NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Zanubrutinib for treating relapsed or refractory mantle cell lymphoma after 1 or more treatments [ID6392]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Zanubrutinib for treating relapsed or refractory mantle cell lymphoma after 1 or more treatments [ID6392]

Contents:

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Company submission** from BeiGene:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submission** from:
   a. Lymphoma Action
   b. Royal College of Pathologists

4. **External Assessment Report** prepared by Birmingham Centre for Evidence and Implementation Science (BCEIS)

5. **External Assessment Group response to factual accuracy check of EAR**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Zanubrutinib for treating relapsed or refractory mantle cell lymphoma after 1 or more treatments ID6392

Document B Company evidence submission

January 2025

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B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The objective of this single technology appraisal (STA) is to evaluate the clinical- and cost-effectiveness of zanubrutinib (brand name BRUKINSA) as a monotherapy for adult patients with relapsed/refractory mantle cell lymphoma (R/R MCL). The marketing authorisation – BRUKINSA as a monotherapy is indicated for the treatment of adult patients with MCL who have received at least one prior therapy – was granted by the Medicines and Healthcare products Regulatory Agency (MHRA) through the International Recognition Procedure (IRP) on 21st November 2024.[1]

This submission covers part of the technology's marketing authorisation, specifically: adult patients with R/R MCL who have received one prior therapy, i.e., as a second line (2L) therapy.

The proposed positioning in the treatment pathway is narrower than the MHRA marketing authorisation. Through engagement with clinical experts it is clear that, in clinical practice, Bruton's tyrosine kinase inhibitors (BTKi) are used almost exclusively for the second line treatment for R/R MCL and there is an unmet need for further effective and well-tolerated BTKi treatment options.[2]

The decision problem addressed in this submission, compared with that defined in the final scope issued by NICE is summarised in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with R/R MCL who have had at least 1 prior therapy	Adults with R/R MCL who have had 1 prior therapy (2L)	The population described in the final scope broadly captures the licensed indication for zanubrutinib. However, the population addressed in this submission is narrower than the marketing authorisation to reflect the population in which zanubrutinib would be used for R/R MCL in UK clinical practice. Zanubrutinib is anticipated to be positioned at 2L therapy, where there is an unmet need for an effective and well-tolerated treatment option, as confirmed by clinical experts. For further details please refer to Section B.1.3.4 Clinical pathway of care and place in therapy
Intervention	Zanubrutinib	As per scope	N/A

Comparator(s)	Established clinical management including but not limited to:
	• After 1 prior therapy
	  ○ Ibrutinib
	• After 2 or more prior therapies
	  ○ Ibrutinib
	  ○ Chemotherapy with or without rituximab
	  ○ Brexucabtagene autoleucel (subject to NICE evaluation)
	  ○ Allogeneic haemopoietic stem cell transplant
		Ibrutinib	Ibrutinib is considered the only appropriate comparator for zanubrutinib in 2L R/R MCL, based on the BSH 2023 and NICE guidelines, past NICE and SMC technology appraisals, real world evidence from the HMRN registry, UK clinical expert opinion[2–6].
			This is the anticipated place of zanubrutinib in the treatment pathway.
			The following therapies are not considered appropriate comparators for reasons provided below:
			• Rituximab with or without chemotherapy
			• Brexucabtagene autoleucel
			• Allogeneic haemopoietic stem cell transplant (alloSCT)
			
			Rituximab with or without chemotherapy

			Ibrutinib is the current SoC in UK clinical practice in 2L R/R MCL, having displaced 'rituximab with or without chemotherapy' following its approval by NICE in 2018.[4] RWE from the HMRN shows that the majority of patients eligible for treatment with zanubrutinib would be those who have received one prior line of therapy (2L). Treatment usage data shows that ibrutinib is the regimen of choice for [redacted] of patients initiating 2L treatment for R/R MCL between [redacted].[7] Zanubrutinib is anticipated to displace ibrutinib as a second-generation Bruton's tyrosine kinase inhibitor (BTKi) therapy, which positions 'rituximab with or without chemotherapy' as subsequent treatment rather than a comparator treatment.[4] Therefore, 'rituximab with or without chemotherapy' should not be considered a comparator against zanubrutinib for this appraisal.

			Brexucabtagene autoleucel The licensed indication for brexucabtagene autoleucel is restricted to patients who have received at least two lines of systemic therapy including a BTKi.[8] Conversely, the trial eligibility criteria for zanubrutinib (BGB-3111-AU-003 and BGB-3111-206)[9,10] excluded patients who had received treatment with a BTKi prior to enrolment. Hence there is no overlap in the eligible populations of the two treatments. This positions brexucabtagene autoleucel at 3L+, beyond zanubrutinib in the treatment pathway, as a subsequent treatment option rather than a relevant comparator. This is reflected in the BSH guidelines which recommend that *"MCL patients who are relapsed or refractory (including stable disease) after anti-CD20 antibody-containing immunochemotherapy and BTKi should be offered Brexu-cel*".[3] Furthermore, brexucabtagene autoleucel is not available via routine commissioning, and hence as per NICE's position statement cannot be considered as a relevant treatment comparator within this appraisal.[3,8]

			AlloSCT Within the RWE from the HMRN no patient underwent a stem cell transplant for R/R MCL, demonstrating that such interventions cannot be considered SoC in the UK. Furthermore, the BSH guidelines clearly recommend alloSCT for only *"fit patients with an appropriate donor following failure with immunochemotherapy, covalent BTKi* [such as zanubrutinib] *and CAR-T failure"* and go on to say: *"The majority of relapsed MCL patients will not be eligible for ASCT or alloSCT",* aligning to the observations from the HMRN cohort.[3]
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	As per scope	N/A

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	A cost-effectiveness analysis in adults with 2L R/R MCL is presented comparing zanubrutinib with ibrutinib. For further details please refer to Section B.3 Cost effectiveness.	N/A

AlloSCT – allogenic stem cell transplant; ASCT – autologous stem cell transplant; BSH – British Society for Haematology; BTKi – Bruton's tyrosine kinase inhibitor; HMRN – Hematological Malignancy Research Network; MCL – mantle cell lymphoma; N/A – not applicable; NHS – National Healthcare Service; NICE – National Institute for Health and Care Excellence; PSS – Personal Social Services; R/R – relapsed refractory; RWE – real world evidence; SMC – Scottish Medicines Consortium; SoC – standard of care; UK – United Kingdom

B.1.2 Description of the technology being evaluated

A description of zanubrutinib is presented in Table 2 and the current Summary Product Characteristics (SmPC) from the MHRA is presented in Appendix C.[1]

Table 2: Technology being appraised

UK approved name and brand name	UK approved name: Zanubrutinib Brand name: BRUKINSA®
Mechanism of action	Zanubrutinib is a next generation, highly selective, small molecule, orally administered, irreversible inhibitor of BTK. BTK is a signalling molecule of the BCR and cytokine receptor pathways. In B cells, BTK signalling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. Zanubrutinib binds with and inhibits BTK which blocks BCR-induced BTK activation. By blocking the signalling pathway, this inhibits the proliferation and survival of malignant B cells.[11] In non-clinical studies, zanubrutinib inhibited malignant B-cell proliferation and reduced tumour growth.[1] Zanubrutinib is specific and selective for BTK and was designed to minimise off-target inhibition of other kinases.
Marketing authorisation/CE mark status	Marketing authorisation for zanubrutinib as a monotherapy for the treatment of adult patients with MCL who have received at least one prior therapy was granted via IRP by the MHRA on 21st November 2024.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The indication associated with this submission: BRUKINSA as a monotherapy is indicated for the treatment of adult patients with MCL who have received at least one prior therapy. Other existing indications: BRUKINSA as a monotherapy is indicated for the treatment of:[1] Adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in the first line treatment for patients unsuitable for chemo-immunotherapy. Adult patients with marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based therapy. Adult patients with chronic lymphocytic leukaemia (CLL). 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.[1]
Method of administration and dosage	The recommended total daily dose of zanubrutinib is 320 mg taken orally either once daily (four x 80 mg capsules) or divided into two doses of 160 mg twice daily (two x 80 mg capsules).[1] Patients should be instructed to swallow the capsules whole with water (with or without food), and not to open, break or chew the capsules.

Additional tests or investigations	No
List price and average cost of a course of treatment	Zanubrutinib is available at a list price of £4,928.65 for a pack of 120 x 80 mg capsules.[12] The average cost of a course of treatment is £4,599.84 per cycle based on the daily dose of zanubrutinib of 320 mg in 28-day cycles in the BGB-3111-206 trial. £4,928.65 / 120 = £41.07 per capsule 320 mg / 80 mg = 4 capsules per patient £41.07 x 4 = £164.28 per patient per day £164.28 x 28 = £4,599.84
Patient access scheme (if applicable)	A simple PAS discount of [redacted] for a pack of 120 x 80 mg capsules.

BCR – B-cell receptor; BTK – Bruton's tyrosine kinase; CLL – chronic lymphocytic leukaemia; FL – follicular lymphoma; IRP – International Regulation Procedure; MCL – mantle cell lymphoma; mg – milligram; MHRA – Medicines and Healthcare products Regulatory Agency; MZL – marginal zone lymphoma; PAS – patient access scheme; SmPC – Summaries of Product Characteristics; UK – United Kingdom; WM - Waldenström's macroglobulinaemia

B.1.3 Health condition and position of the technology in the treatment pathway

Overview of R/R MCL epidemiology and burden

- MCL is a group of indolent non-Hodgkin's lymphoma (NHL) that develop from B cells. It is called 'mantle cell' lymphoma because the abnormal B cells usually develop in a part of the lymph nodes called the 'mantle zone'.[13] It is a rare form of cancer, with an estimated 0.9 new cases of MCL per 100,000 people in the UK each year.[14]
- Most patients diagnosed with MCL will ultimately relapse after initial treatment or become refractory to treatment, progressing to advanced MCL. The course of advanced MCL typically involves a continuing pattern of relapse and remission.[13]
- The broad range of symptoms experienced by patients with MCL pose a significant clinical burden, which impacts patients health-related quality of life (HRQoL).[15] For caregivers, the burden is related to high degrees of stress and fears regarding treatment efficacy and death.[16]

Current clinical pathway of care and unmet need

- Following an initial response to first-line (1L) treatment, the majority of patients with MCL will experience disease relapse or become refractory to 1L treatment and require a second line of therapy. In these instances, UK guidelines recommend ibrutinib as the 2L treatment option for patients with R/R MCL.[3]
- Ibrutinib use represents the standard of care (SoC) for patients with 2L R/R MCL in the UK. Nonetheless, it is associated with considerable tolerability and cardiac safety concerns,[17] and there remains an unmet need for treatment options in 2L R/R MCL with improved tolerability.

Zanubrutinib

- As a next-generation BTKi, zanubrutinib has the potential to address this unmet need, providing an effective treatment with improved tolerability for clinicians and patients in the UK with 2L R/R MCL.

B.1.3.1 Disease overview

NHL refers to a diverse spectrum of cancers that impact the lymphatic system.[18] The lymphatic system plays a crucial role in supporting the immune system, and comprises the lymph vessels, lymph nodes, and other lymphatic organs, including the bone marrow, spleen, and thymus gland. NHL is a heterogeneous group of conditions ranging from indolent (the 'low-grade' type which is slower-growing but usually incurable) to aggressive (the 'high-grade' type which is faster-growing but often curable) disease. The characteristics of NHL reflects the specific lymphoma subtype of the cells from which they originated.[18,19]

MCL is a group of indolent NHL that develop from B cells. It is called 'mantle cell' lymphoma because the abnormal B cells usually develop in a part of the lymph nodes called the 'mantle zone'.[13] MCL can occur at any age but is more common in middle-aged or older people.[13] MCL is a rare form of cancer, with prevalence of 4.2 and annual incidence of 0.9 per 100,000 people in the United Kingdom (UK).[14,20]

The World Health Organisation (WHO) recognises three main subtypes of MCL depending on the tissue type of origin: classical, leukemic nonmodal and in situ mantle cell neoplasia.[21]

The most common symptom in patients with MCL is the development of lumps in several parts of the body, caused by swollen lymph nodes.[13] When symptoms occur, they differ depending on the tissue involved. Additional common symptoms include unexplained weight loss, night sweats, fever, fatigue, prolonged or excessive bleeding, weakened immune system leading to longer times to fight infection.[13]

B.1.3.1.1. Clinical presentation, staging and diagnosis

NHL is staged based on the extent of the disease spread within the body, with stages ranging from I to IV:[22]

- Stage I lymphoma is in a single group of lymph nodes, organ or area outside the lymph system.

- Stage II lymphoma is in two or more groups of lymph nodes, or in another area as well as one group of lymph nodes, but the sites of lymphoma are on the same side of the diaphragm.
- Stage III lymphoma is in two groups of lymph nodes, both above and below the diaphragm.
- Stage IV lymphoma is widespread and may also affect organs such as the bone marrow, lungs or liver.

Frequently used staging systems include the Ann Arbor classification, the Lugano staging system which is a modification of the Ann Arbor system originally developed for gastrointestinal lymphomas, and the fluorodeoxyglucose-positron emission tomography-CT staging.[3,23] The Ann Arbor system was used to stage patients in the two clinical studies for zanubrutinib in R/R MCL – BGB-3111-AU-003 (NCT: NCT02343120) and BGB-3111-206 (NCT: NCT03206970).[9,10] Disease presentation and clinical symptoms of MCL are often unspecific and can vary based on site of involvement as described below.

The type of MCL depends on the site and involvement of lymph nodes and extranodal sites. Classical MCL accounts for most MCL cases and is usually fast growing.[13] Leukemic non-nodal MCL is a less common type of MCL that tends to grow slowly. In situ mantle cell neoplasia (ISMCL) is often found incidentally and in association with other lymphomas.[21,24] ISMCL is associated with a low rate of progression, and its malignant potential seems very limited.[21,25]

The majority of patients diagnosed with MCL will ultimately relapse after initial treatment, or become refractory to treatment, hence progressing to advanced MCL. Real world data from the Haematological Malignancy Research Network (HMRN), the largest UK registry that gathers information on lymphomas and other blood disorders from a population-based patient cohort of around 4 million patients across Yorkshire and Humberside, indicate that [redacted] of patients who received first-line treatment in the registry went on to receive further treatment for R/R MCL.[7] The natural history of advanced MCL is characterised by a continuing pattern of relapse

and remission. Relapse often manifests in more advanced stages as the cancer has spread to lymph nodes.[13] Additionally, the development of resistance to previous treatments also contributes to the increased likelihood of advanced relapse.[13] Once patients with MCL relapse, the relevance of their initial subtype becomes less significant when making treatment decisions and the emphasis shifts to slowing down the progression of the disease rather than its initial cause.[13]

B.1.3.1.2 Epidemiology

MCL is a rare cancer with an estimated prevalence in the UK of 4.2 per 100,000 people and annual incidence of 0.9 people per 100,000 per year.[14,20] MCL can occur at any age but is mostly diagnosed in middle-aged or older patients, with a slight male predominance.[13,14]

The proportion of patients with R/R MCL can vary depending on the stage at diagnosis and other individual patient factors. HMRN data collected from a cohort of [redacted] patients diagnosed with R/R MCL between 1st January 2005 to 31st December 2021, showed that [redacted] patients had received at least one prior treatment.[7]

B.1.3.2 Burden of MCL

While rare, MCL is a chronic disease associated with high disease morbidity and a negative impact on patients' quality of life (QoL). As such, improving or maintaining QoL is vital, especially in patients with more advanced or progressed disease.

B.1.3.2.1 Symptom burden

The symptoms of R/R MCL can be different among people depending on the stage of disease, whether it is an indolent or aggressive type of R/R MCL, and which part(s) of the body are affected.[13] Patients with advanced disease typically have more severe symptoms that substantially impact their QoL, work, and travel.

In a previous NICE appraisal for MCL, UK patient representatives described enduring symptoms, such as fatigue, loss of appetite, weight loss, fever, night sweats and nausea, that can affect their ability to work and take part in their chosen leisure activities.[4] The enlargement of lymph nodes, spleen, and other organs can lead to discomfort and pain, impacting the patient's QoL.[4] Furthermore, in addition to

this physical burden, the mental state of patients is affected and psychological issues such as anxiety, depression and insomnia can arise.[4]

B.1.3.2.2 Impact on quality of life

MCL can significantly impact a patient's QoL due to its symptoms and treatment implications. However, given the rare nature of R/R MCL there is limited literature available that formally quantifies the HRQoL impact of MCL on patients (a systematic literature review [SLR] on HRQoL conducted by the Company identified only six studies), reflecting that MCL is an understudied and underserved disease area.

The HRQoL of MCL patients is significantly reduced due to symptom burden and loss of physical health, mobility and vitality.[15] Moreover, MCL affects different aspects of a patient's life including work, mental health, relationships and travel, all of which contribute to a decreasing QoL.[4]

The typical course of MCL treatment involves alternating periods of systemic treatment followed by short periods of observation and later lines of treatment.[26] This clinical course can contribute to the patient's burden due to fear, anxiety and worry related to the diagnosis, likelihood of relapse and future treatment.[26] For caregivers, the burden is related to high degrees of stress due to lost income, altered activities of daily living, lost sleep, and fears regarding treatment efficacy and death.[16]

Prior to the approval by NICE in 2018 of first-generation BTKi therapy ibrutinib, no targeted treatments were available for patients with R/R MCL,[4] leaving chemotherapy as the only treatment option. The toxicity of chemotherapy (e.g. nausea, vomiting, hair loss, skin irritation, sore mouth, dysphagia, and gastrointestinal problems), can compound the impact on HRQoL. Results of a survey of 294 patients who survived NHL indicated that patients who received chemotherapy experienced worse psychological and social well-being and HRQoL than patients who did not receive chemotherapy.[27]

A study in another rare form of NHL –Waldenström's macroglobulinaemia - demonstrated that patients who received therapy with a BTKi have a higher QoL scores than patients who are not exposed to a BTKi.[28] Therefore, the approval of

ibrutinib by NICE will likely have improved the QoL of patients receiving treatment for 2L R/R MCL. However, ibrutinib treatment can be associated with serious cardiac safety issues, which negatively impact patients QoL. A study published by Shadman *et al.* (2023) demonstrates that zanubrutinib is associated with an improved tolerability profile (68% intolerance events that occurred during ibrutinib treatment did not recur with exposure to zanubrutinib in patients considered intolerant to ibrutinib, and of those that did recur, 70% recurred at a lower grade) compared to patients treated with ibrutinib.[29] Therefore, even with the availability of ibrutinib for patients with 2L R/R MCL, there remains an unmet for a new effective treatment with improved tolerability relative to ibrutinib.

B.1.3.3 Life expectancy

Life expectancy and prognosis for MCL is widely assessed in clinical practice in the UK using the independently validated MCL International Prognostic Index (MIPI), as well as the 'simplified-MIPI' and 'combined MIPI' (MIPI-C) versions of the index.[3,13] The various MIPI prognostic models utilise factors such as age, Eastern Cooperative Oncology Group Performance Score (ECOG PS), Ki-67 proliferation, white blood cell count, lactate dehydrogenase (LDH) level and ability to carry on with normal activities, to calculate a score that can help decide what the most appropriate treatment is and the likely outcome after treatment.[3,13]

MCL often progresses in line with more high grade lymphomas, with median survival ranging between 3.1 and 5 years.[30] Advanced disease and the presence of symptoms are associated with a significantly worse prognosis.[3,26] This is evident in data from a cohort of [redacted] MCL whose disease has relapsed or become refractory to treatment who had median overall survival (OS) of only [redacted] year (95% CI: [redacted]).[7]

B.1.3.4 Clinical pathway of care and place in therapy

Current UK SoC

Often patients with MCL present with asymptomatic, early-stage disease and are generally managed with an active monitoring approach. Treatment is often only initiated once patients develop symptomatic disease. The goal of MCL treatment is to provide remission of symptomatic disease and long-lasting progression-free survival (PFS).[13]

The choice of first-line treatment is dependent on several factors, including MCL subtype, prognostic score, symptoms, disease stage and general health.[13] Localised early-stage disease is generally treated with curative intent with radiotherapy, however patients with advanced and/or disseminated disease require treatment with a systemic therapy.[13]

The BSH and European Society for Medical Oncology (ESMO) guidelines generally recommend rituximab-based chemoimmunotherapy, chemotherapy alone or rituximab monotherapy as systemic therapy for MCL in the first-line setting.[3,23]

Following an initial response to 1L treatment, the majority of patients with MCL will either experience disease relapse or their disease will become resistant to the 1L treatment and will require a second line of therapy. In the HMRN registry, 84% of patients who received 1L treatment went on to receive a 2L treatment for R/R MCL.[7]

UK clinical guidelines recommend ibrutinib as the 2L treatment option for patients with R/R MCL.[3] Ibrutinib was recommended by NICE in 2018 for the treatment of patients with 2L R/R MCL and was deemed cost-effective against established clinical management at that time which included 2L use of rituximab-based chemoimmunotherapy regimens.[4] Following its approval, ibrutinib use has displaced rituximab-based chemoimmunotherapy and now represents SoC for patients with 2L R/R MCL in the UK.

Real world data from the HMRN registry show that [redacted] of patients initiating 2L treatment received ibrutinib therapy (Table 3).[7] This clearly demonstrates that ibrutinib has displaced rituximab with or without chemotherapy and become the SoC

for 2L R/R MCL patients in the UK.[7] Rituximab with or without chemotherapy is now considered as a subsequent therapy only, following BTKi treatment.

Brexucabtagene autoleucel (Brexu-cel) is licensed for R/R MCL patients who have received at least two lines of systemic therapy including a BTKi, i.e. as a 3L+ treatment option.[8] Brexu-cel would therefore not be used in the same treatment line as zanubrutinib but rather as a subsequent line of treatment. Indeed, zanubrutinib clinical trials (BGB-3111-AU-003 and BGB-3111-206)[9,10] excluded patients who had received treatment with a BTKi prior to enrolment and as such there is no overlap in the patient populations eligible for the two treatments.[8] Brexu-cel's positioning as a subsequent treatment option to BTKi including zanubrutinib, rather than as a relevant comparator, is reflected in the BSH guidelines which recommend that *"MCL patients who are relapsed or refractory (including stable disease) after anti-CD20 antibody-containing immunochemotherapy and BTKi should be offered Brexu-cel"*.[3] Furthermore, as Brexu-cel is not currently subject to routine commissioning in the NHS in England, as per NICE's position statement, it should not be considered as a relevant treatment (comparator or subsequent therapy) within this appraisal.[31]

Allogenic stem cell transplant (alloSCT) should also not be considered a comparator for zanubrutinib in patients with R/R MCL. BSH guidelines clearly recommend alloSCT only for *"fit patients with an appropriate donor following failure with immunochemotherapy, covalent BTKi* [such as zanubrutinib] *and CAR-T failure"* and go on to say: *"The majority of relapsed MCL patients will not be eligible for ASCT or alloSCT",* indeed, real world evidence (RWE) from the HMRN show that none of the patients in the cohort examined received stem cell transplant for R/R MCL.[3,7]

Table 3: Second-line treatment for R/R MCL patients

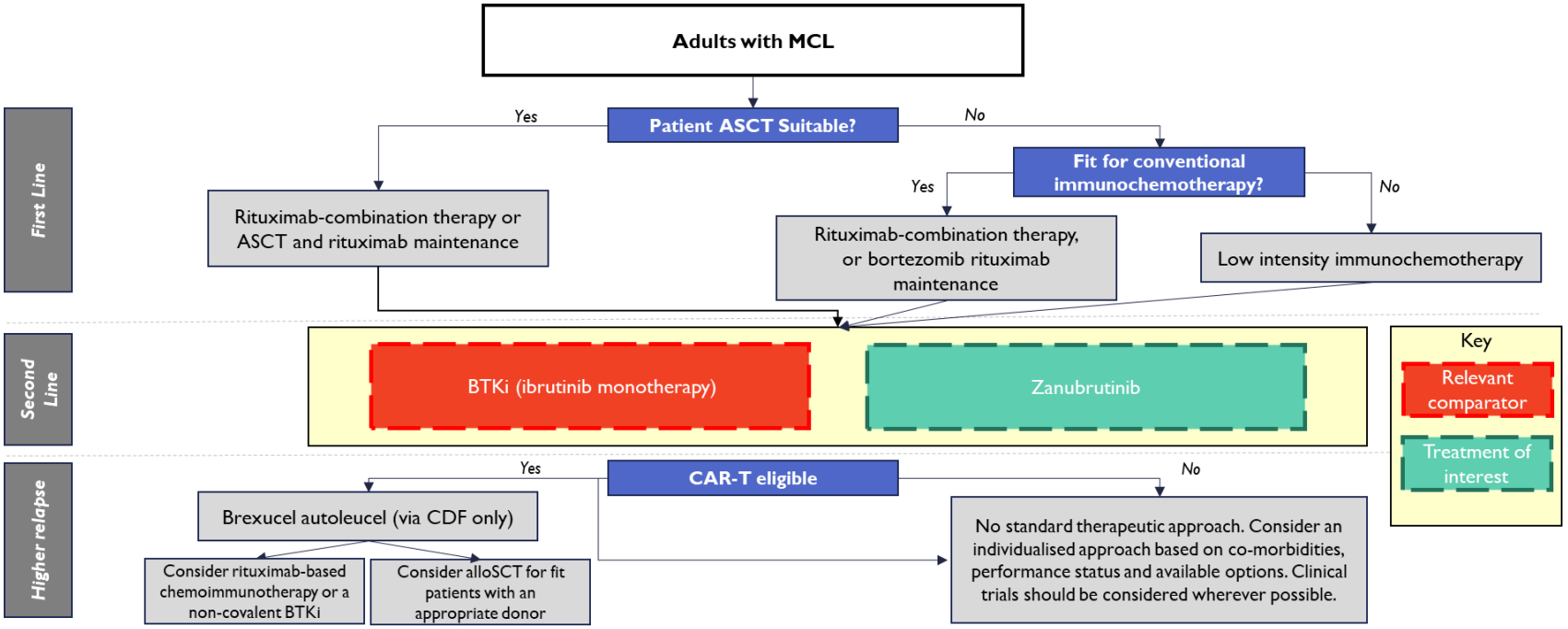
Treatment	2020-2024, n (%)
Total	[redacted]
HD AraC +/- R	[redacted]
FCR	[redacted]
R-CHOP	[redacted]
Chlorambucil	[redacted]
BR	[redacted]
Ibrutinib	[redacted]
Ibrutinib + R	[redacted]
VR-CAP	[redacted]
IVE / rituximab	[redacted]

BR – Bendamustine and rituximab; FCR – fludarabine, cyclophosphamide and rituximab; HD AraC – high-dose cytarabine; IVE – ifosfamide, etoposide and epirubicin; N – number; R – rituximab; R-CHOP – rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R/R MCL – relapsed/refractory mantle cell lymphoma; VR-CAP – frontline bortezomib, rituximab, cyclophosphamide, doxorubicin and prednisone
Source: Bagguley & Smith (2024)[7]

Zanubrutinib place in therapy in MCL

The proposed positioning of zanubrutinib in the MCL treatment pathway is as a treatment option for patients with 2L R/R MCL (Figure 1). According to the BSH guidelines, for patients relapsing after 1L immunochemotherapy a covalent BTKi should be offered. It is further specified that, where there is a choice of BTKi available, treatment should be individualised according to the specific toxicity profile of each treatment.[3] The positioning of zanubrutinib as a treatment to displace ibrutinib is thus in line with clinical guidelines and has been supported by clinicians at a UK advisory board (11th November 2024).[2,3]

Figure 1: Clinical pathway of care and proposed positioning of zanubrutinib



AlloSCT – allogeneic stem cell transplant; BTKi – Bruton tyrosine kinase inhibitor; CAR-T – chimeric antigen receptor T-cell; CDF – Cancer Drugs Fund; MCL – mantle cell lymphoma

B.1.3.5 Clinical guidelines

In the UK, MCL treatment is largely based on the BSH 2023 and NICE 2018 guidelines.[3,4] Whilst the ESMO 2017 guidelines were reviewed, these were considered outdated, as ibrutinib use has become established in UK clinical management of 2L R/R MCL patients, based on the BSH guidelines, HMRN data and clinical expert opinion.[3,7,23]

There are three principal management approaches for newly diagnosed patients with MCL: active monitoring, localised therapy and systemic therapy, with the choice of approach dependent on the disease aetiology, location, stage and presence of symptoms. Patients with MCL can present with asymptomatic, indolent disease that does not require treatment and these patients are generally subject to active monitoring. Treatment is generally initiated in patients with higher grade, symptomatic disease, with the goal of providing remission of symptoms, improvement in quality of life and induction of long-lasting PFS.[13] When treatment is deemed necessary, the choice of treatment depends on a number of factors such as age, patients fitness, MCL subtype, prognostic score, disease stage and general health.[3,13]

The clinical guidelines adopted in the UK recommend the use of rituximab with or without chemotherapy as a 1L treatment. Data on 1L treatments extracted from the HMRN registry show that real-world clinical practice aligns with the guideline recommendations. Following first relapse (R/R MCL), since its introduction to the UK, ibrutinib has become current 2L SoC, displacing rituximab with or without chemotherapy to a subsequent therapy option for those patients whose disease progresses following BTKi treatment.

B.1.3.6 Unmet need

Based on clinical expert opinion, RWE data from the HMRN registry and the BSH 2023 clinical guidelines, ibrutinib is considered the SoC for patients with 2L R/R MCL in the UK. Nonetheless, ibrutinib is associated with considerable tolerability and cardiac safety concerns,[17] and as such, there remains an unmet need for treatment options in 2L R/R MCL with improved tolerability.

As a next-generation BTKi, Zanubrutinib has the potential to address this unmet need, providing an effective treatment with improved tolerability for clinicians and patients in the UK with 2L R/R MCL. See Section B.2 Clinical effectiveness for detail of zanubrutinib efficacy, Section B.2.9 Indirect and mixed treatment comparisons for indirect treatment comparison vs ibrutinib and Section B.2.10 Adverse reactions overview: BGB-3111-AU-003 and BGB-3111- for safety.

B.1.4 Equality considerations

No equality issues are anticipated for the appraisal of zanubrutinib.

B.2 Clinical effectiveness

Summary of clinical effectiveness

- Two single-arm trials of zanubrutinib treatment in R/R MCL, BGB-3111-AU-003 and BGB-3111-206, were identified and pooled to inform this appraisal.
- The BGB-3111-AU-003 trial, an open-label, multiple-dose, multicentre dose escalation (Part 1) and expansion (Part 2) phase I/II study investigates the efficacy of zanubrutinib in patients with B-cell lymphoid malignancies, including R/R MCL (total daily dose of 320 mg). The primary endpoint of the trial was ORR by IRC-assessment and the secondary endpoints were ORR based on INV assessment, PFS, OS, DOR and TTR.
    - At the point of final analysis, ORR by IRC assessment (DCO: 13Dec2018) was 84.4%. As of the latest DCO (31Mar2021), median PFS (INV-assessed) was 21.1 months and 56.3% of patients had progressed or died; median OS was not estimable and 43.8% of patients had died; median DOR (INV-assessed) was 25.2 months and 51.7% of patients had progressed or died; and TTR (INV-assessed) was 2.66 months.
- The BGB-3111-206 trial, an open-label, multicentre, phase II study investigates the efficacy of zanubrutinib (total daily dose of 320 mg) in patients with R/R MCL. The primary endpoint of the trial was overall response rate (ORR) based on independent review committee (IRC) assessment and the secondary endpoints were ORR based on investigator (INV) assessment, PFS, OS, duration of response (DOR) and time to response (TTR).
    - At the point of the final analysis, ORR by IRC assessment (data cut-off [DCO]: 15Feb2019) was 83.7%. As of the latest DCO (08Sept2020), median PFS (INV-assessed) was 33.0 months and 48.8% of patients had progressed or died; median OS was not

estimable and 24.4% of patients had died; median DOR (INV-assessed) was not estimable and 44.4% of patients had progressed or died; and median TTR (INV-assessed) was 2.73 months.

- As no head-to head data for zanubrutinib versus ibrutinib in R/R MCL is available, a clinical SLR was conducted to identify clinical evidence for ibrutinib. Rule *et al.* (2017b) is a pooled analysis study of RAY-MCL3001, SPARK and PCYC-1104 trials and was deemed appropriate to inform this submission.[17]

- An unanchored matching-adjusted indirect comparison (MAIC) was conducted to estimate the relative efficacy of zanubrutinib versus ibrutinib for PFS and OS. Across the base case analysis and scenario analysis results, the MAIC suggested zanubrutinib is more efficacious than ibrutinib.

B.2.1 Identification and selection of relevant studies

A clinical SLR was conducted on the 16th May 2024 and subsequently updated on 16th July 2024 to identify clinical studies investigating treatments for patients with R/R MCL. Full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated are presented in Appendix D.

The SLR conducted was broader than the scope of this submission and as such, studies were only selected for data extraction if they included patients within the decision problem of this appraisal (R/R MCL patients treated with zanubrutinib or ibrutinib). Selected studies were also considered for inclusion in an indirect treatment comparison (ITC), (please refer to Appendix D for further details on justification of extracted studies).

B.2.2 List of relevant clinical effectiveness evidence

The clinical SLR identified six studies of patients with R/R MCL that were relevant to informing the clinical evidence within this submission (Table 4). No randomised

controlled trials (RCTs) were identified for zanubrutinib in R/R MCL. Instead, two single arm studies of zanubrutinib treatment in R/R MCL were identified, for which four publications were extracted: BGB-3111-AU-003 (NCT: NCT02343120)[10] (Tam *et al.* [2021]) and BGB-3111-206 (NCT: NCT03206970)[9] (Song *et al.* [2020], Song *et al.* [2021], Song *et al.* [2022b]).[32–35] For ibrutinib, four studies were identified, for which seven publications were extracted: one RCT - RAY-MCL3001, and three single arm/observational studies - PCYC-1104, Wang *et al.* (2013) and Wang *et al.* (2015); a pooled analysis across three studies, Rule *et al.* (2017); and a named patient programme, McCulloch *et al.* (2021).[17,36–41]

Table 4: Clinical studies identified and extracted in the SLR

Publication source (author, year)	Trial name (if any)	Treatment/ Group (n)	Publication type	Study setting	Study type/phase
RCTs					
Dreyling et al. (2016)[36] Rule *et al.* (2015)[41] Rule *et al.* (2017a)[40]	RAY-MCL3001	Ibrutinib (n=139) and Temsirolimus (n=141)	Journal articles	Multicentre	Phase III
Single arm/observational evidence					
Tam et al. (2021)[35]	BGB-3111-AU-003	Zanubrutinib (n=32)	Journal article	Multicentre	Phase I/II
Song et al. (2020)[32] Song *et al.* (2021)[33] Song *et al.* (2022b)[34]	BGB-311-206	Zanubrutinib (n=86)	Journal articles and conference poster	Multicentre	Phase II
McCulloch et al. (2021)[39]	Not reported	Ibrutinib (n=211)	Journal article	Retrospective multicentre analysis	N/A
Rule et al. (2017b)[17]	Pooled study of: PCYC-1104, SPARK and RAY-MCL3001	Ibrutinib (n=370)	Journal article	Pooled patient-level data analysis	N/A
Wang et al. (2013)[37] and Wang et al. (2015)[38]	PCYC-1104	Ibrutinib (n=111)	Journal articles	Multicentre	Phase II

n – number; N/A – not applicable; RCT – randomised controlled trial; SLR – systematic literature review

As identified in the SLR, the efficacy and safety of zanubrutinib in patients with R/R MCL has been studied in two single arm clinical studies – BGB-3111-AU-003 (NCT: NCT02343120) and BGB-3111-206 (NCT: NCT03206970).[9,10] A summary of the BGB-3111-AU-003 and BGB-3111-206 studies is provided in Table 5. The BGB-3111-AU-003 and BGB-3111-206 studies are discussed in detail in Sections B.2a.3 Summary of methodology of the relevant clinical effectiveness evidence: BGB-3111-

AU-003 and B.2b.3 Summary of methodology of the relevant clinical effectiveness evidence: BGB-3111-206, respectively.

Table 5: Summary of zanubrutinib clinical studies identified in the SLR

Study	BGB-3111-AU-003[35]	BGB-3111-206[32]
Study design	A phase 1/2, open-label, multiple-dose, dose escalation and expansion study	A phase 2, single-arm, open-label, multicentre study
Population	Patients with B-cell lymphoid malignancy, including patients with splenic, nodal, and extranodal MZL, age ≥ 18 years, with ≥1 prior lines of therapy, ECOG PS score of 0-2 with adequate organ functions.	Patients with R/R MCL, aged 18-75 years, with 1-5 prior lines of therapy, ECOG PS score of 0-2 with adequate organ functions.
Intervention(s)	Zanubrutinib monotherapy	Zanubrutinib monotherapy
Comparator(s)	N/A, single arm trial	N/A, single arm trial
Indicate if study supports application for marketing authorisation	Yes	Yes
Indicate if study used in the economic model	Yes	Yes
Rationale if study not used in model	N/A	N/A
Reported outcomes specified in the decision problem	ORR, **OS**, **PFS**, DOR, **safety**	ORR, **OS**, **PFS**, DOR, **safety**
All other reported outcomes	TTR	TTR

CSR – clinical study report; DCO – data cut-off; DOR - duration of response; ECOG PS - Eastern Cooperative Oncology Group performance status; MZL - marginal zone lymphoma; N/A - not applicable; ORR - overall response rate; OS - overall survival; PFS - progression-free survival; R/R – relapsed/refractory mantle cell lymphoma; TTR - time to response
Outcomes in **bold** are used in the economic model.
Source: BGB-3111-206 CSR (DCO: 08Sept2020)[42], BGB-3111-AU-003 CSR (DCO: 31Mar2021)[43]

B.2a.3 Summary of methodology of the relevant clinical effectiveness evidence: BGB-3111-AU-003

B.2a.3.1 Study design

BGB-3111-AU-003 is an international, open-label, multiple-dose, multicentre phase I/II study of zanubrutinib in patients with B-cell lymphoid malignancies, including R/R MCL. The primary trial endpoint was ORR by IRC assessment.[35]

The study was composed of an initial dose escalation phase (Part 1), followed by an expansion phase (Part 2). A total of 32 patients with R/R MCL were exclusively enrolled in Part 2 of the study and received zanubrutinib 320 mg administered once daily or 160 mg twice daily. Consequently, the following discussion of the BGB-3111-AU-003 study will focus solely on the outcomes and insights derived from Part 2, specifically for n=32 patients with R/R MCL. Patients received zanubrutinib until disease progression, intolerance or death, withdrawal of consent, or loss to follow-up. Table 6 provides a summary of the BGB-3111-AU-003 trial methodology.

Table 6: Summary of trial methodology (BGB-3111-AU-003)

Study details	BGB-3111-AU-003; NCT02343120
Location	Australia, New Zealand, Italy, South Korea, the UK, and the USA
Design	Phase I/II, open-label, multiple-dose, multicentre dose escalation (Part 1) and expansion (Part 2) study of zanubrutinib in patients with B-cell lymphoid malignancies, including R/R MCL.
Treatment	Part 1: • Patients received escalating doses of zanubrutinib starting at 40 mg, and escalating to 320 mg once daily, or 160 mg twice daily. Part 2: • The recommended phase 2 dose of zanubrutinib for evaluation was determined to be 320 mg administered once daily or 160 mg twice daily for all subsequent patients enrolled.
Endpoints	Primary endpoint: • ORR (IRC) Secondary endpoints: • ORR (INV) • PFS (IRC and INV) • OS • DOR (IRC and INV) • TTR (IRC and INV)

Study details	BGB-3111-AU-003; NCT02343120
Subgroup analysis	Sex, age group (< 65, ≥ 65, <75 and ≥ 75), disease stage at study entry, ECOG PS (0 versus ≥ 1), number of prior lines of therapy for MCL (< 3 versus ≥ 3), bulky disease (LDi < 10 cm, LDi ≥ 10 cm, LDi < 5 cm, LDi ≥ 5 cm), MIPI (low, intermediate, high), refractory disease (yes versus no), blastoid histology (yes versus no), prior anticancer drug use, baseline extranodal disease, baseline bone marrow involvement and time from end of last regimen to first dose (≥2 years versus 2 years).

CSR – clinical study report; DCO – data cut-off; DOR – duration of response; ECOG PS – Eastern Cooperative Oncology Group performance status; INV – investigator; IRC – independent review committee; LDi – longest transverse diameter of a lesion; MCL – mantle cell lymphoma; mg – milligram; MIPI – mantle cell lymphoma international prognostic index; ORR – overall response rate; OS – overall survival; PFS – progression-free survival; R/R – relapsed or refractory; TTR – time to response; UK – United Kingdom; USA – United States of America

Source: BGB-3111-AU-003 CSR (DCO: 31Mar2021)[43]

B.2a.3.2 Eligibility Criteria

Eligible patients were aged ≥ 18 years with B-cell malignancies meeting the WHO classification, who had received at least one prior line of therapy and have R/R lymphoma. Key inclusion and exclusion criteria for the BGB-3111-AU-003 trial are presented in Table 7.

Table 7: Key eligibility criteria for BGB-3111-AU-003

Key inclusion criteria
• Age 18 years or older • R/R WHO-defined B-lymphoid malignancy, with the exception of Burkitt lymphoma/leukaemia, plasma cell myeloma, acute lymphoblastic leukaemia, lymphoblastic lymphoma, and plasmablastic lymphoma. • Relapsed or refractory disease, following ≥ 1 prior line of therapy, with no higher priority therapy available. • Requirement for treatment in the opinion of the investigator. • ECOG PS score of 0 to 2. • Adequate haematologic, renal and organ functions.
Key exclusion criteria
• Current CNS involvement by lymphoma or leukaemia. • Current histologically transformed disease. • Prior BTK inhibitor treatment. • Allogeneic stem cell transplantation within 6 months or had active graft-versus-host disease requiring ongoing immunosuppression. • Receipt of the following treatment before the first dose of zanubrutinib: corticosteroids given with antineoplastic intent within 7 days, chemotherapy or radiotherapy within 2 weeks, or monoclonal antibody within 4 weeks • Not recovered from toxicity of any prior chemotherapy to Grade 1 or lower. • History of other active malignancies within 2 years of study entry, with the exception of:

• Adequately treated in-situ carcinoma of cervix • Localised basal cell or squamous cell carcinoma of the skin. • Previous malignancy confined and treated locally (surgery or other modality) with curative intent. • Active infections requiring systemic therapy. • HIV or active hepatitis B or C infections • Major surgery within 4 weeks of the first dose of study drug • Cardiovascular disease resulting in New York Heart Association function status of ≥ 3.

BTK – Bruton's tyrosine kinase; CNS – central nervous system; CSR – clinical study report; DCO – data cut-off; ECOG PS – Eastern Cooperative Oncology Group performance status; HIV – human immunodeficiency virus; R/R – relapsed or refractory; WHO – World Health Organisation
Source: BGB-3111-AU-003 CSR (DCO: 31Mar2021)[43]

B.2a.3.3 Outcome measures

The definitions of the outcome measures available in the BGB-3111-AU-003 trial and whether they are used in the economic model are presented in Table 8. No patient reported outcomes were collected for the BGB-3111-AU-003 trial.

Table 8: Outcome measures available from BGB-3111-AU-003

Objective	Definition	Data cut available	Used in economic model
Primary efficacy endpoint			
ORR (IRC)	The proportion of patients achieving a best overall response of CR or PR as determined by IRC in accordance with the Lugano classification. Best overall response was defined as the best response recorded from the start of zanubrutinib until the DCO.	13Dec2018	No
Secondary objectives			
ORR (INV)	The proportion of patients achieving a best overall response of CR or PR as determined by an INV in accordance with the Lugano classification. Best overall response was defined as the best response recorded from the start of zanubrutinib until the DCO.	31Mar2021	No
PFS (IRC and INV)	Time from the first dose of zanubrutinib treatment to the date of first documented progressive disease or death from any cause, whichever occurred first, as determined by IRC or INV assessment.	IRC: 13Dec2018 INV: 31Mar2021	Yes
OS	Time from initiation of zanubrutinib to the date of death from any cause.	31Mar2021	Yes

DOR (IRC and INV)	Time from the date of earliest response (CR or PR) to the date of first documented progressive disease or death from any cause, whichever occurred first, as determined by IRC or INV assessment.	IRC: 13Dec2018 INV: 31Mar2021	No
TTR (IRC and INV)	Time from initiation of zanubrutinib to the date of first documented response (CR or PR), as determined by IRC or INV assessment.	IRC: 13Dec2018 INV: 31Mar2021	No
Safety and tolerability			
Safety and tolerability	AEs classified based on MedDRA (Version 23.0 or higher) and graded according to the NCI-CTCAE (version 4.03)	31Mar2021	Yes

AE – adverse event; CR – complete response; CSR – clinical study report; DCO – data cut-off; DOR – duration of response; INV – investigator; IRC – independent review committee; NCI-CTCAE – National Cancer Institute-Common Terminology Criteria for Adverse Events; ORR – overall response rate; OS – overall survival; PFS – progression-free survival; PR – partial response; TTR – time to response
Source: BGB-3111-AU-003 CSR (DCO: 31Mar2021)[43], BGB-3111 Regulatory summary of clinical efficacy (DCO: 13Dec2018)[44]

B.2a.3.4 Patient characteristics

The demographics and baseline disease characteristics of patients at inclusion are presented in Table 9.

Among patients with R/R MCL taking a total daily dose of 320 mg, the median age was 70.5 years, with 37.5% of patients over 75 years of age. Most patients were from a white ethnic background (87.1%). A significant majority of patients exhibited features indicative of advanced or disseminated disease, including extranodal manifestations (78.1%) and the presence of bulky disease (90.6%).

Among the participants, 25.0% had not responded to prior therapy and were therefore considered refractory. A substantial portion of the patient cohort (56.2%) had undergone one prior line of systemic treatment. Most patients (59.4%) had previously received a R-CHOP/R-CHOPE/R-CHOP-like therapy and 21.9% of patients received hyper-CVAD or hyper-CVAD-like therapy.

Clinical experts in attendance at the advisory board meeting conducted on 11th November 2024 confirmed that the baseline characteristics of patients in the BGB-3111-AU-003 trial appeared to be representative of R/R MCL patients in UK clinical practice.

As per Section B.1.1 Decision problem, this submission covers part of the technology's marketing authorisation, specifically: adult patients with 2L R/R MCL. Given the baseline characteristics and efficacy endpoint results were consistent for patients 2L-only versus ≥ 2L (full trial populations) from the BGB-3111-AU-003 and BGB-3111-206 trials (baseline characteristics: Table 9 and Table 22, respectively, and Section B.2a.6 Clinical effectiveness results of the relevant studies: BGB-3111-AU-003 and Section B.2b.6 Clinical effectiveness results of the relevant studies: BGB-3111-206, respectively), the clinical evidence and model used to inform this appraisal is based on all patients from the BGB-3111-AU-003 and BGB-3111-206 trials (Section B.2.9.1 Data sources) in order to maximise the patient sample used in the analysis. Furthermore, the BGB-3111-AU-003 and BGB-3111-206 trials were not powered to support efficacy endpoint results by line of therapy. As discussed in Section B.2.9Indirect and mixed treatment comparisons.

Table 9: Demographics and baseline disease characteristics (BGB-3111-AU-003)

Characteristics	Zanubrutinib (N = 32)[35,44]	Zanubrutinib 2L-only (N = 18)[45]
Age, years		
Mean (SD)	[redacted]	[redacted]
Median (range)	70.5 (42, 86)	[redacted]
< 65 years	8 (25.0)	[redacted]
≥ 65 to < 75 years	12 (37.5)	[redacted]
≥ 75 years	12 (37.5)	[redacted]
Sex, n (%)		
Male	22 (68.8)	[redacted]
Female	10 (31.3)	[redacted]
Race, n (%)		
White	25 (78.1)	[redacted]
Black or African American	1 (3.1)	[redacted]
Asian	3 (9.4)	[redacted]
Other/multiple	3 (9.4)	[redacted]
ECOG PS, n (%)		
0	15 (46.9)	[redacted]
1	14 (43.8)	[redacted]
2	3 (9.4)	[redacted]
Time from initial diagnosis to first dose (years)		

Characteristics	Zanubrutinib (N = 32)[35,44]	Zanubrutinib 2L-only (N = 18)[45]
Mean (SD)	[redacted]	[redacted]
Median (Range)	[redacted]	[redacted]
Ann Arbor Stage at study entry, n (%)		
I	2 (6.3)	[redacted]
II	1 (3.1)	[redacted]
III	1 (3.1)	[redacted]
IV	28 (87.5)	[redacted]
Disease status to last prior therapy, n (%)[a]		
Relapsed	[redacted]	[redacted]
Refractory	8 (25.0)	[redacted]
Unknown	[redacted]	[redacted]
Bulky disease, n (%)		
Yes (any target lesion LDi > 10 cm)	3 (9.4)	[redacted]
No (all target lesion LDi ≤ 10 cm)	29 (90.6)	[redacted]
Extranodal disease, n (%)[b]		
Yes	25 (78.1)	[redacted]
No	7 (21.9)	[redacted]
MIPI, n (%)[c]		
Low risk	8 (25.0)	[redacted]
Intermediate risk	11 (34.4)	[redacted]
High risk	13 (40.6)	[redacted]
Number of prior therapies		
Median (range)	1.0 (1, 4)	[redacted]
1 prior therapy	18 (56.2)	[redacted]
2 prior therapies	[redacted]	[redacted]
3 prior therapies	[redacted]	[redacted]
4 prior therapies	[redacted]	[redacted]
Time from end of last therapy to study entry, n (%), months		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Patients with any prior radiation therapies, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Prior stem cell transplant, n (%)		
Yes	5 (15.6)	[redacted]

Characteristics	Zanubrutinib (N = 32)[35,44]	Zanubrutinib 2L-only (N = 18)[45]
No	27 (84.4)	[redacted]
Prior systemic regimens, n (%)		
R-CHOP/R-CHOPE/R-CHOP-like	19 (59.4)	[redacted]
DHAP	[redacted]	[redacted]
Hyper-CVAD or hyper-CVAD-like regimen	7 (21.9)	[redacted]
DICE/ICE	[redacted]	[redacted]
Cytarabine	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]
Purine analog	[redacted]	[redacted]
ESHAP	[redacted]	[redacted]
Bendamustine	[redacted]	[redacted]

DCO – data cut-off; DHAP - dexamethasone, cytarabine and cisplatin; DICE – dexamethasone, ifosfamide, cisplatin, etoposide; ECOG PS – Eastern Cooperative Oncology Group performance status; ESHAP – etoposide, methylprednisolone, cytarabine and cisplatin; Hyper-CVAD – cyclophosphamide, vincristine, doxorubicin, and dexamethasone; ICE – ifosfamide, cisplatin and etoposide; LDi – longest transverse diameter of a lesion; MCL – mantle cell lymphoma; MIPI – MCL international prognostic index; N – number; R-CHOP - rituximab plus doxorubicin hydrochloride, vincristine and prednisone; R-CHOPE – rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone and etoposide; SD -standard deviation

[a]Refractory disease is defined as best overall response of stable disease or progressive disease from last prior anticancer treatment regimen.

[b]Defined as patients with extranodal baseline target or nontarget lesions or with baseline bone marrow involvement by biopsy/aspiration per investigator assessment.

[c]MIPI score was calculated for the full population with cutoffs as low (< 5.7), intermediate (≥ 5.7 and < 6.2) and high (≥ 6.2). Simplified MIPI is presented for the 2L-only population.

Source: Tam *et al.,* (2021)[35] / BGB-3111 Regulatory summary of clinical efficacy (DCO: 13Dec2018)[44], BGB-3111-AU-003 data on file (DCO: 31Mar2021)[45]

B.2a.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence: BGB-3111-AU-003

B.2a.4.1 Sample size calculations

A total of 385 patients were enrolled in the expansion cohorts of Part 2. The determination of sample sizes for individual disease cohorts was driven by the goal of obtaining robust insights into the safety profile and precise estimates of response rates for zanubrutinib within specific B-cell malignancies, with a high degree of accuracy. For instance, initial data suggested an expected response rate of 30% for Part 2b (non-germinal centre B-cell like diffuse large B cell lymphoma [DLBCL]). With a cohort of 40 patients, a 95% confidence interval's lower bound would be 17% if the observed response rate were 30%.

B.2a.4.2 Statistical analysis

Table 10 summarises the statistical analyses used in BGB-3111-AU-003. The Safety Analysis Set included all patients who received at least one dose of zanubrutinib. The Efficacy Analysis Set was defined the same as the Safety Analysis set and used to evaluate efficacy.

Table 10: Summary of statistical analyses

Endpoint	Analysis	Population
Primary endpoint analysis		
ORR	Clopper-Pearson 95% CIs The number of patients with a best overall response of CR, PR, stable disease, progressive disease, or not evaluable was summarised. At each timepoint, response by PET was considered the true timepoint response when available. When PET was not available, the timepoint response was determined by CT. The last date of non-progression was defined as the last date with imaging showing no progression	Efficacy analysis set
Secondary endpoint analysis		
CR rate	The proportion of patients who achieved a best overall response of CR	Efficacy analysis set
PFS	The KM method was used to estimate the distribution of PFS for patients with R/R MCL. Quartiles including the median were estimated by KM method along with their 95% CIs by Brookmeyer and Crowley method.	Efficacy analysis set
OS	The KM method was used to estimate the distribution of OS for patients with R/R MCL. Quartiles including the median were estimated by KM method along with their 95% CIs by Brookmeyer and Crowley method.	Efficacy analysis set
DOR	The KM method was used to estimate the distribution of DOR for patients with R/R MCL. Quartiles including the median were estimated by KM method along with their 95% CIs by Brookmeyer and Crowley method.	Efficacy analysis set
TTR	Summarised using sample mean, median and range.	Efficacy analysis set
Safety endpoints		
AEs, SAEs and TEAEs	Graded by NCI-CTCAE v4.03 Classified and coded using MedDRA. Descriptive statistics used to analyse all safety data by treatment group.	Safety analysis set

Endpoint	Analysis	Population
	Descriptive analyses by system organ class, preferred term, maximum severity, and by preferred term only	
Subgroup analyses of efficacy endpoints		
Subgroup analyses	Subgroups including: Sex (male versus female) Age (< 65 versus ≥ 65 years and < 75 versus ≥ 75 years) ECOG PS score (0 versus ≥ 1) MIPI score (low, intermediate, high) Disease stage at study entry (I to III versus IV) Bulky disease (≥ 10 cm versus < 10 cm; ≥ 5 cm versus < 5 cm) Blastoid variant (yes versus no) Bone marrow involvement (yes versus no) Baseline extranodal disease (yes versus no) Refractory disease (yes versus no versus unknown) Number of prior regimens (0 versus 1 to 2 versus ≥ 2)	Efficacy analysis set

AE – adverse event; CI – confidence interval; CR – complete response; CSR – clinical study report; CT – computed tomography; DCO – data cut-off; DOR – duration of response; ECOG PS – Eastern Cooperative Oncology Group performance status; KM – Kaplan-Meier; MIPI – mantle cell lymphoma international prognostic index; NCI-CTCAE - National Cancer Institute-Common Terminology Criteria for Adverse Events; ORR – overall response rate; OS – overall survival; PET – positron emission tomography; PFS – progression-free survival; PR – partial response; R/R MCL – relapsed/refractory mantle cell lymphoma; SAE – Serious adverse event; TEAE – Treatment-emergent adverse event; TTR – time to response
Source: BGB-3111-AU-003 CSR (DCO: 31Mar2021)[43]

B.2a.4.3 Participant flow

Patients with MCL were enrolled in Part 2 of the study only. All 32 patients with R/R MCL received at least one dose of zanubrutinib. At data cut off of 13th December 2018, the median duration of follow-up for patients with R/R MCL was 18.84 months. A total of 10 (31.3%) patients discontinued their study drug due to progressive disease, while eight (25.0%) patients discontinued due to adverse events (AEs), as detailed in Table 11. A total of 10 patients (31.3%) patients discontinued from the study due to death.

Table 11: Patient disposition in BGB-3111-AU-003

Patient disposition	Zanubrutinib (N=32), n (%)
Number of patients treated	32 (100.0)
Patients discontinued from treatment	18 (56.3)
Reason for discontinuation from treatment	
Disease progression	10 (31.3)
Patient withdrew consent	0 (0.0)

Patient disposition	Zanubrutinib (N=32), n (%)
Adverse event	8 (25.0)
Investigator's discretion	0 (0.0)
Patients discontinued from the study	18 (56.3)
Reason for discontinuation from the study	
Death	12 (37.5)
Lost to follow-up	[redacted]
Patient withdrew consent	[redacted]
Adverse event	[redacted]
Other	[redacted]
Median study follow-up time (months)	18.84
Study follow-up time (months) (minimum, maximum)	1.9, 38.2

DCO – data cut-off; N - number
Source: Tam *et al.,* (2021)[35] / BGB-3111 Regulatory summary of clinical efficacy (DCO: 13Dec2018)[44]

B.2a.5 Critical appraisal of the relevant clinical effectiveness evidence: BGB-3111-AU-003

A summary of the quality assessment for the BGB-3111-AU-003 trial is provided in Table 12. The quality assessment was conducted using the criteria for the assessment of risk of bias and generalisability for non-RCTs listed in Section 2.5.2 of the NICE STA user guide.[46,47] Based on the findings from the quality assessment, BGB-3111-AU-003 was a well-designed single arm trial which the appropriate steps taken to minimise bias where possible.[46,47] Based on the findings from the quality assessment, BGB-3111-AU-003 was a well-designed single arm trial which the appropriate steps taken to minimise bias where possible.

Table 12: Quality assessment results for BGB-3111-AU-003

Question	How is the question addressed?	Grade (yes/no/ unclear/NA)
Was the cohort recruited in an acceptable way?	Patients were recruited from six study locations globally based on inclusion and exclusion criteria outlined in Table 7.	Yes

Question	How is the question addressed?	Grade (yes/no/ unclear/NA)
Was the exposure accurately measured to minimise bias?	32 R/R MCL patients in the BGB-3111-AU-003 trial received a total daily dose of 320 mg of zanubrutinib. The median duration of treatment with zanubrutinib was 15.4 months as of the 13th December 2018 data cut-off. The relative dose intensity was 99.92% for patients with R/R MCL receiving a total daily dose of 320 mg of zanubrutinib.	Yes
Was the outcome accurately measured to minimise bias?	Outcomes were accurately measured to minimise bias, as outlined in Table 8. Outcomes were assessed using both IRC and INV assessment to validate outcomes where appropriate.	Yes
Have the authors identified all important confounding factors?	All important confounding factors were considered within pre-planned subgroup analyses. See Section B.2a.6 Clinical effectiveness results of the relevant studies: BGB-3111-AU-003 of the Company Submission for more detail.	Yes
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes, as per the previous question, the confounding factors were identified and taken account for in the analysis.	Yes
Was the follow-up of patients complete?	The BGB-3111-AU-003 trial is complete with no further data cuts planned. The trial design ensured patients were suitably followed up after discontinuation of treatment and/or progression. The median follow-up time for the patients in the R/R MCL population who received 320 mg of zanubrutinib was 18.84 months at a data cut off of 13th December 2018. At the end of treatment, a safety follow-up of 30 ± 7 days after last dose was ensured for both discontinuation due to PD and reasons other than PD. Patients continued efficacy evaluations until PD followed by long-term follow-up for survival every 24 weeks. All patients who discontinued study drug commenced long-term follow-up after progression, which included monitoring for survival status and initiation of new anticancer treatment for MCL and conducting chemistry and haematology assessments. If a patient refused to return for these visits or was unable to do so, every effort was made to contact them to assess the patient's disease status and survival.	Yes
How precise (for example, in terms of confidence interval and p values) are the results?	The primary endpoint of ORR by IRC assessment presented a p-value <0.0001 with a CI of 95%. Medians and other quartiles for all secondary endpoints were estimated by KM method with 95% CIs. See Section B.2a.6 Clinical effectiveness results of the relevant studies: BGB-3111-AU-003 for full details.	Yes

CI – confidence interval; CSR – clinical study report; DCO – data cut-off; INV – investigator; IRC – independent review committee; KM - Kaplan-Meier; MCL – mantle cell lymphoma; mg – milligrams; NA – not applicable; ORR – overall response rate; R/R – relapsed/refractory
Source: BGB-3111-AU-003 CSR (DCO: 31Mar2021)[43]

B.2a.6 Clinical effectiveness results of the relevant studies: BGB-3111-AU-003

The key efficacy outcomes for patients with R/R MCL from BGB-3111-AU-003 for the full trial population and 2L-only are summarised in Table 13. IRC-assessed outcomes are presented based on a cut-off date of 13th December 2018 with a median follow-up 18.84 months. INV-assessed outcomes are presented based on a cut-off date of 31st March 2021, with a median follow-up of 38.92 months. Results from both data cuts are presented below and were consistent with those observed from the BGB-3111-206 trial as presented in Section B.2b.6 Clinical effectiveness results of the relevant studies:

Table 13: Key efficacy outcomes for BGB-3111-AU-003

	Zanubrutinib full trial population (N = 32)		Zanubrutinib 2L-only (N = 18)	
	IRC-assessed (DCO 13Dec2018)[35,44]	INV-assessed (DCO 31Mar2021)[43]	IRC-assessed (DCO 13Dec2018)[45]	INV-assessed (DCO 31Mar2021)[45]
ORR				
ORR (95% CI)	84.4 (67.2, 94.7)	[redacted]	[redacted]	[redacted]
PFS				
Median, months (95% CI)	21.1 (13.2, NE)	[redacted]	[redacted]	[redacted]
DOR				
Median, months (95% CI)	18.53 (12.58, NE)	[redacted]	[redacted]	[redacted]
TTR				
Events, n	27	[redacted]	[redacted]	[redacted]
Median, months (range)	2.76 (1.9, 9.8)	[redacted]	[redacted]	[redacted]
OS (DCO: 31Mar2021)				
Median, months (95% CI)	NR	[redacted]	[redacted]	[redacted]

CI – confidence interval; CSR – clinical study report; DCO – data cut-off; DOR – duration of response; INV – investigator; IRC – independent review committee; NE – not estimable; NR – not reported; ORR – overall response rate; OS – overall survival; PFS – progression-free survival; TTR – time to response
Source: Tam *et al.,* (2021)[35] / BGB-3111 Regulatory summary of clinical efficacy[44], BGB-3111-AU-003 CSR[43], BGB-3111-AU-003 data on file[45]

B.2a.6.1 Primary and key secondary endpoints: ORR

The BGB-3111-AU-003 study met its primary endpoint. As demonstrated in Table 14, ORR by IRC assessment in the full trial population was 84.4% (95% CI: 67.2, 94.7), with eight (25.0%) patients achieving a complete response and 19 (59.4%) patients achieving a partial response, at a median study follow-up of 18.84 months (data cut-off: 13th December 2018). Experts present at a UK advisory board (11th November 2024) noted that with R/R MCL, when a treatment shows a benefit in response rate it would also show a benefit in PFS and OS, which is observed in the BGB-3111-AU-003 trial.[2]

In line with ORR determined by IRC assessment, the ORR determined by INV assessment was [redacted]. The concordance rate between IRC and INV assessments was 93.8% for ORR and 71.9% for best overall response.

Consistent ORR outcomes were demonstrated in patients regardless of whether patients were 2L-only or ≥2L (full trial population), with an ORR for 2L-only patients of [redacted] and [redacted] determined by IRC and INV assessment, respectively.

Table 14: IRC- and INV-assessed response rates in BGB-3111-AU-003

Response category	Zanubrutinib full trial population (N = 32)		Zanubrutinib 2L-only (N = 18)	
	IRC-assessed (DCO 13Dec2018)[35,44]	**INV-assessed (DCO 31 Mar2021)**[43]	**IRC-assessed (DCO 13Dec2018)**	**INV-assessed (DCO 31Mar2021)**[45]
Best overall response, n (%)				
CR	8 (25.0)	[redacted]	[redacted]	[redacted]
PR	19 (59.4)	[redacted]	[redacted]	[redacted]
SD	2 (6.3)	[redacted]	[redacted]	[redacted]
PD	2 (6.3)	[redacted]	[redacted]	[redacted]
Unknown	1 (3.1)[a]	[redacted]	[redacted]	[redacted]
Overall response rate				
ORR, n (%) [95% CI][b]	27 (84.4) [67.2, 94.7]	[redacted]	[redacted]	[redacted]

CI – confidence interval; CR – complete response; CSR – clinical study report; DCO – data cut-off; INV – investigator; IRC – independent review committee; n – number; ORR – overall response rate; PD – progressed disease; PR – partial response; SD – stable disease.
[a]One patient did not provide informed consent for scan collection.
[b] 2-sided Clopper-Pearson 95% CIs.
Source: Tam *et al.,* (2021)[35] / BGB-3111 Regulatory summary of clinical efficacy[44], BGB-3111-AU-003 CSR[43], BGB-3111-AU-003 data on file[45]

B.2a.6.1.1 Sensitivity analysis of the primary endpoint

Sensitivity analysis of the primary endpoint (ORR) is discussed in detail in Section B.2a.7 Subgroup analysis: BGB-3111-AU-003.

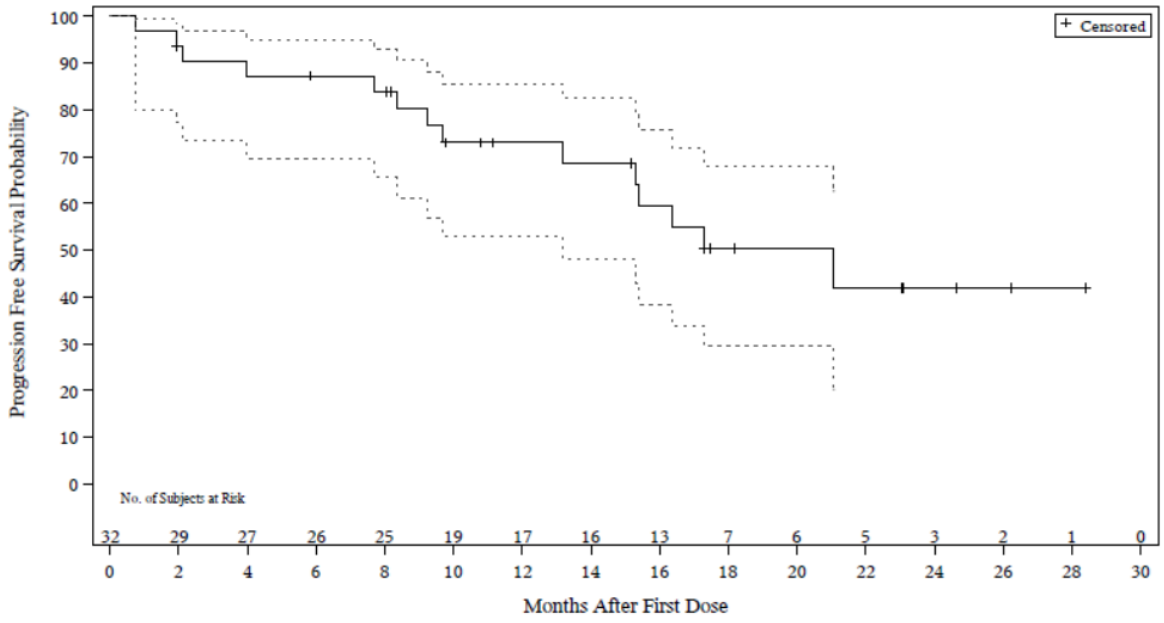
B.2a.6.2 Secondary endpoints

B.2a.6.2.1 Progression-free survival

At a median follow-up of 17.48 months (DCO: 13th December 2018), 14 (43.8%) patients in the full trial population had either progressed or died as per IRC assessment and median PFS was 21.1 months (95% CI: 13.2, NE), as shown in the KM plot presented in Figure 2: Kaplan-Meier plot of PFS by IRC in . As demonstrated in Table 15, the event-free rate was 87.3% ([redacted]) at 6

months, 73.0% ([redacted]) at 12 months and [redacted] at 18 months.

Figure 2: Kaplan-Meier plot of PFS by IRC in BGB-3111-AU-003 (full trial population)



DCO – data cut-off; IRC – independent review committee; PFS – progression-free survival.
Source: Tam *et al.,* (2021)[35] / BGB-3111 Regulatory summary of clinical effectiveness (DCO: 13Dec2018)[44]

In line with the IRC assessment of PFS, [redacted] patients in the full trial population had either progressed or died as per INV assessment and median PFS was [redacted], as shown in the KM plot presented in Figure 3: Kaplan-Meier plot of PFS by INV in BGB-3111-AU-003. The event-free rate was [redacted] at 12 months, [redacted] at 24 months and [redacted] at 48 months.

Figure 3: Kaplan-Meier plot of PFS by INV in BGB-3111-AU-003 (full trial population)

DCO – data cut-off; INV – investigator; PFS – progression-free survival.
Source: BGB-3111-AU-003 CSR (DCO: 31Mar2021)[43]

At a median follow-up of 17.48 months (DCO: 13th December 2018), [redacted] 2L-only patients had either progressed or died as per IRC assessment and median PFS was [redacted], as shown in the KM plot presented in Figure 4. As demonstrated in Table 15, the event-free rate was [redacted] at 6 months, [redacted] at 12 months and [redacted] at 24 months.

Figure 4: Kaplan-Meier plot of PFS by IRC in 2L-only patients in BGB-3111-AU-003

DCO – data cut-off; IRC – independent review committee; PFS – progression-free survival; 2L – second-line
Source: BGB-3111-AU-003 data on file (DCO: 18Dec2018)[45]

In line with the IRC assessment of PFS, [redacted] 2L-only patients had either progressed or died as per INV assessment and median PFS was [redacted], as shown in the KM plot presented in Figure 5. The event-free rate was [redacted] at 12 months, [redacted] at 24 months and [redacted] at 48 months.

Figure 5: Kaplan-Meier plot of PFS by INV in 2L-only patients in BGB-3111-AU-003

DCO – data cut-off; INV – investigator; PFS – progression-free survival; 2L – second-line
Source: BGB-3111-AU-003 data on file (DCO: 31Mar2021)[45]

Table 15: IRC- and INV-assessed PFS in BGB-3111-AU-003

	Zanubrutinib full trial population (N=32)		Zanubrutinib 2L-only (N = 18)	
	IRC-assessed (DCO 13Dec2018)[35,44]	INV-assessed (DCO 31Mar2021)[43]	IRC-assessed (DCO 13Dec2018)[45]	INV-assessed (DCO 31Mar2021)[45]
PFS, n (%)				
Events	14 (43.8)	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS, months (95% CI)[a]	21.1 (13.2, NE)	[redacted]	[redacted]	[redacted]
Event-free Rate at, % (95% CI)[b]				
6 months	87.3 [redacted]	[redacted]	[redacted]	[redacted]
12 months	73.0 [redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]
30 months	[redacted]	[redacted]	[redacted]	[redacted]

	Zanubrutinib full trial population (N=32)		Zanubrutinib 2L-only (N = 18)	
	IRC-assessed (DCO 13Dec2018)[35,44]	INV-assessed (DCO 31Mar2021)[43]	IRC-assessed (DCO 13Dec2018)[45]	INV-assessed (DCO 31Mar2021)[45]
36 months	[redacted]	[redacted]	[redacted]	[redacted]
48 months	[redacted]	[redacted]	[redacted]	[redacted]

CI – confidence interval; CSR – clinical study report; DCO – data cut-off; INV – investigator; IRC – independent review committee; PFS – progression-free survival

[a] Medians and other quartiles are estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.

[b] Event-free rates estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.

Source: Tam *et al.,* (2021)[35] / BGB-3111 Regulatory summary of clinical efficacy[44], BGB-3111-AU-003 CSR[43], BGB-3111-AU-003 data on file[45]

B.2a.6.2.2 Overall survival

At a median follow-up of 45.8 months (95% CI: 42.0, 48.6), in the full trial population [redacted] deaths had occurred, and median OS [redacted], as shown in the KM plot presented in Figure 6: Kaplan-Meier plot of OS in BGB-3111-AU-003. As reported in Table 16, the event-free rate was [redacted] at 12 months, [redacted] at 24 and [redacted] at 48 months.

Figure 6: Kaplan-Meier plot of OS in BGB-3111-AU-003 (full trial population)

DCO – data cut-off; OS – overall survival.

Source: BGB-3111-AU-003 data on file (DCO: 31Mar2021)[45]

At a median follow-up of 36.7 months (DCO 31Mar2021), [redacted] deaths had occurred in 2L-only patients, and median OS [redacted], as shown in the KM plot presented in Figure 7. As reported in Table 16, the event-free rate was [redacted] at 12 months, [redacted] at 24 months and [redacted] at 36 months.

Figure 7: Kaplan-Meier plot of OS in 2L-only patients in BGB-3111-AU-003

DCO – data cut-off; OS – overall survival; 2L – second-line
Source: BGB-3111-AU-003 data on file (DCO: 31Mar2021)[45]

Table 16: OS in BGB-3111-AU-003

	Zanubrutinib full trial population (N = 32) (DCO 31Mar2021)[43]	Zanubrutinib 2L-only (N = 18) (DCO 31Mar2021)[45]
OS		
Deaths, n (%)	[redacted]	[redacted]
Median OS, months (95% CI)[a]	[redacted]	[redacted]
Event-free Rate at, % (95% CI)[b]		
12 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]
48 months	[redacted]	[redacted]

CI – confidence interval; CSR – clinical study report; DCO – data cut-off; N - number; NE – not estimable; OS – overall survival

[a]Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
[a]Event-free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
Source: BGB-3111-AU-003 CSR (DCO: 31Mar2021)[43], BGB-3111-AU-003 data on file[45]

B.2a.6.2.3 Duration of response

At a median follow-up of 14.75 months (DCO: 13th December 2018), [redacted] of the patients in the full trial population who achieved a response had either progressive disease or had died as per IRC assessment as described in Table 17. Median DOR was 18.53 months (95% CI: 18.58, NE), with [redacted] of responders event-free at 18 months after initial response.

In line with IRC-assessed DOR, at a median follow-up of 36.9 months (DCO: 31st March 2021), [redacted] of the patients in the full trial population who achieved a response had either progressive disease or had died as per INV assessment. Median DOR was [redacted] with [redacted] of responders event-free at 30 months after initial response. At this later DCO (DCO: 31st March 2021) median DOR had increased, further demonstrating the durability of response of zanubrutinib.

For the 2L-only population, [redacted] of the patients who achieved a response had either progressive disease or had died as per IRC assessment (DCO: 13th December 2018), and median DOR was not reached, with [redacted] of responders event-free at 18 months after initial response. As per INV assessment (DCO: 31st March 2021), [redacted] of the patients who achieved a response had either progressive disease or had died, and the median DOR was [redacted] with [redacted] of responders event-free at 30 months after initial response.

Table 17: IRC and INV-assessed DOR in BGB-3111-AU-003

	Zanubrutinib full trial population (N=32)		Zanubrutinib 2L-only (N=18)	
	IRC-assessed (DCO 13Dec2018)[35,44]	**INV-assessed (DCO 31Mar2021)**[43]	**IRC-assessed (DCO 13Dec2018)**[45]	**INV-assessed (DCO 31Mar2021)**[45]
DOR, n (%)				
Events	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]
Median DOR, months (95% CI)	18.53 (12.58, NE)	[redacted]	[redacted]	[redacted]
Event-free Rate at, % (95% CI)[a]				
6 months	83.3 [redacted]	[redacted]	[redacted]	[redacted]
12 months	78.7 [redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]
30 months	[redacted]	[redacted]	[redacted]	[redacted]

CI – confidence interval; CSR – clinical study report; DCO – data cut-off; DoR – duration of response; INV – investigator; IRC – independent review committee; N – number; NE – not estimable
Source: Tam *et al.,* (2021)[35] / BGB-3111 Regulatory summary of clinical effectiveness[44], BGB-3111-AU-003 CSR[43], BGB-3111-AU-003 data on file[45]

B.2a.6.2.4 Time to response

As presented in Table 18, median TTR was 2.76 months for all patients (N=32) and [redacted] for 2L-only patients (N=18) by IRC assessment (DCO 13th October 2018). Consistent with IRC assessment, median TTR was [redacted] months for all patients and for 2L-only patients by INV assessment (DCO 31st March 2021).

Table 18: IRC- and INV-assessed TTR in BGB-3111-AU-003

	Zanubrutinib full trial population (N=32)		Zanubrutinib 2L-only (N=18)	
	IRC-assessed (DCO 13Dec2018)[44]	INV-assessed (DCO 31Mar2021)[43]	IRC-assessed (DCO 13Dec2018)[45]	INV-assessed (DCO 31Mar2021)[45]
TTR, months				
n	27	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	2.76 (1.9, 9.8)	[redacted]	[redacted]	[redacted]

CR – complete response; CSR – clinical study report; DCO – data cut-off; INV – investigator; IRC – independent review committee; SD – Standard deviation; TTR – time to response
Source: BGB-3111 Regulatory summary of clinical effectiveness[44], BGB-3111-AU-003 CSR[43], BGB-3111-AU-003 data on file[45]

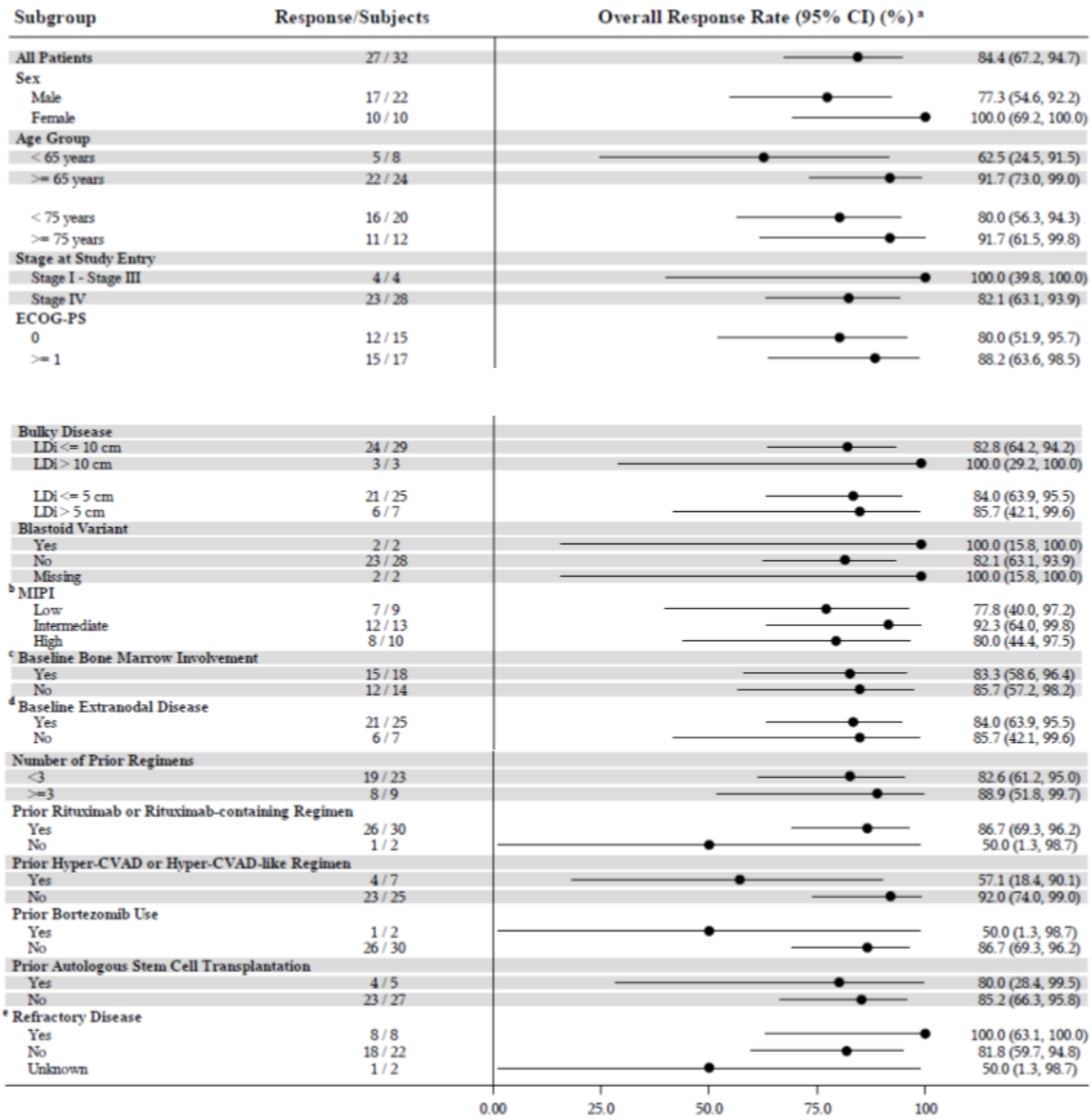
B.2a.6.2.5 Patient reported outcomes

Patient reported outcomes were not collected in the BGB-3111-AU-003 trial.

B.2a.7 Subgroup analysis: BGB-3111-AU-003

As presented in Figure 8, a uniformity in treatment benefits was observed across all pre-specified and post-hoc subgroups in the primary endpoint of IRC-assessed ORR. Despite the limited number of patients in these subgroups, there was a consistent trend towards higher response rates. This trend was even evident in subgroups historically known for having poor responses to treatment, individuals with high-risk prognostic factors (Stage IV disease, bulky disease), and those diagnosed with refractory MCL.

Figure 8: Forest plot of ORR by IRC assessment



CI – confidence interval; DCO – data cut-off; ECOG PS – Eastern Cooperative Oncology Group performance status; hyper-CVAD, hyper fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; IRC – independent review committee; LDi – longest transverse diameter of a lesion; MIPI – MCL international prognostic index; ORR – overall response rate

[a] Two-sided Clopper-Pearson 95% confidence interval

[b] MIPI score was calculated with cutoffs as low (< 5.7), intermediate (5.7 to < 6.2), and high (≥ 6.2).

[c] Bone marrow involvement was derived from baseline bone marrow biopsy/aspiration per investigator assessment.

[d] Extranodal disease is defined as patients with extra-nodal baseline target or non-target lesions, or bone marrow involvement by biopsy per investigator assessment.

Source: Tam *et al.,* (2021)[35] / BGB-3111 Regulatory summary of clinical efficacy (DCO: 13Dec2018)[44]

B.2b.3 *Summary of methodology of the relevant clinical effectiveness evidence: BGB-3111-206*

B.2b.3.1 Study design

BGB-3111-206 is a phase II, single-arm, multicentre, open-label study supporting the clinical value of zanubrutinib in patients with R/R MCL. The primary endpoint was ORR as assessed by an IRC.

The study was composed of an initial screening phase (up to 28 days), a single arm treatment phase, and a follow-up phase. A total of 86 patients (80 planned) were enrolled in the study and received zanubrutinib 160 mg orally twice daily in repeated 28-day cycles. Treatment with zanubrutinib was continued for up to 3 years or until disease progression, unacceptable toxicity, death, withdrawal of consent, loss to follow-up, or study termination. Table 19 summarises the BGB-3111-206 trial methodology, and Figure 9 presents the study design schematic.

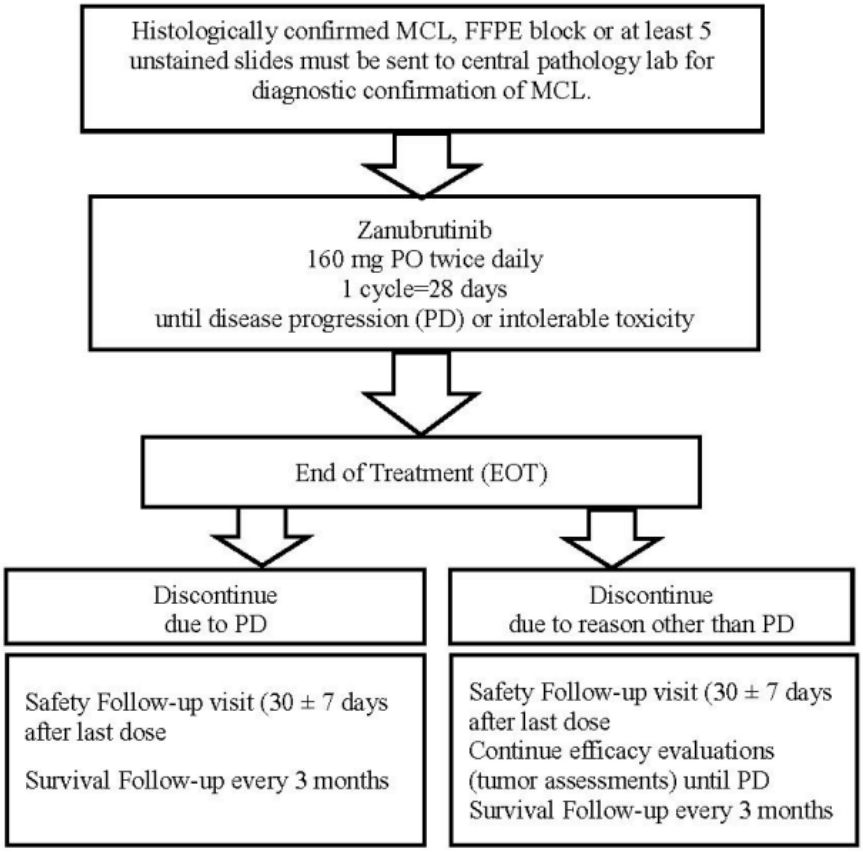
Table 19: Summary of trial methodology (BGB-3111-206)

Study details	**BGB-3111-206; NCT03206970**
Location	China
Design	Single arm, open-label, multicentre phase 2 study of zanubrutinib in patients with R/R MCL.
Treatment	All patients received zanubrutinib 160 mg (two 80-mg capsules) orally twice daily in repeated 28-day treatment cycles for up to three years or until disease progression, unacceptable toxicity, death, withdrawal of consent, loss to follow-up, or study termination by the sponsor.
Endpoints	Primary endpoint: • ORR (IRC) Secondary endpoints: • ORR (INV) • PFS (IRC and INV) • OS • DOR (IRC and INV) • TTR (IRC and INV)

Subgroup analysis	Sex, age group (< 65 versus ≥ 65), disease stage at study entry, ECOG PS(0 versus ≥ 1), number of prior lines of therapy for MCL (< 3 versus ≥ 3), bulky disease (LDi > 10 cm versus LDi ≤ 10 cm), MIPI/MIPI-b (low, intermediate, high), refractory disease (yes versus no), percent of tumour cells positive for Ki-67, blastoid histology (yes versus no), prior anticancer drug use, baseline extranodal disease, baseline bone marrow involvement and gastrointestinal involvement.

CSR – clinical study report; DCO – data cut-off; DOR – duration of response; ECOG PS – Eastern Cooperative Oncology Group performance status; INV – investigator; IRC - independent review committee; Mg- milligrams; MIPI-b - combined biologic mantle cell lymphoma international prognostic index; ORR – overall response rate; OS - overall survival; PFS – progression-free survival; R/R MCL – relapsed/refractory mantle cell lymphoma TTR – time to response
Source: BGB-3111-206 CSR (DCO: 08Sept2020)[42]

Figure 9: BGB-3111-206 schematic and design



CSR – clinical study report; DCO – data cut-off; EOT – end of treatment; FFPE – formalin-fixed paraffin-embedded; MCL – mantle cell lymphoma; PD – progressive disease; PO – oral administration.
Source: BGB-3111-206 CSR (DCO: 08Sept2020)[42]

B.2b.3.2 Eligibility criteria

Eligible patients were aged ≥18 and <75 years with a diagnosis of R/R MCL with experience of one to five prior lines of therapy. Key inclusion and exclusion criteria

for BGB-3111-206 are presented in Table 20. These were well matched with the criteria from the BGB-3111-AU-003 study.

Table 20: Key eligibility criteria for BGB-3111-206

Key inclusion criteria
• Aged 18-75 years. • Diagnostic report had to include evidence of morphological and cyclin D1 or t (11;14). • 1 - 5 prior lines of therapy. • Retrospectively confirmed MCL diagnosis. • ECOG PS of 0-2. • Measurable disease in at least 1 lymph node > 1.5 cm in longest diameter and measurable in 2 perpendicular dimensions. • Documented failure to achieve any response (stable disease or progressive disease during treatment) or documented progressive disease after response to the most recent treatment regimen. • Life expectancy of > 4 months.
Key exclusion criteria
• Current or history of CNS lymphoma. • Prior exposure to a BTK inhibitor. • Corticosteroid therapy in excess of prednisone 10 mg/day or its equivalent with antineoplastic intent within 7 days of the start of study drug. • Chemotherapy, targeted therapy or radiation therapy within 3 weeks before enrolment. • Antineoplastic therapy with Chinese herbal medicine or antibody-based therapies within 4 weeks of the start of study drug. • Cardiovascular disease electrocardiogram findings, active infections requiring antimicrobial therapy (including HIV, hepatitis B or C) or major surgery within 4 weeks of screening.

BTK – Bruton's tyrosine kinase; cm – centimetres; CNS – central nervous system; CSR – clinical study report; DCO – data cut-off; ECOG PS – Eastern Cooperative Oncology Group performance status; HIV – human immunodeficiency virus; MCL – mantle cell lymphoma; mg – milligrams
Source: BGB-3111-206 CSR (DCO: 08Sept2020)[42]

B.2b.3.3 Outcome measures

The definitions of the outcome measures available from the BGB-3111-206 trial and whether they are used in the economic model are presented in Table 21. No patient reported outcomes were collected for the BGB-3111-206 trial.

Table 21: Outcome measures available from BGB-3111-206

Objective	Definition	Data cut available	Used in economic model
Primary objectives			
ORR (IRC)	The proportion of patients who achieved a partial or complete response as determined by an IRC in accordance with the Lugano classification. Best overall response was defined as the best response recorded from the start of zanubrutinib until the study end or start of new anticancer treatment.	15Feb2019	No
Secondary objectives			
ORR (INV)	The proportion of patients who achieved a partial or complete response as determined by an investigator in accordance with the Lugano classification. Best overall response was defined as the best response recorded from the start of zanubrutinib until the DCO.	15Feb2019 08Sep2020	No
PFS (IRC and INV)	The time from the date of the first dose of study drug until documented progressive disease or death from any cause, whichever occurred first.	IRC: 15Feb2019 INV:08Sep2020	Yes
OS	The time from the date of first dose of study drug to death due to any cause.	08Sept2020	Yes
DOR (IRC and INV)	The interval between the date of the earliest qualifying response (complete or partial response) and the date of progressive disease or death from any cause (whichever occurred earlier).	IRC: 15Feb2019 INV:08Sep2020	No
TTR (IRC and INV)	The time between the first dose of study drug to the date of the earliest qualifying response.	IRC: 15Feb2019 INV:08Sep2020	No
Safety and tolerability			
Safety and tolerability	Adverse events were graded for severity using National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03	08Sep2020	Yes

DCO – data cut-off; DOR – duration of response; INV – investigator; IRC – independent review committee; NCI-CTCAE – National Cancer Institute-Common Terminology Criteria for Adverse Events; ORR – overall response rate; OS – overall survival; PFS – progression-free survival; TTR – time to response
Source: BGB-3111-206 CSR (data cut-off: 08Sept2020)[42], Song *et al.* (2020) (data cut-off: 15Feb2019)[32], BGB-3111 Regulatory summary of clinical efficacy (DCO: 31Aug2019)[44]

B.2b.3.4 Patient characteristics

The demographics and baseline disease characteristics of patients enrolled in BGB-3111-206 are presented in Table 22.

The median age was 60.5 years, with 25.6% of individuals 65 years or older. Numerous patients exhibited features indicative of advanced or disseminated disease, including extranodal manifestations (70.9%) and the presence of bulky disease (8.1%). A significant majority (83.7%) displayed an intermediate/high MIPI-b score, a characteristic associated with an unfavourable prognosis marked by reduced PFS in cases of MCL.[3]

A portion of the patient cohort (30.2%) had undergone a minimum of one prior systemic treatment. All patients had previously received a chemotherapy regimen and 74.4% of patients previously received a rituximab or rituximab-containing regimen. The most common therapies received were R-CHOP/R-CHOPE/R-CHOP-like [redacted] and DHAP [redacted]. Among the participants, 52.3% had not responded to prior therapy and were thus considered refractory.

Clinical experts in attendance at the advisory board meeting conducted on 11th November 2024 highlighted that patients in the trial may have been slightly younger (mean: 59.0 years) R/R MCL patients than those commonly encountered in UK clinical practice.[2] Additionally, the experts highlighted a difference in the prior treatments patients received. Clinical experts stated that in UK clinical practice the majority of patients receive a rituximab-containing regimen as first-line treatment for their MCL, however in the BGB-3111-206 trial 25.6% had not received prior rituximab. Clinical experts were reassured that all other baseline characteristics appeared to be aligned with those observed in UK clinical practice. Differences in age were adjusted for as part of the ITC analysis. Rituximab-naivety could not be adjusted for in the ITC, as almost all patients (97%) in the ibrutinib study Rule *et al.* (2017b) received prior rituximab. A sensitivity analysis exploring the clinical effectiveness results upon removing all ‘rituximab-naïve’ patients from the zanubrutinib trial data was conducted, as discussed further in Section B.2.9 Indirect and mixed treatment comparisons.

Furthermore, experts agreed that it would be appropriate to pool data from the BGB-3111-AU-003 and BGB-3111-206 trials to inform this submission, if consistent results were observed in the sensitivity analysis of patients who were not rituximab-naïve.

The results presented in Section B.2.9.5 Results demonstrate that there are consistent MAIC results upon removal of all rituximab-naïve patients, thus confirming the pooling of the two trials as appropriate.

The baseline characteristics and efficacy endpoint results for BGB-3111-206 presented in the following sections are consistent for patients 2L-only versus ≥ 2L (full trial populations), in line with those for BGB-3111-AU-003. As such, the clinical evidence to inform this appraisal uses all patients from BGB-3111-206, in order to maximise the patient sample used in the analysis.

Table 22: Demographics and baseline disease characteristics (BGB-3111-206)

Characteristics	Zanubrutinib full trial population (N=86)[32,42]	Zanubrutinib 2L-only (N=26)[48]
Age, years		
Mean (SD)	[redacted]	[redacted]
Median (range)	60.5 (34, 75)	[redacted]
< 65 years (%)	64 (74.4)	[redacted]
≥ 65 years (%)	22 (25.6)	[redacted]
Sex, n (%)		
Male	67 (77.9)	[redacted]
Female	19 (22.1)	[redacted]
Race, n (%)		
Chinese	86 (100)	[redacted]
ECOG PS, n (%)		
0	60 (69.8)	[redacted]
1	22 (25.6)	[redacted]
2	4 (4.7)	[redacted]
Time from initial diagnosis to study entry (months)[a]		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Ann Arbor Stage at study entry, n (%)		
I	[redacted]	[redacted]
II	[redacted]	[redacted]
III	14 (16.3)	[redacted]
IV	64 (74.4)	[redacted]
Disease status to last prior therapy, n (%)[b]		
Relapsed	41 (47.7)	[redacted]

Refractory	45 (52.3)	[redacted]
Bulky disease, n (%)		
Yes (any target lesion LDi > 10 cm)	7 (8.1)	[redacted]
No (all target lesion LDi ≤ 10 cm)	79 (91.9)	[redacted]
Extranodal disease at study entry, n (%)[c]		
Yes	61 (70.9)	[redacted]
No	25 (29.1)	[redacted]
MIPI-b, n (%)[d]		
Low risk	12 (14.0)	[redacted]
Intermediate risk	39 (45.3)	[redacted]
High risk	33 (38.4)	[redacted]
Missing	2 (2.3)	[redacted]
Ki67-positive cell percentage (n=84)		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
≤ 30%, n (%)	50 (58.1)	[redacted]
> 30%, n (%)	34 (39.5)	[redacted]
Missing	2 (2.3)	[redacted]
Number of prior systemic therapies		
Median (range)	2.0 (1, 4)	[redacted]
1 prior therapy	26 (30.2)	[redacted]
2 prior therapies	[redacted]	[redacted]
3 prior therapies	[redacted]	[redacted]
4 prior therapies	10 (11.6)	[redacted]
Time from end of last therapy to study entry, months		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Patients with any prior radiation therapies, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Prior autologous stem cell transplant, n (%)		
Yes	3 (3.5)	[redacted]
No	83 (96.5)	[redacted]
Prior systemic regimens, n (%)		
R-CHOP/R-CHOPE/R-CHOP-like	[redacted]	[redacted]
Rituximab or rituximab-containing regimen	64 (74.4)	[redacted]

DHAP	[redacted]	[redacted]
Hyper-CVAD or hyper-CVAD-like regimen	13 (15.1)	[redacted]
DICE/ICE	[redacted]	[redacted]
Lenalidomide	12 (14.0)	[redacted]
GDP	[redacted]	[redacted]
Purine analog	[redacted]	[redacted]
Bortezomib	7 (8.1)	[redacted]
GEMOX	[redacted]	[redacted]
ESHAP	[redacted]	[redacted]
Bendamustine	2 (2.3)	[redacted]

CSR – clinical study report; DCO – data cut-off; DHAP - dexamethasone, cytarabine and cisplatin; DICE – dexamethasone, ifosfamide, cisplatin, etoposide; ECOG PS – Eastern Cooperative Oncology Group performance status; ESHAP – etoposide, methylprednisolone, cytarabine and cisplatin; GDP – gemcitabine, dexamethasone and cisplatin; GEMOX – gemcitabine-oxaliplatin; Hyper-CVAD – cyclophosphamide, vincristine, doxorubicin, and dexamethasone; ICE – ifosfamide, cisplatin and etoposide; LDi – longest transverse diameter of a lesion; MIPI-b - combined biologic mantle cell lymphoma international prognostic index; N – number; R-CHOP - rituximab plus doxorubicin hydrochloride, vincristine and prednisone; R-CHOPE – rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone and etoposide; SD -standard deviation

[a] The day of first diagnosis was assumed to be the first day of the month when the day was missing and assumed to be 01 January when the day and month were missing.

[b] As defined by the investigator.

[c] Extranodal disease was defined as biopsy or radiographic evidence of bone marrow or gastrointestinal disease.

[d] MIPI-b score was calculated for the full population with cutoffs as low (< 5.7), intermediate (≥ 5.7 and < 6.5), and high (≥ 6.5) risk. Simplified MIPI is presented for the 2L-only population.

Source: Song *et al.* (2020)[32] / BGB-3111-206 CSR (DCO: 08Sept2020)[42], BGB-3111-206 data on file[48]

B.2b.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence: BGB-3111-206

B.2b.4.1 Sample size calculations

Assuming a null hypothesis with an expected ORR of 40%, a sample comprising 80 patients would yield a statistical power of 70% when considering an alternative hypothesised ORR of 40%. A one-sided alpha level of 0.025 with power >0.99 and exact binomial testing were used.

B.2b.4.2 Statistical analysis

Table 23 summarises the statistical analyses used in BGB-3111-206. The Safety Analysis Set included all patients who were enrolled and received at least one dose of study drug.

Table 23: Summary of pre-specified statistical analyses used in BGB-3111-206

Endpoint	Analysis	Population
Primary endpoint analysis		
ORR	2-sided Clopper-Pearson 95% CI. Binomial exact test with null hypothesised ORR of 40% using a significance level of 0.025 (1-sided). Best overall response was defined as the best response recorded from the start of zanubrutinib until the study end or start of new anticancer treatment. Patients with no post-baseline response assessments (for any reason) were considered non-responders.	Safety Analysis Set
Secondary endpoint analysis		
PFS	KM methodology was used to estimate the median and other quartiles of PFS. Two-sided 95% CIs constructed using generalised Brookmeyer and Crowley method with log-log transformation. PFS rates at selected landmark timepoints determined with corresponding 95% CIs calculated using Greenwood's formula with log-log transformation. Duration of follow-up determined by the reverse KM method.	Safety Analysis Set
OS	KM methodology was used to estimate the median and other quartiles of OS. Two-sided 95% CIs constructed using generalised Brookmeyer and Crowley method with log-log transformation. OS rates at selected landmark timepoints determined with corresponding 95% CIs calculated using Greenwood's formula with log-log transformation. Duration of follow-up determined by the reverse KM method.	Safety Analysis Set
DOR	KM methodology was used to estimate the median and other quartiles and 95% CI. DOR was defined as the interval between the date of the earliest qualifying response (complete or partial response) and the date of progressive disease or death from any cause (whichever occurred earlier).	Safety Analysis Set
TTR	TTR was defined as the time between the first dose of study drug to the date of the earliest qualifying response. KM methodology was used to estimate the median and other quartiles and 95% CI.	Safety Analysis Set
Safety endpoints		
AEs, SAEs and TEAEs	Graded for severity using NCI-CTCAE Version 4.03. Classified and coded using MedDRA. Descriptive analyses by system organ class and preferred.	Safety Analysis Set
Subgroup analyses of efficacy endpoints		

Endpoint	Analysis	Population
Subgroup analysis	Age (< 65 years versus ≥ 65 years). Sex (male versus female). ECOG PS (0 versus ≥ 1). Prior line of systemic therapy (< 3 versus ≥ 3). Bulky disease (LDi > 10 cm versus LDi ≥ 10 cm). MIPI/MIPI-b (low, intermediate, high). Disease status (relapsed versus refractory). Percent of tumour cells positive for Ki-67. Blastoid histology (yes versus no). Prior anticancer drug use. Baseline extranodal disease. Baseline bone marrow involvement. Gastrointestinal involvement.	Safety Analysis Set

AE – adverse event; CI – confidence interval; CSR – clinical study report; DCO – data cut-off; DOR – duration of response; ECOG PS– Eastern Cooperative Oncology Group performance status; KM – Kaplan-Meier; LDi – longest transverse diameter of a lesion; MedRA – Medical Dictionary for Regulatory Activities; MIPI – MCL international prognostic index; MIPI-b – combined biologic MIPI; NCI-CTCAE - National Cancer Institute-Common Terminology Criteria for Adverse Events; ORR – overall response rate; OS – overall survival; PFS – progression-free survival; SAE – serious adverse event; TEAE – treatment-emergent adverse event; TTR – time to response
Source: BGB-311-206 CSR (DCO: 08Sept2020)[42]

B.2b.4.3 Participant flow

A total of 86 patients were enrolled into the BGB-3111-206 study, each of whom received a minimum of one dose of zanubrutinib. The median duration of follow-up for the BGB-3111-206 study was 35.25 months as of the data cut-off of 8th September 2020.[42,42] A total of 37 (43.0%) patients stopped their study drug consumption due to progressive disease, while eight (9.3%) patients discontinued their participation due to adverse events, as detailed in Table 24.

