Single Technology Appraisal

Zanubrutinib for treating marginal zone lymphoma after anti-CD20-based treatment [ID5085]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Zanubrutinib for treating marginal zone lymphoma after anti-CD20-based treatment [ID5085]

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 submissions** from:
   a. Lymphoma Action

4. **Expert personal perspectives** from:
   a. Dr Kim Linton – clinical expert, nominated by BeiGene
   b. Dr Renata Walewska – clinical expert, nominated by the British Society for Haematology
   c. Frank Burroughs – patient expert, nominated by Lymphoma Action

5. **External Assessment Report** prepared by Newcastle NIHR TAR Team
   a. External Assessment Report
   b. EAG addendum

6. **External Assessment Report – factual accuracy check**

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

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Single technology appraisal

Zanubrutinib for treating relapsed or refractory marginal zone lymphoma ID5085

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Company evidence submission

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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 is to evaluate the clinical- and cost-effectiveness of zanubrutinib (brand name BRUKINSA) as a monotherapy for adult patients with relapsed/refractory (R/R) marginal zone lymphoma (MZL) within its marketing authorisation. On the 15th September 2022, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending a change to the terms of the marketing authorisation for zanubrutinib to include the new indication for the treatment of MZL:

- BRUKINSA as monotherapy is indicated for the treatment of adult patients with MZL who have received at least one prior anti-CD20-based therapy.[1]

On the 28th October 2022, marketing authorisation was subsequently granted by the European Medicines Association (EMA), followed by approval by the Medicines and Healthcare products Regulatory Agency (MHRA) through the European Commission Decision Reliance Procedure on the 6th January 2023.[2,3]

This submission covers the technology's full marketing authorisation for the treatment of patients with R/R MZL who have received at least one prior anti-CD20-based therapy. In this context, an anti-CD20 therapy refers to a treatment approach that utilises rituximab, a form of immunotherapy that specifically targets the cluster of differentiation 20 (CD20) protein.

The decision problem is displayed 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 MZL who have had at least 1 prior anti-CD20-based therapy	As per scope	N/A
Intervention	Zanubrutinib	As per scope	N/A
Comparator(s)	• Rituximab with or without chemotherapy • Chemotherapy • Best supportive care • Splenectomy (for splenic marginal zone lymphoma only)	• Rituximab with or without chemotherapy • Chemotherapy	The following treatments listed as comparators within the final scope are not considered appropriate for adults with MZL who have had at least one anti-CD20-based therapy, as confirmed by UK clinical experts in attendance at an advisory board (11th October 2023)[4]: • **Splenectomy**: Splenectomy is not recognised as a treatment option for patients with R/R MZL within the ESMO guidelines. Instead, the guidelines emphasise that splenectomy was traditionally considered as the recommended first-line treatment for patients with splenic MZL. However, as a major, non-curative surgical procedure that may have severe, acute, and potentially fatal downstream complications, it has largely been replaced by rituximab (with or without chemotherapy) and only considered in very select cases where rituximab is not indicated.[5] Data from the HMRN registry shows that out of [redacted] patients diagnosed with MZL between 2005 to 2020, only [redacted] patients had received a splenectomy, which was performed close to diagnosis as part of their first-line treatment.[6] UK clinical experts in attendance an advisory board (11th October 2023) confirmed that splenectomy is not a relevant comparator for this decision problem.[4] • **BSC**: The approach to care for patients with R/R MZL involves active monitoring or systemic treatment. For MZL patients with recurrent

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			disease, ESMO guidelines recommend treatment with rituximab-based CIT or rituximab monotherapy.[5] Feedback gathered from a UK advisory board (11th October 2023) confirmed that BSC is only considered once patients have exhausted all viable treatment options, including clinical trials, and are too frail to tolerate any active therapy. As such, BSC would be considered as end-of-life care and not as a comparator for zanubrutinib in patients able to receive active treatment.
Outcomes	• Overall survival • Progression-free survival • Response rates • Duration of response • Adverse effects of treatment • Health-related quality of life	As per scope	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
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 Personal Social Services 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-utility analysis in adults with MZL who have had at least 1 prior anti-CD20-based therapy is presented comparing zanubrutinib with relevant comparators. For further details please refer to Section B.3 Cost effectiveness.	N/A

BSC – best supportive care; CD20 – cluster of differentiation 20; CIT – chemoimmunotherapy; ESMO – The European Society for Medical Oncology; HMRN - Haematological Malignancy Research Network; MZL – marginal zone lymphoma; N/A – not applicable; NICE – National Institute for Health and Care Excellence; NHS – National Health Service; R/R – relapsed / refractory; UK – United Kingdom

B.1.2 Description of the technology being evaluated

A description of zanubrutinib is presented in Table **2.**

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.[7] In non-clinical studies, zanubrutinib inhibited malignant B-cell proliferation and reduced tumour growth.[2] Zanubrutinib is specific and selective for BTK and was designed to minimise off-target inhibition of other kinases.
Marketing authorisation/CE mark status	On the 15th September 2022, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for zanubrutinib, to include the new indication for the treatment of MZL: • BRUKINSA as monotherapy for the treatment of adult patients with MZL who have received at least one prior anti-CD20-based therapy.[1] On the 28th October 2022, marketing authorisation was subsequently granted by the EMA, followed by approval by the MHRA through the European Commission Decision Reliance Procedure on the 6th January 2023.[2,3]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	BRUKINSA as monotherapy is indicated for the treatment of adult patients with MZL who have received at least one prior anti-CD20-based therapy.[2]
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).[2] 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.[8]
Patient access scheme (if applicable)	[redacted]

Source: Zanubrutinib SmPC.[2]
BCR – B-cell antigen receptor; BTK – Bruton's tyrosine kinase; CD20 – cluster of differentiation 20; CHMP – Committee for Medicinal Products for Human Use; EMA – European Medicines Agency; MZL – Marginal zone lymphoma; PAS – Patient access scheme; SmPC – Summary of Product Characteristics; UK – United Kingdom.

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

B.1.3.1 Disease overview

Non-Hodgkin's lymphoma (NHL) refers to a diverse spectrum of cancers that impact the lymphatic system.[9] 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 reflect the specific lymphoma subtype of the cells from which they originated.[9,10]

MZL is a group of indolent NHL that develops from B lymphocytes that are normally found at the edge of areas of lymph node tissue.[11] MZL can occur at any age, but is mostly diagnosed in the elderly, with an average age at diagnosis between 60 and 70 years.[12] The incidence of MZL is greater in men compared with women, with an annual incidence of 4.1 per 100,000 persons per year in the UK.[13]

The World Health Organisation (WHO) recognises three main subtypes of MZL depending on the tissue type of origin: extranodal (also known as mucosa-associated lymphoid tissue lymphoma or MALT), nodal, and splenic.[14] There are variations in clinical characteristics based on the site of origin of MZL, therefore, MZL subtype can influence the selection of first-line treatment options.[5,15] However, once patients with MZL relapse, the relevance of their initial subtype becomes less significant when making treatment decisions as the emphasis shifts to slowing down the progression of the disease rather than its initial cause.

Symptoms occur only in a minority of patients with MZL at diagnosis and differ depending on the tissue involved. Common symptoms include B symptoms (i.e., fever, weight loss, night sweats), fatigue, lymphadenopathy, splenomegaly and cytopenia. Some site-specific complications may also be present.[16–18]

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:[19]

- 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.

The optimal staging of MZL is subject to ongoing discussion. 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 TNM (tumour, node, metastasis)-based Paris staging system.[20] The Lugano system is the most commonly used staging system in clinical practice, and also is integrated into the treatment algorithms outlined in the European Society for Medical Oncology (ESMO) guidelines.[5] The Lugano system was used to stage patients in the two clinical studies for zanubrutinib in R/R MZL – MAGNOLIA (NCT: NCT03846427) and AU-003 (NCT: NCT02343120).[21,22] A comparison of staging systems is presented in Table 3.

Table 3: Comparison of commonly used staging systems in MZL[20]

Lymphoma Extent	Ann Arbor Stage	Paris Staging	Lugano Staging
Mucosa and submucosal layer	I1E	T1N0M0	I
Muscularis propria, serosal layer	I2E	T2N0M0	I
Penetration beyond serosa	I2E	T3N0M0	I
Direct infiltration of adjacent organs	I2E	T4N0M0	IIE
Locoregional lymph nodes	II1E	T1-T4N1M0	II1
Abdominal lymph nodes (beyond local)	II2E	T1-T4N2M0	II2

Lymphoma Extent	Ann Arbor Stage	Paris Staging	Lugano Staging
Extra-abdominal lymph node spread	IIIE	T1-T4N3M0	IV
Dissemination to distant/non-GI organs	IV	T1-T4N0-N3M1	IV

GI – gastrointestinal; MZL – Marginal zone lymphoma.

Disease presentation and clinical symptoms of MZL are often unspecific and can vary based on site of involvement as described below.

Extranodal MZL

Extranodal MZL can originate at any extranodal site and arises in organs that typically lack lymphoid tissue such as the stomach (most common), thyroid, skin, lungs, and salivary glands. Most patients with extranodal MZL are initially asymptomatic and present with localised (Stage I or II) disease. If symptoms develop, the severity and location of the symptoms are dependent on the location of the lymphoma.[23] Extranodal MZL is frequently associated with chronic inflammation and infectious agents that can give rise to chronic infections, such as *Helicobacter pylori* in gastric extranodal MZL.[24]

Extranodal MZL is often detected during a routine clinical check-up and clinical presentation will differ depending on the tissue involved.[25] In most instances, clinical presentation involves the presence of a slow growing mass, chronic tissue inflammation, chronic infection or autoimmune disorders at the affected organ. Extranodal MZL is typically diagnosed through a biopsy of the affected tissue.[26]

Extranodal MZL often remains localised to the tissue of origin for long periods. However, it can spread to other sites of lymphoid tissues, lymph nodes, or bone marrow. Approximately 30% of patients are diagnosed with advanced stage disease, characterised by multiorgan involvement.[20,27]

Nodal MZL

Nodal MZL can occur in one or more lymph nodes, predominately in the head and neck region.[28] Whilst approximately 60% of patients are diagnosed with advanced stage disease, patients typically present with painless abnormal lymph nodes.[29] Symptoms relate to the swelling of lymph nodes and vary depending on the location

of the lymphoma. Swollen lymph nodes can exert pressure on the airways or oesophagus, leading to challenges in breathing or eating. Additionally, lymph nodes located near nerves can cause severe pain.[28] Nodal MZL is typically diagnosed through a biopsy to remove part or all of the affected lymph node.[28]

A minority of patients present with B symptoms (i.e., fever, night sweats, unintentional weight loss), anaemia or thrombocytopenia once the lymphoma becomes more advanced.[28] Elevated serum levels of lactate dehydrogenase, beta-2 microglobulin or monoclonal immunoglobulin are present in up to half of patients with nodal MZL.

The spleen and other extranodal tissues are not usually involved at presentation, however, spread to these sites may occur in advanced disease. About 30% of patients with nodal MZL show bone marrow involvement.[30]

Splenic MZL

Splenic MZL is characterised by a marginal zone growth pattern in the spleen. Whilst many patients present without symptoms when first diagnosed, splenic MZL is often associated with an enlarged spleen, often discovered during an abdominal examination.[28] Patients with splenic MZL also may present with lymphocytosis or cytopenia caused by the accumulation of lymphoma cells in the spleen hindering the body's ability to generate blood cells.[31]

As with nodal MZL, the bone marrow is a frequently involved site in advanced or disseminated disease.[30] Splenic MZL is typically diagnosed through a combination of blood tests, scans, and bone marrow samples. In rare cases, diagnosis may be made after an operation to remove the spleen.[28]

Advanced stage MZL

Advanced stage MZL is defined as disease that has disseminated from its tissue of origin to different nodal or extranodal sites. In most patients with advanced MZL, the lymphoma spreads from one initial location to other extranodal localisations such as the bone marrow and spleen.[32] Advanced stage MZL is associated with a higher symptomatic burden and worse prognosis.[33]

The natural history of advanced MZL is characterised by a continuing pattern of relapse and remission.[34] When relapse occurs, it is prone to manifesting at an advanced stage due to the slow growing nature of MZL, which can delay the detection of relapses. Additionally, the development of resistance to previous treatments also contributes to the increased likelihood of advanced relapse.[5] Once patients with MZL 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.

B.1.3.1.2 Epidemiology

With an estimated annual incidence of 4.1 per 100,000 persons per year in the UK, MZL is considered an orphan disease.[13] MZL can occur at any age but is mostly diagnosed in patients over 60 years of age, with a slight male predominance. Patients who require systemic therapy due to advanced disease have a median age of 69 years.[35]

The proportion of patients with R/R disease can vary depending on the stage at diagnosis and other individual patient factors. The Haematological Malignancy Research Network (HMRN) is the largest UK registry and gathers information on lymphomas and other blood disorders from a population-based patient cohort. HMRN data collected from a cohort of [redacted] newly patients diagnosed with MZL, between 2005 to 2020, recorded that of [redacted] ([redacted]%) patients were treated with an anti-CD20-based therapy, and of these patients [redacted] ([redacted]%) went on to receive further treatment.[6]

B.1.3.2 Burden of MZL

MZL is a chronic disease associated with high disease morbidity and detriments to quality of life. As such, improving or maintaining quality of life is vital, especially in patients with more advanced or progressed disease.

B.1.3.2.1 Symptom burden

Often patients with MZL initially present with asymptomatic, indolent disease. After the shock of diagnosis, patients can spend a long time in the active monitoring stage, causing anxiety and uncertainty around their prognosis. In a previous NICE appraisal

and in a virtual discussion the Company had during the preparation of this appraisal, UK patient representatives described the uncertainty of active monitoring as stressful, with many people experiencing anxiety. Planning for the future can be challenging for some people due to uncertainty about when they might need to begin treatment or the anxiety of a potential relapse.[36,37]

The symptom burden of MZL can vary depending on the subtype and location of the disease. Common symptoms indicative of MZL include B symptoms (i.e., fever, weight loss, night sweats), fatigue, lymphadenopathy, splenomegaly or cytopenia (anaemia, thrombocytopenia, neutropenia). HMRN data collected from a cohort of [redacted] patients diagnosed with MZL between 2005 to 2020 recorded [redacted] of patients experiencing weight loss and [redacted] experiencing night sweats at the time of diagnosis, highlighting the prevalence of B symptoms.[6]

Site-specific complications are also common. In nodal MZL, lymph nodes located near nerves can cause pain and exert pressure on the airways or the oesophagus, causing difficulty breathing or eating.[28] Gastric extranodal MZL can cause symptoms such as persistent indigestion and stomach pain.[23] Splenic MZL can cause patients to have an enlarged spleen which may put pressure on the stomach causing pain or a feeling of fullness.[28]

In a previous NICE appraisal and in a virtual discussion the Company had during the preparation of this appraisal, UK patient representatives have described 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.[36,37] The enlargement of lymph nodes, spleen, and other organs can lead to discomfort and pain, impacting the patient's quality of life. Furthermore, in addition to this physical burden, the mental state of patients is affected and psychological issues arise. The emotional toll of facing a relapse and undergoing additional treatment with chemotherapy can contribute to heightened distress and anxiety in patients.[36,37] This anxiety is further exacerbated by the lack of approved treatment options in R/R MZL, with no safe and efficacious targeted therapies available.

B.1.3.2.2 Impact on quality of life

MZL can significantly impact a patient's quality of life due to its symptoms and treatment implications. However, there is limited literature available that formally quantifies the health-related quality of life (HRQoL) impact of MZL on patients.

One study of a mixed population of 97 indolent NHL survivors (including 67 with MZL and 27 with follicular lymphoma [FL]), found that NHL survivors reported a lower HRQoL than that of the general population. Patients reported lower physical, role, emotional, cognitive, and social function scores reported using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), highlighting the negative impact on patients. The majority of long-term survivors in the study reported fear of relapse or second malignancy as their most distressing problem, regardless of NHL aggressiveness or stage.[38]

Patients with R/R MZL are likely to have a more significant decrement in HRQoL compared to those who are newly diagnosed.[39] When disease returns after initial treatment, patients are faced with recurring symptoms such as fatigue, night sweats and swollen lymph nodes.[40] Additionally, the emotional burden of an impending relapse, uncertainty related to disease progression, and the need for further treatment can take a toll on their mental well-being. Furthermore, there is a distinct lack of approved treatment options for patients with R/R MZL, which adds to the emotional burden of experiencing a relapse.[5]

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.[41]

B.1.3.3 Life expectancy

The course of MZL is generally indolent with a 5-year overall survival rates ranging between 64% and 75% depending on disease location.[42] Advanced disease and presence of B symptoms are associated with a significantly worse prognosis. HMRN

data collected from a cohort of [redacted] patients diagnosed with MZL between 2005 to 2020 demonstrated a median overall survival of [redacted] years. Additionally, in patients with R/R MZL, median overall survival was [redacted] years from the start of second-line treatment following prior treatment with an anti-CD20 antibody-based regimen.[6]

B.1.3.4 Clinical pathway of care and place in therapy

Often patients with MZL present with asymptomatic, early-stage disease at first and are generally managed with an active monitoring approach. Treatment is often only initiated once patients develop symptomatic disease. The goal of MZL treatment is to provide remission of symptomatic disease and long-lasting progression-free survival (PFS).[5]

The choice of first-line treatment is dependent on several factors, including MZL subtype and disease stage. Localised disease is generally treated with curative intent with pathogen eradication and/or radiotherapy, however patients with advanced and/or disseminated disease require treatment with a systemic therapy.[5]

The ESMO guidelines generally recommend rituximab-based chemoimmunotherapy, chemotherapy alone or rituximab monotherapy as systemic therapy for MZL in the first-line setting.[5] Notably, these treatments are recommended by clinical guidelines for MZL due to their efficacy in other indolent NHL, however relatively few therapies have been specifically tested in MZL, and hence there are no licensed treatments for MZL.[5,43,44]

HMRN data collected from a cohort of [redacted] UK patients who received their MZL diagnosis between 2005 to 2020 supports the use of these treatments in the first-line setting, with particularly high usage of bendamustine-rituximab ([redacted]%), rituximab-cyclophosphamide +/- steroids ([redacted]%), rituximab monotherapy ([redacted]%) and rituximab-cyclophosphamide-vincristine-prednisone (R-CVP) ([redacted]%) in patients starting treatment between 2016-2023, with almost [redacted]% of patients receiving these treatments.[6]

Following an initial response to treatment, some patients with MZL relapse and require additional therapy. In addition, a proportion of patients have disease which is refractory to initial treatment. There is no standard of care for patients with R/R MZL.

Table 4 Clinical guidelines recommend a repetition of rituximab-based chemoimmunotherapy or rituximab monotherapy if prior therapy has achieved a long-term remission of symptomatic disease (>24 months). However, rituximab-based chemoimmunotherapy and rituximab monotherapy are less effective after prior systemic therapy.[25,45,46] In particular, for patients who relapsed quicker (≤ 24 months) or did not respond to prior therapy, therapeutic options become limited and clinical guidelines recommend considering the use of non-approved treatment options through enrolment in clinical trials.[5]

HMRN data collected from a cohort of [redacted] patients diagnosed with MZL between 2005 to 2020 recorded [redacted] patients were treated with an anti-CD20-based therapy, and [redacted] ([redacted]%) of the these patients went on to receive further treatment, the most common ones being bendamustine-rituximab (BR), rituximab monotherapy and R-CVP, used in [redacted], [redacted]% and [redacted] of patients, respectively.[6] (Table 4). Unlike first-line treatment, disease subtype no longer has an impact on treatment decisions, as confirmed by UK clinical experts in attendance at an advisory board (11th October 2023).[4]

Table 4: Relapse/refractory treatment following anti-CD20-based therapy

Treatment	Total n (%)
Total	[redacted]
Bendamustine-rituximab	[redacted]
Ibrutinib	[redacted]
Single agent rituximab	[redacted]
R-CVP	[redacted]
Cyclophosphamide / Rituximab +/- steroid	[redacted]
Chlorambucil	[redacted]
R-CHOP	[redacted]
FCR	[redacted]
Acalabrutinib	[redacted]
Other rituximab-based therapy[1]	[redacted]
Other non-rituximab-based therapy[2]	[redacted]

1 Chlorambucil / Rituximab (n=[redacted]), Gemcitabine / Dexamethasone / Cisplatin / Rituximab (n=[redacted]), IVE / Rituximab (n=[redacted]), Venetoclax / Rituximab (n=[redacted]) 2 Bendamustine (n=[redacted]), CVP (n=[redacted]), Fludarabine (n=[redacted]), Ublituximab / Umbralisib (n=[redacted]), Bendamustine / Methylprednisolone (n=[redacted]), Cyclophosphamide / Prednisolone (n=[redacted]), FC (n=[redacted]), Methotrexate (IT) (n=[redacted]), Pirtobrutinib (n=[redacted]), Tirabrutinib / Idelalisib (n=[redacted]), Tirabrutinib / Entospletinib (n=[redacted]), VCD (n=[redacted]), Velcade / Dexamethasone (n=[redacted]), Vincristine / Prednisolone (n=[redacted]), Zanubrutinib (n=[redacted])

CVP - Cyclophosphamide-vincristine-prednisolone; FC - Fludarabine, cyclophosphamide; FCR – Fludarabine, cyclophosphamide and rituximab; IVE - Ifosfamide-etoposide-epirubicin; R-CVP – Rituximab-cyclophosphamide-

Splenectomy is not considered standard of care for patients with R/R MZL. As highlighted in the ESMO guidelines, splenectomy was traditionally considered as the recommended first-line treatment for patients with splenic MZL.[5] However, splenectomy is not noted as a treatment option in patients with R/R MZL in the current ESMO guidelines. As a major, non-curative surgical procedure that may have severe, acute, and potentially fatal downstream complications, it has largely been replaced by rituximab (with or without chemotherapy) and only considered in very select cases where rituximab is not indicated.[5] Data from the HMRN registry shows that out of [redacted] patients diagnosed with MZL between 2005 to 2020, only [redacted] patients had received a splenectomy, which was mainly performed close to diagnosis as part of their first-line treatment.[6] Feedback gathered from a UK advisory board (11th October 2023) confirmed that splenectomy is not a relevant comparator for this decision problem.[4]

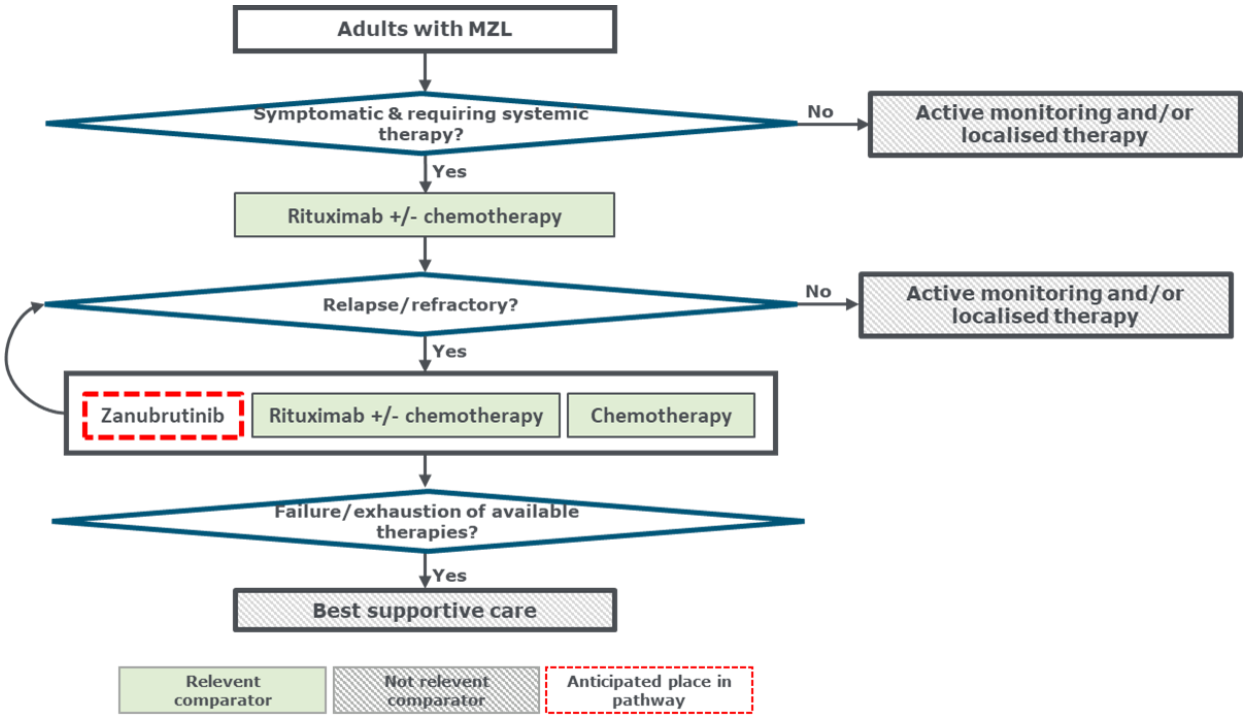
Furthermore, best supportive care (BSC) is not considered a treatment option in patients with R/R MZL since the approach to care for patients involves active monitoring or systemic treatment. For MZL patients with recurrent disease, ESMO guidelines recommend treatment with rituximab-based CIT or rituximab monotherapy.[5] Feedback gathered from a UK advisory board (11th October 2023) confirmed that BSC is rarely given, and would only be considered once a patient has exhausted all viable treatment options, including clinical trials and are too frail to tolerate any active therapy.[47] As such, BSC would be considered as end-of-life care and not as a comparator for zanubrutinib in patients able to receive treatment. This observation was confirmed by data from the HMRN registry, where a cohort of patients receiving BSC ([redacted]) was notably characterised by advanced age (median age of [redacted] years) and poor survival prospects, with a three-year overall survival rate of [redacted]%.[6] BSC for this cohort of patients included interventions such as steroids, blood products, iron, with the majority of patients receiving palliative care only. No patient within the BSC cohort received further chemotherapy.[6]

Zanubrutinib place in therapy in MZL

The proposed positioning of zanubrutinib in the clinical pathway is shown in Figure 1.

It is anticipated that zanubrutinib will be used as a second-line and beyond therapy regimen for patients with R/R MZL, after at least one prior anti-CD20-based therapy. Zanubrutinib can be regarded as a viable alternative treatment to rechallenging with rituximab monotherapy, rituximab-based chemoimmunotherapy or chemotherapy alone.

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



MZL – marginal zone lymphoma.

B.1.3.5 Clinical guidelines

In the UK, MZL treatment is largely based on the ESMO 2020 consensus clinical guidelines.[5] Very recently, the British Society of Haematology (BSH) guidelines on the treatment of MZL were published (November 2023). The Company reviewed the guidelines but due to the short time frame, they were not able to incorporate these guidelines fully into the submission.[48] However, the BSH guidelines are consistent with ESMO guidelines which form the basis of the clinical guidelines section in this appraisal.

There are three principal therapeutic options for MZL: active monitoring, localised therapy and systemic therapy with the choice of approach dependent on the disease aetiology, disease location, presence of symptoms and stage of disease.

Patients with MZL often present with asymptomatic, indolent disease that does not require treatment and these patients are generally managed by an active monitoring approach. Treatment is generally recommended to be initiated in presence of symptomatic disease, with the goal of providing remission of symptomatic disease and long-lasting PFS.[5]

There is no standard of care for patients with MZL who have relapsed after prior systemic therapy, or who have disease which is refractory to initial treatment. The 2020 ESMO guidelines recommend a repetition of treatment with rituximab-based chemoimmunotherapy or rituximab monotherapy if the initial therapy has resulted in a long-term remission of symptomatic disease (> 24 months). If initial therapy has achieved a shorter remission (≤ 24 months), or for patients who do not respond to therapy, therapeutic options become limited and clinical guidelines recommend considering the use of non-approved treatment options through enrolment in clinical trials.[5]

There is a paucity of data supporting the efficacy of rituximab-based therapies for patients with R/R MZL after prior systemic therapy, driven by the fact that MZL is a rare disease, and is often included within clinical trials for broader B-cell malignancies or grouped with FL. When coupled with the indolent nature of the MZL, data is further limited by the need for extended follow-up in trials which poses challenges in trial design and funding. Rituximab-based chemoimmunotherapy and rituximab monotherapy can become less effective after prior systemic therapy since the tumour can become refractory to rituximab-based regimen.[25,45,46] Furthermore, patients who relapse are often older and more frail, and are therefore less able to tolerate intense rituximab-based chemoimmunotherapy regimens in further lines of therapy. Since therapeutic options are limited, off-label treatments are therefore considered on an individual patient basis.[5] This is supported by data from the HMRN registry, which indicates that patients who have relapsed or are refractory after anti-CD20-based therapy are administered various treatments, including off-label options such as ibrutinib, which is prescribed to [redacted]% of these patients.[6,25,45,46]

B.1.3.6 Unmet need

Before the marketing authorisation approval of zanubrutinib in the UK, there was no approved treatment specifically for R/R MZL. Rituximab-based chemoimmunotherapy and rituximab monotherapy are commonly used, however few therapies have been specifically tested in MZL.[5,43,44] In a previous NICE appraisal, UK patient representatives emphasised the lack of treatment options in MZL, where frequent relapses mean most patients quickly exhaust the finite number of chemoimmunotherapy options and become chemo-refractory. Notably, lenalidomide,

the subject of the appraisal, did not receive marketing authorisation for the treatment of MZL. This was further validated through virtual discussions the Company had with patient representatives, where it was highlighted that MZL is a neglected disease which has had less attention in terms of treatment development.[36,37]

While MZL typically exhibits an indolent course, patients with R/R MZL who require systemic treatment tend to experience poorer prognosis and survival outcomes.[35] Limited treatment options exist for these patients, with rituximab-based chemoimmunotherapy or rituximab monotherapy being the only available treatments.[5] However, their efficacy diminishes after prior systemic therapy.[25,45,46] Treatment-related toxicities can further limit the available options, particularly in older and frailer patients. Heavily treated patients with multiple relapses can become chronically immunosuppressed and these patients are no longer suitable for further chemotherapy. In patients who cannot tolerate chemotherapy, treatment is limited to rituximab monotherapy.[43,49] Furthermore, for patients who achieve only short remission or who are refractory to prior rituximab-based therapy, guidelines recommend the use of non-approved treatment options.[5]

In other haematological cancers, a diverse range of treatments are available for patients, with BTKis becoming the standard of care in conditions such as chronic lymphocytic leukaemia (CLL), mantle cell lymphoma (MCL) and Waldenström's macroglobulinaemia (WM).[50–54,46] Despite being widely used in other blood cancers, BTKis are not approved for the treatment of MZL. This disparity highlights the critical gap in the available treatment options for MZL patients. HMRN data demonstrated that ibrutinib is a common second-line treatment, used in [redacted]% of patients receiving treatment following progression from an anti-CD20-based therapy.[6] However, ibrutinib is not licensed for the treatment of patients with R/R MZL, and notably the phase 3 clinical trial (SELENE) for ibrutinib (in combination with BR) in patients with R/R follicular lymphoma or MZL failed to meet its primary endpoint.[55] The reliance on off-label ibrutinib by clinicians highlights the pressing need for an approved and effective targeted therapy in the treatment of MZL.

Feedback gathered from a UK advisory board (11th October 2023) highlighted that there is a desire within the clinical community for an approved targeted therapy, such

as zanubrutinib, for patients with R/R MZL.[4] Furthermore, patient numbers from a UK compassionate use programme (CUP) for zanubrutinib further highlights the unmet need for an approved treatment option, with [redacted] patients enrolled in the programme over 18 months. Whilst, under the conditions of the CUP outcomes for patients receiving zanubrutinib cannot be collected, the requests for zanubrutinib on the CUP reflects patients who have failed primary therapy lines: second-line – 36%; third-line – 30%; fourth-line – 29%; fifth-line – 4%; sixth-line – 1%.

Furthermore, in a virtual discussion the Company had during the preparation of this appraisal, patient representatives expressed excitement about the potential availability of zanubrutinib, as a chemotherapy-free option. Patients emphasised that as a convenient at-home oral tablet, zanubrutinib offered a more accessible and patient-friendly treatment approach.[37]

Therapeutic options for patients with R/R MZL are thus limited and therefore there is an urgent need for a new targeted, chemotherapy-free, and well-tolerated treatment with proven efficacy in this patient population. Zanubrutinib is the only targeted treatment licensed in the UK for R/R MZL and offers a new mechanism of action whilst being an efficacious, safe, and well-tolerated treatment option for patients with R/R MZL.[2]

B.1.4 Equality considerations

No equality issues are anticipated for the appraisal of zanubrutinib.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

A clinical systematic literature review (SLR) was conducted on the 20th February 2023 and subsequently updated on 8th August 2023 to identify clinical studies (clinical trials and real word evidence [RWE] studies) investigating treatments for patients with MZL who require systemic therapy and have received at least one prior anti-CD20-based therapy. 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 extracted if they included patients who had received at least one prior anti-CD20-based therapy and comparators of interest as the focus for this appraisal (Section B.1.3.4 Clinical pathway of care and place in therapy).

B.2.2 List of relevant clinical effectiveness evidence

The SLR identified seven studies of patients with R/R MZL previously treated with anti-CD20-based therapies evaluating either zanubrutinib or one of the comparators of interest of which three were randomised controlled trials (RCTs) and four were single arm trials, with details provided in Table 5.

Table 5: Summary of study characteristics for studies identified in the SLR

Publication source (author, year)	Trial name (if any)	Treatment/ Group (n)	Publication type	Study setting	Study type/phase
RCTs					
Leonard, 2019[56]	AUGMENT NCT01938001	Treatment arm A: lenalidomide + rituximab (n=31) Treatment arm B: rituximab + placebo (n=32)	Journal article	Multicentre	RCT, open-label, phase III
Matasar, 2021[57] Özcan 2021[58]	CHRONOS-3 NCT02367040	Treatment arm A: copanlisib + rituximab (n=66)† Treatment arm B:	Journal article	Multicentre	RCT, open-label, phase III

Publication source (author, year)	Trial name (if any)	Treatment/ Group (n)	Publication type	Study setting	Study type/phase
		rituximab + placebo (n=29)†			
Nastoupil, 2023[59]	SELENE NCT01974440	Treatment arm A: ibrutinib + CIT (n=202) Treatment arm B: placebo + CIT (n=201)	Journal article	Multicentre	RCT, double-blind, phase III
Single arm evidence					
Opat 2021 (MAGNOLIA)[60,61]	MAGNOLIA	Zanubrutinib (N=68)	Journal article	Multicentre	Open-label, phase II
Philips 2022 (AU-003)[62,63]	BGB-3111-AU-003	Zanubrutinib (N=20)	Journal article	Multicentre	Open-label, phase I/II
Kahl, 2010[64]	Kahl, 2010	Bendamustine (N=16)	Journal article	Multicentre	Open-label, Phase III
Coleman, 2021[65] Lansigan, 2022[66]	MAGNIFY NCT01996865	Lenalidomide + rituximab (N=74)	Journal article	Multicentre	Open-label, Phase IIIb

CIT – chemoimmunotherapy; RCT – Randomised controlled trial; SLR – Systematic literature review.
†This study included a wide population of NHL patients, and the MZL-specific characteristics were not available, thus, NHL-specific data are presented.

As identified in the SLR, the efficacy and safety of zanubrutinib in patients with R/R MZL has been studied in two single arm clinical studies – MAGNOLIA (NCT: NCT03846427) and AU-003 (NCT: NCT02343120). A summary of the MAGNOLIA and AU-003 studies is provided in Table 6. The MAGNOLIA and AU-003 studies are discussed in detail in Sections B.2a.3 Summary of methodology of the relevant clinical effectiveness evidence: MAGNOLIA and B.2b.3 Summary of methodology of the relevant clinical effectiveness evidence: AU-003, respectively.

Table 6: Clinical effectiveness evidence for zanubrutinib

Study	MAGNOLIA (Study BGB-3111-214; NCT03846427)	AU-003 (Study BGB-3111-AU-003; NCT02343120)
Study design	A phase 2, single arm, multicentre, open-label study	A phase 1/2, single arm, multicentre, open-label study

Study	MAGNOLIA (Study BGB-3111-214; NCT03846427)	AU-003 (Study BGB-3111-AU-003; NCT02343120)
Population	Patients with histologically confirmed MZL including splenic, nodal, and extranodal subtypes, age ≥ 18 years, with ≥1 prior lines of CD20-based therapy (either as monotherapy or CIT), ECOG PS score of 0-2, adequate organ function based on pre-defined laboratory parameters, and life expectancy of ≥ 6 months.	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.
Intervention(s)	Zanubrutinib monotherapy	Zanubrutinib monotherapy
Comparator(s)	N/A	N/A
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, **HRQoL**, **safety**	ORR**, OS, PFS**, DOR, **safety**
All other reported outcomes	Pharmacokinetics, TTR, TTF, TTNLT	Pharmacokinetics, TTR

CD20 – anti-cluster of differentiation 20; CIT – chemoimmunotherapy; DOR – Duration of response; ECOG PS – Eastern Cooperative Oncology Group Performance Status; HRQoL – Health-related quality of life; MZL – Marginal zone lymphoma; N/A – Not applicable; ORR – Overall response rate; OS – Overall survival; PFS – Progression-free survival; TTNLT – Time to next line of therapy; TTR – Time to response; TTF – Time to treatment failure.
Outcomes in **bold** are used in the economic model.
Source: MAGNOLIA CSR[60], AU-003 CSR[62]

B.2a.3 *Summary of methodology of the relevant clinical effectiveness evidence: MAGNOLIA*

B.2a.3.1 Study design

MAGNOLIA is an international, single arm, multicentre, open-label phase 2 pivotal study supporting the clinical value of zanubrutinib in patients with R/R MZL who have received ≥ 1 prior anti-CD20-based therapy. The primary endpoint was overall response rate (ORR) by Independent Review Committee (IRC) assessment.

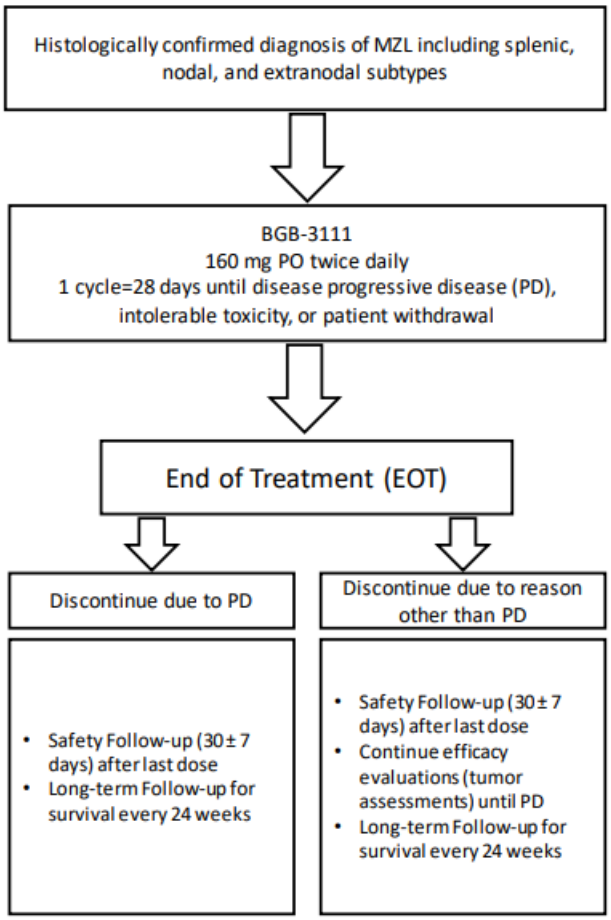
The study was composed of an initial screening phase (up to 35 days), a single arm treatment phase, and a follow-up phase. Sixty-eight patients (65 planned) were enrolled in the study and received zanubrutinib 160 mg orally twice daily in repeated 28-day cycles. Treatment with zanubrutinib was continued until disease progression, unacceptable toxicity, death, withdrawal of consent, or study termination. Table 7 summarises the MAGNOLIA trial methodology, and Figure 2 presents the study design schematic.

Table 7: Summary of trial methodology (MAGNOLIA)

Study details	MAGNOLIA (Study BGB-3111-214; NCT03846427)
Location	Australia, China, Czech Republic, France, Italy, New Zealand, South Korea, the United Kingdom, and the United States
Design	Open-label, single arm, multicentre phase 2 study of zanubrutinib in patients with MZL who were relapsed or refractory after ≥ 1 prior anti-CD20-based therapy.
Treatment	All patients received zanubrutinib 160 mg (two 80-mg capsules) orally twice daily until disease progression, unacceptable toxicity, death, withdrawal of consent, 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) TTF TTNLT
Subgroup analysis	Sex, age group (< 65 versus ≥ 65 years), ECOG PS (0 versus ≥ 1), prior line of therapy for MZL (< 3 versus ≥ 3), and MZL subtypes (extranodal, nodal and splenic).

CD20 – anti-cluster of differentiation 20; DOR – Duration of response; ECOG PS – Eastern Cooperative Oncology Group performance status; INV – Investigator; IRC – Independent Review Committee; MZL – Marginal zone lymphoma; ORR – Overall response rate; OS – Overall survival; PFS – Progression-free survival; TTNLT – Time to next line of therapy; TTR – Time to response; TTF – Time to treatment failure.
Source: MAGNOLIA CSR[60]

Figure 2: BGB-3111-214 MAGNOLIA schematic and design



EOT – End of treatment; MZL – Marginal zone lymphoma; PD – Progressive disease; PO – oral administration.
Source: MAGNOLIA CSR[60]

B.2a.3.2 Eligibility criteria

Eligible patients were aged ≥18 years with a diagnosis of MZL with experience of at least one or more prior lines of anti-CD20-based therapy. Key inclusion and exclusion criteria for MAGNOLIA are presented in Table 8.

Table 8: Key eligibility criteria for MAGNOLIA

Key inclusion criteria
• 18 years or older with histologically confirmed MZL including splenic, nodal, and extranodal subtypes. • At least 1 or more prior lines of therapy, including at least 1 anti-CD20-based therapy (either as monotherapy or as CIT). • Documented failure to achieve at least PR or documented progressive disease after the most recent systemic treatment. • ECOG PS 0-2. • Measurable disease. • Adequate bone marrow and organ function based on pre-defined laboratory parameters.

• Life expectancy of ≥ 6 months.
Key exclusion criteria

• Known transformation to aggressive lymphoma, such as large cell lymphoma.
• Clinically significant cardiovascular disease including:
  ○ Myocardial infarction within 6 months before screening.
  ○ Unstable angina within 3 months before screening.
  ○ New York Heart Association Class III or IV congestive heart failure.
  ○ History of clinically significant arrhythmias.
• Prior malignancy within the past 2 years, except for curatively treated basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in-situ of the cervix or breast, or localised Gleason score 6 prostate cancer.
• History of severe bleeding disorder such as haemophilia A, haemophilia B, von Willebrand disease, or history of spontaneous bleeding requiring blood transfusion or other medical intervention.
• History of stroke or intracranial haemorrhage within 180 days before first dose of study drug.
• Severe or debilitating pulmonary disease.
• Inability to swallow capsules, or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, bariatric surgery procedures, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
• Active fungal, bacterial, and/or viral infection requiring systemic therapy.
• Prior treatment with a BTKi.
• Known central nervous system involvement by lymphoma.
• Active infections requiring systemic therapy, such as HIV, active hepatitis B or C infections.
• Major surgery within 4 weeks of the first dose of study drug.
• Last dose of prior therapy for MZL ≤ 21 days prior to first dose of study drug.

BTKi – Bruton's tyrosine kinase inhibitor; CIT – chemoimmunotherapy; CD20 – anti-cluster of differentiation 20; ECOG PS – Eastern Cooperative Oncology Group Performance Status; HIV – Human immunodeficiency virus; PR – partial response; MZL – Marginal zone lymphoma.
Source: MAGNOLIA CSR[60]

B.2a.3.3 Outcome measures

The definitions of the outcome measures available from the MAGNOLIA trial and whether they were used in the economic model are presented in Table 9.

Table 9: Outcome measures available from MAGNOLIA

Objective	Definition	Data cut available*	Used in economic model
Primary objectives			
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.[67] Best overall response was defined as the best response recorded from the start of zanubrutinib until the DCO.	31 May 2022	No
Secondary objectives			

Objective	Definition	Data cut available*	Used in economic model
ORR (INV)	The proportion of patients achieving a best overall response of CR or PR as determined by an investigator according to the Lugano classification.[67] Best overall response was defined as the best response recorded from the start of zanubrutinib until the DCO.	31 May 2022	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	31 May 2022	Yes
OS	Time from the date of the first dose of zanubrutinib treatment to death due to any cause.	31 May 2022	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.	31 May 2022	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.	31 May 2022	No
TTF	Time from initiation of zanubrutinib to discontinuation of study drug for any reason.	31 May 2022	No
TTNLT	Time from the first dose of zanubrutinib to the start of the first new therapy for MZL.	31 May 2022	No
QoL	Changes from baseline in EORTC QLQ-C30 and EQ-5D-5L scores.	31 May 2022	Yes (EQ-5D data)
Safety and tolerability			
Safety and tolerability	AEs classified based on MedDRA (Version 24.0 or higher) and graded according to the NCI-CTCAE (version 4.03)	31 May 2022	Yes

AE – Adverse events; CR – Complete response; DCO – Data cut-off; DOR – Duration of response; EORTC QLQ-C30 – European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-5L – EuroQol 5-Dimension questionnaire 5 Level; INV – Investigator; IRC – Independent Review Committee; MZL – Marginal zone lymphoma; 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; QoL – Quality of life; TTNLT – Time to next line of therapy; TTR – Time to response; TTF – Time to treatment failure.
*Median follow-up for 31 May 2022 data cut: 27.40 months
Source: MAGNOLIA CSR[60]

B.2a.3.4 Patient characteristics

The demographics and baseline disease characteristics of patients enrolled in MAGNOLIA are presented in Table 10.

The median age was 70 years, with 27.9% of individuals over 75 years old. Among patients enrolled, 38.2% presented with extranodal MZL, 38.2% with nodal MZL, and

17.6% with splenic MZL. Both nodal and extranodal conditions simultaneously occurred in 5.9% of patients, and the investigators were unable to classify the primary MZL subtype.

Numerous patients exhibited features indicative of advanced or disseminated disease, including extranodal manifestations (77.9%) and the presence of bulky disease (36.8%). A significant majority (89.7%) displayed fluorodeoxyglucose (FDG)-avid disease, a characteristic associated with an unfavourable prognosis marked by reduced PFS in cases of MZL.

A substantial portion of the patient cohort ([redacted]%) had undergone a minimum of two prior systemic treatments. All but one patient (88.2%) had previously received a rituximab-based chemoimmunotherapy, with R-CVP (36.8%), BR (32.4%) and R-CHOP (25.0%) the most common therapies received, and 22.1% of patients received rituximab monotherapy in a prior treatment line. Among the participants, 32.4% had not responded to prior therapy and were thus considered refractory.

A total of [redacted] ([redacted]%) patients were included from UK sites. The overall demographics and baseline characteristics of included patients were validated by UK clinicians as being representative of patients who present in UK clinical practice.[4]

Table 10: Demographics and baseline disease characteristics (MAGNOLIA)

Characteristics	Zanubrutinib (N=68)
Age, years	
Mean (SD)	[redacted]
Median (range)	70.0 (37, 95)
< 65 years	27 (39.7)
≥ 65 years and < 75 years	22 (32.4)
≥ 75 years	19 (27.9)
Sex, n (%)	
Male	36 (52.9)
Female	32 (47.1)
Country, n (%)	
Australia	[redacted]
China	[redacted]
Italy	[redacted]
United Kingdom	[redacted]
New Zealand	[redacted]
United States	[redacted]
France	[redacted]

Characteristics	Zanubrutinib (N=68)
Czech Republic	[redacted]
South Korea	[redacted]
ECOG PS n (%)	
0	39 (57.4)
1	24 (35.3)
2	5 (7.4)
Time from initial diagnosis to study entry (months)	
Mean (SD)	[redacted]
Median (range)	[redacted]
Disease subtype, n (%)	
Extranodal MZL	26 (38.2)
Nodal MZL	26 (38.2)
Splenic MZL	12 (17.6)
Unknown[a]	4 (5.9)
Disease status to last prior therapy, n (%)	
Relapsed	[redacted]
Refractory[c]	22 (32.4)
Evidence of FDG-avid disease by IRC, n (%)	
FDG-avid	61 (89.7)
Non-FDG-avid	7 (10.3)
Bulky disease, n (%)	
Yes (any target lesion LDi > 5 cm)	25 (36.8)
No (all target lesion LDi ≤ 5 cm)	43 (63.2)
Extranodal disease at study entry[b], n (%)	
Yes	53 (77.9)
No	15 (22.1)
Number of prior therapies	
Median (range)	2.0 (1, 6)
1 prior therapy	[redacted]
2 prior therapies	[redacted]
≥3 prior therapies	[redacted]
Time from end of last therapy to study entry	
Mean (SD)	[redacted]
Median (range)	20.62 (1.0, 176.6)
≤ 2 Years	[redacted]
> 2 Years	[redacted]
Patients with any prior radiation therapies, n (%)	
Yes	15 (22.1)
No	53 (77.9)
Prior stem cell transplant, n (%)	
Yes	4 (5.9)
No	64 (94.1)
Prior systemic regimens, n (%)	
Rituximab-based chemoimmunotherapy	60 (88.2)
Alkylating agents	58 (85.3)
R-CVP	25 (36.8)
BR	22 (32.4)
R-CHOP	17 (25.0)

Characteristics	Zanubrutinib (N=68)
Rituximab monotherapy	7 (10.3)

BR – bendamustine/rituximab; ECOG PS– Eastern Cooperative Oncology Group performance score; FDG – fluorodeoxyglucose; IRC – Independent Review Committee; LDi, – longest transverse diameter of a lesion; MZL – Marginal zone lymphoma; R-CHOP – Rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; R-CVP – Rituximab + cyclophosphamide + vincristine + prednisone; SD – Standard deviation.
[a] Unknown subtypes in 4 patients who presented with both nodal and extranodal disease.
[b] Extranodal disease was defined as patients with any target or non-target extranodal lesions at baseline or with baseline bone marrow involvement by biopsy/aspiration per investigator assessment.
[c] The proportion of patients with a best response of stable disease or progressive disease to their last prior therapy
Source: MAGNOLIA CSR[60]

B.2a.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence: MAGNOLIA

B.2a.4.1 Sample size calculations

Assuming a null hypothesis with an expected ORR of 30%, a sample comprising 65 patients would yield a statistical power of 82% when considering an alternative hypothesised ORR of 48%. A one-sided alpha level of 0.025 and exact binomial testing were used. The alternative ORR is based on the observed IRC-assessed ORR for another BTKi study in R/R MZL.[68] For an observed ORR of 48% (31/65 patients), the 95% exact binomial confidence interval (CI) is 35% to 60%.

B.2a.4.2 Statistical analysis

Table 11 summarises the statistical analyses used in MAGNOLIA. The Safety Analysis Set included all patients who were enrolled and received at least one dose of study drug. The Efficacy Analysis Set consisted of all patients in the Safety Analysis Set with a confirmed diagnosis of MZL.

Table 11: Summary of pre-specified statistical analyses used in MAGNOLIA

Endpoint	Analysis	Population
Primary endpoint analysis		
ORR	• 2-sided Clopper-Pearson 95% CI. • Binomial exact test with null hypothesised ORR of 30% 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 data cut-off. • Patients with no postbaseline response assessments (for any reason) were considered non-responders.	Efficacy Analysis Set
Secondary endpoint analysis		
PFS	• KM methodology was used to estimate the median and other quartiles of PFS.	Efficacy Analysis Set

Endpoint	Analysis	Population
	• 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.	
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.	Efficacy Analysis Set
DOR	• KM methodology was used to estimate the median and other quartiles and 95% CI.	Efficacy Analysis Set
TTR	• Summarised by sample statistics such as mean, median, and standard deviation for responders only.	Efficacy Analysis Set
TTF	• KM methodology was used to estimate the median and other quartiles of TTF. • Two-sided 95% CIs constructed using generalised Brookmeyer and Crowley method with log-log transformation. • TTF 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.	Efficacy Analysis Set
TTNLT	• KM methodology was used to estimate the median and other quartiles of TTNLT • Two-sided 95% CIs constructed using a generalised Brookmeyer and Crowley method with log-log transformation. • TTNLT 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	Efficacy Analysis Set
Patient reported outcomes		
EORTC QLQ-C30	• Scores at each assessment timepoint and changes from baseline in Global Health Status/Quality of Life scale, 5 functional scales, and 9 symptom scales/items	Efficacy Analysis Set
EQ-5D-5L	• Number and percentage of each level of all 5 dimensions at each assessment timepoint.	Efficacy 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, preferred term, and worst grade.	Safety Analysis Set
Subgroup analyses of efficacy endpoints		

Endpoint	Analysis	Population
Subgroup analysis	• Age (< 65 years versus ≥ 65 years and < 65 years versus 65 to 75 years versus ≥ 75 years). • Sex (male versus female). • ECOG PS – (0 versus ≥ 1). • Prior line of systemic therapy (< 3 versus ≥ 3). • Years since last anti-lymphoma therapy (≤ 2 versus > 2). • Baseline extranodal disease (yes versus no). • Disease status (relapsed versus refractory). • Prior treatment (R-CVP versus R-CHOP versus BR versus all others). • Bulky disease (longest diameter ≤ 5 cm versus > 5 cm and ≤ 10 cm versus > 10 cm). • Baseline LDH (Normal versus Above Normal). • Bone marrow involvement (yes versus no). • MZL subtype (extranodal versus nodal and splenic). • Disease stage (Stage I versus II, III and IV).	Efficacy Analysis Set

AE – Adverse event; BR – Bendamustine + rituximab; CI – Confidence interval; DOR – Duration of response; ECOG PS– Eastern Cooperative Oncology Group performance score; EORTC QLQ-C30 – European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; EQ-5D-5L – EuroQol 5-Dimension questionnaire 5 Level; INV – Investigator; IRC – Independent review committee; ITT – Intention-to-treat; KM – Kaplan-Meier; LDH – Lactate dehydrogenase; MZL – Marginal zone lymphoma; NCI-CTCAE - National Cancer Institute-Common Terminology Criteria for Adverse Events; ORR – Overall response rate; OS – Overall survival; PFS – Progression-free survival; R-CHOP – Rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; R-CVP – Rituximab + cyclophosphamide + vincristine + prednisone; SAE – Serious adverse event; TEAE – Treatment-emergent adverse event; TTF – Time to treatment failure; TTNLT – Time to next line of therapy; TTR – Time to response.
Source: MAGNOLIA CSR[60]

B.2a.4.3 Participant flow

A total of 68 patients were enrolled into the MAGNOLIA study, each of whom received a minimum of one dose of zanubrutinib. The median duration of follow-up for the MAGNOLIA study was 28.0 months. A total of 24 (35.3%) patients halted their study drug consumption due to progressive disease, while five (7.4%) patients discontinued their participation due to adverse events, as detailed in Table 12. At study completion, 31 (45.6%) patients continued with zanubrutinib in the long-term extension (LTE) study, BGB-3111-LTE1, which includes participants with B-cell malignancies from other zanubrutinib trials.[69] The BGB-3111-LTE1 is currently still ongoing with an integrated interim safety report expected in December 2024. A total of two (2.9%) patients discontinued from the study due to COVID-19.

Table 12: Patient disposition in MAGNOLIA

Patient disposition	Zanubrutinib (N = 68) n (%)
Number of patients treated	68 (100.0)
Patients discontinued from treatment	68 (100.0)

Patient disposition	Zanubrutinib (N = 68) n (%)
Reason for discontinuation from treatment	
Sponsor decision to roll over to LTE study	31 (45.6)
Progressive disease	24 (35.3)
Adverse event	5 (7.4)
Related to COVID-19	2 (2.9)
Physician decision[a]	4 (5.9)
Other	3 (4.4)
Study terminated by sponsor/patients not rolling over to LTE[b]	3 (4.4)
Withdrawal by patient	1 (1.5)
Patients remained on study treatment	0
Patients discontinued from the study	68 (100.0)
Reason for discontinuation from the study	
Sponsor decision to roll over to LTE study	[redacted]
Death	[redacted]
Related to COVID-19	[redacted]
Study terminated by sponsor[c]	[redacted]
Withdrawal by patient	[redacted]
Physician decision	[redacted]
Other	[redacted]
Patient declined to be rolled over to BGB-3111-LTE1	[redacted]
Patients remained in study	[redacted]
Median study follow-up timed (months)[d]	28.04
Study follow-up time (months) (minimum, maximum)	1.64, 32.89

LTE – Long-term extension
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] Discontinued due to prohibited medications: One patient required chemotherapy for acute myeloid leukaemia. One patient discontinued due to steroid dependency. One patient required priority treatment for tuberculosis.
[b] Including patients of "Study Terminated by Sponsor, Patient Not Rolling Over," "Study Terminated by Sponsor Patient Not Rolling Over to LTE" and "Study Terminated by Sponsor Patient Not Rolling Over."
[c] These patients did not roll over to BGB-3111-LTE1 study.
[d] 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: MAGNOLIA CSR[60]

B.2a.5 Critical appraisal of the relevant clinical effectiveness evidence: MAGNOLIA

A summary of the quality assessment for the MAGNOLIA trial is provided in Table 13. 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.[70,71] Based on the findings from the quality assessment, MAGNOLIA was a well-designed single arm trial with the appropriate steps taken to minimise bias where possible.

Table 13: Quality assessment results for MAGNOLIA

Question	How is the question addressed?	Grade (yes/no/ unclear/NA)
Was the cohort recruited in an acceptable way?	Patients were recruited from nine study locations based on inclusion and exclusion criteria outlined in Table 8.	Yes
Was the exposure accurately measured to minimise bias?	All 68 patients in the MAGNOLIA trial received at least one dose of zanubrutinib. The median duration of treatment was 24.2 months (range: 0.9 to 32.9 months). The median actual and relative dose intensities were [redacted] mg/day and [redacted]%, respectively.	Yes
Was the outcome accurately measured to minimise bias?	Outcomes were accurately measured to minimise bias as outlined in Table 9. 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 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?	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 an 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 MZL and conducting chemistry and haematology assessments. If a patient refused to return for these visits or was unable to do so, every effort was to be 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 1-sided 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 for full details.	Yes

CI – Confidence interval; INV – Investigator; IRC – Independent review committee; KM - Kaplan-Meier; MZL – Marginal zone lymphoma; NA – Not applicable; ORR – Overall response rate; PD – Progressive disease
Source: MAGNOLIA CSR[60]

B.2a.6 Clinical effectiveness results of the relevant studies: MAGNOLIA

The key efficacy outcomes for patients with R/R MZL from MAGNOLIA are presented in Table 14. As of the data cut-off data 31st May 2022, median follow-up was 28.0 months. Results stratified by MZL subtype can be found within the CSR.[60]

Table 14: Key efficacy outcomes reported in MAGNOLIA

	Zanubrutinib (N = 66)	
	IRC-assessed	**INV-assessed**
ORR		
ORR (%) (95% CI)	68.2 (55.6, 79.1)	75.8 (63.6, 85.5)
PFS		
Events, n (%)	[redacted]	[redacted]
Median, months (95% CI)	[redacted]	[redacted]
DOR		
Median, months (95% CI)	[redacted]	[redacted]
OS		
Events, n (%)	[redacted]	
Median, months (95% CI)	[redacted]	
TTR		
Median, months	[redacted]	[redacted]
TTF		
Events, n (%)	[redacted]	
Median, months (95% CI)	[redacted]	
TTNLT		
Events, n (%)	[redacted]	

CI – Confidence interval; DOR – Duration of response; INV – Investigator; IRC – Independent review committee; NE – Not estimable; ORR – Overall response rate; OS – Overall survival; PFS – Progression-free survival; TTF – Time to treatment failure; TTNLT – Time to next line of therapy; TTR – Time to response.
MAGNOLIA CSR[60]

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

The MAGNOLIA study met its primary endpoint. As demonstrated in Table 15, ORR by IRC assessment was 68.2% (95% CI: 55.6, 79.1), leading to rejection of the pre-specified null hypothesis of 30% with 1-sided p-value < 0.0001. A total of 17 (25.8%) patients achieved a complete response. A large proportion of patients also achieved partial response (42.4%), which was highlighted as a desired outcome by clinical experts at the advisory board. Experts noted that with R/R MZL, the aim of treatment was to control the disease rather than cure patients.[4]

In line with the ORR determined by IRC assessment, the ORR determined by INV assessment was 75.8% (95% CI: 63.6, 85.5). The concordance rate between IRC and INV assessments was [redacted]% for ORR, and [redacted]% for best overall response.

Table 15: IRC- and INV-assessed response rates in MAGNOLIA

Response category	Zanubrutinib (N = 66)	
	IRC-assessed	INV-assessed
Best overall response, n (%)		
CR	17 (25.8)	19 (28.8)
PR	28 (42.4)	31 (47.0)
SD[a]	13 (19.7)	10 (15.2)
Non-PD[b]	1 (1.5)	0 (0.0)
PD	6 (9.1)	5 (7.6)
Discontinued study prior to first assessment	1 (1.5)	1 (1.5)
Overall response rate		
ORR, n (%) [95% CI][c]	45 (68.2) [55.6, 79.1]	50 (75.8) [63.6, 85.5]

CI – Confidence interval; CR – Complete response; INV – Investigator; IRC – Independent review committee; ORR – Overall response rate; PD – Progressive disease; PR – Partial response; SD – Stable disease.
[a] Five (7.6%) patients with a best overall response of stable disease are remaining on study treatment (after 12 to 18 cycles of treatment) as of the data cut-off date.
[b] One patient with FDG-avid disease missed the PET scan at Cycle 3 and was assessed as having non-progressive disease by independent review due to missing PET scan. CT scan results showed stable disease at Cycle 3.
[c] 2-sided Clopper-Pearson 95% CIs.
Source: MAGNOLIA CSR[60]

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

As described in Table 16, exploratory sensitivity analyses were conducted, including assessing ORR based on computerised tomography (CT) assessment and assessing the clinical benefit rate, confirming the robustness of the primary analysis.

Table 16: Results of the sensitivity analysis for IRC-assessed ORR in MAGNOLIA

Analysis	Zanubrutinib (N = 66)
Primary analysis, % (95% CI)	68.2 (55.6, 79.1)
Subgroup analysis	
ORR based on CT assessment, % (95% CI)	66.7 (54.0, 77.8)
Clinical benefit rate (SD + PR + CR), %	90.9

CT – Computerised tomography; CR – Complete response; IRC – Independent review committee; ORR – Overall response rate; PR – Partial response; SD – Stable disease.
Source: MAGNOLIA CSR[60]

B.2a.6.2 Secondary endpoints

B.2a.6.2.1 Progression-free survival

At a median follow-up of 27.4 months, [redacted] patients had either progressed or died as per IRC assessment and median PFS had not been reached, as shown in the Kaplan-Meier (KM) plot presented in Figure 3. As demonstrated in Table 17, the event-free rate was [redacted]% (95% CI: [redacted]) at 12 months and 70.9% (95% CI 57.2, 81.0) at 24 months.

Figure 3: Kaplan-Meier plot of IRC-assessed PFS in MAGNOLIA

CI – Confidence interval; IRC – Independent review committee; PFS – Progression-free survival.
Source: MAGNOLIA CSR[60]

In line with the IRC assessment of PFS, [redacted] patients had either progressed or died as per INV assessment and median PFS had not been reached, as shown in the KM plot presented in Figure 4. The event-free rate was [redacted]% (95% CI: [redacted]) at 12 months and 57.9% (95% CI: 44.8, 68.9) at 24 months.

Figure 4: Kaplan-Meier plot of INV-assessed PFS in MAGNOLIA

CI – Confidence interval; INV – Investigator; PFS – Progression-free survival.
Source: MAGNOLIA CSR[60]

Table 17. IRC- and INV-assessed PFS in MAGNOLIA

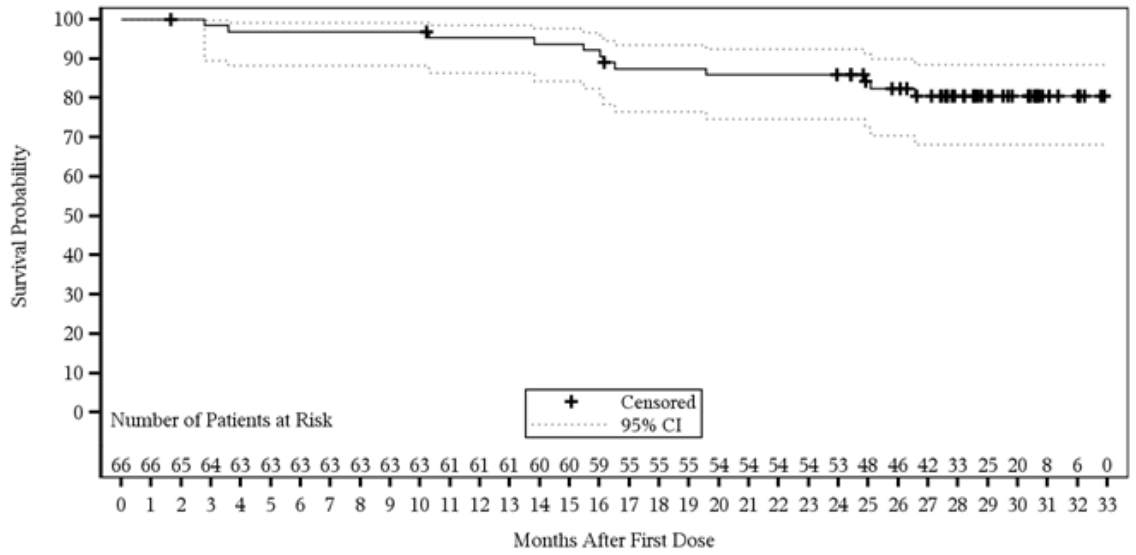
	Zanubrutinib (N = 66)	
	IRC-assessed	**INV-assessed**
PFS, n (%)		
Events	[redacted]	[redacted]
PD	[redacted]	[redacted]
Death	[redacted]	[redacted]
Event-free rate at, % (95% CI)[a]		
6 Months	[redacted]	[redacted]
12 Months	[redacted]	[redacted]
18 Months	[redacted]	[redacted]
24 Months	70.9 (57.2, 81.0)	57.9 (44.8, 68.9)
Median	[redacted]	[redacted]

CI – Confidence interval; INV – Investigator; IRC – Independent review committee; NE – Not estimable; 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: MAGNOLIA CSR[60]

B.2a.6.2.2 Overall survival

At a median follow-up of 28.7 months, 12 deaths had occurred, and median OS had not been reached, as shown in the KM plot presented in Figure 5. As reported in Table 18, the event-free rate was [redacted]% (95% CI [redacted]) at 12 month and 85.9% (95% CI 74.7, 92.4) at 24 months.

Figure 5: Kaplan-Meier plot of OS, MAGNOLIA



CI – Confidence interval; OS – Overall survival.
Source: MAGNOLIA CSR[60]

Table 18: OS in MAGNOLIA

	Zanubrutinib (N = 66)
Overall Survival	
Deaths, n (%)	[redacted]
Event-free rate at, % (95% CI)[a]	
6 months	[redacted]
12 months	[redacted]
18 months	[redacted]
24 months	85.9 (74.7, 92.4)
30 months	[redacted]
Median	NE (NE, NE)

CI – Confidence interval; 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: MAGNOLIA CSR[60]

B.2a.6.2.3 Duration of response

At a median follow-up of 23.4 months, [redacted] of the 45 patients who achieved a response had either progressive disease or had died as per IRC assessment as described in Table 19. Median duration of response (DOR) was not reached with 72.9% (95% CI: 54.4, 84.9) of responders event-free at 24 months after an initial response.

In line with IRC-assessed DOR, at a median follow-up of [redacted] months, [redacted] of the 50 patients who achieved a response had either progressive disease or had died as per

INV assessment. Median DOR was not reached with 60.8% (95% CI: 44.8, 73.6) of responders event-free at 24 months after initial response.

Table 19: IRC- and INV-assessed DOR in MAGNOLIA

	Zanubrutinib (N = 66)	
	IRC-assessed	**INV-assessed**
IRC-assessed DOR, n (%)		
Events	[redacted]	[redacted]
PD	[redacted]	[redacted]
Death	[redacted]	[redacted]
Event-free rate at, (95% CI)[a]		
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	72.9 (54.4, 84.9)	60.8 (44.8, 73.6)
Median	[redacted]	[redacted]

CI – Confidence interval; DOR – Duration of response; INV – Investigator; IRC – Independent review committee; 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: MAGNOLIA CSR[60]

B.2a.6.2.4 Time to response

As presented in Table 20, median time to response (TTR) was 2.8 months by both IRC and INV assessment. Time to complete response was [redacted] months by IRC assessment and [redacted] months by INV assessment.

Table 20: IRC- and INV-assessed TTR in MAGNOLIA

Response Category	Zanubrutinib (N = 66)	
	IRC-assessed	**INV-assessed**
Time to response (months)		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	2.8 (1.7, 11.1)	2.8 (1.7, 16.6)
Time to complete response (months)		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]

INV – Investigator; IRC – Independent review committee; SD – Standard deviation; TTR – Time to response
Source: MAGNOLIA CSR[60]

B.2a.6.2.5 Time to treatment failure

At a median follow-up of 29.7 months, median time to treatment failure (TTF) was [redacted] months (95% CI [redacted]). As presented in Table 21, [redacted] patients discontinued the

treatment, with [redacted] discontinuing due to progressive disease. The event-free rates at 12, 24 and 30 months were [redacted]% (95% CI [redacted]), [redacted]% (95% CI [redacted]) and [redacted]% (95% CI [redacted]), respectively.

Table 21: TTF in MAGNOLIA

	Zanubrutinib (N = 66)
TTF, n (%)	
Events	[redacted]
PD	[redacted]
AE	[redacted]
Physician decision	[redacted]
Other – patients did not roll over to LTE study	[redacted]
Withdrawal by subject	[redacted]
Censored and rolled	[redacted]
Rolled over to LTE study	[redacted]
Event-free rate at, % (95% CI) [a]	
6 months	[redacted]
12 months	[redacted]
18 months	[redacted]
24 months	[redacted]
30 months	[redacted]
Median (95% CI)	[redacted]

AE – Adverse event; CI – Confidence interval; LTE – Long-term extension; NE – Not estimable; PD – Progressed disease; TTF – Time to treatment failure.
[a] Event-free rates were estimated by Kaplan-Meier method with 95% CIs estimated using Greenwood's formula.
Source: MAGNOLIA CSR[60]

B.2a.6.2.6 Time to next line of therapy

At a median follow-up of [redacted] months, median time to next line of therapy (TTNLT) was not reached with only [redacted]% of patients starting a new anticancer therapy for MZL. A total of [redacted] of the patients who were censored, rolled over onto the LTE study for zanubrutinib, and hence continued to receive treatment with the study drug, highlighting the tolerability and safety of zanubrutinib. The event-free rates at 12, 24 and 30 months were [redacted]%, [redacted]% and [redacted]%, respectively.

Table 22: TTNLT in MAGNOLIA

	Zanubrutinib (N = 66)
TTNLT	
Events, n (%)	[redacted]
Event-free rate at, % (95% CI) [a]	
6 months	[redacted]
12 months	[redacted]
18 months	[redacted]

24 months	[redacted]
30 months	[redacted]

CI – Confidence interval; LTE – Long-term extension; MZL – Marginal zone lymphoma; TTNLT – Time to next line of therapy.
Note: Percentages were based on N.
[a] Event-free rates were estimated by Kaplan-Meier method with 95% CIs estimated using Greenwood's formula.
Source: MAGNOLIA CSR[60]

B.2a.6.2.7 Patient reported outcomes

EORTC CLC-C30

The mean change from baseline in EORTC QLQ-C30 is described in Table 23, and plotted for global health status (GHS) in Figure 6. The least squares (LS) mean change from baseline showed a gradual improvement in mean absolute scores for quality of life. The improvement began at Cycle 3 and consistently remained higher than baseline through Cycle 24.

Table 23: Summary of EORTC QLQ-C30 (MAGNOLIA)

PRO endpoint	Zanubrutinib, mean change from baseline (SD)	
	Cycle 12	Cycle 24
GHS/QoL	[redacted]	[redacted]
Physical function	[redacted]	[redacted]
Role function	[redacted]	[redacted]
Emotional functioning	[redacted]	[redacted]
Cognitive functioning	[redacted]	[redacted]
Social functioning	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Nausea and vomiting	[redacted]	[redacted]
Pain	[redacted]	[redacted]

EORTC QLQ-C30 – European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; GHS – Global health status; QoL – Quality of life; SD – Standard deviation
Source: MAGNOLIA CSR[60]

Figure 6: Mean change from baseline* over time for EORTC QLQ-C30: GHS (MAGNOLIA)

CI – Confidence interval; EORTC QLQ-C30 – European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; GHS – Global health status. Note: Only patients with data at both baseline and corresponding postbaseline visit were included in the summary statistics for change from baseline. The bars represent the 95% CI for the mean. *Baseline is defined Cycle 1 Day 1. The questionnaires were completed on Cycle 1 Day 1, end of Cycle 3, and then every 12 weeks for 12 months, and every 24 weeks thereafter.
Source: MAGNOLIA CSR[60]

EQ-5D-5L VAS

A summary of the change from baseline in EQ-5D-5L visual analogue scale (VAS) score is presented in Table 24 and plotted in Figure 7. When using the EQ-5D-5L instrument, mean absolute VAS scores for usual activities slightly improved from baseline and consistently remained higher than baseline through Cycle 24, indicating that quality of life was maintained following treatment with zanubrutinib.

