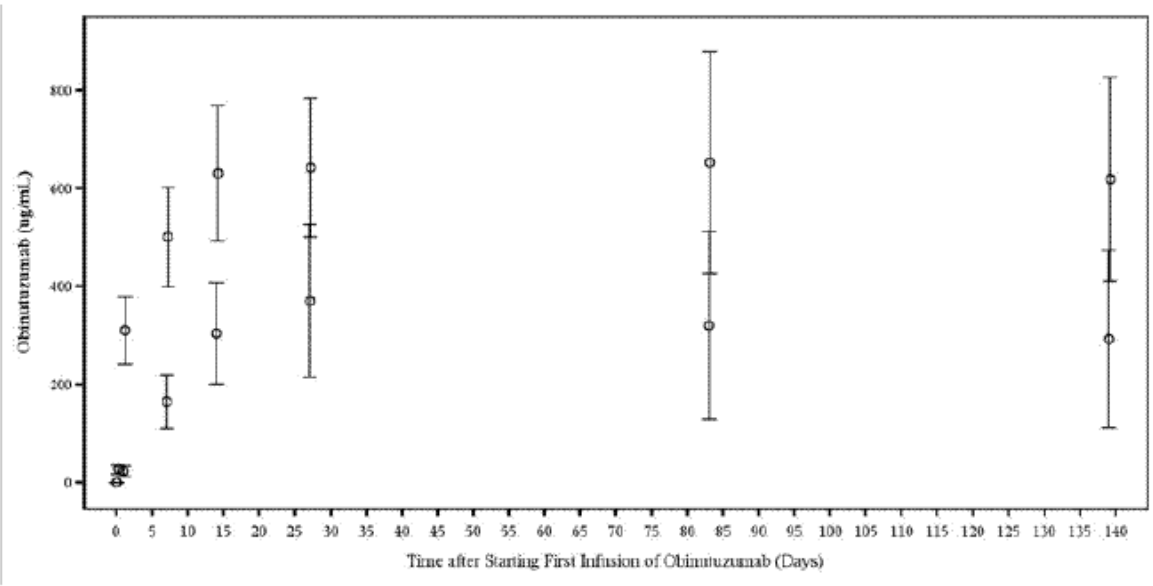
Abbreviations: ACV, arithmetic coefficient of variation; AM, arithmetic mean; AUC, area under the concentration–time curve; $AUC_{0\text{-last}}$, AUC from zero to the last measurable timepoint; $AUC_{0\text{-inf}}$, AUC to extrapolated to infinity; C_{max}, maximum observed plasma concentration; GCV, coefficient of variation of geometric mean; GM, geometric mean; h, hour; n, number of patients; PK, pharmacokinetics; SD, standard deviation; t_{max}, time to maximum observed plasma concentration; $t_{1/2}$, elimination half-life.

[a]Notes: AUC, C_{max} and $t_{1/2}$ are expressed as arithmetic mean± SD, and the t_{max} is expressed as median (minimum, maximum).

Table 8 Summary of steady state PK parameters of zanubrutinib after multiple doses

Dose	Summary	$AUC_{0\text{-last}}$ (ng•h/mL)	$AUC_{0\text{-tau}}$ (ng•h/mL)	C_{max} (ng/mL)	t_{max} (hour)	$t_{1/2}$ (hour)
160 mg BID	n	36	24	36	36	24
	GM	1074.1	1253.7	328.5	1.8	1.8
	GCV (%)	42.1	40.6	52.3	67.0	30.3
	AM [a]	1161.4 ± 464.7	1345.4 ± 506.6	369.1 ± 183.8	1.3 (0-4.3)	1.9 ± 0.6
	ACV (%)	40.0	37.7	49.8	68.8	32.9
320 mg QD	n	75	55	75	75	55
	GM	2003.9	2413.4	580.0	1.9	1.9
	GCV (%)	42.6	37.7	42.6	48.4	31.3
	AM [a]	2167.9 ± 857.7	2566.2 ± 883.2	627.2 ± 245.3	2.0 (0.9-4.3)	2.0 ± 0.6
	ACV (%)	39.6	34.4	39.1	47.1	32.5

Figure 16 Arithmetic mean (+ SD) serum concentration of Obinutuzumab vs time profiles after multiple dose administration



Source: Figure 14.3.6.5.
Note: N: 11 to 12 patients (Cycles 1 and 2); 91 to 101 patients (Cycles 4 to 6).
Database lock date: 27 November 2020.

Pharmacokinetics using human biomaterials

N/A

2.3.3. Pharmacodynamics

No new information has been submitted in this application.

2.3.4. PK/PD modelling

Please refer to Population PK analyses section above

2.3.5. Discussion on clinical pharmacology

Zanubrutinib is a BTK inhibitor approved in the EU as monotherapy for treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy; marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based therapy and chronic lymphocytic leukaemia (CLL). The current type II variation submission concerns approval of zanubrutinib in combination with obinutuzumab for treatment of adult patients with relapsed/refractory (R/R) follicular lymphoma (FL) who have received at least two prior systemic therapies. The pharmacology package included in the present application includes data from a Phase 1b, 2-part open-label study of zanubrutinib and obinutuzumab in patients with R/R disease of various B-cell lymphoid malignancies including FL (study GA101) and a phase 2 study in which R/R FL patients were randomized to obinutuzumab alone or combined with zanubrutinib (study 212).

The bioanalyses conducted in studies BGB-3111-GA101 (Study GA101) and BGB-3111-212 (Study 212) included determination of zanubrutinib and obinutuzumab concentrations. The applied LC-MS/MS methods for determination of zanubrutinib and the ELISA method for determination of obinutuzumab were not evaluated.

The previous final Pop PK model based on data from HV and patients with B-cell malignancies following zanubrutinib monotherapy, was used to fit the concentration data from Studies GA101 and 212 where zanubrutinib was administered in combination with obinutuzumab. Data from 171 FL patients were included in the pooled patient population which also included data from patients with other B-cell malignancies. GA101 included rich and sparse sampled PK data, while PK data from study 212 was sparse. The external fit by the previous model without re-estimation of model parameters, indicate the PK of zanubrutinib in FL patients is comparable to patients with other B-cell malignancies and that combination with obinutuzumab does not affect zanubrutinib PK. In line, colour-coded zanubrutinib concentration-time profiles based on rich PK data from study GA101 indicate that the exposure profile in patients with FL overlaps with those observed in subjects with other types of B-cell lymphoid malignancies.

The exposure-efficacy evaluation of ORR was based on data from Study 212. No relation to exposure measures at steady-state, AUC0-24, Cmax or Cmin was detected by logistic regression modelling. For safety evaluation, data from GA101 and 212 were pooled. No response plots indicated any relation of investigated safety issue to exposure. No exposure-safety relations were further investigated by linear logistic regression models as no trends were observed.

FL patients from Studies 212 and GA-101 all received concomitant treatment with obinutuzumab, however the treatment schedules after 6 months of treatment were not similar in the two studies. Since the individual PK parameter shrinkage values have not been reported for the current PK data, it is not known how well informed the exposure metrics were for the exposure-response and exposure-safety analyses. Nonetheless, even if the shrinkage values had been known, the overall conclusion of lack of

exposure-response-relationships would remain unchanged. Consequently, the issue of non-reported shrinkage values is not pursued.

The different obinituzumab treatments did not seem to influence zanubrutinib exposure, however, is not possible to distinguish between the two regarding safety issues since the safety data were pooled across the two studies. However, no relation of any investigated safety issue to exposure was shown in response plots; hence, this issue will not be further pursued as regards exposure-response for safety. Besides grade ≥3 neutropenia, exposure-safety relations between $AUC_{0\text{-}24h,ss}$ $C_{max,ss}$ and $C_{min,ss}$ versus the following AEs of interest were investigated: Grade ≥3 thrombocytopenia, grade ≥3 anemia, grade ≥3 infections/infestations, all events of secondary primary malignancies, all events of atrial fibrillation and flutter, and major bleeding events. The figures have been assessed but have not been copied to this AR for sake of brevity. No exposure-safety relations were further investigated by linear logistic regression models as no trends were observed.

Overall, and in accordance with previous zanubrutinib submissions, no significant E/R relationsships were observed for ORR or any of the safety endpoints studied. Again, E/R analyses are limited by PK data at only one total daily dose level (320 mg) and by small number of certain events (e.g. n=4 for all events of atrial fibrillation and flutter).

Considering the variability, zanubrutinib exposures in Study GA101 following both single-dose administration of zanubrutinib 160 mg or 320 mg (Part 1) and multiple doses at 160 mg BID or 320 mg once daily (Parts 1 and 2) were consistent with those observed in prior patients with B-cell malignancies treated with zanubrutinib monotherapy - this as per the above referenced PK results from Study BGB-3111-AU-003 submitted with the initial EU MAA in WM. The high variability observed after single dose administration might be due to small number of patients (N=6). In the beginning of the Part 1 of the study, single dose zanubrutinib was given alone on Day1 of Cycle 1 before Obinutuzumab was started on Day 2. The multiple dose pharmacokinetics of zanubrutinib could be sufficiently interpreted based on the pharmacokinetic parameters after single dose. Zanubrutinib possess time-dependency in pharmacokinetics inducing its own metabolism through CYP3A, which could be observed here as slightly lower exposure at steady state compared to single dose PK.

The obinutuzumab concentration-time course data from study GA101 was likewise consistent with that previously reported in patients with non-Hodgkin's lymphoma: Based on the Gazyvaro SmPC, after the Cycle 6 Day 1 infusion in iNHL patients the population PK model predicted median C_{max} value was 539.3 µg/mL which is in good agreement with the observed C_{max} (geometric mean 577.15 µg/ml, CV% 43.52%) for Obinutuzumab on Cycle 6 of the current study. These cross-study comparisons indicate that obinutuzumab had no observable impact on zanubrutinib exposure and vice versa. This is as would be expected for a CD-20 monoclonal antibody (Gayzyvaro EPAR). Exposure parameters (AUC) were not determined for obinutuzumab.

The MAH submitted colour-coded zanubrutinib concentration-time profiles based on rich PK data for patients with FL vs. subjects within the other four disease-specific cohorts combined in study GA101 ('spaghetti plots') for confirmation that PK is comparable in patients with FL compared to in those with other B-cell lymphoid malignancies. Based on the provided figures, the zanubrutinib concentration-time course profile does not appear affected by diagnosis (type of specific B-cell lymphoid malignancy).

2.3.6. Conclusions on clinical pharmacology

The pharmacology data submitted support the extension of the indication in FL. The population PK model and the exposure-response analyses for efficacy and safety of zanubrutinib support the

proposed dose, however keeping in mind that the exposure-response analyses are based on data at only one total daily dose level (320 mg). Based on PK data submitted with the current extension of indication and with the initial (WM) EU MAA, the two proposed zanubrutinib dose regimens, 160 mg twice daily and 320 mg once daily, were found to provide comparable exposure (AUC), and the same posology for the FL indication is considered acceptable based on the efficacy, safety and PK.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

The proposed dose regimen in patients with FL is a 320 mg total daily dose (administered as 160 mg twice daily or 320 mg once daily). This is based on the totality of safety, efficacy, PK, and pharmacodynamics (BTK occupancy data) results from studies BGB-3111-AU-003, BGB-3111-1002, BGB-3111-GA101, and BGB-3111-212.

In Study BGB-3111-AU-003 at dose regimens of 40, 80, 160, and 320 mg once daily and 160 mg twice daily, the maximum tolerated dose was not reached, and no dose-limiting toxicities were observed during the dose-escalation part of the study. Moreover, nearly full occupancy of BTK was achieved in peripheral blood mononuclear cells (PBMCs) of patients at all administered doses, and in lymph node tissue at 160 mg twice daily and 320 mg once daily (BGB-3111-AU-003 Clinical Study Report). Activity has been observed across various B-cell malignancies (including CLL, MCL, WM, and FL) at all tested dose levels. Numerically comparable ORRs have also been observed between the 160 mg twice daily and 320 mg once daily regimens in patients with MCL, WM, and FL (Tam et al 2021; Report BGB-3111-CP-012).

Although the number of FL patients treated with zanubrutinib monotherapy at 320 mg once daily (N = 9) is limited relative to those at 160 mg twice daily dose (N = 50) in BGB-3111-AU-003 and BGB-3111-1002, numerically comparable ORR have been observed between 160 mg twice daily (ORR 33.3% in BGB-3111-AU-003 and 43.5% in BGB-3111-1002) and 320 mg once daily (ORR 50.0% in BGB-3111-AU-003 and 66.7% in BGB-3111-1002) in FL patients (Report BGB-3111-CP-012). Furthermore, no remarkable differences in adverse events between the two regimens in the safety population in Study BGB-3111-AU-003 were observed (Ou et al 2021).

Based on zanubrutinib monotherapy data in R/R FL, the combination of zanubrutinib and obinutuzumab was tested in Phase 1b study BGB-3111-GA101, a proof-of-concept study. The steady-state plasma exposures of zanubrutinib after administration of 160 mg twice daily and 320 mg once daily were also consistent with those in other studies of zanubrutinib monotherapy results, indicating that obinutuzumab had minimal impact on zanubrutinib exposure. As with monotherapy, comparable ORRs and safety profiles were observed in patients with B-cell lymphoma following the two dose regimens (Report BGB-3111-CP-012 and Table 14.3.1.2.6.2 of BGB-3111-GA-101 Clinical Study Report). Intravenous administration of multiple doses of obinutuzumab was delivered to patients according to the package insert (Gazyva [obinutuzumab] US prescribing information 2021). Obinutuzumab exposure nearly reached steady state 15 days after the first infusion. The mean steady-state obinutuzumab Ctrough levels during Cycles 2 to 6 were 292 to 370 µg/mL, and the serum concentration at 4 hours after infusion (Cmax) was 618 to 652 µg/mL during Cycles 2 to 6. These data are consistent with the published data for obinutuzumab monotherapy in patients with B-cell lymphoma (Gibiansky et al 2014), indicating zanubrutinib had minimum impact on obinutuzumab PK. Comparable ORRs and safety profiles were observed in patients with B-cell lymphoma following the two dose regimens (Report BGB-3111-CP-012 and Table 14.3.1.2.6.2 of BGB-3111-GA-101 Clinical Study Report). In addition, comparable ORR in FL patients have been observed between 160 mg twice daily (CR 45%; ORR 75%, N = 20) and 320 mg once daily (CR 43.8%, ORR 68.8%, N = 16) (Report BGB-3111-CP-012). Furthermore, zanubrutinib with

160 mg twice daily dose in concomitant use with obinutuzumab in BGB-3111-212 provided strong evidence of efficacy in patients with R/R FL (CR 39.3%; ORR 69.0%, N = 145, BGB-3111-212 Clinical Study Report).

Additional data support a 320 mg once daily regimen as an option in addition to the 160 mg twice daily regimen for patients with FL. Given the same total daily dose (320 mg) and linear PK, similar AUCs are achieved between the 320 mg once daily and 160 mg twice daily dose. At the 320 mg once daily dose, a sustained and profound BTK inhibition in PBMC and lymph node tissue were also observed. The exposure-response (E-R) analyses indicated that there was no evident E-R relationship between exposure (AUC0-24, Cmax, or Cmin) and safety endpoints (adverse events of interest) in patients with B-cell malignancies (Report BGB-3111-CP-011) and in patients with FL (Report BGB-3111-CP-012). There were no significant relationships between zanubrutinib exposure and adverse events including cytopenia, infections, and bleeding. In addition, the available E-R analysis in patients with FL (Module 2.7.2, Section 3.2 and Report BGB-3111-CP-012) and other B-cell malignancies including MCL (Report BGB-3111-CP-003), WM (Report BGB-3111-CP-007), MZL (Report BGB-3111-CP-009) and CLL/SLL (Report BGB-3111-CP-0011) indicated that efficacy (ORR) does not appear to be significantly impacted by Cmax or Cmin, and therefore the AUC delivered by a 320 mg once daily regimen is expected to result in a similar ORR as that of the 160 mg twice daily regimen.

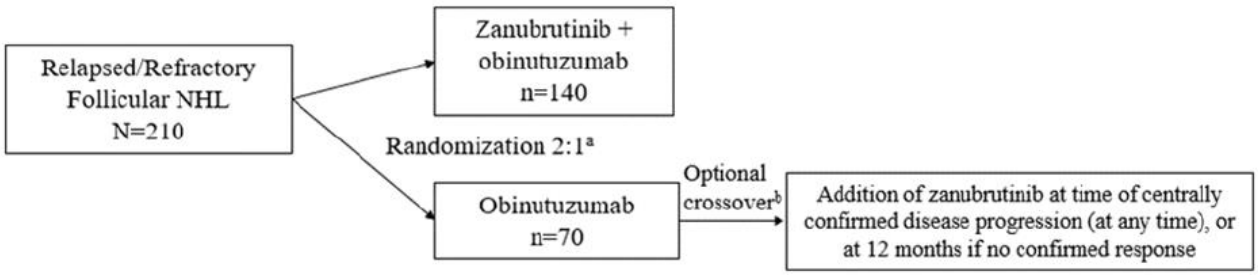
The totality of the data summarized support the recommended dose of a 320 mg total daily dose (as 160 mg twice daily or 320 mg once daily) in combination with obinutuzumab in adult patients with FL. This is based on consistent and sustained BTK occupancy in PBMCs and target tissue, high rates of overall response and complete response in patients with FL in the pivotal study, BGB-3111-212, and a favourable safety and tolerability profile.

2.4.2. Main study

Study BGB-3111-212

An international, phase 2, open-label, randomised study of zanubrutinib (BGB-3111) combined with obinutuzumab (ZO) compared with obinutuzumab monotherapy (O) in relapsed/refractory follicular lymphoma.

Figure 17 Study BGB-3112-212 Study Design



Source: BGB-3111-212 Clinical Study Report.
Abbreviation: NHL, non-Hodgkin lymphoma.
[a] Randomization stratified by the number of prior lines of therapy (2 to 3 versus > 3), rituximab refractory status (yes versus no), and geographic region (China versus ex-China).
[b] Option to add zanubrutinib following independent central confirmation of disease response status.

Methods

Study participants

Key inclusion criteria

1. ≥ 18 years of age at the time of informed consent

2. Histologically confirmed diagnosis of B-cell FL (Grade 1, 2, or 3a) based on the WHO 2008 classification of tumors of hematopoietic and lymphoid tissue

3. ≥ 2 prior systemic treatments for FL

4. Previously received an anti-CD20 antibody and an appropriate alkylator-based combination therapy, including:

    a. Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone

    b. Rituximab, cyclophosphamide, vincristine, and prednisolone

    c. Bendamustine plus rituximab

5. Disease progression after completion of most recent therapy or refractory disease, defined as failure to achieve CR or PR to most recent therapy, and most recent therapy was an appropriate second-line (or later) systemic therapy for FL

6. Presence of measurable disease, defined as ≥ 1 nodal lesion that is > 2 cm in longest diameter, or ≥ 1 extranodal lesion that is > 1 cm in longest diameter

7. Availability of archival tissue confirming diagnosis of B-cell FL (or if archival tissue was not available, a copy of the pathology report confirming diagnosis of B-cell FL was required)

8. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2

9. Life expectancy ≥ 6 months

10. Adequate organ function defined as:

    a. Absolute neutrophil count (ANC) ≥ 1000/mm3, except when neutropenia was assessed by the investigator to be directly due to active lymphoma, in which case ANC must have been ≥ 750/mm3

    b. Platelet > 50,000/mm3 (without growth factor support or transfusion within 7 days)

    c. Creatinine clearance ≥ 30 mL/min (as estimated by the Cockcroft-Gault or Modification of Diet in Renal Disease (MDRD) equation or as measured by nuclear medicine scan or 24-hour urine collection)

    d. Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase, and alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase ≤ 3.0 x upper limit of normal (ULN)

    e. Serum total bilirubin < 2.0 x ULN (unless documented Gilbert's syndrome)

Key exclusion criteria

1. Known central nervous system involvement by leukemia or lymphoma

2. Evidence of transformation from FL to DLBCL or other aggressive histology (such as large cells seen on biopsy or high PET avidity in a single node seen on PET scan)

3. Allogeneic hematopoietic stem cell transplantation within 12 months of study enrollment

4. Prior exposure to a BTK inhibitor

5. Prior malignancy within the past 2 years, except for curatively treated basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast, or localized Gleason score 6 prostate cancer

6. Clinically significant cardiovascular disease, including the following:

a. Myocardial infarction within 6 months before screening

b. Unstable angina within 3 months before screening

c. New York Heart Association Class III or IV congestive heart failure

d. History of clinically significant arrhythmias (eg, sustained ventricular tachycardia, ventricular fibrillation, torsades de pointes)

e. QTcF > 480 milliseconds based on Fridericia's formula

f. History of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place

g. Uncontrolled hypertension as indicated by a minimum of 2 consecutive blood pressure measurements showing systolic blood pressure > 170 mmHg and diastolic blood pressure > 105 mmHg at screening

7. History of severe bleeding disorder such as hemophilia A, hemophilia B, von Willebrand

disease, or history of spontaneous bleeding requiring blood transfusion or other medical

intervention

8. History of stroke or intracranial hemorrhage within 6 months before first dose of study

drug

11. Active fungal, bacterial and/or viral infection requiring systemic therapy

12. Underlying medical conditions that, in the investigator's opinion, rendered the administration of study drug hazardous or obscure the interpretation of safety or efficacy results

21. Requiring ongoing need for corticosteroid treatment. NOTE: Systemic corticosteroids must have been fully tapered off/stopped at least 5 days before the day of first study drug.

Treatments

Zanubrutinib was administered as two 80-mg capsules orally twice a day (160 mg twice a day) with or without food. Patients received daily treatment with zanubrutinib until disease progression, intolerance or death, withdrawal of consent, loss to follow-up, or study termination by sponsor. Each treatment cycle was 28 days.

For both arms obinutuzumab (1000 mg) was administered intravenously on Days 1, 8, and 15 of Cycle 1; on Day 1 of Cycles 2 to 6; and then every 8 weeks for an additional 24 months (maximum total duration of approximately 30 months [20 doses]) or until ICR confirmed disease progression.

At the discretion of the investigator, obinutuzumab may have been administered intravenously on Day 1 (100 mg) and on Day 2 (900 mg) of Cycle 1 instead of 1000 mg on Day 1 of Cycle 1

Crossover

At the discretion of the investigator, patients in Arm B were eligible to receive crossover treatment with zanubrutinib + obinutuzumab either if they experienced ICR-confirmed progressive disease (PD) or if their disease did not respond to therapy with a complete response (CR) or PR after 12 months; however, as of the 25 June 2022 data cut-off date, no patients had crossed over for this latter reason. The PD must have been confirmed by independent central review (ICR). For patients who received crossover treatment, the safety, laboratory, and response evaluation assessments were continued per the schedule of assessments.

Objectives and endpoints

Table 9: Efficacy Objectives and Endpoints for the Pivotal Study (BGB-3111-212)

Study	Objectives	Primary Endpoints	Secondary Endpoints

BGB-3111-212
(Amendment 4.0)
	• To evaluate efficacy, as measured by ORR determined by ICR
	• To evaluate efficacy, as measured by the following:
	  ○ ORR determined by investigator assessment
	  ○ DOR determined by ICR and by investigator assessment
	  ○ PFS determined by ICR and by investigator assessment
	  ○ OS
	  ○ Rate of CR or complete metabolic response determined by ICR and by investigator assessment
	  ○ TTR determined by ICR and by investigator assessment
	  ○ PROs
	• Safety and tolerability
	• PK (zanubrutinib plus obinutuzumab arm only)
		ORR as determined by ICR using the Lugano Classification for NHL	• ORR as determined by investigator assessment
			• DOR as determined by ICR and by investigator assessment
			• PFS as determined by ICR and by investigator assessment
			• OS
			• Rate of CR or complete metabolic response as determined by ICR and by investigator assessment
			• TTR as determined by ICR and by investigator assessment
			• PROs
			• Safety parameters
			• PK parameters: plasma CL/F and AUC_{0-12}

Primary Endpoint

The primary endpoint was overall response rate as determined by independent central review using the Lugano Classification for NHL.

The overall response rate was defined as the proportion of patients who achieved either CR or PR as the best overall response, defined as the best response achieved during the entire follow-up period, until the data cut-off date, the start of a new anticancer therapy, or the crossover date for patients in Arm B who cross over to Arm A.

Secondary Endpoints – duration of response

Duration of response as determined by independent central review and by investigator assessment, defined as the time from the date that response criteria were first met to the date of first documentation of disease progression or death, whichever occurred first. For patients in Arm B who crossed over to Arm A, the disease assessment after the crossover was not included in the derivation.

Efficacy Assessments

Response will be assessed by independent central review and categorized per the Lugano Classification for NHL (Cheson et al 2014). The primary endpoint will be ORR based on independent central review. Investigators will assess response without knowledge of independent central review results. Response parameters will include assessment of lymphadenopathy, hepatomegaly and splenomegaly, blood lymphocyte count, bone marrow aspirate/biopsy, platelet count, haemoglobin level, and neutrophil count. In the event of a treatment delay, disease assessments are to continue per the Schedule of Assessments (Appendix 9). For patients receiving zanubrutinib, refer to Appendix 2 regarding the assessment of disease progression during study drug holds.

Imaging Assessments

All patients must have baseline (within 35 days of randomization) PET/CT scan with contrast of neck, chest, abdomen, and pelvis and any other disease sites. Patients with suspected transformation of disease (eg, a PET/CT with high standardized uptake value-avidity or new onset symptoms) should be fully evaluated prior to enrollment on study.

Screening findings will determine whether patients are followed with contrast-enhanced PET/CT or contrast-enhanced CT only. Patients with disease that is FDG-avid by either site assessment or the central imaging vendor must be followed by PET/CT.

Ideally, and depending on the imaging equipment available, contrast-enhanced CT should occur combined with PET on a single visit. Combined PET/CT may be used in lieu of a CT with contrast only if the CT of the combined PET/CT has been performed with diagnostic quality and contrast is administered. PET/CT scans are required at screening and after Cycles 3, 6, and 12. A PET/CT scan is required to confirm a result on CT scan (CR/PR or disease progression). CT with contrast will be performed at all other tumour assessment timepoints (see Appendix 9, Schedule of Assessments). For patients with a contraindication to receiving CT scan IV-contrast (e.g., contrast allergy, or other medical contraindication such as renal insufficiency), magnetic resonance imaging (MRI) may be used in place of CT scans. For patients being assessed via MRI, a non-contrast chest CT scan is acceptable, and preferred, in place of a chest MRI to evaluate the lung parenchyma. The same imaging technique (i.e., CT, MRI) should be used consistently throughout a patient's time on the study. All efforts will be made to ensure that the imaging equipment, contrast agent, and person (investigator or radiologist) performing the evaluation is kept constant throughout a patient's remaining course on study. All PET/CT scans, CT scans, and MRIs obtained during the study will be collected and reviewed by a central imaging vendor identified to this

trial. De-identified copies of all scans and. radiology reports (including those from screening) must be provided to the sponsor or designee (e.g., central imaging vendor).

Modification from Lugano Classification for NHL (Cheson et al 2014):

Pseudo-progression is defined as an objective tumour response occurring after initial documentation of apparent radiological progressive disease and has been observed in patients receiving a BTK inhibitor for treatment of follicular lymphoma (Salles et al 2016). For patients in either arm, a timepoint finding of "disease progression" will require a confirmatory scan at least 4 weeks after the scan that initially demonstrated possible progression. An exception to the confirmatory scan requirement exists if one or more of the following clear, clinical signs of progression is present and the investigator believes the progression is unequivocal:

a. Clinical symptoms and signs of disease progression (including worsening laboratory values)

b. Deterioration of ECOG performance status

c. Rapid progression of disease or of progressive tumour at critical anatomical sites (e.g., cord compression) that necessitates urgent medical intervention.

Note: If any of the conditions above are present, no confirmatory scan is required to confirm the disease progression.

Due to the potential for pseudoprogression cases in this study, patients in both Arms A and B should remain on study treatment while the patient waits for the confirmation scan results.

Response and Site	PET-CT-Based Response (Patients with FDG-Avid Disease at Screening)	CT-Based Response (Patients Without FDG-Avid Disease at Screening)
Complete	Complete metabolic response	Complete radiologic response (all of the following):
Lymph nodes and extralymphatic sites	Score 1, 2, 3* with or without a residual mass on 5-point scale[†] It is recognized that in Waldeyer's ring or extranodal sites with physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	• Target nodes/nodal masses must regress to ≤ 1.5 cm in longest transverse diameter of a lesion • No extralymphatic sites of disease
Non-measured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology, if indeterminate, immunohistochemistry negative
Partial	Partial metabolic response	Partial remission (all of the following):
Lymph nodes and extralymphatic sites	Score 4 or 5[†] with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	• ≥ 50% decrease in sum of the product of the perpendicular diameters for multiple lesions of up to 6 target measurable nodes and extranodal sites • When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value • When no longer visible, 0 x 0 mm • For a node > 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Non-measured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable

Response and Site	PET-CT-Based Response (Patients with FDG-Avid Disease at Screening)	CT-Based Response (Patients Without FDG-Avid Disease at Screening)
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5† with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in sum of the product of the perpendicular diameters for multiple lesions of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Non-measured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease**	Progressive metabolic disease	Progressive disease requires at least 1 of the following cross product of the longest transverse diameter of a lesion and perpendicular diameter progression: An individual node/lesion must be abnormal with: • longest transverse diameter of a lesion > 1.5 cm and • Increase by ≥ 50% from cross product of the longest transverse diameter of a lesion and perpendicular diameter nadir and • An increase in longest transverse diameter of a lesion or shortest axis perpendicular to the longest transverse diameter of a lesion from nadir o 0.5 cm for lesions ≤ 2 cm o 1.0 cm for lesions > 2 cm • In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline • New or recurrent splenomegaly
Individual target nodes/nodal masses	Score 4 or 5† with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end of treatment assessment	
Non-measured lesions	None	New or clear progression of pre-existing non-measured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	• Regrowth of previously resolved lesions • A new node > 1.5 cm in any axis • A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma • Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: CT, computed tomography; FDG, [18F]fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography.
Modified from Cheson BD, Fisher RJ, Barrington SF, et al. J Clin Oncol 2014;32(27):3059-67.
*A score 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid under treatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal, and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), gastrointestinal involvement, cutaneous lesions, or those noted on palpation. Non-measured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, gastrointestinal tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5-point scale (Deauville Criteria):

- 1: no uptake above background
- 2: uptake ≤ mediastinum
- 3: uptake > mediastinum but ≤ liver
- 4: uptake moderately > liver
- 5: uptake markedly higher than liver and/or new lesions

X. new areas of uptake unlikely to be related to lymphoma

Modification from Lugano Classification for NHL (Cheson et al 2014):

**Pseudoprogression has been observed in patients receiving a BTK inhibitor. For patients in either arm, a timepoint finding of "disease progression" will require a confirmatory scan at least 4 weeks after the scan that demonstrated possible progression. An exception to the confirmatory scan requirement exists if one or more of the clear, clinical signs of progression detailed in Section 5.6 is present and the investigator believes the progression is unequivocal. Patients may continue study treatment while they wait for the confirmation imaging.

Note: Temporary withholding of study drug (eg, for drug-related toxicity, surgery, or intercurrent illness) for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. In such circumstances, and if medically appropriate, patients may resume therapy and relevant clinical, laboratory, and/or radiologic assessments should be performed to document whether tumor control can be maintained or whether actual disease progression has occurred.

Isolated increase in lymph nodes and/or splenomegaly during periods of zanubrutinib hold will not be considered as progressive disease unless confirmed by a repeat imaging studies at least 6 weeks after restarting study drug administration. The response category "indeterminate due to zanubrutinib hold" should be selected for such instances. Following the repeat imaging 6 weeks after restarting study drug, response should be in comparison to the imaging at baseline.

Table 10 Modified PET-CT / CT Lugano responses

PET-Staging Overall (PET + Clinical) Response	CT-Staging Overall (CT + Clinical) Response	Modified PET + CT + Clinical Lugano Overall Response
CMR	CR/PR/SD/NE/PD	CR
PMR	CR/PR/SD/NE/PD	PR
NMR	CR/PR/SD/NE/PD	SD
NE*	CR/PR/SD/NE	Non-PD
NE*	PD	PD
PMD	CR/PR/SD/NE/PD	PD

Sample size

The sample size calculation is based on the comparison of the primary endpoint of ORR in the ITT Population. Assuming ORRA=0.55 and ORRB=0.30, 210 patients will be enrolled in a 2:1 ratio (140 patients in arm A and 70 patients in arm B) to provide a power of approximately 91% in testing ORRA versus ORRB using a normal approximation to binomial distribution with a 2-sided significance level of 0.05 with continuity correction. The sample size calculation is based on methods in Hulley et al, 2013 and Fleiss et al, 1980.

Randomisation

Central randomization (2:1) was used to assign patients to one of the following treatment arms:

- Arm A: zanubrutinib + obinutuzumab

- Arm B: obinutuzumab monotherapy

Randomization was stratified by the number of prior lines of therapy (2 to 3 versus > 3), rituximab-refractory status (yes versus no), and geographic region (China versus ex-China). Patients who were rituximab-refractory were defined as having failed to respond to, or progressed during, any previous rituximab-containing regimen (monotherapy or combined with chemotherapy) or having progressed within 6 months of the last rituximab dose in the induction or maintenance treatment settings. A rituximab-containing regimen included at least 4 weekly doses of rituximab if administered as monotherapy, or at least 4 cycles if given as chemoimmunotherapy. For induction therapy regimens during which a patient had disease progression, the minimum necessary rituximab dose was 1 full cycle (monotherapy or chemoimmunotherapy) or 1 dose of 375 mg/m^2 (maintenance).

Blinding (masking)

Due to the open-label design, blinding was only maintained during treatment allocation and assessments by independent central review.

Statistical methods

The ITT population, consisting of all randomised patients, was used for the efficacy analyses. The per protocol population, defined prior to data base lock, was also used for analysis on the primary endpoint.

Control of type 1 error was only maintained for the analysis of the primary endpoint.

ORR

The comparative analysis of the primary endpoint was done by means Cochran-Mantel-Haenszel test for the null hypothesis, overall response rate for zanubrutinib plus obinutuzumab being less or equal to the overall response rate for obinutuzumab monotherapy, versus the alternative hypothesis of the overall response rate for zanubrutinib plus obinutuzumab being greater than for obinutuzumab monotherapy. Testing was performed by a one-sided test with significance level at 2.5%. In addition, the 95% CI of the odds-ratio of the overall response rate was derived together with Clopper-Pearson 95% CI of the overall response rate per treatment group.

DoR

Descriptive statistics was provided for Duration of response per treatment group.

PFS

PFS was compared by the log-rank test stratified for stratification factors on the randomisation. The following censoring rules was applied:

- PFS for patients without any post-baseline disease assessment will be censored at the time of randomization
- PFS for patients without disease progression or death at the time of analysis will be censored at the time of the last disease assessment
- PFS for patients who are lost to follow-up prior to documented disease progression will be censored at the last disease assessment date
- PFS for patients who start to receive new anticancer therapy will be censored at the last tumor assessment date prior to the introduction of new therapy
- PFS for patients with disease progression or death occurring immediately after two or more missed consecutive disease assessments will be censored at the last assessment tumor assessment before the missed consecutive disease assessments

Overall Survival

OS between the 2 treatment groups will be compared using the same methods employed for the PFS comparison. The distribution of OS (including median and other quartiles) and OS rate at selected timepoints will be estimated by the Kaplan-Meier method.

Complete Response/Complete Metabolic Response

CR rate and complete metabolic response rate will be calculated as the proportion of patients who reached best overall response of CR (complete metabolic response) or higher. The CR and complete metabolic response rate will be compared between treatment groups using Fisher's exact test. A Clopper-Pearson 95% CI of complete response rate and complete metabolic response rate will be constructed per each arm.

Time-to-Response

Time-to-response will be summarized only for responders by sample mean, median and standard deviation for each treatment group.

Patient-Reported Outcomes

The EORTC QLQ-C30 questionnaire will be summarized for each assessment timepoint. The percentage of patients with a clinically meaningful change from baseline in 'global health status/QOL' and functional domains will be summarized as "improved", "stable" or "worsened" and compared between arms A and B.

The data will also be analyzed using repeated measure mixed model to account for missing data under missing at random assumption. Change of EQ-5D-5L score will be summarized descriptively.