Table 24: Patient disposition in BGB-3111-206

Patient disposition	Zanubrutinib (N = 86) n (%)
Number of patients treated	86 (100.0)
Patients discontinued from treatment	86 (100.0)
Reason for discontinuation from treatment	
Study terminated by sponsor	[redacted]
Progressive disease	37 (43.0)
Adverse event	8 (9.3)
Investigator's discretion	1 (1.2)

Patient disposition	Zanubrutinib (N = 86) n (%)
Withdrawal by subject	1 (1.2)
Reason for discontinuation from the study	
Study terminated by sponsor	[redacted]
Death	[redacted]
Withdrawal by subject	[redacted]
Lost to follow-up	[redacted]
Patients remained in study	0
Median study follow-up time (months)[a]	35.25
Study follow-up time (months) (minimum, maximum)	0.3, 41.6

CSR – clinical study report; DCO – data cut-off
Note: All percentages were based on the number of patients treated except for the row "Number of Patients Treated" for which the percentage was calculated based on the number of patients enrolled.
[a] Study follow-up time was defined as the time from the first dose date to the death date or end-of-study date (whichever occurred first) for patients discontinued from the study, or the database cut-off date for ongoing patients.
Source: Song et al. (2022b)[34] / BGB-3111-206 CSR (DCO: 08Sept2020)[42]

B.2b.5 Critical appraisal of the relevant clinical effectiveness evidence: BGB-3111-206

A summary of the quality assessment for the BGB-3111-206 trial is provided in Table 25. The quality assessment was conducted using the criteria for the assessment of risk of bias and generalisability for non-RCTs listed in Section 2.5.2 of the NICE STA user guide.[46,47] Based on the findings from the quality assessment, BGB-3111-206 was a well-designed single arm trial with the appropriate steps taken to minimise bias where possible.[46,47] Based on the findings from the quality assessment, BGB-3111-206 was a well-designed single arm trial with the appropriate steps taken to minimise bias where possible.

Table 25: Quality assessment results for BGB-3111-206

Question	How is the question addressed?	Grade (yes/no/ unclear/NA)
Was the cohort recruited in an acceptable way?	Patients were recruited from 13 study locations in China based on inclusion and exclusion criteria outlined in Table 20.	Yes

Was the exposure accurately measured to minimise bias?	All 86 patients in the BGB-3111-206 trial received at least one dose of zanubrutinib. The median duration of treatment was 27.6 months (range: 0.2 to 41.6 months). The median actual and relative dose intensities were 319.6 mg/day and 99.87%, respectively.	Yes
Was the outcome accurately measured to minimise bias?	Outcomes were accurately measured to minimise bias as outlined in Table 21. Outcomes were assessed using both IRC and INV assessment to validate outcomes where appropriate.	Yes
Have the authors identified all important confounding factors?	All important confounding factors were considered within pre-planned subgroup analyses. See Section B.2b.6 Clinical effectiveness results of the relevant studies: BGB-3111-206 for more details.	Yes
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes, as per the previous question, the confounding factors were identified and taken account for in the analysis.	Yes
Was the follow-up of patients complete?	The BGB-3111-206 trial is complete with no further data cuts planned. The trial design ensured patients were suitably followed up after discontinuation of treatment and/or progression. The median follow-up time was 35.25 months. At the end of treatment, a safety follow-up of 30 ± 7 days after last dose was ensured for both discontinuation due to PD and reasons other than PD. Patients continued efficacy evaluations until PD followed by long-term follow-up for survival every 24 weeks. All patients who discontinued study drug commenced long-term follow-up after progression, which included monitoring for survival status and initiation of new anticancer treatment for MCL and conducting chemistry and haematology assessments. If a patient refused to return for these visits or was unable to do so, every effort was made to contact them to assess the patient's disease status and survival.	Yes
How precise (for example, in terms of confidence interval and p values) are the results?	The primary endpoint of ORR by IRC assessment presented a p-value <0.0001 with a CI of 95%. Medians and other quartiles for all secondary endpoints were estimated by KM method with 95% CIs. See Section B.2b.6 Clinical effectiveness results of the relevant studies: BGB-3111-206 for full details.	Yes

CI – confidence interval; CSR – clinical study report; DCO – data cut-off; INV – investigator; IRC – independent review committee; KM - Kaplan-Meier; MCL – mantle cell lymphoma; mg – milligrams; NA – not applicable; ORR – overall response rate; PD – progressive disease
Source: BGB-3111-206 CSR (DCO: 08Sept2020)[42]

B.2b.6 Clinical effectiveness results of the relevant studies: BGB-3111-206

The key efficacy outcomes for patients with R/R MCL from BGB-3111-206 for the full trial population and 2L-only are presented in Table 26. IRC-assessed outcomes are presented on a cut-off date of 15th February 2019 with a median follow-up of 18.4 months. INV-assessed outcomes are presented on two cut-off dates, an earlier DCO of 31st August 2019 with a median follow-up of 24.84 months and a later DCO of 8th September 2020 with a median overall study follow-up of 35.25 months. Results for both data cuts are presented below and consistent with those observed from the BGB-3111-AU-003 trial as presented in Section B.2b.6 Clinical effectiveness results of the relevant studies: BGB-3111-206.

Table 26: Key efficacy outcomes reported in BGB-3111-206

	Zanubrutinib (N = 86)			**Zanubrutinib 2L-only (N=26)**		
	IRC-assessed (DCO 15Feb2019)[3] [2]	**INV-assessed (DCO 31Aug2019)** [44]	**INV-assessed (DCO 08Sept2020)** [34,42]	**IRC-assessed (DCO 15Feb2019)**[48]	**INV-assessed (DCO 31Aug2019)** [48]	**INV-assessed (DCO 08Sept2020)** [48]
ORR						
ORR (%) (95% CI)	83.7 (74.2, 90.8)	[redacted]	83.7 (74.2, 90.8)	[redacted]	[redacted]	[redacted]
PFS						
Median, months (95% CI)	22.1 (17.4, NE)	[redacted]	33.0 (19.4, NE)	[redacted]	[redacted]	[redacted]
DOR						
Median, months (95% CI)	19.5 (16.6, NE)	[redacted]	NE (24.9, NE)	[redacted]	[redacted]	[redacted]
TTR						
Events, n	86	[redacted]	72	[redacted]	[redacted]	[redacted]
Median, months (range)	2.7 (2.5, 16.6)	[redacted]	2.73 (2.5, 3.0)	[redacted]	[redacted]	[redacted]
OS						
Median, months (95% CI)	NR	[redacted]	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)

CI – confidence interval; CSR – clinical study report; DCO – data cut-off; DOR – duration of response; INV – investigator; IRC – independent review committee; NE – not estimable; NR – not reported; ORR – overall response rate; OS – overall survival; PFS – progression-free survival; TTR – time to response
Source: Song *et al.* (2020)[32], BGB-3111 Regulatory summary of clinical efficacy[44], BGB-3111-206 CSR[42], BGB-3111-206 data on file[48]

B.2b.6.1 Primary and key secondary endpoints: ORR

The BGB-3111-206 study met its primary endpoint. As demonstrated in Table 27, ORR by IRC assessment in the full trial population was 83.7% (95% CI: 74.2, 90.8), leading to rejection of the pre-specified null hypothesis of 40% with 1-sided p-value < 0.0001. A total of 59 (68.6%) patients achieved a complete response and 13 (15.1%) patients achieved a partial response. Clinical experts present at a UK advisory board (11th November 2024) noted that with R/R MCL, when a treatment shows a benefit in response rate it would also show a benefit in PFS, which is observed in the BGB-3111-206 PFS and OS outcomes.[2]

In line with the ORR determined by IRC assessment, the ORR determined by INV assessment was [redacted].

Consistent ORR outcomes were demonstrated in patients regardless of whether patients are 2L-only or ≥2L (full trial population), with an ORR in 2L-only patients of [redacted], using both IRC and INV assessment.

Table 27: IRC- and INV-assessed response rates in BGB-3111-206

Response category	Zanubrutinib in full trial population (N = 86)			Zanubrutinib 2L-only (N = 26)		
	IRC-assessed (DCO 15Feb 2019)[32]	INV-assessed (DCO 31Aug 2019)[44]	INV-assessed (DCO 08Sept 2020)[34,42]	IRC-assessed (DCO 15Feb 2019)[48]	INV-assessed (DCO 31Aug 2019)[48]	INV-assessed (DCO 08Sept 2020)[48]
Best overall response, n (%)						
CR	59 (68.6)	[redacted]	67 (77.9)	[redacted]	[redacted]	[redacted]
PR	13 (15.1)	[redacted]	5 (5.8)	[redacted]	[redacted]	[redacted]
SD	1 (1.2)	[redacted]	1 (1.2)	[redacted]	[redacted]	[redacted]
PD	6 (7.0)	[redacted]	8 (9.3)	[redacted]	[redacted]	[redacted]
Discontinued study prior to first assessment[a]	NR	[redacted]	5 (5.8)	[redacted]	[redacted]	[redacted]
Overall response rate						

ORR, n (%) [95% CI][b]	72 (83.7) [74.2, 90.8]	[redacted]	72 (83.7) [74.2, 90.8]	[redacted]	[redacted]	[redacted]

CI – confidence interval; CSR – clinical study report; CR – complete response; DCO – data cutoff; INV – investigator; IRC – independent review committee; n – number; ORR – overall response rate; PD – progressive disease; PR – partial response; SD – stable disease.
[a] Included subjects discontinued study prior to first post-baseline response assessment.
[b] 2-sided Clopper-Pearson 95% CIs.
Source: Song *et al.* (2020)[32], BGB-3111 regulatory summary of clinical efficacy[44], Song et al. (2022b)[34] / BGB-3111-206 CSR[42], BGB-3111-206 data on file[48]

B.2b.6.1.1 Sensitivity analysis of the primary endpoint

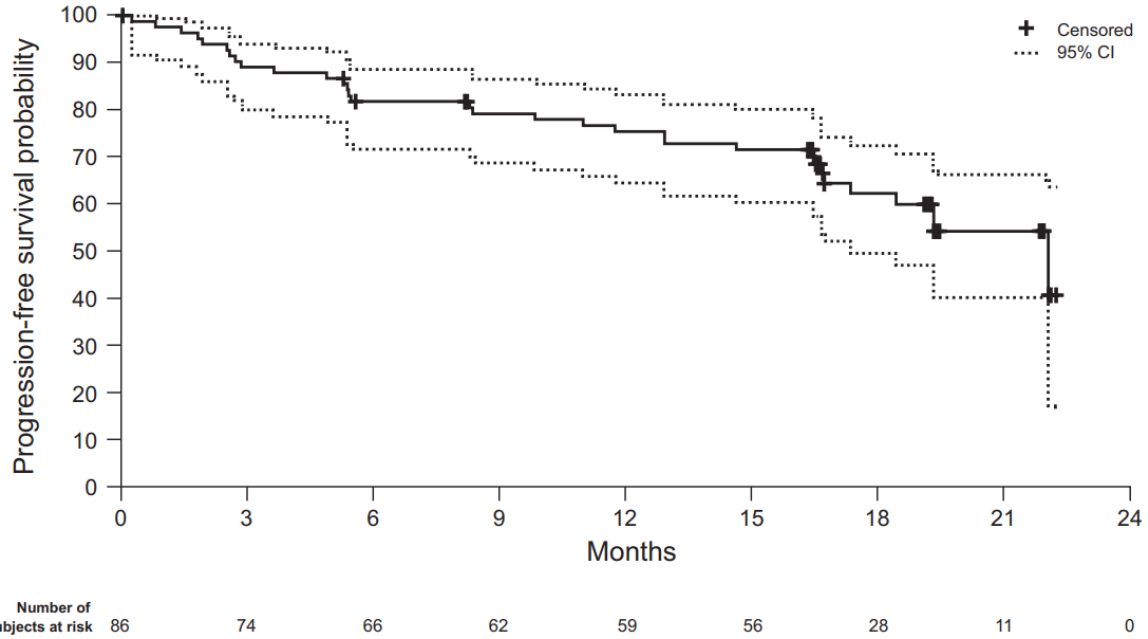
Sensitivity analysis of the primary endpoint (ORR) is discussed in detail in Section B.2b.7 Subgroup analysis: BGB-3111-206.

B.2b.6.2 Secondary endpoints

B.2b.6.2.1 Progression-free survival

At a median follow-up of 19.2 months, IRC-assessed median PFS in the full trial population was 22.1 months, as shown in the Kaplan-Meier (KM) plot presented in Figure 7. As reported in Table 28, the event-free rate (proportion of patients who neither progressed nor died) was 75.5% (95% CI: 65, 83) at 12 months.

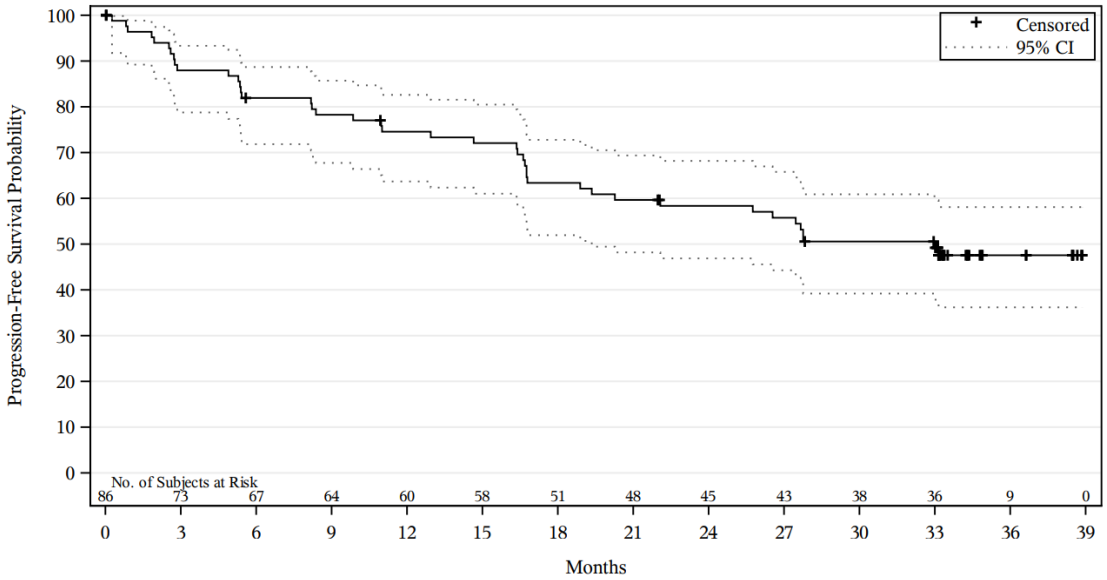
Figure 10: Kaplan-Meier plot of PFS by IRC in BGB-3111-206 (full trial population)



CI – confidence interval; DCO – data cut-off; IRC – independent review committee; PFS – progression-free survival.
Source: Song *et al.* (2020) (DCO: 15Feb2019)[32]

In line with IRC assessment, at a median follow-up of 33.3 months in the full trial population, [redacted] patients had either progressed or died as per INV assessment and median PFS was 33.0 months, as shown in the KM plot presented in Figure 8. The event-free rate was [redacted] at 12 months and 58.3% (95% CI: 46.9, 68.2) at 24 months.

Figure 11: Kaplan-Meier plot of PFS by INV in BGB-3111-206 (full trial population)



CI – confidence interval; DCO – data cut-off; INV – investigator; PFS – progression-free survival.
Source: Song et al. (2022b)[34] / BGB-3111-206 CSR (DCO: 08Sept2020)[42]

For 2L-only patients, IRC-assessed median PFS was [redacted], as shown in the KM plot presented in Figure 12. The event-free rate was [redacted] at 12 months and [redacted] at 18 months.

Figure 12: Kaplan-Meier plot of PFS by IRC in 2L-only patients in BGB-3111-206

[redacted]

2L – second line; DCO – data cut-off; IRC – independent review committee; PFS – progression-free survival
Source: BGB-3111-206 data on file[48]

In line with IRC assessment, [redacted] 2L-only patients had either progressed or died as per INV assessment and median PFS was [redacted], as shown in the KM plot presented in Figure 13. The event-free rate was [redacted] at 12 months and [redacted] at 24 months.

Figure 13: Kaplan-Meier plot of PFS by INV in 2L-only patients in BGB-3111-206

2L – second line; DCO – data cut-off; INV – investigator; PFS – progression-free survival
Source: BGB-3111-206 data on file[48]

Table 28: IRC- and INV-assessed PFS in BGB-3111-206

	Zanubrutinib full trial population (N = 86)			Zanubrutinib 2L-only (N = 26)		
	IRC-assessed (DCO 15Feb 2019)[32]	INV-assessed (DCO 31Aug 2019)[44]	INV-assessed (DCO 08Sep 2020)[34,42]	IRC-assessed (DCO 15Feb 2019)[48]	INV-assessed (DCO 31Aug 2019)[48]	INV-assessed (DCO 08Sep 2020)[48]
PFS, n (%)						
Events	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Median PFS, months (95% CI)	22.1 (17.4, NE)	[redacted]	33.0 (19.4, NE)	[redacted]	[redacted]	[redacted]
Event-free rate at, % (95% CI)[a]						
6 Months	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 Months	75.5 (65, 83)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 Months	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 Months	NR	[redacted]	58.3 (46.9, 68.2)	[redacted]	[redacted]	[redacted]

CI – confidence interval; CSR – clinical study report; DCO – data cutoff; INV – investigator; IRC – independent review committee; NE – not estimable; NR – not reported; PD – progressed disease; PFS – progression-free survival

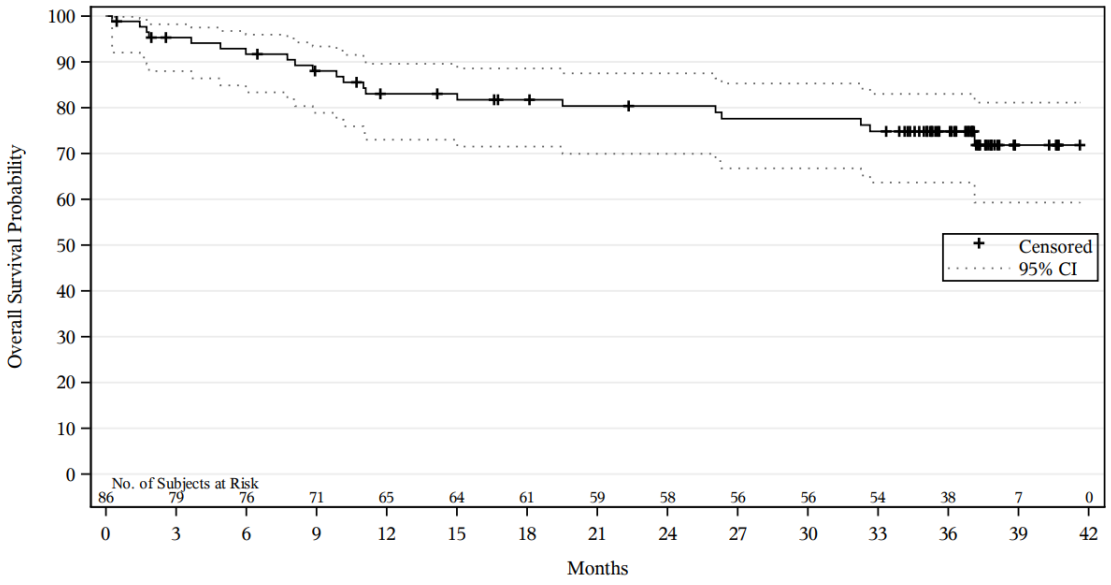
[a] Event-free rates were estimated by Kaplan-Meier method with 95% CIs estimated using Greenwood's formula.

Source: Song *et al.* (2020)[32], BGB-3111 Regulatory summary of clinical efficacy[44], Song et al. (2022b)[34] / BGB-3111-206 CSR[42], BGB-3111-206 data on file[48]

B.2b.6.2.2 Overall survival

At a median follow-up of 36.8 months, 21 deaths had occurred, and median OS had not been reached, as shown in the KM plot presented in Figure 14. As reported in Table 29, the event-free rate was [redacted] at 12 months and 80.4% (95% CI: 69.9, 87.5) at 24 months.

Figure 14: Kaplan-Meier plot of OS in BGB-3111-206 (full trial population)



CI – confidence interval; CSR – clinical study report; DCO – data cut-off; OS – overall survival

Source: Song et al. (2022b)[34] / BGB-3111-206 CSR (DCO: 08Sept2020)[42]

In line with the full population, at a median follow-up of 35.3 months (DCO 08Sept2020), [redacted] deaths had occurred in 2L-only patients, and median OS [redacted], as shown in the KM plot presented in Figure 15. As reported in Table 29, the event-free rate was [redacted] at 12 months, 24 months and 36 months.

Figure 15: Kaplan Meier plot of OS in 2L-only patients in BGB-3111-206

2L – second line; DCO – data cut-off; OS – overall survival
Source: BGB-3111-206 data on file[48]

Table 29: OS in BGB-3111-206

OS	Zanubrutinib in full trial population (N = 86)	Zanubrutinib 2L-only (N = 26)
Deaths, n (%)	21 (24.4)	[redacted]
Median OS, months (95% CI)	NE (NE, NE)	[redacted]
Event-free rate at, % (95% CI)[a]		
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	80.4 (69.9, 87.5)	[redacted]

36 months	74.8 (63.7, 83.0)	[redacted]

CI – confidence interval; CSR – clinical study report; DCO – data cut-off; N – number; NE – not estimable; OS – overall survival

[a] Event-free rates were estimated by Kaplan-Meier method with 95% CIs estimated using Greenwood's formula.

Source: Song et al. (2022b)[34] / BGB-3111-206 CSR (DCO: 08Sept2020)[42], BGB-3111-206 data on file[48]

B.2b.6.2.3 Duration of response

At a median follow-up of 16.4 months, IRC-assessed median DOR in the full trial population was 19.5 months, with 78.3% (95% CI: 67, 86) of responders event-free at 12 months after an initial response.

At a median follow-up of 30.6 months, [redacted] of patients who achieved a response had either progressive disease or had died as per INV assessment. Median DOR was not reached, with [redacted] of responders event-free at 24 months after initial response.

For the 2L-only population, [redacted] of the patients who achieved a response had either progressive disease or had died as per IRC assessment (DCO: 15th February 2019), and median DOR was [redacted], with [redacted] of responders event-free at 18 months after initial response. As per INV assessment (DCO: 8th September 2020), [redacted] of the patients who achieved a response had either progressive disease or had died, and the median DOR was [redacted], with [redacted] of responders event-free at 24 months after initial response.

Table 30: IRC- and INV-assessed DOR in BGB-3111-206

	Zanubrutinib full trial population (N = 86)			**Zanubrutinib 2L-only (N = 26)**		
	IRC-assessed (DCO 15Feb2019)[32]	**INV-assessed (DCO 31Aug 2019)[44]**	**INV-assessed (DCO 08Sept 2020)[34,42]**	**IRC-assessed (DCO 15Feb 2019)[48]**	**INV-assessed (DCO 31Aug 2019)[48]**	**INV-assessed (DCO 08Sep 2020)[48]**
IRC/INV-assessed DOR, n (%)						
Events	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Median DOR, months (95% CI)	19.5 (16.6, NE)	[redacted]	NE (24.9, NE)	[redacted]	[redacted]	[redacted]
Event-free rate at, (95% CI)[a]						
6 months	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months	78.3 (67, 86)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 months	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30 months	NR	[redacted]	57.3 (44.9-67.9)	[redacted]	[redacted]	[redacted]

CI – confidence interval; CSR – clinical study report; DCO -data cut-off; DOR – duration of response; INV – investigator; IRC – independent review committee; N – number; NE – not estimable; PD – progressed disease
[a] Event-free rates were estimated by Kaplan-Meier method with 95% CIs estimated using Greenwood's formula.
Source: Song *et al.* (2020)[32], BGB-3111 Regulatory summary of clinical efficacy[44] and Song et al. (2022b)[34] / BGB-3111-206 CSR[42], BGB-3111-206 data on file[48]

B.2b.6.2.4 Time to response

As presented in Table 31, median TTR by IRC assessment in the full trial population was 2.73 months for the full trial population (N=86) and [redacted] months for the 2L-only population (N=26). INV-assessed TTR was consistent with the IRC-assessed TTR for both the full population and the 2L-only population. Time to complete response by INV was [redacted] months for both the full population and the 2L-only population.

Table 31: INV-assessed TTR in BGB-3111-206

	Zanubrutinib full trial population (N = 86)			**Zanubrutinib 2L-only (N = 26)**		
	IRC-assessed (DCO 15Feb 2019)[32]	**INV-assessed (DCO 31Aug 2019)[44]**	**INV-assessed (DCO 08Sept 2020)**	**IRC-assessed (DCO 15Feb 2019)[48]**	**INV-assessed (DCO 31Aug 2019)[48]**	**INV-assessed (DCO 08Sep 2020)[48]**
TTR (months)						
N	86	72	72	[redacted]	[redacted]	[redacted]
Mean (SD)	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	2.7 (2.5, 16.6)	[redacted]	2.73 (2.5, 3.0)	[redacted]	[redacted]	[redacted]
Time to complete response (months)						

	Zanubrutinib full trial population (N = 86)			Zanubrutinib 2L-only (N = 26)		
	IRC-assessed (DCO 15Feb 2019)[32]	INV-assessed (DCO 31Aug 2019)[44]	INV-assessed (DCO 08Sept 2020)	IRC-assessed (DCO 15Feb 2019)[48]	INV-assessed (DCO 31Aug 2019)[48]	INV-assessed (DCO 08Sep 2020)[48]
N	NR	[redacted]	67	[redacted]	[redacted]	[redacted]
Mean (SD)	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	NR	[redacted]	2.8 (2.5, 16.7)	[redacted]	[redacted]	[redacted]

CSR – clinical study report; DCO – data cutoff; INV – investigator; IRC – independent review committee; n – number; SD – standard deviation; TTR – time to response
Source: Song *et al.* (2020)[32], BGB-3111 Regulatory summary of clinical efficacy[44] and Song et al. (2022b)[34] / BGB-3111-206 CSR[42], BGB-3111-206 data on file

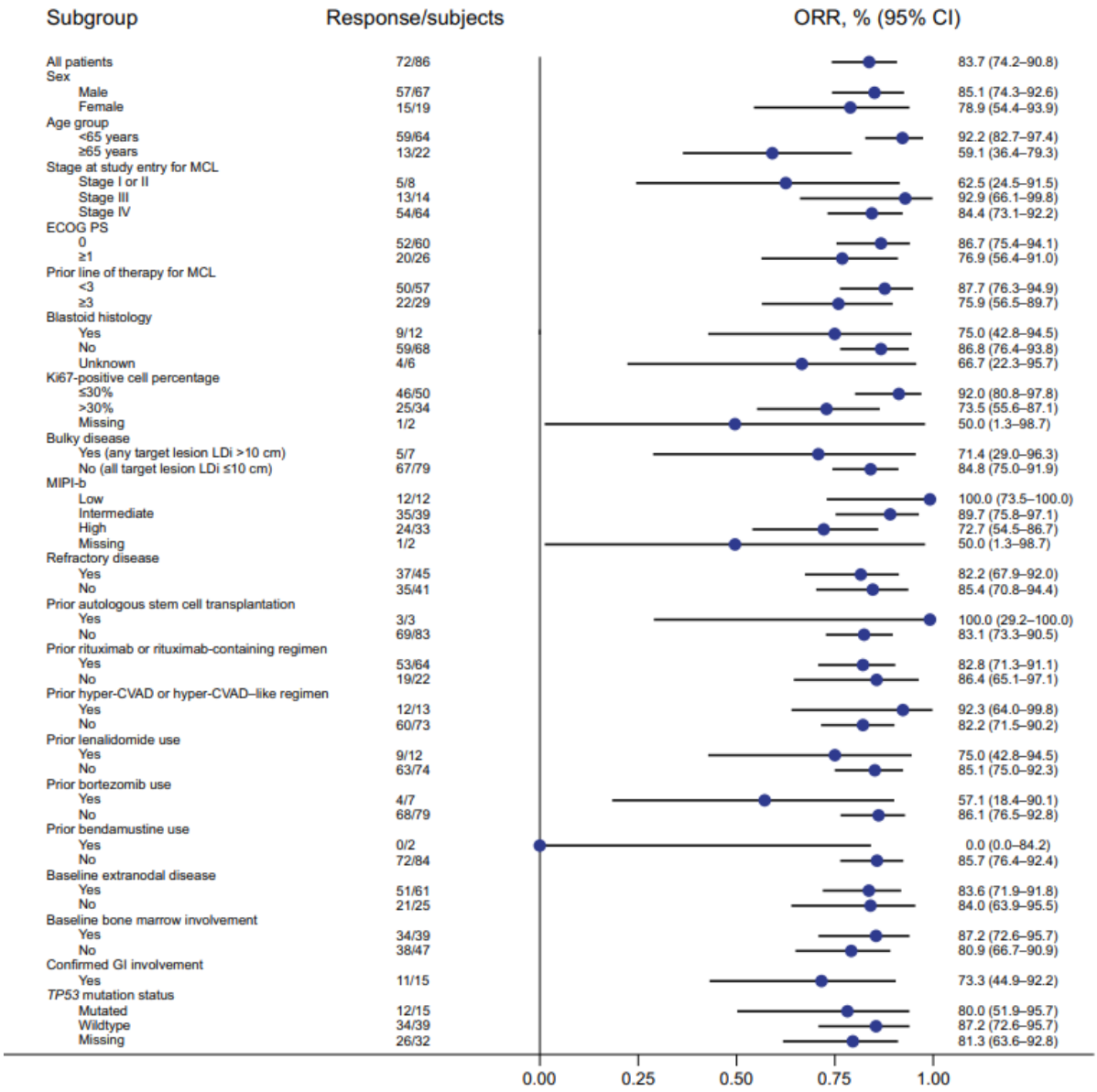
B.2b.6.2.5 Patient reported outcomes

No patient reported outcomes were collected in the BGB-3111-206 trial.

B.2b.7 Subgroup analysis: BGB-3111-206

In line with the subgroup analysis from BGB-3111-AU-003, a uniformity in treatment benefits was observed across all pre-specified and post-hoc subgroups in the primary endpoint of IRC-assessed ORR, as presented in Figure 16. Notably, prior treatment history did not exert a widespread impact on treatment responses. The trends to high response rates were observed even in traditionally poor prognostic groups such as age, bulky disease and high-risk MIPI-b scores. Critical to the population zanubrutinib is being appraised in (2L-only patients), response rates were markedly higher in patients who were <3L at baseline.

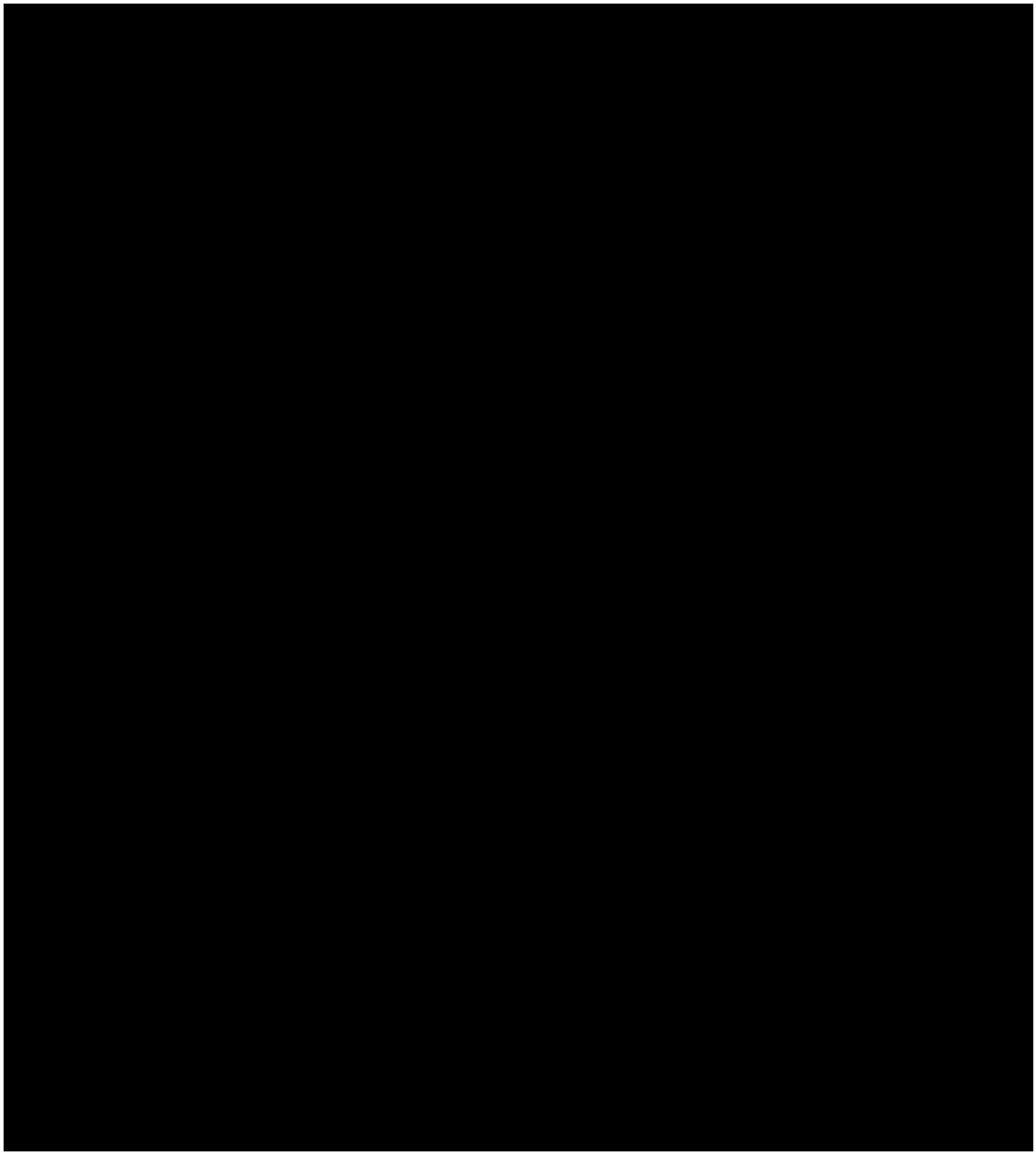
Figure 16: Forest plot of ORR by IRC assessment



CI – confidence interval; DCO -data cut-off; ECOG PS – Eastern Cooperative Oncology Group performance status; GI – gastrointestinal; Hyper-CVAD - cyclophosphamide, vincristine, doxorubicin, and dexamethasone; IRC – independent review committee; LDi – longest transverse diameter of a lesion; MCL – mantle cell lymphoma; MIPI-b - combined biologic mantle cell lymphoma international prognostic index; ORR – overall response rate
Source: Song *et al.* (2020) (DCO: 15Feb2019)[32]

As presented in Figure 17, similarly to IRC-assessment, there is a uniformity in treatment benefits across all subgroups in the endpoint of INV-assessed ORR. Caution should be taken when analysing the subgroup responses due to the low sample size associated with the analyses.

Figure 17: Forest plot of ORR by INV assessment



CI– confidence interval; CSR – clinical study report; DCO – data cut-off; ECOG PS – Eastern Cooperative Oncology Group performance status; GI – gastrointestinal; Hyper-CVAD - cyclophosphamide, vincristine, doxorubicin, and dexamethasone; INV – investigator; LDi – longest transverse diameter of a lesion; MCL – mantle cell lymphoma; MIPI-b - combined biologic mantle cell lymphoma international prognostic index; ORR – overall response rate

[a]2-sided Clopper-Pearson 95% confidence intervals.

[b]MIPI-b score is calculated if Ki-67 is available with cutoffs as low (<5.7), intermediate (≥5.7 and <6.5), and high (≥6.5).

[c]No represents either 1) no GI involvement as confirmed by endoscopy/biopsy or 2) no endoscopy/biopsy performed to confirm GI involvement.

Source: BGB-3111-206 CSR (DCO: 08Sept2020)[42]

B.2.8 Meta-analysis

A formal meta-analysis was not conducted due to the single arm nature of the studies. However, consistent with the published analyses for zanubrutinib in R/R MCL, patient-level data from the BGB-3111-206 and BGB-3111-AU-003 trials were pooled for use in the ITC, see Section B.2.9 Indirect and mixed treatment comparisons for further details.[49]

B.2.9 Indirect and mixed treatment comparisons

This section presents the ITC for zanubrutinib versus ibrutinib.

As discussed in Section B.1.3.4 Clinical pathway of care and place in therapy, ibrutinib is the only appropriate comparator for this appraisal. There are no head-to-head studies of zanubrutinib versus ibrutinib, therefore an ITC was conducted to compare the two treatments and is presented below.

B.2.9.1 Data sources

As discussed in Section B.2a.3 Summary of methodology of the relevant clinical effectiveness evidence: BGB-3111-AU-003 and Section B.2b.3 Summary of methodology of the relevant clinical effectiveness evidence: BGB-3111-206

, two relevant R/R MCL trials studying zanubrutinib monotherapy were identified (BGB-3111-AU-003 and BGB-3111-206). BGB-3111-AU-003 a Phase 1/2 trial in adult patients with B-cell malignancies, was the initiated on the 16th September 2014. Given the positive outcome in the R/R MCL cohort (n=32) (ORR of 84.4%) a subsequent, larger study in this population was initiated, BGB-3111-206.

To increase the sample size for zanubrutinib in the ITC analyses, IPD from the BGB-3111-AU-003 and BGB-3111-206 trials were pooled. This approach is consistent with published analyses evaluating outcomes following treatment with zanubrutinib.[2,49] Furthermore, a comparable pooling approach was submitted as part of the regulatory submission to the MHRA to inform the safety assessment of zanubrutinib. From here-in the pooled IPD is referred to as AU003-206. The trial eligibility criteria (Table 7 and Table 20) and the baseline characteristics (Table 32) were deemed comparable across the two trials. The pooling of the two studies was

confirmed as appropriate by UK clinical and health economic experts in attendance at an advisory board (11th November 2024).[2] As IPD from both zanubrutinib trials were available no adjustments were required to balance the populations of the two trials, the baseline characteristics of the zanubrutinib trials were deemed comparable across the two trials. The pooling of the two studies was confirmed as appropriate by UK clinical and health economic experts in attendance at an advisory board (11th November 2024).[2] As IPD from both zanubrutinib trials were available no adjustments were required to balance the populations of the two trials.

All patients in the zanubrutinib AU003-206 dataset were used in the ITC, i.e., no stratification by 2L (n=44, 37.3%). Given the baseline characteristics and efficacy endpoint results were consistent for patients 2L-only versus ≥2L, all R/R MCL patients were included in the ITC, in order to maximise the patient sample used in the analyses. Furthermore, the BGB-3111-AU-003 and BGB-3111-206 trials were not powered to support efficacy endpoint results by line of therapy.

Table 32: Baseline characteristics of zanubrutinib trials

Characteristics	BGB-3111-AU-003 (N = 32)	BGB-3111-206 (N = 86)	Pooled data (N = 118)
Age, years			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	70.5 (42, 86)	60.5 (34, 75)	[redacted]
Sex, n (%)			
Male	22 (68.8)	67 (77.9)	89 (75.4)
Female	10 (31.3)	19 (22.1)	29 (24.6)
Race, n (%)			
Asian	3 (9.4)	86 (100)	89 (75.4)
Black or African American	1 (3.1)	0 (0.0)	1 (0.8)
White	25 (78.1)	0 (0.0)	25 (21.2)
Other/multiple	3 (9.4)	0 (0.0)	3 (2.5)
ECOG PS, n (%)			
0	15 (46.9)	60 (69.8)	75 (63.6)
1	14 (43.8)	22 (25.6)	36 (30.5)
2	3 (9.4)	4 (4.7)	7 (5.9)
Time from initial diagnosis to study entry (months)[a]			

Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Ann Arbor Stage at study entry, n (%)			
I	2 (6.3)	1 (1.2)	3 (2.5)
II	1 (3.1)	7 (8.1)	8 (6.8)
III	1 (3.1)	14 (16.3)	15 (12.7)
IV	28 (87.5)	64 (74.4)	92 (78.0)
Disease status to last prior therapy, n (%)[b]			
Relapsed	[redacted]	41 (47.7)	[redacted]
Refractory	8 (25.0)	45 (52.3)	53 (45.0)
Unknown	[redacted]	0 (0.0)	[redacted]
Bulky disease, n (%)			
Yes (any target lesion LDi > 10 cm)	3 (9.4)	7 (8.1)	10 (8.5)
No (all target lesion LDi ≤ 10 cm)	29 (90.6)	79 (91.9)	108 (91.5)
Extranodal disease at study entry, n (%)[c]			
Yes	25 (78.1)	61 (70.9)	86 (72.9)
No	7 (21.9)	25 (29.1)	32 (27.1)
MIPI-b, n (%)[d]			
Low risk	8 (25.0)	12 (14.0)	21 (17.8)
Intermediate risk	11 (34.4)	39 (45.3)	52 (44.1)
High risk	13 (40.6)	33 (38.4)	43 (36.4)
Missing	NR	2 (2.3)	2 (1.7)
Ki67-positive cell percentage			
N	NR	84	NR
Mean (SD)	NR	35.4 (18.22)	NR
Median (range)	NR	30.0 (3, 80)	NR
≤ 30%, n (%)	NR	50 (58.1)	NR
> 30%, n (%)	NR	34 (39.5)	NR
Missing	NR	2 (2.3)	NR
Number of prior systemic therapies			
Median (range)	1.0 (1, 4)	2.0 (1, 4)	2.0 (1, 4)
1 prior therapy	18 (56.2)	25 (30.2)	44 (37.3)
2 prior therapies	[redacted]	[redacted]	[redacted]
3 prior therapies	[redacted]	19 (22.1)	[redacted]
4 prior therapies	[redacted]	10 (11.6)	[redacted]

Time from end of last therapy to study entry (months)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Patients with any prior radiation therapies, n (%)			
Yes	[redacted]	8 (9.3)	[redacted]
No	[redacted]	78 (90.7)	[redacted]
Prior stem cell transplant, n (%)			
Yes	5 (15.6)	3 (3.5)	8 (6.8)
No	27 (84.4)	83 (96.5)	110 (93.2)
Prior systemic regimens, n (%)			
Bendamustine	4 (12.5)	2 (2.3)	6 (5.1)
Bortezomib	2 (6.3)	7 (8.1)	9 (7.6)
Cytarabine	[redacted]	[redacted]	[redacted]
DHAP	[redacted]	[redacted]	[redacted]
DICE/ICE	[redacted]	[redacted]	[redacted]
ESHAP	[redacted]	[redacted]	[redacted]
GDP	[redacted]	[redacted]	[redacted]
GEMOX	[redacted]	[redacted]	[redacted]
Hyper-CVAD or hyper-CVAD-like regimen	7 (21.9)	[redacted]	[redacted]
Lenalidomide	[redacted]	12 (14.0)	[redacted]
Purine analog	7 (21.9)	[redacted]	[redacted]
R-CHOP/R-CHOPE/R-CHOP-like	19 (59.4)	[redacted]	[redacted]
R or R-containing regimen	30 (93.8)	64 (74.4)	94 (79.7)

CSR – clinical study report; DCO – data cut-off; DHAP - dexamethasone, cytarabine and cisplatin; DICE – dexamethasone, ifosfamide, cisplatin, etoposide; ECOG PS – Eastern Cooperative Oncology Group performance status; ESHAP – etoposide, methylprednisolone, cytarabine and cisplatin; GDP – gemcitabine, dexamethasone and cisplatin; GEMOX – gemcitabine-oxaliplatin; Hyper-CVAD – cyclophosphamide, vincristine, doxorubicin, and dexamethasone; ICE – ifosfamide, cisplatin and etoposide; LDi – longest transverse diameter of a lesion; MIPI-b - combined biologic mantle cell lymphoma international prognostic index; N – number; R – rituximab; R-CHOP - rituximab plus doxorubicin hydrochloride, vincristine and prednisone; R-CHOPE – rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone and etoposide; SD - standard deviation

[a] The day of first diagnosis was assumed to be the first day of the month when the day was missing and assumed to be 01 January when the day and month were missing.

[b] As defined by the investigator.

[c] Extranodal disease was defined as biopsy or radiographic evidence of bone marrow or gastrointestinal disease.

[d] MIPI-b score was calculated with cutoffs as low (< 5.7), intermediate (≥ 5.7 and < 6.5), and high (≥ 6.5) risk.

Source: Tam *et al.,* (2021)[35] / BGB-3111-206 CSR (DCO: 08Sept2020)[42], Song *et al.* (2020)[32] / BGB-3111-AU-003 CSR (DCO: 31Mar2021)[43], BGB-3111 Regulatory summary of clinical safety[50]

A clinical SLR was conducted to identify data sources for the only appropriate comparator in this appraisal, ibrutinib. There is no significant risk of bias of studies

included in the ITC, further details on the SLR methodology are included in Appendix D. The SLR identified four studies for ibrutinib that may be suitable for inclusion in an ITC (Rule *et al.* [2017b], Dreyling *et al.* [2016], Wang *et al.* [2013 and 2015], McCulloch *et al.* [2021]) (Table 4).[17,36–39] A feasibility assessment concluded the pooled ibrutinib study (Rule *et al.* [2017b], N=370 patients),[17] which included patients from an RCT (RAY-MCL3001 [NCT01646021]) and two single arm studies (PCYC-1104 [NCT01236391] and SPARK [NCT01599949]), was the most appropriate data source to inform the ITC base-case analysis, for the following reasons:

- The pooled analysis includes the largest patient population available for ibrutinib (n=370). The dataset can be considered representative of the UK patient population, with patients from sites across the UK and Europe, across all three studies. Importantly, the analysis includes data from an RCT (RAY-MCL3001), which is considered higher quality evidence than single-arm trials or observational studies.[36,40,41]

- The patient population assessed within Rule *et al.* (2017b),[17] includes patients with R/R MCL who have received at least one prior line of therapy. There is no 2L-only effectiveness data for ibrutinib which is of sufficient quality to inform an indirect treatment comparison versus 2L-only patients in the pooled AU003-206 dataset, further supporting the conduct of an ITC in patients R/R MCL, regardless of whether 2L-only or ≥2L.

- Covariate data was well reported in the publication. The publication also reports PFS and OS KM plots, as required for the ITC.

- In the ibrutinib R/R MCL NICE submission (TA502), the Evidence Analysis Group (EAG) and the committee deemed the pooling of data acceptable, given paucity of evidence for ibrutinib.[4]

- UK clinical experts agreed (at an advisory board conducted on the 11th November 2024) that Rule *et al.* (2017b)[17] was an appropriate data source to inform the ITC of zanubrutinib versus ibrutinib.

B.2.9.2 Choice of ITC

As no head-to-head studies for zanubrutinib and ibrutinib are available, indirect comparison is required. In the absence of IPD for ibrutinib, and since the studies considered for the ITC do not form a connected network, unanchored methods are the only methods feasible for comparison. Therefore, the options considered to inform the comparative efficacy data for zanubrutinib versus ibrutinib were unanchored MAIC and simulated treatment comparison (STC). The key prognostic factors and effect modifiers, presented in Section B.2.9.4 Methodology, were relatively well balanced thus the MAIC and STC methodologies are expected to produce similar results. The MAIC approach has been used in a number of oncology HTAs submitted to and accepted by NICE, most recently the evaluation of zanubrutinib (TA1001) for the treatment of marginal zone lymphoma (MZL), for which a MAIC was conducted on PFS and OS.[51] Consequently, the MAIC methodology was adopted in preference to the STC methodology.

An unanchored MAIC was conducted to compare zanubrutinib and ibrutinib, in line with the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) guidelines and method described by Signorovitch et al. (2012).[52,53] Further details on the MAIC methodology are included in Appendix M.

B.2.9.3 Summary of studies included for the ITC

Study design

A comparison of the BGB-3111-AU-003, BGB-3111-206 and Rule *et al.* (2017b) study design is presented in Table 33.

Table 33: Comparison of study design for BGB-3111-AU-003, BGB-3111-206 and Pooled RAY-MCL3001, PCYC-1104 and SPARK trials

Trial	BGB-3111-AU-003	BGB-3111-206	Pooled RAY-MCL3001, PCYC-1104, SPARK
Study phase and design	Phase I/II, open-label, multiple-dose, dose escalation and expansion study	Phase II, single-arm, open-label, multicentre study	RAY-MCL3001: Phase III, multicentre, randomised, open-label clinical trial

			PCYC-1104: Phase II, open-label, single arm, multicentre study SPARK: Phase II, single-arm, multicentre study
Country/region	USA, Australia, Italy, Republic of Korea, New Zealand and UK	China	RAY-MCL3001: Belgium, Brazil, Canada, Chile, Colombia, Czechia, France, Germany, Hungary, Ireland, Republic of Korea, Mexico, Netherlands, Poland, Portugal, Russian Federation, Spain, Sweden, Taiwan, Ukraine and UK PCYC-1104: USA, Germany, Poland and UK SPARK: USA, Belgium, France, Israel, Poland, Puerto Rico, Russian Federation, Spain and UK
Intervention	Zanubrutinib (320 mg) once daily	Zanubrutinib (320 mg) once daily	Ibrutinib (560 mg)
Comparator	N/A	N/A	RAY-MCL3001: Temsirolimus PCYC-1104: N/A SPARK: N/A
Median follow-up in months (range)	DCO: 13 Dec 2018 - 18.84 months (1.9, 38.2) **DCO: 31 March 2021 – 38.92 (1.9, 56.3)**	DCO: 31 Aug 2019 – 24.84 months (0.3, 30.0) **DCO: 08Sept 2020 – 35.25 (0.3, 41.6)**	24-25 months

Key eligibility criteria	• Aged ≥18 with B-cell malignancies as defined by the WHO classification – containing MCL patient subgroup
	• R/R disease, following ≥1 prior lines of therapy, with no prior exposure to a BTKi
	• ECOG-PS of 0-2
		• Aged 18-75 years
		• 1-5 prior lines of therapy, with no prior exposure to a BTKi
		• Retrospectively confirmed MCL diagnosis
		• ECOG-PS of 0-2
			• Aged ≥18 with confirmed MCL diagnosis
			• RAY-MCL3001:
			  • ≥1 prior R-containing chemotherapy regimen, with no prior exposure to mTOR inhibitors or BTKis
			  • ECOG-PS of 0-1
			• PCYC-1104:
			  • 1-5 prior lines
			  • ECOG-PS of 0-2
			• SPARK:
			  • 1-5 prior lines
			  • ≥1 prior R-containing therapy
			  • ECOG-PS of 0-2
			≥2 cycles of bortezomib therapy (single agent or combination therapy) and have documented progressive disease during or after bortezomib therapy

Outcomes	PFS-IRC (primary methods of assessing PFS), PFS-INV, OS	PFS-IRC (primary methods of assessing PFS), PFS-INV, OS	PFS-IRC, OS

Key publication(s)	CSR[43] and Tam *et al.* (2021)[35]	CSR[42] and Song *et al.* (2020, 2021 and 2022)[32–34]	Rule *et al.* (2017b)[17]

BTKi – Bruton's tyrosine kinase inhibitor; CSR – clinical study report; DCO – data cut-off; ECOG-PS – Eastern Cooperative Oncology Group performance status; INV – investigator; IRC – independent review committee; MCL – mantle cell lymphoma; mg – milligram; mTOR – mammalian target of rapamycin; N/A – not applicable; OS – overall survival; PFS – progression-free survival; R – rituximab; R/R – relapsed/refractory; UK – United Kingdom; USA – United States of America; WHO – World Health Organisation
Source: BGB-3111-AU-003 CSR (DCO:31Mar2021)[43], Tam *et al.*(2021)[35], BGB-3111-206 CSR (DCO: 08Sept2020)[42], Song *et al.* (2020, 2021 and 2022)[32–34], PCYC-1104[38], SPARK[54], RAY-MCL3001[55]

Patient characteristics

The baseline characteristics for the pooled AU003-206 and pooled ibrutinib populations are presented in Table 34. Despite the substantial overlap in the characteristics in the population, a MAIC is still required to account for some differences which are observed.

Table 34: Baseline characteristics for pooled AU003-206 population and pooled RAY-MCL3001, PCYC-1104 and SPARK trials population

Characteristics	AU003-206 pooled population (N = 118)	Rule *et al.* (2017b) ibrutinib pooled population (N = 370)
Age (years), n (%)		
Mean (SD)	[redacted]	66.84 (9.07)
Median (range)	62.0 (34, 86)	67.5
< 65 years	72 (61.0)	139 (37.6)
≥ 65 years	46 (39.0)	231 (62.4)
Sex, n (%)		
Male	89 (75.4)	289 (78.0)
Female	29 (24.6)	81 (22.0)
Race, n (%)		
Asian	89 (75.4)	NR
Black or African American	1 (0.8)	NR
White	25 (21.2)	NR
Other/multiple	3 (2.5)	NR
ECOG PS, n (%)		
0	75 (63.6)	160 (43.0)
1	36 (30.5)	186 (50.0)
2	7 (5.9)	23 (6.0)
3	0 (0.0)	1 (1)
Time from initial diagnosis to study entry (months)[a]		

Mean (SD)	[redacted]	NR
Median (range)	[redacted]	NR
Ann Arbor Stage at study entry, n (%)		
I	3 (2.5)	NR
II	8 (6.8)	NR
III	15 (12.7)	NR
IV	92 (78.0)	NR
Disease status to last prior therapy, n (%)[b]		
Relapsed	[redacted]	NR
Refractory	53 (45.0)	NR
Unknown	[redacted]	NR
Bulky disease, n (%)		
Yes (any target lesion LDi > 10 cm)	10 (8.5)	NR
No (all target lesion LDi ≤ 10 cm)	108 (91.5)	NR
LDi ≥ 5 cm	NR	181 (49)
Extranodal disease at study entry, n (%)[c]		
Yes	86 (72.9)	215 (58.0)
No	32 (27.1)	155 (42.0)
Blastoid variant, n (%)		
Yes	14 (11.9)	44 (12.0)
No	96 (81.3)	56 (88.0)
Unknown	8 (6.8)	0 (0.0)
Bone marrow involvement, n (%)		
Yes	57 (48.3)	170 (46.0)
No	61 (51.7)	200 (54.0)
MIPI/MIPI-b, n (%)[d]		
Low risk (1-3)	21 (17.8)	89 (24.0)
Intermediate risk (4-5)	52 (44.1)	167 (45.0)
High risk (6-11)	43 (36.4)	118 (32.0)
Missing	2 (1.7)	NR
Ki-67		
N	NR	NR
Mean (SD)	NR	NR
Median (range)	NR	NR
≤ 30%, n (%)	NR	NR
> 30%, n (%)	NR	NR
Number of prior systemic therapies		

Median (range)	2.0 (1, 4)	2.0 (1, 9)
1 prior therapy	43 (36.4)	99 (26.8)
2 prior therapies	[redacted]	109 (29.5)
≥ 3 prior therapies	[redacted]	162 (43.8)
Time from end of last therapy to study entry (months)		
Mean (SD)	[redacted]	NR
Median (range)	[redacted]	NR
Patients with any prior radiation therapies, n (%)		
Yes	17 (14.4)	NR
No	101 (85.6)	NR
Prior stem cell transplant, n (%)		
Yes	8 (6.8)	85 (23.0)
No	110 (93.2)	285 (77.0)
Prior systemic regimens, n (%)		
Bendamustine	6 (5.1)	NR
Bortezomib	9 (7.6)	200 (54.0)
Cytarabine	[redacted]	NR
DHAP	[redacted]	NR
DICE/ICE	[redacted]	NR
ESHAP	[redacted]	NR
GDP	[redacted]	NR
GEMOX	[redacted]	NR
Hyper-CVAD or hyper-CVAD-like regimen	[redacted]	NR
Lenalidomide	[redacted]	59 (16.0)
Purine analog	[redacted]	NR
R-CHOP/R-CHOPE/R-CHOP-like	[redacted]	NR
R or R-containing regimen	94 (79.7)	358 (96.8)[e]

CSR – clinical study report; DCO – data cut-off; DHAP - dexamethasone, cytarabine and cisplatin; DICE – dexamethasone, ifosfamide, cisplatin, etoposide; ECOG PS – Eastern Cooperative Oncology Group performance status; ESHAP – etoposide, methylprednisolone, cytarabine and cisplatin; GDP – gemcitabine, dexamethasone and cisplatin; GEMOX – gemcitabine-oxaliplatin; Hyper-CVAD – cyclophosphamide, vincristine, doxorubicin, and dexamethasone; ICE – ifosfamide, cisplatin and etoposide; LDi – longest transverse diameter of a lesion; MIPI-b - combined biologic mantle cell lymphoma international prognostic index; N – number; R – rituximab; R-CHOP - rituximab plus doxorubicin hydrochloride, vincristine and prednisone; R-CHOPE – rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone and etoposide; SD - standard deviation

[a] The day of first diagnosis was assumed to be the first day of the month when the day was missing and assumed to be 01 January when the day and month were missing.

[b] As defined by the investigator.

[c] Extranodal disease was defined as biopsy or radiographic evidence of bone marrow or gastrointestinal disease.

[d] MIPI-b score was calculated with cutoffs as low (< 5.7), intermediate (≥ 5.7 and < 6.5), and high (≥ 6.5) risk.

[e] Value calculated from the individual trials' sources

N.B. Ki67-positive cell not reported for BGB-3111-AU-003 and Rule et al. (2017b), as such these are not presented in the table
Source: Tam *et al.,* (2021)[35] / BGB-3111-206 CSR (DCO: 08Sept2020)[42], Song *et al.* (2020)[32] / BGB-3111-AU-003 CSR (DCO:31Mar2021)[43], BGB-3111-206 CSR (DCO: 08Sept2020)[42], BGB-3111 Regulatory summary of clinical safety[50], PCYC-1104, SPARK[54], RAY-MCL3001[55]

Outcomes

The median study follow-up was very similar across the zanubrutinib BGB-3111-AU-003 and BGB-3111-206 trials at 38.92 and 35.25 months, respectively. Rule *et al.* (2017b) reported a follow-up of 24-25 months. A sensitivity analysis using an earlier DCO, with a shorter follow-up time from the zanubrutinib BGB-3111-AU-003 and BGB-3111-206 trials (18.84 and 24.84 months, respectively) was conducted to understand the impact of using a more comparable follow-up on the results.

The endpoints explored in the ITC were PFS and OS, as they are the outcomes used to inform the treatment effectiveness in the cost-effectiveness model. The zanubrutinib BGB-3111-AU-003 and BGB-3111-206 trials had different DCOs available that used two different methods of assessing PFS (INV and IRC assessed), as presented in Table 35. Rule *et al.* (2017b) reported INV-assessed PFS, thus, to allow for more comparable results across the datasets, DCOs that reported INV-assessed PFS were selected for the zanubrutinib trials. Moreover, it is preferable to use the longest follow-up data to give the best understanding of the long-term PFS, thus the 31 Mar 2021 and 08 Sept 2020 DCOs were used for the MAIC analysis from the BGB-3111-AU-003 and BGB-3111-206 trials, respectively.[2] A sensitivity analysis using IRC-assessed PFS which relies on an earlier DCO of the two trials (see Table 35) was also explored. Endpoint data for OS was collected alongside PFS for each DCO and as the longest follow-up data for OS was preferred in order to give the best understanding of the long-term survival. Therefore, the 31 Mar 2021 and 08 Sept 2020 DCOs were used for the MAIC analysis from the BGB-3111-AU-003 and BGB-3111-206 and trials, respectively.

Table 35: Availability of endpoint data from the trials

Endpoints	Zanubrutinib: BGB-3111-AU-003	Zanubrutinib: BGB-3111-206	Ibrutinib, Rule *et al.* (2017b)
PFS-IRC	1. DCO: 13 Dec 2018 and follow-up: 18.84 months[44]	2. DCO: 15 Feb 2019 and follow-up: 18.4 months[32]	NR – PFS not reported by IRC
PFS-INV	**1. DCO: 31 Mar 2021 and follow-up: 38.92 months**[43]	2. DCO: 31 Aug 2019 and follow-up: 24.84 months[44] **3. DCO: 08 Sept 2020 and follow-up: 35.25 months**[42]	Median duration of follow-up for PCYC-1104, SPARK and RAY was 15.5, 14.9 and 20 months, respectively. Follow-up not reported by PFS or OS endpoints.
OS	**1. DCO: 31 Mar 2021 and follow-up: 38.92 months**[43]	2. DCO: 31 Aug 2019 and follow-up: 24.84 months[44] 3. **DCO: 08 Sept 2020 and follow-up: 35.25 months**[42]	

CSR – clinical study report; DCO – data cut-off; INV – investigator; IRC – independent review committee; NR – not reported; OS – overall survival; PFS – progression-free survival
DCO in **bold** are used for zanubrutinib in the base case analysis. The 31 Mar 2021 and 08 Sept 2020 DCOs were used for the PFS and OS endpoints of the AU-003 and 206 trials, respectively.
Source: BGB-3111-206 CSR (DCO: 15Feb2019)[32], BGB-3111-206 CSR (DCO: 31Aug2019)[44], BGB-3111-206 CSR (DCO: 08Sept2020)[42], BGB-3111-AU-003 CSR (DCO: 13Dec2018)[44], BGB-3111-AU-003 CSR (DCO:31Mar2021)[43], PCYC-1104, SPARK[54], RAY-MCL3001[55]

B.2.9.4 Methodology

As the zanubrutinib trials were both single arm, it was not possible to perform an anchored MAIC and hence an unanchored MAIC was conducted following the NICE DSU guidelines and method described by Signorovitch *et al.*[52,56] This process involved three key steps:

1. Deriving balancing weights for patients in the pooled zanubrutinib population from AU003-206 to match the key population characteristics with prognostic or effect modifying potential the in ibrutinib population using a logistic regression model.

2. Applying balancing weights derived in Step 1 to obtain adjusted outcomes for patients in the pooled zanubrutinib population from AU003-206 to calculate the effective sample size (ESS).

3. Estimating the relative treatment effect between the re-weighted pooled zanubrutinib population from AU003-206 and the ibrutinib population.

Further details on the MAIC methodology are included in Appendix M.

Covariate selection and weighting

The selection of covariates for weighting was informed by a review of the data availability in AU003-206 trials and the ibrutinib study (Rule *et al.* [2017b]),[17] the impact on ESS and UK clinical experts' opinion (at an advisory board conducted on the 11th November 2024).[2]

UK clinical experts opinion highlighted the following covariates as key determinants of prognosis or treatment effect:[2]

- Response to first-line therapy
- Number of prior lines of therapy
- Time from initial diagnosis
- Blastoid status
- ECOG PS
- Ki67
- Mantle Cell Lymphoma International Prognostic (MIPI) index
- Presence of bulky disease
- Presence of extranodal disease
- Prior lenalidomide therapy
- Prior rituximab therapy
- Age

- Gender

The following covariates were highlighted as less important:

- Stage
- Prior stem cell transplant
- GI involvement
- Bone marrow involvement

Covariate data for the ibrutinib pooled population were generated from the baseline characteristics retrieved from either the Rule *et al.* (2017b) publication and supplementary materials or the NICE TA502 submission.[4,17] Age, gender, ECOG performance status, MIPI index and extranodal disease data were retrieved from the NICE TA502 submission.[4] Number of prior lines of therapy, blastoid status, prior stem cell transplant, prior lenalidomide therapy, presence of bulky disease and bone marrow involvement were retrieved from Rule *et al.* (2017b).[17]

It was not possible to include the MIPI index covariate within the matching exercise as there were differences in the variable definition cross the data sources. The zanubrutinib trials reported the MIPI index, while the ibrutinib trial reported the simplified MIPI index. Although the two scores broadly generate the similar prognostic categories of MCL, the clinical expert stated that some patients may be categorised differently in each score.[57] The MIPI index is primarily a function of age and ECOG, and given that both covariates could be included within the matching model, the impact of not including MIPI index is expected to be minimal.[57]

Due to lack of data in Rule *et al.* (2017b), it was not possible to match on response to first-line therapy, time from initial diagnosis or Ki67. According to a UK clinical expert's opinion, presence of bulky disease and blastoid status both correlate with Ki67 and could be included within the matching model, thus the impact of not including Ki67 is expected to be minimal.[57]

Almost all patients in Rule et al. (2017b), had received prior rituximab therapy (100% of patients in RAY-MCL3001, 100% of patients in SPARK and 89% of patients in PCYC-1104), compared with 79.7% of patients in the AU003-206 dataset. Therefore,

it was not appropriate to include prior rituximab therapy as a covariate in the analysis due to the lack of overlap in this characteristic across populations. Instead, the impact of this covariate was explored in a scenario analysis using AU003-206 data removing rituximab-naïve patients versus Rule et al, (2017b).

Based on the above, a matching model was conducted using the following variables:

- Age ≥ 65 (%)
- Male (%)
- ECOG (0 vs. ≥1) (%)
- Bulky disease ≥5 cm (%)
- Blastoid variant (Yes, No)
- Extranodal disease (Yes, No)
- Number of prior lines of therapy (<median of 2 vs >= median of 2) (%)
- Prior lenalidomide (Yes, No) (%)

B.2.9.5 Results

The summary of the population characteristics of the pooled zanubrutinib population (both unweighted and weighted) from AU003-206, and the ibrutinib population are presented in Table 36. After matching for selected covariates, the treatment arms were well balanced. A histogram of weights is included in Appendix M. After weighting, the ESS reduced by [redacted]%, demonstrating considerable overlap between the two patient populations.

Table 36: Summary of the population characteristics before and after matching zanubrutinib versus ibrutinib

Covariate	AU003-206 (N=118), unweighted	AU003-206 (ESS=[redacted]), weighted	Ibrutinib, Rule et al. (2017b), n=370
Age ≥ 65 years (%)	39.0	[redacted]	62.4
Sex: Male (%)	75.4	[redacted]	78.0
ECOG-PS = 0 (%)	63.6	[redacted]	43.0
Bulky disease ≥ 5 cm (%)	39.7	[redacted]	49.0

Covariate	AU003-206 (N=118), unweighted	AU003-206 (ESS=[redacted]), weighted	Ibrutinib, Rule et al. (2017b), n=370
Blastoid variant (%)	11.9	[redacted]	12.0
Extranodal disease (%)	60.2	[redacted]	58.0
Number of prior lines of therapy: >=2 (%)	62.7	[redacted]	73.2
Previous chemotherapy: lenalidomide (%)	[redacted]	[redacted]	16.0

cm – centimetres; CSR – clinical study report; DCO – data cut-off; ECOG PS – Eastern Cooperative Oncology Group performance status; ESS – effective sample size; n - number
Source: Tam *et al.,* (2021)[35] / BGB-3111-AU-003 CSR (DCO: 31Mar2021)[43], Song *et al.* (2020)[32] / BGB-3111-206 CSR (DCO: 08Sept2020)[42], Rule *et al.* (2017b)[17]

The MAIC results for PFS and OS, both before and after matching, are summarised in Table 38.

For PFS, both before (HR: [redacted]) and after (HR: [redacted]) matching**,** a statistically significant difference was observed for zanubrutinib compared to ibrutinib. For OS, both before (HR: [redacted]) and after (HR: [redacted]) matching**,** a statistically significant difference was observed for zanubrutinib compared to ibrutinib.

Figure 18 and Figure 19 present the ibrutinib KM curves, and the unweighted and weighted KM curves for zanubrutinib for PFS and OS, respectively. The zanubrutinib weighted KM curves shift downwards from the unweighted KM curves for both PFS and OS, driven primarily by adjustments for age, ECOG PS, level of pretreatment and bulky disease. Patients in the zanubrutinib trials were slightly younger and less frail (based on ECOG PS), were less heavily pretreated and had smaller tumour mass. In addition to the base-case scenario, four other sensitivity analysis using different zanubrutinib datasets were conducted to explore uncertainty in the zanubrutinib treatment effect (Table 37 outlines the patient numbers before and after matching in the various analysis):

1. MAIC using AU003-206 from an earlier data cut (DCO: 13Dec2018-31Aug2019) (N=118)

2. MAIC using AU003-206 (DCO: 08Sept2020) data removing rituximab-naïve patients (N=94)
3. Naïve unadjusted comparison using BGB-3111-AU-003-only (DCO: 31Mar2021) data. It was not possible to conduct a robust MAIC using AU003-only, based on the number of patients in the trial (N=32), which would have placed reliance on a few data
4. MAIC using BGB-3111-206-only (DCO: 08Sept2020) data (N=86)

Table 37: Summary of the population sizes used in the MAIC analysis before and after matching zanubrutinib versus ibrutinib

Trial - population	Trial, N	N upon MAIC adjustment (ESS)	Trial	N
Zanubrutinib			***Ibrutinib***	
Base case analysis and Sensitivity analysis 1 (earlier data cut)				
AU003/206 - full pooled population	118	[redacted]	Rule *et al.* (2017b)[17]	370
Sensitivity analysis 2: Prior rituximab treated only – generalisable population				
AU003/206 (AU-003; 206)	94 (30; 64)	[redacted]	Rule *et al.* (2017b)[17]	370*
Sensitivity analysis 3: BGB-3111-AU-003 vs. Rule 2017b				
BGB-3111-AU-003	32	N/A**	Rule *et al.* (2017b)[17]	370
Sensitivity analysis 4: 206 vs. Rule 2017b				
BGB-3111-206	86	[redacted]	Rule *et al.* (2017b)[17]	370

ESS – effective sample size; N - number
* 358 (96.8%) of patients in the pooled ibrutinib trials had received prior rituximab therapy, as the Company did not have access to the dataset and the majority of patients had received rituximab, the MAIC sensitivity analysis #2 was conducted using the full dataset in Rule *et al.* (2017b)
** It was not possible to conduct a robust MAIC using AU003-only, based on the number of patients in the trial (N=32), which would have placed reliance on a few data
Source: Tam *et al.,* (2021)[35] / BGB-3111-206 CSR (DCO: 08Sept2020)[42], Song *et al.* (2020)[32] / BGB-3111-AU-003 CSR (DCO: 31Mar2021)[43], Rule *et al.* (2017b)

Given there was no significant impact of using a different DCO, and in accordance with feedback received from experts present at a UK advisory board meeting conducted on 11th November 2024, the most recent DCO with a longer study follow-up was preferred.[2] Results from the scenario analysis excluding rituximab-naïve patients from the base-case MAIC were consistent with the base-case results, showing that a potential lack of generalisability of the AU003-206, in the form of prior

rituximab-therapy does not have an impact on the relative effectiveness of zanubrutinib.. The naïve unadjusted comparison using BGB-3111-AU-003 only data yielded PFS and OS results consistent with the base case analysis, confirming that a benefit is observed in the trial population considered more representative of UK clinical practice. Additionally, the BGB-3111-206 only MAIC analysis yielded PFS and OS results consistent with the base case analysis. A further sensitivity analysis was conducted using a leave-one-out method from the base-case scenario which demonstrated that the MAIC results were consistent upon removing any of the covariates. Further details on the MAIC results are included in Appendix M.

Across all sensitivity analyses performed, the results were consistent with the base case with a statistically significant improved PFS and benefit in OS demonstrated for zanubrutinib compared to ibrutinib with comparable point estimates. Appendix M includes supplementary data for the sensitivity analyses (weighted baseline characteristics, histogram of weights and KM plots).

Table 38: Summary of MAIC results

Analysis	PFS		OS	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Base case – AU003-206 (DCO: 31Mar2021/08Sept2020) (N = 118) versus Rule *et al.* (2017b) (N = 370)[a]				
Pre-matching (N=118)	[redacted]	[redacted]	[redacted]	[redacted]
Model (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analyses 1 – AU003-206 from an earlier data cut (DCO:31Aug2019) (N = 118) versus Rule *et al.* (2017b) (N = 370)[b]				
Pre-matching (N=118)	[redacted]	[redacted]	[redacted]	[redacted]
Model (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analyses 2 – AU003-206 removing rituximab-naïve patients (DCO: 31Mar2021/08Sept2020) (N = 94) versus Rule *et al.* (2017b) (N = 370)[a]				
Pre-matching (N=94)	[redacted]	[redacted]	[redacted]	[redacted]
Model (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]

Analysis	PFS		OS	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Sensitivity analysis 3 –BGB-3111-AU-003 only (DCO: 31Mar2021) (N=32) versus Rule *et al.* (2017b) (N = 370)[a]				
Unadjusted (N=32)	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis 4 – BGB-3111-206 only (DCO: 08Sept2020) (N=86) versus Rule *et al.* (2017b) (N = 370)				
Pre-matching (N=86)	[redacted]	[redacted]	[redacted]	[redacted]
Model (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analyses – leave-one-out approach from base-case analysis				
Age omitted (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Sex: Male omitted (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS omitted (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Bulky disease ≥ 5 cm omitted (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Blastoid variant omitted (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Extranodal disease omitted (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior lines of therapy omitted (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Previous chemotherapy: lenalidomide omitted (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]

CI – confidence interval; cm – centimetres; DCO – data cut-off; ECOG PS – Eastern Cooperative Oncology Group performance status; ESS – effective sample size; HR – Hazard ratio; MAIC – matching-adjusted indirect comparison; n – number; OS – overall survival; PFS – progression-free survival

[a]INV-assessed PFS

[b]IRC-assessed PFS

Figure 18: Kaplan-Meier curves of PFS-INV for MAIC

HR – hazard ratio; INV – investigator; MAIC – matching-adjusted indirect comparison; PFS – progression-free-survival
Source: Indirect treatment comparison of zanubrutinib (AU-003-206) (DCO: 31Mar2021/08Sept2020) versus ibrutinib (Rule *et al.* [2017b]) [58]

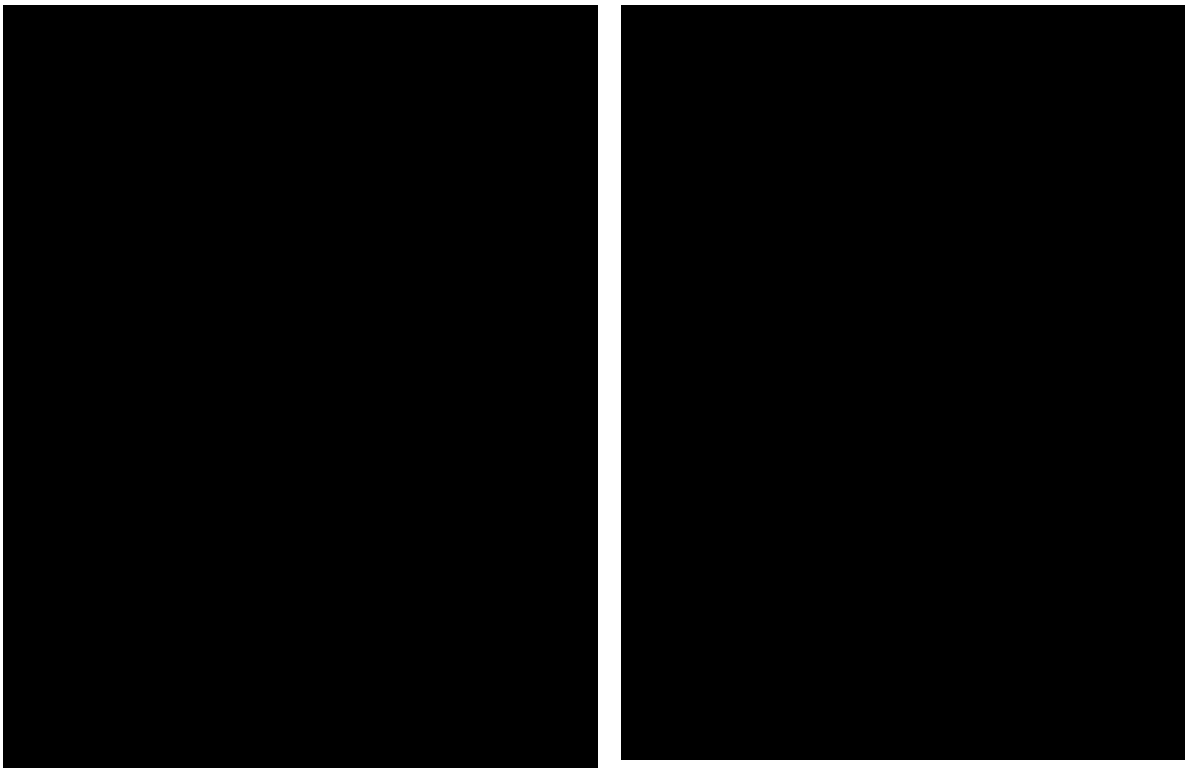
Figure 19: Kaplan-Meier curves of OS for MAIC

HR – hazard ratio; MAIC – matching-adjusted indirect comparison; OS – overall survival
Source: Indirect treatment comparison of zanubrutinib (AU-003-206) (DCO: 31Mar2021/08Sept2020) versus ibrutinib (Rule *et al.* [2017b]) [58]

B.2.9.6 Assessment of proportional hazards

The log cumulative hazard plots and Schoenfeld residuals plots assessing the proportional hazards assumption for the PFS and OS after population adjustment are provided in Figure 20. Initial inspection of the cumulative log-log plots suggests the proportional hazards (PH) assumption can be rejected as the lines cross in both endpoints. In contrast, the Schoenfeld residual plot shows an approximate 0 slope with a p-value>0.05 for both endpoints, suggesting the PH assumption cannot be rejected. Based on the violation of the PH assumption in one of the diagnostic plots reported, it is appropriate to fit independent parametric models (rather than dependent parametric models) to the survival KM data for each both treatment arms for both PFS and OS, see Section B.3.3.1 Time to event analysis for further details.

Figure 20: Cumulative log-log plots (top) and Schoenfeld residual plot (bottom) for OS (left) and PFS (right)



OS – overall survival; PFS – progression-free survival

B.2.9.7 Uncertainties in the indirect and mixed treatment comparisons

An SLR was conducted to identify all relevant publications reporting outcomes for patients treated for R/R MCL who have received treatment with at least one prior line of therapy (see Appendix D for further details). The SLR identified two studies (in four publications) for zanubrutinib (BGB-3111-AU-003 and BGB-3111-206).[32–35] Four studies (in seven publications) potentially relevant to the NICE scope were identified for ibrutinib however, upon assessment only one study was deemed appropriate for inclusion in an ITC (Rule *et al.* [2017b]).[17]

Rule *et al.* (2017b) is a pooled ibrutinib study which included patients from the RCT (RAY-MCL3001) and two single arm studies (PCYC-1104 and SPARK).[17] The data from Rule *et al.* (2017b) is appropriate to the decision problem given it includes the largest patient population available for ibrutinib which is in line with the marketing authorisation of zanubrutinib and considered representative of the UK patient population.

[59]

The leave-one out MAIC analysis showed that upon removal of the 'prior lines of therapy' covariate, the HR is consistent with the base case analysis, demonstrating that the relative difference in zanubrutinib and ibrutinib PFS and OS is consistent in patients in earlier and later lines of therapy, supporting the use of the more complete, full population data from zanubrutinib and ibrutinib trials. Consistent results were observed in the forest plots for patients who were less/more heavily pretreated, as presented in Sections B.2a.7 Subgroup analysis: BGB-3111-AU-003 and B.2b.7 Subgroup analysis: BGB-3111-206 for the BGB-3111-AU-003 and BGB-3111-206 trials, respectively. Given the zanubrutinib trials were not powered to support such analysis, a 2L-only comparison would rely on a small subgroup of zanubrutinib patients (N=44). Given ibrutinib is a relevant comparator in patients at ≥2L (i.e., including 2L and beyond), clinical evidence for ibrutinib and zanubrutinib in patients at ≥2L is the appropriate data to inform decision making.

Dreyling *et al.* (2022)[59], a letter presenting 10-year follow-up of patients in the pooled ibrutinib studies (RAY-MCL3001, PCYC-1104 and SPARK), was identified by clinical experts at an advisory board conducted on the 11th November 2024.[2] PFS and OS KM plots were reported for 2L-only (N=99) and ≥3L (N=271) patients, but not for the full trial population, as such it was not possible to consider this data for a comparison in ≥2L patients (N=370). Dreyling *et al.* (2022) was not identified in the SLR as, being a letter, it did not meet the selection criteria.[59] It would only be possible to adjust for three covariates in a MAIC analysis using the Dreyling *et al.* (2022) dataset as only age, blastoid variant form of MCL and bulky disease are reported. Consequently, any MAIC analysis using Dreyling *et al.* (2022) would not capture important prognostic factors or treatment effect modifiers, identified in the clinically validated list in Section B.2.9.3 Summary of studies included for the ITC.

Having a low ESS for the zanubrutinib arm may introduce uncertainty into the analyses. Therefore, to increase sample size the populations from the BGB-3111-AU-003 and BGB-3111-206 trials were pooled. A sensitivity analysis was conducted using only the BGB-3111-206 trial data. This analysis demonstrated a statistically significant improvement in PFS and OS for zanubrutinib compared to ibrutinib,

consistent with the pooled, base case analysis results. A sensitivity analysis using only the BGB-3111-AU-003 trial was conducted as a naïve, unadjusted analysis, given there were only 32 patients in the BGB-3111-AU-003 trial, a number considered insufficient to inform a MAIC analysis. The unadjusted analysis demonstrates clear improvements in PFS and OS for zanubrutinib compared to ibrutinib, with statistical significance for PFS. According to clinical expert feedback, prior rituximab treatment is an important prognostic factor and treatment effect factor.[2] However, it was not possible to include this covariate in the base-case MAIC due to lack of population overlap. In order to capture the impact of prior rituximab treatment a sensitivity analysis was conducted using the base-case MAIC population with all rituximab naïve patients excluded. This analysis demonstrated a statistically significant improvement in PFS and OS for zanubrutinib compared to ibrutinib.

For the PFS endpoint, differences on the method of assessment (IRC versus INV) may introduce uncertainty into the analyses. However, the sensitivity analyses using PFS-IRC (as opposed to PFS-INV in the base case), demonstrate that regardless of method of PFS assessment, zanubrutinib results in a statistically significant improvement in PFS compared to ibrutinib. Additionally, experts present at a UK advisory board (11th November 2024) confirmed progression is in MCL is particularly apparent, and as such, they expect PFS INV and IRC assessments to produce similar results. For the endpoint of OS, relatively few death events had occurred in BGB-3111-AU-003 and BGB-3111-206. A lack of events may introduce uncertainty into the analysis, however clinical outcomes from both trials support a durable and sustained treatment effect of zanubrutinib, which can increase confidence in MAIC results:

- The follow-up of OS in the BGB-3111-AU-003 and BGB-3111-206 trials was substantially longer than in observed in other ibrutinib trials (RAY-MCL3001 [NCT01646021] PCYC-1104 [NCT01236391] and SPARK [NCT01599949]).
- At 36 months, [redacted]% and 74.8% of patients were alive in BGB-3111-AU-003 and BGB-3111-206, respectively. See Sections B.2a.6.2.2 Overall survival and B.2b.6.2.2 Overall survival for further information.

- A clinically meaningful proportion of patients achieved a partial or complete response in response to treatment across both trials (BGB-3111-AU-003: 84.4%, BGB-3111-206: 83.7%). See Sections B.2a.6.1 Primary and key secondary endpoints: ORR and B.2b.6.1 Primary and key secondary endpoints: ORR for further information.

B.2.9.8 Conclusions

A MAIC comparing zanubrutinib with ibrutinib in patients with R/R MCL was conducted. To increase sample size for the zanubrutinib arm, data from BGB-3111-AU-003 and BGB-3111-206 were pooled. Ibrutinib data were identified through a robust clinical SLR (see Appendix D), and the largest study (n=370) published by Rule *et al.* (2017b)[17] was selected to inform the analysis.

Covariates for matching were selected based on data available and clinical plausibility as validated by UK clinical experts in attendance at an advisory board (11th November 2024), whilst balancing the need to conserve sample size.[2] After matching, the baseline characteristics in AU003-206 were well matched to those reported for the ibrutinib population.

The MAIC analyses consistently demonstrated that treatment with zanubrutinib resulted in a statistically significantly improved PFS and OS compared to ibrutinib. The analysis makes the best use of the data available and is aligned with the NICE DSU guidelines[53] for population adjusted comparisons with the covariate adjustment and outputs validated by UK clinical experts.[2]

The conclusions of the unadjusted and MAIC analysis are consistent with evidence usage of zanubrutinib and ibrutinib in a real-world setting. Phillips *et al.,* (2024) presents a poster of US real-world evidence of time-to-next treatment and OS outcomes in ≥2L patients receiving zanubrutinib versus ibrutinib, both unadjusted and using adjusted approaches.[60] Note time on treatment can be considered a reasonable proxy for progression, as highlighted by clinical experts consulted as part of the advisory board (11th November 2024).[2] Across all time-to-next treatment analyses, a statistically significant HR (zanubrutinib vs ibrutinib) of below 0.7 was estimated and for OS similar (HRs were estimated all below 0.7), with all but the

unadjusted HRs being statistically significant. Crucially, the patients included in this analysis were predominantly 2L at baseline (zanubrutinib: 79%, ibrutininb: 84%), and as such are closely aligned with the population for this appraisal. These real-world outcomes support the conclusion that treatment with zanubrutinib extends time to progression and death when compared to ibrutinib in 2L R/R MCL.

B.2.10 Adverse reactions overview: BGB-3111-AU-003 and BGB-3111-206

Safety analysis from the BGB-3111-AU-003 and BGB-3111-206 trials demonstrated that zanubrutinib in R/R MCL has an acceptable safety and tolerability profile consistent with that observed in other zanubrutinib clinical studies and with the class of BTK inhibitors in general, as well as the disease course of R/R MCL.[42,61–64] The observed AEs were predominantly mild in nature and could be managed with temporary interruptions in treatment. Safety analysis from the BGB-3111-AU-003 and BGB-3111-206 trials demonstrated that zanubrutinib in R/R MCL has an acceptable safety and tolerability profile consistent with that observed in other zanubrutinib clinical studies and with the class of BTK inhibitors in general, as well as the disease course of R/R MCL.[42,61–64] The observed AEs were predominantly mild in nature and could be managed with temporary interruptions in treatment.

B.2a.10 Adverse reactions: BGB-3111-AU-003

The safety results are presented across all patients in the Safety Analysis Set which included those who received at least one dose of study treatment in BGB-3111-AU-003 as of the data cut-off of 31st March 2021.

B.2a.10.1 Dose exposure

At a data cut-off of the 31st March 2021, the median duration of treatment was [redacted] for patients treated with 320 mg of zanubrutinib daily with R/R MCL.[45] The median actual dose intensity was [redacted] mg/day, with a median relative dose intensity of [redacted]%.[45] Among these patients, [redacted] required at least one dose interruption and [redacted] required a dose reduction due to AEs.[45]

B.2a.10.2 Treatment-emergent adverse events

A summary detailing treatment-emergent adverse events (TEAEs) is outlined in Table 38. Whilst [redacted] of patients with R/R MCL experienced at least one TEAE, AEs associated with zanubrutinib were manageable with treatment interruption and supportive care, with [redacted] patients discontinuing zanubrutinib due to treatment-related AEs. A list of the most common AEs is presented in Table 40.

Occurrences of Grade ≥ 3 TEAEs were documented in [redacted] of patients, as presented in Table 41. The most frequently observed Grade ≥3 TEAEs were pneumonia ([redacted]%) and anaemia ([redacted]%).

Table 39: Summary of treatment-emergent and post-treatment AEs in BGB-3111-AU-003

Event	Zanubrutinib (N = 32), n (%)
Patients with at least 1 TEAE	[redacted]
Grade ≥3 TEAEs	[redacted]
Serious TEAEs	[redacted]
TEAEs leading to death	[redacted]
TEAEs leading to study drug discontinuation	[redacted]
TEAEs leading to treatment interruption	[redacted]
TEAEs leading to dose reduction	[redacted]

AE – Adverse event; DCO – data cut-off; n – number; NR – not reported; SAE – serious adverse event
Source: BGB-3111-AU-003 data on file (DCO: 31Mar2021)[45]

Table 40: Treatment-emergent adverse events by system organ class and preferred term reported in BGB-3111-AU-003

System Organ Class Preferred Term	Zanubrutinib (N = 32), n (%)
Patients with at least 1 AE	[redacted]
Gastrointestinal disorders	
Diarrhoea	[redacted]
Constipation	[redacted]
Nausea	[redacted]
Dyspepsia	[redacted]
Gastrooesophageal reflux disease	[redacted]
Abdominal pain	[redacted]
Abdominal pain upper	[redacted]
Hiatus hernia	[redacted]

System Organ Class Preferred Term	Zanubrutinib (N = 32), n (%)
Mouth ulceration	[redacted]
Oral pain	[redacted]
Stomatitis	[redacted]
Vomiting	[redacted]
Infections	
Upper respiratory tract infection	[redacted]
Localised infection	[redacted]
Pneumonia	[redacted]
Urinary tract infection	[redacted]
Nasopharyngitis	[redacted]
Cellulitis	[redacted]
Lower respiratory tract infection	[redacted]
Sinusitis	[redacted]
Conjunctivitis	[redacted]
General disorders and administration site conditions	
Fatigue	[redacted]
Oedema peripheral	[redacted]
Influenza like illness	[redacted]
Chest pain	[redacted]
Peripheral swelling	[redacted]
Pyrexia	[redacted]
Swelling face	[redacted]
Respiratory, thoracic and mediastinal disorders	
Dyspnoea	[redacted]
Cough	[redacted]
Oropharyngeal pain	[redacted]
Pleural effusion	[redacted]
Productive cough	[redacted]
Wheezing	[redacted]
Dyspnoea exertional	[redacted]
Epistaxis	[redacted]
Nasal congestion	[redacted]
Musculoskeletal and connective tissue disorders	
Back pain	[redacted]
Arthralgia	[redacted]
Muscle spams	[redacted]

System Organ Class Preferred Term	Zanubrutinib (N = 32), n (%)
Myalgia	[redacted]
Pain in extremity	[redacted]
Bone pain	[redacted]
Joint effusion	[redacted]
Musculoskeletal chest pain	[redacted]
Muscoluskeletal pain	[redacted]
Skin and subcutaneous tissue disorders	
Rash	[redacted]
Pruritus	[redacted]
Dry skin	[redacted]
Skin lesion	[redacted]
Hyperhidrosis	[redacted]
Rash pruritic	[redacted]
Injury, poisoning and procedural complications	
Contusion	[redacted]
Fall	[redacted]
Procedural pain	[redacted]
Limb injury	[redacted]
Skin laceration	[redacted]
Metabolism and nutrition disorders	
Decreased appetite	[redacted]
Hypokalaemia	[redacted]
Diabetes mellitus	[redacted]
Fluid overload	[redacted]
Hyperkalaemia	[redacted]
Hypermagnesaemia	[redacted]
Hypophosphataemia	[redacted]
Tumour lysis syndrome	[redacted]
Nervous system disorders	
Dizziness	[redacted]
Headache	[redacted]
Presyncope	[redacted]
Burning sensation	[redacted]
Lethargy	[redacted]
Investigations	
Platelet count decreased	[redacted]

System Organ Class Preferred Term	Zanubrutinib (N = 32), n (%)
Blood creatinine increased	[redacted]
Cardiac murmur	[redacted]
Neutrophil count decreased	[redacted]
Blood and lymphatic system disorders	
Anaemia	[redacted]
Neutropenia	[redacted]
Febrile neutropenia	[redacted]
Increased tendency to bruise	[redacted]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Basal cell carcinoma	[redacted]
Melanocytic naevus	[redacted]
Squamous cell carcinoma of skin	[redacted]
Cardiac disorders	
Atrial fibrillation	[redacted]
Pericardial effusion	[redacted]
Renal and urinary disorders	
Haematuria	[redacted]
Acute kidney injury	[redacted]
Micturition urgency	[redacted]
Pollakiuria	[redacted]
Vascular disorders	
Haematoma	[redacted]
Eye disorders	
Vision blurred	[redacted]
Cataract	[redacted]
Dry eye	[redacted]
Psychiatric disorders	
Agitation	[redacted]
Ear and labyrinth disorders	
Ear pain	[redacted]

DCO – data cut-off; n – number; MCL – mantle cell lymphoma; R/R – relapsed/refractory; TEAE – treatment-emergent adverse event
Source: BGB-3111-AU-003 data on file (DCO: 31Mar2021)[45]

Table 41: Treatment-emergent adverse events of Grade 3 or higher by system organ class and preferred term in BGB-3111-AU-003

System Organ Class Preferred Term	Zanubrutinib (N = 32), n (%)
Patients with at least 1 Grade 3 or Higher TEAE	
Infections and infestations	[redacted]
Pneumonia	[redacted]
Cellulitis	[redacted]
Blood and lymphatic system disorders	
Anaemia	[redacted]
Febrile neutropenia	[redacted]
Neutropenia	[redacted]
General disorders and administration site conditions	
Fatigue	[redacted]
Oedema peripheral	[redacted]
Cardiac disorders	
Pericardial effusion	[redacted]
Musculoskeletal and connective tissue disorders	
Myalgia	[redacted]
Metabolism and nutrition disorders	
Tumour lysis syndrome	[redacted]
Renal and urinary disorders	
Acute kidney injury	[redacted]
Respiratory, thoracic and mediastinal disorders	
Pleural effusion	[redacted]
Psychiatric disorders	[redacted]
Agitation	[redacted]
Investigations	
Neutrophil count decreased	[redacted]
Platelet count decreased	[redacted]
Eye disorders	
Cataract	[redacted]

DCO – data cut-off; n – number; MCL – mantle cell lymphoma; R/R – relapsed/refractory; TEAE – treatment-emergent adverse event
Source: BGB-3111-AU-003 data on file (DCO: 31Mar2021)[45]

B.2a.10.3 Serious AEs

Serious TEAEs were reported in [redacted] patients, as presented in Table 39.

B.2a.10.4 Deaths

As of the data cut-off of 31st March 2021, [redacted] patients with R/R MCL had died, [redacted] due to progressive disease, [redacted] due to AEs, [redacted] due to unknown reasons and [redacted] due to other reasons.

B.2b.10 Adverse reactions: BGB-3111-206

The safety results are presented across all patients in the Safety Analysis Set which included those who received at least one dose of study treatment in BGB-3111-206 as of the data cut-off of 8th September 2020.

B.2b.10.1 Dose exposure

The median treatment duration was 27.61 months (range: 0.2, 45.3) for patients treated with zanubrutinib. The median actual dose intensity was 319.61 mg/day, with a median relative dose intensity of 99.87%. Two patients (2.3%) required a dose reduction due to AEs and a total of 24 (27.9%) patients required at least one treatment interruption, 16 (18.6%) due to AEs and 10 (11.6%) due to other reasons.

B.2b.10.2 Treatment-emergent adverse events

A summary detailing TEAEs is outlined in Table 42, 83 (96.5%) patients experienced at least one TEAE, with 50% of TEAEs recorded as Grade 3 or above. AEs associated with zanubrutinib were manageable and reversible with treatment interruption and supportive care, with only eight (9.3%) patients discontinuing zanubrutinib due to treatment-related AEs. A list of the most common AEs is presented in Table 43.

Occurrences of Grade ≥ 3 TEAEs were documented in 50% of patients, as presented in Table 44. The Grade ≥ 3 TEAEs reported most frequently were a decrease in neutrophil count (18.6%), pneumonia (12.8%), a decrease in platelet count (7.0%), a decrease in white blood cell count (7.0%) and anaemia (5.8%).

Table 42: Summary of treatment-emergent and post-treatment adverse events in BGB-3111-206

Event	Zanubrutinib (N = 86), n (%)
Patients with at least 1 AE	83 (96.5)
Grade ≥3 AEs	43 (50.0)
SAEs	25 (29.1)
AEs leading to death	7 (8.1)
AEs leading to study drug discontinuation	8 (9.3)
AEs leading to treatment interruption	16 (18.6)
AEs leading to dose reduction	2 (2.3)
Treatment-related AEs	[redacted]

AE – Adverse event; CSR – clinical study report; DCO – data cut-off; n – number; SAE – serious adverse event
Source: Song et al. (2021)[33] / BGB-3111-206 CSR (DCO: 08Sept2020)[42]

Table 43: Treatment-emergent adverse events by system organ class and preferred term in ≥ 5% of patients (any grade) in BGB-3111-206

System Organ Class Preferred Term	Zanubrutinib (N = 86), n (%)
Treatment-related adverse event	78 (90.7)
Investigations	
Neutrophil count decreased	40 (46.5)
White blood cell count decreased	29 (33.7)
Platelet count decreased	28 (32.6)
Alanine aminotransferase increased	16 (18.6)
Blood urine present	11 (12.8)
Aspartate aminotransferase increased	9 (10.5)
Blood creatinine increased	8 (9.3)
Weight increased	7 (8.1)
Lymphocyte count decreased	5 (5.8)
Infections and infestations	
Upper respiratory tract infection	33 (38.4)
Pneumonia	14 (16.3)
Urinary tract infection	10 (11.6)
Nasopharyngitis	5 (5.8)
Skin and subcutaneous tissue disorders	
Rash	[redacted]
Metabolism and nutrition disorders	
Hypokalaemia	[redacted]
Hyperglycaemia	[redacted]

System Organ Class Preferred Term	Zanubrutinib (N = 86), n (%)
Hyperuricaemia	[redacted]
Gastrointestinal disorders	
Diarrhoea	[redacted]
Constipation	[redacted]
Toothache	[redacted]
Blood and lymphatic system disorders	
Anaemia	15 (17.4)
Thrombocytopenia	8 (9.3)
Leukopenia	[redacted]
Neutropenia	7 (8.1)
General disorders and administration site conditions	
Pyrexia	[redacted]
Respiratory, thoracic and mediastinal disorders	
Cough	[redacted]
Vascular disorders	
Hypertension	13 (15.1)
Psychiatric disorders	
Insomnia	[redacted]
Renal and urinary disorders	
Haematuria	6 (7.0)

CSR – clinical study report; DCO – data cut-off; TEAE – treatment-emergent adverse event
Source: Song et al. (2022b)[34] / BGB-3111-206 CSR (DCO: 08Sept2020)[42]

Table 44: Treatment-emergent adverse events of Grade 3 or higher by system organ class and preferred term in ≥ 2 patients in BGB-3111-206

System Organ Class Preferred Term	Zanubrutinib (N = 86), n (%)
Patients with at least 1 Grade 3 or Higher TEAE	[redacted]
Infections and infestations	
Pneumonia	11 (12.8)
Metabolism and nutrition disorders	
Hyperuricemia	[redacted]
Blood and lymphatic system disorders	
Anaemia	5 (5.8)
Investigations	
Neutrophil count decreased	16 (18.6)
Platelet count decreased	6 (7.0)
White blood cell count decreased	[redacted]

System Organ Class Preferred Term	Zanubrutinib (N = 86), n (%)
Lymphocyte count decreased	[redacted]
General disorders and administration site conditions	
Death	[redacted]
Peripheral swelling	[redacted]
Vascular disorders	
Hypertension	3 (3.5)

CSR – clinical study report; DCO – data cut-off; n – number; TEAE – treatment-emergent adverse event
Source: Song et al. (2022b)[34] / BGB-3111-206 CSR (DCO: 08Sept2020)[42]

B.2b.10.3 Serious AEs

SAEs were reported in 25 (29.1%) patients, as presented in Table 42. The SAEs reported in more than one patient were pneumonia [redacted]%), platelet count decreased ([redacted]%), upper gastrointestinal haemorrhage ([redacted]%) and death ([redacted]%); all other SAEs were reported in [redacted].[42]

B.2b.10.4 Deaths

As of the data cut-off of 8th September 2020, 21 deaths had occurred in the study, of which seven were due to AEs. A total of 13 patients died more than 30 days after their last dose of study drug, which occurred following disease progression (in ten patients), AEs (in one patient) and other reasons (in two patients).

B.2.11 Ongoing studies

There is one ongoing long-term extension trial (BGB-3111-LTE1 [NCT: NCT04170283][65]) of several zanubrutinib trials of B-cell malignancies, including the BGB-3111-AU-003 and BGB-3111-206 trials. Only 12 patients from BGB-3111-AU-003 and 40 patients from the BGB-3111-206 trials were enrolled in the long-term extension trial. The BGB-3111-LTE1 is a safety follow-up and no efficacy outcomes are being collected. Consequently, no efficacy data from BGB-3111-LTE1 is included in this submission.

B.2.12 Interpretation of clinical effectiveness and safety evidence

In the BGB-3111-AU-003 trial, at a median study follow-up period of 18.4 months, patients with R/R MCL treated with zanubrutinib demonstrated an IRC-assessed ORR of 84.4%. Zanubrutinib demonstrated strong and durable PFS and OS with

event-free rates of 73.0% (IRC-assessed) and [redacted]% at 12 months, respectively. DOR and TTR results provide additional evidence of the durable efficacy of zanubrutinib in R/R MCL. Additional data, after a median follow-up of 38.92 months demonstrates consistent results for all key outcomes across data cut. Consistent ORR, PFS, OS, DOR and TTR results were observed in patients 2L-only and ≥2L (full trial population).

In the BGB-3111-206 trial, the primary endpoint was met with zanubrutinib achieving an ORR of 83.7% by IRC assessment, leading to rejection of the pre-specified null hypothesis of 40% with 1-sided p-value < 0.0001. In line with the BGB-3111-AU-003 trial, zanubrutinib also demonstrated strong and durable PFS and OS with event-free rates of 75.5% (IRC-assessed) and [redacted]% at 12 months, respectively. DOR and TTR results further support the durability of zanubrutinib efficacy outcomes in R/R MCL. Additional data, after a median follow-up of 35.25 months demonstrates consistent results for all key outcomes across data cuts. Consistent ORR, PFS, OS, DOR and TTR results were observed in patients 2L-only and ≥2L (full trial population).

Across both BGB-3111-AU-003 and BGB-3111-206, zanubrutinib was shown to be well-tolerated and safe in the treatment of patients with R/R MCL with a safety profile consistent with previously published studies of zanubrutinib in other B-cell malignancies.[61–64]

The AEs were predominantly mild in nature across both trials and could be managed with temporary interruptions in treatment. In the BGB-3111-AU-003 trial, only eight instances of a TEAE leading to treatment discontinuation, and one instance of a TEAE leading to dose reduction were observed. In the BGB-3111-206 trial, only eight instances of TEAE leading to treatment discontinuation and two instances of a TEAE leading to dose reduction were observed.