Table 24: Summary of change in EQ-5D-5L VAS score from baseline (MAGNOLIA)

Change from baseline to	Zanubrutinib, mean change in EQ-5D-5L VAS Score (SD)
Cycle 3	[redacted]
Cycle 6	[redacted]
Cycle 12	[redacted]
Cycle 18	[redacted]
Cycle 24	[redacted]
Cycle 30	[redacted]

EQ-5D-5L – EuroQol 5-Dimension questionnaire 5 Level; VAS – Visual analogue scale.
Source: MAGNOLIA CSR[60]

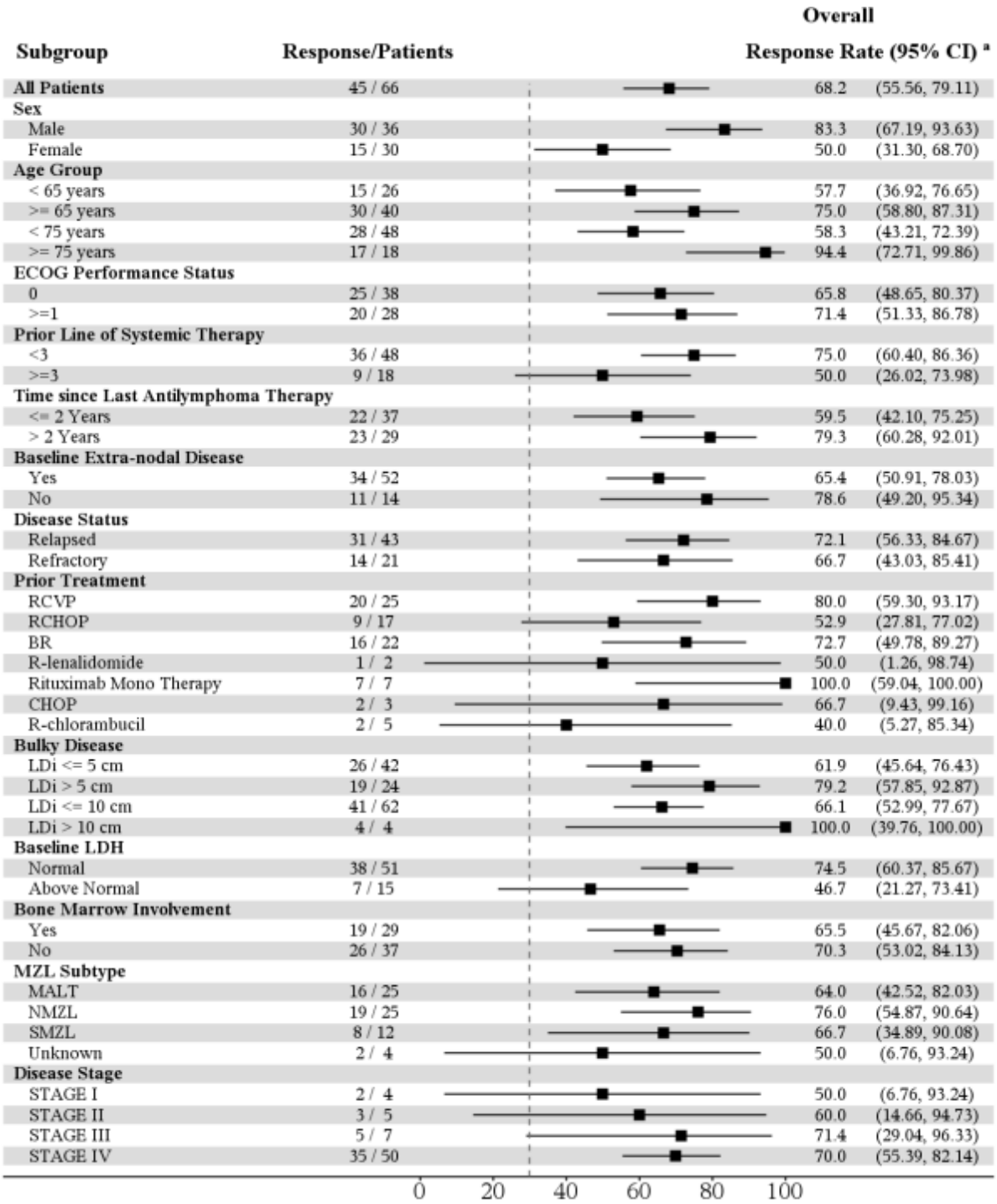
Figure 7: Mean change from baseline over time for EQ-5D-5L VAS score (MAGNOLIA)

CI – Confidence interval; EQ-5D-5L – EuroQol 5-Dimension questionnaire 5 Level; VAS – Visual analogue scale. Note: Only patients with data at both baseline and corresponding postbaseline visit were included in the summary statistics for change from baseline. The bars represent the 95% CI for the mean. *Baseline is defined Cycle 1 Day 1. The questionnaires were completed on Cycle 1 Day 1, end of Cycle 3, and then every 12 weeks for 12 months, and every 24 weeks thereafter.
Source: MAGNOLIA CSR[60]

B.2a.7 Subgroup analysis

As presented in Figure 8, a uniformity in treatment benefits was observed across all subgroups in the primary endpoint of IRC-assessed ORR. Notably, prior treatment history and MZL subtype did not exert a widespread impact on treatment responses. Caution should be taken when analysing the subgroup responses due to the low sample size associated with the analyses.

Figure 8: Forest plot of ORR by IRC assessment



BM – bone marrow; BR – bendamustine + rituximab; CI – confidence interval; ECOG – Eastern Cooperative Oncology Group; IRC – Independent Review Committee; LDH – lactate dehydrogenase; MALT – extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue; NMZL – nodal marginal zone lymphoma; ORR – overall response rate; R – rituximab; R-CHOP – rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; R-CVP – rituximab + cyclophosphamide + vincristine + prednisone; SMZL – splenic marginal zone lymphoma.

[a] 2-sided Clopper-Pearson 95% confidence intervals for Overall response rate.

Source: MAGNOLIA CSR[60]

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

B.2b.3.1 Study design

AU-003 is an international, open-label, multiple-dose, multicentre phase 1/2 study of zanubrutinib in patients with B-cell lymphoid malignancies, including R/R MZL. The primary trial endpoint was ORR by IRC assessment.[62]

The study was composed of an initial dose escalation phase (Part 1), followed by an expansion phase (Part 2). A total of 20 patients with MZL 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 AU-003 study will focus solely on the outcomes and insights derived from Part 2, specifically for patients with MZL. Patients received zanubrutinib until disease progression, intolerance or death, withdrawal of consent, or loss to follow-up. Table 25 provides a summary of the AU-003 trial methodology, and the study schematic is presented in Figure 9.

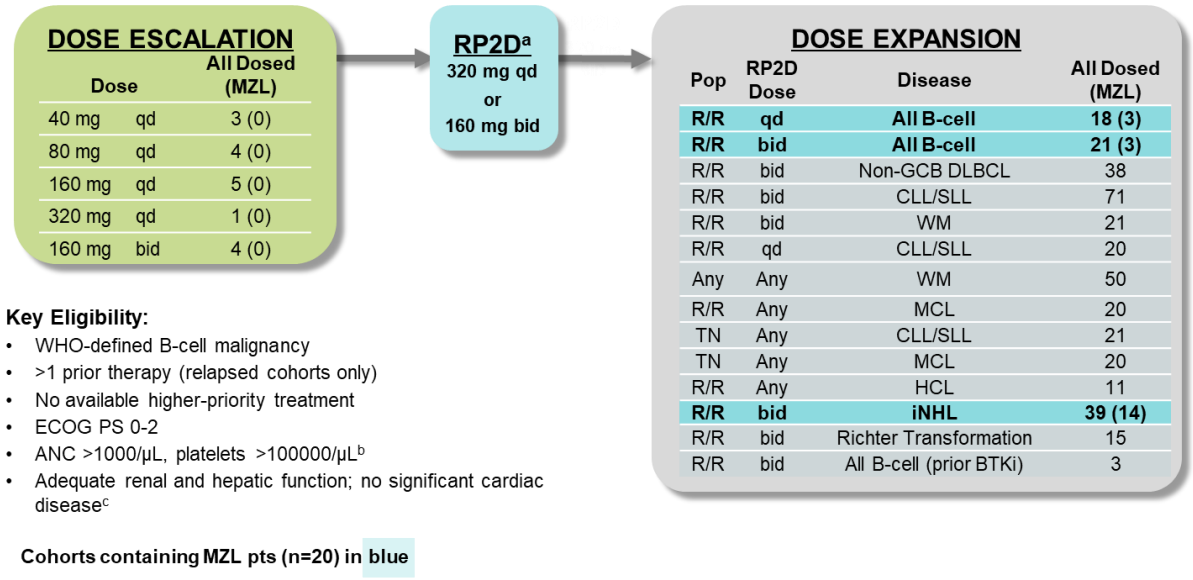
Table 25: Summary of trial methodology (AU-003)

Study details	AU-003 (BGB-3111-AU-003; NCT02343120)
Location	Australia, New Zealand, Italy, South Korea, the UK, and the USA
Design	Phase 1/2, 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 MZL.
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 efficacy endpoints:** • ORR (IRC) **Secondary endpoint:** • DOR (IRC and INV) • PFS (IRC and INV) • TTR (IRC and INV) • ORR (INV) • OS

Study details	AU-003 (BGB-3111-AU-003; NCT02343120)
Subgroup analysis	Sex, age, geographic region, race, ECOG PS, MZL subtype including extranodal, nodal and splenic, disease stage at study entry, bulky disease, baseline bone marrow involvement, baseline extranodal disease, refractory disease, baseline LDH, number of prior regimens, prior R-CVP, prior BR, Prior R-CHOP, prior rituximab monotherapy, prior rituximab-containing chemotherapy and time from end of last regimen to first dose.

BR – Bendamustine + rituximab; DOR – Duration of response; ECOG PS – Eastern Cooperative Oncology Group Performance Status; INV – Investigator; IRC – Independent review committee; LDH – Lactate dehydrogenase; MZL – Marginal zone lymphoma; ORR – Overall response rate; OS – Overall survival; PFS – Progression-free survival; R/R – Relapsed or refractory; R-CHOP – Rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; R-CVP – Rituximab + cyclophosphamide + vincristine + prednisone; TTR – Time to response; UK – United Kingdom; USA – United States of America
Source: AU-003 CSR[62]

Figure 9: AU-003 study schematic and design



bid – Twice daily; BTK – Bruton's tyrosine kinase; DLBCL – diffuse large B-cell lymphoma; GCB – germinal centre B-cell like; iNHL – indolent non-Hodgkin's lymphoma; qd – Once daily; RP2D – Recommended phase 2 dose
Note: Prior anticancer regimens do not include radiotherapy.
Source: AU-003 CSR (2021)[72]

B.2b.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 AU-003 trial are presented in Table 26 and were well matched with the criteria from the MAGNOIA study.

Table 26: Key eligibility criteria for 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. • R/R WHO-defined indolent lymphoma (inclusive of follicular lymphoma, MZL, and MALT lymphoma) • Following ≥ 1 line of therapy, with no therapy of higher priority 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 central nervous system 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; ECOG PS – Eastern Cooperative Oncology Group Performance Status; MALT – Mucosa-associated lymphoid tissue; MZL – Marginal zone lymphoma; R/R – Relapsed or refractory.
Source: AU-003 CSR (2021)[72]

B.2b.3.3 Outcome measures

The definition of the outcome measures available in the AU-003 study and whether they are used in the economic model are presented in Table 27. No QoL data was collected for the AU-003 trial.

Table 27: Outcome measures available from AU-003

Objective	Definition	Datacut 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 an IRC in accordance with the Lugano classification.	02 October 2020	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.	31 March 2021	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 – 02 October 2020 INV – 31 March 2021	Yes
OS	Time from initiation of zanubrutinib to the date of death from any cause.	31 March 2021	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 – 02 October 2020 INV – 31 March 2021	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 – 02 October 2020 INV – 31 March 2021	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)	02 October 2020	Yes

CR – Complete response; 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
*Median follow-up for 02 October 2020 data cut: 35.24 months (range: 8.3 to 59.2 months)
Source: AU-003 CSR (2021)[72] and AU-003 CSR[62]

B.2b.3.4 Patient characteristics

The demographics and baseline disease characteristics of patients at inclusion are presented in Table 28.

Among patients with MZL, the median age was 69.5 years, with 20.0% of patients over 75 years of age, and an even split between male and female participants. Among patients enrolled, 45% presented with extranodal MZL, 25% with nodal MZL, and 30% with splenic MZL.

A significant majority of patients exhibited features indicative of advanced or disseminated disease, including extranodal manifestations (100.0%) and the presence of bulky disease (25.0%).

A substantial portion of the patient cohort (60.0%) had undergone a minimum of two prior systemic treatments. All but one patient (95.0%) had previously received a rituximab-based chemoimmunotherapy, with R-CVP (65.0%), BR (20.0%) and R-CHOP (25.0%) the most common therapies received, and 20.0% of patients received rituximab monotherapy in a prior treatment line. Among the participants, 20.0% had not responded to prior therapy and were therefore considered refractory. The overall demographics and baseline characteristics of included patients were validated by UK clinicians (at an advisory board on the 11th October[4]) as being representative of patients who present in UK clinical practice and were comparable to the patient population included in the pivotal MAGNOLIA trial.

Table 28: Demographics and baseline disease characteristics (AU-003)

Characteristics	Zanubrutinib (N = 20)
Age, years	
Mean (SD)	69.5 (7.47)
Median (range)	69.5 (52, 85)
< 65 years	4 (20.0)
≥ 65 to < 75 years	12 (60.0)
≥ 75 years	4 (20.0)
Sex, n (%)	
Male	10 (50.0)
Female	10 (50.0)
Country, n (%)	
Australia	[redacted]
South Krea	[redacted]
Italy	[redacted]
New Zealand	[redacted]
United States	[redacted]
ECOG PS, n (%)	
0	7 (35.0)
1	11 (55.0)
2	2 (10.0)
Time from initial diagnosis to first dose (years)	
Mean (SD)	[redacted]
Median (Range)	5.97 (0.4, 17.2)
Disease subtype, n (%)	
Extranodal MZL	9 (45.0)
Nodal MZL	5 (25.0)

Characteristics	Zanubrutinib (N = 20)
Splenic MZL	6 (30.0)
Bulky disease, n (%)	
No (any target lesion LDi ≤ 5cm)[a]	15 (75.0)
Yes (all target lesion LDi > 5 cm)	5 (25.0)
Extranodal disease, n (%)[b]	
Yes	20 (100.0)
No	0 (0.0)
Refractory disease, n (%)[c]	
No	15 (75.0)
Yes	4 (20.0)
Unknown	1 (5.0)
Number of prior therapies	
Median (range)	[redacted]
1 prior therapy	8 (40.0)
2 prior therapies	8 (40.0)
≥ 3 prior therapies	4 (20.0)
Time from end of last therapy to first dose, n (%)	
Mean (SD)	[redacted]
Median (range)	[redacted]
≤ 2 years	12 (60.0)
> 2 years	8 (40.0)
Patients with any prior radiation therapies, n (%)	
Yes	1 (5.0)
No	19 (95.0)
Prior stem cell transplant, n (%)	
Yes	0 (0.0)
No	20 (100.0)
Prior systemic regimens, n (%)	
Rituximab-based chemoimmunotherapy	19 (95.0)
R-CVP	13 (65.0)
Alkylating agents	19 (95.0)
BR	4 (20.0)
R-CHOP	5 (25.0)
Rituximab monotherapy	4 (20.0)

BR – Bendamustine + rituximab; ECOG PS – Eastern Cooperative Oncology Group Performance Status; LDi – Longest diameter; MZL – Marginal zone lymphoma; R-CHOP – Rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; R-CVP – Rituximab + cyclophosphamide + vincristine + prednisone; SD – Standard deviation.

[a] Included 4 patients without baseline target lesion.

[b] Extranodal disease is defined as patients with any target or non-target extranodal lesions at baseline, or with baseline bone marrow involvement by biopsy/aspiration per investigator assessment.

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

Source: AU-003 CSR (2021)[72]

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

B.2b.4.1 Sample size calculations

A total of 380 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 [redacted]% for Part 2b (non-germinal centre B-cell like DLBCL). With a cohort of 40 patients, a 95% confidence interval's lower bound would be [redacted]% if the observed response rate were [redacted]%.

B.2b.4.2 Statistical analysis

Table 29 summarises the statistical analyses used in AU-003. The Safety Analysis Set included all patients who were enrolled and received at least one dose of zanubrutinib. The Efficacy Analysis Set included all patients with MZL who received at least one dose of zanubrutinib.

Table 29: 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. • At each imaging timepoint, response by CT and PET was determined. • When PET was not available, the timepoint response was determined by CT only. • The last date of non-progression was defined as the last date with imaging showing no progression	Efficacy analysis set
Secondary endpoint analysis		
PFS	• The KM method was used to estimate the distribution of PFS for patients with MZL. • 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 MZL. • 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 MZL.	Efficacy analysis set

Endpoint	Analysis	Population
	• Quartiles including the median were estimated by KM method along with their 95% CIs by Brookmeyer and Crowley method.	
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. • Descriptive analyses by system organ class, preferred term, maximum severity, and by preferred term only	Safety analysis set
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) • MZL subtype (extranodal, nodal, or splenic) • Disease stage at study entry (I to III versus IV) • Bulky disease (longest traverse diameter [LDi] ≤ 5 cm versus LDi > 5 cm) • Baseline bone marrow involvement (yes versus no) • Baseline extranodal disease (yes versus no) • Refractory disease (yes versus no versus unknown) • Baseline LDH (high versus normal) • Number of prior regimens (1, 2, or ≥ 3) • Prior therapy (R-CVP versus R-CHOP versus rituximab monotherapy versus rituximab-containing chemotherapy) • Time from end of last regimen to first dose (≤ 2 years versus > 2 years)	Efficacy analysis set

AE – Adverse event; CI – Confidence interval; CR – Complete response; CT – Computed tomography; DOR – Duration of response; ECOG PS – Eastern Cooperative Oncology Group Performance Status; ITT – Intention-to-treat; KM – Kaplan-Meier; LDH – Lactate dehydrogenase; LDi – Longest diameter; MZL – Marginal zone lymphoma; ORR – Overall response rate; OS – Overall survival; PET – positron emission tomography; PFS – Progression-free survival; PR – Partial response; R-CHOP – Rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; R-CVP – Rituximab + cyclophosphamide + vincristine + prednisone; SAE – Serious adverse event; TEAE – Treatment-emergent adverse event
Source: AU-003 CSR (2021)[72]

B.2b.4.3 Participant flow

Patients with MZL were enrolled in Part 2 of the study only. All 20 patients with R/R MZL received at least one dose of zanubrutinib. The median duration of follow-up for patients with R/R MZL was 39.24 months. A total of five (25.0%) patients discontinued their study drug due to progressive disease, while one (5.0%) patient discontinued due to adverse events (AEs), as detailed in Table 30. Three (15.0%) patients discontinued from the study due to death.

Table 30: Patient disposition in AU-003

Patient disposition	Zanubrutinib (N=20) n (%)
Number of patients treated	20 (100.0)
Patients discontinued from treatment	20 (100.0)
Reason for discontinuation from treatment	
Disease progression	5 (25.0)
Patient withdrew consent	2 (10.0)
Adverse event	1 (5.0)
Patients remained on study treatment in LTE	[redacted]
Patients discontinued from the study	[redacted]
Reason for discontinuation from the study	
Death	[redacted]
Lost to follow-up	[redacted]
Patient withdrew consent	2 (10.0)
Median study follow-up time (months)	[redacted]
Study follow-up time (months) (minimum, maximum)	[redacted]

LTE – Long-term extension
Source: AU-003 CSR (2021)[72]

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

A summary of the quality assessment for the AU-003 trial is provided in Table 31. 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.[70,71] Based on the findings from the quality assessment, AU-003 was a well-designed single arm trial which the appropriate steps taken to minimise bias where possible.

Table 31: Quality assessment results for 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 based on inclusion and exclusion criteria outlined in Table 26.	Yes
Was the exposure accurately measured to minimise bias?	All 20 MZL patients in the AU-003 trial received at least one dose of zanubrutinib. The median duration of treatment with zanubrutinib was [redacted] months. The relative dose intensity was 97.98% for patients with MZL.	Yes

Question	How is the question addressed?	Grade (yes/no/ unclear/NA)
Was the outcome accurately measured to minimise bias?	Outcomes were accurately measured to minimise bias, as outlined in Table 27. 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 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 median follow-up time for the patients in the MZL population was [redacted] months (range: [redacted] months). At the end of treatment, a safety follow-up occurred within 28 days after the last dose of zanubrutinib (± 7 days). All patients who discontinued study drug commenced long-term follow-up after progression every 3 months.	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 for full details.	Yes

CI – Confidence interval; INV – Investigator; IRC – Independent review committee; KM - Kaplan-Meier; MZL – Marginal zone lymphoma; ORR – Overall response rate.
Source: AU-003 CSR (2021)[72]

B.2b.6 Clinical effectiveness results of the relevant studies: AU-003

The key efficacy outcomes for patients with MZL from AU-003 are summarised in Table 32. IRC- and INV-assessed outcomes are presented based on a cut-off date of 02 October 2020 with a median follow-up 35.2 months. Further data was collected based on INV assessment at a data cut-off date of 31 March 2021, with a median follow-up of [redacted] months. Results from both data cuts are presented below and were consistent with those observed from the MAGNOLIA trial as presented in Section B.2a.6 Clinical effectiveness results of the relevant studies: MAGNOLIA.

Table 32: Key efficacy outcomes for AU-003

	Zanubrutinib (N = 20)		
	IRC-assessed (DCO 02 October 2020)	INV-assessed (DCO 02 October 2020)	INV-assessed (DCO 31 March 2021)
ORR			
ORR (95% CI)	80 (56.3, 94.3)	[redacted]	[redacted]
PFS			
Median, months (95% CI)	NE (20.3, NE)	[redacted]	[redacted]
DOR			
Median, months (95% CI)	[redacted]	[redacted]	[redacted]
TTR			
Events, n	[redacted]	[redacted]	[redacted]
Median, months (range)	2.8	[redacted]	[redacted]
OS (DCO 31 March 2021)			
Deaths, n (%)	[redacted]		

CI – Confidence interval; DCO – Data cut-off; DoR – Duration of response; INV – Investigator; IRC – Independent review committee; MZL – Marginal zone lymphoma; NE – Not estimable; ORR – Overall response rate; OS – Overall survival; PFS – Progression-free survival; TTR – Time to response.
Source: AU-003 CSR (2020)[62], AU-003 CSR (2021)[72]

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

The AU-003 study met its primary endpoint. As demonstrated in Table 33, ORR by IRC assessment was 80.0% (95% CI: 56.3, 94.3), with four (20.0%) patients achieving a complete response, at a median follow-up of 35.2 months (DCO: 02 October 2020). A large proportion of patients also achieved partial response (60.0%), which was highlighted as a desired outcome by clinical experts at the advisory board. Experts noted that with R/R MZL, the aim of treatment was to control the disease rather than cure patients.[4]

In line with ORR determined by IRC assessment, the ORR determined by INV assessment was [redacted]% (95% CI: [redacted]). The concordance rate between IRC and INV assessments was [redacted]% for ORR and [redacted]% for best overall response.

At a median follow-up of 39.2 months (DCO: 31 March 2021), INV-assessed ORR was maintained at [redacted]%. Notably, one patient was able to improve from a partial to complete response.

Table 33: IRC- and INV-assessed response rates in AU-003

Response category	Zanubrutinib (N = 20)		
	IRC-assessed (DCO 02 October 2020)	INV-assessed (DCO 02 October 2020)	INV-assessed (DCO 31 March 2021)
Best overall response, n (%)			
CR	4 (20.0)	[redacted]	[redacted]
PR	12 (60.0)	[redacted]	[redacted]
SD	2 (10.0)	[redacted]	[redacted]
PD	1 (5.0)	[redacted]	[redacted]
Not evaluable[a]	1 (5.0)	[redacted]	[redacted]
Overall response rate			
ORR, n (%) [95% CI][b]	16 (80.0) [56.3, 94.3]	[redacted]	[redacted]

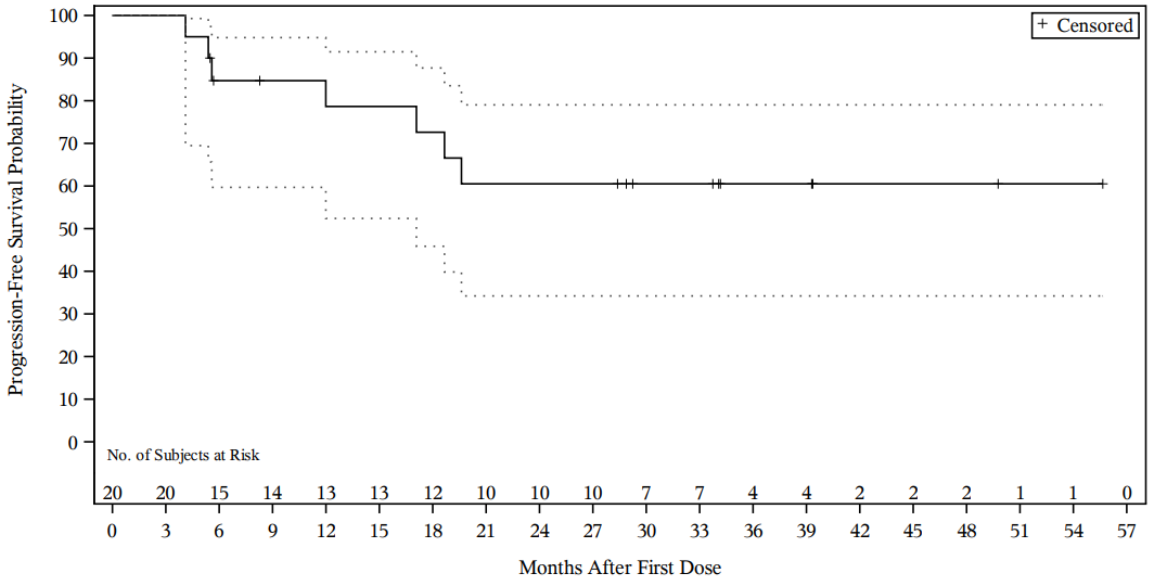
CI – Confidence interval; CR – Complete response; DCO – Data cut-off; INV – Investigator; IRC – Independent review committee; ORR – Overall response rate; PD – Progressed disease; PR – Partial response; SD – Stable disease. [a] For Patient S4208-2-308, the IRC reported no measurable disease, and only splenomegaly was present. Per the IRC charter, if there was no measurable disease, then an assessment of not evaluable was reported. [b] 2-sided Clopper-Pearson 95% CIs.
Source: AU-003 CSR (2020)[62], AU-003 CSR (2021)[72]

B.2b.6.2 Secondary endpoints

B.2b.6.2.1 Progression-free survival

At a median follow-up of 33.8 months (DCO: 02 October 2020), five (25.0%) patients had either progressed or died as per IRC assessment and median PFS had not been reached, as shown in the KM plot presented in Figure 10. As demonstrated in Table 34, the event-free rate was 84.0% (95% CI: 57.9, 94.6) at 12 months, 72.0% (95% CI: 45.0, 87.4) at 24 months and 72.0% (95% CI: 45.0, 87.4) at 36 months.

Figure 10: Kaplan-Meier plot of PFS by IRC in AU-003, DCO 02 October 2020



DCO – Data cut-off; IRC – Independent review committee; PFS – Progression-free survival.
Source: AU-003 CSR (2020)[62]

In line with the IRC assessment of PFS, [redacted] patients had either progressed or died as per INV assessment and median PFS had not been reached, as shown in the KM plot presented in Figure 11. The event-free rate was [redacted]% (95% CI: [redacted]) at 12 months, [redacted]% (95% CI: [redacted]) at 24 months and [redacted]% (95% CI: [redacted]) at 36 months.

Figure 11: Kaplan-Meier plot of PFS by INV in AU-003, DCO 02 October 2020

DCO – Data cut-off; INV – Investigator; PFS – Progression-free survival.
Source: AU-003 CSR (2020)[62]

At a median follow-up duration of 39.2 months (DCO: 31 March 2021), no further progression events were observed as per investigator assessment.

Table 34: IRC- and INV-assessed PFS in AU-003

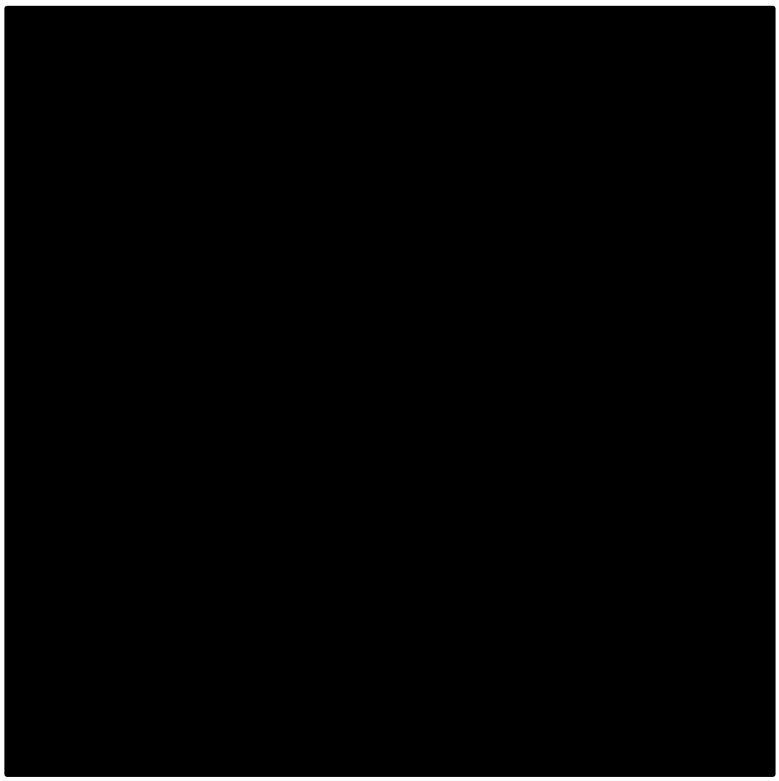
	Zanubrutinib (N=20)		
	IRC-assessed (DCO 02 October 2020)	**INV-assessed (DCO 02 October 2020)**	**INV-assessed (DCO 31 March 2021)**
PFS, n (%)			
Events	5 (25.0)	[redacted]	[redacted]
PD	4 (20.0)	[redacted]	[redacted]
Death	1 (5.0)	[redacted]	[redacted]
Event-free Rate at, % (95% CI)[a]			
6 Months	90.0 (65.6, 97.4)	[redacted]	[redacted]
12 Months	84.0 (57.9, 94.6)	[redacted]	[redacted]
18 Months	[redacted]	[redacted]	[redacted]
24 Months	72.0 (45.0, 87.4)	[redacted]	[redacted]
30 Months	[redacted]	[redacted]	[redacted]
36 Months	72.0 (45.0, 87.4)	[redacted]	[redacted]
Median[b]	NE (20.3, NE)	[redacted]	[redacted]

CI – Confidence interval; DCO – Data cut-off; INV – Investigator; IRC – Independent review committee; MZL – Marginal zone lymphoma; PFS – Progression-free survival.
[a] Event-free rates estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
[b] Medians and other quartiles are estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
Source: AU-003 CSR (2020)[62], AU-003 CSR (2021)[72]

B.2b.6.2.2 Overall survival

At a median follow-up of 39.2 months, three deaths had occurred, and median OS had not been reached, as shown in the KM plot presented in Figure 12. As reported in Table 35, the event-free rate was [redacted]% (95% CI [redacted]) at 12 months, [redacted]% (95% CI [redacted]) at 24 and [redacted]% (95% CI [redacted]) at 36 months.

Figure 12: Kaplan-Meier plot of OS in AU-003



OS – Overall survival.
Source: AU-003 CSR[62]

Table 35: OS in AU-003

	Zanubrutinib (N = 20)
Overall Survival	
Deaths, n (%)	[redacted]
Event-free Rate at, % (95% CI)	
12 months	[redacted]
24 months	[redacted]
36 months	[redacted]

CI – Confidence interval; DCO – Data cut-off; MZL – Marginal zone lymphoma; NE – Not estimable; OS – Overall survival.
Source: AU-003 CSR (2021)[72]

B.2b.6.2.3 Duration of response

At a median follow-up of 31.4 months (DCO: 02 October 2020), [redacted] of the 16 patients who achieved a response had either progressive disease or had died as per IRC assessment as described in Table 36. Median DOR was not reached, with 71.6% (95% CI: 40.3, 88.4) of responders event-free at 30 months after initial response

In line with IRC-assessed DOR, at a median follow-up of 25.8 months, [redacted] of the 17 patients who achieved a response had either progressive disease or had died as per INV assessment. Median DOR was not reached with [redacted]% (95% CI: [redacted]) of responders event-free at 30 months after initial response.

At a median follow-up duration of 39.2 months (DCO: 31 March 2021), DOR improved slightly, further demonstrating the durability of response.

Table 36: IRC and INV-assessed DOR in AU-003

	Zanubrutinib (N = 20)		
	IRC-assessed (DCO 02 October 2020)	**INV-assessed (DCO 02 October 2020)**	**INV-assessed (DCO 31 March 2021)**
DOR, n (%)			
Events	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Median DOR (months) (95% CI)	NE (8.4, NE)	[redacted]	[redacted]
Event-free rate at, (95% CI)			
6 months	87.5 (58.6, 96.7)	[redacted]	[redacted]
12 months	71.6 (40.3, 88.4)	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]
24 months	71.6 (40.3, 88.4)	[redacted]	[redacted]
30 months	71.6 (40.3, 88.4)	[redacted]	[redacted]

CI – Confidence interval; DCO – Data cut-off; DoR – Duration of response; INV – Investigator; IRC – Independent review committee; MZL – Marginal zone lymphoma; NE – Not estimable.
Source: AU-003 CSR (2020)[62], AU-003 CSR (2021)[72]

B.2b.6.2.4 Time to response

As presented in Table 37, median TTR was 2.8 months IRC assessment (DOC 02 October 2020). Consistent with IRC assessment, median TTR was [redacted] months by INV assessment in both data cuts.

Table 37: IRC- and INV-assessed TTR in AU-003

Response Category	Zanubrutinib (N = 20)		
	IRC-assessed (DCO 02 October 2020)	INV-assessed (DCO 02 October 2020)	INV-assessed (DCO 31 March 2021)
TTR, months			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	2.8 (2.6, 23.1)	[redacted]	[redacted]

CR – Complete response; DCO – Data cut-off; INV – Investigator; IRC – Independent review committee; MZL – Marginal zone lymphoma; SD – Standard deviation; TTR – Time to response.
Source: AU-003 CSR (2020)[62], AU-003 CSR (2021)[72]

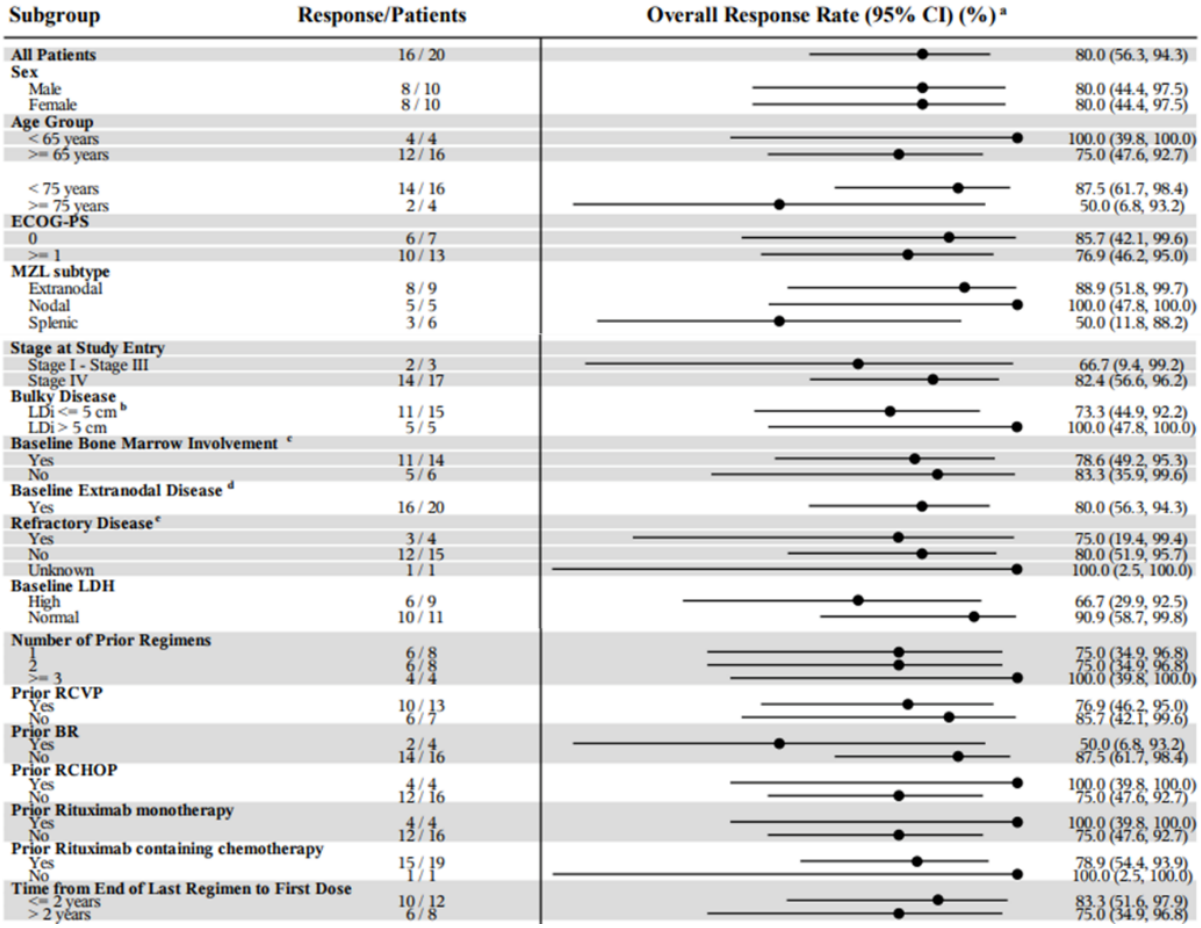
B.2b.6.6 Patient reported outcomes

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

B.2b.7 Subgroup analysis: AU-003

In line with the subgroup analysis from MAGNOLIA, a uniformity in treatment benefits was observed across all subgroups in the primary endpoint of IRC-assessed ORR, as presented in Figure ***13***. 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, such as patients who had undergone extensive prior therapies (≥ 3 prior lines of therapy), individuals with high-risk prognostic factors (Stage IV disease, bulky disease), and those diagnosed with nodal MZL.

Figure 13: Forest plot of ORR by IRC assessment



BR – Bendamustine and rituximab; CI – confidence interval; ECOG PS – Eastern Cooperative Oncology Group performance status; IRC – Independent Review Committee; MZL – Marginal zone lymphoma; ORR – Overall response rate; LDH – Lactate dehydrogenase; LDi – Longest transverse diameter; R-CHOP – Rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisone; R-CVP – Rituximab, cyclophosphamide, vincristine, and prednisone.
Source: AU-003 CSR (2020)[62]

B.2.8 Meta-analysis

A formal meta-analysis was not conducted due to the single arm nature of the studies. However, patient-level data from the MAGNOLIA and AU-003 trials were pooled for use in the indirect treatment comparison (ITC), see below for further details. Data pooling was conducted using data from the 31st May 2022 DCO for MAGNOLIA PFS and OS, the 2nd October 2020 DCO for AU-003 PFS and the 31st March 2021 for AU-003 OS.

B.2.9 Indirect and mixed treatment comparisons

A clinical SLR was performed to identify efficacy and safety evidence for patients with R/R MZL receiving systemic therapy. For further details on the methods and results of this SLR please refer to Appendix D. An assessment of the identified trials for rituximab monotherapy, rituximab in combination with chemotherapy or chemotherapy alone is provided in Table 38:

- One single arm trial assessed an intervention (lenalidomide plus rituximab), that was not licensed for use in MZL, nor was reflective of the treatments observed in the HMRN registry (Table 4) or recommended for off-label use in the ESMO guidelines.[5] Hence, it was not considered appropriate for use in an ITC.
- One single arm trial assessed bendamustine in a mixed patient population, including 16 patients with MZL. However, MZL subgroup baseline characteristics and efficacy outcomes (PFS and OS KM) were not reported, hence prohibiting its use in an ITC.
- One RCT assessed physicians' choice of BR or R-CHOP in patients with MZL, however only an abstract was available and hence insufficient detail was provided to allow for its inclusion in an ITC.
- Two RCTs included a rituximab monotherapy arm, which could be relevant to the decision problem (AUGMENT and CHRONOS-3). However, AUGMENT excluded patients who were refractory to prior rituximab therapy and therefore the patient population was not comparable to patients in MAGNOLIA (32% refractory) or AU-003 (20% refractory).[56] Furthermore, the sample size of the rituximab monotherapy arm in CHRONOS-3 was very small (N=29) with the number at risk

rapidly decreased to only 2 patients remaining at risk of progression by 24 months in comparison with 45 in the pooled zanubrutinib, which would result in substantial uncertainty.[58] Therefore, both trials were not considered appropriate for use in an ITC.

Table 38: Assessment of trials identified in the SLR for use in ITC

Publication source (author, year)	Trial name	Study type/phase	Treatment/Group (n)	Population	Rationale from exclusion from ITC
Leonard, 2019[56]	AUGMENT NCT01938001	RCT, open-label, phase III	Treatment arm A: lenalidomide + rituximab (n=31) Treatment arm B: rituximab + placebo (n=32)	Adults with R/R FL or MZL, excluding patients refractory to rituximab.	In AGUMENT, 97% of patients had relapsed MZL, and only n=1 patient was refractory to prior treatment. Hence the patient population is not comparable to MAGNOLIA (32% refractory) or AU-003 (20% refractory).
Matasar, 2021[57] Özcan 2021[58]	CHRONOS-3 NCT02367040	RCT, open-label, phase III	Treatment arm A: copanlisib + rituximab (n=66) Treatment arm B: rituximab + placebo (n=29)	Adults with MZL relapsed after the last rituximab-containing or other anti-CD20 monoclonal antibody-containing therapy.	Intervention is not licensed for use in R/R MZL,[73] and the intervention is not reflective of SoC observed in HMRN registry. Whilst the intervention is noted once in the ESMO guidelines it is not included within the ESMO treatment pathway recommendations.[5] The population only included relapsed patients with a very small sample size in control arm (N=29). The number at risk rapidly decreased with only 2 patients remaining at risk of progression by 24 months in comparison with 45 in the pooled zanubrutinib, hence any analysis would result in substantial uncertainty.
Nastoupil, 2023[59]	SELENE NCT01974440	RCT, double-blind, phase III	Treatment arm A: ibrutinib + CIT (n=202) Treatment arm B: placebo + CIT (n=201)	Adult patients diagnosed with FL or MZL who had received ≥1 prior line of CIT with an anti-CD20.	Abstract only with mixed population. Insufficient details reported in abstract.

Publication source (author, year)	Trial name	Study type/phase	Treatment/Group (n)	Population	Rationale from exclusion from ITC
Kahl, 2010[64]	Kahl, 2010	Open-label, Phase III	Bendamustine (N=16)	Adults with rituximab-refractory indolent B-cell NHL.	MZL patients grouped into a wider patient population. Baseline characteristics and efficacy outcomes (FSP, OS) not reported for MZL subgroup.
Coleman, 2021[65] Lansigan, 2022[66]	MAGNIFY NCT01996865	Open-label, Phase IIIb	Lenalidomide + rituximab (N=74)	Patients with R/R FL grades 1-3b, transformed FL (tFL), MZL, or MCL	Intervention is not licensed for use in R/R MZL,[74] and the intervention is not reflective of SoC observed in HMRN registry. Whilst it is noted a possible option in the ESMO guidelines it is restricted to patients where rituximab is not feasible,[5] hence the patient population does not align fully with the indication under assessment in this appraisal. MZL patients grouped into a wider patient population. Baseline characteristics and efficacy outcomes (PFS and OS KM) not reported for MZL subgroup.

CD20 – anti-cluster of differentiation 20; CIT – Chemoimmunotherapy; ESMO – European Society for Medical Oncology; FL – Follicular lymphoma; HMRN - Haematological Malignancy Research Network; ITC – Indirect treatment comparison; KM – Kaplan-Meier; MALT – mucosa-associated lymphoid tissue; MCL – Mantle cell lymphoma; MZL – Marginal zone lymphoma; NHL – Non-Hodgkin's lymphoma; OS – overall survival; RCT – Randomised controlled trial; R/R – Relapsed/refractory; SLR – Systematic literature review; SoC – Standard of care.

Given the lack of suitable evidence identified in the SLR for comparator treatments, the Company followed the NICE methods for the hierarchy of clinical evidence and considered real-world evidence as a potential data source.[75]

Through targeted searching, liaising with UK clinical experts and a review of the only previous NICE appraisal (NICE TA627[33]) that included patients with MZL, the Company identified the HMRN registry as an appropriate evidence source to generate comparative efficacy for this appraisal.

The HMRN registry is a suitable source to consider as it represents the largest registry dataset in the UK, and one of the largest across Europe. It is a collaborative venture initiated in 2004 by researchers at the University of York and NHS clinicians working across 14 UK hospitals. The registry includes a regional population of around 4 million people with a similar age and sex profile to the rest of the UK, and a comparable socioeconomic and urban/rural distribution to England. Within the HMRN, clinical practice follows national guidelines; and all haematological cancers and their precursor conditions are diagnosed and coded using the latest WHO ICD-O-3 classification at a single integrated hematopathology laboratory - the internationally recognised Haematological Malignancy Diagnostic Service (HMDS).[76–79]

Clinical experts in attendance at a clinical advisory board conducted in June 2022 by the Company recommended the HMRN as an appropriate source of data for patient characteristics, treatment trends and outcomes for patients receiving treatment for MZL in the UK.[80] The use of the registry to inform the outcomes for comparator treatments in this appraisal was further validated with UK clinical experts at a more recent advisory board conducted by the Company on the 11th October 2023.[34] Furthermore, during NICE TA627, the only existing NICE appraisal which included patients with MZL, the HMRN registry was regarded as a good example of evidence

to inform outcomes in the control arm by both the Evidence Assessment Group (EAG) and the NICE Committee.[33]

Comparable outcomes were available in both the HMRN registry and the zanubrutinib trials, namely PFS and OS. Patient characteristics were available from the HMRN registry to allow an accurate selection of the cohort to align with the eligibility criteria of the zanubrutinib trials. No studies using the HMRN registry were identified in the clinical SLR, therefore the Company engaged with the registry to extract aggregate patient characteristics and anonymised time-to-event individual patient-level data (IPD) relevant to the decision problem.

As both MAGNOLIA and AU-003 were single arm trials it was not possible to create a network for the purposes of a network meta-analysis (NMA) versus the HMRN cohort. In addition, due to data protection laws, IPD data for baseline characteristics could be not obtained from the registry, prohibiting an analysis such as propensity score matching. Therefore, aggregate population adjusted treatment comparisons were necessary to generate comparative effectiveness estimates for zanubrutinib versus comparator treatments following NICE TSD 18.[81]

A matching adjusted indirect comparison (MAIC) was preferred over a simulated treatment comparison (STC) given the recent past precedent in a previous zanubrutinib appraisal (NICE TA833) in a relevant blood cancer, where Committee and the EAG preferred the use of an MAIC over an STC.[82] The appraisal for zanubrutinib in CLL (ID5078) also adopted the MAIC methodology, which was accepted by the EAG and the Committee.[52] Furthermore, the populations of MAGNOLIA-003 and the HMRN cohort demonstrated sufficient comparability to justify the use of a MAIC.

B.2.9.1 Indirect comparison for zanubrutinib versus HMRN treatment basket in R/R MZL

B.2.9.1.1 Methodology

Data sources

To increase the sample size for zanubrutinib in the MAIC analyses, IPD from the MAGNOLIA and AU-003 trials were pooled. A comparable pooling approach was approved during the EMA assessment of zanubrutinib for marketing authorisation, wherein MAGNOLIA and AU-003 data were aggregated for the exposure-efficacy analysis.[83] From here-in the pooled IPD is referred to as MAGNOLIA-003. The trial eligibility criteria and the baseline characteristics (Table 39) were deemed comparable across the two trials. The pooling was validated as appropriate by UK clinical experts in attendance at an advisory board (11th October 2023).[4] As IPD from both zanubrutinib trials were available no adjustments were required to balance the populations of the two trials.

Table 39: Baseline characteristics of zanubrutinib trials

Characteristic		MAGNOLIA (N = 68) n (%)	AU-003 (N = 20) n (%)	Pooled data (N = 88) n (%)
ECOG PS	0	39 (57)	7 (35)	46 (52)
	1	24 (35)	11 (55)	34 (40)
	2	5 (7)	2 (10)	7 (8)
Age	Median (range)	70 (37-95)	70 (52-85)	70 (37-95)
	≥65	41 (60)	16 (80)	57 (65)
Disease stage	III-IV	III-IV: 59 (87)	19 (95)	78 (89)
LDH (U/L)	Above normal	16 (24)	9 (45)	25 (28)
Bulky disease	>5cm	25 (37)	5 (25)	30 (34)
Bone marrow involvement	Yes	29 (43)	14 (70)	43 (49)
Extranodal disease	Yes	53 (78)	20 (100)	73 (83)
Baseline cytopenia	Yes	20 (29)	6 (30)	26 (30)
MZL subtype	MALT/ extranodal	26 (38)	9 (45)	35 (40)

Characteristic		MAGNOLIA (N = 68) n (%)	AU-003 (N = 20) n (%)	Pooled data (N = 88) n (%)
	Nodal	26 (38)	5 (25)	31 (35)
	Splenic	12 (18)	6 (30)	18 (20)
	Unknown	4 (6)	0	4 (5)
Time since last treatment	Month, median (range)	20.6 (1-176.6)	17.3 (1.9-108.7)	20 (1-176.6)
Sex	Male	36 (53)	10 (50)	46 (52)
	Female	32 (47)	10 (50)	42 (48)
Response to last systemic therapy	Refractory	22 (32)	4 (20)	26 (30)
	Relapse	44 (65)	16 (80)	60 (68)
Number of prior therapies	Median (range)	2 (1-6)	2 (1-5)	2 (1-6)
	Immunochemotherapy/other	61 (90)	16 (80)	77 (88)
	Rituximab monotherapy	7 (10)	4 (20)	11 (13)

ECOG PS – Eastern Cooperative Oncology Group Performance Status; IPI – International Prognostic Index; LDH – Lactate Dehydrogenase; MALT – Mucosa-Associated Lymphoid Tissue; MZL – Marginal zone lymphoma; POD – Progression of Disease.
Source: MAGNOLIA CSR[60], AU-003 CSR (2020)[62]

Compared to the clinical trials, less information on patients baseline characteristics and demographics were available from the HMRN registry (though for the outcomes and characteristics that were available there were no issues with missing data and hence imputation was not necessary. There was no imputation of missing data performed for the subgroups and of the total [redacted] patients diagnosed, medical notes were unavailable for [redacted] because they were treated in non-network hospitals [either privately or outside the region] and these were excluded from the remainder of the analysis). In collaboration with the HMRN registry the Company were able to identify a cohort of patients that aligned to the patients included within MAGNOLIA-003. The criteria to identify a cohort aligned to the inclusion/exclusion criteria of the trials is presented in Table 40. The criteria were discussed and validated with UK experts in attendance at an advisory board (11th October 2023).[4] Feedback received from experts at the advisory board was used to improve the selection of subjects from the registry to increase comparability between the HMRN cohort and MAGNOLIA-003.

Figure 14 presents the flow of how the subjects were identified from the HMRN registry.

Table 40: Criteria applied to subjects in the registry to extract a cohort reflective of the patient population in MAGNOLIA-003

Characteristic	Full HMRN cohort	Criteria applied	Rationale
Time of entry into the registry	Enrolled in the registry from 2005 to 2020.	Subjects enrolled in the registry from 2014 onwards.	Clinical practice is expected to have improved since the registry started in 2005, and hence the time periods between the trials and registry were aligned to capture any potential improvements in outcomes. A cut off was applied to only include patients enrolled in the registry from 2014 onwards, the start date of the earlier zanubrutinib trial (AU-003).
ECOG PS	Any ECOG performance status (0-4).	Subjects with ECOG PS ≥ 3 were excluded.	To align with the exclusion criteria of the clinical trials. Note, ECOG PS in the registry was only available at time of enrolment, as opposed to initiation of subsequent treatment after receipt of prior anti-CD20-based therapy. Therefore, an assumption was made that a patient's ECOG PS on enrolment into the registry was an appropriate proxy.
Receipt of at least one prior anti-CD20-based therapy	All patients enrolled in the registry	Only subjects who had received at least one anti-CD20-based therapy	To align with the inclusion/exclusion criteria of the clinical

Characteristic	Full HMRN cohort	Criteria applied	Rationale
	regardless of treatment history.	were included.	trials, and the marketing authorisation of zanubrutinib.
Receiving further treatment beyond prior anti-CD20-based therapy		Only subjects observed to receive further treatment within the registry after receipt of prior anti-CD20-based therapy were included.	Only patients eligible for treatment after receipt of prior anti-CD20-based therapy would reflect the patients enrolled in MAGNOLIA and AU-003.
Receipt of treatments relevant to this appraisal.		Only subjects who were receiving treatments relevant to the comparators to this appraisal were included in the cohort. Targeted treatments such as receipt of BTKi therapy were excluded (n=[redacted] patients were excluded).	To align with the comparators relevant to this appraisal.

BTKi – Bruton tyrosine kinase inhibitor; CD20 – Cluster of differentiate 20; ECOG PS – Eastern Cooperative Oncology Group Performance Status; HMRN – The Haematological Malignancy Research Network; NICE – National Institute for Health and Care Excellence.
Source: MAGNOLIA CSR[60], AU-003 CSR (2020)[62], HMRN registry report[6]

Figure 14: Identification of cohort from HMRN registry

CD20 – Cluster of differentiate 20; ECOG PS – Eastern Cooperative Oncology Group Performance Status; HMRN – The Haematological Malignancy Research Network; NICE – National Institute for Health and Care Excellence.
Source: HMRN registry report[6], BeiGene DoF MAIC model[84]

Table 41 presents details on the individual treatments received by patients with R/R MZL who have received at least one prior anti-CD20-based therapy within the HMRN cohort. The treatments included align with those highlighted in the EMSO 2020 guidelines for the management of patients with advanced R/R MZL (see Table 4).[85] The basket reflects the standard of care patients are receiving in UK clinical practice, as validated by UK experts in attendance at an advisory board (11th October 2023).[4] Patient numbers for individual treatments were deemed too small for use in a MAIC, therefore a MAIC was performed against the basket of treatments within the HMRN cohort.

Table 41: Overview of treatments in HMRN treatment basket

Treatment regimen	% (N=[redacted])
Bendamustine-rituximab	[redacted]
Rituximab monotherapy	[redacted]
Cyclophoshamide-rituximab +/- steroids	[redacted]
R-CVP	[redacted]
Chlorambucil	[redacted]
R-CHOP	[redacted]
FCR	[redacted]
Other rituximab*	[redacted]
Other-non-rituximab**	[redacted]

* Chlorambucil / Rituximab (n=[redacted]), Gemcitabine / Dexamethasone / Cisplatin / Rituximab (n=[redacted]), IVE / Rituximab (n=[redacted]), Venetoclax / Rituximab (n=[redacted]) ** Other-non-rituximab: CVP (n=[redacted]), Bendamustine (n=[redacted]), Bendamustine / Methylprednisolone (n=[redacted]), Cyclophosphamide / Prednisolone (n=[redacted]), Fludarabine (n=[redacted]), VCD (n=[redacted]), Velcade / Dexamethasone (n=[redacted])
FCR – Fludarabine, cyclophosphamide and rituximab; HMRN – The Haematological Malignancy Research Network; R-CHOP – Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP – Rituximab, cyclophosphamide, vincristine, and prednisone; VCD – Velcade, Cyclophosphamide, and Dexamethasone. Source: HMRN registry report[6]

Covariate selection and weighting

The selection of covariates for weighting was informed by a review of a prior technology appraisal in NICE R/R FL/MZL, a review of the data in MAGNOLIA/AU-003 trials and a discussion with UK clinical experts.[86]

The key limiting factor in the selection of covariates was the limited number of patient characteristics available for the HMRN cohort for the following reasons:

- Fewer patient characteristics in general were collected in the HMRN registry compared to the zanubrutinib clinical trials, due to the nature of real-world data collection.
- A number of patient characteristics that were collected were only recorded at time of enrolment into the registry rather than at the time of initiation of therapy after a patient had relapsed or become refractory to their prior anti-CD20 treatment (i.e. equivalent to enrolment in the MAGNOLIA and AU-003 trials).

Therefore, the Company were restricted to patient characteristics that either:

- Were available at the time of initiation of therapy after a patient had relapsed or become refractory to their prior anti-CD20 treatment (e.g. refractory to last therapy, number of lines of prior therapy, POD24 status)
- Could be calculated from the time of enrolment in the registry (e.g. age, time since diagnosis)

Based on the above, a matching model was conducted using all available variables to the Company:

- Number of prior lines of therapy (1 vs 2 vs ≥3)
- Refractory to last therapy (yes vs no)
- Age (mean and variance)
- POD24 (yes or no)
- Median time since diagnosis (< median vs ≥ median)

ECOG status was only available at time of enrolment in the HMRN registry and therefore it was only used a proxy for ECOG status at time of receipt of further therapy (in patients with R/R MZL who have received at least one prior anti-CD20-based therapy) to identify a comparable cohort to the zanubrutinib datasets. ECOG status was therefore not included as a matching covariate.

Clinical UK experts in attendance at an advisory board (11th October 2023) validated the five selected covariates in the matching model. They also agreed with the exploration of a leave-one-out analysis within sensitivity analyses.[4] Additional scenario analyses considered included:

- Matching to MAGNOLIA alone (matching to AU-003 was considered infeasible given the small sample size, n=20).
- The exclusion of chemotherapy alone from the HMRN basket, reducing the sample size to n=[redacted]. Outcomes for patients receiving chemotherapy alone within the HMRN registry were poorer than those receiving rituximab +/- chemotherapy, and exclusion of chemotherapy explores a more conservative analysis.[6] The Company chose to include chemotherapy alone within the base-case analyses to capture the relevant treatment alternatives listed in the final NICE scope (see section B.1.1 Decision problem).

As IPD was available for the zanubrutinib trials, the MAGNOLIA-003 IPD was weighted such that the mean baseline characteristics of interest (covariates) match those reported in a basket of treatments from the HMRN registry. Weights were derived using propensity scores estimated from a logistic regression model. The unadjusted population characteristics of the zanubrutinib populations, in MAGNOLIA-003 and the HMRN cohort, are presented in Table 42.

Table 42: Comparison of unadjusted baseline patient and disease characteristics

Characteristic	MAGNOLIA-003 (N=86)	HMRN population (N=[redacted])
Prior therapies		
2	[redacted]	[redacted]

Characteristic	MAGNOLIA-003 (N=86)	HMRN population (N=[redacted])
3+	[redacted]	[redacted]
Response to last systemic therapy, n (%)		
Refractory	[redacted]	[redacted]
POD24 (%)	[redacted]	[redacted]
Age		
Age ≥ 65 years	[redacted]	[redacted]
Mean age (years)	[redacted]	[redacted]
Prior anti-CD20-based therapy (%)	[redacted]	[redacted]
Time since diagnosis ≥ median (%)	[redacted]	[redacted]
Time since diagnosis – mean (months)	[redacted]	[redacted]
Time since diagnosis – median (months)	[redacted]	[redacted]
Time since last therapy (months)	[redacted]	[redacted]

CD20 – Anti-cluster of differentiation 20; HMRN – The Haematological Malignancy Research Network; MZL – Marginal zone lymphoma; POD24 – Progression of disease within 2 years.
Source: MAGNOLIA CSR[60], AU-003 CSR (2020)[62], HMRN registry report[6]

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.[87,88] This process involved three key steps:

1. Deriving balancing weights for patients in the pooled zanubrutinib population from MAGNOLIA-003 to match the key population characteristics with prognostic or effect modifying potential the in HMRN cohort 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 MAGNOLIA-003 to calculate the effective sample size (ESS).

3. Estimating the relative treatment effect between the re-weighted pooled zanubrutinib population from MAGNOLIA-003 and the population in HMRN.

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

B.2.9.1.2 Results

The summary of the population characteristics of the pooled zanubrutinib population (both unweighted and weighted) from MAGNOLIA-003, and the basket of treatments from HMRN are presented in Table 43. After matching for selected covariates, the treatment arms were well balanced. A histogram of weights is included in Appendix L. After weighting, the ESS reduced by over 50%, however a leave-one-out analysis was conducted to explore the impact of not matching on all variables. An unweighted cox-model was also presented.

Table 43: Summary of the population characteristics before and after matching to the HMRN treatment basket

Characteristics	MAGNOLIA-003 (N=86), unweighted	MAGNOLIA-003 (ESS=[redacted]), weighted	HMRN treatment basket (N=[redacted])
2 lines of prior therapy (%)	[redacted]	[redacted]	[redacted]
3+ lines of prior therapy (%)	[redacted]	[redacted]	[redacted]
Refractory response to last systemic therapy	[redacted]	[redacted]	[redacted]
POD24 (%)	[redacted]	[redacted]	[redacted]
Mean age (years)	[redacted]	[redacted]	[redacted]
Time since diagnosis ≥ median (%)	[redacted]	[redacted]	[redacted]

ESS – Effective sample size; HMRN - Haematological Malignancy Research Network; POD24 – Relapse or progression within 24 months of initiation of systemic therapy. Source: BeiGene DoF MAIC model[84]

The MAIC results for PFS-IRC and OS, both before and after matching, are summarised in Table 44.

For PFS-IRC, both before (HR: [redacted] 95% CI, [redacted], p=[redacted]) and after (HR: [redacted] 95% CI, [redacted], p=[redacted]) matching**,** a statistically significant difference was observed between

zanubrutinib and the HMRN treatment basket. For OS, both before (HR: [redacted] 95% CI, [redacted], p=[redacted]) and after (HR: [redacted] 95% CI, [redacted], p=[redacted]) matching**,** a statistically significant difference was observed between zanubrutinib and the HMRN treatment basket.

Figure 15 and Figure 16 present the HMRN KM curves, and the unweighted and weighted KM curves for zanubrutinib for PFS-IRC and OS, respectively. The zanubrutinib weighted KM curves shift upwards from the unweighted KM curves for both PFS and OS, driven primarily by adjustment for prior lines of treatment, with patients more heavily pre-treated in the unweighted zanubrutinib dataset versus the weighted dataset.

Sensitivity analyses using the leave-one-out method to explore the impact of each covariate in the base-case model and the use of MAGNOLIA only for the zanubrutinib dataset were performed. An additional sensitivity analyses considered the impact of removing chemotherapy alone from the HMRN treatment basket, given that outcomes observed in the HMRN registry in patients receiving non-rituximab-based chemotherapy generally were poorer compared to rituximab +/- chemotherapy regimens.6

The leave-one-out analysis showed that removing any of the covariates from the base case model did not change the pattern of significance in the relative treatment effects and generally yielded comparable point estimates. In addition, the PFS-IRC and OS HRs remained consistent between the base-case analysis, the matching model based on MAGNOLIA alone and the matching model based on the HMRN cohort with chemotherapy alone excluded. Appendix L includes supplementary data for the sensitivity analyses (weighted baseline characteristics, histogram of weights and KM plots).

Table 44: Summary of MAIC results for MAIC using HMRN

Analysis	PFS (IRC)		OS	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Base case – MAGNOLIA-003 versus HMRN treatment basket (N=[redacted])				
Pre-matching (N=86)	[redacted]	[redacted]	[redacted]	[redacted]
Model (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analyses – MAGNOLIA only				
Pre-matching (N=68)	[redacted]	[redacted]	[redacted]	[redacted]
Model (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analyses – MAGNOLIA-003 versus HMRN treatment basket with chemotherapy alone excluded (N=[redacted])				
Pre-matching (N=86)	[redacted]	[redacted]	[redacted]	[redacted]
Model (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis – leave-one-out approach from base-case analysis				
Age omitted (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Response to last prior systemic therapy omitted (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
POD24 omitted (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior lines of therapy omitted (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Time since diagnosis omitted (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]

CI – Confidence interval; ESS – Effective sample size; HMRN – The Haematological Malignancy Research Network; IRC – Independent Review Committee; MAIC – Matching adjusted indirect comparison; OS – Overall survival; PFS – Progression-free survival; POD24 – Progression of disease within 2 years.

Source: BeiGene DoF MAIC model[84]

Figure 15: Kaplan-Meier curves of PFS-IRC for MAIC using HMRN

HMRN – The Haematological Malignancy Research Network; HR – hazard ratio; IRC – Independent review committee; MAIC – Matching adjusted indirect comparison; PFS – Progression-free survival.
Source: BeiGene DoF MAIC model[84]

Figure 16: Kaplan-Meier curves of OS for MAIC using HMRN

HMRN – The Haematological Malignancy Research Network; HR – hazard ratio; IRC – Independent review committee; MAIC – Matching adjusted indirect comparison; OS – Overall survival.
Source: BeiGene DoF MAIC model[84]

B.2.9.1.3 Assessment of proportional hazards

The log cumulative hazard plots and Schoenfeld residuals plots assessing the proportional hazards assumption for the PFS-IRC and OS after population adjustment are provided in Figure 17. While the cumulative log-log plots demonstrate some convergence and divergence, the lines do not cross. In addition, the p-value from the Global Schoenfeld test was >0.05 for both endpoints. Therefore, the null hypothesis that proportional hazards holds between zanubrutinib and the HMRN treatment basket for both PFS and OS cannot be rejected.

Figure 17: Cumulative log-log plots (top) and Schoenfeld residual plot (bottom) for OS (left) and PFS-IRC (right)

IRC – Independent review committee; OS – overall survival; PFS – Progression-free survival
Source: BeiGene DoF MAIC model[84]

B.2.9.1.4 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 MZL who have received treatment with at least one anti-CD20-based therapy (see Appendix D for further details). The SLR identified two studies for zanubrutinib (MAGNOLIA and AU-003).[61,63] Five studies were identified for individual treatments regimens potentially relevant to the NICE scope, however, upon assessment none were deemed appropriate for inclusion in an ITC.

To address the lack of published clinical trial data for the comparators, which, in this case, are off-label treatments, a MAIC utilising real-world evidence from the HMRN registry was considered as appropriate. The use of real-world evidence as opposed to trial data for comparator treatments may introduce uncertainties into the MAIC, however this approach adheres to the hierarchy of evidence as outlined in NICE

methods, which recommends considering real-world evidence when data from trial data is unavailable.[75]

Furthermore, the data from the HMRN registry can be considered high-quality and representative of patients in the UK with R/R MZL, and therefore is appropriate to the decision problem. In collaboration with the HMRN registry, the Company optimised the identification of the HMRN cohort by aligning it with the inclusion and exclusion criteria of the zanubrutinib trials, to increase the comparability of the populations. To increase sample size and hence reduce uncertainty in the MAIC, the use of a HMRN treatment basket in the MAIC was preferred to the use of individual treatments. A sensitivity analysis explored the impact of removing less efficacious chemotherapy regimens from the HMRN treatment basket, with results consistent with the base-case analysis.

Low ESS for the zanubrutinib arm may introduce uncertainty into the analyses. To increase sample size the populations from the MAGNOLIA and AU-003 trials were pooled. Despite the small ESS, zanubrutinib was able to demonstrate a statistically significant improvement in PFS and OS. This was supported by results from sensitivity analyses conducted using the leave-one-out method, using data from MAGNOLIA alone and when chemotherapy treatments were excluded from the HMRN treatment basket.

For the endpoint of OS, relatively few death events had occurred in MAGNOLIA and AU-003. This is expected given the indolent nature of marginal zone lymphoma. 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:

- At 30 months and 36 months, 80.6% and 84.2% of patients were alive in MAGNOLIA and AU-003, respectively. See Section.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 (MAGNOLIA: 68.2%, AU-003: 80%). See Section B.2b.6.1 Primary and key secondary endpoints: ORR and B.2a.6.1 Primary and key secondary endpoints: ORR for further information.

B.2.9.1.4 Conclusion

A MAIC comparing zanubrutinib with a HMRN treatment basket in patients with R/R MZL was conducted. To increase sample size for the zanubrutinib arm, data from MAGNOLIA and AU-003 were pooled. A comparable cohort of patients receiving treatments relevant to this appraisal were extracted from the HMRN registry. The HMRN treatment basket was considered representative of the treatment regimens patients receive in UK clinical practice, as validated by UK clinical experts at an advisory board (11th October 2023).[4]

Covariates for matching were selected based on data available from the HMRN registry and clinical plausibility as validated by UK clinical experts in attendance at an advisory board (11th October 2023), whilst balancing the need to conserve sample size.[4] After matching, the baseline characteristics in MAGNOLIA-003 were well matched to those reported for the HMRN treatment basket.

The MAIC analyses consistently demonstrated that treatment with zanubrutinib resulted in a statistically significantly improved PFS and OS compared to the basket of treatments within the HMRN registry. The analysis makes the best use of the data available and is aligned with the NICE DSU guidelines for population adjusted comparisons with the covariate adjustment and outputs validated by UK clinical experts.[81] There is an urgent unmet need for a new mechanism of action to treat patients with R/R MZL and zanubrutinib offers an efficacious option for this population, displaying improved outcomes compared to current treatment options.

B.2a.10 Adverse reactions: MAGNOLIA

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 MAGNOLIA.

B.2a.10.1 Dose exposure

The median treatment duration was 24.2 months (range: 0.9-32.9) for patients treated with zanubrutinib. The median actual dose intensity was [redacted] mg/day, with a median relative dose intensity of [redacted]%. No patients required a dose reduction, however a total of 25 (36.8%) patients required at least one treatment interruption due to treatment-emergent AEs (TEAE).

B.2a.10.2 Treatment-emergent adverse events

A summary detailing TEAEs is outlined in Table 45. Whilst all patients experienced at least one TEAE, most TEAEs were Grade 1 or 2. AEs associated with zanubrutinib were manageable and reversible with treatment interruption and supportive care and no patient discontinued zanubrutinib due to treatment-related AEs. A list of the most common AEs is presented in Table 46.

Occurrences of Grade ≥ 3 TEAEs were documented in 48.5% of patients, as presented in Table 47. The Grade ≥ 3 TEAEs reported most frequently were neutropenia (8.8%), COVID-19 pneumonia (5.9%), and pneumonia, diarrhoea, and syncope ([redacted]%).

Table 45: Summary of treatment-emergent and post-treatment AEs in MAGNOLIA

Event	Zanubrutinib (N = 68), n (%)
Patients with at least 1 AE	68 (100.0)
Grade ≥3 AEs	33 (48.5)
SAEs	30 (44.1)
AEs leading to death	5 (7.4)
AEs leading to study drug discontinuation	5 (7.4)
AEs leading to treatment interruption	25 (36.8)
AEs leading to dose reduction	0
Treatment-related AEs	[redacted]
AEs due to COVID-19	[redacted]

AE – Adverse event; SAE – Serious adverse event
Source: MAGNOLIA CSR[60]

Table 46: Treatment-emergent adverse events by system organ class and preferred term in ≥ 5% of patients (any grade) in MAGNOLIA

System Organ Class Preferred Term	Zanubrutinib (N = 68), n (%)
Patients with at Least One TEAE	68 (100.0)
Gastrointestinal disorders	[redacted]
Diarrhoea	15 (22.1)
Constipation	[redacted]
Abdominal pain	[redacted]
Nausea	[redacted]
Dyspepsia	[redacted]
Gastroesophageal reflux disease	[redacted]
Vomiting	[redacted]
Infections and infestations	[redacted]
Upper respiratory tract infection	[redacted]
COVID-19	[redacted]
COVID-19 pneumonia	[redacted]
Pneumonia	[redacted]
Tonsillitis	[redacted]
Urinary tract infection	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]
Arthralgia	[redacted]
Back pain	[redacted]
General disorders and administration site conditions	[redacted]
Pyrexia	[redacted]
Fatigue	[redacted]
Injury, poisoning and procedural complications	[redacted]
Contusion	16 (23.5)
Fall	[redacted]
Nervous system disorders	[redacted]
Dizziness	[redacted]

System Organ Class Preferred Term	Zanubrutinib (N = 68), n (%)
Lethargy	[redacted]
Sciatica	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]
Cough	[redacted]
Metabolism and nutrition disorders	[redacted]
Hypokalaemia	[redacted]
Blood and lymphatic system disorders	[redacted]
Thrombocytopenia	[redacted]
Neutropenia	[redacted]
Anaemia	[redacted]
Investigations	[redacted]
Neutrophil count decreased	[redacted]
Platelet count decreased	[redacted]

TEAE – Treatment-emergent adverse event
Source: MAGNOLIA CSR[60]

Table 47: Treatment-emergent adverse events of grade 3 or higher by system organ class and preferred term in ≥ 2 patients in MAGNOLIA

System Organ Class Preferred Term	Zanubrutinib (N = 68), n (%)
Patients with at Least One Grade 3 or Higher TEAE	33 (48.5)
Infections and infestations	15 (22.1)
COVID-19 pneumonia	4 (5.9)
Pneumonia	[redacted]
Gastrointestinal disorders	[redacted]
Diarrhoea	[redacted]
Blood and lymphatic system disorders	[redacted]
Neutropenia	6 (8.8)
Anaemia	[redacted]
Thrombocytopenia	[redacted]
Nervous system disorders	[redacted]
Syncope	[redacted]
Investigations	[redacted]
Neutrophil count decreased	[redacted]
General disorders and administration site conditions	[redacted]
Pyrexia	[redacted]
Vascular disorders	2 (2.9)
Hypertension	2 (2.9)

TEAE – Treatment-emergent adverse event
Source: MAGNOLIA CSR[60]

B.2a.10.3 Serious AEs

Serious AEs (SAE) were reported in 30 (44.1%) patients, as presented in Table 45.

SAEs reported in more than one patient were COVID-19 pneumonia ([redacted]%),

pneumonia ([redacted]%), pyrexia ([redacted]%), syncope ([redacted]%) and fall ([redacted]%); all other serious adverse events were reported in [redacted].

B.2a.10.4 Deaths

As of the data cut-off of 31 May 2022, [redacted] deaths had occurred in the study, of which five were attributed to TEAEs. COVID-19 pneumonia was the most common cause of death, occurring in two patients. All fatal events were assessed by the investigators as unrelated to study drug. [redacted] patients died more than 30 days after their last dose of study drug, which occurred following disease progression (in [redacted] patients) and the start of a new anticancer therapy (in [redacted] patients).

B.2a.10.5 Safety overview

Safety analysis from MAGNOLIA demonstrated that zanubrutinib is tolerable and safe for the treatment of patients with R/R MZL, with a safety profile consistent with previously published studies of zanubrutinib in other B-cell malignancies.[89–92] Aside from COVID-19 events stemming from the global pandemic, no additional new AEs were identified in the safety profile of zanubrutinib. The AEs were predominantly mild in nature and could be managed with temporary interruptions in treatment. Importantly, there were no recorded instances of treatment discontinuation, dose reduction, or fatalities linked to zanubrutinib .