Results

Participant flow

Table 11 ***BGB-3111-212: Patient Disposition and Reasons for Discontinuation (ITT Analysis)***

	Zanubrutinib + Obinutuzumab (N = 145) n (%)	**Obinutuzumab (N = 72) n (%)**	**Total (N = 217) n (%)**
Number of Patients Screened			283
Number of Patients Randomized	145 (100.0)	72 (100.0)	217 (100.0)
Number of Patients Randomized, but Not Treated	2 (1.4)	1 (1.4)	3 (1.4)
Number of Patients Treated	143 (98.6)	71 (98.6)	214 (98.6)
Number of Patients Completed 20 Doses of Obinutuzumab	21 (14.5)	8 (11.1)	29 (13.4)
Number of Patients Discontinued from Treatment [a]	97 (66.9)	65 (90.3)	162 (74.7)
Reason for Discontinuation			
Disease Progression	53 (36.6)	11 (15.3)	64 (29.5)
Adverse Event	27 (18.6)	9 (12.5)	36 (16.6)
Related to COVID-19	6 (4.1)	2 (2.8)	8 (3.7)
Investigator Decision	7 (4.8)	3 (4.2)	10 (4.6)
Related to COVID-19	1 (0.7)	0 (0.0)	1 (0.5)
Patient Withdrew Consent	5 (3.4)	2 (2.8)	7 (3.2)

	Zanubrutinib + Obinutuzumab (N = 145) n (%)	Obinutuzumab (N = 72) n (%)	Total (N = 217) n (%)
Completed 20 Doses of Obinutuzumab	NA	4 (5.6)	4 (1.8)
Other	7 (4.8)	1 (1.4)	8 (3.7)
Crossover to the Combination Treatment	NA	35 (48.6)	35 (16.1)
Disease Progression	NA	19 (26.4)	19 (8.8)
Adverse Event	NA	3 (4.2)	3 (1.4)
Related to COVID-19	NA	3 (4.2)	3 (1.4)
Investigator Decision	NA	1 (1.4)	1 (0.5)
Other	NA	1 (1.4)	1 (0.5)
Number of Patients Remained on Treatment	46 (31.7)	6 (8.3)	52 (24.0)
Number of Patients Discontinued from Study	50 (34.5)	31 (43.1)	81 (37.3)
Reason for Discontinuation			
Death	29 (20.0)	22 (30.6)	51 (23.5)
Related to COVID-19	4 (2.8)	7 (9.7)	11 (5.1)
Patient Withdrew Consent	15 (10.3)	7 (9.7)	22 (10.1)
Lost to Follow-up	3 (2.1)	1 (1.4)	4 (1.8)
Other	3 (2.1)	1 (1.4)	4 (1.8)
Number of Patients Remained in Study	95 (65.5)	41 (56.9)	136 (62.7)
Study Follow-up Time (Months) [b]			
n	145	72	217
Mean (SD)	21.33 (11.636)	20.16 (12.198)	20.94 (11.810)
Median	20.21	20.40	20.21
Q1, Q3	13.08, 30.39	9.97, 29.85	12.02, 30.32
Min, Max	0.1, 46.6	0.1, 46.2	0.1, 46.6

Source: ADSL, DM. Data cutoff: 25JUN2022. Data extraction: 12SEP2022.
Abbreviation: NA, not applicable.
Percentages are based on number of patients randomized.
[a] For patients in zanubrutinib + obinutuzumab arm, both reasons for discontinuation are reported if the end-of-treatment reasons are different. If the end-of-treatment reason is 'completed treatment' for obinutuzumab, only end-of-treatment reason for zanubrutinib is reported.
[b] Study Follow-up Time is defined as the time from the randomization date to the death date or end of study date (whichever occurs first) for patients discontinued from the study, or the database cutoff date for ongoing patients.
/bgb_3111/bgb_3111_212/csr_20220625_fup_12m/dev/pgm/tlfs/ t-ds-i.sas 20OCT2022 12:04 t-14-1-1-1-ds-i.rtf

Table 12 Patient disposition and reasons for discontinuation after crossover - ITT

	Zanubrutinib + Obinutuzumab (N = 35) n (%)
Number of Patients Crossover to the Combination Treatment	35 (100.0)
Number of Patients Discontinued from Treatment after Crossover [a]	24 (68.6)
Disease Progression	19 (54.3)
Adverse Event	3 (8.6)
Related to COVID-19	3 (8.6)
Investigator Decision	1 (2.9)
Other	1 (2.9)
Number of Patients Remained on Treatment after Crossover	11 (31.4)

Source: ADSL. Data cutoff: 25JUN2022. Data extraction: 12SEP2022.
Percentages are based on number of patients crossed over to combination arm.
[a] For patients crossover to zanubrutinib + obinutuzumab arm, both reasons for discontinuation are reported if the end-of-treatment reasons are different. If the end-of-treatment reason is 'completed treatment' for obinutuzumab, only end-of-treatment reason for zanubrutinib is reported.

Recruitment

Subjects were enrolled from 14 November 2017 across 83 centres in 17 countries (AU, BG, BY, CA, CN, CZ, DE, ES, FR, GB, IT, KR, NZ, PO, RU, TW, US). The majority of patients in the ITT analysis set were randomised at sites in Europe (60.8%). The study is ongoing but recruiting has ended.

First patient treated 14 November 2017.

Last patient randomised 25 June 2020.

DCO on 25 June 2022.

Conduct of the study

Several protocol amendments were made during the conduct of the study. Major amendments are summarised here.

Amendment 1 (22 December 2017)

44 patients enrolled in the study under Amendment 1 of the protocol (data on file).

Key changes to the conduct of the study implemented in Amendment 1 (22 December 2017) were as follows:

• Replaced "BGB-3111" with the International Nonproprietary Name, zanubrutinib

• Added that patients in Arm B who experienced progressive disease while receiving obinutuzumab monotherapy were eligible to receive crossover treatment with zanubrutinib plus obinutuzumab

• Added text to clarify how and when tumor assessments were performed

• Modified the definition of adequate organ function for inclusion criterion 10

• Clarified inclusion criterion 11 to add the definition of women of childbearing potential per the Clinical Trial Facilitation Group (CTFG) guidance

• Updated the safety precautions for patients with potential hematologic or nonhematologic toxicities

• Modified the text to ensure step-up and step-down grades for adverse events were recorded in eCRF

• Clarified the reporting of nontreatment emergent adverse events and serious adverse events

Amendment 2 (04 February 2019)

47 patients enrolled in the study under Amendment 2 of the protocol (data on file). Key changes to the conduct of the study implemented in Amendment 2 (04 February 2019) were as follows:

• Added data from a thorough QT study and removed guidance on QT-prolonging medications

• Added data from drug-drug interaction studies and removed guidance on CYP2 metabolized drugs

• Modified inclusion criterion 4c to include a note requiring patients in South Korea to have received prior bendamustine therapy or have been determined by their treating physician to not be medically suitable for bendamustine therapy

• Modified inclusion criterion 5 to eliminate the requirement that patients experience disease progression within 12 months of receiving their last therapy. This revision was made to be consistent with recently approved drugs for which the definition of the population was solely based on the number of prior lines of therapy.

• Added exclusion criterion 21 to exclude patients requiring ongoing corticosteroid treatment

• Added guidance regarding prophylaxis for opportunistic infections

Amendment 3 (30 June 2019)

115 patients enrolled in the study under Amendment 3 of the protocol (data on file). Key changes to the conduct of the study implemented in Amendment 3 (30 June 2019) were as follows:

• Corrected an error in the frequency of tumor assessments (including imaging studies).

Amendment 4 (18 August 2021)

No patients were enrolled in the study under Amendment 4 of the protocol, as enrollment was completed (data on file). Key changes to the conduct of the study implemented in Amendment 4 (18 August 2021) were as follows:

• Changed the timepoint of the primary efficacy analysis from 9 months to 3 months after randomization of the last patient

• Clarified the long-term follow-up assessments required for patients with centrally confirmed disease progression

Changes in the Planned Analyses

First available statistical analysis plan is dated 12 NOV 2021, with an update dated 19 JUL 2022, both of which was only most of subjects were already randomised. Both plans had modifications to the specification of analyses however, the comparative analyses of the primary endpoint, PFS, OS and CR agreed with the specifications from the protocol vers. 1.

The Primary Analysis for this study, reported in a clinical study report with a data cut-off date of

08 October 2021, presented the efficacy and safety results at 3 months after the last patient was randomized into the study (BGB-3111-212 [Data Cutoff Date: 08 October 2021] Clinical Study Report).

Per a request from the US FDA to provide additional follow-up data for duration of response, an Updated Analysis at 12 months after the last patient was randomized into the study was conducted. Updated efficacy and safety analyses with a data cut-off date of 25 June 2022 are presented in the clinical study report.

Baseline data

*Table 13**: Demographics and Baseline Characteristics (ITT Analysis Set)***

	Zanu + Obi (N = 145) n (%)	**Obi (N = 72) n (%)**
Sex, n (%)		
Male	75 (51.7)	33 (45.8)
Female	70 (48.3)	39 (54.2)
Race, n (%)		
White	92 (63.4)	47 (65.3)
Asian	30 (20.7)	17 (23.6)
Other/Not Reported	23 (15.9)	8 (11.1)
Age (years)		
Mean (SD)	61.1 (11.98)	62.9 (12.81)
Median	63.0	65.5

	Zanu + Obi (N = 145) n (%)	Obi (N = 72) n (%)
Q1, Q3	53.0, 70.0	55.5, 72.0
Min, Max	31, 84	32, 88
Age Group, n (%)		
< 60 years	55 (37.9)	24 (33.3)
≥ 60 years	90 (62.1)	48 (66.7)
< 65 years	83 (57.2)	32 (44.4)
≥ 65 years	62 (42.8)	40 (55.6)
< 75 years	130 (89.7)	60 (83.3)
≥ 75 years	15 (10.3)	12 (16.7)
≥ 65 - < 75	47 (32.4)	28 (38.9)
Ethnicity, n (%)		
Hispanic or Latino	4 (2.8)	2 (2.8)
Not Hispanic or Latino	116 (80.0)	60 (83.3)
Not Reported/Unknown	25 (17.2)	10 (13.9)
Geographic Region, n (%)		
Europe	95 (65.5)	37 (51.4)
Asia	30 (20.7)	17 (23.6)
Australia/New Zealand	15 (10.3)	12 (16.7)
North America	5 (3.4)	6 (8.3)
Weight (kg)		
Mean (SD)	75.02 (16.433)	76.81 (17.133)
Median	74.00	77.25
Q1, Q3	64.00, 88.50	63.60, 89.50
Min, Max	40.0, 118.0	47.5, 116.0
BMI (kg/m^2)		
Mean (SD)	26.52 (4.449)	27.41 (5.295)
Median	26.60	27.59
Q1, Q3	23.49, 29.15	23.50, 30.35
Min, Max	15.6, 39.9	17.6, 44.5
ECOG Performance Status, n (%)		
0	86 (59.3)	31 (43.1)
1	54 (37.2)	40 (55.6)
2	5 (3.4)	1 (1.4)

Source: ADSL, ADBASE. Data cutoff: 25JUN2022 (212), 02SEP2020 (GA101), 31MAR2021 (AU003), 30AUG2020 (1002).
Abbreviation: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group.
FL Efficacy Analysis Set includes all FL patients randomized to treatment in BGB-3111-212 or received any dose of zanubrutinib and/or obinutuzumab in BGB-3111-GA101, BGB-3111-AU003 and BGB-3111-1002. All patients received ≥ 2 prior line of therapy.

*Table 14: **Disease History at Study Entry (ITT Analysis Set)***

	BGB-3111-212	
	Zanu + Obi (N = 145) n (%)	Obi (N = 72) n (%)
Time Since Initial Diagnosis to Study Entry (months)		
n	145	72
Mean (SD)	103.99 (71.695)	92.49 (63.884)
Median	90.22	77.24

	BGB-3111-212	
	Zanu + Obi (N = 145) n (%)	**Obi (N = 72) n (%)**
Q1, Q3	48.43, 151.20	47.51, 127.79
Min, Max	5.1, 359.0	6.7, 312.3
FLIPI at Baseline, n (%) [a]		
Low (0-1)	29 (20.0)	9 (12.5)
Intermediate (2)	34 (23.4)	24 (33.3)
High (≥ 3)	77 (53.1)	37 (51.4)
Missing	5 (3.4)	2 (2.8)
Ann Arbor Stage at Baseline, n (%) [b]		
I-II	23 (15.9)	10 (13.9)
III-IV	119 (82.1)	60 (83.3)
Missing	3 (2.1)	2 (2.8)
LDH at Baseline, n (%) [b]		
≤ ULN	93 (64.1)	41 (56.9)
> ULN	49 (33.8)	29 (40.3)
Missing	3 (2.1)	2 (2.8)
Bone Marrow Involvement at Baseline, n (%)		
Absent	103 (71.0)	44 (61.1)
Present	39 (26.9)	26 (36.1)
Missing	3 (2.1)	2 (2.8)
Beta-2 Microglobulin at Baseline, n (%)		
Normal	66 (45.5)	28 (38.9)
Raised	69 (47.6)	37 (51.4)
Unknown	5 (3.4)	3 (4.2)
Missing	5 (3.4)	4 (5.6)
Baseline Bulky Disease, n (%)		
≥ 5 cm	57 (39.3)	31 (43.1)
≥ 10 cm	5 (3.4)	6 (8.3)
B-symptoms, n (%)		
Yes	15 (10.3)	8 (11.1)
No	130 (89.7)	64 (88.9)
Unexplained fever of ≥ 101°F, n (%)		
Yes	2 (1.4)	1 (1.4)
No	143 (98.6)	71 (98.6)
Drenching night sweats, n (%)		
Yes	15 (10.3)	6 (8.3)
No	130 (89.7)	66 (91.7)
Unexplained weight loss > 10% in previous 6 months, n (%)		
Yes	2 (1.4)	1 (1.4)
No	143 (98.6)	71 (98.6)

Source: ADSL, ADBASE. Data cutoff: 25JUN2022 (212), 02SEP2020 (GA101), 31MAR2021 (AU003), 30AUG2020 (1002).

Abbreviation: NR, not reported.

FL Efficacy Analysis Set includes all FL patients randomized to treatment in BGB-3111-212 or received any dose of zanubrutinib and/or obinutuzumab in BGB-3111-GA101, BGB-3111-AU003 and BGB-3111-1002. All patients received ≥ 2 prior lines of therapy.

[a] FLIPI score was calculated using a scoring system that gave 1 point for each of the following risk factors: age ≥ 60 years, Ann Arbor State III or IV, hemoglobin < 120 g/L, > 4 nodal sites, and LDH > ULN.

[b] Only Ann Arbor Stage III-IV and LDH with >ULN at Baseline were collected for BGB-3111-GA101.

Table 15: Prior Anticancer Drug Therapies (ITT Analysis Set)

	BGB-3111-212	
	Zanu + Obi (N = 145) n (%)	**Obi (N = 72) n (%)**
Patients with any Prior Anticancer Therapy, n (%)	145 (100.0)	72 (100.0)
Anti-CD20 mAb	145 (100.0)	72 (100.0)
Rituximab	145 (100.0)	72 (100.0)
Cyclophosphamide	136 (93.8)	68 (94.4)
Anthracyclines or Anthracene-diones	119 (82.1)	58 (80.6)
Anthracyclines	118 (81.4)	57 (79.2)
Bendamustine	79 (54.5)	40 (55.6)
PI3Ki	29 (20.0)	14 (19.4)
Purine analogs	15 (10.3)	9 (12.5)
IMIDs	14 (9.7)	7 (9.7)
Radioimmunotherapy	11 (7.6)	2 (2.8)
Bispecifics	3 (2.1)	0 (0.0)
ADC	2 (1.4)	5 (6.9)
EZH2 inhibitor	2 (1.4)	1 (1.4)
SYKi	2 (1.4)	2 (2.8)
CAR-T	0 (0.0)	1 (1.4)
Venetoclax	0 (0.0)	4 (5.6)
Immunochemotherapy	143 (98.6)	71 (98.6)
Number of Prior Lines		
Mean (SD)	3.10 (1.430)	3.08 (1.361)
Median	3.00	3.00
Q1, Q3	2.00, 4.00	2.00, 3.50
Min, Max	2.0, 11.0	2.0, 9.0
Number of Prior Lines, n (%)		
2	65 (44.8)	30 (41.7)
3	39 (26.9)	24 (33.3)
>3	41 (28.3)	18 (25.0)
Best Response for Last Therapy, n (%)		
Complete Response	52 (35.9)	23 (31.9)
Partial Response	41 (28.3)	19 (26.4)
Stable Disease	26 (17.9)	16 (22.2)
Progressive Disease	21 (14.5)	13 (18.1)
Unknown	5 (3.4)	1 (1.4)
Time from End of Last Therapy to Study Entry (months)		
Mean (SD)	17.21 (21.956)	15.75 (27.505)
Median	8.77	6.28
Q1, Q3	2.84, 22.08	2.41, 17.26
Min, Max	0.2, 116.5	0.7, 197.9
≤ 2 years	110 (75.9)	56 (77.8)
> 2 years	34 (23.4)	16 (22.2)
Missing	1 (0.7)	0 (0.0)
Rituximab-Refractory, n (%) [a]		
Yes	78 (53.8)	36 (50.0)
No	67 (46.2)	36 (50.0)
Unknown	0 (0.0)	0 (0.0)
Refractory to the Most Recent Line of Therapy, n (%) [b]		
Yes	47 (32.4)	29 (40.3)

	BGB-3111-212	
	Zanu + Obi (N = 145) n (%)	**Obi (N = 72) n (%)**
No	93 (64.1)	42 (58.3)
Unknown	5 (3.4)	1 (1.4)
Progression of Disease within 24 Months of Starting the First Line of Therapy, n (%)		
Yes	50 (34.5)	30 (41.7)
No	74 (51.0)	35 (48.6)
Unknown	21 (14.5)	7 (9.7)
Prior Anticancer Radiotherapy, n (%)		
Yes	31 (21.4)	17 (23.6)
No	114 (78.6)	55 (76.4)
Prior Stem Cell Transplant, n (%)		
Yes	32 (22.1)	13 (18.1)
No	113 (77.9)	59 (81.9)

Abbreviation: NR, not reported.
FL Efficacy Analysis Set includes all FL patients randomized to treatment in BGB-3111-212 or received any dose of zanubrutinib and/or obinutuzumab in BGB-3111-GA101, BGB-3111-AU003 and BGB-3111-1002. All patients received ≥ 2 prior line of therapy.
[a] Rituximab-Refractory is defined as patients whose best response to any prior Rituximab treatment was Progressive Disease or Stable Disease.
[b] Refractory to the Most Recent Line of Therapy is defined as patients whose best response to the last prior regimen was Progressive Disease or Stable Disease.

The median number of prior anticancer therapies was 3 lines (range: 2 to 11 lines) and the median time from the end of the last therapy to study entry was 8.0 months (range: 0.2 to 197.9 months).

All patients received ≥ 2 prior lines of therapy and 59 patients (27.2%) received > 3 prior lines of therapy. Approximately one-third of patients (76 patients [35.0%]) reported stable disease (42 patients [19.4%]) or progressive disease (34 patients [15.7%]) as best response to their last therapy.

Seventy-six patients (35.0%) were refractory to their most recent line of therapy (i.e., best response of progressive disease or stable disease), and 141 patients (65.0%) were either not refractory (135 patients [62.2%]) or of unknown status (6 patients [2.8%]).

A total of 147 patients (67.7%) experienced disease progression within 12 months of completing their most recent line of therapy.

All 217 patients in this study received prior rituximab therapy. More than half (114 patients [52.5%]) were refractory to rituximab (defined as failure to respond to, or progression during, any previous rituximab-containing regimen [monotherapy or combined with chemotherapy], or progression within 6 months of the last rituximab dose, in the induction or maintenance treatment settings). The number of patients who were refractory to both rituximab and an alkylating agent were not recorded.

Overall, 214 patients (98.6%) received at least one prior immunochemotherapy regimen; 119 patients (54.8%) received prior bendamustine, 175 patients (80.6%) received prior anthracyclines, 204 patients (94.0%) received prior cyclophosphamide, 43 patients (19.8%) received prior PI3K inhibitors, and 21 patients (9.7%) received prior immunomodulatory drugs (IMiDs; including lenalidomide). Sixty-four patients (29.5%) had prior anticancer surgery, 48 patients (22.1%) had prior anticancer radiotherapy, and 45 patients (20.7%) had prior stem cell transplantation. Of these, 4 patients had allogeneic transplant and the remaining had received autologous transplant.

Numbers analysed

Table 16: Analysis Sets (ITT Analysis Set)

	Obinutuzumab (N = 72) n (%)	Zanubrutinib + Obinutuzumab (N = 145) n (%)	Total (N = 217) n (%)
Intent-to-Treat (ITT) Analysis Set [a]	72 (100.0)	145 (100.0)	217 (100.0)
Safety Analysis Set [b]	71 (98.6)	143 (98.6)	214 (98.6)
Per-Protocol Analysis Set [c]	70 (97.2)	142 (97.9)	212 (97.7)
Pharmacokinetics (PK) Analysis Set [d]	0 (0.0)	142 (97.9)	142 (65.4)

Source: ADSL. Data cutoff: 25JUN2022. Data extraction: 12SEP2022.
[a] The Intent-to-Treat (ITT) Analysis Set includes all patients randomized.
[b] The Safety Analysis Set includes all patients in the ITT Analysis Set who received any dose of any study drug.
[c] The Per-Protocol Analysis Set includes all patients in the ITT Analysis Set who received any dose of study drug and had no critical protocol deviations.
[d] The Pharmacokinetics (PK) Analysis Set includes all zanubrutinib-treated patients who have at least one post-baseline PK concentration measurement.
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Outcomes and estimation

Primary Efficacy Endpoint - ORR

The primary efficacy endpoint was overall response rate as determined by independent central review using the Lugano Classification for NHL.

Table 17:Study BGB-3111-212: Disease Response by Independent Central Review (ITT Analysis Set)

Response Category	Zanubrutinib + Obinutuzumab (N = 145) n (%)	Obinutuzumab (N = 72) n (%)
Best Overall Response, n (%)		
Complete Response	57 (39.3)	14 (19.4)
Partial Response	43 (29.7)	19 (26.4)
Stable Disease	24 (16.6)	14 (19.4)
Non-progressive Disease	3 (2.1)	4 (5.6)
Progressive Disease	13 (9.0)	15 (20.8)
Discontinued Prior to First Tumor Assessment/Not Evaluable	5 (3.4)	6 (8.3)
Overall Response Rate, n (%)	100 (69.0)	33 (45.8)
(95% CI) [a]	(60.8, 76.4)	(34.0, 58.0)
Risk Difference, % (95% CI) [b]	22.7 (9.0, 36.5)	
2-sided p-value [c]	0.0012	
Disease Control Rate, n (%)	124 (85.5)	47 (65.3)
(95% CI) [a]	(78.7, 90.8)	(53.1, 76.1)
Risk Difference, % (95% CI) [b]	20.1 (7.6, 32.6)	
2-sided p-value [c]	0.0007	

Source: ADSL, ADRSIRC. Data cutoff: 25JUN2022. Data extraction: 12SEP2022.
[a] The 95% CI was estimated using the Clopper-Pearson method.
[b] Mantel-Haenszel common risk difference was estimated, along with its 95% CI constructed by a normal approximation and Sato's variance estimator, stratified by rituximab-refractory status, number of prior lines of therapy, and geographic region per IRT.

[c] The p-value was obtained using the Cochran-Mantel-Haenszel method stratified by rituximab-refractory status, number of prior lines of therapy, and geographic region per IRT.
Disease control rate is defined as the proportion of patients who achieved complete response, partial response, or stable disease.
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Table 18: Comparison of ORR, DoR and PFS between the patients who met vs *not met GELF criteria(exploratory subgroup analysis)*

	Zanubrutinib + Obinutuzumab (N = 145)		**Obinutuzumab (N = 72)**	
	Met GELF Criteria (N=83)	**No (N=62)**	**Met GELF Criteria (N=40)**	**No (N=32)**
ORR (95% CI)	62.7 (51.3, 73.0)	77.4 (65.0, 87.1)	45.0 (29.3, 61.5)	46.9 (29.1, 65.3)
Risk Difference (95% CI) [a]	17.7 (-1.0, 36.3)	30.5 (10.4, 50.7)		
P-value [b]	0.0651	0.0030		
Median DoR (95% CI) (Month)[c]	24.7 (8.5, 26.5)	NE (NE, NE)	12.7 (6.1, 21.6)	20.3 (2.7, NE)
Median PFS (95% CI) (Months) [c]	15.2 (9.5, 28.0)	NE (NE, NE)	11.8 (5.6, 17.5)	10.4 (4.3, 16.6)

[a] Mantel-Haenszel common risk difference was estimated, along with its 95% CI constructed by a normal approximation and Sato's variance estimator.

[b] The p-value was obtained using the unstratified Cochran-Mantel-Haenszel method.

[c] Estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.

Source: Q5 response 2nd round.

Table 19: Disease assessment based on CT for patients with non-PD assessment

SUBJID	Arm	VISIT	Assessment Date	Assessment by PET/CT	Assessment by CT	BoR per CT only
0711-001	ZO	CYCLE 3 RESPONSE EVALUATION	5-Jun-20	NON-PD	PR	PR
		CYCLE 6 RESPONSE EVALUATION	7-Sep-20	NON-PD	PR	
		CYCLE 9 RESPONSE EVALUATION	23-Nov-20	NON-PD	PR	
		CYCLE 12 RESPONSE EVALUATION	11-Feb-21	NON-PD	PR	

		CYCLE 15 RESPONSE EVALUATION	13-May-21	NON-PD	PR	
		CYCLE 18 RESPONSE EVALUATION	10-Aug-21	NON-PD	PR	
		UNSCHEDULED 22199.01	29-Nov-21	NON-PD	PR	
		CYCLE 24 RESPONSE EVALUATION	28-Jan-22	NON-PD	PR	
3301-005	O	CYCLE 6 RESPONSE EVALUATION	12-May-21	NON-PD	SD	SD
		UNSCHEDULED 20699.03	17-Jun-21	PD	PD	
3924-005	ZO	UNSCHEDULED 20115.01	18-Mar-20	NON-PD	PR	PR
4426-001	O	CYCLE 3 RESPONSE EVALUATION	25-Nov-19	NON-PD	SD	PR
		CYCLE 6 RESPONSE EVALUATION	27-Jan-20	NON-PD	PR	
		CYCLE 12 RESPONSE EVALUATION	20-Jul-20	NON-PD	PR	
		CYCLE 15 RESPONSE EVALUATION	15-Oct-20	NON-PD	PR	
		CYCLE 18 RESPONSE EVALUATION	4-Jan-21	NON-PD	PR	
		CYCLE 21 RESPONSE EVALUATION	27-Mar-21	NON-PD	PR	
		CYCLE 24 RESPONSE EVALUATION	21-Jun-21	NON-PD	PR	
		LONG-TERM FOLLOW-UP WEEK 24	14-Dec-21	NON-PD	PR	
		LONG-TERM FOLLOW-UP WEEK 48	9-May-22	NON-PD	PR	
4801-003	O	CYCLE 3 RESPONSE EVALUATION	1-Dec-20	NON-PD	SD	SD
6109-002	O	UNSCHEDULED 20201.02	29-Jan-19	NON-PD	SD	SD
8603-001	ZO	CYCLE 3 RESPONSE EVALUATION	30-Jul-20	NON-PD	SD	SD

Eighteen patients achieved a BOR of partial response or complete response per ICR with < 50% reduction in SPD (sum of the products of diameters). All patients had FDG-avid lymphoma and were followed by PET-CT/CT according to the protocol schedule of assessment. The 18 patients had PET-based BOR assessments of partial metabolic response (17 patients) or complete metabolic response (1 patient). For the same time points, CT-based assessments were stable disease (14 patients) and disease progression (4 patients). Per the ICR Charter v2.0, the overall response will default to the PET radiographic response with integrated clinical finding, leading to the BOR as partial response.

There were 18 cases in which the IRC assessed that a complete or partial response had occurred based on the Lugano PET-based criteria, but this assessment would have been discrepant compared to the Lugano CT-based criteria. In this setting, overall response defaulted to the PET-based criteria per the IRC charter, as these PET criteria have been shown to be more predictive of true response.

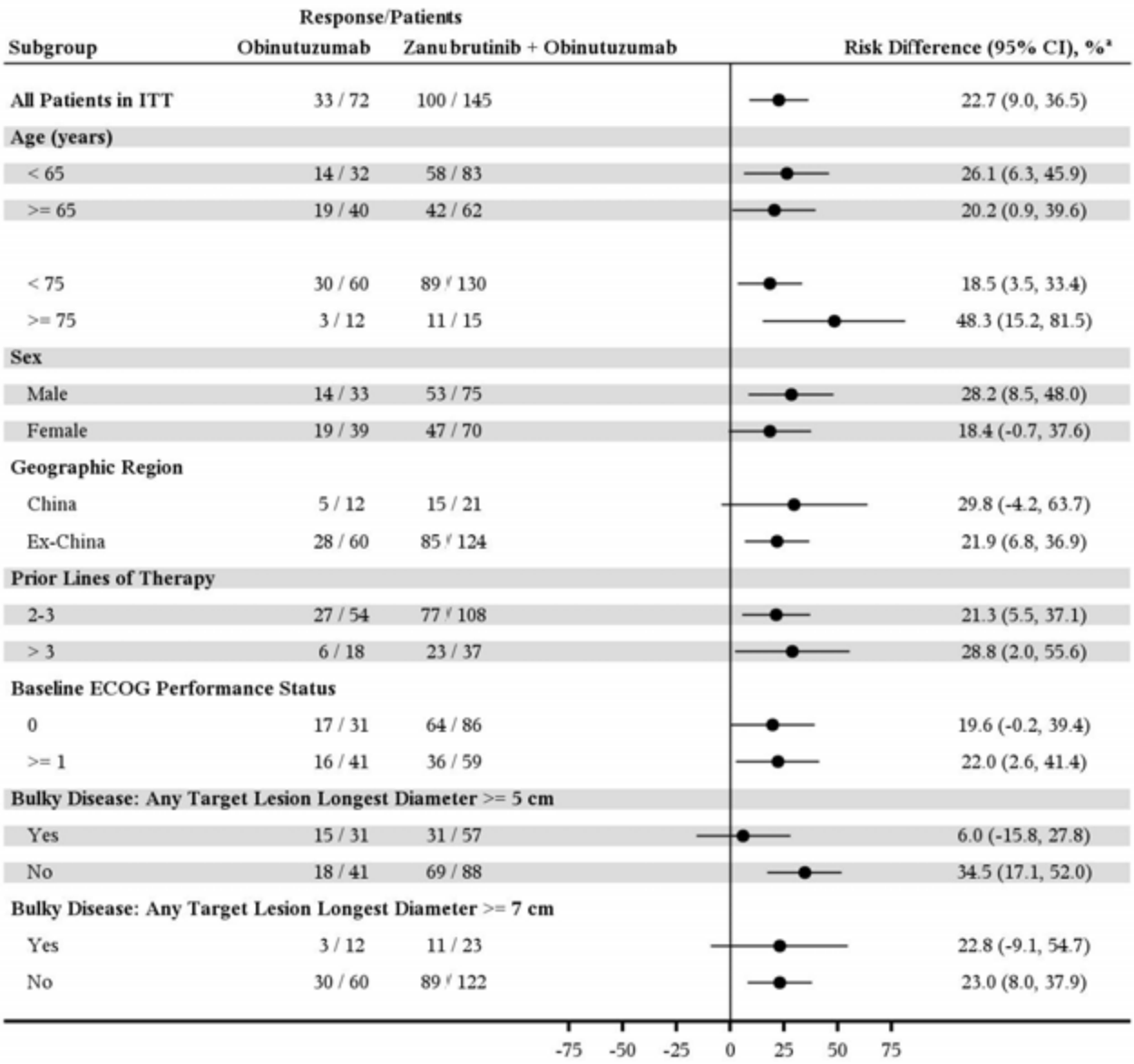
These cases occurred in a 2:1 ratio between the zanubrutinib + obinutuzumab arm and the obinutuzumab monotherapy arms (12 cases and 6 cases, respectively). In 15 of these cases, the discrepancy occurred in the first restaging at Cycle 3. Two cases occurred at the second restaging of Cycle 6, and one occurred late in treatment on an unscheduled scan on Day 312.

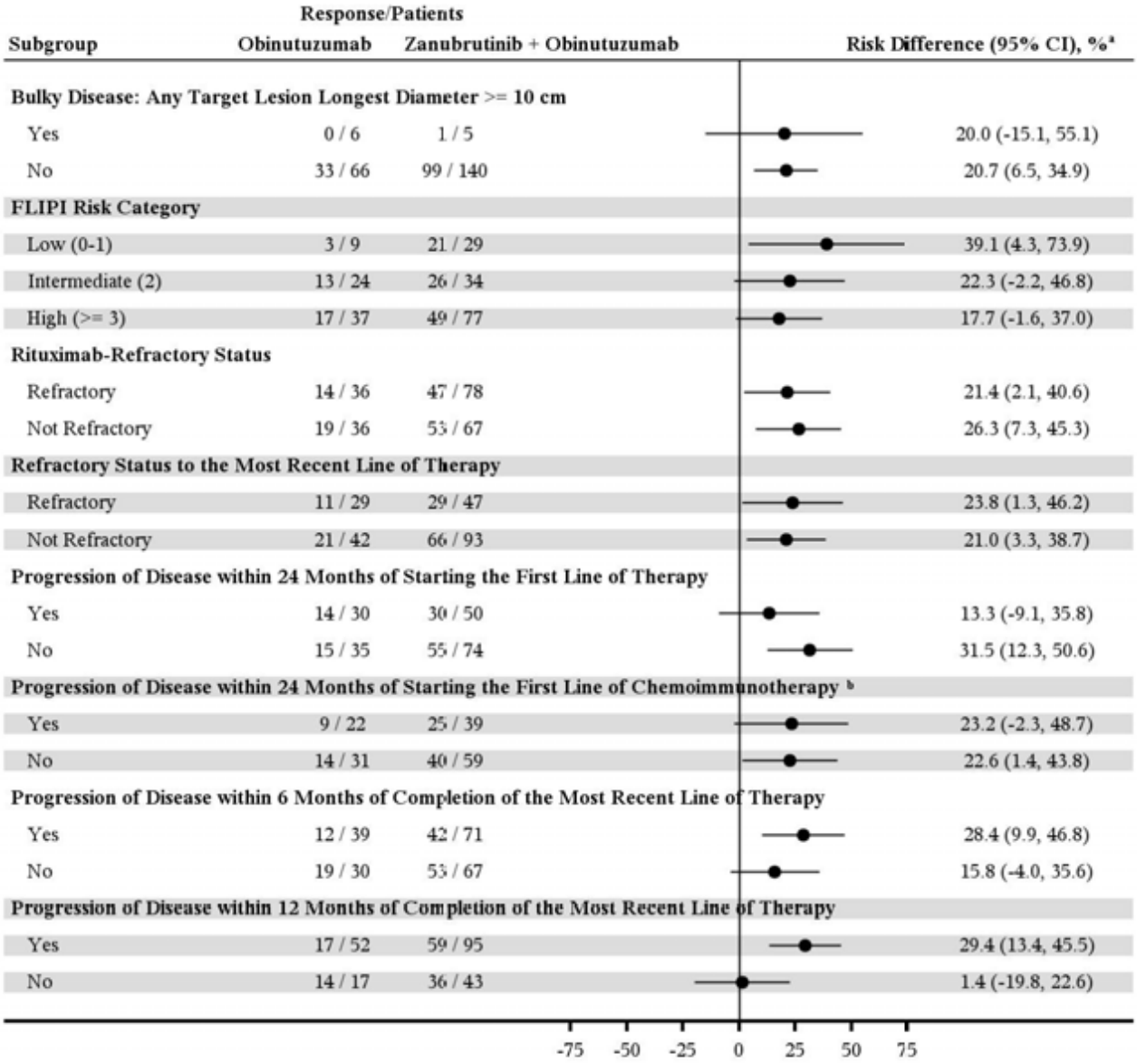
In the majority of cases (12 of 18), PET-based assessment demonstrated CMR or PMR due to decrease in standardized uptake values, and there was concurrent lesion shrinkage. However, the degree of shrinkage was insufficient to qualify for the equivalent CT-based response. In 10 of these cases, PET-based responses showed PMR, but the decrease in lesion sizes was less than 50% (CT-based SD). In one case, PET-based response showed CMR, but the lesions regressed less than 50% (CT-based SD). In one case, PET-based assessment showed PMR based on drop in standardized uptake value, but there was a slight 1% enlargement of SPD (CT-based SD).

In two cases, PET-based assessment showed PMR, but lesions enlarged with change of SPD less than +50% (CT- based SD). In one of these cases, SPD decreased from baseline in the subsequent re-imaging. In the other case, SPD continued to increase in the subsequent scan.

In three of the remaining cases, PET-based assessment was PMR, with CT-based PD based on growth of lesions. In two of these cases, CT-based PD was assessed by the growth of a lesion with increase of SPD > 50%. In one case, PET-based response was PMR, but CT showed a mixed response with shrinkage and growth of different lesions. However, there was new splenomegaly consistent with PD.