Data from the Rule et al. (2017b) study was identified as appropriate to inform the comparative efficacy of zanubrutinib versus ibrutinib in patients with R/R MCL. The MAIC demonstrated that treatment with zanubrutinib is associated with a statistically significant [redacted]% reduction in the risk of INV-assessed disease progression or death versus ibrutinib and a statistically significant [redacted]% reduction in the risk of death versus

ibrutinib. Furthermore, the conclusions of the MAIC analyses are consistent with real-world evidence usage of zanubrutinib and ibrutinib, which demonstrate a significant reduction in time-to-next treatment and death, supporting the conclusion that treatment with zanubrutinib extends time to progression and death when compared to ibrutinib in 2L R/R MCL.[60] The analysis makes the best use of the data available, is reflective of treatments patients receive in UK clinical practice and is aligned with the NICE DSU guidelines for population adjusted comparisons with the covariate adjustment. The MAIC outputs were validated by UK clinical experts at an advisory board.[2]

As highlighted in Section B.1.3.6 Unmet need, ibrutinib is the SoC for patients with 2L R/R MCL in the UK. However, ibrutinib is associated with considerable tolerability and cardiac safety concerns. Zanubrutinib has the potential to address the urgent unmet need for improved treatment options for those with 2L R/R MCL. Zanubrutinib offers an effective option with an improved efficacy, tolerability and safety profile compared to ibrutinib.

B.3 Cost effectiveness

The SLR, conducted on 16th May 2024 with an update performed on the 16th July 2024, identified 20 records that met the cost-effectiveness analysis criteria. Five of these studies were conducted in the UK setting, with two studies exclusively focused on Scotland.

The de novo economic model was developed to compare zanubrutinib to ibrutinib for this appraisal and adopted a partitioned survival model (PSM) structure, as aligned with 12 out of the 20 economic models reviewed as part of the economic SLR.

The model adopted a lifetime time horizon and 3.5% discount rate, as per the NICE reference case.[66] A four-week (28 day) cycle length was applied to accommodate the administration schedule of treatment regimens and a half-cycle correction is applied.

Clinical effectiveness was measured using a pooled population of patients with R/R MCL from BGB-3111-AU-003[32] and BGB-3111-206, two single-arm clinical studies for zanubrutinib.[32,34] The pooled data from BGB-3111-AU-003[32] and BGB-3111-206[34] were adjusted for PFS and OS via an unanchored MAIC to match to the pooled PCYC-1104, SPARK and RAY-MCL3001 ibrutinib studies[17], reflecting the comparator within this appraisal.

HRQoL is informed using utility values derived from NICE TA502[4] for each health state. Health-state resource use is also based on inputs that were previously accepted in NICE TA502[4] and costs were sourced from NHS reference costs for 2022/23.

The CEA demonstrates that patients treated with zanubrutinib accrue an additional [redacted] quality-adjusted life years (QALYs) compared to ibrutinib, at a cost saving of £[redacted]. This corresponds to zanubrutinib dominating ibrutinib, at a PAS discount of [redacted]%.

Sensitivity analyses demonstrated that the economic results are robust to changes in key model outputs with zanubrutinib dominating in all scenarios. Moreover, the model was robust to parameter uncertainty with the mean PSA results lying close to the deterministic results for the base-case and for all scenarios considered.

This cost-effectiveness analysis (CEA) can be considered a robust demonstration of the cost-effectiveness of zanubrutinib for patients with 2L R/R MCL. R/R MCL is a

rare form of non-Hodgkin's lymphoma, which has been historically underserved in the UK with no approved treatment options. There is high unmet need for a well-tolerated and effective chemotherapy-free treatment option. Zanubrutinib is a second-generation BTK inhibitor with improved specificity and selectivity over first-generation BTK inhibitors. The clinical community and patient representatives have expressed excitement that zanubrutinib might become accessible to patients in the UK.[2,67]. The CEA utilises the best available data for zanubrutinib.[2] The economic base-case provides a robust estimate of the cost-effectiveness, and across all scenarios modelled, zanubrutinib dominates ibrutinib, contributed to by the substantial Patient Access Scheme (PAS) in place for zanubrutinib. Results are robust to changes in key model parameters, with mean probabilistic sensitivity analysis (PSA) results lying close to the deterministic results for the base-case and for all scenarios considered.

B.3.1 Published cost-effectiveness studies

An SLR was conducted 16th May 2024, and an update was performed on the 16th of July 2024, to identify all relevant cost-effectiveness studies for the treatment of adult patients with R/R MCL. Full details of the process and methods used to identify and select the economic evidence relevant to the technology being evaluated are presented in Appendix G.

The SLR identified 20 records that met the cost-effectiveness analysis selection criteria, however only five considered a perspective relevant to the decision problem (United Kingdom National Health Service and Personal Social Services [UK NHS and PSS]). Therefore, to maximise the available evidence for this submission all papers were extracted.

Among the 20 studies, eight different perspectives were adopted, all directly related to the region and currency the analysis incorporated. Seven studies used Great British Pounds (GBP) for the region and currency; five studies based in the UK and two exclusively focused on Scotland. The five UK based studies adopted the UK NHS and PSS perspective, two NICE submissions and three independent papers[68–70] and the two Scottish focussed HTA submissions adopted the NHS Scotland and

PSS perspective, both identified through the SMC website. Five studies adopted the Canadian healthcare system perspective; three CADTH HTA submissions described it as the Canadian publicly funded healthcare payer perspective,[71–73] one paper described it as the Canadian Ministry of Health and social perspective,[74] and one paper described it as the Canadian healthcare system perspective.[75] The remaining eight studies considered various perspectives (Greek, Australian, Italian, Chinese and US), all of which outlined the adopted perspective as their respective countries healthcare system.[76–83]

All 20 studies reviewed included the R/R MCL patient population as part of their eligibility criteria, with one study also including R/R indolent non-Hodkins lymphoma (iNHL).[74]

Among the 20 studies selected for extraction, five different interventions were evaluated: brexucabtagene autoleucel (brexu-cel), axicabtagene ciloleucel, ibrutinib, zanubrutinib, acalabrutinib and bendamustine plus rituximab (BR). Brexu-cel was assessed in 13 studies reviewed, with two of these also evaluating axicabtagene ciloleucel.[81,82] Ibrutinib monotherapy was assessed in four studies,[4,5,69,73] while zanubrutinib,[71] acalabrutinib,[79] and BR,[74] were assessed in one study each, respectively.

Excluding the CADTH cost-minimisation analysis, the majority of studies reviewed (12 in total) chose a three-state partitioned survival model (PSM) structure, whilst five adopted a three-state Markov model.[4,69,74,81,82] One study selected a three-state de novo health economic model,[5] and one study referred to a three-state decision analytic model.[75]

A summary of identified cost-effectiveness studies is presented in Table 45.

Table 45: Summary list of published cost-effectiveness studies in R/R MCL identified through the SLR

Study	Cost year (currency)	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained, per LYG etc.)
Simons 2021[83] (Article)	2020 (USD)	PSM consisting of three health states; PFS, post-progression and death	Patients with R/R MCL from the ZUMA-2 trial[84]	KTE-X19 -Total QALYs: 7.39 - Pre-progression: 6.63 - Post-progression: 0.81 SoC: - Total QALYs: 3.65 - Pre-progression: 3.30 - Post-progression: 0.35 KTE-X19 versus SoC (incremental): - QALYs: 3.74 - Pre-progression: 3.33 - Post-progression: 0.46	KTE-X19: - Total costs: $693,832 SoC: -Total costs: $574,263	KTE-X19 versus SoC: - $26,479 per LY gained - $31,985 per QALY Univariate sensitivity analyses: - $32,562 per QALY
Ball 2022[75] (Article)	2021 (CAD)	PSM consisting of the three health states; pre-progression, post-progression and death. The model adopted a one-month (30.44 days) cycle length.	ZUMA-2 trial ITT population, including adult patients with R/R MCL after two or more lines of systemic therapy, including a BTKi[84]	Brexu-cel: - Total QALYs: 8.34 - Pre-progression: 6.23 - Post-progression: 2.14 BSC: - Total QALYs: 1.31 - Pre-progression: 1.27 - Post-progression: 0.05 Brexu-cel versus BSC (incremental):	Brexu-cel: - Total costs: CAD 688,040 BSC: - Total costs: CAD 66,108 Brexu-cel versus BSC (incremental): CAD	Brexu-cel versus BSC: CAD 88,503 per QALY

Study	Cost year (currency)	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained, per LYG etc.)
				- QALYs: 7.03 - Pre-progression: 4.97 - Post-progression: 2.09	621,933	
Petersohn 2022[70] (Article)	2021 (GBP)	PSM consisting of three health states; pre-progression, post-progression and death	Patients with R/R MCL from the ZUMA-2 trial safety population (n=68)[84]	KTE-X19: - Total QALYs: 5.99 - Total LYs: 8.27 SoC: - Total QALYs: 1.48 - Total LYs: 1.98 KTE-X19 versus SoC (incremental): - QALYs: 4.52 - LYs: 6.29	KTE-X19: - Total costs: £385,765 SoC: - Total costs: £79,742 KTE-X19 versus BSC (incremental): £306,023	KTE-X19 versus SoC: - Cost per LY: £48,645 - Cost per QALY: £67,713
Loupas, 2022a[80] (Abstract)	2022 (EUR)	PSM consisting of three health states; pre-progression, post-progression and death	Patients with R/R MCL post-BTKi failure	Brexu-cel: - Total QALYs: 5.42 BAT: - Total QALYs: 1.19 Brexu-cel versus BAT (incremental): - QALYs: 4.23	Brexu-cel versus BAT (incremental): €368,851	Brexu-cel versus BAT: - Cost per QALY: €87,281 - Cost per LY: €62,763

Study	Cost year (currency)	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained, per LYG etc.)
Maglinte, 2021[68] (Abstract)	2019 (GBP)	PSM consisting of three health states; pre-progression, post-progression and death. The model adopted a one-month cycle length.	Patients with R/R MCL from the ZUMA-2 trial[84]	KTE-X19: - Total QALYs: 7.06 - Total LYs: 1.21 SoC: - Total QALYs: 1.48 - Total LYs: 1.62	KTE-X19: - Total costs: £399,160 SoC: - Total costs: £46,485	KTE-X19 versus SoC: - Cost per LY: £43,359 - Cost per QALY: £60,314 KTE-X19 versus SoC (PSA): - Cost per QALY: £61,309
Lachaine, 2013[74] (Abstract)	N/R (CAD)	Markov model consisting of three health states: progression-free, PD, and death. The model adopted a one-month cycle length.	Patients with relapsed iNHL and MCL	N/R	N/R	Bendamustine + rituximab versus fludarabine + rituximab: - Cost per QALY: $38,821 (Ministry of Health perspective) - Cost per QALY: $45,809
Tappenden, 2019[69] (Article)	2014/15 (GBP)	Markov model consisting of three health states: progression-free, PD, and death. The model adopted a	Patients with R/R MCL patients in England, Wales and Northern Ireland.	N/R	N/R	Ibrutinib versus R-chemo (EAG's preferred analysis): -Cost per QALY: £63,340 (overall R/R MCL population)

Study	Cost year (currency)	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained, per LYG etc.)
		28-day cycle length.				- Cost per QALY: £44,711 (patients with one prior treatment) Ibrutinib versus R-chemo (following an updated PAS and later data-cut): -Cost per QALY: £62,650 (overall R/R MCL population) - Cost per QALY: £49,848 (patients with one prior treatment)
NICE TA502, 2018[4] (HTA Company submission)	2016 (GBP)	A de novo Markov model with three health states: pre-progression, post-progression, and death. It used 4-week cycle lengths (with half-cycle corrections)	Adult patients with R/R MCL	Redacted	Redacted	Ibrutinib versus R-CHOP: - Cost per QALY: £75,317 Ibrutinib versus R-CVP: - Cost per QALY: £102,062 Ibrutinib versus RC: - Cost per QALY: £99,642

Study	Cost year (currency)	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained, per LYG etc.)
						Ibrutinib versus FCR: - Cost per QALY: £98, 332
NICE TA677, 2021[85] (HTA Company submission)	2018/19 (GBP)	A PSM with three health states: pre-progression (< 5 years and ≥ 5 years), post-progression and death. The model uses a 1-month cycle length	Adults with R/R MCL who have previously received a BTKi	Redacted	Redacted	Redacted
SMC, 2016[5] (HTA Company submission)	N/R (GBP)	A three-state de novo model with three health states, including: PFS, PPS, and Death.	Adult patients with R/R MCL	N/R	N/R	Ibrutinib versus PC with PAS: -Cost per QALY: £41,798
SMC, 2021[86] (HTA Company submission)	N/R (GBP)	A PSM with three health states, including pre-progression, post-progression and Death	Adult patients with R/R MCL after two or more lines of systemic therapy including a BTKi, from the ZUMA-2 trial mITT population[84]	N/R	Total cost per course: - Tecartus: £316,118	Base case results (with PAS): - Tecartus versus SoC, ICER (cost/QALY): £49,711 Tecartus versus SoC (scenario analyses):

Study	Cost year (currency)	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained, per LYG etc.)
						-Costs per QALY range: £48,679 to £75,805
CADTH, 2022[71] (CADTH Pharmacoeconomic review)	N/R (CAD)	The cost-minimisation analysis focused on drug acquisition costs without detailed modelling of health states	Adult patients with R/R MCL who have received at least one prior therapy	N/R	Annual drug costs per patient: - Ibrutinib: $145,759 - Zanubrutinib: $99,256 Incremental drug costs: - Zanubrutinib: -$46,503	N/R
CADTH, 2021[72] (CADTH Pharmacoeconomic review)	N/R (CAD)	PSM including states for PFS, OS, and progression	Adult patients with R/R MCL after treatment with a BTKi	Brexu-cel: -Total QALYs: 8.334 -BSC: - Total QALYs: 1.318 Brexu-cel versus BSC: -Incremental QALYs: 7.02	Brexu-cel: -Total costs: $693,490 BSC: - Total costs: $65,168 Brexu-cel versus BSC: - Incremental costs: $628,322	Brexu-cel versus BSC: - Cost per QALY: $89,557
CADTH, 2016[73] (CADTH Economic guidance report)	2015 (CAD)	PSM with three health states: pre-progression, post-progression, and death	Patients with R/R MCL	Ibrutinib versus SoC (incremental): - QALYs: 0.86 - LYG: 1.10 Ibrutinib versus SoC	Ibrutinib versus SoC (incremental): - Costs: $173,687	Ibrutinib versus SoC: - Submitter estimated: $201,671 per QALY - EGP reanalysis: $264,142 per QALY

Study	Cost year (currency)	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained, per LYG etc.)
				(incremental, EGP reanalysis): - QALYs: 0.646 - LYG: 0.730		
MSAC, 2021[77] (MSAC public summary)	N/R (AUD)	PSM with three health states: pre-progression, post-progression, and death	Patients with R/R MCL who have failed immunochemotherapy (first line) and BTKi therapy (second line), as well as patients who received immunochemotherapy and were considered unsuitable for BTKi therapy due to predicted intolerance	QALYs over 30-year time horizon: - Brexu-cel arm: 5.090 - Salvage therapy arm: 1.191 - Increment: 3.899 LYs over a 30-year time horizon: - Brexu-cel arm: 6.866 - Salvage therapy arm: 1.540 - Increment: 5.327	N/R	N/R
Marchetti, 2022[78] (Abstract)	N/R (EUR)	A PSM was used to extrapolate OS, PFS, quality-adjusted survival, and healthcare costs of R/R MCL patients	Patients with R/R MCL post BTKi treatment	KTE-X19: - Total LYs: 8.85 - Total QALYs: 6.4 R-BAC: -Total QALYs: 1.20 KTE-X19 versus R-BAC:	Total Costs: - KTE-X19: €411,403 - R-BAC: €74,415 - Incremental Difference: €336,988	KTE-X19 versus R-BAC: - Cost per QALY gained: €64,798 - Cost per LYG: €46,264

Study	Cost year (currency)	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained, per LYG etc.)
				- Incremental QALYs: 5.2 **- Incremental LYs: 7.28**		
Chang, 2024[79] (Poster)	N/R (CNY)	A PSM with three health states: PFS, PD, and death. Cycle length of 28 days	Patients with R/R MCL post-BTKi treatment in China	Base case results: - Acalabrutinib QALYs: 3.70 - Ibrutinib QALYs: 2.92 - Incremental QALYs: 0.78	Total costs: - Acalabrutinib: ¥406,587 - Ibrutinib: ¥504,811 - Incremental costs: -¥98,224	Dominant (exact figure N/R)
Loupas, 2022b[80] (Poster)	2022 (EUR)	Three-state PSM was used, with health states including pre-progression, progression, and death	Patients with R/R MCL post-BTKi failure	Brexu-cel: - Total LYs: 7.48 - Total QALYs: 5.42 BAT: - Total LYs: 1.61 - Total QALYs: 1.19 Incremental LYs: 5.88 Incremental QALYs: 4.23	Total costs: - Brexu-cel: €412,880 - BAT: €44,029 - Incremental: €368,851	Brexu-cel versus BAT: - Incremental cost per LY gained: €62,763 - Incremental cost per QALY gained: €87,281 Brexu-cel versus BAT (applying pricing provisions for public hospitals): - Incremental cost per LYG: €54,291 - Incremental cost per QALY gained: €75,499
Ghanem, 2022a[81] (Abstract)	N/R (USD)	A three-state Markov model with health states including PFS, progression, and	Patients with R/R MCL	Axicabtagene ciloleucel: - Discounted LYs: 9.49 Brexu-cel:	Discounted lifetime costs: - Axicabtagene ciloleucel: $630,890.49 - Brexu-cel:	Axicabtagene ciloleucel versus SoC: - Cost per LYG: $41,255.91

Study	Cost year (currency)	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained, per LYG etc.)
		death. The cycle length is 1 month		- Discounted LYs: 8.99 SoC: - Discounted LYs: 2.6	$673,009.59 - SoC: $346,637.27	Brexu-cel versus SoC: - Cost per LYG $51,075.48
Ghanem, 2022b[82] (Poster)	N/R (USD)	A three-state Markov model with health states including PFS, progression, and death. The cycle length is 1 month	Patients with R/R MCL	N/R	Model results costs: - Axicabtagene ciloleucel: $630,890.49 - Brexu-cel: $673,009.59 -SoC: $346,637.27 - Total Cost: $673,009.59	SoC versus brexu-cel: - Incremental cost per LYG: $51,075 SoC versus Axicabtagene: - Incremental cost per LYG: $41,256 Axicabtagene versus brexu-cel: - Incremental cost per LYG: -$84,238

AUD – Australian Dollar; BAT – best alternative treatment; brexu-cel – brexucabtagene autoleucel: BSC – best supportive care; BTKi – Bruton's tyrosine kinase inhibitor; CAD – Canadian Dollar; CADTH – Canadian Agency for Drugs and Technologies in Health; CNY – Chinese Yen; CVP – cyclophosphamide, vincristine sulfate and prednisone; EAG – evidence assessment group; EGP – economic guidance panel; EUR - Euro; FC – fludarabine and cyclophosphamide; FCM – fludarabine, cyclophosphamide and mitoxantrone; FCR – fludarabine, cyclophosphamide and rituximab; FR – fludarabine and rituximab; GBP – Great British Pound; HTA – health technology assessment; ICER - incremental cost-effectiveness ratio; iNHL – indolent non-Hodgkin's lymphoma; ITT – intention-to-treat; KTE-X19 – brexu-cel: LOT – line of therapy; LY – life year; LYG – life years gained; MCL – mantle cell lymphoma; mITT – modified intention-to-treat; MSAC – Medical Services Advisory Committee; NICE – National Institute of Health and Care Excellence: N/R – not reported; OS – overall survival; PAS – patient access scheme; PC – physicians choice; PD – post-progression; PFS – progression-free survival; PPS – post-progression survival; PSA – probabilistic sensitivity analysis; PSM – partitioned survival model; QALYs - quality-adjusted life years; R-BAC - R-bendamustine, and rituximab, cyclophosphamide, doxorubicin, vincristine plus prednisolone; RC - rituximab and cytarabine; R-CHOP – rituximab, cyclophosphamide, doxorubicin hydrochloride; R-CVP – rituximab, cyclophosphamide, vincristine and prednisolone; R/R – relapsed/refractory; SMC – Scottish Medicines Consortium; SoC – standard of care; US – United States; USD – United States Dollar

B.3.2 Economic analysis

As described in Section B.3.1 Published cost-effectiveness studies, the SLR identified 20 relevant economic studies which revealed the use of four different economic model structures for treatment of R/R MCL. All models used either a Markov, PSM, de novo or decision analytic model approach with three health states, progression-free, post-progression and death, to evaluate the cost-effectiveness of interventions of R/R MCL.

Of the 20 identified economic models reviewed, 12 adopted a three-state PSM structure for their economic analysis, and this informs the choice of PSM model structure for this submission. Among the 12 studies adopting a PSM structure, three adopted a UK NHS and PSS perspective (Petersohn *et al.*, Maglinte and the NICE TA677 submission)[68,70,85] and one adopted a Scotland and PSS perspective (SMC 2021 submission).[86]

The 12 studies adopting a PSM structure investigated the cost-effectiveness of either brexu-cel (11 studies) or ibrutinib (one study).

A de novo economic model was developed for this submission because no existing CEA directly compared zanubrutinib with ibrutinib in 2L R/R MCL. This model is essential to evaluate the cost-effectiveness of zanubrutinib versus ibrutinib in England and Wales.

For advanced and metastatic cancers, the PSM approach is the most commonly used modelling approach to capture the progressive nature of the condition and is a well-established model framework to assess the cost-effectiveness of oncology treatments. Furthermore, the PSM approach is routinely used to inform reimbursement decisions in oncology and it is the most commonly adopted approach for NICE appraisals of advanced or metastatic cancers, accounting for 73% of the oncology appraisals in a recent review for NICE DSU TSD 19.[87,88]

As discussed, PSMs are well understood, partly due to the frequency in which they are used in NICE submissions, but mainly due to their intuitive structure and the

ease of interpreting outcomes (which are usually linked to trial endpoints, OS and PFS).

A PSM is consistent with the approach adopted and accepted by the NICE committee in previous MCL and zanubrutinib NICE health technology assessment submissions (NICE TA677, brexucabtagene autoleucel for treating R/R MCL[85]; NICE TA833, zanubrutinib for treating Waldenstrom's macroglobulinaemia; NICE TA931, zanubrutinib for treating chronic lymphocytic leukaemia, NICE TA1001, zanubrutinib for treating relapsed or refractory marginal zone lymphoma).[51,64,85,89] Although in NICE TA502 the company adopted a Markov model approach to evaluate the cost-effectiveness of ibrutinib in R/R MCL, the EAG noted that the Markov-approach imposes several structural constraints and instead undertook a partitioned survival analysis of their own.[4] Given the EAG's position in TA502, it was concluded that this CEA would adopt a three-state PSM structure. The choice of model structure was validated by clinical and economic experts in attendance at a UK advisory board (11th November 2024) held by the Company, with the model structure deemed suitable for decision making. Additionally, Section B.3.2.5 Model conceptualisation and justification of approach details a more in-depth rationale and model choice justification.

The key characteristics of this economic analysis, in comparison to previous NICE technology evaluations for R/R MCL are presented in Table 46.

Table 46: Features of the economic analysis

Factor	Previous evaluations		Current evaluation	
	TA502[4]	**TA677[85]**	**Chosen values**	**Justification**
Modelling approach	Markov health-state structure, comprising three health states: pre-progression, post-progression and death.	Three-state PSM, comprising three health states: pre-progression, post-progression and death.	Three-state PSM, comprising three health states: PF, PD and death.	PSMs are considered standard practice, with 73% of recent oncology appraisals in the UK assessed using this structure.[90] A PSM structure also aligns with a recent positive MCL appraisal and zanubrutinib NICE appraisals.[51,64,85]
Approval population	Adult patients with R/R MCL.	Adults with R/R MCL who have previously received a BTKi.	Adults with 2L R/R MCL.	To reflect the population zanubrutinib would be used in R/R MCL in UK clinical practice (please refer to Section B.1.1 Decision problem for additional rationale) and validated by clinical experts consulted as part of an advisory board.[2]
Intervention	Ibrutinib	KTE-X19 (brexu-cel)	Zanubrutinib	-

Factor	Previous evaluations		Current evaluation	
	TA502[4]	TA677[85]	Chosen values	Justification
Comparators	• R-CHOP (Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) • R-CVP (Rituximab, cyclophosphamide, vincristine and prednisolone) • FCR (Fludarabine, cyclophosphamide and rituximab) • RC (Rituximab and cytarabine)	• Chemotherapy with or without rituximab • Allogeneic haematopoietic stem cell transplant (AHSCT)	Ibrutinib	In line with the relevant comparators in the final NICE scope (please refer to Section B.1.1 **Decision problem**, description of the technology and clinical care pathway for additional rationale).[91]
Perspective	UK NHS and PSS	UK NHS and PSS	UK NHS and PSS	As per NICE reference case.[66]
Time horizon	15 years	Lifetime horizon (50 years)	Lifetime horizon (32 years)	As per NICE reference case.[66]
Cycle length	28 days	1 month (30.44 days)	28 days	Consistent with the design of the zanubrutinib clinical trials (BGB-3111-AU-003 and BGB-3111-206), which use a period of 4 weeks for drug administration cycles. See Section B.2 **Clinical effectiveness** for further details.
Discount rate	3.5%	3.5%	3.5%	As per NICE reference case.[66]
Half-cycle correction	Yes	No, KTE-X19 acquisition and administration costs are not half-cycle corrected	Yes	The model calculated mid-cycle estimates in each health state by taking the average of patients present at the beginning and end of each cycle.

Factor	Previous evaluations		Current evaluation	
	TA502[4]	**TA677[85]**	**Chosen values**	**Justification**
		Yes, all other costs and outcomes – i.e. those captured after the initial model cycle – are half-cycle corrected		
Source of clinical efficacy	Pooled data from RAY (MCL3001), PCYC-1104 and SPARK (MCL2001)[17], and comparator data from the HMRN registry data[92]	Sourced from the Phase II ZUMA-2 study (Wang et al., NEJM 2020)[93] Comparator data was sourced from the literature base and subsequent ITC	Pooled R/R MCL data from BGB-3111-AU-003 March 2021 DCO and BGB-3111-206 September 2020 DCO, and comparator data from the pooled data of RAY (MCL3001), PCYC1104 and SPARK (MCL2001)[17]	PFS, OS and TTD were derived from pooling the BGB-3111-AU-003 and BGB-3111-206 trials for zanubrutinib. Comparator data were used in the unanchored MAIC comparing ibrutinib with zanubrutinib. See Section B.2 Clinical effectiveness for justification of these data sources.
Safety	Pooled data from RAY (MCL3001), PCYC-1104 and SPARK (MCL2001)[17], published literature, clinical expert input	Sourced from the Phase II ZUMA-2 study (Wang et al., NEJM 2020[93])	Pooled data from BGB-3111-AU-003 December 2021 DCO and BGB-3111-206 September 2020 DCO and comparator data from NICE TA502[4]	Safety outcomes were derived from pooling the BGB-3111-AU-003 and BGB-3111-206 trials for zanubrutinib. See Section B.2 **Clinical effectiveness** further details. Safety outcomes for the comparator were taken from pooled data from NICE TA502.[4]

Factor	Previous evaluations		Current evaluation	
	TA502[4]	**TA677[85]**	**Chosen values**	**Justification**
Utilities	EQ-5D-5L data collected from RAY (MCL3001)[36] and SPARK[94]	EQ-5D-5L data collected from Phase II study, ZUMA-2.[84] Mapped to EQ-5D-3L equivalent utility estimates, using the van Hout algorithm (pre-progression values only).[95]	Sourced from the NICE TA502 ibrutinib submission[4]	Utility data were not collected in the BGB-3111-AU-003 and BGB-3111-206 trials, and alternative sources from the economic SLR contained appropriate health state utility value inputs (in NICE TA502). Thus, the values were aligned with data used in a previously successful NICE submission in the same indication (NICE TA502).[4]
Costs	• Treatment acquisition and administration costs • Health state unit costs • Adverse events costs • Terminal care costs	• Treatment acquisition and administration costs • Health state unit costs • Adverse events costs • Terminal care costs	• Treatment acquisition and administration costs • Subsequent treatment costs • Health state unit costs • Adverse events costs • Terminal care costs • Source of cost data included NHS reference costs, BNF, PSSRU	As per NICE reference case.[66]

Factor	Previous evaluations		Current evaluation	
	TA502[4]	TA677[85]	Chosen values	Justification
Outcomes	• Total QALYs • ICER per QALY gained • Medical resource and related costs • Intervention-related costs • Disease progression/end-of-life related costs • HRQoL	• Total costs • Total LYG • Total QALYs • Incremental costs • Incremental LYGs and QALYs • ICER per QALY gained	• Total (aggregated and disaggregated) costs • Total LYs and QALYs • Incremental costs • Incremental LYs and QALYs • ICER per QALY gained	In line with the final NICE scope for this appraisal and the NICE reference case.[66,91]
Uncertainty	• Probabilistic sensitivity analysis (PSA) • One-way sensitivity analysis (OWSA) • Scenario analysis	• PSA • OWSA • Scenario analysis	• PSA • OWSA • Scenario analysis	As per NICE reference case.[66]

Abbreviations: 2+ - second-line; AHSCT - allogeneic haematopoietic stem cell transplant; BNF – British National Formulary; BTKi – Bruton's tyrosine kinase inhibitor; DCO – data cut off; EQ-5D-3L – EuroQol-5 Dimensions-3 Levels; EQ-5D-5L – EuroQol-5 Dimensions-5 Levels; FCR – fludarabine, cyclophosphamide and rituximab; HMRN – Haematological Malignancy Research Network; HRQoL – health-related quality of life; ICER – incremental cost-effectiveness ratio; ITC – indirect treatment comparison; KTA-X19 – brexucabtagene autoleucel; LY – life year; LYG – life year gain; MAIC – matching adjusted indirect comparison; MCL – mantle cell lymphoma; NEJM – New England Journal of Medicine; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; OS – overall survival; OWSA – one-way sensitivity analysis; PD – progressed disease; PF – progression-free; PFS – progression-free survival; PSA – probabilistic sensitivity analysis; PSM – partitioned survival model; PSS – Personal Social Services; PSSRU - Personal Social Services Resource Use; QALY – quality adjusted life year; RC – rituximab and cytarabine; R-CHOP – rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; R-CVP – rituximab, cyclophosphamide, vincristine and prednisolone; R/R – relapsed / refractory; TA – technology appraisal; TTD – time-to-treatment discontinuation; UK – United Kingdom

B.3.2.1 Patient population

As per Section B.1 Decision problem, description of the technology and clinical care pathway this submission covers part of the technology's marketing authorisation, such that the CEA evaluates the incremental cost-effectiveness of treatment with zanubrutinib compared to ibrutinib in patients with 2L R/R MCL. Given the baseline characteristics and the efficacy endpoint results were consistent for patients 2L-only versus ≥ 2L (full trial population) from the BGB-3111-AU-003 and BGB-3111-206 trials (Sections B.2a.3.4 Patient characteristics, B.2b.3.4 Patient characteristics, B.2a.6 Clinical effectiveness results of the relevant studies: BGB-3111-AU-003 and B.2b.6 Clinical effectiveness results of the relevant studies: BGB-3111-206), the model is based on all patients from the pooled dataset (Section B.2.9.1 Data sources) in order to maximise the patient sample used in the analysis. Furthermore, the BGB-3111-AU-003 and BGB-3111-206 trials were not powered to support efficacy endpoint results by line of therapy. As discussed in Section B.2.9 Indirect and mixed treatment comparisons, in the absence of head-to-head studies for zanubrutinib versus ibrutinib a MAIC analysis was performed to inform the effectiveness inputs for the model. Since the zanubrutinib trial population is adjusted to the ibrutinib trial, the baseline characteristics for the modelled population have been sourced from the ibrutinib technology appraisal for MCL (NICE TA502).[4]

Table 47: Baseline characteristics for modelled population

Characteristic	Mean	Source
Age	68	NICE TA502[4]
BSA (m^2)	1.95	
Proportion male	78%	

BSA – body surface area; m - meter; NICE – National Institute for Health and Care Excellence; SE – standard error; TA – technology appraisal

B.3.2.2 Model structure

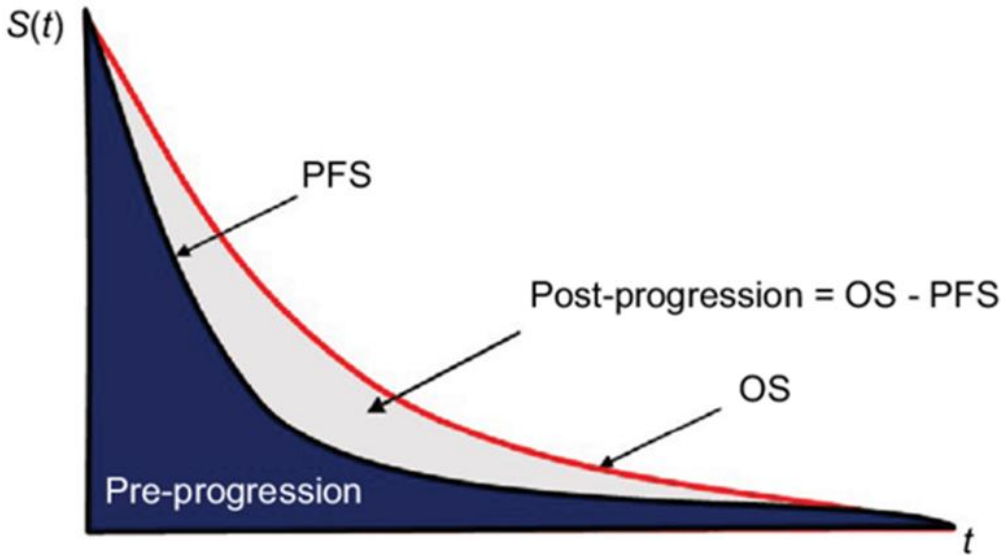
The CEA utilises a PSM structure with three mutually exclusive health states: progression-free (PF), progressed disease (PD), and death, as illustrated in Figure 21. All patients initiate in the PF health state and transition to the PD health state upon disease progression. In a PSM, state occupancy is estimated by extrapolating

trial data for the cumulative probability of PFS and OS for the duration of the time horizon.

A four-week (28 day) cycle length (aligned to the design of the zanubrutinib trials) was used to accommodate the administration schedule of treatment regimens, whilst allowing sufficient granularity to accurately capture differences in cost and health effects between cycles. The model includes a half-cycle correction to account for progression and death events that occur during the 28-day cycle. A lifetime (100 years – baseline age) time horizon allowed long-term treatment costs to be captured.

Total costs of treatments were estimated by combining the proportion of patients in each health state over time with the costs assigned to the respective state. Patients are also assigned a utility value that is associated with their health state. All patients that are in the same health state are assumed to have the same utility value, with the PF health state associated with higher utility than the PD health state. To calculate the ICERs, costs and QALYs were accumulated over the lifetime horizon of the model for each cohort receiving either zanubrutinib or ibrutinib. This data was then used to derive the total costs, total QALYs, and incremental results, including the cost per QALY gained for zanubrutinib compared to ibrutinib. Additionally, the model calculated the cost per life year gained.

Figure 21: Health state structure used in the economic model



OS – overall survival; PD – progressed disease; PF – progression-free; PFS – progression-free survival.

B.3.2.3 Health states

The model structure includes the following health states:

- **PF**: All patients initiate in the PF state and receive treatment until either discontinuation, progression or death. After the first cycle of treatment, patients can discontinue treatment whilst remaining in the PF state until either progression or death. PF captures the costs and consequences of treatment, administration, concomitant therapies and supportive care, monitoring, and adverse events.

- **PD**: The PD state captures patients who have progressed and moved on to a subsequent line of treatment, with patients occupying this health state until death. Therefore, PD captures the costs and consequences of subsequent treatments, monitoring and end of life care.

- **Death**: The death state is an absorbing state, meaning that patients cannot transition out of the health state upon entering.

Overall, the model captures the key elements of care for patients with R/R MCL from the time they begin treatment to when they enter terminal care.

B.3.2.4 Transitions

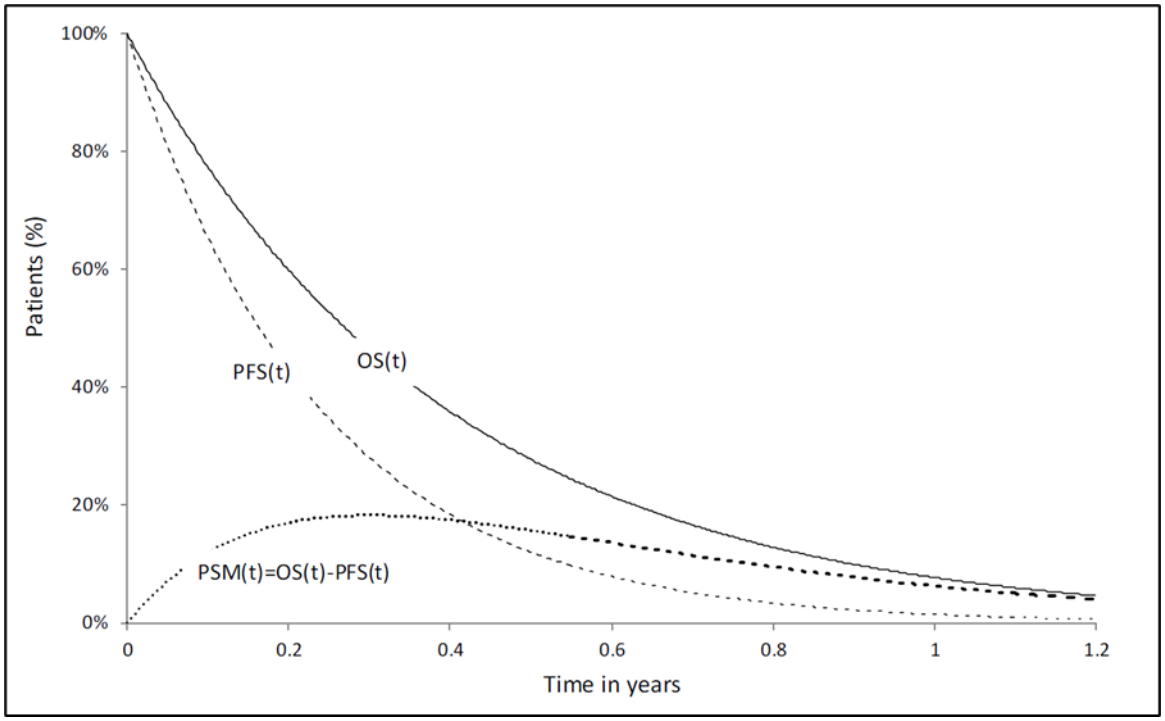
At each model cycle, the number of patients in each independent and mutually exclusive health state is updated with an illustration provided in Figure 22:

- **The proportion of patients who are PF** is represented directly from the PFS(t) curves for each treatment and constrained by OS(t) such that the number of patients who are progression-free cannot exceed the total number of patients alive.

- **The proportion of patients with PD** is calculated by the PSM(t) curve as the difference between OS(t) and PFS(t) to denote all alive patients who are not PF.

- **Death** is calculated as 1-OS(t); that is, all patients who are not alive. In the model, OS(t) is constrained by age- and gender-matched UK general population mortality to ensure the disease-related risk of death does not exceed general population.

Figure 22: Illustration of how the PFS and OS curves are used to estimate health state occupancy in the PSM



OS – overall survival; PFS – progression-free survival; PSM – partitioned survival model
Source: NICE DSU TSD 19 2017[87]

Time on treatment for zanubrutinib and ibrutinib is modelled independently from PFS, allowing patients to discontinue treatment despite remaining in the PF state. The duration of treatment is constrained by PFS, reflecting that zanubrutinib and ibrutinib should be administered until disease progression or unacceptable toxicity, in line with their anticipated and approved license, respectively.[1,96] Clinical experts in attendance at a UK advisory board (11th November 2024) confirmed that the same subsequent treatments (3L+) would be considered for patients following treatment with a BTKi (whether zanubrutinib or ibrutinib). In line with this feedback, subsequent treatment has been modelled equally across both treatment arms, assuming patients in both groups will receive the same therapies following zanubrutinib or ibrutinib. The clinical experts suggested exploring a sensitivity

analysis, including subsequent treatment with CAR-T therapy (brexu-cel), which is presented in Section B.3.11.3 Scenario analysis.

B.3.2.5 Model conceptualisation and justification of approach

The strengths of the partitioned survival approach are well-documented in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 19[87], providing flexibility and directly using time-to-event endpoints available from the clinical trials. The direct reliance of PFS and OS data from trials requires fewer assumptions about the underlying disease process compared with other model approaches.[97] As such, modelling the PFS and OS data as two independent processes allows for a direct calculation of survival without overcomplicating the parameterisation of treatment effectiveness in the model. Overall, the PSM approach is widely used, accepted and understood by health economists and clinicians in oncology, as demonstrated by the cost-effectiveness studies identified in the SLR for this appraisal, with 12 of the 20 studies using a PSM approach.

Furthermore, the PSM approach is routinely used to inform reimbursement decisions in oncology and it is the most commonly adopted approach for NICE appraisals of advanced or metastatic cancers, accounting for 73% of the oncology appraisals in a recent review for NICE DSU TSD 19.[87,88] It is consistent with the approach adopted and accepted by the NICE committee in previous MCL and zanubrutinib NICE health technology assessment submissions (TA677, TA833, TA931 and TA1001).[51,64,85,89] Although in NICE TA502 the company adopted a Markov model approach to evaluate the cost-effectiveness of ibrutinib in R/R MCL, the EAG noted that the Markov-approach imposes several structural constraints and instead undertook a partitioned survival analysis of their own.[4]

As discussed, PSMs are well understood, partly due to the frequency in which they are used in NICE submissions, but mainly due to their intuitive structure and the ease of interpreting outcomes (which are usually linked to trial endpoints, OS and PFS).

The use of a state-transition model (STM) to conduct the CEA would have its own limitations, such as the reliance on post-hoc analysis of PPS and time-to-death

(TTDeath), as well as the long-term extrapolation of such endpoints based on limited events. Critically, it is not possible to inform PPS and TTDeath in an STM in this appraisal as this is not reported in published ibrutinib evidence. The NICE DSU TSD 19 discusses the limitations of the STM, and a comparison of the two model structures has been discussed in detail in a recent NICE appraisals for zanubrutinib (TA833 and TA1001).[51,64,87] Clinician and health economic experts validated the model structure during the advisory board (11th November 2024), as appropriate for decision making.[2]

Therefore, the Company consider the PSM approach to be the most suitable model structure in evaluating the cost-effectiveness of zanubrutinib in 2L R/R MCL.

B.3.2.6 Intervention technology and comparators

The intervention modelled in this CEA is zanubrutinib, administered orally (160 mg twice daily) until disease progression or unacceptable toxicity, as per anticipated licence indication and in line with BGB-3111-AU-003 and BGB-3111-206 trial design.[42,43]

The comparator modelled in this CEA is ibrutinib, administered orally (560 mg once daily) until disease progression or unacceptable toxicity, as per the licensed indication.[96] Ibrutinib is the only appropriate comparator, aligning with BSH 2023 and NICE published guidelines, past NICE and SMC technology appraisals, the current SoC in UK clinical practice and the anticipated place of zanubrutinib in the treatment pathway.[3–6] Moreover, two one-to-one interviews and an advisory board (11th November 2024) with UK clinicians confirmed ibrutinib as the established SoC for the management of 2L R/R MCL.[2,98]

B.3.3 Clinical parameters and variables

Individual survival analyses were required to estimate health state occupancy, as well as to extrapolate the survival curves over the lifetime horizon of the model. The clinical parameters in the model which required survival analyses were: PFS, OS and TTD (for cost calculations only).

B.3.3.1 Time to event analysis

Time to event analysis involved fitting survival functions to patient-level survival data from a pooled population of patients from BGB-3111-AU-003 and BGB-3111-206.[32,34] To maximise the available IPD and increase sample size, BGB-3111-AU-003[32] and BGB-3111-206[34] were pooled, which is consistent with published analyses evaluating outcomes following treatment with zanubrutinib.[49] The pooled data from BGB-3111-AU-003[32] and BGB-3111-206[34] were adjusted for PFS and OS via an unanchored MAIC to match to the pooled PCYC-1104, SPARK and RAY-MCL3001 ibrutinib studies[17], reflecting the comparator within this appraisal (see Section B.2.9 Indirect and mixed treatment comparisons for further details on the MAIC). IPD was adjusted via weights such that the mean baseline characteristics of interest were balanced to those reported in the comparator arm.

In the absence of IPD for the ibrutinib PFS, OS and TTD efficacy endpoints, survival data were reconstructed from published Kaplan-Meier curves, found in the pooled PCYC-1104, SPARK and RAY-MCL3001 ibrutinib studies[17], using a validated two-step approach involving curve digitization and the Guyot algorithm. First, published survival curves were digitized using GetData Graph Digitizer®, extracting coordinates to approximate individual event times. The Guyot algorithm was then applied to reconstruct pseudo-IPD by matching the extracted survival probabilities at each time point with the published survival curve data. This process allowed for the generation of an IPD-based survival curve for ibrutinib that could be compared consistently to zanubrutinib.

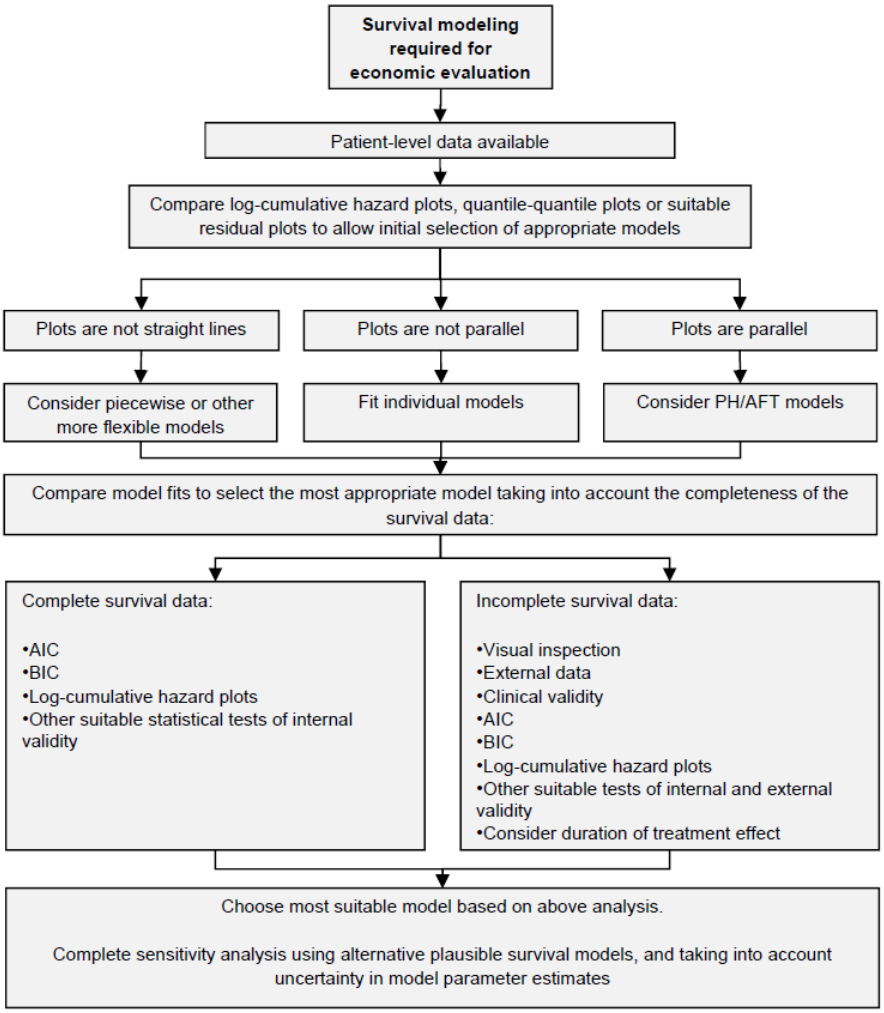
This method is widely accepted for survival curve reconstruction and has been validated to provide reliable approximations when IPD is unavailable, thereby ensuring a robust and comparable estimate of ibrutinib's treatment effect within the economic model.

The survival analysis was conducted in line with the methods recommended by NICE DSU TSD 14[99], using the following distributions: exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma. Given that the zanubrutinib trials were single arm, it was considered appropriate to only fit

independent survival models to the datasets and not consider dependent survival models (which would assume a proportional treatment effect). Additionally, testing of the proportional hazard assumption confirmed its rejection, further supporting the use of independent models, over dependent models, see Section B.2.9 Indirect and mixed treatment comparisons for further details. This decision is consistent with a recent and relevant appraisal for zanubrutinib in R/R MZL (NICE TA1001)[51], whilst also aligning with the feedback received from a survival analysis expert at the advisory board (11th November 2024).[2]

As summarised in Figure 23, the process of selecting a best-fitting distribution involved an assessment of clinical plausibility leveraging clinical expert opinion and comparing to published data (Dreyling et al. 2022[59]), coupled with an assessment of statistical fit via measures such as Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC). The extrapolated curves were also visually compared against BGB-3111-AU-003[32] and BGB-3111-206[34] KM data to assess fit over the observed data period. The most clinically plausible and best-fitting models were selected for the model base-case, with the impact of selecting alternative curves considered in sensitivity analysis.

Figure 23: Survival Model Selection Process Algorithm Presented by NICE DSU TSD-14, and Referenced by Other HTA Agencies



AFT – accelerated failure time; AIC – Akaike information criterion; BIC – Bayesian information criterion; DSU – decision support unit; HTA – health technology assessment; NICE – National Institute for Health and Care Excellence; PH – proportional hazards; TSD – technical support document
Source: NICE DSU TSD-14[99]

B.3.3.2 Progression-free survival

B.3.3.2.1 Zanubrutinib

As per the unanchored MAIC analyses (see Section B.2.9 Indirect and mixed treatment comparisons for further details), extrapolations based on the PFS-INV endpoint were modelled for the zanubrutinib arm using patient level data (PLD) from the pooled BGB-3111-AU-003 and BGB-3111-206 studies (N=118), weighted to the ibrutinib arm sourced from Rule *et al.,* (2017b). For the CEA base-case analysis, the

DCO of March 2021 was used for the BGB-3111-AU-003 study and September 2020 was used for the BGB-3111-206 study.

Assessment of goodness of fit scores

The goodness-of-fit statistics for the PFS-INV endpoint for zanubrutinib is presented in Table 48. Based on both the AIC and BIC statistics, the exponential and generalised gamma distributions provide the best and worst statistical fit, respectively. The Weibull, Gompertz, log-normal and log-logistic distributions are all considered a reasonable statistical fit as they are within five AIC points of the best fitting curve, a criteria used to determine reasonable statistical fit.[100] However, the log-normal and log-logistic appear to have the best statistical fit of these four distributions based on both AIC and BIC.

Table 48: Goodness-of-fit statistics for PFS-INV – zanubrutinib (pooled BGB-3111-AU-003 and BGB-3111-206 trials, N=118, weighted to the ibrutinib arm sourced from Rule 2017b)

Distribution	Zanubrutinib		
	AIC	BIC	Sum of AIC and BIC
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]

AIC – Akaike Information Criteria; BIC – Bayesian Information Criteria; INV – investigator assessed; PFS – Progression-free survival.
Bold indicates the distribution with the best statistical fit.

Fitting of parametric models and visual fit against KM data

The parametric survival extrapolations and KM for PFS for the weighted zanubrutinib analysis is presented in Figure 24. The Gompertz curve provides the most optimistic estimation of PFS. The log-normal, log-logistic and generalised gamma curves all decline at a similar rate over time with [redacted], [redacted] and [redacted] progression-free, respectively, at 10 years. However, it was less significant than the decline observed with the Weibull and exponential estimations, which present the most conservative PFS estimations for patients receiving zanubrutinib. Overall, all of the distributions intersect the KM curve at various points providing a reasonable visual fit. However,

the log-normal, log-logistic and generalised gamma curves provide the closest visual alignment with the KM curve.

Figure 24: KM for PFS-INV overlaid with extrapolated parametric survival curves – zanubrutinib (pooled BGB-3111-AU-003 and BGB-3111-206 trials, N=118, weighted to the ibrutinib arm sourced from Rule 2017b)

INV – investigator assessed; KM – Kaplan Meier; PFS – progression-free survival

An assessment of smoothed hazard plots in Figure 25 demonstrate that hazards for zanubrutinib over time appear to be non-monotonic, i.e. change over time. Therefore, hazards for distributions that can capture a turning point (e.g. AFT models, such as log-normal and log-logistic) are most appropriate for extrapolating PFS. Distributions that assume a constant hazard function or monotonic behaviour (e.g. exponential, Weibull or Gompertz models) cannot capture turning points and are therefore not appropriate for extrapolating PFS.

Figure 25: Smoothed hazard plot for PFS-INV– zanubrutinib (pooled BGB-3111-AU-003 and BGB-3111-206 trials, N=118, weighted to the ibrutinib arm sourced from Rule 2017b)

INV – investigator assessed; KM – Kaplan Meier; PFS – progression-free survival

Long-term clinical plausibility

Sole assessment of the visual and statistical fit was not sufficient to determine the distribution for PFS, therefore, additional clinical validation of landmark survival rates was required. A landmark analysis for the PFS rates for zanubrutinib are presented in Table 49. The clinical experts consulted as part of the advisory board (11th November 2024) provided estimates, based on published data from Dreyling et al.[59], of patients who would be PF at various timepoints (20% at 5 years, 5% at 10 years and 2% at 20 years) following treatment with ibrutinib and commented that that they would expect higher rates of PFS for zanubrutinib at each timepoint, in line with the results from the MAIC analysis (see Section B.2.9 Indirect and mixed treatment comparisons).[2] Upon assessment of the landmark analysis versus the clinical expert estimates for PFS, the exponential and Weibull curves appear to be too conservative particularly at the 20 year timepoint, as both curves estimate that [redacted] of ibrutinib patients will have progressed, whilst clinical experts estimate at least 2% of patients

to be PF at 20 years. The landmark analysis for the remaining curves (log-normal, log-logistic, and generalised gamma) all estimate PFS above the clinician estimates and thus appear to be clinically plausible, with the exception of the Gompertz curve which is likely to be an overestimation of PFS.

Given this, the log-normal, log-logistic, and generalised gamma distributions appear to be the most plausible distributions to model PFS for zanubrutinib.

Table 49: Landmark PFS-INV – zanubrutinib (pooled BGB-3111-AU-003 and BGB-3111-206 trials, N=118, weighted to the ibrutinib arm sourced from Rule 2017b)

Distribution	Median (months)	PFS (%) at landmark timepoints				
		1-year	3-year	5-year	10-year	20-year
KM data	[redacted]	[redacted]	[redacted]	-	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

INV – investigator assessed; KM – Kaplan Meier; PFS – progression-free survival

B.3.3.2.2 Ibrutinib

Extrapolations based on the PFS endpoint were modelled for the ibrutinib arm using data from reconstructed KM sourced from NICE TA502 (N=370) (see further details in Section B.3.3.1 Time to event analysis for methods of reconstruction) a pooled analysis of the three ibrutinib trials (RAY-MCL1001, SPARK and PCYC-1104).[4]

Assessment of goodness of fit scores

The goodness-of-fit statistics for the PFS endpoint for the ibrutinib comparator is presented in Table 50. Based on the AIC and BIC statistics, the generalised gamma and exponential distributions provide the best and worst statistical fit, respectively. The log-normal distribution provides the second-best statistical fit and is the only distribution that is within five AIC points of the best fitting curve. The log-logistic is the third best fitting curve. The exponential, Weibull and Gompertz distributions are all considered an unreasonable statistical fit as they are not within five AIC points of the best fitting curve.[100]

Table 50: Goodness-of-fit statistics for PFS – ibrutinib (pooled RAY-MCL1001, SPARK and PCYC-1104, N=370)

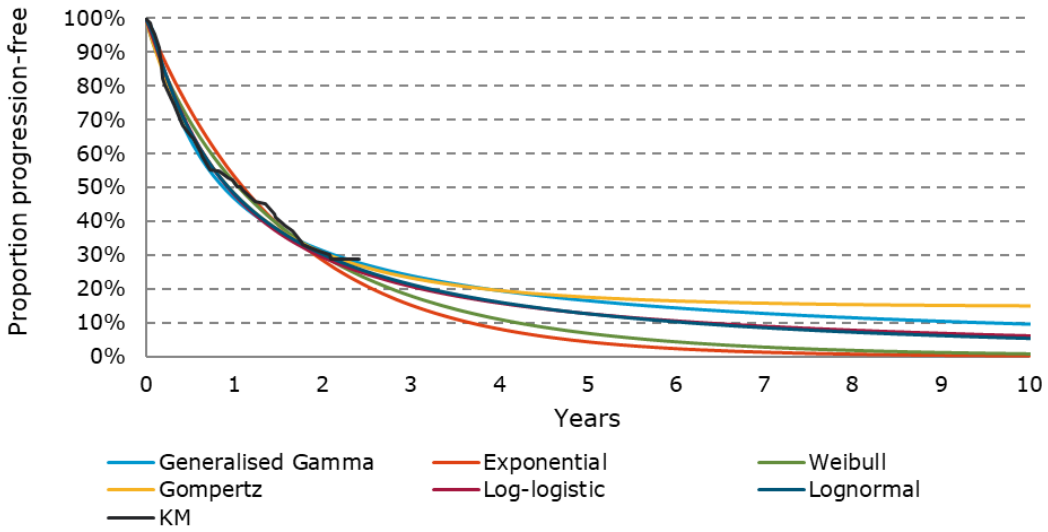
Distribution	Ibrutinib		
	AIC	BIC	Sum of AIC and BIC
Exponential	2132.12	2136.03	4268.14
Weibull	2126.67	2134.50	4261.17
Gompertz	2113.01	2120.83	4233.84
Log-normal	2096.98	**2104.81**	4201.79
Log-logistic	2108.67	2116.49	4225.16
Generalised Gamma	**2093.57**	2105.31	**4198.88**

AIC – Akaike Information Criteria; BIC – Bayesian Information Criteria; PFS – Progression-free survival.
Bold indicates the distribution with the best statistical fit.

Fitting of parametric models and visual fit against KM data

The parametric survival extrapolations and KM for PFS for the pooled ibrutinib analysis is presented in Table 20. The Gompertz curve provides the most optimistic estimation with a PFS plateauing at around 18% by 5 years. In comparison, exponential and Weibull both estimate a PFS of around 0% at 10 years, providing the most conservative estimation. All distributions intersect the KM curve at various time points and appear to provide a good visual fit, with the exception of the Gompertz which assumes an immediate plateau after the follow-up of patients in the trial.

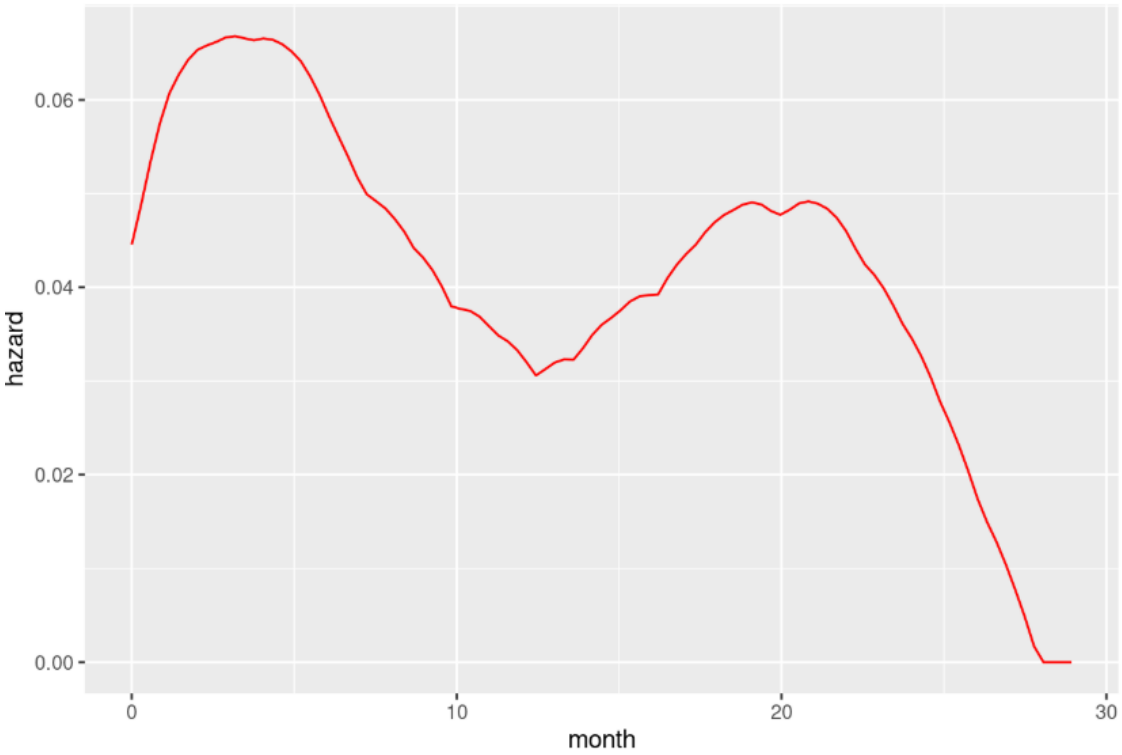
Figure 26: KM for PFS overlaid with extrapolated parametric survival curves – ibrutinib (pooled RAY-MCL1001, SPARK and PCYC-1104, N=370)



KM – Kaplan Meier; PFS – progression-free survival

An assessment of smoothed hazard plots in Figure 27 demonstrate that hazards for ibrutinib over time appear to be non-monotonic, i.e. change over time. Therefore, hazards for distributions that can capture a turning point (e.g. AFT models, such as log-normal and log-logistic) are most appropriate for extrapolating PFS. Distributions that assume a constant hazard function or monotonic behaviour (e.g. exponential, Weibull or Gompertz models) cannot capture turning points and are therefore not appropriate for extrapolating PFS.

Figure 27: Smoothed hazard plot for ibrutinib (pooled RAY-MCL1001, SPARK and PCYC-1104, N=370)



KM – Kaplan Meier; PFS – progression-free survival

Long-term clinical plausibility

Assessment of the visual and statistical fit alone was not sufficient to determine the distribution for PFS, therefore, additional clinical validation of the curve selection was required. Landmark analysis for the PFS rates for zanubrutinib are presented in Table 51. The clinical experts consulted as part of the advisory board (11th November 2024) provided estimates, based on published data from Dreyling et al.[59], for the proportion of ibrutinib patients PF at the following timepoints: 20% at 5 years, 5% at 10 years and 2% at 20 years.[2] All curves appear to give extrapolations in line with the clinical experts estimations, except the exponential, Weibull and Gompertz distributions. The exponential and Weibull distributions estimate that 100% of patients would have progressed at 20 years, which is an underestimation of ibrutinib PFS. Whilst the Gompertz distribution estimates that 4% of patients will be PF at 20 years which is likely an overestimation of ibrutinib PFS. Given this, the log-normal, log-logistic, and generalised gamma distributions appear to be the most plausible distributions to model PFS for ibrutinib.

Table 51: Landmark PFS – ibrutinib (pooled RAY-MCL1001, SPARK and PCYC-1104, N=370)

Distribution	Median (months)	PFS (%) at landmark timepoints				
		1-year	3-year	5-year	10-year	20-year
KM data	13.13	51	-	-	-	-
Exponential	13.80	54	15	4	0	0
Weibull	12.88	52	18	7	1	0
Gompertz	11.96	48	23	16	9	4
Log-normal	11.96	48	21	13	5	2
Log-logistic	11.96	48	21	13	6	2
Generalised Gamma	11.04	47	24	17	9	4

KM – Kaplan-Meier; PFS – progression-free survival

B.3.3.2.3 Summary of selected curves to model PFS

Clinical experts consulted as part of an advisory board (11th November 2024) held by the company recommended that due to the similar mechanism of action between zanubrutinib and ibrutinib, the same parametric survival curves should be selected for both treatment arms.[2] Therefore, in selecting the most appropriate parametric curve the statistical fit, visual fit and clinical plausibility of the extrapolations for PFS in both treatment arms was considered.

Overall, the log-normal distribution was selected for the extrapolation of PFS in the base case. The log-normal distribution provides the second best statistical fit for ibrutinb and a good statistical fit for zanubrutinib. There were no concerns of visual fit for PFS in both arms. In the landmark analysis log-normal curves appears to one of few distributions which are aligned with clinical experts estimates of long-term PFS. Furthermore, the log-normal is an AFT model capable of capturing turning points in hazards, which were observed for PFS in both arms.

The next best fitting curves were log-logistic and generalisation gamma distributions. A sensitivity analysis was conducted using the log-logistic and generalised gamma distributions for PFS in each arm. In the zanubrutinib arm both distributions are within five AIC points to the best statistically fitting curve and are therefore, considered a good statistical fit. In the ibrutinib arm generalised gamma is the best statistically fitting curve. Importantly both curves are able to capture turning points in hazards over time, log-logistic is an AFT model, whilst generalised gamma

distributions can capture both monotonic and non-monotonic hazards. Both curves provided extrapolations in line with clinical experts estimates of long-term PFS. A sensitivity analysis was conducted using these distributions for both zanubrutinib and ibrutinib.

B.3.3.3 Overall survival

B.3.3.3.1 Zanubrutinib

As per the unanchored MAIC analyses (see Section B.2.9 Indirect and mixed treatment comparisons for further details), extrapolations based on the OS endpoint were modelled for the zanubrutinib arm using PLD from the pooled BGB-3111-AU-003 and BGB-3111-206 studies (N=118), weighted to the ibrutinib arm sourced from Rule *et al.* (2017b). As with PFS, DCO's of September 2020 and March 2021 were used for the analysis of BGB-3111-AU-003 and BGB-3111-206 studies, respectively.

Assessment of goodness of fit scores

The goodness-of-fit statistics for the OS endpoint for zanubrutinib is presented in Table 52. Based on both the AIC and BIC statistics, the exponential and generalised gamma distributions provide the best and worst statistical fit, respectively. However, all distributions are considered a reasonable statistic fit as they are within five AIC points of the best fitting curve.[100]

Table 52: Goodness-of-fit statistics for OS – zanubrutinib (pooled BGB-3111-AU-003 and BGB-3111-206 trials, N=118, weighted to the ibrutinib arm sourced from Rule 2017b)

Distribution	Zanubrutinib		
	AIC	BIC	Sum of AIC and BIC
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]

AIC – Akaike Information Criteria; BIC – Bayesian Information Criteria; PFS – progression-free survival.
Bold indicates the distribution with the best statistical fit.

Fitting of parametric models and visual fit against KM data

The parametric survival extrapolations and KM for OS for the weighted zanubrutinib analysis is presented in Figure 28. The log-normal curve provides the most optimistic estimation. The Gompertz, log-logistic and generalised gamma curves decline over time with [redacted], [redacted] and [redacted], respectively, at 20 years. However, it was less significant than the decline observed with the Weibull and exponential estimations, which present the most conservative OS rate for patients receiving zanubrutinib. All distributions intersect the KM curve at various time points and provide a good fit; however, the log-logistic, Gompertz and log-normal curves provide the closest visual alignment with the KM curve.

Figure 28: KM for OS overlaid with extrapolated parametric survival curves – zanubrutinib (pooled BGB-3111-AU-003 and BGB-3111-206 trials, N=118, weighted to the ibrutinib arm sourced from Rule 2017b)

KM – Kaplan Meier; OS – overall survival

An assessment of smoothed hazard plots in Figure 29 demonstrate that hazards for zanubrutinib over time appear to be non-monotonic, i.e. change over time, with multiple turning points. Therefore, hazards for distributions that can capture a turning point (e.g. AFT models, such as log-normal, log-logistic) are most appropriate for extrapolating OS. Distributions that assume a constant hazard function or monotonic behaviour (e.g. exponential, Weibull or Gompertz models) cannot capture turning points and are therefore not appropriate for extrapolating OS.

Figure 29: Smoothed hazard plot for OS– zanubrutinib (pooled BGB-3111-AU-003 and BGB-3111-206 trials, N=118, weighted to the ibrutinib arm sourced from Rule 2017b)

INV – investigator assessed; KM – Kaplan Meier; OS – overall survival

Long-term clinical plausibility

Assessment of the visual and statistical fit alone was not sufficient to determine the distribution for OS, therefore, additional clinical validation of landmark survival rates was required. Landmark OS rates for zanubrutinib are presented in Table 53. The clinical experts consulted as part of the advisory board (11th November 2024) provided estimates, based on published data from Dreyling et al.[59], for patients alive at various timepoints (25% at 5 years, 15% at 10 years and 8% at 20 years) following treatment with ibrutinib. The experts commented that that they would expect a slower decline in patients OS for zanubrutinib at each timepoint compared to ibrutinib, in line with the results from the MAIC analysis (see Section B.2.9 Indirect and mixed treatment comparisons).[2] Upon assessment of the landmark analysis versus the clinical expert estimates for OS, the exponential curve appears to be too conservative particularly at the 20 year timepoint, estimating that [redacted] patients will be alive, whilst clinical experts estimate at least 8% of patients to

be alive at 20 years. The landmark analysis for the remaining curves all estimate OS above the clinician estimates and thus appear to be clinically plausible.

Table 53: Landmark OS – zanubrutinib (pooled BGB-3111-AU-003 and BGB-3111-206 trials, N=118, weighted to the ibrutinib arm sourced from Rule et al. [2017b])

Distribution	Median (months)	OS (%) at landmark timepoints				
		1-year	3-year	5-year	10-year	20-year
KM data	Not reached	[redacted]	[redacted]	-	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

KM – Kaplan Meier; OS – overall survival

B.3.3.3.2 Ibrutinib

Extrapolations based on the OS endpoint were modelled for the ibrutinib arm using reconstructed KM data sourced from Rule 2017b (N=370) (see further details in Section B.3.3.1 Time to event analysis a pooled analysis of the three ibrutinib trials (RAY-MCL1001, SPARK and PCYC-1104).[17]

Assessment of goodness of fit scores

The goodness-of-fit statistics for the OS endpoint for the ibrutinib comparator is presented in Table 54. Based on both the AIC and BIC statistics, the generalised gamma and Weibull distributions provide the best and worst statistical fit, respectively. The log-normal distribution provides the next best fit, based on the AIC and BIC values, as it is within eight and five points of the best-fitting curve. The exponential, Gompertz, Weibull and log-logistic distributions are all considered an unreasonable statistic fit as they are not within five AIC points of the best fitting curve.

Table 54: Goodness-of-fit statistics for OS – ibrutinib (pooled RAY-MCL1001, SPARK and PCYC-1104, N=370)

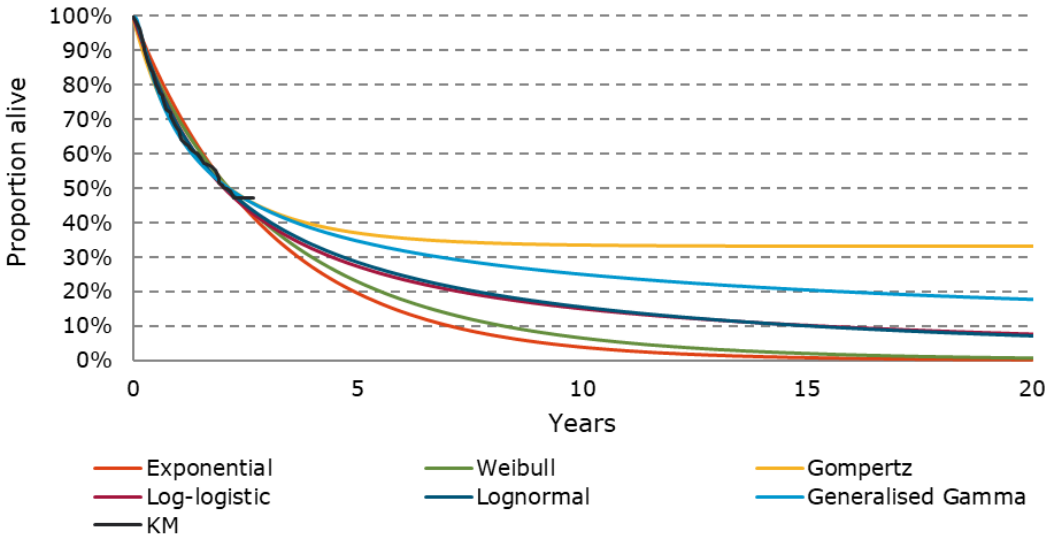
Distribution	Ibrutinib		
	AIC	BIC	Sum of AIC and BIC
Exponential	1829.52	1833.43	3662.94
Weibull	1828.27	1836.10	3664.37
Gompertz	1812.40	1820.22	3632.62
Log-normal	1803.18	1811.01	3614.19
Log-logistic	1814.20	1822.03	3636.23
Generalised Gamma	**1795.70**	**1807.44**	**3603.14**

AIC – Akaike Information Criteria; BIC – Bayesian Information Criteria; OS - overall survival.
Bold indicates the distribution with the best statistical fit.

Fitting of parametric models and visual fit against KM data

The parametric survival extrapolations and KM for OS for the pooled ibrutinib analysis is presented in Figure 30. The Gompertz curve provides the most optimistic estimation with the OS plateauing at around 31% by 10 years. The log-normal, log-logistic and generalised gamma decline over time with 6%, 6% and 11%, respectively, at 20 years. The remaining estimations tend towards zero by 20 years. All distributions intersect the KM curve at various time points; and appear to provide a good visual fit, with the exception of the Gompertz which assumes an immediate plateau after the follow-up of patients in the trial.

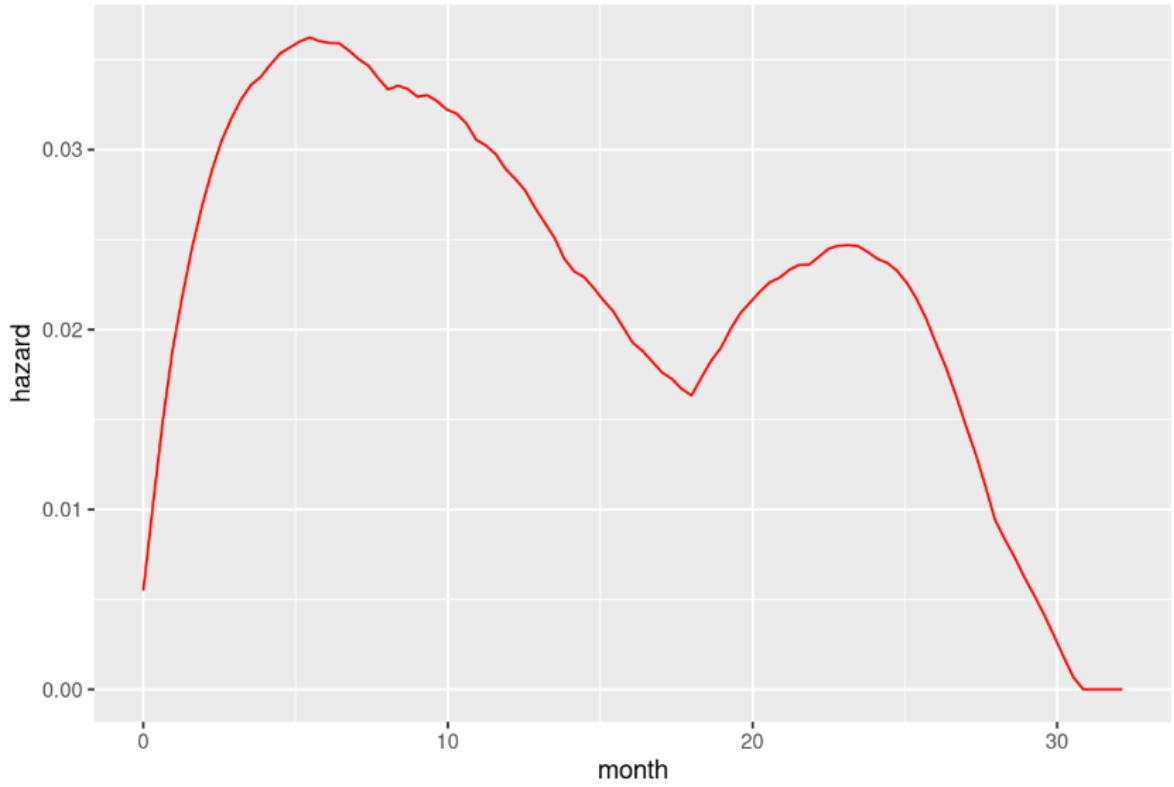
Figure 30: KM for OS overlaid with extrapolated parametric survival curves – ibrutinib (pooled RAY-MCL1001, SPARK and PCYC-1104, N=370)



KM – Kaplan Meier; OS – overall survival

An assessment of smoothed hazard plots in Figure 31 demonstrate that hazards for ibrutinib over time appear to be non-monotonic, i.e. change over time. Therefore, hazards for distributions that can capture a turning point (e.g. AFT models, such as log-normal and log-logistic) are most appropriate for extrapolating OS. Distributions that assume a constant hazard function or monotonic behaviour (e.g. exponential, Weibull or Gompertz models) cannot capture turning points and are therefore not appropriate for extrapolating OS.

Figure 31: Smoothed hazard plot for OS– ibrutinib (pooled RAY-MCL1001, SPARK and PCYC-1104, N=370)



KM – Kaplan Meier; OS – overall survival

Long-term clinical plausibility

Assessment of the visual and statistical fit alone was not sufficient to determine the distribution for OS, therefore, additional clinical validation of the curve selection was required. Landmark analysis for the OS rates for ibrutinib are presented in Table 55. The clinical experts consulted as part of the advisory board (11th November 2024) provided estimates of patients who would be alive at various timepoints (25% at 5 years, 15% at 10 years and 8% at 20 years) following treatment with ibrutinib.[2] The exponential, Weibull, Gompertz and generalised gamma distributions do not appear to provide extrapolations in line with the clinical expert estimations. The exponential and Weibull distributions estimate that almost no patients would be alive at 20 years, which is an underestimation of ibrutinib OS. Whilst the Gompertz, generalised gamma distributions estimates that 14% and 11% of patients will be alive at 20 years, respectively, which is an overestimation of ibrutinib OS. Given this, the log-

normal, log-logistic distributions appear to be the most plausible distributions to model OS for ibrutinib.

Table 55: Landmark OS – ibrutinib (pooled RAY-MCL1001, SPARK and PCYC-1104, N=370)

Distribution	Median (years)	OS (%) at landmark timepoints				
		1-year	3-year	5-year	10-year	20-year
KM data	24.6	67	-	-	-	-
Exponential	25.76	72	38	20	4	0
Weibull	25.76	71	39	23	7	1
Gompertz	26.68	67	44	37	31	14
Log-normal	25.76	68	41	29	16	6
Log- logistic	24.84	69	40	28	15	6
Generalised Gamma	25.76	66	43	35	25	11

KM – Kaplan-Meier; OS – overall survival

B.3.3.3.3 Summary of selected curves to model OS

As with PFS, it was deemed that the same parametric survival curves should be selected for both treatment arms for OS due to the similar mechanism of action between zanubrutinib and ibrutinib, based on clinical expert opinion.[2] Therefore, whilst selecting the most appropriate parametric curve the statistical fit, visual fit and clinician estimate from both treatment arms was considered.

Overall, the log-normal distribution was selected for the extrapolation of OS in the base case. The log-normal distribution provides a good statistical fit for zanubrutinib and is the second-best fitting curve for ibrutinib. The log-normal distribution gives a good visual fit in both arms. In the landmark analysis, the log-normal distribution curves appears to one of few distributions which are aligned with clinical experts estimates of long-term OS, particularly for ibrutinib. Furthermore, the log-normal is an AFT model capable of capturing turning points in hazards, which were observed for OS in both arms. The next best fitting curves were log-logistic and generalisation gamma distributions. A sensitivity analysis was conducted using the log-logistic and generalised gamma distributions for OS in each arm. In the zanubrutinib arm both distributions are within five AIC points to the best statistically fitting curve and are therefore, considered a good statistical fit. In the ibrutinib arm generalised gamma is the best statistically fitting curve. Importantly both curves are able to capture turning

points in hazards over time, log-logistic is an AFT model, whilst generalised gamma distributions can capture both monotonic and non-monotonic hazards. The log-logistic curve provided extrapolations in line with clinical experts estimates of long-term OS, however the generalised gamma curve may over estimate OS for ibrutinib.

B.3.3.4 Time to treatment discontinuation

B.3.3.4.1 Zanubrutinib

Extrapolations based on the TTD endpoint were modelled for the zanubrutinib arm using PLD from the pooled BGB-3111-AU-003 and BGB-3111-206 studies (N=118). As with PFS and OS, DCO's of March 2021 and September 2020 were used for the analysis of BGB-3111-AU-003 and BGB-3111-206 studies, respectively.

Assessment of goodness of fit scores

The goodness-of-fit statistics for the TTD endpoint for zanubrutinib is presented in Table 56. Based on both the AIC and BIC statistics, the generalised gamma distribution provides the best statistical fit. For all other distributions AIC values were greater than five points from the best fitting curve suggesting they are not a reasonable statistic fit.[100]

Table 56: Goodness-of-fit statistics for TTD – zanubrutinib (pooled BGB-3111-AU-003 and BGB-3111-206 trials, N=118)

Distribution	Zanubrutinib		
	AIC	BIC	Sum of AIC and BIC
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]

AIC – Akaike Information Criteria; BIC – Bayesian Information Criteria; TTD – time-to-treatment discontinuation.
Bold indicates the distribution with the best statistical fit.

Fitting of parametric models and visual fit against KM data

The parametric survival extrapolations and KM for TTD for the zanubrutinib analysis is presented in Figure 32. Although each extrapolation intersects the KM curve at least once, none closely align with the KM data or provides an adequate visual fit.

Figure 32: KM for TTD overlaid with extrapolated parametric survival curves – zanubrutinib (pooled BGB-3111-AU-003 and BGB-3111-206 trials, N=118)

KM – Kaplan Meier; TTD – time-to-treatment discontinuation

Long-term clinical plausibility

Clinical validation was performed to understand the appropriateness of the visual assessment. Based on clinical opinion received from the advisory board (11th November 2024), to overcome issues with the poor fit of the TTD extrapolations, TTD was modelled as equal to PFS. Furthermore, it was deemed reasonable to assume patients would receive treatment until progression.[2] Therefore, the model base-case equates TTD to PFS and to explore any uncertainty a scenario models TTD using the KM data from pooled BGB-3111-AU-003 and BGB-3111-206 trials (N=118).

B.3.3.4.2 Ibrutinib

In the base-case, TTD data was sourced from NICE TA502, which in turn is sourced from a pooled analysis of the three ibrutinib trials (RAY-MCL1001, SPARK and PCYC-1104), and were modelled for the ibrutinib arm using reconstruction approach (see further details in Section B.3.3.1 Time to event analysis).[4]

Assessment of goodness of fit scores

The goodness-of-fit statistics for the TTD endpoint for the ibrutinib comparator is presented in Table 57. Based on the AIC and BIC statistics, the generalised gamma distribution provides the best statistical fit (based on summed AIC and BIC). All other distributions are considered an unreasonable statistic fit as they are not within five AIC points of the best fitting curve.[100]

Table 57: Goodness-of-fit statistics for TTD – ibrutinib (pooled RAY-MCL1001, SPARK and PCYC-1104, N=370)

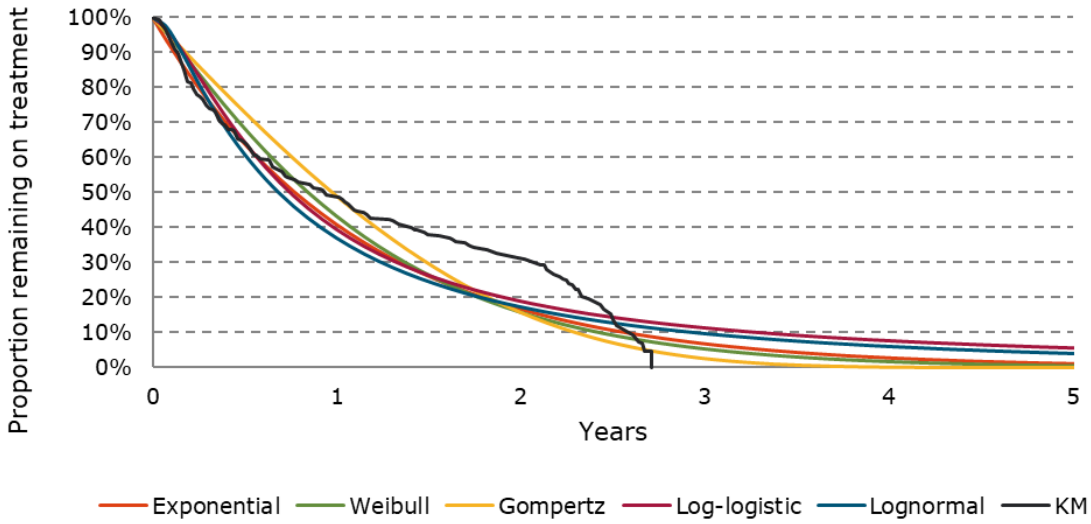
Distribution	Ibrutinib		
	AIC	BIC	Sum of AIC and BIC
Exponential	2724.86	2728.78	5453.64
Weibull	2718.34	2726.17	5,444.51
Gompertz	2689.59	2697.42	5387.01
Log-normal	2771.31	2779.14	5550.45
Log-logistic	2796.76	2804.58	5601.34
Generalised Gamma	**2557.89**	**2569.64**	**5127.53**

AIC – Akaike Information Criteria; BIC – Bayesian Information Criteria; TTD – time-to-treatment discontinuation.
Bold indicates the distribution with the best statistical fit.

Fitting of parametric models and visual fit against KM data

The parametric survival extrapolations and KM for TTD for the pooled ibrutinib analysis is presented in Figure 33. Although each extrapolation intersects the KM curve at least once, none closely align with the KM data or provides an adequate visual fit.

Figure 33: KM for TTD overlaid with extrapolated parametric survival curves – ibrutinib (pooled RAY-MCL1001, SPARK and PCYC-1104, N=370)



KM – Kaplan Meier; TTD – time-to-treatment discontinuation
Note the generalised gamma curve did not converge when fitting the distribution to the KM data, as such the generalised gamma is not presented in the plot

Long-term clinical plausibility

Clinical validation was performed to understand the appropriateness of the visual assessment. Based on clinical opinion received from the advisory board (11th November 2024), to overcome issues with the poor fit of the TTD extrapolations, TTD was modelled as equal to PFS. Furthermore, it was deemed reasonable to assume patients would receive treatment until progression.[2] Therefore, the model base-case equates TTD to PFS and to explore any uncertainty a scenario models TTD using the KM data.

B.3.3.5 Summary of base-case inputs

The data sources and chosen distributions to inform the base case are presented in Table 58. Figure 34 to Figure 36 below present the modelled base-case curves for PFS, OS and TTD by treatment arm. The following adjustments have been made to the curves:

- Restriction of survival by age-gender matched all-cause mortality for both treatment arms, such that the risk of death can never be lower than the risk of general population mortality.[101]
- Restriction of PFS by OS, such that patients cannot be PF for longer than they are alive.

Table 58: Data sources and distributions used to inform base-case clinical parameters

Clinical parameter	Data source	Chosen distribution
PFS: Zanubrutinib	Pooled BGB-3111-AU-003 and BGB-3111-206 for zanubrutinib PFS data, weighted to pooled ibrutinib (RAY-MCL1001, SPARK and PCYC-1104), N=118	Log-normal
PFS: Ibrutinib	Pooled ibrutinib (RAY-MCL1001, SPARK and PCYC-1104) PFS data, N=370	Log-normal
OS: Zanubrutinib	Pooled BGB-3111-AU-003 and BGB-3111-206 for zanubrutinib OS data, weighted to pooled ibrutinib (RAY-MCL1001, SPARK and PCYC-1104), N=118	Log-normal
OS: Ibrutinib	Pooled ibrutinib (RAY-MCL1001, SPARK and PCYC-1104) OS data, N=370	Log-normal
TTD: Zanubrutinib	Pooled BGB-3111-AU-003 and BGB-3111-206 for zanubrutinib PFS data, weighted to pooled ibrutinib (RAY-MCL1001, SPARK and PCYC-1104), N=118	Assumed equal to base case PFS extrapolation
TTD: Ibrutinib	Pooled ibrutinib (RAY-MCL1001, SPARK and PCYC-1104) PFS data, N=370	Assumed equal to base case PFS extrapolation

OS – overall survival; PFS – progression-free survival; TTD – time-to-treatment discontinuation
Source: Rule 2017b[17]

Figure 34: PFS for zanubrutinib and ibrutinib as estimated by the cost-effectiveness model

KM – Kaplan Meier; PFS – progression-free survival

Figure 35: OS for zanubrutinib and ibrutinib as estimated by the cost-effectiveness model

KM – Kaplan Meier; OS – overall survival

Figure 36: TTD for zanubrutinib and ibrutinib as estimated by the cost-effectiveness model

KM – Kaplan Meier; TTD – time-to-treatment discontinuation
Note: TTD for zanubrutinib and ibrutinib is estimated using the base case PFS curves

B.3.4 Measurement and valuation of health effects

As detailed in Section B.1.3.2 Burden of MCL patients with R/R MCL experience a detrimental impact to their HRQoL due to symptom burden and loss of physical health, mobility and vitality.[15] Moreover, MCL affects different aspects of a patient's life including work, mental health, relationships and travel, all of which contribute to a decreasing QoL.[4]

B.3.4.1 Health-related quality-of-life data from clinical trials

No HRQoL data were collected for patients with R/R MCL within the zanubrutinib clinical trials (BGB-3111-AU-003 and BGB-3111-206). In the absence of HRQoL data from the clinical trials, utility values were sourced from the SLR conducted to identify relevant studies reporting the HRQoL of patients with R/R MCL. For further details on the relevant HRQoL data collected from the SLR, see Section B.3.4.3 Health-related quality-of-life studies.

B.3.4.2 Mapping

No mapping has been conducted as HRQoL data were not collected in clinical trials for zanubrutinib.

B.3.4.3 Health-related quality-of-life studies

An SLR was conducted on 16th May 2024, and updated on 16th July 2024, to identify any studies reporting the HRQoL, specifically the utility of patients with R/R MCL and relevant disutility values for the CEA. Full details of the process and methods used to identify and select the economic evidence relevant to the technology being evaluated are presented in Appendix H.

The SLR identified 13 studies reporting on the HRQoL of patients with R/R MCL.

Among the 13 studies selected for extraction, four different interventions were evaluated: liso-cel, brexucabtagene autoleucel (brexu-cel), ibrutinib and acalabrutinib. Brexu-cel was assessed in seven studies reviewed[70,75,77,78,83,85,86], ibrutinib in five[4,5,73,79,102] and liso-cel[103] and acalabrutinib[79] were only assessed in one.

Considering, that the brexu-cel, liso-cel and acalabrutinib treatments are not relevant comparators to the decision problem, only the publications that evaluated ibrutinib's cost-effectiveness are relevant for this appraisal. PFS and PPS EQ-5D utility values relevant to this appraisal were reported in:

- NICE TA502, reported pre-and post-progression utilities as well as the utility decrement associated with R-chem toxicity for patients with R/R MCL treated with ibrutinib.[4]
- Hess 2017, reported mean baseline utility values for patients with R/R MCL treated with ibrutinib.[102]
- SMC 2016, reported the progression-free survival and post-progression utilities for patients with R/R MCL treated with ibrutinib.[5]
- CADTH 2016, reported mean baseline utility values for patients with R/R MCL treated with ibrutinib.[73]

A summary of the relevant identified HRQoL studies is presented in Table 59. A detailed summary of the identified HRQoL studies is presented in Appendix H.

Table 59: Summary of published HRQoL studies

Data source	Patient population	Utility measure	Health state utility value
NICE TA502 2018[4] (HTA Company submission for ibrutinib)	Adult patients with R/R MCL with at least one prior treatment	Elicitation: EQ-5D data collected in clinical trial Evaluation: EQ-5D-5L	Progression-free survival, value, 95% CI: 0.780 (0.762, 0.799) Post-progression, value (95% CI): 0.680 (0.634, 0.727)
Hess 2017[102] (article)	Patients with R/R MCL in the RAY trial (MCL3001)	Elicitation: FACT-Lym and EQ-5D-5L questionnaire Evaluation: EQ-5D-5L, UK TTO weights	Mean baseline utility value, (SD): Ibrutinib: 0.7 (0.2) Temsirolimus: 0.7 (0.2)
SMC 2016[5] (HTA Company submission for ibrutinib)	Adult patients with R/R MCL	Elicitation and evaluation: EQ-5D-5L	Progression-free survival: Ibrutinib: 0.779 PC: 0.730 Post-progression: 0.636
CADTH 2016[73] (CADTH Pharmacoeconomic review of ibrutinib)	Adult patients with R/R MCL from the MCL3001 trial who had received at least one prior rituximab-containing chemotherapy regimen, had documented relapse or disease progression following the last anti-MCL treatment	Elicitation: EQ-5D-5L Evaluation: EQ-5D-5L using UK TTO value set	Mean baseline utility value (SD): Ibrutinib: 0.7 (±0.2) Temsirolimus: 0.7 (±0.2)

CADTH – Canada's Drug and Health Technology Agency; CI – confidence interval; EQ-5D - EuroQol-5 dimensions; EQ-5D-3L – EuroQol-5 dimensions-3 levels; EQ-5D-5L – EuroQol-5 dimensions-5 levels; FACT-Lym – functional assessment of cancer treatment lymphoma; HRQoL – health-related quality of life; HTA – health technology assessment; MCL – mantle cell lymphoma; MSAC – Medical Services Advisory Committee; N/A – not available; N/R – not reported; NICE – National Institute of Health and Care Excellence; QoL – quality of life; R/R - relapsed or refractory; SD – standard deviation; SE – standard error; SMC – Scottish Medicine Consortium; SLR – systematic literature review; TTO – time trade off; UK- United Kingdom; US – United States

B.3.4.4 Age-related disutility

The base case included an age-related adjustment to account for the deterioration in HRQoL with age. The age-related utility adjustment was implemented using the methods described in Hernandez-Alava (2022) and applied to each cycle for the duration of the time horizon, in line with the NICE reference case.[66,104] This approach was validated by clinical experts at an advisory board (11th November 2024).[2]

B.3.4.5 Adverse reactions

The model accounts for the impact of all Grade ≥3 treatment-related AEs occurring in ≥5% of study subjects receiving treatment across treatment arms. The choice of a ≥5% patient threshold is based on the threshold used in TA502[4], which was accepted by the EAG and committee. Moreover, this threshold is sufficient given AEs are not expected to be key model drivers. The Grade ≥3 AEs included in the model are reported in Table 60. During an advisory board (11th November 2024) held by the Company, the clinical experts present agreed with the approach and the AEs included.[2] To inform the zanubrutinib arm, AE rates were derived from the BGB-3111-AU-003 study (DCO: December 2021) and the BGB-3111-206 study (DCO: September 2020) separately and an average rate was calculated.[35,42] To inform the ibrutinib arm, AE rates were derived from NICE TA502[4], which aligns with the efficacy data used in the base-case analysis.

Within the base case, AEs in the model will have an impact on both quality of life and costs. To capture the impact of AEs without adding unnecessary complexity, a simplified assumption was made such that AEs would occur in the first 4 weeks of treatment and costs and QALY losses associated with AEs are applied in the first model cycle only. In addition, only AEs associated with first-line treatment were considered, and AEs associated with subsequent lines were not considered. This assumption is in-line with what has been accepted in previous, relevant appraisals for zanubrutinib (TA833, TA931 and TA1001).[51,64,89]

Table 60: Grade ≥3 treatment-related AEs occurring in ≥5% of patients by treatment arm

Adverse event	Zanubrutinib	Ibrutinib
Pneumonia	[redacted]	8.10%
Anaemia	[redacted]	8.90%
Neutropenia	[redacted]	16.80%
Thrombocytopenia	[redacted]	0.00%
Neutrophil count decreased	[redacted]	0.00%
Platelet count decreased	[redacted]	0.00%
Atrial fibrillation	[redacted]	5.10%
White blood cell count decreased	[redacted]	0.00%
Source	BGB-3111-AU-003 (Tam *et al.* 2021)[35], BGB-3111-206 (CSR)[42]	NICE TA502[4]

AE – adverse event; CSR – clinical study report

B.3.4.5.1 Adverse event disutility

Utility decrements associated with AEs were sourced from the results of the HRQoL SLR detailed in Section B.3.4.3 Health-related quality-of-life studies. The impact of AEs on HRQoL is included in the model by taking the average QALY loss due to AEs for each treatment by considering the treatment-specific AE rates and the mean utility decrements associated with these AEs. All AEs were assumed to occur across the first cycle only.

Table 61: Adverse event disutilities

Adverse event	Disutility	Duration	Source
Pneumonia	0.15	Assumed to occur in the first cycle only	Simons et al (2021)
Anaemia	0.12		Simons et al (2021)
Neutropenia	0.09		Simons et al (2021)
Thrombocytopenia	0.11		Simons et al (2021)
Neutrophil count decreased	0.15		Simons et al (2021)
Platelet count decreased	0.11		Simons et al (2021)
Atrial fibrillation	0.15		Assumed the same at thrombocytopenia
White blood cell count decreased	0.15		Simons et al (2021)

Source: Simons et al 2021[83]

B.3.4.6 Health-related quality-of-life data used in the cost-effectiveness analysis

In the model base-case, the utility values from NICE TA502[4], ibrutinib for treating R/R MCL, are used to inform the HRQoL in the PFS and PD health states in the CEA. The utility values were elicited in the RAY (MCL3001) and SPARK (MCL2001) studies using EQ-5D-5L which is line with the NICE methods. As highlighted in Section B.3.4.3 Health-related quality-of-life studies, the values have been used in multiple other CEAs for patients with R/R MCL, including the NICE TA677[85] for brexucabtagene autoleucel. However, the minimal difference observed in utility scores between the PF and PD health states could lead to an underestimation of the true health utility benefit associated with zanubrutinib. The utility and disutility values applied were deemed appropriate by clinical experts present at an advisory board (November 11th 2024).[2]

To assess any uncertainty in the chosen utility values, scenario analyses were explored using alternative values identified from the HRQoL SLR. Alternative values identified were from the SMC appraisal for ibrutinib in patients with R/R MCL and Simons et al., a study evaluating the cost-effectiveness of KTE-X19 CAR T therapy in patients with R/R MCL.[5,83]

The utilities used in the base case CEA and scenario analyses are presented in Table 62.

Table 62: Summary of utility values for the CEA

State	Utility value: mean (standard error)	95% CI	Source
Base case health state utilities			
PF	0.78	0.762, 0.799	NICE TA502[4]
PD	0.68	0.634, 0.727	
Scenario analysis of health state utilities			
PF	0.78	NR	SMC 2016 (ibrutinib)[5]
PD	0.64	NR	
Scenario analysis of health state utilities			
PF	0.84	NR	Simons *et al.* (2021)[83]
PD	0.74	NR	

CEA – cost-effectiveness analysis; CI – confidence interval; NICE – National Institute for Health and Care Excellence; NR – not reported; PD – progressed disease; PF – progression free; SMC – Scottish Medicines Consortium; TA – technology appraisal

B.3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted on 16th May 2024, with an update was performed on the 16th of July 2024, to identify studies reporting on the cost and resource use of patients with R/R MCL. Full details of the process and methods used to identify and select the cost and resource use data relevant to the technology being evaluated are presented in Appendix I.

The SLR identified 20 studies reporting on the cost and resource use of patients with R/R MCL. The studies most relevant to this submission, as they are applicable to clinical practice in England, include Maglinte *et al.* 2021[68] (UK study), Petersohn *et al.* 2022[70] (UK study), NICE TA502 2018[4] (UK HTA documents), NICE TA677 2021[85] (UK HTA documents), SMC 2016[5] (Scottish HTA documents) and SMC 2021[86] (Scottish HTA documents). These studies provide data directly applicable to the UK context, making them particularly valuable for this submission. See Appendix I for a full breakdown of the relevant studies extracted as part of the SLR.

Consistent with the studies identified in the SLR and other relevant NICE appraisals for zanubrutinib (TA833, TA931 and TA1001)[51,64,89], the following cost categories were included in the model:

- Drug acquisition and administration costs applied for the duration of treatment
- Health-state unit costs and resource use, irrespective of treatment arm
- The cost of AEs applied as a one-off cost in the first cycle
- End of life costs applied as a one-off cost to patients leaving the PD health state

For cost inputs, a UK NHS and PSS perspective was adopted as per the NICE reference case.[66] Unit costs of drug acquisition, administration, resource use, and AE management were based on standard costing sources appropriate for a UK perspective. The types and frequencies of resources associated with disease management and terminal care were derived based on NICE TA502 and were validated with UK clinical experts during an UK HTA advisory board.[4]

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.2 Drug acquisition costs

Drug acquisition costs were based on the dosing regimens presented in Table 63. Costs per pack and cycle are presented in Table 64. Dosing information for zanubrutinib is aligned with its licence and the dosing in the BGB-3111-AU-003 and BGB-3111-206 trials[42,43], whilst the dosing information for ibrutinib is aligned with the SmPC.[1,96] The unit costs were sourced from the British National Formulary (BNF).[12,105]

In the model, the existing PAS price of [redacted] per 30-day pack is used for zanubrutinib, which equates to a simple discount of [redacted]%.

Patients receiving zanubrutinib were treated in line with the PFS curve as derived from the clinical studies. Due to the poor fit of the TTD parametric curves to the KM data, it was considered appropriate to model the treatment discontinuation of zanubrutinib using the PFS curve. Please see Section B.3.3.4 Time to treatment discontinuation

for further details on the modelled TTD for zanubrutinib.

Similarly, patients receiving ibrutinib were treated in line with the PFS data presented in NICE TA502, consistent with the method for modelling zanubrutinib TTD. Please see Section B.3.3.4.2 Ibrutinib for further details.