B.2b.10 Adverse reactions: 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 AU-003.

B.2b.10.1 Dose exposure

At a data cut-off of the 2nd October 2020, the median duration of treatment was 32.1 months (range: 4.5-58.6) for patients treated with zanubrutinib with R/R MZL. The median actual dose intensity was [redacted] mg/day, with a median relative dose intensity of [redacted]%. Among patients with R/R MZL, [redacted] required at least one dose interruption and [redacted] required a dose reduction due to AEs.

In the extended data cut (data cut 31 March 2021) the median duration of treatment was [redacted] months, with a median relative dose intensity of 98.0%. Two patients (10.0%) required a dose reduction due to an AE, and 10 (50.0%) of patients required at least one treatment interruption due to an AE.

B.2b.10.2 Treatment-emergent adverse events

A summary detailing TEAEs is outlined in Table 48. Whilst all patients with MZL experienced at least one TEAE, AEs associated with zanubrutinib were manageable with treatment interruption and supportive care with only [redacted] discontinuing zanubrutinib due to treatment-related AEs. A list of the most common AEs is presented in Table 49.

Occurrences of Grade ≥ 3 TEAEs were documented in 55.0% of patients, as presented in Table 50. Across both data cuts, the most frequently observed Grade ≥3 TEAE were anaemia (15.0%), neutropenia (15.0%), and pyrexia (10.0%).

Table 48: Summary of treatment-emergent and post-treatment AEs in AU-003

	Zanubrutinib (N = 20), n (%)	
	DCO – 02 October 2020	DCO – 31 March 2021
Patients with at least 1 adverse event	20 (100.0)	20 (100.0)
Grade 3 or higher adverse event	11 (55.0)	11 (55.0)
Serious adverse event	[redacted]	[redacted]

	Zanubrutinib (N = 20), n (%)	
	DCO – 02 October 2020	DCO – 31 March 2021
AEs leading to death	0 (0.0)	0 (0.0)
AEs leading to study drug discontinuation	1 (5.0)	[redacted]
AEs leading to treatment interruption	10 (50.0)	10 (50.0)
AEs leading to dose reduction	2 (10.0)	2 (10.0)

AE – Adverse event; NR – Not reported
Source: AU-003 CSR (2020)[62], AU-003 CSR (2021)[72]

Table 49: Adverse events by system organ class and preferred term reported in patients with MZL in AU-003

System Organ Class Preferred Term	Zanubrutinib (N = 20), n (%)	
	DCO: 02 October 2020	DCO: 31 March 2021
Patients with ≥ 1 AE	20 (100.0)	20 (100.0)
Infections and infestations		
Upper respiratory tract infection	6 (30.0)	6 (30.0)
Urinary tract infection	2 (10.0)	2 (10.0)
Pneumonia	[redacted]	[redacted]
Sinusitis	4 (20.0)	4 (20.0)
Nasopharyngitis	5 (25.0)	NR
Escherichia urinary tract infection	[redacted]	[redacted]
Gastrointestinal disorders		
Diarrhoea	7 (35.0)	7 (35.0)
Constipation	[redacted]	[redacted]
Nausea	4 (20.0)	4 (20.0)
Abdominal pain upper	[redacted]	[redacted]
Injury, poisoning and procedural complications		
Contusion	7 (35.0)	7 (35.0)
Musculoskeletal and connective tissue disorders		
Back pain	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Musculoskeletal pain	4 (20.0)	NR
Respiratory, thoracic and mediastinal disorders		
Cough	3 (15.0)	4 (20.0)
General disorders and administration site conditions		
Fatigue	4 (20.0)	4 (20.0)
Pyrexia	5 (25.0)	5 (25.0)
Oedema peripheral	[redacted]	[redacted]
Skin and subcutaneous tissue disorders		
Rash	7 (35.0)	7 (35.0)
Pruritus	[redacted]	[redacted]
Nervous system disorders		
Headache	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]

System Organ Class Preferred Term	Zanubrutinib (N = 20), n (%)	
	DCO: 02 October 2020	DCO: 31 March 2021
Blood and lymphatic system disorders		
Neutropenia	5 (25.0)	5 (25.0)
Anaemia	[redacted]	[redacted]
Renal and urinary disorders		
Haematuria	[redacted]	[redacted]
Vascular disorders		
Hypertension	[redacted]	[redacted]
Psychiatric disorders		
Insomnia	[redacted]	[redacted]

AE – Adverse event; DCO – Data cut-off; MZL – Marginal zone lymphoma.
Source: AU-003 CSR (2020)[62], AU-003 CSR (2021)[72]

Table 50: Grade 3 or higher adverse events reported in > 2% of patients with MZL by system organ class and preferred term in AU-003

System Organ Class Preferred Term	Zanubrutinib (N = 20), n (%)	
	DCO – 02 October 2020	DCO – 31 March 2021
Patients with ≥ 1 Grade 3 or higher AE	11 (55.0)	11 (55.0)
Infections and infestations disorders		
Pneumonia	1 (5.0)	2 (10.0)
Cellulitis	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Influenza	[redacted]	[redacted]
Clostridium difficile colitis	[redacted]	[redacted]
Escherichia sepsis	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]
Skin infection	[redacted]	[redacted]
Carbuncle	[redacted]	[redacted]
Escherichia urinary tract infection	[redacted]	[redacted]
Pyelonephritis	[redacted]	[redacted]
Blood and lymphatic system disorders		
Neutropenia	3 (15.0)	3 (15.0)
Anaemia	3 (15.0)	3 (15.0)
Thrombocytopenia	1 (5.0)	1 (5.0)
Febrile neutropenia	[redacted]	[redacted]
Autoimmune haemolytic anaemia	[redacted]	[redacted]
Gastrointestinal disorders		
Diarrhoea	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Invasive ductal breast carcinoma	[redacted]	[redacted]
Prostate cancer	[redacted]	[redacted]

System Organ Class Preferred Term	Zanubrutinib (N = 20), n (%)	
	DCO – 02 October 2020	DCO – 31 March 2021
Investigations		
Neutrophil count decreased	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
Oxygen saturation decreased	[redacted]	[redacted]
Vascular disorders		
Hypertension	1 (5.0)	1 (5.0)
General disorders and administration site conditions disorders		
Pyrexia	2 (10.0)	2 (10.0)
Asthenia	[redacted]	[redacted]
Non-cardiac chest pain	[redacted]	[redacted]
Pain	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	[redacted]	[redacted]
Acute pulmonary oedema	[redacted]	[redacted]
Haemoptysis	[redacted]	[redacted]
Metabolism and nutrition disorders		
Hypokalaemia	[redacted]	[redacted]
Cardiac disorders		
Stress cardiomyopathy	[redacted]	[redacted]

AE – Adverse event; DCO – Data cut-off; MZL – Marginal zone lymphoma; NR – Not reported
Source: AU-003 CSR (2020)[62], AU-003 CSR (2021)[72]

B.2b.10.3 Serious AEs

As of the data cut-off of 31 March 2021, among patients with R/R MZL, SAEs were reported in [redacted] patients as presented in Table 48. The only serious adverse events occurring in more than one patient were pyrexia ([redacted]%), pneumonia ([redacted]%) and diarrhoea ([redacted]%).

B.2b.10.4 Deaths

As of the data cut-off of 31 March 2021, [redacted] patients with R/R MZL had died, all due to disease progression. [redacted] occurred within 30 days of the last dose of zanubrutinib and the remaining [redacted] occurred more than 30 days after the last dose. No fatal AEs were reported in patients with MZL.

B.2b.10.5 Safety overview

Consistent with the safety analysis from them MAGNOLIA trial, in the AU-003 trial zanubrutinib demonstrated as a tolerable and safe treatment option in patients with

R/R MZL, with a safety profile consistent with previously published studies of zanubrutinib in other B-cell malignancies.[89–92] AE were managed with dose interruptions and only one patient with MZL had an AE which led to discontinuation of the study drug. Importantly, no fatal AEs were reported in patients with MZL.

B.2.11 Ongoing studies

There are no ongoing trials assessing the efficacy of zanubrutinib monotherapy in patients with R/R MZL. No additional data cuts are anticipated for the MAGNOLIA and AU-003 trials.

B.2.12 Interpretation of clinical effectiveness and safety evidence

In the MAGNOLIA trial, the primary endpoint was met with zanubrutinib achieving an ORR of 68.2% by IRC assessment, leading to rejection of the pre-specified null hypothesis of 30% with 1-sided p-value < 0.0001. Zanubrutinib also demonstrated strong and durable PFS and OS with event-free rates of 70.9% (IRC-assessed) and 91.7% at 24 months, respectively. DOR, TTR, TTF and TTNLT results further support the durability of zanubrutinib efficacy outcomes in R/R MZL.

In the AU-003 trial, at a median study follow-up period of 35.2 months, patients with R/R MZL treated with zanubrutinib demonstrated a strong IRC-assessed ORR of 80.0%. In line with the MAGNOLIA trial, zanubrutinib demonstrated strong and durable PFS and OS with event-free rates of 72.0% (IRC-assessed) and 83.9% at 24 months, respectively, after a median follow-up of 35.2 months. DOR and TTR results provide additional evidence of the durable efficacy of zanubrutinib in R/R MZL. Additional data, after a median follow-up of 39.2 months demonstrates consistent results for all key outcomes across datacuts. Notably, median PFS (INV) or median OS had not yet been reached within the data, out to 48 months.

Across both MAGNOLIA and AU-003, zanubrutinib was shown to be well-tolerated and safe in the treatment of patients with R/R MZL with a safety profile consistent with previously published studies of zanubrutinib in other B-cell malignancies.[89–92]

Aside from COVID-19 events stemming from the global pandemic, no additional new AEs were identified in the safety profile of zanubrutinib. The AEs were predominantly mild in nature across both trials and could be managed with temporary interruptions in treatment. Importantly, there were no recorded instances of treatment discontinuation, dose reduction, or fatalities linked to zanubrutinib in the MAGNOLIA trial. In the AU-003 trial, only two instances of a TEAE leading to treatment discontinuation, and two instances of a TEAE leading to dose reduction were observed.

Data from the HMRN registry was identified as appropriate to inform the comparative efficacy of zanubrutinib versus comparator treatments relevant to this appraisal in patients with R/R MZL. The MAIC demonstrated that treatment with zanubrutinib is associated with a statistically significant [redacted]% reduction in the risk of IRC-assessed disease progression or death versus the HMRN treatment basket and a statistically significant [redacted]% reduction in the risk of death versus the HMRN treatment basket. 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 and outputs validated by UK clinical experts.

As highlighted in Section B.1.3.6 Unmet need, there is a clear lack of approved therapies for the treatment of patients with R/R MZL, with most patients exhausting treatment options after failing their first-line therapy. Current guidelines recommend rituximab-based chemotherapies; however, their effectiveness diminishes after prior systemic therapy.[25,45,46] Rituximab monotherapy or enrolment in clinical trials (if available) remain the only options for patients unable to withstand chemotherapy, particularly among the elderly and those heavily treated with chronic immunosuppression.[43,49] In contrast to other haematological cancers, targeted treatments such as BTKis are not approved for MZL, leading to a critical gap in treatment options. The HMRN data demonstrated that ibrutinib is a commonly used second-line treatment, used in [redacted]% of patients receiving treatment following

progression from an anti-CD20-based therapy.[6] The reliance on off-label ibrutinib by clinicians highlights the need for an approved targeted therapy in the treatment of MZL, supported by feedback gathered through a UK advisory board (11th October 2023). Furthermore, in consultation with MZL patient representatives, the Company is aware of the excitement among the patient community about the potential availability of zanubrutinib, a new chemotherapy-free option. In the consultation, patient representatives emphasised that as an at-home oral tablet, zanubrutinib offers a more accessible and convenient treatment option which is more patient-friendly.[37] Therefore, there is an urgent unmet need for a treatment option with a different mechanism of action to treat patients with R/R MZL. Zanubrutinib offers an effective option with improved outcomes and a tolerable safety profile compared to current treatment options.

B.3 Cost effectiveness

This cost-effectiveness analysis (CEA) can be considered a robust demonstration of the cost-effectiveness of zanubrutinib for patients with R/R MZL. R/R MZL is a rare form of blood cancer, which has been historically underserved in the UK with no approved treatment options.[37] There is high unmet need for a tolerable and effective chemotherapy-free treatment option. Zanubrutinib is an innovative, novel treatment, and the first licensed treatment option for R/R MZL in the UK. The clinical community and patient representatives have expressed excitement that zanubrutinib might become accessible to patients in the UK.[4,37] The uptake of zanubrutinib in the CUP further demonstrates the unmet need in R/R MZL. The CEA utilises the best available data for zanubrutinib, and is strengthened by the incorporation of UK registry data, increasing its generalisability to patients in clinical practice.[76–79] The economic base-case provides a highly conservative estimate of the cost-effectiveness, and across all scenarios modelled, the incremental cost-effectiveness ratio (ICER) remains below £30,000 per QALY gained, 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 to identify all relevant cost-effectiveness studies for the treatment of adult patients with R/R MZL. 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 one cost-utility analysis (CUA) from a UK perspective for patients with R/R MZL, a NICE appraisal (TA627) of lenalidomide in combination with rituximab for patients with either FL or MZL. A summary of this study is provided in Table 51. It is important to note that lenalidomide in combination with rituximab was

not granted marketing authorisation in patients with MZL, hence the final NICE guidance recommended it for use in patients with FL only.[86] Cross comparison of the comparators included in NICE TA627 and this appraisal should be considered with caution given the mixed population in NICE TA627. The HMRN registry basket which represents the comparator in this appraisal includes R-CHOP and R-CVP, but not obinutuzumab in combination with bendamustine. Obinutuzumab plus bendamustine was not included in the zanubrutinib analysis because it was not used in the HMRN registry, which collected data from a cohort of [redacted] patients diagnosed with MZL between 2005 to 2020, and it is not indicated in MZL.[6,93]

Table 51: Published cost-effectiveness studies in R/R MZL identified through the SLR

Study	Cost year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
NICE TA627[86]	2018	**Structure:** 3 health state partitioned survival model. **Perspective:** UK NHS and PSS **Time horizon:** Lifetime (40 years) **Discounting:** 3.5% (costs and outcomes)	Adult patients with previously treated FL or MZL (pooled data) who were treated with lenalidomide plus rituximab versus R-CHOP, R-CVP or obinutuzumab plus bendamustine.	NR – Redacted in dossier	NR – Redacted in dossier	FL/MZL population Lenalidomide and rituximab versus: • R-CHOP: £11,471 • R-CVP: £16,814 • Obinutuzumab and bendamustine: £16,960,557

FL – Follicular lymphoma; ICER – Incremental cost-effectiveness ratio; MZL – Marginal zone lymphoma; NHS – National Health Service; NR – Not reported; PSS – Personal Social Services; QALY – Quality-adjusted life year; R-CHOP – Rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone; R-CVP – Rituximab plus cyclophosphamide, vincristine and prednisolone; R/R – Relapsed or refractory; SLR – Systematic literature review; UK – United Kingdom.

B.3.2 Economic analysis

As the SLR did not identify any previous economic evaluations of zanubrutinib in patients with R/R MZL, a de novo economic model was built to assess the cost-effectiveness of zanubrutinib versus HMRN registry basket in this patient population, see section B1 for further details on the comparator. The model was developed in Microsoft Excel® using a three-state partitioned survival model (PSM) structure. The choice of model structure was validated by clinical and economic experts in attendance at an advisory board (11th October 2023) held by the Company, with the model structure deemed suitable for the decision problem.[4] The model structure is also aligned with TA627[86], the only NICE appraisal to consider patients with MZL, as well as other NICE appraisals for lymphoma and blood cancers.[3,4,52,82]

Key characteristics of the economic analysis are presented in Table 52.

Table 52: Features of the economic analysis

Factor	Chosen values	Justification
Modelling approach	PSM; cost-effectiveness	This approach has been applied in several previous HTA submissions for anti-cancer treatments for lymphoma (TA894, TA892, TA627).[86,94,95] It was also the approach taken to model zanubrutinib in similar and relevant blood cancer NICE appraisals (TA833 and ID5078).[52,82]
Approval population	Adults with MZL who have had at least 1 prior anti-CD20-based therapy	Aligned with the licence for zanubrutinib (please refer to Section B.1.1 Decision problem for additional rationale) and the scope of this appraisal.
Intervention	Zanubrutinib	In line with the final NICE scope.
Comparators	HMRN registry basket	In line with the relevant comparators in final NICE scope (please refer to Section B.1.1 Decision problem, description of the technology and clinical care pathway for additional rationale).
Perspective	UK NHS and PSS	Consistent with NICE reference case.[96]
Time horizon	Lifetime	Lifetime horizon (100 years – baseline age) is required to capture all differences in treatment arms in the economic model as per NICE reference case.[96]
Cycle length	28 days	Consistent with design of MAGNOLIA and AU-003, which use a period of 4 weeks for

Factor	Chosen values	Justification
		drug administration cycles. See B.2 Clinical effectiveness for further details.
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.
Source for clinical efficacy	Pooled MAGNOLIA and AU-003; HMRN registry	PFS and OS were derived from pooling the MAGNOLIA and AU-003 trials for zanubrutinib. HMRN registry data were used in the MAIC comparing the treatment basket with zanubrutinib. See B.2 Clinical effectiveness for further details..
Safety	Pooled MAGNOLIA and AU-003; published literature.	MAGNOLIA and AU-003 reflect the safety profile of patients with MZL treated with zanubrutinib. See B.2 Clinical effectiveness for further details. Safety outcomes are not available from the HMRN registry, hence published literature was used.
Utilities	• PF: MAGNOLIA-based utility estimate • PD: CADTH pCODR submission for bendamustine for NHL	EQ-5D-5L data was only recorded whilst patients were progression-free in MAGNOLIA (EQ-5D not recorded in AU-003). EQ-5D-5L data from MAGNOLIA was mapped to EQ-5D-3L as per the NICE reference case.[96] As such, published literature estimates were required for patient with progressed disease.
Costs	• Treatment acquisition and administration • Subsequent treatment costs • Health-state unit costs and resource use • End-of-life • Management of Grade 3 or above adverse events	Consistent with NICE reference case.[96]
Outcomes	• Total (aggregated and disaggregated) costs • Total LYs and QALYs • Incremental costs • Incremental LYs and QALYs • ICER per QALY gained	Consistent with the final scope for this appraisal and the NICE reference case.[96]
Uncertainty	• OWSA • Scenario analysis • Probabilistic sensitivity analysis	Consistent with the NICE reference case.[96]

CADTH – Canadian Agency for Drugs and Technologies in Health; CD20 – cluster of differentiation 20; EQ-5D-5L – EuroQol five dimensions five-level; HMRN – Haematological Malignancy Research Network; HTA – Health technology assessment; ICER – Incremental cost-effectiveness ratio; LY – Life year; MAIC – Matching adjusted indirect comparison; MZL – Marginal zone lymphoma; NHL – Non-Hodgkins's lymphoma; NHS – National Health Service; NICE – National Institute of Health and Care Excellence; OWSA – One-way sensitivity analysis; OS – Overall survival; pCODR – Pan-Canadian Oncology Drug Review; PD – Progressed disease; PF – Progression-free; PFS – Progression-free survival; PSM – Partitioned survival model; PSS – Personal Social Services; QALY – Quality adjusted life year; UK - United Kingdom.

B.3.2.1 Patient population

The CEA evaluates the incremental cost-effectiveness of treatment with zanubrutinib compared with HMRN registry basket in patients with R/R MZL, who have had at least one previous anti-CD20-based therapy. The baseline characteristics for the modelled population are presented in Table 53.

Table 53: Baseline characteristics for modelled population

Characteristics	Mean (SE)	Source
Age (years)	[redacted]	Pooled MAGNOLIA and AU-003 data, that has been matched to HMRN registry basket (base-case MAIC analysis)
BSA (m^2)	[redacted]	
Proportion female	[redacted]	

BSA – Body surface area; m – Metre; MAIC – Matched adjusted indirect treatment comparison; SE – Standard error.

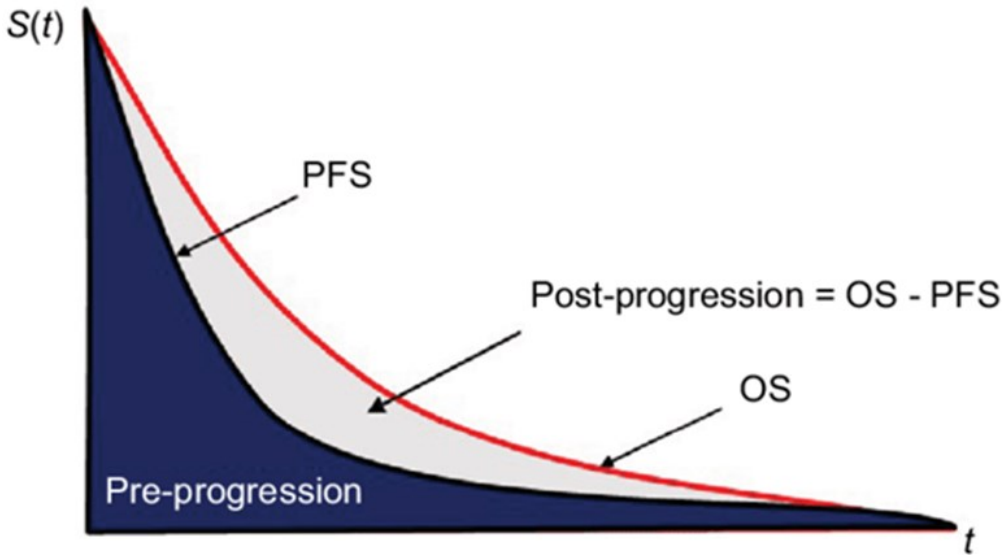
B.3.2.2 Model structure

The CEA utilises a PSM structure with three mutually exclusive health states: progression-free (PF), progressed disease (PD), and death, as illustrated in Figure 18. All patients initiate in the PF health state and can 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 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.

Figure 18: 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.

- **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.

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

B.3.2.4 Transitions

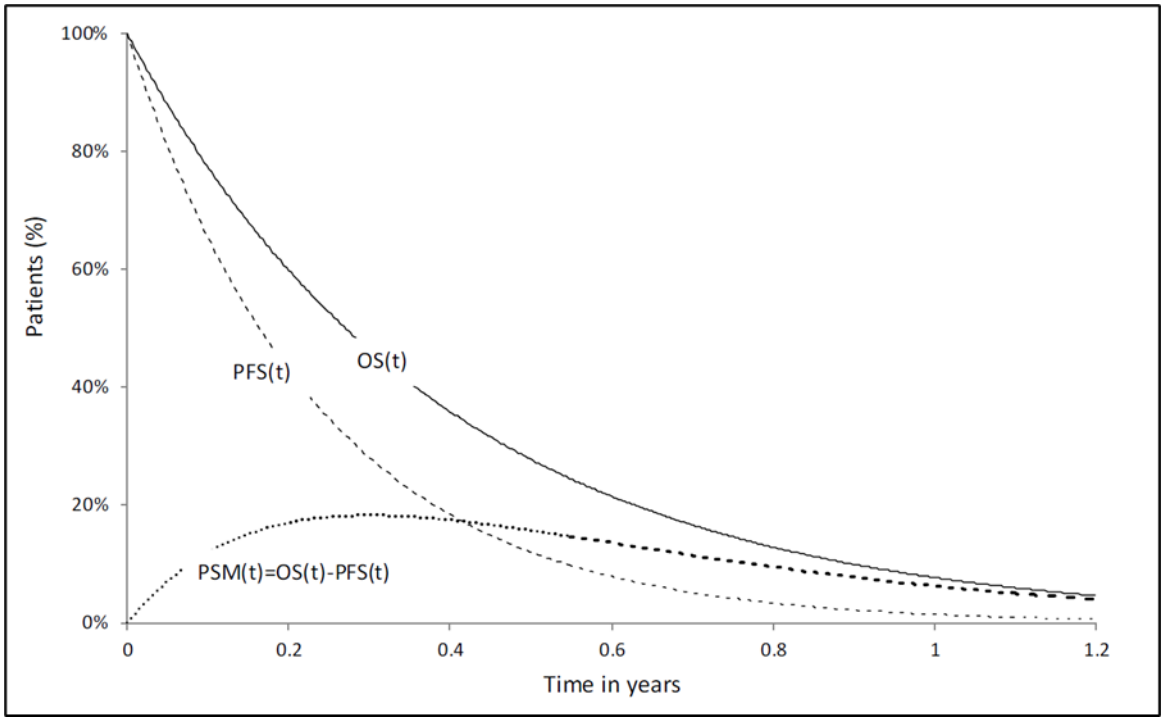
At each model cycle, the number of patients in each independent and mutually exclusive health state is updated with an illustration provided in Figure 19:

- **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 19: 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 2017[97]

Time on primary treatment is modelled independently from PFS for zanubrutinib, allowing patients to discontinue treatment despite remaining in the PF state. However, time on first-line treatment is constrained by PFS, reflecting that zanubrutinib should be administered until disease progression or unacceptable toxicity, in line with its license.[98] In the absence of published time to treatment discontinuation data, patients on HMRN registry basket receive treatment as per the PFS curve, with individual treatment stopping rules applied (i.e. patients will only receive treatments within the basket for a fixed duration of time, in line with anticipated UK clinical practice). Following treatment progression, patients can switch to a subsequent active treatment, modelled as a basket of treatments defined by a weighted distribution based on data from the HMRN registry (see Section B.3.2.6 Intervention technology and comparators). Subsequent treatment costs are applied as a one-time fixed cost to patients entering the PD state, based on the

average time patients are on the subsequent treatment.[52] Treatment-related costs, such as drug acquisition and drug administration costs, are accrued based on the time on treatment.

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 Technical Support Document 19, providing flexibility and directly using time-to-event endpoints available from the clinical trials.[97] The PSM structure is a widely accepted approach that is commonly used in NICE HTAs in oncology,[82,94,95] particularly as it is not necessary to model multiple lines of subsequent therapy given the limited treatment options for patients with R/R MZL (see Section B.1 Decision problem, description of the technology and clinical care pathway for further information on the treatment pathway).

A PSM approach was selected over a semi-Markov approach as explicit modelling of survival on subsequent treatments was not required and data from MAGNOLIA and AU-003 were sufficiently mature to provide robust extrapolations for PFS and OS. In addition, semi-Markov models require the use of alternative trial endpoints including time to progression, pre-progression survival and post-progression survival which can make conducting and interpreting ITCs more difficult, given these endpoints are not as widely reported in the literature. Furthermore, a discrete event simulation was not considered appropriate as these models are highly data intensive. Clinical and economic experts in attendance at an advisory board (11th October 2023) deemed the PSM structure suitable for the decision problem.[4]

B.3.2.6 Intervention technology and comparators

The intervention in the model is zanubrutinib. As highlighted in Section B.1.3.4 Clinical pathway of care and place in therapy, a basket of treatments that captures the range of regimens which patients are receiving in UK for R/R MZL is considered the most appropriate comparator to zanubrutinib (referred to as the HMRN registry basket in the CEA). The treatments included are based on HMRN data collected from cohort of [redacted] newly patients diagnosed with MZL, between 2005 to 2020.[6]

These treatments align with those highlighted in the 2020 ESMO guidelines for the management of patients with advanced R/R MZL.[5] The basket reflects the standard of care patients are receiving in UK clinical practice, as validated by UK experts in attendance at an advisory board (11th October 2023).[4] Details of the treatments included in the HRMN registry basket used in the model can be found in Table 54. It was not possible to include comparisons with individual treatments in the CEA due to a lack of data identified in the SLR, as well as small patient numbers in the HMRN basket for individual treatment regimens, hence prohibiting the completion of a robust ITC.

Table 54: Treatments included in the HMRN registry basket

Treatment regimen	%
Bendamustine-rituximab	[redacted]
Rituximab monotherapy	[redacted]
Cyclophoshamide-rituximab +/- steroids	[redacted]
R-CVP	[redacted]
Chlorambucil	[redacted]
R-CHOP	[redacted]
FCR	[redacted]
Other rituximab*	[redacted]
Other-non-rituximab**	[redacted]

* Chlorambucil / Rituximab (n=3), Gemcitabine / Dexamethasone / Cisplatin / Rituximab (n=1), IVE / Rituximab (n=1), Venetoclax / Rituximab (n=1) ** Other-non-rituximab: CVP (n=3), Bendamustine (n=2), Bendamustine / Methylprednisolone (n=1), Cyclophosphamide / Prednisolone (n=1), Fludarabine (n=1), VCD (n=1), Velcade / Dexamethasone (n=1). FCR – Fludarabine, cyclophosphamide and rituximab; HMRN – The Haematological Malignancy Research Network; R-CHOP – Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP – Rituximab, cyclophosphamide, vincristine, and prednisone; VCD – Velcade, Cyclophosphamide, and Dexamethasone. Source: HMRN registry report[6]

B.3.3 Clinical parameters and variables

Individual survival analyses were required to estimate movement between health states. The key clinical parameters and variables in the model which required separate survival analyses were: PFS, OS and TTD (for cost calculations only).

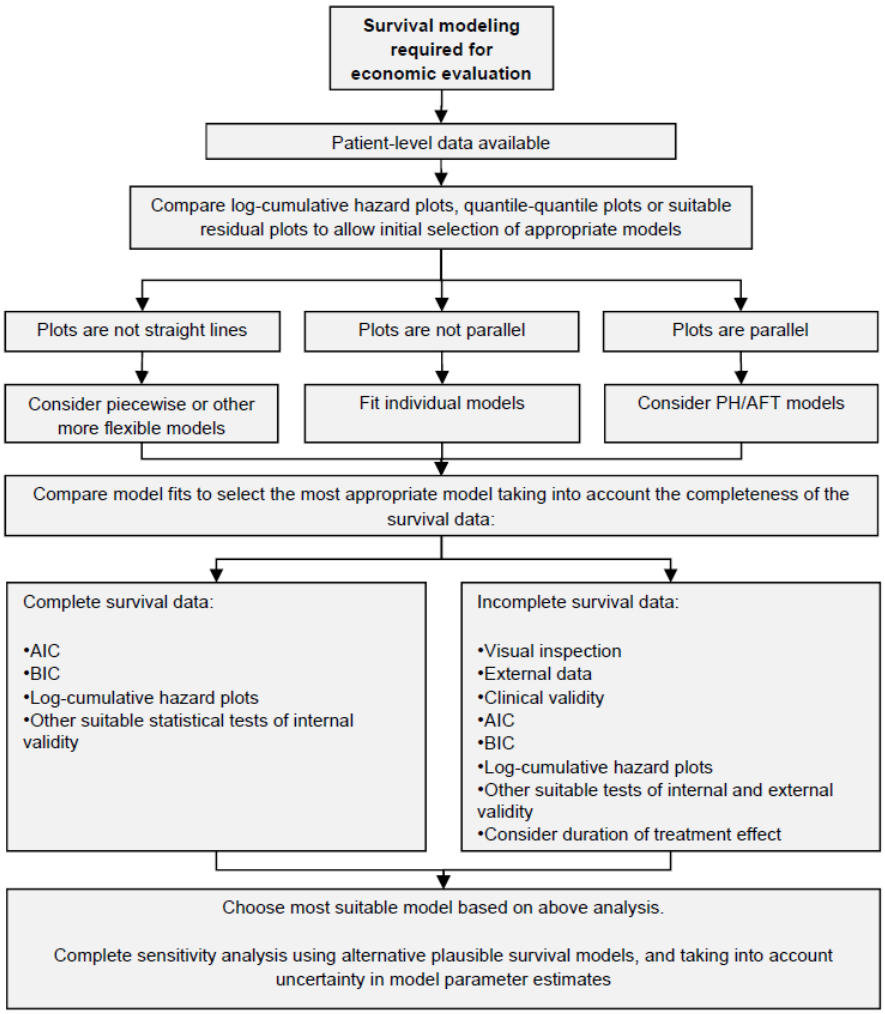
B.3.3.1 Time to event analysis

Time to event analysis involved fitting survival functions to patient-level survival data from a pooled population of patients from MAGNOLIA and AU-003 to estimate long-term extrapolations. Pooled MAGNOLIA-003 data were adjusted via a MAIC (see Section B.2.9 Indirect and mixed treatment comparisons for further details) to match to the HMRN registry basket (N=[redacted]), reflecting the comparator within this appraisal. Individual patient data was adjusted via weights such that the mean baseline characteristics of interest are balanced to those reported in the comparison arm. Scenario analyses were conducted to explore the weighted MAGNOLIA alone data set (adjusted to the HMRN registry basket, N=[redacted]) and the MAGNOLIA-003 weighted dataset adjusted to the restricted HMRN registry basket (N=[redacted]). Please refer to Appendix M for survival analyses outputs for both scenario analyses.

The survival analysis was conducted in line with the methods recommended by NICE DSU 14, using the following distributions: exponential, Weibull, Gompertz, log-logistic, log-normal and gamma.[88] Extrapolations using the generalised gamma curve were considered but did not converge across endpoints for the zanubrutinib dataset, hence could not be included in the model. Given that the zanubrutinib trials were single arm, it was considered appropriate to only fit independent survival models to the datasets and to not consider dependent survival models (which would assume a proportional treatment effect). This decision is aligned with the feedback received from a survival analysis expert at the advisory board (11th October 2023).[4]

As summarised in Figure 20, the process of selecting a best-fitting distribution involved an assessment of clinical plausibility leveraging clinical expert opinion and comparing to real-world data, 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 MAGNOLIA-003 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 20: 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.
Source: NICE DSU TSD-14[99]

B.3.3.2 PFS: HMRN registry basket

To align with the PFS data used to inform the MAIC analyses (see Section B.2.9 Indirect and mixed treatment comparisons), extrapolations based on the HMRN registry data set (N=[redacted]) were produced.

The goodness-of-fit statistics for the PFS endpoint for the HMRN registry basket are presented in Table 55. Based on the AIC and BIC statistics, the Weibull distribution provides the best statistical fit (based on summed AIC and BIC). The Gamma

distribution provides the second-best statistical fit (based on summed AIC and BIC). However, the exponential, Gompertz and log-logistic distributions are considered a reasonable statistical fit as they are within four AIC points of the best fitting curve.[100]

Table 55: Goodness-of-fit statistics for PFS – HMRN registry basket (N=[redacted])

Distribution	HMRN registry basket (Stratified)		
	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]
Gamma	[redacted]	[redacted]	[redacted]

AIC – Akaike Information Criteria; BIC – Bayesian Information Criteria; HMRN – Haematological Malignancy Research Network; PFS – Progression-free survival. **Bold indicates the distribution with the best statistical fit.**

The parametric survival extrapolations and KM for PFS for the HMRN registry basket are presented in Figure 21. The Gompertz, log-logistic and log-normal curves provide the most optimistic estimation with a PFS plateauing at around ~5% by 30 years. All the remaining estimations tend to zero by 30 years.

Figure 21: KM for PFS overlaid with extrapolated parametric survival curves – HMRN registry basket (N=[redacted])

AIC – Akaike Information Criterion; HMRN – Haematological Malignancy Research Network; KM – Kaplan-Meier; PFS – Progression-free survival.

Sole assessment of the visual and statistical fit was not sufficient to determine the distribution for PFS, therefore additional clinical validation of the curve selection was required. The clinical experts consulted as part of the advisory board (11th October 2023) suggested that approximately 20% of patients would be progression-free at 10 years, for patients receiving standard of care.[4] This estimate best aligns with the log-normal and log-logistic curves (Table 56), however all six distributions underestimate PFS at 10 years when compared to this estimate. Clinical experts also indicated that the shape of the hazard for progression in a patient with MZL would exhibit an initial increase before decreasing over time, which also aligns with the hazard profile of accelerated failure time models (e.g. log-logistic and log-normal distributions). Hence, these two curves were considered for the base-case analysis.

Table 56: Landmark PFS – HMRN registry basket (N=[redacted])

Distribution	Median (years)	PFS (%) at landmark timepoints*					
		1-year	2-year	5-year	10-year	20-year	30-year
KM data	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HMRN – Haematological Malignancy Research Network; KM – Kaplan-Meier; PFS – Progression-free survival.

The log-logistic distribution was of better statistical fit than the log-normal distribution (7.28 total AIC and BIC point difference). The log-logistic distribution produced an extrapolation that was a visually good fit to the data, and led to clinically plausible PFS at landmark time points (validated by clinical experts). Therefore, the log-logistic distribution was selected for the extrapolation of PFS in the base case. Sensitivity analyses (see Section B.3.11 Exploring uncertainty) were conducted using the:

- Log-normal distribution, to assess the impact of modelling the most optimistic curve for the HMRN PFS dataset. Note: zanubrutinib is curve is set to the most pessimistic curve choice in this scenario.
- Weibull distribution, to assess the impact of modelling the best statistically fitting curve for the HMRN registry basket.

B.3.3.3 PFS: Zanubrutinib

To align with the PFS endpoint that was used to inform the MAIC analyses (see see Section B.2.9 Indirect and mixed treatment comparisons), extrapolations based on the IRC-assessed PFS endpoint were modelled for the zanubrutinib arm. PFS data was directly derived from pooled patient-level data in the MAGNOLIA and AU-003 trials, weighted to the HMRN registry basket (N=[redacted]). Pooled data was used to increase sample size available to inform the CEA.

The goodness-of-fit statistics for the PFS endpoint for zanubrutinib are presented in Table 57. Based on the AIC and BIC statistics, the exponential curve provides the

best statistical fit (based on summed AIC and BIC). The log-normal provides the second-best fit, with the second lowest total AIC and BIC scores. However, all distributions are considered a reasonable statistical fit as they are within four AIC points of the best fitting curve.[100]

Table 57: Goodness-of-fit statistics for IRC-assessed PFS – zanubrutinib (pooled MAGNOLIA and AU-003 weighted to HMRN basket, N=[redacted])

Distribution	Zanubrutinib (Stratified)		
	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]
Gamma	[redacted]	[redacted]	[redacted]

AIC – Akaike Information Criteria; BIC – Bayesian Information Criteria; HMRN – Haematological Malignancy Research Network; IRC – Independent review committee; PFS – Progression-free survival. **Bold indicates the distribution with the best statistical fit.**

The parametric survival extrapolations and KM for IRC-assessed PFS for zanubrutinib are presented in Figure 22. The Gompertz provides the most optimistic estimation with a tail that exhibits a plateau at ~48% progression-free. The log-normal and log-logistic also feature tails that plateau, however, it was less significant than that observed with the Gompertz estimation. The remaining estimations tend towards zero by 30 years.

Figure 22: KM for IRC-assessed PFS overlaid with extrapolated parametric survival curves – zanubrutinib (pooled MAGNOLIA and AU-003, weighted to HMRN basket, N=[redacted])

HMRN – Haematological Malignancy Research Network; IRC – Independent review committee; KM – Kaplan-Meier; PFS – Progression-free survival.

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. Landmark PFS rates for zanubrutinib are presented in Table 58.

Table 58: Landmark IRC-assessed PFS – zanubrutinib (pooled MAGNOLIA and AU-003, weighted to HMRN basket, N=[redacted])

Distribution	Median (years)	PFS (%) at landmark timepoints*					
		1-year	2-year	5-year	10-year	20-year	30-year
KM data	Not reached	[redacted]	[redacted]	-	-	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HMRN – Haematological Malignancy Research Network; IRC – Independent review committee; KM – Kaplan-Meier; PFS – Progression-free survival.

There is no evidence of a violation in the proportional hazards assumption between zanubrutinib and the HMRN registry basket (N=[redacted]) (please refer to see Section

B.2.9 Indirect and mixed treatment comparisons for further details), hence it may be statistically appropriate to select the same distribution for the treatment arms for PFS. As there was no strong evidence to justify a different choice of curve between zanubrutinib and the HMRN basket for PFS, in line with the NICE DSU guidance, the base-case curve choice for the HMRN registry basket, the log-logistic distribution, was considered for zanubrutinib.[99]

The log-logistic distribution produced an extrapolation that was a statistically and visually good fit to the data, within four total AIC and BIC points of the best fitting curve. The underlying hazard shape of the log-logistic curve also reflects the feedback from UK clinical experts at the advisory board.[4] The log-logistic distribution provides a middle ground estimate for PFS, compared to the other survival extrapolations. Therefore, the log-logistic distribution was selected for the extrapolation of PFS in the base case. A sensitivity analysis was conducted using the:

- Exponential distribution, to assess the impact of modelling the best statistically fitting curve (and also the most pessimistic curve) for zanubrutinib.

B.3.3.4 OS: HMRN registry basket

To align with the OS data used to inform the MAIC analyses (see Section B.2.9 Indirect and mixed treatment comparisons for further details), extrapolations based on the wider HMRN registry data set (N=[redacted]) were produced.

The goodness-of-fit statistics for the OS endpoint for the HMRN registry basket are presented in Table 59. Based on the AIC and BIC statistics, the Gamma curve provides the best statistical fit with the lowest sum of AIC and BIC scores, and the lowest individual AIC and BIC scores. The Weibull provided the second-best statistical fit by both AIC and BIC. However, the exponential, Gompertz, and log-logistic distributions are also considered reasonable statistical fits as they are within four AIC points of the best fitting curve.[100]

Table 59: Goodness-of-fit statistics for OS – HMRN registry basket (N=[redacted])

Distribution	HMRN registry basket (Stratified)		
	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]
Gamma	[redacted]	[redacted]	[redacted]

AIC – Akaike Information Criteria; BIC – Bayesian Information Criteria; HMRN – Haematological Malignancy Research Network; OS – Overall survival. **Bold indicates the distribution with the best statistical fit.**

The parametric survival extrapolations and KM for OS for the HMRN registry basket are presented in Figure 23. The Gompertz and log-normal curves both provide the most optimistic survival, plateauing at ~15% by 30 years. The exponential model provides the most conservative estimations, followed by the Gamma and Weibull models.

Figure 23: KM for OS overlaid with extrapolated parametric survival curves – HMRN registry basket (N=[redacted])

HMRN – Haematological Malignancy Research Network; KM – Kaplan-Meier; OS – overall survival.

Sole assessment of the visual and statistical fit was not sufficient to determine the distribution for PFS, therefore additional clinical validation of the curve selection was required. UK clinical experts expected OS to be around 40% at 10 years.[4] All six

curves underestimate the OS at 10 years compared to the UK clinical expert opinion (Table 60).

Table 60: Landmark OS – HMRN registry basket (N=[redacted])

Distribution	Median (years)	OS (%) at landmark timepoints					
		1-year	2-year	5-year	10-year	20-year	30-year
KM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HMRN – Haematological Malignancy Research Network; KM – Kaplan-Meier; OS – Overall survival.

The log-normal distribution provided the closest estimate to the 40% at 10 years with an estimate of [redacted]%, however the log-normal was the worst statistically fitting curve and hence was not selected for the base-case. The next closest curve ([redacted]%) was the log-logistic which produced an extrapolation that was of good statistical and visual fit to the data. Therefore, the log-logistic distribution was selected for the extrapolation of OS in the base case (validated by clinical experts). Sensitivity analyses were conducted using the:

- Log-normal distribution, to assess the impact of aligning the distribution closer to the clinical UK opinion at the expense of statistical fit. Note: zanubrutinib curve is set to the most pessimistic curve choice in this scenario.

B.3.3.5 OS: Zanubrutinib

OS data was derived from patient-level data in the MAGNOLIA and AU-003 trials, weighted to the HMRN registry basket (N=[redacted]).

The goodness-of-fit statistics for the OS endpoint for zanubrutinib are presented in Table 61. Based on the AIC and BIC statistics, the exponential curve provides the best statistical fit with the lowest sum of AIC and BIC scores, and the lowest individual AIC and BIC scores. The log-normal provided the second-best statistical fit by both AIC and BIC. However, all distributions are considered a reasonable statistical fit as they are within four AIC points of the best fitting curve.[100]

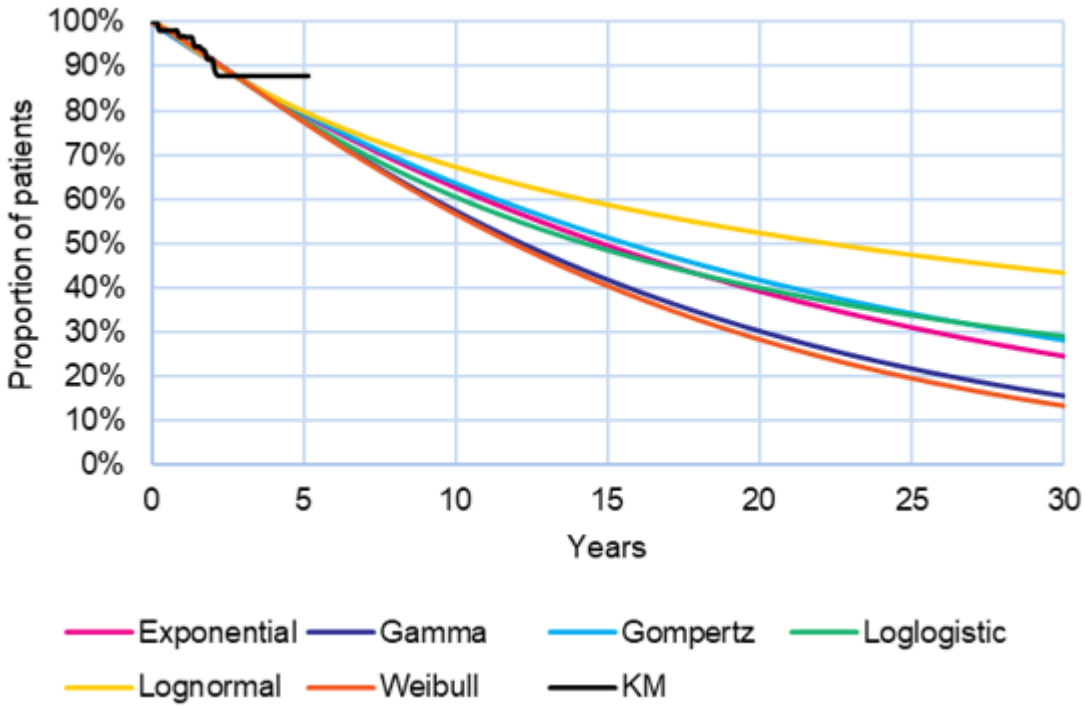
Table 61: Goodness-of-fit statistics for OS – zanubrutinib (pooled MAGNOLIA and AU-003, weighted to HMRN basket, N=[redacted])

Distribution	Zanubrutinib (Stratified)		
	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]
Gamma	[redacted]	[redacted]	[redacted]

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

The parametric survival extrapolations and KM for OS for zanubrutinib are presented in Figure 24. The Weibull model provides the most conservative estimations, followed by the exponential and Gamma models. The log-normal provides the most optimistic estimates for OS.

Figure 24: KM for OS overlaid with extrapolated parametric survival curves – zanubrutinib (pooled MAGNOLIA and AU-003, weighted to HMRN basket, N=[redacted])



HMRN – Haematological Malignancy Research Network; KM – Kaplan-Meier; OS – overall survival.

Sole assessment of the visual and statistical fit was not sufficient to determine the distribution for OS. At an advisory board meeting (11th October 2023), clinical experts suggested that the log-normal, log-logistic and exponential curves could be considered clinically plausible.[4] Landmark OS rates for zanubrutinib are presented in Table 62.

Table 62: Landmark OS – zanubrutinib (pooled MAGNOLIA and AU-003, weighted to HMRN basket, N=[redacted])

Distribution	Median (years)	OS (%) at landmark timepoints					
		1-year	2-year	5-year	10-year	20-year	30-year
KM data	Not reached	[redacted]	[redacted]	-	-	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

KM – Kaplan-Meier; OS – Overall survival.

There is no evidence of a violation in the proportional hazards assumption between zanubrutinib and the HMRN registry basket (N=[redacted]) (please refer to see Section B.2.9 Indirect and mixed treatment comparisons for further details), hence it may be statistically appropriate to select the same distribution for the treatment arms for OS. As there was no strong evidence to justify a different choice of curve between zanubrutinib and the HMRN basket for OS, in line with the NICE DSU guidance, the base-case curve choice for the HMRN registry basket, the log-logistic distribution, was considered for zanubrutinib.[99]

The log-logistic distribution produced an extrapolation that was statistically (<1 AIC point from the best fitting curve) and was a visual good fit to the data. The use of this distribution provides a middle ground estimate of OS, compared to the other survival extrapolations. Sensitivity analyses were conducted using the:

- Exponential distribution, to assess the impact of modelling the best statistically fitting curve for the zanubrutinib arm.

- Weibull distribution, to assess the impact of modelling the most pessimistic curve for zanubrutinib OS.

B.3.3.6 Treatment duration

Given the availability of TTD data from MAGNOLIA and AU-003, extrapolations of TTD are modelled for zanubrutinib time on treatment in the CEM. TTD data was directly derived from pooled patient-level data in the MAGNOLIA and AU-003 trials, weighted to the HMRN registry basket (N=[redacted]).

The goodness-of-fit statistics for the TTD endpoint for zanubrutinib are presented in Table 63. Based on the AIC and BIC statistics, the exponential curve provides the best statistical fit (based on summed AIC and BIC) for TTD data. However, all other distributions are considered a reasonable statistical fit, as they are within four AIC points of the best fitting curve.[100]

Table 63: Goodness-of-fit statistics for TTD – zanubrutinib (pooled MAGNOLIA and AU-003, weighted to HMRN basket, N=[redacted])

Distribution	Zanubrutinib (Stratified)		
	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]
Gamma	[redacted]	[redacted]	[redacted]

AIC – Akaike Information Criteria; BIC – Bayesian Information Criteria; HMRN – Haematological Malignancy Research Network; *TTD – time to treatment discontinuation*. **Bold indicates the distribution with the best statistical fit.**

The parametric survival extrapolations and KM for TTD for zanubrutinib are presented in Figure 25. The Gompertz provides the most optimistic estimation with a tail that exhibits a plateau at ~25% remaining on treatment by 30 years. The log-normal and log-logistic also feature tails that plateau, however, less significantly than was observed with the Gompertz estimation. The remaining estimations tend towards zero by 30 years.

Figure 25: KM for TTD overlaid with extrapolated parametric survival curves – zanubrutinib (pooled MAGNOLIA and AU-003, weighted to HMRN basket, N=[redacted])

KM – Kaplan-Meier; HMRN – Haematological Malignancy Research Network; TTD – time to treatment discontinuation.

Sole assessment of the visual and statistical fit was not sufficient to determine the distribution for TTD, therefore extrapolations are compared for TTD at landmark timepoints. Landmark TTD rates for zanubrutinib are presented in Table 64.

Table 64: Landmark TTD – zanubrutinib (pooled MAGNOLIA and AU-003, weighted to HMRN basket, N=[redacted])

Distribution	Median (years)	TTD (%) at landmark timepoints*					
		1-year	2-year	5-year	10-year	20-year	30-year
KM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

The log-logistic distribution was selected for the extrapolation of TTD in the base case. This distribution was chosen to align with the PFS distribution for zanubrutinib. Additionally, the log-logistic distribution provided a good statistical fit to the data by being within four AIC points of the best fitting curve. The log-logistic was also the

most conservative out of the curves that plateaued (Gompertz, log-logistic, log-normal). A sensitivity analysis was conducted using the exponential distribution, to assess the impact of modelling the best statistically fitting curve for zanubrutinib.

As no TTD data were available in the literature for the HMRN registry basket, it was assumed that patients remained on treatment whilst they were in the progression-free health state only. Whilst this assumption may overestimate the cost of the HMRN registry basket, the impact is expected to be minor given all the HMRN registry basket treatments are fixed duration therapies and hence have relatively low treatment acquisition costs compared to continuous treatment such as zanubrutinib.

B.3.3.7 Relative efficacy

As discussed in Section B.2.9 Indirect and mixed treatment comparisons, a MAIC was conducted which demonstrated a statistically significant improvement in both IRC-assessed PFS and OS for zanubrutinib compared to a basket of treatments that reflects SoC in patients with R/R MZL, as shown in Table 65. Sensitivity analyses were explored using the leave-one-out method to assess the impact of each covariate in the base model. The leave-one-out analysis showed that removing any of the characteristics from the base case model did not change the pattern of significance in the relative treatment effects and generally yielded comparable point estimates. Further sensitivity analyses considered the matching of MAGNOLIA alone to the HMRN dataset and the removal of chemotherapy alone treatments in the basket, with both analyses demonstrating consistent results with the base-case. Please refer to Section B.2.9.1.2 Results for further details.

To capture the relative efficacy between zanubrutinib and the HMRN registry basket, the weighted (based on the MAIC) zanubrutinib MAGNOLIA-003 time-to-event was extrapolated for use in the analysis (please refer to sections B.3.3.1 to B3.3.6 above)

To understand how the model predicts the relative efficacy over time, modelled PFS and OS HRs over the time horizon were estimated, shown in Figure 26. Both figures demonstrate that the HR is tending to 1 over the model time horizon, which indicates

that no further treatment waning assumptions are necessary for the analysis. The assumption regarding treatment waning was validated by clinical experts at an advisory board conducted on the 11th October 2023.[4]

Figure 26: Modelled HRs (zanubrutinib vs HMRN registry basket [N=[redacted]]) over time horizon

HMRN – Haematological Malignancy Research Network; HR – Hazard ratio; OS – Overall survival; PFS – Progression-free survival

Table 65: Summary of MAIC results for zanubrutinib vs HMRN registry basket for patients with R/R MZL

Analysis	PFS (IRC)		OS	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Base case – MAGNOLIA-003 versus HMRN treatment basket (N=[redacted])				
Model (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analyses – MAGNOLIA only				
Model (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analyses – MAGNOLIA-003 versus HMRN treatment basket with chemotherapy alone excluded (N=[redacted])				
Model (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis – leave one out approach from base-case analysis				

Analysis	PFS (IRC)		OS	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age omitted (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Response to last prior systemic therapy omitted (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
POD24 omitted (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior lines of therapy omitted (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Time since diagnosis omitted (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]

CI – Confidence interval; ESS – Effective sample size; HMRN – The Haematological Malignancy Research Network; IRC – Independent Review Committee; MAIC – Matching adjusted indirect comparison; OS – Overall survival; PFS – Progression-free survival; POD24 – Progression of disease within 2 years.
Source: BeiGene DoF MAIC model[84]

B.3.3.8 Summary of base-case inputs

The data sources and chosen distributions to inform the base case are presented in Table 66. Figure 27 to Figure 29 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.
    - A scenario analyses considers applying an increased background mortality risk to reflect that patients with R/R MZL are likely to have an increased risk of death compared to the general population. A standardised mortality ratio (SMR) was applied to the background

morality in the model. A SMR of 1.41 is used, as sourced from NICE appraisal TA649 (polatuzumab vedotin with BR for the treatment of R/R diffuse large B-cell lymphoma), which was recommended as a source by a statistical expert in attendance at the advisory board (11th October 2023).[4,101]

- Restriction of PFS by OS, such that patients cannot be PF for longer than they are alive.

- Restriction of TTD by PFS for zanubrutinib, such that patients cannot remain on treatment for longer than they are PF, as per the licensed indication for zanubrutinib.

Table 66: Data sources and distributions used to inform base-case clinical parameters

Clinical parameter	Data source	Chosen distribution
PFS: Zanubrutinib	Pooled MAGNOLIA and AU-003 for zanubrutinib, weighted to HMRN N=[redacted]	Log-logistic
PFS: HMRN basket	HMRN registry, N=[redacted] population	Log-logistic
OS: Zanubrutinib	Pooled MAGNOLIA and AU-003 for zanubrutinib, weighted to HMRN N=[redacted]	Log-logistic
OS: HMRN basket	HMRN registry, N=[redacted]population	Log-logistic
TTD: Zanubrutinib	TTD for zanubrutinib, weighted to HMRN N=[redacted]	Log-logistic
TTD: HMRN basket	Until progression for HMRN basket for a treatment specific stopping rules are reached	N/A

HMRN – Haematological Malignancy Research Network; OS – Overall survival; PFS – Progression-free survival; TTD – Time to treatment discontinuation; N/A – Not applicable.

Figure 27: PFS for zanubrutinib and HMRN registry basket (N=[redacted]) as estimated by the cost-effectiveness model

HMRN – Haematological Malignancy Research Network; KM – Kaplan-Meier; PFS – Progression-free survival.

Figure 28: OS for zanubrutinib and HMRN registry basket (N=[redacted]) as estimated by the cost-effectiveness model

HMRN – Haematological Malignancy Research Network; KM – Kaplan-Meier; OS – Overall survival.

Figure 29: TTD for zanubrutinib as estimated by the cost-effectiveness model

KM – Kaplan-Meier; TTD – Time-to-treatment discontinuation.

B.3.4 Measurement and valuation of health effects

Patients with R/R MZL typically experience worse HRQoL compared to the general population across several domains including symptom burden, mental functioning, and physical functioning – see Section B.1.3.2 Burden of MZL for further information.

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

The MAGNOLIA trial collected HRQoL data using EQ-5D-5L at baseline, every 12 weeks for 12 months, and every 24 weeks thereafter until disease progression, death, or withdrawal of consent. Given the single-arm nature of MAGNOLIA and that HRQoL data was collected until disease progression as per the trial protocol, it was not feasible to examine the impact of treatment or disease progression on HRQoL based on MAGNOLIA data.[102] As a result, only utility estimates for the PF health state are estimated using mapped MAGNOLIA trial data. PD health state utilities were sourced from published literature.

The mean EQ-5D-5L utility scores over time from MAGNOLIA are presented in Section B2, Figure 7.

B.3.4.2 Mapping

To generate utility scores for the PF health state, the EQ-5D-5L indices were mapped to the EQ-5D-3L indices using the crosswalk algorithm described by Hernandez-Alava (2022) in line with the NICE reference case.[103,104] Once mapped, the EQ-5D-3L utility scores at all visits were analysed using a mixed-effects linear regression with a random intercept for each patient to account for repeated measures. The regression model was adjusted for baseline utility (centred at the mean value of the eligible population) to consider between-patient differences in utilities at baseline.

The predicted utility for the PF health state in the model compared to utilities based on the general population in the UK is presented in Table 67. The PF utility scores were higher than the estimates for age-matched UK general population. As such, the utility value from MAGNOLIA trial appears to lack face validity. This is a common problem in oncology appraisals, with TA689[50] and ID5078[52] reporting the same issue. However, the PF utility estimate is within the range estimated by the AUGMENT trial (the primary data source for pre-progression utilities in TA627 with a mixed FL and MZL population).[56,105] This range was 0.814-0.863 and suggests the PF estimates may have validity.[56,106]

Table 67: Utility Model Including Progression Status as Predictors

Predictor	No. of Patients	No. of Obs.	Coefficient (95% CI)	Source
Predicted utility for health states				
PF	65	357	0.836 (0.792, 0.875)	MAGNOLIA[60]
Mean utility based on published general population UK				
General population irrespective of health status (age 73; 46.5% female)			0.770	Hernández Alava et al. 2022[107]

CI – Confidence interval; Obs – Observations; PF – Progression-free.

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

An SLR was conducted to identify studies reporting on the HRQoL of patients with R/R MZL. Full details of the process and methods used to identify and select the HRQoL data relevant to the technology being evaluated are presented in Appendix

H. The SLR identified three studies reporting on the HRQoL of patients with R/R MZL. A summary of these studies is provided in Table 68.

All three publications reporting utility values considered mixed populations. Whilst MZL was considered in the overall population in all publications, the populations included other non-Hodgkin's lymphomas, such as FL or MCL. Two studies reported HRQoL of patients using EQ-5D instruments directly (CADTH 2012 and NICE TA627).[86,108] The other study (Major 2021)[109] mapped FACT-G and FACT-LYM data to the EQ-5D-5L index using a United States-based validated mapping algorithm.[109] Only one of the studies (NICE TA627)[86] reported utility values for a UK population, the others reported utility values for a US population (Major 2021)[109] and a Canadian population (CADTH 2012).[108] Whilst both the CADTH and NICE submissions included utilities for their post-progression health states, the CADTH submission did not report PF utilities.[108]

Table 68: Summary of published HRQoL studies

Data source	Patient population	Utility measure	Utility value	
			PF health state	PD health state
Major 2021[109]	Patients with iNHL.	Indirect: EQ-5D index	EQ-5D-5L Index HSUV, Mean (SD), Comparative results *Within 6 months of treatment completion:* Rituximab (19 [58%] with MZL): 0.71 (0.07), p=0.087 Bendamustine + rituximab (13 [31%] with MZL): 0.66 (0.09), p=0.087 *6-12 months after treatment completion:* Rituximab (19 [58%] with MZL): 0.72 (0.08), p=0.354 Bendamustine + rituximab (13 [31%] with MZL): 0.69 (0.10), p=0.354	NR
CADTH Bendamustine for iNHL[108]	Adult patients with previously treated relapsed FL, NHL and MCL. Adult patients with previously untreated iNHL or MCL and patients with iNHL or MCL that has relapsed or refractory to treatment that included rituximab.	EQ-5D	NR	0.618 (95% CI: 0.51 to 0.73)

Data source	Patient population	Utility measure	Utility value	
			PF health state	PD health state
NICE TA627[105]	Adult patients with previously treated FL or MZL who had previously received treatment.	EQ-5D-3L	*Progression-free:* R^2 vs. R-CHOP/CVP: 0.863 vs. O-Benda: 0.814	*Post-progression (off treatment):* R^2 vs. R-CHOP/CVP: 0.837 R^2 vs. O-Benda: 0.787 *Post-progression (on treatment)* R^2 vs. R-CHOP/CVP: 0.808 R^2 vs. O-Benda: 0.758

DLBCL – Diffuse large B-cell lymphoma; EQ-5D – European quality-of-life five dimension; FL – Follicular lymphoma; HSUV – Health state utility value; iNHL – Indolent non-Hodgkin lymphoma; MZL – Marginal zone lymphoma; MALT – Mucosa-associated lymphoid tissues; NICE – National Institute of Health and Care Excellence; NR – Not reported; PD – Progressed disease; PF – Progression-free; SE – Standard error.

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.[103,110]

B.3.4.5 Adverse reactions

The model accounts for the impact of all Grade ≥3 treatment-related AEs occurring in ≥2% of study subjects receiving treatment across treatment arms. Events occurring in ≥2% 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. The Grade ≥3 AEs included in the model are reported in Table 69. The pooled MAGNOLIA-003 dataset was used to inform the zanubrutinib arm.

Safety outcomes were not available from the HMRN registry and hence published literature was used to source AE rates for the top three treatments within the HMRN basket (BR, rituximab monotherapy and R-CVP). UK clinical experts in attendance at an advisory board (11th October 2023) indicated that BR and rituximab monotherapy were the most and least toxic treatment options in the basket, respectively. They noted R-CVP would fall in between BR and rituximab monotherapy in terms of toxicity. Therefore, by modelling the toxicity profiles of these three treatments it would reflect the range of toxicity experienced by patients receiving treatment for R/R MZL. The clinical experts recommended that AE rates specifically for BR were applied for the proportion of patients receiving BR in the basket ([redacted]%), and that R-CVP rates and rituximab monotherapy rates were applied to the remaining [redacted]% and [redacted]% of the basket, respectively (note - weights for the AEs were re-proportioned to sum to 100% for the top three treatments in the basket). The clinical SLR identified one trial that included patients treated with BR, the Phase 3 SELENE trial, and no trials for R-CVP. The SELENE trial is limited as patients could receive either BR or R-CHOP within the control arm, and hence no AE rates were available for BR

alone.[111] Furthermore, the trial failed to meet its primary endpoint so limited safety information is published. Given the lack of data identified in the SLR, UK clinical experts recommended that similar blood cancers were explored to identify safety data for BR and R-CVP. Zanubrutinib has directly been compared to BR in patients with previously untreated CLL in the SEQUOIA trial, and UK clinical experts encouraged the Company to extract the rates from SEQUOIA as a proxy for the BR arm.[112] For R-CVP, UK clinical experts highlighted a trial by Oh et al. 2019.[113] This trial investigated R-CVP followed by rituximab monotherapy in patients with advanced MZL. For rituximab monotherapy, CHRONOS-3 was chosen (through identification in the SLR).[114] This trial investigated copanlisib plus rituximab versus placebo plus rituximab in patients with relapsed indolent non-Hodgkin lymphoma. AE rates were extracted from these studies to inform the rates for the proportion of patients in the basket. In Oh et al. 2019, individual AEs were reported for all Grades only, to estimate the proportion of these AEs that were Grade ≥ 3, the proportion of aggregated Grade ≥ 3 were applied to the individual rates as a proxy.

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 simplifying assumption was made such that 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.

Table 69: Grade ≥3 treatment-related AEs occurring in ≥2% of patients by treatment

Adverse event	Zanubrutinib	BR	R-CVP	Rituximab monotherapy	Overall HMRN registry basket
COVID-19 pneumonia	[redacted]	0.00%	0.00%	0.00%	0.00%
Pneumonia	[redacted]	4.41%	0.85%	2.74%	3.27%
Neutropenia	[redacted]	51.10%	1.69%	12.33%	31.52%
Anaemia	[redacted]	1.76%	0.00%	2.74%	1.64%
Thrombocytopenia	[redacted]	7.05%	0.00%	0.00%	3.88%

Adverse event	Zanubrutinib	BR	R-CVP	Rituximab monotherapy	Overall HMRN registry basket
Diarrhoea	[redacted]	1.76%	0.00%	0.00%	0.97%
Neutrophil count decreased	[redacted]	0.00%	0.00%	13.70%	3.35%
Hypertension	[redacted]	4.85%	0.00%	8.90%	4.85%
Pyrexia	[redacted]	3.52%	0.00%	0.00%	1.94%
Rash	[redacted]	2.64%	0.00%	0.00%	1.46%
Infusion-related reaction	[redacted]	2.64%	0.00%	0.00%	1.46%
Hyperglycaemia	[redacted]	0.00%	0.00%	8.22%	2.01%
Source	MAGNOLIA-003[60,62]	SEQUOIA, Tam 2022[112]	Oh et al 2019[113]	CHRONOS-3, Matasar 2021[114]	Weighted calculation

AE – adverse event; BR – bendamustine/rituximab; CSR – clinical study report.

Due to the low incidence rates of AEs and the small sample size in MAGNOLIA and AU-003, estimates of disutility for specific AEs may be inaccurate and susceptible to being skewed by outliers. Therefore, it is more appropriate to estimate the disutility of AEs compared to specific disutilities. 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, the mean utility decrements associated with these AEs, and the mean duration of each AE episode. Utility decrements associated with AEs were estimated from an analysis of MAGNOLIA patient-level data and are assumed to be equal for all AEs. The duration of AEs was derived from the same data source (MAGNOLIA[60]) whenever available and are also assumed to be equal for all AEs. All AE utility decrements were applied in Cycle 1. The utility decrements and duration of AE estimates used in the model are presented in Table 70.

Table 70: Utility decrements and duration estimates

AE	Disutility (SE)	Source	Duration (SE)	Source
Any AE	[redacted]	MAGNOLIA[60]	[redacted]	MAGNOLIA[60]

AE – adverse event; SE – standard error.

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

Utility estimates from the MAGNOLIA trial are used to inform the pre-progression utilities in the cost-effectiveness analysis. Analyses of patient-level data leads to a pre-progression utility value of 0.836. For the purposes of validity, this utility value was compared with the utility estimates derived from the AUGMENT trial, the primary data source for the pre-progression utilities used in TA627 (lenalidomide-rituximab in a mixed FL and MZL population).[56,105] The estimate of 0.836 fell into the range of pre-progression utilities estimated from the AUGMENT trial (0.814 to 0.863) and therefore had face validity.[56,106] However, given that the PF utility exceeded that of the age-gender matched general population (0.772), the PF utility was capped to ensure patients could not have a better HRQoL than the general population. This approach was considered appropriate as it aligned with the approach accepted in relevant previous appraisals, notably NICE appraisal TA627 and NICE ID5078.[52,105]

The MAGNOLIA-based utility estimate for pre-progression survival was then applied to both arms in the cost-effectiveness analysis, conservatively assuming that there was no treatment effect on HRQoL. This assumption was adopted due to the lack of randomised trials directly evaluating HRQoL for zanubrutinib versus the HMRN basket in R/R MZL. Given the uncertainty of this assumption, an exploratory scenario analysis was conducted using treatment-specific pre-progression utility. This scenario analysis was based on the findings of a HRQoL study in WhiMSICAL[115], a global Waldenström's Macroglobulinemia patient-derived data registry capturing treatment and quality of life outcomes. This study showed that BTKi drugs were associated with statistically significantly better HRQoL compared to non-BTKi drugs (i.e., rituximab-based regimens) with mean global scale of 80.1, compared to those not exposed to BTKi who had been treated within 12 months: mean 68.3 ($p = 0.004$), despite the BTKi cohort having undergone a median of 2 prior lines of treatment compared to the non-BTKi cohort (median = 1, $p < 0.001$). The scenario assumes that there was a difference in HRQoL between BTKi and non-BTKi drugs in MZL,

with the difference being calculated using the relative reduction from the WhiMSICAL study[115] (HMRN basket = 0.713 = 0.836 * [68.3 / 80.1]).

It was not plausible to estimate post-progression utility for patients using patient-level trial data from MAGNOLIA, due to the design of the trial. Instead, these utility values have been sourced in from literature. The SLR identified two previous HTA submissions in for the MZL population that could provide post-progression utility estimates: NICE TA627[105] (0.758 to 0.837) and CADTH pan-Canadian Oncology Drug Review (pCODR) for bendamustine for NHL[108] (0.618; 95% CI: 0.51 to 0.73). The post-progression utility value (0.758) used in TA627[105] was deemed to be too high by the ERG as it was higher than the general population utility, despite these patients having MZL. The CADTH pCODR PD utility value was closer to the previously accepted PD utilities in previous zanubrutinib submissions (0.691 and 0.60, for TA833[82] and ID5078[52], respectively). Furthermore, the CADTH PD pCODR utility is very close to the utility value (0.620) preferred by the EAG in TA627, hence adding validity to the PD utility.[86] Therefore, the CADTH pCODR PD utility value was chosen for the base case as it was more closely aligned with previous submissions for zanubrutinib. The utilities used in the cost-effectiveness analysis are presented in Table 71.

In addition to the treatment specific utility scenario, further scenario analyses were explored to assess the impact of utility values on the results:

- Company base-case utility values from NICE TA627[105]:
    - PF: 0.863; PD: 0.808
- EAG utilities values from NICE TA627[105]:
    - PFS: 0.805; PD: 0.620

Table 71: Summary of utility values for the cost-effectiveness analysis base case

State	Utility value: mean (standard error)	95% CI	Source
PF	0.772 (0.021)	(0.729, 0.812)	Utilities estimated from MAGNOLIA,[60] using patient-level trial data, capped by general population utility.
PD	0.618 (0.056)	(0.506, 0.724)	CADTH pCODR submission for bendamustine for NHL[116]

CADTH – Canadian Drug and Heath Technology Agency. CI – Confidence interval; NHL – Non-Hodgkin lymphoma; pCODR – pan-Canadian Oncology Drug Review; PD – Progressed disease; PF – Progression-free. *CI estimated using Beta distribution.

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

An SLR was conducted to identify studies reporting on the cost and resource use of patients with R/R MZL. 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.

Only one study (TA627)[105] was identified from a UK perspective in patients with R/R MZL. Consistent with the study identified in the SLR and other relevant appraisals for zanubrutinib (TA833[82] and ID5078[52]) in similar blood cancers, the following cost categories were included in the model:

- Drug acquisition and administration costs applied for the duration of primary and subsequent treatment
- Health-state unit costs and resource use
- The cost of AEs and terminal care.

For cost inputs, a UK NHS and PSS perspective was adopted as per the NICE reference case.[96] 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, monitoring, and terminal care were derived based on previous NICE appraisals and were validated with UK clinical experts.[4]

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Drug acquisition costs

Drug acquisition costs were based on the dosing regimens presented in Table 72 and Appendix N. Costs per pack and cycle are presented in Table 73 and Appendix N. Dosing information for zanubrutinib is aligned with the SmPC, whilst the dosing information for the HMRN registry basket aligns with their expected use in UK clinical practice. The unit costs were sourced from the BNF. In instances where multiple pack prices were available, the pack price with the lowest cost per mg was used. [redacted].

Patients receiving zanubrutinib were treated in line with the modelled TTD curve. Patients receiving HMRN basket were treated whilst in the progression-free health state, up until treatment specific stopping rules.

Table 72: 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[117]
HMRN Registry basket	See Appendix N for more individual treatments dosing regimens.	See Appendix N

HMRN – Haematological Malignancy Research Network; PD – Progressed disease; IV – Intravenous; SmPC – Summary of Product Characteristics.

In the base case, the model considers wastage for intravenous (IV) drugs for treatments that depend on BSA, as there is a potential that some of the drug will be wasted if perfect vial sharing is not practiced. A BSA of [redacted] m^2 (SE: [redacted] m^2) was calculated from MAGNOLIA-003 pooled data, matched to HMRN registry basket (base-case MAIC analysis). Relative dosing intensity is assumed at [redacted]% for zanubrutinib.[60]

Table 73: 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]
HMRN basket (Rituximab plus / minus chemotherapy and chemotherapy alone: base case, N=[redacted])	See Appendix N				£6,473.07
HMRN basket (Rituximab plus / minus chemotherapy: base case, N=[redacted])	See Appendix N				£9,010.84

HMRN – Haematological Malignancy Research Network; IV – Intravenous; mg – Milligram. Source British National Formulary 2023[118]

B.3.5.1.2 Drug administration costs

Drug administration costs were applied to treatments administered via IV. Medications that were orally administered did not incur administration costs. Unit costs for all categories of administration were based on National Schedule of NHS Costs[119] and are presented in Table 74.

Table 74: Drug administration costs

Description of cost	Use in model	Unit cost (£)	Source
Delivered oral chemotherapy	Administration of zanubrutinib and oral treatments within the basket	0.00	Assumption
Deliver Complex Chemotherapy	Administration of FC, methotrexate, rituximab, bendamustine, gemcitabine, cisplatin, methylprednisolone containing treatments	353.64	NHS 21/22 - SB14Z[119]
Delivered subcutaneous drug	Administration of doxorubicin, cyclophosphamide, vincristine, bortezomib and G-CSF.	0.00	Assumption

FC – Fludarabine and Cyclophosphamide; G-CSF – Granulocyte colony stimulating factor; NHS – National Health Service.

B.3.5.2 Health-state unit costs and resource use

Costs related to routine follow-up and 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) and are presented in Table 75.