Figure 18: Forest Plot of Overall Response Rate by Independent Central Review (ITT Analysis Set)


Response/Patients
Subgroup
Obinutuzumab
Zanubrutinib + Obinutuzumab
Risk Difference (95% CI), %[a]
All Patients in ITT 33 / 72 100 / 145 22.7 (9.0, 36.5)
Age (years)
< 65 14 / 32 58 / 83 26.1 (6.3, 45.9)
>= 65 19 / 40 42 / 62 20.2 (0.9, 39.6)
< 75 30 / 60 89 / 130 18.5 (3.5, 33.4)
>= 75 3 / 12 11 / 15 48.3 (15.2, 81.5)
Sex
Male 14 / 33 53 / 75 28.2 (8.5, 48.0)
Female 19 / 39 47 / 70 18.4 (-0.7, 37.6)
Geographic Region
China 5 / 12 15 / 21 29.8 (-4.2, 63.7)
Ex-China 28 / 60 85 / 124 21.9 (6.8, 36.9)
Prior Lines of Therapy
2-3 27 / 54 77 / 108 21.3 (5.5, 37.1)
> 3 6 / 18 23 / 37 28.8 (2.0, 55.6)
Baseline ECOG Performance Status
0 17 / 31 64 / 86 19.6 (-0.2, 39.4)
>= 1 16 / 41 36 / 59 22.0 (2.6, 41.4)
Bulky Disease: Any Target Lesion Longest Diameter >= 5 cm
Yes 15 / 31 31 / 57 6.0 (-15.8, 27.8)
No 18 / 41 69 / 88 34.5 (17.1, 52.0)
Bulky Disease: Any Target Lesion Longest Diameter >= 7 cm
Yes 3 / 12 11 / 23 22.8 (-9.1, 54.7)
No 30 / 60 89 / 122 23.0 (8.0, 37.9)
-75 -50 -25 0 25 50 75



Data cutoff: 25JUN2022.

a Mantel-Haenszel common risk difference was estimated, along with its 95% CI constructed by a normal approximation and Sato's variance estimator.

b The first line of chemoimmunotherapy includes i) rituximab or obinutuzumab, AND ii) pre-specified chemotherapy.

Analysis of 'All Patients in ITT' is stratified as in the primary disease response analysis. Analysis of all other subgroups are unstratified.

The MAH has provided subgroup analyses and a multivariate logistic regression analysis to support the efficacy findings despite the imbalances observed between treatment arms (more older patients and more patients with poorer performance status (ECOG 1) in arm B). In the multivariate logistic regression analysis performed to explore the relationship between the baseline prognostic factors (no exact details given); neither age nor ECOG performance status (0 vs ≥ 1) turned out to be significant. It seems that the combination therapy was more efficacious than monotherapy also in patients with older age and higher ECOG performance (subgroup analysis of disease response) despite these imbalances. However, due to the imbalances highlighted, this finding needs to be interpreted with caution.

Table 20: Study BGB-3111-212: Disease Response by Investigator (ITT Analysis Set)

Response Category	Zanubrutinib + Obinutuzumab (N = 145) n (%)	Obinutuzumab (N = 72) n (%)
Best Overall Response, n (%)		
Complete Response	43 (29.7)	14 (19.4)
Partial Response	56 (38.6)	17 (23.6)
Stable Disease	20 (13.8)	14 (19.4)
Progressive Disease	20 (13.8)	22 (30.6)
Discontinued Prior to First Tumor Assessment/Not Evaluable	6 (4.1)	5 (6.9)
Overall Response Rate, n (%)	99 (68.3)	31 (43.1)
(95% CI) [a]	(60.0, 75.7)	(31.4, 55.3)
Risk Difference, % (95% CI) [b]	24.9 (11.2, 38.5)	
2-sided p-value [c]	0.0004	

Abbreviations: CI, confidence interval; IRT, interactive response technology.
[a] The 95% CI was estimated using the Clopper-Pearson method.
[b] Mantel-Haenszel common risk difference was estimated, along with its 95% CI constructed by a normal approximation and Sato's variance estimator, stratified by rituximab-refractory status, number of prior lines of therapy, and geographic region per IRT.
[c] The p-value was obtained using the Cochran-Mantel-Haenszel method stratified by rituximab-refractory status, number of prior lines of therapy, and geographic region per IRT.

Concordance

Table 21: Concordance of Best Overall Response by Independent Central Review and Investigator (Intent-to-Treat Analysis Set)

	Overall Response by Independent Central Review								
	Zanubrutinib + Obinutuzumab (N = 145)			Obinutuzumab (N = 72)			Total (N = 217)		
	Responder	Non-Responder	Total	Responder	Non-Responder	Total	Responder	Non-Responder	Total
Overall Response by Investigator									
Responder	92	7	99	26	5	31	118	12	130
Non-Responder	8	38	46	7	34	41	15	72	87
Total	100	45	145	33	39	72	133	84	217
Overall Response			130/145			60/72			190/217
Concordance Rate [a]			(89.7%)			(83.3%)			(87.6%)

Source: ADSL, ADRS, ADRSIRC. Data cutoff: 25JUN2022. Data extraction: 12SEP2022.
Overall response is defined as the proportion of patients who achieved a best overall response of PR or better.
[a] Concordance rate is defined as the proportion of patients with the same overall response based on both assessments.

For patients who achieved an overall response of CR or PR, the concordance rates were 89.7% (130 of 145 patients) for the ZO arm and 83.3% (60 of 72 patients) for to O arm. The concordance rate of overall response of CR or PR for the total population was 87.6% (190 of 217 patients).

*Table 22: **Duration of Response by Independent Central Review (ITT Analysis Set)***

	Obinutuzumab (N = 72)	Zanubrutinib + Obinutuzumab (N = 145)
Duration of Response (DOR)		
Number of Responders	33	100
Events, n (%)	18 (54.5)	29 (29.0)
Progressive Disease	15 (45.5)	23 (23.0)
Death	3 (9.1)	6 (6.0)
Censored, n (%)	15 (45.5)	71 (71.0)
No documented progressive disease/death	9 (27.3)	57 (57.0)
No documented progressive disease/death: Non-protocol anticancer therapy	1 (3.0)	10 (10.0)
No documented progressive disease/death: Withdrew consent/lost to follow-up	0 (0.0)	3 (3.0)
Progressive disease/death after missing ≥ 2 consecutive planned disease assessments	0 (0.0)	1 (1.0)
Crossover to combination treatment	5 (15.2)	0 (0.0)
Follow-up Time (Months)		
Median (95% CI) [a]	23.3 (14.4, 32.7)	16.9 (13.9, 19.4)
(Min, Max)	(0.0, 32.7)	(0.0, 41.2)
Duration of Response (Months) [b]		
Median (95% CI)	14.0 (9.2, 25.1)	NE (25.3, NE)
Q1 (95% CI)	9.0 (2.7, 12.0)	11.5 (5.6, 25.3)
Q3 (95% CI)	26.5 (16.5, NE)	NE (NE, NE)
DOR Rate at, % (95% CI) [c]		
12 months	55.1 (34.4, 71.6)	72.8 (62.1, 80.9)
18 months	41.9 (22.6, 60.1)	69.3 (57.8, 78.2)
24 months	35.9 (17.2, 55.2)	69.3 (57.8, 78.2)
30 months	18.0 (3.7, 41.0)	55.3 (37.5, 69.9)
36 months	NE (NE, NE)	55.3 (37.5, 69.9)

Source: ADSL, ADTTEIRC. Data cutoff: 25JUN2022. Data extraction: 12SEP2022.
Abbreviation: NE, not evaluable.
[a] Median follow-up time was estimated by the reverse Kaplan-Meier method.
[b] Medians and other quartiles of duration of response were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
[c] DOR rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
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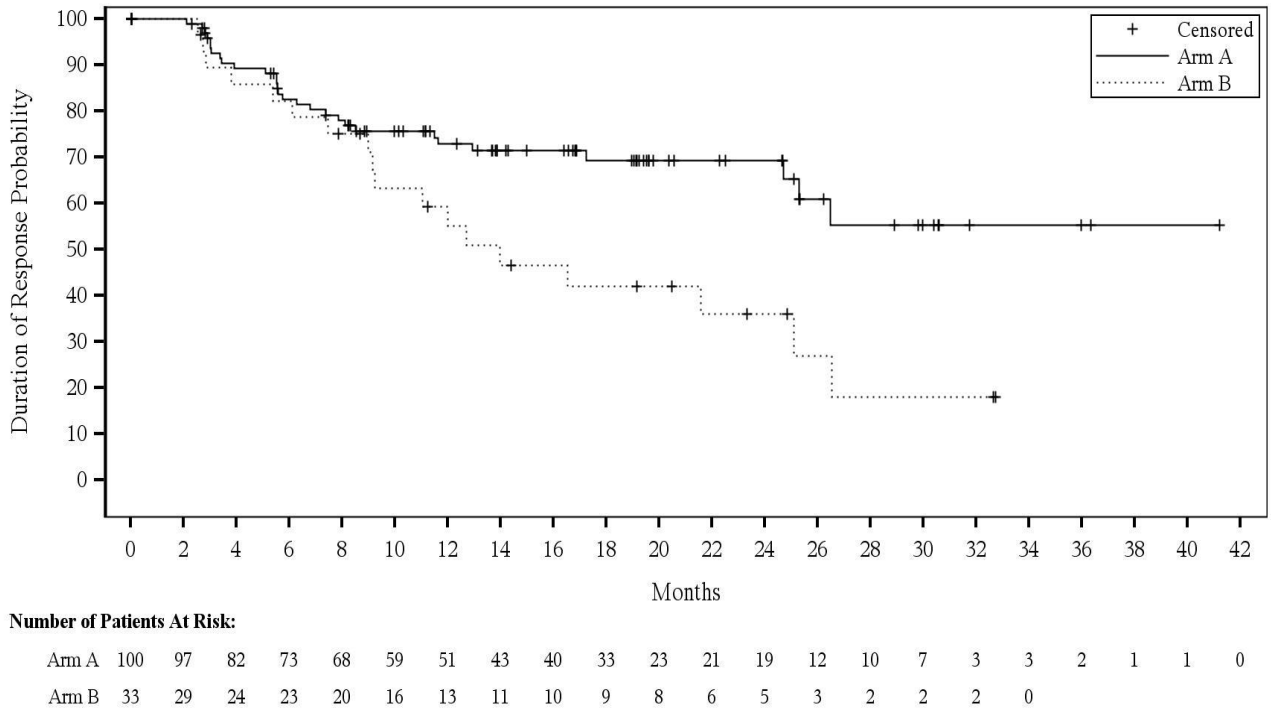
Figure 19: Kaplan-Meier Plot of Duration of Overall Response by Independent Central Review (Intent-to-Treat Analysis Set)



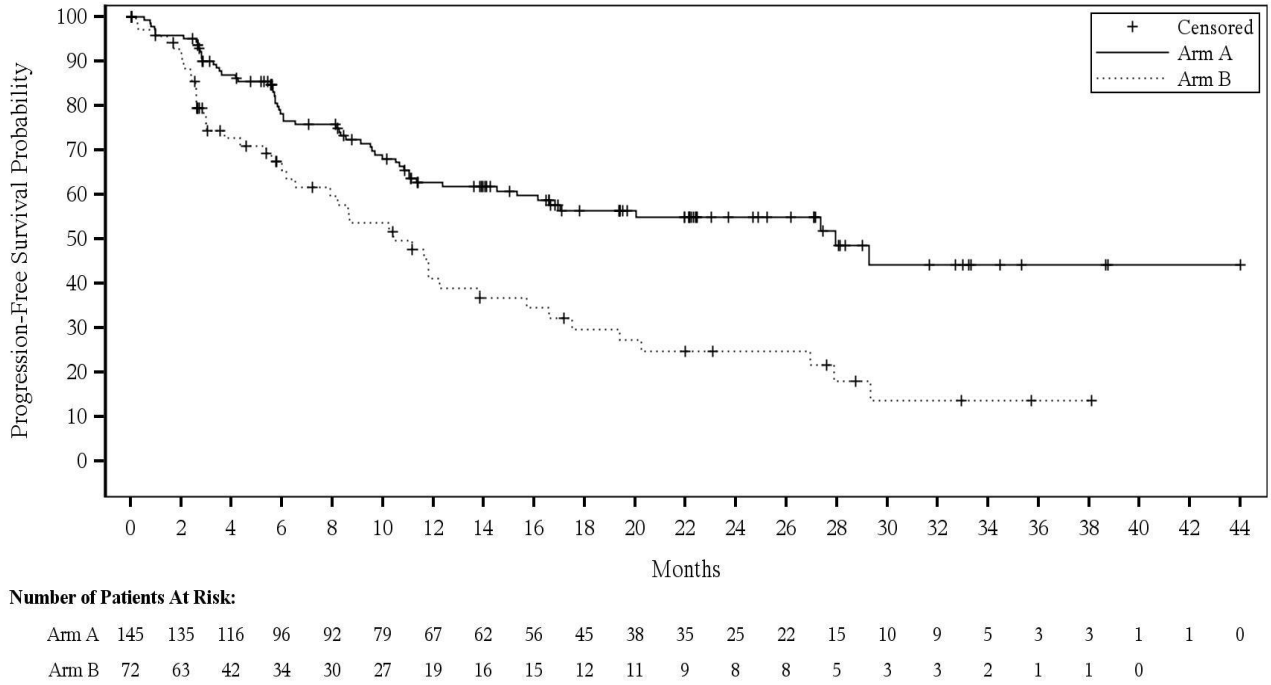
Source: ADSL, ADTTEIRC. Data cutoff: 25JUN2022. Data extraction: 12SEP2022.
Arm A, Zanubrutinib + Obinutuzumab; Arm B, Obinutuzumab.

Table 23: ***Progression-Free Survival by Independent Central Review (ITT Analysis Set)***

	Obinutuzumab (N = 72)	Zanubrutinib + Obinutuzumab (N = 145)
Progression-free Survival (PFS)		
Events, n (%)	44 (61.1)	57 (39.3)
Progressive Disease	37 (51.4)	48 (33.1)
Death	7 (9.7)	9 (6.2)
Censored, n (%)	28 (38.9)	88 (60.7)
No documented progressive disease/death	10 (13.9)	61 (42.1)
No documented progressive disease/death: Non-protocol anticancer therapy	3 (4.2)	17 (11.7)
No documented progressive disease/death: Withdrew consent/lost to follow-up	2 (2.8)	5 (3.4)
No baseline/post-baseline assessment	3 (4.2)	3 (2.1)
Progressive disease/death after missing ≥ 2 consecutive planned disease assessments	0 (0.0)	2 (1.4)
Crossover to combination treatment	10 (13.9)	0 (0.0)
Follow-up Time (Months)		
Median (95% CI) [a]	23.1 (11.2, 32.9)	19.4 (16.7, 22.2)
(Min, Max)	(0.0, 38.1)	(0.0, 44.0)
Hazard Ratio (95% CI) [b]		0.50 (0.33, 0.75)
2-sided p-value [c]		0.0007
Progression-free Survival (Months) [d]		
Median (95% CI)	10.4 (6.5, 13.8)	28.0 (16.1, NE)
Q1 (95% CI)	3.0 (2.4, 6.2)	8.1 (5.7, 10.5)
Q3 (95% CI)	20.2 (13.8, NE)	NE (NE, NE)
PFS Rate at, % (95% CI) [e]		
12 months	41.0 (27.8, 53.8)	62.8 (53.6, 70.6)
18 months	29.7 (17.6, 42.7)	56.3 (46.7, 64.8)
24 months	24.7 (13.5, 37.7)	54.8 (45.1, 63.6)
30 months	13.5 (4.5, 27.5)	44.1 (30.5, 56.9)
36 months	13.5 (4.5, 27.5)	44.1 (30.5, 56.9)

Source: ADSL, ADTTEIRC. Data cutoff: 25JUN2022. Data extraction: 12SEP2022.
Abbreviation: NE, not evaluable.
[a] Median follow-up time was estimated by the reverse Kaplan-Meier method.
[b] The hazard ratio and its 2-sided 95% CI was estimated from a stratified Cox regression model stratified by rituximab-refractory status, number of prior lines of therapy and geographic region per IRT.
[c] The p-value was obtained using a log-rank test stratified by rituximab-refractory status, number of prior lines of therapy and geographic region per IRT.
[d] Medians and other quartiles of progression-free survival were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
[e] PFS rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
/bgb_3111/bgb_3111_212/csr_20220625_fup_12m/dev/pgm/tlfs/t-ef-pfs-i.sas 20OCT2022 12:10 t-14-2-1-3-1-1-ef-pfs-irc-itt-i.rtf

Figure 20:Kaplan-Meier Plot of Progression-Free Survival by ICR (Intent-to-Treat Analysis Set)



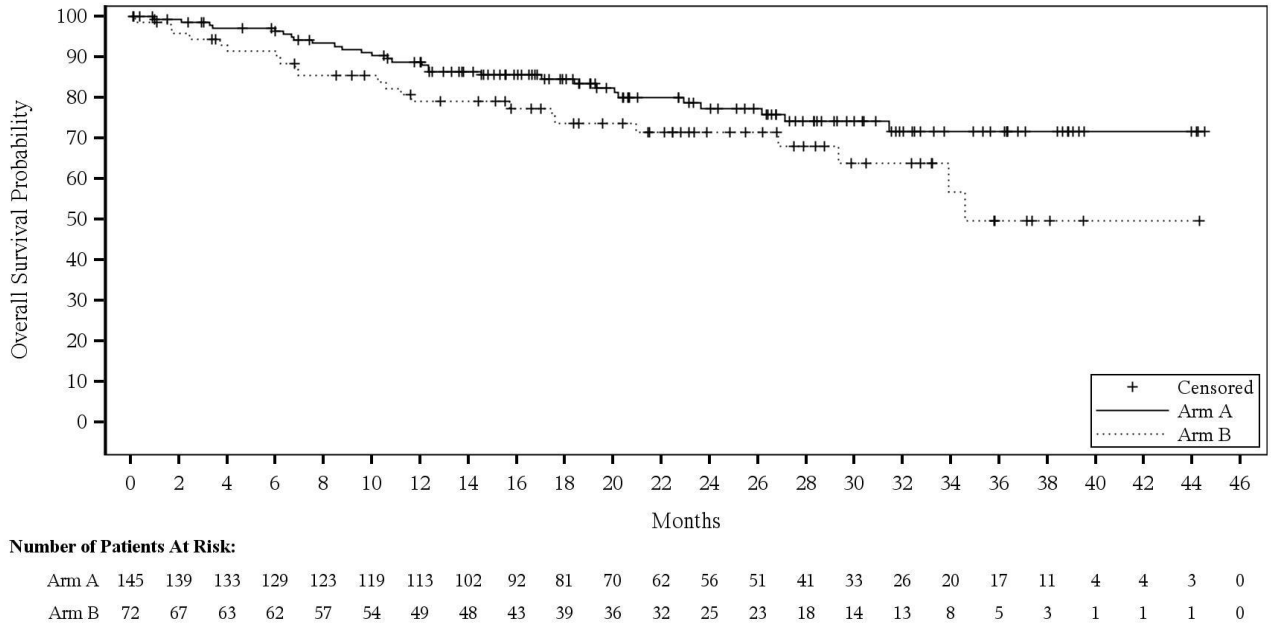
Source: ADSL, ADTTEIRC. Data cutoff: 25JUN2022. Data extraction: 12SEP2022.
Arm A, Zanubrutinib + Obinutuzumab; Arm B, Obinutuzumab.

Table 24: Overall Survival (ITT Analysis Set)

	Zanubrutinib + Obinutuzumab (N = 145)	**Obinutuzumab (N = 72)**
Overall Survival (OS)		
Events (Death), n (%)	29 (20.0)	22 (30.6)
Censored (Alive), n (%)	116 (80.0)	50 (69.4)
Hazard Ratio (95% CI) [a]	0.62 (0.35, 1.07)	
2-sided p-value [b]	0.0845	
OS (Months) [c]		
Median (95% CI)	NE (NE, NE)	34.6 (29.3, NE)
OS Rate at, % (95% CI) [d]		
12 months	88.8 (82.1, 93.1)	79.1 (67.2, 87.0)
18 months	84.6 (77.1, 89.8)	73.5 (60.7, 82.7)
24 months	77.3 (68.0, 84.2)	71.4 (58.3, 81.1)

Abbreviations: CI, confidence interval; IRT, interactive response technology; NE, not evaluable; OS, overall survival.
[a] The hazard ratio and its 2-sided 95% CI was estimated from a stratified Cox regression model stratified by rituximab-refractory status, number of prior lines of therapy and geographic region per IRT.
[b] The p-value was obtained using a log-rank test stratified by rituximab-refractory status, number of prior lines of therapy and geographic region per IRT.
[c] Medians of overall survival were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
[d] OS rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.

Figure 21: Kaplan-Meier Plot of Overall Survival (ITT Analysis Set)



Data cutoff: 25JUN2022
Arm A, Zanubrutinib + Obinutuzumab; Arm B, Obinutuzumab.

Complete Response Rate

The CR rate as assessed by independent central review was 39.3% (95% CI: 31.3, 47.8) in arm ZO and 19.4% (95% CI: 11.1, 30.5) in arm O (Table 14.2.1.5.1 of the BGB-3111-212 Clinical Study Report). The 2-sided p-value was 0.0035.

The CR rate as assessed by the investigator was 29.7% (95% CI: 22.4, 37.8) in arm ZO and 19.4% (95% CI: 11.1, 30.5) in the obinutuzumab monotherapy arm (Table 14.2.1.5.2 of the BGB-3111-212 Clinical Study Report). The 2-sided p-value was 0.1401.

Time to Response

Time to response was defined as the time from randomization to the time of the earliest qualifying response (CR or PR) until the data cut-off date, the start of a new anticancer therapy, or the crossover date for patients who crossed over to receive combination therapy.

As assessed by independent central review, 100 of 145 patients in the combination arm and 33 of 72 patients in the obinutuzumab monotherapy arm reported a PR or CR as their best response. The median time to first response was 2.83 months in both arms, with a range of 2.0 to 23.0 months in the combination arm and a range of 2.5 to 6.5 months in the obinutuzumab monotherapy arm.

As assessed by the investigator, 99 of 145 patients in the combination arm and 31 of 72 patients in the obinutuzumab monotherapy arm reported a PR or CR as their best response. For these patients, the median time to first response was the same in both arms and similar to what was reported by independent central review assessment: 2.83 months, with a range of 2.0 to 19.7 months in the combination arm and a range of 2.5 to 16.6 months in the obinutuzumab monotherapy arm.

Table 25: Time to Response by Independent Central Review (ITT Analysis Set)

	Zanubrutinib + Obinutuzumab (N = 145)	**Obinutuzumab (N = 72)**
Time to First Response (Months)		
n	100	33
Mean (SD)	3.70 (2.722)	3.33 (1.160)
Median	2.83	2.83
Q1, Q3	2.69, 3.24	2.63, 3.15
Min, Max	2.0, 23.0	2.5, 6.5

Data cutoff: 25JUN2022.
Time to response is defined as the time from the randomization date to the date of the earliest qualifying response (complete response or partial response) until the data cut-off date, the start of a new anticancer therapy, or the crossover date for patients in Arm B who cross over to Arm A.

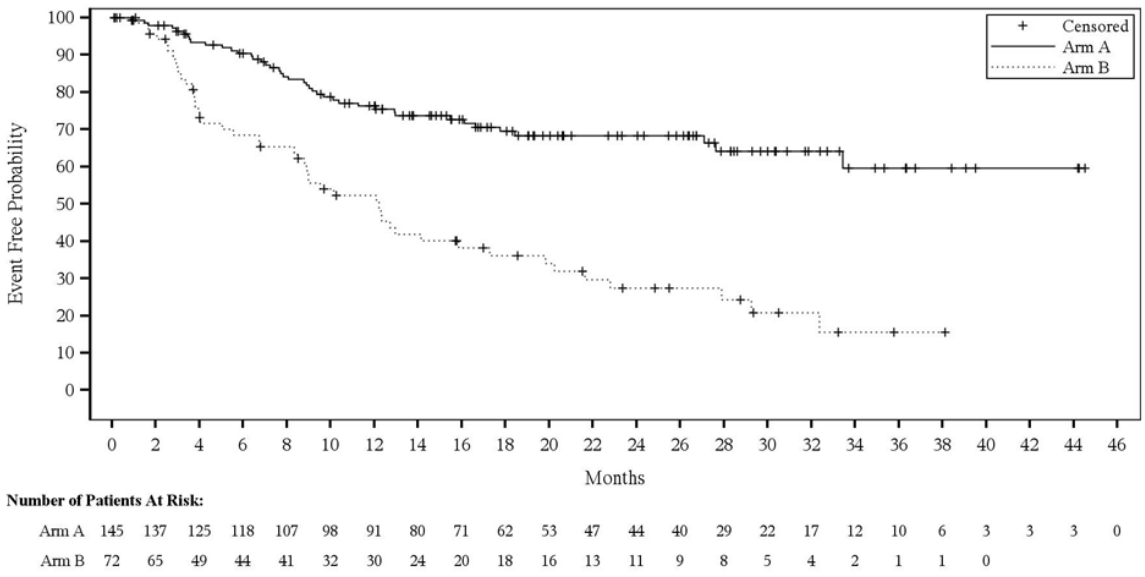
Time to next line of treatment

Table 26: Time to New Anticancer Therapy or Crossover (ITT Analysis Set)

	Obinutuzumab (N = 72)	**Zanubrutinib + Obinutuzumab (N = 145)**
Time to New Anticancer Therapy/Crossover		
Events, n (%)	47 (65.3)	42 (29.0)
New Anticancer Therapy	12 (16.7)	42 (29.0)
Crossover to Combination Treatment	35 (48.6)	NA
Censored, n (%)	25 (34.7)	103 (71.0)
Hazard Ratio (95% CI) [a]		0.34 (0.22, 0.52)
2-sided p-value [b]		<.0001
Time to New Anticancer/Crossover (Months) [c]		
Median (95% CI)	12.2 (8.5, 17.3)	NE (33.4, NE)
Event-Free Rate at, % (95% CI) [d]		
12 months	52.3 (39.4, 63.6)	76.3 (68.0, 82.7)
18 months	36.2 (24.2, 48.2)	69.5 (60.4, 76.9)
24 months	27.4 (16.3, 39.6)	68.3 (59.1, 75.9)
30 months	20.8 (10.3, 33.8)	64.2 (53.6, 72.9)
36 months	15.6 (5.7, 30.1)	59.6 (46.0, 70.8)

Abbreviation: NA, not applicable.
[a] The hazard ratio and its 2-sided 95% CI was estimated from a stratified Cox regression model stratified by rituximab-refractory status, number of prior lines of therapy and geographic region per IRT.
[b] The p-value was obtained using a log-rank test stratified by rituximab-refractory status, number of prior lines of therapy and geographic region per IRT.
[c] Medians time to anticancer/crossover was estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
[d] Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.

Figure 22: Kaplan-Meier Plot of Time to New Anticancer Therapy or Crossover (ITT Analysis Set)



Patient-Reported Outcomes

Compliance rates for the EORTC QLQ-C30 questionnaire in the combination arm were 87% at Week 12 and 85% in Week 24 and in the obinutuzumab monotherapy arm were 80% at Week 12 and 87% in Week 24 (Table 14.2.1.8.2 of the BGB-3111-212 Clinical Study Report). For the EQ-5D-5L questionnaire, the compliance rates in the combination arm were 87% in Week 12 and 84% in Week 24, and in the obinutuzumab monotherapy arm were 81% in Week 12 and 87% in Week 24.

EORTC QLQ-C30

Results of the descriptive analyses, mean changes (standard deviation), from baseline to Week 24, showed that patients in the combination arm had better overall outcomes in symptoms of pain, fatigue, and role functioning compared with patients in the obinutuzumab monotherapy arm. In both arms, symptoms of nausea/vomiting and diarrhoea and physical functioning were maintained (remained stable). While the global health status (GHS) endpoint showed more improvement at Week 12, it maintained (remained stable) in the combination arm and showed higher improvement in the obinutuzumab monotherapy arm by Week 24.

The mean changes (standard deviation [SD]) from baseline to Week 12 and Week 24 for these key endpoints are summarized below:

- GHS/Quality of Life (QoL): At Week 12, 4.023 (16.2440) for the combination arm and -2.222 (16.9856) for the obinutuzumab monotherapy arm. At Week 24, 2.577 (17.3623) for the combination arm and 4.955 (15.1458) for the obinutuzumab monotherapy arm.

- Physical function: At Week 12, 0.361 (13.8192) for the combination arm and -1.449 (13.2526) for the obinutuzumab monotherapy arm. At Week 24, 0.412 (11.4186) for the combination arm and 0.270 (10.2553) for the obinutuzumab monotherapy arm.

- Role function: At Week 12, 2.730 (22.9412) for the combination arm and 1.812 (25.6347) for the obinutuzumab monotherapy arm. At Week 24, 3.093 (17.4022) for the combination arm and -0.901 (21.1352) for the obinutuzumab monotherapy arm.

- Fatigue: At Week 12, -1.947 (19.5647) for the combination arm and 2.657 (19.3424) for the obinutuzumab monotherapy arm. At Week 24, -2.291 (18.4911) for the combination arm and -0.150 (15.0722) for the obinutuzumab monotherapy arm.

- Nausea/Vomiting: At Week 12, -0.855 (10.9085) for the combination arm and 1.812 (7.2250) for the obinutuzumab monotherapy arm. At Week 24, -1.031 (8.9412) for the combination arm and 0.450 (4.7895) for the obinutuzumab monotherapy arm.

- Diarrhoea: At Week 12, 2.609 (19.3197) for the combination arm and 0.758 (25.4049) for the obinutuzumab monotherapy arm. At Week 24, 0.000 (20.4124) for the combination arm and 0.901 (16.6416) for the obinutuzumab monotherapy arm.

- Pain: At Week 12, -1.580 (22.9448) for the combination arm and 1.087 (21.1993) for the obinutuzumab monotherapy arm. At Week 24, -4.983 (16.3450) for the combination arm and -1.351 (23.0332) for the obinutuzumab monotherapy arm.

The results of the mixed model for repeated measure (MMRM) analyses are presented in Table 14.2.1.8.1 of the BGB-3111-212 Clinical Study Report. The results showed better improvements in patients in the combination arm for pain, fatigue, and role functioning by Week 24; observable improvements for GHS were shown at Week 12 only. The LS mean differences (standard error, [95% CI]) at Week 12 and Week 24 for key endpoints are as follows:

- GHS/QoL: Week 12, 6.4 (2.95, [95% CI: 0.6, 12.3]); Week 24, -0.3 (3.18, [95% CI: -6.5, 6.0])

- Physical function: Week 12, 2.2 (2.20, [95% CI: -2.1, 6.5]); Week 24, 0.8 (2.35, [95% CI: -3.8, 5.5])

- Role function: Week 12, 0.7 (3.72, [95% CI: -6.6, 8.1]); Week 24, 5.6 (4.02, [95% CI: -2.3, 13.5])

- Fatigue: Week 12, -4.6 (3.28, [95% CI: -11.1, 1.9]); Week 24, -4.7 (3.50, [95% CI: -11.6, 2.2])

- Nausea/vomiting: Week 12, -2.8 (1.58, [95% CI: -5.9, 0.3]); Week 24, -1.8 (1.69, [95% CI: -5.2, 1.5])

- Diarrhoea: Week 12, 1.6 (3.62, [95% CI: -5.5, 8.8]); Week 24, 0.5 (3.86, [95% CI: -7.1, 8.1])

- Pain: Week 12, -2.0 (3.65, [95% CI: -9.2, 5.2]); Week 24, -4.9 (3.91, [95% CI: -12.6, 2.8])

EQ-5D-5L

A summary of EQ-5D-5L and changes from baseline is summarized in Table 14.2.1.8.3 of the BGB-3111-212 Clinical Study Report. At Week 12, the mean (SD) changes from baseline in visual analogue (VS) scores were 2.4 (16.71) for the combination arm and -0.3 (14.96) for the obinutuzumab monotherapy arm. At Week 24, the mean (SD) changes from baseline in VS scores were 3.1 (15.95) for the combination arm and 2.0 (14.17) for the obinutuzumab monotherapy arm.

Ancillary analyses

NA

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for trial BGB-3111-212

Title: **An International, Phase 2, Open-Label, Randomized Study of BGB-3111 Combined With Obinutuzumab Compared With Obinutuzumab Monotherapy in Relapsed/Refractory Follicular Lymphoma**		
Study identifier	BGB-3111-212 (ROSEWOOD) EudraCT: 2017-001552-54 ClinicalTrials.gov: NCT03332017	
Design	BGB-3111-212 is an ongoing international, phase 2, open-label, randomized, active-control study of zanubrutinib plus obinutuzumab versus obinutuzumab monotherapy in patients with relapsed/refractory follicular lymphoma (FL). Central randomization (2:1) was used to assign patients to one of the following treatment arms: • Arm A: zanubrutinib + obinutuzumab • Arm B: obinutuzumab monotherapy Randomization was stratified by the number of prior lines of therapy (2 to 3 versus > 3), rituximab-refractory status (yes versus no), and geographic region (China versus ex-China).	
	Duration of main phase:	Patients received daily treatment with zanubrutinib until disease progression, intolerance or death, withdrawal of consent, loss to follow-up, or study termination by sponsor. Responding patients may have continued to receive maintenance obinutuzumab for a maximum total duration of approximately 30 months.
	Duration of Run-in phase:	Initial screening phase (up to 35 days) Study treatment must have commenced within 5 days after randomisation
	Duration of Extension phase:	N/A
Hypothesis	Comparing the overall response rates in the combination arm and the obinutuzumab monotherapy arm	
Treatments groups	Arm A (or arm ZO)	Zanubrutinib was administered as two 80-mg capsules orally twice a day (160 mg twice a day). Treatment duration until progressive disease or unacceptable toxicity Obinutuzumab (1000 mg) was administered intravenously on Days 1, 8, and 15 of Cycle 1; on Day 1 of Cycles 2 to 6; and then every 8 weeks for an additional 24 months.
	Arm B (or arm O)	Obinutuzumab (1000 mg) was administered intravenously on Days 1, 8, and 15 of Cycle 1; on Day 1 of Cycles 2 to 6; and then every 8 weeks for an additional 24 months.

Endpoints and definitions	Primary endpoint	ORR rate by ICR	ORR as determined by ICR using the Lugano Classification for NHL
	Secondary endpoint	ORR rate by IA	ORR as determined by investigator assessment
	Secondary endpoint	DOR	DOR as determined by ICR and by investigator assessment
	Secondary endpoint	PFS	PFS as determined by ICR and by investigator assessment
	Secondary endpoint	OS	Overall survival
	Secondary endpoint	CRR or CMR	Rate of CR or complete metabolic response as determined by ICR and by investigator assessment
	Secondary endpoint	TTR	TTR as determined by ICR and by investigator assessment
First dose given Database lock	14 November 2017 25 June 2022 data cut-off date		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	The ITT Analysis Set includes all patients randomized to a treatment arm. Time point: Data cut-off 25 June 2022. Study follow-up: Arm ZO: Median 20.21 months (range: 0.1 to 46.6 months) Arm O: Median 20.40 months (range: 0.1 to 46.2 months)		
Descriptive statistics and estimate variability	Treatment group	Arm A (ZO)	Arm B (O)
	Number of subjects	145 patients randomised	72 patients randomised
	primary endpoint ORR rate by ICR n (%)	100 (69.0)	33 (45.8)
	95% CI	(60.8, 76.4)	(34.0, 58.0)
	ORR rate by IA n (%)	99 (68.3)	31 (43.1)
	95% CI	(60.0, 75.7)	(31.4, 55.3)
	DOR months by ICR median (95% CI)	NE (25.3, NE)	14.0 (9.2, 25.1)
	PFS by ICR, months, Median (95% CI)	28.0 (16.1, NE)	10.4 (6.5, 13.8)
	PFS by IA, months, Median (95% CI)	16.3 months (11.0, 27.4)	5.8 (3.7, 7.9)
	OS by ICR, months, Median (95% CI)	NE (NE, NE)	34.6 (29.3, NE)
	CRR by ICR, n, (%), (95% CI)	57 (39.3%) (31.3, 47.8)	14 (19.4%) (11.1, 30.5)
	TTR, months, median, range	2.83 (2.0, 23.0)	2.83 (2.5, 6.5)
	ORR by ICR	Comparison groups	ZO vs. O

Effect estimate per comparison		ORR risk difference, %	22.7
		95% CI	9.0, 36.0
		p-value (CMH)	0.0012
	PFS by ICR	Comparison groups	ZO vs. O
		Hazard ratio	0.50
		95% CI	0.33, 0.75
		P-value (log-rank test)	0.0007
	PFS by INV	Comparison groups	ZO vs. O
		Hazard ratio	0.50
		95% CI	0.35, 0.71
		P-value (log-rank test)	<0.0001
	OS	Comparison groups	ZO vs. O
		Hazard ratio	0.62
		95% CI	0.35, 1.07
		P-value (log-rank test)	0.0845

Supportive studies

Summary of supportive efficacy data.