The assumptions around modelling of treatment discontinuation was also validated by clinicians as part of an advisory board (11th November 2024).[2]

Table 63: Dosing regimen of treatments included in the economic model

Treatment	Dosing regimen	Source
Zanubrutinib	320 mg once daily (four 80 mg capsules) or 160 mg twice daily (two 80 mg capsules) administered orally until PD or unacceptable toxicity	Zanubrutinib SmPC[1]
Ibrutinib	560 mg once daily administered orally until disease PD or no longer tolerated by the patient	Ibrutinib SmPC[96]

mg – milligram; PD – progressed disease; SmPC – Summary of Product Characteristics

Relative dosing intensity is 100% for zanubrutinib, based on the dose received by patients in the two clinical trials[32,35], and 94.21% for ibrutinib, based on NICE TA502.[4]

Table 64: Drug package price and cost per cycle

Treatment	Dosage strength	Pack size/vial volume	Administration route	Cost per pack (£)	Cost per cycle (£)
Zanubrutinib	80 mg	120	Oral	[redacted]	[redacted]
Ibrutinib	140 mg	28	Oral	1,430.80	5,723.20

Mg – milligram
Source: British National Formulary 2024[105]

B.3.5.1.2 Drug administration costs

Medications that were orally administered did not incur administration costs.

B.3.5.2 Health-state unit costs and resource use

Costs related to disease management included in the model were calculated by multiplying the resource use per cycle by the unit cost for each resource item. Health-state unit costs and resource use are differentiated by health state (i.e., progression status), irrespective of treatment arm, and are presented in Table 65.

Health-state resource use is based on what was previously accepted in NICE TA502.[4] Costs for resource use are sourced from NHS reference costs for 2022/23,

as recommended in the NICE reference case, and inflated to 2024 using inflation indices sourced from Unit Costs of Health and Social Care 2023 (PSSRU).[106] The clinical experts consulted as part of the advisory board (11th November 2024) agreed with this approach but suggested the inclusion of computerised tomography (CT) scans at a resource use of twice per annum.[2]

Table 65: Medical resource unit costs and frequencies

Resource item	Costs		Resource use per cycle		
	Unit (£)	Cost notes*	PF state	PD state	Source
Full blood count	2.94	DAPS05: Haematology	0.36	0.72	NICE TA502[4]
X-ray	44.13	DAPFI: Direct access plain film	0.06	0.06	NICE TA502[4]
Blood glucose	1.73	DAPS04: Clinical biochemistry	0.02	0.00	NICE TA502[4]
LDH	1.73		0.24	0.41	NICE TA502[4]
Lymphocyte counts	2.94	DAPS05: Haematology	0.36	0.72	NICE TA502[4]
Bone marrow exam	519.10	SA33Z: Outpatient Procedures - Diagnostic Bone Marrow Extraction	0.06	0.00	NICE TA502[4]
Haematologist	214.86	WF01A: Consultant Led, Non-admitted fact to face follow-up, Clinical haematology service	0.36	0.72	NICE TA502[4]
Inpatient non-surgical/Medical	4,642.68	Weighted average of Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's with CC Score 0-9 (SA31C-F), Elective and Non-elective inpatient stays	0.03	0.15	NICE TA502[4]
Biopsy	2,649.49	Weighted average Major General Abdominal Procedures, 19 years and over, with CC Score 0 - 10+, (FF51A-FF51E),. Complex General Abdominal Procedures with CC Score 0- 6+ (FF50A-FF50C) and Procedures on the Lymphatic System with CC Score 0- 1+ (WH54A-B), only non-elective short stay and day case for each	0.04	0.00	NICE TA502[4]
Blood transfusion	481.49	SA44A, Clinical haematology, Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over, outpatient procedures	0.06	0.31	NICE TA502[4]
Platelet infusion	481.49		0.00	0.15	NICE TA502[4]
CT scan	172.32	RD22Z: Computerised Tomography Scan of One Area, with Pre- and Post-Contrast	0.15	0.15	Clinical expert opinion from advisory board[2]

*All resource use costs were sourced from the NHS reference costs for 2022/23 and inflated to 2024 using the PSSRU 2023.[106]
CT – computerised tomography; LDH – lactate dehydrogenase; NICE – National Institute for Health and Care Excellence; PD – progressed disease; PF – progression-free; PSSRU – Personal Social Services Research Unit; TA – technology assessment.
Source: PSSRU 2023[106], NICE TA502[4]

B.3.5.3 Adverse reaction unit costs and resource use

As described in Section B.3.4.5 Adverse reactions, the model accounts for the impact of all Grade ≥3 treatment-related AEs occurring in ≥5% of patients receiving treatment. The choice of a ≥5% patient threshold is based on the threshold used in TA502[4], which was accepted by the EAG and committee. During an advisory board (11th November 2024), the clinical experts present agreed with the approach and the AEs included.[2] Moreover, this threshold is sufficient given AEs are not expected to be key model drivers. Total AE costs were calculated as the product of the AE incidence, as presented in Table 60 and the respective unit costs as presented in Table 66. It is assumed that all AEs occur and are resolved in the first cycle (four weeks) of treatment. This assumption is commonly accepted in NICE oncology submissions, including: zanubrutinib for the treatment of CLL, MZL and WM (TA931, TA1001 and TA833)[51,64,89], niraparib 1L and 2L maintenance treatment for patients with ovarian cancer (TA784 and TA673)[107,108], acalabrutinib for the treatment of CLL (TA689)[109], dostarlimab for the treatment of endometrial cancer (TA779)[110] and trastuzumab deruxtecan 1L and 2L for treatment of metastatic breast cancer (TA862 and TA704)[111,112].

The unit costs associated with the management of AEs were sourced from NHS reference costs for 2022/23 and inflated to 2024 using inflation indices sourced from Unit Costs of Health and Social Care 2023 (PSSRU).[106]

Table 66: AE management costs

Adverse event	Cost (£)	Source	Cost notes
Pneumonia	3,163.05	NHS Reference costs 2022/23[113], inflated using PSSRU 2023[106]	Weighted average of Lobar, Atypical or Viral Pneumonia, with Single Intervention, with CC Score 0-7 (DZ11Q), Elective Inpatient, Non-elective inpatient (long and short stay) and Day case
Anaemia	594.04	NHS Reference costs 2022/23[113], inflated using PSSRU 2023[106]	Weighted average of Other Red Blood Cell disorders with CC score 0-5 (SA09K-L), Non-elective inpatient short stay
Neutropenia	626.32	NHS Reference costs 2022/23[113], inflated using PSSRU 2023[106]	Weighted average of Agranulocytisis with CC score 1-13+ (SA35A-E), non-elective inpatient short stay.
Thrombocytopenia	658.93	NHS Reference costs 2022/23[113], inflated using PSSRU 2023[106]	Weighted average of Thrombocytopenia with CC Score 0-8+ (SA12G-K), Non-elective short stay
Neutrophil count decreased	626.32	NHS Reference costs 2022/23[113], inflated using PSSRU 2023[106]	Weighted average of Agranulocytisis with CC score 1-13+ (SA35A-E), non-elective inpatient short stay.
Platelet count decreased	626.32	NHS Reference costs 2022/23[113], inflated using PSSRU 2023[106]	Weighted average of Agranulocytisis with CC score 1-13+ (SA35A-E), non-elective inpatient short stay.
Atrial fibrillation	729.10	NHS Reference costs 2022/23[113], inflated using PSSRU 2023[106]	Weighted average of Arrhythmia or Conduction Disorders, with CC score 0-6 (EB07D-E), Non-elective inpatient - short stay and day case
White blood cell count decreased	626.32	NHS Reference costs 2022/23[113], inflated using PSSRU 2023[106]	Weighted average of Agranulocytisis with CC score 1-13+ (SA35A-E), non-elective inpatient short stay.

CC – Complications and comorbidities; NHS – National Health Service; PSSRU – Personal Social Services Research Unit

B.3.5.4 Miscellaneous unit costs and resource use

B.3.5.4.1 Subsequent treatment costs

Subsequent treatment costs are applied as a one-off cost to each patient that has disease progression. It is assumed that all patients who have disease progression will receive subsequent treatment and that they receive one full course of the treatment in line with the treatment specific stopping rules. In the base-case, the distribution of subsequent treatments is consistent with the treatments received at 3rd-line in UK clinical practice as derived from UK real-world data set (HMRN).[7] The chemotherapy agents included in the subsequent treatment basket were bendamustine + rituximab, high dose cytarabine + rituximab, rituximab monotherapy,

chlorambucil + rituximab, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) and FCR (fludarabine, cyclophosphamide and rituximab). The cost of subsequent treatments is modelled as a weighted distribution of these treatments with the drug acquisition and administration cost per course of therapy presented in Appendix K.

The duration for which patients are treated with individual subsequent treatments is informed using the dosing regimens of each treatment as derived from clinical guidelines. The duration of subsequent treatments is assumed to be equivalent across treatment arms and are presented in Table 67.

This approach was validated by clinical experts in attendance at an advisory board (11th November 2024). The clinical experts suggested exploring a sensitivity analysis, including subsequent treatment with CAR-T therapy (brexu-cel) which is aligned with clinical practice (dependent on the positive recommendation following exit from the Cancer Drugs Fund [CDF][85]) as there was low levels of brexu-cel use in the HMRN RWE dataset. On this basis, the additional cost of brexu-cel was included as a scenario analysis.

Table 67: Duration of each subsequent treatment by treatment cycles

Treatment	Mean duration of treatment (treatment cycles)	Source
Bendamustine + Rituximab	6	NHS clinical commissioning policy[114]
High dose cytarabine + Rituximab	6	NSSG chemotherapy protocol[115]
Rituximab	4	NHS Quick Reference Guide[116]
Chlorambucil + Rituximab	6	NSSG chemotherapy protocol[117]
R-CHOP	6	NSSG chemotherapy protocol[118]
FCR	6	NHS Quick Reference Guide[119]
Brexu-cel	1	EMC SmPC[8]

Brexu-cel; brexucabtagene autoleucel; FCR – fludarabine, cyclophosphamide, rituximab; NHS – National Health Service; R-CHOP – rituximab, cyclophosphamide, doxorubicin, vincristine

The total per patient cost of the subsequent treatment regimen is calculated using the drug acquisition and drug administration costs per treatment regimen, the mean duration of each regimen and the proportion of patients in each treatment arm who are on each chemotherapy. The total per patient cost applied as a one-off subsequent treatment cost is presented in Table 68.

Table 68: Total per patient cost for subsequent treatment (no wastage)

Treatment	Drug acquisition cost per treatment regimen (£)	Drug administration cost per treatment regimen (£)	Base case treatment use – not including CAR-T	Scenario analysis: Treatment use – including CAR-T
Bendamustine + Rituximab	32,485.98	9,320.15	[redacted]	[redacted]
High dose cytarabine + Rituximab	7,187.34	14,633.42	[redacted]	[redacted]
Rituximab	1,257.32	2,221.17	[redacted]	[redacted]
Chlorambucil + Rituximab	2,068.47	3,331.76	[redacted]	[redacted]
R-CHOP	6,582.83	13,327.03	[redacted]	[redacted]
FCR	4,983.19	3,331.76	[redacted]	[redacted]
Brexu-cel (plus pre-treatment regimen)*	346,980.87	0.00	[redacted]	9%
Total per patient cost for subsequent treatment (one-off cost for each treatment arm) (£):			26,692.53	57,074.17

*Total cost of brexu-cel includes the cost of treatment, pre-treatment regimen and administration as derived from NICE TA893[120]
FCR – fludarabine, cyclophosphamide, rituximab; R-CHOP – rituximab, cyclophosphamide, doxorubicin, vincristine

B.3.5.4.1 End of life costs

The costs for end-of-life are applied as a one-off cost to each death event in the model. The cost of end-of-life was source from a research paper conducted by Nuffield trust 2014[121] and inflated to 2024 using inflation indices sourced from Unit Costs of Health and Social Care 2023 (PSSRU).[106] The cost also aligns with the cost used in NICE TA502.[4] This cost was estimated to be £7,286, inflated to £10,084.

B.3.6 Severity

N/A. This appraisal does not qualify for the severity modifiers.

B.3.7 Uncertainty

The key uncertainties in the economic evaluation relate to the immaturity of data and comparative effectiveness data. The long-term extrapolations for OS of zanubrutinib are informed using the clinical data from the BGB-3111-AU-003 and BGB-3111-206 clinical trials and neither trial reached their median OS. To reduce uncertainty in the long-term extrapolation of OS, the Company have validated their curve selection with UK clinical experts at an advisory board (11th November 2024) (see Section B.3.3.1 Time to event analysis) and performed a range of scenario analyses (see Section B.3.11 Exploring uncertainty). Including changing the discounting, varying the time horizon and different parametric survival curves (see Table 76-Table 78 for the full list of deterministic and probabilistic results of the scenario analyses).

In the absence of head-to-head data between zanubrutinib and ibrutinib, an unanchored MAIC was conducted to create a more reliable basis for comparison. The appropriateness of the MAIC methodology, which has been validated by clinical experts, is further confirmed as the baseline characteristics were well matched in the analysis. Sensitivity analyses further confirmed the robustness of these findings, with consistent statistical significance observed across different scenarios, including using different zanubrutinib datasets. Detailed conclusions from the MAIC can be found in Section B.2.9 Indirect and mixed treatment comparisons.

Due to the absence of HRQoL data collected for patients with R/R MCL within the zanubrutinib clinical trials (BGB-3111-AU-003 and BGB-3111-206), an SLR was required to identify data sources that could inform health-state utilities. Scenario analyses were conducted using the data identified in the supplementary sources to provide alternative utility values, offering a more comprehensive assessment of the potential QoL impact. The base case and scenario utility values are detailed in Section B.3.4.6 Health-related quality-of-life data used in the cost-effectiveness analysis , with the resulting ICER estimates and their sensitivity to these utility assumptions presented in Section B.3.11 Exploring uncertainty.

Uncertainty in the model results were explored through extensive deterministic sensitivity analysis (DSA), probabilistic sensitivity analysis (PSA) and scenario

analyses. Exploration of uncertainty through the DSA, PSA and scenario analysis is detailed in Section B.3.11 Exploring uncertainty. To further explore any uncertainty in the clinical efficacy of zanubrutinib and ibrutinib, the Company conducted a cost-comparison between the two treatments, assuming equal efficacy between treatments. For further details and results of the scenario please refer to Section B.3.11 Exploring uncertainty.

B.3.8 Managed access proposal

A managed access proposal is not considered relevant for zanubrutinib for the treatment of patients with R/R MCL.

B.3.9 Summary of base-case analysis inputs and assumptions

B.3.9.1 Summary of base-case analysis inputs

A summary of the key parameters used in the CEA is presented in Table 69.

Table 69: Summary of variables applied in the economic model

Parameter	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Model settings			
Population	Adults with 2L R/R MCL	N/A	B.3.2 Economic analysis
Perspective	Payer (UK NHS and PPS)	N/A	
Time horizon	Lifetime (32 years)	N/A	
Proportion males	78.11%	SE: 0.16 (Beta)	
Starting age in model (years)	68	SE: 14 (Gamma)	
Body surface area (m^2)	1.95	SE: 0.00 (Gamma)	
Half-cycle correction	Yes	Fixed	
Discount rate (costs and outcomes)	3.5%	Fixed but varied in scenario analysis	
Clinical parameters			
Efficacy			
PFS – distribution for zanubrutinib	Log-normal	Normal distribution (Cholesky decomposition)	B.3.3 Clinical parameters and variables
OS – distribution for zanubrutinib	Log-normal		
TTD – distribution for zanubrutinib	Assumed equal to PFS extrapolation		

Parameter	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
PFS – distribution for ibrutinib	Log-normal		
OS – distribution for ibrutinib	Log-normal		
TTD – distribution for ibrutinib	Assumed equal to PFS extrapolation		
Probability of AE – zanubrutinib			
Pneumonia	[redacted]	SE: [redacted](Beta)	KM – Kaplan Meier; TTD – time-to-treatment discontinuation Note: TTD for zanubrutinib and ibrutinib is estimated using the base case PFS curves B.3.4 Measurement and valuation of health effects
Anaemia	[redacted]	SE: [redacted](Beta)	
Neutropenia	[redacted]	SE: [redacted](Beta)	
Thrombocytopenia	[redacted]	SE: [redacted](Beta)	
Neutrophil count decreased	[redacted]	SE: [redacted](Beta)	
Platelet count decreased	[redacted]	SE: [redacted](Beta)	
Atrial fibrillation	[redacted]	SE: [redacted](Beta)	
White blood cell count decreased	[redacted]	SE: [redacted](Beta)	
Probability of AE – ibrutinib			
Pneumonia	8.10%	SE: 0.02 (Beta)	KM – Kaplan Meier; TTD – time-to-treatment discontinuation Note: TTD for zanubrutinib and ibrutinib is estimated using the base case PFS curves B.3.4 Measurement and valuation of health effects
Anaemia	8.90%	SE: 0.02 (Beta)	
Neutropenia	16.80%	SE: 0.03 (Beta)	
Thrombocytopenia	0.00%	SE: 0.00 (Beta)	
Neutrophil count decreased	0.00%	SE: 0.00 (Beta)	
Platelet count decreased	0.00%	SE: 0.00 (Beta)	
Atrial fibrillation	0.00%	SE: 0.01 (Beta)	
White blood cell count decreased	5.10%	SE: 0.00 (Beta)	
Health-related quality-of-life parameters			
Health state utilities			
PF	0.78	SE: 0.01	KM – Kaplan Meier; TTD – time-to-treatment discontinuation Note: TTD for zanubrutinib and ibrutinib is estimated using the base case PFS curves
PD	0.68	SE: 0.02	

Parameter	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
			B.3.4 Measurement and valuation of health effects
Disutilities			
Pneumonia	0.15	SE: 0.03 (Beta)	KM – Kaplan Meier; TTD – time-to-treatment discontinuation Note: TTD for zanubrutinib and ibrutinib is estimated using the base case PFS curves B.3.4 Measurement and valuation of health effects
Anaemia	0.12	SE: 0.02 (Beta)	
Neutropenia	0.09	SE: 0.02 (Beta)	
Thrombocytopenia	0.11	SE: 0.02 (Beta)	
Neutrophil count decreased	0.15	SE: 0.03 (Beta)	
Platelet count decreased	0.11	SE: 0.02 (Beta)	
Atrial fibrillation	0.15	SE: 0.03 (Beta)	
White blood cell count decreased	0.15	SE: 0.03 (Beta)	
Cost parameters			
Health-state resource use per cycle			
Full blood count	PF: 0.36 PD: 0.72	SE:0.07 (Beta) SE: 0.14 (Beta)	B.3.5 Cost and healthcare resource use identification, measurement and valuation
X-ray	PF: 0.06 PD: 0.06	SE: 0.01 (Beta) SE: 0.01 (Beta)	
Blood glucose	PF: 0.02 PD: 0.00	SE: 0.00 (Beta) SE: 0.00 (Beta)	
LDH	PF: 0.24 PD: 0.41	SE: 0.05 (Beta) SE: 0.08 (Beta)	
Lymphocyte counts	PF: 0.36 PD: 0.72	SE: 0.07 (Beta) SE: 0.14 (Beta)	
Bone marrow exam	PF: 0.06 PD: 0.00	SE: 0.01 (Beta) SE: 0.00 (Beta)	
Haematologist	PF: 0.36 PD: 0.72	SE: 0.07 (Beta) SE: 0.14 (Beta)	
Inpatient non-surgical/Medical	PF: 0.03 PD: 0.15	SE: 0.01 (Beta) SE: 0.03 (Beta)	
Biopsy	PF: 0.04 PD: 0.00	SE: 0.01 (Beta) SE: 0.00 (Beta)	
Blood transfusion	PF: 0.06 PD: 0.31	SE: 0.01 (Beta) SE: 0.06 (Beta)	
Platelet infusion	PF: 0.00 PD: 0.15	SE: 0.00 (Beta) SE: 0.03 (Beta)	

Parameter	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
CT scan	PF: 0.15 PD: 0.15	SE: 0.03 (Beta) SE: 0.03 (Beta)	
Health-state unit costs (£)			
Full blood count	2.94	SE: 0.59 (Gamma)	B.3.5 Cost and healthcare resource use identification, measurement and valuation
X-ray	44.13	SE: 8.83 (Gamma)	
Blood glucose	1.73	SE: 0.35 (Gamma)	
LDH	1.73	SE: 0.35 (Gamma)	
Lymphocyte counts	2.94	SE: 0.59 (Gamma)	
Bone marrow exam	519.10	SE: 103.82 (Gamma)	
Haematologist	214.86	SE: 42.97 (Gamma)	
Inpatient non-surgical/Medical	4642.68	SE: 928.54 (Gamma)	
Biopsy	2649.49	SE: 529.00 (Gamma)	
Blood transfusion	481.49	SE: 96.30 (Gamma)	
Platelet infusion	481.49	SE: 96.30 (Gamma)	
CT scan	172.32	SE: 34.46 (Gamma)	
End-of-life costs (£)			
Terminal care	10,083.85	SE: 2,016.77 (Gamma)	B.3.5 Cost and healthcare resource use identification, measurement and valuation
Adverse event costs (£)			
Pneumonia	3,163.05	SE: 632.61 (Gamma)	B.3.5 Cost and healthcare resource use identification, measurement and valuation
Anaemia	594.04	SE: 118.81 (Gamma)	
Neutropenia	626.32	SE: 125.26 (Gamma)	
Thrombocytopenia	658.93	SE: 131.79 (Gamma)	
Neutrophil count decreased	626.32	SE: 125.26 (Gamma)	
Platelet count decreased	626.32	SE: 125.26 (Gamma)	
Atrial fibrillation	729.10	SE: 145.82 (Gamma)	
White blood cell count decreased	626.32	SE: 125.26 (Gamma)	
Treatment acquisition costs (per pack) (£)			
Zanubrutinib cost per pack	[redacted]	Fixed	B.3.5 Cost and healthcare resource use identification, measurement and valuation
Ibrutinib cost per pack	1430.80	Fixed	

Parameter	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Treatment administration costs (£)			
Delivered oral chemotherapy	0.00	N/A	B.3.5 Cost and healthcare resource use identification, measurement and valuation
Total costs excluding CAR-T (base-case) – subsequent treatment one-off (£)			
Zanubrutinib – subsequent treatment costs	26,692.53	SE: 5,338.51 (Gamma)	B.3.5 Cost and healthcare resource use identification, measurement and valuation
Ibrutinib – subsequent treatment costs	26,692.53	SE: 5,338.51 (Gamma)	
Total costs including CAR-T (scenario analysis) – subsequent treatment one-off (£)			
Zanubrutinib – subsequent treatment costs	57,074.17	SE: 11,414.83 (Gamma)	B.3.5 Cost and healthcare resource use identification, measurement and valuation
Ibrutinib – subsequent treatment costs	57,074.17	SE: 11,414.83 (Gamma)	
Proportion per treatment arm – subsequent treatment			
Zanubrutinib – patient proportion receiving subsequent treatment	100%	SE: 20% (Beta)	B.3.5 Cost and healthcare resource use identification, measurement and valuation
Ibrutinib – patient proportion receiving subsequent treatment	100%	SE: 20% (Beta)	

AE – adverse event; CT – computerised tomography; FCR – fludarabine, cyclophosphamide and rituximab; LDH – lactate dehydrogenase; MCL – mantle cell lymphoma; NHS – National Health Service; OS – overall survival; PFS – progression-free survival; PSS – Personal Social Services; R-CHOP; rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R/R – relapsed/refractory; SE – standard error; TTD – time-to-treatment discontinuation; tx – treatment; UK – United Kingdom

B.3.9.2 Assumptions

The key assumptions made in the model base case are presented in Table 70.

Table 70: Key assumptions in the model

Model input	Assumption	Rationale
Model structure	PSM is the most appropriate model structure	The PSM approach can capture disease progression and implications on patients,

Model input	Assumption	Rationale
		which aligns with the pathology of MCL and the expected impact of zanubrutinib on the disease course.
Cycle length	Model cycle of 4 weeks	This is consistent with the treatment dosing schedule for zanubrutinib.[1] It also provides sufficient granularity to observe differences in costs and effects of treatments.
Half-cycle correction	Yes	The model calculated mid-cycle estimates in each health state by taking the average of patients present at the beginning and end of each cycle.
Time horizon	Lifetime	In line with NICE guidance[66] (assumed a 32-year life time horizon based on the age of the patient population from NICE TA502[4], the population the zanubrutinib trial evidence was matched to).
Efficacy	Identification of the most appropriate survival curves describing OS and PFS for zanubrutinib	The most appropriate curves have been identified for the long-term extrapolation of survival and efficacy of zanubrutinib. The methodology and curve selection was validated by clinical experts at an advisory board.[2]
	Identification of the most appropriate survival curves describing OS and PFS for ibrutinib	The most appropriate curves have been identified for the extrapolation of survival and efficacy for ibrutinib. The methodology and curve selection was validated by clinical experts at an advisory board.[2]
	Time on treatment	Given the poor fit of parametric curves to the TTD data, time on treatment was modelled as equal to PFS.
Utilities	Health-state utilities are equal across treatment arms	It is assumed that the utility should only differ by health state.
	Health-state utilities are sourced from NICE TA502.[4]	Given that the zanubrutinib clinical studies did not collect HRQoL data, utility values were source form literature. Values from NICE TA502 were considered the most appropriate values to accurately capture the HRQOL of patients with R/R MCL.[4]
	Age-adjusted utility decrements are modelled.	To capture the decrease in HRQoL with age.
	Disutilities associated with AEs were applied.	Disutilities associated with AEs are sourced from literature and assumed to occur within the first cycle only.
Adverse events	All AEs are assumed to last for the same period of time.	To capture the impact of AEs without adding unnecessary complexity, a simplified assumption was made such that costs and QALY losses associated with AEs are applied in the first model cycle only. This assumption is also in line with what has been accepted in

Model input	Assumption	Rationale
		previous, relevant appraisals for zanubrutinib.[51,64,89]
	Only Grade 3 or Grade 4 AEs occurring in ≥5% patients are included	Events occurring in ≥5% of patients were considered appropriate to capture AEs that would impact patients in a real-world setting where AEs are monitored in a less strict manner compared with a clinical trial setting. Clinical experts at an advisory board agreed with all AEs included.[2]
Treatment costs	No administration costs for zanubrutinib and ibrutinib	Regimens administered orally can be taken by patients at home. It is assumed that no costs are incurred.
	RDIs are sourced from the relevant clinical studies.	RDI for zanubrutinib is an average of the RDI reported in Song et al. (2020) and Tam et al. (2021).[32,35] RDI for ibrutinib is sourced from Rule et al. (2017b).[17]
Subsequent treatment costs	All patients receive subsequent treatment once they move into the PD health state across both treatment arms. The distribution of subsequent treatments is the same across both arms.	In the absence of treatment specific data on subsequent treatment use, assuming all patients receive subsequent treatment avoids bias. The subsequent treatment basket is sourced from data from HMRN.[7]
Health state unit costs and resource use	Health-state unit costs and resource use are assumed equal across treatment arms	It is assumed that monitoring of patients and associated costs will not vary across treatment arms. This is a conservative assumption given the improved clinical efficacy profile of zanubrutinib is likely to require less monitoring from clinicians.

AE – adverse event; HMRN - Haematological Malignancy Research Network; HRs – hazard ratios; KM – Kaplan Meier; MCL – Mantle Cell Lymphoma; NICE – The National Institute of Health and Care Excellence; OS – overall survival; PD – progressed disease; PFS – progression-free survival; PSM – partitioned survival model; RDI – relative dose intensity; TTD – time to treatment discontinuation; UK – United Kingdom

B.3.10 Base-case results

B.3.10.1 Base-case incremental cost-effectiveness analysis results

The base-case results using the list price of ibrutinib and the PAS discount of [redacted]% with a net price of [redacted] per 30-day pack for zanubrutinib are presented in Table 71. Over a lifetime time horizon, treatment with zanubrutinib in patients with 2L R/R MCL was associated with cost savings of £[redacted] and [redacted] incremental QALY gains, resulting in zanubrutinib dominating ibrutinib. The net health benefit (NHB) is displayed in Table 72. The NHB at £20,000 and £30,000 of [redacted] and [redacted], respectively, implies that overall population health would be increased as a result of

introducing zanubrutinib. Disaggregated results from the base-case analysis are presented in Appendix J.

The economic evaluation confirms a robust and favourable cost-effectiveness profile with zanubrutinib dominating ibrutinib in the base case analysis and across all scenarios, with the inclusion of a simple discount. As such the Company maintains that a cost-comparison methodology is the most appropriate approach to appraise zanubrutinib in 2L R/R MCL. Therefore, cost-comparison results are presented in Section B.3.11.3.1 Cost-comparison analysis: zanubrutinib versus ibrutinib. Nevertheless, a full exploration of the cost-effectiveness of zanubrutinib is presented in Section B.3.10.1 Base-case incremental cost-effectiveness analysis results and Section B.3.11 Exploring uncertainty, as requested by NICE at the Decision Problem meeting.

Table 71: Base-case deterministic results in patients with 2L R/R MCL

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Zanubrutinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

ICER – incremental cost-effectiveness ratio; LYG – life years gained; MCL – mantle cell lymphoma; QALYs – quality-adjusted life years; R/R – relapsed or refractory

Table 72: Base-case deterministic results for net health benefit of zanubrutinib in patients with 2L R/R MCL

Technologies	Total costs (£)	Incremental costs (£)	ICER (£/QALY)	NHB at £20,000 (£)	NHB at £30,000 (£)
Zanubrutinib	[redacted]	-	-	-	-
Ibrutinib	[redacted]	[redacted]	Dominating	4.94	4.08

ICER - incremental cost-effectiveness ratio; MCL– mantle cell lymphoma; NHB - net health benefit; R/R – relapsed or refractory

B.3.11 Exploring uncertainty

Uncertainty in the model results were explored through extensive DSA, PSA and scenario analyses.

B.3.11.1 Probabilistic sensitivity analysis

PSA was conducted to assess the impact of parameter uncertainty on the results of the analysis in the model base case; 1,000 simulations were performed, and for each simulation, a value was drawn at random for each variable from its uncertainty distribution simultaneously, and the resulting costs, outcomes, and incremental results were recorded. The model allowed the beta, gamma, log-normal, normal, and Dirichlet distributions to be used dependent on the characteristics of the parameter, and also included Cholesky decomposition matrix calculation fields for modelling pairs of input parameters for which the covariance structure between two variables was known, such as for the survival curves.

Table 73: Distribution options by model parameter for PSA

Parameter	Distribution
Age	Gamma distribution
Proportion of male	Beta distribution
BSA (m^2)	Gamma distribution
TTD, PFS, OS extrapolations	Normal distribution (Cholesky decomposition)
Health state related utility	Beta distribution
Risk of experiencing AEs	Beta distribution
Utility decrement due to AEs	Beta distribution
Treatment acquisition costs	Fixed
Treatment administration costs Health-state unit costs and resource use AE management costs Subsequent treatment costs End of life costs	Gamma distribution

AE – adverse event; BSA – body surface area; OS – overall survival; PFS – progression-free survival; TTD – time-to-treatment discontinuation

The results of the base-case PSA are presented in Table 74, with an incremental cost-effectiveness plane (ICEP) and cost-effectiveness acceptability curve (CEAC) presented in Figure 37 and Figure 38, respectively. Based on the PSA, treatment with zanubrutinib in patients with 2L R/R MCL was associated with incremental savings of £[redacted] and [redacted] incremental QALY gains, resulting in zanubrutinib

dominating ibrutinib. The mean probabilistic results lie close to the deterministic results, indicating that the model is robust to parameter uncertainty. Furthermore, zanubrutinib was [redacted]% cost-effective at a willingness to pay of £30,000 per QALY or more.

Table 74: Base-case PSA results in patients with 2L R/R MCL

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Zanubrutinib	[redacted]	[redacted]	-	-	-
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

ICER – incremental cost-effectiveness ratio; MCL – mantle cell lymphoma; QALYs – quality-adjusted life years; PSA – probabilistic sensitivity analysis; R/R – relapsed or refractory

Figure 37: PSA ICEP for zanubrutinib vs ibrutinib in patients with 2L R/R MCL

ICEP – incremental cost-effectiveness plane; MCL – mantle cell lymphoma; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life year; R/R – relapsed or refractory

Figure 38: PSA CEAC for zanubrutinib vs ibrutinib in patients with 2L R/R MCL

CEAC – cost-effectiveness acceptability curve; MCL – mantle cell lymphoma; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life year; R/R – relapsed or refractory

B.3.11.2 Deterministic sensitivity analysis

DSA was performed to explore the effect of uncertainty associated with varying individual model inputs or groups of individual model inputs on the model results. In the DSA, each variable was systematically increased and decreased based on 95% confidence intervals or published ranges. In the absence of data, the standard error was assumed to be 20% to estimate the 95% confidence intervals.

A tornado diagram was developed to graphically present the parameters which have the greatest effect on the NMB, at the WTP threshold of £30,000 per QALY. The NMB was used as an alternative to the ICER in order to avoid negative ICERs within the OWSA (for when zanubrutinib dominates ibrutinib). The top 10 most sensitive parameters for the NMB of zanubrutinib versus ibrutinib are summarised in Table 75 and Figure 39. The model was most sensitive to ibrutinib PFS and TTD which are varied together as TTD is equalised to PFS. However, adjusting PFS/TTD to the

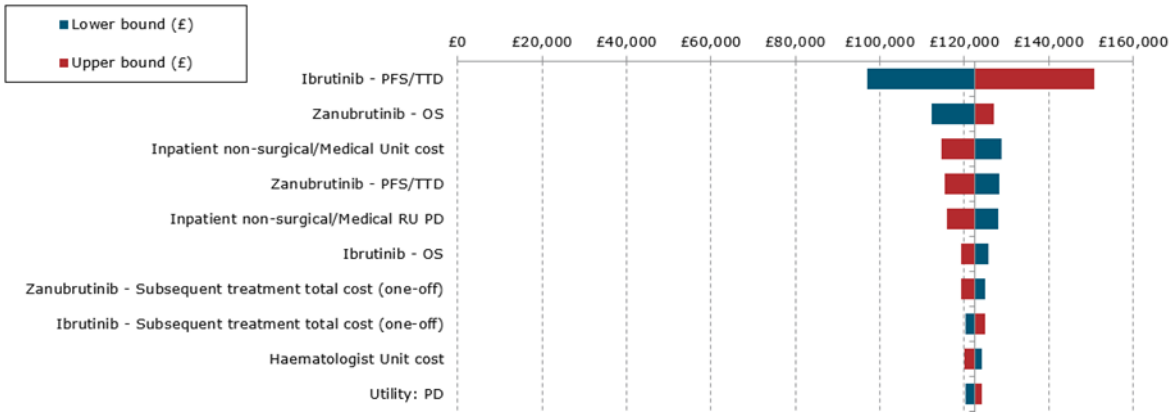
upper or lower bounds still demonstrated a positive NMB, with zanubrutinib providing consistent savings over ibrutinib.

Table 75: DSA results (NMB at WTP £30,000) for zanubrutinib vs ibrutinib in patients with 2L R/R MCL

Parameter name	Lower bound NMB	Upper bound NMB
Ibrutinib - PFS/TTD	£97,176	£150,744
Zanubrutinib - OS	£112,382	£126,838
Inpatient non-surgical/Medical Unit cost	£128,740	£114,578
Zanubrutinib - PFS/TTD	£128,200	£115,551
Inpatient non-surgical/Medical RU PD	£127,767	£115,978
Ibrutinib - OS	£125,615	£119,311
Zanubrutinib - Subsequent treatment total cost (one-off)	£124,848	£119,303
Ibrutinib - Subsequent treatment total cost (one-off)	£120,363	£124,748
Haematologist Unit cost	£124,128	£120,177
Utility: PD	£120,517	£124,113

DSA – deterministic sensitivity analyses; MCL – mantle cell lymphoma; NMB – net monetary benefit; OS – overall survival; PD – progressed disease; PFS – progression-free survival; R/R – relapsed or refractory; RU – resource use; TTD – time-to-treatment discontinuation; WTP – willingness to pay threshold

Figure 39: Tornado plot of DSA results (NMB) for zanubrutinib vs ibrutinib in patients with 2L R/R MCL



DSA – deterministic sensitivity analyses; MCL – mantle cell lymphoma; NMB – net monetary benefit; OS – overall survival; PD – progressed disease; PF – progression free; PFS – progression-free survival; QALY – quality-adjusted life year; RDI – relative dost intensity; R/R – relapsed or refractory; RU – resource use

B.3.11.3 Scenario analysis

Scenario analyses were performed to address and alleviate uncertainty within the base-case inputs and assumptions. Details of each of the included scenario analyses are presented in Table 76. Deterministic and probabilistic scenario analysis

results for zanubrutinib versus ibrutinib are presented in Table 77 and Table 78, respectively. The probabilistic results are consistent with the deterministic results, indicating the robustness of the analyses to parameter uncertainty. In all probabilistic and deterministic scenarios zanubrutinib continued to dominate ibrutinib.

Table 76: Summary of scenario analyses

Base-case	Scenario analysis	Rationale
3.5% discount rate	No discounting	0% discount is assumed for costs to assess the impact of discounting
3.5% discount rate	High discount rates (6%)	6% discount is assumed for costs to assess the impact of discounting
Time horizon: lifetime (32 years)	Time horizon: 20 years	To explore the impact of shortening the time horizon
PFS, OS and TTD from pooled zanubrutinib trials (BGB-3111-AU-003 [DCO: 31Mar2021]) and BGB-3111-206 [DCO: 08Sept2020]), ESS=[redacted]) adjusted through a MAIC to Rule et al. (2017b) (N=370)	PFS, OS and TTD from pooled zanubrutinib trials, **from an earlier data cut** (BGB-3111-AU-003 [DCO: Dec 13, 2018]) and BGB-3111-206 [DCO: Aug 31, 2019]), ESS=[redacted]) adjusted through a MAIC to Rule et al. (2017b) (N=370)	To explore the impact of using an earlier data cut and a different method of assessing PFS (IRC vs. INV).
	PFS, OS and TTD from pooled zanubrutinib trials, **excluding rituximab-naïve patients (ESS=[redacted])** vs. ibrutinib-pooled (n=370) (Rule 2017b)	To explore the impact of removing patients who are less generalisable to UK clinical practice.
	PFS, OS and TTD from **206-only (n=[redacted])** adjusted through a MAIC to Rule et al. (2017b) (N=370)	To explore the impact of removing the AU-003 trial.
PFS distribution: • Zanubrutinib (log-normal) • Ibrutinib (log-normal)	PFS distribution: • Zanubrutinib (log-logistic) • Ibrutinib (log-logistic)	To explore the impact of alternative PFS extrapolations
	PFS distribution: • Zanubrutinib (generalised gamma) • Ibrutinib (generalised gamma)	
OS distribution: • Zanubrutinib (log-normal)	OS distribution: • Zanubrutinib (log-logistic)	To explore the impact of alternative OS extrapolations

Base-case	Scenario analysis	Rationale
• Ibrutinib (log-normal)	• Ibrutinib (log-logistic)	
	OS distribution: • Zanubrutinib (generalised gamma) • Ibrutinib (generalised gamma)	
TTD assumption: TTD is equal to PFS for zanubrutinib and ibrutinib	TTD is equal to the KM data	To explore the impact of alternative TTD data
Utility values: NICE TA502	SMC ibrutinib (2016)	To explore the impact of alternative utility assumptions
	Simons et al. (2021)	
Subsequent treatment costs: Included	Subsequent treatment costs: Excluded	To explore the impact of subsequent treatments
	CAR-T therapy included	To explore the impact of greater subsequent treatment costs

CAR-T – chimeric antigen receptor T-cell; DCO – data cut off; NICE – National Institute for Health and Care Excellence; OS- overall survival; PFS – progression-free survival; SMC – Scottish Medicines Consortium

Table 77: Summary of scenario analyses results for zanubrutinib vs ibrutinib – deterministic

Scenario analysis	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER/QALY (£)
Base case	[redacted]	[redacted]	[redacted]	Dominating
No discounting	[redacted]	[redacted]	[redacted]	Dominating
High discount rates (6%)	[redacted]	[redacted]	[redacted]	Dominating
Time horizon: 20 years	[redacted]	[redacted]	[redacted]	Dominating
PFS, OS and TTD from pooled zanubrutinib trials, **from an earlier data cut** (BGB-3111-AU-003 [DCO: Dec 13, 2018]) and BGB-3111-206 [DCO: Aug 31, 2019]), ESS=[redacted]) adjusted through a MAIC to Rule et al. (2017b) (N=370)	[redacted]	[redacted]	[redacted]	Dominating
PFS, OS and TTD from pooled zanubrutinib trials, **excluding rituximab-**	[redacted]	[redacted]	[redacted]	Dominating

Scenario analysis	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER/QALY (£)
naïve patients (ESS=[redacted]) vs. ibrutinib-pooled (n=370) (Rule 2017b)				
PFS, OS and TTD from **206-only (n=[redacted])** adjusted through a MAIC to Rule et al. (2017b) (N=370)	[redacted]	[redacted]	[redacted]	Dominating
PFS distribution: • Zanubrutinib (log-logistic) • Ibrutinib (log-logistic)	[redacted]	[redacted]	[redacted]	Dominating
PFS distribution: • Zanubrutinib (generalised gamma) • Ibrutinib (generalised gamma)	[redacted]	[redacted]	[redacted]	Dominating
OS distribution: • Zanubrutinib (log-logistic) • Ibrutinib (log-logistic)	[redacted]	[redacted]	[redacted]	Dominating
OS distribution: • Zanubrutinib (generalised gamma) • Ibrutinib (generalised gamma)	[redacted]	[redacted]	[redacted]	Dominating
Zanubrutinib and ibrutinib TTD is equal to the KM data	[redacted]	[redacted]	[redacted]	Dominating
Alternative utility value: SMC 2016	[redacted]	[redacted]	[redacted]	Dominating
Alternative utility value: Simons et al. 2016	[redacted]	[redacted]	[redacted]	Dominating
Subsequent treatment costs: Excluded	[redacted]	[redacted]	[redacted]	Dominating
Subsequent treatment costs: CAR-T included	[redacted]	[redacted]	[redacted]	Dominating

CAR-T - chimeric antigen receptor T-cell; DCO – data cut off; ICER – incremental cost-effectiveness ratio; LYG – life years gained; OS- overall survival; PFS – progression-free survival; SMC – Scottish Medicines Consortium; QALY – quality adjusted life year

Table 78: Summary of scenario analyses results for zanubrutinib vs ibrutinib – probabilistic

Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER/QALY (£)
Base case	[redacted]	[redacted]	Dominating
No discounting	[redacted]	[redacted]	Dominating
High discount rates (6%)	[redacted]	[redacted]	Dominating
Time horizon: 20 years	[redacted]	[redacted]	Dominating
PFS, OS and TTD from pooled zanubrutinib trials, **from an earlier data cut** (BGB-3111-AU-003 [DCO: Dec 13, 2018]) and BGB-3111-206 [DCO: Aug 31, 2019]), ESS=[redacted]) adjusted through a MAIC to Rule et al. (2017b) (N=370)	[redacted]	[redacted]	Dominating
PFS, OS and TTD from pooled zanubrutinib trials, **excluding rituximab-naïve patients (ESS=[redacted])** vs. ibrutinib-pooled (n=370) (Rule 2017b)	[redacted]	[redacted]	Dominating
PFS, OS and TTD from **206-only (n=[redacted])** adjusted through a MAIC to Rule et al. (2017b) (N=370)	[redacted]	[redacted]	Dominating
PFS distribution: • Zanubrutinib (log-logistic) • Ibrutinib (log-logistic)	[redacted]	[redacted]	Dominating
PFS distribution: • Zanubrutinib (generalised gamma) • Ibrutinib	[redacted]	[redacted]	Dominating

Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER/QALY (£)
(generalised gamma)			
OS distribution: • Zanubrutinib (log-logistic) • Ibrutinib (log-logistic)	[redacted]	[redacted]	Dominating
OS distribution: • Zanubrutinib (generalised gamma) • Ibrutinib (generalised gamma)	[redacted]	[redacted]	Dominating
Zanubrutinib and ibrutinib TTD is equal to the KM data	[redacted]	[redacted]	Dominating
Alternative utility value: SMC 2016	[redacted]	[redacted]	Dominating
Alternative utility value: Simons et al. 2016	[redacted]	[redacted]	Dominating
Subsequent treatment costs: Excluded	[redacted]	[redacted]	Dominating
Subsequent treatment costs: CAR-T included	[redacted]	[redacted]	Dominating

CAR-T - chimeric antigen receptor T-cell; DCO – data cut off; ICER – incremental cost-effectiveness ratio; LYG – life years gained; OS- overall survival; PFS – progression-free survival; SMC – Scottish Medicines Consortium; QALY – quality adjusted life year

B.3.11.3.1 Cost-comparison analysis: zanubrutinib versus ibrutinib

Based on the MAIC analyses (Section B.2.9 Indirect and mixed treatment comparisons) and the results of the CEA (Section B.3.10 Base-case results and Section B.3.11 Exploring uncertainty), there is robust evidence that zanubrutinib provides greater health benefits for patients with 2L R/R MCL compared to ibrutinib. However, in order to explore any uncertainty in this assumption, a cost-comparison analysis was conducted to evaluate the cost and resource use associated with the treatment of zanubrutinib compared to ibrutinib i.e. no HRQoL benefit was modelled (no QALYs).

Equal efficacy is assumed across the modelling of PFS and OS in both treatment arms; ibrutinib PFS and OS are assumed to be equal to zanubrutinib PFS and OS. AE rates were assumed to be equal across treatment arms and aligned with the zanubrutinib rates used in the company's base-case CEA (Section B.3.4.5 Adverse reactions). In both treatment arms TTD is modelled as equal to PFS (See Section B.3.3.4 Time to treatment discontinuation

).

The results of the cost-comparison analysis are presented in Table 79. Using the list price of ibrutinib and the PAS discount for zanubrutinib, zanubrutinib is associated with a total cost of £[redacted] and ibrutinib is associated with a total cost of £[redacted], meaning that zanubrutinib is associated with a savings of £[redacted] over a lifetime horizon.

Table 79: Cost-comparison scenario analysis in patients with 2L R/R MCL

Technologies	Total costs	Incremental costs
Zanubrutinib	[redacted]	-
Ibrutinib	[redacted]	[redacted]

MCL – mantle cell lymphoma; R/R – relapsed or refractory

B.3.12 Subgroup analysis

As per the final scope, no subgroup analyses were conducted as subgroups were not considered relevant to this appraisal to evaluate the cost-effectiveness of treatment with zanubrutinib compared with ibrutinib in adult patients with 2L R/R MCL.[91]

Although the target population of this submission is adults with 2L R/R MCL, all patients from the zanubrutinib BGB-3111-AU-003 and BGB-3111-206 clinical trials were incorporated into the CEA. Given the baseline characteristics and efficacy endpoint results were consistent for patients 2L-only versus ≥2L (see Sections: B.2a.3.4 Patient characteristics, B.2b.3.4 Patient characteristics, B.2a.6 Clinical effectiveness results of the relevant studies: BGB-3111-AU-003 and B.2b.6 Clinical effectiveness results of the relevant studies: BGB-3111-206), all R/R MCL patients were included in the ITC and consequently, the economic model in order to maximise the patient sample used in the analyses. Furthermore, the BGB-3111-AU-003 and BGB-3111-206 trials were not powered to support efficacy endpoint results by patients in line of therapy subgroups. See Section B.2.9 Indirect and mixed treatment comparisons for further details.

The company do not consider it necessary to conduct any further subgroup analyses. This aligns with the final scope of NICE TA502 (ibrutinib for R/R MCL), in which no specific subgroups were included.[91,122]

B.3.13 Benefits not captured in the QALY calculation

As a next generation BTK inhibitor, the improved safety profile of zanubrutinib (due to improved selectivity, specificity and reduced inhibition of off-target kinases) compared to existing BTK inhibitors in other relevant blood cancers (WM, CLL and MZL) is anticipated to also apply in MCL.[51,123,124] The clinical and safety outcomes of zanubrutinib in R/R MCL have been demonstrated in two single-arm phase 2 clinical trials, in which zanubrutinib induced durable responses and demonstrated long-term PFS and OS. UK clinical experts at an advisory (11th November 2024) confirmed that

they expected zanubrutinib, in the worst case scenario is expected to be at least as effective in patients with 2L R/R MCL as ibrutinib.

Zanubrutinib's improved tolerability is also apparent in the observed RDI at 100%, whilst the RDI of ibrutinib in the pooled trials was 94%, demonstrating that not all patients can tolerate the recommended dose of ibrutinib. With a higher RDI, zanubrutinib is more likely to deliver optimal therapeutic benefits, ensuring patients receive the full intended dose without interruptions, which can contribute to improved efficacy and potentially better clinical outcomes. This improved tolerability may also lessen the caregiving burden, as caregivers could face fewer demands related to managing side effects. Moreover, the more tolerable safety profile of zanubrutinib may lead to reduced healthcare utilisation, resulting in fewer hospital visits and follow-ups, which could contribute to cost savings and resource efficiencies for the NHS. This benefit would be captured via treatment-dependent resource use analysis. However, in alignment with NICE's approach in TA502, we adopted the more conservative assumption that HCRU varies by health state rather than by treatment arm, and thus did not include it in the model.

A similar argument can be presented regarding the proportion of patients receiving subsequent treatment. In the CEM base-case, the distribution of subsequent treatments algins with the therapies typically received at 3rd-line, post ibrutinib treatment, based on UK clinical practice as derived from real-world HMRN data. Given zanubrutinib's improved PFS and more tolerable safety profile over ibrutinib, patients may experience fewer adverse events and better treatment adherence, potentially reducing the need for disease management support and lowering the overall treatment burden on the patient and NHS resources.

Additionally, zanubrutinib has improved PFS and OS rates over ibrutinib. This not only benefits the patient themselves, but also their caregivers/family members as zanubrutinib patients will remain progression-free for longer, putting less strain on the caregivers/family members. This benefit could be captured via a societal perspective however, this perspective is not included in the analysis.

B.3.14 Validation

B.3.14.1 Validation of cost-effectiveness analysis

Upon completion of the model programming, a rigorous and comprehensive quality check of the model was conducted by an internal health economist not involved with the original programming to ensure the completed model contained no errors and worked as intended. This included validating the logical structure of the model, the expressions and sequences of calculations, and the values of numbers supplied as model inputs.

An extreme-value sensitivity analysis was also conducted on all applicable model inputs. Whilst conducting the analysis, the validator noted the direction and magnitude of change for each extreme value tested and confirmed that this aligned with the expected result (e.g., if all drug cost inputs are set to 0, the model should output total drug costs of 0 as well). The model validation process uncovered minimal discrepancies and no impactful model calculation errors. Feedback from the validation was addressed in the model, and the refined post-validation model was used to generate the results included in this report.

B.3.14.2 Clinician validation/advisory board

Furthermore, the model structure, assumptions, inputs and outputs were validated by UK clinical, economic and statistical experts at an advisory board (11th November 2024) organised by the Company. Feedback from the experts was incorporated into this submission.[2] In particular, the choice of clinical evidence to inform the MAIC, the MAIC methodology and plausibility of the MAIC and survival extrapolations, were validated at the advisory board. A review of treatments for MCL in previous NICE TAs (in particular NICE TA502[4]) and published literature was carried out to further validate the key model assumptions, inputs, and outputs.

B.3.14.3 Validation against clinical trial data

Finally, the modelled outputs were compared to the clinical trial data for validation purposes. Table 80 demonstrates that the predicted survival (using the base case curve selection) aligns well with the observed data for zanubrutinib, which can

increase confidence in the CEA results. As demonstrated, the model predicted PFS and OS closely aligns to the observed data in year 1 and year 3 for both treatments arms. Clinical experts consulted as part of an advisory board (11th November 2024) held by the Company confirmed that PFS is an appropriate source to model TTD.[2]

Table 80: Comparison of modelled and observed survival

Endpoint	Proportion of patients		
	Year 1	Year 3	Year 5
PFS			
Zanubrutinib KM	[redacted]	-	-
Zanubrutinib curve (log-normal)	[redacted]	[redacted]	[redacted]
Ibrutinib KM	51%	-	-
Ibrutinib curve (log-normal)	48%	21%	13%
OS			
Zanubrutinib KM	[redacted]	[redacted]	-
Zanubrutinib curve (log-normal)	[redacted]	[redacted]	[redacted]
Ibrutinib KM	67%	50%	-
Ibrutinib curve (log-normal)	68%	41%	29%

KM – Kaplan-Meier; OS – overall survival; PFS – progression-free survival

B.3.15 Interpretation and conclusions of economic evidence

B.3.15.1 Summary

In the base-case analysis, treatment with zanubrutinib in patients with 2L R/R MCL was associated with cost savings of £[redacted] and [redacted] incremental QALY gains resulting in zanubrutinib dominating ibrutinib. The NHB at £20,000 and £30,000 of [redacted] and [redacted], respectively, implies that overall population health would be increased as a result of introducing zanubrutinib. Results are robust to changes in key model parameters, with zanubrutinib continuing to dominate ibrutinib for all scenarios (including highly pessimistic survival curve scenarios for zanubrutinib). The model was robust to parameter uncertainty with the mean PSA results lying close to the deterministic results for the base-case and for all scenarios considered. Zanubrutinib was [redacted]% cost-effective at a willingness to pay of £30,000 per QALY or more.

B.3.15.2 Strengths and weaknesses

The main strengths of the analyses are:

- The 3-health state PSM structure directly aligns with the time-to-event endpoints available from the clinical data sources. The PSM structure is a widely accepted approach that has been used in previous NICE HTAs in oncology,[64,109,125] and reflects the disease progression of MCL. The model structure was validated as appropriated by UK experts at an advisory board (11th November 2024).

- Efficacy data for zanubrutinib is informed by pooled data from the BGB-3111-AU-003 and BGB-3111-206 clinical trials.[42,43] These trials measured key outcomes, such as PFS, OS and AE rates, that are used in the model.[42,43] The baseline characteristics were deemed representative of a UK patient population by UK clinical experts at an advisory board on the 11th of November 2024, with the exception of the higher number of younger patients and patients who were rituximab-naïve (25.6%) in BGB-3111-206.[2] In order to reduce any concerns around generalisability, age was adjusted for in the base case MAIC. Additionally, a scenario MAIC conducted using pooled data from the BGB-3111-AU-003 and BGB-3111-206 trials with rituximab-naïve patients removed and demonstrated results consistent with the company's base-case analysis, demonstrating that aligning the sampled population to be even more reflective of the UK patient population provides the same statistically significant benefit. See Section B.2.9.5 Results for further details of the MAIC scenarios.

- Clinical effectiveness data for the comparator arm (ibrutinib) was estimated using pooled data from the RAY (MCL3001), SPARK (MCL2001) and PCYC-1104 clinical trials from Rule et al. (2017b)[17]. The pooled dataset is large (n=370) and the committee in NICE TA502 concluded that pooling the data was appropriate. Furthermore, it was possible to generate a robust MAIC analysis of the zanubrutinib trial data to the pooled ibrutinib data (both in the base case and sensitivity analysis datasets).

- The model included cost categories appropriate for a UK NHS and PPS perspective, with costs and resource use inputs sourced from appropriate UK based sources and inflated to a 2023/24 cost year where necessary. Drug administration, AE and resource use costs were obtained from NHS reference costs, whilst drug acquisition costs were taken from the BNF.[12,105,113]

- The clinical outcomes predicted by the model and the assumptions underpinning it were ratified by UK clinical expert opinion at an advisory board (11th November 2024).[2,98] The modelled clinical outcomes align well with the trial data (see Appendix J).

While the model has many strengths, some limitations remain:

- Clinical benefits beyond the duration of the trials were estimated through the fitting of parametric distributions to patient level data to estimate PFS and OS, over a lifetime horizon. These estimates may give rise to uncertainty in the efficacy results, but the approach taken was appropriate given the inherent limitation of short-term trial durations. The methods for survival extrapolation follow the NICE DSU guidelines and the extrapolations were validated by external UK clinical experts. To explore uncertainty in the results, scenario analyses considered alternative parametric distributions, which were found to have no significant impact on the results, with zanubrutinib dominating ibrutinib and remaining cost-saving.

- Both of the zanubrutinib trials were single arm, which means that there is no direct treatment comparison of zanubrutinib versus ibrutinib, which may introduce uncertainty. This shortcoming was addressed by conducting an unanchored MAIC analysis (adjusting the zanubrutinib dataset to ibrutinib) to generate comparative effectiveness results. The MAIC base case demonstrated that treatment with zanubrutinib resulted in a statistically significant benefit in both PFS and OS versus ibrutinib. Extensive scenario analyses confirmed the consistency of these analyses to the base-case results from the MAIC, including the use of alternate datasets.

- In the absence of direct HRQoL data from both the zanubrutinib and ibrutinib trials, an SLR was conducted to identify additional data sources that could better inform health-state utilities. The values used were sourced from the TA502 submission which were previously accepted by the ERG.[4] Scenario analyses were conducted using alternative, SLR identified data sources and these demonstrated that zanubrutinib continues to dominate ibrutinib.

B.3.15.3 Conclusion

In conclusion, this submission demonstrates the clinical and cost-effectiveness of zanubrutinib versus ibrutinib (that reflects standard of care in the UK). The economic evaluation confirms a robust and favourable cost-effectiveness profile with zanubrutinib dominating ibrutinib in the base case analysis and across all scenarios, with the inclusion of a simple discount. As such the Company maintains that a cost-comparison methodology is the most appropriate approach to appraise zanubrutinib in 2L R/R MCL.

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B.5 Appendices

Please refer to standalone appendix documents, submitted alongside this Company submission.

Appendix C: Summary of product characteristics

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource use studies

Appendix J: Clinical outcomes and disaggregated results

Appendix K: Price details of treatments included in the submission

Appendix L: Checklist of confidential information

Appendix M: Supplementary MAIC

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Zanubrutinib for treating relapsed or refractory mantle cell lymphoma [ID6892]

Summary of Information for Patients (SIP)

January 2025

File name	Version	Contains confidential information	Date
ID6392_Zanubrutinb for treating rrMCL _SIP_v1.0_(10Jan_FINAL)	1.0	No	10 January 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the grey text included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers. Additional prompts for the company have been in red text to further advise on the type of information which may be most relevant and the level of detail needed. You may delete the red text.

1a) Name of the medicine (generic and brand name):

Generic name: Zanubrutinib Brand name: BRUKINSA

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

BRUKINSA as a monotherapy for the treatment of adult patients with mantle cell lymphoma who have received at least one prior therapy

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

On the 21st November 2024, zanubrutinib monotherapy was approved in the UK for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy by the Medicines and Healthcare products Regulatory Agency through the International Recognition Procedure.[1]

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

None

SECTION 2: Current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation should include country-level information where needed to provide local country-level context.

Please focus this submission on the **main indication (condition and the population who would use the treatment)** being assessed by NICE rather than sub-groups, as this could distract from the focus of the SIP and the NICE review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen.

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Non-Hodgkin's lymphoma refers to a variety of cancers that affect the lymphatic system.[2] The lymphatic system is part of the body's immune system and helps protect people from infection and disease. There are two main types of non-Hodgkin's lymphoma: indolent, which grows slowly but is harder to cure, and aggressive, which grows quickly but is more likely to be curable. The characteristics of non-Hodgkin's lymphoma are influenced by the cells in which the cancer originally started.[2,3]

Mantle cell lymphoma is a group of indolent non-Hodgkin's lymphoma that develops from B cells. It is called 'mantle cell' lymphoma because the abnormal B cells usually develop in a part of the lymph nodes called the 'mantle zone'.[4] Mantle cell lymphoma can occur at any age but is more common in middle-aged or older people.[4] The incidence of mantle cell lymphoma is greater in men compared to women.[4] In the United Kingdom (UK), approximately 0.9 new patients are diagnosed with mantle cell lymphoma for every 100,000 people per year.[5]

The World Health Organisation recognises three main subtypes of mantle cell lymphoma, which are dependent on the tissue where the lymphoma originated from[6]:

- Classical, usually involves lymph nodes and other extranodal sites
- Leukemic nonmodal, usually involves the blood, bone marrow and spleen. These cases are frequently clinically indolent; however, secondary abnormalities, often involving a mutation of the TP53 gene, may occur and lead to very aggressive disease.
- In situ mantle cell neoplasia, characterised by the presence of cancer cells in the inner mantle zones of lymphoid tissues.

Each type of mantle cell lymphoma has unique features, which can influence the choice of initial treatment a patient may receive.

The most common symptom in patients with mantle cell lymphoma is the development of lumps in several parts of the body, caused by swollen lymph nodes.[4] When symptoms occur, they differ depending on the tissue involved. Additional common symptoms include unexplained weight loss, night sweats, fever, fatigue, prolonged or excessive bleeding, weakened immune system leading to longer times to fight infection.[4]

When the disease has progressed beyond its tissue of origin to other locations in the body the disease is defined as advanced stage disease. Mantle cell lymphoma is associated with cycles of relapse and remission. When a patient experiences a relapse, it is often when the disease is at an advanced stage.[4]

Mantle cell lymphoma can significantly impact a patient's quality of life due to its symptoms and treatment implications.[7] When the disease returns after initial treatment, symptoms can worsen and new ones may appear, compounding the impact on patient's quality of life.[7] The emotional burden of living with a relapse, uncertainty related to disease progression, and the need for further treatment can take a toll on a patient's mental well-being.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Initially patients with early-stage disease mantle cell lymphoma may appear asymptomatic, hence the presence of disease is often detected during a routine clinical check-up. Clinical presentation will differ depending on the tissue involved.[4]

In most instances, when a patient does present as symptomatic the signs of mantle cell lymphoma involve the presence of swollen lymph nodes or an enlarged spleen. A minority of patients present with symptoms such as fever, night sweats and/or unintentional weight loss, once the lymphoma becomes more advanced.[4]

Mantle cell lymphoma is usually diagnosed with a biopsy, a medical procedure where a small sample of the affected tissue is taken and examined under a microscope to understand the extent of the disease.[4] If patients have leukemic mantle cell lymphoma, the lymphoma may be diagnosed through a blood test.[4]

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For

example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Often patients with mantle cell lymphoma present without symptoms if their disease is at an early stage. In these cases, clinicians usually watch the condition closely without starting treatment right away. Treatment begins when symptoms appear, such as, lymph nodes becoming very large, or the if lymphoma starts to affect a patient's organs or blood counts. When this occurs, the main goal is to manage symptoms and to help patients have longer periods without the disease getting worse.[4,8]

The choice of first-line treatment is dependent on several factors, including the age and fitness of the patient, symptoms experienced and disease staging.

Commonly used first-line treatments for mantle cell lymphoma are:[9]

- Rituximab-based chemotherapy
- Rituximab monotherapy
- Non-rituximab-based chemotherapy
- Autologous stem cell transplant (ASCT) consolidation treatment following chemotherapy induction (for younger patients [<65 years of age] who are deemed fit enough for ASCT)

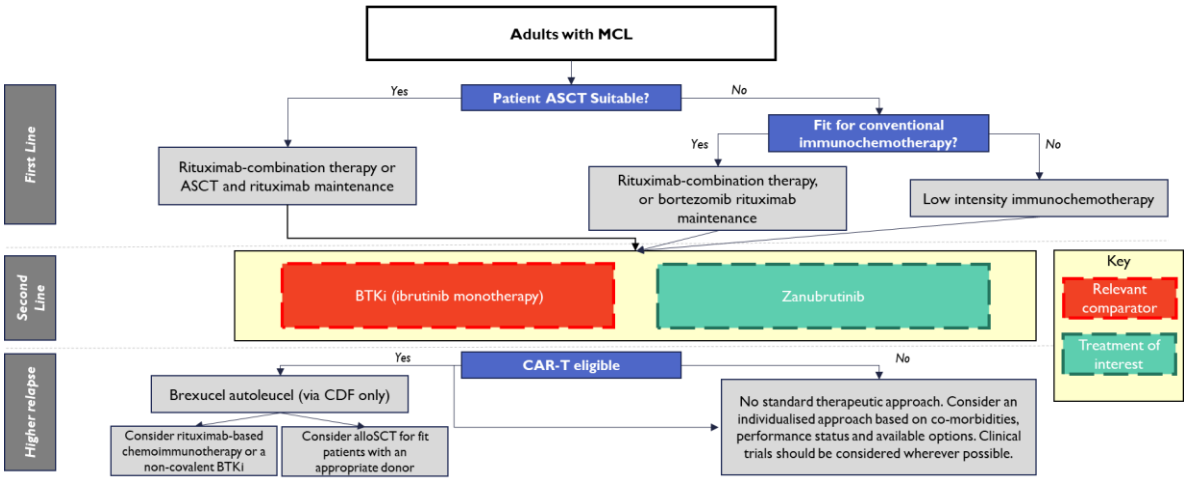
Following initial treatment, lymphoma can come back (relapsed) or not respond to the treatment (refractory disease). Clinical guidelines from the British Society of Haematology (published in 2023) recommend the use of ibrutinib monotherapy after a patient relapses when on first-line treatment which is typically immunochemotherapy (e.g rituximab with or without chemotherapy). This is aligned to the National Institute for Health and Care Excellence (NICE) recommendation to use ibrutinib monotherapy for patients with MCL who have received one prior line of therapy. [7] A small proportion of patients may receive rituximab with or without chemotherapy at first relapse, however the numbers are small (<5%), confirming that ibrutinib is the standard of care for second-line treatment.[10]

Following failure to respond to the second treatment received (2L), patients will be offered a different treatment (3L). 3L treatment options include rituximab with or without chemotherapy, or cell therapy with brexucabtagene autoleucel. However, brexucabtagene autoleucel is only recommended for reimbursement by NICE in patients who have previously received a Bruton tyrosine kinase (BTK) inhibitor (such as zanubrutinib or ibrutinib), therefore patients who are eligible for zanubrutinib are not also eligible for

brexucabtagene autoleucel at the same point in their treatment pathway.[9,11]

Zanubrutinib is expected to be used in line with the marketing authorisation, as a treatment for patients with relapsed or refractory mantle cell lymphoma, after at least one prior therapy.[1] As such, zanubrutinib will be entering the clinical pathway of care at second line, and based on feedback from clinical experts may displace ibrutinib use, as presented in Figure 1.[10]

Figure 1: Clinical pathway of care and proposed positioning of zanubrutinib



N.B. Ibrutinib is only recommended by NICE as a second line treatment
MCL – mantle cell lymphoma.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Patient-based evidence about living with mantle cell lymphoma was gathered as part of the NICE appraisal of ibrutinib (NICE TA502[7]). UK patient representatives described:

- the lack of treatment options in mantle cell lymphoma, where frequent relapses mean most patients quickly exhaust the finite number of chemotherapy options and become chemo-refractory (where their disease does not respond to chemotherapy).
- enduring symptoms, such as fatigue, night sweats and weight loss, that can affect their ability to work and take part in their chosen leisure activities. The enlargement of lymph nodes, spleen, and other organs can lead to discomfort and pain, impacting the patient's quality of life.[4]

- the burden on caregivers' day-to-day life, as the time and energy spent caring for the patients reduces their ability to fulfil obligations and contribute financially to the household.

Despite being the current standard of care second-line treatment option, ibrutinib is also associated with a high toxicity profile and has a range of debilitating side-effects such as diarrhoea, fatigue, cough and thrombocytopenia, which have a detrimental impact on patients' quality of life.[12] Compared to new and more innovative treatments, such as zanubrutinib, ibrutinib may not be as effective in achieving fuller and longer remissions. As such, there is a considerable unmet need for patients with mantle cell lymphoma.

SECTION 3: The treatment

Note to authors: Please complete each section with a concise overview of the key details and data, including plain language explanations of any scientific methods or terminology. Please provide all references at the end of the template. Graphs or images may be used to accompany text if they will help to convey information more clearly.

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Zanubrutinib is a next-generation BTK inhibitor. BTK is a protein that plays a key role in the B-cell receptor signalling pathway which helps cancer cells grow and survive. By blocking BTK, zanubrutinib helps kill and reduce the number of cancer cells, which can slow down the worsening of cancer.[8,13]

The Summary of Product Characteristics can be found here:

https://mhraproducts4853.blob.core.windows.net/docs/8fe909146aefae92425140ba9d1827e49013f9ec

A patient information leaflet, prepared by BeiGene, can be found here:

https://www.brukinsa.com/patient-information.pdf

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

N/A. For patients with R/R MCL zanubrutinib is not intended to be used in combination with any other medicines.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Consistent with existing licensed indications for zanubrutinib and the MCL trials relevant to this NICE submission (BGB-3111-206 and BGB-3111-AU-003), the recommended dose of zanubrutinib is 320 mg per day.[1,8,13] This can be taken as four 80 mg capsules once a day, or as two 80 mg capsules twice a day.

Patients must swallow the capsules whole with water (with or without food), and not open, break or chew the capsules. Zanubrutinib should be taken until a patient's disease progresses (as determined by their clinician) or until unacceptable toxicity/side effects are experienced by the patient.

Zanubrutinib is a simple oral regimen and does not require frequent hospital visits. This limits the disruption to both patients' and caregivers' lives who avoid having to travel to the hospital for treatment.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Zanubrutinib has been investigated in mantle cell lymphoma in two single arm trials, BGB-3111-206 and BGB-3111-AU-003. A summary of the key clinical trials for zanubrutinib is presented in Table 1.

Table 1: Clinical effectiveness evidence

Study title	BGB-3111-206[8,14]	BGB-3111-AU-003[13,15]
Study design	A phase 2, single arm, multicentre, open-label study	A phase 1/2, single arm, multicentre, open-label study
Population	Patients with mantle cell lymphoma who have received at least one prior line of therapy	Patients with B-cell lymphoid malignancy, including patients with mantle cell lymphoma who have received at least one prior line of therapy
Intervention(s)	Zanubrutinib (N=86)	Zanubrutinib, R/R MCL cohort (N=32)

Comparator(s)	Not applicable, trial was single arm only	Not applicable, trial was single arm only
Key inclusion criteria	• Age ≥ 18-75 years • Confirmed mantle cell lymphoma (any subtype) • At least one prior line of therapy • Documented failure to an objective response or documented progressive disease after an objective response to the most recent regimen • ECOG Performance Status score of 0-2 • Measurable disease • Adequate hematologic, renal and liver function • Life expectancy of at least 4 months	• Age ≥ 18 years • Relapsed or refractory WHO-defined indolent lymphoma (inclusive of mantle cell lymphoma) • At least one prior line of therapy, with no therapy of higher priority available • ECOG Performance Status score of 0-2 • Adequate haematologic, renal and liver function
Key exclusion criteria	• Current central nervous system involvement by lymphoma or leukaemia • Prior treatment with a BTKi • History of other active malignancies within 2 years of study entry, with the exception of: ○ Adequately treated in-situ carcinoma of cervix ○ Localised basal cell or squamous cell carcinoma of the skin ○ Previous malignancy confined and treated locally (surgery or other modality) with curative intent • Currently significant cardiovascular disease	• Current central nervous system involvement by lymphoma or leukaemia • Prior treatment with a BTKi • Allogeneic stem cell transplantation within 6 months or had active graft-versus-host disease requiring ongoing immunosuppression • Not recovered from toxicity of any prior chemotherapy to Grade 1 or lower • History of other active malignancies within 2 years of study entry, with the exception of: ○ Adequately treated in-situ carcinoma of cervix ○ Localised basal cell or squamous cell carcinoma of the skin ○ Previous malignancy confined and treated locally (surgery or other modality) with curative intent • Cardiovascular disease resulting in NYHA status of 3 or more
Completion date	September 08, 2020	March 31, 2021
Outcomes	• ORR: 83.7% • Median PFS: 27.5 months	• ORR: 84.4% • Median PFS: 21.1 months

	• Median OS: Not reached, 80.2% alive at a median follow-up of 24.9 months • Patients with at least one adverse event: 83 (96.5%) • Patients with at least one grade ≥3 adverse event: 34 (41.9%) • Most common grade ≥3 adverse event: lung infection - 8 (9.3%), neutropenia - 17 (19.8%), leukopenia - 6 (7.0%) and anaemia - 5 (5.8%)	• Median OS: 27.2 months, 62.5% alive at a median follow-up of 22.0 months • Patients with at least one adverse event: 31 (96.9%) • Patients with at least one grade ≥3 adverse event: 19 (59.5%) • Most common grade ≥3 adverse event: infections – 6 (18.8%), anaemia – 4 (12.5%) and, pneumonia, myalgia and neutropenia all at 3 (9.4%)

BTKi – Bruton's Tyrosine Kinase inhibitor; ECOG – Eastern Cooperative Oncology Group; N/A – not applicable; NYHA – New York Heart Association; WHO – World Health Organisation.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Zanubrutinib as a monotherapy has been investigated in mantle cell lymphoma in two single arm trials, BGB-3111-206 and BGB-3111-AU-003.[17,18] These studies looked at how effective zanubrutinib is in reducing or eliminating tumours in patients with relapsed or refractory mantle cell lymphoma.

BGB-3111-206

The primary outcome measured in the BGB-3111-206 trial was overall response rate. Overall response rate measures the proportion of patients who have a response to treatment (i.e. the proportion of patients whose tumour disappears or is significantly reduced by a drug). In the BGB-3111-206 trial, 83.7% of patients treated with zanubrutinib had a tumour that completely disappeared or was partially reduced. There was no difference by mantle cell lymphoma subtype, and 77.9% of patients achieved complete tumour remission. As mantle cell lymphoma is considered an indolent uncurable disease, this represents a high proportion of patients with either complete tumour remission or partial response. High response rates were also observed in known poor prognostic groups such as patients over the age of 65 years of age, patients with target lesions of more than 10cm and patients with refractory disease. For further information on overall response rate in the BGB-3111-206 trial please see Document B, Sections B.2.a.6.1.

Progression-free survival and overall survival were also captured in the BGB-3111-206 trial. Progression-free survival measures the length of time after starting treatment that a patient lives with a disease without it progressing. In BGB-3111-206 trial, 50% of patients remained progression-free for at least 33.0 months. Overall survival measures the length of time after starting treatment that a patient is alive. As mantle cell lymphoma follows an indolent disease course, few death events occurred in the BGB-3111-206 trial. After a median follow-up of 36.8 months, 74.8% patients were alive after 36 months, and median overall survival was not reached. For further information on progression-free survival and overall survival in BGB-3111-206 trial, please see Document B, Sections B.2b.6.2.1 and Sections B.2b.6.2.1, respectively.

BGB-3111-AU-003

The primary outcome measured in the BGB-3111-AU-003 trial was also overall response rate. In BGB-3111-AU-003, 84.4% of patients treated with zanubrutinib had a tumour that completely disappeared or was partially reduced. Aligned to the BGB-3111-206 trial, there was no difference by mantle cell lymphoma subtype and 25.0% of patients achieved complete tumour remission, along with 59.4% who achieved a partial response. As mantle cell lymphoma is considered an indolent disease and uncurable, this represents a high proportion of patients with either complete tumour remission or partial response. For further information on overall response rate in the BGB-3111-AU-003 trial, please see Document B, Sections B.2.3.1.

Progression-free survival and overall survival results were consistent with observations from the BGB-3111-206 trial. In the BGB-3111-AU-003 trial, 43.8% of patients had progressed after a median follow-up of 17.5 months and 50.4% of patients were progression-free at 18 months. After a median follow-up of 22.0 months, 62.5% patients were alive. For further information on progression-free survival and overall survival in BGB-3111-AU-003, please see Document B, Sections B.2b.3.2.1 and Sections B.2b.3.2.1.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Quality of life data was not collected in the BGB-3111-206 or the BGB-3111-AU-003 trials. However, patients receiving zanubrutinib have a better disease control (in terms of both progression-free survival and overall survival) when compared with ibrutinib, as

demonstrated in the ibrutinib and zanubrutinib trials in MCL.[8,12,13] Zanubrutinib is also associated with fewer toxicity concerns compared with ibrutinib, as demonstrated in a BGB-3111-215 study and from head-to-head data from other relevant blood cancers (ASPEN and ALPINE trials).[19–21] As such, lower disease burden and treatment toxicity with zanubrutinib treatment, versus ibrutinib, would be expected to result in patients sustaining a higher quality of life for longer.

Compared to rituximab with or without chemotherapy, zanubrutinib is anticipated to have a reduced toxicity burden driven by an improved safety profile. Hence patient quality of life is not expected to be negatively impacted through the use of zanubrutinib over chemotherapy-based regimens. This is supported by clinical trials in other relevant blood cancers (SEQUOIA).[22]

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Safety analysis from the BGB-3111-206 and BGB-3111-AU-003 trials demonstrated that zanubrutinib is well tolerated and suggests a favourable benefit-risk profile for the treatment of patients with relapsed or refractory mantle cell lymphoma. The safety profile is consistent with previously published studies of zanubrutinib in similar blood cancers.[21,23–25] The most common side effects reported were decreased neutrophil, white blood cell and platelet count, upper respiratory tract infection, rash and diarrhoea.[16,18] The adverse events were consistent with the types of events expected for patients with R/R MCL. Adverse events leading to death and treatment discontinuation were consistent with those reported in the pivotal trial for ibrutinib: RAY-MCL3001.[26]

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration.

- Zanubrutinib is a simple oral regimen and does not require frequent hospital visits, which will offer an additional treatment option for those whose disease has not responded adequately to first line therapy.

- Zanubrutinib prolongs time until disease progression and death, and has shown that most patients will achieve a partial response, and some will achieve complete remission following treatment.[8,13]
- As a second generation BTKi, zanubrutinib has the potential to reduce the rate of discontinuation due to intolerance or adverse events experienced following ibrutinib treatment.[19]
- Adverse events associated with zanubrutinib are more tolerable and manageable for patients than those associated with ibrutinib.[19]

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

BTK inhibitors are associated with a number of class-specific side effects including bleeding, hypertension, atrial fibrillation, arthralgias, skin rash, and diarrhoea. The risk of cardiac adverse events and tolerability issues often leads to high level of treatment discontinuation. However, adverse events associated with zanubrutinib appear to be more tolerable and manageable for patients than those associated with other BTK inhibitors across a range of blood cancers.[19]

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

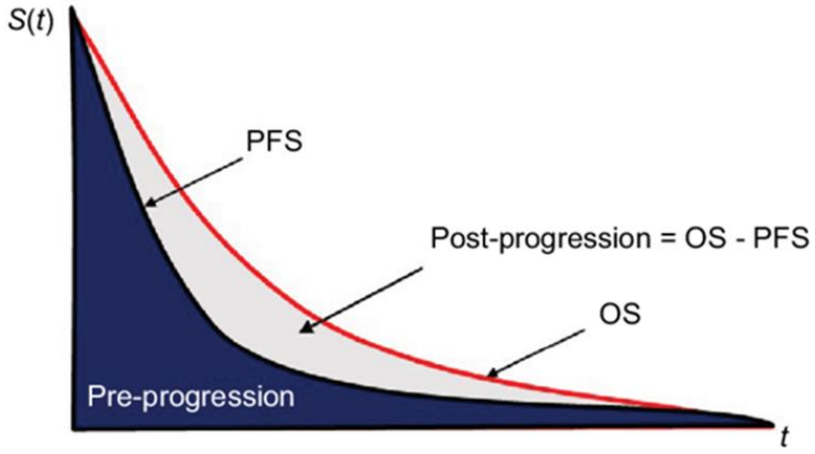
In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

<u>How the model reflects the condition</u>

A cost-effectiveness model was developed to evaluate the costs and survival benefits of using zanubrutinib to treat patients with relapsed or refractory mantle cell lymphoma who have received at least one prior therapy when compared to ibrutinib. The model tracks patients as they move from being in a progression-free state to a progressed disease state or until death occurs (Figure 2). The model calculates the cost of the initial treatment, one line of subsequent treatment (given at disease progression), disease management, adverse events, and end-of-life care and the associated outcomes for patients in terms of survival and their quality of life.

Figure 2: Health state structure used in the economic model



OS – overall survival; PD – Progressed disease; PF – Progression-free.

Modelling how much a treatment extends life

As highlighted in Sections 3e and 3g, zanubrutinib delays the progression of the disease, extends survival and is more tolerable compared to current treatment options. Published trial evidence was used to inform outcomes for ibrutinib. These data sources were compared to trial data from the BGB-3111-206 and BGB-3111-AU-003 trials. Data were projected over a 30-year time horizon using standard methods for extrapolation and survival was capped by the survival observed in the general UK population.

Modelling how much a treatment improves quality of life

Zanubrutinib is anticipated to have improved efficacy compared to the currently available treatment options. As such, patients are expected to be progression-free and survive for a longer period. Patients experience better quality of life whilst progression-free than when with progressed disease. In addition, the improved safety profile of zanubrutinib compared to other treatment options will result in improved quality of life through a reduction in the number of adverse events experienced. Quality of life was modelled to decrease with age as per standard modelling assumptions.

Modelling how the costs of treatment differ with the new treatment

When comparing to ibrutinib, zanubrutinib was associated with substantially lower treatment acquisition costs, in addition to improved progression-free and overall survival.

Uncertainty

The key uncertainties in the economic model relate to the prediction of long-term survival estimates. However, sensitivity analyses were performed to explore alternative assumptions for long-term survival. Individual model inputs were varied to explore the sensitivity of the model to certain inputs and analyses were run where model parameters were varied according to set statistical distributions. In addition, the impact of alternative assumptions was tested.

Cost-effectiveness results

In patients with relapsed or refractory mantle cell lymphoma:

- When comparing to ibrutinib for patients who have received one prior treatment line, over a lifetime time horizon, treatment with zanubrutinib resulted in fewer costs for the National Health Service (NHS), as well as greater survival and improved quality of life. Hence zanubrutinib can be considered a cost-effective use of NHS resources according to the criteria outlined by NICE.[27]

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Zanubrutinib is a second-generation BTK inhibitor with improved specificity and selectivity over first-generation BTK inhibitors. The clinical and safety outcomes of zanubrutinib in R/R MCL have been demonstrated in two single-arm phase 2 clinical trials, in which zanubrutinib induced durable responses and demonstrated long-term progression-free survival and overall survival.[8,13] As a second-generation BTK inhibitor, zanubrutinib has also demonstrated better tolerability over existing BTK inhibitors in other relevant blood cancers.[19]

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
There are no significant equality considerations associated with this appraisal.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Information about mantle cell lymphoma:

- What is mantle cell lymphoma: https://www.lls.org/research/mantle-cell-lymphoma-mcl
- Symptoms of mantle cell lymphoma: https://www.cancercenter.com/cancer-types/non-hodgkin-lymphoma/types/mantle-cell-lymphoma

Treatment guidelines:

- British Society for Haematology guidelines: https://b-s-h.org.uk/guidelines/guidelines/diagnosis-and-management-of-mantle-cell-lymphoma
- European Society for Medical Oncology guidelines: https://www.annalsofoncology.org/article/S0923-7534(19)42151-0/fulltext

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

- **Bruton tyrosine kinase:** a protein that plays a key role in the B-cell receptor signalling pathway which helps cancer cells grow and survive.
- **Monotherapy:** the use of a single drug to treat a particular disorder or disease.

- **Non-Hodgkin's Lymphoma:** a variety of cancers that affect the lymphatic system
- **Overall response rate:** the proportion of patients who have a response to treatment i.e. the proportion of patients whose tumour disappears or is significantly reduced by a drug.
- **Overall survival:** the length of time after starting treatment that a patient is alive.
- **Progression-free survival:** The length of time after starting treatment that a patient lives with a disease without it progressing.
- **Single arm trial:** A single-arm clinical trial is a type of medical research study where all participants receive the same treatment. There is no comparison group, like a placebo or different treatment group, which is common in other types of trials.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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7. NICE. Single Technology Appraisal: Ibrutinib for treating relapsed or refractory mantle cell lymphoma [TA502] [Internet]. 2018. Available from: https://www.nice.org.uk/guidance/ta502/resources/ibrutinib-for-treating-relapsed-or-refractory-mantle-cell-lymphoma-pdf-82606716182725

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Zanubrutinib for treating relapsed or refractory mantle cell lymphoma after 1 or more treatments [ID6392]

Clarification questions

February 2025

File name	Version	Contains confidential information	Date
ID6392 zanubrutinib EAG clarification questions_Company_response_17Feb25	1	Yes	17/02/2025

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Studies of clinical effectiveness

A1. Priority question: Please provide baseline characteristics and full results for the > 2L subgroup of the two zanubrutinib studies.

The >2L subgroup is outside of the proposed population submitted in the CS, particularly as ibrutinib is not recommended by the National Institute for Health and Care Excellence (NICE) in patients following 2L of therapy. The Company's proposed positioning for zanubrutinib in England and Wales is for patients at 2L, which is aligned with the population NICE recommended for ibrutinib.[1] As such the Company maintain that data for the >2L subgroup is not relevant to the decision making in this appraisal.

The Company would also like to highlight that the baseline characteristics and full efficacy results for the relapsed/refractory mantle cell lymphoma (R/R MCL) and 2L-only populations are presented in the CS. From the data presented the baseline characteristics of >2L patients can be calculated. Furthermore, differences in the efficacy outcomes between the 2L-only and full R/R MCL population can be inferred. The median progression-free survival (mPFS) in 2L-only patients appears to be

shorter than in the full population, using the latest data cuts (BGB-3111-AU-003: mPFS - [redacted] [95% confidence intervals [CI] [redacted], [redacted]] in 2L only patients vs. 21.1 [13.2, NE] in the full population and BGB-3111-206: mPFS - [redacted] [redacted] for 2L only patients vs. 33.0 [19.4, NE] in the full population). OS appears to be comparable across populations, with median OS not met in 2L-only or the full population. Given mPFS appears to be higher for the full population, it is clear that narrowing the proposed population to 2L-only patients does not bias the trial results in favour of zanubrutinib. One the contrary, positioning in 2L-only may bias the results in favour of ibrutinib for PFS. See Table 1 for a presentation of the PFS and OS efficacy outcomes for zanubrutinib trials.

Table 1: PFS and OS efficacy outcomes for zanubrutinib trials (full population and 2L-only)

	BGB-3111-AU-003 (DCO: 31st March 2021)		BGB-3111-206 (DCO: 8th September 2020)	
	Full population	2L-only	Full population	2L-only
Median PFS, months (95% CI)	21.1 (13.2, NE)	[redacted]	33.0 (19.4, NE)	[redacted]
Median OS, months (95% CI)	NE (15.4, NE)	[redacted]	NE (NE, NE)	NE (NE, NE)

CI – confidence interval; DCO – data cut-off; NE – not estimable; OS – overall survival; PFS – progression-free survival

In response to A11 and B12 clarification questions, the Company have presented clinical and cost-effectiveness results using 2L-only trial evidence for zanubrutinib and ibrutinib. The results using 2L-only trial data are consistent with the full population results, with zanubrutinib extending time to progression and OS, and also dominating ibrutinib in the cost-effectiveness analysis, as presented in the CS. As such, these results demonstrate the same conclusions would be expected in the >2L population.

The Company maintains that, given zanubrutinib is likely to provide similar or greater health benefits to ibrutinib in the treatment of 2L R/R MCL at similar or lower cost, a cost-comparison methodology is the most appropriate approach to appraise zanubrutinib vs ibrutinib in 2L R/R MCL.

A2. For study BGB-3111-AU-003, reference 35 states sixteen treatment-naïve MCL patients and 37 R/R MCL patients were enrolled in parts 1 and 2, and that one patient from phase 1 and 31 patients from phase 2 are reported in the

publication. However, the CSR for BGB-3111-AU-003 (reference 43) implies 57 patients with MCL were enrolled. CS B.2a.3.1 states 'A total of 32 patients with R/R MCL were exclusively enrolled in Part 2'. Please explain these apparent differences. Please explain how many patients with MCL and RR/MCL were enrolled in each phase of the study, what the starting dose was, and which of these patients comprise the 32 patients reported in the CS.

Reference 35 reports clinical trial data as of the data cut-off (DCO) of 13th December 2018, whereas the CSR (reference 43) reports clinical trial data as of the DCO of 31st August 2021. For the earlier DCO (reference 35), 53 MCL patients were enrolled in the study, of whom 16 were treatment-naïve and 37 had R/R MCL. The later DCO data (reference 43) reports that 57 MCL patients were enrolled in the study, of whom 20 were treatment-naïve and 37 had R/R MCL. The difference therefore relates to the additional four treatment-naïve patients enrolling in the study between the two DCO dates. Given the scope of the CS is R/R MCL, this has no impact on the analyses.

As of the latest DCO date (31Aug2021), six R/R MCL patients were enrolled in Part 1 of the study, and 31 R/R MCL and 20 MCL patients were enrolled in Part 2.

The starting dose of R/R MCL patients (N=37) enrolled in the study (parts 1 and 2) is as follows:[2]

- Part 1:
    - 40 mg once daily (QD) (n = [redacted])
    - 80 mg QD (n = [redacted])
    - 160 mg QD (n = [redacted])
    - 320 mg QD (n = [redacted])
- Part 2:
    - 160 mg twice daily (n = [redacted])
    - 320 mg QD (n = [redacted])

The Company acknowledges that the statement 'A total of 32 patients with R/R MCL were exclusively enrolled in Part 2' in the Company Submission B.2a.3.1 is not accurate. The 32 R/R MCL patients reported in the submission comprise, [redacted] patient from Part 1 who received 320 mg QD, [redacted] patients from Part 2 who received 320 mg QD and [redacted] patients from Part 2 who received 160 mg twice daily. The five patients who received a total dose of <320 mg daily were not included in the summary of the clinical effectiveness or cost-effectiveness in the CS.

A3. How many UK patients were in the overall RR/MCL population of BGB-3111-AU-003, and in the 2L and >2L subgroups?

There were no UK patients in the R/R MCL population of BGB-3111-AU-003. Table 2 presents the distribution of R/R MCL patient by country and line of therapy.

Table 2: Patient disposition by country and prior lines of therapy

Geographic region	1 prior line of therapy, n (%)	2 prior lines of therapy, n (%)	>2 prior lines of therapy, n (%)
Australia	[redacted]	[redacted]	[redacted]
Korea	[redacted]	[redacted]	[redacted]
New Zealand	[redacted]	[redacted]	[redacted]
United States of America	[redacted]	[redacted]	[redacted]

N – number

As described in CS Section B.2a.3.4, clinical experts in attendance at the advisory board meeting conducted on 11th November 2024 confirmed that the baseline characteristics of patients in the BGB-3111-AU-003 trial appeared to be representative of R/R MCL patients in UK clinical practice.[3]

A4. In Table 9 the median number of prior therapies in the 2L subgroup (n=18) was [redacted], but 100% had 1 prior therapy, please explain the difference. Similarly, please explain why the median in the full population is not greater than 1.0.

The Company would like to correct the typographical error in CS Table 9 and Table 22. The median number of prior therapies in the 2L subgroup (n=18) should read: [redacted] instead of: [redacted]

For clarity, the median number of prior lines of therapy in the full population is [redacted] since this is the middle value in the ordered dataset.

A5. For Tables 13 and 26:

- **Please confirm whether OS was IRC-assessed as stated in the column heading.**
- **Please explain the abbreviation 'NR'.**
- **Please explain why IRC-assessed OS in the full population is 'NR' when it is available for the second-line only subgroup?**
- **Please provide data for the full population for both studies if available.**

The Company acknowledges that the column headings in Tables 13 and 26 of the CS may be confusing. To clarify, the reference to 'IRC/INV-assessed' in the table headings is relevant only to the objective response rate (ORR), PFS, duration of response (DOR) and time to response (TTR) endpoints and the method of assessment (IRC on INV) differed between the DCOs. The overall survival (OS) endpoint was not subject to assessment by either investigator (INV), or independent review committee (IRC) and as such, only the different DCO dates in the column headings are relevant to the median OS data presented in the tables.

The abbreviation 'NR' used in the tables is an abbreviation for 'not reported' as the median OS for the full population in the BGB-3111-AU-003 and BGB-3111-206 trials was not reported in the relevant publications and CSRs. Further to the EAG's request however, the Company have conducted the analyses to provide these values (based on data on file) and provided them below in Table 3 and Table 4.

Table 3: Overall survival BGB-3111-AU-003 (CS Table 13)

	Zanubrutinib full trial population (N = 32)		Zanubrutinib 2L-only (N = 18)	
	DCO 13Dec2018[2,4]	DCO 31Mar2021[5]	DCO 13Dec2018[6]	DCO 31Mar2021[6]
Median, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

CI – confidence interval; CSR – clinical study report; DCO – data cut-off; NE – not estimable; OS – overall survival
Source: Tam *et al.* (2021)[4] / BGB-3111 Regulatory summary of clinical efficacy[2], BGB-3111-AU-003 CSR[5], BGB-3111-AU-003 data on file[6]

Table 4: Overall survival BGB-3111-206 (CS Table 26)

	Zanubrutinib full population (N = 86)			Zanubrutinib 2L-only (N = 26)		
	DCO 15Feb2019[7]	DCO 31Aug2019[2]	DCO 08Sept2020[8,9]	DCO 15Feb2019[10]	DCO 31Aug2019[10]	DCO 08Sept2020[10]
Median, months (95% CI)	[redacted]	[redacted]	NE (NE, NE)	[redacted]	[redacted]	[redacted]

CI – confidence interval; CSR – clinical study report; DCO – data cut-off; NE – not estimable; OS – overall survival
Source: Song *et al.* (2020)[7], Song *et al.* (2022)[9], BGB-3111 Regulatory summary of clinical efficacy[2], BGB-3111-206 CSR[8], BGB-3111-206 data on file[10]

For the BGB-3111-AU-003 trial, median OS was reached in the earlier DCO (13Dec2018), but not at the later DCO (31Mar2021), as the median OS is based on the number of patients at risk at the DCOs (following censoring). The median OS for BGB-3111-206 was not reached at any of the DCOs.

The median OS data for the 2L-only populations was sourced from data on file for the preparation of the CS. The median OS results from the later DCOs (BGB-3111-AU-003: 31Mar2021 and BGB-3111-206: 08Sept2020) are considered most appropriate for decision-making rather than the results from the earlier DCOs.

A6. In Table 32 the mean time since end of last therapy was [redacted] in the pooled data column. Please explain why this is higher than the mean reported in study BGB-3111-206, given the mean was NR in study BGB-3111-AU-003?

The mean time since end of last therapy for the BGB-3111-AU-003 trial is not reported in Table 32 of the CS, instead NR (abbreviation of 'not reported'), as the relevant publications and CSR did not report this data. However, the Company has now provided the data below. Additionally, the Company has identified a slight error

in the pooled AU003-206 population mean time since end of last therapy and has corrected this below:

- BGB-3111-AU-003: [redacted]
- Pooled data: [redacted], instead of [redacted]

A7. In B.2b.4.1 the sample size calculation for BGB-3111-206 states ORR of 40% as both the null and alternative hypothesis. Additionally, 70% and 99% power are both mentioned. Please clarify the sample size calculation and show mathematically how the required sample size was obtained.

The sample size calculations for BGB-3111-206 were based primarily on the desired level of precision for the estimate for ORR (the primary endpoint for the trial). Assuming an ORR of 70% in this study compared with a historical control overall response rate of 40%, approximately 80 patients would be required to demonstrate statistical significance at a 1-sided alpha of 0.025 with power > 0.99, using a binomial exact test.

The following procedure was followed to calculate the sample size:

- Assume type I error α and type II error β, the historical response rate p_0 and target response rate p_1, the sample size n and corresponding critical value x_0 satisfy the conditions in the equations below.

Equation 1: Significance Level Condition

$$\sum_{x=x_0}^{n} \binom{n}{x} p_0^x (1-p_0)^{n-x} \leq \alpha$$

And

$$\sum_{x=x_0-1}^{n} \binom{n}{x} p_0^x (1-p_0)^{n-x} > \alpha \quad (1)$$

Equation 2: Power Condition

$$\sum_{x=x_0}^{n} \binom{n}{x} p_1^x (1-p_1)^{n-x} \geq 1-\beta \quad (2)$$

- The n can be found via grid search. Starting from a small initial value of n, x_0 is obtained using equations (1) and then adding in n, x_0 to equation (2) and check whether the power criteria is satisfied or not.

Indirect treatment comparison

A8. Section B.2.9.4: was multiplicity/multiple testing accounted for in all analyses, and specifically in the ITC analyses? If so, please provide details. If not, please re-evaluate the results using appropriate corrections to ensure the robustness of the conclusions. Please justify your choice of appropriate corrections.

The Company did not apply specific multiplicity adjustments in the indirect treatment comparison (ITC) analyses, as the risk of multiplicity is considered low for the following reasons:

- The ITC includes only one comparator and two outcomes (PFS and OS). Multiplicity is a greater concern in more complex networks or analyses involving multiple comparators and endpoints.
- The matched-adjusted indirect treatment comparison (MAIC) results demonstrated strong statistical significance for both PFS and OS, with p-values <0.01 in the base case (Table 38 in the CS). This level of significance was also consistent in Sensitivity Analyses #1 and #2 and leave-one-out analysis (based on the base-case settings), suggesting that the results are unlikely to be due to chance alone.
- PFS and OS are highly correlated, as PFS and OS often tracked together. This reduces the potential impact of multiple testing, as a true effect in one outcome is likely to be reflected in the other.

Given the above considerations, the Company maintains that no additional multiplicity adjustments are necessary, and the conclusions regarding comparative effectiveness remain robust.

A9. Priority question: Please provide an STC with the pooled studies, and with BGB-3111-AU-003 only.

As per the CS (Section B.2.9.2 and Appendix M), the Company maintains that a MAIC approach is appropriate for generating the comparative effectiveness of zanubrutinib versus ibrutinib. A MAIC methodology was adopted in preference to the STC methodology for the reasons below:

- The key prognostic factors and treatment effect modifiers, presented in Section B.2.9.4, were relatively well balanced thus the MAIC and STC methodologies are expected to produce similar results.
- The MAIC approach has been used in a number of oncology health technology appraisals (HTAs) submitted to and accepted by NICE, most recently the evaluation of zanubrutinib (TA1001) for the treatment of marginal zone lymphoma (MZL), for which a MAIC was conducted on PFS and OS.[11]
- While still a relevant methodology, STCs have not been used in many HTAs submitted to and accepted by NICE.

A robust unanchored MAIC was conducted in line with the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) guidelines and method described by Signorovitch *et al.* (2012).[12,13] Based on the reasons provided, the Company maintains that the MAIC analysis is sufficient to inform decision making and concludes that treatment with zanubrutinib extends time to progression and OS when compared to ibrutinib in 2L R/R MCL. Additionally, clinical experts and health economic experts in attendance at the advisory board meeting conducted on 11th November 2024 agreed that a MAIC approach was appropriate to estimate the relative effectiveness of zanubrutinib versus iburutinib in 2L R/R MCL.[3]

A10. Can you confirm whether the relationships between the treatment effect modifiers and prognostic factors with the outcomes (OS and PFS) were evaluated for complexity, such as through interaction testing or assessments of nonlinearity? If so, could you provide details on the methods used and whether any significant interactions or nonlinear effects were identified?

The Company adjusted for key prognostic factors and treatment effect modifiers, which were identified and clinically validated with clinical experts at an advisory board conducted on the 11th November 2024.[3]

To assess the impact of covariate selection, a leave-one-out analysis was conducted, where each adjusted covariate was sequentially removed to explore its effect on the treatment comparison and the effective sample size (ESS). The leave-one-out analysis produced hazard ratios (HRs) that were consistent with the base-case analysis, indicating that the findings were robust to the inclusion or exclusion of specific covariates (see Section M2 in Appendix M for further details).

The Company did not formally assess interactions between treatment and prognostic factors due to the limitations of the MAIC approach. In a MAIC, only individual patient data (IPD) for the BGB-3111-AU-003 and BGB-3111-206 trials was available, while the Rule *et al.* (2017b)[14] data is based on published aggregate outcomes. This prevents direct interaction testing between treatment and covariates across both datasets.

Nonlinearity was not explicitly tested because the primary goal of the MAIC was to balance key prognostic factors between populations, rather than to model complex relationships. While nonlinearity was not explicitly tested, the MAIC methodology applies a weighted rebalancing of patient characteristics to minimise confounding. Given that clinically validated prognostic factors and treatment effect modifiers were used and that the leave-one-out analysis confirmed the robustness of results, the Company maintains that the conclusions of the MAIC analysis are robust; treatment with zanubrutinib extends time to progression and OS when compared to ibrutinib in 2L R/R MCL.

A11. Priority question: Please repeat the MAIC using 2L only data from the zanubrutinib and ibrutinib studies. Please consider and justify choice of data for ibrutinib, including from the publication by Dreyling 2022 (Hemasphere 2022. 6: E712).

As discussed in the CS, Dreyling *et al.* (2022) was not identified in the systematic literature review (SLR) as, being a letter, it did not meet the selection criteria.[15] Dreyling *et al.* (2022) was instead identified by clinical experts at an advisory board conducted on the 11th November 2024.[3] The Company believe the letter which presents 10-year follow-up of patients in pooled ibrutinib studies (RAY-MCL3001, PCYC-1104 and SPARK) is relevant for the appraisal of zanubrutinib versus ibrutinib, as it:

- Uses the same ibrutinib R/R MCL dataset as Rule *et al.* (2017b), but with longer follow-up, to 10 years.
- Presents 2L PFS and OS Kaplan-Meier (KM), to inform the clinical effectiveness of an unanchored analysis in patients at 2L (relevant to the proposed positioning of zanubrutinib).

However, based on the covariate data presented in the letter, it is only possible to adjust for three covariates in a MAIC analysis: age, blastoid variant form of MCL and bulky disease. Consequently, any MAIC analysis using Dreyling *et al.* (2022) would not capture important prognostic factors or treatment effect modifiers, identified in the clinically validated list in Section B.2.9.3 of the CS.

As per the EAGs request, the Company has conducted a MAIC analysis using Dreyling *et al.* (2022) and the methods and results of the comparison are presented below.

The Dreyling *et al.* (2022) MAIC analysis was informed using 2L data from the pooled zanubrutinib population (AU003-206) (N=44), from the most recent DCOs (BGB-3111-AU-003: 31Mar2021 and BGB-3111-AU-206: 08Sept2020). Whilst for ibrutinib, the 2L data from 99 patients as reported in Dreyling *et al.* (2022) was used (Figure 1A and Figure 1B).

The summary of the population characteristics of the pooled zanubrutinib population (both unweighted and weighted) from AU003-206, and the ibrutinib population Dreyling *et al.* (2022) are presented in Table 5. After matching for selected covariates, the treatment arms were well balanced. A histogram of weights is included in Figure 1. After weighting, the ESS reduced by [redacted] %, demonstrating considerable overlap between the two patient populations. However, as mentioned above, only three covariates were adjusted for, and other key prognostic factors could not be accounted for.