Health-state resource use is based on what was previously accepted in NICE TA627 and the recommendations in the ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of marginal zone lymphoma.[5,105] Costs for resource use are sourced from NHS reference costs for 2021/22, as recommended in the NICE reference case.[75,119]

The clinical experts consulted as part of the advisory board (11th October 2023) suggested that due to zanubrutinib having a better safety profile, the zanubrutinib arm would accrue lower health state resources compared to the HMRN basket arm.[4] However, the resource use was equalised across treatment arms as a conservative assumption.

Table 75: Medical resource unit costs and frequencies

Resource item	Costs		Resource use per cycle		
	Unit (£)	Source	PF state	PD state	Source
Haematologist visit	209.41	NHS ref costs 21/22[119]	0.23	0.92	NICE TA627[105] Zucca et al. (2020)[5]
Full blood count	2.96	NHS ref costs 21/22[119]	0.23	0.92	NICE TA627[105] Zucca et al. (2020)[5]
Patient history/ physical exam	221.48	NHS ref costs 21/22[119]	0.23	0.92	NICE TA627[105] Zucca et al. (2020)[5]
Urea and electrolytes	1.55	NHS ref costs 21/22[119]	0.23	0.92	NICE TA627[105] Zucca et al. (2020)[5]
Liver function tests	1.55	NHS ref costs 21/22[119]	0.23	0.92	NICE TA627[105] Zucca et al. (2020)[5]
Calcium	1.55	NHS ref costs 21/22[119]	0.23	0.92	NICE TA627[105] Zucca et al. (2020)[5]
Serum IgG, IgA, IgM and electrophoresis	7.61	NHS ref costs 21/22[119]	0.23	0.92	NICE TA627[105] Zucca et al. (2020)[5]
LDH test	1.55	NHS ref costs 21/22[119]	0.23	0.92	NICE TA627[105] Zucca et al. (2020)[5]

Ig – immunoglobulin; LDH – lactate dehydrogenase; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; PD – Progressed disease; PF – Progression-free.

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 ≥2% of patients receiving treatment. Total AE costs were calculated as the product of the AE incidence, as presented in Table 69, and the respective unit cost as presented in Table 76. It is assumed that all AEs occur and are resolved in the first cycle (four weeks) of treatment and only AEs associated with first-line treatment were considered. This assumption is commonly accepted in NICE oncology submissions, including: niraparib first-line and second-line maintenance treatment for patients with ovarian cancer (TA784[120] and TA673[121]), acalabrutinib for the treatment of CLL (TA689[50]), zanubrutinib for the treatment of CLL and WM (ID5078[52] and TA833[82]), dostarlimab for the treatment of endometrial cancer (TA779[122]) and trastuzumab deruxtecan first-line and second-line for treatment of metastatic breast cancer (TA862[123] and TA704[124]).

Table 76: AE management costs

Adverse event	Cost (£)	Source	Comment
COVID-19 pneumonia	741.08	National Cost Collection: National Schedule of NHS costs - Year 2021-22: DX11A	Non-elective short stay
Pneumonia	668.60	National Cost Collection: National Schedule of NHS costs - Year 2021-22: DZ11K-V	Weighted average of non-elective short stay
Neutropenia	627.97	National Cost Collection: National Schedule of NHS costs - Year 2021-22: SA35A-E	Weighted average of non-elective short stay
Anaemia	615.42	National Cost Collection: National Schedule of NHS costs - Year 2021-22: SA09K-L	Weighted average of non-elective short stay
Thrombocytopenia	627.97	National Cost Collection: National Schedule of NHS costs - Year 2021-22: SA35A-E	Assumed to be the same as Neutropenia
Diarrhoea	562.16	National Cost Collection: National Schedule of NHS costs - Year 2021-22: WJ07A-D	Weighted average of non-elective short stay
Decreased neutrophil count	542.77	National Cost Collection: National Schedule of NHS costs - Year 2021-22: SA08G-J	Weighted average of non-elective short stay
Hypertension	424.60	National Cost Collection: National Schedule of NHS costs - Year 2021-22: EB04Z	Non-elective short stay
Pyrexia	588.82	National Cost Collection: National Schedule of NHS costs - Year 2021-22: FD10A-M	Weighted average of non-elective short stay
Rash	387.71	National Cost Collection: National Schedule of NHS costs - Year 2021-22: JD07K	Non-elective short stay
Infusion-related reaction	439.22	National Cost Collection: National Schedule of NHS costs - Year 2021-22: WH05Z	Non-elective short stay
Hyperglycaemia	500.02	National Cost Collection: National Schedule of NHS costs - Year 2021-22: WH13A-B	Weighted average of non-elective short stay

AE – Adverse event; NHS – National Health Service.
Source: NHS Cost Collection: National Schedule of NHS costs[119]

B.3.5.4 Miscellaneous unit costs and resource use

B.3.5.4.1 Subsequent treatment cost

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. The drug acquisition and administration cost per course of therapy is as per the calculations presented in Appendix N. The proportion of subsequent treatments was informed by HMRN registry data for patients receiving third-line treatment.[6] The treatments included in the subsequent treatment basket are listed in Table 77.

Based on UK clinical expert opinion and reflective of the treatment pathway in the UK, subsequent treatment usage was equalised across both arms within the analysis.[4] UK clinical experts also noted that less toxic agents (e.g. rituximab monotherapy, R-CVP, chlorambucil) are likely to be used in later lines of therapy, validating the HMRN registry data in which more than 60% of patients received these treatments.[4]

Table 77: Subsequent treatment costs and weightings

Treatment	Drug acquisition cost per course of therapy (£)	Drug administration cost per course of therapy (£)	Treatment use[6]
Single agent Rituximab	£7,195.55	£2,333.79	[redacted]
Bendamustine / Rituximab	£6,414.54	£5,845.13	[redacted]
R-CVP	£8,392.19	£2,927.12	[redacted]
Chlorambucil	£196.58	£0.00	[redacted]
R-CHOP	£17,984.32	£5,146.96	[redacted]
Chlorambucil / Rituximab	£7,962.01	£1,594.74	[redacted]

R-CHOP – Rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone; R-CVP – Rituximab plus cyclophosphamide, vincristine and prednisolone. Source: see Appendix N

B.3.5.4.2 Terminal care costs

Costs for terminal care are applied as a one-off cost to each death event in the model. The cost of end of life care was sourced from Round, Jones and Morris 2015, identified from the manufacturer submissions for NICE TA429, TA561, TA627 and TA689 and estimated the direct and indirect cost for lung, breast, colorectal and prostate patients at the end of life in England and Wales.[50,51,105,125,126] These costs were added together (£6,083) and inflated from a 2013/2014 to a 2022/2023 price year using the NHS Cost Inflation Index.[127,128] The terminal cost applied in the analysis is £7,155.15.

B.3.6 Severity

N/A. Given the indolent nature of R/R MZL, 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. The long-term extrapolations for zanubrutinib are informed by less than half of the trial population and therefore are associated with uncertainty. The data is more mature within the HMRN registry basket, with the median being reached for both PFS and OS. To reduce uncertainty in the long-term extrapolation, the Company have validated their curve selection with UK clinical experts at an advisory board (11th October 2023) and performed a range of scenario analyses (including modelling the most pessimistic curves for zanubrutinib PFS and OS) to reflect alternative datasets and survival curve choices.[4]

In addition to data immaturity, as indicated by the lack of evidence identified in the SLR, it is clear that R/R MZL is a disease area which historically has been poorly studied. This has resulted in a lack of clinical and cost-effectiveness data to support the development of an economic model for zanubrutinib patients with R/R MZL. To reduce uncertainty, the Company have validated the inputs and assumptions of the economic model with UK experts at an advisory board (11th October 2023).[4]

Furthermore, the uncertainty in the model results were explored through extensive deterministic sensitivity analysis (DSA), probabilistic sensitivity analysis (PSA) and scenario analyses. 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.

In the PSA, values were drawn at random for each variable from its uncertainty distribution. The model allowed the beta, gamma, log-normal, normal, and Dirichlet distributions to be used, 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 78).

Several scenario analyses were also performed to assess the impact of alternative assumptions and data sources which were not captured within the DSA and PSA.

Table 78: Distribution options by model parameter for PSA

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

AE – Adverse event; BSA – Body surface area; OS – Overall survival; PFS – Progression-free survival; TTD – Time to discontinuation.

B.3.8 Managed access proposal

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

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 79.

Table 79: 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	Patients with R/R MZL who have received at least one prior line of anti-CD20 treatment (MAGNOLIA and AU-003 pooled)	N/A	B.3.2 Economic analysis
Perspective	Payer (UK NHS and PPS)	N/A	
Time horizon	Lifetime (27 years)	Not modelled, explored in scenario analyses only	
Proportion females	[redacted]%	SE: [redacted]% (Beta)	
Starting age in model (years)	73	Fixed	
Body surface area (m^2)	[redacted]	SE: [redacted] (Gamma)	
Half-cycle correction	Yes	Fixed	
Discount rate (cost and outcomes)	3.5%	Fixed	
Clinical parameters			
Efficacy			
PFS – distribution for zanubrutinib	Log-logistic	Cholesky decomposition matrix	B.3.3 Clinical parameters and variables
OS – distribution for zanubrutinib	Log-logistic		
Treatment duration for zanubrutinib	Log-logistic		

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 HMRN basket	Log-logistic		
OS – distribution for HMRN basket	Log-logistic		
Probability of AE – zanubrutinib			
COVID-19 pneumonia	[redacted]	SE: [redacted]% (Beta)	B.3.4 Measurement and valuation of health effects
Pneumonia	[redacted]	SE: [redacted]% (Beta)	
Neutropenia	[redacted]	SE: [redacted]% (Beta)	
Anaemia	[redacted]	SE: [redacted]% (Beta)	
Thrombocytopenia	[redacted]	SE: [redacted]% (Beta)	
Diarrhoea	[redacted]	SE: [redacted]% (Beta)	
Neutrophil count decreased	[redacted]	SE: [redacted]% (Beta)	
Hypertension	[redacted]	SE: [redacted]% (Beta)	
Pyrexia	[redacted]	SE: [redacted]% (Beta)	
Rash	[redacted]	SE: [redacted]% (Beta)	
Infusion-related reaction	[redacted]	SE: [redacted]% (Beta)	
Hyperglycaemia	[redacted]	SE: [redacted]% (Beta)	
Probability of AE – HMRN basket			
COVID-19 pneumonia	0.00%	SE: 0% (Beta)	B.3.4 Measurement and valuation of health effects
Pneumonia	3.27%	SE: 0.65% (Beta)	
Neutropenia	31.52%	SE: 6.30% (Beta)	
Anaemia	1.64%	SE: 0.33% (Beta)	
Thrombocytopenia	3.88%	SE: 0.78% (Beta)	
Diarrhoea	0.97%	SE: 0.19% (Beta)	
Neutrophil count decreased	3.35%	SE: 0.67% (Beta)	
Hypertension	4.85%	SE: 0.97% (Beta)	
Pyrexia	1.94%	SE: 0.39% (Beta)	
Rash	1.46%	SE: 0.29% (Beta)	
Infusion-related reaction	1.46%	SE: 0.29% (Beta)	
Hyperglycaemia	2.01%	SE: 0.40% (Beta)	
Duration of adverse event (days)			
All AEs	[redacted]	SE: [redacted] (Gamma)	B.3.4 Measurement and valuation

Parameter	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
			of health effects
Health-related quality-of-life parameters			
Health state utilities			
PF	0.772	SE: 0.021 (Beta)	B.3.4 Measurement and valuation of health effects
PD	0.618	SE: 0.056 (Beta)	
Disutilities			
All AEs	[redacted]	SE: [redacted] (Beta)	B.3.4 Measurement and valuation of health effects
Cost parameters			
Health-state resource use			
Haematologist visit	PF: 0.23 PD: 0.92	SE: 0.05 (Gamma) SE: 0.18 (Gamma)	B.3.5 Cost and healthcare resource use identification
Diagnostic: full blood count	PF: 0.23 PD: 0.92	SE: 0.05 (Gamma) SE: 0.18 (Gamma)	
Diagnostic: patient history/physical exam	PF: 0.23 PD: 0.92	SE: 0.05 (Gamma) SE: 0.18 (Gamma)	
Diagnostic: urea and electrolytes	PF: 0.23 PD: 0.92	SE: 0.05 (Gamma) SE: 0.18 (Gamma)	
Diagnostic: liver function tests	PF: 0.23 PD: 0.92	SE: 0.05 (Gamma) SE: 0.18 (Gamma)	
Diagnostic: calcium	PF: 0.23 PD: 0.92	SE: 0.05 (Gamma) SE: 0.18 (Gamma)	
Diagnostic: serum IgG, IgA, IgM and electrophoresis	PF: 0.23 PD: 0.92	SE: 0.05 (Gamma) SE: 0.18 (Gamma)	
Diagnostic: lactate dehydrogenase (LDH) test	PF: 0.23 PD: 0.92	SE: 0.05 (Gamma) SE: 0.18 (Gamma)	
Health-state unit costs (£)			
Haematologist visit	209.41	SE: 41.88 (Gamma)	B.3.5 Cost and healthcare
Diagnostic: full blood count	2.96	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 submission
Diagnostic: patient history/physical exam	221.48	SE: 44.3 (Gamma)	resource use identification
Diagnostic: urea and electrolytes	1.55	SE: 0.31 (Gamma)	
Diagnostic: liver function tests	1.55	SE: 0.31 (Gamma)	
Diagnostic: calcium	1.55	SE: 0.31 (Gamma)	
Diagnostic: serum IgG, IgA, IgM and electrophoresis	7.61	SE: 1.52 (Gamma)	
Diagnostic: lactate dehydrogenase (LDH) test	1.55	SE: 0.31 (Gamma)	
End-of-life costs (£)			
Terminal care	7,155.15	SE: 1,431.03 (Gamma)	B.3.5 Cost and healthcare resource use identification
Adverse event costs (£)			
COVID-19 pneumonia	741.08	SE: 148.22 (Gamma)	B.3.5 Cost and healthcare resource use identification
Pneumonia	668.60	SE: 133.72 (Gamma)	
Neutropenia	627.97	SE: 125.59 (Gamma)	
Anaemia	615.42	SE: 123.08 (Gamma)	
Thrombocytopenia	627.97	SE: 125.59 (Gamma)	
Diarrhoea	562.16	SE: 112.43 (Gamma)	
Decreased neutrophil count	542.77	SE: 108.55 (Gamma)	
Hypertension	424.60	SE: 84.92 (Gamma)	
Pyrexia	588.82	SE: 117.76 (Gamma)	
Rash	387.71	SE: 77.54 (Gamma)	
Infusion-related reaction	439.22	SE: 87.84 (Gamma)	
Hyperglycaemia	500.02	SE: 100.00 (Gamma)	
Treatment acquisition costs (£)			
Zanubrutinib cost per pack	[redacted]	Fixed	B.3.5 Cost and healthcare resource use identification
HMRN-[redacted] basket total one-off cost	6,473.07	Fixed	
HMRN-[redacted] basket total one-off cost	9,010.84	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	SE: 0 (Gamma)	B.3.5 Cost and healthcare resource use identification
Deliver Complex Chemotherapy	353.64	SE: 70.73 (Gamma)	
Delivered subcutaneous drug	0.00	SE: 0 (Gamma)	
Treatment acquisition costs – subsequent treatment per cycle (£)			
Drug cost per cycle: Single agent Rituximab	7,195.55	SE :1,471 (Gamma)	B.3.5 Cost and healthcare resource use identification
Drug cost per cycle: Bendamustine / Rituximab	6,414.54	SE: 1,312 (Gamma)	
Drug cost per cycle: R-CVP	8,392.19	SE: 1,7159 (Gamma)	
Drug cost per cycle: Chlorambucil	196.58	SE: 39 (Gamma)	
Drug cost per cycle: R-CHOP	17,984.32	SE: 3,676 (Gamma)	
Drug cost per cycle: Chlorambucil / Rituximab	7,962.01	SE: 1,6260 (Gamma)	
Treatment administration costs – subsequent treatment per cycle (£)			
Admin. cost per cycle: Single agent Rituximab	£2,333.79	SE :467 (Gamma)	B.3.5 Cost and healthcare resource use identification
Admin. cost per cycle: Bendamustine / Rituximab	£5,845.13	SE: 1,169 (Gamma)	
Admin. cost per cycle: R-CVP	£2,927.12	SE: 585 (Gamma)	
Admin. cost per cycle: Chlorambucil	£0.00	SE: 0 (Gamma)	
Admin. cost per cycle: R-CHOP	£5,146.96	SE: 1,029 (Gamma)	
Admin. cost per cycle: Chlorambucil / Rituximab	£1,594.74	SE: 319 (Gamma)	
Distribution of subsequent treatment (%)			

Parameter	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Zanubrutinib proportion receiving subsequent treatment	100	SE: 0 (Beta)	B.3.5 Cost and healthcare resource use identification
Subsequent tx use following Zanubrutinib: Single agent Rituximab	[redacted]	SE: 7.35 (Beta)	
Subsequent tx use following Zanubrutinib: Bendamustine / Rituximab	[redacted]	SE: 5.29 (Beta)	
Subsequent tx use following Zanubrutinib: R-CVP	[redacted]	SE: 2.94 (Beta)	
Subsequent tx use following Zanubrutinib: Chlorambucil	[redacted]	SE: 2.06 (Beta)	
Subsequent tx use following Zanubrutinib: R-CHOP	[redacted]	SE: 1.47 (Beta)	
Subsequent tx use following Zanubrutinib: Chlorambucil / Rituximab	[redacted]	SE: 0.88 (Beta)	
HMRN basket proportion receiving subsequent treatment	100	SE: 0 (Beta)	
Subsequent tx use following Rituximab +/- chemotherapy, Chemotherapy alone: Single agent Rituximab	[redacted]	SE: 7.35 (Beta)	
Subsequent tx use following Rituximab	[redacted]	SE: 5.29 (Beta)	

Parameter	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
+/- chemotherapy, Chemotherapy alone: Bendamustine / Rituximab			
Subsequent tx use following Rituximab +/- chemotherapy, Chemotherapy alone: R-CVP	[redacted]	SE: 2.94 (Beta)	
Subsequent tx use following Rituximab +/- chemotherapy, Chemotherapy alone: Chlorambucil	[redacted]	SE: 2.06 (Beta)	
Subsequent tx use following Rituximab +/- chemotherapy, Chemotherapy alone R-CHOP	[redacted]	SE: 1.47 (Beta)	
Subsequent tx use following Rituximab +/- chemotherapy, Chemotherapy alone: Chlorambucil / Rituximab	[redacted]	SE: 0.88 (Beta)	

AE – Adverse Event; HMRN – Haematological Malignancy Research Network; LDH – Lactate dehydrogenase; N/A – Not applicable; NHS – National Health Service; OS – Overall survival; PD – Progressed disease; PF – Progression-free; PFS – Progression-free survival; PPS – Personal Social Services; R-CHOP – Rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone; R-CVP – Rituximab plus cyclophosphamide, vincristine and prednisolone; SE – Standard error; TTD – Time to treatment discontinuation; UK – United Kingdom.

B.3.9.2 Assumptions

The key assumptions made in the model base case are presented in Table 80.

Table 80: 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, which aligns with the pathology of MZL and the expected impact of zanubrutinib on the

Model input	Assumption	Rationale
		disease course.
Cycle length	Model cycle of 4 weeks	This is consistent with the treatment dosing schedule for zanubrutinib.[117] 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[103] (assumed a 27-year life time horizon based on the age of the patient population from pooled MAGNOLIA and AU-003 trial data.
Efficacy	Identification of the most appropriate survival curves describing OS, PFS and TTD	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.
	Identification of the most appropriate survival curves describing OS and PFS for HMRN registry basket	The most appropriate curves have been identified for the extrapolation of survival and efficacy for the HMRN registry basket. The methodology and curve selection was validated by clinical experts at an advisory board
	No treatment waning is applied in the analysis	The model structure naturally wanes the efficacy of zanubrutinib over the time horizon with the HRs of both PFS and OS tending to 1.
Utilities	Progression-free utility is equal across treatment arms	The utility value was derived from disease severity and therefore should only differ by health-state.
	Progressed disease utilities from CADTH pCODR bendamustine for NHL are representative of UK MZL patients in the progressed disease state	The estimates of PD utility from the CADTH HTA fall within the range of accepted progressed disease utilities in previous zanubrutinib NICE submissions (0.60-0.691).[82] Furthermore, the progressed disease utility decrement is in similar to the utility values accepted in TA833.[82]
	Age-adjusted utility decrements are modelled.	To capture the decrease in HRQoL with age.
	All AEs lead to the same disutility regardless of the AE	Due to the low incidence rates of AEs and the small sample size in MAGNOLIA and AU-003, estimates of disutility for specific AEs is inaccurate and susceptible to being skewed by outliers. Therefore, it was more appropriate

Model input	Assumption	Rationale
		to estimate the disutility of AEs generally compared to specific disutilities.
Adverse events	All AEs are assumed to last for the same period of time	Due to the low incidence rates of AEs and the small sample size in MAGNOLIA and AU-003, estimates of AE duration for specific AEs is inaccurate and susceptible to being skewed by outliers. Therefore, it was more appropriate to estimate the duration of AEs generally compared to AE-specific durations.
	Only Grade 3 or Grade 4 AEs occurring in ≥2% patients are included	Events occurring in ≥2% 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
Treatment duration	PFS is used to model time on treatment for treatments within the HMRN basket, up until treatment specific stopping rules.	In the absence of TTD data in MZL patients from the HMRN registry, PFS was deemed a suitable proxy for treatment costs. The impact is expected to be minor on the analyses given that all treatments within the basket are fixed duration and not treatment to progression.
Treatment costs	No administration costs for zanubrutinib.	Regimens administered orally can be taken by patients at home. It is assumed that no costs are incurred.
	All HMRN registry basket RDIs are 100%	In the absence of treatment specific data on RDI for all treatments, assuming constant RDI for all treatments avoids bias.
	100% wastage was assumed for treatments that are based on BSA (included in the HMRN registry basket) and not for oral treatments.	As MZL is a relatively uncommon disease it was assumed that no vial sharing would occur for treatments are delivered intravenously, as no other patient would receive the remainder of non-exhausted vials. No wastage would occur for oral treatments as patients would receive the exact number of tablets they need for treatment.
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.
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 safety profile of zanubrutinib and

Model input	Assumption	Rationale
		its simple administration is likely to require less monitoring from clinicians.

AE – Adverse event; CADTH – Canadian Drug and Heath Technology Agency; HMRN – Haematological Malignancy Research Network; HR – Hazard ratio; MZL – Marginal zone lymphoma; NICE – National Institute for Health and Care Excellence; OS – Overall survival; pCODR – pan-Canadian Oncology Drug Review; PD – Progressed disease; PFS – Progression-free survival; PSM – Partitioned survival model; RDI – Relative dose intensity; TTD – Time to treatment discontinuation.

B.3.10 Base-case results

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

The base-case results are presented in Table 81. Over a lifetime time horizon, treatment with zanubrutinib in patients with R/R MZL was associated with an ICER of £26,197 per person, compared to the HMRN registry basket. Disaggregated results from the base-case analysis are presented in Appendix J.

Table 81: Base-case deterministic results in patients with R/R MZL

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
HMRN registry basket	[redacted]	[redacted]	[redacted]	-	-	-	-
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,197

ICER – incremental cost-effectiveness ratio; HMRN – Haematological Malignancy Research Network; LYG – Life years gained; MZL – marginal zone lymphoma; QALYs – Quality-adjusted life years; R/R – Relapsed or refractory.

Table 82: Base-case deterministic results for net health benefit of zanubrutinib in patients with R/R MZL

Technologies	Total costs (£)	Incremental costs (£)	ICER (£)	NHB at £20,000	NHB at £30,000
HMRN registry basket	[redacted]	-	-	-	-
Zanubrutinib	[redacted]	[redacted]	26,197	-0.88	0.36

ICER, incremental cost-effectiveness ratio; HMRN – Haematological Malignancy Research Network; MZL – marginal zone lymphoma; NHB, net health benefit; R/R – Relapsed or refractory.

B.3.11 Exploring uncertainty

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 results of the base-case PSA are presented in Table 83, with an incremental cost-effectiveness plane (ICEP) and cost-effectiveness acceptability curve (CEAC) presented in Figure 30: PSA ICEP for zanubrutinib vs HMRN registry basket in patients with R/R MZL and Figure 31, respectively. Based on the PSA, treatment with zanubrutinib in patients with R/R MZL was associated with incremental costs of £[redacted] and [redacted] incremental QALYs, with a corresponding ICER of £26,775, compared with the HMRN registry basket. The mean probabilistic results lie close to the deterministic results, indicating that the model is robust to parameter uncertainty.

Table 83: Base-case PSA results in patients with R/R MZL

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
HMRN registry basket	[redacted]	[redacted]	-	-	-
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	26,775

ICER, incremental cost-effectiveness ratio; HMRN – Haematological Malignancy Research Network; MZL – marginal zone lymphoma; QALYs – Quality-adjusted life years; PSA – Probabilistic sensitivity analysis; R/R – Relapsed or refractory.

Figure 30: PSA ICEP for zanubrutinib vs HMRN registry basket in patients with R/R MZL

ICEP – incremental cost-effectiveness plane; HMRN – Haematological Malignancy Research Network; MZL – marginal zone lymphoma; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life year; R/R – relapsed/refractory.

Figure 31: PSA CEAC for zanubrutinib vs HMRN registry basket in patients with R/R MZL

CEAC – Cost-effectiveness acceptability curve; HMRN – Haematological Malignancy Research Network; MZL – marginal zone lymphoma; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life year; R/R – relapsed/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. The results of the DSA are summarised in Table 84 and Figure 32 versus HMRN registry basket. The most influential factors on the DSA were PF utility, PF healthcare resource use (HRU) patient history/physical exam and PF HRU haematologist visit.

Table 84: DSA results (ICER) for zanubrutinib vs HMRN registry basket in patients with R/R MZL

Parameter name	Lower bound ICER (£)	Upper bound ICER (£)
PF utility	£27,789	£24,860
PF HRU patient history/physical exam	£25,865	£26,601
PF HRU haematologist visit	£25,883	£26,579
Cost for patient history/physical exam	£25,930	£26,522
Cost for haematologist visit	£25,944	£26,504
PD utility	£25,998	£26,389
Cost for terminal care	£26,314	£26,055
Single agent Rituximab subsequent treat use following HMRN basket	£26,278	£26,110

Parameter name	Lower bound ICER (£)	Upper bound ICER (£)
BR subsequent treat use following HMRN basket	£26,270	£26,115
Single agent Rituximab subsequent treat use following zanubrutinib	£26,127	£26,274

BR – bendamustine/rituximab; DSA – deterministic sensitivity analyses; HRU – Healthcare resource use; HMRN – Haematological Malignancy Research Network; MZL – marginal zone lymphoma; PD – Progressed disease; PF – Progression free; R/R – relapsed or refractory.

Figure 32: Tornado plot of DSA results (ICER) for zanubrutinib vs HMRN registry basket in patients with R/R MZL

BR – bendamustine/rituximab; DSA – deterministic sensitivity analyses; ICER – incremental cost-effectiveness ratio; HRU – Healthcare resource use; HMRN – Haematological Malignancy Research Network; MZL – marginal zone lymphoma; PFS – Progression-free survival; PPS – post-progression survival; QALY – quality-adjusted life year; R/R – relapsed or refractory; tx – treatment.

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 85. Deterministic and probabilistic scenario analysis results for zanubrutinib versus the HMRN registry basket are presented in Table 86 and Table 87, respectively. The probabilistic results lie are consistent with the deterministic results, indicating the robustness of the analyses to parameter uncertainty. All scenarios both probabilistic and deterministic remained below £30,000 per QALY gained.

Table 85: 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: 27 years	Time horizon: 20 years	To explore the impact of shortening the time horizon
MAGNOLIA-003, weighted to HMRN N=[redacted] dataset	MAGNOLIA, weighted to HMRN N=[redacted] dataset	To explore the impact of alternative datasets for efficacy
MAGNOLIA-003, weighted to HMRN N=[redacted] dataset	MAGNOLIA-003, weighted to HMRN N=[redacted] dataset	
Age-gender matched background mortality restriction applied	Adjusted (by SMR=1.41) age-gender matched background mortality restriction applied	To explore the impact of assuming that patients with MZL have an increased background mortality compared to the general population
PFS distribution: • Zanubrutinib: Log-logistic • HMRN registry basket: Log-logistic	PFS distribution (statistical fit HMRN): • Zanubrutinib: Weibull¥ • HMRN registry basket: Weibull¥	To explore the impact of alternative PFS extrapolations
	PFS distribution (most conservative analysis): • Zanubrutinib: Exponential** • HMRN registry basket: Log-normal*	
	PFS distribution (statistical fit zanubrutinib): • Zanubrutinib: Exponential** • HMRN registry basket: Exponential**	
OS distribution: • Zanubrutinib: Log-logistic • HMRN registry basket: Log-logistic	OS distribution (statistical fit zanubrutinib): • Zanubrutinib: Exponentialβ • HMRN registry basket: Exponentialβ**	To explore the impact of alternative OS extrapolations
	OS distribution (most conservative analysis):	

Base-case	Scenario analysis	Rationale
	• Zanubrutinib: Weibull** • HMRN registry basket: log-normal*	
TTD distribution: • Zanubrutinib: log-logistic	TTD distribution: • Zanubrutinib: Exponential	To explore the impact of an alternative TTD distribution
HRQoL	Treatment specific utilities	To explore the impact of alternative utility assumptions
	NICE TA627 Company utilities	
	NICE TA627 EAG utilities	
	Exclude age adjustment	
	Model MAGNOLIA trial utility	
Wastage applied	Wastage not applied	To explore the impact of wastage
AE applied (cost and QALYs)	AEs not applied (costs and QALYs)	To explore the impact of the treatment safety profiles

AE – Adverse event; EAG – External assessment group; HMRN – Haematological Malignancy Research Network; MZL – Marginal zone lymphoma; NICE – National Institute for Health and Care Excellence; OS – Overall survival; PFS – Progression-free survival; QALY – Quality-adjusted life year; SMR – Standardised mortality ratio. *Most optimistic curve choice. **Most pessimistic curve choice (note for zanubrutinib this curve choice also represents the best statistically fitting curve for PFS). ¥Best statistical fit for HMRN. βBest statistical fit for zanubrutinib.

Table 86: Summary of scenario analyses results for zanubrutinib vs HMRN registry basket – deterministic

Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER/QALY (£)
Base case	[redacted]	[redacted]	26,197
No discounting	[redacted]	[redacted]	25,139
High discount rates (6%)	[redacted]	[redacted]	26,969
Time horizon: 20 years	[redacted]	[redacted]	26,378
MAGNOLIA, weighted to HMRN N=[redacted] dataset	[redacted]	[redacted]	29,272
MAGNOLIA-003, weighted to HMRN N=[redacted] dataset	[redacted]	[redacted]	26,661
Adjusted (by SMR=1.41) age-gender matched background mortality restriction applied	[redacted]	[redacted]	27,999
PFS distribution (statistical fit HMRN): • Zanubrutinib: Weibull¥ • HMRN registry basket:	[redacted]	[redacted]	25,867

Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER/QALY (£)
Weibull¥			
PFS distribution (most conservative analysis): • Zanubrutinib: Exponential** • HMRN registry basket: Log-normal*	[redacted]	[redacted]	29,228
PFS distribution (statistical fit zanubrutinib): • Zanubrutinib: Exponential** • HMRN registry basket: Exponential**	[redacted]	[redacted]	26,040
OS distribution (statistical fit zanubrutinib): • Zanubrutinib: Exponentialβ • HMRN registry basket: Exponentialβ**	[redacted]	[redacted]	22,792
OS distribution (most conservative analysis): • Zanubrutinib: Weibull** • HMRN registry basket: log-normal*	[redacted]	[redacted]	27,170
TTD distribution: • Zanubrutinib: Exponential	[redacted]	[redacted]	18,935
Treatment specific utilities	[redacted]	[redacted]	23,063
NICE TA627 Company utilities	[redacted]	[redacted]	23,590
NICE TA627 EAG utilities	[redacted]	[redacted]	25,069
Exclude age adjustment	[redacted]	[redacted]	24,910
Exclude restrict of MAGNOLIA PF utility by age-sex matched general population	[redacted]	[redacted]	24,100
Wastage not applied	[redacted]	[redacted]	26,075
AEs not applied (costs and QALYs)	[redacted]	[redacted]	26,227

AE – Adverse event; HMRN – Haematological Malignancy Research Network; ICER – Incremental cost-effectiveness ratio; IRC – Independent review committee; LYG – Life year gained; MAIC – Matching-adjusted indirect comparison; NICE – National Institute of Health and Care Excellence; OS – overall survival; PFS – Progression-free survival; R/R – Relapsed/refractory; QALY – Quality-adjusted life year; SMR – standardised mortality ratio; TTD – Time to treatment discontinuation. *Most optimistic curve choice. **Most pessimistic curve choice (note for zanubrutinib this curve choice also represents the best statistically fitting curve for PFS). ¥Best statistical fit for HMRN. βBest statistical fit for zanubrutinib.

Table 87: Summary of scenario analyses results for zanubrutinib vs HMRN registry basket – probabilistic

Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER/QALY (£)
Base case	[redacted]	[redacted]	26,775
No discounting	[redacted]	[redacted]	25,587
High discount rates (6%)	[redacted]	[redacted]	27,484
Time horizon: 20 years	[redacted]	[redacted]	27,883
MAGNOLIA, weighted to HMRN N=[redacted] dataset	[redacted]	[redacted]	29,043
MAGNOLIA-003, weighted to HMRN N=[redacted] dataset	[redacted]	[redacted]	27,861
Adjusted (by SMR=1.41) age-gender matched background mortality restriction applied	[redacted]	[redacted]	29,601
PFS distribution (statistical fit HMRN): • Zanubrutinib: Weibull¥ • HMRN registry basket: Weibull¥	[redacted]	[redacted]	26,660
PFS distribution (most conservative analysis): • Zanubrutinib: Exponential** • HMRN registry basket: Log-normal*	[redacted]	[redacted]	30,152
PFS distribution (statistical fit zanubrutinib): • Zanubrutinib: Exponential** • HMRN registry basket: Exponential**	[redacted]	[redacted]	25,253
OS distribution (statistical fit zanubrutinib): • Zanubrutinib: Exponentialβ • HMRN registry basket: Exponentialβ**	[redacted]	[redacted]	23,233
OS distribution (most conservative analysis): • Zanubrutinib: Weibull** • HMRN registry basket: log-normal*	[redacted]	[redacted]	27,578

Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER/QALY (£)
TTD distribution: • Zanubrutinib: Exponential	[redacted]	[redacted]	20,767
Treatment specific utilities	[redacted]	[redacted]	23,899
NICE TA627 Company utilities	[redacted]	[redacted]	24,714
NICE TA627 EAG utilities	[redacted]	[redacted]	26,382
Exclude age adjustment	[redacted]	[redacted]	25,449
Exclude restrict of MAGNOLIA PF utility by age-sex matched general population	[redacted]	[redacted]	25,047
Wastage not applied	[redacted]	[redacted]	26,589
AEs not applied (costs and QALYs)	[redacted]	[redacted]	26,454

AE – Adverse event; HMRN – Haematological Malignancy Research Network; ICER – Incremental cost-effectiveness ratio; NICE – National Institute for Health and Care Excellence; OS – Overall survival; PFS – Progression-free survival; QALY – Quality-adjusted life year; SMR – Standardised mortality ratio. *Most optimistic curve choice. **Most pessimistic curve choice (note for zanubrutinib this curve choice also represents the best statistically fitting curve for PFS). ¥Best statistical fit for HMRN. βBest statistical fit for zanubrutinib.

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 a HMRN registry basket in adult patients with R/R MZL.

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 chemoimmunotherapy in other relevant blood cancers (WM and CLL) is anticipated to also apply in MZL.[112,129] UK clinical experts at an advisory (11th October 2023) confirmed that they expected zanubrutinib to be better tolerated in patients with R/R MZL than the current standard of care, rituximab- and chemotherapy-based treatments.[4] The clinical SLR highlighted a lack of safety data for the treatments within the HMRN registry basket, and no further safety data is available from the HMRN registry. Therefore, the analyses relied on the published

safety profiles of the top three most used treatments in the basket (BR, R-CVP and rituximab monotherapy). Notably, only AEs of any Grade were available for R-CVP, so the rates were reduced by the total proportion of Grade 3 AEs. Given the lack of AE data for the comparator, it is likely that the analysis underestimates the improvement in the safety profile of zanubrutinib compared to standard of care treatments.

Furthermore, zanubrutinib is a simple oral regimen that can be administered in the home. Therefore, patients will not have to travel to hospital to receive treatment. The reduction in hospital visits will benefit the patient from an economic and HRQoL perspective and will also result in cost savings from an NHS resource perspective. The analysis conservatively assumes the same resource use across zanubrutinib and the HMRN registry basket, hence does not capture the benefit of the simple oral administration of zanubrutinib.

Additionally, zanubrutinib has improved PFS and OS rates over the HMRN registry basket. This not only benefits the patient themselves, but their caregivers/family members as well since zanubrutinib patients will remain progression-free for longer, putting less strain on the caregivers/family members. This benefit would 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.

Furthermore, the model structure, assumptions, model inputs and outputs were validated by UK clinical experts, economic and statistical experts in attendance at an advisory board (11th October 2023) organised by the Company, and feedback from the experts was incorporated into this submission.[4] In particular, the survival extrapolations, choice of comparator and the ITC results were validated at the advisory board. A review of treatments for MZL in previous NICE TAs and published literature was carried out to further validate the key model assumptions, inputs, and outputs.

Finally, the modelled outputs were compared to the clinical trial data for validation purposes. Table 88 demonstrates that the predicted survival aligns well with the observed data for zanubrutinib, which can increase the confidence in the CEA results. The model predicted PFS and OS which closely aligned to the observed data in year 1 for the HMRN registry basket but slightly underestimated the survival in year 2, and overestimated the survival by year 5. The overestimation carries through into the tail of the curve, favouring the HMRN registry basket. Therefore, the incremental benefit of zanubrutinib can be considered conservative.

Table 88: Comparison of modelled and observed survival

Endpoint	Proportion of patients		
	Year 1	Year 2	Year 5
PFS			
Zanubrutinib KM	[redacted]	[redacted]	-
Zanubrutinib curve	[redacted]	[redacted]	[redacted]
HMRN KM	[redacted]	[redacted]	[redacted]
HMRN curve	[redacted]	[redacted]	[redacted]
OS			
Zanubrutinib KM	[redacted]	[redacted]	[redacted]
Zanubrutinib curve	[redacted]	[redacted]	[redacted]
HMRN KM	[redacted]	[redacted]	[redacted]
HMRN curve	[redacted]	[redacted]	[redacted]

HMRN – Haematological Malignancy Research Network; KM – Kaplan-Meier; OS – Overall survival.

B.3.15 Interpretation and conclusions of economic evidence

B.3.15.1 Summary

In the base-case analysis, zanubrutinib was associated with [redacted] incremental QALYs, and £[redacted] incremental costs, compared with the HMRN registry basket. The corresponding ICER was below a willingness-to-pay threshold of £30,000, at £26,197 per QALY gained. The base-case provides a conservative estimate of the cost-effectiveness of zanubrutinib, with potential benefits in safety, HRQoL and resource use not captured in the analysis. Results are robust to changes in key model parameters, with the ICERs for all scenarios ran below £30,000 per QALY gained (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 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, [50,82,105] and reflects the disease progression of MZL. The model structure was validated as appropriated by UK experts at an advisory board (11th October 2023).[4]

- Efficacy data for zanubrutinib is informed by pooled data from the MAGNOLIA and AU-003 clinical trials. These trials measured key outcomes, such as PFS, OS, TTD and AE rates, that are used in the model. The baseline characteristics were deemed representative of a UK patient population by UK clinical experts at an advisory board on the 11th October 2023.[4] Clinical effectiveness data for the comparator arm (the HMRN registry basket) was estimated using data from the largest UK registry for patients with MZL and is therefore reflective of clinical practice in the UK. Furthermore, the zanubrutinib trial data were matched to the baseline characteristics of the HMRN cohort (via a MAIC), further increasing the generalisability of the data to the UK population.

- 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 2022/23 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.

- The clinical outcomes predicted by the model and the assumptions underpinning it were ratified by UK clinical expert opinion at an advisory board (11th October 2023).[4] 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, OS, and TTD over a lifetime horizon. This assumption may have led to uncertainty in the efficacy results, but it is appropriate due to 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.[4,97] To explore uncertainty in the results, scenario analyses considered alternative parametric distributions, which were found to have no significant impact on the results.

- Both of the zanubrutinib trials were single arm, which means that there is no direct treatment comparison of zanubrutinib and relevant comparators, which may introduce uncertainty. This was addressed by conducting a MAIC analysis to adjust the zanubrutinib dataset to the HMRN registry basket 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 the HMRN registry basket. Extensive scenario analyses confirmed the consistency of these analyses to the base-case results from the MAIC.

- Due to the design of the MAGNOLIA and AU-003 trials, no patient level HRQoL data was collected for patients once their disease had progressed. This meant that it was necessary to source utility values for the PD disease state from published literature and previous HTA submissions. Whilst this would not normally be an issue, there have been few HRQoL studies for patients with MZL. The utilities used in the CEA were taken from a CADTH pCODR HTA in patients with indolent NHL in Canada and therefore may not be as easily generalisable to the UK.[108] However, the PD value used falls between the values accepted in previous zanubrutinib HTAs in the UK in

relevant blood cancers, and is close to the EAG's preferred utility in NICE appraisal TA627.[86] Sensitivity analyses show that variation of PD utility does not have a significant impact on the CE results with the ICER ranging from £25,998/QALY to £26,389/QALY. Therefore, whilst the PD utility value used may be uncertain, it should not impact the interpretation of the results.

- There was a lack of published data on AEs for the treatments within the HMRN registry basket. Therefore, on advice from UK clinical experts,[4] the analysis relies on the AE profile of the top three used treatments in the basket (BR, R-CVP and rituximab monotherapy). However, the analysis is not sensitive to the impact of AEs, as confirmed by scenario analyses where the safety profile of zanubrutinib and the HMRN registry basket is excluded.

In conclusion, this submission demonstrates the clinical and cost-effectiveness of zanubrutinib versus the HMRN registry basket (that reflects standard of care in the UK). The economic evaluation confirms a robust and favourable cost-effectiveness profile with a base case ICER of £26,197, in the presence of a simple discount.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Zanubrutinib for treating relapsed or refractory marginal zone lymphoma [ID5085]

Summary of Information for Patients (SIP)

November 2023

File name	Version	Contains confidential information	Date
ID5085_Zanubrutinb for treatment relapsed refractory marginal zone lymphoma_SIP_(FINAL_28Nov23)	1.0	No	28th November 2023

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 monotherapy is indicated for the treatment of adult patients with marginal zone lymphoma who have received at least one prior anti-CD20-based 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 15th September 2022, the Committee for Medicinal Products for Human Use recommended that the existing marketing authorisation be changed to include a new indication for the treatment of adult patients with marginal zone lymphoma who have received at least one prior anti-CD20-based therapy (i.e. rituximab-based therapy) https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-brukinsa-ii-02_en.pdf Zanubrutinib as a monotherapy is indicated for the treatment of adult patients with marginal zone lymphoma who have received at least one prior anti-CD20-based therapy in Europe following approval by the European Medicines Association on the 28th October

2022. On the 6th January 2023, zanubrutinib was also approved in the UK for the same indication by the Medicines and Healthcare products Regulatory Agency through the European Commission Decision Reliance Procedure.[1,2]

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.[3] 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.[3,4]

Marginal zone lymphoma is a group of indolent non-Hodgkin's lymphoma that develops at the edge of areas of lymph node tissue within the lymphatic system.[5] Marginal zone lymphoma can occur at any age but is more common in people over 60 years of age.[6] The incidence of marginal zone lymphoma is greater in men compared to women. In the UK, approximately 4.1 new patients are diagnosed with marginal zone lymphoma for every 100,000 people per year.[7]

The World Health Organisation recognises three main subtypes of marginal zone lymphoma depending on the tissue type of origin[8]:

- Extranodal (also known as mucosa-associated lymphoid tissue lymphoma or MALT), usually starts in organs outside the lymph nodes
- Nodal, the rarest type starting in lymph nodes
- Splenic, originates in the spleen and splenic.

Each type of marginal zone lymphoma has unique features and starts in different locations, which can influence the choice of treatment a patient may receive.

Patients with marginal zone lymphoma often present without symptoms. After the shock of diagnosis, patients can spend a long time being actively monitored by their clinician. Not receiving treatment can cause anxiety among patients and uncertainty around their outlook. When symptoms occur, they differ depending on the tissue involved. Common symptoms include weight loss, night sweats, swollen lymph nodes, an enlarged spleen and a reduced number of red blood cells or white blood cells.[9–11]

When the disease has progressed beyond its tissue of origin to other locations in the body the disease is defined as advanced stage disease. Marginal zone 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.[12] Once a patient with marginal zone lymphoma experiences relapse, the relevance of their initial subtype becomes less important when making treatment decisions. As patients receive additional treatment, they may develop resistance to previous treatments which contributes to the increased likelihood of further relapses.[13]

Marginal zone lymphoma can significantly impact a patient's quality of life due to its symptoms and treatment implications. When the disease returns after initial treatment, patients are faced with symptoms such as fatigue, night sweats and swollen lymph nodes. In addition, the toxicity of chemotherapy (e.g. nausea, vomiting, hair loss, skin irritation, sore mouth, difficulties swallowing, and gastrointestinal problems), can compound the impact on patient's quality of life. 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. Furthermore, there is a lack of approved treatment options for patients with relapsed or refractory disease, which adds to the emotional burden of experiencing a relapse.[14]

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?

As most patients will not experience symptoms with early stage disease, marginal zone lymphoma is often detected during a routine clinical check-up and clinical presentation will differ depending on the tissue involved.[15]

In most instances, the signs of marginal zone lymphoma involve the presence of a slow growing mass, chronic tissue inflammation/infection or autoimmune disorders at the affected organ, abnormal lymph nodes or an enlarged spleen. A minority of patients present with symptoms such as fever, night sweats, unintentional weight loss, iron deficiency or low platelets (red or white blood cells) once the lymphoma becomes more advanced.[16]

Marginal zone 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.

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 marginal zone lymphoma present without symptoms if their disease is at an early-stage. In these cases, doctors usually watch the condition closely without starting treatment right away. Treatment begins when symptoms appear, with the main goals being to manage symptoms and to help patients have longer periods without the disease getting worse.[13]

The choice of first-line treatment is dependent on several factors, including marginal zone lymphoma subtype and disease stage. For lymphoma that is localised (only in one area), doctors might use radiation therapy aiming for a cure. However, if the disease has spread to more areas, a more widespread treatment approach, called systemic therapy, is used.[13]

The commonly used first-line treatments for marginal zone lymphoma are:[13,17]

- Rituximab-based chemotherapy
- Rituximab monotherapy
- Non-rituximab-based chemotherapy.

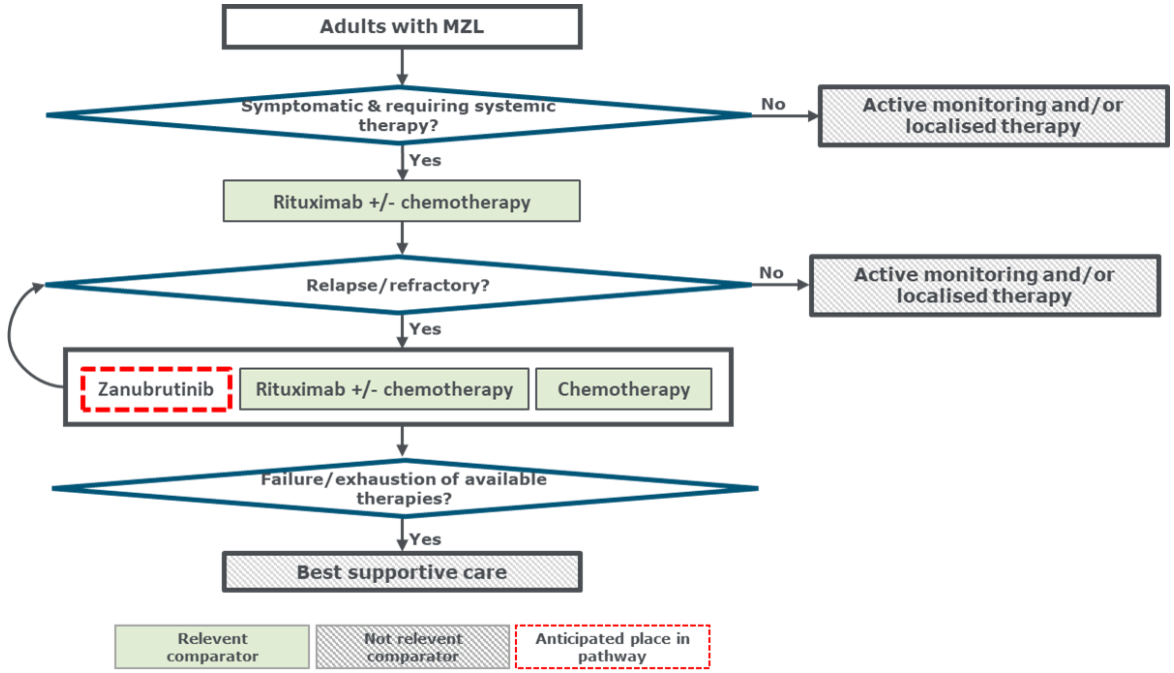
Rituximab-based treatments are generally recommended because they work well in similar types of lymphoma, however relatively few therapies have been specifically tested in marginal zone lymphoma.[13,18,19]

Following an initial response to treatment, lymphoma can come back (relapsed) or not respond to the treatment (refractory disease). There is no standard of care for patients with marginal zone lymphoma who have who have relapsed or refractory disease.

Recent clinical guidelines from the European Society for Medical Oncology, published in 2020, suggest that if a patient's marginal zone lymphoma did not get worse for more than 24 months after the first rituximab-based treatment, doctors might recommend repeating the same treatment. However, if the disease returns or worsens within those 24 months, or didn’t respond at all initially, the guidelines recommend considering other options, such as enrolling in clinical trials for treatments that are not yet approved.[13]

Zanubrutinib is only treatment that is licensed for marginal zone lymphoma and it is anticipated that zanubrutinib will be used in line with the marketing authorisation, as a second-line and beyond therapy regimen for patients with relapsed or refractory marginal zone lymphoma, after at least one prior anti-CD20 antibody-based regimen (i.e. rituximab-based therapy). Zanubrutinib can be regarded as an alternative treatment to rechallenging with rituximab monotherapy, rituximab-based chemotherapy or chemotherapy alone as presented in
Figure **1**.

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



MZL – marginal zone 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 marginal zone lymphoma was gathered during a recent NICE appraisal (NICE TA627[20]).[21] UK patient representatives described:

- the uncertainty of active monitoring as stressful and noted that many people experience anxiety. Some people find it hard to plan for the future because they do not know if or when they may need to start treatment.
- the lack of treatment options in marginal zone 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.
- the impact on the mental state of patients with psychological issues arising. The emotional toll of facing a relapse and undergoing additional treatment can contribute to heightened distress and anxiety in patients.

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 Bruton tyrosine kinase (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. The Summary of Product Characteristics can be found here: https://www.ema.europa.eu/en/documents/product-information/brukinsa-epar-product-information_en.pdf 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.**
Currently, 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?
The recommended dose of zanubrutinib is 320 mg per day. 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 marginal zone lymphoma in two single arm trials, MAGNOLIA and AU-003. A summary of the key clinical trials for zanubrutinib is presented in Table 1.

Table 1: Clinical effectiveness evidence

Study title	**MAGNOLIA**[22]	**AU-003**[23]
Study design	A phase 2, single arm, multicentre, open-label study	A phase 1/2, single arm, multicentre, open-label study
Population	Patients with marginal zone lymphoma who have received at least one prior lines of CD20-based therapy	Patients with B-cell lymphoid malignancy, including patients with marginal zone lymphoma who have received at least one prior lines of therapy
Intervention(s)	Zanubrutinib (N=68)	Zanubrutinib (N=20)
Comparator(s)	Not applicable, trial was single arm only	Not applicable, trial was single arm only
Key inclusion criteria	• Confirmed marginal zone lymphoma (any subtype) • At least one prior lines of therapy, including at least one anti-CD20-based therapy regimen (either as monotherapy or as chemoimmunotherapy) • Documented failure to achieve at least partial response or documented progressive disease after the most recent systemic treatment • ECOG Performance Status score of 0-2 • Measurable disease • Adequate bone marrow and organ function • Life expectancy of at least 6 months	• Relapsed or refractory WHO-defined indolent lymphoma (inclusive of marginal zone 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 organ function

Key exclusion criteria	• 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
		• 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	May 04, 2022	March 31, 2021

BTKi – Bruton's Tyrosine Kinase inhibitor; CD20 – anti-cluster of differentiation 20; 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 marginal zone lymphoma in two single arm trials, MAGNOLIA and AU-003.[22,23] These studies looked at how effective zanubrutinib is in reducing or eliminating tumours in patients with relapsed or refractory marginal zone lymphoma.

MAGNOLIA

The key outcome measured in MAGNOLIA 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 MAGNOLIA, 68.2% of patients treated with zanubrutinib had a tumour that completely disappeared or was partially reduced. The MAGNOLIA population was heavily pre-treated, and the response rate demonstrated that zanubrutinib was effective in even more pre-treated patients. There was no difference by marginal zone lymphoma subtype, and

25.8% of patients achieved complete tumour remission along with 42.4% who achieved a partial response. As marginal zone lymphoma is considered an indolent disease and uncurable, this represents a high proportion of patients with complete tumour remission and partial response. High response rates were also observed in patients who are known to respond poorly; patients over the age of 75 years of age, target lesions of more than 5cm, refractory disease and nodal marginal zone lymphoma. For further information on overall response rate in MAGNOLIA, please see Document B, Sections B.2a.6.1.

Progression-free survival measures the length of time after starting treatment that a patient lives with a disease without it progressing. In MAGNOLIA, 30.3% of patients progressed after a median follow-up of 27.4 months and 70.9% of patients were progression-free at 24 months. For further information on progression-free survival in MAGNOLIA, please see Document B, Sections B.2a.6.2.

Overall survival was also measured in MAGNOLIA i.e. the length of time after starting treatment that a patient is alive. As marginal zone lymphoma is a long-term chronic illness, few death events occurred in MAGNOLIA (18.2%) at a median follow-up of 28.7 months and 85.9% of patients were alive at 24 months. All fatal events were assessed by the investigators as unrelated to study drug and the majority of patients died more than 30 days after their last dose of study drug. For further information on overall survival in MAGNOLIA, please see Document B, Sections B.2a.6.2.

AU-003
The key outcome measured in AU-003 was also overall response rate. In AU-003, 80.0% of patients treated with zanubrutinib had a tumour that completely disappeared or was partially reduced. The AU-003 population was also heavily pre-treated, and the response rate demonstrated that zanubrutinib was effective in even more pre-treated patients. There was no difference by marginal zone lymphoma subtype and 20.0% of patients achieved complete tumour remission, along with 60.0% who achieved a partial response. As marginal zone lymphoma is considered an indolent disease and uncurable, this represents a high proportion of patients with complete tumour remission. For further information on overall response rate in AU-003, please see Document B, Sections B.2b.6.1.

In AU-003, 25.0% of patients progressed after a median follow-up of 33.8 months and 72.0% of patients were progression-free at 36 months. For further information on progression-free survival in AU-003, please see Document B, Sections B.2b.6.2.

As marginal zone lymphoma is a long-term chronic illness, few death events occurred in AU-003 (15.0%) at a median follow-up of 39.2 months and 84.2% of patients were alive at 36 months. All fatal events were assessed by the investigators as unrelated to study drug and only one patient died within 30 days of their last dose of study drug. For further information on overall survival in AU-003, please see Document B, Sections B.2b.6.2.

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.

Patients in MAGNOLIA were asked to complete two questionnaires about their quality of life, the EORTC-QLQ-C30 (cancer-specific questionnaire) and the EQ-5D-5L (general health questionnaire). Both questionnaires are commonly used and include questions about multiple topics which contribute to quality of life.

Patients reported slightly improved quality of life from baseline using the EORTC-QLQ-C30 questionnaire and remained higher than baseline throughout the questionnaire follow-up. When using the EQ-5D-5L instrument, patients reported improvements in usual activities such as work, study, housework, family or leisure activities, from baseline. This improvement remained consistently higher than baseline throughout, indicating that quality of life was maintained following treatment with zanubrutinib.

Quality of life data was not collected in AU-003.

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 MAGNOLIA and 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 marginal zone lymphoma. The safety profile is consistent with previously published studies of zanubrutinib in similar cancers.[24–27]. The most common side effects reported are diarrhoea, confusion, and rash. Aside from COVID-19 events stemming from the global pandemic, no additional new adverse events were identified in the safety profile of zanubrutinib. The adverse events were predominantly mild in nature and could be managed with temporary dose interruptions in treatment. Only one instance of treatment discontinuation due to zanubrutinib was reported. Notably no fatal adverse events were reported in patients taking zanubrutinib.

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.
- Zanubrutinib is the only licensed treatment option for refractory or relapsed marginal zone lymphoma.
- Zanubrutinib offers a new targeted, chemotherapy-free mechanism of action.
- Zanubrutinib has the potential to reduce the rate of discontinuation due to intolerance or adverse events experienced with chemotherapy treatment.
- Adverse events associated with zanubrutinib are more tolerable and manageable for patients than those associated with chemotherapy.
- Zanubrutinib has shown that most patients will achieve a partial response, and some will achieve complete remission.
- Zanubrutinib has shown to improve patients' quality of life, which was sustained throughout the trials.

- Zanubrutinib offers additional treatment option for physicians to make the best choice for their patients.

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.

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:

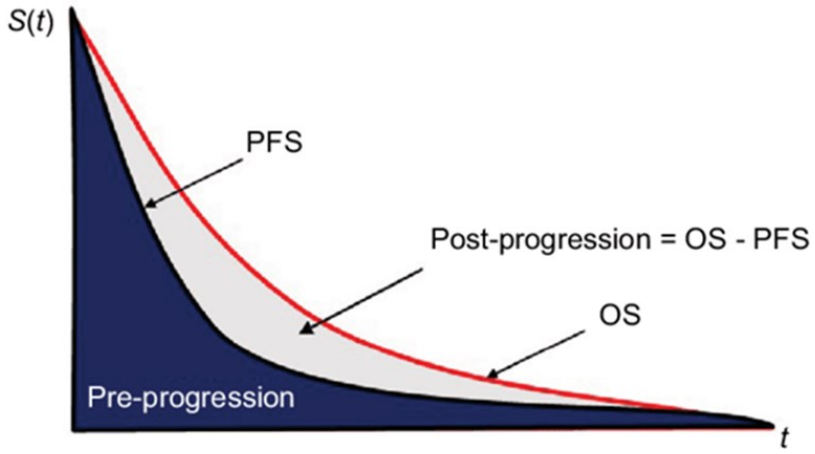
- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you 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 model was developed to evaluate the costs and survival benefits of using zanubrutinib to treat patients with relapsed or refractory marginal zone lymphoma who have received at least one prior anti-CD20-based therapy when compared to a basket of treatments including rituximab with or without chemotherapy and chemotherapy alone.

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, is more tolerable and improves survival. Real-world data from a UK registry was used to inform outcomes for the basket of currently available treatment options and a comparison was conducted comparing to trial data from the MAGNOLIA and AU-003 trials. Data for zanubrutinib from the trials and from the real-world registry were projected over a 30-year time horizon using standard methods 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 of time. Patients experience better quality of life whilst progression-free than when with progressed disease. In addition, the improved safety of zanubrutinib 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

The treatment acquisition costs associated with zanubrutinib were greater compared to the currently available treatment options. In addition, the disease management costs were greater than currently available treatment options. However, this was due to improved survival on zanubrutinib. Adverse event costs, subsequent treatment costs and end-of-life costs were lower for zanubrutinib due to improved safety, reduced disease progression and improved survival compared to currently available treatment options, respectively.

Uncertainty

The key uncertainties in the economic model relate to extrapolating both the trial and the real-world data. 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

Over a lifetime time horizon, treatment with zanubrutinib resulted in greater costs (due to the extended survival) for the National Health Service compared to a basket of currently used rituximab- or chemotherapy-based treatments in patients with relapsed or refractory marginal zone lymphoma who have received at least one prior anti-CD20-based therapy. However, zanubrutinib resulted in greater survival and improved quality of life and can be considered a cost-effective use of NHS resources according to the criteria outlined by NICE.

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 considered an innovative 'step change' in the management of relapsed or refractory marginal zone lymphoma as the first targeted therapy to be licensed for this patient population. The introduction of zanubrutinib would offer a new chemotherapy-free treatment mechanism of action, expanding treatment choice for marginal zone lymphoma patients and enabling greater patient autonomy and ability to make more tailored treatment decisions. Zanubrutinib does not require frequent hospital visits as is the case with chemotherapy which require intravenous administration, leading to improvements in quality of life for patients and reduced burden on caregivers. These benefits related to expanded treatment choice and reduced burden of administration for patients and their caregivers might not be adequately captured by calculations in the economic model.

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. However, whilst targeted therapies are considered the standard of care in similar blood cancers, no targeted therapies are available for patients with marginal zone lymphoma. This disparity highlights the critical gap in the available treatment options for marginal zone lymphoma patients. There is a high unmet need for a new chemotherapy-free, and well-tolerated treatment with proven efficacy.

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 marginal zone lymphoma:

- What is marginal zone lymphoma; https://www.lls.org/research/marginal-zone-lymphoma-mzl
- Symptoms of marginal zone lymphoma: https://www.cancercenter.com/cancer-types/non-hodgkin-lymphoma/types/marginal-zone-lymphoma

Treatment guidelines:

- European Society for Medical Oncology guidelines: https://www.esmo.org/guidelines/guidelines-by-topic/esmo-clinical-practice-guidelines-haematological-malignancies/marginal-zone-lymphoma

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.

Overall survival: the length of time after starting treatment that a patient is alive.

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.

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:

1. BRUKINSA 80 mg hard capsules - Summary of Product Characteristics (SmPC) - (emc). https://www.medicines.org.uk/emc/product/14001/smpc#gref.
2. BeiGene. *BeiGene. Press release. 2023*.
3. Cancer Research UK. Non-Hodgkin lymphoma statistics. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/non-hodgkin-lymphoma (2015).
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19. Buske. Nodales Marginalzonen Lymphom. *Onkopedia* https://www.onkopedia.com/de/onkopedia/guidelines/nodales-marginalzonen-lymphom.
20. NICE. Lenalidomide for treated follicular lymphoma and marginal zone lymphoma [ID1374]. Committee Papers.
21. BeiGene. DoF. Virtual discussion with patient representatives. (2023).
22. Opat, S. *et al.* The MAGNOLIA Trial: Zanubrutinib, a Next-Generation Bruton Tyrosine Kinase Inhibitor, Demonstrates Safety and Efficacy in Relapsed/Refractory Marginal Zone Lymphoma. *Clin Cancer Res* **27**, 6323–6332 (2021).

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25. Project information | Zanubrutinib for treating Waldenström's macroglobulinaemia [ID1427] | Guidance | NICE. https://www.nice.org.uk/guidance/indevelopment/gid-ta10705.
26. Tam, C. S. *et al.* Pooled safety analysis of zanubrutinib monotherapy in patients with B-cell malignancies. *Blood advances* **6**, 1296–1308 (2022).
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Zanubrutinib for treating relapsed or refractory marginal zone lymphoma [ID5085]

Clarification questions

January 2024

File name	Version	Contains confidential information	Date
ID5085 zanubrutinib MZL clarification letter v1[AClC]	**1**	**Yes**	**13/12/2023**

Notes for company

Highlighting in the template

Square brackets and [redacted] 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 [redacted] 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

Literature searches

A1. Please provide the earliest date searched for each of the databases (for example, 'from inception' or 'from 2000'). Please provide this information for each database in the clinical SLR, the economic SLR and the HRQoL SLR.

The clinical, economic and health related quality of life (HRQoL) systematic literature reviews (SLRs) presented as part of the Company Submission (CS) searched databases from their inception (Table 1).

Table 1: Inception dates for databases searched in the Company SLRs

Database	Inception year	SLR		
		Clinical	Economic	HRQoL
EMBASE via Ovid	1974	✓	✓	✓
MEDLINE and MEDLINE In-Process via Ovid	1946	✓	✓	✓
CENTRAL	1996	✓	×	✓
CDSR	2005	✓	×	×
EconLit	1969	×	✓	×
NHS EED	1995	×	✓	✓
APA PsycInfo	1895	×	×	✓

Abbreviations: APA - American Psychological Association; CDSR – Cochrane Database of Systematic Reviews; CENTRAL – Cochrane Central Register of Controlled Trials; NHS EED – National Health Service Economic Evaluation Database; SLR - Systematic literature review

A2. Please cite the source of any published search filters that have been used in all databases (e.g. Appendix D, Table 2, lines 4, 24, 46 for EMBASE). Please provide

this information where appropriate for both clinical (Appendix D) and economic/HRQoL searches (Appendix G).

A number of different published search filters were used to inform the search filters for the clinical, economic and HRQoL SLRs.

In the clinical SLR, the source of the search filters used for each database are as follows:

- EMBASE, MEDLINE In-Process randomised controlled trials filter used the SIGN search filter for randomised controlled trials.[1]
- EMBASE, MEDLINE observational studies filter used the SIGN search filter for observational studies.[2]

In the economic SLR, the source of the search filters used for each database are as follows:

- EMBASE search filter used the CADTH search filters for Economic Evaluations & Models (EMBASE).[3]
- MEDLINE and MEDLINE In-Process search filter used the CADTH search filters for Economic Evaluations & Models (MEDLINE).[4]
- CENTRAL search filter was translated from the CADTH Economic Evaluations & Models (MEDLINE) search filter.[4]

In the HRQoL SLR, the source of the search filters used for each database are as follows:

- EMBASE via Ovid used the CADTH Economic - Health Utilities / Quality of Life - Broad – EMBASE search filter.[5]
- MEDLINE and MEDLINE In-Process used the CADTH Economic - Health Utilities / Quality of Life - MEDLINE search filter.[6]

Clinical trials

A3. Company submission (CS), Section B.1.3.5 (p.23). The British Society of Haematology (BSH) guidelines for the treatment of marginal zone lymphoma (MZL) were published in November 2023.[1] In the CS, it states that the company "*reviewed the guidelines but due to the short time frame, were not able to incorporate these guidelines fully into the submission"* (p.23). It further explains that *"the BSH guidelines are consistent with ESMO guidelines which form the basis of the clinical guideline section in this appraisal"* (p.23). Please provide a summary of any differences between the treatment pathway for R/R MZL detailed in the BSH and ESMO guidelines, and any implications this has on the clinical and cost effectiveness evidence presented in the submission.

Based on the latest available guidance, the British Society of Haematology (BSH) guidelines are consistent with the European Society for Medical Oncology (ESMO) guidelines for the treatment approach to managing relapsed/refractory (R/R) marginal zone lymphoma (MZL).[7,8] A summary of each set of guidelines are presented in Table 2. There are no major differences between the ESMO and BSH guidelines, with both making almost identical recommendations about treatments. Furthermore, the advisory board conducted by the Company (11th October 2023) involved the lead author of the guidelines and another co-author (Renata Walewska and Harriet Walter), with both experts in agreement that the composition of the Haematological Malignancy Research Network (HMRN) basket of treatments was reflective of UK clinical practice.[7,9]

The HMRN treatment basket appears to be well aligned with the BSH guidelines. Given the similarity of the recommendations made by the two sets of guidelines there is unlikely to be any implication for the clinical and cost-effectiveness evidence presented in the submission.

Table 2: Comparison of ESMO and BSH guidelines for R/R MZL

Category	ESMO guidelines[8]	BSH guidelines[7]	Key difference
Active surveillance	Asymptomatic patients may be observed (watch-and-wait).	Active monitoring should be considered for asymptomatic patients with relapsed disease (any stage).	None
Radiotherapy	Radiotherapy for MZL patients with localised relapses.	Radiotherapy for localised symptomatic relapse.	None
Systemic treatment	If systemic treatment is required: A prior used chemoimmunotherapy can be repeated after long initial remissions (≥24 months). An alternative chemoimmunotherapy can be used if a long initial remission has not been achieved. Therapies to consider include rituximab-chlorambucil, bendamustine-rituximab, rituximab monotherapy and rituximab-lenalidomide.	Systematic therapy options include immunotherapy (e.g. rituximab monotherapy), chemoimmunotherapy (e.g. R- chlorambucil, BR, R-CVP, R-CHOP) or chemotherapy alone (e.g. chlorambucil). Immunochemotherapy is specifically noted as an effective option for patient specific strategies for POD24 disease (relapse or progression within 24 months of initiation of systemic therapy). Single agents (e.g. rituximab monotherapy) is an option for symptomatic relapsed SMZL and MALT who have achieved a durable response to prior treatment. This represents the majority of patients diagnosed with MZL, as over 60% are diagnosed with MALT and 20% are diagnosed with splenic MZL disease.	There is no substantial difference between the two guidelines. In general, the recommended treatments (CIT, immunotherapy and chemotherapy) are consistent, one difference being that the BSH does not mention rituximab-lenalidomide, which is not used for R/R MZL in the UK, as demonstrated by the HMRN registry.[10] Therefore, there is no concern for the clinical and cost-effectiveness presented.
ASCT	ASCT may be considered in fit patients with clinically aggressive relapse.	ASCT can be considered for chemosensitive relapsed MZL in selected fit patients, but benefits should be weighed against the availability of alternative novel approaches. Consolidation ASCT is an option for selected fit patients with MZL, and high-grade transformation had been ruled out for patients experiencing early relapse after immunochemotherapy.	There is a slight difference in eligibility for ASCT but given that ASCT is not considered a relevant comparator to this submission as per the final NICE scope, this has no implications on the clinical and cost-effectiveness evidence.[11]
Splenectomy	The ESMO guidelines explain that splenectomy was traditionally considered as the recommended first treatment for patients with SMZL, however its use has	Splenectomy is an option for selected patients with relapsed splenic MZL when rituximab monotherapy is ineffective or contraindicated.	BSH guidelines suggest a splenectomy may be appropriate in a small sub-group of relapsed splenic MZL patients who are not eligible for rituximab monotherapy.

Category	ESMO guidelines[8]	BSH guidelines[7]	Key difference
	declined in recent years with it largely being replaced with rituximab monotherapy in the first-line setting. The ESMO guidelines do not recommend splenectomy as a treatment option for patients with R/R MZL.		The HMRN registry shows that out of [redacted] patients diagnosed with MZL between 2005 to 2020, only [redacted] patients had received a splenectomy, which was performed close to diagnosis as part of their first-line treatment.[10] This is less than 2% of the total patient population, and hence the use of splenectomy is not expected to impact the clinical and cost-effectiveness evidence submitted as part of this appraisal. Furthermore, UK clinicians (Renata Walewska and Harriet Walter) confirmed that splenectomy is not relevant for the scope of this submission at a UK advisory board.[9]
Non-chemotherapy targeted treatments through clinical trials	Non-approved targeted therapies, within clinical trial settings, should be considered for patients who have exhaustive prior treatment options.	Targeted therapies, ideally within a clinical trial, should be offered to patients with multiple relapsed disease who are unsuitable for standard therapy. Licensed option includes zanubrutinib only.	None

Abbreviations: ASCT – autologous stem-cell transplantation; BR – bendamustine plus rituximab; BSH – British Society of Haematology; CIT – Chemoimmunotherapy; ESMO – European Society for Medical Oncology; HMRN – Haematological Malignancy Research Network; MALT – mucosa-associated lymphoid tissue; MZL – marginal zone lymphoma; NICE – National Institute For Health and Care Excellence; POD24 – progression of disease within 24 months; R-CVP – rituximab plus cyclophosphamide plus vincristine plus prednisolone; R-CHOP – rituximab plus cyclophosphamide plus doxorubicin plus vincristine plus prednisolone; R/R – relapsed or refractory; SMZL – splenic marginal zone lymphoma.

A4. CS, Section B.1.3.2.1 (p.17). Please provide a summary of the discussion with patient representatives that the company undertook (reference 37). Please provide the data on file. If not, please clarify what extra information this relates to and provide the full report.

As part of the CS the Company included reference 37, which presents the minutes from a virtual discussion with patient representatives. Please note this reference has also been included as part of the reference pack for this set of responses to clarification questions. As BeiGene data on file, the virtual discussion should be treated as CIC.

A5. Priority Question: CS, Section B.1.3.4 (p.21). Please provide a summary of the advisory board feedback from the meeting on 11th October 2023. The EAG assume this is covered by reference 4 in the company submission (p.179). If so, please provide the data on file. If not, please clarify what extra information this relates to and provide the full report.

As part of the CS the Company included reference 4, which is the advisory board meeting report. A new version of this report (which removes an internal comment that was erroneously left in) has been included as part of the reference pack for this set of responses to clarification questions. As BeiGene data on file, the advisory report should be treated as CIC.

A6. Priority Question: CS, Section B.2a.6.2.7 (p.48). Please provide further information regarding the EORTC CLC-C30 and EQ-5D-5L collected as part of the MAGNOLIA trial, specifically:

a. **For both the EORTC CLC-C30 and EQ-5D-5L, please provide the completion rates at each time point.**

The completion and compliance rates for each time point for European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire. (EORTC QLQ-C30) and EuroQoL-Five Dimensions-Five Levels (EQ-5D-5L) are provided in Table 3 and Table 4, respectively. Additionally for completeness, the completion and compliance rates for EQ-5D-5L visual analogue scale (VAS) are presented in Table 5.

The Company would also like to identify an error made in the CS for the labelling of EORTC endpoint data which was labelled as EORTC CLC-C30. The data should in fact be labelled EORTC QLQ-C30.

Table 3: EORTC QLQ-C30 completion and compliance rate by assessment point in MAGNOLIA

Assessment point	Completion	Compliance
Cycle 1 day 1	[redacted]	[redacted]
Cycle 03	[redacted]	[redacted]
Cycle 06	[redacted]	[redacted]
Cycle 09	[redacted]	[redacted]
Cycle 12	[redacted]	[redacted]
Cycle 18	[redacted]	[redacted]
Cycle 24	[redacted]	[redacted]
Cycle 30	[redacted]	[redacted]
Safety follow-up	[redacted]	[redacted]

Abbreviations: EORTC QLQ-C30 – European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire.