Table 27: Analysis of Disease Response in Zanubrutinib Clinical Studies (FL Efficacy Analysis Set)

	BGB-3111-212 by ICR		BGB-3111-GA101	BGB-3111-AU-003	BGB-3111-1002
Response Category	**Zanubrutinib + Obinutuzumab (N = 145)**	**Obinutuzumab (N = 72)**	**Zanubrutinib + Obinutuzumab (N = 24)**	**Zanubrutinib (N = 26)**	**Zanubrutinib (N = 23)**
Best Overall Response, n (%)					
Complete Response	57 (39.3)	14 (19.4)	12 (50.0)	4 (15.4)	4 (17.4)
Partial Response	43 (29.7)	19 (26.4)	4 (16.7)	6 (23.1)	7 (30.4)
Stable Disease	24 (16.6)	14 (19.4)	5 (20.8)	8 (30.8)	6 (26.1)
Non-progressive Disease [a]	3 (2.1)	4 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
Progressive Disease	13 (9.0)	15 (20.8)	3 (12.5)	5 (19.2)	4 (17.4)
Discontinued Prior to First Tumor Assessment/Not Evaluable	5 (3.4)	6 (8.3)	0 (0.0)	3 (11.5)	2 (8.7)
Overall Response Rate, n (%)	100 (69.0)	33 (45.8)	16 (66.7)	10 (38.5)	11 (47.8)
(95% CI) [b]	(60.8, 76.4)	(34.0, 58.0)	(44.7, 84.4)	(20.2, 59.4)	(26.8, 69.4)
Complete Response Rate, n (%)	57 (39.3)	14 (19.4)	12 (50.0)	4 (15.4)	4 (17.4)
(95% CI) [b]	(31.3, 47.8)	(11.1, 30.5)	(29.1, 70.9)	(4.4, 34.9)	(5.0, 38.8)

Source: Table 26 in Module 2.7.3
Abbreviations: CI, confidence interval; CT, computed tomography.
FL Efficacy Analysis Set includes all FL patients randomized to treatment in BGB-3111-212 or received any dose of zanubrutinib and/or obinutuzumab in BGB-3111-GA101, BGB-3111-AU-003, and BGB-3111-1002. All patients received ≥ 2 prior lines of therapy.
The disease response from BGB-3111-GA101, BGB-3111-AU-003, and BGB-3111-1002 were assessed by investigator.
[a] The designation of Non-progressive Disease is assigned if PET exam was missed or was received but was deemed not evaluable and criteria at least for Stable Disease designation were met by CT exam.
[b] The 95% CI was estimated using the Clopper-Pearson method.

2.4.3. Discussion on clinical efficacy

In support of the extension of indication for zanubrutinib is: *"BRUKINSA in combination with obinutuzumab is indicated for the treatment of adult patients with refractory or relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies"* the MAH submitted data from study BGB-3111-212: a phase 2, open-label, 2:1 randomized controlled trial of ZO compared with obinutuzumab monotherapy (O).

The MAH had also submitted supportive studies, but they have been disregarded in the efficacy assessment of ZO, either because the regimen was zanubrutinib monotherapy or with obinutuzumab in a different regimen (fewer obinutuzumab treatment doses) than in the pivotal 212 study.

Design and conduct of clinical studies

The study population was enrolled according to reasonable criteria. Patients must have confirmed diagnosis FL (grade 1, 2, or 3a) according to the WHO 2008 classification and must have received ≥ 2 prior systemic treatments for FL, including an anti-CD20 antibody and an appropriate alkylator-based combination therapy. The choice of required prior immunochemotherapies is supported and is reflective of practice in first and second line FL treatment in a European setting.

Disease progression after completion of most recent therapy or refractory disease was a requirement. From the clinical perspective, it is important to point out that in follicular lymphoma, disease progression does not necessarily equate treatment need. Because the natural course of the disease is characterised by spontaneous regressions in some cases and varies significantly from case to case, therapy should be initiated upon the development of symptoms, including B symptoms (unexplained fever >38°C, drenching night sweats or loss of >10% body weight within 6 months), hematopoietic impairment, bulky disease, vital organ compression, ascites, pleural effusion or rapid lymphoma progression. (ESMO FL guideline, Dreyling et al., annals of oncology, 2020).

By including patients with disease progression but potentially without treatment need as defined in the ESMO guideline or by the GELF criteria, there is risk of selection bias of a study population with a greater likelihood of high ORR and better PFS because of a underlying more indolent (or less aggressive) disease.

Prior treatment with a BTK inhibitor was an exclusion criterion while prior treatment with obinutuzumab was not. Unfortunately, not excluding patients previously treated with obinutuzumab (or at least defining a time limit regarding prior exposure) allowed inclusion of patients who might have been randomised to a monotherapy treatment they potentially could benefit very little from or if at all.

Treatment

The proposed dose of zanubrutinib in combination with obinutuzumab in the treatment of follicular lymphoma is 320 mg once daily or 160 mg BID and is thus identical to the recommended doses in the approved indications: Waldenström's macroglobulinaemia, MZL and CLL. For both arms obinutuzumab (1000 mg) was administered intravenously on Days 1, 8, and 15 of Cycle 1; on Day 1 of Cycles 2 to 6; and then every 8 weeks for an additional 24 months (maximum total duration of approximately 30 months [20 doses]) or until ICR confirmed disease progression. Once started, no end date was defined for zanubrutinib BID (except for disease progression, intolerance or death, withdrawal of consent, loss to follow-up, or study termination by sponsor).

Obinutuzumab monotherapy was chosen as comparator in study 212. Obinutuzumab monotherapy for FL is not an EMA or FDA approved therapy (only as maintenance therapy after initial combination therapy). A phase II randomized trial failed to demonstrate a PFS or OS benefit with obinutuzumab when compared with rituximab in 175 patients with relapsed indolent B cell lymphoma (85 percent FL). Among patients with follicular lymphoma (n = 149), ORR seemed higher for obinutuzumab than rituximab (44.6% v 33.3%; P = .08). This observation was also demonstrated by a blinded independent review

panel that measured a higher ORR for obinutuzumab (44.6% v 26.7%; P = .01). However, this difference did not translate into an improvement in progression-free survival. No new safety signals were observed for obinutuzumab, and the incidence of adverse events was balanced between arms, with the exception of infusion-related reactions and cough, which were higher in the obinutuzumab arm. (GAUSS study, Sehn et al., J Clin Onc 2015).

Efficacy of obinutuzumab in rituximab-refractory FL has previously been established in the GADOLIN study: In rituximab-refractory cases or remissions lasting less than 6 months, obinutuzumab in combination with bendamustine (plus obinutuzumab maintenance) showed improved PFS and OS in comparison with bendamustine only. (Gadolin study, Cheson et al., J Clin Oncol., 2018).

In the GALLIUM study, obinutuzumab (immunochemotherapy and maintenance for 2 years) resulted in significantly prolonged PFS in comparison with rituximab in 1st line treatment of FL. There was no OS benefit.

In clinical practice anti-CD20 monotherapy for R/R FL is mostly reserved for comorbid patients who are poor candidates for chemoimmunotherapy due to toxicity concerns or who have low tumour burden or a phenotype of slowly progressing disease (typically over years).

The study population in study 212 had low ECOG PS and a median age under 65 years and it could be argued that most of these patients would be insufficiently treated with anti-CD20 monotherapy in clinical practice. On the other hand, the study population had disease that had progressed after at least two systemic treatment lines (including chemoimmunotherapy) and novel monotherapy and combination therapy options are desirable in this setting where surviving patients eventually will have exhausted treatment options.

Although open-label and not placebo-controlled, the trial design makes it possible to assess the efficacy of zanubrutinib in combination with obinutuzumab in comparison with obinutuzumab monotherapy. This said, double-blinding could have been possible in this case, with IV obinutuzumab as backbone in both arms and zanubrutinib vs. oral placebo.

At the discretion of the investigator, patients in the obinutuzumab monotherapy arm were eligible to receive crossover to treatment with zanubrutinib + obinutuzumab either if they experienced ICR-confirmed progressive disease (PD) or if their disease did not respond to therapy with a complete response (CR) or PR after 12 months. According to the MAH, only one patient crossed over for this latter reason.

The OS result will nevertheless be confounded by crossover, as will be the PFS analyses to the extent that crossover in fact could have taken place before IRC-confirmed progression. It should be noted that in the scientific advice given by EMA in 2017, the CHMP recommended against crossover.

The primary endpoint was overall response rate as determined by independent central review using the Lugano Classification for NHL. Key secondary endpoints include ORR as determined by investigator assessment, DOR as determined by ICR and by investigator assessment, PFS as determined by ICR and by investigator assessment and OS analysis. Overall, the endpoints are supported. If the study is of adequate size, ORR if backed up by DOR and PFS can provide clinically relevant data that potentially can support a benefit/risk assessment. At the data cut-off patients had had the opportunity to be treated for at least 12 months, hence the data is considered final for the assessment of ORR. The DoR and PFS effects observed from the study population are, however, still subject to uncertainty due to relative data immaturity. Hence submi updated efficacy data as a post authorisation recommendation was requested and has been confirmed by the MAH.

The MAH had introduced a response category called non-progressive disease into to the IRC charter, which is not part of the Lugano classification system used for assessment of responses in FL. Apart from this deviation both IRC and the investigator were required to use the 2014 Lugano response criteria.

The study was appropriately powered to demonstrate a s difference in the primary endpoint ORR between treatment arms with 91% probability assuming that the true ORR in the arm A and arm B are 0.55 and 0.3, respectively. Using a 2:1 ratio, 140 and 70 patients were to be enrolled to arm A and arm B. respectively. The observed ORR are higher than those used for sample size calculation, however, the difference in ORR between the arms corresponds to what was expected.

Four amendments were made to the protocol. Summaries can be found in section 5.4 conduct of the study. Crossover option was added in amendment 1. In amendment 2, inclusion criterion 5 was modified to eliminate the requirement that patients experience disease progression within 12 months of receiving their last therapy. Although this modification can alter the study population it is supported as there is no need to exclude patients who had disease progression more than 12 months after receiving their last therapy. In amendment 2, exclusion criterion 21 was added to exclude patients requiring ongoing corticosteroid treatment. This is not an uncommon exclusion criterion in clinical trials in follicular lymphoma.

The median age was 64.0 years. Most patients were ≥ 60 years of age (63.6%). Of note, despite randomisation, there was an imbalance in age; with arm O having more patients ≥ 65 years old compared with arm ZO (55.6% versus 42.8%, respectively).

The ZO arm had more males than females and was slightly younger; 61.1 vs. 62.9 years. In spite of randomisation, there was an imbalance with regard to ECOG performance status. For ECOG PS 0 there were more patients in the ZO arm (59.3% vs. 43.1%) and fewer with ECOG PS 1 (37.2% vs. 55.6%).

It cannot be excluded that the imbalances regarding ECOG PS status and patients ≥ 65 years old could have affected study outcomes and favoured the ZO arm that had more patients under 65 years of age and more patients with ECOG PS 0.

The median time since initial diagnosis to study entry was 86.2 months (range: 5.1 to 359.0 months). At screening (not at initial diagnosis), most patients had a Follicular Lymphoma International Prognostic Index (FLIPI) risk of intermediate or high (172 patients [79.2%]) and were Ann Arbor Stage III or IV (179 patients [82.5%]).

The median number of prior anticancer therapies was 3 lines (range: 2 to 11 lines). Median time from end of last therapy was higher in the ZO arm (8.77 months vs. 6.28 months), but both medians were low. Best response for last therapy was balanced between study arms with slightly more in the ZO arm achieving CR or PR (64.2% vs. 58.3%). Less patients in the ZO arm were refractory to the most recent line of therapy (32.4% vs. 40.3%) suggesting a potential increased likelihood of a better response to next treatment (ZO). Less patients in the ZO arm had progression of disease within 24 months (POD24) of starting the first line of therapy (34.5% vs 41.7%).

The prior therapies given to the study population was as expected in patients with R/R follicular lymphoma who have received minimum two prior lines of systemic therapy. Prior treatments were balanced between study arms. Disease history and prior treatment information shows that there was a high proportion of patients with stage III or IV disease, a median of 3 prior lines of therapy and a median time from end of last therapy till study entry of 8 months indicating that the study population could be considered as having a poor prognosis. Some patients had a long remission before entering study 212 but the majority had progressed or had refractory disease within 12 months indicating selection of a patient population where new longer lasting remissions might not be easily attainable. Although the patients were randomised, there were imbalances in the study populations favouring the ZO arm with

regard to best response for last therapy, refractoriness to most recent line of therapy and POD24, age, and ECOG status.

Efficacy data and additional analyses

ORR

The study met its primary endpoint with ORR (patients achieving a CR or PR) as assessed by ICR of 69.0% (95% CI: 60.8, 76.4) in the ZO arm and 45.8% (95% CI: 34.0, 58.0) in the O arm (using the Lugano Classification for NHL). The risk difference was 22.7% (95% CI: 9.0, 36.5), and the 2-sided p-value was 0.0012. ORR results were more favourable in patients who did not meet GELF criteria vs. those who did. In arm ZO, the ORR in patients who met GELF criteria was 62.7% (51.3, 73.0) vs. patients who did not meet GELF criteria was 77.4% (65.0, 87.1).

The risk difference between arm ZO and arm O for patients who met GELF criteria was 17.7% (-1.0, 36.3). For patients who did not meet GELF criteria the risk difference was 30.5% (10.4, 50.7).

The ICR could assign to a fabricated response category called non-progressive disease. However, this response category is not part of the Lugano classification for NHL and the investigator could not assign this response category. However, a sensitivity analysis revealed no impact on the primary endpoint by this fabricated response category.

Subgroup analyses of disease response by ICR showed higher overall response rates in arm ZO across all subgroups including older patients and patients with ECOG PS 1, which were groups where there was imbalance despite randomisation.

ORR by investigator was overall concordant with ICR assessment. A requested sensitivity analyses reassigning the fabricated response category non-progressive disease with a CT based response showed results consistent with the primary analysis.

While obinutuzumab might be a subpar comparator in younger fit patients, study indicates 212 that zanubrutinib in combination with obinutuzumab shows superior ORR in comparison with obinutuzumab monotherapy in a patient population deemed to have a poor prognosis due to progression after at least two prior systemic therapies and with a proclivity to early relapse.

DOR

As assessed by independent central review for the ITT Analysis Set, the median duration of response was not reached (95% CI: 25.3 months, not evaluable [NE]) in arm ZO with a median follow-up time of 16.9 months (range: 0.0 to 41.2 months) and 14.0 months (95% CI: 9.2, 25.1 months) in arm O with a median follow-up time of 23.3 months (range: 0.0 to 32.7 months). There was a high degree of censoring (71%) in the ZO arm.

PFS

As assessed by the ICR, the median PFS was 28.0 months (95% CI: 16.1, NE) in arm ZO with a median follow-up time of 19.4 months (range: 0.0 to 44.0 months). In arm O median PFS was 10.4 months (95% CI: 6.5, 13.8) with a median follow-up time of 23.1 months (range: 0.0 to 38.1 months). 60.7% and 38.9% were censored respectively.

The hazard ratio was 0.50 (95% CI: 0.33, 0.75) with a 2-sided p-value of 0.0007.

As assessed by the investigator for the ITT Analysis Set, median PFS was higher in arm ZO: 16.3 months (95% CI: 11.0, 27.4) with a median follow-up time of 22.2 months (range: 0.0 to 38.8 months) in arm

ZO and 5.8 months (95% CI: 3.7, 7.9) with a median follow-up time of 23.1 months (range: 0.0 to 38.1 months) in arm O.

The PFS difference between treatment arms for patients who met GELF criteria was limited, 15.2m (9.5, 28.0) in arm ZO vs 11.8 (5.6, 17.5) in arm O.

The MAH has provided additional results for DoR and PFS based on EMA guideline on censoring. For both endpoints the results of the analysis of the predefined censor rule and the censor rule required by EMA were quite similar in both treatment groups.

In conclusion, zanubrutinib in combination with obinutuzumab shows superior PFS in comparison with obinutuzumab monotherapy. However, it is noted that PFS estimates and rate of censoring vary considerably between the ICR and the investigator assessment but additional requested sensitivity analyses confirmed the primary analyses done by the MAH. Robust data on DOR and PFS could support the efficacy of zanubrutinib in combination with obinutuzumab for FL based on the primary endpoint of ORR. At this point, DOR and PFS data are considered supportive but uncertainties remain due to the relative data immaturity. The MAH will submit updated efficacy data (DOR, PFS, OS) post authorisation following a CHMP recommendation.

Median OS was not reached in arm ZO and was 34.6 months (95% CI: 29.3, NE) in arm O. Median follow-up times were similar: 23.3 months (range: 0.1 to 44.5 months) in arm ZO and 23.9 months (range: 0.1 to 44.3 months) in arm O. The hazard ratio was 0.62 (95% CI: 0.35, 1.07) with a 2-sided p-value of 0.0845. No OS detriment was observed.

Crossover from arm O to ZO was allowed by the investigator. Apparently 35 patients from the O arm were crossed over to the ZO upon progression. Crossover confounds the OS analysis. Additionally, it can be assumed that there will potentially be imbalances in post-protocol therapy between study arms which can confound OS analysis further. Benefit in terms of increased OS has not been demonstrated, and due to extensive cross-over between the treatment arm the final OS data are not likely to be conclusive.

In the supportive study GA101 obinutuzumab was only given for the first 6 cycles (8 infusions instead of 20 in study 212). This limits the value of the study as supportive efficacy data because treatments are not fully comparable across the two studies.

Having this limitation in mind, ORR and CR rates from study GA101 are supportive of the main study.

The zanubrutinib monotherapy studies (003 and 1002) are not considered supportive with regard to evaluating the efficacy of combination therapy with zanubrutinib and obinutuzumab.

Although follicular lymphoma tends to behave as an indolent disease, the targeted population is deemed to have a poor prognosis due to progression after at least two prior systemic therapies and with a proclivity to early relapse. In patients with multiple relapsed FL, effective and easily manageable treatment options are limited. While FL behaves as a chronic, incurable disease albeit with a long natural history and survival often measured in decades, disease eventually relapses. Further treatment options are thus needed, especially in patients with symptomatic relapse / rapid progression after previous therapy.

2.4.4. Conclusions on the clinical efficacy

Treatment with zanubrutinib in combination with obinutuzumab in adult patients with relapsed FL who have previously received at least two systemic therapies, displayed a statistically significant and clinically meaningful benefit over obinutuzumab in terms of ORR. This improvement in the primary endpoint was supported by DoR and PFS.

While the observed responses appear to be durable, uncertainty remains regarding the duration of these effects due to limited follow-up. Study BGB-3111-212 is ongoing. The MAH will submit updated efficacy (ORR, DoR, PFS) post-authorisation - in Q4-2024, following a recommendation from the CHMP.

2.5. Clinical safety

Introduction

The safety database includes additional safety data from the following 4 studies:

• **Study BGB-3111-212**: an additional 4 months of safety data are provided in the pivotal study, with a data cutoff date of 25 October 2022 compared to 25 June 2022 in the original SCS.

• **Study BGB-3111-304**: an additional 6 months of safety data are provided, with a data cutoff date of 07 March 2022 compared to 07 September 2021 in the original SCS.

• **Study BGB-3111-305**: an additional 8 months of safety data are provided, with a data cutoff date of 08 August 2022 compared to 01 December 2021 in the original SCS.

• **Study BGB-3111-LTE1**: an additional 3.5 months of safety data are provided, with a data cutoff date of 17 October 2022 compared to 01 July 2022 in the original SCS.

As of the latest safety update, original and updated safety data are presented in the tables for the following 4 patient groups:

• **Study BGB-3111-212** (zanubrutinib + obinutuzumab; Arm A, n = 143 patients)

• **Study BGB-3111-212** (obinutuzumab; Arm B, n = 71 patients)

• **All Patients** (zanubrutinib monotherapy; n = 1550 patients)

• **FL Patients**, within the **All Patients** group (zanubrutinib monotherapy)

Table 1: Studies Included in the Summary of Clinical Safety

Study Location	Study Design	Population	Zanubrutinib Starting Dose	Number of Treated Patients			First Patient First Dose/ Data Cutoff Date/ Study Status [a]
				Zanubrutinib		Comparator	
				FL	All		
Pivotal study							
BGB-3111-212 (AU, BY, CA, CN, EU [BG, CZ, DE, ES, FR, IT, PO], GB, KR, NZ, RU, TW, US)	Phase 2, randomized, open-label, multicenter study	Patients with R/R FL	160 mg BID	143 (in combination with obinutuzumab)	143	Obinutuzumab 71	14 November 2017/ 25 October2022/ Ongoing
Supportive combination therapy study							
BGB-3111-GA101 (AU, KR, US)	Phase 1b, open-label, multicenter study	Patients with R/R B-cell malignancies	160 mg BID or 320 mg QD	36 (in combination with obinutuzumab)	119	N/A	13 January 2016/ 02 September 2020/ Closed
Supportive monotherapy safety studies							
BGB-3111-AU-003 (AU, IT, KR, NZ, US, UK)	Phase 1/2, single-arm, dose escalation and cohort expansion	Patients with R/R or TN CLL/SLL, DLBCL, FL, HCL, MALT, MCL, MZL, NHL, RT, or WM	40 mg QD starting dose up to160 mg BID or 320 mg QD	33	373 (includes only patients receiving 160 mg BID or 320 mg QD)	N/A	16 September 2014/ 31 March 2021/ Closed
BGB-3111-1002 (China)	Phase 1, single-arm	Patients with R/R CLL/SLL, MCL, WM/LPL, FL, MZL, HCL, or nGCB DLBCL	160 mg BID or 320 mg QD	26	44	N/A	05 July 2016/ 30 August 2020/ Closed

Study Location	Study Design	Population	Zanubrutinib Starting Dose	Number of Treated Patients			First Patient First Dose/ Data Cutoff Date/ Study Status [a]
				Zanubrutinib		Comparator	
				FL	All		
BGB-3111-205 (China)	Phase 2, single-arm	Patients with R/R CLL/SLL	160 mg BID	N/A	91	N/A	09 March 2017/ 11 September 2020/ Closed
BGB-3111-206 (China)	Phase 2, single-arm	Patients with R/R MCL	160 mg BID	N/A	86	N/A	02 March 2017/ 08 September 2020/ Closed
BGB-3111-210 (China)	Phase 2, single-arm	Patients with R/R WM	160 mg BID	N/A	44	N/A	31 August 2017/ 11 January 2021/ Closed
BGB-3111-214 (AU, CN, EU [CZ, FR, IT], KR, NZ, UK, US)	Phase 2, open-label, single-arm study	Patients with R/R MZL	160 mg BID	N/A	68	N/A	19 February 2019/ 04 May 2022/ Closed
BGB-3111-302 (AU, EU [CZ, DE, ES, FR, GR, IT, NL, PO, SW], UK, US)	Phase 3, randomized, open-label, multicenter study	Patients with R/R or TN WM	160 mg BID	N/A	129	98 (ibrutinib)	25 January 2017/ 21 June 2022/ Closed
BGB-3111-304 (AU, CN, EU [AT, BE, CZ, ES, FR, IT, PO, SW], NZ, RU, UK, US)	Phase 3, randomized, open-label, multicenter study	Patients with TN CLL/SLL	160 mg BID	N/A	391	265 (B + R)	31 October 2017/ 07 March 2022/ Ongoing

Study Location	Study Design	Population	Zanubrutinib Starting Dose	Number of Treated Patients			First Patient First Dose/ Data Cutoff Date/ Study Status [a]
				Zanubrutinib		Comparator	
				FL	All		
BGB-3111-305 (AU, CN, EU [BE, CZ, DE, ES, FR, IT, NL, PO, SW], TR, NZ, UK, US)	Phase 3, randomized, open-label, multicenter study	Patients with R/R CLL/SLL	160 mg BID	N/A	324	324 (ibrutinib)	01 November 2018 08 August 2022/ Ongoing
BGB-3111-LTE1 [b]	Long-term extension	Patients with B-cell malignancies who were previously enrolled in a BeiGene parent study	Initial dosing regimen of 160 mg BID or 320 mg QD, as received in the parent study	BGB-3111-AU-003 n = 9 BGB-3111-1002 n = 4	373 BGB-3111-AU-003 n = 176 BGB-3111-1002 n = 9 BGB-3111-205 n = 58 BGB-3111-206 n = 37 BGB-3111-210 n = 20 BGB-3111-214 n = 24 BGB-3111-302 n = 49	N/A	Data cutoff 07 October 2022/ Ongoing
Total Patients in the Integrated Safety Population				**238**	**1550** [c]	N/A	N/A

Abbreviations: AT, Austria; AU, Australia; BE, Belgium; BG, Bulgaria; BID, twice a day; B+R, bendamustine and rituximab; BY, Belarus; CA, Canada; CLL, chronic lymphocytic leukemia; CN, China; CZ, Czech Republic; DE, Germany; DLBCL, diffuse large B-cell lymphoma; ES, Spain; EU, European Union; FL, follicular lymphoma; FR, France; GB, Great Britain; GR, Greece; HCL, hairy cell leukemia; IT, Italy; KR, Korea; LPL, lymphoplasmacytic lymphoma; LTE, long-term extension; MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma;; N/A, not applicable; nGCB, non-germinal center B-cell-like; NHL, non-Hodgkin lymphoma; NL, Netherlands; NZ, New Zealand; PO, Poland; QD, once a day; R/R, relapsed or refractory; RT, Richter's transformation; RU, Russia; SLL, small lymphocytic lymphoma; SW, Sweden; TN, treatment-naive; TR, Turkey; TW, Taiwan; UK, United Kingdom; US, United States; WM, Waldenström macroglobulinemia.

[a] Study status of "Closed" indicates that the study is complete, and no additional clinical study report will be submitted.

[b] Safety data collected from LTE1 study for 373 patients who were dosed at either 160 mg BID or 320 mg QD in the parent studies (BGB-3111-AU-003, BGB-3111-1002, BGB-3111-205, BGB-3111-206, BGB-3111-210, BGB-3111-214, and BGB-3111-302) are grouped with data from the parent studies in all data summaries and analysis described herein. The LTE data of a patient who discontinued the parent study due to "patient diagnosed with other cancer that needed treatment" on 18 September 2017 and then enrolled in LTE study for zanubrutinib treatment was not included.

[c] This total only includes patients receiving zanubrutinib monotherapy and excludes patients from BGB-3111-212 and BGB-3111-GA101.

Study BGB-3111-212 is an ongoing international, Phase 2, open-label, randomized, active control study of zanubrutinib plus obinutuzumab versus obinutuzumab monotherapy in patients with R/R FL. This study is being conducted in 17 countries worldwide.

For combination therapy studies BGB-3111-212 and BGB 3111 GA101, a treatment-emergent adverse event was defined as an adverse event with an onset date or an increase in severity on or after the first dose of study treatment until 30 or 90 days after the last dose of zanubrutinib or obinutuzumab, respectively, or before initiation of a new anticancer therapy, whichever occurred first; this definition also applied to patients in Study BGB-3111-212 who crossed over from obinutuzumab monotherapy to zanubrutinib plus obinutuzumab combination therapy.

For zanubrutinib monotherapy studies, a treatment-emergent adverse event was defined as an adverse event with an onset date or an increase in severity on or after the first dose of zanubrutinib until 30 days

after the last dose of zanubrutinib or before initiation of a new anticancer therapy, whichever occurred first.

Worsening of an event to Grade 5 beyond 30 or 90 days after the last dose of zanubrutinib or obinutuzumab, respectively, was also considered a treatment-emergent adverse event if it occurred before initiation of a new anticancer therapy. Only those adverse events that were treatment emergent are included in the summary tables.

Patient exposure

Table 28 Summary of treatment exposure (SAS)

	Original				Update			
	Combination Therapy Trials		Monotherapy Trials		Combination Therapy Trials		Monotherapy Trials	
	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
Number of Treatment Cycles (Zanubrutinib) [a]								
n	143	NA	1550	59	143		1550	59
Mean (SD)	16.16 (11.448)		33.20 (21.162)	19.14 (22.327)	17.46 (12.777)		36.78 (21.960)	19.67 (23.462)
Median	13.21		31.07	9.07	13.43		37.41	9.07
Q1, Q3	6.43, 25.04		16.29, 48.00	4.00, 24.00	6.43, 26.68		20.32, 50.07	4.00, 24.00
Min, Max	0.5, 47.9		0.1, 93.9	0.1, 82.1	0.5, 52.3		0.1, 97.8	0.1, 86.0
Number of Treatment Cycles (Zanubrutinib) [a], n (%)								
< 3 cycles	14 (9.8)	NA	87 (5.6)	9 (15.3)	14 (9.8)	NA	87 (5.6)	9 (15.3)
3 - < 6 cycles	17 (11.9)	NA	71 (4.6)	9 (15.3)	17 (11.9)	NA	71 (4.6)	9 (15.3)
6 - < 9 cycles	19 (13.3)	NA	59 (3.8)	8 (13.6)	19 (13.3)	NA	59 (3.8)	8 (13.6)
9 - < 12 cycles	12 (8.4)	NA	55 (3.5)	11 (18.6)	12 (8.4)	NA	49 (3.2)	11 (18.6)
12 - < 24 cycles	44 (30.8)	NA	264 (17.0)	7 (11.9)	37 (25.9)	NA	189 (12.2)	7 (11.9)
24 - < 30 cycles	16 (11.2)	NA	181 (11.7)	3 (5.1)	15 (10.5)	NA	128 (8.3)	3 (5.1)
≥ 30 cycles	21 (14.7)	NA	833 (53.7)	12 (20.3)	29 (20.3)	NA	967 (62.4)	12 (20.3)
Duration of Treatment (Zanubrutinib) (months) [b]								
n	143	NA	1550	59	143	NA	1550	59
Mean (SD)	14.86 (10.532)		30.54 (19.467)	17.61 (20.539)	16.07 (11.754)		33.83 (20.202)	18.09 (21.583)
Median	12.16		28.58	8.34	12.35		34.41	8.34
Q1, Q3	5.91, 23.03		14.98, 44.16	3.68, 22.08	5.91, 24.54		18.69, 46.06	3.68, 22.08
Min, Max	0.5, 44.1		0.1, 86.4	0.1, 75.6	0.5, 48.1		0.1, 90.0	0.1, 79.1

	Original				Update			
	Combination Therapy Trials		Monotherapy Trials		Combination Therapy Trials		Monotherapy Trials	
	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
Duration of Treatment (Zanubrutinib) (months) [b], n (%)								
< 3 months	19 (13.3)	NA	104 (6.7)	13 (22.0)	19 (13.3)	NA	104 (6.7)	13 (22.0)
3 - < 6 months	18 (12.6)	NA	76 (4.9)	7 (11.9)	18 (12.6)	NA	76 (4.9)	7 (11.9)
6 - < 9 months	16 (11.2)	NA	59 (3.8)	11 (18.6)	16 (11.2)	NA	57 (3.7)	11 (18.6)
9 - < 12 months	18 (12.6)	NA	55 (3.5)	7 (11.9)	17 (11.9)	NA	43 (2.8)	7 (11.9)
12 - < 24 months	38 (26.6)	NA	277 (17.9)	9 (15.3)	36 (25.2)	NA	235 (15.2)	9 (15.3)
24 - < 36 months	28 (19.6)	NA	496 (32.0)	3 (5.1)	28 (19.6)	NA	338 (21.8)	3 (5.1)
≥ 36 months	6 (4.2)	NA	483 (31.2)	9 (15.3)	9 (6.3)	NA	697 (45.0)	9 (15.3)
Cumulative Dose (Zanubrutinib) (g)								
n	143	NA	1550	59	143	NA	1550	59
Mean (SD)	136.04 (99.264)		282.31 (185.644)	167.42 (197.347)	145.80 (109.504)		311.62 (193.105)	172.05 (207.501)
Median	114.56		264.56	81.12	116.16		318.40	81.12
Q1, Q3	53.76, 200.80		138.08, 379.20	35.68, 198.40	53.76, 222.08		161.92, 410.72	35.68, 198.40
Min, Max	4.6, 429.3		1.0, 836.0	1.3, 728.6	4.6, 468.3		1.0, 870.6	1.3, 763.1
Actual Dose Intensity (Zanubrutinib) (mg/day) [c]								
n	143	NA	1550	59	143	NA	1550	59
Mean (SD)	300.01 (42.797)		302.94 (37.158)	310.85 (15.202)	299.30 (42.922)		301.90 (38.145)	310.84 (15.208)
Median	316.44		316.34	318.57	316.36		315.10	318.57
Q1, Q3	305.20, 320.00		306.47, 319.60	308.55, 320.00	302.10, 320.00		305.00, 319.33	308.55, 320.00
Min, Max	98.2, 320.0		46.7, 353.3	262.2, 320.0	98.2, 320.0		46.7, 531.0	262.2, 320.0
Relative Dose Intensity (Zanubrutinib) (%) [d]								
n	143	NA	1550	59	143	NA	1550	59
Mean (SD)	93.75 (13.374)		94.68 (11.606)	97.16 (4.761)	93.53 (13.413)		94.35 (11.915)	97.16 (4.763)
Median	98.89		98.87	99.63	98.86		98.48	99.63

	Original				Update			
	Combination Therapy Trials		Monotherapy Trials		Combination Therapy Trials		Monotherapy Trials	
	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
Q1, Q3	95.37, 100.00		95.80, 99.88	96.42, 100.00	94.41, 100.00		95.32, 99.80	96.40, 100.00
Min, Max	30.7, 100.0		14.6, 110.4	81.9, 100.0	30.7, 100.0		14.6, 165.9	81.9, 100.0
Number of Infusions (Obinutuzumab)								
n	143	71	NA	NA	143	71	NA	NA
Mean (SD)	11.94 (5.234)	9.61 (5.151)			12.24 (5.428)	9.69 (5.277)		
Median	11.00	9.00			11.00	9.00		
Q1, Q3	8.00, 16.00	5.00, 13.00			8.00, 17.00	5.00, 13.00		
Min, Max	3.0, 20.0	3.0, 20.0			3.0, 20.0	3.0, 20.0		
Number of Infusions (Obinutuzumab), n (%)								
1-3	6 (4.2)	3 (4.2)	NA	NA	6 (4.2)	3 (4.2)	NA	NA
4-8	41 (28.7)	31 (43.7)	NA	NA	41 (28.7)	31 (43.7)	NA	NA
≥9	96 (67.1)	37 (52.1)	NA	NA	96 (67.1)	37 (52.1)	NA	NA
Duration of Treatment (Obinutuzumab) (months) [b]								
n	143	71	NA	NA	143	71	NA	NA
Mean (SD)	13.10 (9.245)	9.31 (8.760)			13.71 (9.763)	9.49 (9.070)		
Median	10.61	6.47			10.61	6.47		
Q1, Q3	4.63, 21.26	2.07, 13.83			4.63, 23.20	2.07, 13.83		
Min, Max	0.3, 30.3	0.1, 28.7			0.3, 34.3	0.1, 31.5		
Duration of Treatment (Obinutuzumab) (months) [b], n (%)								
< 3 months	22 (15.4)	25 (35.2)	NA	NA	22 (15.4)	25 (35.2)	NA	NA
3 - < 6 months	24 (16.8)	7 (9.9)	NA	NA	24 (16.8)	7 (9.9)	NA	NA
6 - < 9 months	15 (10.5)	12 (16.9)	NA	NA	15 (10.5)	12 (16.9)	NA	NA
9 - < 12 months	14 (9.8)	8 (11.3)	NA	NA	13 (9.1)	8 (11.3)	NA	NA

	Original				Update			
	Combination Therapy Trials		Monotherapy Trials		Combination Therapy Trials		Monotherapy Trials	
	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
12 - < 24 months	37 (25.9)	11 (15.5)	NA	NA	35 (24.5)	10 (14.1)	NA	NA
24 - < 36 months	31 (21.7)	8 (11.3)	NA	NA	34 (23.8)	9 (12.7)	NA	NA
≥ 36 months	0 (0.0)	0 (0.0)	NA	NA	0 (0.0)	0 (0.0)	NA	NA
Relative Infusion Frequency (Obinutuzumab) (%)								
n	143	71	NA	NA	143	71	NA	NA
Mean (SD)	99.54 (2.224)	99.14 (5.431)			99.37 (2.774)	99.14 (5.431)		
Median	100.00	100.00			100.00	100.00		
Q1, Q3	100.00, 100.00	100.00, 100.00			100.00, 100.00	100.00, 100.00		
Min, Max	80.0, 100.0	55.6, 100.0			80.0, 100.0	55.6, 100.0		
Patients with Dose Reduction (Zanubrutinib), n (%)	16 (11.2)	NA	198 (12.8)	1 (1.7)	19 (13.3)	NA	235 (15.2)	1 (1.7)
Reason for Dose reduction [e]								
Adverse Event	13 (9.1)	NA	149 (9.6)	1 (1.7)	15 (10.5)	NA	166 (10.7)	1 (1.7)
PI Decision	6 (4.2)	NA	24 (1.5)	0 (0.0)	6 (4.2)	NA	28 (1.8)	0 (0.0)
Held for Procedure	0 (0.0)	NA	8 (0.5)	0 (0.0)	0 (0.0)	NA	13 (0.8)	0 (0.0)
Subject Forgot/Error	0 (0.0)	NA	5 (0.3)	0 (0.0)	0 (0.0)	NA	6 (0.4)	0 (0.0)
Other	1 (0.7)	NA	29 (1.9)	0 (0.0)	3 (2.1)	NA	43 (2.8)	0 (0.0)
Number of Dose Reductions (Zanubrutinib)								
n	16	NA	198	1	19	NA	235	1
Mean (SD)	1.69 (0.873)		1.38 (0.757)	1.00 (NE)	1.63 (0.831)		1.38 (0.732)	1.00 (NE)
Median	1.50		1.00	1.00	1.00		1.00	1.00
Q1, Q3	1.00, 2.00		1.00, 2.00	1.00, 1.00	1.00, 2.00		1.00, 2.00	1.00, 1.00
Min, Max	1.0, 4.0		1.0, 6.0	1.0, 1.0	1.0, 4.0		1.0, 6.0	1.0, 1.0
Number of Dose Reductions (Zanubrutinib), n (%)								

	Original				Update			
	Combination Therapy Trials		Monotherapy Trials		Combination Therapy Trials		Monotherapy Trials	
	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
1	8 (5.6)	NA	144 (9.3)	1 (1.7)	10 (7.0)	NA	170 (11.0)	1 (1.7)
2	6 (4.2)	NA	39 (2.5)	0 (0.0)	7 (4.9)	NA	48 (3.1)	0 (0.0)
3	1 (0.7)	NA	11 (0.7)	0 (0.0)	1 (0.7)	NA	13 (0.8)	0 (0.0)
≥4	1 (0.7)	NA	4 (0.3)	0 (0.0)	1 (0.7)	NA	4 (0.3)	0 (0.0)
Patients with Dose Interruption (Zanubrutinib), n (%)	77 (53.8)	NA	903 (58.3)	26 (44.1)	82 (57.3)	NA	945 (61.0)	26 (44.1)
Reason for Dose Interruption [e]								
Adverse Event	58 (40.6)	NA	643 (41.5)	14 (23.7)	63 (44.1)	NA	690 (44.5)	14 (23.7)
COVID-19 Infection	8 (5.6)	NA	27 (1.7)	0 (0.0)	13 (9.1)	NA	36 (2.3)	0 (0.0)
Number of Dose Interruption (Zanubrutinib)								
n	77	NA	903	26	82	NA	945	26
Mean (SD)	2.91 (2.843)		2.58 (2.331)	2.69 (3.484)	2.98 (2.867)		2.70 (2.407)	2.69 (3.484)
Median	2.00		2.00	2.00	2.00		2.00	2.00
Q1, Q3	1.00, 4.00		1.00, 3.00	1.00, 2.00	1.00, 4.00		1.00, 3.00	1.00, 2.00
Min, Max	1.0, 14.0		1.0, 20.0	1.0, 18.0	1.0, 14.0		1.0, 21.0	1.0, 18.0
Number of Dose Interruption (Zanubrutinib), n (%)								
1	35 (24.5)	NA	371 (23.9)	10 (16.9)	35 (24.5)	NA	362 (23.4)	10 (16.9)
2	12 (8.4)	NA	224 (14.5)	11 (18.6)	15 (10.5)	NA	239 (15.4)	11 (18.6)
3	8 (5.6)	NA	114 (7.4)	1 (1.7)	8 (5.6)	NA	124 (8.0)	1 (1.7)
≥4	22 (15.4)	NA	194 (12.5)	4 (6.8)	24 (16.8)	NA	220 (14.2)	4 (6.8)
Duration of Dose Interruption (Zanubrutinib) (days) [f]								
n	76	NA	902	26	80	NA	944	26
Mean (SD)	26.35 (30.803)		29.19 (34.926)	21.92 (25.813)	31.01 (35.526)		30.72 (35.649)	21.92 (25.813)
Median	12.25		18.00	12.00	15.25		19.00	12.00

	Original				Update			
	Combination Therapy Trials		Monotherapy Trials		Combination Therapy Trials		Monotherapy Trials	
	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
Q1, Q3	2.75, 42.50		7.50, 37.00	5.00, 27.00	4.00, 52.75		8.00, 39.00	5.00, 27.00
Min, Max	0.5, 115.0		1.0, 389.0	1.0, 95.0	0.5, 193.0		1.0, 389.0	1.0, 95.0

Source: ADSL, ADEXSUM. Data cutoff: 25OCT2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304).