Table 5: Summary of the population characteristics before and after matching zanubrutinib versus ibrutinib (AU003-206 [DCO: 31Mar2021/08Sept2020] [N=44] versus Dreyling *et al.* [2022] N=99)

Characteristics	AU003-206 (N=44), unweighted	AU003-206 (ESS= [redacted]), weighted	Dreyling *et al.* (2022) (N=99)
Age ≥ 70 years (%)	[redacted]	[redacted]	44.4
Bulky disease ≥ 5 cm (%)	[redacted]	[redacted]	39.4
Blastoid variant form of MCL (%)	[redacted]	[redacted]	6.0

cm – centimetres; DCO – data cut-off; ESS – effective sample size; MCL – mantle cell lymphoma; N - number

Figure 1: Histogram of normalised weights (AU003-206 [DCO: 31Mar2021/08Sept2020] [N=44] versus Dreyling *et al.* [2022] N=99)

DCO – data cut-off; ESS – effective sample size

Figure 2 and Figure 3 present the ibrutinib KM curves, and the unweighted and weighted KM curves for zanubrutinib for PFS and OS, respectively. For PFS, both before (HR: [redacted]) and after (HR: [redacted]) matching**,** zanubrutinib extends time to progression, compared to ibrutinib, although the result is not statistically significant. For OS, both before (HR: [redacted]) and after (HR: [redacted]) matching**,** zanubrutinib appears to extend survival, compared to ibrutinib, although the result is not statistically significant. In the KM curve figures (Figure 2 and Figure 3) the zanubrutinib weighted KM curves shift downwards only slightly from the unweighted KM curves for both PFS and OS, and this is driven by adjustments for three covariates only (age, bulky disease and blastoid variant).

The PFS and OS results of the unweighted and weighted analyses for the 2L comparison (using Dreyling *et al.* [2022]), whilst not statistically significant, are consistent with the base-case analysis, in the full R/R MCL population (using Rule *et al.* [2017b]). Importantly, the base-case MAIC outputs were validated by UK clinical

experts at an advisory board.[3] The Company would contend that any conclusions made on the overall effectiveness of zanubrutinib relative to ibrutinib using the Dreyling *et al*. (2022) dataset are likely to be associated with a reasonably high degree of uncertainty. In addition to the lack of matching covariates, the comparison is based on only 44 patients from the pooled AU003-206 dataset, as such, wide confidence intervals for the HR are to be expected. Furthermore, the length of follow-up for ibrutinib as reported in the Dreyling *et al.* (2022) is substantially longer (up to 10 years) compared to the zanubrutinib trials (median follow-up of 38.92 months for BGB-3111-AU-003 and a median of 35.25 months for the BGB-3111-206). In contrast in the base-case comparison using Rule *et al.* (2017b), a median follow-up was reported for PCYC-1104, SPARK and RAY were 15.5, 14.9 and 20 months, respectively, which is more aligned with the follow-up in the zanubrutinib trials.

Consequently, the Company maintains that the base-case analysis (using Rule *et al.* [2017b]) is the most appropriate for decision making in this appraisal, given the limitations of a comparison using the Dreyling *et al.* (2022) dataset (primarily in the number of covariates, but also the number of patients and length of follow-up as described) and the strengths of the Rule *et al.* (2017b), as discussed in Section B.2.12 of the CS.

Figure 2: KM curves of PFS-INV before and after matching for zanubrutinib (AU003-206 [DCO: 31Mar2021/08Sept2020] [N=44] versus Dreyling *et al.* [2022] N=99)

DCO – data cut-off; HR – Hazard Ratio; INV – investigator; KM – Kaplan-Meier; PFS – progression-free survival

Figure 3: KM curves of OS before and after matching for zanubrutinib (AU003-206 [DCO: 31Mar2021/08Sept2020] [N=44] versus Dreyling *et al.* [2022] N=99)

DCO – data cut-off; HR – Hazard Ratio; KM – Kaplan-Meier; OS – overall Survival

Adverse events

A12. Priority question: The CS make the case that zanubrutinib should displace ibrutinib because of safety issues with ibrutinib. Please provide an ITC of zanubrutinib versus ibrutinib comparing adverse events of grade ≥3 occurring in >2% of patients.

As discussed in the CS, the Company maintains that zanubrutinib should, over time, displace ibrutinib in treating new 2L R/R MCL patients, based on an improved efficacy, tolerability and safety profile compared to ibrutinib. The Company has conducted an ITC of zanubrutinib versus ibrutinib comparing treatment-emerging adverse events (TEAEs) of grade ≥ 3 occurring in >2% of patients as per the EAG's request, presented below.

To inform the ITC, data from the pooled zanubrutinib population (AU003-206) (N=118) from the most recent DCOs (BGB-3111-AU-003: 31Mar2021 and BGB-3111-AU-206: 08Sept2020) was used. Whilst for ibrutinib, data from Rule *et al.* (2017b) was used. These data are consistent with those used to inform the base-case PFS and OS MAIC analysis, as presented in B.2.9 in the CS.

The summary of the characteristics of the pooled zanubrutinib population (both unweighted and weighted) from AU003-206 and the ibrutinib population Rule *et al.* (2017b) are presented in Table 6, in line with the characteristics presented in Table 36 of the CS.

Table 6: Summary of the population characteristics before and after matching zanubrutinib versus ibrutinib

Covariate	AU003-206 (N=118), unweighted	AU003-206 (ESS=[redacted]) weighted	Ibrutinib, Rule *et al.* (2017b) (n=370)
Age ≥ 65 years (%)	39.0	[redacted]	62.4
Sex: Male (%)	75.4	[redacted]	78.0
ECOG-PS = 0 (%)	63.6	[redacted]	43.0
Bulky disease ≥ 5 cm (%)	39.7	[redacted]	49.0
Blastoid variant (%)	11.9	[redacted]	12.0
Extranodal disease (%)	60.2	[redacted]	58.0

Covariate	AU003-206 (N=118), unweighted	AU003-206 (ESS=[redacted]) weighted	Ibrutinib, Rule *et al.* (2017b) (n=370)
Number of prior lines of therapy: >=2 (%)	62.7	[redacted]	73.2
Previous chemotherapy: lenalidomide (%)	[redacted]	[redacted]	16.0

cm – centimetres; CSR – clinical study report; DCO – data cut-off; ECOG-PS – Eastern Cooperative Oncology Group performance status; ESS – effective sample size; n - number
Source: Tam *et al.,* (2021)[4] / BGB-3111-AU-003 CSR (DCO: 31Mar2021)[5], Song *et al.* (2020)[7] / BGB-3111-206 CSR (DCO: 08Sept2020)[8], Rule *et al.* (2017b)[14]

To conduct the analysis, TEAEs ≥ grade 3 occurring in at least 2% of patients in the pooled zanubrutinib population, were matched to the TEAEs ≥ grade 3 reported in the ibrutinib population. Importantly, in the ibrutinib population no ≥ grade 3 TEAEs were reported for myalgia, hyperuricaemia, hypertension, neutrophil count decreased, platelet count decreased and white blood cell count decreased. As such, it is not possible to produce a MAIC analyses for these particular outcomes. The MAIC safety analyses have been conducted and produced for the following four outcomes, and Table 7 presents the unweighted AU003-206 pooled zanubrutinib values as well as the MAIC results.

- For ≥ grade 3 TEAEs, both before (OR: [redacted], p-value: [redacted]) and after (OR: [redacted], p-value: [redacted]) matching**,** a statistically significant (to a 95% confidence limit) difference was observed in favour of zanubrutinib compared to ibrutinib.
- For ≥ grade 3 pneumonia, both before (OR: [redacted], p-value: [redacted]) and after (OR: [redacted], p-value: [redacted]) matching, a difference was observed for zanubrutinib compared to ibrutinib, in favour of ibrutinib. This difference was only statistically significant (to a 95% confidence limit) after matching.
- For ≥ grade 3 neutropenia, both before (OR: [redacted], p-value: [redacted]) and after (OR: [redacted], p-value: [redacted]) matching**,** a statistically significant (to a 95% confidence limit) difference was observed in favour of zanubrutinib compared to ibrutinib.
- For ≥ grade 3 anaemia, before matching a difference was observed for zanubrutinib compared to ibrutinib, in favour of zanubrutinib (OR: [redacted], p-value: [redacted]), although this difference was not statistically significant (to a 95% confidence limit). Similarly, after matching a difference was observed for zanubrutinib compared to ibrutinib, but in favour of ibrutinib (OR: [redacted], p-

value: [redacted]). However, this difference was not statistically significant (to a 95% confidence limit).

Table 7: MAIC of zanubrutinib vs. ibrutinib comparing TEAEs of grade ≥3

TEAEs	AU003-206 (n=118), unweighted	AU003-206 (ESS=[redacted]) weighted	Ibrutinib, Rule *et al.* (2017b) (n=370)	Unweighted results			Weighted results		
				OR	OR (LB, UB)	p-value	OR	OR (LB, UB)	p-value
TEAE ≥ grade 3	[redacted]	[redacted]	71.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Specific TEAE ≥ grade 3 occurring in >2% of patients									
Pneumonia	[redacted]	[redacted]	8.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	16.49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	8.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperuricaemia	[redacted]	[redacted]	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MAIC – matching-adjusted indirect comparison; n – number; NR – not reported; OR – odds ratio; TEAE – treatment-emergent adverse event

A13. Priority question: Please provide any available safety data from the ongoing study BGB-3111-LTE1.

Safety data from the ongoing BGB-3111-LTE1 study are available in the Brown *et al*. (2023) poster 'Characterization of Zanubrutinib Safety/Tolerability Profile and Comparison With Ibrutinib Profile in Patients With B-Cell Malignancies: Post Hoc Analysis of a Large Clinical Trial Safety Database' presented at the European Haematology Association congress in 2023.[16] This publication presents a pooled analysis of safety outcomes from clinical trials for zanubrutinib monotherapy for 1,550 patients, across various indications: chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), MCL, MZL, Waldenström macroglobulinemia (WM), follicular lymphoma (FL), and other B-cell malignancies. The analysis covered 10 different clinical trials, including BGB-3111-206 and BGB-3111-AU-003. Additionally, 337 patients from BGB-3111-LTE1 were included in the dataset.

Importantly, in all 10 studies patients received 320 mg daily dose of zanubrutinib, aligned to the dosing used in this appraisal.

Safety outcome data is presented for ibrutinib from the ASPEN (WM) and ALPINE (R/R CLL/SLL) trials.

In line with the BGB-3111-AU-003 and BGB-3111-206 safety data presented in the CS, the Brown *et al.* (2023) pooled safety analyses shows that zanubrutinib has an acceptable safety and tolerability profile.[16] The median duration of treatment was 34.4 months (range: 0.1, 90.0) for zanubrutinib, with 45% of patients receiving zanubrutinib for more than 36 months. For ibrutinib, the median duration of treatment was 25.7 months (range:0.1, 59.3), with only 25.4% of patients receiving treatment for more than 36 months.[16] When comparing the duration of treatment across pooled head-to-head studies of zanubrutinib versus ibrutinib, patients appear to be receiving zanubrutinib treatment for longer. Whilst duration of treatment is linked heavily to time to progression, the results suggest that patients may be less able to tolerate ibrutinib for as long as zanubrutinib.

When comparing pooled head-to-head studies of zanubrutinib versus ibrutinib, rates of TEAEs and cardiac TEAEs leading to discontinuation and death due to TEAEs and cardiac TEAEs were lower with zanubrutinib than ibrutinib. In the zanubrutinib arm, the number of patients with at least one TEAE leading to:

- A dose reduction was 156 (10.1%)
- A dose interruption was 791 (51.0%)
- Treatment discontinuation was 211 (13.6%)
- Treatment discontinuation due to cardiac TEAE was 16 (1.0%)

While in the ibrutinib arm, the number of patients with at least one TEAE leading to:

- A dose reduction was 81 (19.2%)
- A dose interruption was 249 (59.0%)
- Treatment discontinuation was 93 (22.0%)

- Treatment discontinuation due to a cardiac TEAE was 18 (4.3%)

Death due to TEAEs occurred in 113 (7.3%) zanubrutinib patients compared to 43 (10.2%) ibrutinib patients. Death due to cardiac TEAEs occurred in 12 (0.8%) zanubrutinib patients compared to 7 (1.7%) ibrutinib patients.[16]

Exposure-adjusted incidence rates (EAIRs) of adverse events of special interests (AESIs), including infection, with zanubrutinib were lower than with ibrutinib in the ASPEN/ALPINE trial study populations, except for 1 AESI (neutropenia). Moreover, EAIRs of atrial fibrillation and infections were significantly lower with zanubrutinib than with ibrutinib (P<0.0001 and P=0.0098, respectively).[16]

A14. Please provide safety data (n/N and %) from study BGB-3111-AU-003 for: 1) patients with all indications receiving total daily doses of 320 mg; and 2) RR/MCL patients receiving totally daily doses of 320 mg.

Safety data for:

1. Patients with all indications in the BGB-3111-AU-003 study planned to receive total daily doses of 320 mg, is presented below.

2. R/R MCL patients planned to receive total daily doses of 320 mg is presented in the CS Section B.2a.10.

In the BGB-3111-AU-003 study, 373 patients were treated for B-cell lymphoid malignancies with a planned total daily dose of 320 mg, of whom 32 were R/R MCL patients. At the DCO of 31st March 2021, the median duration of treatment was [redacted] for patients across all indications (N=373). The median relative dose intensity was [redacted] %. Table 8 and Table 9 present data for TEAEs and post-treatment adverse events.

Table 8: Summary of treatment-emergent and post-treatment adverse events in patients from all indications receiving 320 mg in BGB-3111-AU-003

Event	Zanubrutinib (N = [redacted]), n (%)
Patients with at least 1 TEAE	[redacted]
Grade ≥3 TEAEs	[redacted]
Serious TEAEs	[redacted]
TEAEs leading to death	[redacted]
TEAEs leading to study drug discontinuation	[redacted]

TEAEs leading to treatment interruption	[redacted]
TEAEs leading to dose reduction	[redacted]

AE – Adverse event; DCO – data cut-off; mg – milligrams; n – number; NR – not reported; SAE – serious adverse event

Table 9: TEAEs of Grade 3 or higher by system organ class and preferred term in patients from all indications receiving 320 mg in BGB-3111-AU-003

System Organ Class Preferred Term	Zanubrutinib (N = [redacted]), n (%)
Neutropenia	[redacted]
Anaemia	[redacted]
Pneumonia	[redacted]
Major haemorrhage	[redacted]
Bleeding	[redacted]
Thrombocytopenia	[redacted]
Opportunistic infections	[redacted]
Myalgia	[redacted]
Tumour lysis syndrome	[redacted]
Peripheral oedema	[redacted]

Mg – milligrams; n – number

As of the DCO of 31st March 2021, 95 patients in all indications planned to receive 320 mg daily had died, [redacted] due to progressive disease, [redacted] due to adverse events and [redacted] due to unknown or other reasons.

Section B: Clarification on cost-effectiveness data

Updated company base case

In response to Question B9 the Company has updated the base-case cost-effectiveness analysis, with an updated unit cost for the haematologist visit. The update results in a minimal change to the total incremental costs (<£20), with the same conclusions around cost-effectiveness, as zanubrutinib dominates ibrutinib. The incremental results for the CS and update in response to the clarification comments are presented in Table 10 (Patient Access Scheme [PAS] price).

Table 10: Summary of updates to CEM base case in response to EAG clarification questions

Clarification Question	Update to CEM base case	Cost-effectiveness analysis base-case results	Change from CS base-case results, in response to EAG clarification questions

CS base case at submission		Incr. costs (£): [redacted] Incr. QALYs: [redacted] **ICER: Dominating**	-
B9	Unit cost for haematologist (WF01A, clinical haematologist service) updated from £200.74 to £201.43	Incr. costs (£): [redacted] Incr. QALYs: [redacted] **ICER: Dominating**	Incr. costs (£): +£[redacted] Incr. QALYs: Unchanged **ICER: Unchanged**

CEM – cost-effectiveness model; EAG – External Assessment Group; ICER – incremental cost-effectiveness ratio; Incr. – Incremental; QALYs – quality-adjusted life years

The updated Company deterministic base-case results (PAS price) are presented in Table 11.

Table 11: Updated base-case deterministic results in patients with 2L R/R MCL (PAS price)*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Zanubrutinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

ICER – incremental cost-effectiveness ratio; LYG – life years gained; MCL – mantle cell lymphoma; PAS – patient access scheme; QALYs – quality-adjusted life years; R/R – relapsed or refractory
*Base case updated based on response to B9 (updated resource use unit cost)

Clinical parameters

B1. Section B.3.3.1: Please provide one table detailing the accuracy between the company's reconstructed IPD of ibrutinib compared with the actual data. This should include a comparison of the number of events identified by the reconstruction algorithm compared with the observed number of events, the median PFS/OS, and a comparison of the numbers at risk tables in the Kaplan-Meier plots.

The Company has provided a comparison of the actual ibrutinib data and the Company's reconstructed IPD of ibrutinib, Table 12 below. To reconstruct the KM curves for ibrutinib, the Company used the 'GetData Digitizer' software, ensuring that the guidance points necessary for successfully applying the Guyot algorithm for IPD reconstruction were followed:

- The initial point was added at (0,1) as no patients have experienced an event or have been censored at the beginning of the study therefore the probability of survival was 100%.
- Points were monotonic decreasing throughout the digitised dataset.
- Points were added along the entire curve, ensuring that a point was placed at each drop in the curve. For consistency, the points were located at the bottom left-hand corner of each drop.
- Points were placed just before each time interval and on the time interval.

The Guyot algorithm was then used to generate the reconstructed IPD from the KM data. To apply the Guyot algorithm to the KM data, an online application developed by Zhou *et al.* is used.[17]

A key validation step in assessing the accuracy of the reconstructed IPD is to compare the number of events to the original published value. While experience suggests that the reconstructed number of events should be close to the published value (±3 for a KM curve of reasonable resolution), Rule *et al.* (2017b) does not report the number of events or patients at risk.[14] This limitation meant that validation relied on comparing the median PFS and OS, which were found to be very similar and within an acceptable range of variation (i.e. the median PFS or OS did not deviate by more than 0.5 months from the reported medians). This outcome supports the accuracy of the reconstruction. The Company has provided a comparison of the reported ibrutinib PFS and OS KM summary data and the Company's reconstructed PFS and OS IPD of ibrutinib in Table 12.

Table 12: Comparison of actual ibrutinib data vs. reconstructed IPD

	Observed ibrutinib data (Rule *et al.* [2017b]) (N=370)	Reconstructed ibrutinib IPD from Rule *et al.* [2017b] (N=370)
Number of events	NR	264
Median PFS (months)	12.8	13.13
Median OS (months)	25.0	24.6

IPD – individual patient data; NR – not reported; OS – overall survival; PFS – progression-free survival

Additionally, the Company conducted extensive sensitivity analysis which demonstrates that the overall cost-effectiveness results remain robust to changes in

the key parameters, includes the following sensitivity analysis relevant to the ibrutinib PFS and OS data:

- Deterministic sensitivity analysis (DSA)
- Probabilistic sensitivity analysis (PSA)
- Scenario analysis using alternative PFS and OS distributions for ibrutinib and zanubrutinib) – log-logistic and generalised Gamma

These analyses confirm that any differences between the published KM data and the reconstructed data do not impact the cost-effectiveness conclusions.

While data reconstruction inherently has limitations, particularly when key survival metrics such as patients at risk or number of events are unavailable, the Company adhered to the standard Guyot procedure and achieved a comparable reconstruction, based on the similarity in median PFS and OS. Furthermore, the sensitivity analysis results demonstrate that the overall cost-effectiveness results remain robust to varying PFS and OS for ibrutinib. As such, the Company maintains that the reconstruction presented is appropriate for use in the analysis and subsequent decision making.

B2. Priority question: Please provide the Kaplan-Meier plot with the numbers at risk table for time-to-treatment discontinuation for the pooled zanubrutinib trials that was used for the TTD survival modelling in CS B.3.3.4.

Figure 4 presents the KM plot of TTD in AU003-206 pooled population, including the number of patients at risk. The KM data corresponds to the TTD data presented in the CS B.3.3.4.

Figure 4: Kaplan-Meier plot of TTD in AU003-206 pooled population (full trial population)

DCO – data cut-off; TTD – time-to-treatment discontinuation
Source: BGB-3111-AU-003 data on file (DCO: 31Mar2021)[6] and BGB-3111-206 data on file (DCO: 08Sept2020)[10]

B3. Section B.3.3: please rerun the survival analysis modelling for the BGB-3111-AU-003 trial only. Additionally, please provide the unadjusted and adjusted Kaplan-Meier plots to the EAG, with the numbers at risk.

The Company has presented the BGB-3111-AU-003 PFS and OS results in the CS (Section B.2a.6.2.1 and B.2a.6.2.2). As discussed in the CS, it is not feasible to conduct a robust MAIC analysis using only the BGB-3111-AU-003 trial alone given the trial population size (N=32). However, an unadjusted comparison was conducted versus Rule *et al.* (2017) which demonstrated results consistent with the base case with improved PFS and benefit in OS (albeit not statistically significant) for zanubrutinib compared to ibrutinib.

The results of the unadjusted BGB-3111-AU-003 comparison are available in Section B.2.9.5 and corresponding KM plots are presented in Appendix M Section M2.4. A cost-effectiveness scenario using unadjusted BGB-3111-AU-003 PFS and OS data for zanubrutinib is presented in response to clarification question B12.

Model structure

B4. Priority question: In section B.3.3, the EAG notes that, visually, the parametric models do not look to fit the overserved KM plots well, zanubrutinib in particular. Were flexible models considered, such as spline or piecewise models?

The Company can confirm that flexible models, such as spline or piecewise models, were considered in the modelling of zanubrutinib and ibrutinib in the cost-effectiveness analysis. The Company maintains that application of flexible models is not appropriate in the base-case analysis and scenario analyses for this appraisal, given the parametric models fitted provide a reasonable fit to the observed KM plots for PFS and OS. As demonstrated in Section B.3.3 of the CS, the parametric models appear to pass through the tails of the KM curves well, for both zanubrutinib and ibrutinib, despite the small patient numbers in the later timepoints. For zanubrutinib PFS, the parametric models pass through the KM data at numerous timepoints, with a close fit at 1.5 years and 4 years (Figure 24 in the CS). However, at other timepoints the parametric curves pass underneath the KM data suggesting the curves are a conservative estimation of zanubrutinib PFS. Furthermore, for zanubrutinib OS, the parametric models provide a close fit to the KM data throughout the first 2 years with numerous points of intersection thereafter until the end of the KM curve at 5 years (Figure 28 in the CS). In line with the PFS extrapolation, the parametric curves appear to pass underneath the KM data, suggesting the curves are a conservative estimation of zanubrutinib OS. Following an assessment of the parametric curves, the log-normal (PFS and OS) curves were selected in the base-case analysis for zanubrutinib based on visual and statistical fit, and clinical plausibility (Section B.3.3.2.1 and B.3.3.3.1). Furthermore, an assessment of the smoothed hazard plots was also conducted to inform the base-case curve selection. Based on the non-monotonic nature of the zanubrutinib PFS and OS hazards over time, the Company considered accelerated time failure models (such as log-normal and log-logistic distributions) appropriate for both outcomes.

Additionally, given the small number of patients and events in the zanubrutinib clinical studies, the Company consider that increasing the complexity of the models

used to extrapolate survival data is not appropriate, especially given that there are a large number of patients still yet to have an OS event.

The choice of parametric curves applied in the base-case cost-effectiveness analysis was validated by clinical experts for both treatment arms via the advisory board (11th November 2024). In instances where the parametric curve may have provided a poor fit, such as in the modelling of TTD, the clinical opinion received as part of the advisory board was followed and TTD was modelled as equal to PFS.

Therefore, given the reasons above, it was not considered necessary or appropriate to explore flexible models for the modelling of PFS, OS and TTD as part of this appraisal. Furthermore, the Company maintains that the parametric models likely provide a conservative estimate of zanubrutinib's effectiveness, given the parametric PFS and OS curves pass below the KM data.

B5. Priority question: Please amend/update the economic model to allow the incorporation of flexible modelling, namely splines and piecewise models.

As discussed as part of the Company's response to Question B4, the Company maintains that standard parametric modelling approaches are appropriate to model zanubrutinib and ibrutinib PFS and OS, and as such it is not necessary to explore flexible modelling as part of this appraisal, therefore the functionality has not been incorporated into the cost-effectiveness model.

Model Inputs

B6. Priority question: The EAG notes that the baseline characteristics for the modelled population (i.e., age, percentage males, body surface area (BSA)) have been sourced from NICE TA502. The company has provided data on age and percentage males for the BGB-3111-AU-003, BGB-3111-206 populations and for the pooled dataset. Please can the company also provide the BSA values for the same populations (i.e., BGB-3111-AU-003, BGB-3111-206 populations and pooled dataset)

The BSA values for the BGB-3111-AU-003, BGB-3111-206 populations and the AU003-206 pooled dataset are reported in Table 13. The Company would like to highlight that the BSA calculations only inform the subsequent treatment acquisition

cost calculations and have no bearing over the acquisition costs of zanubrutinib or ibrutinib, meaning that changes in BSA results in a minimal change in incremental costs in the cost-effectiveness analysis.

Table 13: BSA values from the BGB-3111-AU-003, BGB-3111-206 populations and the AU003-206 pooled dataset

Characteristic	BGB-3111-AU-003 (N=32)	BGB-3111-206 (N=86)	AU003-206 pooled (N=118)
BSA, m^2			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]

BSA – body surface area; m^2 – meters squared; SD – standard deviation
Source: BGB-3111-AU-003 data on file (DCO: 31Mar2021)[6], BGB-3111-206 data on file (DCO:08Sept2020)[10]

B7. Priority question: Can the company clarify which of the tables from reference 7 (CS document B, HMRN real-world dataset) was used to derive the proportions of patients receiving subsequent therapy used in the economic model? The proportions used in economic model are shown on Table 68.

The Company acknowledges an error in the reference provided for reference 7 in the CS Document B reference pack. While reference 7 correctly cites the Haematological Malignancy Research Network (HMRN) report on the clinical management and outcome of MCL, the specific figures used to derive the proportions of patients receiving subsequent therapy was sourced from a supplementary appendix to the main report.[18] Figure 5 presents the data used to derive the proportions of patients receiving subsequent therapy from the supplementary appendix, specifically the patients receiving third-line (3L) therapy, for patients who received 2L ibrutinib.

The Company has already provided the supplementary appendix “HMRN MCL Report - supplementary appendix“ via NICE. Docs and via email following the clarification call with the EAG.

Figure 5: Sankey diagram for lines of chemotherapy (grouped) for patients included in relapsed/refractory subgroup and treated with ibrutinib at 2L

CVPR – Rituximab, cyclophosphamide, vincristine and prednisone; FCR – fludarabine, cyclophosphamide and rituximab; HD AraC – high dose cytarabine; HMRN – Haematological Malignancy Research Network; MCL – mantle cell lymphoma; R-CHOP – rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
Source: HMRN report on the clinical management and outcome of MCL, supplementary appendix[18]

B8. Priority question: In the HMRN (real-world dataset) some patients received ibrutinib at 3rd line. Can the company explain how these patients were 're-distributed' to the other subsequent treatments used in the economic model?

The Company adapted the rates of 3L treatment use in the HMRN to ensure that it reflected for current UK clinical practice, based on the supplementary appendix presented in the Company response to B7.[18] Table 14 presents the 3L treatments in the HMRN registry data, before and after reweighting. The reweighted breakdown of 3L treatment was used to inform the weighted average subsequent therapy cost in the cost-effectiveness model (CEM).

There were six patients who received ibrutinib at 3L line, given that all patients are expected to receive ibrutinib at 2L, the proportion of patients receiving ibrutinib at 3L was removed and the break down was reweighted.

There was one patient who received CAR-T at 3L, given that brexucabtagene autoleucel (brexu-cel) (the only NICE recommended CAR-T treatment for R/R MCL)

is not recommended for routine commissioning, the proportion of patients receiving CAR-T at 3L was removed for the base case and the break down was reweighted. Note 3L CAR-T usage was instead explored in a scenario analysis, presented in the CS.

Table 14: 3L line treatments in the HMRN registry data, before and after reweighting

	HMRN registry 3L treatments (N=[redacted])	HMRN registry 3L treatments (N=[redacted]), redistributed
Bendamustine + Rituximab	[redacted]	[redacted]
High dose cytarabine + Rituximab	[redacted]	[redacted]
Rituximab	[redacted]	[redacted]
Chlorambucil + Rituximab	[redacted]	[redacted]
R-CHOP	[redacted]	[redacted]
FCR	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]
Brexu-cel	[redacted]	[redacted]

3L – third-line; Brexu-cel – brexucabtagene autoleucel; FCR – fludarabine, cyclophosphamide and rituximab; HMRN – Haematological Malignancy Research Network; R-CHOP – rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

B9. Please confirm the unit cost (before uprating) for haematologist (WF01A, clinical haematologist service) applied in model is correct

The Company acknowledges the costing error in the CEM data store sheet in cell D63/64. The Company can confirm that the unit cost for haematologist (WF01A, clinical haematologist service), sourced from the NHS national cost collection data publication 2022/2023, (before uprating) is £201.43.[19] As a result, the unit cost in the CEM has been updated from £200.74 to £201.43. Therefore, once inflated to 2024 prices the unit cost in Table 65 of the CS has increased from £214.86 to £215.59.

This single unit cost update has minimal impact on total costs. Specifically:

- It increases the incremental healthcare resource use cost of zanubrutinib versus ibrutinib by £17, from £[redacted] to £[redacted].
- It reduces the incremental cost of zanubrutinib by £18, from -£[redacted] to -£[redacted].

Importantly, the incremental cost-effectiveness ratio (ICER) remains dominating following the update of the haematologist unit cost. For the Company's updated base-case results, please see Table 11.

Model assumptions

B10. The company stated that the model begins with a hypothetical cohort of people aged 68, and that the time horizon is 32 years (calculated as 418 cycles). Could the company confirm that costs incurred, and benefits accrued in the last cycle (cycle 418) are captured in the calculation of total costs and outcomes (Refer to 'Trace (Zanubrutinib)' and 'Trace (Ibrutinib)'

The Company can confirm that the costs incurred, and benefits accrued in the 418th cycle are fully captured in the calculation of total costs and outcomes. The base-case results in the CEM include the first cycle (cycle 0), therefore, the 418th cycle is labelled as cycle 417 on row 426 of the 'Trace (Zanubrutinib)' and 'Trace (Ibrutinib)' sheets in the CEM.

To further reassure the EAG that the 32-year time horizon is fully captured in the base-case cost-effectiveness analysis, the Company has conducted a scenario analysis increasing the number of cycles included in the calculation of costs and benefits by one cycle.

As presented in Table 15, increasing the number of cycles by one has a minimal impact on the updated base-case ICER, decreasing the incremental cost savings by £[redacted] from [redacted] (Table 10, Company's updated base case) to [redacted]. The change to the incremental QALYs is less the [redacted]. Importantly, zanubrutinib continues to dominate ibrutinib after increasing the number of cycles by one.

Table 15: Scenario deterministic results applying 419 cycles using the Company's updated base case*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

ICER – incremental cost-effectiveness ratio; LYG – life years gained; MCL – mantle cell lymphoma; QALYs – quality-adjusted life years; R/R – relapsed or refractory
*Base case updated based on response to B9 (updated resource use unit cost)

B11. Can the company confirm that treatment waning was not considered in the base-case analysis or explored in scenario analysis?

The Company can confirm that treatment waning was not considered in the modelling of zanubrutinib and ibrutinib in the cost-effectiveness analysis.

The Company maintains that application of treatment effect waning is not appropriate for the base-case analysis or explored in scenario analysis for this appraisal.

Zanubrutinib demonstrated strong and durable PFS and OS in both the BGB-3111-AU-003 and BGB-3111-206 trials. Additionally, the smoothed hazard plots assessed for zanubrutinib (Figures 25 and 29 in the CS) did not clearly highlight any treatment effect waning.

Furthermore, in the NICE TA502 appraisal of ibrutinib for the treatment of R/R MCL, the EAG did not identify any issues regarding treatment effect waning, and this was subsequently accepted by the NICE committee and clinical experts.[1] Given that zanubrutinib and ibrutinib belong to the same medicine class, i.e. Bruton's tyrosine kinase inhibitor (BTKi), and the NICE committee and clinical experts previously accepted that the inclusion of a treatment effect waning was not necessary, the Company believes it is reasonable to consider that the treatment effect for zanubrutinib is sustained over time. Moreover, during the advisory board conducted by the Company (11th November 2024), clinicians did not raise any concerns regarding treatment effect waning with zanubrutinib.[3]

As such, it is assumed that a natural waning of the treatment effect of zanubrutinib over the time horizon is intuitively captured within the survival analysis presented in the CS (Section B.3.3).

In conclusion, the Company does not consider it relevant or reasonable to consider treatment waning in either the base case or scenario analysis.

Exploratory analyses

B12. Priority question: Please provide scenario analyses using:

- **The 2L only population**
- **The BGB-3111-AU-003 trial only**

2L only population scenario

The Company has conducted a MAIC analysis for 2L-only patients, comparing AU003-206 (N=44) versus Dreyling *et al.* (2022) (N=99), as presented in response to A11. The corresponding exploratory cost-effectiveness analysis, with the zanubrutinib (pooled AU003-206 N=44, weighted to the ibrutinib arm sourced from Dreyling *et al.* [2022] [N=44]) is presented below.

The assumptions, inputs and data sources for the cost-effectiveness analysis scenario using Dreyling *et al.* (2022) are as per the methods in the CS, Section B3, with the exception of the inputs and settings noted in Table 16 and Table 17 respectively.

Table 16: Data input sources for exploratory cost-effectiveness analysis using 2L data - AU003-206 (N=44) and Dreyling *et al.* (2022) (N=99)

Data input	Source	Location in cost-effectiveness model
AU003-206 survival extrapolations for PFS, OS and TTD	Weighted AU003-206 population, as per MAIC presented in A11. TTD is assumed equal to PFS based on clinical expert opinion.	Please refer to the drop-down "2L only; AU-003: 31Mar2021; 206: 08Sept2020" in 'Settings' Sheet, cell E41.
Ibrutinib survival extrapolations for PFS, OS and TTD	Dreyling *et al.* (2022) 2L population. TTD is assumed equal to PFS based on clinical expert opinion.	Please refer to the drop-down "2L only; Dreyling (2022)" in 'Settings' Sheet, cell E47.

MAIC – matching-adjusted indirect comparison; OS – overall survival; PFS – progression-free survival; TTD – time-to-treatment discontinuation

Table 17: Settings for exploratory cost-effectiveness analysis using the 2L data - AU003-206 (N=44) and Dreyling *et al.* (2022) (N=99)

Parameter	Setting	Justification
PFS distribution choice	Log-normal for both treatment arms (in line with the base-case PFS distribution for zanubrutinib and ibrutinib)	• Log-normal is of good statistical fit (best fitting score for ibrutinib and 2nd best fitting score for zanubrutinib, within <1 AIC point of best fitting extrapolation [Exponential]).

Parameter	Setting	Justification
		• Visually good fit to the observed data for both arms.
OS distribution choice	Log-normal for both treatment arms (in line with the base-case OS distribution for zanubrutinib and ibrutinib)	• Log-normal is of good statistical fit (best fitting score for ibrutinib and 2nd best fitting score for zanubrutinib within <1 AIC point of best fitting extrapolation [Exponential]). • Visually good fit to the observed data for both arms.
TTD distribution choice	Assumed equal to PFS	• TTD is set equal to PFS for both treatment arms, as patients are assumed to receive treatment until progression, in line with the base-case assumptions.

Abbreviations: AE – adverse event; AIC – Akaike information criteria; MAIC – matching-adjusted indirect comparison; OS – overall survival; PFS – progression-free survival; TTD – time-to-treatment discontinuation; UK – United Kingdom

In this scenario analysis, when compared to ibrutinib, zanubrutinib is associated with [redacted] incremental QALYs and incremental cost savings of £ [redacted] over the lifetime time horizon, resulting in zanubrutinib dominating ibrutinib (using the list price for ibrutinib and the PAS discount for zanubrutinib, Table 18). This result supports the Company's base-case conclusion, that zanubrutinib is a cost-effective use of NHS resources versus current standard of care for patients with 2L R/R MCL in the UK.

Regardless, the Company maintains that the base-case analysis (using Rule *et al.* [2017b] [N=370] in R/R MCL patients) is more appropriate for decision making in this appraisal, given the limitations of a comparison using the Dreyling *et al.* (2022) dataset (primarily in the number of covariates, but also the number of patients and length of follow-up) and the strengths of the Rule *et al.* (2017b) (see the Company's response to clarification question A11 for further details).

Table 18: Scenario deterministic results (2L-only population) using the Company's updated base case*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Zanubrutinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

2L – second-line; ICER – incremental cost-effectiveness ratio; LYG – life years gained; MCL – mantle cell lymphoma; QALYs – quality-adjusted life years; R/R – relapsed or refractory
*Base case updated based on response to B9 (updated resource use unit cost)

BGB-3111-AU-003 trial only scenario

As discussed in the CS, it is not feasible to conduct a robust MAIC analysis using the BGB-3111-AU-003 trial alone given the trial population size (N=32). However, an unadjusted comparison was conducted versus Rule *et al.* (2017). The corresponding exploratory cost-effectiveness analysis, with the zanubrutinib (BGB-3111-AU-003 N=32 (unadjusted), compared to the ibrutinib arm sourced from Rule *et al.* [2017b] [N=370]) is presented below.

The assumptions, inputs and data sources for the cost-effectiveness analysis scenario using BGB-3111-AU-003 only are as per the methods in the CS, Section B3, with the exception of the inputs and settings noted in Table 19 and Table 20 respectively. Note, the assumptions, inputs and data sources related to ibrutinib are unchanged in this scenario.

Table 19: Data input sources for exploratory cost-effectiveness analysis using unadjusted BGB-3111-AU-003 only (N=32) data versus ibrutinib (Rule *et al.* [2017b] [N=370])

Data input	Source	Location in cost-effectiveness model
AU-003 survival extrapolations for PFS, OS and TTD	Unadjusted AU-003 population, as per Company's response to Question B3 and Section B.2.9.5. of the CS.	Please refer to the drop-down "003 only (unadjusted): 31Mar2021" in 'Settings' Sheet, cell E41.

MAIC – matching-adjusted indirect comparison; OS – overall survival; PFS – progression-free survival; TTD – time-to-treatment discontinuation

Table 20: Settings for exploratory cost-effectiveness analysis using unadjusted BGB-3111-AU-003 effectiveness data, only (N=32)

Parameter	Setting	Justification
PFS distribution choice	Zanubrutinib: log-normal (in line with the base-case PFS distribution for zanubrutinib and ibrutinib)	• Log-normal is of good statistical fit (3rd best fitting score for zanubrutinib treatment arm, within < 2 AIC points of best fitting model [Exponential]). • Visually good fit to the observed data for both arms.
OS distribution choice	Zanubrutinib: log-normal (in line with the base-case OS distribution for zanubrutinib and ibrutinib)	• Log-normal is of good statistical fit (2nd best fitting score for zanubrutinib, within < 2 AIC points of best fitting curve [Exponential]) • Visually good fit to the observed data for both arms.
TTD distribution choice	Assumed equal to PFS	• TTD is set equal to PFS for both treatment arms, as patients are assumed to receive treatment until progression, in line with the base-case assumptions

Abbreviations: AE – adverse event; AIC – Akaike information criteria; MAIC – matching-adjusted indirect comparison; OS – overall survival; PFS – progression-free survival; TTD – time-to-treatment discontinuation; UK – United Kingdom

In this scenario analysis, when compared to ibrutinib, zanubrutinib is associated with [redacted] incremental QALYs and incremental cost savings of £[redacted] over the lifetime time horizon, resulting in zanubrutinib dominating ibrutinib (using the list price for ibrutinib and the PAS discount for zanubrutinib, Table 21). This result supports the Company's base-case conclusion, that zanubrutinib is a cost-effective use of NHS resources versus current standard of care for patients with 2L R/R MCL in the UK.

Regardless, the Company maintains that the base-case analysis (using the pooled BGB-3111-AU-003 and BGB-3111-206 zanubrutinib data in R/R MCL patients) is the most appropriate for decision making in this appraisal, as it allows the largest number of patients to be used (N=118, instead of N=32) and adjustment to the ibrutinib dataset (Rule *et al.* [2017b] [N=370]) through the MAIC analyses.

Table 21: Scenario deterministic results (BGB-3111-AU-003 only unadjusted) using the Company's updated base case*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Zanubrutinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

ICER – incremental cost-effectiveness ratio; LYG – life years gained; MCL – mantle cell lymphoma; QALYs – quality-adjusted life years; R/R – relapsed or refractory
*Base-case updated based on response to B9 (updated resource use unit cost)

B13. Please provide sensitivity/scenario analyses using all IRC-assessed outcomes in the model (not just PFS as in Table 76 and 77).

The Company maintains that the use of INV-assessed outcomes is appropriate, rather than IRC-assessed outcomes, for the base-case cost-effectiveness analysis. This is because there is longer follow-up of PFS for zanubrutinib available when assessed via INV (median follow-up: 38.92 months and 35.25 months for BGB-3111-AU-003 and BGB-3111-206, respectively). IRC-assessed PFS was only collected until an earlier DCO (BGB-3111-AU-003 December 13th 2018 [18.84 month median follow-up] and BGB-3111-206 August 31st 2019 [24.84 month median follow-up]). The Company considers it most appropriate to utilise the more complete PFS data for the cost-effectiveness analysis. Furthermore, there is little difference between

IRC and INV-assessed outcomes for zanubrutinib (as show in Table 13 and Table 26 in the CS) and minimal impact on the cost-effectiveness analysis is presented in Table 77 in the CS, with the scenario "PFS, OS and TTD from pooled zanubrutinib trials, from an earlier data cut". This scenario allows PFS IRC-assessed outcomes to be modelled rather than INV-assessed outcomes.

Nevertheless, the Company has reproduced Table 76 and 77 for the scenario when using IRC-assessed PFS, these are presented in Table 22 and Table 23. Note: PFS is the only outcome in the CEM assessed by the IRC, however modelling this scenario uses PFS data (and OS data) from an earlier time point.

The deterministic scenario analysis results when using IRC-assessed PFS (Table 23) are consistent with the base-case scenario results, with zanubrutinib dominating ibrutinib, in all scenarios.

In conclusion, the Company maintains that the longer-term follow-up data using INV-assessed PFS is more appropriate for the base-case analysis of zanubrutinib versus ibrutinib as it provides more robust survival extrapolations, based on more mature data.

Table 22: Summary of scenario analyses using the earlier DCO (i.e. IRC-assessed PFS)

Base case	Scenario analysis	Rationale
3.5% discount rate	No discounting	0% discount is assumed for costs to assess the impact of discounting
3.5% discount rate	High discount rates (6%)	6% discount is assumed for costs to assess the impact of discounting
Time horizon: lifetime (32 years)	Time horizon: 20 years	To explore the impact of shortening the time horizon
PFS, OS and TTD from pooled zanubrutinib trials (BGB-3111-AU-003 [DCO: 13Dec2018]) and BGB-3111-206 [DCO: 31Aug2019]), ESS=[redacted]) adjusted through a MAIC to Rule *et al.* (2017b) (N=370)	PFS, OS and TTD from pooled zanubrutinib trials, **excluding rituximab-naïve patients (ESS=[redacted])** vs. ibrutinib-pooled (n=370) (Rule 2017b)	To explore the impact of removing patients who are less generalisable to UK clinical practice
	PFS, OS and TTD from **206-only (n=[redacted])** adjusted through a MAIC to Rule *et al*. (2017b) (N=370)	To explore the impact of removing the AU-003 trial
PFS distribution:	PFS distribution:	To explore the impact of

Base case	Scenario analysis	Rationale
• Zanubrutinib (log-normal) • Ibrutinib (log-normal)	• Zanubrutinib (log-logistic) • Ibrutinib (log-logistic)	alternative plausible PFS extrapolations
	PFS distribution: • Zanubrutinib (generalised gamma) • Ibrutinib (generalised gamma)	
OS distribution: • Zanubrutinib (log-normal) • Ibrutinib (log-normal)	OS distribution: • Zanubrutinib (log-logistic) • Ibrutinib (log-logistic)	To explore the impact of alternative plausible OS extrapolations
TTD assumption: TTD is equal to PFS for zanubrutinib and ibrutinib	TTD is equal to the KM data	To explore the impact of alternative TTD data
Utility values: NICE TA502	SMC ibrutinib (2016)	To explore the impact of alternative utility assumptions
	Simons *et al.* (2021)	
Subsequent treatment costs: Included	Subsequent treatment costs: Excluded	To explore the impact of subsequent treatments
	CAR-T therapy included	To explore the impact of greater subsequent treatment costs

N.B. Setting the OS distribution to generalised gamma for both zanubrutinib and ibrutinib, as had previously been explored in the scenario analyses in Section B.3.11 of the CS, has not been explored in this scenario analysis. Using the generalised gamma curve for zanubrutinib OS provides long-term survival estimates that are clinically plausible or reflective of clinical practice. Given the clinical implausibility, this scenario has not been included in Table 22.
CAR-T – chimeric antigen receptor T-cell; DCO – data cut-off; NICE – National Institute for Health and Care Excellence; OS- overall survival; PFS – progression-free survival; SMC – Scottish Medicines Consortium

Table 23: Summary of scenario analyses results with an earlier DCO of the base-case pooled zanubrutinib trial data* (i.e. IRC-assessed PFS)

Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER/QALY (£)
Base case	[redacted]	[redacted]	Dominating
No discounting	[redacted]	[redacted]	Dominating
High discount rates (6%)	[redacted]	[redacted]	Dominating
Time horizon: 20 years	[redacted]	[redacted]	Dominating
PFS, OS and TTD from pooled zanubrutinib trials, **excluding rituximab-naïve patients (ESS=[redacted])** vs. ibrutinib-pooled (n=370) (Rule 2017b)	N/A**	N/A**	N/A**
PFS, OS and TTD from	N/A**	N/A**	N/A**

Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER/QALY (£)
206-only (n=[redacted]) adjusted through a MAIC to Rule *et al.* (2017b) (N=370)			
PFS distribution: • Zanubrutinib (log-logistic) • Ibrutinib (log-logistic)	[redacted]	[redacted]	Dominating
PFS distribution: • Zanubrutinib (generalised gamma) • Ibrutinib (generalised gamma)	[redacted]	[redacted]	Dominating
OS distribution: • Zanubrutinib (log-logistic) • Ibrutinib (log-logistic)	[redacted]	[redacted]	Dominating
Zanubrutinib and ibrutinib TTD is equal to the KM data	[redacted]	[redacted]	Dominating
Alternative utility value: SMC 2016	[redacted]	[redacted]	Dominating
Alternative utility value: Simons *et al.* 2016	[redacted]	[redacted]	Dominating
Subsequent treatment costs: Excluded	[redacted]	[redacted]	Dominating
Subsequent treatment costs: CAR-T included	[redacted]	[redacted]	Dominating

*Base case updated based on response to B9 (updated resource use unit cost)
**These scenarios use INV-assessed PFS, as such no scenario has been run based on these analyses.
DCO – data cut-off; ICER – incremental cost-effectiveness ratio; IRC – independent review committee; LYG – life years gained; MCL – mantle cell lymphoma; OS – overall survival; PFS – progression-free survival; QALYs – quality-adjusted life years; R/R – relapsed or refractory

B14. Priority question: Can the company clarify how the following 3 scenarios presented in Tables 77 and 78 were run in the model, as it is not clear in the 'controls' worksheet which data source options are being selected.

- **Scenario 1: PFS, OS and TTD from pooled zanubrutinib trials, from an earlier data cut (BGB-3111-AU-003 [DCO: Dec 13, 2018]) and BGB-3111-206 [DCO: Aug 31, 2019]), ESS=[redacted]) adjusted through a MAIC to Rule et al. (2017b) (N=370),**

- **Scenario 2: PFS, OS and TTD from pooled zanubrutinib trials, excluding rituximab-naïve patients (ESS=[redacted]) vs. ibrutinib-pooled (n=370) (Rule 2017b),**
- **Scenario 3: PFS, OS and TTD from 206-only (n=[redacted]) adjusted through a MAIC to Rule et al. (2017b) (N=370).**

The scenarios highlighted by the EAG as part of this question were presented only in Document B of the CS and were not added as options in the Company's CEM submitted on 14th January 2025. The Company have now included the three scenarios as options in an updated version of the model "ID6392_Zanubrutinib in rrMCL_cost-effectiveness model_14Feb25_V1.0_CQ_updates.xlsm". The EAG can find the switch for these scenarios in cell E41 of the 'Settings' Sheet. As stated above, the results of these three scenarios have already been presented in Table 77 and Table 78 of Document B of the CS.

Section C: Textual clarification and additional points

C1. In section B.2.9.2, the CS states "There is no 2L-only effectiveness data for ibrutinib which is of sufficient quality to inform an indirect treatment comparison versus 2L-only patients in the pooled AU003-206 dataset". Please explain the process for excluding studies on the basis of quality.

The Company has presented a full description of the methods used to identify relevant clinical evidence for zanubrutinib and ibrutinib in the CS, based on the results of the SLR (as presented in Section B.2.9 and further information is available Appendix D, Section D2). This includes the assessment of each study based on trial design, inclusion/exclusion criteria, baseline characteristics, PFS and OS outcomes reported and a quality assessment (as reported in Appendix D, Section D4).

Four relevant studies were identified for ibrutinib (Rule *et al.* [2017b], Dreyling *et al.* [2016], Wang *et al.* [2013 and 2015], McCulloch *et al.* [2021]).[14,20–23] McCulloch *et al.* (2021), a real-world evidence (RWE) study, was the only study which presented PFS and OS KM data for 2L patients, the remaining studies presented PFS and OS in the full R/R MCL population.

Whilst McCulloch *et al.* (2021) presents 2L-only data, which is relevant, the Company considers Rule *et al.* (2017b) (N=370) to the most appropriate data source to provide the clinical evidence for ibrutinib. This conclusion was arrived at having considered the following:

- Data Quality: Trial-based datasets (such as Rule *et al.* [2017b]) are preferred over RWE (such as McCulloch *et al.* [2021]) within HTA given their prospective design and controlled measurement of outcomes. Importantly, the Rule *et al.* (2017b) analysis includes data from an RCT (RAY-MCL3001), which is considered higher quality evidence than single-arm trials or observational studies.

- Clinical Validation: UK clinical experts confirmed (at an advisory board conducted on the 11th November 2024) that Rule *et al.* (2017b) was an appropriate data source to inform the ITC of zanubrutinib versus ibrutinib.[3]

- Precedent: In the ibrutinib R/R MCL NICE submission (TA502), the EAG and the committee deemed Rule *et al.* (2017b) to be acceptable for decision making.[1]

The Company also assessed Dreyling *et al.* (2022), a letter presenting data for 2L-only patients in the pooled ibrutinib RAY-MCL3001, PCYC-1104 and SPARK studies. This source was not identified in the SLR due publication type (a letter), rather by clinical experts at an advisory board conducted on the 11th November 2024.[3] Dreyling *et al.* (2022) was not considered by the Company of sufficient quality to inform the clinical evidence for ibrutinib based on the level of covariate data reported (only three relevant prognostic factors could be matched to the zanubrutinib dataset). The Company maintains its position that the data derived from Dreyling *et al.* (2022) is insufficient to conduct a robust MAIC against zanubrutinib.

Nonetheless, the Company has conducted a MAIC analysis using Dreyling *et al.* (2022) and the methods and results of the comparison are presented in response to A11. The PFS and OS results of the unweighted and weighted analyses for the 2L comparison (using Dreyling *et al.* [2022]), whilst not statistically significant, are consistent with the base-case analysis, in the full R/R MCL population (using Rule *et al.* [2017b]).

In conclusion, the Company maintains that the base-case analysis (using Rule *et al.* [2017b]) is the most appropriate for decision making in this appraisal, given the limitations of a comparison using the Dreyling *et al.* (2022) dataset (primarily in the number of covariates, but also the number of patients and length of follow-up) and the strengths of the Rule *et al.* (2017b), as discussed above and in Section B.2.12 of the CS.

C2. Please clarify the apparent mistype in the B.2.9.4. Methodology section point 1: "... effect modifying potential *the in* ibrutinib population..."

The Company acknowledges the mistype error in the B.2.9.4. Methodology section point 1, as it should state "… effect modifying potential in the ibrutinib population…".

C3. The EAG is aware of the Reference pack notes for Document B provided by the company, justifying the absence of files for five references. Reference 48 is missing from this list but does not have an associated file; please provide and documentation/report for this analysis. Please also provide any documentation/report for analysis in references 45 and 58. Please provide these as soon as possible and prior to the clarification responses.

The Company has already provided a response to this question via email (5th February 2025), due to its high priority status. Please find the response below.

The references in question (45, 48 and 58) correspond to analysis outputs from BGB-3111-AU-003, BGB-3111-206 and the ITC results of zanubrutinib (AU003-206) vs ibrutinib (Rule *et al.* [2017b]) - DCO 2020/2021, respectively. As such, there are no files the Company can provide. However, summaries and descriptions of these data, including follow-up duration and date, have already been included in Document B.

C4. Please provide the supplementary appendix for Dreyling 2016. Please provide this as soon as possible and prior to the clarification responses.

The Company has already provided a response to this question via email (5th February 2025), due to its high priority status. Please find the response below.

The Company acknowledges the omission of the supplementary appendix for Dreyling 2016 in the initial submission and has provided the document via email, due to its high priority status.

C5. Priority question: Reference 43 (CSR for BGB-3111-AU-003) data cut is October 2020, so data do not align with data in the CS. Please provide the CSRs or other reports for the data cuts reported in the CS (IRC-assessed 13 Dec 2018 and INV-assessed 31 March 2021) for the n=32 patients reported in the CS. Please provide this as soon as possible and prior to the clarification responses.

The Company has already provided a response to this question via email on 5th February 2025, due to its high priority status. Please find the response below.

The Company apologises for any confusion surrounding the different data cuts for the zanubrutinib trials. The Company can confirm that the only available CSR files correspond to the 31st March 2021 data cut-off (BGB-3111-AU-003) and the 8th September 2020 data cut-off (BGB-3111-206). Additionally, a regulatory summary of clinical efficacy file exists with a December 2018 data cut-off, covering both BGB-3111-AU-003 and BGB-3111-206. This document is included in the Document B reference pack (reference 44).

C6. CS Table 1, Column 2 states: 'Chemotherapy with or without rituximab'- please clarify whether this should state 'Rituximab with or without chemotherapy'.

The Company acknowledges the typographical error in CS Table 1 Column 2, as it should state 'Rituximab with or without chemotherapy', in line with the final NICE scope. This is a typographical error and has no bearing over the evidence and results presented in the Company Submission.

C7. Please describe the process (e.g. number of reviewers, was it planned *a priori* etc) for identifying studies of ibrutinib and zanubrutinib at the final stage of study selection for the ITC. Please also confirm the number of publications

as there appears to be a discrepancy between CS Appendix D Table 7 and Table 8.

To identify studies of ibrutinib and zanubrutinib at the final stage of study selection for the ITC, the availability, relevance and quality of data reported in each study was assessed and concluded by two reviewers.

Discrepancies were resolved through discussion or by consulting a third reviewer, when necessary. The process was not planned a priori, and instead the most complete and appropriate studies to generate a robust ITC were selected.

The final list of relevant studies, including the Company's proposed base-case dataset for zanubrutinib and ibrutinib (as presented below), was presented to and validated by clinical experts present at an advisory board meeting conducted on 11th November 2024.[3]

For zanubrutinib, it was deemed appropriate to use BGB-3111-AU-003[4,5] and BGB-3111-206[7–9,24] pooled data in the ITC, as this represents the largest patient population treated with zanubrutinib.

For ibrutinib, the Rule *et al.* (2017b) pooled analysis of PCYC-1104, SPARK and RAY-MCL3001 was deemed the most appropriate data to be used in the ITC, as it includes the largest patient population. Importantly, the analysis includes data from an RCT (RAY-MCL3001), which is considered higher quality evidence than single-arm trials or observational studies. See CS Section B2.9.1 for further information.

The Company acknowledges the discrepancy on the CS Appendix D Table 7 and Table 8. The total number of publications should be 11, as per Table 8. For clarity Table 7 cites one extra publication for BGB-3111-206 and four extra publications for RAY-MCL3001. These publications are relevant to the studies, but are supplementary to informing the clinical evidence in the CS.

The correct list of publications relevant to the CS, for the six key studies are as follows:

- BGB-3111-AU-003: 1 publication[4]
- BGB-3111-206: 3 publications[7, 9,24]

- RAY-MCL3001: 3 publications[23,25,26]
- PCYC-1104: 2 publications[20,22]
- Pooled of PCYC-1104, SPARK and RAY-MCL3001: 1 publication[14]
- McCulloch *et al.* (2021)[21]

C8. Appendix D1.5: please clarify the number of records excluded for questions 1 and 2 (it appears that 270 were identified and 54 of these were ibrutinib or zanubrutinib, but the text (D2.1) and PRISMA Figure 1 state 215 were excluded).

The Company acknowledges the typographical error in Appendix D2.1. At second-pass screening, 119 records (n_1=116; n_2=3) were excluded for question 1 and 97 records (n_1=94; n_2=3) were excluded for question 2, totalling 216 records excluded (as per Section D1.5 and PRISMA Figure 1).

C9. Appendix D1.4 states non-RCTs were quality assessed according to CRD guidance and the Downs and Black Checklist for Clinical Trial Quality Assessment. Please provide the completed Downs and Black Checklists for all non-RCTs.

The Company apologises for any confusion regarding the non-RCT checklist. All non-RCTs were quality assessed according to the Critical Appraisal Skills Programme (CASP) checklist for cohort studies, not the Downs and Black Checklist.[27] The Company considers that the CASP checklist is relevant for assessing the quality of non-RCTs, however the Company have now completed the Downs and Black Checklist for all non-RCTs in Table 24.

Table 24: Quality assessment of non-RCT studies according to Downs and Black Checklist

Studies/ Questions	BGB-3111-AU-003 (NCT02343120)	BGB-3111-206 (NCT03206970)	PCYC-1104 (NCT01236391)	Ibrutinib-pooled (PCYC-1104, SPARK, RAY – MCL3001)	McCulloch *et al.* (2021)[21]

Publication(s)	CSR, Tam *et al.* (2021)[4,5]	CSR, Song *et al.* (2020), Song *et al.* (2021), Song *et al.* (2022b)[7–9,24]	Wang *et al.* (2013), Wang *et al.* (2015)[20,22]	Rule *et al.* (2017b)[14]	N/A
Reporting section					
Q1. Is the hypothesis/aim/objective of the study clearly described?	1	1	1	1	1
Q2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	1	1	1	1	1
Q3. Are the characteristics of the patients included in the study clearly described?	1	1	1	1	1
Q4. Are the interventions of interest clearly described?	1	1	1	1	1
Q5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	1	1	0	0	0
Q6. Are the main findings of the study clearly described?	1	1	1	1	1
Q7. Does the study provide estimates of the random variability in the data for the main outcomes?	1	1	1	1	1
Q8. Have all important adverse events that may be a consequence of the intervention been reported?	1	1	1	1	1
Q9. Have the characteristics of patients lost to follow-up been described?	0	0	0	0	0
Q10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.01?	1	1	0	0	0
Reporting subtotal	**9**	**9**	**7**	**7**	**7**
External validity section					

Q11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	1	1	1	N/A – pooled analysis	N/A – retrospective study of anonymised patient data
Q12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	0 – unable to determine	0 – unable to determine	0– unable to determine	N/A – pooled analysis	0 – unable to determine
Q13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	1	1	1	1	1
Q14. Was an attempt made to blind study subjects to the intervention they have received?	0 – single-arm trial	0 – single-arm trial	0 – single-arm trial	0 – pooled analysis including single armed trial	0 – single-arm trial
Q15. Was an attempt made to blind those measuring the main outcomes of the intervention?	0 – single-arm trial	0 – single-arm trial	0 – single-arm trial	0 – pooled analysis including single armed trial	0 – single-arm trial
Q16. If any of the results of the study were based on “data dredging”, was this made clear?	1	1	1	1	1
Q17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	1	1	1	1	1
Q18. Were the statistical tests used to assess the main outcomes appropriate?	1	1	1	1	1
Q19. Was compliance with the intervention/s reliable?	1	1	1	1	1
Q20. Were the main outcome measures used accurate (valid and reliable)?	1	1	1	1	1
External validity subtotal	**7**	**7**	**7**	**6**	**6**

Internal validity section					
Q21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	0	0	0	0	0
Q22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	0	0	0	0	0
Q23. Were study subjects randomised to intervention groups?	0	0	0	0	0
Q24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	0	0	0	0	0
Q25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	1	1	0	0	0
Q26. Were losses of patients to follow-up taken into account?	1	1	1	1	1
Internal validity subtotal	**2**	**2**	**1**	**1**	**1**
Power section					
Q27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	0	5	4	0 – pooled analysis	0
Power validity subtotal	0	5	4	0	0
Total score	18	23	19	14	14

CSR – clinical study report; RCT – randomised controlled trial

The Rule *et al.* (2017b) is a pooled analysis which includes patients from three studies, one randomised controlled trial (RAY-MCL3001 [NCT01646021]), and two single-arm studies (PCYC-1104 [NCT01236391] and SPARK [NCT01599949]). As a

pooled analysis, the publication is not expected to report each study's methods in great level of detail, justifying a lower total score on the Downs and Black Checklist. Even so, the Company maintains that the Rule *et al.* (2017b) pooled analysis is the most appropriate data source to inform the ITC base-case analysis, as it includes high-quality data for the largest patient population available for ibrutinib.

C10. Appendix G states that 21 records were included in the cost-effectiveness SR, but CS Doc B, section 3.1 states that 20 records were included. Please clarify the number of included records and if 20, please provide the full reference and reason for exclusion for the removed study.

The Company acknowledges the typographical error in CS Document B Section 3.1. A total of 21 records were included in the cost-effectiveness SLR, as per Appendix G and the PRISMA diagram (Appendix G, Figure 1).

Additionally, the Company would like to clarify that the study Marchetti *et al.* (2023) is still included in Appendix G and this study was used to support the use of a partitioned survival model (PSM) in the cost-effectiveness analysis.[28] Marchetti *et al.* (2023) is a cost-effectiveness study of brexucabtagene autoleucel for R/R MCL, modelled using a PSM approach.[28]

C11. Appendix I states that 21 records were included in the cost and resource use SR, but CS Doc B, section 3.5 states that 20 records were included. Please clarify the number of included records and if 20, please provide the full reference and reason for exclusion for the removed study.

The Company acknowledges the typographical error in CS Document B Section 3.5. A total of 21 records were included in the cost and resource use SLR, as per Appendix I and the PRISMA diagram (Appendix I, Figure 1). This does not impact the studies described in further detail in the CS which are applicable to clinical practice in England (n=6).

C12. Appendix References. Please supply.ris files for the references in Appendices D, G, H, I and K.

The Company have provided the relevant .ris files for each of the appendices alongside these clarification question responses, in the zipped folder named ("QC12 RIS files").

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Zanubrutinib for treating relapsed or refractory mantle cell lymphoma after 1 or more treatments [ID6392]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Lymphoma Action
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Lymphoma Action is a national charity, established in 1986, registered in England and Wales and in Scotland. We provide high quality information, advice and support to people affected by lymphoma – the 5th most common cancer in the UK. We also provide education, training and support to healthcare practitioners caring for lymphoma patients. In addition, we engage in policy and lobbying work at government level and within the National Health Service with the aim of improving the patient journey and experience of people affected by lymphoma. We are the only charity in the UK dedicated to lymphoma. Our mission is to make sure no one faces lymphoma alone. Lymphoma Action is not a membership organisation. We are funded from a variety of sources; predominantly fundraising activity with some limited sponsorship and commercial activity. We have a policy for working with healthcare and pharmaceutical companies – those that provide products, drugs or services to patients on a commercial or profit-making basis. The total amount of financial support from healthcare companies will not exceed 20% of our total budgeted income for the financial year (this includes donations, gifts in kind, sponsorship etc) and there is also a financial cap of £50,000 of support from individual healthcare companies per annum (excluding employee fundraising), unless approval to accept a higher amount is granted by the Board of Trustees.

	This policy and approach ensures that under no circumstances will these companies influence our strategic direction, activities or the content of the information we provide to people affected by lymphoma.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	BeiGene £20,561.34 Contribution towards our Lymphoma Essentials and Preparing for Treatment online services and sponsorship of Lymphoma Management course for HCPs. Payment for patient volunteer expenses to attend BeiGene event.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	We spoke to members of our community to understand their experiences of living with the types of non-Hodgkin lymphoma mentioned in this appraisal. We combined the information gathered from this, along with our experiences of working with these patients and their carers.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Lymphoma is a type of blood cancer, where white blood cells known as lymphocytes grow out of control. It is the 5th most common type of cancer in the UK. There are two main types of lymphoma: non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). NHL is the most common type, with around 14,200 people diagnosed each year in the UK. There are around 60 different types of NHL which can be classified in two main ways. Firstly, they can be grouped into low-grade and high-grade based on how fast they grow. Secondly, they can be grouped depending on the type of lymphocyte they developed from: B cells or T cells. B-cell lymphomas are much more common, accounting for 90% of cases. Mantle cell lymphoma (MCL) is a type of NHL which develops from B cells found in the mantle zone of lymph nodes. It mainly affects lymph nodes but can also spread to other parts of the body such as bone marrow, spleen, bowel and liver. MCL is a rare cancer with around 600 people being diagnosed each year in the UK. It tends to be a cancer of later years, with most people diagnosed being middle-aged or older. MCL often grows very quickly, which means symptoms can develop fast. These can include swollen lymph nodes, abdominal pain or a feeling of fullness due to an enlarged spleen, or symptoms arising from lymphoma cells invading the bone marrow. This can include bruising or bleeding, being more prone to infections, or symptoms of anaemia. Some people also have what is known as B-symptoms which can include weight loss, night sweats or fever. Fatigue is also a common symptom of mantle cell lymphoma, but one which is often overlooked. MCL unfortunately almost always relapses at some point after initial treatment, and then multiple times after this. Most people with MCL will require more than one line of treatment, and often the aim is to achieve as much time as possible cancer free in between these treatments. The psychological impact of a diagnosis of MCL is enormous. Patients have described insomnia, anxiety and a constant fear of dying to us. Much of this fear is due to this high risk of relapse, and

	running out of viable treatment options. Patients and those close to them live with this fear which obviously adds to this impact. *"The diagnosis has been very difficult to deal with, mainly due to the short overall survival statistics and the uncertainty surrounding response to chemo because of the heterogeneity of the disease and the unknown remission duration. I have young children, and I am scared to leave them without a father."* The family and friends of people with MCL also have their lives turned upside down and can struggle with the diagnosis given to their loved one. They have to be there emotionally but also practically, often taking on the burden of day-to-day activities, "*My wife will have a lot to deal with, looking after the children and picking up the things that I won't be able to help with during my very aggressive treatment"*. Carers can feel powerless to help, especially as MCL is a cancer which is likely to come back despite responding to treatment – one of our patients talked about the "*inevitable relapse*".

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	The treatment for MCL varies according to several factors which include the stage, prognostic score or symptoms of the lymphoma, along with the patient's age and overall health. In some cases, for example when patients have very few symptoms as the lymphoma is growing slowly, no active treatment is required. This is called active monitoring, or 'watch and wait'. If treatment is required, in most cases this is chemotherapy in combination with immunotherapy such as rituximab. If patients are fit enough, they will be given an intensive regimen including cytarabine. This can be effective and helps to prevent the MCL from spreading, but it can be incredibly difficult to endure. *"The side-effects (of my chemotherapy) were insomnia and extreme tiredness plus hair loss".* If patients are less fit, they may be offered an alternative chemotherapy regimen such as R-CHOP (rituximab, cyclophosphamide, doxorubicin (or hydroxydaunorubicin), vincristine (Oncovin®) and prednisolone), bendamustine plus rituximab or VR-CAP (a version of R-CHOP which includes a targeted drug called bortezomib). If patients respond well to chemotherapy, they may be offered an autologous stem cell transplant (SCT). This requires intensive chemotherapy and patients have to be fit enough which is often not the case. In almost all cases, despite treatment MCL will unfortunately relapse. This can happen on multiple occasions, requiring many different treatment regimens. Possible treatments at this point include the targeted treatment ibrutinib, a different chemotherapy regimen to the one previously received, CAR-T therapy, a donor stem cell transplant or taking part in a clinical trial. Not all of these treatments are suitable options for everyone and patients and their carers worry about running out of options. *"I think if you have TP53 mutation, people are being put through unnecessary/ineffective chemo regimens and auto SCT for very little benefit."*

8. Is there an unmet need for patients with this condition?	MCL is a very difficult cancer to live with. It can act like a high-grade lymphoma by growing quickly and causing significant symptoms, but also like a low-grade lymphoma often relapsing after treatment requiring various treatment regimens, "*It is very hard to live with this type of lymphoma, as although I am in remission I know it will come back at some point".* With this in mind, patients want multiple treatment options open to them, especially ones which can be tolerated by most patients. They feel that there is currently an unmet need for this, which adds to the fear that the treatment options that they are offered will either not provide a long-term remission, or will cause intolerable side effects: "*We need as many treatments at our disposal as possible given the high relapse rate. This is especially important for younger patients.*" *"I think the more options for treatment for this condition there are the better, so that clinicians can help patients decide which treatment is best tailored to their personal life at the time".* *"Obviously we'd all hope for a cure with a treatment that did not endanger life and had fewer side effect."* *"Yes, there is an unmet need. The perfect treatment would be something with relatively little side effects."* "*I think newer BTK inhibitors should be offered in second line instead of ibrutinib which has cardiac toxicity. BTK inhibitors may also offer a good first line treatment with fewer side effects than chemo (as per windows 2 trial in US).*" *"Given that people with MCL need repeated treatments, attention should be given to reducing the burden of treatment (for example chemo-free approaches, MRD testing to inform auto SCT etc). Additional sequencing for gene mutations other than in TP53 may identify additional patients who may*

	not respond well to chemo and who should go straight to BTK inhibition. Bispecifics should be considered as another potential tool." These views were confirmed by the recent 2024 Lymphoma Coalition survey, which shows that 72% of patient respondents and 80% of carer respondents (total respondents 1204; 3% MCL) rated fewer side effects/more tolerable side effects during treatment as important, or very important.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	As already stated, patients struggle with the side effects of the current treatment options open to them. They feel that zanubrutinib may provide an option which is more tolerable: *"It has a better safety profile than ibrutinib and therefore represents a better option for second line treatment."* Another advantage is that zanubrutinib offers another oral option. Some current treatment options can only be given intravenously which require recurrent, often daily, hospital appointments. This can be incredibly disruptive for both the patient, and those around them and can also be financially difficult: *"It is a treatment which can be used at home and therefore appears to represent a very convenient option."* *"Using a less invasive treatment makes a huge difference to the patient."*

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patients felt that any side effects may be a disadvantage of this treatment. However, our patients felt that if these side effects were not worse than the disease itself it was worth it: *"I have heard that some people have had to discontinue because of side effects but I don't see any major drawbacks."*

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	One patient suggested that: *"I think TP53 mutated people will benefit more - they are unlikely to have a durable response to current first line therapies so need the best available BTK inhibitor with the least side effects given that they are likely to have less time to recover from first line treatment."*

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Our patients could not think of any equality issues but felt that all patients should be able to access all the best treatment options available.

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Mantle cell lymphoma is a complex condition which often relapses after treatment • Current treatment options have significant short and long term side effects • Patients want multiple treatment options open to them • Treatment options that can be taken orally at home are very welcome to patients • Patients would welcome a treatment which prolongs time between relapses, but also does not have intolerable side effects

Thank you for your time.

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NICE National Institute for Health and Care Excellence

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Zanubrutinib for treating relapsed or refractory mantle cell lymphoma after 1 or more treatments [ID6392]

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About you

1. Your name	[redacted]
2. Name of organisation	The Royal College of Pathologists and [redacted]
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	FRCPath Representative. NHS We are a medical royal college, we make money from many different areas, likes exams, events etc. we get no funding as such from NO manufacturer and other relevant companies.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Stop progression / induce remission / improve QoL To control mantle cell lymphoma i.e. induce response/remission. To prevent progression of mantle cell lymphoma i.e. to prolong progression free survival and overall surival
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Overall response rate (by Cheson criteria) of ~70% +
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – survival is poor in relapsed MCL Yes – most patients still die of their disease i.e. MCL rather unrelated causes

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Ibrutinib monotherapy in 2L to progression or toxicity. It is NICE approved only in 2L and has near universal use 2L. Standard first line treatment is rituximab plus chemotherapy.

	All patients at present outside of a clinical trial receive ibrutinib at first relapse as this is where NICE have approved its use.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	MCL BSH Guideline 2023, BJH, Eyre et al. https://pubmed.ncbi.nlm.nih.gov/37880821/ Yes, MCL BSH Guidelines, 2024. Eyre TA et al BJH 2024.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes very well defined. Chemoimmunotherapy 1L, BTK inhibitor 2L. Avaliable BTKi at present is Ibrutinib monotherapy. Well defined. 1L immunochemotherapy +/- rituximab maintenance. 2L covalent BTK inhibitor (Ibrutinib as per NICE approval). 3L is less well defined but antiCD19 CAR-T treatment is an option for patients fit enough for this treatment.
9c. What impact would the technology have on the current pathway of care?	There was be large scale change over from ibrutinib to zanubrutinib 2L. Zanubrutinib is known to be better tolerated than ibrutinib and there is no evidence that zanubrutinib responses and duration of response would be worse. It would have the potential to switch the BTK inhibitor from ibrutinib to zanubrutinib and potentially expand the access to it for patients beyond 2nd line.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
10a. How does healthcare resource use differ between the technology and current care?	No difference. Less toxicity with Zanubrutinib Very little. Both are oral BTK inhibitors. Zanubrutinib is known to have an improved cardiac safety profile compared to ibrutinib
10b. In what clinical setting should the technology be used? (For example,	Secondary care lymphoma clinics

primary or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil outside of what is already used in the NHS for pts having ibrutinib Nil specific. Zanubrutinib is a commonly used, well understood agent, currently NICE approved in waldeonstroms macroglobulinaemia, marginal zone lymphoma and CLL.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes as above Yes – its safer than ibrutinib and no reason to suggest that it is not at least as effect in MCL.
11a. Do you expect the technology to increase length of life more than current care?	Hard to say but certainly no worse than current SoC. Diffucult to suggest that zanubrutinib would improve survival compared to ibrutinib. No comparative data available in MCL.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes – zanubrutinib is safer than ibrutinib and no reason to suggest that it is not at least as effect in MCL. There are randomised trials in WM and CLL to strongly suggest this.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There are groups of pts that don't respond as well to BTKi than others e.g. blastoid disease, TP53 mutated MCL, but this is true for all BTKi. No patient group that I would not use Zanubrutinib compared to ibrutinib. This appraisal has to potential to switch prescribing across the UK for this indication.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or	Easier - zanubrutinib is safer than ibrutinib

healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Not specifically Standard rules for BTK inhibitors would apply – i.e. no different from the current standard
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and	Yes Yes – it's a more selective, safer BTK inhibitor than the current standard

how might it improve the way that current need is met?	
16a. Is the technology a 'step-change' in the management of the condition?	Yes
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes – many pts with MCL struggle with toxicities of ibrutinib
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Most pts tolerate zanubrutinib well with few adverse effects.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes in the sense that the data for ibrutinib and zanubrutinib monotherapy in from the R/R MCL space. That said there is a relative lack of zanubrutinib data for MCL pts treated in the West/Europe. The main pivotal data set was from China.
18a. If not, how could the results be extrapolated to the UK setting?	Data from CLL, WM, MZL all provides strong evidence of zanubrutinib efficacy and tolerability and includes many pts treated in the West/Europe.
18b. What, in your view, are the most important	Overall response rate, CR rate, tolerability, overall survival, PFS. All are measured and reported.

outcomes, and were they measured in the trials?	
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No - we know a lot about the tolerability profile of zanubrutinib from CLL, WM, MCL, MZL data.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA502 and TA677?	No
21. How do data on real-world experience compare with the trial data?	N/A No comparative data available

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Zanubrutinib is highly effective, well tolerated 2nd generation BTKi • Data supporting Zanubrutinib in R/R MCL is excellent • Zanubrutinib is clearly known to be better tolerated than ibrutinib • There would be widespread, rapid change to zanubrutinib from ibrutinib in R/R MCL if this was funded • Zanubrutinib is likely to be at least as effective as ibrutinib in the absence of randomised head to head RCTs in R/R MCL. • Efficacy for ibrutinib in 2L MCL is excellent and NICE approved. • Data from the relapsed refractory MCL setting suggests zanubrutinib response rates and PFS is at least as effective although no head-to-head studies of zanubrutinib vs ibrutinib have been performed. • Zanubrutinib is a more efficacious BTKi than ibrutinib in other low grade B cell lymphoid cancers: CLL and WM where randomised trials have demonstrated this clearly. • Zanubrutinib is known to be safer than ibrutinib in randomised trials in CLL and WM. • Based on these key points, if NICE approved, zanubrutinib would be used in place of ibrutinib in a widespread fashion across the UK with a change in new prescribing occurring immediately and consistently

Thank you for your time.

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External Assessment Group's report

Title: *Zanubrutinib for treating relapsed or refractory mantle cell lymphoma after 1 or more treatments: EAG Report*

Produced by	Birmingham Centre for Evidence and Implementation Science
Authors	Mandy Maredza, Health Economist, University of Birmingham Mubarak Patel, Research Fellow, University of Birmingham Iman Ghosh, Research Associate, University of Birmingham Emma Loveman, Systematic Review Consultant, Effective Evidence LLP Rachel Court, Senior Information Specialist, University of Birmingham Jill Colquitt, Systematic Review Consultant, Effective Evidence LLP
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Date completed	09/04/2025

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Declared competing interests of the authors
None.

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Please refer to the International Committee of Medical Journal Editors (ICMJE) ***Uniform Requirements for Manuscripts Submitted to Biomedical Journals see*** ***http://www.icmje.org/***

All authors read and accepted the final report. JC compiled the report and supported the review of the clinical evidence. MP reviewed the ITC and statistical analysis in the clinical and cost-effectiveness sections. MM reviewed the economics of the submission, revised the company model and provided the cost effectiveness estimates. EL and IG reviewed the clinical evidence. RC reviewed the company's literature searches and conducted additional searches.

Please note that: Sections highlighted in [redacted] are '[redacted]. Sections highlighted in [redacted]. Figures that are CIC have been bordered with blue. Depersonalised Data (DPD) is highlighted in pink.

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Executive Summary

1 Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 0 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.2 to 1.5 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1: Summary of key issues

ID	Summary of issue	Report sections
Issue 1	The population in the company's decision problem is narrower than defined in the NICE scope and marketing authorisation	2.42.4
Issue 2	Limitations of the included zanubrutinib studies	3.2.8
Issue 3	Poor fit of company's preferred models to observed data	4.2.6
Issue 4	Uncertain degree of overall survival benefit	4.2.6
Issue 5	Resource use levels for outpatient visits, blood tests and scans not reflective of clinical practice	4.2.9
Issue 6	Adverse events rates applied in model	4.2.8
Issue 7	Suitability of baseline characteristics of modelled population in economic model	4.2.3

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are choice of survival models to estimate long-term PFS, OS and TTD, source of data for adverse event rates for BGB-3111-AU-003 trial and estimates of resource usage for outpatient visits, blood tests and scans.

Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Parametric model fit to PFS and OS data.
- Baseline characteristics of modelled population

Overall, the technology is modelled to affect costs by:

- Parametric model fit to PFS, OS and TTD data
- Frequency of resource use in progression-free and progressed disease health state
- Frequency of adverse events

The modelling assumptions that have the greatest effect on the ICER are:

- N/A. The ICER remained [redacted]

1.2 The decision problem: summary of the EAG's key issues

Issue 1: The population is narrower than the NICE scope

Report section	2.4
Description of issue and why the EAG has identified it as important	The populations in the two key studies submitted as evidence of clinical effectiveness by the company match the NICE final scope and the marketing authorisation for zanubrutinib (adults with at least 1 prior therapy). However, the CS addresses the narrower population of adults who have had only 1 prior line of therapy (2L) and presents subgroup data for these patients. Despite this, the company's ITC of zanubrutinib versus ibrutinib and the economic model use data from ≥2L patients.
What alternative approach has the EAG suggested?	Requested subgroup analysis for the 2L-only population during clarification (Clarification B12)
What is the expected effect on the cost-effectiveness estimates?	Incremental QALYs [redacted] by [redacted]%. ICERs showed zanubrutinib remained [redacted], [redacted] i.e., [redacted]
What additional evidence or analyses might help to resolve this key issue?	Ideally, future clinical trials on zanubrutinib, focussed on the R/R MCL 2L population could provide additional evidence, (increase sample sizes) and allow ITC analyses with 2L-only cohort that are sufficiently powered for efficacy estimates.

1.3 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 2: Limitations of the included zanubrutinib studies

Report section	3.23.2.8
Description of issue and why the EAG has identified it as important	Concerns remain about the reliability of information coming from the two included zanubrutinib studies. The small sample sizes, numerous data cuts and issues with not being able to validate many of the data reduce the EAG certainty in the interpretation of the results. The populations of the trials may also differ compared to expected real-world use in NHS practice and there were no UK participants. In addition, no data on quality of life has been provided.
What alternative approach has the EAG suggested?	With the exception of baseline characteristics used in the economic model the EAG is unable to meaningfully explore the impact of these concerns. The EAG explored the impact on the ICER of using the baseline characteristics of the pooled zanubrutinib trials rather than data from NICE appraisal TA502, by simultaneously varying age, BSA and proportion males.
What is the expected effect on the cost-effectiveness estimates?	The ICER using the baseline characteristics from zanubrutinib did not change the overall outcome, although the EAG discusses the impact in costs and QALYs in section 0. The impact of these concerns is difficult to estimate beyond acknowledging the high degree of uncertainty.
What additional evidence or analyses might help to resolve this key issue?	Further evidence to reduce the uncertainty in the data would be required.

1.4 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 3: Poor fit of company's preferred models to observed data

Report section	4.2.6
Description of issue and why the EAG has identified it as important	Poor fit of the preferred parametric models to the observed Kaplan-Meier data and the lack of consideration of more flexible modelling approaches. The company's preferred base case models are a poor visual fit with the observed KM curves, underestimating survival at certain points and failing to capture changes in hazard over time, especially in the zanubrutinib models. Despite this poor visual fit, the company did not present results of flexible models, such as spline-based models, which could have provided a better fit to and representation of the observed KM data. This issue raises concerns about the reliability of the extrapolated survival estimates and their impact on the overall cost-effectiveness results.
What alternative approach has the EAG suggested?	Exploration of flexible models
What is the expected effect on the cost-effectiveness estimates?	Generally, [redacted] QALY gains, significant impact observed with OS assumptions for both zanubrutinib and ibrutinib. Cost-savings generally [redacted] and highest impact also observed with OS. Zanubrutinib remained [redacted]
What additional evidence or analyses might help to resolve this key issue?	Longer follow-up or ideally head-to-head trials would provide improved estimates of zanubrutinib benefit.

Issue 4: Uncertain degree of overall survival benefit

Report section	4.2.6
Description of issue and why the EAG has identified it as important	The company models a long-term survival benefit for zanubrutinib that appears inconsistent with what could be observed in clinical practice, particularly considering the short-term follow-up (38.92 months at DCO March 2021) for BGB-3111-AU-003 trial and 35.25 months for BGB-3111-206. EAG clinical expert's opinion indicated that estimates in CS beyond 5 years appeared overly optimistic
What alternative approach has the EAG suggested?	The EAG's choice of the most plausible OS models in both treatment arms are based on the plausible long-term (5-year) estimates as judged by the EAG's clinical experts, as well as statistical and visual fit.
What is the expected effect on the cost-effectiveness estimates?	Applying the EAG's preferred OS assumptions to the company's base case [redacted] both the incremental costs and benefits (QALY gains) but cost-effectiveness conclusion remains the same
What additional evidence or analyses might help to resolve this key issue?	Additional follow-up would assist with reducing the uncertainty about the future OS benefit of zanubrutinib.

Issue 5: Resource use levels for outpatient visits, blood tests and scans not reflective of clinical practice

Report section	4.2.9
Description of issue and why the EAG has identified it as important	The EAG considers that the 7
What alternative approach has the EAG suggested?	The EAG has conducted a scenario analysis using alternative estimates provided by the EAG clinical expert.
What is the expected effect on the cost-effectiveness estimates?	The cost-savings are marginally [redacted] for zanubrutinib
What additional evidence or analyses might help to resolve this key issue?	Real-world evidence on resource usage in patients with R/R MCL on BTKi therapies could aid in better understanding resource use patterns.

Issue 6: Adverse events rates applied in economic model

Report section	4.2.8
Description of issue and why the EAG has identified it as important	Two issues identified related to adverse events (AE) included in model. • AE rates used in economic model for BGB-3111-AU-003 trial based on earlier datacut not (DCO: December 2021) as stated in company's narrative (B.3.4.5). • Costs are likely underestimated in the company's cost-effectiveness results. EAG's clinical expert commented that the incidence of infections, appears under-estimated for zanubrutinib possibly due to the small sample size (N=118; unweighted) and short-term follow-up period. The CS included AEs occurring in >5% of population.
What alternative approach has the EAG suggested?	• The EAG updated AE data in model to reflect rates reported for the 31March 2021 DCO in CS • The EAG conducted a scenario analysis whereby grade 3 AEs occurring in ≥2% of the patients are included in analysis. This is in line with previous appraisals (TA963) whereby appraising committee concluded that given the small sample size, it was appropriate to include the broader range of AEs (those affecting at least 2% of people) in economic analysis
What is the expected effect on the cost-effectiveness estimates?	There is negligible impact on costs and no impact on ICER
What additional evidence or analyses might help to resolve this key issue?	Longer-term follow-up data may resolve uncertainty

1.5 Other key issues: summary of the EAG's view

Issue 7: Suitability of baseline characteristics of modelled population in economic model

Report section	4.2.3
Description of issue and why the EAG has identified it as important	Modelled baseline characteristics in economic model derived from TA502 and differ markedly from the pooled zanubrutinib pivotal trials.
What alternative approach has the EAG suggested?	Scenario analysis using baseline characteristics from pooled zanubrutinib studies
What is the expected effect on the cost-effectiveness estimates?	[redacted] in QALY gains but [redacted] cost-savings for zanubrutinib
What additional evidence or analyses might help to resolve this key issue?	Real world databases showing real world characteristics, treatment patterns of patients with R/R MCL.

1.6 Summary of EAG's preferred assumptions and resulting ICER

Since the ICER, after implementing EAG's preferred assumptions, showed that zanubrutinib [redacted] ibrutinib across all scenarios (i.e., is [redacted], and [redacted]), the impact (direction of change) in costs and QALYs (percentage change) is shown instead (see Table 2).

Table 2: Summary of EAG's preferred assumptions and ICER

Preferred assumption	Section in EAG report	Incremental Costs (Direction of Change)	Incremental QALYs (%Change)	Cumulative ICER £/QALY
Company base-case (post-clarification)	*5.1*	[redacted]	[redacted]	[redacted]
Flexible models for modelling PFS, OS, TTD for both zanubrutinib and ibrutinib[1]				
Zanubrutinib				
EAG 01: 2-knot normal to model zanubrutinib PFS	*4.2.6.1*	[redacted]	[redacted]	[redacted]
EAG 02: 1-knot normal to model zanubrutinib OS	4.2.6.1	[redacted]	[redacted]	[redacted]
EAG 03: TTD for zanubrutinib assumed equal to PFS	4.2.6.1	[redacted]	[redacted]	[redacted]
Ibrutinib				
EAG 04: 2-knot odds to model ibrutinib PFS	4.2.6.1	[redacted]	[redacted]	[redacted]
EAG 05: 2-knot normal to model ibrutinib OS	4.2.6.1	[redacted]	[redacted]	[redacted]
EAG 06: TTD assumed equal to ibrutinib PFS	4.2.6.1	[redacted]	[redacted]	[redacted]
Alternative health state resource use assumptions				
EAG 07[a]: Alternative assumptions on frequency of resource use in the progression-free and progressed diseased state for blood glucose tests, LDH tests, lymphocyte counts, haematolgist's visit, biopsy and CT scans. as per EAG's clinical expert's opinion	4.2.10	[redacted]	[redacted]	[redacted]

Preferred assumption	Section in EAG report	Incremental Costs (Direction of Change)	Incremental QALYs (%Change)	Cumulative ICER £/QALY
EAG 08[b]: Incidence of adverse events based on March 2021 datacut for AU003 trial	*4.2.8*	[redacted]	[redacted]	[redacted]
Cumulative impact of all changes (EAG01 – EAG08)		[redacted]	[redacted]	[redacted]

[a] Potential models were all chosen based on good statistical and visual fit to both KM and hazard plots and plausibility of the long-term survival estimates compared to the EAG's clinical experts' opinions. [b] Based on EAG's clinical experts' opinion. [redacted] means zanubrutinib is [redacted] and [redacted] than ibrutinib.
[redacted] implies [redacted] in favour of zanubrutinib

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Abbreviations

2L	Second line treatment
AE	Adverse event
AIC	Akaike information criterion
alloSCT	Allogeneic haemopoietic stem cell transplant
ASCT	Autologous stem cell transfer
BCR	B-cell receptor
BIC	Bayesian information criterion
BSA	Body surface area
BTKi	Bruton's tyrosine kinase inhibitor
BMI	Body mass index
BNF	British National Formulary
CDF	Cancer Drugs Fund
CASP	Critical Appraisal Skills Programme
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CRD	Centre for reviews and dissemination
CS	Company submission
CSR	Clinical study report
DCO	Data cut-off
DOR	Duration of response
EAG	External assessment group
ECOG	Eastern Cooperative Oncology Group
ESS	Effective sample size
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICEP	Incremental cost-effectiveness plane
ICER	Incremental cost-effectiveness ratio
IPSW	Inverse probability of sampling weight
IRC	Independent review committee
ISMCL	In situ mantle cell neoplasia
INV	Investigator
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IPD	Individual patient data
KM	Kaplan-Meier
LY	Life year
LYG	Life years gained
MAIC	Matching-adjusted indirect comparison
MCL	Mantle cell lymphoma

MIPI	MCL International Prognostic Index
MZL	Marginal zone lymphoma
NMB	Net monetary benefit
NE	Not estimable
NHL	Non-Hodgkin lymphoma
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NR	Not reported
ORR	Overall response rate
OS	Overall survival
PAS	Patient access scheme
PD	Progressive disease
PFS	Progression-free survival
PH	Proportional hazards
PRO	Patient reported outcome
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal social service
PT	Preferred term
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
R/R	Relapsed or refractory
RWE	Real-world evidence
SAE	Serious adverse event
SAP	Statistical analysis plan
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
SOC	System organ class
STA	Single technology appraisal
STC	Simulated treatment comparison
TA	Technology appraisal
TEAE	Treatment emergent adverse events
TEMs	Treatment effect modifiers
TTD	Time to treatment discontinuation
TTR	Time to response
UK	United Kingdom
WTP	Willingness to pay

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

Remit of the appraisal

To appraise the clinical and cost-effectiveness of zanubrutinib within its marketing authorisation for the treatment of relapsed or refractory (R/R) mantle cell lymphoma (MCL).

Condition, symptoms and economic burden

MCL is a rare type of B cell non-Hodgkin lymphoma (NHL), which is a cancer of the lymphatic system. The most common symptom is one or more painless swellings in the neck, armpit or groin, caused by enlarged lymph nodes. Other symptoms include heavy night sweats, high temperature with no obvious cause, and weight loss. MCL can develop outside of the lymph nodes, if this occurs the symptoms will depend on where it grows.[1]

The company accurately reports a prevalence of 4.2 and an annual incidence of 0.9 per 100,000 people in the United Kingdom (UK).[2, 3] There are 590 estimated cases per year in the UK; 410 of these are men.[3] The CS describe this as a 'slight male predominance'. MCL is very rare in young people and is most common in those over 70 years. In CS B.1.3.1.1, the company reports real world data from the Haematological Malignancy Research Network (HMRN) (citing [redacted]), supplied with the CS), a UK registry of a population-based patient cohort of around 4 million patients from Yorkshire and Humberside, indicating that [redacted] of patients who received first-line treatment in the registry went on to receive further treatment for R/R MCL. The same reference is cited in section CS B.1.3.1.2, where it is stated that [redacted] of a cohort of [redacted] patients diagnosed with R/R MCL had received at least one prior treatment. On checking the reference, it appears that the latter figure is correct. Lymphoma Action states that MCL 'almost always' needs more treatment after remission with first-line treatment.[4]

2.2 Background

Critique of the company's description of the health condition

The EAG agrees with the company's description of the health condition. NHL is graded as indolent (low grade, slow growing) or aggressive / high grade (fast growing).[3] The EAG notes that MCL looks like a low grade lymphoma under the microscope, but often grows like a high grade lymphoma.[1]

The CS describes the main types of MCL as classical, leukemic non-nodal and in situ mantle cell neoplasia.[5] Classical MCL is the most common and is usually fast growing, whereas leukemic non-nodal MCL is less common and slower growing.[4] In situ mantle cell neoplasia (ISMCL) is described as often found incidentally and in association with other lymphomas, and is associated with a low rate of progression.[5-7] The EAG clinical advisor explained that, whilst fewer patients with leukemic, non-nodal MCL may need treatment, the management approach when treatment is needed is not affected by the type of MCL.

A description of staging of NHL can be found in CS section B.1.3.1.1. The CS mentions three staging systems: the Ann Arbor classification, the Lugano staging system (a modification of the Ann Arbor system), and the fluorodeoxyglucose-positron emission tomography-CT staging system, and states that Ann Arbor was used in the clinical studies included in the CS.

Quality of Life

The symptom burden of MCL and the impact on quality of life (QoL) are described in CS B.1.3.2, with the company reporting experiences of patient representatives from NICE TA502 of ibrutinib for R/R MCL.[8] The company notes that there is limited health-related quality of life (HRQoL) literature on R/R MCL due the rare nature of the condition, stating that a literature review conducted by the company identified only six studies. However, these are not summarised in the background.

The company refers to one systematic review,[9] stating that HRQoL of MCL patients is significantly reduced due to symptom burden and loss of physical health, mobility and vitality. The EAG notes that the systematic review is not specific to MCL, it is a broad review of haematological cancers including NHL, but considers it reasonable to assume the conclusions apply to MCL.

The company also refers to a survey[10] that found worse HRQoL in NHL patients who received chemotherapy than those did not. The EAG notes that this study is included in the review[9] already mentioned, and that the review also notes that one study found improvements in some aspects of HRQoL in aggressive NHL during chemotherapy. Better QoL in patients with Waldenström's macroglobulinaemia, a rare form of NHL, in those with a Bruton's Kinase Inhibitor (BTKi) (e.g. ibrutinib) than those not exposed was found in another study.[11] The EAG notes that HRQoL was assessed in NICE TA502 of ibrutinib for R/R MCL. A clinically meaningful improvement in lymphoma symptoms, measured by FACT-Lym, a cancer-specific, non-preference based HRQoL measure, was achieved by 62% of patients treated with ibrutinib compared with 35.5% of patients treated with the trial comparator, temsirolimus. A statistically significant difference in EQ-5D utility score favouring ibrutinib over temsirolimus was also found.[8]

Other statements regarding QoL in CS section B.1.3.2.2 are from patient information websites from charities (Macmillan cancer support;[12] Lymphoma Action[13]), rather than evidence from peer review publications.

The company states that ibrutinib can be associated with serious cardiac safety issues, which negatively impact patients' QoL, but does not support this statement with references. However, a study demonstrating that zanubrutinib is associated with an improved tolerability profile compared with ibrutinib is cited.[14] This was a study of 82 patients with B-cell malignancies (n=4 with MCL) who were intolerant of ibrutinib and/or acalabrutinib, with a median 2 prior therapies (range 1 to 12), which concluded that zanubrutinib may provide clinical benefit to patients previously intolerant of other BTKis.[14]

Life expectancy

CS section B.1.3.3 states 'MCL often progresses in line with more high grade lymphomas, with median survival ranging between 3.1 and 5 years.[15]' The EAG notes that the values are not available at the company's cited source, but considers them comparable to another source.[16] Median overall survival for R/R MCL patients in the HMRN registry (n=[redacted]) was only [redacted] year (95% CI: [redacted]) (data reported in [redacted], supplied with the CS).

2.3 Critique of the company's overview of the position of the technology in the treatment pathway

Current treatment pathway

The company describes first-line treatment of MCL in CS section B.1.3.4 and CS Figure 1. The EAG clinical advisor agrees that this is an accurate description of UK clinical practice.

Standard of care for R/R MCL at second line is now the BTKi ibrutinib, following its recommendation by NICE in 2018.[8] The company provides data from the HMRN registry showing that [redacted] of patients initiating 2L treatment received ibrutinib therapy (CS Table 3). Although the size of the sample was small (n=[redacted]), the EAG clinical advisor agrees with the company that very few patients would not receive ibrutinib at second line. Where this is the case, it would usually be due to specific health issues of the individual patient. The EAG clinical advisor explained that patients can usually only have one BTKi, although they can have a second BTKi if they are intolerant of the first.

The company justifies the exclusion of other potential comparators listed in the NICE scope (rituximab with or without chemotherapy, brexucabtagene autoleucel and allogenic stem cell transplant) in CS section B.1.3.4. The EAG agrees with the company's justification.

Zanubrutinib

Zanubrutinib is described in CS Table 2 as a next generation, highly selective, small molecule, orally administered, irreversible inhibitor of Bruton's tyrosine kinase (BTK), a signalling molecule of the B-cell receptor (BCR) and cytokine receptor pathways. The CS states that '*zanubrutinib binds with and inhibits BTK which blocks BCR-induced BTK activation. By blocking the signalling pathway, this inhibits the proliferation and survival of malignant B cells*.'

Zanubrutinib is indicated as a monotherapy for the treatment of adult patients with MCL who have received at least one prior therapy, with marketing authorisation granted on 21st November 2024. Other indications are:[17]

- Adults with Waldenström's macroglobulinaemia who have received at least one prior therapy, or in the first line treatment for patients unsuitable for chemo-immunotherapy.
- Adults with marginal zone lymphoma who have received at least one prior anti-CD20-based therapy.
- Adults with chronic lymphocytic leukaemia.
- In combination with obinutuzumab for adult patients with refractory or relapsed follicular lymphoma who have received at least two prior systemic therapies.

Proposed placement of zanubrutinib

The proposed positioning of zanubrutinib in the MCL treatment pathway is as a treatment option for patients at second line, that is for patients who have relapsed after first line immunochemotherapy or who are refractory to treatment. The company has positioned it as a treatment to displace ibrutinib. The company appropriately cites the British Society for Haematology (BSH) Guidelines:[18]

- Patients relapsing after first-line immunochemotherapy should be offered a covalent BTKi.
- Offer ibrutinib monotherapy as an approved and reimbursed standard of care option in the United Kingdom at first relapse.
- Where the choice of ibrutinib, acalabrutinib or zanubrutinib is available, treatment should be individualised based on the specific toxicity profile of each agent.
- Where a covalent BTKi has been used in first line as continuous therapy [e.g. through clinical trials or early access schemes], consider clinical trials or immunochemotherapy at first relapse.

2.4 Critique of company's definition of decision problem

The decision problem in the company's submission has some differences to the final NICE scope. The population in the company's decision is narrower than the NICE scope and only one comparator (ibrutinib) is considered. The EAG considers that the comparator is appropriate for the population under consideration.

Table 3: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with R/R MCL who have had at least 1 prior therapy	Adults with R/R MCL who have had 1 prior therapy (2L)	The population described in the final scope broadly captures the licensed indication for zanubrutinib. However, the population addressed in this submission is narrower than the marketing authorisation to reflect the population in which zanubrutinib would be used for R/R MCL in UK clinical practice. Zanubrutinib is anticipated to be positioned at 2L therapy, where there is an unmet need for an effective and well-tolerated treatment option, as confirmed by clinical experts.	The populations in the two key studies submitted as evidence of clinical effectiveness by the company match the NICE final scope and the marketing authorisation for zanubrutinib (adults with at least 1 prior therapy). However, the CS addresses the narrower population of adults who have had 1 prior line of therapy (2L) and presents subgroup data for these patients. Despite this, the company's ITC of zanubrutinib versus ibrutinib and the economic model use data from ≥2L patients. The company provided analyses using the 2L only population in response to EAG clarifications A11 and B12. It is difficult to assess the generalizability of the studies to UK clinical practice due to the small sample sizes. One of the studies was conducted in China. The other study was multinational with no UK patients (clarification A3). Participants in this trial were younger, which

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				means they may be better able tolerate treatment.
Intervention	Zanubrutinib	As per scope	N/A	The intervention matches the NICE scope. Zanubrutinib as a monotherapy is indicated for the treatment of adult patients with MCL who have received at least one prior therapy (authorisation granted 21/11/2024). The recommended total daily dose is 320 mg taken orally, either once daily or 160 mg twice daily.