Table 4: EQ-5D-5L completion and compliance rate by assessment point in MAGNOLIA

Assessment point	Completion	Compliance
Cycle 1 day 1	[redacted]	[redacted]
Cycle 03	[redacted]	[redacted]
Cycle 06	[redacted]	[redacted]
Cycle 09	[redacted]	[redacted]
Cycle 12	[redacted]	[redacted]
Cycle 18	[redacted]	[redacted]
Cycle 24	[redacted]	[redacted]
Cycle 30	[redacted]	[redacted]
Safety follow-up	[redacted]	[redacted]

Abbreviations: EQ-5D-5L – EuroQol 5 Dimensions 5 Levels.

Table 5: EQ-5D-5L VAS completion and compliance rate by assessment point in MAGNOLIA

Assessment point	Completion	Compliance
Cycle 1 day 1	[redacted]	[redacted]
Cycle 03	[redacted]	[redacted]
Cycle 06	[redacted]	[redacted]
Cycle 09	[redacted]	[redacted]
Cycle 12	[redacted]	[redacted]

Assessment point	Completion	Compliance
Cycle 18	[redacted]	[redacted]
Cycle 24	[redacted]	[redacted]
Cycle 30	[redacted]	[redacted]
Safety follow-up	[redacted]	[redacted]

Abbreviations: EQ-5D-5L – EuroQol 5 Dimensions 5 Levels; VAS – visual analogue scale.

b. Please provide details of any methods used to account for missing data (if applicable) and justify the use of these methods.

In general, missing data collected in the trial was not imputed at the data level. Given the high completion and completion rates over the trial follow-up for EORTC QLQ-C30 and EQ-5D-5L and VAS (see response to A6a for details), no management of missing data was required.

c. For both the EORTC CLC-C30 and EQ-5D-5L, please provide the mean dimension scores (and standard deviations) at each available time point (not mean change from baseline).

The EORTC QLQ-C30 mean dimension scores and standard deviations are reported in the Clinical Study Report (CSR), in Table 14.2.1.6. The EQ-5D-5L mean dimension scores and standard deviations are reported in the CSR, in Table 14.2.1.4. The CSR is provided again in the clarification response reference pack.

d. For the EQ-5D-5L, please provide the mean utility score (and standard deviation) at each available time point (not mean change from baseline).

The mean utility scores for EQ-5D-5L collected in MAGNOLIA are presented below in Table 6.

Table 6: EQ-5D-5L averages at each time point

Assessment point	Statistics	Overall
Cycle 1 Day 1	Number of observations	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	Q1, Q3	[redacted]
	Min, Max	[redacted]
Cycle 3 Day 28	Number of observations	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	Q1, Q3	[redacted]
	Min, Max	[redacted]
Cycle 6 Day 28	Number of observations	[redacted]

Assessment point	Statistics	Overall
	Mean (SD)	[redacted]
	Median	[redacted]
	Q1, Q3	[redacted]
	Min, Max	[redacted]
Cycle 9 Day 28	Number of observations	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	Q1, Q3	[redacted]
	Min, Max	[redacted]
Cycle 12 Day 28	Number of observations	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	Q1, Q3	[redacted]
	Min, Max	[redacted]
Cycle 18 Day 28	Number of observations	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	Q1, Q3	[redacted]
	Min, Max	[redacted]
Cycle 24 Day 28	Number of observations	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	Q1, Q3	[redacted]
	Min, Max	[redacted]
Cycle 30 Day 28	n	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	Q1, Q3	[redacted]
	Min, Max	[redacted]

Abbreviations: AE – adverse event; EQ-5D-5L – EuroQol 5 dimensions 5 levels; Max – maximum; Min – Minimum; NA – Not applicable; OR – overall response; Q – quarter; SD – standard deviation.

e. Please provide the mean EQ-5D-5L VAS score (and standard deviation) at each available time point (not mean change from baseline).

The EQ-5D-5L VAS score and standard deviations at each time point are reported in the CSR, in Table 14.2.1.5. The CSR is provided again in the clarification response reference pack.

Indirect treatment comparisons

A7. Priority Question: CS, Section B.2.8 (p.70). Please clarify whether both stages of the AU-003 trial were used within the MAIC.

Only data from the expansion phase of AU-003 (Part 2) were included in the submission and hence within the matching adjusted indirect comparisons (MAIC), following determination of the optimal dose of zanubrutinib, as detailed in Section B.2b.3.1 (p.52) of the CS.

A8. CS, Section B.2.8 (p.70). Where multiple IPD populations exist for the same treatment, NICE Decision Support Unit (DSU) Guidelines 18 caution against pooling the data and state that: “A better option in this scenario, in the absence of MAIC methodology which accounts for clustering, is to perform identical MAICs based on each IPD population, and then pool the relative effect estimates (on the linear predictor scale) with standard meta-analysis methods” (p.42).[2] Please further clarify why pooling the data from MAGNOLIA and AU-003 was considered appropriate and explain how clustering effects within the MAIC were accounted for.

The Company pooled data from MAGNOLIA and AU-003 due to the relatively small sample sizes in the trials (MAGNOLIA n=68 patients, AU-003 n=20 patients). This increased the patient numbers available for the analysis, to reduce the reliance on a small number of patient data and to increase the certainty in the results. The method of pooling of data was validated as appropriate by UK clinical experts in attendance at an advisory board (11th October 2023).[9]

Table 7 presents a comparison of the MAGNOLIA and AU-003 patient baseline characteristics. The comparison indicates that the characteristics were largely consistent between the trials, with only statistically significant differences observed in the presence of bone marrow involvement (yes/no) and extranodal disease (yes/no), with respective p-values of [redacted] and [redacted]. This result could be attributed to the small patient numbers in AU-003 and the high proportion of bone marrow: yes and extranodal: yes within this population. However, importantly, these attributes were not identified by the UK clinical experts at the advisory board as key prognostic factors or treatment effect modifiers.[9] Furthermore, clinical endpoint analyses for overall response rate (ORR) in MAGNOLIA (CS, B.2a.7 [Figure 8]) and AU-003 (CS, B.2b.7 [Figure 13]) demonstrates that these characteristics di0d not influence patient outcomes with the confidence intervals overlapping for these subgroups and the overall population. From this, it can be inferred that patient prognosis or treatment effect of zanubrutinib would not likely be confounded by these two characteristics and that differences in the baseline characteristics of the two trials do not make it inappropriate to pool the data.

It should also be noted that in the CS, a scenario analysis was conducted to match the HMRN basket to MAGNOLIA alone. This approach was considered infeasible for

AU-003 given the small sample size (N=20). The small sample size (N=20) in AU-003 also therefore prohibits the Company from conducting identical MAICs on each individual patient data (IPD) population and subsequently pooling outcomes through a meta-analysis. The results for the MAIC with MAGNOLIA alone are presented in the CS Appendix L (p.7-11). The scenario analyses demonstrated that the MAIC results remains consistent with the base-case analysis, with zanubrutinib demonstrating statistically significantly improvements in progression-free survival (PFS) and overall survival (OS) compared to the HMRN comparator basket.

Table 7: Patient characteristics comparison between MAGNOLIA and AU-003

Characteristic	MAGNOLIA		AU-003		p-value
	Number of patients	Number in category [n (%)]	Number of patients	Number in category [n (%)]	
ECOG 0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG 1					
ECOG 2					
Age <65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age ≥65 years					
Stage 1 or 2 cancer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage 3 or 4 cancer	[redacted]	[redacted]	[redacted]	[redacted]	
LDH low	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LDH high					
Bulky disease (node ≤5cm)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bulky disease (node >5cm)	[redacted]	[redacted]	[redacted]	[redacted]	
Bone marrow disease: no	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone marrow disease: yes	[redacted]	[redacted]	[redacted]	[redacted]	
Extranodal disease: no	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extranodal disease: yes	[redacted]	[redacted]	[redacted]	[redacted]	
B symptoms: no	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B symptoms: yes	[redacted]	[redacted]	[redacted]	[redacted]	
Cytopenia: no	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cytopenia: yes					
MALT subtype	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nodal subtype					
Splenic subtype					
Unknown subtype	[redacted]	[redacted]	[redacted]	[redacted]	
Time since last treatment ≤2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	MAGNOLIA		AU-003		p-value
	Number of patients	Number in category [n (%)]	Number of patients	Number in category [n (%)]	
Time since last treatment >2 years	[redacted]	[redacted]	[redacted]	[redacted]	
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female					
Response: refractory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response: relapse	[redacted]	[redacted]	[redacted]	[redacted]	
Number of prior LOT: 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior LOT: 2	[redacted]	[redacted]	[redacted]	[redacted]	
Number of prior LOT: >2	[redacted]	[redacted]	[redacted]	[redacted]	
Prior antiCD20 treatment: no	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior antiCD20 treatment: yes	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: ECOG – Eastern Cooperative Oncology Group; LDH – lactate dehydrogenase; LOT – line of therapy; MALT – extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue; SMZL – splenic marginal zone lymphoma; Tx – treatment.

A9. CS, Section B.2.9 (p.72-3). Please clarify whether the company asked the authors of the five clinical trials excluded from the MAIC analysis for additional data regarding MZL participants (e.g. baseline or outcome data).

The Company was acutely aware of ensuring timely treatment access for patients, and hence the authors of the identified trials were not asked for additional data regarding the MZL participants. It was deemed that it would have taken too long for the data from the authors to be received, assessed, analysed and populated into the CS, assuming they would be willing to share such information.

Importantly, the Company prioritised engagement with the HMRN registry as it was considered a more reliable data source (as validated by UK clinical experts, please refer to Section B.2.9.1.1 of the CS for further details) compared to the clinical trials identified, as it represents real-world treatment usage and outcomes for patients with R/R MZL in the UK.

A10. Priority Question: CS, Section B.2.9 (p.72-3). Clinical advice to the EAG has highlighted that it would be clinically appropriate to compare relapsed and refractory MZL participants. Further to this point, please conduct MAICs with both relapsed and refractory participants included from the identified clinical trials presented in CS, Table 38.

As per the CS (Table 38), the Company maintains that additional MAICs utilising trials identified as part of the clinical SLR are either not feasible or not appropriate for the following reasons.

- The trials reported insufficient data on outcomes and baseline characteristics for patients with MZL to facilitate a comparison with MAGNOLIA-003 (SELENE[12] Kahl, 2010[13] and MAGNIFY[14,15]). The two trial patient populations included a mix of patients (SELENE: follicular lymphoma [FL] and MZL; MAGNIFY: FL, MZL and small lymphocytic lymphoma [SLL]). Both trials did not report baseline characteristics nor efficacy outcomes specifically for MZL patients. Despite both FL and MZL being indolent forms of non-Hodgkin's lymphoma (NHL), these are distinct conditions which are managed differently with different outcomes and prognosis in UK clinical practice, as validated by UK clinical experts in an advisory board.[9]

- The AUGMENT and CHRONOS-3 trial populations insufficiently overlapped with population enrolled in MAGNOLIA and AU-003, specifically when considering that both trials enrolled patients with relapse disease only. As patients with relapsed disease are likely to have improved outcomes compared to patients with refractory disease given their disease is still yet to become refractory to immunotherapy treatment, any comparison conducted utilising data from AUGMENT or CHRONOS-3 would bias in favour of rituximab monotherapy.

Given the limitations with the studies identified in the SLR, the Company explored the use of real-world evidence (aligned with the NICE reference case).[16] The HMRN registry was identified as an appropriate data set to inform the comparator arm within the submission. The registry collects data from patients receiving treatment for R/R MZL in the UK, and hence is highly generalisable to the decision problem. Furthermore, UK clinical experts validated the use of the registry to inform the

effectiveness of the control arm within the submission.[9] Please refer to CS, Section B.2.9, for further discussion on the identification and the use of the HMRN registry data set.

In response to this question and question A13, the Company extracted data from the HMRN registry patients receiving immunotherapy alone (namely rituximab monotherapy). See response to question A13 for further details.

In a comparison to the data in the HMRN registry, the AUGMENT and CHRONOS-3 trials did not appear to adequately reflect UK clinical practice. Table 8 presents a comparison of the baseline characteristics from the two rituximab monotherapy trial arms with a subset of patients in the HMRN registry who had received rituximab monotherapy only (N=[redacted]). There was poor overlap in the AUGMENT and CHRONOS-3 trial patient populations with that of the HMRN registry (N=[redacted]).

AUGMENT

Patients in the AUGMENT trial were notably younger (59% aged 65 or older and median age of 66 years) than those in the subset of rituximab monotherapy HMRN patients (N =[redacted]) ([redacted]% aged 65 or older and median age of [redacted] years). This was in line with clinical opinion provided to the EAG (question A14) that rituximab monotherapy is often reserved for very elderly patients who cannot tolerate chemotherapy. Given patients in the AUGMENT trial were younger, they were more likely to have a better prognosis than patients in UK clinical practice. This is evident when comparing OS rates between the AUGMENT trial and the HMRN N=[redacted] dataset. Survival in AUGMENT was higher than in the HMRN dataset, further indicating that patients enrolled in AUGMENT are not reflective of UK clinical practice and hence are not generalisable to the decision problem.

Furthermore, only 81% of the patient population in the AUGMENT trial had received treatment with a prior anti-CD20 regimen. This is not aligned with the scope of this appraisal, nor the licensed indication for zanubrutinib.[17]

CHRONOS-03

As with the AUGMENT trial, the CHRONOS-3 population were younger (median age of 63 years) than those in the subset of rituximab-receiving HMRN patients (N = [redacted]) (median age of [redacted] years). Patients in the CHRONOS-03 trial had also received fewer prior systemic therapies (1: 66%; 2: 21% and ≥3: 14%) than the HMRN data set (2: [redacted]% and 3: [redacted]%). As such, the younger, earlier line patients in the CHRONOS-3 trial are more likely to have a better prognosis than those in UK clinical practice. However, all patients enrolled in CHRONOS-3 had received prior treatment with an anti-CD20 regimen, in line with the HMRN data set.

Based on the observable differences between the populations, the Company considers that CHRONOS-3 and AUGMENT do not adequately reflect the characteristics of patients receiving treatment for R/R MZL in UK clinical practice, meaning any MAIC using these two trials would be highly uncertain and not generalisable to the decision problem. Instead, the Company maintains that the HMRN registry basket (N=[redacted]) is the only appropriate data set to inform effectiveness of the comparator arm within the submission, as a source clinically validated with UK clinical experts.[9]

Table 8: Comparison of cohorts from the HMRN registry

Characteristic	HMRN cohort N=[redacted] 'Immunotherapy only' (rituximab monotherapy)	AUGMENT N=32 (rituximab monotherapy)	CHRONOS-3 N=29 (rituximab monotherapy)
Baseline characteristics			
Prior therapies (%)			
1	[redacted]	-	66
2	[redacted]	-	21
3+	[redacted]	16	14
Response to last systemic therapy (%)			
Refractory	[redacted]	3	0
Relapse	[redacted]	97	100
POD24	[redacted]	-	-
Age			
Age ≥ 65 years (%)	[redacted]	59	-
Median age (years)	[redacted]	66	63
Mean age (years)	[redacted]	-	-
Prior therapy			
Prior anti-CD20-based therapy (%)	[redacted]	81	100
Time since diagnosis – mean (months)	[redacted]	-	-

Time since diagnosis – median (months)	[redacted]	-	72
Time since last therapy (months)	[redacted]	-	31
Time since last therapy - ≤2 years	[redacted]	44	-

Abbreviations: HMRN – The Haematological Malignancy Research Network.
Source: HMRN registry report addendum January 2024[18]; AUGMENT[19] CHRONOS-3[20]

However, to alleviate concerns by the EAG or the NICE Committee, the Company have conducted an exploratory MAIC analysis of MAGNOLIA-003 versus CHRONOS-3. CHRONOS-3 was deemed more suitable than AUGMENT because 100% of patients had received treatment with a prior anti-CD20 regimen and hence aligned with the licensed indication for zanubrutinib.[17]

The MAIC methodology is aligned with the methods presented in the CS submission, Section B2.9, and Appendix L. Table 9 compares the study design and eligibility criteria of CHRONOS-3, MAGNOLIA and AU-003. The unadjusted population characteristics of the zanubrutinib populations in MAGNOLIA and AU-003 and the rituximab monotherapy arm of CHRONOS-3 are presented in Table 10. The patient characteristics were well balanced between MAGNOLIA, AU-003 and CHRONOS-3 though 97% patients in CHRONOS-3 receiving rituximab had relapsed disease and the median age was 7 years younger than the zanubrutinib trials, which will likely lead to results that favour rituximab monotherapy.

Table 9: Comparison of key trial characteristics of MAIC using CHRONOS-3

	AU-003	MAGNOLIA	CHRONOS-3
Study design			
Patient population	R/R MZL (splenic, nodal or extranodal)	R/R MZL (splenic, nodal or extranodal)	R/R MZL (splenic, nodal or extranodal)
Phase	I/II	II	III
Study design	Single arm, open-label	Single arm, open-label	RCT, double-blind
Median follow-up	35.2 months	28.0 months	18.0 months
Definition of relapse	NR	Documented failure to achieve at least partial response or documented PD after, the most recent systemic treatment	Recurrence after CR or presented progression after PR from last rituximab, rituximab-containing, or anti-CD20-based therapy
Definition of refractory	Best overall response of SD or PD from last prior anticancer treatment regimen	Best response of SD or PD to their last prior anticancer treatment regimen	NR
Outcome definition			

	AU-003	MAGNOLIA	CHRONOS-3
Outcomes of interest	PFS, OS	PFS, OS	PFS, OS
Eligibility criteria			
Age	≥18 years	≥18 years	≥18 years
Adequate organ function	Adequate baseline laboratory values	Adequate baseline laboratory values	Adequate baseline laboratory values
ECOG PS	0-2	0-2	0-2
CNS involvement	Not eligible	Not eligible	Not eligible
Prior therapy	≥1 prior line of therapy No previous exposure to a BTK inhibitor	≥1 prior line of therapy, including at least one prior anti-CD20-based regimen No previous exposure to a BTK inhibitor	Relapsed following prior rituximab- or anti-CD20-based regimen

BTK – Bruton's tyrosine kinase; CD20 – Anti-cluster of differentiation 20; CR – Complete response; ECOG PS – Eastern Cooperative Oncology Group Performance Status; MZL – Marginal zone lymphoma; NR – Not reported OS – Overall survival; PD – Progressed disease; PFS – Progression-free survival; PR – Partial response; R/R – Relapsed or refractory; RCT – Randomised control trial; SD – Stable disease.
Source: MAGNOLIA CSR[19], AU-003 CSR[21], Özcan 2021[20]

Table 10: Comparison of unadjusted baseline patient and disease characteristics of MAIC using CHRONOS-3

Characteristic	MAGNOLIA Zanubrutinib (N=68)	AU-003 Zanubrutinib (N=20)	CHRONOS-3 Rituximab (N=29)
Age			
Median (range)	[redacted]	[redacted]	63 (46-76)
MZL subtype, n (%)			
Extranodal	[redacted]	[redacted]	11 (38)
Nodal	[redacted]	[redacted]	12 (41)
Splenic	[redacted]	[redacted]	6 (21)
Unknown	[redacted]	[redacted]	0
Time since last treatment			
Median, months (range)	[redacted]	[redacted]	31 (4-161)
Time since initial diagnosis			
Median, moths (range)	[redacted]	[redacted]	72 (13-237)
Sex, n (%)			
Male	[redacted]	[redacted]	12 (41)
Female	[redacted]	[redacted]	17 (59)
Response to last systemic therapy, n (%)			
Refractory	[redacted]	[redacted]	0 (0)
Relapsed	[redacted]	[redacted]	29 (100)
Prior therapies			
Median (range)	[redacted]	[redacted]	1
1	[redacted]	[redacted]	19 (66)
2	[redacted]	[redacted]	6 (21)
3+	[redacted]	[redacted]	4 (14)
Prior anti-CD20 therapy, n (%)	[redacted]	[redacted]	29 (100)

CD20 – Anti-cluster of differentiation 20; ECOG PS – Eastern Cooperative Oncology Group Performance Status; MZL – Marginal zone lymphoma.
Source: MAGNOLIA CSR[19], AU-003 CSR[21], Özcan 2021[20]

Covariate selection for matching variables was limited by reporting in the CHRONOS-3 trial. The model matched on the following covariates:

- number of prior lines of therapy (1 vs 2 vs >2)
- MZL subtype (extranodal vs nodal vs splenic)
- response to last prior systemic therapy (relapse – yes vs no)
- age

The covariates were consistent with those included in the MAICs versus the HMRN datasets, except for the exclusion of POD24 status as it was not available from the CHRONOS-3 trial and the inclusion of MZL subtype, which was not available from the HMRN registry.

The summary of the population characteristics of the pooled zanubrutinib population (both unweighted and weighted) from MAGNOLIA and AU-003 and rituximab monotherapy from CHRONOS-3 are presented in Table 11. After matching, all matched baseline characteristics were balanced (i.e. statistically equivalent) between the trials.

Table 11: Summary of the population characteristics before and after matching using CHRONOS-3

Characteristics	Pooled zanubrutinib population, unweighted	Pooled zanubrutinib population, weighted	Rituximab monotherapy
	N = 86	ESS = [redacted]	N = 29
2 prior treatment lines (%)	[redacted]	[redacted]	20.7
≥3 prior treatment lines (%)	[redacted]	[redacted]	13.8
MZL subtype: Nodal (%)	[redacted]	[redacted]	41.4
MZL subtype: Splenic (%)	[redacted]	[redacted]	20.7
Relapse to last therapy, relapse (%)	[redacted]	[redacted]	100
Median age, years	[redacted]	[redacted]	63

ESS – Effective sample size; MZL – Marginal zone lymphoma.
Source: MAGNOLIA CSR[19], AU-003 CSR[21], Özcan 2021[20]

The MAIC results for PFS and OS both before and after matching are summarised in Table 12. For PFS, the point estimates for before and after matching are very similar. Before and after matching. a statistically significant difference was observed between zanubrutinib and rituximab monotherapy (HR: [redacted]; 95% CI, [redacted], [redacted]). For OS, the point estimates before and after matching are also very similar. Before and after matching, a numerical improvement for OS was observed, however the results were not statistically significant (HR: [redacted]; 95% CI, [redacted], [redacted]).

Table 12: Summary of MAIC results for MAIC using CHRONOS-3

	PFS		OS	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Pre-matching	[redacted]	[redacted]	[redacted]	[redacted]
Model	[redacted]	[redacted]	[redacted]	[redacted]

CI – confidence interval; OS – overall survival; PFS – progression-free survival.

The KM curves of PFS for rituximab monotherapy and zanubrutinib (both pre- and post- adjustment) are presented in Figure 1 and the KM curves for OS are presented in Figure 2. The KM for OS displayed a drop-off in survival for patients treated with rituximab monotherapy, suggesting that a statistically significant improvement in OS could be observed with longer data follow-up in the zanubrutinib trials. Despite the low effective sample size (ESS) after matching, the consistency between the adjusted and unadjusted curve helps to address uncertainty in the analysis. However, the Company considers this MAIC exploratory only and advised that the results are interpreted with caution, given the small sample sizes across both arms, the enrolment of relapsed patients only in CHRONOS-3 and the differences between CHRONOS-3 and patients receiving rituximab monotherapy in UK clinical practice. As such the Company maintains that the base-case approach of assessing rituximab monotherapy with the standard of care basket via the HMRN N=[redacted] cohort is the most appropriate approach.

Figure 1: Kaplan-Meier curves of PFS for MAIC using CHRONOS-3

HR – Hazard ratio; MAIC – Matching-adjusted indirect comparisons; OS – overall survival; PFS – progression-free survival.

Figure 2: Kaplan-Meier curves of OS for MAIC using CHRONOS-3

HR – Hazard ratio; MAIC – Matching-adjusted indirect comparisons; OS – overall survival.

A11. Priority Question: CS, Section B.2.9 (p.72). The EAG note that a full paper of the SELENE trial (NCT01974440) has recently been published.[3] Please:

- **Comment on the suitability of a comparison between MAGNOLIA-003 and the SELENE trial within a MAIC.**
- **Provide methods and results from a MAIC between MAGNOLIA-003 and the SELENE trial, if deemed sufficiently similar.**

At the time of initial submission, only the abstract for the SELENE trial was available, which had insufficient details for an MAIC. On evaluation of the full publication, SELENE is still not suitable for a MAIC against MAGNOLIA-003 as there are neither Kaplan Meier plots reported for PFS or OS, nor baseline characteristics for MZL patients only, as mentioned in Clarification Question A10.[12]

A12. CS, Section B.2.9.1.1, Table 40 (p.78-9). The CS describes criteria applied to the HMRN registry to extract a cohort reflective of the patient population in MAGNOLIA-003. Only subjects enrolled in the registry from 2014 to 2020 were used to capture any changes in clinical practice and subsequent outcome improvements. Please clarify whether the company intends on using later data cuts from the registry (i.e. after 2020).

The median time for MZL patients to receive second-line therapy within the registry is [redacted] years, and hence there was time lag between diagnosis and analysis in order to capture patients receiving treatment for R/R disease. To reflect this time lag, a cut-off of 2020 for the date of diagnosis was selected by the registry, and hence patients included in the cohort were diagnosed on or before 2020. All patients within the cohort were followed up to 2022 to ensure that outcomes associated with their treatment for R/R disease were captured. The registry confirmed that they have not processed patients diagnosed from 2021 onwards yet, however it is expected that these patients will not have reached second-line therapy yet.

Please note in CS, Section B.2.9, the year 2020 was referred to be the Company as date of enrolment which was incorrect. The year 2020 reflects the cutoff date for date of diagnosis for inclusion in the registry cohort.

A13. Priority Question: CS, Section B.2.9.1.1, Table 41 (p.80-1). Clinical advice to the EAG has highlighted that it would not be clinically appropriate to combine immunotherapy regimens with chemotherapy and chemoimmunotherapy regimens. Please provide separate MAIC results for:

- **zanubrutinib versus immunotherapy regimens; and**
- **zanubrutinib versus chemotherapy and chemoimmunotherapy regimens.**

The Company considers the cohorts extracted from the HMRN registry as part of the CS, which have been used to inform the relative effectiveness of zanubrutinib versus relevant comparator treatments ('rituximab +/- chemotherapy, chemotherapy alone'), to be reflective of the standard of care patients are receiving for the treatment of R/R MZL in the UK. The treatments included align with those highlighted in the EMSO 2020 and BSH 2023 guidelines for the management of patients with R/R MZL (see response to A3 for further details). Furthermore, UK clinical experts in attendance at an advisory board (11th October 2023) validated the composition of the basket as reflective of UK standard of care.[9] Please refer to Section B.2.9.1.1 of the CS for further details.

However, in response to this question from the EAG, in collaboration with the HMRN registry, the Company extracted data on the following cohorts, as per the original selection criteria presented in the CS (Section B.2.9.1.1, Table 40):

- Patients receiving immunotherapy regimens only (N=[redacted])
- Patients receiving chemotherapy or chemoimmunotherapy (N=[redacted])

Table 13 presents data on the treatment regimens, baseline characteristics and outcomes for the above noted cohorts, plus the original HMRN N=[redacted] (rituximab +-/ chemotherapy, chemotherapy alone) and HMRN N=[redacted] (rituximab +/- chemotherapy) cohorts, which was included as a scenario analysis in the CS.

The data shows that the HMRN 'chemotherapy and chemoimmunotherapy' N=[redacted] cohort is well aligned to the HMRN N=[redacted] and N=[redacted] cohorts (included in the CS). Outcomes are slightly poorer for receiving 'chemotherapy and

chemoimmunotherapy'; however, across all three cohorts there is a less than 10% difference in the PFS and OS rates at 1, 3 and 5 years.

Given that the outcomes were poorer in the HMRN N=[redacted] cohort, the existing MAICs conducted by the Company (versus the HMRN N=[redacted] and HMRN =[redacted]) can be considered more conservative analyses when estimating the relative treatment effect of zanubrutinib versus standard of care in the UK. As such, the Company have not revised the existing MAICs to consider the HMRN N=[redacted] cohort. It is likely that an updated MAIC would improve the relative effectiveness of zanubrutinib, and hence improve the cost-effectiveness of zanubrutinib.

For the cohort of patients who received immunotherapy alone (N=[redacted], namely rituximab monotherapy), patients appear to be older (mean age of [redacted] years versus [redacted] years) and more heavily pre-treated ([redacted]% have received 2 prior treatment lines versus [redacted]%) compared to patients who did not receive immunotherapy alone. In addition, a smaller proportion of patients were refractory to their last therapy ([redacted]% versus [redacted]%). This indicates that despite an older and more heavily pre-treated cohort, patients are continuing to respond to treatment, with a higher ORR compared to patients not receiving immunotherapy only ([redacted]% versus [redacted]%).[18] Improved outcomes following treatment with immunotherapy is also seen on PFS and OS, with higher survival rates at years 1, 3 and 5 compared to patients not receiving immunotherapy only. However, at year 6 the outcomes become more comparable across the cohorts with ~30% OS rate for the N=[redacted], N=[redacted] and N=[redacted] cohort. This indicates that despite strong initial outcomes after treatment with immunotherapy alone, the outcomes are not durable. The Company acknowledges that there are differences in outcomes observed for patients receiving immunotherapy alone, but due to the extremely small sample size, it was not feasible to conduct an MAIC. However, the Company have ran an exploratory MAIC analysis versus rituximab monotherapy (using data from the CHRONOS-3 trial) to alleviate concerns by the EAG. Please refer to response A10 for further details.

Table 13: Comparison of cohorts from the HMRN registry

Characteristic	HMRN cohort N=[redacted] 'Immunotherapy only'	HMRN cohort N=[redacted] 'chemotherapy and	HMRN cohort N=[redacted] (as per CS) 'rituximab+/chemotherapy,	HMRN cohort N=[redacted] (as per CS) 'rituximab+/-chemotherapy'

		chemoimmunotherapy'	chemotherapy alone'	
Treatment regimens in basket (%)				
Bendamustine plus rituximab	-	[redacted]	[redacted]	[redacted]
Rituximab monotherapy	[redacted]	-	[redacted]	[redacted]
R-CVP	-	[redacted]	[redacted]	[redacted]
Chlorambucil	-	[redacted]	[redacted]	-
Cyclophosphamide/rituximab +/- steroid	-	[redacted]	[redacted]	[redacted]
R-CHOP	-	[redacted]	[redacted]	[redacted]
FCR	-	[redacted]	[redacted]	[redacted]
Other rituximab	-	[redacted][1]	[redacted][3]	[redacted][5]
Other non-rituximab	-	[redacted][2]	[redacted][4]	-
Baseline characteristics				
Prior therapies (%)				
2	[redacted]	[redacted]	[redacted]	[redacted]
3+	[redacted]	[redacted]	[redacted]	[redacted]
Response to last systemic therapy (%)				
Refractory	[redacted]	[redacted]	[redacted]	[redacted]
POD24	[redacted]	[redacted]	[redacted]	[redacted]
Age				
Age ≥ 65 years	[redacted]	[redacted]	[redacted]	[redacted]
Mean age (years)	[redacted]	[redacted]	[redacted]	[redacted]
Prior therapy				
Prior anti-CD20-based therapy (%)	[redacted]	[redacted]	[redacted]	[redacted]
Time since diagnosis – mean (months)	[redacted]	[redacted]	[redacted]	[redacted]
Time since diagnosis – median (months)	[redacted]	[redacted]	[redacted]	[redacted]
Time since last therapy (months)	[redacted]	[redacted]	[redacted]	[redacted]
Outcomes				
PFS, % at 1 year	[redacted]	[redacted]	[redacted]	[redacted]
PFS, % at 3 years	[redacted]	[redacted]	[redacted]	[redacted]
PFS, % at 5 years	[redacted]	[redacted]	[redacted]	[redacted]
PFS, % at 6 years	[redacted]	[redacted]	[redacted]	[redacted]
OS, % at 1 year	[redacted]	[redacted]	[redacted]	[redacted]
OS, % at 3 years	[redacted]	[redacted]	[redacted]	[redacted]
OS, % at 5 years	[redacted]	[redacted]	[redacted]	[redacted]
OS, % at 6 years	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FCR – Fludarabine, cyclophosphamide and rituximab; HMRN – The Haematological Malignancy Research Network; IVE – Ifosfamide-etoposide-epirubicin; PFS – Progression-free survival; POD24 – Progression of disease within 2 years; OS – Overall survival; R-CHOP – Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP – Rituximab, cyclophosphamide, vincristine, and prednisone; VCD – Velcade, Cyclophosphamide, and Dexamethasone.

1. Chlorambucil / Rituximab (n=[redacted]), Gemcitabine / Dexamethasone / Cisplatin / Rituximab (n=[redacted]), IVE / Rituximab (n=[redacted]). 2. CVP (n=[redacted]), Bendamustine (n=[redacted]), Bendamustine / Methylprednisolone (n=[redacted]), Cyclophosphamide / Prednisolone (n=[redacted]), Fludarabine (n=[redacted]), VCD (n=[redacted]). **3.** Chlorambucil / Rituximab (n=[redacted]), Gemcitabine / Dexamethasone / Cisplatin / Rituximab (n=[redacted]), IVE / Rituximab (n=[redacted]), Venetoclax /

Rituximab (n=[redacted]). **4.** Other-non-rituximab: CVP (n=[redacted]), Bendamustine (n=[redacted]), Bendamustine / Methylprednisolone (n=[redacted]), Cyclophosphamide / Prednisolone (n=[redacted]), Fludarabine (n=[redacted]), VCD (n=[redacted]), Velcade / Dexamethasone (n=[redacted]). **5.** Chlorambucil / Rituximab (n=[redacted]), Gemcitabine / Dexamethasone / Cisplatin / Rituximab (n=[redacted]), IVE / Rituximab (n=[redacted]), Venetoclax / Rituximab (n=[redacted]). * Kaplan Meier analysis has not been conducted beyond a 5-year timepoint for the HMRN cohort N=[redacted] 'chemotherapy and chemoimmunotherapy'. Source: HMRN registry report November 2023[10], HMRN registry report addendum January 2024[18]

A14. Priority Question: CS, Section B.2.9.1.1, Table 41 (p.80-1). Clinical advice to the EAG has also highlighted that the following regimens would not be used in NHS clinical practice for R/R MZL:

- **Rituximab monotherapy (first line or only used for very elderly patients who cannot tolerate chemotherapy)**
- **Chlorambucil**
- **FCR**
- **Gemcitabine / dexamethasone / cisplatin / rituximab (only used in high-grade relapse where MZL is accompanied by another condition)**
- **IVE / rituximab**
- **Venetoclax / rituximab (venetoclax not available for this indication via the NHS)**
- **CVP (normally given with rituximab)**
- **Bendamustine (normally given with rituximab)**
- **Bendamustine / methylprednisolone (normally given with rituximab)**
- **Cyclophosphamide / prednisolone (normally given with rituximab)**
- **Fludarabine**
- **VCD**
- **Velcade / dexamethasone**

Please update the MAIC analyses to remove these regimens and include only those regimens common in NHS practice for R/R MZL.

As noted in response to question A14, the Company considers the cohorts extracted from the HMRN registry as part of the CS, which have been used to inform the relative effectiveness of zanubrutinib versus relevant comparator treatments ('rituximab +/- chemotherapy, chemotherapy alone'), to be reflective of the standard of care patients are receiving for the treatment of R/R MZL in the UK. Importantly, the HMRN registry collects data from patients in UK NHS clinical practice and hence is reflective of commonly used regimens in the UK. Please refer to Section B.2.9.1.1

of the CS for further discussion on the suitability of the HMRN registry. Furthermore, the Company validated the composition of the HMRN registry basket with two leading UK clinicians:

- Renata Walewska, Consultant Haematologist and lead author of the 2023 BSH guidelines.[7]
- Harriet Walter, Consultant Medical Oncologist and co-author of the 2023 BSH guidelines.[7]

However, in response to this question from the EAG, in collaboration with the HMRN registry, the Company have restricted HMRN N=[redacted] basket to remove the regimens listed by the EAG in question A14, as per the original selection criteria presented in the CS (Section B.2.9.1.1, Table 40).

Table 14 presents data on the treatment regimens, baseline characteristics and outcomes for the above noted cohort, plus the original HMRN N=[redacted] (rituximab +-/ chemotherapy, chemotherapy alone) and HMRN N=[redacted] (rituximab +/- chemotherapy) cohorts, which was included a scenario analysis in the CS.

The data shows that the HMRN 'restricted regimen' N=[redacted] cohort is in general well aligned to the HMRN N=[redacted] and N=[redacted] cohorts (included in the CS). However, longer-term outcomes are poorer for the restricted cohort, with 5-year PFS and OS rates notably lower than the HMRN N=[redacted] and HMRN N=[redacted] cohorts.

Given that the longer-term outcomes were poorer in the HMRN N=[redacted] cohort, the existing MAICs conducted by the Company (versus the HMRN N=[redacted] and HMRN =[redacted]) can be considered more conservative analyses when estimating the relative treatment effect of zanubrutinib versus standard of care in the UK. As such, the Company have not revised the existing MAICs to consider the HMRN N=[redacted] cohort. It is likely that an updated MAIC would improve the relative effectiveness of zanubrutinib, and hence improve the cost-effectiveness of zanubrutinib.

Table 14: Comparison of cohorts from the HMRN registry

Characteristic	HMRN cohort N=[redacted] 'regimen restricted basket'	HMRN cohort N=[redacted] (as per CS) 'rituximab+/chemotherapy, chemotherapy alone'	HMRN cohort N=[redacted] (as per CS) 'rituximab+/- chemotherapy'
Treatment regimens (%)			
Bendamustine plus rituximab	[redacted]	[redacted]	[redacted]
Rituximab monotherapy	-	[redacted]	[redacted]
R-CVP	[redacted]	[redacted]	[redacted]
Chlorambucil	-	[redacted]	[redacted]
Cyclophosphamide/rituximab +/- steroid	[redacted]	[redacted]	[redacted]
R-CHOP	[redacted]	[redacted]	[redacted]
FCR	[redacted]	[redacted]	[redacted]
Other rituximab	[redacted][1]	[redacted][2]	[redacted][4]
Other non-rituximab	-	[redacted][3]	[redacted]
Baseline characteristics			
Prior therapies (%)			
2	[redacted]	[redacted]	[redacted]
3+	[redacted]	[redacted]	[redacted]
Response to last systemic therapy (%)			
Refractory	[redacted]	[redacted]	[redacted]
POD24	[redacted]	[redacted]	[redacted]
Age			
Age ≥ 65 years	[redacted]	[redacted]	[redacted]
Mean age (years)	[redacted]	[redacted]	[redacted]
Prior therapy			
Prior anti-CD20-based therapy (%)	[redacted]	[redacted]	[redacted]
Time since diagnosis – mean (months)	[redacted]	[redacted]	[redacted]
Time since diagnosis – median (months)	[redacted]	[redacted]	[redacted]
Time since last therapy (months)	[redacted]	[redacted]	[redacted]
Outcomes			
PFS, % at 1 year	[redacted]	[redacted]	[redacted]
PFS, % at 3 years	[redacted]	[redacted]	[redacted]
PFS, % at 5 years	[redacted]	[redacted]	[redacted]
OS, % at 1 year	[redacted]	[redacted]	[redacted]
OS, % at 3 years	[redacted]	[redacted]	[redacted]
OS, % at 5 years	[redacted]	[redacted]	[redacted]

Abbreviations: FCR – Fludarabine, cyclophosphamide and rituximab; HMRN – The Haematological Malignancy Research Network; IVE – Ifosfamide-etoposide-epirubicin; PFS – Progression-free survival; POD24 – Progression of disease within 2 years; OS – Overall survival; R-CHOP – Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP – Rituximab, cyclophosphamide, vincristine, and prednisone; VCD – Velcade, Cyclophosphamide, and Dexamethasone.

1. Chlorambucil / Rituximab (n=[redacted]). **2.** Chlorambucil / Rituximab (n=[redacted]), Gemcitabine / Dexamethasone / Cisplatin / Rituximab (n=[redacted]), IVE / Rituximab (n=[redacted]), Venetoclax / Rituximab (n=[redacted]). **3.** Other-non-rituximab: CVP (n=[redacted]), Bendamustine (n=[redacted]), Bendamustine / Methylprednisolone (n=[redacted]), Cyclophosphamide / Prednisolone (n=[redacted]), Fludarabine (n=[redacted]), VCD (n=[redacted]), Velcade / Dexamethasone (n=[redacted]). **4.** Chlorambucil / Rituximab (n=[redacted]), Gemcitabine / Dexamethasone / Cisplatin / Rituximab (n=[redacted]), IVE / Rituximab (n=[redacted]), Venetoclax / Rituximab (n=[redacted]).

Source: HMRN registry report November 2023[10], HMRN registry report addendum January 2024[18]

A15. CS, Section B.2.9.1.2, Table 44 (p.86-7); Appendix L2.3 (p.11). Please confirm which chemotherapy regimens were excluded from the HMRN basket of treatments within this sensitivity analysis.

Within this sensitivity analysis, all chemotherapy regimens that did not include rituximab were excluded from the HMRN basket, to reduce the basket size to n=[redacted]. These were the following:

- Chlorambucil
- Bendamustine
- Cyclophosphamide, Vincristine, Prednisolone (CVP)
- Fludarabine
- Bendamustine / Methylprednisolone
- Cyclophosphamide / Prednisolone
- Methotrexate
- Bortezomib, Cyclophosphamide and Dexamethasone (VCD)
- Bortezomib / Dexamethasone

Section B: Clarification on cost-effectiveness data

Model Structure

B1. Priority Question: CS, Section 3.2.2 (p.109). Partitioned Survival Models (PSMs) are frequently used in diseases which have short PFS and OS. In the company model, a significant proportion of the patients are predicted to remain in the PFS health state for a long period of time. NICE Decision Support Unit (DSU) technical support document (TSD) 19 recommends the use of a State Transition Model (STM) alongside a PSM to verify the plausibility of the PSM extrapolations. Please further comment on the limitations of a PSM in this

context and further justify the use of a PSM rather than a STM, in particular in relation to:

a. **The assumption of structural independence between the PFS and OS endpoints.**
b. **The fact that PFS and OS are secondary endpoints in the MAGNOLIA and AU-003 trials.**

The Company considered both the partitioned survival model (PSM) and state transition model (STM) structure during the model conceptualisation phase. Based on the reasoning presented in Document B, Section B.3.2, the PSM was selected as the most appropriate structure and therefore was used for the cost-effectiveness model.

The PSM approach is widely used, accepted, and understood by health economists and clinicians. The PSM approach is consistent with the approaches adopted and accepted by the National Institute For Health and Care Excellence (NICE) committee, in previous lymphoma and zanubrutinib NICE health technology assessment submissions (TA627, TA649, TA833 and TA933).[22–25] 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 Technical Support Document (TSD) 19.[26,27]

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 an STM to conduct the cost-effectiveness analysis would have its own limitations, such as the reliance on post-hoc analysis of post-progression survival (PPS) and time-to-pre-progression death (TTDeath), and the long-term extrapolation of such endpoints based on limited events, Therefore, it may not be able to alleviate the uncertainty associated with a PSM. The NICE DSU Technical Support Document 19 discusses the limitations of the STM, and a comparison of the two model structures has been discussed in detail in a recent NICE appraisal for zanubrutinib (TA833).[23,26]

Structural independence between PFS and OS

PSMs operate with the assumption that PFS and OS are structurally independent, which is a widely acknowledged limitation of the modelling approach. This is because PFS and OS are fundamentally dependent on each other as they include the same events (pre-progression deaths), progression is often prognostic for mortality, and they are structurally dependent (e.g. death cannot be followed by progression). Assuming independence of PFS and OS means that extrapolations ignore potential dependency between endpoints and create uncertainty. However, NICE TSD 19 accepts that for the within trial period these dependencies will be reflected in the data and results will be closely reflected in the PSM results.[26] Furthermore, the Company accounted for dependency within the extrapolated period by restricting the PFS hazard rate by the OS hazard rate such that the risk of progression was never greater than the risk of death.

The HMRN data used is mature with median PFS and OS being reached for both endpoints. This means that extrapolations will account for less than half of the patients and therefore the structural independence of PFS and OS is less relevant.

For zanubrutinib, the structural independency assumption may be more impactful for extrapolations as data is less mature than for the HMRN basket. However, as MAGNOLIA and AU-003 data is less mature, it is likely to overestimate the hazard of death for zanubrutinib and will therefore lead to more conservative estimates of OS. As described in NICE TSD 19,[26] this is because extrapolation of the hazard of death is based on the observed within trial hazard of death, which is likely increasing as patients progress and prognostically become more at risk.

To further limit the impact of independence between OS and PFS, and in line with NICE TSD 19, the Company validated all extrapolations with UK clinical experts at an advisory board (11th October 2023).[9] Additionally, the Company performed a range of scenario analyses (including modelling the most pessimistic curves for zanubrutinib PFS and OS) to reflect alternative datasets and survival curve choices. These sensitivity analyses demonstrated that, regardless of which curves were chosen for the extrapolations, zanubrutinib remained cost-effective at the £30,000 threshold (CS, B.3.11.3 [Table 86]).

Use of secondary outcomes

The endpoints of PFS and OS are widely used and accepted by clinicians and health economists in the modelling of clinical outcomes for health technology assessments. Previous submissions in oncology, lymphoma and for zanubrutinib have consistently used these two endpoints in their respective submissions (TA627, TA649, TA833 and TA931).[22–25]

The fact that PFS and OS are secondary endpoints in the MAGNOLIA and AU-003 trials is irrelevant, as they are the most clinically meaningful endpoints for use in the Company's cost-effectiveness model. Recent and relevant NICE appraisals for zanubrutinib, TA833 and TA931, had included both PFS and OS despite them being secondary endpoints in their respective trials (ASPEN and ALPINE).[23,25] Additionally, TA894 (relapsed or refractory low-grade non-Hodgkin lymphoma), TA677 (relapsed or refractory mantle cell lymphoma) and TA883 (relapsed or refractory diffuse large B-cell lymphoma) all informed their PSM models with PFS and OS from clinical trials, where they were secondary endpoints.[28–30] Whilst the EAG questioned the use of secondary endpoints in TA833, the NICE committee ultimately accepted the use of such secondary endpoints and the PSM approach as suitable for decision making. Furthermore, PFS and OS are essential to the functioning of the PSM model as without these outcomes there is no difference in treatment effectiveness beyond AE.

B2. Priority Question: CS, Section B.3.3 (p.114). Please provide updated economic results (and accompanying model/s) considering the additional MAIC analysis requested as part of questions A11, A13 and A14.

The economic model has been updated to include an exploratory comparison versus rituximab monotherapy using CHRONOS-3 trial data, as documented in response to question A10. The existing HMRN MAICs have not been revised as requested in questions A13 and A14, hence no further model updates have been made. Please refer to responses to questions A13 and A14 for justification.

The assumptions, inputs and data sources for the exploratory cost-effectiveness analysis versus rituximab monotherapy are as per the methods in the CS, Section B3, with the exception of the inputs noted in Table 15. The settings applied for the

exploratory cost-effectiveness analysis versus rituximab monotherapy are as per the methods in the CS, Section B3, with the exception of the settings noted in Table 16.

Table 15: Data input sources for exploratory cost-effectiveness analysis versus rituximab monotherapy

Data input	Source	Data file/reference details
MAGNOLIA-003 survival extrapolations for PFS, OS and TTD	Weighted MAGNOLIA-003 to CHRONOS-3 population, as per MAIC presented in A10	Please refer to file "*MAGNOLIA-003 weighted to CHRONOS-3 survival extrapolations*" within Company reference pack for survival analysis outputs
Rituximab monotherapy survival extrapolations for PFS, OS and TTD	CHRONOS-3 population, as per MAIC presented in A10. TTD is assumed equal to PFS given lack of TTD available from literature	Please refer to file "*CHRONOS-3 survival extrapolations.zip*" within Company reference pack for survival analysis outputs

Abbreviations: MAIC – matching adjusted indirect comparison; OS – Overall survival; PFS – Progression-free survival; TTD – Time to treatment discontinuation

Table 16: Settings for exploratory cost-effectiveness analysis versus rituximab monotherapy

Parameter	Setting	Justification
Baseline characteristics	Mean age: [redacted] years Proportion female: [redacted]% BSA: [redacted] m^2	Weighted baseline characteristics as per MAIC presented in question A10
Time horizon	[redacted] years	100 years – baseline age
Comparator arm treatment costs	100% rituximab monotherapy	To reflect efficacy source for comparator
PFS distribution choice	Log-normal for both treatment arms	• Based on clinical expert opinion and the responses presented to question B3b the hazard rate for PFS is expected to have a turning point, hence AFT models are appropriate. • Log-normal is of good statistical fit (2nd best fitting score for both treatment arms within < 1 AIC score of best fitting model). • Visually good fit to the observed data for both arms.
OS curves	Log-normal for both treatment arms	• Based on clinical expert opinion and the responses presented to question B3b the hazard rate for OS is expected to have a turning point, hence AFT models are appropriate. • Log-normal is of good statistical fit (best fit for CHRONOS and 2nd best fit for zanubrutinib within < 1

Parameter	Setting	Justification
		AIC score of best fitting curve) • Visually good fit to the observed data for both arms.
TTD curves	Log-normal for zanubrutinib Assumed equal to PFS for rituximab monotherapy	• Aligned with curve for PFS for zanubrutinib • In absence of published TTD data, TTD is set equal to PFS for rituximab monotherapy. Patients only receive the cost of one regimen of rituximab monotherapy.
Subsequent treatment basket	Exclude rituximab monotherapy retreatment for rituximab monotherapy arm	Aligns anticipated UK treatment pathway.
Safety profile	Model only AEs from rituximab monotherapy only for comparator arm.	Reflective of comparator arm safety profile.

Abbreviations: AE – Adverse event; MAIC – matching adjusted indirect comparison; OS – Overall survival; PFS – Progression-free survival; TTD – Time to treatment discontinuation; UK – United Kingdom

In this exploratory scenario analysis, when compared to rituximab monotherapy, zanubrutinib is associated with [redacted] incremental QALYs and [redacted] incremental costs, with an ICER of £25,906 (Table 17). Therefore, zanubrutinib remains cost-effective at the £30,000 per QALY threshold. 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 R/R MZL in the UK.

Table 17: Exploratory scenario analysis results versus rituximab monotherapy (CHRONOS-3)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Base case							
Rituximab monotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25,906

Abbreviations: ICER – incremental cost-effectiveness ratio;; LYG – Life years gained; MZL – marginal zone lymphoma; QALYs – Quality-adjusted life years; R/R – Relapsed or refractory.

Time to Event Analysis

B3. Priority Question: CS, Section B.3.3.1 (p.115). The data from the MAGNOLIA and AU-003 trials are immature, and therefore extrapolating beyond the trial period(s) is difficult and subject to considerable uncertainty.

a. **Throughout Section B.3.3.1, the CS states that clinical expert opinion at the UK advisory board (on 11th October 2023) helped to inform the choice of survival model. Please provide full details of the discussions regarding the choices of various survival models at the UK advisory board, including any meeting notes or minutes if available.**

As part of the CS the Company included reference 4, which is the advisory board meeting report. A new version of this report (which removes an internal comment that was erroneously left in) has been included as part of the reference pack for this set of responses to clarification questions. As BeiGene data on file, the advisory report should be treated as CIC.

b. **Please provide additional diagnostic plots to assess the visual fit of the parametric survival distributions using the observed data, including:**

- **Smoothed hazard vs time**
- **LN(smoothed hazard) vs time**
- **LN(cumulative hazard) vs LN(time)**

Smoothed hazard versus time

Figure 3 and Figure 4 present the smoothed hazard versus time for the extrapolated parametric survival distributions plots for zanubrutinib OS and PFS (MAGNOLIA-003 weighted to HMRN N=[redacted]), respectively. The corresponding plots for the HMRN basket (N=[redacted]) OS and PFS are presented in Figure 5 and Figure 6, respectively.

The plateau of the parametric survival distributions at end of the observed hazard functions can be attributed to the high levels of censoring observed in the tails of the KM data, particularly for the zanubrutinib arm. Given the high level of censoring the smoothed hazard should be interpreted with caution. The observed OS and PFS

hazard functions in Figure 3 to Figure 6 exhibit turning points, which is aligned with input from UK clinical experts in attendance at an advisory board (11th October 2023) who indicated that for patients with MZL there may be an initial period where the hazard rate is higher as more deaths/progression events occur, followed by a decrease in the hazard rate over time.[9] As such, accelerated failure time (AFT) models were chosen to extrapolate PFS and OS for both treatment arms to allow for an extrapolated hazard which can be non-monotonic (e.g. hazards that exhibiting turning points). Tails of the observed hazard curves, for example for MAGNOLIA-003 weighted to HMRN N=[redacted] PFS (Figure 4), should be interpretated with caution given that it is informed by potentially low numbers at risk and influenced by higher censoring rates in the tails of the KM curves.

In Figure 3 to Figure 6, the hazard rate estimations for Weibull, gamma, Gompertz, and exponential distributions are either monotonically increasing, constant, or monotonically decreasing. Only the log-logistic and log-normal distributions exhibit turning points in the hazard rate (across all endpoints and treatment arms). Therefore, the smoothed hazard function plots support the Company's base-case curve choice for PFS and OS across both treatment arms.

Smoothed hazard rate plots versus time for populations included as scenario analyses (MAGNOLIA alone weighted to HMRN N=[redacted], MAGNOLIA-003 weighted to HMRN N=[redacted] and HMRN N=[redacted]) are included within the reference pack (file name "ID5085_Zanubrutinib MZL_B3_Hazardplots"). The conclusions remain consistent with the base-case population.

Figure 3: OS smoothed hazard versus time – zanubrutinib (pooled MAGNOLIA-003 weighted to HMRN basket, N=[redacted])

Abbreviations: HMRN – Haematological Malignancy Research Network; OS – overall survival. Note. All extrapolated curves are included on the plots however in some cases they overlay one another so can appear hard to view.

Figure 4: PFS smoothed hazard versus time – zanubrutinib (pooled MAGNOLIA-003 weighted to HMRN basket, N=[redacted])

Abbreviations: HMRN – Haematological Malignancy Research Network; PFS – progression-free survival. Note. All extrapolated curves are included on the plots however in some cases they overlay one another so can appear hard to view.

Figure 5: OS smoothed hazard versus time – HMRN registry basket (N=[redacted])

Abbreviations: HMRN – Haematological Malignancy Research Network; OS – overall survival. Note. All extrapolated curves are included on the plots however in some cases they overlay one another so can appear hard to view.

Figure 6: PFS smoothed hazard versus time – HMRN registry basket (N=[redacted])

Abbreviations: HMRN – Haematological Malignancy Research Network; PFS – progression-free survival. Note. All extrapolated curves are included on the plots however in some cases they overlay one another so can appear hard to view.

LN(smoothed hazard) versus time

Figure 7 and Figure 8 present the logarithm of the smoothed hazard versus time for the extrapolated parametric survival distributions for zanubrutinib OS and PFS, respectively. The corresponding plots for the HMRN basket (N=[redacted]) OS and PFS are presented in Figure 9 and Figure 10, respectively. Across all treatment arms and endpoints, the observed hazard aligns well with the extrapolated hazard, with all curves sitting closely together. Therefore, these requested diagnostic plots do not aid the assessment of visual fit of the extrapolations as well as the smoothed hazard versus time plot s (presented above). Deviations in the tails of the observed hazard should be interpreted with caution given that they are informed by potentially low numbers at risk and influenced by higher censoring rates in the tails of the KM curves.

The logarithm of the smoothed hazard rate plots versus time for populations included as scenario analyses (MAGNOLIA alone weighted to HMRN N=[redacted], MAGNOLIA-003 weighted to HMRN N=[redacted] and HMRN N=[redacted]) are included within the reference pack (file name “ID5085_Zanubrutinib MZL_B3_Hazardplots”). The conclusions remain consistent with the base-case population.

Figure 7: OS LN(smoothed hazard) versus time – zanubrutinib (pooled MAGNOLIA and AU-003 weighted to HMRN basket, N=[redacted])

Abbreviations: HMRN – Haematological Malignancy Research Network; OS – overall survival. Note. All extrapolated curves are included on the plots however in some cases they overlay one another so can appear hard to view.

Figure 8: PFS LN(smoothed hazard) versus time – zanubrutinib (pooled MAGNOLIA-003 weighted to HMRN basket, N=[redacted])

Abbreviations: HMRN – Haematological Malignancy Research Network; PFS – progression-free survival. Note. All extrapolated curves are included on the plots however in some cases they overlay one another so can appear hard to view.

Figure 9: OS LN(smoothed hazard) versus time – HMRN registry basket (N=[redacted])

Abbreviations: HMRN – Haematological Malignancy Research Network; OS – overall survival. Note. All extrapolated curves are included on the plots however in some cases they overlay one another so can appear hard to view.

Figure 10: PFS LN(smoothed hazard) versus time – HMRN registry basket (N=[redacted])

Abbreviations: HMRN – Haematological Malignancy Research Network; PFS – progression-free survival. Note. All extrapolated curves are included on the plots however in some cases they overlay one another so can appear hard to view.

LN(cumulative hazard) vs LN(time)

Figure 11 and Figure 12 present the logarithm of the smoothed hazard versus logarithm of time for the extrapolated parametric survival distributions for zanubrutinib OS and PFS, respectively. The corresponding plots for the HMRN basket (N=[redacted]) OS and PFS are presented in Figure 13 and Figure 14, respectively

For the zanubrutinib figures, the gradient of the observed hazard line aligns well with the gradient of the extrapolated hazards. However, the observed hazard sits away from the extrapolated curves. For the HMRN data, the observed hazard line gradient also aligns well with the extrapolated curves, with the observe hazard sitting slightly closer to the extrapolated hazard lines. This could be driven by the fact the HMRN dataset is more mature than the zanubrutinib dataset.

The logarithm of the smoothed hazard rate plots versus the logarithm of time for populations included as scenario analyses (MAGNOLIA alone weighted to HMRN N=[redacted], MAGNOLIA-003 weighted to HMRN N=[redacted] and HMRN N=[redacted]) are included within the reference pack (file name “ID5085_Zanubrutinib MZL_B3_Hazardplots”). The conclusions remain consistent with the base-case populations.

Figure 11: OS LN(cumulative hazard) versus LN(time) – zanubrutinib (pooled MAGNOLIA-003 weighted to HMRN basket, N=[redacted])

Abbreviations: HMRN – Haematological Malignancy Research Network; OS – overall survival. Note. All extrapolated curves are included on the plots however in some cases they overlay one another so can appear hard to view.

Figure 12: PFS LN(cumulative hazard) versus LN(time) – zanubrutinib (pooled MAGNOLIA-003 weighted to HMRN basket, N=[redacted])

Abbreviations: HMRN – Haematological Malignancy Research Network; PFS – progression-free survival.

Figure 13: OS LN(cumulative hazard) versus LN(time) – HMRN registry basket (N=[redacted])

Abbreviations: HMRN – Haematological Malignancy Research Network; OS – overall survival. Note. All extrapolated curves are included on the plots however in some cases they overlay one another so can appear hard to view.

Figure 14: PFS LN(cumulative hazard) versus LN(time) – HMRN registry basket (N=[redacted])

Abbreviations: HMRN – Haematological Malignancy Research Network; PFS – progression-free survival. Note. All extrapolated curves are included on the plots however in some cases they overlay one another so can appear hard to view.

B4. CS, Section B.3.3.2, Table 55 (p.117). The sum of the AIC and BIC is presented and used to justify the choices of several distributions over others. Please further justify the methodological robustness of using this combined metric, including references to previous related studies that have used it.

Both the Akaike information criterion (AIC) and Bayesian information criterion (BIC) are measures of the statistical fit of a model to the observed data. Both information criteria are regularly used in NICE submissions to help inform the decision on which curve should be selected to model PFS and OS. In addition to using the sum of AIC and BIC to inform curve selection, the individual values and how close these were from the lowest values were used these to help inform the curve selection. Following engagement with a health economics expert from PenTAG in this clarification period, the Company were advised that in principle, curves with an AIC within 5 points of the best fitting curve (the lowest AIC) and those with a BIC within 5 points of the best fitting curve (the lowest BIC) could all be considered to fit the data strongly enough to be considered for extrapolation.[31] Table 18 summarises the lowest AIC and BIC scores and which curves could be considered as they are within 5 points of the respective information criterion.

Table 18: Acceptable curves based on AIC and BIC scores

Outcome	AIC	BIC
HMRN – PFS	Curve with the lowest value (i.e., best statistical fit): Weibull (545.9) Curves within 5 points of the lowest value: All except log-normal	Curve with the lowest value (i.e., best statistical fit): Exponential (550.6) Curves within 5 points of the lowest value: All except log-normal
Zanubrutinib – PFS	Curve with the lowest value (i.e., best statistical fit): Exponential (86.6) Curves within 5 points of the lowest value: All	Curve with the lowest value (i.e., best statistical fit): Exponential (89.2) Curves within 5 points of the lowest value: All
HMRN – OS	Curve with the lowest value (i.e., best statistical fit): Gamma (523.5) Curves within 5 points of the lowest value: All except log-normal	Curve with the lowest value (i.e., best statistical fit): Gamma (528.5) Curves within 5 points of the lowest value: All except log-normal
Zanubrutinib – OS	Curve with the lowest value (i.e., best statistical fit): Exponential (58.1)	Curve with the lowest value (i.e., best statistical fit): Exponential (60.5) Curves within 5 points of the lowest value:

Outcome	AIC	BIC
	Curves within 5 points of the lowest value: All	All

Abbreviations: AIC – Akaike Information Criterion; BIC – Bayesian Information Criterion; HMRN – Haematological Malignancy Research Network; OS – overall survival; PFS – progression-free survival.

Based on statistical fit alone, all curves, except log-normal for HMRN outcomes, could be considered for the extrapolations of PFS and OS. However, the AIC and BIC scores alone are insufficient to formulate a decision on which curve to select. This is because the AIC and BIC scores measure the goodness-of-fit of the models to the observed data and do not consider how clinically plausible the long-term extrapolations are, as this data is unobserved. For example, the Gompertz curve for zanubrutinib PFS has acceptable individual AIC and BIC scores, but it predicts that PFS at 30 years is nearly half ([redacted]%), which is clinically implausible. Therefore, as stated in Sections B.3.3.2 to B.3.3.5 of the CS, sole assessment of the statistical fit was not sufficient to determine the distribution for outcomes. These sections detail further how curves for extrapolations were selected based on statistical assessment, visual assessment, clinical expert opinion and landmark survival estimates.

Given that curve selection is not solely based on AIC and BIC scores, but instead considers a wider range of assessments, the Company maintains that the extrapolated curves selected are the most appropriate curves. This decision remains the same, irrespective of the decision to use the sum of AIC and BIC scores, or individual AIC and BIC scores.

B5. Priority Question: CS, Section B.3.3.7 (p.130). The CS states that as the HRs tend to 1 over the model time horizon no treatment waning assumptions are necessary for the analysis.

a. **Please provide further evidence that no treatment waning assumptions are necessary.**

As detailed in the CS, no treatment waning was included in the model, as the survival analysis (CS B.3.3) demonstrate a natural waning of the treatment effect of zanubrutinib over the time horizon with the OS hazard ratio (HR) tending towards 1. Figure 15 shows how the OS HR changes throughout the time horizon of the model in the base case, with the HR consistently increasing and tending towards 1. The decision to follow this approach was informed by health economic expert opinion

obtained at an advisory board conducted by the Company (11th October 2023).[9] The approach to omit additional treatment waning on top of the natural observed waning in the model aligns with what has been accepted in previous zanubrutinib NICE submissions (TA833 and TA931).[23,25]

Figure 15: OS HR for zanubrutinib over the time horizon of the model

Abbreviations: HR – hazard ratio; OS – overall survival.

However, to alleviate any potential concerns by the EAG and the NICE Committee on the impact of treatment waning, the Company have programmed the scenarios as requested by the EAG in part b of this question. Treatment waning functionality has only been programmed for OS, given that zanubrutinib is administered until progression, and as such it is appropriate to assume that treatment waning does not occur whilst patients remain on treatment. Across all treatment waning scenarios conducted in response to B5b, the incremental cost-effectiveness ratio (ICER) remains below £30,000, except for one clinically implausible scenario where it was assumed that treatment waning would begin once median TTD was reached for zanubrutinib in which the ICER increased to £32,362.

b. **Please provide full details of the discussions regarding the treatment waning assumption at the UK advisory board on 11th October 2023, including any meeting notes or minutes if available.**

The advisory board report has been provided in the reference pack as: "DoF_UK HTA Advisory Board for zanubrutinib for RR MZL_BeiGene 2023". No further meeting minutes or notes are available.

c. **Please provide additional results for scenarios assuming different lengths of treatment waning:**

- **Extrapolated median TTD of zanubrutinib from log-logistic distribution used in base case ([redacted]).**
- **5-year cut-off used in previous TA appraisals in the same disease area (e.g. TA627).**
- **Extrapolated median PFS of zanubrutinib from log-logistic distribution used in base case ([redacted]).**

Extrapolated median TTD of zanubrutinib from log-logistic distribution used in base case ([redacted])

The Company considers that application of treatment waning at the extrapolated median time to treatment discontinuation (TTD) time point to be clinically inappropriate, as this assumes that 50% of patients would continue to receive treatment without gaining any benefit from zanubrutinib. From a clinical perspective, this is implausible as clinicians would not keep patients on treatment while there is no observed benefit.

However, despite the clinically implausibility of the assumption, the Company has explored a scenario where treatment waning is applied at [redacted]. The results of the scenario are presented in Table 19. As a result of applying this assumption, the ICER increases by £6,165 to £32,362 compared to the base-case ICER of £26,197. Implementing treatment waning so early, leads to a sudden spike in the OS HR, before it quickly tends towards 1, as shown in Figure 16. In this scenario, half of the patients remain on treatment with zanubrutinib, accruing treatment costs, whilst

gaining no benefit. This leads to the increase in the ICER, as costs remain constant and quality-adjusted life years (QALYs) decrease compared to the base case as patients are unable to gain treatment benefits for as long.

Figure 16: Hazard ratios of OS for zanubrutinib - treatment waning applied at median TTD ([redacted])

Abbreviations: OS – overall survival; TTD – time to treatment discontinuation.

5-year cut-off used in previous TA appraisals in the same disease area (e.g. TA627)

As per the licensed indication for zanubrutinib, patients continue to receive treatment until disease progression.[17] Therefore, applying treatment waning at 5 years will affect the [redacted]% of patients still receiving treatment with zanubrutinib. These patients would continue to incur treatment costs despite gaining no clinical benefit, which, as highlighted in the previous scenario, is clinically implausible.

For rituximab-lenalidomide (the treatment under evaluation in TA627) patients are treated for a fixed duration, whereas as noted above, zanubrutinib is indicated until disease progression. In addition, whilst a 5-year cut-off for treatment benefit was applied and accepted in TA627, there is no clear justification or evidence to support this assumption.[22] Furthermore, applying a 5-year cut off for treatment effect results in a sudden spike in the OS HR, as shown by Figure 17. As such the Company

maintains that applying treatment waning at this arbitrary point is not evidence-based and hence is inappropriate.

Despite this, the Company has explored a scenario where treatment waning is applied at 5 years, which the Company considers to be an inappropriate assumption. The results of the scenario are presented in Table 19. The ICER increases by £1,947 to £28,144 compared to the base-case ICER of £26,197, with zanubrutinib remaining cost-effective at the £30,000 cost-effectiveness threshold.

Figure 17: Hazard ratios of OS for zanubrutinib - treatment waning applied at same point as TA627 (5 years)

Abbreviations: HR – hazard ratio; OS – overall survival.

Extrapolated median PFS of zanubrutinib from log-logistic distribution used in base case ( )

In line with the responses above, the Company consider it inappropriate to assume treatment waning would begin once median PFS has been reached. Given that MZL is an indolent cancer, half of patients are still yet to progress at this point and are still gaining a treatment benefit from zanubrutinib. There is no evidence to support that treatment waning would occur at , therefore the timepoint appears to be arbitrary and not evidence based.

However, the Company has explored a scenario where treatment waning is applied at the extrapolated median PFS for zanubrutinib ( ), which the Company considers

to be highly conservative. The results of the scenario are presented in Table 19. The ICER increases by £150 to £26,347 compared to the base-case ICER of £26,197. Despite the conservative assumption, zanubrutinib remained cost-effective at the £30,000 cost-effectiveness threshold.

Table 19: Cost-effectiveness results in patients with R/R MZL – scenarios for different lengths of treatment waning applied

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Base-case							
HMRN registry basket	[redacted]	[redacted]	[redacted]	-	-	-	-
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,197
Treatment waning applied at extrapolated median TTD of zanubrutinib from log-logistic distribution used in base case ([redacted])							
HMRN registry basket	[redacted]	[redacted]	[redacted]	-	-	-	-
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32,362
Treatment waning applied at 5-year cut-off							
HMRN registry basket	[redacted]	[redacted]	[redacted]	-	-	-	-
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	28,144
Treatment waning applied at extrapolated median PFS of zanubrutinib from log-logistic distribution used in base case ([redacted])							
HMRN registry basket	[redacted]	[redacted]	[redacted]	-	-	-	-
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,347

Abbreviations: ICER – incremental cost-effectiveness ratio; HMRN – Haematological Malignancy Research Network; LYG – Life years gained; MZL – marginal zone lymphoma; PFS – progression-free survival; QALYs – Quality-adjusted life years; R/R – Relapsed or refractory; TTD – time to treatment discontinuation.

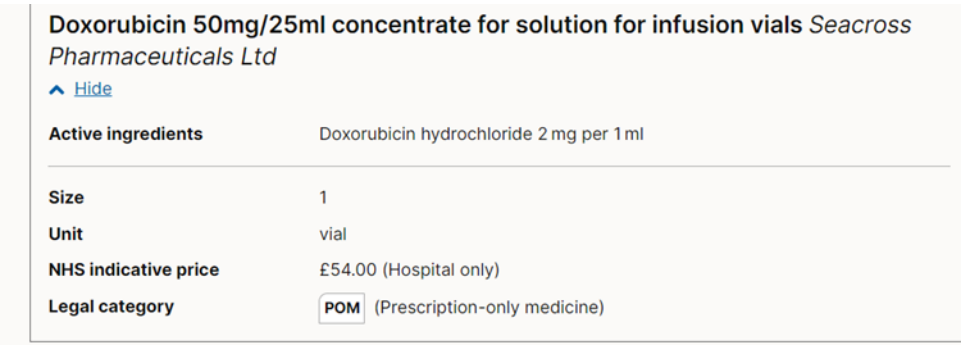
d. Please update the economic model so that the different treatment waning scenarios can be easily tested by the EAG.

The Company has updated the model so that the EAG can test the different treatment waning scenarios as well as other scenarios for Clarification Questions B6-10, B12-13, B15b and B17. These switches are located in the 'EAG switches' tab, in Column C. See Clarification Questions B5c for details on the treatment waning scenario results.

Resource Use

B6. CS, Section B.3.5.1 (p.146); Appendix N, Table 2 (p.2). The CS states the cost of 50mg of doxorubicin (from the company Seacross Pharmaceuticals Ltd) as £712.49.

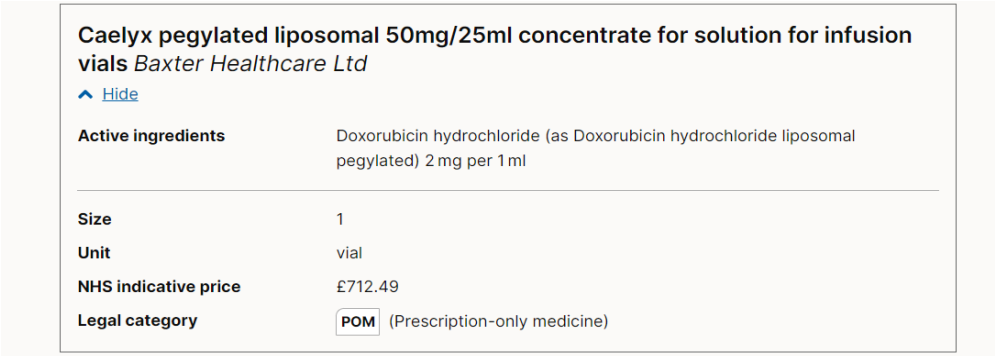
On the BNF website, the unit price for 50mg/25ml of doxorubicin from Seacross Pharmaceuticals Ltd, is given as £54. The CS states that "where multiple pack prices were available, the pack price with the lowest cost per mg was used". The EAG note that this higher price (of £712.49) relates to a product from Baxter.



Doxorubicin 50mg/25ml concentrate for solution for infusion vials *Seacross Pharmaceuticals Ltd*

Hide

Active ingredients	Doxorubicin hydrochloride 2 mg per 1 ml
Size	1
Unit	vial
NHS indicative price	£54.00 (Hospital only)
Legal category	POM (Prescription-only medicine)



Caelyx pegylated liposomal 50mg/25ml concentrate for solution for infusion vials *Baxter Healthcare Ltd*

Hide

Active ingredients	Doxorubicin hydrochloride (as Doxorubicin hydrochloride liposomal pegylated) 2 mg per 1 ml
Size	1
Unit	vial
NHS indicative price	£712.49
Legal category	POM (Prescription-only medicine)

Please:

a. Clarify which price and source is correct.

b. Correct the model and associated output if an error has been made.

Please note that the response to this question will cover questions B6-B9.

At the time of submission in November 2023, the drug acquisition costs included in the model were reflective of the cheapest per mg drug costs for each treatment. Since the submission date, it appears that the British National Formulary (BNF) website has updated the costs and suppliers for some of the treatments included in the model. Therefore, at the time of the submission the drug costs included were accurate to the best of the Company's knowledge. A PDF has been attached with screenshots of the BNF drug prices at the time of submission (see "BNF_drug_prices_November_2023.pdf" in the reference pack). However, following

the latest updates to the BNF, a scenario where all treatment costs identified in questions B6-B9 have been updated has been explored and included in the updated cost-effectiveness model. Table 20 shows the prices included in the scenario, with the results of the scenario presented in Table 21. As a result of this change, the ICER increases by £144 to £26,341 compared to the base-case ICER of £26,197. Given the minor impact on the ICER, the Company has retained the original unit costs in the base-case analysis.