Abbreviations: FL, Follicular Lymphoma; NA, not applicable; Obi, Obinutuzumab; Zanu, Zanubrutinib.

N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD and/or obinutuzumab. Percentages are based on N, unless otherwise specified.

[a] Number of treatment cycles is defined as duration of treatment (days) divided by 28.

[b] Duration of exposure (months) was calculated as (last dose date - first dose date + 1)/30.4375, where data cutoff date is used as last dose date for ongoing patients.

[c] Actual dose intensity (mg/day) is defined as the cumulative dose administration (mg) received by a patient divided by the duration of exposure (days).

[d] Relative dose intensity is defined as the ratio of the actual dose intensity (mg/day) and the planned dose intensity (mg/day).

[e] A patient may be counted in more than one row. Multiple reduction due to same reasons were counted once per patient in each row.

[f] Duration was calculated for patients with dose interruption only.

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Table 5: Demographics and Baseline Characteristics (Safety Analysis Set)

	Combination Therapy Trials				Monotherapy Trials	
	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	BGB-3111-GA101 Zanu + Obi (N = 36) n (%)	Pool Zanu + Obi (N = 179) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
Sex, n (%)						
Male	73 (51.0)	33 (46.5)	22 (61.1)	95 (53.1)	1027 (66.3)	29 (49.2)
Female	70 (49.0)	38 (53.5)	14 (38.9)	84 (46.9)	523 (33.7)	30 (50.8)
Race, n (%)						
White	90 (62.9)	47 (66.2)	29 (80.6)	119 (66.5)	1032 (66.6)	19 (32.2)
Asian	30 (21.0)	16 (22.5)	7 (19.4)	37 (20.7)	424 (27.4)	35 (59.3)
Not Reported	23 (16.1)	8 (11.3)	0 (0.0)	23 (12.8)	40 (2.6)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	53 (3.4)	4 (6.8)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (1.7)
Age (years)						
n	143	71	36	179	1550	59
Mean (SD)	61.0 (11.98)	62.8 (12.85)	59.1 (14.38)	60.6 (12.48)	66.2 (10.71)	55.1 (12.35)
Median	63.0	65.0	58.5	62.0	67.0	57.0
Q1, Q3	53.0, 70.0	55.0, 72.0	46.0, 69.5	51.0, 70.0	60.0, 73.0	46.0, 65.0
Min, Max	31, 84	32, 88	34, 86	31, 86	20, 95	28, 79
Age Group, n (%)						
< 60 years	55 (38.5)	24 (33.8)	19 (52.8)	74 (41.3)	364 (23.5)	34 (57.6)
≥ 60 years	88 (61.5)	47 (66.2)	17 (47.2)	105 (58.7)	1186 (76.5)	25 (42.4)
< 65 years	83 (58.0)	32 (45.1)	24 (66.7)	107 (59.8)	600 (38.7)	44 (74.6)
≥ 65 years	60 (42.0)	39 (54.9)	12 (33.3)	72 (40.2)	950 (61.3)	15 (25.4)
< 75 years	129 (90.2)	59 (83.1)	29 (80.6)	158 (88.3)	1215 (78.4)	58 (98.3)
≥ 75 years	14 (9.8)	12 (16.9)	7 (19.4)	21 (11.7)	335 (21.6)	1 (1.7)
≥ 65 and < 75 years	46 (32.2)	27 (38.0)	5 (13.9)	51 (28.5)	615 (39.7)	14 (23.7)
Geographic Region, n (%) [a]						
North America	5 (3.5)	6 (8.5)	4 (11.1)	9 (5.0)	179 (11.5)	10 (16.9)
Europe	93 (65.0)	37 (52.1)	0 (0.0)	93 (52.0)	551 (35.5)	1 (1.7)
Australia/New Zealand	15 (10.5)	12 (16.9)	26 (72.2)	41 (22.9)	414 (26.7)	15 (25.4)
Asia	30 (21.0)	16 (22.5)	6 (16.7)	36 (20.1)	406 (26.2)	33 (55.9)
Weight (kg)						
n	143	71	36	179	1549	59
Mean (SD)	74.90 (16.459)	77.18 (16.951)	78.62 (16.570)	75.65 (16.502)	75.25 (16.998)	70.42 (16.616)
Median	74.00	77.40	78.55	74.00	73.00	67.30
Q1, Q3	64.00, 88.50	64.00, 90.00	67.55, 87.25	64.00, 88.50	63.00, 85.00	58.00, 83.00
Min, Max	40.0, 118.0	47.5, 116.0	46.9, 114.7	40.0, 118.0	36.0, 149.0	36.0, 117.4
Height (cm)						
n	142	71	36	178	1533	59

Data cutoff: 25JUN2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 01JUL2022(LTE1), 01DEC2021(305), 07SEP2021(304). Abbreviations: BMI, Body Mass Index; ECOG, Eastern Cooperative Oncology Group; FL, Follicular Lymphoma; Obi, Obinutuzumab; Zanu, Zanubrutinib. N = number of patients who received zanubrutinib

at the initial dose of 160 mg BID or 320 mg QD and/or obinutuzumab.

Table 29 Prior Anticancer therapies

	Combination Therapy Trials				Monotherapy Trials	
	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	BGB-3111-GA101 Zanu + Obi (N = 36) n (%)	Pool Zanu + Obi (N = 179) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
Patients with any Prior Anticancer Drug Therapy, n (%)	143 (100.0)	71 (100.0)	36 (100.0)	179 (100.0)	1068 (68.9)	59 (100.0)
Number of Prior Lines [a]						
n	143	71	36	179	1068	59
Mean (SD)	3.1 (1.44)	3.1 (1.36)	2.5 (1.78)	3.0 (1.53)	2.1 (1.44)	3.3 (1.67)
Median	3.0	3.0	2.0	3.0	2.0	3.0
Q1, Q3	2.0, 4.0	2.0, 4.0	1.0, 3.0	2.0, 4.0	1.0, 3.0	2.0, 4.0
Min, Max	2, 11	2, 9	1, 9	1, 11	1, 12	1, 8
Number of Prior Lines, n (%) [a]						
1	0 (0.0)	0 (0.0)	12 (33.3)	12 (6.7)	496 (46.4)	10 (16.9)
2	65 (45.5)	29 (40.8)	11 (30.6)	76 (42.5)	276 (25.8)	11 (18.6)
3	37 (25.9)	24 (33.8)	7 (19.4)	44 (24.6)	151 (14.1)	14 (23.7)
>3	41 (28.7)	18 (25.4)	6 (16.7)	47 (26.3)	145 (13.6)	24 (40.7)
Patients with any Prior Anticancer Radiotherapy, n (%)						
Yes	31 (21.7)	17 (23.9)	9 (25.0)	40 (22.3)	87 (5.6)	11 (18.6)
No	112 (78.3)	54 (76.1)	0 (0.0)	112 (62.6)	1463 (94.4)	48 (81.4)
Patients with any Prior Stem Cell Transplant, n (%)						
Yes	32 (22.4)	13 (18.3)	NA	NA	43 (2.8)	6 (10.2)
No	111 (77.6)	58 (81.7)	NA	NA	1506 (97.2)	53 (89.8)
Unknown	0 (0.0)	0 (0.0)	NA	NA	1 (0.1)	0 (0.0)

Source: ADSL, ADBASE. Data cutoff: 25JUN2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 01JUL2022(LTE1), 01DEC2021(305), 07SEP2021(304).
Abbreviations: FL, Follicular Lymphoma; NA, not applicable; Obi, Obinutuzumab; Zanu, Zanubrutinib.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD and/or obinutuzumab.
[a] n is number of patients with prior lines of therapy/regimens.
Patients with any Prior Stem Cell Transplant was not collected in study GA101.

Adverse events

For combination therapy studies BGB-3111-212 and BGB 3111 GA101, a treatment-emergent adverse event was defined as an adverse event with an onset date or an increase in severity on or after the first dose of study treatment until 30 or 90 days after the last dose of zanubrutinib or obinutuzumab, respectively, or before initiation of a new anticancer therapy, whichever occurred first; this definition also applied to patients in Study BGB-3111-212 who crossed over from obinutuzumab monotherapy to zanubrutinib plus obinutuzumab combination therapy.

For zanubrutinib monotherapy studies, a treatment-emergent adverse event was defined as an adverse event with an onset date or an increase in severity on or after the first dose of zanubrutinib until 30 days

after the last dose of zanubrutinib or before initiation of a new anticancer therapy, whichever occurred first.

Table 30 Overall summary of TEAEs (SAS)

	Original				Update			
	Combination Therapy Trials		Monotherapy Trials		Combination Therapy Trials		Monotherapy Trials	
	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
Patients With at Least One TEAE	135 (94.4)	64 (90.1)	1514 (97.7)	57 (96.6)	135 (94.4)	64 (90.1)	1518 (97.9)	57 (96.6)
Grade 3 or Higher	90 (62.9)	34 (47.9)	994 (64.1)	36 (61.0)	94 (65.7)	34 (47.9)	1037 (66.9)	38 (64.4)
Serious	58 (40.6)	22 (31.0)	708 (45.7)	18 (30.5)	64 (44.8)	22 (31.0)	763 (49.2)	19 (32.2)
Leading to Death	12 (8.4)	7 (9.9)	100 (6.5)	1 (1.7)	14 (9.8)	7 (9.9)	113 (7.3)	1 (1.7)
Leading to Treatment Discontinuation	23 (16.1)	8 (11.3)	190 (12.3)	4 (6.8)	26 (18.2)	8 (11.3)	211 (13.6)	4 (6.8)
Leading to Zanubrutinib Discontinuation	21 (14.7)	NA	190 (12.3)	4 (6.8)	24 (16.8)	NA	211 (13.6)	4 (6.8)
Leading to Obinutuzumab Discontinuation	21 (14.7)	8 (11.3)	NA	NA	24 (16.8)	8 (11.3)	NA	NA
Leading to Dose Modification	75 (52.4)	31 (43.7)	749 (48.3)	17 (28.8)	79 (55.2)	31 (43.7)	811 (52.3)	18 (30.5)
Leading to Dose Reduction	13 (9.1)	NA	139 (9.0)	1 (1.7)	15 (10.5)	NA	156 (10.1)	1 (1.7)

	Original				Update			
	Combination Therapy Trials		Monotherapy Trials		Combination Therapy Trials		Monotherapy Trials	
	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
Leading to Dose Interruption	74 (51.7)	31 (43.7)	733 (47.3)	16 (27.1)	78 (54.5)	31 (43.7)	791 (51.0)	17 (28.8)
Treatment-Related	105 (73.4)	49 (69.0)	1222 (78.8)	49 (83.1)	106 (74.1)	49 (69.0)	1231 (79.4)	49 (83.1)
Treatment-Related Grade 3 or Higher	53 (37.1)	19 (26.8)	533 (34.4)	16 (27.1)	55 (38.5)	19 (26.8)	553 (35.7)	17 (28.8)
Treatment-Related Serious	18 (12.6)	8 (11.3)	250 (16.1)	5 (8.5)	20 (14.0)	8 (11.3)	266 (17.2)	5 (8.5)
Treatment-Related Leading to Death	0 (0.0)	1 (1.4)	22 (1.4)	1 (1.7)	1 (0.7)	1 (1.4)	24 (1.5)	1 (1.7)
Zanubrutinib-Related Leading to Zanubrutinib Discontinuation	8 (5.6)	NA	70 (4.5)	1 (1.7)	10 (7.0)	NA	77 (5.0)	1 (1.7)
Zanubrutinib-Related Leading to Obinutuzumab Discontinuation	9 (6.3)	NA	NA	NA	11 (7.7)	NA	NA	NA
Obinutuzumab-Related Leading to Zanubrutinib Discontinuation	7 (4.9)	NA	NA	NA	8 (5.6)	NA	NA	NA
Obinutuzumab-Related Leading to Obinutuzumab Discontinuation	8 (5.6)	3 (4.2)	NA	NA	9 (6.3)	3 (4.2)	NA	NA
Patients With at Least One AESI	116 (81.1)	46 (64.8)	1385 (89.4)	52 (88.1)	118 (82.5)	46 (64.8)	1404 (90.6)	52 (88.1)
Grade 3 or Higher AESI	77 (53.8)	24 (33.8)	800 (51.6)	27 (45.8)	82 (57.3)	24 (33.8)	847 (54.6)	29 (49.2)
Serious AESI	40 (28.0)	13 (18.3)	518 (33.4)	12 (20.3)	47 (32.9)	13 (18.3)	567 (36.6)	13 (22.0)

Source: ADSL, ADAE. Data cutoff: 25OCT2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304).
Abbreviations: AESI, adverse event of special interest; FL, Follicular Lymphoma; NA, not applicable; Obi, Obinutuzumab; TEAE, treatment-emergent adverse event; Zanu, Zanubrutinib.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD and/or obinutuzumab.
Percentages are based on N, unless otherwise specified.
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to last zanubrutinib dose date + 30 days/last obinutuzumab infusion date + 90 days or initiation of new anti-cancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond last zanubrutinib dose date + 30 days/last obinutuzumab infusion date + 90 days and prior to initiation of new anti-cancer therapy is also considered as treatment-emergent.
Dose delay (collected in study BGB-3111-212 only) was merged to dose interruption.
Adverse events were graded by NCI-CTCAE (v5.0 in LTE1 study and v4.03 in all other studies), except for hematologic toxicities in BGB-3111-304 and -305 studies where IWCLL 2008 Grading Scale were used.
Treatment-related TEAEs include those events considered by the investigator to be related, probably or possibly related, or with missing assessment of the causal relationship.

Table 31 Overall summary of TEAEs : first 6 months

(Safety Analysis Set)

	Combination Therapy Trials				Monotherapy Trials	
	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	BGB-3111-GA101 Zanu + Obi (N = 36) n (%)	Pool Zanu + Obi (N = 179) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
Patients With at Least One TEAE	125 (87.4)	63 (88.7)	35 (97.2)	160 (89.4)	1431 (92.3)	57 (96.6)
Grade 3 or Higher	64 (44.8)	26 (36.6)	14 (38.9)	78 (43.6)	555 (35.8)	25 (42.4)
Serious	30 (21.0)	15 (21.1)	7 (19.4)	37 (20.7)	302 (19.5)	12 (20.3)
Leading to Death	4 (2.8)	5 (7.0)	0 (0.0)	4 (2.2)	34 (2.2)	1 (1.7)

Common Adverse Events

Table 32: TEAEs in in 10≥ of patients

Patient Group by System Organ Class and Preferred Term (Safety Analysis Set)

	Original				Update			
	Combination Therapy Trials		Monotherapy Trials		Combination Therapy Trials		Monotherapy Trials	
System Organ Class Preferred Term	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
Patients With at Least One TEAE	135 (94.4)	64 (90.1)	1514 (97.7)	57 (96.6)	135 (94.4)	64 (90.1)	1518 (97.9)	57 (96.6)
Infections and infestations	79 (55.2)	29 (40.8)	1096 (70.7)	32 (54.2)	83 (58.0)	30 (42.3)	1153 (74.4)	32 (54.2)
Pneumonia	17 (11.9)	5 (7.0)	209 (13.5)	7 (11.9)	18 (12.6)	5 (7.0)	224 (14.5)	8 (13.6)
COVID-19	14 (9.8)	7 (9.9)	129 (8.3)	0 (0.0)	18 (12.6)	7 (9.9)	208 (13.4)	0 (0.0)
Urinary tract infection	12 (8.4)	4 (5.6)	202 (13.0)	10 (16.9)	13 (9.1)	4 (5.6)	212 (13.7)	10 (16.9)
Upper respiratory tract infection	10 (7.0)	4 (5.6)	449 (29.0)	16 (27.1)	10 (7.0)	4 (5.6)	461 (29.7)	16 (27.1)
Gastrointestinal disorders	66 (46.2)	30 (42.3)	869 (56.1)	21 (35.6)	67 (46.9)	31 (43.7)	895 (57.7)	21 (35.6)
Diarrhoea	26 (18.2)	12 (16.9)	309 (19.9)	4 (6.8)	27 (18.9)	13 (18.3)	327 (21.1)	4 (6.8)
Constipation	19 (13.3)	6 (8.5)	203 (13.1)	6 (10.2)	19 (13.3)	6 (8.5)	210 (13.5)	6 (10.2)
Nausea	13 (9.1)	10 (14.1)	175 (11.3)	9 (15.3)	13 (9.1)	11 (15.5)	179 (11.5)	9 (15.3)
Abdominal pain	11 (7.7)	8 (11.3)	96 (6.2)	3 (5.1)	11 (7.7)	8 (11.3)	99 (6.4)	3 (5.1)
General disorders and administration site conditions	58 (40.6)	33 (46.5)	606 (39.1)	16 (27.1)	58 (40.6)	34 (47.9)	642 (41.4)	16 (27.1)
Fatigue	22 (15.4)	10 (14.1)	199 (12.8)	7 (11.9)	22 (15.4)	10 (14.1)	212 (13.7)	7 (11.9)
Pyrexia	19 (13.3)	14 (19.7)	169 (10.9)	5 (8.5)	19 (13.3)	14 (19.7)	180 (11.6)	5 (8.5)
Asthenia	17 (11.9)	6 (8.5)	59 (3.8)	1 (1.7)	17 (11.9)	6 (8.5)	60 (3.9)	1 (1.7)
Blood and lymphatic system disorders	54 (37.8)	20 (28.2)	542 (35.0)	26 (44.1)	57 (39.9)	21 (29.6)	562 (36.3)	26 (44.1)
Thrombocytopenia	28 (19.6)	7 (9.9)	130 (8.4)	2 (3.4)	30 (21.0)	7 (9.9)	135 (8.7)	2 (3.4)
Neutropenia	19 (13.3)	12 (16.9)	232 (15.0)	6 (10.2)	19 (13.3)	12 (16.9)	240 (15.5)	6 (10.2)
Anaemia	16 (11.2)	7 (9.9)	229 (14.8)	15 (25.4)	17 (11.9)	7 (9.9)	240 (15.5)	15 (25.4)

	Original				Update			
	Combination Therapy Trials		Monotherapy Trials		Combination Therapy Trials		Monotherapy Trials	
System Organ Class Preferred Term	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
Investigations	51 (35.7)	20 (28.2)	570 (36.8)	32 (54.2)	51 (35.7)	20 (28.2)	598 (38.6)	32 (54.2)
Platelet count decreased	25 (17.5)	10 (14.1)	149 (9.6)	7 (11.9)	26 (18.2)	10 (14.1)	155 (10.0)	7 (11.9)
Neutrophil count decreased	23 (16.1)	8 (11.3)	243 (15.7)	14 (23.7)	24 (16.8)	8 (11.3)	245 (15.8)	14 (23.7)
White blood cell count decreased	14 (9.8)	4 (5.6)	87 (5.6)	10 (16.9)	15 (10.5)	4 (5.6)	88 (5.7)	10 (16.9)
Skin and subcutaneous tissue disorders	45 (31.5)	18 (25.4)	771 (49.7)	26 (44.1)	45 (31.5)	18 (25.4)	795 (51.3)	26 (44.1)
Rash	6 (4.2)	4 (5.6)	251 (16.2)	10 (16.9)	8 (5.6)	4 (5.6)	257 (16.6)	10 (16.9)
Musculoskeletal and connective tissue disorders	44 (30.8)	22 (31.0)	622 (40.1)	15 (25.4)	46 (32.2)	22 (31.0)	648 (41.8)	15 (25.4)
Back pain	15 (10.5)	4 (5.6)	173 (11.2)	4 (6.8)	15 (10.5)	4 (5.6)	179 (11.5)	4 (6.8)
Arthralgia	6 (4.2)	5 (7.0)	226 (14.6)	4 (6.8)	6 (4.2)	5 (7.0)	233 (15.0)	4 (6.8)
Respiratory, thoracic and mediastinal disorders	43 (30.1)	22 (31.0)	641 (41.4)	20 (33.9)	43 (30.1)	22 (31.0)	659 (42.5)	20 (33.9)
Cough	18 (12.6)	9 (12.7)	267 (17.2)	11 (18.6)	18 (12.6)	9 (12.7)	281 (18.1)	11 (18.6)
Dyspnoea	16 (11.2)	7 (9.9)	97 (6.3)	5 (8.5)	16 (11.2)	7 (9.9)	100 (6.5)	5 (8.5)
Nervous system disorders	33 (23.1)	17 (23.9)	508 (32.8)	11 (18.6)	33 (23.1)	17 (23.9)	528 (34.1)	11 (18.6)
Headache	6 (4.2)	2 (2.8)	173 (11.2)	5 (8.5)	6 (4.2)	2 (2.8)	179 (11.5)	5 (8.5)
Injury, poisoning and procedural complications	29 (20.3)	13 (18.3)	557 (35.9)	12 (20.3)	30 (21.0)	13 (18.3)	571 (36.8)	12 (20.3)
Contusion	11 (7.7)	2 (2.8)	300 (19.4)	8 (13.6)	12 (8.4)	2 (2.8)	303 (19.5)	8 (13.6)
Vascular disorders	16 (11.2)	10 (14.1)	370 (23.9)	5 (8.5)	16 (11.2)	10 (14.1)	397 (25.6)	6 (10.2)
Hypertension	5 (3.5)	4 (5.6)	220 (14.2)	3 (5.1)	5 (3.5)	4 (5.6)	242 (15.6)	4 (6.8)
Renal and urinary disorders	12 (8.4)	5 (7.0)	314 (20.3)	15 (25.4)	12 (8.4)	5 (7.0)	327 (21.1)	15 (25.4)
Haematuria	1 (0.7)	1 (1.4)	159 (10.3)	7 (11.9)	1 (0.7)	1 (1.4)	166 (10.7)	7 (11.9)

Source: ADSL, ADAE. Data cutoff: 25OCT2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304).
Abbreviations: FL, Follicular Lymphoma; Obi, Obinutuzumab; TEAE, treatment-emergent adverse event; Zanu, Zanubrutinib.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD and/or obinutuzumab.

Percentages are based on N, unless otherwise specified.
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to last zanubrutinib dose date + 30 days/last obinutuzumab infusion date + 90 days or initiation of new anti-cancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond last zanubrutinib dose date + 30 days/last obinutuzumab infusion date + 90 days and prior to initiation of new anti-cancer therapy is also considered as treatment-emergent. Patients with multiple events for a given preferred term and with multiple preferred terms within a system organ class are counted only once at the preferred term and system organ class levels, respectively. Events are sorted by decreasing frequency first by system organ class and then by preferred term within each system organ class in the original 'BGB-3111-212 Zanu + Obi' column.

Table 33 ***Treatment-Related Adverse Events in ≥10 %*** **of Patients in Any Patient Group by System Organ Class and Preferred Term (Safety Analysis Set)**

	Original				Update			
	Combination Therapy Trials		Monotherapy Trials		Combination Therapy Trials		Monotherapy Trials	
System Organ Class Preferred Term	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
Patients With at Least One Treatment-Related TEAE	105 (73.4)	49 (69.0)	1222 (78.8)	49 (83.1)	106 (74.1)	49 (69.0)	1231 (79.4)	49 (83.1)
Blood and lymphatic system disorders	40 (28.0)	18 (25.4)	370 (23.9)	15 (25.4)	42 (29.4)	18 (25.4)	380 (24.5)	15 (25.4)
Thrombocytopenia	23 (16.1)	7 (9.9)	87 (5.6)	2 (3.4)	24 (16.8)	7 (9.9)	87 (5.6)	2 (3.4)
Neutropenia	14 (9.8)	11 (15.5)	181 (11.7)	4 (6.8)	14 (9.8)	11 (15.5)	186 (12.0)	4 (6.8)
Anaemia	8 (5.6)	2 (2.8)	112 (7.2)	8 (13.6)	8 (5.6)	2 (2.8)	115 (7.4)	8 (13.6)
Investigations	37 (25.9)	12 (16.9)	357 (23.0)	21 (35.6)	38 (26.6)	12 (16.9)	361 (23.3)	21 (35.6)
Platelet count decreased	24 (16.8)	8 (11.3)	125 (8.1)	6 (10.2)	25 (17.5)	8 (11.3)	131 (8.5)	6 (10.2)
Neutrophil count decreased	21 (14.7)	6 (8.5)	223 (14.4)	12 (20.3)	22 (15.4)	6 (8.5)	225 (14.5)	12 (20.3)
White blood cell count decreased	14 (9.8)	3 (4.2)	79 (5.1)	9 (15.3)	15 (10.5)	3 (4.2)	80 (5.2)	9 (15.3)
Gastrointestinal disorders	31 (21.7)	12 (16.9)	349 (22.5)	9 (15.3)	31 (21.7)	12 (16.9)	358 (23.1)	9 (15.3)
Nausea	3 (2.1)	5 (7.0)	63 (4.1)	6 (10.2)	3 (2.1)	5 (7.0)	63 (4.1)	6 (10.2)
Skin and subcutaneous tissue disorders	29 (20.3)	7 (9.9)	441 (28.5)	19 (32.2)	30 (21.0)	7 (9.9)	446 (28.8)	19 (32.2)
Rash	5 (3.5)	1 (1.4)	133 (8.6)	10 (16.9)	6 (4.2)	1 (1.4)	136 (8.8)	10 (16.9)
Infections and infestations	28 (19.6)	12 (16.9)	422 (27.2)	13 (22.0)	30 (21.0)	12 (16.9)	447 (28.8)	13 (22.0)
Upper respiratory tract infection	4 (2.8)	0 (0.0)	118 (7.6)	7 (11.9)	4 (2.8)	0 (0.0)	123 (7.9)	7 (11.9)
Injury, poisoning and procedural complications	11 (7.7)	7 (9.9)	250 (16.1)	5 (8.5)	11 (7.7)	7 (9.9)	253 (16.3)	5 (8.5)
Contusion	7 (4.9)	0 (0.0)	219 (14.1)	5 (8.5)	7 (4.9)	0 (0.0)	221 (14.3)	5 (8.5)

Source: ADSL, ADAE. Data cutoff: 25OCT2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304).

Abbreviations: FL, Follicular Lymphoma; Obi, Obinutuzumab; TEAE, treatment-emergent adverse event; Zanu, Zanubrutinib.

N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD and/or obinutuzumab. Percentages are based on N, unless otherwise specified.
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to last zanubrutinib dose date + 30 days/last obinutuzumab infusion date + 90 days or initiation of new anti-cancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond last zanubrutinib dose date + 30 days/last obinutuzumab infusion date + 90 days and prior to initiation of new anti-cancer therapy is also considered as treatment-emergent. Patients with multiple events for a given preferred term and with multiple preferred terms within a system organ class are counted only once at the preferred term and system organ class levels, respectively. Events are sorted by decreasing frequency first by system organ class and then by preferred term within each system organ class in the original 'BGB-3111-212 Zanu + Obi' column.
Treatment-related TEAEs include those events considered by the investigator to be related, probably or possibly related, or with missing assessment of the causal relationship.

Table 34 Grade 3 or higher Adverse events in ≥ 3%

of Patients in Any Patient Group by System Organ Class and Preferred Term (Safety Analysis Set)

	Original				Update			
	Combination Therapy Trials		Monotherapy Trials		Combination Therapy Trials		Monotherapy Trials	
System Organ Class Preferred Term	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
Patients With at Least One Grade 3 or Higher TEAE	90 (62.9)	34 (47.9)	994 (64.1)	36 (61.0)	94 (65.7)	34 (47.9)	1037 (66.9)	38 (64.4)
Infections and infestations	39 (27.3)	10 (14.1)	404 (26.1)	14 (23.7)	45 (31.5)	10 (14.1)	448 (28.9)	15 (25.4)
Pneumonia	14 (9.8)	3 (4.2)	122 (7.9)	4 (6.8)	15 (10.5)	3 (4.2)	130 (8.4)	5 (8.5)
COVID-19	8 (5.6)	2 (2.8)	40 (2.6)	0 (0.0)	10 (7.0)	2 (2.8)	59 (3.8)	0 (0.0)
COVID-19 pneumonia	5 (3.5)	2 (2.8)	37 (2.4)	0 (0.0)	6 (4.2)	2 (2.8)	55 (3.5)	0 (0.0)
Urinary tract infection	1 (0.7)	0 (0.0)	33 (2.1)	7 (11.9)	2 (1.4)	0 (0.0)	34 (2.2)	7 (11.9)
Cellulitis	0 (0.0)	1 (1.4)	27 (1.7)	2 (3.4)	0 (0.0)	1 (1.4)	27 (1.7)	2 (3.4)
Sepsis	0 (0.0)	0 (0.0)	19 (1.2)	2 (3.4)	0 (0.0)	0 (0.0)	19 (1.2)	2 (3.4)
Blood and lymphatic system disorders	32 (22.4)	14 (19.7)	287 (18.5)	12 (20.3)	33 (23.1)	14 (19.7)	297 (19.2)	12 (20.3)
Neutropenia	16 (11.2)	10 (14.1)	169 (10.9)	6 (10.2)	16 (11.2)	10 (14.1)	175 (11.3)	6 (10.2)
Thrombocytopenia	13 (9.1)	1 (1.4)	53 (3.4)	2 (3.4)	14 (9.8)	1 (1.4)	55 (3.5)	2 (3.4)
Anaemia	7 (4.9)	4 (5.6)	88 (5.7)	8 (13.6)	7 (4.9)	4 (5.6)	88 (5.7)	8 (13.6)
Investigations	27 (18.9)	12 (16.9)	205 (13.2)	10 (16.9)	27 (18.9)	12 (16.9)	213 (13.7)	10 (16.9)
Neutrophil count decreased	19 (13.3)	6 (8.5)	140 (9.0)	5 (8.5)	19 (13.3)	6 (8.5)	144 (9.3)	5 (8.5)
Platelet count decreased	10 (7.0)	4 (5.6)	46 (3.0)	0 (0.0)	10 (7.0)	4 (5.6)	46 (3.0)	0 (0.0)
White blood cell count decreased	5 (3.5)	1 (1.4)	20 (1.3)	0 (0.0)	5 (3.5)	1 (1.4)	22 (1.4)	0 (0.0)
White blood cell count increased	0 (0.0)	0 (0.0)	4 (0.3)	3 (5.1)	0 (0.0)	0 (0.0)	4 (0.3)	3 (5.1)
Respiratory, thoracic and mediastinal disorders	9 (6.3)	4 (5.6)	77 (5.0)	5 (8.5)	10 (7.0)	4 (5.6)	80 (5.2)	5 (8.5)

	Original				Update			
	Combination Therapy Trials		Monotherapy Trials		Combination Therapy Trials		Monotherapy Trials	
System Organ Class Preferred Term	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
Asthma	1 (0.7)	0 (0.0)	3 (0.2)	2 (3.4)	1 (0.7)	0 (0.0)	3 (0.2)	2 (3.4)
Injury, poisoning and procedural complications	4 (2.8)	4 (5.6)	74 (4.8)	0 (0.0)	4 (2.8)	4 (5.6)	80 (5.2)	0 (0.0)
Infusion related reaction	1 (0.7)	3 (4.2)	1 (0.1)	0 (0.0)	1 (0.7)	3 (4.2)	1 (0.1)	0 (0.0)
Vascular disorders	3 (2.1)	1 (1.4)	139 (9.0)	3 (5.1)	3 (2.1)	1 (1.4)	150 (9.7)	4 (6.8)
Hypertension	1 (0.7)	1 (1.4)	114 (7.4)	2 (3.4)	1 (0.7)	1 (1.4)	125 (8.1)	3 (5.1)

Source: ADSL, ADAE. Data cutoff: 25OCT2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304).
Abbreviations: FL, Follicular Lymphoma; Obi, Obinutuzumab; TEAE, treatment-emergent adverse event; Zanu, Zanubrutinib.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD and/or obinutuzumab.
Percentages are based on N, unless otherwise specified.
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to last zanubrutinib dose date + 30 days/last obinutuzumab infusion date + 90 days or initiation of new anti-cancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond last zanubrutinib dose date + 30 days/last obinutuzumab infusion date + 90 days and prior to initiation of new anti-cancer therapy is also considered as treatment-emergent.
Patients with multiple events for a given preferred term and with multiple preferred terms within a system organ class are counted only once at the preferred term and system organ class levels, respectively. Events are sorted by decreasing frequency first by system organ class and then by preferred term within each system organ class in the original 'BGB-3111-212 Zanu + Obi' column.
Adverse events were graded by NCI-CTCAE (v5.0 in LTE1 study and v4.03 in all other studies), except for hematologic toxicities in BGB-3111-304 and -305 studies where IWCLL 2008 Grading Scale were used.
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/bgb_3111/filing_fl_2023_90d/iss/dev/pgm/tlfs/t-teae-soc-pt-i.sas 12JAN2023 01:50 t-12-teae-soc-pt-grd3-3-i.rtf

Adverse Events of Special Interest

Table 35 Adverse Events of Special Interest

Adverse Event of Special Interest Category	Search Criteria
Hemorrhage (including minor bleeding such as Contusion and Petechiae)	Haemorrhage terms (excluding laboratory terms) (SMQ) Narrow
Major hemorrhage - defined as serious or ≥ Grade 3 bleeding at any site, or central nervous system bleeding of any grade	Major haemorrhage: • All Subdural haematoma PT, Subdural haemorrhage PT • All haemorrhage PTs if adverse event SOC is "Nervous system disorders" or • Serious or ≥ Grade 3 haemorrhage PT if adverse event SOC is not "Nervous system disorders"
Atrial fibrillation and flutter	Atrial fibrillation PT, Atrial flutter PT
Hypertension	Hypertension (SMQ) Narrow
Second primary malignancies *Skin cancers*	Malignant tumours (SMQ) Narrow Subcategory - Skin malignant tumours (SMQ) narrow
Tumor lysis syndrome	Tumour lysis syndrome (SMQ) Narrow
Infections *Opportunistic infections*	Infections: Infections and Infestations SOC Subcategory - Opportunistic infections: Opportunistic infections (SMQ) Narrow
Cytopenia	
Neutropenia	Neutropenia PT, Neutrophil count decreased PT, Febrile neutropenia PT, Agranulocytosis PT, Neutropenic infection PT, Neutropenic sepsis PT
Thrombocytopenia	Thrombocytopenia PT, Platelet count decreased PT
Anemia	Anaemia PT, Haemoglobin decreased PT

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term; SMQ, Standardized MedDRA Query; SOC, System Organ Class.