Comparator(s)	Established clinical management including but not limited to:
	• After 1 prior therapy
	  ○ Ibrutinib
	• After 2 or more prior therapies
	  ○ Ibrutinib
	  ○ Chemotherapy with or without rituximab
	  ○ Brexucabtagene autoleucel (subject to NICE evaluation)
		Ibrutinib	Ibrutinib is considered the only appropriate comparator for zanubrutinib in 2L R/R MCL, based on the BSH 2023 and NICE guidelines, past NICE and SMC technology appraisals, real world evidence from the HMRN registry, UK clinical expert opinion (Advisory Board Report for zanubrutinib monotherapy in patients with R/R MCL, provided with the CS).[8, 18-20]
			
			This is the anticipated place of zanubrutinib in the treatment pathway.
			The following therapies are not considered appropriate comparators for reasons provided below:
				The EAG agrees that ibrutinib is the appropriate comparator at 2L. Ibrutinib is generally considered standard of care, and very few patients receive alternatives (usually due to specific health issues of the patient). The EAG clinical advisor agrees with the company's justification for the exclusion of other comparators.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	Allogeneic haemopoietic stem cell transplant		• Rituximab with or without chemotherapy • Brexucabtagene autoleucel • Allogeneic haemopoietic stem cell transplant (alloSCT) **Rituximab with or without chemotherapy** Ibrutinib is the current SoC in UK clinical practice in 2L R/R MCL, having displaced 'rituximab with or without chemotherapy' following its approval by NICE in 2018.[8] RWE from the HMRN shows that the majority of patients eligible for treatment with zanubrutinib would be those who have received one prior line of therapy (2L). Treatment usage data shows that ibrutinib is the regimen of choice for [redacted] of patients initiating 2L treatment for R/R MCL between [redacted] (data reported in [redacted], supplied with the CS). Zanubrutinib is anticipated to displace ibrutinib as a second-generation Bruton's tyrosine	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			kinase inhibitor (BTKi) therapy, which positions 'rituximab with or without chemotherapy' as subsequent treatment rather than a comparator treatment.[8] Therefore, 'rituximab with or without chemotherapy' should not be considered a comparator against zanubrutinib for this appraisal. **Brexucabtagene autoleucel** The licensed indication for brexucabtagene autoleucel is restricted to patients who have received at least two lines of systemic therapy including a BTKi.[21] Conversely, the trial eligibility criteria for zanubrutinib (BGB-3111-AU-003 and BGB-3111-206)[22, 23] excluded patients who had received treatment with a BTKi prior to enrolment. Hence there is no overlap in the eligible populations of the two treatments. This positions brexucabtagene autoleucel at 3L+, beyond zanubrutinib in the treatment pathway, as a subsequent treatment option rather than a relevant comparator. This is reflected in the BSH guidelines which recommend that *"MCL patients who are relapsed*	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			or refractory (including stable disease) after anti-CD20 antibody-containing immunochemotherapy and BTKi should be offered Brexu-cel". [18] Furthermore, brexucabtagene autoleucel is not available via routine commissioning, and hence as per NICE's position statement cannot be considered as a relevant treatment comparator within this appraisal.[18, 21] **AlloSCT** Within the RWE from the HMRN no patient underwent a stem cell transplant for R/R MCL, demonstrating that such interventions cannot be considered SoC in the UK. Furthermore, the BSH guidelines clearly recommend alloSCT for only *"fit patients with an appropriate donor following failure with immunochemotherapy, covalent BTKi* [such as zanubrutinib] *and CAR-T failure"* and go on to say: *"The majority of relapsed MCL patients will not be eligible for ASCT or alloSCT",* aligning to the observations from the HMRN cohort.[18]	
Outcomes	The outcome measures to be considered include:	As per scope	N/A	Health-related quality of life was not assessed in the zanubrutinib studies, but the company's

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment Health-related quality of life			decision problem does not note this. Utility values in the economic model are sourced from NICE TA502 of ibrutinib for R/R MCL.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS	A cost-effectiveness analysis in adults with 2L R/R MCL is presented comparing zanubrutinib with ibrutinib.	N/A	Follows NICE approach.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.			
Subgroups	None specified.	N/A	N/A	N/A
Special considerations including issues related to equity or equality	None specified.	N/A	N/A	N/A

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The CS undertook a systematic literature review (SLR) to identify studies investigating any treatments for people with R/R MCL, described in CS Appendix D.

3.1.1 Search strategies

The search strategy reflects the breadth of the SLR's aims. Searches in three bibliographic databases (MEDLINE, Embase and CENTRAL) were originally run on 16th of May 2024 and last updated on 16th July 2024. Appropriately, searches of these databases included both free text and controlled language terms. Suitable terms for MCL were included and no intervention or comparator terms were used to restrict the search, but there is a major error in the Relapsing/Remitting line of the MEDLINE and Embase search (run using Embase.com); "AND adj:ti,ab AND" occurs twice. The EAG tested a targeted version of the CS search (with zanubrutinib or ibrutinib added) and found that terms for prior treatment and the relevant lines of treatment were not contributing to the search. Therefore, a small proportion of potentially relevant records that do not additionally have terms for relapse, refractory, recurrent or resistant (or are indexed with relevant thesaurus terms)) will have been missed. The search of CENTRAL does not contain this error. The EAG's check of records not retrieved due to this error (for zanubrutinib or ibrutinib only) indicates that it has not had an impact on the overall clinical effectiveness SLR (see section 3.6.1).

Recognised and cited search filters for clinical trials and observational studies were applied appropriately. However, there is no filter for SLRs/ITCs meaning they were not specifically sought as a source of primary studies or to compare results. No date or language limits were used.

In addition to bibliographic database searches, the CS states that searches of relevant conferences and trials registers were undertaken in June 2024. Although the search month and source names are provided in Appendix D (and the EAG can confirm these are relevant sources) and numbers included from each source are given in the PRISMA flow diagram (Appendix D, Figure 1), the CS does not provide any more details on these searches (e.g. date limits, exact search terms, initial number of hits) and therefore the EAG cannot provide further commentary other than that they lack some transparency.

3.1.2 SLR methods

The EAG considered the steps taken to identify studies for the SLR (inclusion criteria, selection) to be generally appropriate (Table 4), despite some concerns about the searches. The SLR was initially broader than the decision problem, but additional steps were taken to only include studies with people with R/R MCL treated with zanubrutinib or ibrutinib. However, the processes for assessing potential studies at this stage was not clearly reported and the EAG considers that these additional criteria were likely not pre-stated criteria. The EAG has checked all the studies excluded at this additional stage and considers they were appropriate exclusions, because they did not provide enough details of the treatment effect modifiers relevant to the comparison.

Table 4: Summary of SLR methods EAG assessment of robustness

Systematic review step	EAG assessment of robustness of methods
Searches CS Appendix D section D1.	Unclear. Searches of several suitable sources are reported, although the reporting of grey literature searches lacked some transparency. Mainly, appropriate search terms are used. An error in the search of two sources does not appear to have made an impact overall on the amount of relevant records retrieved for zanubrutinib or ibrutinib. SLRs/ITCs were not specifically sought as alternative sources of primary studies or to compare results.
Inclusion criteria B.2.1; CS Appendix D Tables 4 and 5; CS Section B2.9.1 (ITC)	The inclusion criteria were generally appropriate for the decision problem. The SLR inclusion criteria were reported in two separate tables, one for RCTs and one for observational studies but apart from the study design the criteria were the same. The criteria were broader than the NICE scope, however, at a subsequent stage only studies which met the decision problem were eligible. The criteria for these do not appear to have been pre-stated at the outset of the SLR.
Screening CS Appendix D, section D1.3	Appropriate: the citations were screened by two reviewers, conflicts were resolved by a third independent reviewer, with any citations that were unclear retrieved for full paper selection.

Selection of included studies CS Appendix D, section D1.3	Unclear. Full texts assessed against the selection criteria by two independent reviewers, with arbitration of disagreements by a third independent reviewer. The CS assessment of the feasibility of studies for the ITC, was not using pre-defined selection criteria (Clarification C7). The EAG has checked the excluded studies lists, including those excluded from the ITC, and although additional studies of ibrutinib were available there were insufficient data on the treatment effect modifiers of relevance to the appraisal. The EAG are satisfied that the pooled ibrutinib study[24] was appropriate to inform the ITC base-case which included those with any prior line of therapy. One study of ibrutinib was excluded as it was reported in the form of a letter.[25] This is a longer-term follow-up of the pooled ibrutinib study[24] chosen by the company for the ITC. The excluded study has data for the population of relevance to the decision problem and in response to clarification question A11 the company have undertaken an indirect comparison using these data, see section 3.3. The CS stated that there was no data of sufficient quality to inform the ITC in 2L only patients, the EAG requested clarification of the process for excluding studies based on quality (clarification C1). The company response reiterates the reasons for inclusion / exclusion but the process applied was not provided. The EAG considers that the process to exclude based on quality was not pre-defined.
Data extraction CS Appendix D, section D1.4	Appropriate: data was extracted into a data collection form by a single reviewer and validated by a second reviewer, with discrepancies resolved through discussion or consultation with a third reviewer.
Tools for quality assessment CS Appendix D, section D1.4 and CS Sections B.2a.5 and B.2b.5	Appropriate. The CS appendix states that CRD report guidance and the Downs and Black tools for non-randomised controlled studies were used to assess risk of bias. The CS cites the CASP checklist and the NICE user guide. The questions presented reflect the latter. In response to clarification question C9 the company reported that the Downs and Black tool was not used, but the company did then provide a full assessment using Downs and Black at clarification.
Evidence synthesis CS Section B2.2-9; CS Appendix D, section D2	Unclear. The CS provides summary tables and narrative descriptions of the included studies. The two included zanubrutinib studies were pooled. The CS cites a recent publication[26] which presents pooled analyses of the two studies where participant data were divided into two groups

	based on the line of treatment line 2L only; later-lines and the inverse propensity score weighting (IPSW) method was used to balance the baseline covariates between the groups. In this publication patient-level data for those with no missing baseline covariates (age, sex, BMI, ECOG performance status, disease stage, blastoid variant, MIPI score, bulky disease, extranodal and bone marrow involvement) were pooled. The CS states only that patient-level data were pooled and that no adjustments were required to balance the populations of the two trials as baseline characteristics were comparable. In Song 2023, the pooled zanubrutinib population initially has 112 patients, and after applying IPSW to balance covariates between treatment-line subgroups, the ESS was reduced to 91 patients. In contrast, the CS reported a pooled zanubrutinib population of 118 patients. The larger pooled population in the CS suggests that additional patients were included beyond those included in Song 2023. Song 2023 excluded those with missing data, and the larger pooled population in the CS suggests that these were included. If the CS included these additional six patients without the appropriate adjustments, it could introduce selection bias and impact the comparability of the pooled population used in the ITC.

CASP: Critical Appraisal Skills Programme; CRD: Centre for Reviews and Dissemination; IPSW: inverse probability of sampling weight

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation

The source of evidence for the assessment of clinical effectiveness of zanubrutinib for the treatment of R/R MCL was obtained from two key studies, BGB-3111-AU-003 (NCT02343120) (2021 CSR for BGB-3111-AU-003, provided with the CS) and BGB-3111-206 (NCT03206970) (2021 CSR for BGB-3111-206, provided with the CS) and four associated publications (Tam *et al.* [2021]),[27] Song *et al.* [2020],[28] Song *et al.* [2021],[29] Song *et al.* [2022][30]). The studies were summarised in CS Table 5 with further detailed descriptions in CS Sections B.2a.3 and B.2b.3.

3.2.1 BGB-3111-AU-003 and BGB-3111-206

The BGB-3111-AU-003 study is a phase 1/2, open label, single arm, multicentre study consisting of a phase of dose escalation (part 1) and a phase of dose expansion (part 2), Table 5. The study included participants with various B-cell lymphoid malignancies who had at least one prior therapy; for the purpose of the company decision problem, the CS focuses on participants with R/R MCL who received a total daily dose of zanubrutinib of 320 mg (n=32) and similarly the EAG assessment considers these participants, predominantly from part 2 (n=1 from part 1) of the study. R/R MCL participants were treated with 320mg oral zanubrutinib once daily or 160mg oral zanubrutinib twice daily in 28 day cycles until disease progression, unacceptable toxicity, death, withdrawal of consent or loss to follow up. Participants in BGB-3111-AU-003 were recruited from Australia, New Zealand, Italy, South Korea, US, and UK, however the number of UK population was not explicitly reported in the CS. In response to the EAG's request for clarification (clarification A3) the company stated that there were no UK participants. This may be a generalisability concern, discussed further in section 3.2.8. Of the 32 participants included, 18 received zanubrutinib at second line (2L) only (herein referred to as the 2L-subgroup). This small sample size raises concerns for the EAG regarding the potential for random variation in results and lack of power. See section 3.2.3 for quality assessment of study BGB-3111-AU-003.

As can be seen in Table 5, BGB-3111-206 is a phase 2 open label, single arm, multicentre study. Study participants with R/R MCL who had between one and five prior therapies received oral zanubrutinib160 mg twice daily in 28-day cycles for up to 3 years or until disease progression, unacceptable toxicity, or study termination by the sponsor. The cohort size for overall study (N=86) was larger than BGB-3111-AU-003, but in the 2L-subgroup the sample size was still small (n=26). The study was undertaken in China, the impact of this is unclear but there may be differences in health care practices which could have a bearing on results, see section 3.2.8. See section 3.2.3 for quality assessment of study BGB-3111-206.

Eligibility criteria for participants in the two studies can be seen in Table 5. Criteria were broadly similar for age; in BGB-3111-AU-003, participants were ≥18 years old; in BGB-3111-206 participants were aged 18 to 75 years. The permitted range of

Eastern Cooperative Oncology Group performance status (ECOG PS) was the same in the two studies (0-2). Adequate organ function was required for entry into both studies although there were some differences in required levels. Study BGB-3111-AU-003 required adequate haematologic function (neutrophil count ≥1.0 × 10^9/L, platelet count ≥50 × 10^9/L), renal function (measured or estimated creatinine clearance ≥30 mL/min), and liver function (transaminase levels ≤3× the upper limit of normal [ULN], total bilirubin ≤1.5× ULN). Study BGB-3111-206 required adequate organ function (creatinine clearance ≥30 mL/min, transaminase levels ≤2.5× UPL, total bilirubin ≤1.5× UPL), and specific blood counts (neutrophil count ≥1 × 10^9/L, platelet count ≥75 × 10^9/L or ≥50 × 10^9/L for bone marrow involvement), without recent growth factor support or transfusion. The differences in requirement criteria are unlikely to impact overall prognosis of the disease. In both studies, included participants had R/R MCL with no prior exposure to a BTK inhibitor. BGB-3111-206 participants were additionally required to have measurable disease (lymph node ≥1.5 cm on CT/MRI). The implications of this are unclear, but the EAG clinical adviser considered that in the context of the small sample this would not have any important implication.

Key efficacy outcomes such as ORR, PFS, and DOR, were assessed in both studies by an independent review committee (IRC) and investigator (INV) evaluation, though reported at different data cut-off (DCO) points, see 3.2.2 and Table 6 for more details. The EAG notes that IRC assessment is recommended by regulatory authorities for independent verification of outcomes using medical imaging. The aim is to minimise unintentional bias that site investigators may be subject to, such as additional patient information or the anticipated study outcome, although in some cases IRC assessment may introduce bias such as informative censoring.[31, 32] There is evidence to suggest that INV may overestimate response rates compared with IRC.[31]

The IRC members as reported in the CSR for BGB-3111-AU-003 were [redacted] who retrospectively evaluated the radiological findings in accordance with the Lugano classification (2018 CSR for study BGB-3111-AU-003, supplied after clarifications).

[redacted]

[redacted] (2021 CSR for BGB-3111-AU-003, provided with the CS). For study BGB-3111-206, efficacy measures assessed by IRC also use the Lugano classification. However, specific details regarding the agreement methodology and investigator roles were not reported in the CSR available to the EAG (2021 CSR for BGB-3111-206, provided with the CS).

The median follow-up times were comparable in both studies. The median follow-up time for IRC assessment in BGB-3111-AU-003 was 18.84 months (DCO on 13th December 2018) and for the INV assessment 38.92 months (DCO on 31st March 2021). Similarly, BGB-3111-206 reported the IRC assessed median follow-up at 18.4 months (DCO 15 February 2019) and an INV assessed median follow-up at 35.25 months (DCO 8th September 2020). BGB-3111-206 provided an additional DCO for INV reporting at a median follow up of 24.84 months (DCO 31 August 2019); see CS Section B.2b.6.

Table 5: Characteristics of included zanubrutinib studies

	BGB-3111-AU-003	**BGB-3111-206**
Study details	Tam et al. 2021[27] NCT02343120 Australia, New Zealand, South Korea, US, and UK (24 sites in 6 countries) Between 22 September 2014 and 22 March 2018	Song et al. 2020,[28] Song et al. 2021,[29] Song et al. 2022[30] NCT03206970 China (13 clinical sites) Between March 2, 2017 and September 27, 2017
Study design	Open-label, multiple doses, multicentre phase I/II study composed of initial dose escalation phase (Part 1; in various B-cell lymphoid malignancies, not relevant here) followed by expansion phase (Part 2-enrolled patients in disease specific cohorts including R/R MCL)	Phase II, single-arm, multicentre, open-label study
Intervention	In part-2 zanubrutinib orally, 320mg once or 160mg twice daily in 28-day cycles, until progression or unacceptable toxicity, death, withdrawal of consent or loss to follow up	Zanubrutinib orally 160 mg twice daily in 28-day cycles for up to 3 years or until disease progression, unacceptable toxicity, death, withdrawal of consent, or study termination

Sample size	In part-2 (N=32), One Part 1 patient received 320 mg QD, [redacted] Part 2 patients received 320 mg QD, and [redacted] Part 2 patients received 160 mg BID. (Clarification response A2)	N=86 The company clarified the sample size calculation in response to clarification A7 since there were mistypes in the CS. Assuming ORR=70% compared to a historical ORR=40%, around 80 patients will be required at a one-sided alpha=2.5% and power >99%.
Population	• ≥18 years old • R/R MCL without prior exposure to BTK inhibitor therapy • ECOG PS 0-2 • Adequate haematologic, renal and liver function	• Aged 18 to 75 years. • 1 - 5 prior lines of therapy. • Retrospectively confirmed MCL diagnosis. • ECOG PS of 0-2. • Measurable disease in at least 1 lymph node >1.5 cm in longest diameter and measurable in 2 perpendicular dimensions. • Failure to achieve any response or progressive disease after the most recent treatment regimen. • No prior BTK inhibitor • Adequate organ liver function • Life expectancy of > 4 months.
Subgroup of relevance to decision problem	N=18 Adult patients with R/R MCL and 2L (only) prior therapy	N=26 Adult patients with R/R MCL and 2L (only) prior therapy
Duration of follow-up	IRC assessed Median follow-up time 18.84 months (DCO on 13th December 2018) INV assessed median follow up 38.92 months (DCO on 31st March 2021)	IRC assessed median follow-up 18.4 months (DCO 15 February 2019). INV assessed median follow-up 24.84 months (DCO 31 August 2019) and 35.25 months (DCO 8th September 2020).
Outcomes	**ORR:** The proportion of patients achieving a best overall response of CR or PR as determined by either IRC or INV **PFS** (IRC and INV): Time from the first dose of zanubrutinib treatment to the date of first documented progressive disease or death from any cause, whichever occurred first **OS**: Time from initiation of zanubrutinib to the date of death from any cause. **DOR** (IRC and INV): Time from the date of earliest response (CR or PR) to the date of first documented progressive disease or death from any cause, whichever occurred first. **TTR** (IRC and INV): Time from initiation of zanubrutinib to the date of first documented response (CR or PR).	

Source: Adapted from Tam et al 2021,[27] CS Table 6, CS Table 7, CS Table 8, Song et al 2020,[28] CS Table 19, CS Table 20, and CS Table 21. *Abbreviations:* BTK – Bruton's tyrosine kinase; cm – centimetres; DCO – data cut-off; DOR – duration of response; ECOG PS – Eastern Cooperative Oncology Group performance status; INV – investigator; IRC - independent review committee; ORR – overall response rate; OS - overall survival; PFS – progression-free survival; R/R MCL – relapsed/refractory mantle cell lymphoma TTR – time to response; UK – United Kingdom; USA – United States of America

3.2.2 Data-cuts

DCOs, assessor (IRC or INV), median follow-up, and associated CSRs and references are summarised in Table 6 for the full population (≥1 prior line of therapy) of each study. No CSRs or other sources of data were available for the 2-L only subgroup of either study; the references cited by the company (CS reference 45 and 48) are raw clinical data taken directly from the trial and there is no formal file (Clarification response C3). The EAG is therefore unable to validate the 2L-only data.

The rationale for reporting IRC- or INV-assessed outcomes at each DCO is not given in the CS, but some explanation can be found in the regulatory summary of clinical efficacy (BeiGene 2020 Regulatory summary of clinical safety for the BGB-3111-206 and AU-003 trials, provided with the CS) and CSR for BGB-3111-206 (2024 CSR for BGB-3111-206 clinical evidence, provided with the CS). Concordance between IRC and INV assessments was measured in both studies (see section 3.2.6.2), with the CSR for BGB-3111-206 stating that

[redacted] (2024 CSR for BGB-3111-206 clinical evidence, provided with the CS).

BGB-3111-AU-003

The CS presents two DCOs for study BGB-3111-AU-003: 13 December 2018 (IRC-assessed) and 31 March 2021 (INV-assessed) (CS Table 13). Data from the first DCO are published in Tam 2021,[27] and are available in the confidential regulatory summary of clinical efficacy (BeiGene 2020 Regulatory summary of clinical efficacy for the BGB-3111-206 and AU-003 trials) provided by the company. The second DCO presented in the CS cites the CSR (2021 CSR for BGB-3111-AU-003, provided with the CS) for study BGB-3111-AU-003, but the CSR provided with the CS has a different DCO (02 October 2020) to the CS, and does not report data for the subgroup of patients with R/R MCL who had a 320 mg total daily dose of zanubrutinib (n=32, referred to as the 'full trial population' in the CS). The company provided the CSR for the 13 December 2018 DCO, after initially stating that 'the only available CSR file for [BGB-3111-]AU-003 has a data cut off of the 31st March 2021' (Company response to urgent clarification questions 05/02/025, Clarification C5).

The CSR for the 31st March 2021 was requested by the EAG but not provided (Clarification C5) until after submission of the EAG report. The EAG was able to validate the clinical effectiveness data at this DCO during the factual accuracy check. However, the 31st March 2021 CSR does not report adverse event data for the R/R MCL 320 mg daily dose cohort, therefore the EAG is unable to validate adverse event data at this DCO.

BGB-3111-206

Three DCOs are presented in the CS for study BGB-3111-206 (CS Table 26). The first presented DCO at 15 February 2019 (median follow-up 18 months) was IRC-assessed, and was published in Song 2020a.[28] INV-assessed (but not IRC-assessed) outcomes at the 31 August 2019 DCO were provided in the regulatory summary of clinical efficacy (BeiGene 2020 Regulatory summary of clinical efficacy for the BGB-3111-206 and AU-003 trials). Only INV-assessments were analysed at the study end date (08 September 2020) and presented in the CSR (2021 CSR for BGB-3111-206, provided with the CS) and published in Song 2022.[30]

Table 6: Data-cuts and related evidence for the full trial populations

DCO in CS	Assessed	Follow-up, months	CSR (full population)	Other sources (full population)
Study BGB-3111-AU-003				
13 December 2018	IRC	18.84	Yes[a]	Tam 2021[27] Regulatory summary [c]
31 March 2021	INV	38.92	Partial[b]	None
Study BGB-3111-206				
15 February 2019	IRC	18.4	No	Song 2020[28]
31 August 2019	INV	24.84	No	Regulatory summary [c]
08 September 2020	INV	35.25	Yes	Song 2021[29] Song 2022[30]

[a] Provided in response to EAG follow-up of company response to urgent clarification questions. [b] CS cites CSR (2021 CSR for BGB-3111-AU-003, provided with the CS), but the DCO is 2nd October 2020; correct CSR was requested but not provided at clarification (Clarification question C5); CSR for 31st March 2021 was provided after submission of the EAG report, but does not report patient disposition, dose exposure or adverse events for the R/R MCL 320 mg daily dose cohort. [c] BeiGene 2020 Regulatory summary of clinical efficacy for the BGB-3111-206 and AU-003 trials, provided with the CS.

3.2.3 Quality assessment

Quality assessment of the zanubrutinib studies is presented in CS section B.2a.5 and B.2b.5, and in CS Appendix D Table 17, using criteria recommended by NICE.[33, 34] The CS Appendix also stated that the studies were assessed using the Downs and Black checklist,[35] but this was not presented. In response to clarification question C9, the company confirmed that all non-RCT studies, including trials BGB-3111-AU-003 and BGB-3111-206, were initially assessed with the CASP checklist only. However, the company provided the completed Downs and Black checklist in clarification response C9 Table 24. Based on the findings of the quality assessment, both studies are described by the company as well-designed single arm trials with the appropriate steps taken to minimise bias where possible. A comparison of the company's assessment and the EAG's assessment of the studies using NICE recommended criteria can be seen in Appendix 9.1 Table 52. The company's assessment using the Down's and Black checklist was also checked but is not reproduced here. The EAG agrees with most of the company's judgements, but notes the following concerns. A comparison between investigator-assessed (INV) and independent review committee (IRC) reported outcomes is not possible for all IRC assessed outcomes in study BGB-3111-AU-003, as outcomes are reported at different time points. Concordance rate was 93.8% for ORR and 71.9% for best overall response, suggesting there may be some bias in assessments. BGB-3111-206 was undertaken exclusively in China, and although the EAG clinical expert did not have any concerns regarding the effects of race, there may be differences in health care or other unknown factors that could affect generalisability. Secondary endpoints were estimated by KM method with 95% CIs. However, the upper limits for PFS and OS are not estimable introducing some uncertainty in precision of these results. Longer follow-up may decrease uncertainty in the estimates.

3.2.4 Participant flow

Patient disposition in the zanubrutinib studies is summarised in Table 7. Patient disposition for the 32 participants with R/R MCL receiving a total daily dose of 320 mg zanubrutinib enrolled in either Phase 1 or Phase 2 of study BGB-3111-AU-003 is presented in the CS for the first DCO of 13th December 2018 only (CS Section B.2a.4.3); data from the 31st March 2021 DCO are not reported in the CS andthe CSR provided by the company (after submission of the EAG report) for this DCO does not report these data for the R/R MCL 320 mg daily dose cohort. Patient disposition at the third (final) DCO of 8th September 2020 is presented in CS Section B.2b.4.3 for study BGB-3111-206.

There appears to be a discrepancy in the number of study discontinuations in BGB-3111-AU-003 due to death between the narrative in CS B.2a.4.3 (n=10, 31.3%, also reported in the CSR (2018 CSR for study BGB-3111-AU-003, supplied after clarifications) and regulatory summary (BeiGene 2020 Regulatory summary of clinical safety for the BGB-3111-206 and AU-003 trials, provided with the CS)) and CS Table 11 (n=12, 37.5%, also reported in Tam 2021[27]). The numbers discontinued from the study also differ between CS Table 11 and the 2018 CSR, and the reasons for study discontinuation in CS Table 11 (n=17) do not equal the total discontinued (n=18); the reason for this is unclear.

Discontinuation from treatment due to disease progression occurred in 31.3% and 43.0% of patients in studies BGB-3111-AU-003 and BGB-3111-206, respectively. Treatment discontinuation due to adverse events occurred in a higher proportion of patients in BGB-3111-AU-003 (25.0%) than BGB-3111-206 (9.3%). In study BGB-3111-206 all (100%) participants discontinued treatment and discontinued the study; the reason was due to termination of the study by the sponsor in 45.3% and 57.0% of participants, respectively. [redacted]. Outcomes occurring after termination of the study are therefore unknown, and it is uncertain what impact this will have on the results.

Table 7: Patient disposition

Patient disposition, n (%)	BGB-3111-AU-003 (N=32)	BGB-3111-206 (N = 86)
Median study follow-up, months	18.84 (range 1.9, 38.2)	35.25 (range 0.3, 41)
Patients discontinued from treatment	18 (56.3)	86 (100.0)
Reason for discontinuation from treatment		
Study terminated by sponsor		[redacted][a]
Disease progression	10 (31.3)	37 (43.0)
Patient withdrawal	0 (0.0)	1 (1.2)
Adverse event	8 (25.0)	8 (9.3)
Investigator's discretion	0 (0.0)	1 (1.2)
Patients discontinued from the study	18 (56.3)/CSR[b] [redacted]	86 (100.0)
Reason for discontinuation from the study		
Study terminated by sponsor		[redacted][a]
Death	12 (37.5)/CSR[b] [redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Patient withdrawal	[redacted]	[redacted]
Adverse event	[redacted]	
Other	[redacted]	

Source: adapted from CS Table 11 and 24.[a]

[redacted] [b]2018 CSR for study BGB-3111-AU-003, supplied after clarifications.

3.2.5 Baseline characteristics of the included zanubrutinib studies

CS Section B.2a.3.4 and CS Table 9 present the baseline demographic details for participants in Part 2 of the BGB-3111-AU-003 study (N=32), while CS Section B.2b.3.4 and CS Table 22 provide patient characteristics for the total population in the BGB-3111-206 study. Both tables also include data specific to the 2L R/R MCL subgroups. The EAG has summarised key baseline characteristics of the study populations in Table 8 and has verified values for the total trial population against the CSR (2021 CSR for BGB-3111-AU-003 and 2021 CSR for BGB-3111-206, provided with the CS). The EAG is unable to verify the data for the 2L R/R MCL subgroups of either study. For completeness of the critique of the populations in the studies the EAG requested in clarification question A1 the baseline statistics for the >2L subgroup, however, the company declined to provide these stating that the request fell outside the proposed scope. Instead, they suggested inferring the data from the

reported demographic statistics of the total population. As a result, the EAG opted not to conduct additional secondary analyses of these characteristics.

BGB-3111-206 had a larger cohort than BGB-3111-AU-003 (n=86 versus n=32), including within the 2L R/R MCL subgroup (n=26 versus n=18). The EAG considers any notable differences between the participants in the two studies, however, caution is required in interpreting any differences owing to the small sample sizes. The mean age of participants in the full populations of BGB-3111-AU-003 was [redacted] than in BGB-3111-206, with median ages of 70.5 (range 42, 86) and 60.5 (range 34, 75), in study BGB-3111-AU-003 and BGB-3111-206 respectively.

[redacted]. The EAG clinical advisor highlighted that age is a key factor in treatment outcomes and tolerability, with younger patients generally experiencing better prognoses, discussed further in section 3.2.8. As can be seen in Table 8, study BGB-3111-206 included only Asian participants (specifically Chinese as this was where the study was conducted), the race of participants in BGB-3111-AU-003 was predominantly White. The EAG requested at clarification (question A2), how many participants were from the UK, the company confirmed that no UK patients were included in Part 2 of the study. Clinical advice to the EAG is that race does not impact treatment outcomes, however, there may be generalisability factors in terms of healthcare system differences in these studies, discussed in section 3.2.8.

BGB-3111-AU-003 included a higher proportion of patients with ECOG PS stage 1 than study BGB-3111-206 (43.8% vs. 25.6%) and ECOG PS stage 2 (9.4% vs. 4.7%). A [redacted] was seen in the 2L subgroups, see Table 8. The time from initial diagnosis to first dose was [redacted] in BGB-3111-AU-003 than in BGB-311-206, potentially relating to the different healthcare systems in the countries included in the two studies. In study BGB-3111-AU-003 there was a [redacted] proportion of participants with relapsed disease in both the overall group and the 2L only groups than study BGB-3111-206, see Table 8.

The EAG clinical advisor emphasised that the number of prior therapies significantly impacts treatment outcomes. Regarding prior treatments, most patients in BGB-3111-206 ([redacted] in the total group; [redacted] in the 2L subgroup) had received R-

CHOP/R-CHOPE/R-CHOP-like therapy. In contrast, in BGB-3111-AU-003, 19 (59.4) of the total Part 2 participants and [redacted] of the 2L subgroup had received these treatments. This again may reflect differences in healthcare practices in the countries where the studies took place. In the UK, treatment guidelines for younger patients recommend intensive chemotherapy including high dose cytarabine followed by an autologous stem cell transplant (for example the Nordic Protocol);[36] R-CHOP is typically recommended for older patients. Therefore, there are concerns about possible differences in health care systems between these studies and UK practice, discussed in section 3.2.8.

Regarding other disease characteristics, small variations in the proportions of patients with bulky disease, extra-nodal involvement and Ann Arbor stage were noted, though these differences are likely due to the small sample sizes, see Table 8. The 2L subgroup of study BGB-3111-206 had a [redacted] however, clinical advice to the EAG was that the MIPI-b score has limited relevance in single arm trials and relapsed MCL patients.

Aside from the age of the participants, the EAG clinical advice indicated that other reported baseline characteristics were generally comparable to the UK population.

Table 8: Baseline characteristics of included zanubrutinib studies

Characteristic	BGB-3111-AU-003, N=32	BGB-3111-AU-003 2L subgroup, n=18[a]	BGB-3111-206, N=86	BGB-3111-206 2L subgroup, n=26[a]
Age, years				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	70.5 (42, 86)	[redacted]	60.5 (34, 75)	[redacted]
Male Sex, n (%)	22 (68.8)	[redacted]	67 (77.9)	[redacted]
Race, n (%)				
White	25 (78.1)[b]	[redacted]	-	-
Black or African American	1 (3.1)	[redacted]	-	-
Asian	3 (9.4)	[redacted]	86 (100)	[redacted]
Other/multiple	3 (9.4)	[redacted]	-	-
ECOG PS, n (%)				
0	15 (46.9)	[redacted]	60 (69.8)	[redacted]
1	14 (43.8)	[redacted]	22 (25.6)	[redacted]
2	3 (9.4)	[redacted]	4 (4.7)	[redacted]
Time from initial diagnosis to first dose (years)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (Range)	[redacted]	[redacted]	[redacted]	[redacted]
Ann Arbor Stage study entry, n (%)				
I	2 (6.3)	[redacted]	[redacted]	[redacted]
II	1 (3.1)	[redacted]	[redacted]	[redacted]
III	1 (3.1)	[redacted]	14 (16.3)	[redacted]
IV	28 (87.5)	[redacted]	64 (74.4)	[redacted]
Disease status, n (%)				
Relapsed	[redacted]	[redacted]	41 (47.7)	[redacted]
Refractory	8 (25.0)	[redacted]	45 (52.3)	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	-
Bulky disease, n (%) (any target lesion LDi > 10 cm)	3 (9.4)	[redacted]	7 (8.1)	[redacted]
Extranodal disease, n (%)	25 (78.1)	[redacted]	61 (70.9)	[redacted]
MIPI, n (%)[d]				

Characteristic	BGB-3111-AU-003, N=32	BGB-3111-AU-003 2L subgroup, n=18[a]	BGB-3111-206, N=86	BGB-3111-206 2L subgroup, n=26[a]
Low risk	9 (28.1)	[redacted]	12 (14.0)	[redacted]
Intermediate risk	13 (40.6)	[redacted]	39 (45.3)	[redacted]
High risk	10 (31.3)	[redacted]	33 (38.4)	[redacted]
Missing	0 (0.0)		2 (2.3)	[redacted]
Prior therapies[e]				
Median (range)	1.0 (1, 4)	[redacted][f]	2.0 (1, 4)	[redacted][f]
1 prior therapy	18 (56.2)	[redacted]	26 (30.2)	[redacted]
2 prior therapies	[redacted]	[redacted]	[redacted]	[redacted]
3 prior therapies	[redacted]	[redacted]	[redacted]	[redacted]
4 prior therapies	[redacted]	[redacted]	10 (11.6)	[redacted]
Time from end of last therapy to study entry, n (%), months				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Prior therapy, n (%)				
Stem cell transplant	5 (15.6)	[redacted]	3 (3.5)	[redacted]
R-CHOP/R-CHOPE/R-CHOP-like	19 (59.4)	[redacted]	[redacted]	[redacted]
DHAP	[redacted]	[redacted]	[redacted]	[redacted]
Hyper-CVAD or hyper-CVAD-like regimen	7 (21.9)	[redacted]	13 (15.1)	[redacted]
Cytarabine	[redacted]	[redacted]	-	-
Purine analog	[redacted]	[redacted]	[redacted]	[redacted]
Bendamustine	[redacted]	[redacted]	2 (2.3)	[redacted]
Rituximab or Rituximab-containing regimen	30 (93.8)		64 (74.4)	[redacted]

Source: Adapted from CS Table 9, Tam et al 2021,[27] Song et al 2020,[28] CS Table 22 and CSRs (2021 CSR for BGB-3111-AU-003 and 2021 CSR for BGB-3111-206, provided with the CS)
[a] EAG was not able to validate the data with CSRs
[b] The data do not match with that in Tam 2021,[27] but the EAG considers the CS as the correct data
[c] Data reported in months; The day of first diagnosis was assumed to be the first day of the month when the day was missing and assumed to be 01 January when the day and month were missing
[d] MIPI score, presented in the CS Section B.2a.3.4 Table 9, was calculated using the threshold of low (< 5.7), intermediate (≥ 5.7 and < 6.2) and high (≥ 6.2) for the full population (where MIPI was reported as: Low risk 8 (25.0), Intermediate risk 11 (34.4), High risk 13 (40.6). However, these thresholds do not align with those reported in the CSRs and Tam et al 2021.[27]
[e] The EAG was unable to fully verify these data owing to differences in reporting thresholds in the relevant publications and CSRs, but the EAG considers these data from the CS to be the correct data.
[f] The data originally presented in CS Section B.2a.3.4, Table 9, was reported as [redacted]. Upon clarification (A4), the company acknowledged this as a typographical error.

DHAP - dexamethasone, cytarabine and cisplatin; ECOG PS – Eastern Cooperative Oncology Group performance status; Hyper-CVAD – cyclophosphamide, vincristine, doxorubicin, and dexamethasone; LDi – longest transverse diameter of a lesion; MIPI-b - combined biologic mantle cell lymphoma international prognostic index; N – number; R-CHOP - rituximab plus doxorubicin hydrochloride, vincristine and prednisone; R-CHOPE – rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone and etoposide; SD -standard deviation

3.2.6 Clinical effectiveness results

3.2.6.1 Overview of results

Key results from the zanubrutinib studies are summarised in Table 9, with outcomes used in the economic model in bold font. Individual outcomes are discussed below.

Results are presented for the overall population (≥1 prior line of therapy) and the 2L-only subgroup. For completeness, the EAG requested results for the >2L subgroup, but these were not provided as the company maintained they could be calculated and inferred from the presented populations (Clarification A1).

Table 9: Overview of key efficacy outcomes

BGB-3111-AU-003				
Median, months (95% CI)[a]	**Zanubrutinib full trial population (N = 32)**		**Zanubrutinib 2L-only (N = 18)**	
	IRC-assessed	**INV-assessed**	**IRC-assessed[d]**	**INV-assessed[d]**
DCO (follow-up)	**13 Dec 2018 (18.84 months[h])**	**31 Mar 2021 (38.92 months)**	**13 Dec 2018 (18.84 months[h])**	**31 Mar 2021 (38.92 months)**
ORR, %	84.4 (67.2, 94.7)	[redacted]	[redacted]	[redacted]
PFS	**21.1 (13.2, NE) [b]**	[redacted] [b]	[redacted] [b]	[redacted] [b]
DOR	18.53 (12.58, NE)	[redacted]	[redacted]	[redacted]
TTR, events, n	27	[redacted]	[redacted]	[redacted]
TTR (range)	2.76 (1.9, 9.8)	[redacted]	[redacted]	[redacted]
OS[c]	[redacted] [e]	[redacted] [b]	[redacted]	[redacted] [b]

BGB-3111-206						
Median, months (95% CI)[a]	**Zanubrutinib (N = 86)**			**Zanubrutinib 2L-only (N = 26)**		
	IRC-assessed	**INV-assessed**	**INV-assessed**	**IRC-assessed[d]**	**INV-assessed[d]**	**INV-assessed[d]**
DCO (follow-up)	**15Feb2019 (18.4 months)**	**31Aug2019 (24.84 months)**	**08Sept2020 (35.25 months)**	**15Feb2019 (18.4 months)**	**31Aug2019 (24.84 months)**	**08Sept2020 (35.25 months)**
ORR, %	83.7 (74.2, 90.8)	[redacted]	83.7 (74.2, 90.8)	[redacted]	[redacted]	[redacted]
PFS	**22.1 (17.4, NE)[b]**	[redacted]	**33.0 (19.4, NE) [b]**	[redacted]	[redacted]	[redacted]
DOR	19.5 (16.6, NE)	[redacted]	NE (24.9, NE)	[redacted]	[redacted]	[redacted]
TTR events, n	86	[redacted]	72	[redacted]	[redacted]	[redacted]
TRR (range)	2.7 (2.5, 16.6)	[redacted]	2.73 (2.5, 3.0)	[redacted]	[redacted]	[redacted]
OS[c]	[redacted] [f]	[redacted] [g]	**NE (NE, NE)[b]**	NE (NE, NE)	NE (NE, NE)	**NE (NE, NE)[b]**

Source: Adapted from CS Tables 13 and 26. [a] Unless stated otherwise. [b] Outcomes in bold used in the economic model (source: CS Tables 8 and 21). [c] not subject to assessment by either investigator, or independent review committee, therefore only the different DCO dates in the column headings are relevant to the median OS (Clarification A5). [d] No report provided, EAG unable to validate data. [e] NR in CS Table 13 but available in CSR (2018 CSR for study BGB-3111-AU-003, supplied after clarifications) and regulatory summary (BeiGene 2020 Regulatory summary of clinical safety for the BGB-3111-206 and AU-003 trials, provided with the CS). [f] Clarification A5. [g] NR in CS Table 26 but reported in regulatory summary (BeiGene 2020 Regulatory summary of clinical safety for the BGB-3111-206 and AU-003 trials, provided with the CS) and Clarification A5.[h] Follow-up for PFS median 17.48 months estimated by reverse Kaplan-Meier method.
CI – confidence interval; CSR – clinical study report; DCO – data cut-off; DOR – duration of response; INV – investigator; IRC – independent review committee; NE – not estimable; NR – not reported; ORR – overall response rate; OS – overall survival; PFS – progression-free survival; TTR – time to response

3.2.6.2 Response rates

Response rates are summarised in Table 10. In the full population, IRC-assessed ORR (primary outcome) was 84.4% (95% CI 67.2, 94.7) at 18.8 months follow-up, and INV-assessed ORR was [redacted] at 38.9 months follow-up.

The CS reports concordance rates between IRC and INV assessments of 93.8% for ORR and 71.9% for best overall response (CS B.2a.6.1) at the 13 December 2018 DCO. Concordance is [redacted] than in BGB-3111-206 (see below). The EAG was unable to identify evidence in the literature to determine an acceptable level of concordance in NHL.

The EAG notes that data for INV-assessed ORR and best response in CS Tables 13 and 14 (DCO 31st March 2021, median follow-up 38.9 months) [redacted] published in Tam 2021[27] and presented in the December 2018 CSR (2018 CSR for study BGB-3111-AU-003, supplied after clarifications).

For the 2L-only subgroup, ORR was [redacted] by IRC assessment at 18.8 months follow-up and [redacted] by INV assessment at 38.9 months follow-up. As stated above, the EAG is unable to verify these data.

Response rates for BGB-3111-206 are summarised in Table 10. In the full population, IRC-assessed ORR (primary outcome) was 83.7% (95% CI 74.2, 90.8) at 18.4 months follow-up, and remained the same by investigator assessment at 35.25 months follow-up. ORR in the 2L-only subgroup was [redacted] at each DCO; the EAG is unable to verify these data.

Concordance is not reported in the CS for study BGB-3111-206, but the regulatory summary of clinical efficacy (BeiGene 2020 Regulatory summary of clinical safety for the BGB-3111-206 and AU-003 trials, provided with the CS) reports a concordance rate between IRC and INV assessment at both the first and second DCOs of [redacted] for ORR and [redacted] for best response, and median duration of response was [redacted] (2024 CSR for BGB-3111-206 clinical evidence, provided with the CS). [redacted] (2024 CSR for BGB-3111-206 clinical evidence, provided with the CS). The EAG considers this to be appropriate.

The EAG notes that for the full trial populations, complete response was achieved in [redacted] of participants in BGB-3111-AU-003 compared with 77.9% in BGB-3111-206. For the 2L-only subgroup, these values were [redacted] and [redacted], respectively.

Table 10: IRC- and INV assessed response rates

BGB-3111-AU-003				
Best overall response, n (%)	**Zanubrutinib full trial population (N = 32)**		**Zanubrutinib 2L-only (N = 18)**	
	IRC-assessed	**INV-assessed**	**IRC-assessed**	**INV-assessed**
DCO	**13 Dec 2018**	**31 Mar 2021**	**13 Dec 2018[d]**	**31 Mar 2021[d]**
Follow-up	**18.84 months**	**38.92 months**	**18.84 months**	**38.92 months**
CR	8 (25.0)	[redacted]	[redacted]	[redacted]
PR	19 (59.4)	[redacted]	[redacted]	[redacted]
SD	2 (6.3)	[redacted]	[redacted]	[redacted]
PD	2 (6.3)	[redacted]	[redacted]	[redacted]
Unknown	1 (3.1)[a]	[redacted]	[redacted]	[redacted]
ORR, n (%) [95% CI][b]	27 (84.4) [67.2, 94.7]	[redacted]	[redacted]	[redacted]

BGB-3111-206						
	Zanubrutinib (N = 86)			**Zanubrutinib 2L-only (N = 26)**		
	IRC-assessed	**INV-assessed**	**INV-assessed**	**IRC-assessed**	**INV-assessed**	**INV-assessed**
DCO	**15 Feb 2019**	**31 Aug 2019**	**08 Sept 2020**	**15 Feb 2019[d]**	**31 Aug 2019[d]**	**08 Sept 2020[d]**
Follow-up	**18.4**	**24.84**	**35.25**	**18.4**	**24.84**	**35.25**
CR	59 (68.6)	[redacted]	67 (77.9)	[redacted]	[redacted]	[redacted]
PR	13 (15.1)	[redacted]	5 (5.8)	[redacted]	[redacted]	[redacted]
SD	1 (1.2)	[redacted]	1 (1.2)	[redacted]	[redacted]	[redacted]
PD	6 (7.0)	[redacted]	8 (9.3)	[redacted]	[redacted]	[redacted]
Discontinued [c]	NR	[redacted]	5 (5.8)	[redacted]	[redacted]	[redacted]
ORR, n (%) [95% CI][b]	72 (83.7) [74.2, 90.8]	[redacted]	72 (83.7) [74.2, 90.8]	[redacted]	[redacted]	[redacted]

Source: adapted from CS Table 14 and 27. CI – confidence interval; CR – complete response; DCO – data cut-off; INV – investigator; IRC – independent review committee; n – number; PD – progressed disease; PR – partial response; SD – stable disease. [a]One patient did not provide informed consent for scan collection. [b] 2-sided Clopper-Pearson 95% CIs. [c] Discontinued study prior to first assessment [d] No report provided, EAG unable to validate data.

3.2.6.3 Progression free survival

In the full trial population of BGB-3111-AU-003, median IRC-assessed PFS at the December 2018 DCO was 21.1 months, which was [redacted] the INV-assessed PFS median at the March 2021 DCO. For [redacted], which means that the median PFS is [redacted]. At the December 2018 data-cut with a median follow-up of [redacted] months, median INV-assessed PFS was lower at [redacted] months. The [redacted] from the December 2018 data cut to the March 2021 data cut could be due to immaturity of data at the earlier data cutoff, a more robust estimation over time, or a potential treatment benefit over time. In BGB-3111-206, IRC-assessed median PFS was 22.1 months (95% CI: 17.4, NE) at the first DCO, and INV-assessed median PFS was [redacted], which used the August 2019 data cut. With the September 2020 data cut, median PFS [redacted] to 33 months. In this study, median PFS when INV-assessed was [redacted] than IRC-assessed, but there are [redacted] between the two assessors. When comparing the two studies, there are [redacted] between PFS, although the median PFS in BGB-3111-206 is [redacted].

In the 2L-only cohort, median PFS was [redacted] in BGB-3111-206 for either assessor, and was [redacted]. However, the lower bounds of the confidence intervals suggests that the 2L-only patients are associated with [redacted] PFS in BGB-3111-206 than in BGB-3111-AU-003.

3.2.6.4 Duration of response

In BGB-3111-AU-003, median IRC-assessed duration of response was 18.53 months (12.58, NE) at the December 2018 DCO and INV-assessed DOR was [redacted] at the December 2018 DCO and [redacted]) at the March 2021 DCO. In BGB-3111-206, median IRC-assessed DOR was 19.5 months (16.6, NE). Median INV-assessed DOR at the August 2019 data cut was [redacted] at the first DCO, and at the September 2020 DCO it was NE

(24.9, NE). In BGB-3111-206, the INV-assessed DOR was [redacted] than the IRC-assessed DOR. In BGB-3111-AU-003, when comparing the same DCOs, INV-assessed DOR is [redacted] than the IRC-assessed DOR. There were [redacted] between DOR between studies when comparing the same assessor, however a true comparison and statistical conclusion requires further follow-up and more event data due to the [redacted] in the confidence intervals.

In the 2L cohort, only the INV-assessed DOR of BGB-3111-AU-003 had an [redacted], with a median DOR of [redacted] months, all other DORs in both studies were [redacted].

3.2.6.5 Time to response

Median TTR was [redacted] across both trials. In BGB-3111-AU-003, the TTR between the different assessors were [redacted]. 27 patients had an IRC-assessed response (84%), compared to [redacted] when INV-assessed. The median TTR for the IRC-assessed outcome at the December 2018 DCO was 2.76 months with a range of 1.9 to 9.8 months, compared to [redacted] and the [redacted] in the INV-assessed outcome at December 2018 and the March 2021 DCOs.

In BGB-3111-206, there was a [redacted] between the IRC- and INV-assessed number of TTR events. The IRC reported 100% of participants had a response at the first DCO, while the investigator reported [redacted] patients ([redacted]) at the final DCO. However, there was [redacted] the assessors for the median TTR, [redacted] months.

In the 2L only cohort, there were [redacted] between the assessors across both trials and between trials.

3.2.6.6 Overall survival

Median overall survival was not subject to assessment by either INV or IRC (clarification A5), and [redacted].

The EAG notes that in Clarification response Table 1, study BGB-3111-AU-003, OS for the full population and 2L-only population has been transposed compared with that reported in CS Table 13. The EAG has checked the CSR, which indicates that CS Table 13 has the correct value and Clarification response Table 1 is incorrect.

3.2.6.7 Patient reported outcomes

Patient reported outcomes were not assessed by either zanubrutinib study.

3.2.6.8 Subgroups

The CS reports subgroup analyses of IRC-assessed ORR at the shorter follow-up of the 13 December 2018 DCO for BGB-3111-AU-003 in section B.2a.7 and CS Figure 8. For study BGB-3111-206, IRC-assessed ORR at the first reported DCO is presented in CS Figure 16, and INV-assessed ORR at the last DCO is presented Figure 17. The EAG notes very minor differences between the two DCOs in the number of patients with a response in some of the categories. Overall, in both studies responses among subgroups were reasonably consistent, although some subgroups had small sample sizes and no test for interaction was performed. No subgroups were noted in the NICE decision problem.

3.2.7 Adverse events

This section summarises adverse events in BGB-3111-AU-003 and BGB-3111-206. Further information on adverse events can be found in:

- Section 3.4.10: ITC of zanubrutinib versus ibrutinib comparing grade ≥3 adverse events in R/R MCL.
- Section 3.6.2: grade ≥3 adverse events in ten pooled zanubrutinib studies (in any indication).

- 3.6.3: a head-to-head comparison of zanubrutinib versus ibrutinib in chronic lymphocytic leukaemia/small lymphocytic lymphoma and Waldenström macroglobulinemia from two pooled RCTs.

3.2.7.1 Overview of adverse events

Adverse events are reported in the CS at the 31st March 2021 data-cut (median 38.9 months follow-up) for study BGB-3111-AU-003. The company did not provide a CSR for this DCO (requested at Clarification C5) until after submission of the EAG report, but on checking the CSR during the factual accuracy check the EAG found that it does not report any dose exposure or adverse event data for the R/R MCL 320 mg daily dose cohort (n=32). The EAG is therefore unable to validate these data. For study BGB-3111-206, adverse events are reported at the final data cut of 8th September 2020 with median 35.3 months follow-up (2024 CSR for BGB-3111-206 clinical evidence, provided with the CS).[30]

Dose exposure is summarised in Table 11. Median actual dose intensity and relative dose intensity were similar between the two studies. A [redacted] of patients experienced at least one dose interruption in BGB-3111-AU-003.

An overview of adverse events in both studies is presented in Table 12; further detail about these is summarised below.

In addition, the EAG requested safety data from patients with all indications in study BGB-3111-AU-003 who received total daily doses of 320 mg (Clarification A14). This is presented in Table 12 and Table 13 for the 31st March 2021 DCO, median duration of treatment [redacted]. The EAG is unable to verify these data.

Table 11: Dose exposure

	BGB-3111-AU-003	**BGB-3111-206**
	Zanubrutinib N = 32	**Zanubrutinib N = 86**
Median duration of treatment	[redacted]	27.61 months (range: 0.2, 45.3[a])
Median actual dose intensity (min, max), mg/day	[redacted]	319.61 ([redacted])
Median relative dose intensity[a] (min, max)	[redacted]%	99.87% ([redacted])

At least one dose interruption	[redacted]	24 (27.9%)
Dose reduction due to AEs	[redacted]	2 (2.3%)

Source: adapted from CS B.2a.10.1, B.2b.10.1, and CSR (2021 CSR for BGB-3111-206, provided with the CS). [a] 41.6 in Song 2022[30]

[redacted] [a] defined as the ratio of the actual dose intensity (mg/day) and the planned dose intensity (320 mg/day).

Table 12: Overview of treatment-emergent and post-treatment AEs

Event	BGB-3111-AU-003	BGB-3111-206	BGB-3111-AU-003
	Zanubrutinib N = 32	Zanubrutinib N = 86	All indications N = 373
Patients with ≥ 1 TEAE	[redacted]	83 (96.5)	[redacted]
Grade ≥3 TEAEs	[redacted]	43 (50.0)	[redacted]
Serious TEAEs	[redacted]	25 (29.1)	[redacted]
TEAEs leading to death	[redacted]	7 (8.1)	[redacted]
TEAEs leading to study drug discontinuation	[redacted]	8 (9.3)	[redacted]
TEAEs leading to treatment interruption	[redacted]	16 (18.6)	[redacted]
TEAEs leading to dose reduction	[redacted]	2 (2.3)	[redacted]
Treatment-related AEs	[redacted]	[redacted]	[redacted]

Source: adapted from CS Tables 39 and 42, and Clarification A14.

3.2.7.2 Deaths and serious adverse events

In study BGB-3111-AU-003, [redacted] patients with R/R MCL had died by the 31st March 2021 DCO; [redacted] of the deaths were due to adverse events. Serious TEAEs occurred in [redacted] patients, details of these are not reported in the CS. Clarification A14 narrative states that among patients with all indications in BGB-3111-AU-003, [redacted] of the 95 deaths were due to adverse events, although Clarification Table 8 reports [redacted] TEAEs leading to death.

In study BGB-3111-206, 21 patients had died by the final DCO; seven of the deaths were due to adverse events. Serious adverse events (SAEs) were reported in 29.1% of patients. Pneumonia ([redacted]), platelet count decreased ([redacted]), upper gastrointestinal haemorrhage ([redacted]) and death ([redacted] were the only events occurring in more than one patient.

3.2.7.3 Treatment-related adverse events

Treatment-related adverse events leading to discontinuation of zanubrutinib occurred in [redacted] of patients in study BGB-3111-AU-003 but only 9.3% of patients in BGB-3111-206. Among patients with all indications in BGB-3111-AU-003, [redacted] of patients discontinued due to adverse events. Further information on treatment-related adverse events is not presented in the CS, but events by grade are available in the CSR for study BGB-3111-206.(2024 CSR for BGB-3111-206 clinical evidence, provided with the CS) At least one treatment-related adverse event was experienced by [redacted] of patients; these were Grade 3, 4 and 5 in [redacted] and [redacted], respectively.

3.2.7.4 Grade 3 or higher adverse events

At least one Grade 3 or higher adverse event was experienced by [redacted] and 50% of patients in studies BGB-3111-AU-003 and BGB-3111-206, respectively. Among patients with all indications in BGB-3111-AU-003, [redacted] had at least one Grade 3 or higher adverse event. The most common events in BGB-3111-AU-003 were pneumonia ([redacted], anaemia ([redacted]) and myalgia ([redacted]), and in BGB-3111-206 were neutrophil count decreased (18.6%), pneumonia (12.8%), platelet count decreased (7.0%), and white blood cell count decreased ([redacted]) (see Table 13 for details). The most common Grade 3 or higher adverse events in the all indication participants of BGB-3111-AU-003 were neutropenia ([redacted]), anaemia ([redacted]) and pneumonia ([redacted]).

The company's economic model included grade ≥3 adverse events occurring in ≥5% of participants. CS section B.3.4.5 states that AE rates were derived from BGB-3111-AU-003 (DCO: December 2021) and BGB-3111-206 study (DCO September 2020) separately and an average rate was calculated. However, the company actually uses the first DCO (December 2018) published in Tam 2021,[27] as cited in CS Table 60. The values for this study presented in Table 13 for the December 2021 DCO therefore differ from the values used in the company's base case, see section 4.2.8 for further details.

Table 13: Treatment-emergent adverse events of Grade 3 or higher by system organ class and preferred term in ≥ 2 patients

System Organ Class Preferred Term, n (%)	BGB-3111-AU-003	BGB-3111-206	BGB-3111-AU-003
	Zanubrutinib (N = 32)	Zanubrutinib (N = 86)	All indications (N = 373)
≥1 Grade 3 or higher TEAE	[redacted]	43 (50.0)	[redacted]
Infections and infestations	[redacted]		
Pneumonia[a]	[redacted]	11 (12.8)	[redacted]
Cellulitis	[redacted]		
Opportunistic infections			[redacted]
Blood and lymphatic system disorders			
Anaemia[a]	[redacted]	5 (5.8)	[redacted]
Febrile neutropenia	[redacted]		
Neutropenia[a]	[redacted]		[redacted]
Thrombocytopenia[a]			[redacted]
General disorders and administration site conditions			
Fatigue	[redacted]		
Oedema peripheral	[redacted]	[redacted]	[redacted]
Death		[redacted]	
Cardiac disorders			
Pericardial effusion	[redacted]		
Musculoskeletal and connective tissue disorders			
Myalgia	[redacted]		[redacted]
Metabolism and nutrition disorders			
Tumour lysis syndrome	[redacted]		[redacted]
Hyperuricemia		[redacted]	
Renal and urinary disorders			
Acute kidney injury	[redacted]		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion	[redacted]		
Psychiatric disorders	[redacted]		
Agitation	[redacted]		
Investigations			
Neutrophil count decreased[a]	[redacted]	16 (18.6)	
Platelet count decreased[a]	[redacted]	6 (7.0)	
White blood cell count decreased[a]		[redacted]	

System Organ Class Preferred Term, n (%)	BGB-3111-AU-003	BGB-3111-206	BGB-3111-AU-003
	Zanubrutinib (N = 32)	Zanubrutinib (N = 86)	All indications (N = 373)
Lymphocyte count decreased		[redacted]	
Eye disorders			
Cataract	[redacted]		
Vascular disorders			
Hypertension		3 (3.5)	
Major haemorrhage			[redacted]
Bleeding			[redacted]

Source: CS Tables 41 and 44, Clarification A14 and Song 2022.[30] [a] Grade ≥3 adverse events included in the economic mode (CS Table 60).

3.2.7.5 **Common adverse events of any grade**

Treatment-emergent adverse events of any grade are listed in Table 14. The most common events in study BGB-3111-AU-003 were diarrhoea ([redacted]), constipation ([redacted]) and upper respiratory tract infection ([redacted]), and in in BGB-3111-206 were neutrophil count decreased (46.5%), upper respiratory tract infection (38.4%), rash ([redacted]), white blood cell count decreased (33.7%) and platelet count decreased (32.6%). Commonly reported TEAEs were not reported for the all-indication participants from study BGB-3111-AU-003.

Table 14: Treatment-emergent events (any grade) by system organ class and preferred term reported in ≥ 10% of patients in either study[a]

System Organ Class Preferred Term, n (%)	BGB-3111-AU-2003	BGB-3111-206
	Zanubrutinib (N = 32)	Zanubrutinib (N = 86)
Patients with at least 1 AE	[redacted]	[redacted]
Gastrointestinal disorders		
Diarrhoea	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Nausea	[redacted]	
Dyspepsia	[redacted]	
Infections		
Upper respiratory tract infection	[redacted]	33 (38.4)
Localised infection	[redacted]	
Pneumonia	[redacted]	14 (16.3)
Urinary tract infection	[redacted]	10 (11.6)
Nasopharyngitis	[redacted]	5 (5.8)
General disorders and administration site conditions		
Fatigue	[redacted]	
Oedema peripheral	[redacted]	
Influenza like illness	[redacted]	
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	[redacted]	
Cough	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	
Pleural effusion	[redacted]	
Productive cough	[redacted]	
Wheezing	[redacted]	
Musculoskeletal and connective tissue disorders		
Back pain	[redacted]	
Arthralgia	[redacted]	
Muscle spams	[redacted]	
Myalgia	[redacted]	
Skin and subcutaneous tissue disorders		
Rash	[redacted]	[redacted]
Pruritus	[redacted]	
Injury, poisoning and procedural complications		

System Organ Class Preferred Term, n (%)	BGB-3111-AU-2003	BGB-3111-206
	Zanubrutinib (N = 32)	Zanubrutinib (N = 86)
Contusion	[redacted]	
Fall	[redacted]	
Metabolism and nutrition disorders		
Decreased appetite	[redacted]	
Hypokalaemia	[redacted]	[redacted]
Hyperglycaemia		[redacted]
Hyperuricaemia		[redacted]
Nervous system disorders		
Dizziness	[redacted]	
Investigations		
Platelet count decreased	[redacted]	28 (32.6)
Neutrophil count decreased	[redacted]	40 (46.5)
White blood cell count decreased		29 (33.7)
Alanine aminotransferase increased		16 (18.6)
Blood urine present		11 (12.8)
Aspartate aminotransferase increased		9 (10.5)
Blood and lymphatic system disorders		
Anaemia	[redacted]	15 (17.4)
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Basal cell carcinoma	[redacted]	
Renal and urinary disorders		
Haematuria	[redacted]	6 (7.0)
Vascular disorders		
Hypertension		13 (15.1)

Source: adapted from CS Tables 40 and 43, CSRs for BGB-3111-AU-003 and BGB-3111-206.
[a] Events occurring in <10 patients can be seen in CS Tables 40 and 43. [b] 14 (16.3) in Song 2022.[30]

3.2.8 Summary of uncertainties in the zanubrutinib evidence base

The EAG has identified a number of uncertainties which potentially affect the reliability of the clinical effectiveness evidence for zanubrutinib. These uncertainties are likely to relate to the small sample sizes of the studies, which ranged from 32 to 86 in the overall populations with R/R MCL and 18 to 26 in the subgroups of relevance to the decision problem (2L only). These uncertainties are as follows:

Data for each study were analysed at different DCOs (2 for study BGB-3111-AU-003; 3 for study BGB-3111-206) and by different assessors (IRC and INV). No discussion of the risk of multiplicity is made in the CS. At clarification (A8) the company were asked about multiplicity testing in all analyses, but the response focused only on multiplicity in the ITC. Concordance between IRC and INV was [redacted] in study BGB-3111-AU-003 than in study BGB-3111-206, but the EAG was unable to determine what an acceptable level of concordance is.

There are notable differences in the ages of the participants between the two studies. Age is a key factor in MCL treatment outcomes and younger people generally experience better prognoses. The differences in age may have influenced the outcomes of the respective studies. The study populations are also younger than the relevant population in the UK, which affects the representativeness of the studies.

There were no UK participants in either study. It is difficult to quantify whether there are differences in health care practices between study locations, but there appears to be slight differences in the time since diagnosis and the proportions with relapsed MCL between the studies, which may reflect different practices. In addition, the prior treatments used in the studies may not be reflective of those typically used in UK practice.

There were some differences in the rates of discontinuations and reasons for discontinuations from the studies, which the EAG is unable to substantiate. In addition, a large proportion of participants in study BGB-3111-206 discontinued due to the planned termination of the study by the sponsor, which means that outcomes occurring after study termination are unknown.

There are some inconsistencies between the studies in the results of the efficacy outcomes. Although ORR rates were similar, the ratio of complete response to partial response were different between the two studies for the both the overall groups and the 2L-only subgroups.

The EAG is unable to validate any data presented for the 2-L subgroups of either study or patient disposition, dose exposure and adverse event data for the 31st March 2021 DCO of study BGB-3111-AU-003.

3.3 Critique of trials identified and included in the indirect comparison

A meta-analysis was not performed due to both zanubrutinib studies, BGB-3111-AU-003 and BGB-3111-206, being single-arm studies, hence there are no studies with pairwise comparison to ibrutinib. Consequently, the company performed population-adjusted methods using individualised patient data (IPD) from the zanubrutinib studies to match the pooled population of the two zanubrutinib studies to any potential studies of the comparator in this STA, ibrutinib.

3.3.1 Company's search strategy

The company described their clinical SLR in Appendix D of the CS, see section 3.1.1 for the EAG critique of this. Four studies of ibrutinib were identified for potential inclusion in the ITC: Rule et al. 2017b,[24] Dreyling et al. 2016,[37] Wang et al. 2013[38] and 2015,[39] (PCYC-1104) and McCulloch et al. 2021.[40]

After conducting a feasibility assessment (CS section B.2.9.1), the company included the Rule et al. 2017b publication,[24] which pooled three ibrutinib studies, RAY-MCL-3001,[41] PCYC-1104,[39] and SPARK,[42] in the ITC analyses. The reasons given for including this study was that it was the largest patient population available for ibrutinib (370 patients after pooling), included patients with at least one prior line of therapy for R/R MCL, reported OS and PFS, and was used in NICE TA502 where it was deemed acceptable for pooling due to the paucity of ibrutinib studies. The EAG agrees with the choice of the pooled ibrutinib study.

3.3.2 Comparison of included studies

The EAG presents a summary of the trials identified and included in the indirect comparisons: BGB-3111-AU-003 and BGB-3111-206 for the safety and efficacy of zanubrutinib, and RAY-MCL 3001, PCYC-1104, and SPARK for the safety and efficacy of ibrutinib. Table 15 presents the study designs, Table 16 the baseline characteristics that were identified as important treatment effect modifiers (TEMs by the company in CS section B.2.9.4, and Table 17 a comparison of the outcomes of each included study.

3.3.2.1 Study design

The sample sizes of the studies vary significantly, with from BGB-3111-AU-003 having the smallest cohort at 32 patients (18 in the 2L setting) in BGB-3111-AU-003 while RAY-MCL 3001 having the largest at to 139 patients in RAY-MCL 3001 in the ibrutinib arm. The studies started at different times and have differing follow-up, with BGB-3111-AU-003 having the longest follow-up (38.92 months) and SPARK (14.9 months) with the shortest, see Table 8. These discrepancies could affect the maturity of survival data and outcome comparisons.

RAY-MCL 3001 is the only phase III study with a comparator, thus patients were randomised to either ibrutinib or temsirolimus.

Most of the inclusion criteria were broadly similar across the trials except BGB-3111-206 included patients aged 18-75 years while the other studies had no explicit upper limit, and there were differences in prior treatment histories. For example, SPARK required prior bortezomib treatment, while PCYC-1104 and RAY-MCL 30001 required at least one rituximab-containing regimen.

Study locations varied, however all but the two zanubrutinib studies included UK patients. BGB-3111-AU-003 and RAY-MCL 3001 were conducted across multiple continents, PCYC-1104 was limited to four countries, SPARK to nine, and BGB-3111-206 was conducted exclusively in China.

3.3.2.2 Treatment effect modifiers

There is considerable variation in the proportion of relapsed and refractory patients in the included studies (Table 9), ranging from 74% relapsed in RAY-MCL 3001 to 47.7% in BGB-3111-206. The proportion of relapsed patients was not reported in PCYC-1104 or SPARK.

Ibrutinib studies tended to have patients with more prior lines of therapy, suggesting a more heavily pre-treated population compared to the two zanubrutinib studies. Patients in the zanubrutinib studies had between one and four prior lines of therapy, whereas RAY-MCL 3001 ranged from one to nine, and SPARK ranged one to eight.

The mean/median time from initial diagnosis were broadly similar between the studies, though it was not reported in PCYC-1104. BGB-3111-AU-003 showed the [redacted] mean duration.

The prevalence of blastoid cases were relatively similar across studies.

Patients with an ECOG PS of 0 were different between studies, ranging from 35% in SPARK to 69.8% in BGB-3111-206. However, combining ECOG PS 0 and 1 shows similar probabilities across the five studies, suggesting patient fitness is generally comparable.

Ki67 status was only reported in BGB-3111-206, therefore there is a gap in understanding the tumour proliferation across the different cohorts.

Risk stratification using MIPI index varied across the studies, with the ibrutinib studies showing a mix of high-risk patients compared to the zanubrutinib studies, Table 8.

The presence of bulky disease above 10 cm was relatively low in the zanubrutinib studies; PCYC-1104, and SPARK. RAY-MCL 3001 reported bulky disease greater or smaller than 5 cm where these groups were almost split evenly. It is therefore difficult to compare between the zanubrutinib and ibrutinib populations.

There is a difference between the studies with respect to the presence of extranodal disease. Higher rates of extranodal disease were seen in the zanubrutinib studies which indicates more advanced disease stages compared to the ibrutinib studies.

Zero patients in BGB-3111-AU-003 had prior lenalidomide and rituximab therapy. In the other four studies, the proportions of lenalidomide and rituximab therapy were different, with the former ranging from 0% to 24%, and the latter ranging from 0% to 100%.

The age of patients varied, with the zanubrutinib studies generally including older patients. All studies were male dominated, ranging from 69% to 87%.

3.3.2.3 Outcomes

The EAG has summarised any differences in the key outcomes from the included studies, described in more detail in Table 10.

- Best overall response:
    - [redacted] difference between the two zanubrutinib trials. Complete response achieved in [redacted] in BGB-3111-AU-003 compared to 77.9% in BGB-3111-206.

- Progression-free survival:
  - [redacted] proportion of patients progress in BGB-3111-AU-003 compared to BGB-3111-206 ([redacted] vs [redacted]), and lower median PFS ([redacted] vs [redacted]), however results [redacted].
- Overall survival:
  - [redacted] proportion of patients progress in BGB-3111-AU-003 compared to BGB-3111-206 ([redacted] vs 24%), the [redacted] for either study.
  - In the ibrutinib studies, RAY-MCL 3001 had a median OS of 30 months, while PCYC-1104 reported 22.5 months. SPARK's OS data was not available.
- Duration of response:
  - The median DOR in BGB-3111-AU-003 was [redacted] months and was not estimable in BGB-3111-206.
  - No significant difference in the ibrutinib studies, although RAY-MCL 3001 had the highest median DOR.
- Time to response:
  - [redacted] between the zanubrutinib studies.
  - Was not reported in RAY-MCL 3001. PCYC-1104 reported a median of 5.5 months (time to complete response), while SPARK had a median of 2.1 months).

The zanubrutinib studies show generally [redacted] compared to the ibrutinib studies.

3.3.2.4 Comparison of variables used in ITC

Due to the ibrutinib studies not reporting all the TEMs identified by the company, only some of the TEMs could be adjusted for in the MAIC. These were: number of prior lines of therapy, blastoid status, ECOG PS, presence of bulky disease, presence of extranodal disease, prior lenalidomide therapy, age, and gender.

The differences in prior treatment exposure, age, and prior lenalidomide therapy suggest some challenges in achieving complete comparability between the pooled populations and may influence the results, however the other TEMs were similar

across studies, therefore a MAIC is an appropriate method to improve the comparability given the available data.

Table 15: Study design and characteristics of the studies included in the ITC

Study design	BGB-3111-AU-003	BGB-3111-206	RAY-MCL 3001	PCYC-1104	SPARK
Population and size	ITT = 32 (2L = 18)	ITT = 86	Ibrutinib ITT =139	ITT = 111	ITT = 120
Start date	September 2014	March 2017	December 2012	February 2011	July 2012
End date	March 2021	August 2020	December 2016	January 2014	Unclear
Median follow-up	38.92 months	35.25 months	20 months	15.3 months 26.7 months (final analysis)	14.9 months
Phase	1/2	2	3	2	2
Treatment	Zanubrutinib 320 mg orally QD	Zanubrutinib 320 mg orally QD	Ibrutinb 4x140mg (560 mg) orally QD	Ibrutinb 4x140mg (560 mg) orally QD	Ibrutinb 4x140mg (560 mg) orally QD
Comparator	NA	NA	Temsirolimus Cycle 1: 175 mg IV QW Cycle 2+: 75 mg IV QW	NA	NA
Randomisation	NA	NA	Yes	NA	NA

Study design	BGB-3111-AU-003	BGB-3111-206	RAY-MCL 3001	PCYC-1104	SPARK
Key inclusion criteria	• ≥18 years old • R/R MCL • ECOG PS 0-2 • Adequate haematologic, renal and liver function	• Aged 18 to 75 years. • 1 - 5 prior lines of therapy. • Retrospectively confirmed MCL diagnosis. • ECOG PS 0-2. • Measurable disease in at least 1 lymph node >1.5 cm in longest diameter and measurable in 2 perpendicular dimensions.	≥1 previous rituximab containing chemotherapy regimen relapse or disease progression after the last treatment measurable disease by Revised Response Criteria for Malignant Lymphoma ECOG Ps 0 or 1	confirmed diagnosis of MCL with cyclin D1 overexpression or translocation breakpoints at t(11;14) measurable disease (lymph-node diameter, ≥2 cm) ≥1 but no more than 5 previous lines of treatment ECOG 2 or less	MCL with ≥ 1 measurable site of disease according to Revised Response Criteria for Malignant Lymphoma Received ≥1 rituximab-containing chemotherapy regimen but no more than 5 prior regimens Received ≥2 cycles of bortezomib therapy ECOG PS 0-2
Key exclusion criteria	Prior exposure to BTK inhibitor therapy	• Current or history of CNS lymphoma. • Prior exposure to a BTK inhibitor.	chemotherapy, radiation, or other investigational drugs within 3 weeks antibody treatment within 4 weeks immunoconjugates	NR	Prior treatment with ibrutinib or other BTK inhibitors Prior chemotherapy within 3 weeks, nitrosoureas within 6 weeks, therapeutic

Study design	BGB-3111-AU-003	BGB-3111-206	RAY-MCL 3001	PCYC-1104	SPARK
			within 10 weeks previous treatment with mTOR or BTK inhibitors		anticancer antibodies within 4 weeks, radio- or toxin-immunoconjugates within 10 weeks, radiation therapy or investigational agents within 3 weeks, or major surgery within 4 weeks Known central nervous system lymphoma
Location	6 countries including the UK*; 4 continents	China	21 countries including the UK; 4 continents	4 countries including the UK; 2 continents	9 countries including the UK; 3 continents
Funding	BeiGene	BeiGene	Janssen	Pharmacyclics and Janssen Biotech	Janssen
*At the clarification stage, it was confirmed that in the MCL population there were no UK patients in BGB-3111-AU-003.					

Table 16: Baseline characteristics of TEMS included in the ITC

TEM	BGB-3111-AU-003	BGB-3111-206	RAY-MCL 3001[1]	PCYC-1104[2]	SPARK[3]	Included in MAIC?
Population and size	ITT = 32	ITT = 86	Ibrutinib ITT =139	ITT = 111	ITT = 120	
Response to first line therapy	[redacted]	Relapsed 41 (47.7%) Refractory 45 (52.3%)	Relapsed 103 (74%) Refractory 36 (26%)	Relapsed: NR Refractory: 50 (45%)	NR	
Number of prior lines of therapy	Median (range): 1.0 (1, 4)	Median (range): 2.0 (1, 4)	Median (range): 2.0 (1, 9)	Median (range): 3 (1, 5)	Median (range): 2 (1, 8)	Yes
Time from initial diagnosis (years)	[redacted]	Mean (SD): 3.0 (2.02)	Median: 3.24		Median 43.9 months (time to first dose) Range: 6.8 to 189.6 months	
Blastoid status	[redacted]	[redacted]	Blastoid: 16 (12%) Non-blastoid: 123 (88%)	Blastoid: 17 (15.3%)	Blastoid histology: 11 (9.17%)	Yes
ECOG PS	0: 46.9%	0: 69.8%	0: 48.2%	0 or 1: 99 (89%)	0: 35%	Yes
	1: 43.8%	1: 25.6%	1: 51.1%		1: 55.8%	
	2: 9.4%	2: 4.7%	2: 0.7%	2: 11 (10%)	2: 9.2%	
Ki67	NR	[redacted]	NR	NR	NR	
MIPI index	Low: 25.0%	Low: 14.0%	Low: 31.7%	Low: 15 (14%)	Low: 23.7%	
	Int: 34.4%	Int: 45.3%	Int: 46.8%	Int: 42 (38%)	Int: 48.3%	
	High: 40.6%	High: 38.4%	High: 21.6%	High: 54 (49%)	High: 28.0%	
	>10cm: 9.4%	>10cm: 8.1%	< 5cm: 64 (46%)			Yes

TEM	BGB-3111-AU-003	BGB-3111-206	RAY-MCL 3001[1]	PCYC-1104[2]	SPARK[3]	Included in MAIC?
Presence of bulky disease	≤10cm: 90.6%	≤10cm: 91.9%	≥ 5 cm: 74 (53%)	≥ 5 cm: 43 (38.7%) ≥10 cm: 9 (8%)	≥ 5cm: 52.5% ≥10 cm: 17 (14.2%)	
Presence of extranodal disease	78.10%	70.90%	83 (59.7%)	54%	72 (60.0%)	Yes
Prior lenalidomide therapy	0%	14.00%	6%	24%	19%	Yes
Prior rituximab therapy	0%	74.40%	100%	89%	100%	
Age	[redacted]	[redacted]	Median (range): 67.0 (39, 84)	Median (range): 68 (40-84)	67.5 (35-85)	Yes
Gender	Male: 68.8%	Male: 77.9%	Male: 71.9%	Male: 77%	Male: 86.7%	Yes

[1] From Table 17 of TA502, Dreyline 2016, and Rule 2017 supplementary material
[2] From Wang 2013, Wang 2015, and Rule 2017 supplementary material
[3] From TA502 and Rule 2017 supplementary material

Table 17: Clinical outcomes of trials included in indirect comparison

Outcomes	BGB-3111-AU-003	BGB-3111-206	RAY-MCL 3001	PCYC-1104	SPARK
Population and size	ITT = 32	ITT = 86	Ibrutinib ITT =139	ITT = 111	ITT = 120
Data cut	(INV) 31/03/2021	(INV) 08/09/2020			
Objective response rate	[redacted]	83.7% (74.2, 90.8)	77% 1L: 75.4%	67% (57.1%, 75.3%)	62.7% (53.7%, 71.8%)
Best overall response					
Complete	[redacted]	67 (77.9%)	23%[4]	23% (15.1%, 31.4%)	20.9% (13.3%, 28.5%)
Partial	[redacted]	5 (5.8%)	74 (53.2%)[1,4]	Final: 49 (44.1%) Primary: 52 (47%)	41.8% (32.6%, 51.0%)
Stable	[redacted]	1 (1.2%)	15 (10.8%)[1,4]	16 (14.4%)	14.5% (.0%, 21.1%)
Progressed	[redacted]	8 (9.3%)	15 (10.8%)[1,4]	19 (17.1%)	22.7% (14.9%, 30.6%)
Unknown	[redacted]	5 (5.8%)			
Progression-free survival					
Events	[redacted]	[redacted]	NR		
Median (months)	[redacted]	33.0 (19.4, NE)	15.6 (10.6 to 25.1)	13 (7.0, 17.5)[2]	10.5 (4.4 ,15)[1]
Overall survival					
Events	[redacted]	21 (24.4%)			
Median (months)	[redacted]	NE (NE, NE)	30.3 (19.1 to 42.1)	22.5 (13.7, NE)	NE
Duration of response					
Events	[redacted]	[redacted]			
Median (months)	[redacted]	NE (24.9, NE)	23.1 (16.2 to 28.1)	17.5 (4.9, NE)	14.9
Time to response					
Mean	[redacted]	[redacted]			
Median (months)	[redacted]	2.73 (2.5, 3.0)		5.5[3] (Range: 1.7, 24.7)	2.1 (1.3, 6.3)

Outcomes	BGB-3111-AU-003	BGB-3111-206	RAY-MCL 3001	PCYC-1104	SPARK
[1] Outcomes are Independent Review Committee (IRC)-assessed [2] at median follow-up of 26.7 months [3] time to complete response [4] complete responses at 39 months follow-up; partial, stable, progressed response at 20 months follow-up					

3.4 Methods used in company's ITC

3.4.1 Unanchored network

As both zanubrutinib studies were single arm, comparison to any studies of ibrutinib would result in an unanchored network. Of the three studies in the pooled ibrutinib studies, only RAY-MCL3001 was a phase III multicentre, open-label RCT with temsirolimus as the comparator. The other two ibrutinib studies in this pooled study were PCYC-1104 and SPARK, both phase II single-arm studies.

3.4.2 Matching-adjusted indirect comparisons (MAICs)

MAICs involve reweighting IPD from one study to match the baseline characteristics of a comparator study, enabling a fairer comparison between treatments. In this case, IPD was used from the zanubrutinib studies to reweight the pooled populations of BGB-3111-AU-003 and BGB-3111-206 (BGB003-206) to match important TEMs from the pooled RAY-MCL3001, PCYC-1104, and SPARK studies. The quality of the results depends on the overlap between populations, indicated by the effective sample size (ESS) and the choice of variables for matching.

An important assumption of the MAIC approach is that there are no unobserved differences between the studies that could confound the comparison of outcomes. While the adjustment accounts for observed TEMs, any unmeasured confounders remain a potential source of bias. One specific concern is that supportive care practices may have improved over time, meaning that patients in the ibrutinib trials (conducted earlier) may have had access to different management strategies than those in the more recent zanubrutinib trials. If survival outcomes have improved over time due to better supportive treatments rather than differences in drug efficacy, this could lead to a systematic bias in favour of zanubrutinib.

The company's weighting algorithm is described in Appendix M.1.3 and used a propensity score-type logistic regression model to derive the weights which were used to weight the characteristics of patients from the pooled zanubrutinib trials to that of the pooled ibrutinib trials.

3.4.3 Simulated Treatment Comparison (STC)

STCs, like MAICs, are also used when head-to-head clinical trial data are unavailable. The method involves using IPD from one trial and aggregate data from another, applying models to adjust for baseline differences and create a comparable patient population. This adjustment helps estimate treatment effects in a way that accounts for imbalances between studies. STCs are generally considered less robust than MAICs but can be useful when MAICs are infeasible,

The company considered STCs in the decision problem meeting as a potential choice for the ITC but ultimately chose the MAIC. The company stated that both methods “are expected to produce similar results”, and since the MAIC has been used in similar STAs, the MAIC method was preferred.

The EAG requested the company’s feasibility assessment, methods, and results for the STC during the clarification stage to ensure transparency in the selection of the ITC method. However, the company did not provide a feasibility assessment comparing the appropriateness of STC versus MAIC for this specific analysis. Without such an assessment, it is unclear whether STC was fully explored as a viable alternative.

3.4.4 MAIC vs STC

During the DPM stage, the company considered using either the MAIC or STC approach but chose the MAIC method due to, according to the company, the key TEMs being balanced between the zanubrutinib and ibrutinib studies, both approaches expected to produce similar results, and the wide use of the MAIC in HTA submissions. The following Table 18 compares key features of the MAIC and STC approaches. MAICs are generally simpler than STCs, however have limited generalisability in comparison.

The company’s decision to use the MAIC over the STC is reasonable if the relationship between the outcomes and the effect modifiers or prognostic factors are relatively straightforward (i.e. limited significant interactions between covariates). The EAG requested the company to perform additional analyses to clarify these covariate-outcome relationships. The absence of strong interactions between covariates and outcomes would support the company’s use of the MAIC.

Table 18: Comparison of MAIC and STC methods

	Matching-adjusted indirect comparison	Simulated treatment comparison
Methodology	Uses propensity score weighting to reweight IPD to match aggregate-level summary statistics of the comparator groups(s). Focuses on balancing the baseline characteristics between populations using weights derived from matching.	Fits a regression model on the IPD to adjust for treatment effect modifiers and prognostic variables, allowing predictions for outcomes in the comparator population(s).
Input data	IPD for one treatment, aggregate data for the others.	IPD for one treatment, aggregate data for the others.
Results output	Produces weighted treatment effect estimates.	Produces regression-based treatment effects estimates.
Key assumptions	All effect modifiers and prognostic variables are accounted for. Cannot adjust for unmeasured confounders.	The model used to predict outcomes is correctly specified and captures the covariate-outcome relationship. Also, cannot adjust for unmeasured confounders, but could potentially handle complex data relationships if specified.

3.4.5 Naïve comparison

A naïve comparison is an unadjusted analysis comparing outcomes between treatments without accounting for potential confounding factors or differences in baseline characteristics between the study populations. This type of comparison assumes that the populations are sufficiently similar to allow direct comparison of outcomes, but it is prone to bias if this assumption does not hold. This method was used in sensitivity analyses to compare BGB-3111-AU-003 only to the pooled studies from Rule 2017 since the BGB-3111-AU-003 study only had 32 participants, therefore after adjusting the ESS would be very small and reduce the robustness of any results.

3.4.6 Sensitivity analyses

The company performed five sensitivity analyses to assess the robustness of the base case MAIC results and the impact of different assumptions on the estimated treatment effects.

These were:

1. Using data from an earlier data cut (31st August 2019) for AU003-206
2. Removing rituximab-naïve patients from AU003-206
3. Using data from BGB-3111-AU-003 only
4. Using data from BGB-3111-206 only
5. Leave one out approach from the base case: omitted one of the TEMs and re-running the analysis, and repeating this for all eight factors

3.4.7 Company's feasibility assessment

The company concluded, in section B.2.9.2, that the most appropriate choice of ITC is the unanchored MAIC, due to the following:

- No head-to-head studies comparing the safety and efficacy of zanubrutinib versus ibrutinib.
- Availability of IPD for zanubrutinib, but only aggregate data for ibrutinib.
- MAIC used more in HTAs compared to STCs, though both expected to produce similar results.

3.4.8 Results

The results of the base case MAIC, as well as the sensitivity analysis MAICs, were presented in Table 38 of CS B.2.9.5, and are presented as forest plots by the EAG in Figure 1 and Figure 2.

For PFS, both the unadjusted and adjusted base case analyses resulted in a [redacted]. In the adjusted analyses, patients on zanubrutinib had [redacted] odds of disease progression compared to ibrutinib. The sensitivity analyses all resulted in [redacted] hazard ratios and the [redacted] that patients on zanubrutinib had [redacted] odds of progression compared to patients on ibrutinib.

For OS, both the unadjusted and adjusted base case analyses resulted in [redacted]. In the adjusted analyses, patients on zanubrutinib had a [redacted] odds of death compared to ibrutinib. The sensitivity analyses all resulted in [redacted] except the HR from the naïve-comparison of sensitivity analysis [redacted], using [redacted] which was [redacted] despite showing a [redacted] in the odds of death for zanubrutinib compared to ibrutinib.

Figure 1: Results of the company's MAIC analysis for PFS (from CS Table 38, B.2.9.5)

Figure 2: Results of the company's MAIC analysis for OS (from CS Table 38, B.2.9.5)

3.4.9 Adverse events MAIC

In the CS, the company makes the case that zanubrutinib should eventually displace ibrutinib in treating new second-line R/R MCL patients based on efficacy, tolerability, and safety. Due to this, the EAG requested the company conduct an ITC comparing adverse events of grade ≥3 occurring in >2% of patients, which the company provided in response to clarification A12.

The same pooled population of BGB-003-206 was used to compare the relevant adverse event data from Rule et al. 2017b, thus an ESS of [redacted] was achieved after adjustment, the same ESS for the PFS and OS MAICs.

Due to the lack of reporting every adverse event in Rule et al. 2017b, comparisons would only be made for the following:

- ≥Grade 3 TEAEs
- ≥Grade 3 pneumonia
- ≥Grade 3 neutropenia
- ≥Grade 3 anaemia

The EAG tabulated the safety data from the individual zanubrutinib and ibrutinib studies and presented the results in Table 19. The data for ibrutinib appears to be mainly from RAY-MCL 3001, with PCYC-1104 and SPARK only reporting TEAEs leading to study drug discontinuation. This reinforces the company's choice in only comparing the treatments for four safety-related outcomes.

The majority of patients in each study with data had at least one TEAE, with [redacted] having a TEAE grade 3 or more. [redacted] of patients in BGB-3111-AU-003 had a TEAE leading to study drug discontinuation, and in BGB-3111-206 this was 9.3%, compared to 6.5-16.7% in the ibrutinib studies. Additionally, [redacted] of BGB-3111-AU-003 patients had TEAEs leading to dose reductions, compared to 2.3% in BGB-3111-206, and 3.6% in RAY-MCL 3001.

Table 19: Safety data for the studies included in the ITC

Safety	BGB-3111-AU-003	BGB-3111-206	RAY-MCL 3001[1]	PCYC-1104[2]	SPARK[3]
Population and size	ITT = 32	ITT = 86	Ibrutinib ITT =139	ITT = 111	ITT = 120
Patients with at least 1 TEAE	[redacted]	83 (96.5%)	138 (99.3%)		
Grade ≥3 TEAEs	[redacted]	43 (50.0%)	94 (67.6%)		
Serious TEAEs	[redacted]	25 (29.1%)			
TEAEs leading to death	[redacted]	7 (8.1%)			
TEAEs leading to study drug discontinuation	[redacted]	8 (9.3%)	9 (6.5%)	8 (7%)	20 (16.7%)
TEAEs leading to treatment interruption	[redacted]	16 (18.6%)			
TEAEs leading to dose reduction	[redacted]	2 (2.3%)	5 (3.6%)		
Treatment-related AEs		[redacted]			

[1] From Table 17 of TA502 and Dreyling 2016
[2] From Wang 2013 and Wang 2015
[3] From TA502

3.4.10 Results of TEAEs MAIC

The results of the TEAEs MAIC are presented in Table 7 of the company's Clarification Responses document. The proportion of patients who experienced the

TEAE outcomes used in the MAIC pre- and post-adjustment are presented in Table 20 and the results presented in Figure 3.

Post-adjustment, zanubrutinib patients has [redacted]. This is reflected in the results where zanubrutinib had [redacted] of any TEAE ≥ grade 3 and neutropenia compared to ibrutinib. Conversely, zanubrutinib had [redacted] of pneumonia compared to ibrutinib, and there was [redacted] between treatments for anaemia.

Table 20: Comparison of TEAEs before and after MAIC adjustment

TEAEs	AU003-206 (n=118), unweighted	AU003-206 (ESS=[redacted]) weighted	Ibrutinib, Rule et al. (2017b) (n=370)
TEAE ≥ grade 3	[redacted]	[redacted]	71.6
Pneumonia	[redacted]	[redacted]	8.9
Neutropenia	[redacted]	[redacted]	16.49
Anaemia	[redacted]	[redacted]	8.1

[redacted]

Figure 3: Results of the company's MAIC analysis for TEAEs (Clarification A12 Table 7)

3.4.11 Company's conclusions

The results of the MAIC demonstrated that treatment with zanubrutinib resulted in statistically significant improvements in PFS and OS compared to treatment with

ibrutinib, however the results of the TEAE MAIC were mixed. The company used the results from the base-case MAIC to weight the KM plots for zanubrutinib (Figure 18 and 19 in CS B.2.9.5) which were then modelled using parametric survival models in CS B.3.3. The EAG discusses the company's survival modelling in section 3.2.6.

3.5 EAG's critique of company's ITC

3.5.1 Feasibility assessment

3.5.1.1 Study characteristics

The company presented a comparison of the pooled zanubrutinib and ibrutinib studies in Table 34 of CS B.2.9.3. The company stated that there was "substantial overlap" between the two populations, however there were a few key differences between the pooled studies.

Statistical analysis of the baseline characteristics indicates that the AU003-206 population was significantly younger than the Rule et al. population, with a lower mean and median age. Additionally, the AU003-206 cohort had better ECOG performance status, with a higher proportion of patients classified as ECOG 0. The AU003-206 population also had a significantly higher rate of extranodal disease at study entry.

Conversely, the Rule et al. population had a greater proportion of patients who had undergone prior stem cell transplant and were more heavily pretreated, with a higher percentage of patients receiving ≥3 prior systemic therapies. Prior exposure to bortezomib and rituximab-containing regimens was also significantly more common in the Rule et al. cohort.

Due to these differences, the EAG tabulated the study characteristics of each of the five studies separately to provide a clearer picture of patient populations and ensure a more accurate comparison.

3.5.1.2 Effective sample size

Table 36 of the CS document B presents the covariate balance between the post-matched AU003-206 populations compared to the pooled ibrutinib studies from Rule et al. 2017. In each case, the covariates matched to one decimal place. The effective

sample size of the matched population was [redacted], down from the unweighted population of 118, representing a [redacted] reduction. The company stated that such a reduction demonstrated “considerable overlap”, however, in the EAG’s opinion, a [redacted] reduction is quite substantial and indicates a significant portion of the original population were either down weighted or excluded during the matching process. Conversely, an ESS of [redacted] is reasonably large and, if the treatment effect is strong, should be sufficient to draw meaningful conclusions from.

3.5.1.3 Study design

The zanubrutinib studies have longer follow-up compared to the three ibrutinib studies. The efficacy of zanubrutinib is derived from two single-arm studies, while ibrutinib data comes from two single-arm studies (SPARK and PCYC-1104) and an open-label phase 3 RCT (RAY-MCL-3001). The inclusion of an RCT introduces a difference since RCTs include a comparator arm, reducing selection bias and allowing for more robust causal inference. Single-arm studies lack these; thus they are more susceptible to confounding.

3.5.2 Pooling of zanubrutinib studies

The two zanubrutinib studies that were pooled, BGB-3111-AU-003 and BGB-3111-206, have a few differences which may affect the comparability of the pooled dataset to the pooled ibrutinib studies. Compared to BGB-3111-206, some key differences in the patients from BGB-3111-AU-003 were:

- A [redacted] proportion of relapsed patients ([redacted]) and [redacted] refractory patients ([redacted]) compared to BGB-3111-206 ([redacted] and [redacted], respectively) suggesting a [redacted] treatment-resistant population in comparison.
- A lower median of prior lines of therapies.
- A [redacted] mean time from initial diagnosis.
- A [redacted] proportion of blastoid cases.
- A higher proportion of ECOG 2 patients.
- A lower proportion of intermediate and high-risk patients using the MIPI index.
- No patients with prior lenalidomide or rituximab therapy.
- [redacted] mean age.
- Slightly lower proportion of males, though both studies male-dominated.

While the two studies are broadly similar, the notable differences mentioned above may introduce some heterogeneity in the pooled dataset. As BGB-3111-206 accounts for most of the patients in the pooled zanubrutinib population (86/118 = 73%), its baseline characteristics will have a greater influence on the overall pooled zanubrutinib population. However, the pooling is still reasonable, though with some limitations in comparability.

3.5.3 Pooling of ibrutinib studies

The three ibrutinib studies that were pooled, RAY-MCL-3001, PCYC-1104, and SPARK, have a few differences in characteristics. All three studies have a similar sample size, thus the pooled ibrutinib population will not be heavily weighted by one study.

- RAY-MCL 3001 had a lower proportion of refractory patients (26%) compared to PCYC-1104 at 45%. This was not reported for SPARK.
- PCYC-1104 patients had the highest median of prior lines of therapy, while SPARK and RAY-MCL 1104 patients had wider ranges.
- PCYC-1104 and SPARK had similar highest proportions of patients with ECOG 2 (10% and 9.2%, respectively), while in RAY-MCL 1004 it was significantly lower at 0.7%.
- PCYC-1104 had the highest proportion of high-risk MIPI patients (49%) compared to SPARK (28%) and RAY-MCL 1004 (21.6%).
- PCYC-1104 had the highest proportion of prior lenalidomide exposure (24%), followed by SPARK (19%) and RAY-MCL 3001 (6%).

While the differences exist, the three studies are broadly comparable to pool for an ITC.

3.5.4 STCs and covariate-outcome relationships

In response to clarification question A10, the company acknowledged that interactions between treatment and prognostic factors were not formally assessed, stating that the published aggregate data available in Rule et al. 2017 “prevents direct interaction testing between treatment and covariates across both datasets”. This raises a few concerns regarding choosing the MAIC over the STC.

While the MAIC approach does not allow for direct interaction testing across datasets, this does not prevent the possibility of exploring interactions within the available IPD for the zanubrutinib studies, which could have provided insight into whether the key TEMs influenced outcomes in a way that might impact the validity of the adjusted comparisons. Without this assessment, the assumption that treatment effects are consistent across subgroups remains unverified.

Similarly, the company confirmed that nonlinearity was not explicitly tested, stating "Nonlinearity was not explicitly tested because the primary goal of the MAIC was to balance key prognostic factors between populations, rather than to model complex relationships." This assumed that the relationships between prognostic factors and outcomes are linear, which may not hold.

The company described the leave-one-out analysis conducted to assess the impact of covariate selection, stating that "The leave-one-out analysis produced hazard ratios (HRs) that were consistent with the base-case analysis, indicating that the findings were robust to the inclusion or exclusion of specific covariates." However, this does not address whether interactions exist between covariates or whether nonlinear relationships affect treatment outcomes. Consistent HRs do not necessarily indicate that all relevant covariate relationships have been appropriately accounted for in the MAIC, questioning the robustness of the results.

The company asserts that the MAIC was preferable to the STC by stating that "The key prognostic factors and treatment effect modifiers, presented in Section B.2.9.4, were relatively well balanced thus the MAIC and STC methodologies are expected to produce similar results." Again, this argument assumes that balance was adequately achieved without providing quantitative evidence of covariate distributions post-weighting, and the lack of formal interaction testing means that any residual confounding due to unmeasured interactions remains unaddressed.

Another reason for choosing the MAIC, the company states that "The MAIC approach has been used in a number of oncology health technology appraisals (HTAs) submitted to and accepted by NICE, most recently the evaluation of zanubrutinib (TA1001) for the treatment of marginal zone lymphoma (MZL)." While precedent can be relevant, it does not establish methodological justification. The appropriateness of an indirect treatment comparison (ITC) method should be

determined by the characteristics of the data rather than by past appraisals. The fact that NICE has accepted MAICs in prior oncology HTAs does not inherently validate its use in this specific case, particularly when an alternative method such as STC could have potentially provided a more robust adjustment for treatment effect modifiers.

Additionally, the company states that “While still a relevant methodology, STCs have not been used in many HTAs submitted to and accepted by NICE.” This argument is not relevant, as the frequency of STC usage in previous submissions does not determine its suitability for a given dataset. If an STC could have better accounted for potential residual confounding, its relative lack of prior use should not determine its use.

The company also highlighted that expert clinicians and health economist supported the use of the MAIC approach, however this does not replace statistical validation. The lack of interaction and nonlinearity testing means that the MAIC results rely on assumptions that remain unverified.

3.5.5 Results

The company presented the results of the main and sensitivity analysis MAICs in Table 38 of B.2.9.5. Across both outcomes and all analyses, zanubrutinib was associated with a [redacted] for both PFS and OS, at the 5% level, except for [redacted] between the treatments.

3.5.6 Conclusion of EAG’s critique

3.5.6.1 PFS and OS MAIC

The ITC results consistently [redacted] zanubrutinib over ibrutinib for PFS and OS, suggesting efficacy [redacted] for zanubrutinib.

The main issues with the ITC are related to the reporting of the TEMs in the ibrutinib studies. Of the 13 TEMs identified by the company’s experts, only eight were used for the adjustments, which will introduce residual confounding and could potentially bias the estimated treatment effect between to two treatments. The direction of this bias is unknown and, depending on whether the imbalance favours zanubrutinib or ibrutinib, it could either overestimate or underestimate the treatment effect. However, this is a limitation of the evidence base and not the methods.

3.5.6.2 TEAE MAIC

The company was transparent in its choice of outcomes based on the available data. Although some AEs that were experienced by a [redacted] proportion of BGB-003-206 patients, such as neutrophil count decreased, were not analysed in the MAIC, it was only due to that not being reported in Rule et al. 2017b. The MAIC procedure followed the same approach as the PFS and OS MAICs, resulting in the [redacted] ESS and the EAG considers this sufficiently large to draw meaningful conclusions despite the almost [redacted] reduction from the original sample size. Results are clinically meaningful, for example [redacted] neutropenia risk with zanubrutinib, but [redacted] pneumonia risk. The latter, for example, needs further exploration as it could offset tolerability benefits.

3.6 Additional work on clinical effectiveness undertaken by the EAG

3.6.1 Searches

The CS SLR searches were last undertaken on 16th July 2024 (CS Appendix D). The EAG therefore ran a targeted update search to the company SLR, focusing on studies of zanubrutinib and ibrutinib for R/R MCL. The EAG targeted searches were conducted on two databases, Medline and Embase. See Appendix 9.2.1 for detailed search strategy.

After duplicates were removed there were 96 references to screen. An initial screening of titles and abstracts focusing on studies in R/R MCL by two EAG team members reduced the number of references to 38 studies. Two independent reviewers then conducted title and abstract screening using a modification of the CS SLR eligibility criteria focusing only on studies assessing safety or efficacy of zanubrutinib or ibrutinib. Any disagreements were resolved through discussion. Ten full texts were retrieved for full review against the modified eligibility criteria by two independent EAG reviewers. Any disagreements were resolved by discussion. Of these ten studies, two met the inclusion criteria.

Lu et al 2024[43] conducted a single-centre retrospective study to evaluate the safety and efficacy of second-generation BTK inhibitors, zanubrutinib and acalabrutinib, in people with R/R MCL. The study included a total cohort of 30 participants, all of whom were followed for a minimum duration of nine months. Among the 30 participants, only eight received zanubrutinib. The mean age of those receiving

zanubrutinib was 65 years (range 52–82), with a predominance of male participants (62.5%). Regarding prior treatment history, 75% (six out of eight participants) had received three or more lines of therapy. The remaining two participants had received either one or two prior lines of therapy. Only safety outcomes were reported, no grade 3 or higher adverse events were reported among the zanubrutinib-treated participants. The most observed adverse event of any grade was fatigue, which was reported in 75%. The study therefore does not provide any additional data of relevance to the appraisal.

Maruyama et al 2024[44] was a real-world study reporting the effectiveness and safety of ibrutinib in R/R MCL from Japan. The EAG considered that the study did not provide any additional data of relevance to the appraisal, as the population was older, exclusively Japanese, and had a higher median number of prior therapies compared to the pooled zanubrutinib population. Furthermore, the publication only reported a subset of the key TEMs identified by the company, limiting its suitability for an adjusted comparison. While this study could be considered for an exploratory scenario, the expected low ESS and lack of robust adjustment potential reduce its applicability.

The EAG also undertook an additional test search (see Appendix 9.2.2) to correct the error in the execution of the company searches discussed in 3.1.1. The test search identified 113 titles and abstracts and these were screened by two reviewers. Two potential additional studies were identified for the clinical effectiveness review. These two studies were published as abstracts, Shah 2024[45] and Phillips 2024.[46] Shah 2024 used an STC to compare the efficacy of zanubrutinib (using pooled BGB-003-206 data) with acalabrutinib; while Phillips 2024 was a retrospective real-world study investigating the comparative effectiveness of zanubrutinib, acalabrutinib, and ibrutinib. The EAG believes the Phillips' study could have some relevance to this submission since it provides real-world evidence in patients with R/R MCL. This study suggests zanubrutinib has significantly longer time-to-next treatment and overall survival compared to ibrutinib, supporting the company's conclusions from the MAIC, whilst also having more participants in the study (607 total, 107 for zanubrutinib). Potential limitations, however, are that it is a retrospective observational study, meaning there may be confounders that were not fully

controlled, and that it was conducted in the USA, so generalisability to the UK needs to be considered.