Table 20: Comparison of November 2023 BNF prices and the latest prices for selected treatments

Treatment	Base-case price	Updated price
Doxorubicin	£712.49 for 2mg per 1ml	£54.00 for 2mg per 1ml
Mesna	£441.15 per 1,000mg	£527.10 per 1,000mg
Gemcitabine	£13.09 per 1,000mg	£162.00 per 1,000mg
Ifosfamide	£115.79 per 1,000mg	£151.49 per 1,000mg

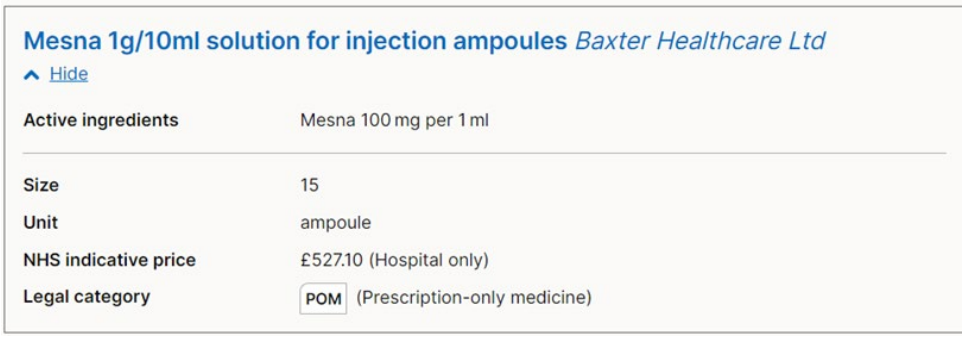
Abbreviations: mg – milligram; ml – millilitre.

Table 21*:* Scenario analysis results with updated treatment acquisition costs in patients with R/R MZL

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Base-case							
HMRN registry basket	[redacted]	[redacted]	[redacted]	-	-	-	-
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,197
Updated treatment acquisition costs							
HMRN registry basket	[redacted]	[redacted]	[redacted]	-	-	-	-
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,341

Abbreviations: BNF – British National Formulary; ICER – incremental cost-effectiveness ratio; HMRN – Haematological Malignancy Research Network; LYG – Life years gained; MZL – marginal zone lymphoma; QALYs – Quality-adjusted life years; R/R – Relapsed or refractory

B7. CS, Section B.3.5.1 (p.146); Appendix N, Table 2 (p.3). The cost for 1000mg of Mesna (from the company Baxter Healthcare Ltd) is stated as £441.15. On the BNF website, the unit price of 1000mg of Mesna from Baxter Healthcare Ltd is given as £527.10.



Mesna 1g/10ml solution for injection ampoules *Baxter Healthcare Ltd*

Hide

Active ingredients	Mesna 100 mg per 1 ml
Size	15
Unit	ampoule
NHS indicative price	£527.10 (Hospital only)
Legal category	POM (Prescription-only medicine)

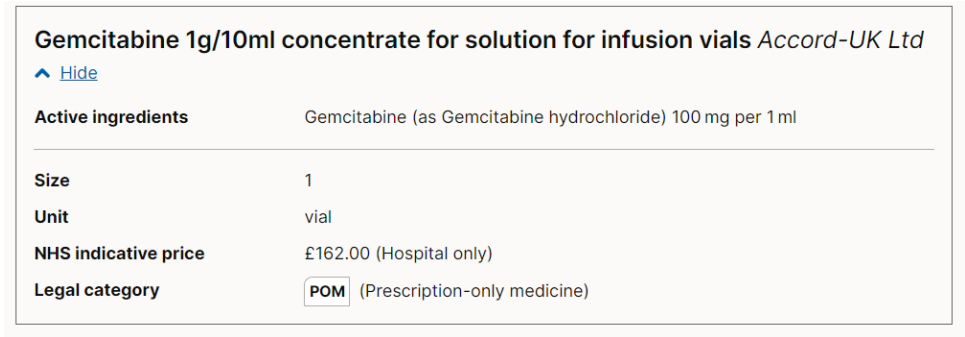
Please:

a. Clarify the source of the £441.15 price for 1000mg of Mesna.

b. Correct the model and associated output if an error has been made.

Please see the response to question B6a.

B8. CS, Section B.3.5.1 (p.146); Appendix N, Table 2 (p.3). The cost for 1000mg of gemcitabine (from the company Accord-UK Ltd) is stated as £13.09. On the BNF website, the unit price of 1000mg of gemcitabine from Accord-UK Ltd is given as £162.00.



Gemcitabine 1g/10ml concentrate for solution for infusion vials *Accord-UK Ltd*

Hide

Active ingredients	Gemcitabine (as Gemcitabine hydrochloride) 100 mg per 1 ml
Size	1
Unit	vial
NHS indicative price	£162.00 (Hospital only)
Legal category	POM (Prescription-only medicine)

Please:

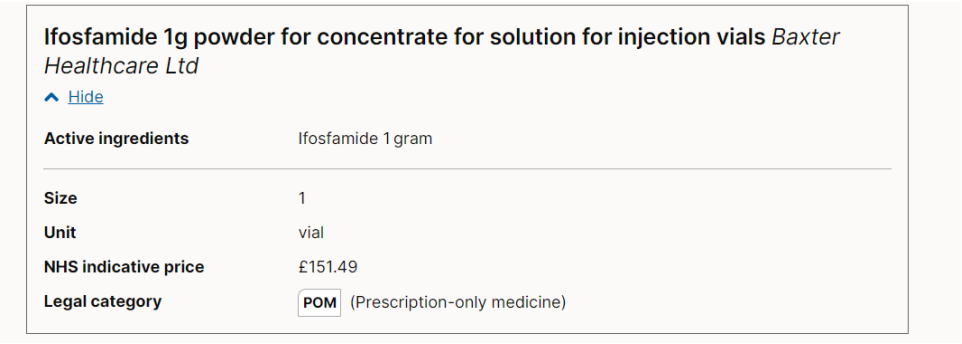
a. Clarify the source of the £162.00 price for 1000mg of gemcitabine.

b. Correct the model and associated output if an error has been made.

Please see the response to question B6a.

B9. CS, Section B.3.5.1 (p.146); Appendix N, Table 2 (p.3). The cost for ifosfamide 1000mg (from the company Baxter Healthcare Ltd) is stated as £115.79. On the BNF

website, the unit price of 1000mg of ifosfamide from Baxter Healthcare Ltd is given as £151.49.



Please:

a. Clarify the source of the £151.49 price for 1000mg of ifosfamide.

b. Correct the model and associated output if an error has been made.

Please see the response to question B6a.

B10. CS, Section B.3.5.1 (p.146); Appendix N, Table 2 (p.3). The per pack cost of G-CSF is stated as £312.69 (from the company Chugai). The EAG was unable to locate this cost from the BNF. Please:

a. Clarify the source of the £312.69 price for G-CSF.

The per pack cost of G-CSF of £312.69 (produced by Chugai) was obtained from the BNF website in November 2023. The Company understands that the values reported by the BNF have been updated since the submission date. A PDF has been attached with screenshots of the BNF drug prices at the time of submission (see "BNF_drug_prices_November_2023.pdf" in the reference pack).

B11. CS, Section B.3.5.2 (p.148). The health state resource use is partially based on the recommendations in the ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up for marginal zone lymphoma.

a. Please comment on whether there are differences between the ESMO Clinical Practice Guidelines and the recently published BSH Guidelines in relation to recommended health care resource use, in particular, for the estimates of

"Haematologist Visits" and "Patient History/Physical Exam", as these are shown to be key drivers in the deterministic sensitivity analysis (DSA).

The DSA tornado plot shows that frequency of patient history/physical exams and haematologist visits for progression-free patients are two of the top variables that the ICER is most sensitive to. Despite this, changes in these variables leads to a minor impact on the ICER. The submission assumed a standard deviation of 20% of the mean value for both. Deterministic sensitivity analyses for PFS health resource use are presented in Table 22. Despite being the variables that the ICER is second and third most sensitive to, these variables only lead to changes of <2% in the ICER. The minimal variation in the incremental analyses suggests that the cost-effectiveness analysis (CEA) is not that sensitive to these variables and hence they are not key drivers of the results.

Table 22: Scenario analysis results for PFS HRU: patient history/physical exam and haematologist visits, in patients with R/R MZL

	Base-case	Lower bound	Upper bound
HRU: PFS Patient History/Physical Exam, per 28 days	Value: 0.23 ICER: £26,197	Value: 0.149 ICER: £25,865 Change from base case: -£332 (-1.3%)	Value: 0.329 ICER: £26,601 Change from base case: £404 (1.5%)
HRU: PFS Haematologist Visits, per 28 days	Value: 0.23 ICER: £26,197	Value: 0.149 ICER: £25,883 Change from base case: -£314 (-1.2%)	Value: 0.329 ICER: £26,579 Change from base case: £382 (1.4%)

Abbreviations: HRU – health resource use; ICER – incremental cost-effectiveness ratio; PFS – progression-free survival.

The recently published BSH guidelines make no specific recommendations on the management of R/R MZL with respect to healthcare resource use, including haematologist visits and patient history/physical examinations. Therefore, the Company believes that no additional sensitivity analyses are required to capture the BSH guidelines. Furthermore, the Company maintains that the healthcare resource use included in the submission accurately reflects UK clinical practice as it was informed by ESMO guidelines, a previous NICE HTA submission in R/R MZL (TA627), before being validated by UK clinicians at an advisory board (11th October 2023).[2,4,9]

b. If there are differences between the ESMO Clinical Practice Guidelines and the BSH Guidelines in relation to health care resource use, please update the economic model to take into account these recommendations and report the updated results as additional scenario analyses.

As stated in part 11a, the BSH guidelines make no specific recommendations on the management of R/R MZL with respect to healthcare resource use, including haematologist visits and patient history/physical examinations. Therefore, the Company believes that no additional sensitivity analyses are required to capture the BSH guidelines.

B12. CS, Section B.3.5.2 (p.148). The CS states that "costs for resource use are sourced from NHS reference costs for 2021/22". Please clarify whether these costs were inflated to the 2022/23 cost year and the specific method they used to inflate these costs.

The terminal care unit cost sourced from TA627 was inflated to a 2022/23 cost year using inflation indices from Jones & Burns, 2021 and Jones et al. 2023.[32,33] The remaining resource use activities unit costs were sourced from the 2021/22 NHS reference costs, the most recently published NHS reference costs tariff.[34] However, these unit costs were not inflated to a 2022/23 cost year, despite the statement in the CS. Table 23 presents the NHS reference costs inflated to 2023, with Table 24 presenting a scenario analyses of the results when using the inflated NHS reference costs. As a result of inflating the unit costs, the ICER increases by £42 to £26,239, compared to the base-case ICER of £26,197. The minimal variation in the incremental analyses suggests that the CEA is not that sensitive to resource use costs and that they are not key drivers of the results. Given the minor change in the ICER, the Company have retained their base-case inputs from the 2021/22 NHS reference costs.

Table 23: Inflated NHS reference costs for healthcare resource use (cost year 2023)

Category	NHS reference cost 2021/22[34]	Cost inflated to 2023, using inflation indices[32,33]
Haematologist visit	£209.41	£215.11
Diagnostic: full blood count	£2.96	£3.04
Diagnostic: patient history/physical exam	£221.48	£227.50

Category	NHS reference cost 2021/22[34]	Cost inflated to 2023, using inflation indices[32,33]
Diagnostic: U & E	£1.55	£1.59
Diagnostic: LFT	£1.55	£1.59
Diagnostic: calcium	£1.55	£1.59
Diagnostic: serum IgG, IgA, IgM and electrophoresis	£7.61	£7.81
Diagnostic: LDH test	£1.55	£1.59

Abbreviations: IgA – immunoglobulin A; IgG – immunoglobulin G, IgM – immunoglobulin M; LDH – lactate dehydrogenase; LFT – liver function tests; NHS – National Health Service; U & E – urea and electrolytes.

Table 24: Scenario analysis results for inflated NHS reference unit costs, in patients with R/R MZL

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Base case							
HMRN registry basket	[redacted]	[redacted]	[redacted]	-	-	-	-
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,197
Using NHS references costs inflated to 2023 cost year for resource use							
HMRN registry basket	[redacted]	[redacted]	[redacted]	-	-	-	-
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,239

Abbreviations: ICER – incremental cost-effectiveness ratio; HMRN – Haematological Malignancy Research Network; LYG – Life years gained; MZL – marginal zone lymphoma; NHS – National Health Service; QALYs – Quality-adjusted life years; R/R – Relapsed or refractory.

B13. CS, Section B.3.5.4.1 (p.151). Subsequent treatment costs have been included in the model as a one-off cost to each patient who have disease progression. Please:

a. Justify that the subsequent treatments included in the economic analyses are relevant to the population stated in the decision problem, paying particular attention to the recently published BSH guidelines.

In the CS, subsequent treatment costs are informed by HMRN registry data in patients who are at their third-line treatment.[10] This includes the basket of treatments and the proportion of patients receiving each treatment. As the data is sourced from patients with MZL receiving treatment in the UK, the HMRN represents the best real-world source to inform the subsequent treatment assumptions. Furthermore, the subsequent treatment assumptions were validated as reflective of clinical practice by UK experts at an advisory board (11th October 2023).[9] The list of treatments included in the subsequent treatment basket are presented in Table 77 of the CS.

As discussed in A3, there are very few differences between the recently published BSH guidelines and the ESMO guidelines (that were used to inform the CS). The BSH guidelines make no additional recommendations on which treatments should be given to patients following treatment within the decision problem paradigm (zanubrutinib or rituximab ± chemotherapy / chemotherapy alone). Considering this and that the HMRN registry data was validated with UK experts,[9] the Company maintains that the subsequent treatments assumptions within the model are reflective of UK clinical practice in R/R MZL.

b. Further justify why the duration of subsequent treatments were not considered in the economic model.

In the cost-effectiveness model, it is assumed that patients receive one complete regimen of each respective subsequent treatment. The duration of each subsequent treatment is captured within the drug administration and acquisition of the complete regimen through the dosing schedule (modelled to align with each treatment's recommended dose) and is then applied as a one-off cost upon progression.

c. Further justify why any differences in these subsequent treatments by treatment arm was not considered in the economic model.

The HMRN data is reflective of current UK clinical practice, as validated by UK clinical experts, therefore the Company consider it the most appropriate data source to inform subsequent treatment assumptions within the model.[9]

Given the lack of approved treatments in MZL and the frequent reuse of front-line MZL treatments, the available subsequent treatments are unlikely to differ by treatment arm.

Furthermore, the weightings of each subsequent treatment regimen is considered reflective of current UK clinical practice following validation by UK clinical experts.[9,10] Applying different weightings for the basket for each arm was not feasible given that zanubrutinib is not routinely available for use in England and Wales for the treatment of MZL, and hence no data is available on how zanubrutinib might impact the downstream treatment pathway.

Finally, as there is no head-to-head trial data comparing the proportion of patients receiving subsequent treatments following zanubrutinib compared with relevant comparator treatments, assuming that it is equal across the arms is the least biased approach to capture subsequent treatment costs. Other alternative approaches to capture subsequent treatment were considered infeasible due to a lack of available data. Therefore, the Company maintains that the current approach is the most appropriate method with data available.

d. Provide appropriate scenario analyses which relax the assumption of a one-off subsequent treatment cost to each patient who have disease progression.

The Company has explored a number of scenarios to assess the impact of the subsequent treatment assumptions, with the aim of alleviating any uncertainty inherent in the analyses.

The first scenario, presented in Table 25, explores the **removal of all subsequent treatment costs from the model**, which results in an ICER increase of £78, (ICER: £26,275) compared to the base-case ICER of £26,197.

The second scenario, presented in Table 25, explores the **removal of subsequent treatment costs for patients in the zanubrutinib arm-only,** which results in an ICER decrease of £571 (ICER: £25,626) compared to the base-case ICER of £26,197.

The third scenario, presented in Table 25, explores the **removal of subsequent treatment costs for the HMRN basket arm-only**, which results in an ICER increase of £649 (ICER: £26,846) compared to the base-case ICER of £26,197.

These three scenarios demonstrate that the assumptions made to the proportion of patients that receive subsequent treatments do not drive cost-effectiveness in the model. The extreme assumptions in scenarios 2 and 3, where subsequent treatment is removed from one arm, only leads to a 2.2% decrease and a 2.5% increase in the ICER compared to the base case.

Given the lack of evidence to determine the proportion of patients that should receive subsequent treatment in each arm, and the insensitivity of the ICER to changes in the proportions, the Company maintains that the assumption of all patients receiving the same subsequent treatment is appropriate.

Table 25: Base-case deterministic results in patients with R/R MZL

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Base case							
HMRN registry basket	[redacted]	[redacted]	[redacted]	-	-	-	-
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,197
Scenario 1: no patients receive subsequent treatment in either arm							
HMRN registry basket	[redacted]	[redacted]	[redacted]	-	-	-	-
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,275
Scenario 2: no patients in the zanubrutinib arm receive subsequent treatment, but all patients in the HMRN Registry basket arm receive subsequent treatment							
HMRN registry basket	[redacted]	[redacted]	[redacted]	-	-	-	-
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25,626
Scenario 3: all patients in the zanubrutinib arm receive subsequent treatment, but no patients in the HMRN Registry basket arm receive subsequent treatment							
HMRN registry basket	[redacted]	[redacted]	[redacted]	-	-	-	-
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,846

Abbreviations: ICER – incremental cost-effectiveness ratio; HMRN – Haematological Malignancy Research Network; LYG – Life years gained; MZL – marginal zone lymphoma; QALYs – Quality-adjusted life years; R/R – Relapsed or refractory.

e. Provide appropriate scenario analyses which relax the assumption of no difference in the subsequent treatment across treatment arm.

The Company has provided scenarios where the assumption of no difference in subsequent treatment across treatment arms is relaxed in part B13.d.

Health Related Quality of Life

B14. Priority Question: CS, Section B.3.4.2 (p.136). The EQ-5D-5L results from the MAGNOLIA trial were mapped to the EQ-5D-3L using the Hernandez-Alava (2022) algorithm and then predicted using a mixed-effects linear regression model. Please provide further details of this regression model, including the full regression output.

Utility scores collected during the MAGNOLIA clinical trial were converted from EQ-5D-5L using Hernández's mapping algorithm, in line with the NICE reference case.[16,35] This data included all patients in the efficacy analysis set (n=66), who provided at least one complete EQ-5D-5L measurement. As reported in the CSR and the CS, EQ-5D data was only collected until disease progression in MAGNOLIA, as per the clinical trial protocol, and therefore utilities were only estimated for pre-progression.

In the utility analysis, a linear mixed-effect model (LMM) with random intercepts was estimated to account for the longitudinal and hierarchical nature of data (level 1 = repeated measures; level 2 = patient). The model included utility score as a dependent variable. The covariate investigated was:

- Ongoing grade ≥3 adverse event (AE) (ae_i) – binary variable equal to 1 if the date of EQ-5D- assessment falls in between the start and end date of any grade ≥3 adverse event

Table 26: Utility regression model specification

Model	Specification
Model	$U_{it} = \alpha + \beta_1 ae_{it} + \varepsilon_{it}$

Where the term U_{it} denotes the EQ-5D-5L utility value measured for patient *i* at time *t* and ε_{it} is the residual random error for patient *i* at time *t*.

No missing data imputation is applied with the assumption of missing at random (MAR). Table 27 below presents the regression outcomes for the model. For the health state of PFS, the intercept of [redacted] reflects the utility score. The decrement associated with experiencing an adverse event (AE) is applied within the model as a disutility.

Table 27: Estimated coefficients, variance-covariance matrix, and fit statistics

Variable	Parameter estimate					Variance-covariance		Fit statistics	
	Coefficient	SE	Df	t statistics	p-value	Intercept	AE	AIC	BIC
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: AE – adverse event; AIC – Akaike Information Criterion; BIC – Bayesian Information Criterion; Df – degrees of freedom; SE – standard error.

B15. Priority Question: CS, Section B. 3.4.2 (p.136). As stated in the CS, the estimated utility value for the PF health state from the MAGNOLIA trial lacks face validity. Please:

a. Comment further on the possible reasons for this lack of face validity.

The utility values for the PFS health collected from MAGNOLIA were compared with age-matched UK population utility (using Hernández-Alava et al. 2022[35]) in line with the NICE reference case.[16]. As discussed in the CS (Table 67 p.136), the progression-free (PF) utility scores were higher than the estimates for age-matched UK population. A possible reason may be a 'trial effect' or 'Hawthorne effect', whereby the participants were aware that they are part of a study so may have consciously or subconsciously altered their responses in the EQ-5D-5L complete forms. This is a common problem in oncology appraisals, with NICE TA689[36] and NICE TA931[25] reporting the same issue. To address this issue, the PF utility values were capped by that of the age-gender matched general population to ensure patients could not have a better HRQoL than the general population. This approach was considered appropriate as it aligned with the approach accepted in relevant previous appraisals, notably NICE appraisal TA627[22] and TA931[25] and was validated by UK experts in an advisory board (11th October 2023).[9]

b. Conduct a scenario analysis using a utility value for the PF health state from the Major (2021) study and report the results.

Scenario analyses have been conducted and presented in Table 28 using the four PF utility values reported in the Major (2021) study as requested by the EAG.[37] The study reports PF utility values for the two trial arms (rituximab and bendamustine + rituximab) at two different timepoints: at 6 months of treatment completion and in 6-

12 months of treatment completion. Applying the four Major (2021) PF utility values produce ICER results that range from £28,158 to £30,844. Based on the cost-effectiveness threshold at £30,000 per QALY gained, zanubrutinib is cost-effective in all but one of the scenarios (when using a 0.66 PF utility value). Given that the utility values are not summarised across both trial arms and do not consider HRQoL over longer time horizons (e.g., up to 12 months of treatment completion or longer) it is unclear how relevant the PF utility values are for use in the Company's cost-effectiveness model. Notably, taking an average of the four utility values results in a PF utility value of 0.7, yields an ICER below a £30,000 per QALY gained threshold.

Table 28: Scenario results using Major (2021) PF utility values, in patients with R/R MZL

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Base-case							
HMRN registry basket	[redacted]	[redacted]	[redacted]	-	-	-	-
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,197
Scenario deterministic results using PF utility values for within 6 months of treatment completion (rituximab arm: 0.71)							
HMRN registry basket	[redacted]	[redacted]	[redacted]	-	-	-	-
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	28,572
Scenario deterministic results using PF utility values for within 6 months of treatment completion (bendamustine + rituximab arm: 0.66)							
HMRN registry basket	[redacted]	[redacted]	[redacted]	-	-	-	-
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	30,844
Scenario deterministic results using PF utility values for 6-12 months after treatment completion (rituximab arm: 0.72)							
HMRN registry basket	[redacted]	[redacted]	[redacted]	-	-	-	-
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	28,158
Scenario deterministic results using PF utility values for 6-12 months after treatment completion (bendamustine + rituximab arm: 0.69)							
HMRN registry basket	[redacted]	[redacted]	[redacted]	-	-	-	-
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,439

Abbreviations: ICER – incremental cost-effectiveness ratio; HMRN – Haematological Malignancy Research Network; LYG – Life years gained; MZL – marginal zone lymphoma; PF: progression-free; QALYs – Quality-adjusted life years; R/R – Relapsed or refractory.

B16. Priority Question: CS, Section B.3.4.2 (p.136). Please provide further justification for the use of the CADTH utility value for the PD health state in the base case, considering the perspective of the study is not aligned to this decision problem.

Due to the design of the MAGNOLIA and AU-003 trials, no utility data were collected for patients with progressed disease (PD), therefore it was not possible to estimate post-progression utility for patients using the data from the MAGNOLIA or AU-003 trials.

As such an SLR was conducted to identify published literature and previous health technology assessment submissions reporting on the HRQoL data for patients with R/R MZL. Full details of the process and methods used to identify and select the HRQoL data are presented in Appendix H of the CS. The SLR identified three studies which reported HRQoL for patients with R/R MZL (see Table 68 in the CS). Of these:

- Major (2021)[37] did not report PD utilities and therefore could not be used to inform the PD health state utility value.
- The CADTH appraisal of bendamustine for NHL (2012)[38], in which PD utilities values were derived from two previous studies of patients with FL in the UK.[39,40] Despite the utilities being collected from a different NHL condition, the PD value falls within the values accepted in previous zanubrutinib NICE submissions (0.60-0.691)[25] in the UK in relevant blood cancers, and is close to the EAG's preferred utility in the NICE appraisal TA627.[22] Furthermore, the PD utility value is similar to the utility values accepted in TA833.[23]
- TA627[22] PD utilities values from AUGMENT,[41] were not appropriate to use as they were higher than the general population utility, as the Company has highlighted in the CS (Section B.3.4.6).

In summary, the PD utility from the CADTH appraisal of bendamustine for NHL (2012) were selected over the NICE TA627 PD utility, as it was deemed to be the only clinically appropriate utility available from literature, and due to the closeness to the EAG's preferred utility in the NICE TA627 appraisal. Furthermore, the base-case

PD utility value was validated as appropriate by UK experts in attendance at an advisory board conducted by the Company (11th October 2023).[9] It should also be noted that sensitivity analyses demonstrated that altering of PD utility values within the DSA does not have a significant impact on the cost-effectiveness results, with the ICER ranging from £25,998 to £26,389. Therefore, any uncertainty relating to the PD utility value does not impact the overall conclusion, with zanubrutinib remaining cost-effective at the £30,000 per QALY gained threshold.

Adverse Events

B17. Priority Question: CS, Section B.3.4.5 (Page 142). The CS states that "due to the low incidence rates of AEs and the small sample size in MAGNOLIA and AU-003, estimates of disutility for specific AEs may be inaccurate and susceptible to being skewed by outliers" and a simplifying assumption is made that all AEs have the same disutility value ([redacted]) and duration ([redacted]). Please:

a. **Comment further on the potential bias arising from this simplifying assumption.**

The likelihood of bias arising from the use of the simplified assumption is minimal as the duration and disutility of AEs do not drive the model results. To further explore this, the Company has provided two scenarios where the upper and lower bound values from the DSA of both the AE disutilities and AE durations are applied. These results are presented in Table 30. As a result of using upper and lower bound values, the ICER decreases by £13 to £26,184 and increases by £6 to £26,203, respectively, compared to the base-case ICER of £26,197.

b. **Provide a scenario analysis with AE specific disutility and duration estimates for all AEs, appropriately sourced from the wider literature.**

The Company obtained AE disutility and duration estimates from published literature, as outlined in Table 29. These sources predominantly include technology appraisals and NICE guidelines. In the absence of data, assumptions were made for COVID-19 pneumonia disutility and duration, as well as hyperglycaemia duration. It was assumed that, given COVID-19 pneumonia is a type of pneumonia, it would share

the same disutility and duration as pneumonia. Additionally, hyperglycaemia was assumed to have the same duration as hypoglycaemia as they are both related to blood sugar levels. The duration was based on hypoglycaemia events experienced by non-intensive care unit (ICU) patients, as described in Dhatariya et al. 2020.[42]

Table 29: AE disutilities and durations sourced from wider literature

AE	Disutility	Disutility source/assumption	Duration (days)	Duration source/assumption
COVID19 pneumonia	-0.1950	Assumed to be the same as pneumonia	18.20	Assumed to be the same as pneumonia
Pneumonia	-0.1950	TA931[25]	18.20	TA931[25]
Neutropenia	-0.1630	TA931[25]	15.09	TA931[25]
Anaemia	-0.0900	TA931[25]	23.21	TA931[25]
Thrombocytopenia	-0.1100	TA931[25]	23.21	TA931[25]
Diarrhoea	-0.1030	NG115[43]	4.00	NG115[43]
Neutrophil count decreased	-0.1630	TA931[25]	15.09	TA931[25]
Hypertension	-0.0200	TA931[25]	21.00	TA931[25]
Pyrexia	-0.0297	Chirikov et al. 2019[44]	1.00	Chirikov et al. 2019[44]
Rash	-0.0325	TA258 PAS[45]	28.00	Chirikov et al. 2019[44]
Infusion-related reaction	-0.0110	Chirikov et al. 2019[44]	1.00	Chirikov et al. 2019[44]
Hyperglycaemia	-0.062	NG28[46]	4.10	Assumption[a] based on Dhatariya et al. 2020[42]

Abbreviations: AE – adverse event; ICU – Intensive Care Unit; NICE – National Institute For Health and Care Excellence; NG – NICE guideline; PAS – patient access scheme; TA – technology appraisal. [a] Assumed hyperglycaemia duration is the same as the increase length of hospital stay for non-ICU patients who experience hospital acquired hypoglycaemia compared to those who do not.

The Company has presented the results of the scenario where the values sourced from published literature have been applied to the AE disutilities and AE durations in Table 30. As a result, the ICER increases by £1 to £26,198 compared to the base-case ICER of £26,197, demonstrating that the ICER is not sensitive to changes in AE disutilities or durations, and as such the model base case remains unchanged.

Table 30: Scenario analysis results for AE disutilities and durations in patients with R/R MZL

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Base case							
HMRN registry basket	[redacted]	[redacted]	[redacted]	-	-	-	-
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,197
Upper bound values							

HMRN registry basket	[redacted]	[redacted]	[redacted]	-	-	-	-
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,184
Lower bound values							
HMRN registry basket	[redacted]	[redacted]	[redacted]	-	-	-	-
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,203
Published literature							
HMRN registry basket	[redacted]	[redacted]	[redacted]	-	-	-	-
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,198

Abbreviations: ICER – incremental cost-effectiveness ratio; HMRN – Haematological Malignancy Research Network; LYG – Life years gained; MZL – marginal zone lymphoma; QALYs – Quality-adjusted life years; R/R – Relapsed or refractory.

Model Validation

B18. CS, Figure 32 (p.167). There are minor discrepancies between the numbers presented in Figure 32 and the numbers generated by manually changing the individual cells to the upper and lower bounds specified in the Tornado plot presented in the 'DSA' tab of the model. For example, manually changing cell F13 of the 'Utilities' tab of the model changes the ICER reported in cell G4 to [redacted], slightly different to the [redacted] figure reported in Figure 32 of the company submission and the Tornado diagram reported in the 'DSA' tab of the model. Please provide an updated model with no such discrepancies.

The DSA incorporates values with more than the two decimal places shown in the tornado diagram. The upper and lower parameter values, used in the DSA, illustrated in the CS, Figure 32 (p.167), can be viewed in the hidden 'Inputs' tab, columns I and J. Upon testing the values with their full decimal precision, they yield identical results as those presented in the tornado diagram.

B19. Section B.3.2.5 (p.107). Please provide a completed copy of the Assessment of the Validation Status of Health Economic Decision Models (AdViSHE) tool.

The Company is unsure what the "Section B.3.2.5 (p.107)" refers to in the clarification question, however upon reviewing the AdViSHE tool the Company would like to provide more assurances over the rigour of the model both conceptually and technically. Whilst there is not sufficient time to fill out the AdViSHE in this response,

in the development of the economic model, the Company has covered all parts of the tool, as follows:

Part A (conceptual model), B (input data validation) and D (operational validation) in the tool

In ensuring the model received appropriate and sufficient validation, external validation was sought for the model structure, assumptions, inputs and outputs with both UK clinical experts and health economic experts as part of the advisory board.[9] The advisory board report contains details of how a comprehensive validation of the model was conducted and any follow up actions taken by BeiGene as per the feedback received in the advisory board.

Part C (validation of the computerised model)

To ensure technical rigour of the analyses, including avoidance of errors, the model has undergone review by two programmers external to the conceptualisation and development team. Each programmer used their own quality check template which includes tests for extreme values, trace calculations and unit values sourcing, and was in line with health economics best practice. The results of the technical quality check have been submitted as two Excel files as part of the reference pack to these responses (Precision_model CEM QC checklist_zanubrutinib_MZL and FIECON_model CEM QC checklist_zanubrutinib_MZL).

Budget Impact Analysis

B20. BIA Submission, Section 5. Uptake and Market Share (p.20). The BIA submission states that: “in year 1 zanubrutinib will displace off-label use of ibrutinib ([redacted]), as a licensed BTKi, and reach at maximum market share of [redacted] by year [redacted]”. Please provide further justification for the assumptions regarding market share.

The market share estimates provided in the budget impact analysis are predictions based on BeiGene market research. Given that zanubrutinib is not yet available in the UK for the treatment of MZL, there is no available data to inform the expected market share. However, when varying the market shares up to a 75% peak market share by year 5, the budget impact remains below the NHS Budget Impact Test

threshold. This has further been confirmed by the NICE Resource Impact Assessment team through the Budget Impact Assessment.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Zanubrutinib for treating relapsed or refractory marginal zone lymphoma [ID5085]

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

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- 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 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. The 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. https://lymphoma-action.org.uk/about-us-how-we-work-policies-and-terms-use/working-healthcare-and-pharmaceutical-companies

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.**	Funding received in 2022 Beigene – none Aspen Pharma – none Baxter Healthcare – none Celltrion Healthcare - none Dr Reddy's Laboratories – none Hospira – none Medac GmBH – none Pfizer - £300 Roche - £26000 Sandoz Ltd – none Seacross Pharmaceuticals – none Zentiva – none
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 marginal zone lymphoma.

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?	Lymphomas are cancers of the immune system and develop when lymphocytes grow out of control. It is the 5th most common type of cancer in the UK. There are two main types: Hodgkin (HL) and non-Hodgkin lymphoma (NHL), the most common being non-Hodgkin lymphoma with around 14000 people being diagnosed with it every year. It encompasses a range of different types which can either be aggressive or slow growing. Marginal cell lymphoma (MZL) is one of these slow-growing lymphomas. It develops from B -cells in the edge of lymphoid tissues called the marginal zone. There are three types of MZL: • Mucosa-associated lymphoid tissue (MALT) lymphoma • Nodal marginal zone lymphoma • Splenic marginal zone lymphoma MALT lymphoma is the most common type of MZL, affecting 8 out of every 100 people diagnosed with NHL. It occurs in the mucosa associated lymphoid tissue, which is collections of lymphocytes in the moist protective layer that lines a lot of the body such as the mouth, gut, and airways. MALT lymphoma occurs when abnormal lymphocytes collect in these areas. It is most commonly found in the stomach. MALT lymphoma does not tend to cause the symptoms usually associated with lymphoma, such as swollen lymph nodes. People with MALT lymphoma in the stomach can experience persistent indigestion, abdominal pain, nausea or weight loss. It can also cause bleeding in the stomach which leads to anaemia and its associated symptoms of fatigue or shortness of breath. People with non-gastric MALT often have no symptoms at all but they may have problems with their eye, cough, lumps in the mouth or jaw or unusual patches on the skin. Nodal MZL lymphoma develops in lymph nodes and as such causes swollen lymph nodes, usually in the neck. It can also cause weight loss, night sweats and fever. Splenic MZL may not cause any symptoms, or symptoms due to an enlarged spleen. These can be abdominal pain, feeling of fullness or pain under the ribs. It can also cause symptoms from anaemia such as tiredness, or from low platelets, such as bruising.

	The uncertainty and anxiety of a family member's diagnosis has an impact on family members. One patient said *"my diagnosis with MZL had a huge impact on my wife, not only the shock and anxiety but getting used to me being at home all the time… financially it has also had an impact."* The diagnosis has an ongoing impact on family members and is hard to not think about frequently- *"the experience for my two children was also stressful and it is always in the back of everyone's minds."*

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	MZL is rare, and this makes it difficult to determine exactly which treatment to give. The treatment for marginal zone lymphomas often starts with treating an underlying viral cause such as hepatitis C or H-pylori. This treatment can be successful for some, but ongoing treatment is dependent on the individual, their general health and symptoms being experienced. Many patients go on to Active Monitoring (watch and wait) which we know is a very anxious time for them and their families, waiting for the day when symptoms warrant treatment. Treatment with radiotherapy or chemo-immunotherapy such as rituximab plus R-CVP, with follow up maintenance treatment can offer lasting remission, but relapse is common and clinical trials are few due to the relatively low numbers of people with MZL. Our patients tell us about a perceived lack of treatment options for them as a rare sub-group, and the toxicity of the current treatments, with enduring fatigue, often exacerbated by the need for regular hospital visits. Our patients wish for more options in treatment, especially when first line treatments have not been successful. They told us: • *"Any treatment that has lower toxicity and offers the strong possibility of good quality of life would be amazing."* • *"I think we need a medication that is effective but doesn't need hospital visits as often. It would be very beneficial to know that there was a treatment like Zanubrutinib available that you could take at home."* • *"It needs to be easier to take treatments at home so that hospitals and staff are freed to treat other patients who require it."*
8. Is there an unmet need for patients with this condition?	The unmet needs for patients with this condition include providing more specified treatment pathways for rarer diagnoses and enabling more treatment option after the first line treatment has not been successful. Our patient community told us: • *"There should be definitive pathways for the rarer lymphomas with all patients being seen in centres where there is a special interest so that the most appropriate treatments can be offered."* • *"There is no one size fits all at the moment."*

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	There were many advantages of the technology that our patient community outlined. The main advantage of this technology that patients identified were around quality of life and not having to go into hospital for the treatment which can be stressful, time consuming and a financial burden. Our patient told us: • *"This drug could help ensure that the lymphoma didn't progress, reduce visits to hospital, allow patients to keep their jobs without having to get time off for hospital visits etc."* • *"It could help patients emotionally by giving them a sense of control and a better quality of life."* • *"It could also help families because it won't be as stressful for them seeing you have cannulas inserted."* • *"In the long run it could save money by patients not requiring hospital treatment. It could also give them a better opportunity to carry on with daily living as best they can, as it can be tolerated well."* • *- "Less visits to the hospital would be an advantage for both patient and carer. All drugs have side effects but if they are less than the current chemotherapy that would be a big bonus."*

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	One of our patients noted that fatigue from this technology could have an impact on the patient: *"I suspect that tiredness would be a side effect- this can be very negative on quality of life and needs understanding and support."*

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.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	One of our patients made a point to consider around quality of life when considering this technology: *"quality of life is equally as important as longevity- sometimes more important."*

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• A diagnosis of MZL has a significant impact on the quality of life of patients. • There is an unmet need for treatment options following unsuccessful first line treatment. • Multiple treatment options are favourable, especially in rarer lymphoma where less trials are occurring. • Home administration and less reported toxicity are key factors when choosing a treatment option. • Treatment options are already proving advantageous and should be more widely available.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Zanubrutinib for treating relapsed or refractory marginal zone lymphoma [ID5085]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Friday 29 March**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating marginal zone lymphoma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Kim Linton
2. Name of organisation	The Christie NHS Foundation Trust
3. Job title or position	Clinical Senior Lecturer
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with marginal zone lymphoma? ☐ A specialist in the clinical evidence base for marginal zone lymphoma or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.) I have not seen the company submission
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	none
8. What is the main aim of treatment for marginal zone lymphoma?	To delay or prevent relapse or progression using the most effective and least toxic therapy available.

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. 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)	• PFS lasting 18 months or longer • PFS to Zanubrutinib lasting longer than PFS to previous line of therapy for relapsed disease • Delayed time to next treatment
10. In your view, is there an unmet need for patients and healthcare professionals in marginal zone lymphoma?	Yes, treatment options are limited to standard immunochemotherapy or rituximab alone for a minority of selected patients with relapsed SMZL/MALT subtypes. Older or frailer patients (who make up the majority of patients with r/r MZL) may not have any options after receiving non-intensive first line treatment (such as R; R-chlorambucil; RCVP) if they are not candidates for more intensive RCHOP or R-bendamustine. There is a significant unmet need for well tolerated novel agents for these patients.
11. How is marginal zone lymphoma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.) • What impact would the technology have on the current pathway of care?	• We have recently published the BCSH Guideline for the management of marginal zone lymphomas (Walewska et al, Br J Haematolo. 2024 Jan;204(1):86-107 • Treatment selection is limited to rituximab monotherapy (for a small group of selected patients) or immunochemotherapy (R-chlorambucil; R-CVP ; R-CHOP; R-bendamustine). Treatment choice depends on disease stage, MZL subtype, previous therapies, age and fitness, tolerance of previous treatment, availability of trials and clinician experience. The pathway of care is not well defined leading to differences in opinion between professionals (my experience is in England) • Access to zanubrutinib, which has demonstrated activity and safety across all MZL subtypes, patient age and fitness groups, would standardise care at relapse
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	• The technology, zanubrutinib, is not in routine use. Access has been possible in England via a compassionate use programme which ha, to my knowledge, been very well supported • Specialist lymphoma clinics in tertiary care

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	• No special facilities or equipment required (oral therapy). • Staff will need training in the management of side effects of this class of drug, however minimal impact to NHS staff as this class of drug (BTK inhibitors) is already widely used in clinical practise for treating lymphomas and most staff are very experienced
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	• Yes. Outcome data for zanubrutinib appear to produce higher response rates and longer PFS compared to other options, which may translate to longer survival, but comparisons with other therapies are limited by lack of published outcome data for commonly used regimens such as RCVP/RCHOP and R-chlorambucil. • It should be noted that regimens with published efficacy e.g. R-bendamustine are unsuitable for older and frailer patients who make up the majority of patients with r/r MZL • Also note that rituximab monotherapy is only a valid comparator for MALT and splenic MZL subtypes • Other regimens with published activity in r/r MZL e.g. ibrutinib and rituximab-lenalidomide are not available in England.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not to my knowledge
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use?	• Easier to use as current care is mostly given intravenously • More acceptable to patients due to oral dosing, favourable side effect profile and low monitoring requirements

(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	• Patients are monitored for safety, initially monthly while they are established on therapy. Patients who are tolerating treatment and achieving response (the majority of patients) can step down to 3 monthly reviews in the outpatient clinic, which reduces health care utilisation and improves the patient experience
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	• No special rules outside of standard stopping if there is unacceptable toxicity or the drug is not producing an objective radiological response and/or clinical benefit • No additional testing e.g. mutation testing, is required
17. 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? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Unable to comment as I have not seen the QALY calculation
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	• This is an innovative 'step-change' treatment in a treatment pathway addressing unmet need for patients with no available options and standardising care and pathways
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	• Minimally. This is a well tolerated treatment with a favourable side effect profile compared to first generation BTKis. Only 4/68 (5.8%) patients in the pivotal trial discontinued Zanubrutinib due to adverse events which compares favourably to rates for FDA approved options – ibrutinib (17%) and R-lenalidomide (15%)

20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	• Yes, very much so • PFS is the most important endpoint in my view and this was an important secondary endpoint in the pivotal phase 2 trial. • N/A • No
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Very closely based on anecdotal experience from the compassionate access programme. The trial population broadly reflects real world patients (median age of the trial population was 70 years, including 28% aged >75; 32% had refractory disease, all subtypes were represented. Perhaps more patients in real world practice would have ECOG 2, which only made up 7% of the trial population, but outcomes were very similar in subsets with ECOG 1 vs >=1
23. NICE considers whether there are any equalities issues at each stage of an evaluation. 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	No disadvantaged groups

belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. 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.	

NICE National Institute for Health and Care Excellence

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

This is an innovative treatment addressing unmet need

This treatment will standardise management of relapsed and refractory MZL in England

The drug is very well tolerated with low rates of discontinuation due to adverse events

This drug is suitable to use across the full range of patients presenting with relapsed and refractory MZL

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Zanubrutinib for treating relapsed or refractory marginal zone lymphoma [ID5085]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Friday 29 March**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1: Treating marginal zone lymphoma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Renata Walewska
2. Name of organisation	
3. Job title or position	Consultant Haematologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with marginal zone lymphoma? ☐ A specialist in the clinical evidence base for marginal zone lymphoma or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	none

8. What is the main aim of treatment for marginal zone lymphoma? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	the main aim of treatment is to achieve complete remission (CR) or partial remission (PR), improve symptoms (weight loss, sweats at night), signs (pancytopenia, associated autoimmune complications, threat of obstruction to vital organs, e.g. lesion threatening kidneys)
9. 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)	Response criteria SMZL, as per https://doi.org/10.1111/bjh.19064, table 10

Complete response	Resolution of splenomegaly (spleen length <13 cm)
	Resolution of cytopenias, with Hb >120 g/L, platelets >100 × 10^9/L, neutrophils >1.5 × 10^9/L
	No evidence of clonal B-cell population in peripheral blood by flow cytometry
	No evidence of bone marrow infiltration by immunohistochemistry
	No residual FDG-avid disease above background by PET (if positive at pretreatment assessment)
Partial response	≥50% Regression of measurable disease
	No new sites of disease
	10%–99% Improvement of cytopenias
	10%–99% Reduction of bone marrow infiltration
Stable disease/no change	≤10% Improvement in disease parameters

	Progressive disease >10% Increase in measurable disease from nadir or best response Progressive disease Reappearance of any measurable disease **Tumour Measurement Response Criteria** **WHO Criteria (1979)** Measure the sum of the products of diameters (SPD), bidimensional Complete Response: tumour not detected for at least 4 weeks Partial Response: ≥50% reduction in the SPD from baseline also confirmed at 4 weeks Progressive Disease: ≥25% increase in tumour size in one or more lesions Stable Disease: Neither partial response nor progressive disease Source: WHO handbook for reporting results of cancer treatment. Geneva (Switzerland): World Health Organization Offset Publication No. 48; 1979
10. In your view, is there an unmet need for patients and healthcare professionals in marginal zone lymphoma?	Yes, there is an unmet need for these indications. MZL is an orphan disease amongst all other B cell lymphomas when the only treatment available is chemoimmunotherapy (CIT), unlike CLL, MCL, and WM. Up to 17% of splenic marginal zone lymphomas have been reported to harbour 17p aberration https://doi.org/10.1016/j.pathol.2019.08.012, (these patients are refractory to CIT and should only be offered non-CIT type of therapy, yet there is a complete lack of non-CIT options for these patients.

	In addition, approximately 30% of patients will not achieve CR. Bendamustine-based therapies are only reserved for young fit patients; the immunosuppression is very significant, and even young patients experience 25% serious adverse events.
11. How is marginal zone lymphoma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.) • What impact would the technology have on the current pathway of care?	The recent British Society for Haematology guidelines: **https://doi.org/10.1111/bjh.19064** ESMO guidelines https://doi.org/10.1016/j.annonc.2019.10.010, Canadian prospective https://www.mdpi.com/1718-7729/30/2/135 The options for SMZL in the front line are: Rituximab monotherapy, splenectomy (for young, fit patients with minimal bone marrow involvement), CIT in the form of RCVP, for very young, fit patients R Bendamustine. The treatment for the nodal MZL follows the treatment algorithm for Follicular Lymphoma: RCHOP, RCVP, RB. The second line options are non-existent, and we are forced to reuse the first line. In all treatment situations, when the CIT is used in the second line, remissions are shorter than in the first line, the adverse events are more pronounced, and there is also an increased risk of clonal evolution leading to transformation. Therefore, the CIT should not be used in the second line and availability of targeted therapy would be welcomed in this group of patients.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	Zanubrutinib is currently available as the Free of Charge medication scheme for relapsed MZL patients funded by the company. Otherwise, no targeted therapies are available in this setting; as mentioned before, the only option is to reuse CIT from the front line. The zanubrutinib treatment would be delivered through secondary care in haematology outpatients.

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	No investment is needed to deliver the treatment; this type of treatment will save on day case time and infusion time.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	The results from the clinical trial are impressive: Opat *et al.*, Clinical Cancer Research 2021: ORR 68%, CR 26%, PFS 83% at 1 year, OS 95% at 1 year. I would expect this technology to improve quality of life, help patients getting back to work, and certainly improve OS and PFS.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Any patients requiring treatment for the relapsed disease, especially ones with short remission post-CIT, patients with TP53 aberrations.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current	The tolerability of this second-generation BTKi is excellent; patients can be seen infrequently in the clinic for repeat prescriptions, and those visits can be done remotely. There are interactions with CYP34a inhibitors and inducers, in clinical practice, the main issue is if patient requires concomitant azole treatment for fungal infections (quite rare occurrence) and treatment with calcium channel blockers for hypertension.

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)	Clinicians are accustomed to these interactions since we have been using ibrutinib for more than 10 years in chronic lymphocytic leukaemia (CLL)
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Stop and start will depend on unexpectable toxicities and progressive disease. These can be re-assessed every 3-4 months when the patient is reviewed for re-prescribing. The prescriber assesses adverse events and for possible disease progression. This is the mainstay of clinical practice.
17. 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? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Zanubrutinib offers ease of administration and dose adjustments in case of adverse events.
18. Do you consider the technology to be innovative in	Zanubrutinib is an important mode of treatment for these patients.

its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	It will reduce disease volume, in turn improve symptoms, quality of life.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	One of the most common side effects is neutropenia, which can be controlled with dose reduction (the pharmacokinetics of this product are excellent and give a good range of dose adjustments with still good drug occupancy on the BTK target.it is important to empower patients to monitor for hypertension.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do	The MAGNOLIA study enrolled mainly in the Western world, and treated 68 patients at 31 sites across 9 countries (Australia, China, Czech Republic, France, Italy, New Zealand, South Korea, the United Kingdom, and the United States) The latest update of this study reported no additional late-onset toxicities and no new safety signals observed after longer treatment duration and follow-up.

they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Ibrutinib RR RWD in US: https://jhoonline.biomedcentral.com/articles/10.1186/s13045-022-01316-1 Describes effectiveness of Ibrutinib, a first generation of BTK inhibitor in this disease in relapsed disease, 58% achieved overall response and 17% with complete response; the median PFS and OS were 29 and 71.4 months, patients with complex cytogenetics had inferior PFS and OS; these are similar data we have seen in CLL treated with Ibrutinib. Ibrutinib TN in RWD in US, 12 patients age range 52-86, ORR 83%, and CR 42%, responses were durable, PFS at 3 years was 55.6%, this study also mirrors experience of BTKi in front line in CLL, the outcomes tend to be better in earlier lines of therapy https://ashpublications.org/bloodadvances/article/-8/3/549/506612/Outcomes-of-marginal-zone-lymphoma-treated-with. German registry: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8453851/ This study presents 175 cases and reflects German routine practice: rituximab-bendamustine (BR) for a median of 6 cycles was the most frequently used first-line (76%) and second-line treatment (36%).The ORR for patients encompassing any positive response was 81%. For patients with MALT and non-MALT MZL, respectively, 5-years PFS was 69% (95% CI 52%–81%) and 66% (95% CI 56%–75%), 5-years OS 79% (95% CI 65%–89%) and 75% (95% CI 66%–83%). Cox proportional hazards models showed a significantly increased risk of mortality for higher age in all patient groups. US registry https://www.sciencedirect.com/science/article/pii/S0006497121049855

	This study examines real-world treatment patterns, costs and healthcare resource utilization for patients with different lymphomas (MCL, WM, CLL, MZL), as well as identify disparities and risk factors associated with costs incurred in US hospitals. There were 2,655 MZL, with age range of (69.3 ± 33.8 years). Non-white patients have significantly longer mean LOS (length of stay) days compared with white patients (CLL: 18.3 vs. 14.8; MCL: 21.7 vs. 18.3; MZL: 21.6 vs. 18.5; WM 19.0 vs. 14.5). Across the 4 lymphoma types, multivariable regression confirmed the descriptive results and demonstrated that higher hospitals costs were associated with patients who were non-white, Hispanic/Latino, treated in hospitals located in the Northeast or West, or had Medicaid; statistically significant increased cost of care was also noted for patients who received targeted therapy or supportive care, such as blood transfusion or GCSF. There is significantly high total hospital costs once patients with MCL, WM, MZL, and CLL patients were hospitalised, with significantly higher impact to minority populations Given the increased availability of effective oral therapeutics, optimal and timely disease control in the outpatient setting can potentially prevent or decrease hospitalisations and reduce economic burden on healthcare systems and payors. Health economics US DOI: 10.1200/JCO.2022.40.16_suppl.e18730 "Real-world treatment patterns and economic burden of patient with MZL" this study was conducted using the IBM MarketScan® commercial and Medicare supplemental claims dataset, 2491 MZL pts, (median age = 63; 52% male), A total of 1,781 (72%) pts received first-line (1L), 518 (29%) pts received second-line (2L) and 239 (13%) pts received third-line (3L) therapies. Overall MZL patients had PPPM (per-patient-per-month) 4.6 outpatient visits, 0.5 hospitalisation, and mean length of stay of 2.6 days. Total PPPM healthcare cost was $19,895.8. Multivariable regression showed that baseline comorbidities (AF, renal disease, neutropenia) and treatment discontinuation were significant predictors of higher costs and HRU (healthcare resource utilisation). The closing conclusion was: MZL patients incur high economic burden.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when	I am not aware of any issues with inequalities.

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. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people.	

Please consider whether these issues are different from issues with current care and why. 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.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Zanubrutinib for treating relapsed or refractory marginal zone lymphoma [ID5085]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with marginal zone lymphoma or caring for a patient with marginal zone lymphoma. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

NICE National Institute for Health and Care Excellence

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Friday 29 March 2024**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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Part 1: Living with this condition or caring for a patient with marginal zone lymphoma

Table 1 About you, marginal zone lymphoma, current treatments and equality

1. Your name	Frank Burroughs
2. Are you (please tick all that apply)	☒ A patient with marginal zone lymphoma? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with marginal zone lymphoma? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Lymphoma Action
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the

	expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with marginal zone lymphoma? **If you are a carer (for someone with marginal zone lymphoma) please share your experience of caring for them**	I was diagnosed with stage 4 extra-nodal MZL in the summer of 2018. I had been feeling run down and tired for some time. I had no idea that it was lymphoma as I had no visible swollen lymph nodes. Several years before, I experienced a constant upset stomach, sudden weight loss and night sweats. These symptoms lasted for about 8 weeks. Oddly, they stopped as suddenly as they started. When I was diagnosed it began to make sense. The news came as a big shock as my sister had died from NHL in 2013 after a short illness. I naturally feared the worst. I coped well with the chemotherapy, but I did feel poorly for the six months of treatment. I decided to retire as I did not feel well enough to carry on working. Since ending my treatment, I enjoy a high quality of life. I have been able to get fit and lose the weight that I put on from the steroids. I exercise regularly and have had no repeat of my earlier symptoms. I have a good idea of what to look out for should the disease come back or transform.
7a. What do you think of the current treatments and care available for marginal zone lymphoma on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	a. Looking back, I believe it took far too long to get to the point of having an accurate diagnosis. I had a 60th birthday check-up with my GP in February 2018, but I did not start chemotherapy until September. By then my disease had progressed to stage 4 and I was seriously unwell. It seems to me that a big part of the delay was caused by each individual step happening in sequence, with a wait of several weeks for each appointment, followed by several weeks more waiting for the results. While each individual step may have met its NHS service standard, put them all together and the delay was unacceptable. (I had an ultrasound scan, a urology check-up, a full scan,

	and a biopsy). The quality of care could have been improved if some of these steps had taken place together at a 'super-clinic' rather than in sequence. After my diagnosis, the area below my lung needed to be drained and my chemotherapy could not start until this happened. The care that I received from the haematology team at Southmead Hospital once I got to that point was excellent. And the coordination with Respiratory and Urology worked well too, as specialists in these areas were needed to make sure that what was showing up on my left kidney and right lung were indeed lymphoma and not something else entirely. The treatments that I received (RCVP, followed by maintenance Rituximab) worked well and drove the disease back. I tolerated the treatment well. There are no overall long-term side effects other than deterioration in my overall kidney function. b. I had the benefit of being treated at a major regional hospital that had Haematology, Respiratory and Urology specialist units on site. Others may not get the same quality of care. My sister, for example, had part of her care delivered by her local hospital in Yorkshire, and for the remainder of her care she travelled to the major regional centre in Leeds. It may have advantages for all NHL care to be given in stronger regional centres which have access to a range of specialists and all the resources necessary.
8. If there are disadvantages for patients of current NHS treatments for marginal zone lymphoma (for example, how they are given or taken, side effects of treatment, and any others) please describe these	The toxicity of chemotherapy is a concern as it may have contributed to the impairment of my kidney function. I do worry whether I will be able to tolerate further treatment of this sort should my disease relapse. During the treatment, I travelled to Southmead Hospital on many occasions. At some points, I was there once a week. The hospital is about an hour's drive away. Some eldery patients I know find driving across a city such as Bristol to be very difficult. Having the opportunity to have a drug that can be taken at home would be very beneficial for some patients and would free up time and space at the hospital.
9a. If there are advantages of zanubrutinib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your	The main advantage is the possibility of avoiding the toxicity associated with chemotherapy together with the chance of further good quality of life.

ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does zanubrutinib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
10. If there are disadvantages of zanubrutinib over current treatments on the NHS please describe these. For example, are there any risks with zanubrutinib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I'm not aware of any substantial risks with Zanubrutinib.
11. Are there any groups of patients who might benefit more from zanubrutinib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Patients that do not have access to transport would benefit from being able to take the drug at home daily and make only occasional visits to hospital.
12. Are there any potential equality issues that should be taken into account when considering marginal zone lymphoma and zanubrutinib? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	NA

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.	
13. Are there any other issues that you would like the committee to consider?	NA

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- The quality of care for MZL NHL could be improved by accelerating the time it takes reach a diagnosis and start treatment.
- The quality of care that I received during treatment was excellent and as my hospital was a major regional centre it had the ability to coordinate care effectively across the teams I needed, including Haematology, Respiratory and Urology.
- Chemotherapy (RCVP) was effective at treating my disease although further treatment comes with risks of side effects.
- Zanubrutinib is an effective treatment that brings the possibility of good quality of life with less toxicity and lower risks.
- Taking Zanubrutinib at home is an attractive option that reduces hospital visits.

Thank you for your time.

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Zanubrutinib for treating relapsed or refractory marginal zone lymphoma [ID5085]

Produced by Newcastle University

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Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Any de-personalised data are highlighted in pink throughout the report.

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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Gurdeep S Sagoo acted as project lead. Katie Thomson acted as lead effectiveness reviewer. Tomos Robinson acted as lead health economist. Fiona Beyer acted as lead reviewer of the literature search methods. Eugenie Evelynne Johnson and Cyril Onwuelazu Uteh acted as assistant effectiveness reviewers. Najmeh Moradi acted as assistant health economics reviewer. Alex Inskip assisted in reviewing the literature search methods.

Abbreviations

AdViSHE	Assessment of the Validation Status of Health Economic Decision Models
AE	Adverse event
AIC	Akaike's Information Criterion
anti-CD20	Anti-cluster of differentiation 20
ASCT	Autologous stem cell transplant
BIC	Bayesian Information Criterion
BM	Bone marrow
BNF	British National Formulary
BR	Bendamustine-rituximab
BSA	Body surface area
BSC	Best supportive care
BSH	British Society for Haematology
BTKi	Bruton tyrosine kinase inhibitor
CADTH	Canadian Agency for Drugs and Technology in Health
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CI	Confidence interval
CIT	Chemoimmunotherapy
CR	Complete response
CS	Company submission
CSR	Clinical study report
CT	Chemotherapy
CUA	Cost-utility analysis
CVP	Cyclophosphamide, vincristine and prednisolone
DCO	Data cut-off
DES	Discrete event simulation
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	Evidence Assessment Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eMIT	Electronic market information tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire
EQ-5D	EuroQol 5 Dimension
EQ-5D-5L	EuroQol 5 Dimension 5 Level
ESMO	European Society for Medical Oncology
ESS	Effective sample size
EU	European Union
FACT-G	Functional Assessment of Cancer Therapy - General
FACT-LYM	Functional Assessment of Cancer Therapy - Lymphoma
FCR	Fludarabine, cyclophosphamide and rituximab
FL	Follicular lymphoma
G-CSF	Granulocyte colony stimulating factor
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
INAHTA	International Network of Agencies for Health Technology Assessment
iNHL	Indolent non-Hodgkin lymphoma
INV	Investigator-assessed

IRC	Independent review committee
ITC	Indirect treatment comparison
KM	Kaplan-Meier
IVE	Ifosfamide, etoposide, epirubicin
LDH	Lactate dehydrogenase
LDi	Longest transverse diameter
LN	Natural Logarithm
LTE	Long-term extension
LYG	Life years gained
m	Metre
MAIC	Matching-adjusted indirect comparison
MALT	Mucosa-associated lymphoid tissue
MRD	Minimal residual disease
MZL	Marginal zone lymphoma
NE	Not estimable
NHB	Net health benefit
NHL	Non-Hodgkin lymphoma
NHS	National Health Service
NHS-EED	National Health Service-Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analyses
NMB	Net monetary benefit
NMZL	Nodal marginal zone lymphoma
O-Benda	Obinutuzimab + bendamustine
ONS	Office for National Statistics
ORR	Overall response rate
OS	Overall survival
PAS	Patient Access Scheme
pCODR	Pan-Canadian Oncology Drug Review
PD	Progressed disease
PfC	Points for clarification
PFS	Progression-free survival
PK	Pharmacokinetics
POD24	Progression of disease within 24 months
PPS	Post-progression survival
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal social services
QALY	Quality-adjusted life year
QoL	Quality of life
R^2	Lenalidomide + rituximab
R-CHOP	Rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone
RCT	Randomised controlled trial
R-CVP	Rituximab + cyclophosphamide + vincristine + prednisone
ROBINS-I	Risk Of Bias in Non-randomised Studies – of Interventions
R/R	Relapsed or refractory
SAE	Serious adverse event
SE	Standard error
SIGN	Scottish Intercollegiate Guidelines Network
SLL	Small lymphocytic lymphoma
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMR	Standardised mortality ratio

SMZL	Splenic marginal zone lymphoma
STA	Single technology appraisal
STM	State transition model
TEAE	Treatment-emergent adverse event
TSD	Technical support document
TTD	Time to discontinuation
TTF	Time to treatment failure
TTNLT	Time to next line of therapy
TTR	Time to response
UK	United Kingdom
USA	United States of America
VCD	Bortezomib (Velcade), cyclophosphamide and dexamethasone

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1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence 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 1.2 presents the key model outcomes. Section 1.3 relates to the clinical effectiveness, and Section 1.4 relates to the cost effectiveness. A summary of the results is presented in Section 1.5.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main EAG report, see Sections 2 (decision problem), 3 (clinical effectiveness) and 4-6 (cost effectiveness) for more details.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1: Summary of key issues

ID5085	Summary of issue	Report sections
1	Uncertainty due to lack of an RCT	3.2, 3.4
2	Uncertainty in the results of the MAIC	3.3
3	The choice of a partitioned survival model	4.2.2
4	Uncertain PFS and OS predictions for zanubrutinib	3.2, 4.2.6
5	Uncertainty in the choice of parametric survival functions used in the economic model	4.2.6
6	Uncertainty in the utility values for the PFS and PD health states used in the economic model	4.2.8

Abbreviations: MAIC = matching-adjusted indirect comparison; RCT = randomised controlled trial; PD = progressed disease; PFS = progression-free survival

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are 1) the use of updated costs; 2) AEs; and 3) the use of an alternative utility value for the PD health state. In addition, the EAG performed exploratory scenario analyses to explore the impact of alternative parametric survival curves.

1.2 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 incremental cost effectiveness ratio (ICER) is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing overall survival (OS);
- Increasing progression-free survival (PFS).

Overall, the technology is modelled to affect costs by:

- Higher unit price than current treatments

The modelling assumptions that have the greatest effect on the ICER are:

- Use of the pooled MAGNOLIA-003 dataset for treatment effectiveness;

- Inclusion of age-sex matched background mortality restriction;
- Choice of parametric survival curves for PFS.

1.3 The clinical effectiveness evidence: summary of the EAG's key issues

Table 1.2: Key issue [1] – Uncertainty due to lack of RCT evidence

Report section	**3.2, 3.4**
Description of issue and why the EAG has identified it as important	The clinical effectiveness evidence of zanubrutinib for R/R MZL patients is derived from two single-arm clinical trials, AU-003 and MAGNOLIA, which are Phase 1/2 and 2, respectively. In certain rare diseases, including rare cancers, it is not unusual for clinical data from such trials to be used as pivotal evidence in marketing authorisation applications or health technology assessments. However, such single-arm trials are subject to methodological limitations necessitating comparison with other data to demonstrate treatment benefit. Furthermore, the lack of an available RCT has methodological implications for the MAIC (see Key Issue 2 for further discussion).
What alternative approach has the EAG suggested?	The EAG suggests no alternative approach.
What is the expected effect on the cost effectiveness estimates?	We believe this to be a currently unresolvable issue that is a cause of great uncertainty. The effect on the cost effectiveness estimate is unclear.
What additional evidence or analyses might help to resolve this key issue?	Additional real-world evidence data could be routinely collected if zanubrutinib was to be given a NICE recommendation. These data could be used to revisit conclusions about effectiveness and cost-effectiveness for patients with R/R MZL.
Abbreviations: EAG = Evidence Assessment Group; HMRN = Haematological Malignancy Research Network; MAIC = matching-adjusted indirect comparison; MZL = marginal zone lymphoma; NICE = National Institute for Health and Care Excellence; RCT = randomised controlled trial; R/R = relapsed or refractory	

Table 1.3: Key issue [2] – Uncertainty in the results of the MAIC

Report section	**3.3**
Description of issue and why the EAG has identified it as important	The company claim zanubrutinib is superior to a basket of treatments taken from the HMRN registry in the CS in terms of both PFS (IRC) and OS. However, the EAG note that the MAIC is subject to methodological limitations that leave the results open to uncertainty. These include: 1.) The use of an unanchored MAIC, which is inherently open to uncertainty. This is particularly challenging for this condition due a lack of epidemiological data and therefore difficult to rule out and quantify the impact of important unknown confounders and effect modifiers. 2.) The lack of participant characteristics available from the HMRN registry basket of treatments to adequately compare and adjust using data from the pooled MAGNOLIA-003 trials. This is particularly challenging for this condition due to a lack of epidemiological data and therefore it is difficult to rule out and

Report section	3.3
	quantify the impact of important unknown confounders and effect modifiers. 3.) Only five covariates were included within the MAIC model due to the lack of available baseline data from the HMRN registry. As a result of these methodological limitations, the EAG believes that the results of the MAIC are open to a large amount of uncertainty.
What alternative approach has the EAG suggested?	With regards the MAIC methodology, the EAG have no suggested alternatives. As there is no RCT evidence, any MAIC conducted by the company would be unanchored and therefore subject to uncertainty (see Key Issue 1). The EAG also acknowledge that, due to the lack of demographic information available from the HMRN registry, issues surrounding the comparability of MAGNOLIA-003 with patients in the HMRN registry and the lack of covariates available to match within the MAIC is difficult to resolve.
What is the expected effect on the cost effectiveness estimates?	Due to the uncertainties, lack of an alternative approach and lack of further available data, the EAG are unable to comment on whether more evidence would either increase or reduce the incremental cost-effectiveness ratios (ICERs).
What additional evidence or analyses might help to resolve this key issue?	Further comparable evidence with zanubrutinib for patients with R/R MZL may facilitate further MAICs with other treatments. An RCT of zanubrunitib in patients with R/R MZL may help enable the conduct of an anchored MAIC in the future (see Key Issue 1). Additionally, further real-world evidence surrounding treatment effectiveness in the MZL population may facilitate further comparisons.
Abbreviations: EAG = Evidence Assessment Group; HMRN = Haematological Malignancy Research Network; ICER = incremental cost-effectiveness ratio; IRC = independent review committee; OS = overall survival; MAIC = matching-adjusted indirect comparison; MZL = marginal zone lymphoma; PFS = progression-free survival; RCT = randomised controlled trial; R/R = relapsed or refractory	

1.4 The cost effectiveness evidence: summary of the EAG's key issues

Table 1.4 Key issue [3] - The choice of a partitioned survival model

Report section	4.2.2
Description of issue and why the EAG has identified it as important	The choice of a partitioned survival model (PSM). PSMs are commonly used in advanced or metastatic cancers and have been accepted by NICE in a number of previous health technology appraisal submissions. However, PSMs have a key methodological limitation in that in these models, health state occupancy is based on a set of non-mutually exclusive survival curves. This has a number of implications, principally that the extrapolations produced from these survival curves may not be appropriate.
What alternative approach has the EAG suggested?	The EAG have suggested that a state transition model (STM) could be a more appropriate model structure for the decision

Report section	4.2.2
	problem, however, acknowledge that data limitations may inhibit the parametrisation of such a model in this specific context.
What is the expected effect on the cost effectiveness estimates?	The effect on the cost effectiveness estimates is unclear.
What additional evidence or analyses might help to resolve this key issue?	A STM presented alongside the existing PSM could resolve the uncertainty related to the model structure. The EAG acknowledge that data limitations may inhibit the parametrisation of such a model in this specific context.
Abbreviations: EAG = Evidence Assessment Group; PSM = Partitioned survival model;	

Table 1.5: Key issue [4] - Uncertain PFS and OS predictions for zanubrutinib

Report section	3.2.1.2, 3.2.2.3.1, 3.4, 4.2.6
Description of issue and why the EAG has identified it as important	The primary efficacy outcomes for MAGNOLIA and AU-003 were ORR, with PFS and OS being secondary outcomes. Sufficient ORR events occurred to conduct the final analysis on the primary outcome. [redacted] As noted in Key Issue 3, PFS and OS are the key inputs in the PSM used by the company to demonstrate cost effectiveness. The small numbers of patients to have progressed or died by the end of the MAGNOLIA and AU-003 clinical trials are a cause of inherent uncertainty in the cost effectiveness analysis, as it makes long term predictions very difficult.
What alternative approach has the EAG suggested?	The EAG is not able to resolve the uncertainty caused by data immaturity.
What is the expected effect on the cost effectiveness estimates?	The effect on the cost effectiveness estimates is unclear.
What additional evidence or analyses might help to resolve this key issue?	Collection of long-term follow-up data. The long-term extension study which patients from both MAGNOLIA and AU-003 have been moved onto may be able to provide further evidence.
Abbreviations: DCO = data cut-off; EAG = Evidence Assessment Group; INV = investigator-assessed; IRC = independent review committee; PSM = partitioned survival model; PFS = progression-free survival; ORR = overall response rate; OS = overall survival	

Table 1.6: Key Issue [5] Uncertainty in the choice of parametric survival curve

Report section	4.2.6
Description of issue and why the EAG has identified it as important	As noted in Key Issue 4, the estimates for PFS and OS for zanubrutinib are subject to considerable uncertainty given the immaturity of the data and small number of PFS and OS events in the MAGNOLIA and AU-003 trials. As a consequence of this, the extrapolations for these outcomes are also extremely

Report section	4.2.6
	uncertain, with significant heterogeneity in the predictions from different parametric survival curves with almost identical statistical fit. This issue is particularly pertinent in a PSM framework, given that the results will be particularly sensitive to the predictions of PFS and OS. Although the data from the HMRN registry basket is more mature, the EAG again note that there is heterogeneity between the long-term PFS and OS predictions from different parametric curves with almost identical statistical fit. Furthermore, there is a lack of concurrence between the estimates from the various parametric survival curves and clinical expert opinion gathered by both the company and the EAG.
What alternative approach has the EAG suggested?	The EAG have explored alternative survival curves in the EAG scenario analysis.
What is the expected effect on the cost effectiveness estimates?	The EAG scenario analyses increases or decreases the ICER depending on the specific scenario.
What additional evidence or analyses might help to resolve this key issue?	The EAG has no suggestions for additional analysis.
Abbreviations: EAG = Evidence Assessment Group; HMRN = Haematological Malignancy Research Network; ICER = incremental cost-effectiveness ratio; PFS = progression-free survival; OS = overall survival	

Table 1.7: Key Issue [6] Uncertainty in the utility values for the PFS and PD health states

Report section	4.2.8
Description of issue and why the EAG has identified it as important	Different sources were used by the company to inform health state utility values in the economic model. The utility value for the PFS state was estimated from the MAGNOLIA trial. The company argued that this health utility value lacked face validity when compared to utility values from the age-sex matched general population, and therefore the company capped this value at the age-sex matched general population level. The utility value for the PD health state was taken from CADTH pCODR submission for bendamustine for NHL. The PD utility value from CADTH pCODR is uncertain, as the study it is taken from is a different clinical condition in a Canadian population, and therefore not aligned to the decision problem. Although scenario analyses were undertaken to address the uncertainty around both values, these utility values are a source of uncertainty.
What alternative approach has the EAG suggested?	The EAG has explored alternative HRQoL utility values in the EAG base-case and EAG scenario analyses.
What is the expected effect on the cost effectiveness estimates?	The use of the EAG preferred utility values increases the ICER.
What additional evidence or analyses might help to resolve this key issue?	Additional evidence about the HRQoL of MZL patients in the UK may help to resolve this issue.

Report section	4.2.8
Abbreviations: CADTH = Canada's Drug and Health Technology Agency; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; NHL = non-Hodgkin lymphoma; PD = progressed disease; PFS = progression-free survival	

1.5 Summary of the EAG's view

The EAG base-case included the EAG's preferred assumptions. Based on the deterministic results, the ICER for zanubrutinib was £26,612 per QALY gained. The probabilistic EAG base-case with 1,000 replications indicated that zanubrutinib has a [redacted] chance of being cost-effective compared to the HMRN basket at a willingness to pay threshold of £20,000 per QALY gained and a [redacted] chance of being cost-effective at a willingness to pay threshold of £30,000 per QALY gained. The probabilistic EAG base-case with 5,000 replications indicated that zanubrutinib has a [redacted] chance of being cost-effective compared to the HMRN basket at a willingness to pay threshold of £20,000 per QALY gained and a [redacted] chance of being cost-effective at a willingness to pay threshold of £30,000 per QALY gained.

The most influential scenario analyses were:

1) the use of the MAGNOLIA trial data only for zanubrutinib rather than the pooled MAGNOLIA-003 dataset;
2) the inclusion of age-sex matched background mortality restriction; and
3) implementing the most conservative parametric survival curves for PFS.

The EAG identified several issues with the cost-effectiveness analysis, including the use of a PSM despite their methodological limitations, the immaturity of the PFS and OS data from the key clinical trials and consequential uncertainty related to the long-term predictions from the parametric survival analyses and uncertainty related to the utility values used in the model. There is also considerable uncertainty related to the unanchored MAIC used to match the data from the zanubrutinib trials to the data from the HMRN registry. Given these various issues, overall the EAG consider the cost-effectiveness results to be subject to considerable uncertainty.

Table 1.8 and Table 1.9 summarise the company's and EAG's base-case results.