Table 36 Overall Summary of TEAEs of special interest

(Safety Analysis Set)

	Original				Update			
	Combination Therapy Trials		Monotherapy Trials		Combination Therapy Trials		Monotherapy Trials	
	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
Patients With at Least One TEAE of Special Interest	116 (81.1)	46 (64.8)	1385 (89.4)	52 (88.1)	118 (82.5)	46 (64.8)	1404 (90.6)	52 (88.1)
Grade 3 or Higher	77 (53.8)	24 (33.8)	800 (51.6)	27 (45.8)	82 (57.3)	24 (33.8)	847 (54.6)	29 (49.2)
Serious	40 (28.0)	13 (18.3)	518 (33.4)	12 (20.3)	47 (32.9)	13 (18.3)	567 (36.6)	13 (22.0)
Leading to Death	7 (4.9)	4 (5.6)	69 (4.5)	1 (1.7)	9 (6.3)	4 (5.6)	79 (5.1)	1 (1.7)
Leading to Treatment Discontinuation	16 (11.2)	7 (9.9)	125 (8.1)	2 (3.4)	18 (12.6)	7 (9.9)	138 (8.9)	2 (3.4)
Leading to Zanubrutinib Discontinuation	14 (9.8)	NA	125 (8.1)	2 (3.4)	16 (11.2)	NA	138 (8.9)	2 (3.4)
Leading to Obinutuzumab Discontinuation	15 (10.5)	7 (9.9)	NA	NA	17 (11.9)	7 (9.9)	NA	NA
Leading to Dose Modification	53 (37.1)	16 (22.5)	552 (35.6)	13 (22.0)	57 (39.9)	15 (21.1)	615 (39.7)	13 (22.0)
Leading to Dose Reduction	10 (7.0)	NA	91 (5.9)	1 (1.7)	11 (7.7)	NA	103 (6.6)	1 (1.7)
Leading to Dose Interruption	52 (36.4)	16 (22.5)	536 (34.6)	12 (20.3)	56 (39.2)	15 (21.1)	595 (38.4)	12 (20.3)
Treatment-Related of Special Interest	81 (56.6)	32 (45.1)	1021 (65.9)	37 (62.7)	83 (58.0)	32 (45.1)	1038 (67.0)	37 (62.7)
Treatment-Related Grade 3 or Higher	46 (32.2)	16 (22.5)	465 (30.0)	13 (22.0)	48 (33.6)	16 (22.5)	486 (31.4)	14 (23.7)
Treatment-Related Serious	15 (10.5)	6 (8.5)	214 (13.8)	3 (5.1)	17 (11.9)	6 (8.5)	228 (14.7)	3 (5.1)
Treatment-Related Leading to Death	0 (0.0)	0 (0.0)	18 (1.2)	1 (1.7)	1 (0.7)	0 (0.0)	20 (1.3)	1 (1.7)
Zanubrutinib-Related Leading to Zanubrutinib Discontinuation	6 (4.2)	NA	43 (2.8)	1 (1.7)	7 (4.9)	NA	49 (3.2)	1 (1.7)
Zanubrutinib-Related Leading to Obinutuzumab Discontinuation	7 (4.9)	NA	NA	NA	8 (5.6)	NA	NA	NA
Obinutuzumab-Related Leading to Zanubrutinib Discontinuation	5 (3.5)	NA	NA	NA	5 (3.5)	NA	NA	NA
Obinutuzumab-Related Leading to Obinutuzumab Discontinuation	6 (4.2)	3 (4.2)	NA	NA	6 (4.2)	3 (4.2)	NA	NA

Source: ADSL, ADAE. Data cutoff: 25OCT2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304).
Abbreviations: FL, Follicular Lymphoma; NA, not applicable; Obi, Obinutuzumab; TEAE, treatment-emergent adverse event; Zanu, Zanubrutinib.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD and/or obinutuzumab. Percentages are based on N, unless otherwise specified.
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to last zanubrutinib dose date + 30 days/last obinutuzumab infusion date + 90 days or initiation of new anti-cancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond last zanubrutinib dose date + 30 days/last

obinutuzumab infusion date + 90 days and prior to initiation of new anti-cancer therapy is also considered as treatment-emergent.
Dose delay (collected in study BGB-3111-212 only) was merged to dose interruption.
Adverse events were graded by NCI-CTCAE (v5.0 in LTE1 study and v4.03 in all other studies), except for hematologic toxicities in BGB-3111-304 and -305 studies where IWCLL 2008 Grading Scale were used.
Treatment-related TEAEs include those events considered by the investigator to be related, probably or possibly related, or with missing assessment of the causal relationship.

Table 37 TEAEs of special interest by category (SAS)

	Original				Update			
	Combination Therapy Trials		Monotherapy Trials		Combination Therapy Trials		Monotherapy Trials	
AESI Category	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
Patients With at Least One TEAE of Special Interest	116 (81.1)	46 (64.8)	1385 (89.4)	52 (88.1)	118 (82.5)	46 (64.8)	1404 (90.6)	52 (88.1)
Anemia	16 (11.2)	7 (9.9)	236 (15.2)	15 (25.4)	17 (11.9)	7 (9.9)	247 (15.9)	15 (25.4)
Atrial fibrillation and flutter	4 (2.8)	1 (1.4)	72 (4.6)	0 (0.0)	4 (2.8)	1 (1.4)	75 (4.8)	0 (0.0)
Hemorrhage	40 (28.0)	9 (12.7)	785 (50.6)	25 (42.4)	40 (28.0)	9 (12.7)	799 (51.5)	25 (42.4)
Major hemorrhage	2 (1.4)	2 (2.8)	81 (5.2)	2 (3.4)	2 (1.4)	2 (2.8)	88 (5.7)	2 (3.4)
Hypertension	6 (4.2)	4 (5.6)	235 (15.2)	3 (5.1)	6 (4.2)	4 (5.6)	259 (16.7)	4 (6.8)
Infections	79 (55.2)	29 (40.8)	1096 (70.7)	32 (54.2)	83 (58.0)	30 (42.3)	1153 (74.4)	32 (54.2)
Opportunistic infections	4 (2.8)	0 (0.0)	36 (2.3)	1 (1.7)	4 (2.8)	0 (0.0)	38 (2.5)	1 (1.7)
Neutropenia	43 (30.1)	20 (28.2)	458 (29.5)	19 (32.2)	44 (30.8)	20 (28.2)	467 (30.1)	19 (32.2)
Second primary malignancies	9 (6.3)	3 (4.2)	228 (14.7)	3 (5.1)	11 (7.7)	3 (4.2)	248 (16.0)	3 (5.1)
Skin cancers	5 (3.5)	2 (2.8)	136 (8.8)	1 (1.7)	6 (4.2)	2 (2.8)	148 (9.5)	1 (1.7)
Thrombocytopenia	51 (35.7)	17 (23.9)	265 (17.1)	9 (15.3)	53 (37.1)	17 (23.9)	274 (17.7)	9 (15.3)
Tumor lysis syndrome	0 (0.0)	1 (1.4)	5 (0.3)	0 (0.0)	0 (0.0)	1 (1.4)	5 (0.3)	0 (0.0)

Source: ADSL, ADAE. Data cutoff: 25OCT2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304).
Abbreviations: FL, Follicular Lymphoma; Obi, Obinutuzumab; TEAE, treatment-emergent adverse event; Zanu, Zanubrutinib.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD and/or obinutuzumab.
Percentages are based on N, unless otherwise specified.
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to last zanubrutinib dose date + 30 days/last obinutuzumab infusion date + 90 days or initiation of new anti-cancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond last zanubrutinib dose date + 30 days/last obinutuzumab infusion date + 90 days and prior to initiation of new anti-cancer therapy is also considered as treatment-emergent.

Serious adverse event/deaths/other significant events

Deaths

Table 38 Summary of all Deaths (SAS)

	Initial				Update			
	Combination Therapy Trials		Monotherapy Trials		Combination Therapy Trials		Monotherapy Trials	
Death Summary	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
All Deaths	29 (20.3)	22 (31.0)	254 (16.4)	12 (20.3)	35 (24.5)	25 (35.2)	285 (18.4)	13 (22.0)
Cause of death								
Adverse event	12 (8.4)	12 (16.9)	87 (5.6)	1 (1.7)	14 (9.8)	12 (16.9)	104 (6.7)	1 (1.7)
Related to COVID-19	3 (2.1)	6 (8.5)	19 (1.2)	0 (0.0)	3 (2.1)	6 (8.5)	29 (1.9)	0 (0.0)
Disease progression	12 (8.4)	7 (9.9)	111 (7.2)	8 (13.6)	12 (8.4)	9 (12.7)	118 (7.6)	8 (13.6)
Related to COVID-19	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Other	5 (3.5)	2 (2.8)	29 (1.9)	0 (0.0)	7 (4.9)	3 (4.2)	33 (2.1)	0 (0.0)
Related to COVID-19	1 (0.7)	1 (1.4)	0 (0.0)	0 (0.0)	2 (1.4)	1 (1.4)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	1 (1.4)	27 (1.7)	3 (5.1)	2 (1.4)	1 (1.4)	30 (1.9)	4 (6.8)
Deaths ≤30/90 days after last dose date [a]	13 (9.1)	14 (19.7)	101 (6.5)	4 (6.8)	15 (10.5)	14 (19.7)	113 (7.3)	4 (6.8)
Cause of death								
Adverse event	12 (8.4)	10 (14.1)	69 (4.5)	1 (1.7)	14 (9.8)	10 (14.1)	78 (5.0)	1 (1.7)
Related to COVID-19	3 (2.1)	4 (5.6)	16 (1.0)	0 (0.0)	3 (2.1)	4 (5.6)	21 (1.4)	0 (0.0)
Disease progression	1 (0.7)	4 (5.6)	24 (1.5)	3 (5.1)	1 (0.7)	4 (5.6)	26 (1.7)	3 (5.1)
Other	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)	5 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.4)	0 (0.0)
Deaths >30/90 days after last dose date [b]	16 (11.2)	8 (11.3)	153 (9.9)	8 (13.6)	20 (14.0)	11 (15.5)	172 (11.1)	9 (15.3)
Cause of death								
Disease progression	11 (7.7)	3 (4.2)	87 (5.6)	5 (8.5)	11 (7.7)	5 (7.0)	92 (5.9)	5 (8.5)
Related to COVID-19	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Other	5 (3.5)	2 (2.8)	26 (1.7)	0 (0.0)	7 (4.9)	3 (4.2)	30 (1.9)	0 (0.0)
Related to COVID-19	1 (0.7)	1 (1.4)	0 (0.0)	0 (0.0)	2 (1.4)	1 (1.4)	0 (0.0)	0 (0.0)
Adverse event	0 (0.0)	2 (2.8)	18 (1.2)	0 (0.0)	0 (0.0)	2 (2.8)	26 (1.7)	0 (0.0)
Related to COVID-19	0 (0.0)	2 (2.8)	3 (0.2)	0 (0.0)	0 (0.0)	2 (2.8)	8 (0.5)	0 (0.0)
Unknown	0 (0.0)	1 (1.4)	22 (1.4)	3 (5.1)	2 (1.4)	1 (1.4)	24 (1.5)	4 (6.8)

Source: ADSL. Data cutoff: 25OCT2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304).

Abbreviations: FL, Follicular Lymphoma; Obi, Obinutuzumab; Zanu, Zanubrutinib.

N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD and/or obinutuzumab.

Percentages are based on N, unless otherwise specified.

[a] Death within 30 days of last dose of zanubrutinib or within 90 days of last dose of obinutuzumab.

[b] Death after 30 days of last dose of zanubrutinib and after 90 days of last dose of obinutuzumab.

Table 39 TEAEs leading to Death by SOC and PT (SAS)

	Original				Update			
	Combination Therapy Trials		Monotherapy Trials		Combination Therapy Trials		Monotherapy Trials	
System Organ Class Preferred Term	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
Patients With at Least One TEAE Leading to Death	12 (8.4)	7 (9.9)	100 (6.5)	1 (1.7)	14 (9.8)	7 (9.9)	113 (7.3)	1 (1.7)
Infections and infestations	6 (4.2)	3 (4.2)	50 (3.2)	1 (1.7)	7 (4.9)	3 (4.2)	57 (3.7)	1 (1.7)
COVID-19	2 (1.4)	1 (1.4)	14 (0.9)	0 (0.0)	2 (1.4)	1 (1.4)	14 (0.9)	0 (0.0)
COVID-19 pneumonia	1 (0.7)	1 (1.4)	7 (0.5)	0 (0.0)	1 (0.7)	1 (1.4)	13 (0.8)	0 (0.0)
Pneumonia	1 (0.7)	0 (0.0)	12 (0.8)	1 (1.7)	2 (1.4)	0 (0.0)	13 (0.8)	1 (1.7)
Pulmonary mucormycosis	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Septic shock	1 (0.7)	1 (1.4)	2 (0.1)	0 (0.0)	1 (0.7)	1 (1.4)	2 (0.1)	0 (0.0)
Acute hepatitis B	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Arthritis bacterial	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Bacteraemia	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Bacterial sepsis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Endocarditis	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Escherichia sepsis	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Infection	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Lower respiratory tract infection bacterial	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Pneumonia bacterial	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Pneumonia cryptococcal	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Pneumonia fungal	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Pneumonia influenzal	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Pneumonia pseudomonal	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Pneumonia staphylococcal	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Respiratory tract infection	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Scedosporium infection	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Sepsis	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)
Septic encephalopathy	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	3 (2.1)	1 (1.4)	7 (0.5)	0 (0.0)	3 (2.1)	1 (1.4)	8 (0.5)	0 (0.0)
Dyspnoea	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumothorax	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory failure	1 (0.7)	1 (1.4)	5 (0.3)	0 (0.0)	1 (0.7)	1 (1.4)	5 (0.3)	0 (0.0)
Acute respiratory failure	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Bronchiectasis	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Pulmonary oedema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
General disorders and administration site conditions	2 (1.4)	1 (1.4)	16 (1.0)	0 (0.0)	2 (1.4)	1 (1.4)	17 (1.1)	0 (0.0)

	Original				Update			
	Combination Therapy Trials		Monotherapy Trials		Combination Therapy Trials		Monotherapy Trials	
System Organ Class Preferred Term	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
Death	1 (0.7)	1 (1.4)	7 (0.5)	0 (0.0)	1 (0.7)	1 (1.4)	8 (0.5)	0 (0.0)
Multiple organ dysfunction syndrome	1 (0.7)	0 (0.0)	7 (0.5)	0 (0.0)	1 (0.7)	0 (0.0)	7 (0.5)	0 (0.0)
Malaise	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.7)	0 (0.0)	13 (0.8)	0 (0.0)	2 (1.4)	0 (0.0)	14 (0.9)	0 (0.0)
Metastatic neoplasm	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Acute myeloid leukaemia	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Adenocarcinoma gastric	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Adenocarcinoma of colon	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Adenocarcinoma pancreas	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Breast cancer metastatic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lung neoplasm malignant	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Lung squamous cell carcinoma recurrent	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Lymphoma transformation	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Metastatic malignant melanoma	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Metastatic squamous cell carcinoma	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Neuroendocrine carcinoma	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Neuroendocrine carcinoma of prostate	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Skin squamous cell carcinoma recurrent	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Squamous cell carcinoma of lung	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Psychiatric disorders	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Completed suicide	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	0 (0.0)	1 (1.4)	1 (0.1)	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.1)	0 (0.0)
Anaemia	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)
Bone marrow necrosis	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Cardiac disorders	0 (0.0)	1 (1.4)	11 (0.7)	0 (0.0)	0 (0.0)	1 (1.4)	12 (0.8)	0 (0.0)
Acute myocardial infarction	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Cardiac arrest	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Cardiac failure	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Cardiac failure congestive	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Cardiogenic shock	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Cardiomegaly	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Cardiopulmonary failure	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)

	Original				Update			
	Combination Therapy Trials		Monotherapy Trials		Combination Therapy Trials		Monotherapy Trials	
System Organ Class Preferred Term	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
Hypertensive heart disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Myocardial infarction	0 (0.0)	1 (1.4)	1 (0.1)	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.1)	0 (0.0)
Pulseless electrical activity	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Colitis	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Jaundice	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Immune system disorders	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)
Anaphylactic reaction	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	4 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.3)	0 (0.0)
Brain herniation	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Craniocerebral injury	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Fall	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Road traffic accident	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Subdural haematoma	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Tumour lysis syndrome	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Mobility decreased	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Nervous system disorders	0 (0.0)	0 (0.0)	5 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.4)	0 (0.0)
Central nervous system lesion	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Cerebral haemorrhage	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Cerebral infarction	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Haemorrhagic transformation stroke	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Ischaemic stroke	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Renal and urinary disorders	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)
Acute kidney injury	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Renal failure	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Urinary tract obstruction	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Toxic epidermal necrolysis	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Vascular disorders	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Aortic aneurysm rupture	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Aortic dissection	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)

Source: ADSL, ADAE. Data cutoff: 25OCT2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304).
Abbreviations: FL, Follicular Lymphoma; Obi, Obinutuzumab; TEAE, treatment-emergent adverse event; Zanu, Zanubrutinib.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD and/or obinutuzumab.

Percentages are based on N, unless otherwise specified.
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to last zanubrutinib dose date + 30 days/last obinutuzumab infusion date + 90 days or initiation of new anti-cancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond last zanubrutinib dose date + 30 days/last obinutuzumab infusion date + 90 days and prior to initiation of new anti-cancer therapy is also considered as treatment-emergent. Patients with multiple events for a given preferred term and with multiple preferred terms within a system organ class are counted only once at the preferred term and system organ class levels, respectively. Events are sorted by decreasing frequency first by system organ class and then by preferred term within each system organ class in the original 'BGB-3111-212 Zanu + Obi' column.

Study 212:

In the ZO group, 35 (24.5%) patients died while on study. Overall, 14 (9.8%) patients had adverse events leading to death, an increase of 2 patients from the original SCS; the new adverse events leading to death were Pneumonia and Adenocarcinoma pancreas (1 patient each).

Study 212/Combination therapy:

The overall incidence of adverse events was similar between the combination arm and the obinutuzumab monotherapy arm and, consistent with this the incidence of adverse events leading to death was comparable in zanubrutinib + obinutuzumab group with that found in obinutuzumab monotherapy group. The small sizes of the patient groups add uncertainty to these findings.

The MAH has provided the requested narratives for all patients who died in study 212. Generally, if not due to PD, the fatal AEs were most frequently due to infections, which is common in these patients both due to the disease itself as well as prior and current treatment. One patient had a "metastatic neoplasm" and one patient died due to AML.

In the **monotherapy pool** 78/1550 patients died within 30 days after the last dose of zanubrutinib or within 90 days after the last dose of obinutuzumab due to an adverse event. Not unexpectedly in a late line lymphoma population the most frequent cause was related to infections including COVID-19.

Serious adverse events

Table 40

Table 14: Serious Treatment-Emergent Adverse Events Reported in ≥ 1% of Patients in Any Patient Group by System Organ Class and Preferred Term (Safety Analysis Set)

	Original				Update			
	Combination Therapy Trials		Monotherapy Trials		Combination Therapy Trials		Monotherapy Trials	
System Organ Class Preferred Term	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
Patients With at Least One Serious TEAE	58 (40.6)	22 (31.0)	708 (45.7)	18 (30.5)	64 (44.8)	22 (31.0)	763 (49.2)	19 (32.2)
Infections and infestations	36 (25.2)	8 (11.3)	368 (23.7)	11 (18.6)	42 (29.4)	8 (11.3)	409 (26.4)	12 (20.3)
Pneumonia	12 (8.4)	2 (2.8)	117 (7.5)	4 (6.8)	13 (9.1)	2 (2.8)	127 (8.2)	5 (8.5)
COVID-19	8 (5.6)	2 (2.8)	35 (2.3)	0 (0.0)	10 (7.0)	2 (2.8)	50 (3.2)	0 (0.0)
COVID-19 pneumonia	6 (4.2)	3 (4.2)	38 (2.5)	0 (0.0)	7 (4.9)	3 (4.2)	58 (3.7)	0 (0.0)
Lower respiratory tract infection	2 (1.4)	0 (0.0)	12 (0.8)	0 (0.0)	2 (1.4)	0 (0.0)	12 (0.8)	0 (0.0)
Anal abscess	1 (0.7)	0 (0.0)	2 (0.1)	0 (0.0)	2 (1.4)	0 (0.0)	2 (0.1)	0 (0.0)
Gastroenteritis	1 (0.7)	1 (1.4)	6 (0.4)	0 (0.0)	1 (0.7)	1 (1.4)	6 (0.4)	0 (0.0)
Septic shock	1 (0.7)	1 (1.4)	3 (0.2)	0 (0.0)	2 (1.4)	1 (1.4)	3 (0.2)	0 (0.0)
Urinary tract infection	1 (0.7)	0 (0.0)	27 (1.7)	4 (6.8)	2 (1.4)	0 (0.0)	29 (1.9)	4 (6.8)
Bacteraemia	0 (0.0)	0 (0.0)	4 (0.3)	1 (1.7)	0 (0.0)	0 (0.0)	4 (0.3)	1 (1.7)
Cellulitis	0 (0.0)	1 (1.4)	23 (1.5)	2 (3.4)	0 (0.0)	1 (1.4)	23 (1.5)	2 (3.4)
Complicated appendicitis	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)
Gastroenteritis viral	0 (0.0)	0 (0.0)	2 (0.1)	1 (1.7)	0 (0.0)	0 (0.0)	2 (0.1)	1 (1.7)
Hepatitis E	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)
Influenza	0 (0.0)	0 (0.0)	7 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	8 (0.5)	1 (1.7)
Pleural infection	0 (0.0)	0 (0.0)	1 (0.1)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.1)	1 (1.7)
Pneumonia bacterial	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	2 (0.1)	0 (0.0)
Scrotal infection	0 (0.0)	0 (0.0)	2 (0.1)	1 (1.7)	0 (0.0)	0 (0.0)	2 (0.1)	1 (1.7)
Sepsis	0 (0.0)	0 (0.0)	18 (1.2)	2 (3.4)	0 (0.0)	0 (0.0)	18 (1.2)	2 (3.4)

	Original				Update			
	Combination Therapy Trials		Monotherapy Trials		Combination Therapy Trials		Monotherapy Trials	
System Organ Class Preferred Term	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (5.6)	0 (0.0)	99 (6.4)	2 (3.4)	9 (6.3)	0 (0.0)	108 (7.0)	2 (3.4)
Myelodysplastic syndrome	2 (1.4)	0 (0.0)	1 (0.1)	0 (0.0)	2 (1.4)	0 (0.0)	1 (0.1)	0 (0.0)
Tumour pain	2 (1.4)	0 (0.0)	2 (0.1)	1 (1.7)	2 (1.4)	0 (0.0)	2 (0.1)	1 (1.7)
Metastases to central nervous system	0 (0.0)	0 (0.0)	1 (0.1)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.1)	1 (1.7)
Sarcomatoid carcinoma of the lung	0 (0.0)	0 (0.0)	1 (0.1)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.1)	1 (1.7)
General disorders and administration site conditions	7 (4.9)	4 (5.6)	59 (3.8)	1 (1.7)	7 (4.9)	4 (5.6)	62 (4.0)	1 (1.7)
Pyrexia	2 (1.4)	2 (2.8)	27 (1.7)	1 (1.7)	2 (1.4)	2 (2.8)	27 (1.7)	1 (1.7)
Death	1 (0.7)	1 (1.4)	7 (0.5)	0 (0.0)	1 (0.7)	1 (1.4)	8 (0.5)	0 (0.0)
Influenza like illness	0 (0.0)	1 (1.4)	1 (0.1)	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.1)	0 (0.0)
Gastrointestinal disorders	6 (4.2)	4 (5.6)	74 (4.8)	2 (3.4)	7 (4.9)	4 (5.6)	79 (5.1)	2 (3.4)
Colitis	1 (0.7)	1 (1.4)	4 (0.3)	0 (0.0)	1 (0.7)	1 (1.4)	5 (0.3)	0 (0.0)
Diarrhoea	1 (0.7)	1 (1.4)	8 (0.5)	0 (0.0)	1 (0.7)	1 (1.4)	8 (0.5)	0 (0.0)
Ascites	0 (0.0)	0 (0.0)	1 (0.1)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.1)	1 (1.7)
Nausea	0 (0.0)	1 (1.4)	2 (0.1)	1 (1.7)	0 (0.0)	1 (1.4)	3 (0.2)	1 (1.7)
Upper gastrointestinal haemorrhage	0 (0.0)	1 (1.4)	4 (0.3)	0 (0.0)	0 (0.0)	1 (1.4)	4 (0.3)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	6 (4.2)	3 (4.2)	67 (4.3)	4 (6.8)	7 (4.9)	3 (4.2)	70 (4.5)	4 (6.8)
Pleural effusion	2 (1.4)	0 (0.0)	18 (1.2)	1 (1.7)	2 (1.4)	0 (0.0)	19 (1.2)	1 (1.7)
Respiratory failure	1 (0.7)	1 (1.4)	9 (0.6)	0 (0.0)	1 (0.7)	1 (1.4)	9 (0.6)	0 (0.0)
Asthma	0 (0.0)	0 (0.0)	3 (0.2)	1 (1.7)	0 (0.0)	0 (0.0)	3 (0.2)	1 (1.7)
Chronic obstructive pulmonary disease	0 (0.0)	1 (1.4)	4 (0.3)	1 (1.7)	0 (0.0)	1 (1.4)	4 (0.3)	1 (1.7)
Hypoxia	0 (0.0)	1 (1.4)	2 (0.1)	0 (0.0)	0 (0.0)	1 (1.4)	3 (0.2)	0 (0.0)
Pneumonia aspiration	0 (0.0)	0 (0.0)	2 (0.1)	1 (1.7)	0 (0.0)	0 (0.0)	2 (0.1)	1 (1.7)
Injury, poisoning and procedural complications	4 (2.8)	2 (2.8)	73 (4.7)	0 (0.0)	4 (2.8)	2 (2.8)	79 (5.1)	0 (0.0)
Fall	1 (0.7)	1 (1.4)	16 (1.0)	0 (0.0)	1 (0.7)	1 (1.4)	18 (1.2)	0 (0.0)
Infusion related reaction	1 (0.7)	1 (1.4)	0 (0.0)	0 (0.0)	1 (0.7)	1 (1.4)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	3 (2.1)	2 (2.8)	67 (4.3)	1 (1.7)	3 (2.1)	2 (2.8)	71 (4.6)	1 (1.7)
Thrombocytopenia	2 (1.4)	0 (0.0)	5 (0.3)	0 (0.0)	2 (1.4)	0 (0.0)	5 (0.3)	0 (0.0)
Febrile neutropenia	1 (0.7)	0 (0.0)	16 (1.0)	0 (0.0)	1 (0.7)	0 (0.0)	17 (1.1)	0 (0.0)
Anaemia	0 (0.0)	1 (1.4)	24 (1.5)	0 (0.0)	0 (0.0)	1 (1.4)	25 (1.6)	0 (0.0)
Lymphadenopathy	0 (0.0)	0 (0.0)	2 (0.1)	1 (1.7)	0 (0.0)	0 (0.0)	2 (0.1)	1 (1.7)
Necrotic lymphadenopathy	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)

	Original				Update			
	Combination Therapy Trials		Monotherapy Trials		Combination Therapy Trials		Monotherapy Trials	
System Organ Class Preferred Term	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
Cardiac disorders	3 (2.1)	2 (2.8)	79 (5.1)	1 (1.7)	4 (2.8)	2 (2.8)	83 (5.4)	1 (1.7)
Atrial fibrillation	2 (1.4)	1 (1.4)	20 (1.3)	0 (0.0)	2 (1.4)	1 (1.4)	21 (1.4)	0 (0.0)
Myocardial infarction	0 (0.0)	1 (1.4)	4 (0.3)	0 (0.0)	0 (0.0)	1 (1.4)	4 (0.3)	0 (0.0)
Myocardial ischaemia	0 (0.0)	0 (0.0)	4 (0.3)	1 (1.7)	0 (0.0)	0 (0.0)	5 (0.3)	1 (1.7)
Musculoskeletal and connective tissue disorders	2 (1.4)	0 (0.0)	31 (2.0)	1 (1.7)	2 (1.4)	0 (0.0)	34 (2.2)	1 (1.7)
Intervertebral disc protrusion	0 (0.0)	0 (0.0)	2 (0.1)	1 (1.7)	0 (0.0)	0 (0.0)	2 (0.1)	1 (1.7)
Nervous system disorders	2 (1.4)	1 (1.4)	59 (3.8)	0 (0.0)	3 (2.1)	1 (1.4)	65 (4.2)	0 (0.0)
Syncope	0 (0.0)	1 (1.4)	14 (0.9)	0 (0.0)	0 (0.0)	1 (1.4)	14 (0.9)	0 (0.0)
Psychiatric disorders	1 (0.7)	0 (0.0)	11 (0.7)	1 (1.7)	1 (0.7)	0 (0.0)	11 (0.7)	1 (1.7)
Anxiety	0 (0.0)	0 (0.0)	2 (0.1)	1 (1.7)	0 (0.0)	0 (0.0)	2 (0.1)	1 (1.7)
Immune system disorders	0 (0.0)	1 (1.4)	1 (0.1)	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.1)	0 (0.0)
Anaphylactic reaction	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)
Investigations	0 (0.0)	1 (1.4)	18 (1.2)	0 (0.0)	0 (0.0)	1 (1.4)	21 (1.4)	0 (0.0)
Amylase increased	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)
Lipase increased	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	0 (0.0)	2 (2.8)	23 (1.5)	1 (1.7)	1 (0.7)	2 (2.8)	27 (1.7)	1 (1.7)
Hyperglycaemia	0 (0.0)	0 (0.0)	1 (0.1)	1 (1.7)	0 (0.0)	0 (0.0)	3 (0.2)	1 (1.7)
Hypoglycaemia	0 (0.0)	1 (1.4)	1 (0.1)	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.1)	0 (0.0)
Tumour lysis syndrome	0 (0.0)	1 (1.4)	4 (0.3)	0 (0.0)	0 (0.0)	1 (1.4)	4 (0.3)	0 (0.0)
Renal and urinary disorders	0 (0.0)	1 (1.4)	40 (2.6)	2 (3.4)	0 (0.0)	1 (1.4)	42 (2.7)	2 (3.4)
Acute kidney injury	0 (0.0)	0 (0.0)	10 (0.6)	1 (1.7)	0 (0.0)	0 (0.0)	10 (0.6)	1 (1.7)
Haematuria	0 (0.0)	1 (1.4)	10 (0.6)	1 (1.7)	0 (0.0)	1 (1.4)	12 (0.8)	1 (1.7)
Hydronephrosis	0 (0.0)	0 (0.0)	3 (0.2)	1 (1.7)	0 (0.0)	0 (0.0)	3 (0.2)	1 (1.7)
Surgical and medical procedures	0 (0.0)	0 (0.0)	1 (0.1)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.1)	1 (1.7)
Abortion induced	0 (0.0)	0 (0.0)	1 (0.1)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.1)	1 (1.7)

Source: ADSL, ADAE. Data cutoff: 25OCT2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304).

Abbreviations: FL, Follicular Lymphoma; Obi, Obinutuzumab; TEAE, treatment-emergent adverse event; Zanu, Zanubrutinib.

N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD and/or obinutuzumab. Percentages are based on N, unless otherwise specified.

TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to last zanubrutinib dose date + 30 days/last obinutuzumab infusion date + 90 days or initiation of new anti-cancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond last zanubrutinib dose date + 30 days/last obinutuzumab infusion date + 90 days and prior to initiation of new anti-cancer therapy is also considered as treatment-emergent.

Patients with multiple events for a given preferred term and with multiple preferred terms within a system organ class are counted only once at the preferred term and system organ class levels, respectively. Events are sorted by decreasing frequency first by system organ class and then by preferred term within each system organ class in the original 'BGB-3111-212 Zanu + Obi' column. MedDRA Version: 24.0.

/bgb_3111/filing_fl_2023_90d/iss/dev/pgm/tlfs/t-teae-soc-pt-i.sas 12JAN2023 01:50 t-15-ser-teae-soc-pt-1-i.rtf

The majority of SAEs belonged to the SOC Infections and Infestations for both the combination and monotherapy treatment.

Study 212/combination therapy:

Overall there were more SAEs in the ZO arm compared to the O arm with the most frequent belonging to the SOC Infections and Infestations with the frequency in the ZO arm being more than twice that of the O arm.

Monotherapy pool:

There were overall more SAEs in the monotherapy pool compared to the combination therapy pool despite the added obinutuzumab in the latter. This is most likely due to the more than double exposure in the monotherapy pool, as previously explained.

Laboratory findings

Table 41 Select Laboratory abnormalities (≥ 20% zanubrutinib) that worsened from baseline (SAS)

	BGB-3111-212 Zanu + Obi (N = 143)		BGB-3111-212 Obi (N = 71)	
Laboratory Abnormality	**All Grades n (%)**	**Grade 3 or 4 n (%)**	**All Grades n (%)**	**Grade 3 or 4 n (%)**
Hematologic Abnormalities				
Hemoglobin decreased	38 (31.1)	1 (0.8)	13 (22.8)	0 (0.0)
Platelets decreased	79 (64.8)	14 (11.5)	24 (42.9)	6 (10.7)
Neutrophils decreased	57 (46.7)	21 (17.2)	24 (42.1)	8 (14.0)
Chemistry Abnormalities				
Alanine Aminotransferase increased	28 (23.0)	0 (0.0)	16 (27.6)	0 (0.0)
Glucose increased	65 (53.3)	10 (8.2)	24 (41.4)	5 (8.6)
Phosphate decreased	26 (21.3)	1 (0.8)	8 (13.8)	0 (0.0)

Source: ADSL, ADLB. Data cutoff: 25JUN2022(212).
Abbreviations: Obi, Obinutuzumab; Zanu, Zanubrutinib.
/bgb_3111/filing_fl_2022/iss/dev/pgm/tlfs/t-lab-abn-212-i.sas 20OCT2022 05:33 t-38-lab-abn-212-i.rtf

Table 42

Table 41: Shifts in ≥ 2 Toxicity Grades From Baseline to the Worst Postbaseline Grade for Selected Chemistry Parameters (Safety Analysis Set)

	Combination Therapy Trials				Monotherapy Trials	
	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	BGB-3111-GA101 Zanu + Obi (N = 36) n (%)	Pool Zanu + Obi (N = 179) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
Alkaline Phosphatase (U/L)						
n	122	59	36	158	1550	59
High directionality	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	16 (1.0)	1 (1.7)
Alanine Aminotransferase (U/L)						
n	122	59	36	158	1550	59
High directionality	1 (0.8)	1 (1.7)	0 (0.0)	1 (0.6)	43 (2.8)	0 (0.0)
Aspartate Aminotransferase (U/L)						
n	122	59	36	158	1550	59
High directionality	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	30 (1.9)	0 (0.0)
Albumin (g/L)						
n	122	59	36	158	1550	59
Low directionality	0 (0.0)	2 (3.4)	2 (5.6)	2 (1.3)	51 (3.3)	1 (1.7)
Bilirubin (umol/L)						
n	122	59	36	158	1550	59
High directionality	1 (0.8)	0 (0.0)	2 (5.6)	3 (1.9)	55 (3.5)	0 (0.0)
Calcium (mmol/L)						
n	122	59	36	158	1550	59
Low directionality	6 (4.9)	3 (5.1)	2 (5.6)	8 (5.1)	64 (4.1)	3 (5.1)
High directionality	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (0.6)	0 (0.0)
Creatinine (umol/L)						
n	122	59	36	158	1550	59
High directionality	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.6)	33 (2.1)	3 (5.1)
Glucose (mmol/L)						
n	122	59	36	158	1549	59
Low directionality	0 (0.0)	2 (3.4)	2 (5.6)	2 (1.3)	32 (2.1)	1 (1.7)
High directionality	10 (8.2)	6 (10.2)	6 (16.7)	16 (10.1)	135 (8.7)	5 (8.5)
Potassium (mmol/L)						
n	122	59	36	158	1550	59
Low directionality	0 (0.0)	2 (3.4)	0 (0.0)	0 (0.0)	28 (1.8)	0 (0.0)
High directionality	2 (1.6)	1 (1.7)	1 (2.8)	3 (1.9)	52 (3.4)	0 (0.0)
Sodium (mmol/L)						
n	122	59	36	158	1550	59
Low directionality	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.6)	47 (3.0)	1 (1.7)
High directionality	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.5)	0 (0.0)
Magnesium (mmol/L)						
n	122	59	36	158	1550	59
Low directionality	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.5)	0 (0.0)
High directionality	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (0.6)	0 (0.0)

	Combination Therapy Trials				Monotherapy Trials	
	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	BGB-3111-GA101 Zanu + Obi (N = 36) n (%)	Pool Zanu + Obi (N = 179) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
Phosphate (mmol/L)						
n	122	59	36	158	1509	59
Low directionality	26 (21.3)	8 (13.6)	8 (22.2)	34 (21.5)	315 (20.9)	11 (18.6)
Urate (umol/L)						
n	NA*	NA*	36	36	767	59
High directionality	NA*	NA*	1 (2.8)	1 (2.8)	22 (2.9)	2 (3.4)

Source: ADSL, ADLB. Data cutoff: 25JUN2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 01JUL2022(LTE1), 01DEC2021(305), 07SEP2021(304).
Abbreviations: FL, Follicular Lymphoma; NA, not applicable; Obi, Obinutuzumab; Zanu, Zanubrutinib.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD and/or obinutuzumab.
Percentages are based on n, number of patients with at least one assessment at baseline or any time postbaseline, respectively.
Postbaseline laboratory results were summarized up to 30 days following study drug discontinuation or initiation of new anticancer therapy, whichever comes first.
Laboratory results are graded using CTCAE v4.03.
*Urate was not collected in study 212.
/bgb_3111/filing_fl_2022/iss/dev/pgm/tlfs/t-chem-abn-shift2-i.sas 15NOV2022 21:30 t-37-chem-abn-shift2-i.rtf

Potential Hy's Law Cases:

Liver function test results were evaluated for all patients who received zanubrutinib and/or obinutuzumab for evidence of potential drug-induced liver injury per Hy's Law criteria. Hy's law criteria requires ALT or AST values > 3 x upper limit of normal (ULN) and total bilirubin values > 2 x ULN.