For the Shah 2024 abstract, while the comparison of zanubrutinib of acalabrutinib in R/R MCL is not directly relevant to the scope of the appraisal, the EAG considered that while this study does not inform the zanubrutinib versus ibrutinib comparison, it may offer contextual information on comparative analyses in R/R MCL. For example, the TEMs and prognostic factors adjusted for in this STC may be relevant for assessing zanubrutinib versus ibrutinib. However, as an unanchored STC, the findings are subject to potential residual confounding, and further methodological details are not available in the abstract for full appraisal.

3.6.2 Adverse events: ten pooled zanubrutinib studies in any indication

The CS cites an ongoing long-term extension safety follow-up study of several zanubrutinib trials of B-cell malignancies (BGB-3111-LTE1[47]), which includes 12 patients from BGB-3111-AU-003 and 40 patients from BGB-3111-206. No safety data or details of publications from BGB-3111-LTE1 were presented in the CS. The EAG requested any available safety data from BGB-3111-LTE1 in Clarification A13. In response, the company narratively summarised results from a poster presentation[48] reporting a pooled analysis of 1550 patients from ten clinical studies of zanubrutinib, including BGB-3111-AU-003, BGB-3111-206 and BGB-3111-LTE1. This also reported events from two RCTs that compared zanubrutinib head-to-head with ibrutinib in other indications (ASPEN and ALPINE), see section 3.6.3.

As grade 3 adverse events are important to the economic model, the EAG has tabulated grade ≥3 adverse events occurring in any indication reported in the poster presentation,[48] see Table 21. Similar to studies BGB-3111-AU-003 and BGB-3111-206, pneumonia was one of the most common grade ≥3 events, occurring in 8.4% of participants. However, hypertension appeared to be more common than in the R/R MCL studies alone, occurring in 8.1% of participants with any indication. Hypertension was not included in the company's economic model. The EAG clinical expert noted that ethnic differences between the studies may play a role, as

hypertension would be expected to be lower among Chinese participants (study BGB-3111-206).

Table 21: Most common non-haematologic TEAEs of grade ≥3 reported in ≥5% of patients: pooled zanubrutinib studies in all indications

Grade ≥3 event, %	All indications (N=1550)
Pneumonia	8.4
Hypertension	8.1
Upper respiratory tract infection	1.9
Diarrhoea	1.8
Arthralgia	0.8
Rash	0.3
Cough	0.1

Source: Adapted from Brown 2024.[48]

3.6.3 Adverse events: comparison between zanubrutinib and ibrutinib

The EAG critique of the company's ITC of zanubrutinib and ibrutinib grade ≥3 events in R/R MCL is described above in sections 1.1.1 and 3.4.10.

As stated earlier, Clarification response A13 narratively summarises a poster presentation[48] reporting two pooled RCTs that compared zanubrutinib head-to-head with ibrutinib in other B-cell malignancies (ASPEN: Waldenström macroglobulinemia and ALPINE: chronic lymphocytic leukaemia/small lymphocytic lymphoma). However, the company reports zanubrutinib data from ten pooled studies (n=1550) in any indication, rather than just the pooled RCT data. The EAG considers that the pooled RCT data is most appropriate for a comparison; this is presented in Table 22. Median duration of treatment was longer with zanubrutinib, and TEAES leading to dose reduction, dose interruption and treatment discontinuation were slightly lower. Deaths due to any TEAE or to a cardiac TEAE were also slightly lower with zanubrutinib.

The poster presentation[48] also reports exposure-adjusted incidence rates of adverse events of special interest (any grade) from the pooled RCTs. The only event

occurring more often in zanubrutinib than ibrutinib was neutropenia (1.32 vs 1.05 persons per 100 person months).

Table 22: Adverse events from two pooled RCTs

Event, n (%)	**ASPEN/ALPINE RCTs**	
	Zanubrutinib (n=425)	**Ibrutinib (N=422)**
Duration of treatment, median (range), months	32.6 (0.4-68.7)	25.7 (0.1-59.3)
TEAE leading to dose reduction	59 (13.9)	81 (19.2)
TEAE leading to dose interruption	230 (54.1)	249 (59.0)
TEAE leading to treatment discontinuation	60 (14.1)	93 (22.0)
TEAE leading to treatment discontinuation due to cardiac TEAE	2 (0.5)	18 (4.3)
Death due to any TEAE	37 (8.7)	43 (10.2)
Death due to cardiac TEAE	1 (0.2)	7 (1.7)

Source: Adapted from Brown 2023.[48]

3.7 Conclusions of the clinical effectiveness section

The CS presents evidence from two single-arm studies of zanubrutinib for people with R/R MCL. The CS decision problem is focused on zanubrutinib as 2L treatment; however results are presented for the wider population of R/R MCL (with one or more prior therapies) as well as for the subgroups at 2L-only. The sample sizes of the full populations and the 2L-only subgroups are small, and the EAG has been unable to verify any of the 2L-only data presented in the CS. Results of the two studies suggest good rates of overall response to treatment, although there were differences in the proportions achieving complete response between the two studies. A [redacted] proportion of patients progressed in study BGB-3111-AU-003 than in BGB-3111-206 ([redacted]), and there was a [redacted] median PFS ([redacted]), however, these results [redacted]. Adverse event rates overall were broadly similar between the two studies, however [redacted] participants in study BGB-3111-AU-003 experienced Grade 3 or higher adverse events, serious adverse events and adverse events leading to dose reduction/interruption or discontinuation.

Although the quality of these two studies is acceptable, the findings are from single arm studies and therefore any conclusions are caveated. In addition, as discussed in section 3.2.8, there are several uncertainties around the studies that needs to be considered when interpreting the results.

The CS conducted an SLR to identify possible studies of relevance to the decision problem and in particular for an indirect comparison with the comparator ibrutinib. The EAG is satisfied that all relevant studies for the indirect comparison were included in the CS.

Results of the ITC suggest that zanubrutinib offers PFS and OS [redacted] over ibrutinib. However, limitations in the reporting of TEMs in the ibrutinib studies introduces residual confounding. The TEAE ITC was limited by data availability but followed a consistent approach with the PFS and OS MAICs and results were considered robust. Clinically meaningful differences were observed, including a [redacted] risk of neutropenia but a [redacted] risk of pneumonia with zanubrutinib, the latter warranting further investigation.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The CS provides detailed reports of three systematic literature reviews (SLRs), aimed at identifying economic evaluations (CS Appendix G) health state utility values and health-related quality of life data (CS Appendix H) and studies describing costs and resource use (CS Appendix I), all relating to population with MCL who received ≥1 lines of therapy.

4.1.1 Search strategies

Searches for these three SLRs were undertaken in conjunction with searches for the clinical SLR (see section 3.1.1), on 16th of May 2024 and last updated on 16th July 2024. In addition to relevant medical bibliographic databases (MEDLINE, Embase), other appropriate databases and sources were searched. The error in the MEDLINE and Embase search described in section 3.1.1 does not appear to have had an impact on the overall cost effectiveness SLR; of the two additional potentially relevant records identified in EAG testing, one is a cost-minimisation analysis and the other a budget impact analysis. Both studies were conference abstracts and did not exactly meet the CS inclusion criteria.

4.1.2 Inclusion/exclusion criteria used in the study selection

The inclusion and exclusion criteria for the review of cost-effectiveness evidence, health state utility values, and costs and resource are presented in Table 8 of CS Appendix G, Table 9 of CS Appendix G, and Table 10 of CS Appendix G.

- The EAG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies.

4.1.3 Included/ excluded studies in the cost-effectiveness review

A total of 21 publications, reporting 8 published analyses, 5 conference proceedings and 8 HTAs were included in the cost-effectiveness review. Details of these studies are provided in Table 45 of the CS.

- It is worth noting that that there is a slight mismatch between CS Document B and CS Appendix G in the reported total number of studies or records included for extraction (21 vs. 20) and published analyses included in review (12 vs. 13). The EAG believes this is because the company interchangeably uses the terminology studies and records in reporting and the discrepancy is because both the abstract and accompanying poster were identified for Loupas 2022 and Ghanem 2022, which were extracted as separate records (but are the same study). The mismatch in reporting has no impact on the cost-effectiveness review.

The search for health state utility values resulted in 13 included studies, four of which were considered relevant for this appraisal. The EAG considers the rationale for final studies included appropriate.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

The eligibility criteria were suitable for the SLR performed. The SLR search strategies were comprehensive enough despite some limitations highlighted above. An updated EAG search yielded only 2 potentially relevant studies missed by the company's search, but these studies did not exactly meet the inclusion criteria. The EAG considers the company's submitted economic evaluation evidence comprehensive.

4.2.1 NICE reference case checklist

The EAG assessment against the NICE reference case checklist is presented in Table 23.

Table 23: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – 32 years
Synthesis of evidence on health effects	Based on systematic review	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes. However, EQ-5D data was not collected in the pivotal zanubrutinib trials but based on TA502
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes, but based on external data (same comment as above).
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

Element of health technology assessment	Reference case	EAG comment on company's submission
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

The company constructed a *de novo* cost-utility model using partitioned survival with a four-weekly cycle length (28 days) and a 32-year time horizon. The model defines three health states: progression free survival (PFS), progressed disease (PD) and death (absorbing health state) (Figure 4). All patients entered the model in the PFS state and remained there until disease progression or death. The CS notes that patients received treatment in the PF state until either discontinuation, progression or death. However, since time to treatment discontinuation (TTD) was set equal to PFS in the base case analysis (detailed explanation in section 4.2.6) patients were assumed to receive treatment unless they progressed.

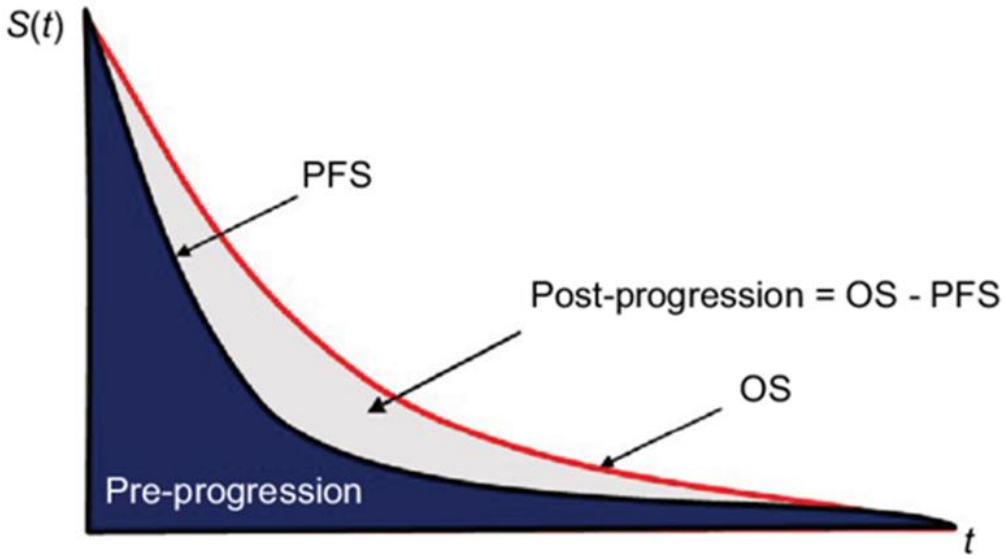

Figure 4: Health state structure used in the company's economic model

Source: CS Figure 21

The partitioned survival method uses "area under the curve" approach, where the number of patients in each health state at a given time point is taken directly from survival curves fitted to the clinical data. The PFS curves indicate, for each time

point, the proportion of patients who have not progressed or died whilst the OS curves indicate the proportion of patients who are alive at a given time point. The proportion of patients in the PD state was calculated as the difference between the proportion of living patients (OS health state) and the proportion of patients who were both living and pre-progression (PFS health state). The OS and PFS curves were determined by fitting parametric models to the combined data from BGB-3111-AU-003 and BGB-3111-206 trials adjusted to the ibrutinib dataset (Rule 2017[24]) throughout the MAIC analysis. For the ibrutinib arm, OS and PFS distribution were determined by fitting parametric models to reconstructed KM curves from the pooled ibrutinib studies (RAY-MCL3001, PCYC-1104 and SPARK).

TTD in the PFS state for the zanubrutinib and ibrutinib arms were set equal to PFS in the model's base case. The company's justification for taking this approach was that it overcame issues of poor fit observed with the TTD extrapolations. Furthermore, the assumption of PFS as a proxy for TTD was supported by clinical experts at an advisory board. A detailed discussion is provided in section 4.2.6.

No treatment waning effect was applied in the model. At clarification (B11), the company noted the following reasons for not exploring treatment waning in ether the base case or scenario analyses. First, the company stated that "*Zanubrutinib demonstrated strong and durable PFS and OS in both the BGB-3111-AU-003 and BGB-3111-206 trials* and *additionally, the smoothed hazard plots assessed for zanubrutinib (Figures 25 and 29 in the CS) did not clearly highlight any treatment effect waning"*. Secondly, the company indicated that because the EAG and the appraisal committee for TA502 (ibrutinib appraisal) did not raise any issue with the lack of treatment waning effect assumption, the same would apply for zanubrutinib since the same technologies belong to the same drug class. Thirdly, the company's clinical experts did not raise any concerns regarding treatment effect waning with zanubrutinib during the advisory board meeting. However, the clinical expert consulted by EAG highlighted that not exploring treatment effect waning was not a reasonable approach as patients stop treatment for toxicity and when they do the disease returns within months.

EAG Comments

Assuming time on treatment is equal to PFS could overestimate the proportion of patients remaining on treatment and subsequently treatment costs. This is because the approach does not consider treatment discontinuations prior to disease progression for reasons such as withdrawal from the trial.

- Since there is no stopping rule for zanubrutinib and ibrutinib, using KM data on TTD and assuming that the study follow-up period is the maximum possible "time on treatment" for each patient in the analysis could resolve some of the uncertainties with modelling TTD. However, long-term estimates based on this approach underestimated TTD beyond 3 years as per EAG's clinical expert's opinion. Both the company and EAG (section 4.2.6.11) explored alternative TTD assumptions and impact on ICER.

- While the EAG understands the decision by the company not to apply a treatment waning effect, the data is very immature, and the potential impact of applying treatment waning effect should be considered in decision-making. However, this would apply for both treatments as they belong to the same class and the impact on ICER may not be significant.

    - Uncertainties regarding the need of a treatment waning effect are best resolved by long-term outcomes on OS and PFS.

4.2.3 Population

The patient population considered in the model is specifically: adult patients with R/R MCL who have received one prior therapy, i.e., as a second line (2L only) therapy. The population is *partially* in line with the marketing authorisation (MA): treatment of adult patients with MCL who have received at least one prior therapy. i.e., (2L+) therapy. It is important to note that whilst the modelled population is for 2L only, the efficacy data from the pooled zanubrutinib trials was based on pooled data for patients who received zanubrutinib as 2L and >2L therapy. At clarification, the EAG requested the baseline characteristics and efficacy results for the >2L population (clarification question A1) to assess if inclusion of this data would introduce any bias

to the efficacy results. The company did not provide the data stating the following: the >2L population was outside the proposed population submitted in the CS, baseline characteristics can be calculated from the data provided and efficacy results for this subgroup can be inferred.

- The EAG prefers not to infer the results of the >2L population and maintains that without access to the data it is unclear whether the population (2L only) and the data modelled (2L+) are not biased in any direction by inclusion of >2L patients. In response to clarification question B12, the company provided a cost-effectiveness scenario analyses using the 2L population only of the pooled zanubrutinib trials (AU003-206 N=44, weighted to the ibrutinib arm sourced from Dreyling *et al.* [2022] [N=99]) and used results of that analyses as supporting evidence that inclusion of patients who received zanubrutinib at third-line plus does not change the base case cost-effectiveness conclusions.

As described in section 3.2, the submission mainly relies on two single arm studies: (i) BGB-3111-206 – a single arm, open-label, multicentre phase 2 study of zanubrutinib in patients with R/R MCL conducted in China and (ii) BGB-3111-AU-003 – A phase I/II, open-label, multiple-dose, multicentre dose escalation (Part 1) and expansion (Part 2) study of zanubrutinib in patients with B-cell lymphoid malignancies, including R/R MCL. The pooled data for these 2 studies (n= 118, unweighted; N=[redacted], weighted sample size in MAIC analysis) provided data on the use of, and clinical efficacy, safety, and time on treatment of zanubrutinib for treatment of adult patients in the intended population.

- A detailed EAG critique of these trials is provided in section 3.2.

Baseline patient parameters for the modelled populations were derived from the comparator treatment, ibrutinib technology appraisal for MCL (NICE TA502) (i.e., mean age: 68 years; baseline BSA:1.95 m^2; and proportion of males in the cohort: 78.0%. (Table 47 CS). The company justified this approach on the basis that it aligned the baseline patient parameters in the model with the survival data estimated from in the MAIC. The baseline characteristics are markedly different to those of the pooled zanubrutinib trials (Table 24 below).

- The EAG's clinical advisor questioned the choice of source for baseline characteristics in the company's model. At clarification (question B6), the EAG requested missing baseline characteristics (i.e., BSA) from the pooled zanubrutinib trials. The EAG conducted a scenario analysis using baseline characteristics of the pooled zanubrutinib trials instead of TA502 (see section 0).

Table 24: Baseline characteristics of zanubrutinib trials

Characteristic	Mean	Source
Age	[redacted]	CS Table 32 and Clarification Response B6
BSA (m^2)	[redacted]	
Proportion male	[redacted]	

BSA – body surface area.

  - It is important to determine which of the baseline characteristics are reasonably similar to the UK treatment population to provide a valid comparison

For the comparator treatment, efficacy estimates were drawn from the pooled ibrutinib trials (Pooled RAY-MCL3001, PCYC-1104, SPARK) as reported in Rule (2017b). A detailed EAG critique of these trials and comparisons is provided in Section 3.3.

4.2.4 Interventions and comparators

The description of comparators in the NICE scope is as follows: ibrutinib (after 1 prior therapy); ibrutinib, chemotherapy with or without rituximab; brexucabtagene autoleucel (subject to NICE evaluation) and allogeneic haemopoietic stem cell transplant (after 2 or more prior therapies) (see Summary of decision problem). The company's base case compares zanubrutinib with ibrutinib, partly reflecting the description of comparators in the NICE scope but aligning with the comparator for the proposed population in the CS.

  - The EAG's clinical advisor agrees with the choice of comparator for this appraisal.

4.2.5 Perspective, time horizon and discounting

The perspective is as per NICE reference case, with benefits from a patient perspective and costs from an NHS and personal social services (PSS) perspective. In the base-case, costs and benefits were discounted at an annual rate of 3.5% in line with NICE reference case used and discount applied is in line with NICE reference case. The time horizon is 32 years which is sufficient to capture the extrapolated OS curves given model cohort age.

4.2.6 Survival modelling

4.2.6.1 Overview

This section presents the company's and EAG's preferred models. While the company presented results for parametric models only, the EAG explored both parametric and spline models. Table 25 presents the preferred base case models for each treatment and outcome, Table 26 presents the expected PFS and OS up to five-years, and Table 27 presents the models used in scenario analyses. The EAG's critique of the company's survival modelling approach is presented in section 4.2.6.5, followed by the EAG's modelling approach.

Selected models

Table 25: Summary of the preferred models by company and EAG

Treatment	Outcome	Company	EAG
Zanubrutinib	PFS	Log-normal	2-knot normal
	OS	Log-normal	1-knot normal
	TTD	Same as PFS	Same as PFS
Ibrutinib	PFS	Log-normal	2-knot odds
	OS	Log-normal	2-knot normal
	TTD	Same as PFS	Same as PFS

Survival extrapolations

Table 26: Survival extrapolations at key timepoints up to five years (%)

		Survival (%)			
Treatment	**Model**	**1-year**	**2-year**	**3-year**	**5-year**
Progression-free survival					
Zanubrutinib	Company	[redacted]	[redacted]	[redacted]	[redacted]
	EAG	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	Company	[redacted]	[redacted]	[redacted]	[redacted]
	EAG	[redacted]	[redacted]	[redacted]	[redacted]
Overall survival					
Zanubrutinib	Company	[redacted]	[redacted]	[redacted]	[redacted]
	EAG	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	Company	[redacted]	[redacted]	[redacted]	[redacted]
	EAG	[redacted]	[redacted]	[redacted]	[redacted]
Time to treatment discontinuation (equivalent to PFS)					
Zanubrutinib	Company	[redacted]	[redacted]	[redacted]	[redacted]
	EAG	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	Company	[redacted]	[redacted]	[redacted]	[redacted]
	EAG	[redacted]	[redacted]	[redacted]	[redacted]

Scenario analysis models

The company and EAG undertook scenario analyses to assess how the ICER changes when using different survival curves. The company described their scenario analysis models in Table 76 of CS B.3.11.3 and are also presented in Table 27 along with the EAG's scenario analysis models.

Table 27: Scenario analysis curves chosen by the company and EAG

	Company	EAG
Progression-free survival		
Scenario 1	Zanubrutinib: Log-logistic Ibrutinib: Log-logistic	Zanubrutinib: Log-logistic Ibrutinib: 2-knot normal
Scenario 2	Zanubrutinib: Generalised gamma Ibrutinib: Generalised gamma	
Overall survival		
Scenario 3	Zanubrutinib: Log-logistic Ibrutinib: Log-logistic	Zanubrutinib: Log-logistic Ibrutinib: 3-knot normal
Scenario 4	Zanubrutinib: Generalised gamma Ibrutinib: Generalised gamma	
Time to treatment discontinuation		
Scenario 5*	Zanubrutinib: using KM data Ibrutinib: Using KM data	Zanubrutinib: 3-knot normal Ibrutinib: 3-knot hazard
Scenario 6**		Zanubruinib and ibrutinib: Generalised gamma model fit on pooled zanubrutinb + ibrutinib population using PFS data
*The EAG's first scenario analysis for TTD used the best fitting model on the observed TTD KM data from the pooled zanubrutinib and pooled ibrutinib studies separately **The EAG's second scenario analysis for TTD was done by fitting models on a combined zanubrutinib + ibrutinib data for PFS and assumed TTD is equal for both treatment and that PFS = TTD.		

4.2.6.2 Company's survival analysis methods

Survival models were fit to the zanubrutinib and ibrutinib data to extract long-term PFS, OS, and TTD estimates, up to 20 years, by the company. The company did not have access to the KM IPD from the any of the three ibrutinib trials that were pooled, therefore the company reconstructed the IPD by digitising the published KM plots and reconstructed the KM IPD in line with the methods of Guyot et al.[49]

Standard parametric models were fit to the observed KM data from the zanubrutinib trials and the reconstructed KM data of the pooled ibrutinib trials. These are fit from time zero until the end of the study and beyond to extrapolate expected survival up

to 20 years. The parametric models fitted were the exponential, Weibull, log-normal, log-logistic, Gompertz, and generalised gamma models.

The EAG asked the company during the clarifications stage whether they considered flexible models, such as splines or piecewise models. The company responded in clarification response B4 that they were considered, however maintain that the parametric models used in the economic base case provide reasonable fit, and that in the instances where the curves pass below the zanubrutinib KM data, this means that the company's parametric models are underestimating survival, therefore providing conservative estimates. Furthermore, the company did not add functionality to their economic model to allow the use of flexible models in their response to clarification B5.

4.2.6.3 Company's assumptions and model fit

Model fit was based on criteria in line with NICE Decision Support Unit Technical Support Document 14. This included an assessment of proportional hazards using Schoenfeld's residuals, time-dependent hazard ratio, and cumulative hazard plots, visual fit to the Kaplan-Meier plot, and goodness-of-fit statistics (Akaike information criterion (AIC) and Bayesian information criterion (BIC)). Additionally, the underlying hazard functions and the clinical plausibility of the extrapolated outcomes were evaluated. Other good-fitting models were included in scenario analyses.

The company performed an assessment of proportional hazards (PH) and presented the results in Figure 20 of CS B.2.9.6. The plots of the Schoenfeld residuals are reasonably flat and the corresponding p-values of the global Schoenfeld test are greater than 0.05, suggesting that the proportional hazards assumption was not violated. Conversely, the cumulative log-log plots for zanubrutinib and ibrutinib cross more than once for each outcome, suggesting a violation of the PH assumption. Since one of the tests concluded a violation of the PH assumption, the company fitted separate models to each treatment for each outcome.

It should be noted that the company presented the sum of AIC and BIC, however it is not appropriate to sum them as this gives them equal weighting and assumed they measure the same thing while there are subtle differences between the two. The AIC focuses on model fit while penalising complexity, while BIC introduces a stronger penalty for complexity, especially in cases with larger sample sizes. By combining

these values, the company risks misrepresenting the trade-off between model fit and complexity, as each criterion serves slightly different purposes and is sensitive to different factors. Instead, models with low AIC and low BIC should be considered for the base case separately. This would ensure that model selection appropriately balances goodness-of-fit with complexity instead of being influenced by an arbitrary combined metric of goodness-of-fit.

Since the company had the Kaplan-Meier (KM) IPD for the two zanubrutinib studies but not for the pooled ibrutinib studies, they reconstructed the pseudo-IPD by digitising the respective PFS, OS, and time-on-treatment curves for the pooled ibrutinib studies using standard methods for reconstructing IPD.

4.2.6.4 BGB-3111-AU-003 only modelling

The EAG requested the company to rerun the survival modelling using only the BGB-3111-AU-003 study, as this study had UK participants. However, the company later clarified that there were no UK patients in the MCL population (clarification A3). The company responded to clarification question B3 that only an unadjusted comparison was included due to the study already having a low sample size, thus an adjusted comparison will decrease the ESS further. The company provided the KM plots for this comparison in Section B.2.9.5 in the CS. At clarification the Company provided parametric survival analysis of the unadjusted BGB-3111-AU-003 data (B12)."

The EAG does not anticipate a difference in conclusions from the economic model if only this data was used (such as in a scenario analysis), but since the results of the ITC analyses using this study only has borderline significant for PFS and not significant for OS, survival estimates for zanubrutinib and ibrutinib would be closer, reducing the ICER.

4.2.6.5 EAG's critique and key concerns

Poor visual fit for parametric models to observed Kaplan-Meier (KM) data

The company presented the parametric survival curves with the KM plots for PFS and OS overlaid for each treatment and outcome. These were presented in CS document B Figure 24 for zanubrutinib PFS-INV, Figure 26 for ibrutinib PFS, Figure

28 for zanubrutinib OS, and Figure 30 for ibrutinib OS (with zanubrutinib weighted to the ibrutinib population in Figures 24 and 28).

In the EAG's opinion, the parametric curves show acceptable visual fit to the observed KM data for ibrutinib OS only, the remaining three figures do not. This issue is more significant in the two zanubrutinib figures. In the PFS figure (Figure 24 of CS), all the curves underestimate PFS for the majority of the observed trial period, while in the OS figure (Figure 28 of CS), all the parametric curves underestimate OS around halfway during the observed trial period. Additionally, due to the nature of the parametric models, they are unable to deal with the sudden changes in slope well, both in the KM and the hazard plots.

Flexible models

The above limitation regarding poor parametric fit suggests that the company's choice of parametric models may not be the most appropriate for capturing the complex hazard functions observed in the trial data. The poor visual fit, particularly for zanubrutinib, indicates that the parametric models fail to adequately reflect the underlying survival trends, leading to potential biases in long-term extrapolations.

Given these limitations, the company should have presented the results of using flexible modelling approaches in their submission and considered them for use in their economic model, since they can better accommodate changes in hazard over time.

Long-term survival plausibility

Another concern with the company's survival modelling approach is the time horizon used for assessing the plausibility of long-term survival estimates. The company evaluated survival predictions at 5, 10, and 20 years; however, based on input from the EAG's clinical expert, this approach is not appropriate for this disease area and felt that considering survival estimates beyond 5 years—let alone 10 or 20 years—is not clinically meaningful.

This is supported by the zanubrutinib trial data, where the median follow-up for PFS and OS is approximately 35–39 months, and the median PFS was 33 months for BGB-3111-206. While the median OS was not reached, the available data do not justify reliable projections extending to 10 or 20 years. Given the aggressive nature

of R/R MCL, long-term extrapolations over such extended periods introduce significant uncertainty and may not provide a realistic basis for decision making. Instead, the focus should be on more clinically relevant time points, such as two to five years, which align with expert opinion and better reflect the expected disease course in this population.

Assessment of the Proportional Hazards assumption for PFS and OS

As mentioned above, the company performed an assessment of the PH assumption and concluded that, due to different conclusions by different tests, it would be appropriate to fit different curves to each treatment. In general, when the results of PH assumption tests are inconclusive or result in different conclusions, it is appropriate to fit separate models for each treatment and outcome. Despite this, the company chose the same parametric distribution (log-normal) for all models in the base case. This decision implies an implicit assumption of a common hazard shape between the treatments, which does not fully address the non-proportionality suggested by the cumulative log-log plots. By constraining all models to follow the same hazard function form, the company may have limited the flexibility of the extrapolation and potentially introduced biases in long-term survival estimates. The EAG feels this is, in part, a key limitation of the company's modelling approach which only considered parametric models and did not consider flexible models.

Potential issue: Time to treatment discontinuation (TTD)

The company assumed that TTD is equal to PFS for both treatments, based on clinical validation from an advisory board (November 2024). This assumption was made to address the poor fit of the TTD extrapolations from the parametric survival models to the observed TTD KM and the company justified this decision by stating that it is reasonable to assume patients would remain on treatment until disease progression. However, this may not necessarily reflect real-world practice and treatment patterns. Patients may discontinue treatment before progression due to adverse events, intolerance to treatment, clinical discretion, or other reasons. Thus, assuming that TTD equals PFS may overestimate treatment duration and costs, especially so if non-progression-related discontinuations are common in practice.

However, according to the EAG's experts, the observed KM data for the pooled ibrutinib studies are pessimistic and unrealistic in real practice. Patients are likely to

stay on ibrutinib compared to other drugs in other settings, and since it is effective, would expect the TTD for ibrutinib to be closer to that of zanubrutinib, and certainly longer than the three years as observed in Rule et al.

Considering the EAG experts' input, the EAG stayed consistent with the assumption used in the company's TTD base case and performed two scenario analyses. The first was modelling on the observed KM data on the pooled zanubrutinib and ibrutinib studies. The second was by pooling the reconstructed PFS KM data of zanubrutinib and ibrutinib and selecting the best-fitting curve based on this new pooled data, assuming equal TTD between treatments. This approach is in line with the EAG expert's view that time on ibrutinib and zanubrutinib should be similar.

Minor issue: Multiplicity

The EAG asked the company during the clarification stage if they had considered multiple testing and the issue of inflating type I error (false positive), specifically in the ITC analyses. The company considered it a low risk due to there being one comparator and two outcomes (more if including the TEAEs MAIC), the results of the ITC demonstrating strong statistical significance, and since PFS and OS are highly correlated.

In the EAG's view, while the risk of multiplicity is lower in simple ITCs, adjustments should still be done when considering statistical significance. The correlation between PFS and OS does not guarantee that the treatment effects will be identical. However, since the results of the sensitivity analyses support the company's claim that the results are robust to different assumptions, it is reasonable to assume it is not an issue in this case.

4.2.6.6 EAG's survival analysis methods

In the absence of readily available KM IPD for either treatment, the EAG digitised the PFS and OS KM plots of these studies to generate pseudo-IPD. These plots were taken from the following locations:

- Zanubrutinib PFS-INV: weighted zanubrutinib curve (in blue) from CS B.2.9.5 Figure 18
- Zanubrutinib OS: weighted zanubrutinib curve (in blue) from CS B.2.9.5 Figure 19

- Ibrutinib PFS: Figure 1 (left) from the Rule et al. 2017 publication
- Ibrutinib OS: Figure 1 (right) from the Rule et al. 2017 publication
- Zanubrutinib TTD: Figure 4 in the company's clarification response to question B2 (for scenario analysis)
- Ibrutinib TTD: Figure 44 (page 299 of 339 of company evidence submission) of 'Ibrutinib for treating relapsed or refractory mantle cell lymphoma [ID753]' committee papers (for scenario analysis)

The EAG considered the company's fitted models, namely the zanubrutinib models presented in Figure 34, Figure 35, and Figure 36 of CS B.3.3.5, were poor visual fits compared to the adjusted KM data (raw KM data for TTD). Therefore, the EAG explored fitting spline models to the zanubrutinib KM data. The EAG also considered piecewise models which use the observed KM data up to a cut-off point in the data, after which survival models are fit. However, the EAG did not fit piecewise models as fitting piecewise models to the adjusted zanubrutinib population means reducing an already small cohort further. Although this is only an issue for zanubrutinib, the EAG did not fit piecewise models to ibrutinib data for consistency.

To reconstruct the IPD, the EAG used the 'ipdfc' package in STATA SE 18 (64-bit) to reconstruct the pseudo-IPD and fit the survival models in R version 4.4.2 using the 'flexsurv' package.

Reconstructed KM pseudo-IPD may vary slightly due to differences in individual practice in digitisation precision, and use of different software packages, and reconstruction methods, resulting in similar but not identical outcomes compared to the results presented. The optimum method would be to use the observed KM IPD, however this was not available to the EAG for any of the treatments and was only available to the company for zanubrutinib. The company provided a table in response to clarification question B1 detailing the accuracy of their digitising to the observed ibrutinib data and compared to the EAG's reconstructions these were all similar. Thus, any impact on the extrapolations is likely to be minimal.

Table 28 lists the potential models chosen as the EAG's preferred models for each treatment and outcome. In all cases, the potential models were chosen based on good statistical and visual fit to both KM and hazard plots. These potential models were then judged by how plausible the long-term survival extrapolations were

compared to the EAG's clinical experts' opinions. In cases where multiple models were reasonable and resulted in similar estimates, the simpler of the models were chosen.

4.2.6.7 EAG's assumptions and model fit

The EAG tested the PH assumption using the same test of Schoenfeld's residuals and global test and found the PH assumption not violated. However, assessing the PH assumption using cumulative log-log plots (for OS only) and time-dependent covariates resulted in sufficient evidence to reject the PH assumption. Since the tests resulted in opposing conclusions regarding proportional hazards, the EAG fit separate models to each treatment. The results of the PH tests are presented in Appendix Table 53 for PFS and Table 54 for OS.

4.2.6.8 EAG's potential model choice

Table 28 presents the models investigated as potential EAG base case models, and a justification for those choices.

Table 28: EAG's justification for chosen model

Treatment, outcome	Potential models	Justification
For base case analyses		
Zanubrutinib, PFS (also used for TTD)	Log-normal Log-logistic Generalised gamma 1-knot hazards 1-knot odds 1-knot normal 2-knot hazards 2-knot odds **2-knot normal**	**Parametric model fit**: all models acceptable fit **Parametric model hazards**: log-normal, log-logistic, and generalised gamma follow general shape of observed hazards **Spline model fit**: higher knot models fit best **Spline model hazards**: 1- and 2-knot models follow shape of observed hazards best **Statistical fit**: all models well-fitting
Zanubrutinib, OS	Exponential Weibull Log-normal Log-logistic Gompertz Gamma 1-knot hazards 1-knot odds **1-knot normal**	**Parametric model fit**: acceptable fit, though these curves underestimate OS at certain periods during the trials **Parametric model hazards**: models follow general trend of hazards except the sudden increase of hazards around 35 months **Spline model fit**: better visual fit but still issue with underestimating OS at certain points **Spline model hazards**: spline hazards follow trend and >1-knot models somewhat accounts for sudden jump in observed hazards **Statistical fit**: Exponential model best, all but 3-knot spline models acceptable in terms of AIC, while all parametric models except generalised gamma acceptable for BIC also
Ibrutinib, PFS (also used for TTD)	2-knot hazards **2-knot odds** 2-knot normal	**Parametric model fit**: overall poor fit **Parametric model hazards**: only generalised gamma fits observed hazards up to 10 months, after which all models have poor fit **Spline model fit**: >1-knot models show good visual fit **Spline model hazards**: >1-knot spline hazards show better fit to observed hazards, but still issue after 10 months **Statistical fit**: 2-knot normal spline model best, >1-knot spline and generalised gamma models also acceptable
Ibrutinib, OS	Generalised gamma 1-knot normal **2-knot normal** 3-knot normal	**Parametric model fit**: generalised gamma and Gompertz model acceptable fit **Parametric model hazards**: generalised gamma and Gompertz

		models fit well until the sudden drop in observed hazards around 25 months **Spline model fit**: all models visually fit the observed data well **Spline model hazards**: better fit to observed hazards but issue post-25 months remains **Statistical fit**: generalised gamma model best fit, normal splines models also acceptable
For TTD Scenarios		
Zanubrutinib, TTD	3-knot hazards 3-knot odds **3-knot normal**	**Parametric model fit**: poor visual fit **Parametric model hazards**: all models poor fit **Spline model fit**: 3-knot models good fit except for bump in KM plot around 30 to 40 months **Spline model hazards**: 3-knot hazard models best fit **Statistical fit**: 3-knot normal model has lowest AIC and lowest BIC, other 3-knot models also good fit
Ibrutinib, TTD	**3-knot hazards**	**Parametric model fit**: poor fit **Parametric model hazards**: poor fit **Spline model fit**: 3-knot models good fit, though underestimates TTD after 2 years **Spline model hazards**: 2- and 3-knot hazard models reasonable fit during trial length **Statistical fit**: 3-knot hazard has lowest AIC and BIC; no other models are good-fitting
Zanubrutinib and ibrutinib PFS combined	**Generalised gamma** 3-knot hazards 2-knot odds 3-knot odds 2-knot normal 3-knot normal	**Parametric model fit**: Log-normal, log-logistic, Gompertz. And generalised gamma model good fit **Parametric model hazards**: same models above good fit **Spline model fit**: all good fit, higher-knot models better fits **Spline model hazards**: higher-knot models fit well but 1-knot models able closer to hazards after around 25 months **Statistical fit**: 2-knot normal model best fitting. 2- and 3-knot odds model, 3-knot normal, 3-knot hazards, and generalised gamma also acceptable.
Chosen model denoted in **bold**		

4.2.6.9 Company and EAG curves

This section plots the EAG's preferred curves with the company's preferred curves to compare the survival estimates.

4.2.6.10 EAG's and company's base case curves

Figure 5, Figure 6 and Figure 7 present the EAG's and Company's base case

Figure 5: EAG's and company's preferred PFS curves

Figure 6: EAG's and company’s preferred OS curves

Figure 7. EAG's and company's preferred TTD curves

4.2.6.11 EAG's base case and scenario models

Figure 8,

Figure 9 and

Figure 10 presents the EAG's base case and scenario analysis models overlaying

Figure 8: EAG's preferred and scenario PFS curves

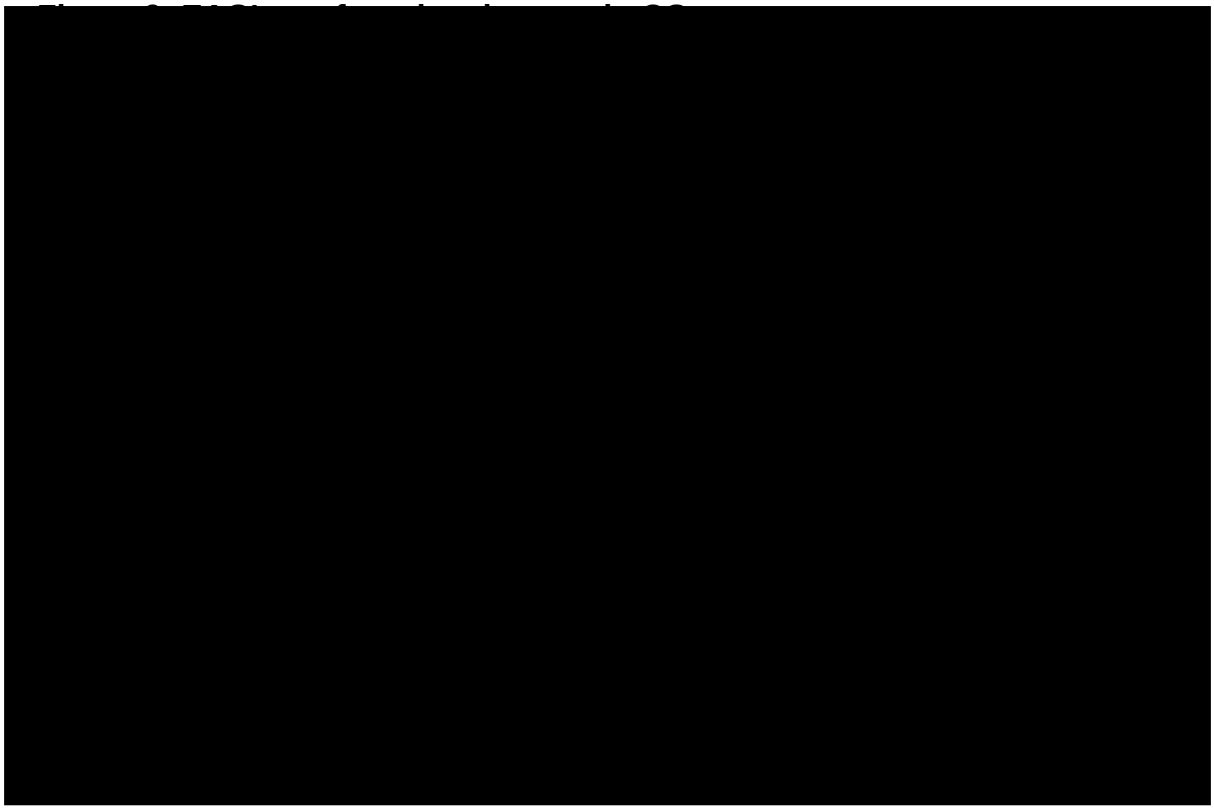

Figure 10. EAG's preferred and scenario TTD curves

4.2.6.12 All base case and scenario analysis models

Figure 11,

Figure 12 and Figure 13 present all of the EAG's and company's models for each outcome.

Figure 13. All the EAG and company models for TTD

Figure 11: All the EAG and company models for PFS

Figure 12: All the EAG and company models for OS

Figure 13. All the EAG and company models for TTD

4.2.7 Health related quality of life

HRQoL was sourced from NICE TA502 via a SLR as no HRQoL data were collected for patients with R/R MCL within the zanubrutinib clinical trials (BGB-3111-AU-003 and BGB-3111-206).

4.2.7.1 Health-related quality of life data identified in the review

According to the CS, the SLR identified a total of 13 studies which reported health state utility values (HSUVs) associated with patients with R/R MCL in the 2L treatment setting. Among these studies, four different interventions were evaluated: liso-cel (assessed in one study), brexucabtagene autoleucel (brexu-cel) (assessed in seven studies), ibrutinib (assessed in five studies) and acalabrutinib (assessed in one study. Out of these, the company considered the utility values of the studies that evaluated the cost-effectiveness of ibrutinib as most relevant i.e., NICE TA502; Hess 2017; SMC 2016 and CADTH 2016. The utility values from NICE TA502 were chosen in the base case analyses and the rest explored via scenario analyses. A summary of the HRQoL is presented in Table 29.

Table 29: Summary of HRQoL identified through company's SLR

Data source	Patient population	Utility measure	Health state utility value
NICE TA502 2018 (HTA Company submission for ibrutinib)	Adult patients with R/R MCL with at least one prior treatment	Elicitation: EQ-5D data collected in clinical trial Evaluation: EQ-5D-5L	Progression-free survival, value, 95% CI: 0.780 (0.762, 0.799) Post-progression, value (95% CI): 0.680 (0.634, 0.727)
Hess 2017 (article)	Patients with R/R MCL in the RAY trial (MCL3001)	Elicitation: FACT-Lym and EQ-5D-5L questionnaire Evaluation: EQ-5D-5L, UK TTO weights	Mean baseline utility value, (SD): Ibrutinib: 0.7 (0.2) Temsirolimus: 0.7 (0.2)
SMC 2016 (HTA Company submission for ibrutinib)	Adult patients with R/R MCL	Elicitation and evaluation: EQ-5D-5L	Progression-free survival: Ibrutinib: 0.779 PC: 0.730 Post-progression: 0.636
CADTH 2016 (CADTH Pharmacoeconomic review of ibrutinib)	Adult patients with R/R MCL from the MCL3001 trial who had received at least one prior rituximab-containing chemotherapy regimen, had documented relapse or disease progression following the last anti-MCL treatment	Elicitation: EQ-5D-5L Evaluation: EQ-5D-5L using UK TTO value set	Mean baseline utility value (SD): Ibrutinib: 0.7 (±0.2) Temsirolimus: 0.7 (±0.2)

4.2.7.2 Health state utility values

The utility values from NICE TA502[8] were used to inform the health states in the model for zanubrutinib and ibrutinib and utility values from the SMC 2016[19] and Simons 2021[50] studies were tested in scenario analyses (Table 30). However, it is unclear to the EAG why the company explored the utility values from Simons 2021 as this study is not amongst the ones the company considered relevant for this appraisal. Simons et al (2021) did not assess either ibrutinib or zanubrutinib, and the health state utilities obtained from ZUMA-2 trial applied the US tariff; and no PPS utilities were collected in ZUMA 2 but were indirectly derived from NICE TA502.

Table 30: Summary of utility values for the CAE explored in the model

State	Utility value: mean (standard error)	95% CI	Source
Base case health state utilities			
PF	0.78	0.762, 0.799	NICE TA502[8]
PD	0.68	0.634, 0.727	
Scenario analysis of health state utilities			
PF	0.78	NR	SMC 2016 (ibrutinib)[19]
PD	0.64	NR	
Scenario analysis of health state utilities			
PF	0.84	NR	Simons *et al.* (2021)[50]
PD	0.74	NR	

Source: Table 65 (CS)
CEA – cost-effectiveness analysis; CI – confidence interval; NICE – National Institute for Health and Care Excellence; NR – not reported; PD – progressed disease; PF – progression free; SMC – Scottish Medicines Consortium; TA – technology appraisal

- The EAG's clinical advisor noted that using the utility values from the ibrutinib study was a reasonable approach as zanubrutinib is likely to only slightly fare better in the mobility domain of the EQ-5D but not elsewhere

4.2.8 Adverse events applied in economic model and associated disutilities

Section 3.2.7 presents a detailed critique of adverse events data presented in the CS. Of relevance to the cost-effectiveness section is the apparent mismatch between the data used in economic model for BGB-3111-AU-003 (reported in table 60 CS) versus the company's narrative in section B.3.4.5. The company stated that "*AE rates were derived from the BGB-3111-AU-003 study (DCO: December 2021)".* However, the AE data reported in Tam (2021)[27] appear to be from an earlier datacut.

The impact of AEs is captured in the model by taking the average QALY loss due to AEs for each treatment by considering the treatment-specific AE rates and the mean utility decrements associated with these AEs. It was assumed that all AEs occur

within the first cycle only. In NICE TA502, the company did not apply utility decrements due to AEs and argued that this would result in double-counting the QALY loss as the EQ-5D data were collected in the ibrutinib trials and any utility decrement would have been captured in the reporting of EQ-5D data. The EAG and appraising committee of TA502 did not seem to have an issue with this approach.

Adverse event disutilities were sourced from Simons et al 2021.[50] However, Simons et al 2021 cites the source of adverse events as NICE technology appraisal 559,[51] which the EAG note has since been replaced with NICE technology appraisal 872.[52]

Table 31: Adverse events disutilities

Adverse event	Disutility	Duration	Source
Pneumonia	0.15	Assumed to occur in the first cycle only	Simons et al (2021)[50]
Anaemia	0.12		Simons et al (2021)[50]
Neutropenia	0.09		Simons et al (2021)[50]
Thrombocytopenia	0.11		Simons et al (2021)[50]
Neutrophil count decreased	0.15		Simons et al (2021)[50]
Platelet count decreased	0.11		Simons et al (2021)[50]
Atrial fibrillation	0.15		Assumed the same at thrombocytopenia
White blood cell count decreased	0.15		Simons et al (2021)[50]

4.2.9 Resources and costs

The CS provides a detailed report of the costing approach, including the assumptions and sources used to measure and value resource use for zanubrutinib and ibrutinib. The following cost categories were included in the model:

- Drug acquisition and administration costs applied for the duration of treatment
- Health-state unit costs and resource use, irrespective of treatment arm
- The cost of AEs applied as a one-off cost in the first cycle
- End of life costs applied as a one-off cost to patients leaving the PD health state

EAG Comments

- The cost categories included are sufficient to capture the costs associated with treatment for both zanubrutinib and ibrutinib.
- The EAG's clinical advisor commented that AEs are observed within the first 6 months and whilst the company's approach follows previous technology appraisals, applying AE costs within the first cycle is unlikely to capture the 'true' costs of treating adverse events.

Intervention and comparator costs

Drug acquisition costs

The drug acquisition costs for both treatments were based on the dosing regimens detailed in Table 32 below. Dosing schedule for zanubrutinib followed that in BGB-3111-AU-003 and BGB-3111-206 trials (2021 CSR for BGB-3111-AU-003 and 2021 CSR for BGB-3111-206, provided with the CS), whilst the dosing schedule for ibrutinib was as detailed in the Summary of Product Characteristics (SmPC).[53] Unit costs were sourced from the British National Formulary (BNF).[54, 55]

A patient access scheme (PAS), comprising a discount of [redacted] was applied to zanubrutinib's drug acquisition costs i.e., [redacted] (PAS price) per 30-day pack (Table 33). The list price of ibrutinib (£1,430.80 per 7-day pack) was applied in the model.

Table 32: Dosing regimen of treatments included in the economic model

Treatment	Dosing regimen	Source
Zanubrutinib	320 mg once daily (four 80 mg capsules) or 160 mg twice daily (two 80 mg capsules) administered orally until PD or unacceptable toxicity	Zanubrutinib SmPC[17]
Ibrutinib	560 mg once daily administered orally until disease PD or no longer tolerated by the patient	Ibrutinib SmPC[53]

Source: CS Table 63. PD – progressed disease; SmPC – Summary of Product Characteristics

Relative dosing intensity was assumed to be 100% for zanubrutinib, based on data from the two clinical trials.[27, 28] Relative dosing intensity for ibrutinib was 94.21%, based on NICE TA502.[8]

Table 33: Drug package price and cost per cycle

Treatment	Dosage strength	Pack size/vial volume	Administration route	Cost per pack (£)	Cost per cycle (£)
Zanubrutinib	80 mg	120	Oral	[redacted]	[redacted]
Ibrutinib	140 mg	28	Oral	1,430.80	5,723.20

No administration costs were included in analysis for drugs that are administered orally.

Intervention and comparator costs

Subsequent treatments were included in the model as an average one-off cost to patients entering the progressed disease heath state, taking into account the mean duration of treatment, the proportion assumed to use each treatment option (i.e. treatments available at third and subsequent lines of R/R MCL treatment) and the costs. Duration of treatment was assumed similar for both treatments.

The CS stated that data on subsequent therapy use were derived from a UK real-world data set (HMRN) (data reported in [redacted], supplied with

the CS). The company clarified that proportions of patients receiving subsequent therapy was sourced from figure 2 of supplementary appendix to the main report (clarification question B7). The chemotherapy agents included in the subsequent treatment basket were bendamustine + rituximab, high dose cytarabine + rituximab, rituximab monotherapy, chlorambucil + rituximab, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) and FCR (fludarabine, cyclophosphamide and rituximab) (Table 35). The cost of subsequent treatments were modelled as a weighted distribution of these treatments (Table 34) with the drug acquisition and administration cost per course of therapy. The company states that the approach was validated by clinicians who attended the Clinical Advisory Board. Based on the company's clinical experts' opinion, a scenario analysis was conducted exploring the impact of including CAR-T therapy (brexu-cel), as subsequent treatment. This will align with clinical practice if brexu-cel receives positive recommendation following exit from the Cancer Drugs Fund (CDF).[56]

Table 34: Proportion of patients on subsequent treatment in progressed disease state

Treatment	Base case treatment use – not including CAR-T	Scenario analysis: Treatment use – including CAR-T
Bendamustine + Rituximab	[redacted]	[redacted]
High dose cytarabine + Rituximab	[redacted]	[redacted]
Rituximab	[redacted]	[redacted]
Chlorambucil + Rituximab	[redacted]	[redacted]
R-CHOP	[redacted]	[redacted]
FCR	[redacted]	[redacted]
Brexu-cel	[redacted]	9%

The disaggregated drug acquisition and administration costs are shown in Table 35. The total per-patient cost of subsequent treatment (included as a once-off treatment costs at the first cycle) were £26,692.53 in the base case analysis and £57,074.17 for the scenario analysis where subsequent treatment includes CAR-T.

Table 35: Total per patient cost for subsequent treatment (no wastage)

Treatment	Drug acquisition cost per treatment regimen (£)	Drug administration cost per treatment regimen (£)
Bendamustine + Rituximab	32,485.98	9,320.15
High dose cytarabine + Rituximab	7,187.34	14,633.42
Rituximab	1,257.32	2,221.17
Chlorambucil + Rituximab	2,068.47	3,331.76
R-CHOP	6,582.83	13,327.03
FCR	4,983.19	3,331.76
Brexu-cel (plus pre-treatment regimen)[a]	346,980.87	0.00

Source: CS Table 68. [a]Total cost of brexu-cel includes the cost of treatment, pre-treatment regimen and administration as derived from NICE TA893.[120] FCR – fludarabine, cyclophosphamide, rituximab; R-CHOP – rituximab, cyclophosphamide, doxorubicin, vincristine.

Health state unit costs and resource use

Disease-related management costs in the progression-free and progressed disease state were calculated by multiplying the resource use per cycle by the unit cost of each resource item. Resource use was assumed to be similar across treatment arms (Table 36). According to the CS, health state resource use was based on what was previously accepted in TA502. The clinical experts the Company consulted as part of the advisory board (2024) generally agreed with the estimates from NICE TA502. According to TA502, resource use was derived from a clinical survey of one hundred actively practicing NHS haematologists, of which 52 provided complete or partial responses to the survey The survey recorded estimates of resource use for patients who had complete response, partial response, stable disease and were in post-progression state. Mean resource use in the progression free state was calculated by weighting the response rates for ibrutinib and R-chemo according to the distribution of overall response rate.

Table 36: Total resource use per cycle and health state costs used in the company's model

Resource item	Resource use per cycle (cycle = 28days)			EAG's clinical expert opinion
	PF state	PD state	Source	
Full blood count	0.36	0.72	NICE TA502	Reasonable estimate
X-ray	0.06	0.06	NICE TA502	Reasonable estimate
Blood glucose	0.02	0.00	NICE TA502	No reason to undertake one
Lactase dehydrogenase	0.24	0.41	NICE TA502	LDH in progression-free state – every 6 months (0.15) PD – *"No particular reason to do more than one (i.e., do at disease progression, then no reason to do again ever)" i.e., 0.08*
Lymphocyte counts	0.36	0.72	NICE TA502	*Intrinsic part of FBC and so should not be listed as a separate test (this is double counting)*
Bone marrow exam	0.06	0.00	NICE TA502	PF state – *"no reason to do bone marrow in this setting"*
Haematologist	0.36	0.72	NICE TA502	OK for PF state Could be slightly higher for PD state (probably every 4 weeks) therefore 1.0
Inpatient non-surgical/Medical	0.03	0.15	NICE TA502	Reasonable
Biopsy	0.04	0.00	NICE TA502	No reason to do this
Blood transfusion	0.06	0.31	NICE TA502	Reasonable
Platelet infusion	0.00	0.15	NICE TA502	Reasonable
CT scan	0.15	0.15	Clinical expert opinion from advisory board (Advisory Board Report for zanubrutinib monotherapy in	PF State –"*Feels too often. If patient is clinically well no need to do CT scan at all. However common to do one after 4-6 cycles on treatment, then if going well, no need to repeat (maybe after 1 year)".*

Resource item	Resource use per cycle (cycle = 28days)			EAG's clinical expert opinion
	PF state	PD state	Source	
			patients with R/R MCL, provided with the CS)	

NICE TA502[8]

EAG Comments

The company's approach to estimating resource use and costs is reasonable.

The EAG's clinical expert queried some of the resource items and frequencies in the company's mode (comments in Table 36). A scenario analysis was run, reflecting the alternative resource use assumptions as per EAG's clinical expert's opinion.

4.2.10 Summary of company's base case analysis assumptions and inputs

A summary of the company's base case analysis and assumptions is provided in Table 37.

Table 37: Base case analysis inputs and main assumptions

Parameter	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in company submission
Model settings			
Population	Adults with 2L R/R MCL	N/A	B.3.2
Perspective	Payer (UK NHS and PPS)	N/A	
Time horizon	Lifetime (32 years)	N/A	
Proportion males	78.11%	SE: 0.16 (Beta)	
Starting age in model (years)	68	SE: 14 (Gamma)	
Body surface area (m^2)	1.95	SE: 0.00 (Gamma)	
Half-cycle correction	Yes	Fixed	
Discount rate (costs and outcomes)	3.5%	Fixed but varied in scenario analysis	
Clinical parameters			
Efficacy			
PFS – distribution for zanubrutinib	Log-normal	Normal distribution (Cholesky decomposition)	B.3.3
OS – distribution for zanubrutinib	Log-normal		
TTD – distribution for zanubrutinib	Assumed equal to PFS extrapolation		
PFS – distribution for ibrutinib	Log-normal		

Parameter	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in company submission
OS – distribution for ibrutinib	Log-normal		
TTD – distribution for ibrutinib	Assumed equal to PFS extrapolation		
Probability of AE – zanubrutinib			
Pneumonia	[redacted]	SE: [redacted] (Beta)	B.3.4
Anaemia	[redacted]	SE: [redacted] (Beta)	
Neutropenia	[redacted]	SE: [redacted] (Beta)	
Thrombocytopenia	[redacted]	SE: [redacted] (Beta)	
Neutrophil count decreased	[redacted]	SE: [redacted] (Beta)	
Platelet count decreased	[redacted]	SE: [redacted] (Beta)	
Atrial fibrillation	[redacted]	SE: [redacted] (Beta)	
White blood cell count decreased	[redacted]	SE: [redacted] (Beta)	
Probability of AE – ibrutinib			
Pneumonia	8.10%	SE: 0.02 (Beta)	B.3.4
Anaemia	8.90%	SE: 0.02 (Beta)	
Neutropenia	16.80%	SE: 0.03 (Beta)	
Thrombocytopenia	0.00%	SE: 0.00 (Beta)	
Neutrophil count decreased	0.00%	SE: 0.00 (Beta)	
Platelet count decreased	0.00%	SE: 0.00 (Beta)	
Atrial fibrillation	0.00%	SE: 0.01 (Beta)	
White blood cell count decreased	5.10%	SE: 0.00 (Beta)	

Parameter	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in company submission
Health-related quality-of-life parameters			
Health state utilities			
PF	0.78	SE: 0.01	B.3.4
PD	0.68	SE: 0.02	
Pneumonia	0.15	SE: 0.03 (Beta)	B.3.4
Anaemia	0.12	SE: 0.02 (Beta)	
Neutropenia	0.09	SE: 0.02 (Beta)	
Thrombocytopenia	0.11	SE: 0.02 (Beta)	
Neutrophil count decreased	0.15	SE: 0.03 (Beta)	
Platelet count decreased	0.11	SE: 0.02 (Beta)	
Atrial fibrillation	0.15	SE: 0.03 (Beta)	
White blood cell count decreased	0.15	SE: 0.03 (Beta)	
Cost parameters			
Health-state resource use per cycle			
Full blood count	PF: 0.36 PD: 0.72	SE:0.07 (Beta) SE: 0.14 (Beta)	B.3.5
X-ray	PF: 0.06 PD: 0.06	SE: 0.01 (Beta) SE: 0.01 (Beta)	
Blood glucose	PF: 0.02 PD: 0.00	SE: 0.00 (Beta) SE: 0.00 (Beta)	

Parameter	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in company submission
LDH	PF: 0.24 PD: 0.41	SE: 0.05 (Beta) SE: 0.08 (Beta)	
Lymphocyte counts	PF: 0.36 PD: 0.72	SE: 0.07 (Beta) SE: 0.14 (Beta)	
Bone marrow exam	PF: 0.06 PD: 0.00	SE: 0.01 (Beta) SE: 0.00 (Beta)	
Haematologist	PF: 0.36 PD: 0.72	SE: 0.07 (Beta) SE: 0.14 (Beta)	
Inpatient non-surgical/Medical	PF: 0.03 PD: 0.15	SE: 0.01 (Beta) SE: 0.03 (Beta)	
Biopsy	PF: 0.04 PD: 0.00	SE: 0.01 (Beta) SE: 0.00 (Beta)	
Blood transfusion	PF: 0.06 PD: 0.31	SE: 0.01 (Beta) SE: 0.06 (Beta)	
Platelet infusion	PF: 0.00 PD: 0.15	SE: 0.00 (Beta) SE: 0.03 (Beta)	
CT scan	PF: 0.15 PD: 0.15	SE: 0.03 (Beta) SE: 0.03 (Beta)	
Health-state unit costs (£)			
Full blood count	2.94	SE: 0.59 (Gamma)	B.3.5
X-ray	44.13	SE: 8.83 (Gamma)	
Blood glucose	1.73	SE: 0.35 (Gamma)	
LDH	1.73	SE: 0.35 (Gamma)	
Lymphocyte counts	2.94	SE: 0.59 (Gamma)	

Parameter	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in company submission
Bone marrow exam	519.10	SE: 103.82 (Gamma)	
Haematologist	214.86	SE: 42.97 (Gamma)	
Inpatient non-surgical/Medical	4642.68	SE: 928.54 (Gamma)	
Biopsy	2649.49	SE: 529.00 (Gamma)	
Blood transfusion	481.49	SE: 96.30 (Gamma)	
Platelet infusion	481.49	SE: 96.30 (Gamma)	
CT scan	172.32	SE: 34.46 (Gamma)	
End-of-life costs (£)			
Terminal care	10,083.85	SE: 2,016.77 (Gamma)	B.3.5
Adverse event costs (£)			
Pneumonia	3,163.05	SE: 632.61 (Gamma)	B.3.5
Anaemia	594.04	SE: 118.81 (Gamma)	
Neutropenia	626.32	SE: 125.26 (Gamma)	
Thrombocytopenia	658.93	SE: 131.79 (Gamma)	
Neutrophil count decreased	626.32	SE: 125.26 (Gamma)	
Platelet count decreased	626.32	SE: 125.26 (Gamma)	
Atrial fibrillation	729.10	SE: 145.82 (Gamma)	
White blood cell count decreased	626.32	SE: 125.26 (Gamma)	
Treatment acquisition costs (per pack) (£)			
Zanubrutinib cost per pack	[redacted]	Fixed	B.3.5
Ibrutinib cost per pack	1430.80	Fixed	

Parameter	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in company submission
Total costs excluding CAR-T (base-case) – subsequent treatment one-off (£)			
Zanubrutinib – subsequent treatment costs	26,692.53	SE: 5,338.51 (Gamma)	B.3.5
Ibrutinib – subsequent treatment costs	26,692.53	SE: 5,338.51 (Gamma)	
Total costs including CAR-T (scenario analysis) – subsequent treatment one-off (£)			
Zanubrutinib – subsequent treatment costs	57,074.17	SE: 11,414.83 (Gamma)	B.3.5
Ibrutinib – subsequent treatment costs	57,074.17	SE: 11,414.83 (Gamma)	
Proportion per treatment arm – subsequent treatment			
Zanubrutinib – patient proportion receiving subsequent treatment	100%	SE: 20% (Beta)	B.3.5
Ibrutinib – patient proportion receiving subsequent treatment	100%	SE: 20% (Beta)	

4.2.11 Severity

In its submission, the company could not provide evidence that a QALY weighting should be applied for this appraisal. A QALY weight is an additional weight applied to QALY gains for severe diseases. Whether QALY weighting applies depends on the absolute and proportional QALY shortfalls. Absolute shortfall is defined as the number of future QALYs that are lost by people living with the disease and on current standard of care and proportional shortfall is defined as the proportion of future QALYs that are lost by people living with the disease and on current standard of care. For example, if the proportional QALY shortfall is ≥0.95 or absolute QALY shortfall ≥18, the incremental QALYs are multiplied by a weighting of 1.7 (see Table 38 below).

Table 38: QALY weightings for severity

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1	Less than 0.85	Less than 12
X1.2	0.85 to 0.95	12 to 18
X1.7	At least 0.95	At least 18

The company submission (Document B) did not provide any explanation on the company's QALY shortfall analysis though the model included a reference to the QALY shortfall calculator. The EAG was unable to replicate the values shown in the model but performed an independent analysis which resulted in the same conclusion that QALY weighting does not apply for this appraisal

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The discounted life years gained (LYG) and quality adjust life years (QALYs), total and incremental costs, between zanubrutinib and ibrutinib are presented in Table 39 and Table 40 for deterministic and probabilistic analyses respectively. The results presented are for the company's revised base case post-clarifications, amended to

reflect the updated haematologist visit cost (in response to clarification question B9). The revised base case resulted in a minor change in incremental costs [redacted]).

Table 39: Updated base-case deterministic results in patients with 2L R/R MCL (PAS price)[a]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Zanubrutinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

[a]Base case updated based on response to B9 (updated resource use unit cost). ICER – incremental cost-effectiveness ratio; LYG – life years gained; MCL – mantle cell lymphoma; PAS – patient access scheme; QALYs – quality-adjusted life years; R/R – relapsed or refractory

5.1 Company's sensitivity analyses

Uncertainty was explored via probabilistic sensitivity analysis, scenario analyses and univariate sensitivity analyses.

One thousand simulations were performed for the PSA, allowing values to be randomly drawn for each variable, for every simulation. The results of the PSA are shown in Table 40 below. The corresponding incremental cost-effectiveness scatterplot and cost-effectiveness acceptability curves are shown in Figure 14 and Figure 15 below. The scatterplot shows that the majority of iterations fall within the South-East quadrant indicating that zanubrutinib is both less costly and more effective than ibrutinib at a WTP threshold of £30,000 per QALY.

Table 40: Base-case PSA results in patients with 2L R/R MCL

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Zanubrutinib	[redacted]	[redacted]	-	-	-
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

ICER – incremental cost-effectiveness ratio; MCL – mantle cell lymphoma; QALYs – quality-adjusted life years; PSA – probabilistic sensitivity analysis; R/R – relapsed or refractory

Figure 14: Cost-effectiveness scatterplot for zanubrutinib vs ibrutinib in patients with 2L R/R MCL

ICEP – incremental cost-effectiveness plane; MCL – mantle cell lymphoma; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life year; R/R – relapsed or refractory

Figure 15: PSA CEAC for zanubrutinib vs ibrutinib in patients with 2L R/R MCL

CEAC – cost-effectiveness acceptability curve; MCL – mantle cell lymphoma; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life year; R/R – relapsed or refractory

Univariate sensitivity analysis was performed for each parameter in the model. The analysis was performed for each parameter and results presented using a tornado diagram showing its impact on NMB at a threshold of £30,000 per QALY as shown in Table 41 and Figure 16.

Table 41: Univariate sensitivity results (NMB at WTP £30,000) for zanubrutinib vs ibrutinib in patients with 2L R/R MCL

Parameter name	Lower bound NMB	Upper bound NMB
[redacted]	[redacted]	[redacted]

DSA – deterministic sensitivity analyses; MCL – mantle cell lymphoma; NMB – net monetary benefit; OS – overall survival; PD – progressed disease; PFS – progression-free survival; R/R – relapsed or refractory; RU – resource use; TTD – time-to-treatment discontinuation; WTP – willingness to pay threshold

Figure 16: Tornado plot of DSA results (NMB) for zanubrutinib vs ibrutinib in patients with 2L R/R MCL

The company presented a range of scenario analysis including the sensitivity of cost-effectiveness estimates to alternative parametric distributions, alternative health state utility sources, impact of using different method to assess PFS, using an earlier data cut for efficacy data, including CAR-T as subsequent therapy (Table 42). At clarification, the company also provided scenario analyses using the 2L only population of the zanubrutinib trials and data from BGB-3111-AU-003 trial only (Clarification question B12).

Table 42: Summary of scenario analyses

Base-case	Scenario analysis	Rationale
3.5% discount rate	No discounting	0% discount is assumed for costs to assess the impact of discounting
3.5% discount rate	High discount rates (6%)	6% discount is assumed for costs to assess the impact of discounting
Time horizon: lifetime (32 years)	Time horizon: 20 years	To explore the impact of shortening the time horizon
PFS, OS and TTD from pooled zanubrutinib trials (BGB-3111-AU-003 [DCO: 31Mar2021]) and BGB-3111-206 [DCO: 08Sept2020]), ESS=[redacted]) adjusted through a MAIC to Rule et al. (2017b) (N=370)	PFS, OS and TTD from pooled zanubrutinib trials, **from an earlier data cut** (BGB-3111-AU-003 [DCO: Dec 13, 2018]) and BGB-3111-206 [DCO: Aug 31, 2019]), ESS=[redacted]) adjusted through a MAIC to Rule et al. (2017b) (N=370)	To explore the impact of using an earlier data cut and a different method of assessing PFS (IRC vs. INV).
	PFS, OS and TTD from pooled zanubrutinib trials, **excluding rituximab-naïve patients (ESS=[redacted])** vs. ibrutinib-pooled (n=370) (Rule 2017b)	To explore the impact of removing patients who are less generalisable to UK clinical practice.
	PFS, OS and TTD from **206-only (n=[redacted])** adjusted through a MAIC to Rule et al. (2017b) (N=370)	To explore the impact of removing the AU-003 trial.
PFS distribution: Zanubrutinib (log-normal) Ibrutinib (log-normal)	PFS distribution: Zanubrutinib (log-logistic) Ibrutinib (log-logistic)	To explore the impact of alternative PFS extrapolations
	PFS distribution: Zanubrutinib (generalised gamma) Ibrutinib (generalised gamma)	
OS distribution: Zanubrutinib (log-normal) Ibrutinib (log-normal)	OS distribution: Zanubrutinib (log-logistic) Ibrutinib (log-logistic)	To explore the impact of alternative OS extrapolations
	OS distribution: Zanubrutinib (generalised	

Base-case	Scenario analysis	Rationale
	gamma) Ibrutinib (generalised gamma)	
TTD assumption: TTD is equal to PFS for zanubrutinib and ibrutinib	TTD is equal to the KM data	To explore the impact of alternative TTD data
Utility values: NICE TA502	SMC ibrutinib (2016)	To explore the impact of alternative utility assumptions
	Simons et al. (2021)[50]	
Subsequent treatment costs: Included	Subsequent treatment costs: Excluded	To explore the impact of subsequent treatments
	CAR-T therapy included	To explore the impact of greater subsequent treatment costs

CAR-T – chimeric antigen receptor T-cell; DCO – data cut off; NICE – National Institute for Health and Care Excellence; OS- overall survival; PFS – progression-free survival; SMC – Scottish Medicines Consortium

Table 43: Summary of scenario analyses results for zanubrutinib: deterministic

Scenario analysis	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER/QALY (£)
Base case	[redacted]	[redacted]	[redacted]	Dominating
No discounting	[redacted]	[redacted]	[redacted]	Dominating
High discount rates (6%)	[redacted]	[redacted]	[redacted]	Dominating
Time horizon: 20 years	[redacted]	[redacted]	[redacted]	Dominating
PFS, OS and TTD from pooled zanubrutinib trials, **from an earlier data cut** (BGB-3111-AU-003 [DCO: Dec 13, 2018]) and BGB-3111-206 [DCO: Aug 31, 2019]), ESS=[redacted]) adjusted through a MAIC to Rule et al. (2017b) (N=370)	[redacted]	[redacted]	[redacted]	Dominating
PFS, OS and TTD from pooled zanubrutinib trials, **excluding rituximab-naïve patients (ESS=[redacted])** vs. ibrutinib-pooled (n=370) (Rule 2017b)	[redacted]	[redacted]	[redacted]	Dominating
PFS, OS and TTD from **206-only (n=[redacted])** adjusted through a MAIC to Rule et al. (2017b) (N=370)	[redacted]	[redacted]	[redacted]	Dominating
PFS distribution: Zanubrutinib (log-logistic) Ibrutinib (log-logistic)	[redacted]	[redacted]	[redacted]	Dominating
PFS distribution: Zanubrutinib (generalised gamma) Ibrutinib	[redacted]	[redacted]	[redacted]	Dominating

Scenario analysis	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER/QALY (£)
(generalised gamma)				
OS distribution: Zanubrutinib (log-logistic) Ibrutinib (log-logistic)	[redacted]	[redacted]	[redacted]	Dominating
OS distribution: Zanubrutinib (generalised gamma) Ibrutinib (generalised gamma)	[redacted]	[redacted]	[redacted]	Dominating
Zanubrutinib and ibrutinib TTD is equal to the KM data	[redacted]	[redacted]	[redacted]	Dominating
Alternative utility value: SMC 2016[19]	[redacted]	[redacted]	[redacted]	Dominating
Alternative utility value: Simons et al. 2021[50]	[redacted]	[redacted]	[redacted]	Dominating
Subsequent treatment costs: Excluded	[redacted]	[redacted]	[redacted]	Dominating
Subsequent treatment costs: CAR-T included	[redacted]	[redacted]	[redacted]	Dominating

CAR-T - chimeric antigen receptor T-cell; DCO – data cut off; ICER – incremental cost-effectiveness ratio; LYG – life years gained; OS- overall survival; PFS – progression-free survival; SMC – Scottish Medicines Consortium; QALY – quality adjusted life year

Table 44: Summary of scenario analyses results for zanubrutinib vs ibrutinib - probabilistic

Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER/QALY (£)
Base case	[redacted]	[redacted]	Dominating
No discounting	[redacted]	[redacted]	Dominating
High discount rates (6%)	[redacted]	[redacted]	Dominating
Time horizon: 20 years	[redacted]	[redacted]	Dominating
PFS, OS and TTD from pooled zanubrutinib trials, **from an earlier data cut** (BGB-3111-AU-003 [DCO: Dec 13, 2018]) and BGB-3111-206 [DCO: Aug 31, 2019]), ESS=[redacted]) adjusted through a MAIC to Rule et al. (2017b) (N=370)	[redacted]	[redacted]	Dominating
PFS, OS and TTD from pooled zanubrutinib trials, **excluding rituximab-naïve patients (ESS=[redacted])** vs. ibrutinib-pooled (n=370) (Rule 2017b)	[redacted]	[redacted]	Dominating
PFS, OS and TTD from **206-only (n=[redacted])** adjusted through a MAIC to Rule et al. (2017b) (N=370)	[redacted]	[redacted]	Dominating
PFS distribution: Zanubrutinib (log-logistic) Ibrutinib (log-logistic)	[redacted]	[redacted]	Dominating
PFS distribution: Zanubrutinib (generalised gamma) Ibrutinib	[redacted]	[redacted]	Dominating

Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER/QALY (£)
(generalised gamma)			
OS distribution: Zanubrutinib (log-logistic) Ibrutinib (log-logistic)	[redacted]	[redacted]	Dominating
OS distribution: Zanubrutinib (generalised gamma) Ibrutinib (generalised gamma)	[redacted]	[redacted]	Dominating
Zanubrutinib and ibrutinib TTD is equal to the KM data	[redacted]	[redacted]	Dominating
Alternative utility value: SMC 2016	[redacted]	[redacted]	Dominating
Alternative utility value: Simons et al. 2016	[redacted]	[redacted]	Dominating
Subsequent treatment costs: Excluded	[redacted]	[redacted]	Dominating
Subsequent treatment costs: CAR-T included	[redacted]	[redacted]	Dominating

CAR-T - chimeric antigen receptor T-cell; DCO – data cut off; ICER – incremental cost-effectiveness ratio; LYG – life years gained; OS- overall survival; PFS – progression-free survival; SMC – Scottish Medicines Consortium; QALY – quality adjusted life year

Table 45: Scenario deterministic results (2L-only population) using the company's updated base case*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Zanubrutinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

2L – second-line; ICER – incremental cost-effectiveness ratio; LYG – life years gained; MCL – mantle cell lymphoma; QALYs – quality-adjusted life years; R/R – relapsed or refractory
*Base case updated based on response to B9 (updated resource use unit cost)

Whilst acknowledging the limitations of the 2L analysis, notably a smaller sample size (n=44), which affects robustness of MAIC analysis, the results of the 2L subgroup analysis provided during clarification are important for this appraisal as the target population for this assessment is adults with 2L R/R MCL. The results indicate that QALY gains are significantly reduced when the efficacy inputs are based on the 2L only population of the pooled zanubrutinib trials (i.e., [redacted] incremental QALYs for 2L only population vs. [redacted] QALYs for base case). The company highlighted the limitations of the analysis in clarification response B12 i.e., small sample size, ibrutinib data source used which had limited covariates for matching in MAIC analysis. Whilst the EAG agrees that these factors impact on the robustness of analysis, it could not explore whether differences in QALY gains could also be partly explained by the differing baseline characteristics and indeed efficacy results of the 2L only vs. >2L population. The EAG requested the baseline statistics for the >2L subgroup but the company declined to provide these stating that the request fell outside the proposed scope. As such, any bias either in favour of, or against that inclusion of >2L subgroup could not be explored.

Thus, whilst the EAG agree that the results should be interpreted with caution, we maintain that the results highlight the uncertainty with the base case analysis, owing to amongst other things, choice of efficacy inputs used.

Table 46: Scenario deterministic results (BGB-3111-AU-003 only adjusted) using the company's updated base case*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Zanubrutinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

ICER – incremental cost-effectiveness ratio; LYG – life years gained; MCL – mantle cell lymphoma; QALYs – quality-adjusted life years; R/R – relapsed or refractory
*Base-case updated based on response to B9 (updated resource use unit cost)

Using data from the BGB-3111-AU-003 only study, also had a significant impact on QALY gains. The company offers similar explanation to the 2L-only subgroup analysis on why these results need to be interpreted cautiously. It's worth noting, that base-case cost-effectiveness results using the BGB-3111-206 only population (conducted in China), showed [redacted] QALY gains for that scenario.

EAG Comments

- The EAG notes that although the overall cost-effectiveness conclusions for the scenario analyses remain similar to the company's base case analysis (Table 43; Table 44; Table 45; Table 46), the QALY estimates were most sensitive to the choice of parametric curves chosen for both PFS and OS for the two treatments, the data source used (BGB-3111-206 or BGB-3111-AU-003 only) vs. pooled zanubrutinib trial population and also the subgroup population (2L only) vs full trial population (≥2L) from the pooled zanubrutinib trials.

5.1.1.1 Cost-comparison analysis

The company conducted a cost-comparison analysis, assuming equal efficacy for both treatment arms and specifically that PFS, OS and AE rates observed will be as reported for the pooled zanubrutinib trials. At zanubrutinib PAS price, and ibrutinib list price, the results showed that zanubrutinib is associated with a savings of £[redacted] over a lifetime horizon.

EAG Comments

- As a scenario analysis, the company's approach to cost-comparison analysis appears reasonable.
- Cost-comparison analysis is likely the most appropriate analytical approach for this appraisal.
    - Feedback from the EAG clinical expert was that LYG for zanubrutinib reported in the CS appear overly optimistic, particularly considering the

duration of follow-up in the trials. The EAG clinical expert's opinion indicated that LYG are likely similar for both treatments. Furthermore, it was highlighted that health-related quality of life benefits (as measured by the EQ-5D instrument) are likely to be similar across the EQ-5D domains except for mobility, which would be expected to be better for zanubrutinib. The EAG's exploratory analyses (section 0) indicate the cost-effectiveness analysis is subject to significant uncertainty and QALY gains are very likely overly estimated for zanubrutinib but unlikely to be [redacted] than that of ibrutinib.

  - It is important to note that the cost-comparison analysis may bias against zanubrutinib in terms of adverse event treatment-related costs as zanubrutinib appears to have a better safety profile as emphasized by the clinical experts.

- A more robust cost-comparison analysis, that explores varying assumptions may provide a better indication of the cost-savings associated with zanubrutinib.

5.1.2 Model validation and face validity check

The EAG conducted an extensive review of the model submitted by the company. The model appears to reflect the assumptions made by the company and contained clinical aspects necessary to address the decision problem. The EAG sought clinical validation of (i) the model assumptions (both EAG and company's) and (ii) model's output ((LYG, QALYs) and relevant economic outcomes (e.g., treatment costs)).

6 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

Table 47 summarises the main issues highlighted by the EAG throughout this report that could impact zanubrutinib's cost-effectiveness. It shows the expected direction of bias introduced by these issues and whether these are examined in any exploratory analyses or incorporated in the EAG base-case.

Table 47: Main EAG critique of company's submitted economic evaluation

Issue	Likely direction of bias introduced in costs/QALYs	EAG Analyses	Addressed in company analyses
Population, intervention and comparators, perspective, and time horizon (Section 4.2.3- 4.2.5)			
The baseline characteristics of the modelled population are derived from the comparator treatment and differ markedly from those of the pooled zanubrutinib studies	NA	Scenarios	No
Treatment effectiveness and extrapolation (Section 4.2.6)			
Magnitude of benefit following parametric extrapolation of OS for zanubrutinib not supported by evidence	+	Base-case Scenarios	Scenarios
Potential bias in estimating the proportion of patients remaining on zanubrutinib treatment	+	Scenarios	Yes, different TTD assumption explored
Extrapolation of zanubrutinib OS	+	Base case Scenarios	Yes but no flexible models explored
Extrapolation of zanubrutinib PFS	+	Base Case Scenarios	Yes but no flexible models explored
Extrapolation of ibrutinib PFS	+ and -	Base-case Scenarios	Yes but no flexible models explored
Extrapolation of ibrutinib OS	+ and -	Base-case Scenarios	Yes but no flexible models explored
Extrapolation of TTD	+ and -	Base-case Scenarios	Yes
Adverse events (Section 4.2.8)			
Incidence of grade 3 and 4 adverse events included in model likely underestimate some AEs (e.g., infections) for zanubrutinib due to the short follow-up period; likely to affect HRQoL estimates	+/-	Scenarios	No
Incidence of grade ≥3 AEs for AU-003 trial included in model	+	Base Case	No

likely underestimates AEs as earlier data cut used			

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Based on our critique of the company's economic model, the EAG made changes to the company's model to explore the impact of individual changes to the company's base case results. The suggested changes along with the EAG's justifications are presented below:

- **Using baseline characteristics from the pooled zanubrutinib populations in the model**

  This exploratory analysis draws on our critique of the company's choice of baseline characteristics to include in model given the apparent differences with baseline characteristics used in the model that are based on TA502 (NICE appraisal for ibrutinib)

- **A different approach to extrapolating PFS for both treatment arms**

Section 4.2.6 provided an in-depth justification for EAG's preferred PFS extrapolations to reflect EAG's clinical experts' opinions of what would be a more plausible clinical benefit of the technologies and also the best fitting models according to EAG's assessments.

- **A different approach to extrapolating OS**

This exploratory analysis draws on EAG's clinical experts' opinions of what would be considered a clinically plausible benefit (long-term survival) at different years alongside the EAG's assessment of best fitting models. Detailed critique and justification for model choice are provided in Sections 4.2.6

Briefly, the EAG's experts' opinion indicated that benefit of zanubrutinib was likely overestimated, and they preferred EAG's extrapolations with lower survival beyond 5

years. Therefore, the EAG chose a different approach to the extrapolation of OS as detailed in Table 25, Table 27, and **Error! Reference source not found.**.

- **Exploring uncertainty around some of the resource utilisation estimates in both treatment arms.**

The EAG's clinical experts emphasised that some of the resource use inputs were over/under-reported, particularly haematologist's visits. A scenario analysis was conducted using estimates provided by the EAG's clinical experts (see Table 36).

- **Evaluate the impact of using AE rates from latest DCO for BGB-3111-AU-003.**

In section 4.2.8, it was highlighted that there was an apparent mismatch between the data used in economic model for BGB-3111-AU-003 (reported in table 60 CS) versus the company's narrative in section B.3.4.5. A scenario analysis was conducted using data from the March 2021 datacut to take advantage of the longer-follow up and also match the company's narrative.

- **Explore impact on ICER of including grade ≥3 AEs occurring in ≥2% of population in the economic model**

Section 4.2.8 also highlights that the cost of AEs incorporated into the model may have been underestimated by the company as only the AEs of grade 3+ occurring in ≥ 5% of patients in the trial were included. The EAG conducted an additional scenario analysis on AE to capture grade 3 AEs occurring in ≥2% of the patients. This is in line with previous appraisals (TA963) whereby the appraising committee concluded that given the small sample size, it was appropriate to include the broader range of AEs (those affecting at least 2% of people) in economic analysis.

Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

Table 48 below shows the EAG's main scenario analyses and the impact on costs and QALYs. Since the ICER showed that zanubrutinib [redacted] ibrutinib across all scenarios (i.e., is [redacted], and [redacted]), the impact (percentage change) in QALYs and direction of change in cost-savings for zanubrutinib is shown instead.

Table 48: EAG exploratory analyses

Parameter varied	Base case value	Scenario value	Rationale	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	% change in incremental costs	% change in incremental QALYs
Company base case (post clarifications)				[redacted]	[redacted]	[redacted]		
Baseline characteristics used in economic model	Age = 68 years Percentage males = 78.11 BSA = 1.95	Age = [redacted] years Percentage males= [redacted] BSA = [redacted]	Estimating impact when baseline age is reflective of population in pooled zanubrutinib trials .	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Preferred models/ extrapolation by treatment arm and outcome								
Zanubrutinib PFS	PFS: Log-normal	PFS Scenario 1 *(EAG Base Case):* 2-knot normal	Best fitting model to model long-term survival chosen by EAG experts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		PFS Scenario 2: Log-logistic		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Zanubrutinib OS	OS: Log-normal	OS Scenario 1 *(EAG Base Case):* 1-knot normal	Best fitting to model long-term survival as chosen by EAG experts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		OS Scenario 2: Log-logistic		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Parameter varied	Base case value	Scenario value	Rationale	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	% change in incremental costs	% change in incremental QALYs
Zanubrutinib TTD	TTD = PFS	TTD Scenario 1 (EAG Base Case):	Based on EAG's expert opinion on best fitting to model long-term TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		TTD Scenario 2: 3-knot normal		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		TTD Scenario 3: Generalised gamma model fit on pooled zanubrutinib + ibrutinib population using PFS data		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib PFS	PFS: Log-normal	Scenario 1 PFS (EAG Base Case): 2 knot odds	Best fitting model to long-term estimates chosen by EAG experts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Scenario 2: 2-knot normal		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib OS	OS: Log-normal	Scenario 1 OS (EAG	Best overall fitting model,	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Parameter varied	Base case value	Scenario value	Rationale	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	% change in incremental costs	% change in incremental QALYs
		Base Case): 2-knot normal	selected by EAG's expert					
		Scenario 2: 3-knot normal		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib TTD	TTD =PFS	Scenario 1 (EAG Base Case): PFS=TTD	Based on EAG's expert opinion on best fitting to model long-term TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Scenario 2: 3-knot hazard data		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Scenario 3: Generalised gamma model fit on pooled zanubrutinb + ibrutinib population using PFS		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use frequency per health state in	As per table 65 (CS)	Scenario: As per Table 36 (EAG report)	EAG Clinical expert's opinion.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Parameter varied	Base case value	Scenario value	Rationale	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	% change in incremental costs	% change in incremental QALYs
both treatment arms								
Source of data for adverse events of grade 3+ in ≥ 5% of patients in AU003 trial	Based on Tam (2021) – earlier data cut	Based on latest data cut (Dec 2021) as presented in CS	Align with company's narrative in B.3.4.5 which states use of latest data cut not the earlier data cut subsequently used in model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range of adverse events included in economic model	Grade 3+ AES in ≥ 5% of patients in AU003-206	Grade 3+ AEs in ≥ 2% of patients in AU003-206	To capture clinically important AEs potentially underestimated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.2 EAG's preferred assumptions and revised base case

Based on all considerations in Section 4.2 of this report (summarised in Table 47), the EAG defined a new base case. The adjustments made to the company model are described below and impact on QALYs and incremental costs summarised in Table 49.

Table 49: EAG's preferred model assumptions

Preferred assumption	Section in EAG report	Incremental Costs (Direction of change)	Incremental QALYs (% Change)	Cumulative ICER £/QALY
Company base-case (post-clarification)		[redacted]	[redacted]	[redacted]
Flexible models for modelling PFS, OS, TTD for both zanubrutinib and ibrutinib[1]				
Zanubrutinib				
EAG 01: 2-knot normal to model zanubrutinib PFS	*4.2.6.1*	[redacted]	[redacted]	[redacted]
EAG 02: 1-knot normal to model zanubrutinib OS	*4.2.6.1*	[redacted]	[redacted]	[redacted]
EAG 03: TTD for zanubrutinib assumed equal to PFS	*4.2.6.1*	[redacted]	[redacted]	[redacted]
Ibrutinib				
EAG 04: 2-knot odds to model ibrutinib PFS	*4.2.6.1*	[redacted]	[redacted]	[redacted]
EAG 05: 2-knot normal to model ibrutinib OS	*4.2.6.1*	[redacted]	[redacted]	[redacted]
EAG 06: TTD assumed equal to ibrutinib PFS	*4.2.6.1*	[redacted]	[redacted]	[redacted]
Alternative health state resource use assumptions				

Preferred assumption	Section in EAG report	Incremental Costs (Direction of change)	Incremental QALYs (% Change)	Cumulative ICER £/QALY
Company base-case (post-clarification)		[redacted]	[redacted]	[redacted]
EAG 07[a]: Alternative assumptions on frequency of resource use in the progression-free and progressed diseased state for blood glucose tests, LDH tests, lymphocyte counts, haematologist's visit, biopsy and CT scans. as per EAG's clinical expert's opinion	*4.2.10*	[redacted]	[redacted]	[redacted]
EAG 08[b]: Incidence of adverse events based on December 2021 DCO for AU003 trial	*4.2.8*	[redacted]	[redacted]	[redacted]
Cumulative impact of all changes (EAG01 – EAG08)				

[a] Potential models were all chosen based on good statistical and visual fit to both KM and hazard plots and plausibility of the long-term survival estimates compared to the EAG's clinical experts' opinions. [b]Based on EAG's clinical experts' opinion. [redacted] means zanubrutinib is [redacted] and [redacted] than ibrutinib

[redacted] means in favour of zanubrutinib; converse is true [redacted].

Note: None of the EAG's preferred assumptions resulted in zanubrutinib's lifetime costs being [redacted] than ibrutinib's even for those scenarios were cost-savings were [redacted] compared to company's base case

6.2.1 EAG deterministic base case results

The cumulative effect of all EAG changes on deterministic cost-effectiveness results is shown in Table 50 .

- The EAG emphasises that all EAG analyses are conditional upon the MAIC, for which uncertainty could not be incorporated into the economic model.

Table 50: Deterministic EAG base cost-effectiveness results with zanubrutinib PAS discount

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs of Zanubrutinib (£)	Incremental LYG of Zanubrutinib	Incremental QALYs of Zanubrutinib	ICER (£) of Zanubrutinib (QALYs)
Zanubrutinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Deterministic incremental costs were [redacted] and incremental QALYs were [redacted] which resulted in zanubrutinib [redacted] ibrutinib.

6.2.2 EAG's Probabilistic base case cost-effectiveness results

The EAG's base case was subjected to a probabilistic sensitivity analysis using 10,000 iterations drawn from the EAG parametric assumptions. The probabilistic incremental costs were [redacted] and incremental QALYs were [redacted] resulting in ibrutinib being [redacted]. The probability of zanubrutinib being cost-effective at £30,000 threshold is [redacted]. The EAG's cost-effectiveness scatterplots is presented in Figure 17.

Table 51: Probabilistic EAG base cost-effectiveness results with zanubrutinib PAS discount

	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	Cost per QALY (£)
Zanubrutinib	[redacted]	[redacted]	-	-	-
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 17: Cost-effectiveness scatterplot comparing zanubrutinib to ibrutinib, EAG's base case

6.3 Conclusions of the cost effectiveness section

In summary, the model constructed by the company appears to be logical.

The EAG has the following concerns regarding the cost-effectiveness analysis (as detailed in Section 1.1):

- Uncertainty in the estimates of relative effectiveness of zanubrutinib compared with ibrutinib obtained from the MAIC; the EAG could not quantify the uncertainty in the model.
- Choice of data source to inform efficacy estimates which results in widely varying estimates of QALY gains.
    - This is particularly pronounced for the 2L subgroup analysis where the company's QALY gains are reduced by [redacted]; the EAG acknowledges

limitations of the analysis but maintain the subgroup results provide an indication of the wide uncertainty in company's base case estimates.

- Use of data from ≥2L population of the pooled zanubrutinib trials and not the 2L only population for which the company submission is focussed on; the EAG could not quantify the direction of bias that inclusion of >2L population introduces to the cost-effectiveness estimates.

Other important factors that had an impact on the cost-effectiveness results (either costs or QALYs) included:

- Choice of extrapolations to model PFS, OS and TTD. The company did not explore flexible models which the EAG considered to be the best-fitting models to provide reasonable estimates of long-term survival as per EAG clinical expert's opinion.

- Source of baseline characteristics included in model.

The EAG has presented scenarios with a preferred base-case analysis. The ICER has remained [redacted] for zanubrutinib; the EAG maintains the results should be interpreted with caution due to uncertainty, particularly in the ITC, that could not be quantified in the model.

The company presents a case for a cost-comparison analysis instead of full cost-utility analysis. The EAG believes that a cost-comparison analysis is a reasonable approach for this appraisal as feedback from clinical experts combined with the EAG's own exploratory analyses indicate that LYG and QALY gains are likely similar for both treatments, but it is unlikely that zanubrutinib will be [redacted] than ibrutinib.

7 SEVERITY MODIFIERS

The CS states that the appraisal does not qualify for severity modifiers.

8 REFERENCES

1. Cancer Research UK. *Mantle cell lymphoma*. 2024. URL: https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/types/mantle-cell (Accessed 4 March 2025).

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9 Appendices

9.1 Comparison of company and EAG quality assessment of zanubrutinib studies

Table 52: Critical appraisal of the zanubrutinib studies

Question	Company Assessment	EAG Assessment
BGB-3111-AU-003		
Was the cohort recruited in an acceptable way?	Yes Patients were recruited from six study locations globally based on inclusion and exclusion criteria outlined in CS Table 7.	Yes Patients were recruited from six study locations from (24 sites in 6 countries.). The eligibility criteria were reported in CS Table 7.
Was the exposure accurately measured to minimise bias?	Yes 32 R/R MCL patients in the BGB-3111-AU-003 trial received a total daily dose of 320 mg of zanubrutinib. The median duration of treatment with zanubrutinib was 15.4 months as of the 13th of December 2018 data cut-off. The relative dose intensity was 99.92% for patients with R/R MCL receiving a total daily dose of 320 mg of zanubrutinib.	Yes It was not clearly reported in the CS how many of the 32 patients had participated in Phase 1 of the study and what dose they received in Phase 1. This was explained in clarification response A2.
Was the outcome accurately measured to minimise bias?	Yes Outcomes were accurately measured to minimise bias, as outlined in CS Table 8. Outcomes were assessed using both IRC and INV assessment to validate outcomes where appropriate.	Unclear A direct comparison between INV and IRC assessments is not possible for all IRC assessed outcomes, as outcomes are reported at different time points. Concordance rate was 93.8% for ORR and 71.9% for best overall response. This suggests there may be some bias in assessments.
Have the authors identified all important confounding factors?	Yes All-important confounding factors were considered within pre-planned subgroup analyses. See Section B.2a.6 of the Company Submission for more detail.	Yes The CS reported confounding factors in CS section B.2a.4.2 and provided outcome from subgroup analysis in CS Figure 8. This analysis was in accordance with the preplanned analysis plan.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes Yes, as per the previous question, the confounding factors were identified and taken account for in the analysis.	Yes The confounding factors identified in CS section B.2a.4.2 are analysed in B.2a.7 and in CS Figure 8
Was the follow-up of patients complete?	Yes The BGB-3111-AU-003 trial is complete with no further data cuts planned. The trial design ensured patients were suitably followed up after	Unclear The reasons for patient withdrawal from the study are outlined in CS Table 11 under patient disposition. However, the total number of discontinuations does not sum to 18 (56.3%)

	discontinuation of treatment and/or progression. The median follow-up time for the patients in the R/R MCL population who received 320 mg of zanubrutinib was 18.84 months at a data cut off of 13th December 2018. At the end of treatment, a safety follow-up of 30 ± 7 days after last dose was ensured for both discontinuation due to PD and reasons other than PD. Patients continued efficacy evaluations until PD followed by long-term follow-up for survival every 24 weeks. All patients who discontinued study drug commenced long-term follow-up after progression, which included monitoring for survival status and initiation of new anticancer treatment for MCL and conducting chemistry and haematology assessments. If a patient refused to return for these visits or was unable to do so, every effort was made to contact them to assess the patient's disease status and survival.	Was the follow-up long enough? Unclear The median follow-up time for the R/R MCL population who received 320 mg of zanubrutinib was 38.32 months at a data cut off of 31st March 2021 for investigator assessed outcomes (shorter for IRC-assessed outcomes). However, PFS and DOR for subgroup 2L only (n=18) were not estimable at data cut-off of 13th December 2018 CS Table 13) for IRC-assessment, which raises question about length of follow up for these outcomes.
How precise (for example, in terms of confidence interval and p values) are the results?	Yes The primary endpoint of ORR by IRC assessment presented a p-value <0.0001 with a CI of 95%. Medians and other quartiles for all secondary endpoints were estimated by KM method with 95% CIs. See CS Section B.2a.6 for full details.	Unclear The primary end point of ORR was reported with a 95% CI in the CS section B.2a.6. Secondary endpoints were estimated by KM method with 95% CI. However, the upper limits for PFS and OS are not estimable introducing some uncertainty in precision.
BGB-3111-206		
Was the cohort recruited in an acceptable way?	Yes Patients were recruited from 13 study locations in China based on inclusion and exclusion criteria outlined in CS Table 20.	Unclear Patients were recruited from 13 centres in China. This might limit the generalisability of the study findings, although the EAG clinical expert did not have any concerns regarding the effects of race, there may differences in health care or other factors.
Was the exposure accurately measured to minimise bias?	Yes All 86 patients in the BGB-3111-206 trial received at least one dose of zanubrutinib. The median duration of treatment was 27.6 months (range: 0.2 to 41.6 months). The median actual and relative dose intensities were 319.6 mg/day and 99.87%, respectively	Yes The recruited patients (n=86) received oral zanubrutinib at a dose of 160 mg twice daily with a median duration of treatment 27.6 months (range, 0.2-41.6).
Was the outcome accurately measured to minimise bias?	Yes Outcomes were accurately measured to minimise bias as outlined in CS Table 21. Outcomes were assessed using both IRC and INV assessment to validate outcomes where appropriate.	Yes Concordance rates between INV and IRC at each DCO were reported, and were [redacted] for ORR and [redacted] for best overall response, and median duration of response [redacted] (2024 CSR for BGB-3111-206 clinical evidence and BeiGene 2020 Regulatory summary of

		clinical safety for the BGB-3111-206 and AU-003 trials, provided with the CS)
Have the authors identified all important confounding factors?	Yes All-important confounding factors were considered within pre-planned subgroup analyses. See Section B.2b.6 for more details.	Yes The CS reported confounding factors in CS section B.2b.4.2 and provided outcome from subgroup analysis in CS Figure 16. This analysis was in accordance with the preplanned analysis plan.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes Yes, as per the previous question, the confounding factors were identified and taken account for in the analysis.	Yes The confounding factors identified in CS section B.2b.4.2 are analysed in B.2b.7 and in CS Figure 16
Was the follow-up of patients complete?	Yes The BGB-3111-206 trial is complete with no further data cuts planned. The trial design ensured patients were suitably followed up after discontinuation of treatment and/or progression. The median follow-up time was 35.25 months.[a] At the end of treatment, a safety follow-up of 30 ± 7 days after last dose was ensured for both discontinuation due to PD and reasons other than PD. Patients continued efficacy evaluations until PD followed by long-term follow-up for survival every 24 weeks. All patients who discontinued study drug commenced long-term follow-up after progression, which included monitoring for survival status and initiation of new anticancer treatment for MCL and conducting chemistry and haematology assessments. If a patient refused to return for these visits or was unable to do so, every effort was made to contact them to assess the patient's disease status and survival.	Yes CS Table 24 reports patient disposition with reasons for discontinuation. Was the follow-up long enough? Unclear Median follow-up was 35.25 months at DCO 8th September 2020 for investigator assessed outcomes. However, some of measures were not estimable (NE) at this DCO or the shorter DCO for IRC assessed outcomes (CS Table 26), which raises questions about length of follow up.
How precise (for example, in terms of confidence interval and p values) are the results?	Yes The primary endpoint of ORR by IRC assessment presented a p-value <0.0001 with a CI of 95%. Medians and other quartiles for all secondary endpoints were estimated by KM method with 95% CIs. See Section B.2b.6 for full details.	Unclear The primary end point of ORR was reported with a 95% CI and 1-sided p-value < 0.0001 in the CS section B.2b.6.1. Secondary endpoints were estimated by KM method with 95% CI However, the upper limits for PFS and OS are not estimable introducing some uncertainty in precision.

[a]The median follow-up time given in CS Appendix D Table 17 was 24.84 months, but this refers to an earlier data cut.
Source: adapted from CS Tables 12 and 25, and CS Appendix D Table 16 and CSR (2024 CSR for BGB-3111-206 clinical evidence, provided with the CS).