Table 1.8: Summary of company's base-case results

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)
Company base-case (Deterministic)	[redacted]	[redacted]	26,197
Company base-case (Probabilistic – 1000 replications)	[redacted]	[redacted]	27,217
Company base-case (Probabilistic – 5000 replications)	[redacted]	[redacted]	26,814
Source: Produced by the EAG. Abbreviations: CS = company submission; HMRN = Haematological Malignancy Research Network; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years			

Table 1.9: Summary of EAG's base-case results

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)
EAG base-case (Deterministic)	[redacted]	[redacted]	26,612
EAG Base-Case (Probabilistic – 1000 replications)	[redacted]	[redacted]	27,141
EAG base-case (Probabilistic – 5000 replications)	[redacted]	[redacted]	27,238

Source: Produced by the EAG.
Abbreviations: CS = company submission; HMRN = Haematological Malignancy Research Network; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years

2 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (as presented by the company)

	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 MZL who have had at least 1 prior anti-CD20-based therapy	As per scope	N/A	The population is in line with the NICE scope.
Intervention	Zanubrutinib	As per scope	N/A	The population is in line with the NICE scope.
Comparator(s)	• Rituximab with or without chemotherapy • Chemotherapy • Best supportive care • Splenectomy (for splenic marginal zone lymphoma only)	• Rituximab with or without chemotherapy • Chemotherapy	The following treatments listed as comparators within the final scope are not considered appropriate for adults with MZL who have had at least one anti-CD20-based therapy, as confirmed by UK clinical experts in attendance at an advisory board (11th October 2023):[1] Splenectomy: Splenectomy is not recognised as a treatment option for patients with R/R MZL within the ESMO guidelines. Instead, the guidelines emphasise that splenectomy was traditionally considered as the recommended first-line treatment for patients with splenic MZL. However, as a major, non-curative surgical procedure that may have severe, acute, and potentially fatal downstream complications, it has largely been replaced by rituximab (with or without chemotherapy) and only considered in very select cases where rituximab is	The comparators are largely in line with the NICE scope. Clinical advice to the EAG has highlighted rituximab may have only limited use in this patient population. The updated BSH guidance states the specific circumstances that the use of single agent rituximab and splenectomy might be considered relevant.[3] The EAG agree with the company that BSC is not appropriate, and whilst the use of a splenectomy might prove helpful for some R/R MZL patients, for the majority, these treatments are typically not used in English NHS practice. Further information is provided in Section 2.1.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
			not indicated.5 Data from the HMRN registry shows that out of [redacted] patients diagnosed with MZL between 2005 to 2020, only [redacted] patients had received a splenectomy, which was performed close to diagnosis as part of their first-line treatment.6 UK clinical experts in attendance an advisory board (11th October 2023) confirmed that splenectomy is not a relevant comparator for this decision problem.[1] **BSC**: The approach to care for patients with R/R MZL involves active monitoring or systemic treatment. For MZL patients with recurrent disease, ESMO guidelines recommend treatment with rituximab-based CIT or rituximab monotherapy.[2] Feedback gathered from a UK advisory board (11th October 2023) confirmed that BSC is only considered once patients have exhausted all viable treatment options, including clinical trials, and are too frail to tolerate any active therapy. As such, BSC would be considered as end-of-life care and not as a comparator for zanubrutinib in patients able to receive active treatment.	
Outcomes	• Overall survival • Progression-free survival • Response rates	As per scope	N/A	MAGNOLIA included all outcomes as reported in the NICE decision problem. This

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
	• Duration of response • Adverse effects of treatment • Health-related quality of life			included OS, PFS, response rates (ORR and TTR), DOR, adverse effects of treatment (AEs, SAEs and TEAEs) and HRQoL (EORTC QLQ-C30 and EQ-5D-5L) amongst others (see Table 11, CS Document B for full list).[4] AU-003 included outcomes related to OS, PFS, response rates (ORR and TTR), DOR and adverse effects (AEs) amongst others (see CS Table 27, Document B for full list).[4] The EAG are satisfied that the outcomes across the two clinical trials match the decision problem.
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	A cost-utility analysis in adults with MZL who have had at least 1 prior anti-CD20-based therapy is presented comparing zanubrutinib with relevant comparators. For further details please refer to Section B.3 Cost effectiveness.[4].	N/A	The cost-effectiveness of the treatments was expressed in terms of quality-adjusted life years with a lifetime time horizon. Costs were considered from an NHS and Personal Social Services perspective and were taken from appropriate sources.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
	outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services 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.			The EAG are satisfied that the cost effectiveness analysis was conducted in line with NICE scope.

Source: CS Table 1 (Section B.1.1, p.8-10)[4]

Abbreviations: AE = adverse event; BSC = best supportive care; BSH = British Society for Haematology; CIT = chemoimmunotherapy; CS = company submission; DOR = duration of response; EAG = Evidence Assessment Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire; ESMO = European Society for Medical Oncology; HMRN = Haematological Malignancy Research Network; MZL = marginal zone lymphoma; N/A = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; ORR = overall response rate; OS = overall survival; R/R = relapsed/refractory; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TTR = time to response

2.1 Comparators

The description of the comparator detailed by the company is largely in line with the NICE scope.[5] It includes rituximab (with or without chemotherapy) and chemotherapy.

Clinical advice to the EAG indicated that rituximab monotherapy may not be a relevant comparison in the majority of R/R MZL patients, the exception being very elderly patients who are not able to tolerate chemotherapy. The most recent British Society for Haematology (BSH) guidance states that rituximab monotherapy is an "*option for patients with symptomatic relapsed splenic MZL and extranodal MZL/mucosa-associated lymphoid who have previously achieved a durable response to rituximab monotherapy*" (p. 16).[3]

In the CS, the use of BSC was also not considered as an appropriate comparison.[4] This was only deemed an option for patients who had exhausted other treatments and were considered end-of-life. Clinical advice to the EAG confirmed this as an appropriate assumption. Treatment with a splenectomy (for splenic MZL only) was also considered inappropriate in the CS.[4] Clinical advice again confirmed to the EAG that this is acceptable. However, the EAG note that, in the most recent (BSH) guidance,[3] splenectomy may be an option for *"selected patients with re-lapsed splenic MZL when rituximab monotherapy is ineffective or contraindicated"* (p. 16). Data from the United States indicates that approximately 9% of MZL cases were splenic,[6] so it is likely that splenectomy is only an appropriate treatment option for very few patients. This was confirmed by the company's analysis of the HMRN registry, which illustrated that of the [redacted] patients diagnosed with MZL between 2005 and 2020, [redacted] patients ([redacted]%) had received a splenectomy. As such, the EAG finds it acceptable that splenectomy was not considered an appropriate comparator in the CS.

In the CS,[4] treatment of MZL was said to predominantly follow the ESMO 2020 consensus clinical guidelines.[7] During submission of the CS, the most recent guidance from the BSH was published.[3] The company describes how, due to the short time frame, "*they were not able to incorporate these guidelines fully into submission however, the BSH guidelines are consistent with ESMO guidelines*" (p.23).[4] In response to clarification (Question A3), the company provided key differences between the ESMO and BSH guidance (see Table 2, PfC response).[8] The company reiterate that there are no major differences between the ESMO and BSH guidelines, and treatment recommendations are "*almost identical"* (p.4). They go on to say that the HMRN treatment basket appears to be "*well aligned with the BSH guidelines*" (p.4), and therefore they don't anticipate any implications for the clinical and cost-effectiveness evidence presented in the CS.[8] The EAG are broadly supportive of this assertion. Some treatments such as autologous stem cell transplant (ASCT) were identified in the BSH guidance as an option for selected fit patients with MZL,[3] however, this wasn't considered a relevant comparator in the final scope.[5] As such, the EAG are satisfied that the comparators listed in the NICE scope are those most typically seen in UK clinical practice.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The CS describes a systematic literature review (SLR) conducted to identify evidence on the efficacy and safety outcomes associated with R/R MZL. The methods of the SLR are detailed in Appendix D of the CS.[9] The SLR is broader than the NICE scope, focusing on two research questions concerning:

i. the clinical and safety of systemic treatments for MZL in patients with R/R disease requiring systemic therapy after previously receiving at least one anti-CD20-based therapy;

ii. the epidemiology of R/R MZL after previously receiving at least one anti-CD20-based therapy. No protocol was reported.

Table 3.1 details a summary of the EAG's critique of the methods used by the company to identify evidence relevant to the decision problem. The EAG's assessments (detailed in bold) are on a three-point Likert scale (key issue, some concerns or appropriate).

Table 3.1: Summary of the EAG's critique of the methods implemented by the company to identify evidence relevant to the decision problem.

Systematic review step	Section in CS where methods are reported	EAG's assessment of the robustness of methods
Data sources	Appendix D1.2, p.1-11 Appendix G1.2, p.1-15	**Some concerns** An appropriate range of bibliographic databases were used. One relevant conference was omitted and only the most recent two years of conference abstracts were searched.
Search strategies	Appendix D1.2, p.1-11 Appendix G1.2, p.1-15	**Some concerns** Search strategies were well reported. Certain thesaurus headings and abbreviations were omitted from some search strategies. Clinicaltrials.gov was restricted to 'completed studies'. All of these minor issues individually risked missing relevant studies, but taken as a whole the searches are likely to have captured most relevant material.
Inclusion criteria	Appendix D1.3, p.12-13	**Some concerns** The SLR had a broader inclusion criterion compared with that specified in the NICE scope.[5] Whilst the EAG are satisfied that the population/intervention/comparator are appropriate, there remains some concern with the study design/additional limits components of the inclusion criteria. These are discussed in more detail in Sections 3.1.1.1 and 3.1.2.
Screening	Appendix D1.3.1, D1.3.2, D1.4, p. 14-17	**Appropriate** Screening was done in duplicate, with disagreements arbitrated by a third reviewer. The flow of studies through the review is shown in the accompanying PRISMA flow charts (original SLR, and update). Seven studies were identified from the SLR, four were single arm clinical trials, and three were RCTs.[9]

		The EAG finds the approaches adopted in the CS robust and the screening of studies with reference to the NICE scope appropriate.
Data extraction	Appendix D1.3.3, p.14	**Some concerns** The CS stated data extraction was performed by a single investigator in Excel, and validated by a second, senior investigator with discrepancies resolved through discussion with a third reviewer.[9] The company are the sponsors of the two clinical trials identified from the SLR and, as such, have direct access to the trial data. The EAG finds this approach acceptable. An important aspect of collating data for inclusion in the SLR is seeking out key unpublished information that is missing from reports of included studies. This was not undertaken, and was justified by the company. This is further described in Section 3.1.3.
Quality assessment of included study or studies	Appendix D1.3.4, p.14-15	**Appropriate** Quality assessment was conducted by a single investigator and validated by a second, senior investigator. Discrepancies were resolved after discussion with a third reviewer. Only studies which had full-text articles were quality appraised, which encompassed MAGNOLIA and AU-003. The Downs and Black checklist were used.[10] The quality assessment judgements using the Downs and Black checklist[10] were considered adequate by the EAG. An alternative more robust assessment tool such as the Cochrane ROBINS-I would have been more appropriate, however it is unlikely any key concerns would have been highlighted.
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ROBINS-I = Risk Of Bias in Non-randomised Studies – of Interventions		

3.1.1 Search strategies for clinical effectiveness SLR

Searches were conducted separately for clinical effectiveness (reported in Appendix D), and for economics (cost effectiveness and cost resource use) and health-related quality of life (Appendix G and I). Searches were appraised by the EAG using the Peer Review of Electronic Search Strategies (PRESS) checklist.[11] All of these searches contained a concept relating to MZL which is discussed in this Section. Critique of the searches for cost effectiveness and health-related quality of life, aside from the MZL portion of the strategies, can be found in Sections 4.1.1 and 4.2.9.1 respectively. Searches were conducted from the inception date of databases until November-December 2022, and updated in August 2023, so they can be considered up to date.

3.1.1.1 Sources

The clinical effectiveness search used an appropriate range of sources: Embase, MEDLINE, Cochrane databases, and trials registries. A range of conference abstracts was searched, but the BSH was omitted; clinical advice to the EAG suggested that this could have included relevant material. The search also only looked at the last two meetings for each conference; anything that was presented at a conference before this but not subsequently published in a peer-reviewed publication would have been missed.

3.1.1.2 MZL concept

The clinical effectiveness search strategy contained concepts for MZL, relapsing and refractory disease, and study designs.

In the Embase searches, the Emtree thesaurus heading Marginal Zone Lymphoma/ was not exploded (e.g., Appendix D Table 2 Search line 1[9]). Embase records indexed with narrower headings (e.g., MALT lymphoma/) would not have been retrieved by the unexploded search. Whilst the additional title/abstract/keyword field search lines will have retrieved some records with those headings, some results may have been missed.

Across all sources, there are missing abbreviations from the range of MZL search terms (e.g., Appendix D Table 2 Search line 2[9]); for example, 'EZML', 'SMZL' and 'NMZL' are not used. Records that contain only these abbreviations and not 'MZL' or a full 'marginal zone lymphoma' term in the fields searched would not have been retrieved.

In searches that were run on the Ovid platform, for the MZL terms (e.g., Appendix D Table 2 Search line 2[9]) the kw field tag was used for keyword searching rather than kf – this means the results retrieved would have to include the words listed as complete keywords, whereas, for example, results with 'splenic marginal zone lymphoma' in the keyword field would be missed.

3.1.1.3 Relapsed/refractory concept

In the MEDLINE and Embase searches, the search line representing relapsed/refractory disease (Appendix D, Table 2, 3, 4, 6, search line 4[9]) appears to have been developed on MEDLINE and used verbatim on Embase and CENTRAL. Whilst it is likely that other title/abstract search terms would have identified most relevant material, results containing relevant Emtree headings that do not map to MeSH headings, e.g. Refractory disease/ could have been missed.

3.1.1.4 Study designs concept

Published search filters from SIGN were used to restrict the results to randomised controlled trials (RCTs) and observational study designs.[12] The MEDLINE version of the filter in the company searches omits the term Prospective Study/ from the RCT filter, so it would have missed records indexed with this heading if they didn't contain other indexing and keywords in the filter.

In the Embase search, line 22 pertaining to real world evidence, registries or electronic health records is omitted from the search. None of these study designs would have been retrieved from the Embase search, although they would have been from the MEDLINE search.

3.1.1.5 Restrictions to searches

In Clinicaltrials.gov (Appendix D Table 7[9]) the search was limited to 'completed studies', which would have missed studies that have published results before completion. The search also used a truncation symbol when truncation is not supported – although it should still function adequately due to the platform's automatic use of synonyms.

Without comprehensive testing, it is difficult for the EAG to quantify the effects that all the issues mentioned may have had on search results, but it seems likely the effects would be relatively minor. Overall, the EAG is satisfied that the search for clinical effectiveness studies was conducted appropriately.

3.1.2 Inclusion criteria

The SLR inclusion criteria are presented in Table 3.2. Overall, the inclusion criteria shown match the decision problem. BSC was included as a possible comparator in the SLR (although was deemed not appropriate in the company's interpretation of the decision problem), alongside splenectomy (for splenic MZL). Furthermore, studies with fewer than 10 patients per arm were excluded as the company noted the lack of robustness of these studies and that they are not powered to detect effects.[4] Excluding studies with fewer than 10 patients per arm may increase the robustness of the research, though considering the numbers of MZL patients in the SLR is small, it may have been beneficial to have included these studies and conduct sensitivity analyses to check the overall robustness of the results.

A range of relevant publication types were deemed eligible, including full-text journal publications and conference abstracts from the two most recent meetings from key conferences (see Table 3.2). Whilst it is helpful that conference abstracts were considered (and indeed one was found to be potentially eligible),[13] as study authors were not contacted to ascertain whether additional data were available (Question A9),[8] some conference abstracts could not be included in the MAIC as there was insufficient information presented in the abstracts alone (see Section 3.3.2 for further commentary).

Table 3.2: Selection criteria for clinical studies in SLR

Selection criteria	Inclusion criteria	Exclusion criteria

Population	○ Adults (≥18 years) with R/R MZL previously treated with anti-CD20 therapy
	○ Mixed population studies must meet at least one criterion:
	  ○ Subgroup data available for population of interest
	  ○ Population of interest comprising ≥80% of analysed population
		• Patients <18 years old
		• Patients who are treatment-naïve
		• Patients who received first-line therapy not including any anti-CD20 agent
		• Follicular lymphoma

Interventions	○ Efficacy and safety: Any systemic therapy used for the treatment of R/R MZL (chemotherapy, immunotherapy, or chemoimmunotherapy) ○ Epidemiology: Any/none required	• Efficacy and safety: Any non-systemic treatments, any other therapies not used to treat MZL • Epidemiology: Not applicable
Comparators	○ Any; including best supportive care, placebo, any active treatment, or none required	• Not applicable

Outcomes	○ Epidemiology:
	  ○ Incidence
	  ○ Prevalence
	  ○ Mortality
	○ Efficacy:
	  ○ PFS
	  ○ OS
	  ○ Response outcomes (ORR, CR, PR, TTR, DOR, MRD negativity)
	○ Safety:
	  ○ Treatment discontinuation due to AEs
	  ○ Total Grade 3+/serious AEs
		• PK/pharmacodynamics outcomes
		• Any other outcomes not listed as the outcomes of interest

	○ Specific Grade 3+/serious AEs, limited to: ▪ BTKI-specific: atrial fibrillation, bleeding, hypertension, arthralgias, infections, and diarrhoea ▪ CD20 monoclonal antibodies-specific: infusion related, cardiovascular events, pulmonary events, renal toxicity, bowel obstruction/perforation, and cytopenia, secondary malignancies	
Study design	○ Phase II or III clinical trials (e.g., RCTs, single-arm trials, non-randomised studies) ○ Observational studies (prospective or retrospective, including surveys and questionnaires) ○ Subgroup analyses of relevant studies¥	• Phase I and dose escalation studies • Economic evaluations • Case reports and case series • Studies with fewer than 10 patients per arm† • Narrative reviews • In vitro and ex vivo studies • Qualitative studies • Genetic studies and cellular/molecular studies • SLRs and NMAs will be excluded, but if any are found, the reference lists will be cross checked*
Additional limits	○ Time limit: None ○ Geographical limits: None ○ Language: English-only ○ Publication type: Full-text journal publications, conference abstracts from two most recent meetings from key conferences	• Letters to the editor • Editorials • Comments • Notes • Erratum • Trial protocol • Guidelines

Source: Table 9, Appendix D[9]

*Systematic reviews and meta-analyses were tagged separately during the screening phase, and the list of included studies from each publication will be reviewed to identify any additionally relevant randomised controlled trials (RCTs) not otherwise captured by the database searches. These publications themselves will not be included in the SLR.

†Studies that evaluated fewer than 10 patients lack the robustness and are not powered to detect effects.

¥ Subgroup analyses will be listed but data will not be extracted.

Abbreviations: AE = Adverse event; BTKI = Bruton tyrosine kinase inhibitor; CR = Complete response; MALT = Mucosa-associated lymphoid tissue; MRD = Minimal residual disease; MZL = Marginal zone lymphoma; NMA = Network meta-analyses; NMZL = Nodal marginal zone lymphoma; ORR = Overall response rate; OS = Overall survival; PFS = Progression-free survival; PK = Pharmacokinetics; PR = Partial response; RCT = Randomised controlled trials; R/R=– Relapsed/refractory; SLR = Systematic literature review; SMZL = Splenic marginal zone lymphoma; TTR = Time to response

3.1.3 Data extraction

Following the selection of the seven unique studies that met the NICE decision problem,[5] a further five studies were excluded for inclusion in the MAIC. One study was excluded as it was an abstract only with a mixed population,[14] and another study was excluded as MZL patients were grouped into a wider patient population[15] (two further studies were excluded based on the interventions not being licensed for use in R/R MZL,[16-19] while another study was excluded as the majority of patients had relapsed MZL and the company considered this not to reflect the patient population of MAGNOLIA and AU-003).[20]

As detailed in the Cochrane Handbook,[21] contacting study authors to obtain or confirm data makes the review more complete, potentially enhances precision and reduces the impact of reporting biases. In response to the points for clarification (PfC),[8] the company stated that the authors of the identified trials were not asked for additional data regarding the MZL participants. The company's justification is that it would have taken too long for the data from the authors to be populated into the CS and that timely patient access was prioritised (Question A9). This has important implications as to whether all relevant data were extracted and subsequently included in the MAIC, which is discussed further in Section 3.3.2.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

Two trials are included in the CS, MAGNOLIA and AU-003,[4] which are summarised below. Both are multicentre, single-arm trials in Phase 1/2 (AU-003) and Phase 2 (MAGNOLIA) clinical development. [redacted].[1] Single-arm trials are useful to obtain preliminary evidence of the efficacy of the treatment and to collect safety data but are generally not used as confirmation of efficacy. In certain rare diseases, including rare cancers, it is not unusual for clinical data from such trials to be used as pivotal evidence in marketing authorisation applications or health technology assessments. The company provided quality assessments of the MAGNOLIA and AU-003 studies 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 (details found in Section B.2a.5 and B.2b.5, respectively).[22] The assessments, which the EAG were satisfied with, indicated that both trials were well-designed, with the appropriate steps taken to minimise bias. However, single-arm trials such as MAGNOLIA and AU-003 are however subject to methodological limitations which necessitate comparison with other data to demonstrate treatment benefit. As such, it was necessary to use a matched subset of the HMRN trial registry to compare outcomes for patients not on treatment with zanubrutinib (see Section 3.3.3 for further details). The uncertainty arising due to a lack of RCT evidence is highlighted in Key Issue 1.

3.2.1 MAGNOLIA trial

Part of the evidence for the effectiveness of zanubrutinib in patients MZL came from the MAGNOLIA (NCT03846427) trial. MAGNOLIA is an international, multicentre, single-arm, open-label, completed Phase 2 study. Zanubrutinib was administered as oral capsules (two 80 mg capsules) twice daily until progressive disease, unacceptable toxicity, death, withdrawal of consent, or study termination by the sponsor. The trial was conducted in 31 centres across nine countries including Australia, China, Czech Republic, France, Italy, New Zealand, South Korea, the UK and the US. A summary of the EAG critique on the design, conduct and analysis of the trial is presented in Table 3.3.

Table 3.3: Summary of the EAG's critique on the design, conduct and analysis of the MAGNOLIA trial

Aspect of trial design or conduct	Section in CS where methods are reported	EAG's assessment of the robustness of methods
Treatment	B.2a.3.1, p.29/30	**Appropriate** The trial comprised of an initial screening phase lasting up to 35 days, followed by a single-arm treatment phase and a follow-up phase. The treatment phase involved an oral dose of 160 mg zanubrutinib twice daily in repeated 28-day cycles until progressive disease, unacceptable toxicity, death, withdrawal of consent, or study termination by the sponsor. The EAG agree that the treatment daily dose was in line with the recommended total daily dose for zanubrutinib.[23]
Randomisation	Not applicable.	
Concealment of treatment allocation	Not applicable.	
Eligibility criteria	B.2a.3.2, Table 8, p.31/32	**Appropriate** Eligible patients were aged 18 years and older with histologically confirmed MZL (including splenic, nodal and extranodal subtypes), had previously received at least one prior line of therapy (including anti-CD20-based therapy taken either as monotherapy or CIT), and had documented failure to achieve PR or documented progressive disease following the most recent systemic treatment were recruited. The EAG agrees that this was in line with the NICE decision problem.[5]
Blinding	Not applicable.	
Baseline characteristics	B.2a.3.4, Table 10, p.33 - 36	**Appropriate** The median age of the included patients was 70.0 years, with 41 of the 68 included patients (60%) aged 65 years and above, and 19 out of 68 patients (28%) aged 75 years and above. [redacted] of the 68 patients were recruited from the UK and an additional [redacted] from three other EU countries. From the 68 recruited patients, 26 presented with extranodal MZL, 26 with nodal MZL, 12 with splenic MZL and four with an unknown disease subtype. Over half of patients at baseline (n=39; 57.4) had an ECOG PS of 0 (24 patients or 35.3% had an ECOG PS of 1 and five patients or 7.4% had a ECOG PS of 2). The EAG considers the target population and baseline characteristics relevant to the UK population, based on independent clinical advice to the EAG.[4]
Dropouts	B.2a.4.3, Table 12, p.38/39	**Some concerns** A total of 68 patients were recruited for the study and were followed up for a median duration of 28 months. A total of five patients discontinued treatment due to AEs, 24 discontinued due to progressive disease, two discontinued

		treatment due to COVID-19, four patients discontinued treatment due to physician decision, and 31 patients continued into a LTE (BGB-3111-LTE1) study of zanubrutinib, which is ongoing, with an integrated interim safety report expected in December 2024.[4] A complete list of the participants' flow, and further discussion is presented in Table 3.4 and Section 3.2.1.1 below. Whilst the patient flow seems appropriate, and the extension or 'roll-over' of patients participating in MAGNOLIA to the LTE study is typical of early phase oncology trials, the EAG cannot be sure of the impact or results of the LTE study. It is likely however, that the extension trial would provide valuable patient data over the coming years.
Outcome assessment	B.2a.3.3, Table 9, p.32/33	**Appropriate** The study reported outcomes included ORR (primary outcome measure), PFS, OS, DOR, QoL and AEs. Of these, PFS, OS, HRQoL and AEs were included in the economic model. The primary outcome was determined according to the Lugano classification and the proportion of patients achieving the best overall response of CR or PR was noted. The Lugano classification is the current staging system for non-Hodgkin's lymphoma in adults.[24] The EAG finds all the reported outcomes to be in line with those documented in the NICE decision problem.[5]
Statistical analyses	B.2a.4.1/ B.2a.4.2, Table 11, p.36 - 38	**Appropriate** Sample size calculations were estimated using a one-sided alpha level of 0.025 and exact binomial testing. Details on how each outcome of interest was analysed are presented in CS Section B.2a.4.2.[4] The EAG is satisfied that the statistical analyses presented in the CS are appropriate.
Results	B.2a.6, p.41-50	**Appropriate** The study's key efficacy outcomes for patients with R/R MZL, were assessed by both the IRC and INV. ORR by IRC assessment (the study's primary endpoint) was 68.2% (95% CI: 55.6, 79.1) at a DCO of 31 May 2022 with a median follow-up duration of 28 months. A total of 17 (25.8%) and 28 (42.4%) patients achieved CR and PR respectively. However, the median PFS and median OS (secondary endpoints) were not reached at a median follow-up of 27.4 months and 28.7 months, respectively. HRQoL was also reported for MAGNOLIA. EORTC QLQ-C30 demonstrated an improvement from Cycle 3 which was sustained through Cycle 24. EQ-5D-5L VAS was also used to document quality of life, and again showed a slight improvement from baseline which was sustained through to Cycle 24, again demonstrating that HRQoL was maintained following treatment with zanubrutinib.[4] Further discussion can be found in CS Section B.2a.6.[4], and in Section 3.2.1.2 below.
Subgroup analyses	B.2a.4.2, Table 11,	**Some concerns**

	p.38	The company reported subgroup analysis which included: age, sex, ECOG PS, prior line of systemic therapy (< 3 versus ≥ 3), years since last anti-lymphoma therapy (≤ 2 versus > 2), disease status, prior treatment (R-CVP versus R-CHOP versus BR versus all others), bulky disease (longest diameter ≤ 5 cm versus > 5 cm and ≤ 10 cm versus > 10 cm), bone marrow involvement, disease stage (stage I versus II, III and IV), MZL subtype (extranodal versus nodal versus splenic), baseline extranodal disease, baseline LDH.[4] Whilst all the confidence intervals overlap, indicating no statistically significant difference in outcomes, there is tentative evidence of a possible difference in response between sexes (males: 83.3, 95% CI 67.19, 93.63; females: 50.0, 95% CI 31.30, 68.70). It is unclear to the EAG what may have caused the difference. Further real-world evidence may help understand any differential treatment effect by subgroups. Further discussion can be found in Section 4.2.1.3 below.
Abbreviations: AEs = adverse events; BR = bendamustine-rituximab; anti-CD20 = anti-cluster of differentiation 20; CIT = chemoimmunotherapy; CR = complete response; CS = company submission; DOR = duration of response; EAG = Evidence Assessment Group; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; EU = European Union; EQ-5D-5L= EuroQol 5-Dimension questionnaire; HRQoL = health-related quality of life; INV = investigator assessed; IRC = independent review committee; LDH = lactate dehydrogenase; MZL = marginal zone lymphoma; NICE = National Institute for Health and Care Excellence; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; QoL = quality of life; R/R = relapsed or refractory; R-CHOP = rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; R-CVP = rituximab + cyclophosphamide + vincristine + prednisone; UK = United Kingdom; VAS = visual analogue scale.		

3.2.1.1 Dropouts

Table 3.4 shows the patient disposition in MAGNOLIA. A total of 31 (45.6%) patients were discontinued from treatment and enrolled on an ongoing long-term extension (LTE) study of zanubrutinib (for which they continued treatment). The number of patients who discontinued treatment due to adverse events was five (7.4%), while 24 (35.3%) patients discontinued treatment due to progressive disease.[4]

The LTE study (BGB-3111; NCT04170283), is a single group assignment, non-randomised, open label study with an estimated study completion of December 2028.[25] The CS report that an integrated interim safety report is expected in December 2024,[4] and therefore not ready for this submission. Adverse events, alongside PFS, DOR and OS (time frame, up to five years) will be collated during this trial. Although no further DCOs are planned in MAGNOLIA, the LTE study offers an opportunity to collate further efficacy and safety outcomes and reduce uncertainty, particularly concerning survival in the medium to long term.

Table 3.4: Patient disposition in MAGNOLIA

Patient disposition	Zanubrutinib (N = 68) n (%)
Number of patients treated	68 (100.0)
Patients discontinued from treatment	68 (100.0)

Reason for discontinuation from treatment	
Sponsor decision to roll over to LTE study	31 (45.6)
Progressive disease	24 (35.3)
Adverse event	5 (7.4)
Related to COVID-19	2 (2.9)
Physician decision[a]	4 (5.9)
Other	3 (4.4)
Study terminated by sponsor/patients not rolling over to LTE[b]	3 (4.4)
Withdrawal by patient	1 (1.5)
Patients remained on study treatment	0
Patients discontinued from the study	68 (100.0)
Reason for discontinuation from the study	
Sponsor decision to roll over to LTE study	[redacted]
Death	[redacted]
Related to COVID-19	[redacted]
Study terminated by sponsor[c]	[redacted]
Withdrawal by patient	[redacted]
Physician decision	[redacted]
Other	[redacted]
Patient declined to be rolled over to BGB-3111-LTE1	[redacted]
Patients remained in study	[redacted]
Median study follow-up timed (months)[d]	28.04
Study follow-up time (months) (minimum, maximum)	1.64, 32.89

Source: Table 12, CS Document B[4]
Abbreviations: LTE = Long-term extension
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] Discontinued due to prohibited medications: One patient required chemotherapy for acute myeloid leukaemia. One patient discontinued due to steroid dependency. One patient required priority treatment for tuberculosis.
[b] Including patients of "Study Terminated by Sponsor, Patient Not Rolling Over," "Study Terminated by Sponsor Patient Not Rolling Over to LTE" and "Study Terminated by Sponsor Patient Not Rolling Over."
[c] These patients did not roll over to BGB-3111-LTE1 study.
[d] 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.

3.2.1.2 Results

The key efficacy outcomes for patients with R/R MZL in the MAGNOLIA study are presented below in Table 3.5 (both primary and secondary outcomes). The primary endpoint (ORR) as reported by the independent review committee and the investigator were 68.2% (55.6, 79.1) and 75.8% (63.6, 85.5), respectively.

Table 3.5: Key Efficacy Outcomes Reported in MAGNOLIA

	Zanubrutinib (N = 66)

	IRC-assessed	INV-assessed
ORR		
ORR (%) (95% CI)	68.2 (55.6, 79.1)	75.8 (63.6, 85.5)
PFS		
Events, n (%)	[redacted]	[redacted]
Median, months (95% CI)	[redacted]	[redacted]
DOR		
Median, months (95% CI)	[redacted]	[redacted]
OS		
Events, n (%)	[redacted]	
Median, months (95% CI)	[redacted]	
TTR		
Median, months	[redacted]	[redacted]
TTF		
Events, n (%)	[redacted]	
Median, months (95% CI)	[redacted]	
TTNLT		
Events, n (%)	[redacted]	

Source: CS Document B, Table 14[4]
Abbreviations: CI = confidence interval; DOR = duration of response; INV = investigator; IRC = independent review committee; NE = not estimable; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; TTF = time to treatment failure; TTNLT = time to next line of therapy; TTR = time to response.

The safety results containing treatment-emergent adverse events as presented by the company are shown in Table 3.6 and Table 3.7 below. All patients experienced at least one TEAE, and most TEAE were Grade 1 or 2. The Grade ≥ 3 TEAEs most frequently reported were neutropenia (8.8%), COVID-19 pneumonia (5.9%), and pneumonia, diarrhoea, and syncope ([redacted]%). Clinical advice to the EAG suggested the adverse events seen in MAGNOLIA were typical of treatment with zanubrutinib.

Table 3.6: Summary of treatment-emergent and post-treatment AEs in MAGNOLIA

Event	Zanubrutinib (N = 68), n (%)
Patients with at least 1 AE	68 (100.0)
Grade ≥ 3 AEs	33 (48.5)
SAEs	30 (44.1)
AEs leading to death	5 (7.4)
AEs leading to study drug discontinuation	5 (7.4)
AEs leading to treatment interruption	25 (36.8)
AEs leading to dose reduction	0
Treatment-related AEs	[redacted]
AEs due to COVID-19	[redacted]

Source: CS Document B, Table 45[4]
Abbreviations: AE = adverse event; SAE = serious adverse event

Table 3.7: Treatment-emergent adverse events by system organ class and preferred term in ≥ 5% of patients (any grade) in MAGNOLIA

System Organ Class Preferred Term	Zanubrutinib (N = 68), n (%)
Patients with at Least One TEAE	68 (100.0)
Gastrointestinal disorders	[redacted]
Diarrhoea	15 (22.1)
Constipation	[redacted]
Abdominal pain	[redacted]
Nausea	[redacted]
Dyspepsia	[redacted]
Gastroesophageal reflux disease	[redacted]
Vomiting	[redacted]
Infections and infestations	[redacted]
Upper respiratory tract infection	[redacted]
COVID-19	[redacted]
COVID-19 pneumonia	[redacted]
Pneumonia	[redacted]
Tonsillitis	[redacted]
Urinary tract infection	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]
Arthralgia	[redacted]
Back pain	[redacted]
General disorders and administration site conditions	[redacted]
Pyrexia	[redacted]
Fatigue	[redacted]
Injury, poisoning and procedural complications	[redacted]
Contusion	16 (23.5)
Fall	[redacted]
Nervous system disorders	[redacted]
Dizziness	[redacted]
Lethargy	[redacted]
Sciatica	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]
Cough	[redacted]
Metabolism and nutrition disorders	[redacted]
Hypokalaemia	[redacted]
Blood and lymphatic system disorders	[redacted]
Thrombocytopenia	[redacted]
Neutropenia	[redacted]

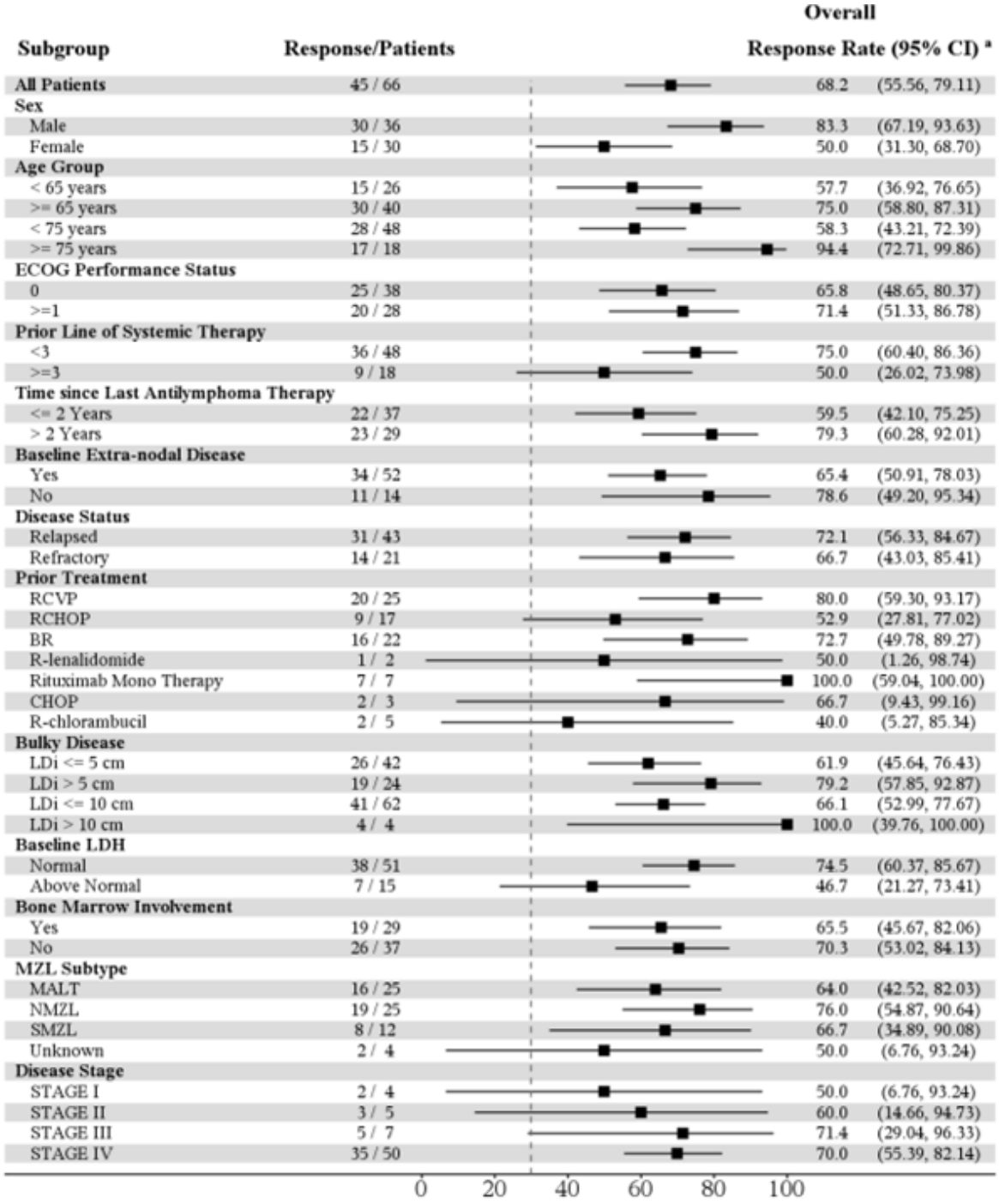
Anaemia	[redacted]
Investigations	[redacted]
Neutrophil count decreased	[redacted]
Platelet count decreased	[redacted]

Source: CS Document B, Table 46[4]
Abbreviations: TEAE = treatment-emergent adverse event

3.2.1.3 Subgroup analysis

No subgroup analysis was specified in the NICE scope.[5] The forest plots for the subgroup analysis of ORR by IRC assessment is shown in Figure 3.1. Treatment with zanubrutinib was shown to be broadly comparable across all patient subgroups, owing to the wide confidence intervals attributable to low patient numbers (n = 66 patients; 45 responses). Notably, female patients appear have considerably worse ORR compared to males (ORR 83.3, 95% CI 67.19 to 93.63, n = 30 and ORR 50.0, 95% CI 31.30 to 68.70, n = 15 for males and females, respectively). It is unclear to the EAG what may have caused the differences however, it is important to note that the confidence intervals overlap indicating no statistically significant difference in outcomes. Further real-world evidence may help understand any differential treatment effect by subgroups.

Figure 3.1: Forest plot of ORR by IRC assessment



Source: CS, Figure 8;[4] MAGNOLIA CSR[26]

Abbreviations: BM = bone marrow; BR = bendamustine + rituximab; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; IRC = Independent Review Committee; LDH = lactate dehydrogenase; MALT = extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue; NMZL = nodal marginal zone lymphoma; ORR = overall response rate; R = rituximab; R-CHOP = rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; R-CVP = rituximab + cyclophosphamide + vincristine + prednisone; SMZL = splenic marginal zone lymphoma.

a 2-sided Clopper-Pearson 95% confidence intervals for overall response rate.

3.2.2 AU-003 trial

The second key trial for which evidence of the effectiveness of zanubrutinib in patients with B-cell lymphoid malignancies, including R/R MZL, was AU-003. AU-003 is an international, open-label, multiple-dose, multicentre phase 1/2 study (NCT02343120). Participants were recruited from Australia, South Korea, Italy, New Zealand, and the United States. Table 3.8 summarises the EAG's critique of the methods and results of AU-003.

Table 3.8: Summary of the EAG's critique on the design, conduct and analysis of the AU-003 trial

Aspect of trial design or conduct	Section in CS where methods are reported	EAG's assessment of the robustness of methods
Treatment	B.2b.3.1, p.52-53	**Appropriate** The trial comprised a dose escalation phase (Part 1), followed by an expansion phase (Part 2) where 320 mg zanubrutinib was administered daily. The company state that only the outcomes and insights from Part 2 are reported in the company submission,[4] and this is confirmed in the PfC response (Question A7).[8] The EAG are satisfied that treatment with zanubrutinib reported for AU-003 in the CS matches the recommended treatment dosage.
Randomisation	Not applicable.	
Concealment of treatment allocation	Not applicable.	
Eligibility criteria	B.2b.3.2, Table 26, p.53-54	**Appropriate** 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.[4] The EAG note that out of the 380 participants enrolled in the study (encompassing all those with B-cell lymphoid malignancies), 20 were selected who met the R/R MZL population specified in the NICE scope.[5] The company note that the eligibility criteria were well matched with the criteria from the MAGNOLIA study.[4] The EAG are satisfied that the eligibility criteria for those patients meeting the R/R MZL subset of B-cell lymphoid malignancies included in the trial is appropriate.
Blinding	Not applicable.	
Baseline characteristics	B.2b.3.4, Table 28, p.56-57	**Appropriate** The majority of the 20 patients enrolled who had MZL were aged between 65 and 75 (n=12, 60%), and [redacted] patients were drawn from Australia. [redacted] Clinical advice also highlighted that the patients enrolled to AU-003 had a poorer level of functioning (as measured by ECOG PS Scale) compared to patients in MAGNOLIA. Thirty five percent of patients (n=7) in AU-003 had a ECOG PS of '0' as opposed to 57.4% of patients in MAGNOLIA (n=39).

		Clinical advice to the EAG has confirmed that the demographic and baseline disease characteristics are however typical of that seen in UK clinical practice.
Dropouts	B.2b.4.3, Table 30, p. 59-60.	**Some concerns** Of the 20 patients enrolled with R/R MZL, [redacted] discontinued from AU-003 but continued study treatment in the LTE study. In addition, owing to the immaturity of the survival data (which were secondary endpoint outcomes, see Section 3.2.2.2), there remains uncertainty on the impact of the dropouts on the reporting of outcomes in AU-003 and, therefore, the robustness of the trial and its use in subsequent modelling. Further information is provided in Section 3.2.2.1.
Outcomes	B.2b.3.3, Table 27, p. 54-55.	**Appropriate** The outcomes reported in the trial include ORR, DOR, PFS, TTR, OS and adverse effects (related to safety and tolerability), which are all included in the decision problem.[4] HRQoL is reported in the decision problem yet is not collected as part of the trial. Given the nature of phase 1/2 trials, is it unsurprising that HRQoL was not included. The datacut available was either 02 October 2020 or 31 March 2021. No further DCOs are planned.[4] The EAG is satisfied that the outcomes are appropriate, given the trial phase and acknowledge that data related to HRQoL was collected in MAGNOLIA. As such, all trial outcomes reported in the NICE scope are reflected in the two clinical trials.
Statistical analyses	B.2b.4, p.58-59.	**Appropriate** The CS reports that sample sizes for individual disease cohorts was determined to provide robust estimates of response rates and safety profiles.[4] Of the 380 patients enrolled in the expansion cohort of AU-003 Part 2, 20 were included in the R/R MZL cohort used for the CS.[4,27] The sample sizes for individual disease cohorts were 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"* (CS, p.58).[4] The EAG finds this approach acceptable. For all primary and secondary outcomes, the efficacy analysis set was used (which included all patients with MZL who received at least one dose of zanubrutinib).[4] For safety outcomes, the safety analysis set was used (including all patients enrolled and received at least one dose of zanubrutinib).[4] The EAG are satisfied that the correct datasets were used for the respective analyses.
Results	B.2b.6, Tables 33-37, Figure 13; B.2b.10, p.61-69.	**Some concerns** The primary endpoint, ORR, was met. However, from the perspective of survival outcomes (PFS, OS), the datasets may be considered relatively immature. This in part, reflects the prognostic nature of MZL as a slow growing form of non-Hodgkin lymphoma (NHL). The most reported ≥3 Grade

		adverse events were neutropenia ([redacted]) and anaemia ([redacted]). Further information is provided in Section 3.2.2.2
Subgroup analyses	B.2b.3, Table 25, p.52-53	**Appropriate** No subgroup analyses were specified in the decision problem.[5] Subgroup analysis presented in the CS comprised sex, age, geographic region, race, ECOG PS, MZL subtype including extranodal, nodal and splenic, disease stage at study entry, bulky disease, baseline bone marrow involvement, baseline extranodal disease, refractory disease, baseline LDH, number of prior regimens, prior R-CVP, prior BR, Prior R-CHOP, prior rituximab monotherapy, prior rituximab-containing chemotherapy and time from end of last regimen to first dose. Treatment with zanubrutinib was shown to be broadly comparable across all patient subgroups, owing to the wide confidence intervals attributable to low patient numbers (n=20). However, the results do suggest a likely improvement in ORR for participants under 75 years old compared with those 75 years and older (< 75 years, ORR 87.5: 95% CI 61.7 to 98.4, n=16; ≥ 75 years, ORR 50.0: 95% CI 6.8 to 93.2, n=4), nodal versus splenic MZL subtypes (nodal, ORR 100.0: 95% CI 47.8 to 100.0, n=5; splenic, ORR 50.0: 95% CI 11.8 to 88.2, n=6), and prior treatment with bendamustine rituximab (BR) (no BR treatment, ORR 87.5: 95% CI 61.7 to 98.4, n=4; BR treatment, ORR 50.0: 95% CI 6.8 to 93.2, n=16). The EAG are satisfied that the results of the subgroup analyses are adequate and expected given the number of patients enrolled in AU-003. Low patient numbers mean these analyses have high levels of uncertainty, and no inferences can be made as to which groups may respond better/worse to treatment with zanubrutinib.
Abbreviations: CS = company submission; DOR = duration of response; EAG = Evidence Assessment Group; OS = overall survival; PfC = points for clarification; PFS = progression-free survival; TTR = time to response.		

3.2.2.1 Dropouts

Table 3.9 describes the patient disposition in AU-003. Five patients discontinued owing to disease progression, two withdrew their consent, one withdrew because of adverse events and a further [redacted] remained on study treatment in the LTE study (NCT04170283, as described in Section 3.2.1.1). Of the five patients who discontinued treatment, [redacted] died. The company state: *"there are no ongoing trials assessing the efficacy of zanubrutinib monotherapy in patients with R/R MZL"* and *"no additional data cuts are anticipated for the MAGNOLIA and AU-003 trials"* (p.101).[4]

Table 3.9: Patient disposition in AU-003

Patient disposition	**Zanubrutinib (N=20) n (%)**
Number of patients treated	20 (100.0)
Patients discontinued from treatment	20 (100.0)
Reason for discontinuation from treatment	
Disease progression	5 (25.0)
Patient withdrew consent	2 (10.0)

Adverse event	1 (5.0)
Patients remained on study treatment in LTE	[redacted]
Patients discontinued from the study	[redacted]
Reason for discontinuation from the study	
Death	[redacted]
Lost to follow-up	[redacted]
Patient withdrew consent	2 (10.0)
Median study follow-up time (months)	[redacted]
Study follow-up time (months) (minimum, maximum)	[redacted]
Source: CS Document B, Table 30[4] Abbreviations: CS = company submission; LTE = long-term extension	

Over [redacted] remained on study treatment in the LTE study. This expansion trial encompasses participants with B-cell malignancies who currently participated or are participating in a BeiGene parent study.[25] In the CS, it is stated that an interim safety report for the LTE study is expected in December 2024,[4] and therefore not ready for this submission. It is unclear to the EAG whether results from the LTE will be reported for MZL patients specifically, or grouped with other B-cell malignancies.

Given the relatively small numbers of patients involved in the trial, and the immaturity of the data (see Section 3.2.2.2), there remains uncertainty surrounding the AU-003 trial results. Future interim and final DCOs for the LTE study may reduce uncertainty.

3.2.2.2 Results

3.2.2.2.1 Efficacy outcomes

Key efficacy outcomes for AU-003 are provided in Table 3.10. The primary endpoint for AU-003 was ORR, defined as *"the number of patients with a best overall response of complete response (CR), partial response (PR), stable disease, progressive disease, or not evaluable"* (p.58).[4] By IRC assessment, ORR was 80% (95% CI 56.4 to 94.3), which equated to 16 patients, with four patients (20%) achieving a complete response. ORR by INV (at DCO on 02 October 2020 (median follow up 35.2 months) and 31 March 2021 (median follow-up of 39.2 months) was [redacted].

Table 3.10: Key efficacy outcomes for AU-003

	Zanubrutinib (N = 20)		
	IRC-assessed (DCO 02 October 2020)	**INV-assessed (DCO 02 October 2020)**	**INV-assessed (DCO 31 March 2021)**
ORR			
ORR (95% CI)	16 (56.3, 94.3)	[redacted]	[redacted]
PFS			
Median, months (95% CI)	NE (20.3, NE)	[redacted]	[redacted]
DOR			
Median, months (95% CI)	[redacted]	[redacted]	[redacted]

TTR			
Events, n	[redacted]	[redacted]	[redacted]
Median, months (range)	2.8	[redacted]	[redacted]
OS (DCO 31 March 2021)			
Deaths, n (%)	[redacted]		
Source: CS Document B, Table 32;[4] AU-003 CSR[28], AU-003 CSR[29] Abbreviations: CI = confidence interval; CS = company submission; CSR = clinical study report; DCO = data cut-off; DoR = duration of response; INV = investigator; IRC = independent review committee; MZL = marginal zone lymphoma; NE = not estimable; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; TTR = time to response.			

For PFS and [redacted] were not estimable. The results from the analysis are therefore uncertain and they may not reflect the true estimates of the relative effectiveness that will become estimable when sufficient data are available.

At the DCO dated 02 October 2020 (median follow up 33.8 months), five (25%) patients had either progressed or died as per IRC assessment, and median PFS had not been reached. The event-free rate was 84.0%, (95% CI 57.9 to 94.6) at 12 months, 72.0% (95% CI 45.0 to 87.4) at 24 months and 72.0% (95% CI 45.0 to 87.4) at 36 months.[4] (see Figures 11 and 12 in the CS for Kaplan-Meier plots of PFS assessed by IRC and INV respectively). At median follow-up of 31.4 months (DCO 02 October 2020), [redacted] patients had died and median OS had not been reached (see Section B.2b.6.2.2 for further details).[4]

The immaturity of the data results in considerable uncertainty surrounding the PFS and OS extrapolations for AU-003. These issues are further explored in the MAIC which pooled data from AU-003 with MAGNOLIA (see Section 3.3.1).

3.2.2.2.2 Safety outcomes

At the DCO 31 March 2021, the median duration of treatment was [redacted] months. During this time, two patients (10%) required a dose reduction due to an AE, and 10 patients (50%) required at least one treatment interruption due to an AE. All patients experienced at last one TEAE, and the CS reports that AEs with zanubrutinib were '*manageable with treatment interruption and supportive care with* [redacted] *discontinuing zanubrutinib due to a treatment-related AE'* (p.97).[4] Grade 3 or higher TEAEs were identified in 55.0% of patients, with anaemia (15.0%), neutropenia (15.0%) and pyrexia (10.0%) being the most common.[4]

The CS stated that, consistent with the results from MAGNOLIA, zanubrutinib demonstrated a safe and tolerable treatment option in patients with R/R MZL.[4] Whilst the safety events are clearly discussed in the CS, the small sample size of AU-003 makes interpretation of this trial alone problematic. However, the results do appear to be consistent with both MAGNOLIA, and other B-cell malignancy trials,[30-32] and thus the EAG do not have any concerns with the safety data presented. Due to the nature of AU-003 being single-arm, the EAG cannot ascertain whether the safety profile of zanubrutinib is better/worse than comparators currently used in the treatment of R/R MZL.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

In the absence of head-to-head trial evidence for the NICE scope comparisons involving zanubrutinib in participants with R/R MZL, the company conducted an ITC in the form of a MAIC (CS Section B.2.8).[4] The company used pooled data from the MAGNOLIA and AU-003 trials (henceforth known as MAGNOLIA-003) and compared with a basket of treatments from the HMRN registry. Table 3.11 presents a summary of the EAG's comments regarding the methodology of the MAIC, with key points expanded upon in the following sections.

Table 3.11: Summary of the methodology of the company's MAIC and EAG comments

Aspect of MAIC design or conduct	CS Section	EAG comment
Statistical methods	B.2.9.1.1, p.84; Appendix L, Section L1.3 (p.2-5)	**Key issue 2** The company performed an unanchored MAIC using the guidance from the NICE DSU and the method described by Signorovitch *et al*.[33,34] The EAG note that unanchored MAICs are inherently subject to uncertainty but believe the approach was appropriate due to the lack of comparative data available. The EAG also asked the company to clarify how clustering effects from pooling data from MAGNOLIA and AU-003 were accounted for. See Section 3.3.1 for further comment.
Pooling of the MAGNOLIA and AU-003 trial data	B.2.9.1, p.76-81; PfC question A8	**Appropriate** To increase the sample size for zanubrutnib, the company pooled data from MAGNOLIA and AU-003 (known as MAGNOLIA-003). As the company clarified that only data from Part 2 of AU-003 were used when pooling with data from the MAGNOLIA trial,[8] the EAG considers the trials to be sufficiently similar to pool.
Studies excluded from the MAIC	B.2.9, p.70-3; PfC questions A9-11	**Some concerns** The company excluded five trials (AUGMENT,[20] CHRONOS-3,[16,17] SELENE,[13] Kahl 2010,[15] and MAGNIFY).[18,19] The EAG have concerns surrounding the exclusion of these trials from the MAICs and asked the company to further clarify their rationale in the PfC (questions A9-11).[8] See Section 3.3.2 for further comment.
Comparison with the HMRN basket of treatments	B.2.9.1, p.76-81	**Some concerns** The company compared the pooled MAGNOLIA-003 data with a basket of treatments using data from the HMRN registry. The EAG are concerned about the pooling of immunotherapy, CIT and chemotherapy regimens into a single comparator and the effect this may have on the results of the MAIC. Furthermore, the EAG have concerns surrounding the applicability of some of the therapies contained within the HMRN treatment basket to current NHS practice. See Section 3.3.3 for further EAG comment.

Study characteristics and demographics	B.2.9.1.1, p.76-81; 83; 85	**Key Issue 2** Few participant characteristics were available from the HMRN registry basket of treatments used as the comparator and many of the characteristics were only recorded at time of enrolment into the registry rather than time of initiation of therapy after a patient was R/R to anti-CD20 treatment. The EAG have concerns that this limits the comparability of the HMRN registry basket to the MAGNOLIA-003 data but accepts that there was little the company could have done to resolve this issue.
Covariates included in the MAIC	B.2.9.1.1, p.81-2	**Key Issue 2** Only five covariates were included within the MAIC matching process: number of prior lines of therapy (1 versus 2 versus ≥ 3); refractory to last therapy (yes versus no); age (mean and variance); POD24 (yes or no); median time since diagnosis (< median versus ≥ median). The EAG are concerned that the lack of covariates included within the MAIC introduces the possibility of residual bias and a potential lack of comparability between MAGNOLIA-003 and the HMRN treatment basket. See Section 3.3.4 for further details.
Results	B.2.9.1.2, p.84-92	**Some concerns** The company state that zanubrutinib demonstrated a statistically significant improvement in PFS and OS compared with the HMRN treatment basket, which remained robust to the leave-out-one sensitivity analyses. However, the EAG note that, due to the methodological limitations outlined in Sections 3.3.1 and 3.3.4 below, there is substantial uncertainty surrounding these results.
Sensitivity analyses	Appendix L, Section L2.2 to L2.4 (p.7-26	**Some concerns** The company conducted sensitivity analyses on the MAIC by only using the MAGNOLIA data, excluding chemotherapy alone regimens from the HMRN basket of treatments and using a leave-out-one approach on the five covariates included. The EAG believe these sensitivity analyses were appropriate but also reiterate that there is substantial uncertainty in the sensitivity analysis results due to the methodological issues outlined in Sections 3.3.1 and 3.3.4 below.

Source: CS;[4] CS Appendix L;[35] response to PfCs[8]

Abbreviations: CS = company submission; DCO = data cut-off; EAG = Evidence Assessment Group; HMRN = Haematological Malignancy Research Network; MAIC = matching-adjusted indirect comparison; NHS = National Health Service; OS = overall survival; PfC = points for clarification; PFS = progression-free survival; POD24 = progression of disease within 24 months

3.3.1 Pooling of the MAGNOLIA and AU-003 data

The EAG asked the company to clarify whether data from both stages of the AU-003 trial were used when pooling with the MAGNOLIA trial. The company responded that only data from the extension phase of AU-003 were included in the submission and, hence, within the MAIC.[8]

The company pooled data from the MAGNOLIA and AU-003 studies into a single dataset (MAGNOLIA-003). NICE DSU Technical Document 18 states that: "*A better option in this scenario, in the absence of MAIC methodology which accounts for clustering, is to perform identical MAICs based on each IPD population, and then pool the relative effect estimates (on the linear predictor scale) with standard meta-analysis methods*" (p.42).[33] The EAG asked the company to clarify the methods used to pool MAGNOLIA and AU-003 and requested analyses based on the recommendations from the NICE DSU. The company noted that the method of pooling data from both trials was considered appropriate by UK clinical experts in attendance at an advisory board (11 October 2023) and that baseline characteristics between MAGNOLIA and AU-003 were largely consistent, providing a comparison of patient characteristics between the two trials.[8]

The company noted that the only statistically significant differences between MAGNOLIA and AU-003 were for the presence of bone marrow involvement and extranodal disease, noting that these attributes were not identified by the UK clinical experts at the advisory board as key prognostic factors or treatment effect modifiers.[8] Clinical advice to the EAG agreed that the bone marrow involvement or extanodal disease were not key prognostic factors or effect modifiers for MZL and so the EAG are satisfied with the comparability of MAGNOLIA and AU-003.

3.3.2 Studies excluded from the MAIC

The company excluded five trials from the MAIC (AUGMENT,[20] CHRONOS-3,[16,17] SELENE,[13] Kahl 2010,[15] and MAGNIFY).[18,19] In CS Section B.2.9 (Table 38),[4] the company justified their reasons for excluding these studies from the MAIC. Firstly, the EAG asked whether the company had approached the authors of the five clinical trials for additional data surrounding participants with MZL (PfC, question A9).[8] The company responded that they did not approach study authors for additional information regarding the five trials, stating that it would have taken too long for data from the authors to be received, assessed, analysed and populated into the CS, assuming they would be willing to share such information. Instead, they prioritised engagement with the HMRN registry as it was considered a more reliable data source by UK clinical experts in consultation with the company (see CS Section B.2.9.1.1 for further details).

Clinical advice to the EAG noted that it would be clinically appropriate to compare relapsed and refractory MZL patients within the MAIC. As such, the EAG requested that the company conduct additional MAICs that included both relapsed and refractory participants from the five clinical trials excluded from the CS (PfC, question A10).[8] In response, the company conducted an exploratory MAIC analysis comparing against CHRONOS-03. However, the company maintained that additional MAICs with these trials were not feasible or appropriate. For the SELENE and MAGNIFY studies, the company noted that both trials included a mixture of either MZL and follicular lymphoma (FL) participants (SELENE) or MZL, FL and small lymphocytic lymphoma (SLL; MAGNIFY), with neither trial reporting baseline nor efficacy outcomes only for MZL. The EAG note that, in Table 10 of the PfCs, the proportion of relapsed participants in MAGNOLIA was [redacted], while in AU-003 the proportion was [redacted]. As such, it may have been possible to conduct exploratory MAICs with the other trials, though the EAG appreciate these would still have been subject to the same uncertainties as the MAIC with the HMRN treatment basket.

3.3.2.1 Comparability of the SELENE trial with MAGNOLIA-003

A full publication of the results from the SELENE trial has become available since the time of original submission of the CS.[14] As such, the EAG asked the company to comment on the comparability of the SELENE trial with MAGNOLIA-003 for comparison within a MAIC, and to conduct a MAIC between SELENE and MAGNOLIA-003 if they were deemed sufficiently similar (PfC, question A11).[8] The company responded that, on evaluation of the full publication of the SELENE study, neither Kaplan-Meier plots for PFS or OS nor baseline characteristics for MZL were reported. As such, the company did not deem SELENE to be suitable for a MAIC against MAGNOLIA-003 (PfC, question A11).[8] The EAG agrees that a MAIC would not have been feasible using the published data from the SELENE trial.

3.3.2.2 Comparability of the AUGMENT and CHRONOS-3 trials with MAGNOLIA-003

The company also noted that the AUGMENT and CHRONOS-3 trial populations insufficiently overlapped with those in MAGNOLIA and AU-003, particularly since both trials enrolled patients with relapsed disease only (PfC, question A10).[8] The company noted that patients with relapsed disease are likely to have improved outcomes compared with patients with refractory disease and, as such, any comparisons would favour rituximab monotherapy. As noted in Section 3.3.2 above, Table 10 of the PfCs[8] shows that the proportion of relapsed participants in MAGNOLIA was [redacted], while in AU-003 the proportion was [redacted]. However, further clinical advice provided to the EAG suggested that those with refractory disease would be less responsive to treatment compared with relapsed patients.

To further highlight how the HMRN registry was more aligned to UK clinical practice, the company provided a comparison of baseline characteristics between participants in AUGMENT, CHRONOS-3 and [redacted] participants receiving rituximab monotherapy from the HMRN cohort (PfC, question A10, Table 8).[8] The company stated that neither CHRONOS-3 nor AUGMENT adequately reflected characteristics of patients receiving treatment for R/R MZL in UK clinical practice. In the case of AUGMENT, the company noted that the population were significantly younger (59% aged 65 or older and median age of 66 years) than those in a subset of rituximab monotherapy HMRN patients (N = [redacted]) ([redacted]% aged 65 or older and median age of [redacted] years) and that only 81% of the patient population had received a prior anti-CD20 regimen, which was not aligned with the scope of the appraisal or the licensed indication for zanubrutinib.

The company also conducted an exploratory MAIC with MAGNOLIA-003 and CHRONOS-3 in response to the PfC (Question A10).[8] This is discussed further in Section 3.3.2.3 below.

3.3.2.3 The company's exploratory MAIC comparing MAGNOLIA-003 with CHRONOS-3

The company conducted an exploratory MAIC between MAGNOLIA-003 and CHRONOS-3, stating that CHRONOS-3 was more applicable to the licensed indication for zanubrutinib than AUGMENT as all participants had received prior treatment with an anti-CD20 regimen (PfC, question A10).[8] The MAIC was conducted with the same methodology as those used in the CS. The company provided a comparison of key trial characteristics between AU-003, MAGNOLIA and CHRONOS-3 (PfC, question A10, Table 9),[8] and unadjusted population characteristics of MAGNOLIA, AU-003 and the rituximab monotherapy arm of CHRONOS-3 (PfC, question A10, Table 10).[8]

Covariates used within the exploratory MAIC were: number of prior lines of therapy (1 vs 2 vs > 2); MZL subtype (extranodal versus nodal versus splenic); response to last prior systemic therapy (relapse – yes versus no); and age. The company noted that these covariates were consistent with the HMRN registry basket, except for the exclusion of POD24 status, as this was not available from CHRONOS-

3, and the inclusion of MZL subtype, as this was not available from the HMRN registry basket (PfC, question A10).[8] Weighted and unweighted populations from MAGNOLIA-003 and CHRONOS-3 were presented in the company's response to the PfC (question A10, Table 11).[8] The results of the exploratory MAIC were presented by the company in Table 12 of the response to the PfC, which is replicated in Table 3.12 below.

Table 3.12: Summary of MAIC results between MAGNOLIA-003 and CHRONOS-3

	PFS		OS	
	Hazard ratio (95% CI)	**P-value**	**Hazard ratio (95% CI)**	**P-value**
Pre-matching	[redacted]	[redacted]	[redacted]	[redacted]
Model	[redacted]	[redacted]	[redacted]	[redacted]

Source: PfC, question A10 (Table 12)[8]
Abbreviations: CI = confidence interval; MAIC = matching-adjusted indirect comparison; OS = overall survival; PfC = points for clarification; PFS = progression-free survival

The EAG note that the results of the exploratory MAIC favour zanubrutinib for both PFS and OS, though also note that there is substantial uncertainty in the 95% CIs for OS (neither pre-matching nor MAIC models were statistically significant). As this exploratory MAIC followed the same methodology as in the CS, which is appropriate given the lack of available comparative data and the single-arm nature of the MAGNOLIA and AU-003 trials, it is unanchored and therefore open to considerable uncertainty. However, the EAG acknowledge that the company described the MAIC comparing MAGNOLIA-003 with CHRONOS-3 to be exploratory.

3.3.3 Comparability of the HMRN treatment basket with MAGNOLIA-003

3.3.3.1 Cut-off date for eligibility in HMRN treatment basket

The company used data from the HMRN registry to compare the efficacy of zanubrutinib in the pooled MAGNOLIA-003 data with a basket of immunotherapy, chemoimmunotherapy (CIT) and chemotherapy treatments. The EAG have concerns relating to the use of the HMRN registry treatment basket as the comparator for the MAIC. The EAG highlighted that only participants enrolled in the HMRN registry from 2014 to 2020 were eligible for inclusion in the treatment basket and asked the company in the PfC (question A12).[8] The company responded to note that 2020 was the cut-off date for diagnosis for inclusion in the registry cohort, not the date of enrolment. Furthermore, the company clarified that a cut-off of 2020 for date of diagnosis was selected by the registry, with all patients within this cohort having been followed up to 2022. The company also noted that the registry have not yet processed patients diagnosed post-2021, though it is expected that many of these patients would still not have reached second-line therapy. The EAG are satisfied by this response.

3.3.3.2 Combinations of interventions included in the HMRN treatment basket

The HMRN basket of treatments contained 18 different immunotherapy, CIT, and chemotherapy regimens. Clinical advice to the EAG highlighted that it would be inappropriate to combine immunotherapy regimens with CIT and chemotherapy regimens within the same treatment basket. As such, the EAG asked the company to provide separate MAICs for zanubrutinib versus immunotherapies and zanubrutinib versus CIT and chemotherapies (PfC question A13).[8] The company responded by extracting data from the HMRN registry for patients receiving immunotherapy regimens only (N=[redacted]) and those receiving chemotherapy or chemoimmunotherapy (N=[redacted]), presenting a comparison of

baseline characteristics between these baskets and the original HMRN treatment basket (N=[redacted]) and HMRN basket with rituximab with or without chemotherapy (N=[redacted]) in Table 13 of the clarification letter.[8] The company noted that because outcomes were poorer for the HMRN N=[redacted] cohort, they considered the existing MAICs to be a more conservative estimate of relative treatment effect of zanubrutinib versus standard care in the UK and therefore did not present an additional MAIC analysis. Although this is partly true, it is difficult to assess whether this comparison is more conservative compared with other potential comparators. This is because such a judgment would require assessment of complex interactions between varying patterns of known and unknown confounders and effect modifiers, as well as a difficult to quantify impact on the generalisability of this comparator. The EAG cannot comment further, though note that additional evidence may reduce some of the uncertainties surrounding this issue.

For the HMRN N=[redacted] cohort (rituximab monotherapy), the company noted that the small sample size meant a MAIC was unfeasible.[8] However, as previously noted in Section 3.3.2.3 above, the company performed an exploratory analysis versus rituximab monotherapy using data from the CHRONOS-3 trial.[8]

3.3.3.3 Applicability of HMRN treatment basket regimens used in the MAIC

Clinical advice to the EAG also suggested that the following treatment regimens included in the HMRN treatment basket would not be in common use within UK clinical practice:

- rituximab monotherapy (as this would usually be used in first-line settings or in the very old who cannot tolerate chemotherapy);
- chlorambucil;
- fludarabine, cyclophosphamide and rituximab (FCR);
- gemcitabine/ dexamethasone/ cisplatin/ rituximab (as this would only be used in high-grade relapses where MZL is accompanied by another condition);
- ifosfamide, epirubicin and etoposide (IVE)/rituximab;
- venetoclax/ rituximab (as venetoclax is not available for this indication via the NHS);
- cyclophosphamide, vincristine and prednisolone (CVP);
- bendamustine;
- bendamustine/ methulprednisolone;
- cyclophosphamide/ prednisolone;
- fludarabine;
- bortezomib (Velcade), cyclophosphamide and dexamethasone (VCD); and
- velcade/ dexamethasone.

As such, the EAG asked the company to repeat the MAIC analyses removing these regimens from the HMRN treatment baskets (PfC, question A14).[8] The company responded by providing a restricted HMRN registry basket of N=[redacted], excluding the regimens listed by the EAG above.[8] The company noted that the restricted regimen cohort was well-aligned to the full HMRN basket of N=[redacted] and the N=[redacted] HMRN cohort with only participants treated with rituximab with or without chemotherapy.[8] However, because longer-term outcomes were poorer in the HMRN restricted regimen cohort, they considered the existing MAICs in the CS to be more conservative when assessing the relative treatment effect of zanubrutinib.[8] The EAG cannot comment further, though additional evidence may reduce some of the uncertainties surrounding this issue.

3.3.4 Covariates included within the MAIC

Only five covariates were included within the MAIC matching process: number of prior lines of therapy (1 versus 2 versus ≥ 3); refractory to last therapy (yes versus no); age (mean and variance); POD24 (yes or no); median time since diagnosis (< median versus ≥ median; CS Section B.2.9.1.1, p.81-2).[4] The covariates included in the MAIC were validated during an advisory board of UK experts on 11 October 2023.[1] The company did not include ECOG PS as a covariate within the MAIC as it was only available at the time of enrolment into the HMRN registry (CS Section B.2.9.1.1, p.82).[4] Clinical advice to the EAG noted that TP53 mutation may also have been a relevant prognostic variable for MZL, which could not be included within the MAIC due to the lack of data available from the HMRN registry. However, UK clinical experts in attendance at an advisory board for zanubrutnib did not highlight the presence of TP53 mutation as a key covariate.[1]

The EAG appreciate that the lack of covariates included within the MAIC was because several patient characteristics that were collected in the HMRN registry were only recorded at the time of enrolment rather than at the time of initiation of therapy once a patient had become R/R to prior anti-CD20 treatment (CS Section B.2.9.1.1, p.81-2).[4] However, the EAG have concerns regarding the lack of covariates within the MAIC and their potential impact on the results. The NICE DSU guidance on conducting unanchored MAICs states that "*the weighting model must include every effect modifier and prognostic variable*" (p.35), though also note that this assumption is "*largely considered to be implausibly strong*" (p.42).[33] Though the company acknowledge the lack of covariates within the MAIC, the EAG note that the lack of adjustment and weighting for covariates within the unanchored MAIC introduces greater uncertainty in the overall results.

Furthermore, the EAG note that, when weighted against the HMRN treatment basket, the ESS of the pooled MAGNOLIA-003 data dropped from 86 to [redacted] (see Table 43, CS Section B.2.9.1.2, p.85).[4] NICE DSU Technical Document 18 states: "*However, small effective sample sizes are an indication that the weights are highly variable due to a lack of population overlap, and that the estimate may be unstable*" (p.27).[33] As such, the EAG believe that the substantial decrease in ESS is suggestive of an overall lack of overlap between the MAGNOLIA-003 and HMRN registry basket data, further increasing the uncertainty surrounding the results of the MAIC.

Table 3.13: Summary of the MAGNOLIA-003 population characteristics before and after matching to the HMRN treatment basket

Characteristics	MAGNOLIA-003 (N=86), unweighted	MAGNOLIA-003 (ESS=[redacted]), weighted	HMRN treatment basket (N=[redacted])
2 lines of prior therapy (%)	[redacted]	[redacted]	[redacted]
3+ lines of prior therapy (%)	[redacted]	[redacted]	[redacted]
Refractory response to last systemic therapy	[redacted]	[redacted]	[redacted]
POD24 (%)	[redacted]	[redacted]	[redacted]
Mean age (years)	[redacted]	[redacted]	[redacted]
Time since diagnosis ≥ median (%)	[redacted]	[redacted]	[redacted]
Source: CS Section B.2.9.1.2, Table 43, p.85[4]			

Characteristics	MAGNOLIA-003 (N=86), unweighted	MAGNOLIA-003 (ESS=[redacted]), weighted	HMRN treatment basket (N=[redacted])
Abbreviations: CS = company submission; ESS = Effective sample size; HMRN = Haematological Malignancy Research Network; POD24 = Relapse or progression within 24 months of initiation of systemic therapy			

3.4 Conclusions of the clinical effectiveness section

A SLR was conducted to identify literature relevant to the NICE scope.[5] A broader SLR encompassing wider inclusion criteria was undertaken initially. Despite several minor concerns with the search strategies, the EAG is satisfied that most relevant studies are likely to have been retrieved. From the 24 studies identified, seven studies matched the NICE scope, of which two single-arm trials reporting the efficacy and safety of zanubrutinib in R/R MZL patients previously treated with anti-CD20 therapy were used in the CS.[4]

The MAGNOLIA and AU-003 studies used in the CS comprise populations which are considered generalisable to that seen in NHS clinical practice. Whilst not uncommon in rare diseases, including rare cancers, single-arm trials are subject to methodological limitations. Although, the EAG are satisfied with the conduct of the trials, and the evidence the company provided to minimise bias, uncertainty is inherently introduced when using an external control group to assess effectiveness The evidence from MAGNOLIA and AU-003 is compared a historical control (subset of the HMRN registry) to facilitate comparability of survival and other outcome measures with patients not treated with zanubrutinib.

MAGNOLIA was a multicentre, single-arm, open-label Phase 2 study that evaluated the efficacy, safety, and tolerability of zanubrutinib in patients with R/R MZL (NCT03846427). The study recruited 68 patients and had a median follow-up duration of 28 months at DCO of 31 May 2022. The efficacy and safety results for 66 patients were included in the CS. All trial outcomes were in line with the outcomes identified in the NICE scope. The study met its primary endpoint (ORR), with 17 (25.8%) and 28 (42.4%) achieving CR and PR respectively (IRC-assessed). The secondary endpoint data on PFS indicated that at a median follow-up of 27.4 months, median PFS was not reached, while [redacted] patients had either progressed or died (IRC-assessed). Similarly, data on OS indicated that at a median follow-up of 28.7 months, median OS was not reached, while [redacted] patients had died.