In Study BGB-3111-212, no cases of Hy's law were observed.

Haematology

The overall incidences of abnormal laboratory values were similar between the combination arm of Study 212 and the zanubrutinib monotherapy group. However, decreased neutrophil and platelet count were common and zanubrutinib adds to this known obinutuzumab. Neutropenia and thrombocytopenia as AEs have been discussed previously.

Chemistry

No clinically relevant differences between patient groups were observed for serum chemistry analytes of interest for postbaseline shifts of ≥ 2 toxicity grades. Increases of ≥ 2 toxicity grades in ALT or AST were reported in less than 3% of patients in every patient group; no ≥ 2 toxicity-grade shifts in AST were reported in study 212.

Safety in special populations

Age:

Table 43 Overall Summary of TEAEs by age

Table 38: Overall Summary of Treatment-Emergent Adverse Events by Age Category (Safety Analysis Set)

	Original						Update					
	BGB-3111-212 Zanu + Obi (N = 143)		BGB-3111-212 Obi (N = 71)		All Patients (N = 1550)		BGB-3111-212 Zanu + Obi (N = 143)		BGB-3111-212 Obi (N = 71)		All Patients (N = 1550)	
	< 65 years (N = 83) n (%)	≥ 65 years (N = 60) n (%)	< 65 years (N = 32) n (%)	≥ 65 years (N = 39) n (%)	< 65 years (N = 600) n (%)	≥ 65 years (N = 950) n (%)	< 65 years (N = 83) n (%)	≥ 65 years (N = 60) n (%)	< 65 years (N = 32) n (%)	≥ 65 years (N = 39) n (%)	< 65 years (N = 600) n (%)	≥ 65 years (N = 950) n (%)
Patients With at Least One TEAE	78 (94.0)	57 (95.0)	29 (90.6)	35 (89.7)	581 (96.8)	933 (98.2)	78 (94.0)	57 (95.0)	29 (90.6)	35 (89.7)	582 (97.0)	936 (98.5)
Grade 3 or Higher	49 (59.0)	41 (68.3)	16 (50.0)	18 (46.2)	363 (60.5)	631 (66.4)	52 (62.7)	42 (70.0)	16 (50.0)	18 (46.2)	376 (62.7)	661 (69.6)
Serious	31 (37.3)	27 (45.0)	7 (21.9)	15 (38.5)	233 (38.8)	475 (50.0)	34 (41.0)	30 (50.0)	7 (21.9)	15 (38.5)	249 (41.5)	514 (54.1)
Leading to Death	6 (7.2)	6 (10.0)	4 (12.5)	3 (7.7)	19 (3.2)	81 (8.5)	7 (8.4)	7 (11.7)	4 (12.5)	3 (7.7)	21 (3.5)	92 (9.7)
Leading to Treatment Discontinuation	11 (13.3)	12 (20.0)	5 (15.6)	3 (7.7)	50 (8.3)	140 (14.7)	12 (14.5)	14 (23.3)	5 (15.6)	3 (7.7)	52 (8.7)	159 (16.7)
Leading to Zanubrutinib Discontinuation	11 (13.3)	10 (16.7)	NA	NA	50 (8.3)	140 (14.7)	12 (14.5)	12 (20.0)	NA	NA	52 (8.7)	159 (16.7)
Leading to Obinutuzumab Discontinuation	9 (10.8)	12 (20.0)	5 (15.6)	3 (7.7)	NA	NA	10 (12.0)	14 (23.3)	5 (15.6)	3 (7.7)	NA	NA
Leading to Dose Modification	40 (48.2)	35 (58.3)	16 (50.0)	15 (38.5)	249 (41.5)	500 (52.6)	42 (50.6)	37 (61.7)	16 (50.0)	15 (38.5)	273 (45.5)	538 (56.6)
Leading to Dose Reduction	4 (4.8)	9 (15.0)	NA	NA	43 (7.2)	96 (10.1)	5 (6.0)	10 (16.7)	NA	NA	51 (8.5)	105 (11.1)
Leading to Dose Interruption	39 (47.0)	35 (58.3)	16 (50.0)	15 (38.5)	245 (40.8)	488 (51.4)	41 (49.4)	37 (61.7)	16 (50.0)	15 (38.5)	266 (44.3)	525 (55.3)
Treatment-Related	59 (71.1)	46 (76.7)	23 (71.9)	26 (66.7)	476 (79.3)	746 (78.5)	60 (72.3)	46 (76.7)	23 (71.9)	26 (66.7)	478 (79.7)	753 (79.3)
Treatment-Related Grade 3 or Higher	30 (36.1)	23 (38.3)	8 (25.0)	11 (28.2)	212 (35.3)	321 (33.8)	32 (38.6)	23 (38.3)	8 (25.0)	11 (28.2)	215 (35.8)	338 (35.6)
Treatment-Related Serious	10 (12.0)	8 (13.3)	1 (3.1)	7 (17.9)	93 (15.5)	157 (16.5)	12 (14.5)	8 (13.3)	1 (3.1)	7 (17.9)	98 (16.3)	168 (17.7)

	Original						Update					
	BGB-3111-212 Zanu + Obi (N = 143)		BGB-3111-212 Obi (N = 71)		All Patients (N = 1550)		BGB-3111-212 Zanu + Obi (N = 143)		BGB-3111-212 Obi (N = 71)		All Patients (N = 1550)	
	< 65 years (N = 83) n (%)	≥ 65 years (N = 60) n (%)	< 65 years (N = 32) n (%)	≥ 65 years (N = 39) n (%)	< 65 years (N = 600) n (%)	≥ 65 years (N = 950) n (%)	< 65 years (N = 83) n (%)	≥ 65 years (N = 60) n (%)	< 65 years (N = 32) n (%)	≥ 65 years (N = 39) n (%)	< 65 years (N = 600) n (%)	≥ 65 years (N = 950) n (%)
Treatment-Related Leading to Death	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	6 (1.0)	16 (1.7)	1 (1.2)	0 (0.0)	0 (0.0)	1 (2.6)	6 (1.0)	18 (1.9)
Zanubrutinib-Related Leading to Zanubrutinib Discontinuation	6 (7.2)	2 (3.3)	NA	NA	18 (3.0)	52 (5.5)	7 (8.4)	3 (5.0)	NA	NA	19 (3.2)	58 (6.1)
Zanubrutinib-Related Leading to Obinutuzumab Discontinuation	6 (7.2)	3 (5.0)	NA	NA	NA	NA	7 (8.4)	4 (6.7)	NA	NA	NA	NA
Obinutuzumab-Related Leading to Zanubrutinib Discontinuation	5 (6.0)	2 (3.3)	NA	NA	NA	NA	6 (7.2)	2 (3.3)	NA	NA	NA	NA
Obinutuzumab-Related Leading to Obinutuzumab Discontinuation	6 (7.2)	2 (3.3)	1 (3.1)	2 (5.1)	NA	NA	7 (8.4)	2 (3.3)	1 (3.1)	2 (5.1)	NA	NA
Patients With at Least One AESI	65 (78.3)	51 (85.0)	20 (62.5)	26 (66.7)	527 (87.8)	858 (90.3)	67 (80.7)	51 (85.0)	20 (62.5)	26 (66.7)	534 (89.0)	870 (91.6)
Grade 3 or Higher AESI	42 (50.6)	35 (58.3)	11 (34.4)	13 (33.3)	298 (49.7)	502 (52.8)	45 (54.2)	37 (61.7)	11 (34.4)	13 (33.3)	311 (51.8)	536 (56.4)
Serious AESI	19 (22.9)	21 (35.0)	3 (9.4)	10 (25.6)	182 (30.3)	336 (35.4)	22 (26.5)	25 (41.7)	3 (9.4)	10 (25.6)	192 (32.0)	375 (39.5)

Source: ADSL, ADAE. Data cutoff: 25OCT2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304).
Abbreviations: AESI, adverse event of special interest; FL, Follicular Lymphoma; NA, not applicable; Obi, Obinutuzumab; TEAE, treatment-emergent adverse event; Zanu, Zanubrutinib.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD and/or obinutuzumab.
Percentages are based on N, unless otherwise specified.
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to last zanubrutinib dose date + 30 days/last obinutuzumab infusion date + 90 days or initiation of new anti-cancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond last zanubrutinib dose date + 30 days/last obinutuzumab infusion date + 90 days and prior to initiation of new anti-cancer therapy is also considered as treatment-emergent.

Dose delay (collected in study BGB-3111-212 only) was merged to dose interruption.
Adverse events were graded by NCI-CTCAE (v5.0 in LTE1 study and v4.03 in all other studies), except for hematologic toxicities in BGB-3111-304 and -305 studies where IWCLL 2008 Grading Scale were used.

Table 44

Table 39: Treatment-Emergent Adverse Events Reported by ≥ 10% and ≥ 5 of patients in Any Age Category by System Organ Class and Preferred Term (Safety Analysis Set)

	Original						Update					
	BGB-3111-212 Zanu + Obi (N = 143)		BGB-3111-212 Obi (N = 71)		All Patients (N = 1550)		BGB-3111-212 Zanu + Obi (N = 143)		BGB-3111-212 Obi (N = 71)		All Patients (N = 1550)	
System Organ Class Preferred Term	< 65 years (N = 83) n (%)	≥ 65 years (N = 60) n (%)	< 65 years (N = 32) n (%)	≥ 65 years (N = 39) n (%)	< 65 years (N = 600) n (%)	≥ 65 years (N = 950) n (%)	< 65 years (N = 83) n (%)	≥ 65 years (N = 60) n (%)	< 65 years (N = 32) n (%)	≥ 65 years (N = 39) n (%)	< 65 years (N = 600) n (%)	≥ 65 years (N = 950) n (%)
Patients With at Least One TEAE	78 (94.0)	57 (95.0)	29 (90.6)	35 (89.7)	581 (96.8)	933 (98.2)	78 (94.0)	57 (95.0)	29 (90.6)	35 (89.7)	582 (97.0)	936 (98.5)
Infections and infestations	43 (51.8)	36 (60.0)	13 (40.6)	16 (41.0)	429 (71.5)	667 (70.2)	46 (55.4)	37 (61.7)	14 (43.8)	16 (41.0)	445 (74.2)	708 (74.5)
Pneumonia	9 (10.8)	8 (13.3)	0 (0.0)	5 (12.8)	93 (15.5)	116 (12.2)	10 (12.0)	8 (13.3)	0 (0.0)	5 (12.8)	96 (16.0)	128 (13.5)
COVID-19	7 (8.4)	7 (11.7)	3 (9.4)	4 (10.3)	57 (9.5)	72 (7.6)	10 (12.0)	8 (13.3)	3 (9.4)	4 (10.3)	93 (15.5)	115 (12.1)
Urinary tract infection	7 (8.4)	5 (8.3)	0 (0.0)	4 (10.3)	68 (11.3)	134 (14.1)	7 (8.4)	6 (10.0)	0 (0.0)	4 (10.3)	71 (11.8)	141 (14.8)
Upper respiratory tract infection	5 (6.0)	5 (8.3)	1 (3.1)	3 (7.7)	227 (37.8)	222 (23.4)	5 (6.0)	5 (8.3)	1 (3.1)	3 (7.7)	232 (38.7)	229 (24.1)
Nasopharyngitis	4 (4.8)	7 (11.7)	0 (0.0)	2 (5.1)	40 (6.7)	64 (6.7)	4 (4.8)	7 (11.7)	0 (0.0)	2 (5.1)	42 (7.0)	69 (7.3)
Gastrointestinal disorders	33 (39.8)	33 (55.0)	12 (37.5)	18 (46.2)	327 (54.5)	542 (57.1)	33 (39.8)	34 (56.7)	12 (37.5)	19 (48.7)	336 (56.0)	559 (58.8)
Diarrhoea	15 (18.1)	11 (18.3)	5 (15.6)	7 (17.9)	121 (20.2)	188 (19.8)	15 (18.1)	12 (20.0)	6 (18.8)	7 (17.9)	129 (21.5)	198 (20.8)
Constipation	12 (14.5)	7 (11.7)	2 (6.3)	4 (10.3)	51 (8.5)	152 (16.0)	12 (14.5)	7 (11.7)	2 (6.3)	4 (10.3)	53 (8.8)	157 (16.5)
Nausea	8 (9.6)	5 (8.3)	5 (15.6)	5 (12.8)	58 (9.7)	117 (12.3)	8 (9.6)	5 (8.3)	5 (15.6)	6 (15.4)	59 (9.8)	120 (12.6)
Abdominal pain	4 (4.8)	7 (11.7)	4 (12.5)	4 (10.3)	36 (6.0)	60 (6.3)	4 (4.8)	7 (11.7)	4 (12.5)	4 (10.3)	37 (6.2)	62 (6.5)
Blood and lymphatic system disorders	32 (38.6)	22 (36.7)	7 (21.9)	13 (33.3)	222 (37.0)	320 (33.7)	33 (39.8)	24 (40.0)	8 (25.0)	13 (33.3)	227 (37.8)	335 (35.3)

	Original						Update					
	BGB-3111-212 Zanu + Obi (N = 143)		BGB-3111-212 Obi (N = 71)		All Patients (N = 1550)		BGB-3111-212 Zanu + Obi (N = 143)		BGB-3111-212 Obi (N = 71)		All Patients (N = 1550)	
System Organ Class Preferred Term	< 65 years (N = 83) n (%)	≥ 65 years (N = 60) n (%)	< 65 years (N = 32) n (%)	≥ 65 years (N = 39) n (%)	< 65 years (N = 600) n (%)	≥ 65 years (N = 950) n (%)	< 65 years (N = 83) n (%)	≥ 65 years (N = 60) n (%)	< 65 years (N = 32) n (%)	≥ 65 years (N = 39) n (%)	< 65 years (N = 600) n (%)	≥ 65 years (N = 950) n (%)
Thrombocytopenia	14 (16.9)	14 (23.3)	2 (6.3)	5 (12.8)	48 (8.0)	82 (8.6)	15 (18.1)	15 (25.0)	2 (6.3)	5 (12.8)	50 (8.3)	85 (8.9)
Neutropenia	12 (14.5)	7 (11.7)	4 (12.5)	8 (20.5)	94 (15.7)	138 (14.5)	12 (14.5)	7 (11.7)	4 (12.5)	8 (20.5)	98 (16.3)	142 (14.9)
Anaemia	9 (10.8)	7 (11.7)	1 (3.1)	6 (15.4)	98 (16.3)	131 (13.8)	9 (10.8)	8 (13.3)	1 (3.1)	6 (15.4)	101 (16.8)	139 (14.6)
General disorders and administration site conditions	30 (36.1)	28 (46.7)	16 (50.0)	17 (43.6)	223 (37.2)	383 (40.3)	30 (36.1)	28 (46.7)	16 (50.0)	18 (46.2)	235 (39.2)	407 (42.8)
Fatigue	12 (14.5)	10 (16.7)	5 (15.6)	5 (12.8)	71 (11.8)	128 (13.5)	12 (14.5)	10 (16.7)	5 (15.6)	5 (12.8)	74 (12.3)	138 (14.5)
Pyrexia	11 (13.3)	8 (13.3)	6 (18.8)	8 (20.5)	68 (11.3)	101 (10.6)	11 (13.3)	8 (13.3)	6 (18.8)	8 (20.5)	71 (11.8)	109 (11.5)
Asthenia	8 (9.6)	9 (15.0)	2 (6.3)	4 (10.3)	20 (3.3)	39 (4.1)	8 (9.6)	9 (15.0)	2 (6.3)	4 (10.3)	20 (3.3)	40 (4.2)
Oedema peripheral	1 (1.2)	2 (3.3)	0 (0.0)	4 (10.3)	24 (4.0)	108 (11.4)	1 (1.2)	2 (3.3)	0 (0.0)	4 (10.3)	28 (4.7)	116 (12.2)
Investigations	30 (36.1)	21 (35.0)	10 (31.3)	10 (25.6)	282 (47.0)	288 (30.3)	30 (36.1)	21 (35.0)	10 (31.3)	10 (25.6)	291 (48.5)	307 (32.3)
Neutrophil count decreased	15 (18.1)	8 (13.3)	5 (15.6)	3 (7.7)	143 (23.8)	100 (10.5)	16 (19.3)	8 (13.3)	5 (15.6)	3 (7.7)	143 (23.8)	102 (10.7)
Platelet count decreased	15 (18.1)	10 (16.7)	3 (9.4)	7 (17.9)	82 (13.7)	67 (7.1)	15 (18.1)	11 (18.3)	3 (9.4)	7 (17.9)	84 (14.0)	71 (7.5)
White blood cell count decreased	11 (13.3)	3 (5.0)	3 (9.4)	1 (2.6)	65 (10.8)	22 (2.3)	12 (14.5)	3 (5.0)	3 (9.4)	1 (2.6)	65 (10.8)	23 (2.4)
Musculoskeletal and connective tissue disorders	25 (30.1)	19 (31.7)	6 (18.8)	16 (41.0)	214 (35.7)	408 (42.9)	27 (32.5)	19 (31.7)	6 (18.8)	16 (41.0)	226 (37.7)	422 (44.4)
Back pain	7 (8.4)	8 (13.3)	1 (3.1)	3 (7.7)	63 (10.5)	110 (11.6)	7 (8.4)	8 (13.3)	1 (3.1)	3 (7.7)	68 (11.3)	111 (11.7)

	Original						Update					
	BGB-3111-212 Zanu + Obi (N = 143)		BGB-3111-212 Obi (N = 71)		All Patients (N = 1550)		BGB-3111-212 Zanu + Obi (N = 143)		BGB-3111-212 Obi (N = 71)		All Patients (N = 1550)	
System Organ Class Preferred Term	< 65 years (N = 83) n (%)	≥ 65 years (N = 60) n (%)	< 65 years (N = 32) n (%)	≥ 65 years (N = 39) n (%)	< 65 years (N = 600) n (%)	≥ 65 years (N = 950) n (%)	< 65 years (N = 83) n (%)	≥ 65 years (N = 60) n (%)	< 65 years (N = 32) n (%)	≥ 65 years (N = 39) n (%)	< 65 years (N = 600) n (%)	≥ 65 years (N = 950) n (%)
Arthralgia	3 (3.6)	3 (5.0)	1 (3.1)	4 (10.3)	80 (13.3)	146 (15.4)	3 (3.6)	3 (5.0)	1 (3.1)	4 (10.3)	84 (14.0)	149 (15.7)
Respiratory, thoracic and mediastinal disorders	22 (26.5)	21 (35.0)	10 (31.3)	12 (30.8)	221 (36.8)	420 (44.2)	22 (26.5)	21 (35.0)	10 (31.3)	12 (30.8)	228 (38.0)	431 (45.4)
Cough	13 (15.7)	5 (8.3)	4 (12.5)	5 (12.8)	104 (17.3)	163 (17.2)	13 (15.7)	5 (8.3)	4 (12.5)	5 (12.8)	105 (17.5)	176 (18.5)
Dyspnoea	6 (7.2)	10 (16.7)	4 (12.5)	3 (7.7)	25 (4.2)	72 (7.6)	6 (7.2)	10 (16.7)	4 (12.5)	3 (7.7)	25 (4.2)	75 (7.9)
Skin and subcutaneous tissue disorders	20 (24.1)	25 (41.7)	9 (28.1)	9 (23.1)	303 (50.5)	468 (49.3)	20 (24.1)	25 (41.7)	9 (28.1)	9 (23.1)	311 (51.8)	484 (50.9)
Rash	3 (3.6)	3 (5.0)	1 (3.1)	3 (7.7)	109 (18.2)	142 (14.9)	3 (3.6)	5 (8.3)	1 (3.1)	3 (7.7)	110 (18.3)	147 (15.5)
Metabolism and nutrition disorders	19 (22.9)	17 (28.3)	11 (34.4)	9 (23.1)	203 (33.8)	297 (31.3)	21 (25.3)	17 (28.3)	11 (34.4)	9 (23.1)	211 (35.2)	310 (32.6)
Hypokalaemia	4 (4.8)	5 (8.3)	1 (3.1)	2 (5.1)	51 (8.5)	62 (6.5)	5 (6.0)	6 (10.0)	1 (3.1)	2 (5.1)	53 (8.8)	64 (6.7)
Nervous system disorders	15 (18.1)	18 (30.0)	7 (21.9)	10 (25.6)	174 (29.0)	334 (35.2)	15 (18.1)	18 (30.0)	7 (21.9)	10 (25.6)	179 (29.8)	349 (36.7)
Headache	2 (2.4)	4 (6.7)	1 (3.1)	1 (2.6)	82 (13.7)	91 (9.6)	2 (2.4)	4 (6.7)	1 (3.1)	1 (2.6)	83 (13.8)	96 (10.1)
Dizziness	0 (0.0)	4 (6.7)	1 (3.1)	3 (7.7)	35 (5.8)	96 (10.1)	0 (0.0)	4 (6.7)	1 (3.1)	3 (7.7)	36 (6.0)	101 (10.6)
Injury, poisoning and procedural complications	11 (13.3)	18 (30.0)	6 (18.8)	7 (17.9)	174 (29.0)	383 (40.3)	12 (14.5)	18 (30.0)	6 (18.8)	7 (17.9)	179 (29.8)	392 (41.3)
Contusion	6 (7.2)	5 (8.3)	1 (3.1)	1 (2.6)	78 (13.0)	222 (23.4)	7 (8.4)	5 (8.3)	1 (3.1)	1 (2.6)	79 (13.2)	224 (23.6)
Infusion related reaction	3 (3.6)	1 (1.7)	5 (15.6)	2 (5.1)	4 (0.7)	3 (0.3)	3 (3.6)	1 (1.7)	5 (15.6)	2 (5.1)	4 (0.7)	3 (0.3)
Fall	1 (1.2)	6 (10.0)	0 (0.0)	4 (10.3)	16 (2.7)	84 (8.8)	1 (1.2)	6 (10.0)	0 (0.0)	4 (10.3)	16 (2.7)	88 (9.3)
Vascular disorders	7 (8.4)	9 (15.0)	4 (12.5)	6 (15.4)	99 (16.5)	271 (28.5)	7 (8.4)	9 (15.0)	4 (12.5)	6 (15.4)	111 (18.5)	286 (30.1)

	Original						Update					
	BGB-3111-212 Zanu + Obi (N = 143)		BGB-3111-212 Obi (N = 71)		All Patients (N = 1550)		BGB-3111-212 Zanu + Obi (N = 143)		BGB-3111-212 Obi (N = 71)		All Patients (N = 1550)	
System Organ Class Preferred Term	< 65 years (N = 83) n (%)	≥ 65 years (N = 60) n (%)	< 65 years (N = 32) n (%)	≥ 65 years (N = 39) n (%)	< 65 years (N = 600) n (%)	≥ 65 years (N = 950) n (%)	< 65 years (N = 83) n (%)	≥ 65 years (N = 60) n (%)	< 65 years (N = 32) n (%)	≥ 65 years (N = 39) n (%)	< 65 years (N = 600) n (%)	≥ 65 years (N = 950) n (%)
Hypertension	2 (2.4)	3 (5.0)	2 (6.3)	2 (5.1)	71 (11.8)	149 (15.7)	2 (2.4)	3 (5.0)	2 (6.3)	2 (5.1)	81 (13.5)	161 (16.9)
Renal and urinary disorders	5 (6.0)	7 (11.7)	1 (3.1)	4 (10.3)	121 (20.2)	193 (20.3)	5 (6.0)	7 (11.7)	1 (3.1)	4 (10.3)	124 (20.7)	203 (21.4)
Haematuria	0 (0.0)	1 (1.7)	0 (0.0)	1 (2.6)	67 (11.2)	92 (9.7)	0 (0.0)	1 (1.7)	0 (0.0)	1 (2.6)	69 (11.5)	97 (10.2)

Source: ADSL, ADAE. Data cutoff: 25OCT2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304).
Abbreviations: FL, Follicular Lymphoma; Obi, Obinutuzumab; TEAE, treatment-emergent adverse event; Zanu, Zanubrutinib.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD and/or obinutuzumab.
Percentages are based on N, unless otherwise specified.
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to last zanubrutinib dose date + 30 days/last obinutuzumab infusion date + 90 days or initiation of new anti-cancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond last zanubrutinib dose date + 30 days/last obinutuzumab infusion date + 90 days and prior to initiation of new anti-cancer therapy is also considered as treatment-emergent.
Patients with multiple events for a given preferred term and with multiple preferred terms within a system organ class are counted only once at the preferred term and system organ class levels, respectively. Events are sorted by decreasing frequency first by system organ class and then by preferred term within each system organ class in the original 'BGB-3111-212 Zanu + Obi' column.

Table 45

Table 43: Treatment-Emergent Adverse Events Reported by ≥ 10% and ≥ 5 of patients in Any Age Category by System Organ Class and Preferred Term (Safety Analysis Set)

	BGB-3111-212 Zanu + Obi (N = 143)		BGB-3111-212 Obi (N = 71)		BGB-3111-GA101 Zanu + Obi (N = 36)		Pool Zanu + Obi (N = 179)		All Patients (N = 1550)		FL Patients (N = 59)	
System Organ Class Preferred Term	< 65 years (N = 83) n (%)	≥ 65 years (N = 60) n (%)	< 65 years (N = 32) n (%)	≥ 65 years (N = 39) n (%)	< 65 years (N = 24) n (%)	≥ 65 years (N = 12) n (%)	< 65 years (N = 107) n (%)	≥ 65 years (N = 72) n (%)	< 65 years (N = 600) n (%)	≥ 65 years (N = 950) n (%)	< 65 years (N = 44) n (%)	≥ 65 years (N = 15) n (%)
Patients With at Least One TEAE	78 (94.0)	57 (95.0)	29 (90.6)	35 (89.7)	24 (100.0)	12 (100.0)	102 (95.3)	69 (95.8)	581 (96.8)	933 (98.2)	42 (95.5)	15 (100.0)
Infections and infestations	43 (51.8)	36 (60.0)	13 (40.6)	16 (41.0)	14 (58.3)	10 (83.3)	57 (53.3)	46 (63.9)	429 (71.5)	667 (70.2)	22 (50.0)	10 (66.7)
Upper respiratory tract infection	5 (6.0)	5 (8.3)	1 (3.1)	3 (7.7)	8 (33.3)	5 (41.7)	13 (12.1)	10 (13.9)	227 (37.8)	222 (23.4)	11 (25.0)	5 (33.3)
Pneumonia	9 (10.8)	8 (13.3)	0 (0.0)	5 (12.8)	2 (8.3)	1 (8.3)	11 (10.3)	9 (12.5)	93 (15.5)	116 (12.2)	4 (9.1)	3 (20.0)
Urinary tract infection	7 (8.4)	5 (8.3)	0 (0.0)	4 (10.3)	2 (8.3)	0 (0.0)	9 (8.4)	5 (6.9)	68 (11.3)	134 (14.1)	5 (11.4)	5 (33.3)
COVID-19	7 (8.4)	7 (11.7)	3 (9.4)	4 (10.3)	0 (0.0)	0 (0.0)	7 (6.5)	7 (9.7)	57 (9.5)	72 (7.6)	0 (0.0)	0 (0.0)
Nasopharyngitis	4 (4.8)	7 (11.7)	0 (0.0)	2 (5.1)	1 (4.2)	2 (16.7)	5 (4.7)	9 (12.5)	40 (6.7)	64 (6.7)	4 (9.1)	0 (0.0)
Gastrointestinal disorders	33 (39.8)	33 (55.0)	12 (37.5)	18 (46.2)	16 (66.7)	5 (41.7)	49 (45.8)	38 (52.8)	327 (54.5)	542 (57.1)	14 (31.8)	7 (46.7)
Diarrhoea	15 (18.1)	11 (18.3)	5 (15.6)	7 (17.9)	5 (20.8)	2 (16.7)	20 (18.7)	13 (18.1)	121 (20.2)	188 (19.8)	4 (9.1)	0 (0.0)
Constipation	12 (14.5)	7 (11.7)	2 (6.3)	4 (10.3)	3 (12.5)	1 (8.3)	15 (14.0)	8 (11.1)	51 (8.5)	152 (16.0)	3 (6.8)	3 (20.0)
Nausea	8 (9.6)	5 (8.3)	5 (15.6)	5 (12.8)	6 (25.0)	1 (8.3)	14 (13.1)	6 (8.3)	58 (9.7)	117 (12.3)	7 (15.9)	2 (13.3)
Abdominal pain	4 (4.8)	7 (11.7)	4 (12.5)	4 (10.3)	2 (8.3)	1 (8.3)	6 (5.6)	8 (11.1)	36 (6.0)	60 (6.3)	2 (4.5)	1 (6.7)
Blood and lymphatic system disorders	32 (38.6)	22 (36.7)	7 (21.9)	13 (33.3)	7 (29.2)	6 (50.0)	39 (36.4)	28 (38.9)	222 (37.0)	320 (33.7)	19 (43.2)	7 (46.7)
Thrombocytopenia	14 (16.9)	14 (23.3)	2 (6.3)	5 (12.8)	4 (16.7)	5 (41.7)	18 (16.8)	19 (26.4)	48 (8.0)	82 (8.6)	1 (2.3)	1 (6.7)

	BGB-3111-212 Zanu + Obi (N = 143)		BGB-3111-212 Obi (N = 71)		BGB-3111-GA101 Zanu + Obi (N = 36)		Pool Zanu + Obi (N = 179)		All Patients (N = 1550)		FL Patients (N = 59)	
System Organ Class Preferred Term	< 65 years (N = 83) n (%)	≥ 65 years (N = 60) n (%)	< 65 years (N = 32) n (%)	≥ 65 years (N = 39) n (%)	< 65 years (N = 24) n (%)	≥ 65 years (N = 12) n (%)	< 65 years (N = 107) n (%)	≥ 65 years (N = 72) n (%)	< 65 years (N = 600) n (%)	≥ 65 years (N = 950) n (%)	< 65 years (N = 44) n (%)	≥ 65 years (N = 15) n (%)
Neutropenia	12 (14.5)	7 (11.7)	4 (12.5)	8 (20.5)	3 (12.5)	4 (33.3)	15 (14.0)	11 (15.3)	94 (15.7)	138 (14.5)	5 (11.4)	1 (6.7)
Anaemia	9 (10.8)	7 (11.7)	1 (3.1)	6 (15.4)	2 (8.3)	1 (8.3)	11 (10.3)	8 (11.1)	98 (16.3)	131 (13.8)	10 (22.7)	5 (33.3)
General disorders and administration site conditions	30 (36.1)	28 (46.7)	16 (50.0)	17 (43.6)	9 (37.5)	7 (58.3)	39 (36.4)	35 (48.6)	223 (37.2)	383 (40.3)	11 (25.0)	5 (33.3)
Fatigue	12 (14.5)	10 (16.7)	5 (15.6)	5 (12.8)	6 (25.0)	3 (25.0)	18 (16.8)	13 (18.1)	71 (11.8)	128 (13.5)	5 (11.4)	2 (13.3)
Pyrexia	11 (13.3)	8 (13.3)	6 (18.8)	8 (20.5)	1 (4.2)	2 (16.7)	12 (11.2)	10 (13.9)	68 (11.3)	101 (10.6)	1 (2.3)	4 (26.7)
Asthenia	8 (9.6)	9 (15.0)	2 (6.3)	4 (10.3)	0 (0.0)	0 (0.0)	8 (7.5)	9 (12.5)	20 (3.3)	39 (4.1)	1 (2.3)	0 (0.0)
Oedema peripheral	1 (1.2)	2 (3.3)	0 (0.0)	4 (10.3)	1 (4.2)	2 (16.7)	2 (1.9)	4 (5.6)	24 (4.0)	108 (11.4)	1 (2.3)	1 (6.7)
Respiratory, thoracic and mediastinal disorders	22 (26.5)	21 (35.0)	10 (31.3)	12 (30.8)	15 (62.5)	7 (58.3)	37 (34.6)	28 (38.9)	221 (36.8)	420 (44.2)	13 (29.5)	7 (46.7)
Cough	13 (15.7)	5 (8.3)	4 (12.5)	5 (12.8)	7 (29.2)	2 (16.7)	20 (18.7)	7 (9.7)	104 (17.3)	163 (17.2)	8 (18.2)	3 (20.0)
Dyspnoea	6 (7.2)	10 (16.7)	4 (12.5)	3 (7.7)	2 (8.3)	1 (8.3)	8 (7.5)	11 (15.3)	25 (4.2)	72 (7.6)	2 (4.5)	3 (20.0)
Productive cough	0 (0.0)	2 (3.3)	0 (0.0)	1 (2.6)	6 (25.0)	1 (8.3)	6 (5.6)	3 (4.2)	24 (4.0)	39 (4.1)	3 (6.8)	0 (0.0)
Investigations	30 (36.1)	21 (35.0)	10 (31.3)	10 (25.6)	5 (20.8)	1 (8.3)	35 (32.7)	22 (30.6)	282 (47.0)	288 (30.3)	26 (59.1)	6 (40.0)
Platelet count decreased	15 (18.1)	10 (16.7)	3 (9.4)	7 (17.9)	3 (12.5)	0 (0.0)	18 (16.8)	10 (13.9)	82 (13.7)	67 (7.1)	7 (15.9)	0 (0.0)
Neutrophil count decreased	15 (18.1)	8 (13.3)	5 (15.6)	3 (7.7)	1 (4.2)	0 (0.0)	16 (15.0)	8 (11.1)	143 (23.8)	100 (10.5)	12 (27.3)	2 (13.3)