CI – confidence interval; CS- company submission; DCO – data cut-off; INV – investigator; IRC – independent review committee; KM - Kaplan-Meier; ORR – overall response rate; OS- overall survival PD – progressive disease; PFS – progression-free survival; R/R MCL – relapsed/refractory mantle cell lymphoma

9.2 Additional EAG searches

9.2.1 EAG update search

Embase <1974 to 2025 February 11>
Ovid MEDLINE(R) ALL <1946 to February 11, 2025>

1 mantle cell lymphoma/ or Lymphoma, Mantle-Cell/ 20341
2 (mantle cell and lymphom*).ti,ab,kf,kw. 20119
3 mcl.ti,ab,kf,kw. 39120
4 1 or 2 or 3 53704
5 (relaps* or refract* or recurren* or resistant or ((prior or previous or previously or experienced) adj3 (treatment or treated or therapy or therapies or line or lines or exposed or exposure)) or ((second or 2nd or third or 3rd or fourth or 4th) adj3 (line or lines))).ti,ab,kf,kw. or exp treatment failure/ or exp recurrence/ 4830842
6 4 and 5 15133
7 (zanubrutinib or Brukinsa).mp. 2072
8 6 and 7 295
9 (ibrutinib or Imbruvica).mp. 18597
10 6 and 9 2134
11 8 or 10 2217
12 limit 11 to yr="2024 -Current" 131
13 remove duplicates from 12 96

Total after Information Specialist filtered out definitely irrelevant records (e.g. case studies, non MCL, animal studies): 38

9.2.2 EAG testing impact of error in CS SLR searches of MEDLINE and Embase

Embase <1974 to 2025 March 05>
Ovid MEDLINE(R) ALL <1946 to March 05, 2025>

Search with error in line 5	1	mantle cell lymphoma/ or Lymphoma, Mantle-Cell/ 20493
	2	(mantle cell and lymphom*).ti,ab. 20035
	3	mcl.ti,ab. 39163
	4	1 or 2 or 3 53874
	5	(relaps* or refract* or recurren* or resistant or ((prior or previous or previously or experienced) and "adj" and (treatment or treated or therapy or therapies or line or lines or exposed or exposure)) or ((second or 2nd or third or 3rd or fourth or 4th) and "adj" and (line or lines))).ti,ab. or exp treatment failure/ or exp recurrence/ 4429050
	6	4 and 5 14274

	7	(zanubrutinib or Brukinsa).mp. 2129
	8	6 and 7 278
	9	(ibrutinib or Imbruvica).mp. 18831
	10	6 and 9 2006
	11	8 or 10 2083
	12	remove duplicates from 11 1636 [search with error in line 5]
Search without error	13	mantle cell lymphoma/ or Lymphoma, Mantle-Cell/ 20493
	14	(mantle cell and lymphom*).ti,ab,kf,kw. 20199
	15	mcl.ti,ab,kf,kw. 39551
	16	13 or 14 or 15 54283
	17	(relaps* or refract* or recurren* or resistant or ((prior or previous or previously or experienced) adj3 (treatment or treated or therapy or therapies or line or lines or exposed or exposure)) or ((second or 2nd or third or 3rd or fourth or 4th) adj3 (line or lines))).ti,ab,kf,kw. or exp treatment failure/ or exp recurrence/ 4865290
	18	16 and 17 15235
	19	(zanubrutinib or Brukinsa).mp. 2129
	20	18 and 19 296
	21	(ibrutinib or Imbruvica).mp. 18831
	22	18 and 21 2146
	23	20 or 22 2229
	24	remove duplicates from 23 1756 [search without error]
	25	24 not 12 120

Downloaded to EndNote and removed further 7 duplicates.
Total: 113 (sent to reviewers for check)

9.3 Proportional hazards testing

9.3.1 Progression-free survival

Table 53: Summary of proportional hazards assumption tests for PFS

Test	Conclusion of proportional hazards assumption
Cumulative hazard plots	Assumption not violated No obvious crossing between the curves
Global Schoenfeld test	Assumption not violated [redacted]
Schoenfeld residuals plot	Assumption not violated Lowess smoother flat line around 0
Time-dependent covariate	Assumption violated P < 0.0001

Figure 18: Cumulative hazard functions of zanubrutinib and ibrutinib for PFS

Figure 19: Schoenfeld residuals plot for PFS

9.3.2 Overall survival

Table 54: Summary of proportional hazards assumption tests for OS

Test	Conclusion of proportional hazards assumption
Cumulative hazard plots	Assumption violated Crossings between the curves near start of study
Global Schoenfeld test	Assumption not violated [redacted]
Schoenfeld residuals plot	Assumption not violated Lowess smoother flat line around 0
Time-dependent covariate	Assumption violated P < 0.0001

[redacted]

Figure 20: Cumulative hazard functions of zanubrutinib and ibrutinib for OS

Figure 21: Schoenfeld residuals plot for OS

9.4 Zanubrutinib PFS

9.4.1 Estimated Kaplan-Meier survival

Table 55: Estimated monthly survival from KM plot (zanubrutinib PFS)

Months	Survival	Months	Survival	Months	Survival
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9.4.2 Statistical fit

The log-normal model had the lowest AIC, and the exponential model had the lowest BIC. All the other models had a similar AIC to the log-normal, and the parametric models had a similar BIC to the exponential except for the generalised gamma model.

Table 56: Statistical model fit (zanubrutinib PFS)

Model	AIC	BIC	AIC rank	BIC rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Hazards k=1	[redacted]	[redacted]	[redacted]	[redacted]
Hazards k=2	[redacted]	[redacted]	[redacted]	[redacted]
Hazards k=3	[redacted]	[redacted]	[redacted]	[redacted]
Odds k=1	[redacted]	[redacted]	[redacted]	[redacted]
Odds k=2	[redacted]	[redacted]	[redacted]	[redacted]
Odds k=3	[redacted]	[redacted]	[redacted]	[redacted]
Normal k=1	[redacted]	[redacted]	[redacted]	[redacted]
Normal k=2	[redacted]	[redacted]	[redacted]	[redacted]
Normal k=3	[redacted]	[redacted]	[redacted]	[redacted]

9.4.3 Parametric model visual fit

The parametric models generally have good fit to the observed data. The models overestimate PFS around 16 to 25 months, after which they start to disperse. Up to 20 years, the exponential, Weibull, and gamma models estimate [redacted] PFS (i.e. everyone progresses disease), while the Gompertz model is the most optimistic.

Figure 22: Parametric model fit over trial length (zanubrutinib PFS)

Figure 23: Parametric model fit over 20 years (zanubrutinib PFS)

9.4.4 Parametric model hazards

Compared to the hazards from the observed PFS KM data of the pooled zanubrutinib trials, the log-normal, log-logistic, and generalised gamma models follow the general shape of the observed hazards.

Figure 24: Parametric model hazard functions with observed hazards overlaid in black (zanubrutinib PFS)

9.4.5 Spline model visual fit

The spline models also visually fit the observed KM data well and, due to the nature of the higher-knot models, are able to deal with the various ‘bumps’ in the KM plot.

Figure 25: Spline model fit over trial length (zanubrutinib PFS)

9.4.6 Spline model hazards

Compared to the hazards from the observed PFS KM data of the pooled zanubrutinib trials, the 1- and 2-knot models follow the general shape of the observed hazards. The 3-knot models conform more to the observed hazards after around 26-27 moths, but up to that point differs in shape.

Figure 26: Spline model hazard functions with observed hazards overlaid in black (zanubrutinib PFS)

9.5 Zanubrutinib OS

9.5.1 Estimated Kaplan-Meier survival

Table 57: Estimated monthly survival from KM plot (zanubrutinib OS)

Months	Survival	Months	Survival	Months	Survival
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9.5.2 Statistical fit

The exponential model had the lowest AIC and lowest BIC. All the other models had a similar AIC to the exponential except for the 3-knot spline models, and the parametric models had a similar BIC to the exponential except for the generalised gamma model.

Table 58: Statistical model fit (zanubrutinib OS)

Model	AIC	BIC	AIC rank	BIC rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Hazards k=1	[redacted]	[redacted]	[redacted]	[redacted]
Hazards k=2	[redacted]	[redacted]	[redacted]	[redacted]
Hazards k=3	[redacted]	[redacted]	[redacted]	[redacted]
Odds k=1	[redacted]	[redacted]	[redacted]	[redacted]
Odds k=2	[redacted]	[redacted]	[redacted]	[redacted]
Odds k=3	[redacted]	[redacted]	[redacted]	[redacted]
Normal k=1	[redacted]	[redacted]	[redacted]	[redacted]
Normal k=2	[redacted]	[redacted]	[redacted]	[redacted]
Normal k=3	[redacted]	[redacted]	[redacted]	[redacted]

9.5.3 Parametric model visual fit

The parametric models have decent fit to the observed KM data, although they underestimate OS in the pooled zanubrutinib trials in various places. Up to 20 years, there is a wide range of estimated survival between the parametric models, with only the generalised gamma model predicting zero survivors up to 20 years.

Figure 27: Parametric model fit over trial length (zanubrutinib OS)

Figure 28: Parametric model fit over 20 years (zanubrutinib OS)

9.5.4 Parametric model hazards

Compared to the hazards from the observed OS KM data of the pooled zanubrutinib trials, the log-logistic model follows the general shape of the observed hazards best, followed by the log-normal except at the beginning of the trial.

Figure 29: Parametric model hazard functions with observed hazards overlaid in black (zanubrutinib OS)

9.5.5 Spline model visual fit

The spline models fit well to the KM data but run into similar issues as the parametric models where is underestimates survival at some time points.

Figure 30: Spline model fit over trial length (zanubrutinib OS)

9.5.6 Spline model hazards

Most of the hazards of the spline models fit the observed OS hazards from the zanubrutinib trials well. The 2- and 3-knot models capture the dip in the hazards well up to around 24 months, while increasing and then slowly decreases at the end of the trial period. The 1-knot spline models trend downwards throughout the plot and do not capture the sudden increase in observed hazards around 35 months.

Figure 31: Spline model hazard functions with observed hazards overlaid in black (zanubrutinib OS)

9.6 Zanubrutinib TTD

9.6.1 Estimated Kaplan-Meier survival

Table 59: Estimated monthly survival from KM plot (zanubrutinib TTD)

Months	Survival	Months	Survival	Months	Survival
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9.6.2 Statistical fit

Table 60: Statistical model fit (zanubrutinib TTD)

Model	AIC	BIC	AIC rank	BIC rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Hazards k=1	[redacted]	[redacted]	[redacted]	[redacted]
Hazards k=2	[redacted]	[redacted]	[redacted]	[redacted]
Hazards k=3	[redacted]	[redacted]	[redacted]	[redacted]
Odds k=1	[redacted]	[redacted]	[redacted]	[redacted]
Odds k=2	[redacted]	[redacted]	[redacted]	[redacted]
Odds k=3	[redacted]	[redacted]	[redacted]	[redacted]
Normal k=1	[redacted]	[redacted]	[redacted]	[redacted]
Normal k=2	[redacted]	[redacted]	[redacted]	[redacted]
Normal k=3	[redacted]	[redacted]	[redacted]	[redacted]

9.6.3 Parametric model visual fit

Figure 32: Parametric model fit over trial length (zanubrutinib TTD)

9.6.4 Parametric model hazards

Figure 33: Parametric model hazard functions with observed hazards overlaid in black (zanubrutinib TTD)

9.6.5 Spline model visual fit

Figure 34: Spline model fit over trial length (zanubrutinib TTD)

Spline model hazards

Figure 35: Spline model hazard functions with observed hazards overlaid in black (zanubrutinib TTD)

9.7 Ibrutinib PFS

9.7.1 Estimated Kaplan-Meier survival

Table 61: Estimated monthly survival from KM plot (ibrutinib PFS)

Months	Survival	Months	Survival	Months	Survival
0	100	10	55.1	20	37.5
1	97.6	11	54.3	21	35.6
2	93.2	12	52.9	22	33.7
3	81.1	13	50.5	23	32.8
4	75.7	14	49.6	24	31.4
5	68.6	15	46.1	25	30.9
6	66.2	16	45.8	26	29
7	62.2	17	44.7	27	29
8	60	18	41.4	28	29
9	55.9	19	39.7		

9.7.2 Statistical fit

The 2-knot normal spline model had the lowest AIC and lowest BIC. The other 2- and 3-knot spline models had a similar AIC to the 2-knot normal model, while the generalised gamma, 2-knot hazards, 2- and 3-knot odds, and 3-knot normal models had a similar BIC to the 2-knot normal model.

Table 62: Statistical model fit (ibrutinib PFS)

Model	AIC	BIC	AIC rank	BIC rank
Exponential	2109.696	2113.61		
Weibull	2106.657	2114.484		
Log-normal	2070.486	2078.313		
Log-logistic	2084.903	2092.73		
Gompertz	2091.641	2099.468		
Generalised Gamma	2059.089	2070.829		Similar
Gamma	2109.624	2117.451		
Hazards k=1	2071.2	2082.94		
Hazards k=2	2054.365	2070.019	Similar	Similar
Hazards k=3	2053.386	2072.954	Similar	
Odds k=1	2070.437	2082.178		
Odds k=2	2052.27	2067.924	Similar	Similar
Odds k=3	2051.693	2071.261	Similar	Similar
Normal k=1	2061.777	2073.517		
Normal k=2	**2051.086**	**2066.74**	**Best**	**Best**
Normal k=3	2051.861	2071.429	Similar	Similar

9.7.3 Parametric model visual fit

The parametric models generally have poor fit to the observed PFS KM data in the pooled ibrutinib studies. While models such as the generalised gamma model fits the KM data well up to around 10 months, it underestimates PFS afterwards, and other models like the exponential or Weibull overestimate PFS prior to 10 months but then is in line with the KM data after.

Up to 20 years, the exponential, Weibull, and gamma models estimate [redacted] PFS (i.e. everyone progresses disease), while the Gompertz model is the most optimistic followed by the generalised gamma.

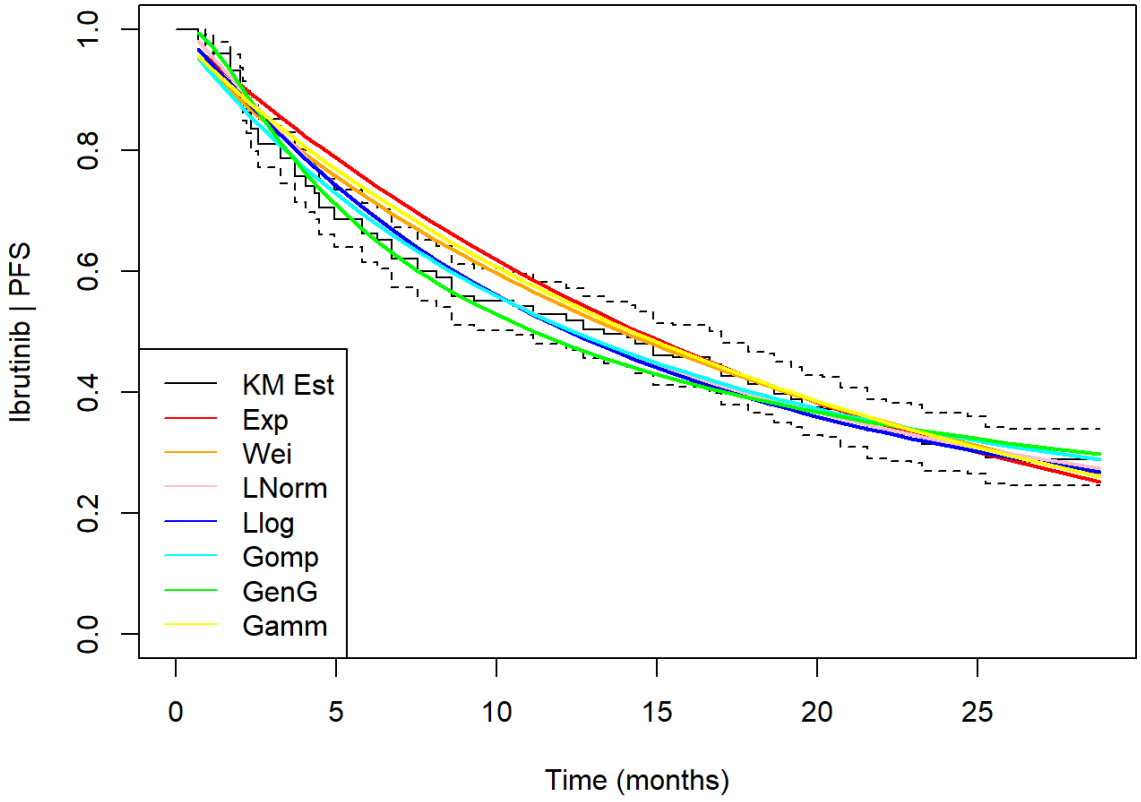

Figure 36: Parametric model fit over trial length (ibrutinib PFS)

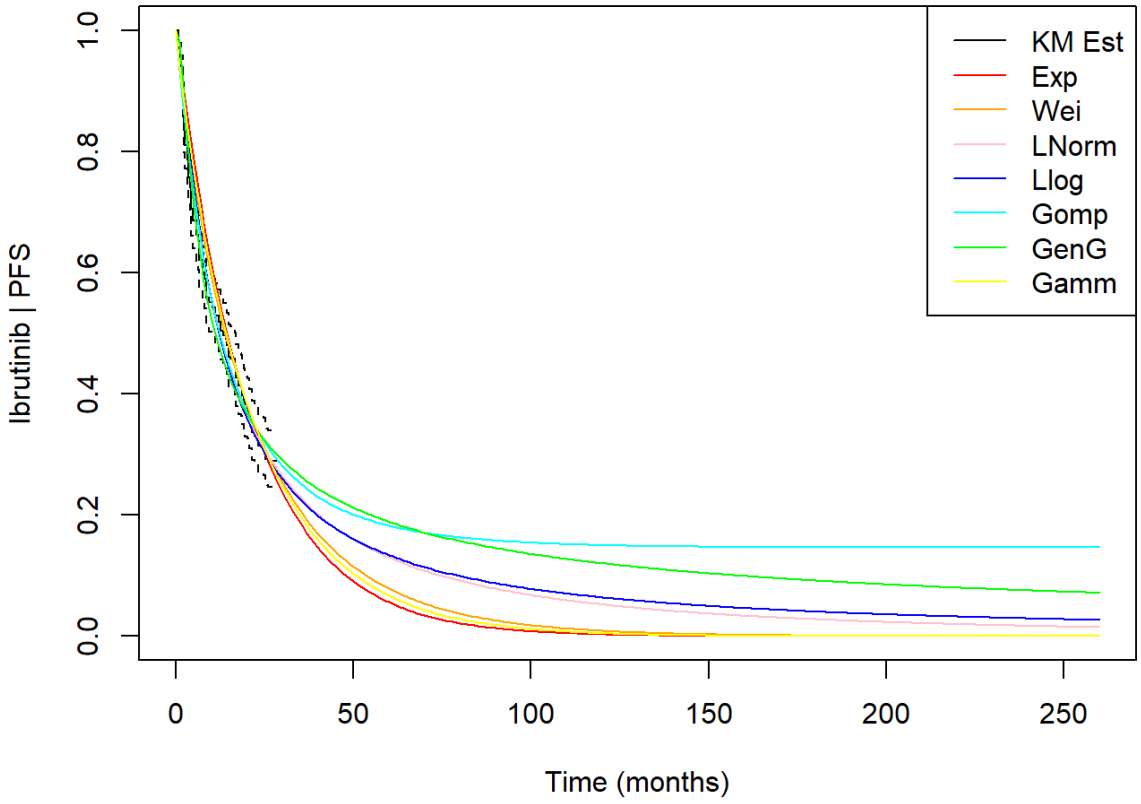

Figure 37: Parametric model fit over 20 years (ibrutinib PFS)

9.7.4 Parametric model hazards

Compared to the hazards from the observed PFS KM data of the pooled ibrutinib trials, the generalised gamma models follow the general shape of the observed hazards up to around 12 to 13 months, after which the trial's hazards increase before decreasing again. Otherwise, none of the parametric models' hazards follows the observed hazards, though the hazards of some models do trend downwards over time.

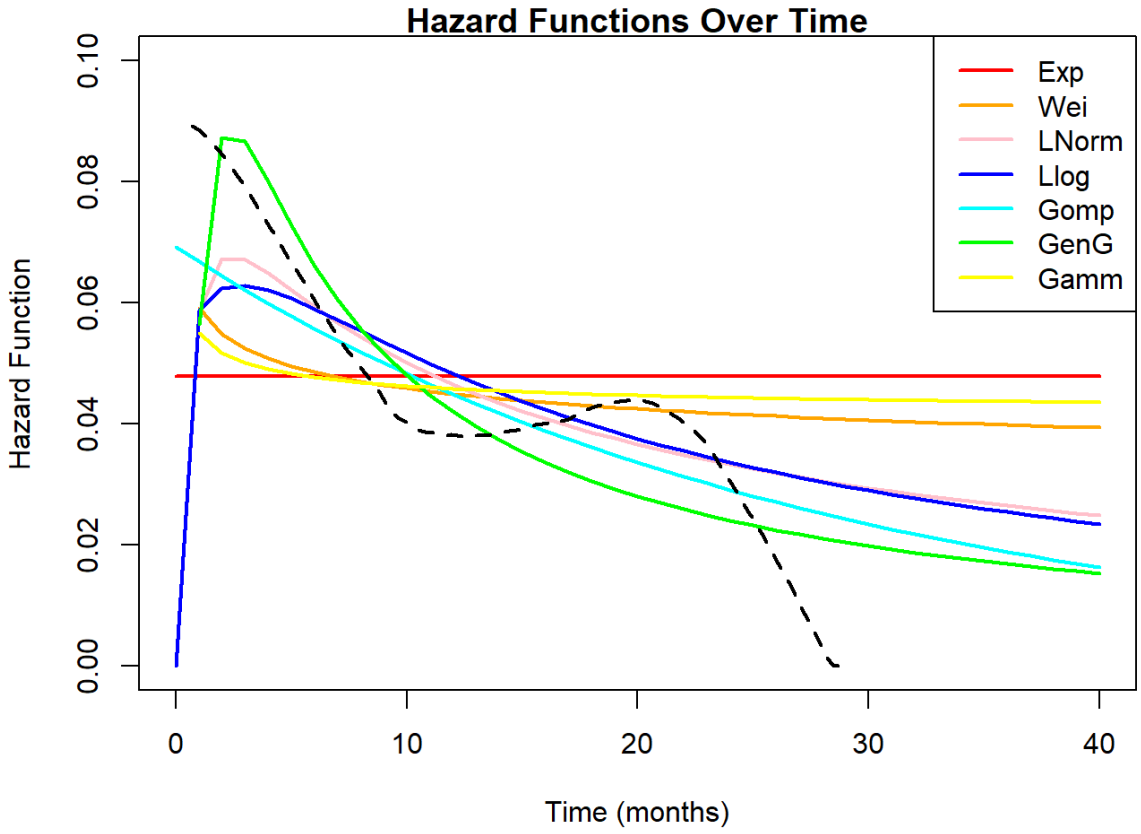

Figure 38: Parametric model hazard functions with observed hazards overlaid in black (ibrutinib PFS)

9.7.5 Spline model visual fit

The 2- and 3-knot spline models have good fit to the data, while the 1-knot spline models underestimate PFS during the middle of the pooled trial period.

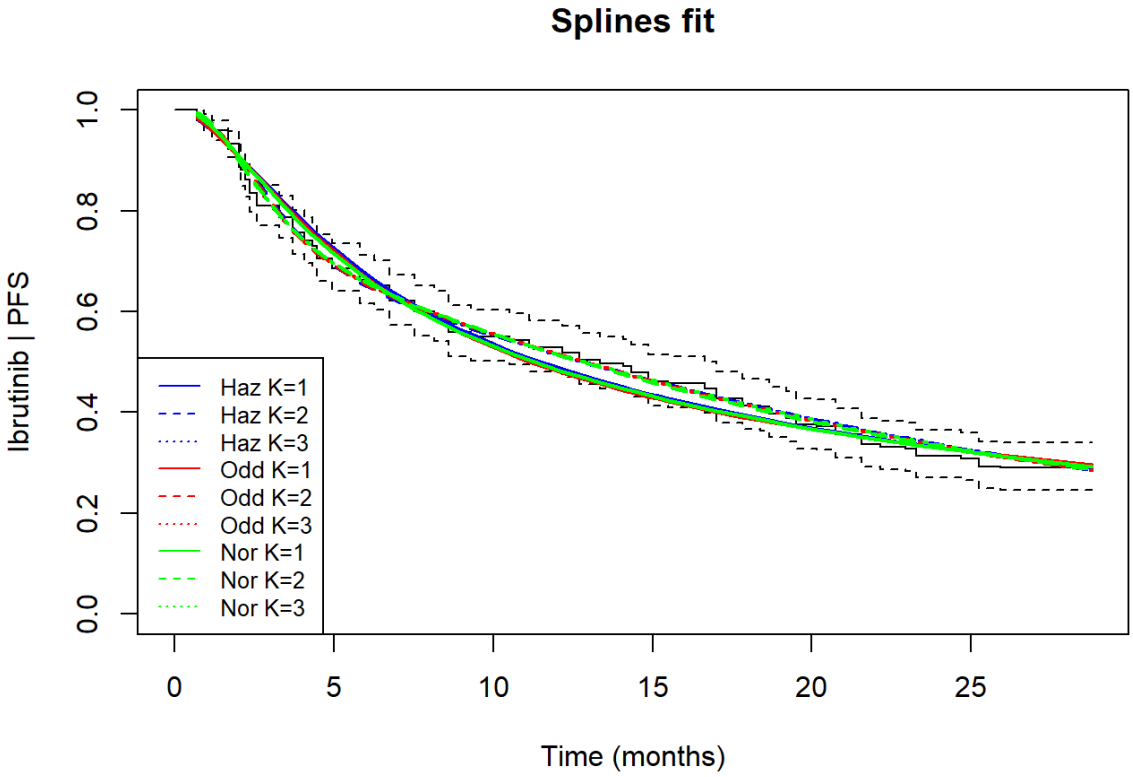

Figure 39: Spline model fit over trial length (ibrutinib PFS)

Spline model hazards

The 2- and 3-knot spline models' hazards follows the general trend of the observed hazards, the 1-knot models also follow the trend but not as well.

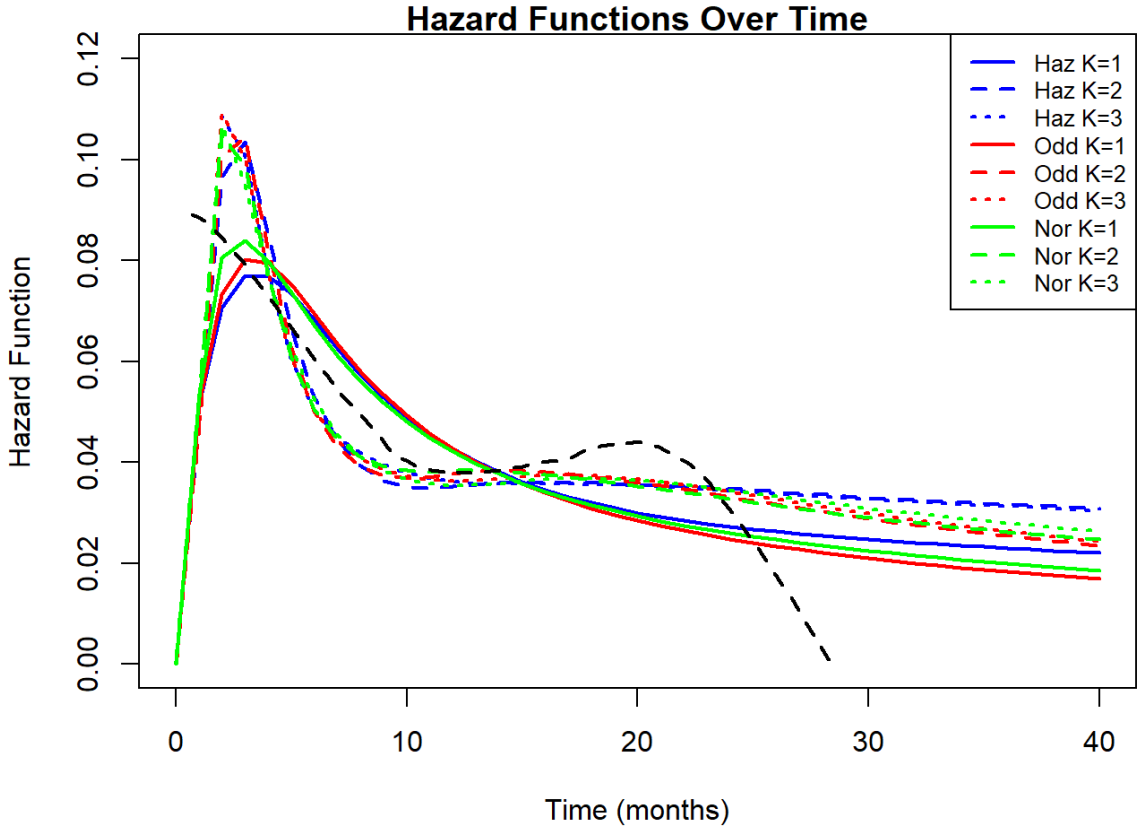

Figure 40: Spline model hazard functions with observed hazards overlaid in black (ibrutinib PFS)

9.8 Ibrutinib OS

9.8.1 Estimated Kaplan-Meier survival

Table 63: Estimated monthly survival from KM plot (ibrutinib OS)

Months	Survival	Months	Survival	Months	Survival
0	100	11	70.8	22	56.2
1	100	12	68.8	23	55.3
2	98.1	13	66.8	24	51.7
3	93.7	14	63.5	25	50.8
4	88.7	15	62.6	26	49.7
5	86.5	16	62.1	27	49.4
6	84.5	17	61.2	28	47.5
7	80.9	18	59.8	29	47.2
8	77.5	19	59	30	47.2
9	76.4	20	57	31	47.2
10	73.9	21	57	32	47.2

9.8.2 Statistical fit

The generalised gamma model had the lowest AIC and lowest BIC. Only the 1-knot normal model had a similar AIC and BIC, and the 2- and 3-knot normal models had a similar BIC.

Table 64: Statistical model fit (ibrutinib OS)

Model	AIC	BIC	AIC rank	BIC rank
Exponential	1782.801	1786.714		
Weibull	1784.065	1791.892		
Log-normal	1755.722	1763.549		
Log-logistic	1768.634	1776.461		
Gompertz	1771.143	1778.97		
Generalised Gamma	**1741.068**	**1752.809**	**Best**	**Best**
Gamma	1784.763	1792.59		
Hazards k=1	1747.416	1759.157		
Hazards k=2	1747.899	1763.553		
Hazards k=3	1746.94	1766.508		
Odds k=1	1746.379	1758.119		
Odds k=2	1746.941	1762.595		
Odds k=3	1746.23	1765.798		
Normal k=1	1743.306	1755.047	Similar	Similar
Normal k=2	1744.924	1760.578	Similar	
Normal k=3	1745.524	1765.092	Similar	

9.8.3 Parametric model visual fit

The parametric models generally fit poorly to the observed OS KM data for the pooled ibrutinib studies. The generalised gamma model fits well, as does the Gompertz, while the others overestimate OS. Up to 20 years, the exponential, Weibull, and gamma models estimate no survivors, then log-logistic and log-normal models estimate around 10% survival, while the Gompertz and generalised gamma models are the most optimistic with around 30% and 20% survival, respectively.

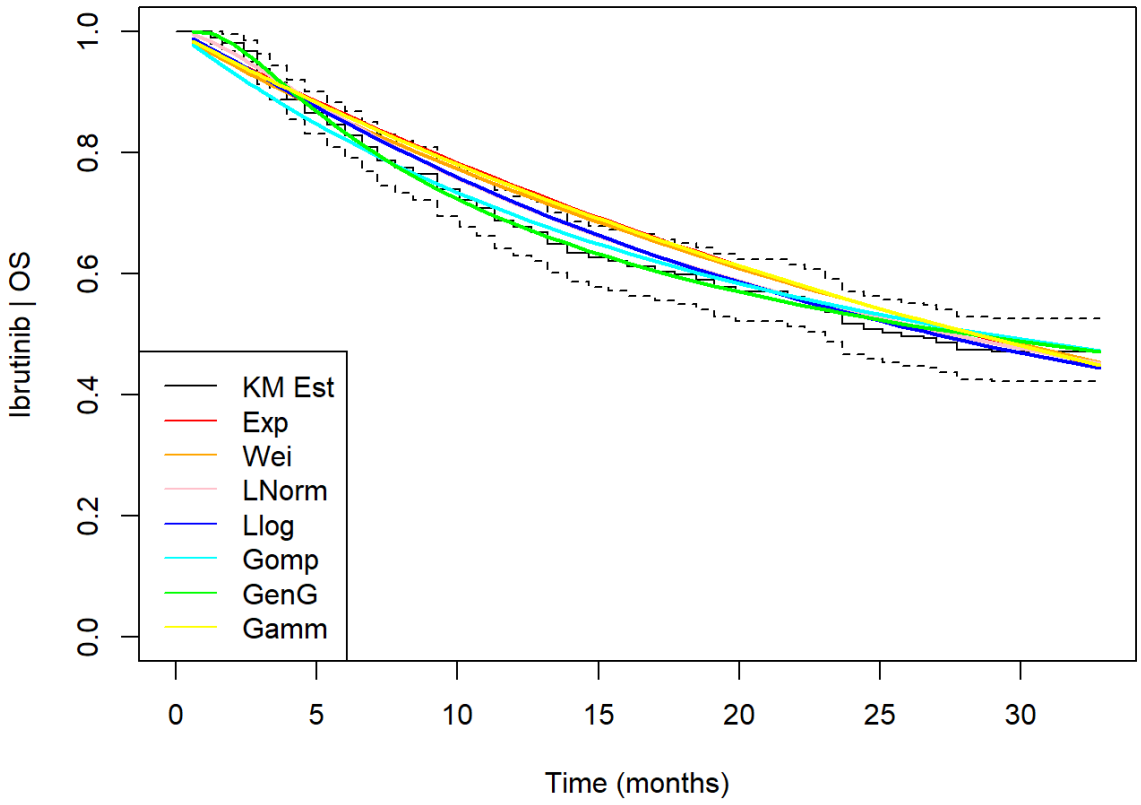

Figure 41: Parametric model fit over trial length (ibrutinib OS)

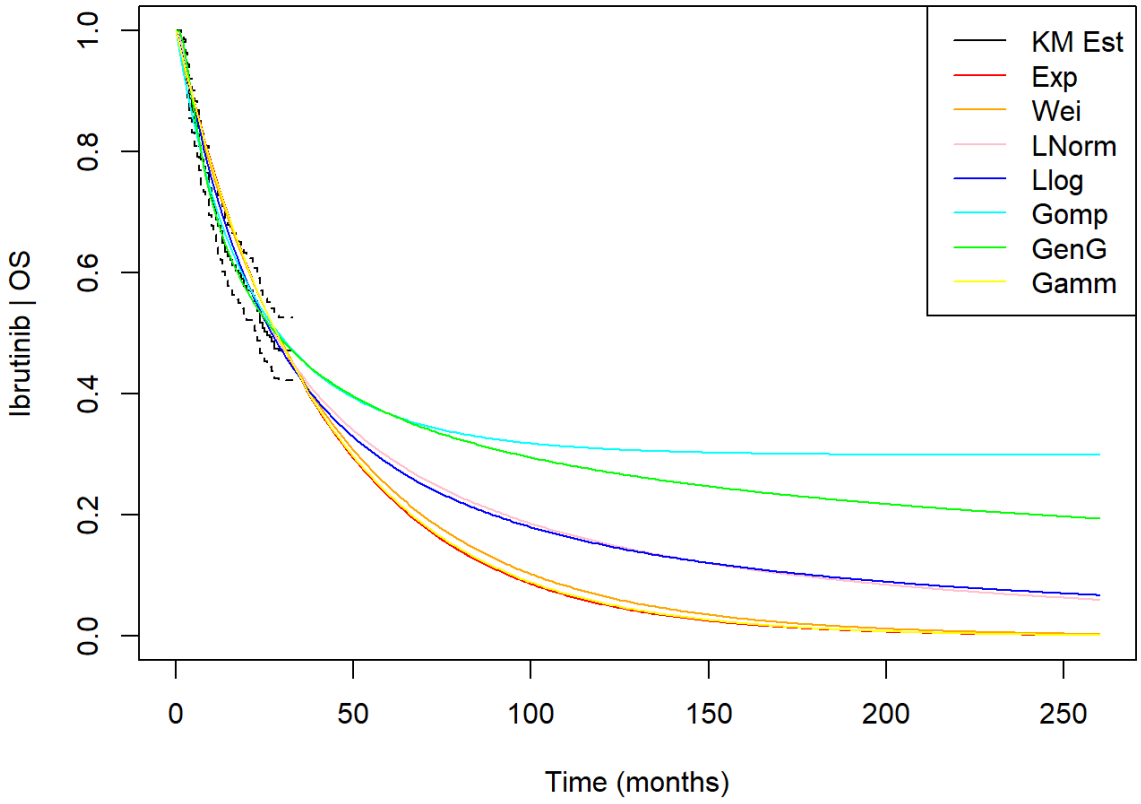

Figure 42: Parametric model fit over 20 years (ibrutinib OS)

9.8.4 Parametric model hazards

Compared to the hazards from the observed OS KM data of the pooled ibrutinib trials, the Gompertz and the generalised gamma models follow the general shape of the observed hazards up to around 27 months. From that point on, the trial's OS hazards decreases sharply, while the Gompertz and generalised gamma hazards gradually decreases.

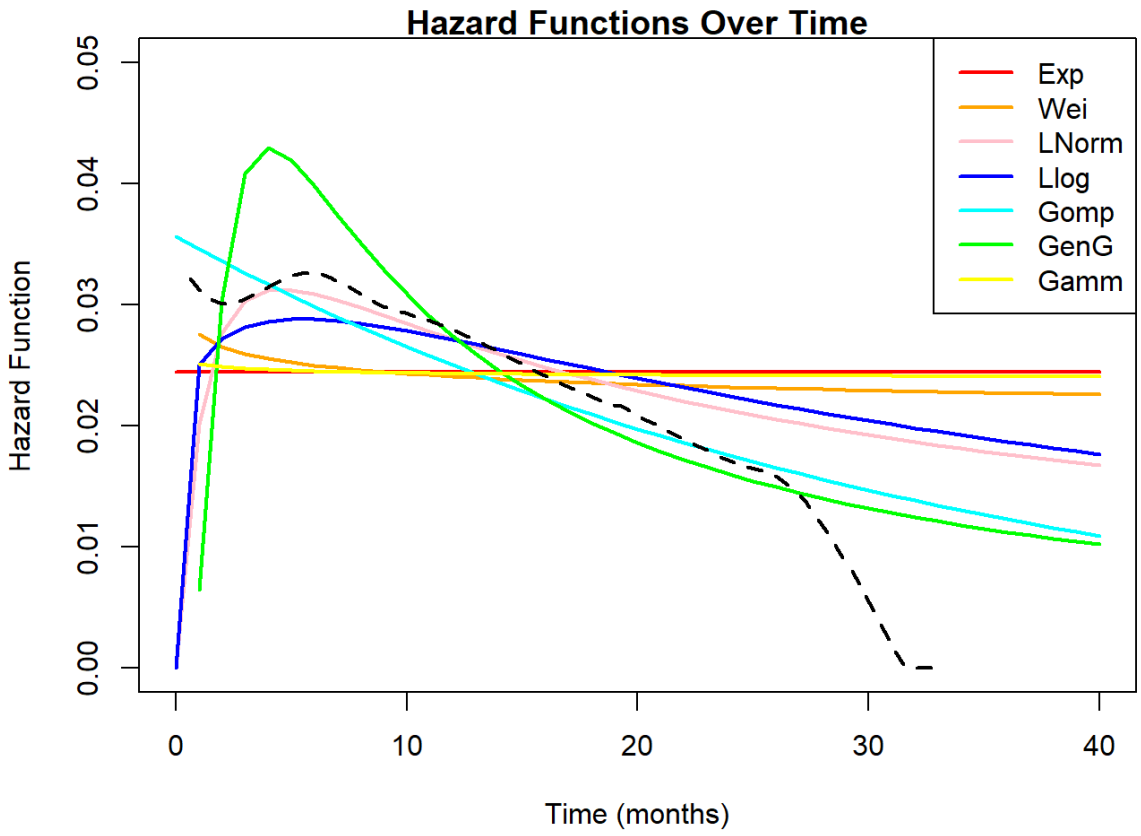

Figure 43: Parametric model hazard functions with observed hazards overlaid in black (ibrutinib OS)

9.8.5 Spline model visual fit

All of the spline models look to fit the observed KM data well.

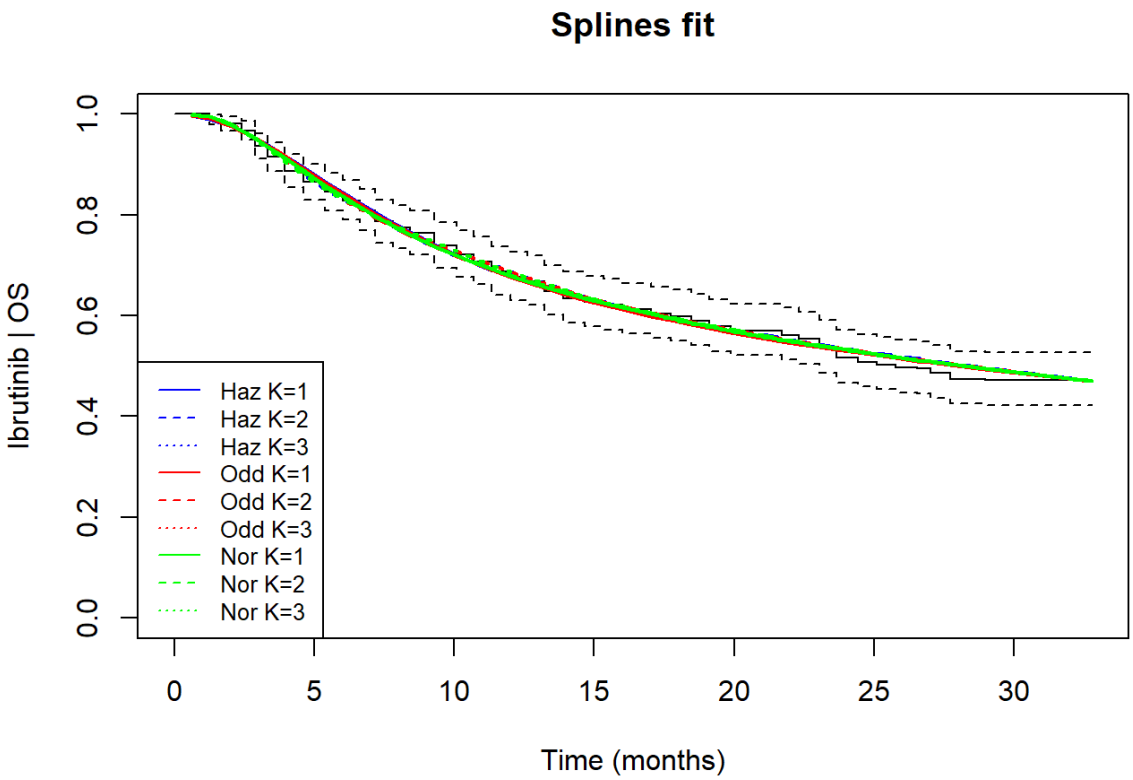

Figure 44: Spline model fit over trial length (ibrutinib OS)

9.8.6 Spline model hazards

All of the spline models follow the trend of the observed hazards from around 10 to 27 months, but before 10 months and after 27 months, the splines models' hazards are much higher than the observed hazards.

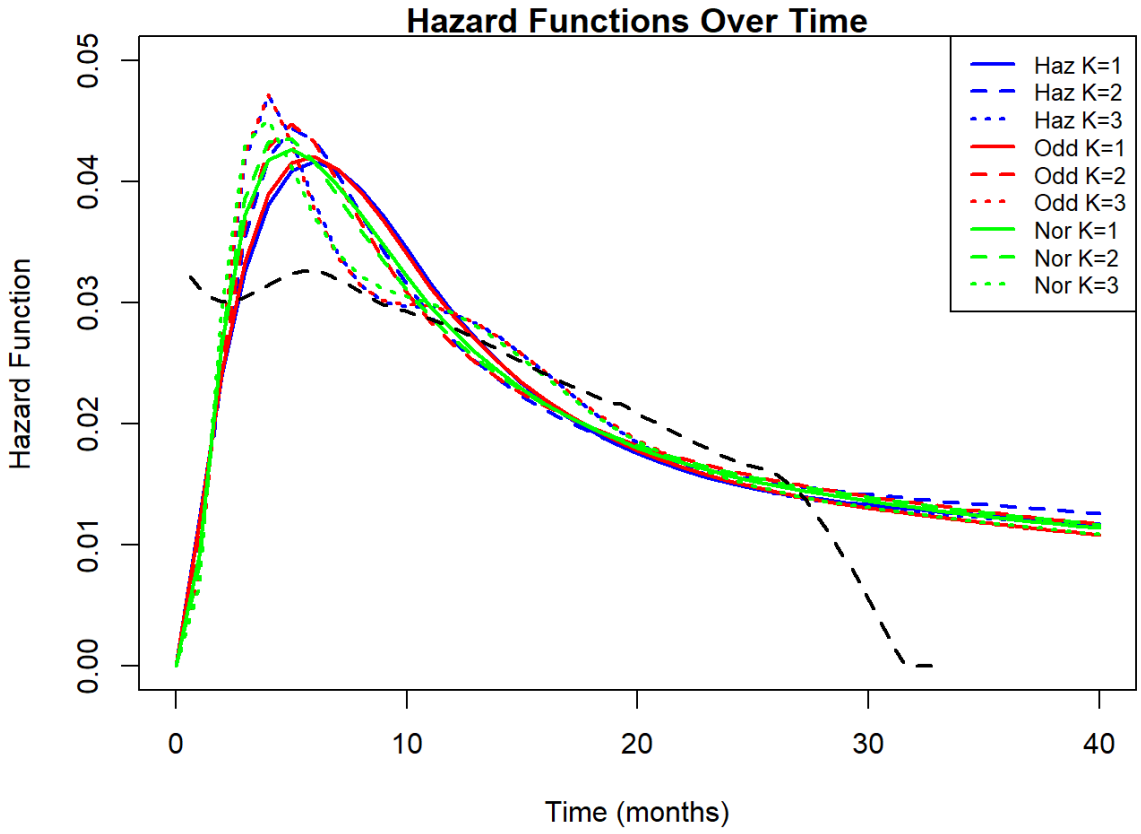

Figure 45: Spline model hazard functions with observed hazards overlaid in black (ibrutinib OS)

9.9 Ibrutinib TTD

9.9.1 Estimated Kaplan-Meier survival

Table 65: Estimated monthly survival from KM plot (ibrutinib TTD)

Months	Survival	Months	Survival
0	100	17	40.8
1	100	18	39.5
2	98.6	19	38.1
3	89.7	20	37.3
4	81.1	21	35.9
5	73	22	34.6
6	68.6	23	32.4
7	64.9	24	31.6
8	61.6	25	30.5
9	58.1	26	28.9
10	54.6	27	26.2
11	52.2	28	23.8
12	51.1	29	20.3
13	48.6	30	17.8
14	44.6	31	11.4
15	42.7	32	8.4
16	42.2		

9.9.2 Statistical fit

Table 66: Statistical model fit (ibrutinib TTD)

Model	AIC	BIC	AIC rank	BIC rank
Exponential	2747.948	2751.861		
Weibull	2707.303	2715.13		
Log-normal	2727.996	2735.823		
Log-logistic	2763.585	2771.412		
Gompertz	2690.326	2698.153		
Generalised Gamma	2590.789	2602.529		
Gamma	2710.256	2718.083		
Hazards k=1	2708.901	2720.641		
Hazards k=2	2581.07	2596.724		
Hazards k=3	2547.278	2566.845	**Best**	**Best**
Odds k=1	2762.679	2774.42		
Odds k=2	2627.381	2643.035		
Odds k=3	2585.372	2604.939		
Normal k=1	2724.766	2736.506		
Normal k=2	2603.619	2619.273		
Normal k=3	2603.838	2623.405		

9.9.3 Parametric model visual fit

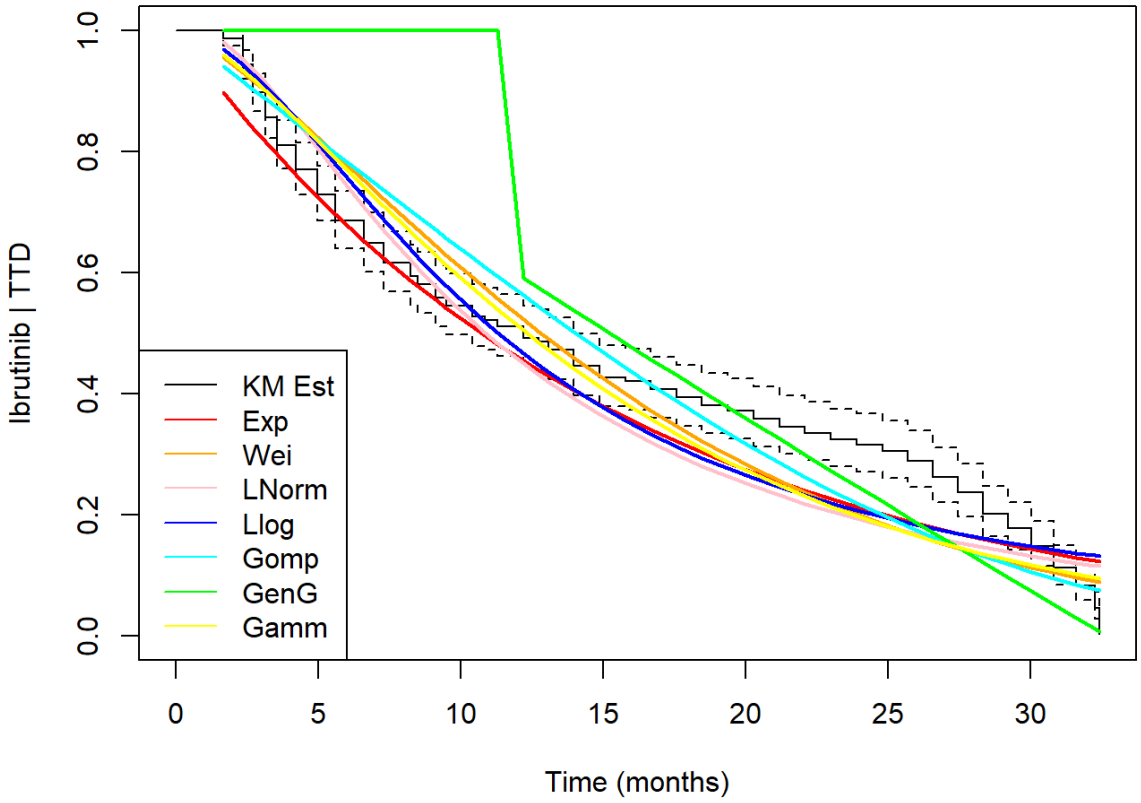

Figure 46: Parametric model fit over trial length (ibrutinib TTD)

9.9.4 Parametric model hazards

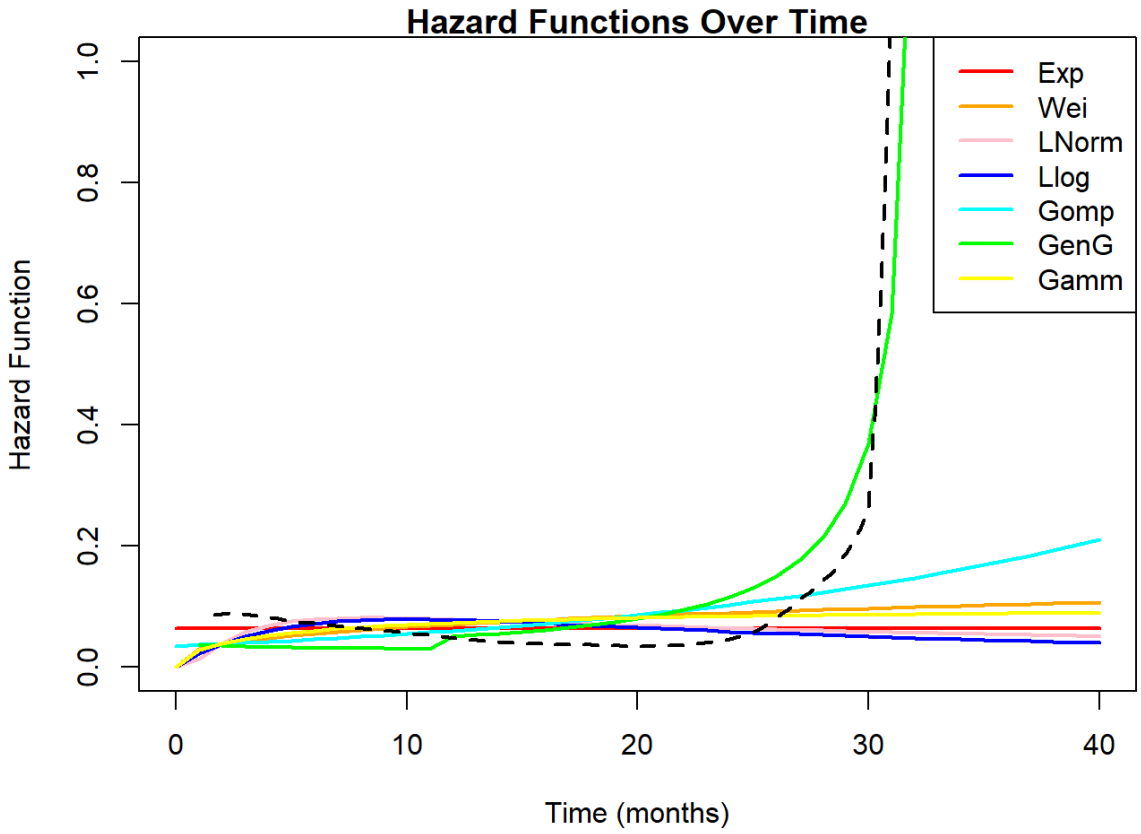

Figure 47: Parametric model hazard functions with observed hazards overlaid in black (ibrutinib TTD)

9.9.5 Spline model visual fit

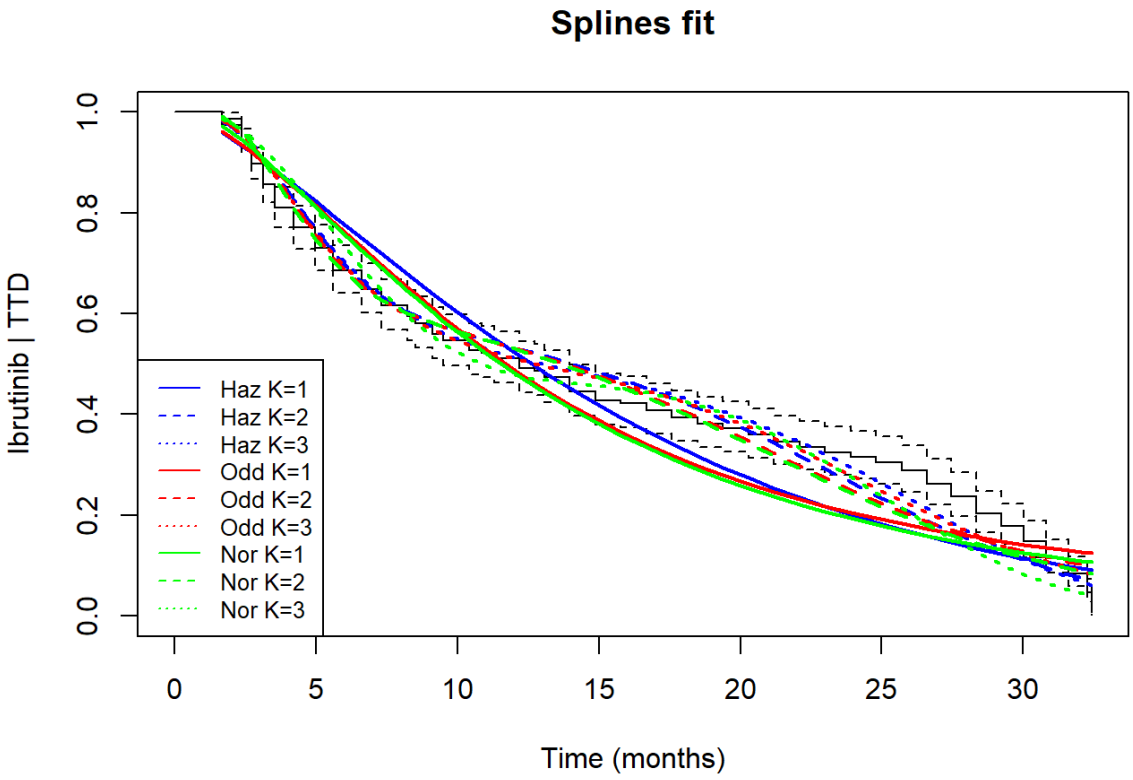

Figure 48: Spline model fit over trial length (ibrutinib TTD)

9.9.6 Spline model hazards

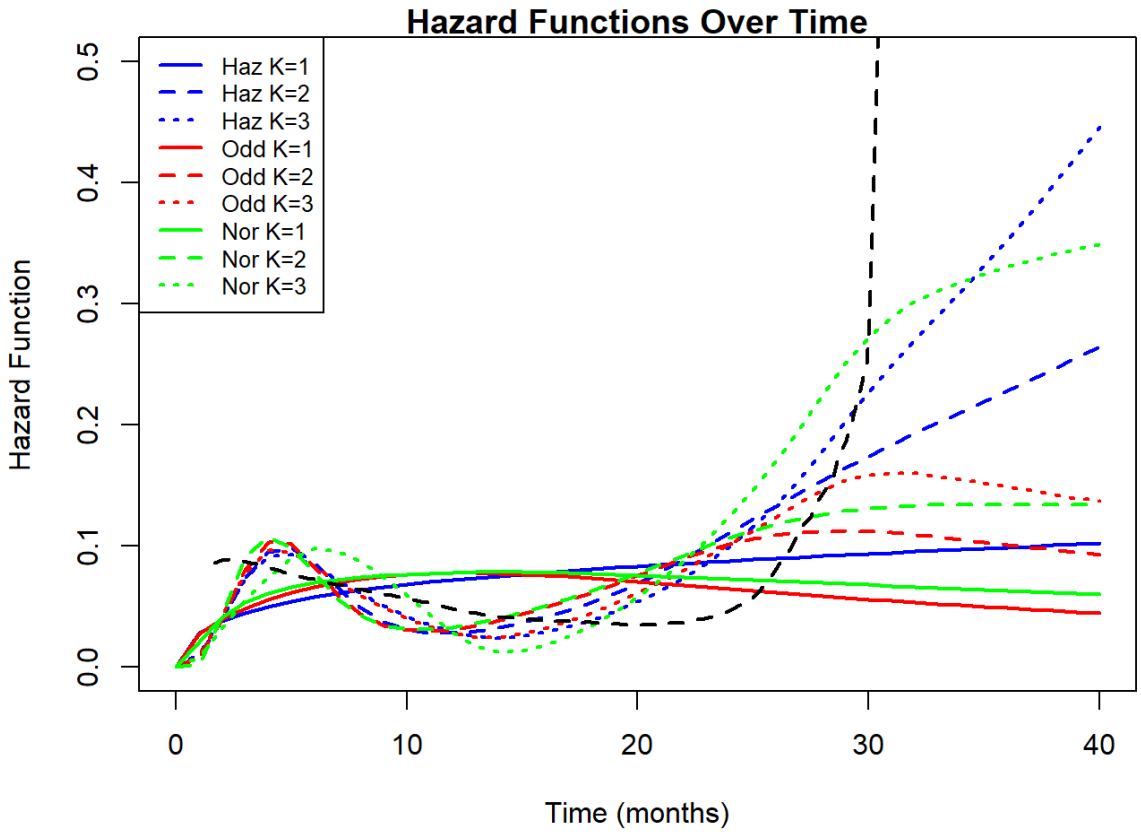

Figure 49: Spline model hazard functions with observed hazards overlaid in black (ibrutinib TTD)

9.10 Zanubrutinib + Ibrutinib pooled TTD

Using the assumption that the TTD model will be equivalent to the best-fitting PFS model and assuming time on ibrutinib is the same as time on zanubrutunib, hence the PFS datasets for both treatments were combined.

9.10.1 Estimated Kaplan-Meier survival

Table 67: Estimated monthly survival from KM plot (combined zanubrutinib and ibrutinib PFS data)

Months	Survival	Months	Survival	Months	Survival
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9.10.2 Statistical fit

The 2-knot normal spline model had the lowest AIC and the lowest BIC. Other similar models were the generalised gamma, 3-knot hazards, 2-knot odds, 3-knot odds, and 3-knot normal models.

Table 68: Statistical model fit (combined zanubrutinib and ibrutinib PFS data)

Model	AIC	BIC	AIC rank	BIC rank
Exponential	[redacted]	[redacted]		
Weibull	[redacted]	[redacted]		
Log-normal	[redacted]	[redacted]		
Log-logistic	[redacted]	[redacted]		
Gompertz	[redacted]	[redacted]		
Generalised Gamma	[redacted]	[redacted]		
Gamma	[redacted]	[redacted]		
Hazards k=1	[redacted]	[redacted]		

Hazards k=2	[redacted]	[redacted]		
Hazards k=3	[redacted]	[redacted]	Similar	
Odds k=1	[redacted]	[redacted]		
Odds k=2	[redacted]	[redacted]	Similar	Similar
Odds k=3	[redacted]	[redacted]	Similar	Similar
Normal k=1	[redacted]	[redacted]		
Normal k=2	[redacted]	[redacted]	**Best**	**Best**
Normal k=3	[redacted]	[redacted]	Similar	

9.10.3 Parametric model visual fit

Figure 50: Parametric model fit over trial length (combined zanubrutinib and ibrutinib PFS data)

9.10.4 Parametric model hazards

The log-normal, log-logistic, Gompertz, and generalised gamma model hazards reasonably fir the observed hazards well.

Figure 51: Parametric model hazard functions with observed hazards overlaid in black (combined zanubrutinib and ibrutinib PFS data)

9.10.5 Spline model visual fit

Figure 52: Spline model fit over trial length (combined zanubrutinib and ibrutinib PFS data)

9.10.6 Spline model hazards

All spline model hazards fit the observed hazards well except the bump in hazards near the beginning of the combined trial periods.

Figure 53: Spline model hazard functions with observed hazards overlaid in black (combined zanubrutinib and ibrutinib PFS data)

Single Technology Appraisal

Zanubrutinib for treating relapsed or refractory mantle cell lymphoma after 1 or more treatments [ID6392]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 28 March 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Opening response to the EAG's report

The Company would like to thank the EAG for the thorough assessment of the evidence submitted. The Company acknowledges the EAG's assessment of the cost-utility analysis which showed that zanubrutinib dominates ibrutinib (i.e., is more effective and less costly) across all scenarios considered. We also welcome the EAG's conclusion that a cost-comparison analysis is an appropriate approach to appraise zanubrutinib in 2L R/R MCL.

The Company agrees that a cost-comparison methodology is an appropriate approach to appraise zanubrutinib in 2L R/R MCL, given zanubrutinib is likely to provide at least similar or greater health benefits to ibrutinib at a lower cost. This approach would reduce uncertainty across the evidence base, since equal efficacy, safety and in turn resource use would be assumed in a cost-comparison analysis. As a result, it would alleviate the issues raised by the EAG regarding: the fit of the parametric models, the long-term overall survival benefit and the resource use levels, adverse events and baseline characteristics applied in the model.

As part of the company submission, a cost-comparison analysis between zanubrutinib and ibrutinib was already presented, see Section B.3.11.3.1 for further details. Based on feedback from the EAG on the appropriateness of the cost-comparison approach, the Company has reproduced the cost-comparison analysis, incorporating the minor change to the Company base case in response to clarification question B9 (to reflect the updated haematologist visit cost). The updated cost-comparison analysis is presented below in Table 1. At zanubrutinib PAS price, and ibrutinib list price, the results show that zanubrutinib is associated with a saving of [redacted] over a lifetime horizon (Note: the minor change impacts the total costs per treatment only since equal efficacy and resource use is assumed).

Table 1: Cost-comparison analysis in patients with 2L R/R MCL

Technologies	Total costs	Incremental costs
Zanubrutinib	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]

2L – second-line; MCL – mantle cell lymphoma; R/R – relapsed or refractory.

1. Factual inaccuracies– Clinical

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.2, p. 24: "Median survival for MCL ranges between 3.1 and 5 years."	The Company cannot verify the median survival range for patients with MCL from the source (https://www.cancerresearchuk.org/). The Company request the EAG check the estimates from the source are correct.	The values are not available at the source referenced.	The survival range and source are cited by the company in CS section B.1.3.3. The EAG agrees that the values are not available at

			the source referenced by the company, but notes that source cites another reference (https://hmrn.org/statistics/survival). The EAG had previously checked the company's values against the survival curves in the second reference and

			considered them comparable. Reworded to: ‘CS section B.1.3.3 states ‘MCL often progresses in line with more high grade lymphomas, with median survival ranging between 3.1 and 5 years’. The EAG notes that the values are not available at the company’s cited source, but

			considers them comparable to another source (https://hmrn.org/statistics/survival).
Section 3.1.1, p. 35: “Suitable terms for MCL were included and no intervention or comparator terms were used to restrict the search, but there is a major error in the Relapsing/Remitting line of the MEDLINE and Embase search (run using Embase.com); “AND adj:ti,ab AND” occurs twice.”	The Company request that the text is amended to: “Suitable terms for MCL were included and no intervention or comparator terms were used to restrict the search, but there is a ~~**major**~~ error in the Relapsing/Remitting line of the MEDLINE and Embase search (run using Embase.com); “AND adj:ti,ab AND” occurs twice.”	The wording should reflect the EAG’s conclusion that this error “has not had an impact on the overall clinical effectivene	Not a factual error. Regardless of the impact of the error on the SLR overall, it is the EAG’s opinion that this was a major error in the search strategy.

		ss SLR" (Section 3.1.1, p. 25).	
Section 3.2.1, p. 40: "Study BGB-3111-AU-003 required adequate haematologic function (neutrophil count >1.0 × 10^9/L, platelet count ≥50 × 10^9/L), renal function (measured or estimated creatinine clearance ≥30 mL/min), and liver function (transaminase levels ≤3× the upper limit of normal [ULN], total bilirubin ≤1.5× ULN)."	The Company request that the text is amended to: "Study BGB-3111-AU-003 required adequate haematologic function (neutrophil count **≥**1.0 × 10^9/L, platelet count ≥50 × 10^9/L), renal function (measured or estimated creatinine clearance ≥30 mL/min), and liver function (transaminase levels ≤3× the upper limit of normal [ULN], total bilirubin ≤1.5× ULN)."	Typographical error.	Typographical error corrected.
Section 3.2.1, p. 40: "Study BGB-3111-206 required adequate organ function, and specific blood counts (neutrophil count ≥1 × 10^9/L, platelet count ≥75	The Company request that the text is amended to: "Study BGB-3111-206 required adequate organ function **(creatinine clearance ≥30**	Correction to reflect all the available informatio	Not a factual error, but additional details

× 10^9/L or ≥50 × 10^9/L for bone marrow involvement), without recent growth factor support or transfusion.”	**mL/min, transaminase levels ≤2.5× UPL, total bilirubin ≤1.5× UPL)**, and specific blood counts (neutrophil count ≥1 × 10^9/L, platelet count ≥75 × 10^9/L or ≥50 × 10^9/L for bone marrow involvement), without recent growth factor support or transfusion.”	n for the BGB-3111-206 trial (available at: BeiGene. Brukinsa. Clinical Study Report BGB-3111-206 trial. 2021), relevant for the compariso n of inclusion	added for information.

		criteria between the two zanubrutinib trials.	
Section 3.2.1, p. 40: "The IRC members as reported in the CSR for BGB-3111-AU-003 were [redacted]) who retrospectively evaluated the radiological findings in accordance with the Lugano classification (2018 CSR for study BGB-3111-AU-003, supplied after clarifications)."	The Company request that the text is amended to: "The IRC members as reported in the CSR for BGB-3111-AU-003 [redacted] who retrospectively evaluated the radiological findings in accordance with the Lugano classification (2018 CSR for study BGB-3111-AU-003, supplied after clarifications)."	Typographical error.	No change needed. The submitted version of the report says: …were [redacted] who retrospectively…

Section 3.2.1, Table 5, p. 41: *Study details row/BGB-3111-206 column:* "Song et al. 2020, Song et al. 2021, Song et al. 2022[27] Song, 2021 #27}[29] NCT03206970"	The Company request that the text is amended to: "Song et al. 2020**[27]**, Song et al. 2021**[28]**, Song et al. 2022**[29]** ~~**Song, et al. 2021 #27}[29]**~~ NCT03206970"	Typographical error and references are missing.	References corrected.
Section 3.2.1, Table 5, p. 43: *Sample size row/BGB-3111-206 column:* "N=86T"	The Company request that the text is amended to: "N=86~~T~~"	Typographical error.	Typographical error corrected.
Section 3.2.2, p. 43: "Concordance between IRC and INV assessments was measured in both studies (see section 3.2.6.2), with the CSR for BGB-3111-206 stating that [redacted] (2024 CSR for	The Company request that the text is amended to: "Concordance between IRC and INV assessments was measured in both studies (see section 3.2.6.2), with the CSR for BGB-3111-206 stating that [redacted]	Typographical error.	Typographical error corrected.

BGB-3111-206 clinical evidence, provided with the CS).”	[redacted] (2024 CSR for BGB-3111-206 clinical evidence, provided with the CS).”		

Sections: *3.2.2, p. 43:* "The second DCO presented in the CS cites the CSR (2021 CSR for BGB-3111-AU-003, provided with the CS) for study BGB-3111-AU-003, but the CSR has a different DCO (02 October 2020) to the CS, and does not report data for the subgroup of patients with R/R MCL who had a 320 mg total daily dose of zanubrutinib (n=32, referred to as the 'full trial population' in the CS). The company provided the CSR for the 13 December 2018 DCO, after initially stating that 'the only available CSR file for [BGB-3111-]AU-003 has a data cut off of the 31st March 2021' (Company response to urgent clarification questions 05/02/025, Clarification C5). The CSR for the 31st March 2021 was requested by the EAG but not provided (Clarification C5). The EAG is	These statements from the EAG relate to an inability to verify data from the AU-003 CSR (dated 31 March 2021). The Company request that the statements are updated upon review of the correct CSR file provided.	The Company acknowledge the error in BGB-3111-AU-003 CSR file provided in the reference pack '43_CONFIDENTIAL_BeiGene_AU-003_CSR_2021'. In the CS the	The EAG notes that the company was informed in Clarification A5 that 'Reference 43 (CSR for BGB-3111-AU-003) data cut is October 2020, so data do not align with data in the CS.' The EAG thanks the company for providing the CSR for the March 2021 after submission of the EAG report.

therefore unable to validate the data at this DCO." *3.2.2, Table 6, p. 44:* a) 31 March 2021 row/CSR (full population) and Other sources (full population) columns: "No[b]; None" b) Table footer: "[b] CS cites CSR (2021 CSR for BGB-3111-AU-003, provided with the CS), but the DCO is 2nd October 2020; correct CSR requested but not provided (Clarification question C5)." *3.2.4, p. 45:* "Patient disposition for the 32 participants with R/R MCL receiving a total daily dose of 320 mg zanubrutinib enrolled in either Phase 1 or Phase 2 of study BGB-3111-AU-003 is presented in the CS for the first DCO		Company erroneously provided an earlier data cut (DCO: 2 October 2020) of the BGB-3111-AU-003 trial which do not present results relevant to R/R MCL cohort of patients. Additionall	However, the EAG notes that this CSR reports clinical effectiveness data for the R/R MCL 320 mg daily dose cohort (n=32), but not adverse event data. The EAG has examined the statements listed by the company and updated them as follows: 3.2.2 p.43 text edited to reflect

of 13th December 2018 only (CS Section B.2a.4.3); data from the 31st March 2021 DCO are not reported in the CS and no CSR was provided for this data cut." *3.2.4, Table 7, p. 46 – Table footer:* "[b]2018 CSR for study BGB-3111-AU-003, supplied after clarifications." *3.2.6.1, Table 9, p. 54 – Table footer:* "[e] NR in CS Table 13 but available in CSR (2018 CSR for study BGB-3111-AU-003, supplied after clarifications) and regulatory summary (BeiGene 2020 Regulatory summary of clinical safety for the BGB-3111-206 and AU-003 trials, provided with the CS)." *3.2.6.2, p. 54:* "The EAG is unable to validate the INV-assessed data for the 31st March 2021 DCO.		y at clarification response the Company did not rectify this error by providing the correct file. The correct version of the CSR file (DCO: 31 March 2021) to	the new CSR reports clinical effectiveness data but not adverse event data.

”*3.2.6.2, Table 10, p. 55:* “[d] No report provided, EAG unable to validate data.” *3.2.6.6, p. 58:* “… but the EAG is unable to validate which is correct (as discussed in section 3.2.2, no published or CSR data were available for the 2L only population, and the CSR for the 31st March 2021 DCO was not provided).” *3.2.7.1, p. 59:* “The company did not provide a CSR for this DCO (Clarification C5) therefore the EAG is unable to validate these data.” *3.2.8, p. 66:* “The EAG is unable to validate any data presented for the 2-L subgroups of either study or the investigator-assessed data for the 31st March 2021 DCO of study BGB-3111-AU-003.”		replace reference 43 was provided to NICE on the 25th of March. The Company apologises for any confusion and hope the correct CSR can be used to verify the BGB-3111-AU-003 data	

3.3.2.4, Table 15, p.72 – End date row/BGB-3111-AU-003 column: "Unclear".		and, therefore, the statements can be updated.	3.2.2, Table 6, a) Row 31 March 2021 changed to 'Partial' , because the CSR provided by the company after submission of the EAG report does not report dose exposure or adverse events data for the R/R MCL 320 mg daily dose cohort.

			b) Footnote [b] edited 'CSR for 31st March 2021 was provided after submission of the EAG report, but does not report patient disposition, dose exposure or adverse events for the R/R MCL 320 mg daily dose cohort'.

			3.2.4 p. 45: The CSR provide by the company (after submission of the EAG report) for the March 2021 DCO does not report these data for the R/R MCL 320 mg daily dose cohort.

			Statement not removed. Sentence edited to clarify this.

			Table 7 footnote [b]: This is correct, no change needed. 3.2.6.1, Table 9, p. 54 – Table footer [e]: This footnote refers to the 2018 DCO

			and is correct, no change needed. Cross-reference to footnote [d] removed for the 31 March 2021 DCO (footnote still applies to the 2L subgroup).

			3.2.6.2, p. 54. This statement has been removed. 3.2.6.2, Table 10, p. 55 footnote[d]: Cross-reference to footnote [d] removed for the 31 March 2021

			DCO (footnote still applies to the 2L subgroup). 3.2.6.6, p. 58: The EAG has checked the CSR and can confirm that CS Table 13 is correct, and the value in Clarification response Table 1 is incorrect. Sentence

			updated to reflect this. 3.2.7.1 p.59 The CSR provided by the company after submission of the EAG report (DCO March 2021) does not report adverse event

			data for the R/R MCL 320 mg daily dose cohort, therefore the statement is correct and cannot be removed. Statement edited to explain this. 3.2.8, p. 66: The CSR provided by the company after submission of the EAG report (DCO March 2021) does not report patient

			disposition, dose exposure or adverse event data for the R/R MCL 320 mg daily dose cohort. Statement edited to reflect this. 3.3.2.4, Table 15 End date row/BGB-3111-AU-003 column: Table updated with information from the CSR

			provided by the company after submission of the EAG report (‘Unclear’ changed to ‘March 2021’).

Section 3.2.5, p. 48: "A [redacted] was seen in the 2L subgroups, see Table X."	The Company request that the text is amended to: "A [redacted] was seen in the 2L subgroups, see **Table 8**."	Typographical error.	Typographical error corrected.
Section 3.2.6.3, p. 56: "At the December 2018 data-cut with a median follow-up of [redacted] months, median INV-assessed PFS was lower at [redacted] months. The improvement from the December 2018 data cut to the March 2021 data cut could be due to immaturity of data at the earlier data cutoff, a more robust estimation over time, or a potential treatment benefit over time."	The Company request that the statement is removed.	At the December 2018 data-cut, the PFS results reported were assessed by IRC, not INV. The median follow-up	Page 112 of the CSR reports INV-assessed PFS for the R/R MCL patients in the 320 mg total daily dose cohort. The EAG has checked the statement against the CSR and considers it to be correct. No change made.

		of [redacted] months and respective PFS values included in the source for this data-cut refers to the IRC-assessed PFS for N=37 R/R MCL patients who received doses	

		other than the 320mg total daily dose relevant for this appraisal. Meaning the data provided is not using the relevant 320mg patient group (N=32). Furthermore, the wording	

		does not include the correct method to assess PFS, which is INV-assessed.	
Section 3.2.6.4, p. 57: "In BGB-3111-AU-003, median IRC-assessed duration of response was 18.53 months (12.58, NE) at the December 2018 DCO and INV-assessed DOR was [redacted] at the December 2018 DCO and [redacted] at the March 2021 DCO."	The Company request that the text is amended to: "In BGB-3111-AU-003, median IRC-assessed duration of response was 18.53 months (12.58, NE) at the December 2018 DCO and INV-assessed DOR was [redacted] ~~**at the December 2018 DCO and**~~ [redacted] at the March 2021 DCO."	At the December 2018 data-cut, DOR was assessed by IRC, not INV. As such, the	INV-assessed DOR was reported in CSR Table 14.2.1.1.2.2. The EAG has checked the text against the CSR and considers it

		statement should be amended.	to be correct. No change made.
Section 3.2.6.4, p.57: “In BGB-3111-AU-003, when comparing the same DCOs, INV-assessed DOR is [redacted] than the IRN-assessed DOR.”	The Company notes a typographical error “...IRN-assessed...” which should read “...IRC-assessed...” but nonetheless request that the statement is removed.	For the BGB-3111-AU-003 study, the earlier DCO of December 2018 reports IRC-assessed DOR only and the latest DCO of March	The CSR reports INV-assessed DOR at the December 2018 DCO. Statement not removed. Typographical error corrected.

		2021 reports INV-assessed DOR only. No other results for different methods of assessing DOR are reported in each source. Thus, the statement should be removed.	

Section 3.2.6.6, p. 57: “[redacted]”	The Company request that the text is amended to: “[redacted]”	The Company would like to clarify that OS was not subject to assessment by either INV or IRC, as per response to clarification question A5.	Sentence edited as follows: Median overall survival was not subject to assessment by either INV or IRC (clarification A5), [redacted]

Section 3.2.7.2, p. 60: "In study BGB-AU-003, [redacted] patients with R/R MCL had died by the 31st March 2021 DCO"	The Company request that the text is amended to: "In study **BGB-3111-AU-003**, [redacted] patients with R/R MCL had died by the 31st March 2021 DCO"	Typographical error.	Typographical error corrected.
Section 3.2.7.4, p. 61: "At least one Grade 3 or higher adverse event was experienced by 68.9% and [redacted] of patients in studies BGB-3111-AU-003 and BGB-3111-206, respectively"	The Company request that the text is amended to: "At least one Grade 3 or higher adverse event was experienced by [redacted] and 50% of patients in studies BGB-3111-AU-003 and BGB-3111-206, respectively"	Typographical error. Note: confidential marking correction is detailed in Section 3, below.	Typographical error and confidential marking corrected.
Section 3.3.2.4, p.70: "These were: number of prior lines of therapy, blastoid status, ECOG PS, presence of bulky	The Company request that the text is amended to:	Typographical error.	Typographical error corrected.

disease, presence of bulky disease, presence of extranodal disease, prior lenalidomide therapy, age, and gender."	"These were: number of prior lines of therapy, blastoid status, ECOG PS, presence of bulky disease, ~~**presence of bulky disease,**~~ presence of extranodal disease, prior lenalidomide therapy, age, and gender."		
Section 3.5.3, p.91: "SPARK had the highest proportion of prior lenalidomide exposure (24%), followed by PCYC-1104 (19%) and RAY-MCL 3001 (6%)."	The Company request that the text is amended to: "**PCYC-1104** had the highest proportion of prior lenalidomide exposure (24%), followed by **SPARK** (19%) and RAY-MCL 3001 (6%)."	Typographical error.	Typographical error corrected.
Section 3.5.4, p. 92 *"*Consistent HRs do not necessarily indicate that all relevant covariate relationships have been appropriately accounted for in the MAIC, question its robustness."	The Company request that the text is amended to: *"*Consistent HRs do not necessarily indicate that all relevant covariate relationships have been appropriately accounted for in the MAIC~~,~~ ~~**questions its robustness**~~."	The Company suggest removing the final part of the sentence as is it	Text amended to: "Consistent HRs do not necessarily indicate that all relevant

		does not read well.	covariate relationships have been appropriately accounted for in the MAIC, questioning the robustness of the results”
Section 3.6.1, p.94: “Any disagreements were resolved though discussion.”	The Company request that the text is amended to: “Any disagreements were resolved **through** discussion.”	Typographical error.	Typographical error corrected.
Section 9.1, Table 52, p. 180:	The Company request that the text is amended to:	Typographical error.	Typographical error corrected.

’Was the follow-up of patients complete?’ row/EAG assessment column: “However, PSF and DOR for subgroup 2L only (n=18) were not estimable at data cut off of13th December 2018 CS Table 13) for IRC-assessment, which raises question about length of follow up for these outcomes.”	“However, **PFS** and DOR for subgroup 2L only (n=18) were not estimable at data **cut-off of** 13th December 2018 **(**CS Table 13) for **IRC-assessment**, which raises question about length of follow up for these outcomes.”		

2. Factual inaccuracies – Cost-effectiveness

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Section 4.2.2, p. 103: *“*However, since time to treatment discontinuation (TTD) was set equal to PFS in the base case analysis	The Company request that the text is amended to: *“*However, since time to treatment discontinuation (TTD) was set equal to PFS in the base case analysis (detailed explanation in	Typographical error.	Typographical error amended as follows: *“*However, since time to treatment discontinuation (TTD) was set equal to PFS in the base case analysis

(detailed explanation in section **Error! Reference source not found.** patients were assumed to receive treatment unless they progressed.”	section **Error! Reference source not found.** patients were assumed to receive treatment unless they progressed**)**.”		(detailed explanation in section **Error! Reference source not found.)** patients were assumed to receive treatment unless they progressed.”
Section 4.2.2, p. 104: “The OS and PFS curves were determined by fitting parametric models to the combined data from BGB-3111-AU-003 and BGB-3111-206 trials.”	The Company request that the text is amended to: “The OS and PFS curves were determined by fitting parametric models to the combined data from BGB-3111-AU-003 and BGB-3111-206 trials **adjusted to the ibrutinib dataset (Rule *et al.* [2017b]) throughout the MAIC analysis**”	It is important to clarify that the parametric curves were fitted to MAIC-adjusted data. Without this clarification, it may be inferred that only a naïve comparison was conducted.	Not a factual error, but additional detail added as requested by the company.

Section 4.2.2, p. 104: "The company's justification for taking this approach was that it overcame issues of poor fit observed with the TTD extrapolations."	The Company request that the text is amended to: "The company's justification for taking this approach was that it overcame issues of poor fit observed with the TTD extrapolations. **Furthermore, the assumption of PFS as a proxy for TTD was supported by clinical experts at an advisory board**.**"**	Importantly, the justification for using PFS was supported by clinical experts.	Not a factual error, but additional detail added as requested by the company.
Section 4.2.2, p. 105: "However, long-term estimates based on this approach underestimated TTD beyond 3 years as er	The Company request that the text is amended to: "However, long-term estimates based on this approach underestimated TTD beyond 3	Typographical error.	Text amended as requested by the company

EAG's clinical expert's opinion."	years as **per** EAG's clinical expert's opinion."		
Section 4.2.3, p. 106: "In response to clarification question B12, the company provided a cost-effectiveness scenario analyses using the 2L population only of the pooled zanubrutinib trials (AU003-206 N=44, weighted to the ibrutinib arm sourced from Dreyling *et al.* [2022] [N=44]) and used results of that analyses as supporting evidence	The Company request that the text is amended to: "In response to clarification question B12, the company provided a cost-effectiveness scenario analyses using the 2L population only of the pooled zanubrutinib trials (AU003-206 N=44, weighted to the ibrutinib arm sourced from Dreyling *et al.* [2022] [N=**99**]) and used results of that analyses as supporting evidence that inclusion of patients who received zanubrutinib at third-line plus	Incorrect number of 2L patients from Dreyling *et al.* (2022).	Text amended as requested by the company

that inclusion of patients who received zanubrutinib at third-line plus does not change the base case cost-effectiveness conclusions.”	does not change the base case cost-effectiveness conclusions.”		
Section 4.2.3, p. 106: “Baseline patient parameters for the modelled populations were derived from the comparator treatment, ibrutinib technology appraisal for MCL (NICE TA502) (i.e., mean age: 68 years; baseline BSA:1.95 m^2;	The Company request that the text is amended to: “Baseline patient parameters for the modelled populations were derived from the comparator treatment, ibrutinib technology appraisal for MCL (NICE TA502) (i.e., mean age: 68 years; baseline BSA: 1.95 m^2; and proportion of males in the cohort: 78.0%**)** (Table 47 CS). **This approach was chosen to align**	The EAG has omitted the Company’s justification for selecting TA502 baseline characteristics for the model baseline characteristics. Furthermore, the Company maintains the selection of the NICE baseline characteristics TA502 (based on the pooled ibrutinib studies [N=370]) for the model is appropriate to ensure consistent datasets are used to inform both	Text has been amended to: “The company justified this approach on the basis that it aligned the baseline patient parameters in the model with the survival data estimated from in the MAIC”

and proportion of males in the cohort: 78.0%. (Table 47 CS). The baseline characteristics are markedly different to those of the pooled zanubrutinib trials (**Error! Reference source not found.** below)."	**the baseline patient parameters in the model with the survival data estimated from in the MAIC.** The baseline characteristics are markedly different from those of the pooled zanubrutinib trials (Table 24 below).	the baseline characteristics and survival data in the model.	
Section 4.2.6, p. 109: "The company described their scenario analysis models in Table 76 of CS B.3.1.1.3 and are also presented in **Error!**	The Company request that the text is amended to: "The company described their scenario analysis models in Table 76 of CS **B.3.11.3** and are also presented in **Error! Reference source not found.**	Typographical error.	Typographical error corrected.

Reference source not found. along with the EAG's scenario analysis models."	along with the EAG's scenario analysis models."		
Section 4.2.6.3, p. 111: "It should be noted that the company presented the sum of AIC and BIC, however it is not appropriate to sum them as this gives them equal weighting and assumed they measure the same thing while there are subtle differences between the two. The AIC focuses on model fit while	The Company request that the text is amended to: "It should be noted that the company presented the sum of AIC and BIC **for illustrative purposes only**, ~~**however**~~ **and the combined AIC and BIC were not used to determine statistical fit."**~~**it is not appropriate to sum them as this gives them equal weighting and assumed they measure the same thing while there are subtle differences between the two. The AIC**~~	The Company considered statistical fit of the curves based on individual AIC and BIC scores, as discussed in the interpretation of AIC and BIC scores in the CS. The combined AIC and BIC scores were presented for illustrative purposes, only.	Not a factual error, no change made.

penalising complexity, while BIC introduces a stronger penalty for complexity, especially in cases with larger sample sizes. By combining these values, the company risks misrepresenting the trade-off between model fit and complexity, as each criterion serves slightly different purposes and is sensitive to different factors. Instead, models with low AIC and low BIC should be considered for the base case separately. This	**~~focuses on model fit while penalising complexity, while BIC introduces a stronger penalty for complexity, especially in cases with larger sample sizes. By combining these values, the company risks misrepresenting the trade-off between model fit and complexity, as each criterion serves slightly different purposes and is sensitive to different factors. Instead, models with low AIC and low BIC should be considered for the base case separately. This would ensure that model selection appropriately balances goodness-of-fit with complexity instead of being~~**		

would ensure that model selection appropriately balances goodness-of-fit with complexity instead of being influenced by an arbitrary combined metric of goodness-of-fit.”	~~**influenced by an arbitrary combined metric of goodness-of-fit.**~~		
Section 4.2.6.4, p. 112: “The company provided the KM plots for this comparison but did not conduct survival modelling for this comparison.”	The Company request that the text is amended to: “The company provided the KM plots for this comparison ~~**but did not conduct survival modelling for this comparison**~~ **in Section B.2.9.5 in the CS. At clarification the Company**	The Company provided the parametric survival analysis of the unadjusted BGB-3111-AU-003 data in response to clarification question B12.	Factual error corrected.

	provided parametric survival analysis of the unadjusted BGB-3111-AU-003 data (B12)."		
Section 4.2.6.5, p.113: "This is supported by the zanubrutinib trial data, where the median follow-up for PFS and OS is approximately 35–38 months, and the median PFS was 33 months."	The Company request that the text is amended to: "This is supported by the zanubrutinib trial data, where the median follow-up for PFS and OS is approximately 35–**39** months, and the median PFS was 33 months **for BGB-3111-206**."	There is a typographical error in the number of months of follow-up for the BGB-3111-AU-003 trial follow-up. Additionally, the EAG has not included the trial name when referring to specific trial data.	Typographical error corrected.
Section 4.2.6.8, Table 28, p. 117: *Zanubrutinib, OS row/Potential models column:*	The Company request that the text is amended to: "Exponential Weibull Log-normal Log-logistic Gompertz **Generalised gamma**	Typographical error, gamma distribution was listed instead of generalised gamma.	Not factual error, gamma model was the correct model considered.

"Exponential Weibull Log-normal Log-logistic Gompertz Gamma 1-knot hazards 1-knot odds **1-knot normal"**	1-knot hazards 1-knot odds **1-knot normal**"		
Section 4.2.6.8, Table 28, p. 118: Zanubrutinib, TDD row/Justification column "**Spline model fit**: 3-knot models fit good fit except for bump in KM plot around 30 to 40 months"	The Company request that the text is amended to: "**Spline model fit**: 3-knot models fit good ~~**fit**~~ except for bump in KM plot around 30 to 40 months"	Typographical error.	Typographical error corrected.
Section 4.2.6.12, p. 126:	The Company request that the text is amended to:	Typographical error.	Formatting issue corrected.

"Figure 11, Figure 12 and [image] Figure 13. All the EAG and company models for TTD present all of the EAG's and company's models for each outcome"	"Figure 11, Figure 12 and **[image]** Figure 13**~~. All the EAG and company models for TTD~~** present all of the EAG's and company's models for each outcome"		
Section 4.2.9, p. 136: "According to the CS, health state resource use was based on what was previously accepted in TA502. No further details were provided in the CS document B."	The Company request that the text is amended to: "According to the CS, health state resource use was based on what was previously accepted in TA502. **The clinical experts the Company consulted as part of the advisory board (2024) generally agreed with the estimates from NICE TA502. ~~No~~**	The Company shared the health care resource use from NICE TA502 with clinical experts at an advisory board (2024) to understand whether the estimates were reflective of UK clinical practice. Clinical experts agreed with the estimates but suggested inclusion of computerised tomography (CT) scans at a resource use of twice per annum.	Text amended as requested by the company

	~~**further details were provided in the CS document B**~~.	This is documented in the CS Section B.3.5.2 (page 179) and in the advisory board report (Reference "*2: BeiGene. Advisory Board Report for zanubrutinib monotherapy in patients with R/R MCL [Data on file]. 2024*"). However, the Company acknowledge this may not have been made clear in the CS.	
Section 4.2.10, Table 37, p. 139: PFS – distribution for zanubrutinib row/Measurement of uncertainty and distribution: confidence	The Company request that the text is amended to: "**Normal** distribution (Cholesky decomposition)"	Typographical error.	Typographical error corrected

interval (distribution) column “Normjal distribution (Cholesky decomposition)”			
Section 5.1, p. 146: “…amended to reflect the updated the haematologist visit cost …”	The Company request that the text is amended to: “…amended to reflect the updated ~~**the**~~ haematologist visit cost …”	Typographical error.	Typographical error corrected.
Section 5.1, p. 148: “Univariate sensitivity analysis was performed on 10 parameters considered to be most	The Company request that the text is amended to: “Univariate sensitivity analysis was performed for ~~**10 parameters considered to be most influential by the**~~	This sentence does not reflect how the univariate analysis was conducted. For clarity, the univariate sensitivity analysis was performed for each parameter considered and the 10 most sensitive parameters were	Text amended as requested by the company

influential by the company.”	~~**company**~~ **each parameter in the model**.”	presented in a table and tornado diagram.	
Section 5.1, p. 148: “The analysis was performed for each comparator …”	The Company request that the text is amended to: “The analysis was performed for each **parameter** …”	Typographical error.	Typographical error corrected
Section 5.1, Table 41, p. 148: *Table caption:* “Table 41: Univariate sensitivity results (MNB at WTP £30,000) for zanubrutinib vs ibrutinib in patients with 2L R/R MCL**”**	The Company request that the text is amended to: “Table 41: Univariate sensitivity results (**NMB** at WTP £30,000) for zanubrutinib vs ibrutinib in patients with 2L R/R MCL”	Typographical error.	Typographical error corrected.

Section 5.1, p. 156: "… we maintain that the results highlight the significant uncertainty with the base case analysis …"	The Company request that the text is amended to: "… we maintain that the results highlight the ~~**significant**~~ uncertainty with the base case analysis …"	The Company maintains that the uncertainties in the economic evaluation were thoroughly explored in the unanchored MAIC with several sensitivity analyses, as well as extensive model sensitivity analyses, including deterministic, probabilistic, and scenario analyses. Importantly, zanubrutinib dominates ibrutinib in both the Company's and EAG's base case and sensitivity analyses.	Text amended as requested by the company.
Section 6, Table 47, p. 159: *Extrapolation of zanubrutinib OS row/Issues column:*	The Company request that the text is amended to: "Extrapolation of **ibrutinib** OS"	Typographical error.	Text amended as requested by the company.

"Extrapolation of zanubrutinib OS"			
Section 6.1, p.161: "Explore impact on ICER of including grade 3 AEs occurring in ≥2% of population in the economic model"	The Company request that the text is amended to: "Explore impact on ICER of including **grade ≥3** AEs occurring in ≥2% of population in the economic model"	Typographical error.	Text amended as requested by the company.
Section 6.1, Table 48	The Company request the EAG update the formatting of the table to read easier.	Formatting error.	The table has been re-formatted.
Section 6.1, Table 48, p. 162: *Baseline characteristics used in the economic model row/Incremental*	The Company request the EAG check the alternative baseline characteristics exploratory scenario analysis and amend the text to (if agreement of the error): Incremental costs (£) "[redacted]"	The Company arrives at different results when using the pooled zanubrutinib baseline characteristics presented in Table 48 of the EAGs Exploratory analysis. Note the Company has	The EAG apologises for the error and amended the text to reflect the correct values

costs (£) and % Change in QALYs columns: Incremental costs (£) "[redacted]" Incremental QLAYs "[redacted]" % Change in QALYs [redacted]"	Incremental QALYs "[redacted]" % Change in QALYs [redacted]"	used the Company's updated CEM, shared with the EAG following post clarification questions, ("*ID6392_Zanubrutinib in rrMCL_cost-effectiveness model_CQ response_v1.0_17Feb25_CON*")	
Section 6.1, Table 48, p. 162: *Range of adverse events included in the economic model row/Base case value column:*	The Company request that the text is amended to: "Grade 3**+** AES in ≥5% of patients in AU003-206"	Typographical error.	Text amended as requested by the company

“Grade 3 AES in ≥5% of patients in AU003-206”			

3. Confidential marking corrections

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 3.2.6.5, p.57: “However, there was no difference between the assessors for the median TTR, both at [redacted] months.”	The median IRC-assessed TTR for the BGB-3111-206 is publicly available. Thus, by disclosing that there is no difference between the assessors for the median TTR, INV-assessed TTR can be inferred.	“However, there was [redacted] the assessors for the median TTR, [redacted] months.”	Amended as requested.

Section 3.2.7.2, p. 60: "In study BGB-AU-003, [redacted] patients with R/R MCL had died by the 31st March 2021 DCO; three of the deaths were due to adverse events."	Death due to AEs from the BGB-3111-AU-003 trial has not yet been published and is considered confidential. Note: a typographical error in the same text has been identified and is summarised in Section 1, above.	"In study BGB-3111-AU-003, [redacted] patients with R/R MCL had died by the 31st March 2021 DCO; [redacted] of the deaths were due to adverse events."	Amended as requested.
Section 3.2.7.4, p.61: "At least one Grade 3 or higher adverse event was experienced by 68.9% and [redacted] of patients in studies BGB-3111-AU-003 and BGB-3111-206, respectively."	Incidence of grade 3 or higher adverse events for the BGB-3111-AU-003 trial has not yet been published and is considered confidential.	"At least one Grade 3 or higher adverse event was experienced by [redacted] and 50% of patients in studies BGB-3111-AU-003 and BGB-3111-206, respectively."	Amended as requested.

	Conversely, it is publicly available for the BGB-3111-206 trial. Note: a typographical error in the same text has been identified and is summarised in Section 1, above.		
Section 3.2.7.4, p. 61: "The most common events in BGB-3111-AU-003 were pneumonia ([redacted]), anaemia ([redacted]) and myalgia ([redacted]), and in BGB-3111-206 were neutrophil count decreased (18.6%), pneumonia (12.8%), platelet count decreased (7.0%), and white blood cell count	Incidence of white blood cell count decreased from the BGB-3111-206 trial has not yet been published and is considered confidential.	"The most common events in BGB-3111-AU-003 were pneumonia ([redacted]), anaemia ([redacted]) and myalgia ([redacted]), and in BGB-3111-206 were neutrophil count decreased (18.6%), pneumonia (12.8%), platelet count decreased (7.0%), and white blood cell count decreased ([redacted]) (see Table 13 for details)."	Amended as requested.

decreased (7.0%) (see Table 13 for details)."			
Section 3.2.7.4, Table 13, p. 62: *White blood cell count decreased[a] row/BGB-3111-206 column:* "6 (7.0)"	Incidence of white blood cell count decreased from the BGB-3111-206 trial has not yet been published and is considered confidential.	"[redacted]"	Amended as requested.
Section 3.2.7.5, p.63: "The most common events in study BGB-3111-AU-003 were diarrhoea ([redacted]), constipation ([redacted]) and upper respiratory tract infection ([redacted]), and in in BGB-3111-206 were neutrophil count decreased (46.5%), upper respiratory tract infection (38.4%),	Incidence of rash from the BGB-3111-206 trial has not yet been published and is considered confidential.	"The most common events in study BGB-3111-AU-003 were diarrhoea ([redacted]), constipation ([redacted]) and upper respiratory tract infection ([redacted]), and in in BGB-3111-206 were neutrophil count decreased (46.5%), upper respiratory tract infection (38.4%), rash ([redacted]), white blood cell count	Amended as requested.

rash (36.0%), white blood cell count decreased (33.7%) and platelet count decreased (32.6%).”		decreased (33.7%) and platelet count decreased (32.6%).“	
Section 3.4.8, p.83: “The sensitivity analyses all resulted in [redacted] except the HR from the naïve-comparison of sensitivity analysis [redacted], using [redacted] which was [redacted] despite showing a [redacted] in the odds of death for zanubrutinib compared to ibrutinib.”	Indirect treatment comparison results have not yet been published and are considered confidential.	“The sensitivity analyses all resulted in [redacted] except the HR from the naïve-comparison of sensitivity analysis [redacted], using [redacted] which was [redacted] despite showing a [redacted] in the odds of death for zanubrutinib compared to ibrutinib.”	Amended as requested.
Section 4.2.3, Table 24, p. 107 Age, BSA (m^2) and proportion male rows/Mean column “Age: [redacted]	The baseline characteristics for the pooled zanubrutinib trials has not yet been published and is	“Age: [redacted] BSA (m^2): [redacted] Proportion male: [redacted]”	Amended as requested.

BSA (m^2): [redacted] Proportion male: [redacted]”	considered confidential. Therefore, the Company would request the baseline characteristics are underlined as well as highlighted per confidential mark-up convention.		
Section 4.2.6, Table 26, p. 109	The Company’s zanubrutinib survival extrapolations have not yet been published and are considered confidential. Therefore, the Company would request that all the Company’s survival extrapolations for	-	Amended as requested.

	zanubrutinib at key timepoints to be underlined and highlighted blue.		
Section 4.2.6: a) *Figure 5, p. 120* b) *Figure 6, p.121* *c) Figure 7, p. 122* *d) Figure 8, p.123* *e) Figure 9, p. 124* *f) Figure 10, p. 125* *g) Figure 11, p. 127* *h) Figure 12, p. 128* *i) Figure 13, p. 129*	The Company's zanubrutinib survival extrapolation curves have not yet been published and are considered confidential. Therefore, the Company would request that all the figures which Company's extrapolations for PFS, OS or TTD are underlined and highlighted blue.	-	Amended as requested.

Section 4.2.9, p. 133: "…comprising a discount of [redacted] was applied to zanubrutinib's drug acquisition costs …"	The PAS discount for zanubrutinib is considered strictly confidential. Therefore, the Company would request the PAS discount to be underlined as well as highlighted as per mark-up convention.	"… comprising a discount of [redacted] was applied to zanubrutinib's drug acquisition costs …"	Amended as requested.
Section 5.1 *a) Table 41, p. 148* *b) Figure 16, p. 149*	The Company's univariate sensitivity analysis results have not yet been published and are considered confidential. Therefore, the Company would request all the data and parameter names	-	Amended as requested. However, company did not mark the sensitivity analyses as confidential in CS.

	in Table 41, and Figure 16 to be underlined and highlighted blue.		
Section 6.1, Table 48, p. 162-166	The Company request all confidential highlighted information is underlined as well as highlighted as per mark-up convention.	-	Amended as requested.
Section 6.1, Table 49, p. 167: footnote	The Company request all confidential highlighted information is underlined as well as highlighted as per mark-up convention.	-	Amended as requested.
Section 6.2.1, Table 51, p. 169:	The Company request the confidential highlighted information	“[redacted]”	Amended as requested.

Ibrutinib row/ICER (£) of Zanubrutinib (QALYs) column: "[redacted]"	is underlined as well as highlighted as per mark-up convention.		
Section 9.1, Table 52, p.180: 'Was the outcome accurately measured to minimise bias?' row/EAG Assessment column "Concordance rates between INV and IRC at each DCO were reported, and were [redacted] for ORR and [redacted] for best overall response, and median duration of response [redacted] (2024 CSR for BGB-3111-206 clinical evidence and BeiGene 2020 Regulatory summary of clinical safety	The Company requests that non-confidential text is not be underlined.	"Concordance rates between INV and IRC at each DCO were reported, and were [redacted] for ORR and [redacted] for best overall response, and median duration of response [redacted] (2024 CSR for BGB-3111-206 clinical evidence and BeiGene 2020 Regulatory summary of clinical safety for the BGB-3111-206 and AU-003 trials, provided with the CS)"	Amended as requested.

for the BGB-3111-206 and AU-003 trials, provided with the CS)”			