	BGB-3111-212 Zanu + Obi (N = 143)		BGB-3111-212 Obi (N = 71)		BGB-3111-GA101 Zanu + Obi (N = 36)		Pool Zanu + Obi (N = 179)		All Patients (N = 1550)		FL Patients (N = 59)	
System Organ Class Preferred Term	< 65 years (N = 83) n (%)	≥ 65 years (N = 60) n (%)	< 65 years (N = 32) n (%)	≥ 65 years (N = 39) n (%)	< 65 years (N = 24) n (%)	≥ 65 years (N = 12) n (%)	< 65 years (N = 107) n (%)	≥ 65 years (N = 72) n (%)	< 65 years (N = 600) n (%)	≥ 65 years (N = 950) n (%)	< 65 years (N = 44) n (%)	≥ 65 years (N = 15) n (%)
White blood cell count decreased	11 (13.3)	3 (5.0)	3 (9.4)	1 (2.6)	0 (0.0)	0 (0.0)	11 (10.3)	3 (4.2)	65 (10.8)	22 (2.3)	8 (18.2)	2 (13.3)
Musculoskeletal and connective tissue disorders	25 (30.1)	19 (31.7)	6 (18.8)	16 (41.0)	10 (41.7)	3 (25.0)	35 (32.7)	22 (30.6)	214 (35.7)	408 (42.9)	9 (20.5)	6 (40.0)
Back pain	7 (8.4)	8 (13.3)	1 (3.1)	3 (7.7)	4 (16.7)	1 (8.3)	11 (10.3)	9 (12.5)	63 (10.5)	110 (11.6)	2 (4.5)	2 (13.3)
Arthralgia	3 (3.6)	3 (5.0)	1 (3.1)	4 (10.3)	4 (16.7)	2 (16.7)	7 (6.5)	5 (6.9)	80 (13.3)	146 (15.4)	4 (9.1)	0 (0.0)
Skin and subcutaneous tissue disorders	20 (24.1)	25 (41.7)	9 (28.1)	9 (23.1)	11 (45.8)	8 (66.7)	31 (29.0)	33 (45.8)	303 (50.5)	468 (49.3)	20 (45.5)	6 (40.0)
Rash	3 (3.6)	3 (5.0)	1 (3.1)	3 (7.7)	5 (20.8)	3 (25.0)	8 (7.5)	6 (8.3)	109 (18.2)	142 (14.9)	10 (22.7)	0 (0.0)
Nervous system disorders	15 (18.1)	18 (30.0)	7 (21.9)	10 (25.6)	10 (41.7)	7 (58.3)	25 (23.4)	25 (34.7)	174 (29.0)	334 (35.2)	7 (15.9)	4 (26.7)
Headache	2 (2.4)	4 (6.7)	1 (3.1)	1 (2.6)	5 (20.8)	0 (0.0)	7 (6.5)	4 (5.6)	82 (13.7)	91 (9.6)	4 (9.1)	1 (6.7)
Dizziness	0 (0.0)	4 (6.7)	1 (3.1)	3 (7.7)	2 (8.3)	2 (16.7)	2 (1.9)	6 (8.3)	35 (5.8)	96 (10.1)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	11 (13.3)	18 (30.0)	6 (18.8)	7 (17.9)	11 (45.8)	6 (50.0)	22 (20.6)	24 (33.3)	174 (29.0)	383 (40.3)	4 (9.1)	8 (53.3)
Contusion	6 (7.2)	5 (8.3)	1 (3.1)	1 (2.6)	8 (33.3)	3 (25.0)	14 (13.1)	8 (11.1)	78 (13.0)	222 (23.4)	1 (2.3)	7 (46.7)
Fall	1 (1.2)	6 (10.0)	0 (0.0)	4 (10.3)	2 (8.3)	1 (8.3)	3 (2.8)	7 (9.7)	16 (2.7)	84 (8.8)	0 (0.0)	3 (20.0)
Infusion related reaction	3 (3.6)	1 (1.7)	5 (15.6)	2 (5.1)	0 (0.0)	0 (0.0)	3 (2.8)	1 (1.4)	4 (0.7)	3 (0.3)	0 (0.0)	0 (0.0)
Renal and urinary disorders	5 (6.0)	7 (11.7)	1 (3.1)	4 (10.3)	2 (8.3)	2 (16.7)	7 (6.5)	9 (12.5)	121 (20.2)	193 (20.3)	10 (22.7)	5 (33.3)
Haematuria	0 (0.0)	1 (1.7)	0 (0.0)	1 (2.6)	0 (0.0)	1 (8.3)	0 (0.0)	2 (2.8)	67 (11.2)	92 (9.7)	3 (6.8)	4 (26.7)

	BGB-3111-212 Zanu + Obi (N = 143)		BGB-3111-212 Obi (N = 71)		BGB-3111-GA101 Zanu + Obi (N = 36)		Pool Zanu + Obi (N = 179)		All Patients (N = 1550)		FL Patients (N = 59)	
System Organ Class Preferred Term	< 65 years (N = 83) n (%)	≥ 65 years (N = 60) n (%)	< 65 years (N = 32) n (%)	≥ 65 years (N = 39) n (%)	< 65 years (N = 24) n (%)	≥ 65 years (N = 12) n (%)	< 65 years (N = 107) n (%)	≥ 65 years (N = 72) n (%)	< 65 years (N = 600) n (%)	≥ 65 years (N = 950) n (%)	< 65 years (N = 44) n (%)	≥ 65 years (N = 15) n (%)
Vascular disorders	7 (8.4)	9 (15.0)	4 (12.5)	6 (15.4)	0 (0.0)	4 (33.3)	7 (6.5)	13 (18.1)	99 (16.5)	271 (28.5)	4 (9.1)	1 (6.7)
Hypertension	2 (2.4)	3 (5.0)	2 (6.3)	2 (5.1)	0 (0.0)	3 (25.0)	2 (1.9)	6 (8.3)	71 (11.8)	149 (15.7)	3 (6.8)	0 (0.0)

Source: ADSL, ADAE. Data cutoff: 25JUN2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 01JUL2022(LTE1), 01DEC2021(305), 07SEP2021(304).
Abbreviations: FL, Follicular Lymphoma; Obi, Obinutuzumab; TEAE, treatment-emergent adverse event; Zanu, Zanubrutinib.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD and/or obinutuzumab. Percentages are based on N, unless otherwise specified.
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to last zanubrutinib dose date + 30 days/last obinutuzumab infusion date + 90 days or initiation of new anti-cancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond last zanubrutinib dose date + 30 days/last obinutuzumab infusion date + 90 days and prior to initiation of new anti-cancer therapy is also considered as treatment-emergent.
Patients with multiple events for a given preferred term and with multiple preferred terms within a system organ class are counted only once at the preferred term and system organ class levels, respectively. Events are sorted by decreasing frequency first by system organ class and then by preferred term within each system organ class in the 'Pool' column.
MedDRA Version: 24.0.
/bgb_3111/filing_fl_2022/iss/dev/pgm/tlfs/t-teae-sum-sub-i.sas 20OCT2022 05:33 t-40-teae-soc-pt-age-10-5-i.rtf

Race:

Table 46

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Table 2.7.4.2.14.1
Overall Summary of Treatment-Emergent Adverse Events by Race
(Safety Analysis Set)

	BGB-3111-212 Zanu + Obi (N = 143)			BGB-3111-212 Obi (N = 71)			BGB-3111-GA101 Zanu + Obi (N = 36)		Pool Zanu + Obi (N = 179)			All Patients (N = 1550)			FL Patients (N = 59)		
	White (N = 90) n (%)	Asian (N = 30) n (%)	Other (N = 23) n (%)	White (N = 47) n (%)	Asian (N = 16) n (%)	Other (N = 8) n (%)	White (N = 29) n (%)	Asian (N = 7) n (%)	White (N = 119) n (%)	Asian (N = 37) n (%)	Other (N = 23) n (%)	White (N = 1032) n (%)	Asian (N = 424) n (%)	Other (N = 93) n (%)	White (N = 19) n (%)	Asian (N = 35) n (%)	Other (N = 4) n (%)
Patients With at Least One TEAE	85 (94.4)	27 (90.0)	23 (100.0)	42 (89.4)	15 (93.8)	7 (87.5)	29 (100.0)	7 (100.0)	114 (95.8)	34 (91.9)	23 (100.0)	1005 (97.4)	415 (97.9)	93 (100.0)	19 (100.0)	33 (94.3)	4 (100.0)
Grade 3 or Higher	59 (65.6)	15 (50.0)	16 (69.6)	26 (55.3)	4 (25.0)	4 (50.0)	15 (51.7)	5 (71.4)	74 (62.2)	20 (54.1)	16 (69.6)	659 (63.9)	272 (64.2)	62 (66.7)	13 (68.4)	19 (54.3)	3 (75.0)
Serious	41 (45.6)	8 (26.7)	9 (39.1)	17 (36.2)	2 (12.5)	3 (37.5)	11 (37.9)	2 (28.6)	52 (43.7)	10 (27.0)	9 (39.1)	477 (46.2)	182 (42.9)	48 (51.6)	7 (36.8)	7 (20.0)	3 (75.0)
Leading to Death	6 (6.7)	3 (10.0)	3 (13.0)	6 (12.8)	1 (6.3)	0 (0.0)	1 (3.4)	0 (0.0)	7 (5.9)	3 (8.1)	3 (13.0)	72 (7.0)	20 (4.7)	8 (8.6)	0 (0.0)	0 (0.0)	1 (25.0)

Region: China vs Ex-China

Table 47

Table 44: Overview of TEAEs of China versus Ex-China (Safety Analysis Set) in BGB-3111-212

	Zanubrutinib + Obinutuzumab		Obinutuzumab	
	CHINA (N = 21)	EX-CHINA (N = 122)	CHINA (N = 12)	EX-CHINA (N = 59)
Patients With at Least One TEAE	19 (90.5)	116 (95.1)	11 (91.7)	53 (89.8)
Grade 3 or Higher	10 (47.6)	84 (68.9)	3 (25.0)	31 (52.5)
Serious	5 (23.8)	59 (48.4)	2 (16.7)	20 (33.9)
Leading to Death	1 (4.8)	13 (10.7)	1 (8.3)	6 (10.2)
Leading to Treatment Discontinuation	3 (14.3)	23 (18.9)	0 (0.0)	8 (13.6)
Leading to Dose Reduction	0 (0.0)	15 (12.3)	NA	NA
Leading to Dose Interruption	6 (28.6)	64 (52.5)	5 (41.7)	13 (22.0)

Source: ADSL, ADAE. Data cutoff: 25OCT2022. Data extraction: 15DEC2022.
Abbreviation: TEAE, treatment-emergent adverse event.
Adverse event grades were evaluated based on NCI-CTCAE Version 4.03.
/bgb_3111/bgb_3111_212/rtq_20230524_ema/dev/pgm/tlfs/t-teae-summ-ema.sas 20JUL2023 08:40 t-14-3-1-2-1-1-2-teae-summ-bychn-ema.rtf

Safety related to drug-drug interactions and other interactions

Obinutuzumab did not appear to influence zanubrutinib exposure and vice versa (see section on clinical pharmacology).

Discontinuation due to adverse events

Table 48 TEAEs leading to treatment discontinuation

Reported in ≥ 2 Patients in Any Patient Group by System Organ Class and Preferred Term (Safety Analysis Set)

	Original				Update			
	Combination Therapy Trials		Monotherapy Trials		Combination Therapy Trials		Monotherapy Trials	
System Organ Class Preferred Term	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
Patients With at Least One TEAE Leading to Treatment Discontinuation	23 (16.1)	8 (11.3)	190 (12.3)	4 (6.8)	26 (18.2)	8 (11.3)	211 (13.6)	4 (6.8)
Infections and infestations	12 (8.4)	5 (7.0)	61 (3.9)	1 (1.7)	13 (9.1)	5 (7.0)	70 (4.5)	1 (1.7)
COVID-19	4 (2.8)	1 (1.4)	13 (0.8)	0 (0.0)	4 (2.8)	1 (1.4)	13 (0.8)	0 (0.0)
Pneumonia	4 (2.8)	1 (1.4)	17 (1.1)	1 (1.7)	4 (2.8)	1 (1.4)	19 (1.2)	1 (1.7)
COVID-19 pneumonia	2 (1.4)	1 (1.4)	7 (0.5)	0 (0.0)	2 (1.4)	1 (1.4)	15 (1.0)	0 (0.0)
Infection	1 (0.7)	0 (0.0)	2 (0.1)	0 (0.0)	1 (0.7)	0 (0.0)	2 (0.1)	0 (0.0)
Hepatitis B	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)
Pneumonia cryptococcal	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (2.8)	0 (0.0)	45 (2.9)	2 (3.4)	5 (3.5)	0 (0.0)	48 (3.1)	2 (3.4)
Myelodysplastic syndrome	2 (1.4)	0 (0.0)	2 (0.1)	0 (0.0)	2 (1.4)	0 (0.0)	2 (0.1)	0 (0.0)
Acute myeloid leukaemia	1 (0.7)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.7)	0 (0.0)	2 (0.1)	0 (0.0)
Breast cancer	1 (0.7)	0 (0.0)	4 (0.3)	0 (0.0)	1 (0.7)	0 (0.0)	4 (0.3)	0 (0.0)
Adenocarcinoma gastric	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Adenocarcinoma of colon	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Chronic myeloid leukaemia	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Colon cancer	0 (0.0)	0 (0.0)	2 (0.1)	1 (1.7)	0 (0.0)	0 (0.0)	2 (0.1)	1 (1.7)
Lung adenocarcinoma	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Neuroendocrine carcinoma	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Rectal cancer	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Squamous cell carcinoma of lung	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Investigations	3 (2.1)	0 (0.0)	2 (0.1)	0 (0.0)	3 (2.1)	0 (0.0)	2 (0.1)	0 (0.0)
Neutrophil count decreased	2 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Platelet count decreased	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	3 (2.1)	1 (1.4)	16 (1.0)	0 (0.0)	3 (2.1)	1 (1.4)	18 (1.2)	0 (0.0)

	Original				Update			
	Combination Therapy Trials		Monotherapy Trials		Combination Therapy Trials		Monotherapy Trials	
System Organ Class Preferred Term	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Patients (N = 1550) n (%)	FL Patients (N = 59) n (%)
Respiratory failure	1 (0.7)	1 (1.4)	4 (0.3)	0 (0.0)	1 (0.7)	1 (1.4)	4 (0.3)	0 (0.0)
Pleural effusion	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Pneumonitis	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)
General disorders and administration site conditions	1 (0.7)	0 (0.0)	9 (0.6)	0 (0.0)	1 (0.7)	0 (0.0)	11 (0.7)	0 (0.0)
Death	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)
Multiple organ dysfunction syndrome	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)
Pyrexia	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Nervous system disorders	1 (0.7)	0 (0.0)	12 (0.8)	0 (0.0)	2 (1.4)	0 (0.0)	14 (0.9)	0 (0.0)
Cerebral haemorrhage	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.3)	0 (0.0)
Haemorrhage intracranial	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Blood and lymphatic system disorders	0 (0.0)	2 (2.8)	7 (0.5)	0 (0.0)	0 (0.0)	2 (2.8)	8 (0.5)	0 (0.0)
Anaemia	0 (0.0)	1 (1.4)	2 (0.1)	0 (0.0)	0 (0.0)	1 (1.4)	2 (0.1)	0 (0.0)
Neutropenia	0 (0.0)	1 (1.4)	2 (0.1)	0 (0.0)	0 (0.0)	1 (1.4)	2 (0.1)	0 (0.0)
Thrombocytopenia	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Cardiac disorders	0 (0.0)	2 (2.8)	15 (1.0)	0 (0.0)	0 (0.0)	2 (2.8)	16 (1.0)	0 (0.0)
Atrial fibrillation	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Cardiac arrest	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Cardiac failure	0 (0.0)	1 (1.4)	1 (0.1)	0 (0.0)	0 (0.0)	1 (1.4)	2 (0.1)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	8 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	9 (0.6)	0 (0.0)
Diarrhoea	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	6 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.4)	0 (0.0)
Subdural haemorrhage	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Renal and urinary disorders	0 (0.0)	0 (0.0)	9 (0.6)	1 (1.7)	0 (0.0)	0 (0.0)	9 (0.6)	1 (1.7)
Acute kidney injury	0 (0.0)	0 (0.0)	2 (0.1)	1 (1.7)	0 (0.0)	0 (0.0)	2 (0.1)	1 (1.7)
Haematuria	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	9 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	9 (0.6)	0 (0.0)
Pruritus	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Purpura	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)

Source: ADSL, ADAE. Data cutoff: 25OCT2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304).

Abbreviations: FL, Follicular Lymphoma; Obi, Obinutuzumab; TEAE, treatment-emergent adverse event; Zanu, Zanubrutinib.

N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD and/or obinutuzumab. Percentages are based on N, unless otherwise specified.

TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to last zanubrutinib dose date + 30 days/last obinutuzumab infusion date + 90 days or initiation of new anti-cancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond last zanubrutinib dose date + 30 days/last

obinutuzumab infusion date + 90 days and prior to initiation of new anti-cancer therapy is also considered as treatment-emergent. Patients with multiple events for a given preferred term and with multiple preferred terms within a system organ class are counted only once at the preferred term and system organ class levels, respectively. Events are sorted by decreasing frequency first by system organ class and then by preferred term within each system organ class in the original 'BGB-3111-212 Zanu + Obi' column.

Dose reduction:

In the **Study BGB-3111-212 (zanubrutinib + obinutuzumab)** group, 15 (10.5%) patients reported ≥ 1 dose reduction of zanubrutinib because of an adverse event. The most common adverse events leading to dose reduction were Thrombocytopenia and Platelet count decreased (3 [2.1%] patients each) as well as Neutropenia (2 [1.4%] patients). All other adverse events leading to dose reduction were reported in a single patient each.

In the **All Patients** group, 156 (10.1%) patients reported ≥ 1 dose reduction because of an adverse event. The most common adverse events leading to dose reduction were Pneumonia (16 [1.0%] patients), Diarrhoea (12 [0.8%] patients), Neutropenia (10 [0.6%] patients), and Atrial fibrillation (9 [0.6%] patients).

Dose interruption:

In the **Study BGB-3111-212 (zanubrutinib + obinutuzumab)** group, 78 (54.5%)patients reported ≥ 1 dose interruption because of an adverse event, an increase of 4 patients from the original SCS. The most common events were COVID-19 (12 [8.4%] patients), Pneumonia (8 [5.6%] patients), and Thrombocytopenia and Pyrexia (6 [4.2%] patients each).

In the **Study BGB-3111-212 (obinutuzumab)** group, 31 (43.7%) patients had ≥ 1 dose interruption because of an adverse event, no change from the original SCS (**Error! Reference source not found.**). The most common events were Infusion related reaction (6 [8.5%] patients), Neutropenia (4 [5.6%] patients), and Abdominal pain, Neutrophil count decreased, Platelet count decreased, and Chills (3 [4.2%] patients each).

In the **All Patients** group, 733 (47.3%) patients reported ≥ 1 dose interruption because of an adverse event. The most common events were Neutropenia (80 [5.2%] patients), Pneumonia (73 [4.7%] patients), COVID-19 (53 [3.4%] patients), Diarrhoea (38 [2.5%] patients), and COVID-19 pneumonia and Vomiting (31 [2.0%] patients each).

Post marketing experience

There are no postmarketing data for zanubrutinib plus obinutuzumab combination therapy.

2.5.1. Discussion on clinical safety

The safety assessment consists of two parts: One for safety in FL patients receiving the combination of zanubrutinib and obinutuzumab (ZO; compared to obinutuzumab monotherapy; O) and an update of the entire zanubrutinib monotherapy population of 1550 R/R patients with B-cell malignancies in the currently approved SmPC.

The pivotal study for the combination regimen was study 212 (ZO; N=143, O; N=71) with support from study GA101 (N=36). Treatment with zanubrutinib and obinutuzumab was open label. In study 212, patients received zanubrutinib 160 mg twice a day orally and obinutuzumab 1000 mg intravenously on Days 1, 8, and 15 of Cycle 1; on Day 1 of Cycles 2 to 6; and then every 8 weeks for a maximal total of 20 infusions. In the supportive study GA101 obinutuzumab was only given for the first 6 cycles (a maximum of 8 infusions instead of a maximum of 20 infusions), so the AE profile is not directly comparable between the two studies, which is why study 212 is the main study for safety assessment

of the ZO combination regimen. The difference in treatment doses between the two studies is clearly shown in Table 3/SCS were patients in study 212 (which is ongoing) received a median of 13 cycles of zanubrutinib and 11 doses of obinutuzumab, whereas in study GA101, patients received 29 cycles of zanubrutinib but only 9 doses of obinutuzumab. Thus, the safety population for the ZO combination is based on study 212 and the MAH has updated the SmPC accordingly.

For the monotherapy pool an update using the most recent DCO for the studies included was provided.

Exposure:

Combination therapy: For study 212 (DCO 25 October 2022) the median duration of zanubrutinib treatment was 12.35 months (0.5 to 48.1 months). Patients completed a median of 13.43 zanubrutinib treatment cycles (range: 0.5 to 52.3 cycles) and a median of 11.0 obinutuzumab infusions (3.0 to 20.0 infusions) with a median relative dose intensity for zanubrutinib of 98.9% (30.7% to 100.0%). In the obinutuzumab arm patients completed a median of 9.0 infusions (range: 3.0 to 20.0 infusions). Dose reductions of obinutuzumab were not allowed in the study.

Monotherapy safety pool: In the All Patients monotherapy group, the median duration of zanubrutinib treatment was 34.41 months (range: 0.1 to 90.0 months). Patients completed a median of 37.41 zanubrutinib treatment cycles (range: 0.1 to 97.8 cycles). A total of 1270 (82%) patients had ≥ 12 months of treatment, 1035 (66.8%) patients had ≥ 24 months of treatment, and 697 (45%) patients had ≥ 36 months of treatment.

For the FL patients in the monotherapy pool (N=59) the median duration of treatment was markedly lower (8.34 months) than in the entire monotherapy pool (N=1550; 34.41 months) limiting the value of a comparison between the All patients monotherapy pool and the FL patients in this pool.

Baseline and disease characteristics:

In study 212 the baseline and disease characteristics where generally comparable between the two arms: One possible significant difference favouring the ZO arm was a higher percentage of patients with ECOG 0 (59.4% vs 43.7%).

There were some differences between the ZO arm of study 212 and the monotherapy pool: The median age was 63.0 and 67.0 and ECOG 0 was 59.4% and 44.6%, respectively. The number of prior treatments were 3 and 2, respectively. The main difference lies in the exposure time, as previously described.

Adverse events:

Reported adverse events were consistent with the known safety profile of zanubrutinib monotherapy, and there were no unexpected findings. At the same time it is worth noticing that the patient populations in the studies concerning follicular lymphoma (FL) were relatively small and, thus, any unexpected signals were unlikely to be identified.

Combination therapy: The addition of zanubrutinib to obinutuzumab did not substantially increase toxicity compared to single-agent obinutuzumab, although some differences were seen: In study 212 there were higher frequencies of the All grades AEs Infections (by SOC) and thrombocytopenia in the ZO arm compared to the O arm. AEs of ≥Grade 3 and SAEs in the SOC Infections and Infestations were the most frequent event occurring twice as frequent in the ZO arm compared to the O arm. The frequency was similar to the monotherapy pool but here the duration of exposure to zanubrutinib is more than double the exposure in study 212 and the high ≥Grade 3 infection frequency for the ZO combination is thus a cause for concern. Updated safety data was requested, but as 90% of patients in the O arm and 67% in the ZO arm have discontinued the study at the DCO of 25 June 2022 this will not be of much additional value for the comparison to the obinutuzumab arm given the low number of patients left in

this arm, but data from the ZO arm may be compared to the zanubrutinib monotherapy pool; there was a small rise in AE incidences with +4 months longer follow up but no new ADRs.

Pronounced thrombocytopenia was reported more frequently in the combination therapy groups than in the monotherapy groups. However, despite the decrease in platelet count no increase in the incidence of haemorrhage was observed, which could be due to the small size of the population. Thrombocytopenia and haemorrhage are described in the SmPC.

Monotherapy safety pool: There were minor increases in various AE frequencies, but no change to the cruder adverse reaction frequency groups (Very common, Common etc.) were observed neither for the All Grades nor the ≥ Grade 3 categories.

Combination therapy: There were 14 AEs leading to death in the ZO arm: Generally, if not due to PD the fatal AEs were due to infections (Table 13/uSCS), which is common in these patients both due to the disease itself as well as prior and current treatment.

In the *monotherapy pool* 78/1550 patients died within 30 days after the last dose of zanubrutinib due to an adverse event. Not unexpectedly in a late line lymphoma population the main cause was related to infections including COVID-19.

The MAH has made an update on the summary of adverse events (the ”All Zanubrutinib” safety data set) with new data cut offs (the SmPC document). The data set contains the total 1550 patients, and the median duration of exposure has increased after the previous approved SmPC version from 22.95 months to 34.41 months: No change to the cruder adverse reactions frequency groups (Very common, Common etc.) were observed neither for the All Grades nor the ≥Grade 3 categories.

As the number of patients in other race categories than White and Asian were few, the comparison was limited to these categories. In the monotherapy pool the proportion of patients experiencing adverse events was similar in White patients and in Asian patients across all patient groups, - whereas for study 212 a rather large difference is seen for eg. SAEs in both arms between White and Asian race.

Approximately 2/3 of the patients in study 212 were from Europe and 1/5 were from the Asian region. One of the three stratification factors was geographic region (China versus ex-China). The rates of ≥ Grade 3 adverse events, serious adverse events, TEAE leading to death, treatment discontinuation, and dose reduction were lower in the China group similarly in both ZO and O arms. It is agreed, that this may in part be due to the China patients being 7 or 10 years younger than the global patients. It could also be partly due to underreporting. Whatever the explanation the China patients contribute to a lower incidence of these adverse events, which is not ideal, but is not considered to have an impact on the benefit-risk.

The most common AEs leading to discontinuation were preferred terms in the SOC Infections and Infestations both in the combination treatment and the monotherapy pool. Despite the shorter exposure in study 212 the frequency was higher than in the monotherapy pool; this could be due to both the ZO combination as well as the fact that study 212 was conducted to a larger part during the COVID-19 pandemic compared to the monotherapy pool as COVID-19 infections were higher in study 212 (both arms although higher in the ZO arm) compared to the monotherapy pool. Despite this, it is considered safe to conclude that the combination of ZO enhances the risk of infection compared to obinutuzumab monotherapy.

2.5.2. Conclusions on clinical safety

Based on the dossier with the DCO of 25-OCT-2022, the safety results in the combination regimen were consistent with the known safety profile of zanubrutinib and obinutuzumab with no unexpected findings. With the updated data (median duration of exposure of 34.41 months) in the m*onotherapy pool,* no new or unanticipated safety signals were seen.

The MAH will submit updated safety data from the ROSEWOOD study (BGB-3111-212) post-authorisation in Q4-2024 following a recommendation from the CHMP.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 5.0 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 5.0 with the following content:

Safety concerns

Table 49 Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	• Haemorrhage • Infections (including lower respiratory tract infections and hepatitis B reactivation) • Cardiac arrhythmia, mainly presenting as atrial fibrillation and flutter
Important potential risks	• Second primary malignancies (other than non-melanoma skin cancer) • Second primary non-melanoma skin cancer • Drug-drug interaction with CYP3A inducers • Teratogenicity
Missing information	• Safety in patients with severe hepatic impairment • Safety in patients with severe renal impairment/on dialysis • Long-term safety (> 2 years)

Pharmacovigilance plan

Table 50 Summary Table of Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				
Category 3 – Required additional pharmacovigilance activities				
BGB-3111-LTE1 An Open-label, Multicenter, Long-term Extension Study of Zanubrutinib (BGB-3111) Regimens in Patients with B-cell Malignancies Ongoing	To evaluate the long-term safety of zanubrutinib, as monotherapy or in combination, in patients with B-cell malignancies who participated in a BeiGene parent study for zanubrutinib.	Long-term safety (> 2 years)	Information on study progress in PSURs: Interim report submission: Estimated study completion date: Final report submission:	In each periodic report until study completion December 2025 December 2026 Planned June 2027

Risk minimisation measures

Not applicable.

2.7. Update of the Product information

As a consequence of this new indication, 4.1, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This is an extension of indication for *zanubrutinib in combination with obinutuzumab in the treatment of adult patients with refractory or relapsed follicular lymphoma who have received at least two prior systemic therapies.*

3.1.2. Available therapies and unmet medical need

Medical treatment for R/R follicular lymphoma depends on the stage and severity of the disease, as well as the age and overall health status of the patient, prior therapies and responses and response durations to prior therapies. Treatment options typically include rituximab monotherapy, or combinations of anti-CD20 monoclonal antibodies (rituximab, obinutuzumab) with chemotherapeutic agents (such as cyclophosphamide, doxorubicin, vincristine, bendamustine). Commonly used regimens are R-bendamustine, R-CVP and R-CHOP. Autologous or allogeneic stem cell transplant is also a treatment option in selected cases. Additional treatment options include the PI3K-δ inhibitor idelalisib, the PI3K inhibitor duvelisib, lenalidomide (in combination with rituximab), the bispecific antibody mosunetuzumab and the CAR-T therapies axicabtagene ciloleucel and Tisagenlecleucel.

With each relapse of FL, the duration of remission tends to be shorter. Acceptable options for patients with R/R FL eventually become somewhat limited and may not be accessible for all patients, either because of advanced patient age (precluding use of stem cell transplantation, chemotherapy, or cellular therapy), or limited bone marrow reserve following prior therapies or comorbidities (e.g., hepatic, renal, pulmonary or cardiac impairment). Thus, treatments capable of inducing high rates of durable responses with favourable safety and tolerability profiles are still needed in the high-risk population of patients with R/R FL, especially in second or later relapse.

To date, there are no BTK inhibitors approved in EU for the treatment of follicular lymphoma.

3.1.3. Main clinical studies

Study 212 is an ongoing international, phase 2, open-label, randomized, active-control study of zanubrutinib plus obinutuzumab versus obinutuzumab monotherapy in patients with relapsed/refractory follicular lymphoma (FL). Patients were above 18 years of age, had a histologically confirmed diagnosis of B-cell FL (Grade 1, 2, or 3a) and had received ≥ 2 prior systemic treatments for FL (including an anti-CD20 antibody and an appropriate alkylator-based combination therapy). Central randomization (2:1) was used to assign patients to one of the following treatment arms:

• Arm A (arm ZO): zanubrutinib + obinutuzumab

• Arm B (arm O): obinutuzumab monotherapy

Zanubrutinib was administered as two 80-mg capsules orally twice a day (160 mg twice a day). Each treatment cycle was 28 days. Treatment duration was until progressive disease or unacceptable toxicity. Obinutuzumab (1000 mg) was administered intravenously on Days 1, 8, and 15 of Cycle 1; on Day 1 of Cycles 2 to 6; and then every 8 weeks for an additional 24 months.

Primary endpoint was ORR as determined by ICR using the Lugano Classification for NHL.

Key secondary endpoints included ORR as determined by investigator assessment, DOR as determined by ICR and by investigator assessment, and PFS as determined by ICR and by investigator assessment.

3.2. Favourable effects

The study met its primary endpoint: ORR as assessed by ICR was 69.0% in arm ZO and 45.8% in arm O. ORR risk difference was 22.7% (95% CI: 9.0, 36.0, p-value (CMH) 0.0012). ORR assessed by investigator was concordant. Responses were observed across most predefined subgroups.

Median DOR by ICR was not reached in arm ZO and was 14.0 months in arm O (median FU 17 and 23 months, respectively, and 22% events across arms).

Median PFS by ICR was 28.0 months in arm ZO and was 10.4 months in arm O (median FU 19 and 23 months, respectively, and 47% events across arms).

Acknowledging possible confounding due to cross-over (35 out of 72 patients from O to ZO), median OS was not reached in arm ZO and was 34.6 months in arm O (median FU around 23 months and 23% events across arms).

3.3. Uncertainties and limitations about favourable effects

PFS estimates and rate of censoring vary considerably between the ICR and the investigator assessment. Due to the short follow-up, uncertainties regarding PFS and DoR estimates remain and the MAH will provide updated efficacy data as a post authorisation recommendation.

Due to open label design of the study, the value and interpretation of PROs is very limited.

The MAH will submit updated efficacy (ORR, DoR, PFS) data from the ROSEWOOD study (BGB-3111-212) post-authorisation following a recommendation from the CHMP.

3.4. Unfavourable effects

In the combination study 212 there were higher frequencies of the All grades AEs Infections (by SOC) in the ZO arm compared to the O arm. AEs of ≥ Grade 3 and SAEs in the SOC Infections and Infestations were the most frequent event, occurring twice as frequent in the ZO arm compared to the O arm. The frequency was similar to the monotherapy pool but here the duration of exposure to zanubrutinib is more than double the exposure in study 212 and the high ≥ Grade 3 infection frequency for the ZO combination is thus a cause for concern. Updated safety data was requested, but since 90% of patients in the O arm and 67% in the ZO arm have discontinued the study at the DCO of 25 June 2022, this will not be of much additional value for the comparison to the obinutuzumab arm given the low number of patients left in this arm, but data from the ZO arm may be compared to the zanubrutinib monotherapy pool: there was a small rise in AE incidences with +4 months longer follow up but no new ADRs.

3.5. Uncertainties and limitations about unfavourable effects

In the combination study 212 (DCO 25 October 2022) the median duration of zanubrutinib treatment was only 12.35 months (0.5 to 48.1 months). Results from the monotherapy pool has shown that adverse events increase gradually with time on treatment, so higher AE frequencies in the ZO combination could

be expected, as demonstrated with the +4 months update. Furthermore, the small number of patients in study 212 represents some uncertainty.

The MAH will submit safety data from the ROSEWOOD study (BGB-3111-212) as a post-authorisation commitment following a recommendation from the CHMP.

3.6. Effects Table

Table 2. Effects Table for Zanubrutinib + obinutuzumab [data cut-off: 25JUN2022 (efficacy) and 25OCT2022 (safety)]

Effect	Short descrip-tion	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Endpoints			Zanubrutinib + obinutuzumab **N = 145**	Obinutuzumab **N = 72**	Randomised (2:1), open-label, multicentre trial with 217 patients	Pivotal trial BGB-3111-212
Primary endpoint	ORR (CR+PR)	No. (%) 95% CI	100 (69.0%) (60.8, 76.4)	33 (45.8%) (34.0, 58.0)	ORR risk difference 22.7% 95% CI 9.0, 36.0 P-value 0.0012	
Secondary endpoint	DOR	Median (95% CI)	NE (25.3, NE)	14.0 (9.2, 25.1)	Short follow-up, high degree of censoring	
Secondary endpoint	PFS by ICR	Median (95% CI)	28.0 (16.1, NE)	10.4 (6.5, 13.8)	Short follow-up, high degree of censoring	
Secondary endpoint	PFS by INV	Median (95% CI)	16.3 (11.0, 27.4)	5.8 (3.7, 7.9)	Short follow-up, high degree of censoring	
Unfavourable Effects						
			Zanubrutinib (Z) + obinutuzumab (O) **N = 143**	Obinutuzumab **N = 71**		
SAE		% (N)	44.8 (64)	31.0 (22)	Short FU; higher frequency in Z monotherapy pool with longer FU.	Table 7/uSCS
AE leading to death		% (N)	9.8 (14)	9.9 (7)	Short FU. Missing narratives; OC raised.	
≥ Grade 3 AE		% (N)	65.7 (94)	47.9 (34)	Short FU	
Dis-continuation		% (N)	18.2 (26)	11.3 (8)	Short FU	
Infections & Infestations (SOC)	Any AE ≥ Grade 3 SAE	% (N)	58.0 (83) 31.5 (45) 29.4 (42)	42.3 (30) 14.1 (10) 11.3 (8)	Pneumonia and COVID-19 the most frequent PTs. Study conducted during the COVID-19 pandemic. AESI	Table 9, 11, and 14/uSCS
Blood & lymphatic system	Any AE ≥ Grade 3	% (N)	39.9 (57) 23.1 (33)	29.6 (21) 19.7 (14)	Neutropenia and thrombocytopenia mainly.	Table 9 and 14/uSCS

Effect	Short descrip-tion	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
disorders (SOC)					AESI	
Afli (PT)	Any AE	% (N)	2.8 (4)	1.4 (1)	Short FU AESI	Table 19/uSCS
Investigations Absolute neutrophil count decreased	Any AE ≥ Grade 3	% (N)	47.5 (58) 18.0 (21)	42.1 (24) 14.0 (8)	AESI	Table 2.7.4.3.3. ISS
Platelets Decreased	Any AE ≥ Grade 3	% (N)	64.8 (79) 11.5 (14)	42.9 (24) 10.7 (6)	AESI	Table 2.7.4.3.3. ISS

Abbreviations: AESI adverse event of special interest; Afli atrial fibrillation or flutter; CI confidence interval; CR complete response; DOR duration of response; FU follow-up; ICR independent central review; INV investigator; PFS progression free survival; PT preferred term; SAE serious adverse events; SCS summary of clinical safety; uSCS updated SCS; TEAE treatment-emergent adverse events;

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The use of zanubrutinib in combination with obinutuzumab demonstrated an improvement of efficacy compared to obinutuzumab monotherapy regimens with significantly more patients achieving response (CR or PR); 69.0% vs. 45.8% (2-sided p-value of 0.0012). Considering the poor prognosis of multiple relapsed FL, the observed magnitude of PFS difference (while immature) is also considered clinically meaningful.

The observed responses appeared to be durable: the median DoR was longer in the arm A (zanubrutinib combination with obinutuzumab) compared to the arm B (obinutuzumab alone), with median duration of response was not reached in arm A. The DoR data are also considered immature.

The OS data are immature and due to extensive cross-over between the treatment arms, OS data will be of limited value and difficult to interpret. The MAH will submit updated efficacy data following a recommendation from the CHMP.

The combination of zanubrutinib and obinutuzumab has added to the known toxicity of the individual medicines, however, the adverse events appear manageable and given the relatively poor prognosis in the third line FL setting, is considered acceptable.

3.7.2. Balance of benefits and risks

Efficacy with regard to ORR for zanubrutinib in combination with obinutuzumab can be considered clinically relevant in this patient population (third line setting) and is supported by DoR and PFS estimates.

The majority of adverse events observed are considered manageable in the clinical setting.

3.7.3. Additional considerations on the benefit-risk balance

3.8. Conclusions

The overall B/R of Brukinsa is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include in combination with obinutuzumab treatment of adult patients with relapsed or refractory follicular lymphoma who have received at least two prior systemic treatments for BRUKINSA; based on results from studies BGB-3111-212 and BGB-3111-GA101-001. BGB-3111-212 is an ongoing international, Phase 2, open-label, randomized (2:1), active control study of zanubrutinib plus obinutuzumab (Arm A) versus obinutuzumab monotherapy (Arm B) in patients with R/R FL. The primary efficacy endpoint is overall response rate (ORR); while BGB-3111-GA101-001 is 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. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 5.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Brukinsa is not similar to Gazyvaro, Lunsumio, Kymriah and Yescarta within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR

module "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Brukinsa-H-C-4978-II-0014'