AU-003 was a single group assignment, dose escalation and expansion Phase 1/2 study to investigate the safety and pharmacokinetics of zanubrutinib in patients with B-cell lymphoid malignancies (NCT02343120). The efficacy and safety results for 20 patients with R/R MZL were included in the CS. Excluding HRQoL, all outcomes identified in the NICE scope were trial outcomes, including ORR (the primary endpoint). Whilst ORR was met, with four (20.0%) and twelve patients (60.0%) having a CR and PR, respectively (IRC-assessed, DCO 02 October 2020), data for secondary outcomes including PFS and OS can be considered relatively immature. Using the same DCO, the median PFS was not reached, and five patients had progressed disease or died. The OS data is also very immature (events have occurred in 15.0% of the population).

The EAG were satisfied that study quality for both trials was acceptable, however the lack of a randomised trial severely limits any conclusions on the effectiveness of zanubrutinib in patients with R/R MZL.

The company conducted a MAIC by pooling data from MAGNOLIA and AU-003 together (MAGNOLIA-003) and comparing with a basket of treatments taken from the HMRN registry. The company reported that, compared with this basket of treatments, the MAIC demonstrated a statistically

significant difference in PFS-IRC and OS in favour of zanubrutinib. However, the EAG believe the results of the MAIC uncertain due to methodological issues. Although unavoidable when using data from single-arm studies, conducting an unanchored MAIC inherently means that the results are open to considerable uncertainty. Furthermore, the lack of demographic variables available from the HMRN basket of treatments means that only five covariates were available to match participants on which violates the key assumption underlying unanchored MAICs (that all prognostic factors and effect modifiers are adjusted for). This means there are uncertainties surrounding the comparability of participants within the HMRN basket of treatments and those in MAGNOLIA-003.

In conclusion, the study quality of the two trials included in the effectiveness review is satisfactory. Both were early phase, and as such ORR was the primary outcome. Secondary outcomes of PFS and OS were not estimable by DCO for either trial. Patients continued treatment in the LTE study and results for these key survival outcomes will become evident over the coming years. However, the implication of using single-arm trials to determine the clinical effectiveness of zanubrutinib in R/R MZL patients is compromised compared to using an RCT. Whilst single-arm studies are not uncommon in trials for rare diseases and cancers, and the company provided evidence that the studies were well-designed which minimised bias where possible, there is inherent uncertainty associated with the resultant need to use an unanchored MAIC to facilitate comparison with other treatments for R/R MZL. Furthermore, comparison with the treatment basket derived from the HMRN registry adds further uncertainty to the results of the MAIC due to the lack of covariates available to match with MAGNOLIA-003. These uncertainties feed into the cost-effectiveness results, which is discussed in the following sections.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies.

4.1.1 Search strategies for cost effectiveness SLR

Searches were conducted separately for economics (cost-effectiveness and cost resource use) and HRQoL (Appendix G). The EAG's critique of HRQoL searches are in Section 4.2.9.1. while the EAG's critique of the way the MZL concept was searched in all searches (clinical effectiveness, economic, and HRQoL) can be found in Section 3.1.1.2.

4.1.1.1 Sources

For the economic search, the company searched a reasonable range of databases and grey sources: Embase, MEDLINE, NHS-EED, EconLit, CEA Registry, HTA agencies, and INAHTA. For the EAG's assessment of conference sources used in the CS, see Section 3.1.1.1.

4.1.1.2 Search filters

Searches were restricted to economic studies using a variation of the CADTH filter for Economic Evaluations & Models.[36,37] The CADTH filter uses the keyword heading word field (.kf) in the lines pertaining to keywords, whereas the company searches in Embase uses the keyword heading field (.kw) (e.g. CS Appendix G, Table 2, search line 16).[38] The latter (.kw) is less sensitive, only returning results if the whole keyword heading matches exactly (e.g. "markov.kw" does not include results with "markov model" as a keyword, whereas "markov.kf" does). The filter was updated in June 2023 to include "exp Economic Model/" but it is feasible that this was not available at the time the company ran the searches. Additional terms relating to absenteeism have been added to the filter, which would add to the results but not restrict what the filter would otherwise retrieve.

Without comprehensive testing, it is difficult for the EAG to quantify the effects that all the issues mentioned may have had on search results, but it seems likely the effects would be relatively minor. Overall, the EAG is satisfied that the search for economic studies was conducted appropriately.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.1: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Population	As per NICE scope.	In line with NICE reference case.
Comparators	Therapies routinely used in the National Health Service (NHS), including technologies regarded as current best practice.	In contrast to the NICE scope, the model does not include best supportive care or splenectomy (for splenic MZL only). As noted in Section 3.1, the EAG finds this acceptable.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers.	In line with NICE reference case.

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on costs	NHS and PSS.	In line with NICE reference case.
Type of economic evaluation	Cost utility analysis with fully incremental analysis.	In line with NICE reference case.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared.	In line with NICE reference case.
Synthesis of evidence on health effects	Based on systematic review.	In line with NICE reference case.
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.	In line with NICE reference case.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers.	As the EQ-5D-5L estimate for the PF health state from the MAGNOLIA trial was considered to lack face validity, the utility value was capped at the age and gender matched estimate for the general population. The EQ-5D-5L estimate for the PD health state is sourced from a CADTH pan-Canadian Oncology Drug Review for bendamustine for NHL.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population.	The utility value for the PD health state is from a Canadian population (CADTH 2012).
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	In line with NICE reference case.
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	In line with NICE reference case.
Discounting	The same annual rate for both costs and health effects (currently 3.5%).	In line with NICE reference case.

Source: Produced by EAG
Abbreviations: CADTH = Canadian Agency for Drugs and Technology in Health; EAG = Evidence Assessment Group; NHL = Non-Hodgkin lymphoma; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PD = progressed disease; PF = progression-free; PSS = Personal Social Services; QALY = quality-adjusted life year; UK = United Kingdom

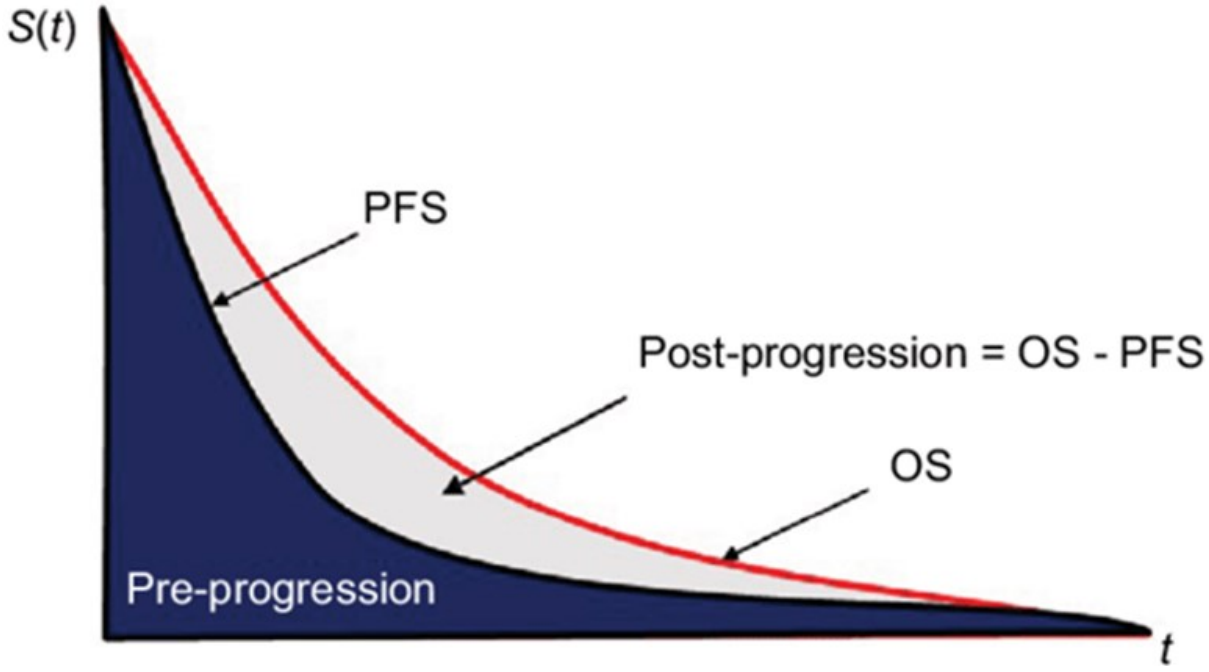
4.2.2 Model structure

The company developed a partitioned survival model (PSM) in Microsoft Excel® to project the long-term clinical and economic consequences of zanubrutinib for treating relapsed or refractory marginal zone lymphoma.

4.2.2.1 Health states/events and transitions

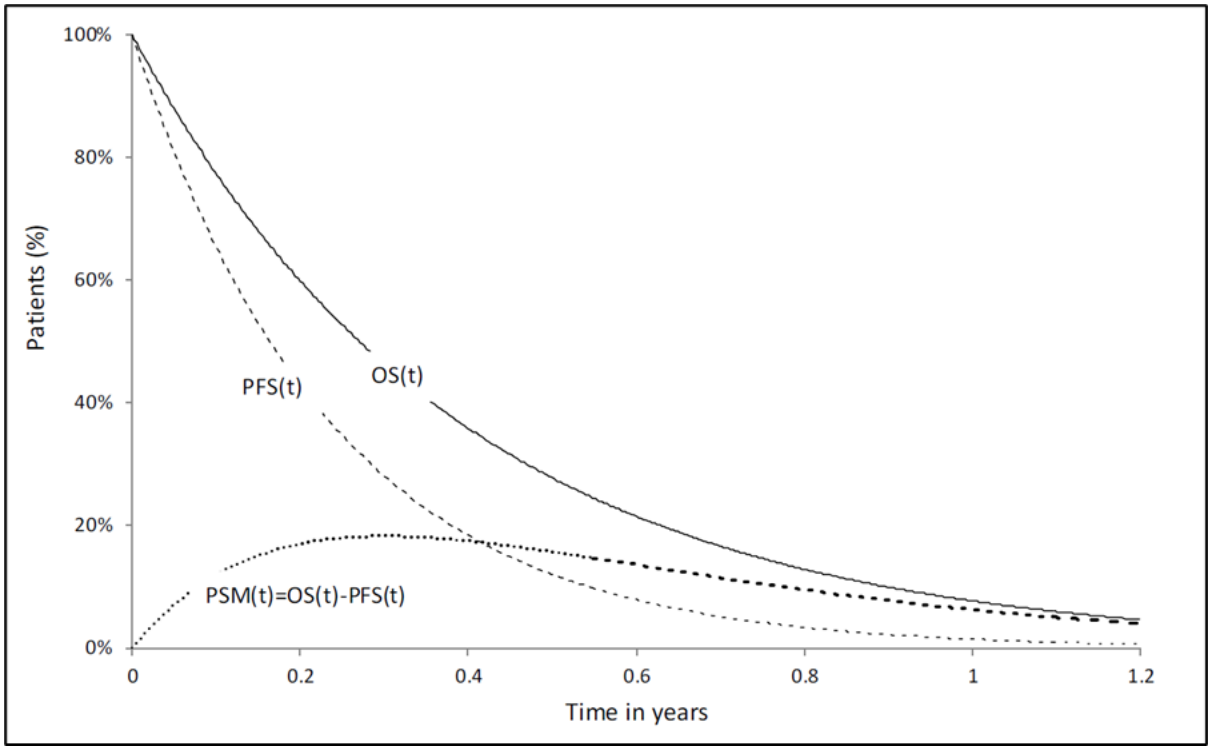
The PSM consisted of three mutually exclusive health states: progression-free (PF), progressed disease (PD) and death, as shown in **Figure 4.1**. All patients started in the PF state. From the PF state, patients could then either remain in this PF state, transition to PD health state upon disease progression, or the death state if mortality occurred. State occupancy of these health states was determined by estimating the cumulative probability of PFS and OS by extrapolating the data from the MAGNOLIA and AU-003 single-arm trials and the HMRN registry basket respectively. An illustration of how the PFS and OS curves were used to estimate health state occupancy in the PSM is shown in Figure 4.2.

Figure 4.1: Model structure



Source: CS Section B.3.2.2, Figure 18, p.110[4]
Abbreviations: CS = company submission; OS = Overall survival; PD = progressed disease; PF = progression-free; PFS = progression-free survival.

Figure 4.2: Illustration of how the PFS and OS curves are used to estimate health state occupancy in the PSM



Source: CS Section B.3.2.4, Figure 19, p.112[4]
Abbreviations: CS = company submission; OS = overall survival; PD = progressed disease; PF = progression-free; PFS = progression-free survival; PSM = partitioned survival model.

The EAG has some concerns regarding the choice of a PSM, given the assumptions that underpin this modelling framework.

The company justified their choice of using a PSM modelling framework by stating that:

- the PSM structure is a widely accepted approach commonly used in NICE HTAs in oncology;
- that it is not necessary to model subsequent lines of treatment given the limited treatment options for patients with R/R MZL;
- the PSM approach was selected over the semi-Markov approach as explicit modelling on subsequent treatments was not required and the data from the MAGNOLIA and AU-003 trials were sufficiently mature to provide robust extrapolations for PFS and OS;
- semi-Markov approaches require the use of alternative trial endpoints, which can make conducting ITCs more difficult; and
- a Discrete Event Simulation (DES) was not considered due to the high data intensity.

The EAG agrees with the company that PSMs are commonly used in NICE HTAs in oncology. However, the EAG is of the opinion that a State Transition Model (STM) could be a more appropriate modelling framework for the decision problem. The principal reason for this is that the PSM approach independently models PFS and OS. [redacted] In contrast to a PSM, an STM includes the probability of death during both the PFS and PD states, with OS depending on disease progression and the likelihood of dying in

each state. Furthermore, many of the clinical conditions for which PSMs have previously been used have a relatively short PFS and OS, whereas the PFS and OS predicted in the company's economic model are much longer. The EAG is of the opinion that, given a sufficient evidence base, an STM could give more accurate cost-effectiveness results than a PSM. The EAG acknowledge that data limitations may inhibit the parametrisation of such a model in this specific context. The EAG agrees that a DES is a very data intensive method and is therefore not appropriate in this instance.

The EAG asked the company to further justify their choice of model structure (PfCs, question B1).[8] In their response, the company stated that they considered the use of an STM during the model conceptualisation phase but the PSM was ultimately selected as the most appropriate model structure. The company reiterated that the PSM structure is widely used and consistent with the approaches previously used in NICE appraisals. Furthermore, the company noted that the STM structure has its own limitations and may not be able to alleviate the uncertainty associated with a PSM. The company further argued that, given the data from MAGNOLIA and AU-003 is less mature than the data from the HMRN basket, it will likely overestimate the hazard of death for zanubrutinib as it is based on the observed within-trial hazard of death, which is likely to increase as patients progress. The company argued that this will lead to a more conservative estimate of OS for zanubrutinib.

Overall, the EAG has concerns over the PSM modelling framework used by the company. The EAG acknowledges the PSM structure is consistent with the approaches previously accepted by NICE in similar assessments, and that data limitations may inhibit the parameterisation of an STM in this specific context. However, the EAG ultimately considers an STM to be the preferred model structure for the decision problem.

4.2.3 Population

The baseline characteristics for the modelled population are shown in Table 4.2. The EAG is satisfied that this broadly represents the population at risk, which was confirmed by expert clinical opinion obtained by the EAG.

Table 4.2: Baseline characteristics in economic model

Characteristics	Mean (SE)	Source
Age (years)	[redacted]	Pooled MAGNOLIA and AU-003 data matched to the HMRN registry basket (base-case MAIC analysis)
BSA (m^2)	[redacted]	
Proportion female	[redacted]	

Source: CS Section B.3.2.1 Table 53, p.109[4]

Abbreviations: BSA = Body surface area; CS = company submission; m = metre; MAIC = matching-adjusted indirect treatment comparison; SE = standard error.

4.2.4 Interventions and comparators

See Table 4.1 for further EAG comment relating to the interventions and comparators.

4.2.5 Perspective, time horizon and discounting

As per scope.

4.2.6 Treatment effectiveness and extrapolation

The evidence on treatment effectiveness used for the intervention and comparators in the economic model are the combined MAGNOLIA-003 cohort for zanubrutinib (adjusted using the MAIC discussed in Section 3.3) and the HMRN registry data for the comparators.

The company used survival analysis on PFS and OS to extrapolate the treatment effectiveness for zanubrutinib and the comparators from the HMRN registry basket beyond the available trial data. The company also used survival analysis on the time to discontinuation (TTD) to estimate the treatment duration for zanubrutinib. These survival analyses are discussed in detail in Section 4.2.7.

As no TTD data were available in the literature for the HMRN registry basket, the company assumed that patients remained on treatment only whilst in the PFS health state. As noted by the company, it is possible that this assumption will overestimate the cost of the HMRN registry basket. The EAG agree with the company that this overestimation is likely to be relatively low and, consequently, is likely to have little substantial impact on the ICER.

4.2.7 Time to event analysis

The company's survival analysis methods largely followed the recommendations from the NICE DSU TSD 14.[39] Kaplan-Meier data were fit across six parametric distributions to predict survival over the modelled time horizon: exponential; Weibull; Gompertz; log-normal; log-logistic; and gamma. Kaplan-Meier data from the combined MAGNOLIA-003 and HMRN registry data were used as a reference. The most plausible distribution was selected based on an assessment of:

- goodness of fit (Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC));
- visual inspection comparing the estimates to the MAGNOLIA-003 KM data; and
- clinical plausibility, leveraging clinical expert opinion.

Following a request from the EAG (PfC, question B3b)[8], the following additional diagnostic plots were provided by the company for the EAG to further assess the survival model choices made by the company.

- Smoothed hazard versus time
- LN (smoothed hazard) versus time
- LN (cumulative hazard) versus LN (time)

These diagnostic plots are shown in Appendix 1.

A summary of the company's choice of parametric survival model is shown in Table 4.3. The EAG's assessment of these choices is presented in the following sections.

Table 4.3: Summary of the company's choice of parametric survival model

Parameter	CS Section	Company choice of parametric survival model
PFS: HMRN registry basket	B.3.3.2 (p.116)	Log-logistic
PFS: zanubrutinib	B.3.3.3 (p.119)	Log-logistic
OS: HMRN registry basket	B.3.3.4 (p.122)	Log-logistic
OS: zanubrutinib	B.3.3.5 (p.125)	Log-logistic
TTD: zanubrutinib	B.3.3.5 (p.127)	Log-logistic
Source: Produced by the EAG.		

Parameter	CS Section	Company choice of parametric survival model
Abbreviations: OS = overall survival; PFS = progression-free survival; TTD = time to discontinuation		

4.2.7.1 PFS: HMRN registry data

Goodness-of-fit statistics, landmark PFS rates and the parametric survival extrapolations are shown in Table 4.4, Table 4.5 and Figure 4.3.

The company justified the choice of survival curve by stating:

- ~20% of patients would be progression-free at 10 years, which best aligned with the log-normal and log-logistic curves;
- the shape of hazard for progression aligns with accelerated failure time models;
- log-logistic was chosen over log-normal due to its lower AIC and BIC scores, both individual and combined; and
- that PFS was clinically plausible at landmark time-points.

The EAG consider the Exponential, Gamma, Gompertz and Weibull distributions to visually fit the KM data better than the log-logistic distribution and log-normal distributions. [redacted][1] Clinical expert opinion gathered by the EAG suggested that this estimate of 20% was "*about right*". All six parametric survival curves underestimated the OS at 10 years compared to this expert opinion. Given the lack of concurrence between the OS rates estimated by the clinical experts and the KM data, the EAG consider the choice of parametric survival function to be subject to considerable uncertainty. As expert advice gathered by the company recommended that [redacted][1] the EAG consider the reasoning for choosing the log-logistic curve over the log-normal curve to be questionable. However, given this inherent uncertainty, the EAG consider the company choice of curve in the base-case to be satisfactory.

Table 4.4: Goodness-of-fit statistics for PFS – HMRN registry basket

Distribution	HMRN registry basket (Stratified)		
	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]
Gamma	[redacted]	[redacted]	[redacted]

Source: CS Section B.3.3.2 Table 55, p.117[4]

Abbreviations: AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria; CS = company submission; HMRN = Haematological Malignancy Research Network; PFS = Progression-free survival.
Bold indicates the distribution with the best statistical fit.

Table 4.5: Landmark PFS – HMRN registry basket

Distribution	Median (Years)	PFS (% at landmark timepoints)					
		1-year	2-year	5-year	10-year	20-year	30-year
KM Data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS Section B.3.3.2 Table 56, p.119[4]
Abbreviations: CS = company submission; HMRN = Haematological Malignancy Research Network; KM = Kaplan-Meier; PFS = progression-free survival

Figure 4.3: KM for PFS overlaid with extrapolated parametric survival curves – HMRN registry basket

Source: CS Section B.3.3.2, Figure 21, p.118[4]
Abbreviations: CS = company submission; KM = Kaplan-Meier

4.2.7.2 PFS: zanubrutinib

Goodness-of-fit statistics, landmark PFS rates and the parametric survival extrapolations are shown in Table 4.6, Table 4.7 and Figure 4.4. The company justified their choice of survival curve by stating that:

- due to no violation of the proportional hazards assumption, it was appropriate to select the same distribution for both treatment arms of the PFS;

- there was no strong evidence to justify a different choice of curve between the two treatment arms; and
- underlying shape of the hazard function reflected feedback from advisory board.

Due to the immaturity of the data, the EAG consider it extremely difficult to assess the curve choice through visual fit. Expert clinician opinion gathered by the EAG noted that although the landmark PFS rates calculated from the log-logistic distribution seemed "*reasonable*", estimating beyond this time point was "*difficult to say*". The EAG consider the choice of curve to be subject to considerable uncertainty. However, given this inherent uncertainty, the EAG consider the company choice of curve in the base-case to be satisfactory. The EAG note that the choice of the log-logistic curve by the company is conservative in nature compared to the log-normal distribution, which exhibits a similar hazard shape.

Table 4.6: Goodness-of-fit statistics for PFS – zanubrutinib

Distribution	Zanubrutinib (Stratified)		
	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]
Gamma	[redacted]	[redacted]	[redacted]

Source: CS Section B.3.3.3 Table 57, p.120[4]

Abbreviations: AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria; CS = company submission; HMRN – Haematological Malignancy Research Network; PFS = progression-free survival.
Bold indicates the distribution with the best statistical fit.

Table 4.7: Landmark PFS – zanubrutinib

Distribution	Median (Years)	PFS (% at landmark timepoints)					
		1-year	2-year	5-year	10-year	20-year	30-year
KM Data	Not reached	[redacted]	[redacted]	-	-	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS Section B.3.3.3 Table 58, p.121[4]
Abbreviations: CS = company submission; HMRN = Haematological Malignancy Research Network; KM = Kaplan-Meier; PFS = progression-free survival

Figure 4.4: KM for PFS overlaid with extrapolated parametric survival curves – zanubrutinib

Source: CS Section B.3.3.3, Figure 22, p.121[4]
Abbreviations: CS = company submission; KM = Kaplan-Meier

4.2.7.3 OS: HMRN registry basket

Goodness-of-fit statistics, landmark PFS rates and the parametric survival extrapolations are shown in Table 4.8, Table 4.9 and Figure 4.5. The company justified their choice of survival curve by stating that:

- the advisory board suggested that OS would be ~ 40% at 10 years, which aligned best with the log-normal and log-logistic curve; and
- the log-logistic curve was chosen as it had the best statistical fit of those curves, which were closest to the predictions of the clinical experts.

Due to the immaturity of the data, the EAG consider it extremely difficult to assess the curve choice through visual fit. [redacted] Clinical expert opinion gathered by the EAG suggested that 40% seemed "*a bit low*" and that they expected the OS rate to be "*between 60% and 70%*". All six parametric survival curves fit by the company underestimated OS at 10 years compared to this expert opinion, with the log-normal and log-logistic curves closest to this estimate. Given the lack of concurrence between the OS rates estimated by the clinical experts and the KM data, the EAG consider the choice of parametric survival function to be subject to considerable uncertainty. [redacted][1] the EAG consider the reasoning for choosing the log-logistic curve over the log-normal curve to be questionable. However, given this inherent uncertainty, the EAG consider the company choice of curve in the base-case to be satisfactory.

Table 4.8: Goodness-of-fit statistics for OS – HMRN registry basket

Distribution	HMRN registry basket (Stratified)		
	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]
Gamma	[redacted]	[redacted]	[redacted]

Source: CS Section B.3.3.4 Table 59, p.123[4]

Abbreviations: AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria; HMRN = Haematological Malignancy Research Network; OS = overall survival.
Bold indicates the distribution with the best statistical fit.

Table 4.9: Landmark OS – HMRN registry basket

Distribution	Median (Years)	PFS (% at landmark timepoints)					
		1-year	2-year	5-year	10-year	20-year	30-year
KM Data	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS Section B.3.3.4 Table 60, p.124[4]
Abbreviations: CS = company submission; HMRN = Haematological Malignancy Research Network; KM = Kaplan-Meier; OS = overall survival.

Figure 4.5: KM for OS overlaid with extrapolated parametric survival curves – HMRN registry basket

Source: CS Section B.3.3.4, Figure 23, p.124[4]
Abbreviations: CS = company submission; HMRN = Haematological Malignancy Research Network; KM = Kaplan-Meier; OS = overall survival

4.2.7.4 OS: zanubrutinib

Goodness-of-fit statistics, landmark OS rates and the parametric survival extrapolations for zanubrutinib are shown in Table 4.10, Table 4.11 and Figure 4.6. The company justified their choice of survival curve by stating that:

- the clinical advisory board suggested that the log-normal, log-logistic, and exponential curves could be considered clinically plausible; and
- there was no strong evidence to justify a different choice of curve between the two treatment arms.

Due to the immaturity of the data, the EAG consider it extremely difficult to assess the curve choice through visual fit. Expert clinician opinion gathered by the EAG noted that, although the landmark OS rates calculated from the log-logistic distribution seemed "*reasonable*", estimating beyond this time point was "*difficult to say*". The EAG consider the choice of curve to be subject to considerable uncertainty. However, given this inherent uncertainty the EAG consider the company choice of curve in the base-case to be satisfactory. The EAG note that the choice of the log-logistic curve is conservative in nature compared to the log-normal distribution, which was also considered clinically plausible.

Table 4.10: Goodness-of-fit statistics for OS – zanubrutinib

Distribution	Zanubrutinib (Stratified)		
	AIC	BIC	Sum of AIC and BIC
Exponential	[redacted]	[redacted]	[redacted]

Distribution	Zanubrutinib (Stratified)		
	AIC	BIC	Sum of AIC and BIC
Weibull	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]

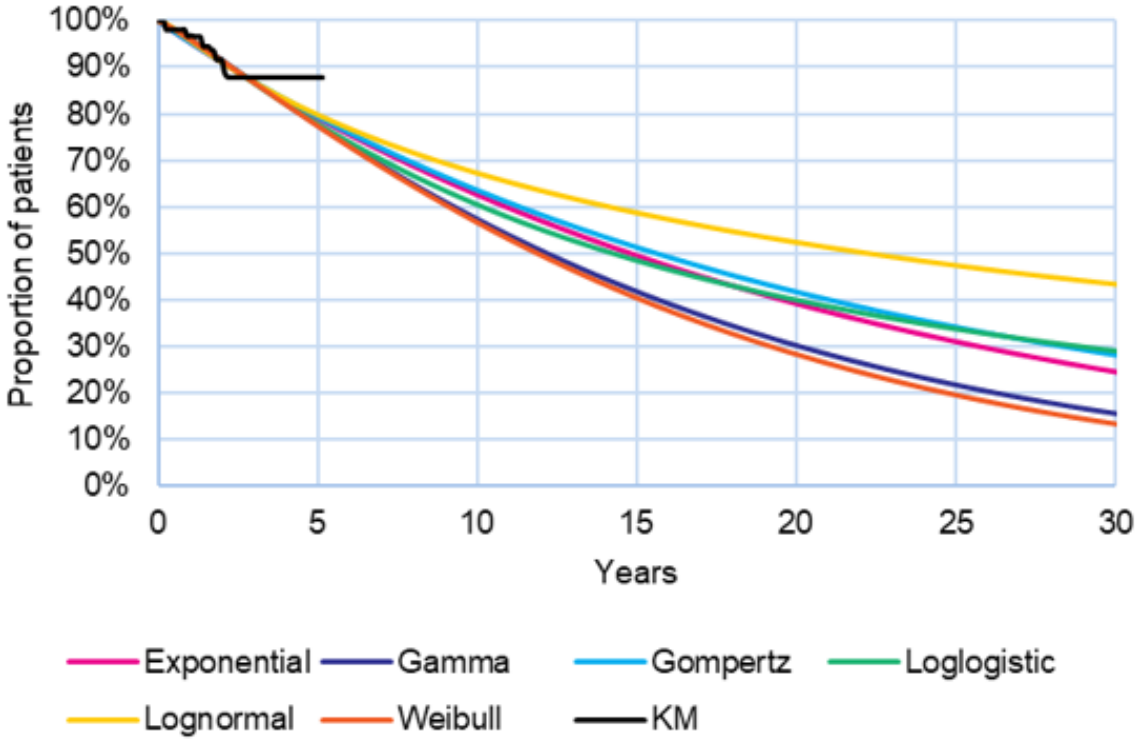
Source: CS Section B.3.3.4 Table 61, p.125[4]
Abbreviations: AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria; CS = company submission; HMRN = Haematological Malignancy Research Network; OS = overall survival. **Bold indicates the distribution with the best statistical fit.**

Table 4.11: Landmark OS – zanubrutinib

Distribution	Median (Years)	OS (% at landmark timepoints)					
		1-year	2-year	5-year	10-year	20-year	30-year
KM Data	Not reached	[redacted]	[redacted]	-	-	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS Section B.3.3.4 Table 62, p.127[4]
Abbreviations: CS = company submission; HMRN = Haematological Malignancy Research Network; KM = Kaplan-Meier; OS = overall survival.

Figure 4.6: KM for OS overlaid with extrapolated parametric survival curves – zanubrutinib



Source: CS Section B.3.3.5, Figure 24, p.126[4]
Abbreviations: CS = company submission; KM = Kaplan-Meier; OS = overall survival

4.2.7.5 TTD for zanubrutinib

Goodness-of-fit statistics,landmark TTD rates and the parametric survival extrapolations for zanubrutinib are shown in Table 4.12, Table 4.13and Figure 4.7. The company justified their choice of survival curve by stating that:

- the log-logistic curve is one of the three curves (along with the Gompertz and log-normal) that plateau rather than tend to zero; and
- the log-logistic curve is in line with the choice of distribution for the PFS for zanubrutinib.

Due to the immaturity of the data, the EAG consider it extremely difficult to assess the curve choice through visual fit. The EAG note that the expert opinion gathered by the company did not specifically discuss the potential TTD rates for patients treated with zanubrutinib, instead concentrating on whether it was reasonable to use TTD data to model duration for zanubrutinib patients. The EAG consider the choice of curve to be subject to considerable uncertainty. However, given this inherent uncertainty the EAG consider the choice of curve to be satisfactory. The EAG note that the choice of the log-logistic curve is optimistic compared to the log-normal curve, which exhibits an almost identical hazard shape.

Table 4.12: Goodness-of-fit statistics for TTD – zanubrutinib

Distribution	HMRN registry basket (Stratified)		
	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]
Gamma	[redacted]	[redacted]	[redacted]

Source: CS Section B.3.3.6 Table 63, p.128[4]
Abbreviations: AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria; CS = company submission; HMRN = Haematological Malignancy Research Network; TTD = time to discontinuation. **Bold indicates the distribution with the best statistical fit.**

Table 4.13: Landmark TTD – zanubrutinib

Distribution	Median (Years)	TTD (% at landmark timepoints)					
		1-year	2-year	5-year	10-year	20-year	30-year
KM Data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS Section B.3.3.4 Table 64, p.129[4]
Abbreviations: = Kaplan-Meier; TTD = Time to Treatment Discontinuation

Figure 4.7: KM for TTD overlaid with extrapolated parametric survival curves – zanubrutinib

Source: CS Section B.3.3.6, Figure 25, p.129[4]
Abbreviations: KM – Kaplan-Meier

4.2.7.6 Adjustments to the survival curves

The company made several further adjustments to the survival curves selected for use in the base-case analysis.[4]

- Restriction of survival by age-gender matched all-cause mortality for both treatment arms.
- Restriction of PFS by OS, such that patients cannot be PF for longer than they are alive.
- Restriction of TTD by PFS for zanubrutinib.

The EAG consider these adjustments to be appropriate. In the case of restricted survival by age-gender matched all-cause mortality, the EAG note that by not applying a standardised mortality ratio (SMR) in the base-case analysis, the company are assuming that the background (non-cancer) mortality risk for patients with R/R MZL is the same as the age and gender matched general population. Expert clinical advice gathered by the EAG confirmed that this assumption was appropriate.

The company state that as the HRs tend to 1 over the model time horizon no additional treatment waning assumptions are necessary for the analysis.[4] This is illustrated graphically in Figure 4.8.

Figure 4.8: Modelled HRs (zanubrutinib vesus HMRN registry basket) over time horizon

Source: CS Section B.3.3.7, Figure 26, p.131[4]
Abbreviations: CS = company submission; HMRN = Haematological Malignancy Research Network; HR = hazard ratio; OS = overall survival; PFS = progression-free survival

As part of the clarification process (PfC, question B5),[8] the EAG requested that the company provide further evidence that no treatment waning assumptions were necessary, and also requested that they provide additional scenario analyses assuming several different lengths of treatment waning. As part of their response, the company demonstrated the additional scenario analyses made relatively little difference to the ICER and argued that these additional scenarios were clinically implausible. The company further reiterated that the OS HR tending towards 1 demonstrated a natural waning of treatment effect over the model time horizon, with this assumption accepted in previous zanubrutinib NICE submissions.[40,41] The EAG is satisfied with this assumption but notes that treatment waning is subject to uncertainty. Clinical expert opinion gathered by the EAG noted that, due to a lack of data, estimating treatment waning for zanubrutinib was difficult.

4.2.7.7 Summary of EAG's view on time to event analysis

Overall, the EAG is satisfied that the company carried out the survival analysis and extrapolation methods in line with current best practice.[39] However, the EAG has concerns related to the immaturity of the trial data and the consequential uncertainty related to the choice of survival curves for the PFS, OS, and TTD parameters.

Due to the relative absence of mature evidence, the EAG consider it very difficult to make long term predictions regarding PFS and OS for those patients receiving zanubrutinib. This is illustrated by the significant heterogeneity between the long-term PFS and OS predictions from the different parametric curves, which all have almost identical statistical fits based on the AIC and BIC. For instance, the log-normal distribution predicts the OS proportion to be [redacted] at 20 years, whereas the Weibull distribution predicts the same proportion to be [redacted]. Furthermore, the Gompertz distribution predicts the PFS proportion to be [redacted], at 20 years, whereas the exponential distribution predicts the PFS to be [redacted]. The EAG acknowledge that the choice between different survival curves makes relatively little

difference on the ICERs but note that, in the case of OS, this could partially be due to the restriction of survival by age-gender matched all-cause mortality. The EAG questions the assumption that the data from the MAGNOLIA and AU-003 trials were sufficiently mature to provide robust extrapolations for the PFS and OS health states, considering that the economic model predicts that a significant proportion of the patients will be in the PFS and OS health states at 20 years. The lack of maturity in the data can be exemplified by the fact that, as noted in Tables 14 and 32 of the CS,[4] median PFS was not estimable in the MAGNOLIA trial. The EAG considers the extrapolations of the data from the MAGNOLIA and AU-003 trials to be subject to considerable uncertainty.

Although the evidence from the HMRN registry is more mature, the EAG again note there is heterogeneity between the long-term PFS and OS predictions from the different parametric curves, which again all have almost identical statistical fits based on the AIC and BIC. For instance, the Gompertz distribution predicts the OS proportion to be [redacted] at 20 years, whereas the Exponential distribution predicts the same proportion to be [redacted]. Moreover, the log-normal distribution predicts the PFS proportion to be [redacted] at 20 years, whereas the Exponential distribution predicts the same proportion to be [redacted] Furthermore, there was a lack of concordance between the expert opinion gathered by both the company and the EAG and the estimates from the various survival models, with all six survival curves underestimating the PFS and OS compared with the clinical expert opinion. The EAG considers the extrapolations of the data from the HMRN registry to be subject to uncertainty.

Throughout Sections B.3.3.2 to B.3.3.5 of the CS, the sum of the AIC and BIC is presented alongside the individual AIC and BIC values. As part of the PfC (question B4)[1], the EAG asked the company to further justify the use of this combined metric, including references to previous studies that have used this combined metric. In response, the company did not justify the use of the combined metric, and instead reiterated the common use of the AIC and BIC in NICE submissions, the other methods used to inform curve selection in the CS.[1] The EAG note that although they find the use of this combined AIC/BIC metric to be unusual, its use has limited impact on the final choice of survival function and, therefore, the cost-effectiveness results.

4.2.8 Adverse events

The cost-effectiveness model (CEM) accounted for the impact of all Grade ≥ 3 treatment-related AEs which occurred in ≥ 2% of patients receiving treatment.[4] Table 4.14 shows the incidence rates of AEs for zanubrutinib, alongside three selected treatments taken from the HMRN registry basket and the overall HMRN registry basket.

Table 4.14: Grade ≥ 3 treatment-related AEs occurring in ≥ 2% of patients by treatment.

AE	Zanubrutinib	BR	R-CVP	Rituximab monotherapy	Overall HMRN registry basket
Neutropenia	[redacted]	51.10%	1.69%	12.33%	31.52%
Anaemia	[redacted]	1.76%	0.00%	2.74%	1.64%
COVID-19 pneumonia	[redacted]	0.00%	0.00%	0.00%	0.00%
Pneumonia	[redacted]	4.41%	0.85%	2.74%	3.27%

Diarrhoea	[redacted]	1.76%	0.00%	0.00%	0.97%
Pyrexia	[redacted]	3.52%	0.00%	0.00%	1.94%
Thrombocytopenia	[redacted]	7.05%	0.00%	0.00%	3.88%
Neutrophil count decreased	[redacted]	0.00%	0.00%	13.70%	3.35%
Hypertension	[redacted]	4.85%	0.00%	8.90%	4.85%
Rash	[redacted]	2.64%	0.00%	0.00%	1.46%
Infusion-related reaction	[redacted]	2.64%	0.00%	0.00%	1.46%
Hyperglycaemia	[redacted]	0.00%	0.00%	8.22%	2.01%
Source	MAGNOLIA-003[26,28]	SEQUOIA, Tam 2022[42]	Oh et al 2019[43]	CHRONOS-3, Matasar 2021[44]	Weighted calculation

Source: CS Section B.3.4.5 Table 69, p.141[4]
Abbreviations: AE = adverse event; BR = bendamustine-rituximab; CS = company submission; HMRN = Haematological Malignancy Research Network; R-CVP = rituximab + cyclophosphamide + vincristine + prednisone

The AE profiles of zanubrutinib and the comparators were derived from several sources. The AE profiles for zanubrutinib were taken from the pooled MAGNOLIA-003 dataset. As safety outcomes were not available from the HMRN registry, published literature was used to source the AE rates for the top three treatments within the registry basket (BR, rituximab monotherapy and R-CVP). The company justified their approach by noting that these treatments reflected the range of toxicities experienced by patients receiving treatment for R/R MZL, [redacted][1] The clinical experts further recommended that AE rates for BR were applied to the proportion of patients receiving this treatment in the basket ([redacted]), with the proportions for CVP and rituximab monotherapy being assigned to the remaining [redacted] and [redacted] of the basket. Table 4.15 presents the weights of treatments in the basket. The EAG consider this approach to be appropriate.

Table 4.15: Weights of the selected treatments within HMRN basket

Intervention	R-CVP	BR	Rituximab monotherapy	HMRN Basket %
Basket proportion	[redacted]	[redacted]	[redacted]	[redacted]
Weighted proportion	[redacted]	[redacted]	[redacted]	100%

Source: Produced by the EAG, adapted from the CEM[45]
Abbreviations: BR = bendamustine-rituximab; CS = company submission; HMRN = Haematological Malignancy Research Network; R-CVP = rituximab + cyclophosphamide + vincristine + prednisone

The AE profile of rituximab monotherapy was taken from the CHRONOS-3 trial,[44] identified through the SLR. CHRONOS-3 compared copanlisib plus rituximab against placebo plus rituximab in patients with relapsed indolent non-Hodgkin lymphoma. The AE profile for R-CVP was taken from Oh *et al*.,[43] [redacted] This was a phase 2 study of R-CVP followed by rituximab maintenance therapy for patients with stage III/IV CD20-positive advanced MZL who had responded to first-line R-CVP. The AE profile of BR was taken from the SEQUOIA trial,[42] [redacted] SEQUOIA compared zanubrutinib with BR for patients with previously untreated CLL. Given the very limited number of previous studies in R/R MZL, the EAG consider these sources to be appropriate.

4.2.8.1 Impact of AEs on HRQoL

Utility decrements associated with Grade ≥ 3 AEs were included in the CEM. Specifically, the average QALY loss due to AEs was estimated for treatment options by considering treatment-specific AE rates, mean utility decrements associated with AEs, and the mean duration of AE episodes.[4]

The company used two sets of simplifying assumptions in relation to these AEs. Firstly, the costs and disutilities associated with AEs were applied in the first model cycle only and only for first-line treatments, with AEs for subsequent lines of treatment not considered. This implicitly assumes that AEs only occur once and are resolved in the first cycle, with no persisting impacts on individuals over time. The EAG note that this is a strong assumption, and that it is very likely that adopting this approach underestimates the impact of AEs in the CEM. However, the EAG acknowledge that this assumption has been accepted in previous submissions to NICE for zanubrutinib.[40,41] [redacted]

The second set of assumptions used by the company in relation to the AEs is that all AEs included in the CEM were assumed to have the same disutility ([redacted]) and duration ([redacted]; see Table 4.16). In the company's response to the PfC (question B14), the company showed that the utility decrement was estimated using a linear mixed-effect model, with the utility score as a dependent variable and a binary variable for a grade ≥ 3 AE in the preceding period as a covariate.[8]

Table 4.16: AE disutility and duration estimates

AE	Disutility (SE)	Duration (SE)	Source
Any AE	[redacted]	[redacted]	MAGNOLIA[26]
Source: CS Section B.3.4.5 Table 70, p.142[4] Abbreviations: AE = adverse event; SE =standard error			

The company justified this assumption by noting that the low incidence rates of AEs and the small sample size in both the MAGNOLIA and AU-003 trials meant that estimates of disutility for specific AEs may be inaccurate and susceptible to outliers. During the clarification process, the EAG raised concerns regarding the rationality and potential biases arising from this simplified assumption, considering the diverse range of AEs included in the model. The EAG therefore asked the company to conduct an additional scenario analysis using AE disutility and duration estimates sourced from the wider literature to explore the uncertainty related to their simplified assumption (PfC, question B17).[8]

In response, the company conducted a scenario analysis with disutilities and durations sourced from the wider literature, which are shown in Table 4.17.

Table 4.17: Updated AE disutility and duration estimates

Adverse Event	Disutility	Disutility source/assumption	Duration (days)	Duration source/assumption
COVID-19	-0.1950	Assumed to be the same as pneumonia	18.20	Assumed to be the same as pneumonia
Pneumonia	-0.1950	TA931[41]	18.20	TA931[41]
Neutropenia	-0.1630	TA931[41]	15.09	TA931[41]
Anaemia	-0.0900	TA931[41]	23.21	TA931[41]
Thrombocytopenia	-0.1100	TA931[41]	23.21	TA931[41]
Diarrhoea	-0.1030	NG115[46]	4.00	NG115[46]
Neutrophil count decreased	-0.1630	TA931[41]	15.09	TA931[41]
Hypertension	-0.0200	TA931[41]	21.00	TA931[41]
Pyrexia	-0.0297	Chirikov et al. 2019[47]	1.00	Chirikov et al. 2019[47]
Rash	-0.0325	TA258 PAS[48]	28.00	Chirikov et al. 2019[47]
Infusion-related reaction	-0.0110	Chirikov et al. 2019[47]	1.00	Chirikov et al. 2019[47]
Hyperglycaemia	-0.062	NG28[49]	4.10	Assumption[a] based on Dhatariya et al. 2020

Source: PfCs, Table 29,[8]
Abbreviations: AE = adverse event; NG= NICE guideline; TA= technology appraisal; PAS = Patient Access Scheme; PfC = points for clarification
[a]Assumed hyperglycaemia duration is the same as the increase length of hospital stay for non-ICU patients who experience hospital acquired hypoglycaemia compared to those who do not.

4.2.8.2 Impact of AEs on cost

Costs associated with Grade ≥ 3 AEs were included in the CEM. Specifically, these costs were estimated by multiplying the AE incidence by the respective unit cost.[4] As previously noted, costs were applied in the first model cycle only. Although this is a strong assumption, as noted in Section 4.2.8.1, given the minor impact on the cost-effectiveness results the EAG are satisfied with this assumption.

Table 4.18 presents the unit costs associated with managing AEs and their sources. The EAG note that, in the CS, the unit costs for AEs were sourced from NHS reference costs for 2021/22;[50] these were not

inflated to the 2022/23 cost year. During the clarification process, the company provided inflated costs to the EAG (PfC, question B12).[8]

Table 4.18: AE management costs

Adverse event	Cost (UK £)	Source	Comment
COVID-19 pneumonia	741.08	National Cost Collection: National Schedule of NHS costs - Year 2021-22: DX11A[50]	Non-elective short stay
Pneumonia	668.60	National Cost Collection: National Schedule of NHS costs - Year 2021-22: DZ11K-V[50]	Weighted average of non-elective short stay
Neutropenia	627.97	National Cost Collection: National Schedule of NHS costs - Year 2021-22: SA35A-E[50]	Weighted average of non-elective short stay
Anaemia	615.42	National Cost Collection: National Schedule of NHS costs - Year 2021-22: SA09K-L[50]	Weighted average of non-elective short stay
Thrombocytopenia	627.97	National Cost Collection: National Schedule of NHS costs - Year 2021-22: SA35A-E[50]	Assumed to be the same as Neutropenia
Diarrhoea	562.16	National Cost Collection: National Schedule of NHS costs - Year 2021-22: WJ07A-D[50]	Weighted average of non-elective short stay
Decreased neutrophil count	542.77	National Cost Collection: National Schedule of NHS costs - Year 2021-22: SA08G-J[50]	Weighted average of non-elective short stay
Hypertension	424.60	National Cost Collection: National Schedule of NHS costs - Year 2021-22: EB04Z[50]	Non-elective short stay
Pyrexia	588.82	National Cost Collection: National Schedule of NHS costs - Year 2021-22: FD10A-M[50]	Weighted average of non-elective short stay
Rash	387.71	National Cost Collection: National Schedule of NHS costs - Year 2021-22: JD07K[50]	Non-elective short stay
Infusion-related reaction	439.22	National Cost Collection: National Schedule of NHS costs - Year 2021-22: WH05Z[50]	Non-elective short stay
Hyperglycaemia	500.02	National Cost Collection: National Schedule of NHS costs - Year 2021-22: WH13A-B[50]	Weighted average of non-elective short stay

Source: CS Section B.3.5.3 Table 76, p.149[4]
Abbreviations: AE = adverse event; CS = company submission

4.2.9 Health-related quality of life

4.2.9.1 Searches for health-related quality of life SLR

The company conducted separate searches for the HRQoL SLR. A reasonable range of databases were searched: Embase, MEDLINE, EconLit, PsycINFO and CENTRAL. For the EAG's evaluation of

conference sources, see Section 3.1.1.1. The EAG's critique of the way the MZL concept was searched in all searches (clinical effectiveness, economic, and health-related quality of life) can be found in Section 3.1.1.2. The company restricted searches to HRQoL studies using the CADTH filter for health utilities/quality of life.[51] This filter was updated in June 2023 but it is feasible that this was not available at the time the company ran the searches. Overall, the EAG is satisfied that the search for HRQoL studies was conducted appropriately.

4.2.9.2 Health-related quality of life data identified in the review

The company stated that they conducted an SLR on 29 December 2022 (updated on 8 August 2023) to identify studies reporting on the HRQoL of patients with R/R MZL (CS Appendix H).[52] By updating the SLR, the number of included studies increased from seven to nine unique studies. In total, the company included three studies for their utility values for the cost-effectiveness analysis (CEA).

- Major 2021[53]: In this study, the HRQoL of patients with iNHL in a US population was assessed using THE FACT-G and FACT-LYM instruments and mapped on to the EQ-5D-5L index.
- CADTH 2012[54]: In this HTA submission, the HRQoL of patients with previously treated, relapsed FL, NHL and MCL, patients with previously untreated iNHL or MCL and patients with iNHL or MCL that was relapsed or refractory to treatment was assessed in a Canadian population using the EQ-5D instrument.
- NICE TA627[55]: In this HTA submission, the HRQoL of patients with previously treated FL or MZL who had previously received treatment was reported in the UK population using the EQ-5D-3L.

4.2.9.3 Progression-free health state utility value

The pre-progression health state utility value was estimated from the MAGNOLIA trial.[26] In this trial, the HRQoL of patients was assessed using the EQ-5D-5L and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) at different time points until disease progression. Due to the absence of post-progression data on the patients' HRQoL, the MAGNOLIA patient-level data were exclusively used for estimating the PF health state utility value.

To estimate the PF health state utility value from the MAGNOLIA trial, the results of the EQ-5D-5L from the trial was mapped to the EQ-5D-3L using the Hernandez-Alava (2022) algorithm,[56] then predicted using a mixed-effects linear regression model. During the clarification process, the EAG requested further details of this regression model, including the full regression output (PfC, question B14). This regression output was provided by the company and is shown in Table 4.19,[8] with the intercept reflecting the utility score. The company confirmed that these data included all patients in the efficacy analysis set (n=66) who provided at least one complete EQ-5D-5L measurement, and that no imputation of missing data was implemented. The EAG note the lack of independent variables included in this regression model and are of the opinion that variables such as age, sex and number of completed visits may have been useful additions. However, the EAG also acknowledge that the impact of the utility value estimate would probably have been minimal.

Table 4.19: Regression model results on PF utility estimation

Variable	Parameter estimate			Fit statistics	
	Coefficient	SE	p-value	AIC	BIC

Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE	[redacted]	[redacted]	[redacted]		

Source: PfCs, Table 27[8]
Abbreviations: AE = adverse event; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; PF = progression-free; PfC = points for clarification; SE = standard error.

Although the company argue that the utility estimate fell in the range of the pre-progressive utilities estimated from the AUGMENT trial (the source of the utility values in TA627),[20] because the estimate of [redacted] exceeded that of the age-gender match general population (0.772), the company capped the PF utility value to ensure that the patient's HRQoL could not be higher than the general population. The company noted that this is aligned with the approach accepted in relevant previous NICE appraisals.[41,55]

The EAG are concerned by the face validity of this utility value from the MAGNOLIA trial. When asked to comment on the possible reasons for this (PfC, question B15)[8], the company noted that it could be due to a "*trial effect*" or "*Hawthorne effect*" and that this is a common problem with oncology appraisals, reiterating that their approach was in line with previous NICE appraisals.

Given the lack of a randomised trial (an issue discussed in Section 3.4), in the company base-case the PF utility value was applied to both arms in the cost-effectiveness analysis. The EAG are satisfied by this simplifying assumption. Given the uncertainty, the company conducted an exploratory scenario analysis using the findings of a HRQoL study, WhiMISCAL,[57] a global Waldenstrom's Macroglobulinemia registry. The company calculated a relative difference in HRQoL between those taking BTKi drugs and those taking non-BTKi drugs using the EORTC QLQ-C30 global scale. Given the difference in clinical condition and the use of a non preference-based measure in calculating this relative difference, the EAG has concerns about the validity of this scenario analysis.

4.2.9.4 PD health state utility value

Given the lack of post-progression utility data from MAGNOLIA, the PD utility value was obtained from the published literature. As mentioned in Section B.3.4.3 of the CS (p.137),[4] the company identified three studies in their SLR of HRQoL in patients with R/R MZL. Two of them were HTA appraisals, including NICE TA627 (in the UK population),[55] and CADTH (in the Canadian population).[54] The other study mapped FACT-G and FACT-LYM data from a US population to the EQ-5D-5L index using a United States-based validated mapping algorithm.[53] Table 4.20 shows the utility values obtained from these studies.

Table 4.20: Health state utility values

Data source	Health state utility value	
	PF	**PD**
NICE TA627[55]	R^2 vs. R-CHOP/CVP: 0.863 vs. O-Benda: 0.814	Post-progression (off treatment): R^2 vs. R-CHOP/CVP: 0.837 R^2vs. O-Benda: 0.787 Post-progression (on treatment)

Data source	Health state utility value	
	PF	**PD**
		R^2 vs. R-CHOP/CVP: 0.808 R^2 vs. O-Benda: 0.758
CADTH[54]	NR	Bendamustine for iNHL 0.618 (95% CI: 0.51 to 0.73)
Major 2021[53]	Mean (SD) Within 6 months of treatment completion: Rituximab (19 [58%] with MZL): 0.71 (0.07), p=0.087 Bendamustine + rituximab (13 [31%] with MZL): 0.66 (0.09), p=0.087 6-12 months after treatment completion: Rituximab (19 [58%] with MZL): 0.72 (0.08), p=0.354 Bendamustine + rituximab (13 [31%] with MZL): 0.69 (0.10), p=0.354	NR

Source: Produced by the EAG, adapted from CS Table 68, p.138[4]

Abbreviations: CADTH = Canadian Agency for Drugs and Technologies in Health; CI = confidence interval; CS = company submission; PD= progressed disease; PF = progression-free; iNHL = indolent non-Hodgkin lymphoma; MZL = marginal zone lymphoma; NICE = National Institute for Health and Care Excellence; NR = not reported; O-Benda = obinutuzimab + bendamustine; PD = progressed disease; PF = progression-free; R^2 = lenalidomide + rituximab; R-CHOP = rituximab + cyclophosphamide + doxorubicin + vincristine + prednisolone; R-CVP = rituximab + cyclophosphamide + vincristine + prednisolone; SD = standard deviation; SE = Standard error

The company chose the CADTH pan-Canadian Oncology Drug Review (pCODR) PD utility value in their base-case. The company argued that the utility estimates from TA627 were deemed to be too high by the EAG in that appraisal,[55] as they were higher than the general population utility despite the patients having MZL. The company further argued that the CADTH pCODR PD utility values were closer to previously accepted PD utilities in previous zanubrutinib submissions, including TA833 (0.691) and ID5078 (0.60),[4,40,41] as well as close to the utility value preferred by the EAG in TA627.[55] During the clarification process (PfC, question B16),[8] the EAG asked the company to further justify the use of the CADTH utility value for the PD health state, and also conduct scenario analyses around this value. In response, the company stated that although this value was obtained from a different NHL condition, the value falls within the values accepted in previous zanubrutinib NICE submissions (0.60 - 0.691), is close to the EAG's preferred utility value in TA627[55] and was validated by the expert on the advisory board.[1] In response, the company conducted a series of scenario analyses, stating that the alteration of

the PD utility did not have a significant impact on the cost effectiveness results. Table 4.21 presents the utility values used in the CEM.

Table 4.21: Health state utility values in base-case analysis

Health state	Utility value (SE)	95% CI	Source
PF	0.772 (0.021)	(0.729, 0.812)	MAGNOLIA[26], capped by general population utility
PD	0.618 (0.056)	(0.506, 0.724)	CADTH pCODR submission for bendamustine for NHL[54]

Source: CS Section B.3.4.6 Table 71, p.145[4]

Abbreviations: CI = confidence interval; PD= progressed disease; PF = progression free; SE =standard error; CADTH = Canadian Drug and Heath Technology Agency; NHL= non-Hodgkin lymphoma; pCODR = pan-Canadian Oncology Drug Review.

The EAG are concerned that by using utility values for the PF and PD from two different populations, the decrement between the PF and PD utility values for this population is uncertain. The EAG note that the utility decrements for the PF and PD utility values in TA627 (between 0.026 and 0.056 depending on the specific comparison) are significantly lower than the utility decrement between the PF and PD utilities used in this submission (0.154). The EAG acknowledge that the utility values from TA627 were deemed to be too high by the EAG for that submission. However, the EAG notes that this is the only study with estimates of the utility decrement for a population closely comparable to the population in this study.

Overall, although the EAG acknowledge that there is very limited literature related to HRQoL for patients with MZL, the EAG also consider the utility values used in the economic model to be subject to uncertainty, principally due to the lack of face validity for the PF utility value and the source of the PD utility value. Although the company have conducted a range of scenario analyses around these values, an alternative value for the PD health state is included in the EAG base-case, presented in Section 6.1.1.

4.2.10 Costs and resource use

4.2.10.1 Searches for costs and resource use

The company conducted searches for costs and resource use as part of the economic searches; the EAG's evaluation of these are presented in Section 4.1.1.

4.2.10.2 Drug acquisition costs

The company estimated a cost per pack and a cost per cycle based on information on the unit price of drugs and dosing regimens. The dosing regimen for zanubrutinib was assumed to be 320 mg once daily (four 80 mg capsules) or 160 mg twice daily (two 80 mg capsules) administered orally until PD or the occurrence of unacceptable toxicity, aligned with the drug's Summary of Product Characteristics (SmPC).[23] The dosing information for the HMRN registry basket aligns with the expected use in UK clinical practice.[58] The cost of zanubrutinib was based on the existing confidential PAS price. Unit costs for the HMRN registry basket were sourced from the British National Formulary (BNF).[59] Patients receiving zanubrutinib were treated in line with the modelled TTD curve discussed in Section 4.2.7.5.

Patients receiving treatments in the HMRN basket were treated whilst in the PF health state only, using treatment specific stopping rules.

As shown in Table 4.22, along with zanubrutinib the company provided a cost per cycle for the HMRN basket for the two main treatment regimens (rituximab plus/minus chemotherapy and chemotherapy alone, and rituximab plus/minus chemotherapy). In the cases of availability of multiple pack prices for a drug, the lowest price was chosen for calculating the drugs acquisition cost of the comparator. Other assumptions applied were a body surface area (BSA) of [redacted] and a relative dosing intensity of [redacted] for zanubrutinib. The EAG are satisfied with these assumptions.

Table 4.22: Zanubrutinib and HMRN basket cost per cycle in the base-case analysis

Treatment	Dosage strength	Administration	Pack size	Cost per per pack (£)	Cost per cycle (£)	Assumptions
Zanubrutinib	Capsule, 80 mg	Oral	120	[redacted]	[redacted]	PAS discount: [redacted] Relative dosing intensity: [redacted] Dosing information: SmPC Treatment rule: until PD or unacceptable toxicity
Rituximab plus/minus chemotherapy and chemotherapy alone	CS Appendix N[58]				6473.07	Unit price: BNF[59] Dosing information: HMRN basket BSA: [redacted] Treatment rule: until treatment specific stopping rules
Rituximab plus/minus chemotherapy	CS Appendix N[58]				9010.84	

Source: Produced by the EAG, adapted from the CS Section B.3.5.1.1 Tables 72 -73, p.146[4]
Abbreviations: BNF = British National Formulary; BSA = body surface area; CS = company submission; HMRN = Haematological Malignancy Research Network; mg = milligram; PAS = Patient Access Scheme; PD = progressed disease; SmPC = Summary of Product Characteristics

The EAG noticed some minor discrepancies between the pricing of some medications in the HMRN basket and the prices reported in the BNF[59] for doxorubicin, Mesna, gemcitabine, and ifosfamide (PfC, questions B6-B9).[8] The company provided updated unit costs during the clarification process,[8] attributing these discrepancies to recent updates in the cost and suppliers in the BNF, which occurred after the submission (November 2023). Table 4.23 shows both the initial prices used in the company base-case model and the updated prices provided by the company. The company provided an additional scenario analysis using these updated prices (see Section 5.2).

Table 4.23: Updated medicine prices in HMRN basket

Treatment	Base-case price	Updated price

Doxorubicin	£712.49	£54.00
Mesna	£441.15	£527.10
Gemcitabine	£13.09	£162.00
Ifosfamide	£115.79	£151.49
Source: PfCs Table 20,[8] Abbreviations: HMRN = Haematological Malignancy Research Network; mg = milligram; ml = millilitre.		

As requested by NICE, the EAG updated the prices for several drugs to align with eMIT[60] rather than the BNF (as used by the company in their analysis). Table 4.24 shows the prices used in the base-case by the company alongside the updated prices from eMIT.[60] These updated prices are used as part of the EAG base-case (Section 6).

Table 4.24: Updated drug prices from eMIT

Treatment	Base-case price (BNF)	Updated price (eMIT)
Bendamustine	£27.75	£27.19
Cisplatin	£50.22	£9.53
Cyclophosphamide	£15.22	£12.96
Cyclophosphamide Oral	£139	£50.08
Dexamethasone	£84.70	£35.95
Doxorubicin	£712.49	£9.73
Epirubicin	£347.55	£25.66
Etoposide	£11.50	£4.21
Gemcitabine	£13.09	£14.26
Mesna	£441.15	£449.67
Methotrexate	£380.00	£171.89
Methyl-prednisolone	£4.75	£4.76
Prednisolone	£42.30	£12.39
Vincristine	£133.33	£33.89
Source: Produced by EAG, based on information provided by NICE. Abbreviations: HMRN = Haematological Malignancy Research Network; mg = milligram; ml = millilitre.		

4.2.10.2.1 Wastage, vial sharing and drug administration costs

As zanubrutinib is administered orally, the company assumed no wastage on medication consumption. For the treatments in the HMRN registry, a 100% wastage rate was applied for intravenously-

administered drugs, as there is the potential that some of the drug will be wasted if perfect vial sharing is not practiced. The EAG are satisfied with this assumption.

The EAG also requested clarification from the company regarding the price year (PfC, question B12).[8] The company stated that that they did not inflate the unit costs to a 2022/23 cost year. Moreover, after inflating the prices, the company decided to retain an unchanged economic model due to minimal variation in the ICER value.[8]. The EAG used the updated costs in the EAG base-case.

The company assumed that medications taken orally or subcutaneously did not incur any administration costs, while drugs administered intravenously were subject to drug administration costs. These costs are shown in Table 4.25. The EAG has no concerns regarding this assumption on administration costs.

Table 4.25: Administration costs for zanubrutinib and the HMRN basket

Description of cost	Drugs	Unit cost (£)	Source
Delivery of oral chemotherapy	zanubrutinib and oral medications in HMRN basket	0.00	Assumption
Delivery of subcutaneous drug	doxorubicin, cyclophosphamide, vincristine, bortezomib and G-CSF.	0.00	Assumption
Delivery of complex Chemotherapy	fludarabine and cyclophosphamide, methotrexate, rituximab, bendamustine, gemcitabine, cisplatin, methylprednisolone containing treatments	353.64	NHS 21/22 - SB14Z[50]

Source: CS Section B.3.5.1.2 Table 74, p.148 [4]
Abbreviations: CS = company submission; G-CSF = granulocyte colony stimulating factor; HMRN = Haematological Malignancy Research Network; NHS = National Health Service

4.2.10.3 Monitoring and disease management costs

The company calculated the cost per cycle of disease managing and follow-up monitoring for PF and PD health states. It was assumed in the economic model that resource use in the zanubrutinib arm and the HMRN basket arm are the same, although they expected lower resource use in the intervention arm due to the better safety profile of zanubrutinib.[4]

The company assumed a Haematologist visit every four months when patients are in the PF state and one Haematologist visit per month when patients are in the PD health state, which is equal to 0.23 and 0.92 visits per cycle in the PF and PD states, respectively. The sources of resource use were NICE TA627,[55] as well as ESMO guidelines for diagnosis, treatment, and follow-up of MZL treatment.[7] The EAG are satisfied with these assumptions regarding medical resource use. The source of the unit costs was the NHS reference costs 21/22.[50] The EAG note that the unit costs were not inflated to the 2022/23 in the base-case model;[4] in the PfCs, the company decided to retain the unchanged economic model due to minimal variation in the ICER value.[8] The EAG included the updated inflated costs in the EAG base-case.

Table 4.26 presents the information on resource use and unit cost for each health state.

Table 4.26: Medical resource unit costs and frequencies

Treatment	Unit cost	Source	PF state	PD state	Source
Haematologist visit	209.41	NHS ref costs 21/22[50]	0.23	0.92	NICE TA627[55] Zucca *et al.*[2]
Full blood count	2.96				
Patient history/ physical exam	221.48				
Urea and electrolytes	1.55				
Liver function tests	1.55				
Calcium	1.55				
Serum IgG, IgA, IgM and electrophoresis	7.61				
LDH test	1.55				

Source: CS Section B.3.5.2 Table 75, p.149[4]
Abbreviations: Ig = immunoglobulin; LDH = lactate dehydrogenase; NHS = National Health Service; NICE= National Institute for Health and Care Excellence; PD = progressed disease; PF = progression-free.

The EAG requested further explanation from the company regarding the assumptions made regarding resource use (PfC, question B11)[8], considering the recently published BSH Guidelines,[3] in particular for the estimates of 'Haematologist Visits' and 'Patient History/Physical Exam', as these two items are the most expensive resources and are shown to be drivers in the company DSA. The company indicated that the BSH guidelines make no specific recommendations on the management of R/R MZL with respect to healthcare resource use, stated that the frequency of resource use was based on the ESMO guideline,[7] TA627[55] and that the HMRN basket could accurately reflect the UK clinical practice. The company further stated that these assumptions were also validated by UK clinicians at an advisory board meeting (11 October 2023).[1] The company further provided a set of additional scenario analyses regarding this resource use; this is discussed further in Section 5.2.3.[8]

4.2.10.4 Subsequent treatment costs

As shown in Table 4.27, the company provided a list of the top six subsequent treatments, drug acquisition, and administration costs per course of therapy for each treatment and applied this to all patients with disease progression. These drug acquisition costs were based on the regimen provided for the selected six treatments in HMRN basket, as shown in CS Appendix N.[58] The frequency of subsequent treatment use was based on the proportion of patients in the HMRN basket receiving third-line treatment. The company assumed that the resource usage of the subsequent treatments was equal between patients on zanubrutinib and those in the comparator arm. The cost of subsequent treatment was included in the model as a one-off cost.

Table 4.27: Subsequent treatment costs and weightings

Treatment	Drug acquisition cost per course of therapy (£)	Drug administration cost per course of therapy (£)	Treatment use

Single agent rituximab	£7195.55	£2333.79	[redacted]
Bendamustine / Rituximab	£6414.54	£5845.13	[redacted]
R-CVP	£8392.19	£2927.12	[redacted]
Chlorambucil	£196.58	£0.00	[redacted]
R-CHOP	£17,984.32	£5146.96	[redacted]
Chlorambucil / rituximab	£7962.01	£1594.74	[redacted]
Source: CS Section B.3.5.4 Table 77, p.151[4] Abbreviations: R-CVP = Rituximab plus cyclophosphamide, vincristine and prednisolone; R-CHOP = Rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone			

During the clarification process (PfC, question B13)[8], the EAG requested that the company consider how the recently published BSH guidelines[3] may potentially change the recommendations for treatment and follow up of MZL and therefore the estimates of health care utilisation in the CS. In their response, the company indicated that the updated guidelines made no specific recommendations on the management of R/R MZL with respect to healthcare resource use and that the estimates informed by the ESMO guidelines accurately reflects UK clinical practice. The EAG is satisfied by this response.

4.2.10.5 Adverse effects costs

Please see section 4.2.7.2 for discussion on the impact of AEs on costs.

4.2.10.6 Terminal care costs

The company applied the cost of terminal care (£7155.15) in the base-case analysis as one-off cost to each death in the model, sourced from Round *et al*.[61] and inflated to a 2022/23 price year using the NHS Cost Inflation Index.[4] The EAG is satisfied with the company's approach.

5 COST-EFFECTIVENESS RESULTS

5.1 Company's cost-effectiveness results

The company's deterministic base-case cost effectiveness results, which include the confidential patient access scheme (PAS) price for zanubrutinib are shown in Table 5.1, Table 5.2 and Table 5.3. The base-case results amount to £26,197 per QALY for zanubrutinib when compared to the HMRN registry basket. The net health benefit (NHB) is -0.88 at the £20,000 QALY threshold and 0.36 at £30,000 threshold. The net monetary benefit (NMB) is -£17,569 at the £20,000 QALY threshold and £10,780 at £30,000 QALY threshold.

Table 5.1: Company base-case cost-effectiveness results

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
HMRN registry basket	[redacted]	[redacted]	[redacted]	-	-	-	-
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,197

Source: CS Section B.3.10.1 Table 81, p.163[4]
Abbreviations: CS = company submission; HMRN = Haematological Malignancy Research Network; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years

Table 5.2: Company base-case results for net health benefit

Technology	Total costs (£)	Incremental costs (£)	ICER (£)	NHB at £20,000	NHB at £30,000
HMRN registry basket	[redacted]	-	-	-	-
Zanubrutinib	[redacted]	[redacted]	26,197	-0.88	0.36

Source: CS Section B.3.10.1 Table 82, p.163[4]
Abbreviations: CS = company submission; HMRN = Haematological Malignancy Research Network; ICER = incremental cost-effectiveness ratio; NHB = net health benefit

Table 5.3: Company base-case results for net monetary benefit

Technology	Total costs (£)	Incremental costs (£)	ICER (£)	NMB at £20,000 (£)	NMB at £30,000 (£)
HMRN registry basket	[redacted]	-	-	-	-
Zanubrutinib	[redacted]	[redacted]	26,197	-17,569	10,780

Source: Produced by the EAG, based on information from the company CEM[45]
Abbreviations: ICER = incremental cost-effectiveness ratio; HMRN = Haematological Malignancy Research Network; NMB = net monetary benefit

5.2 Company's sensitivity analyses

To explore the uncertainty in their cost-effectiveness analysis, the company conducted a probabilistic sensitivity analysis (PSA), a deterministic sensitivity analysis (DSA), and a scenario analysis.

5.2.1 Probabilistic Sensitivity Analysis (PSA)

The PSA was conducted to assess the impact of parameter uncertainty in the model base-case. The PSA used 1000 simulations. The results from the PSA are shown in Table 5.4, with the incremental cost-effectiveness plane (ICEP) and cost-effectiveness acceptability curve (CEAC) presented in Figure 5.1 and Figure 5.2, respectively. The base-case probabilistic results amount to £26,775 per QALY for zanubrutinib when compared to the HMRN registry basket. The company stated that, as the mean probabilistic results were close to the deterministic results, this indicated that the model was robust to parameter uncertainty.

Table 5.4: Results from the company's probabilistic sensitivity analysis

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
HMRN registry basket	[redacted]	[redacted]	-	-	-
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	26,775

Source: CS Section B.3.11.1 Table 83, p.165[4]
Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; HMRN = Haematological Malignancy Research Network; QALYs = Quality-adjusted life years

Figure 5.1: Company's incremental cost-effectiveness plane

Source: CS Section B.3.11.1, Figure 30, p.165[4]
Abbreviations: QALY = quality-adjusted life year.

Figure 5.2: Company's cost-effectiveness acceptability curve

Source: CS Section B.3.11.1, Figure 31, p.166[4]
Abbreviations: QALY = quality-adjusted life year.

Although not explicitly stated in section B.3.11.1 of the CS,[4] the results from the CEAC in the CEM imply that zanubrutinib has a [redacted] chance of being cost-effective at a willingness to pay of £20,000 per QALY and a [redacted] chance of being cost-effective at a willingness to pay of £30,000 per QALY.

The EAG was concerned that the number of simulations used (1,000) was low. The EAG ran the company model with 5000 simulations (the maximum permittable in the CEM), where the ICER changed to £26,814 per QALY for zanubrutinib when compared to the HMRN registry basket. This represents an increase in the ICER of £39 compared to the ICER estimated with 1000 simulations in the CS. The deterministic and probabilistic results lie relatively close to each other and the EAG are therefore satisfied that the CEM is robust in terms of parameter uncertainty.

5.2.2 Deterministic Sensitivity Analysis (DSA)

The DSA was performed to explore the effect of uncertainty associated with varying individual model inputs. The results from the DSA are shown in Table 5.5 with a Tornado plot of the DSA results shown in
Figure 5.3.

Table 5.5 Company's deterministic sensitivity analysis

Parameter name	Lower bound ICER (£)	Upper bound ICER (£)
PF utility	27,789	24,860
PF HRU patient history/physical exam	25,865	26,601
PF HRU haematologist visit	25,883	26,579
Cost for patient history/physical exam	25,930	26,522
Cost for haematologist visit	25,944	26,504
PD utility	25,998	26,389
Cost for terminal care	26,314	26,055
Single agent rituximab subsequent treat use following HMRN basket	26,278	26,110
BR subsequent treat use following HMRN basket	26,270	26,115
Single agent rituximab subsequent treat use following zanubrutinib	26,127	26,274

Source: CS Section B.3.11.2, Table 84, p.166[4]
Abbreviations: BR = bendamustine-rituximab; CS = company submission; DSA = deterministic sensitivity analyses; HRU = healthcare resource use; HMRN = Haematological Malignancy Research Network; ICER = incremental cost-effectiveness ratio; PD – Progressed disease; PF = progression free.

Figure 5.3: Company's tornado plot

Source: CS Section B.3.11.2, Figure 32, p.167[4]
Abbreviations: BR = bendamustine/rituximab; HRU = healthcare resource use; PFS = progression-free survival; PPS = post-progression survival; QALY = quality-adjusted life year; tx – treatment.

The most influential factors on the DSA were reported as being PF utility, PF healthcare resource use (HRU), patient history/physical exam, and PF HRU haematologist visit. The EAG are satisfied that the DSA was conducted appropriately.

5.2.3 Scenario analyses

Scenario analyses were performed by the company in the CS[4] to address the uncertainty within the base-case inputs and assumptions. The results of the scenario analyses (deterministic and probabilistic) are shown in Table 5.6 and Table 5.7.

Table 5.6: Scenario analysis performed by the company (deterministic)

Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER/QALY (£)
Base-case	[redacted]	[redacted]	26,197
No discounting	[redacted]	[redacted]	25,139
High discount rates (6%)	[redacted]	[redacted]	26,969
Time horizon: 20 years	[redacted]	[redacted]	26,378
MAGNOLIA, weighted to HMRN N=[redacted] dataset	[redacted]	[redacted]	29,272
MAGNOLIA-003, weighted to HMRN N=[redacted] dataset	[redacted]	[redacted]	26,661

Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER/QALY (£)
Adjusted (by SMR=1.41) age-gender matched background mortality restriction applied	[redacted]	[redacted]	27,999
PFS distribution (statistical fit HMRN): • Zanubrutinib: Weibull[¥] HMRN registry basket: Weibull[¥]	[redacted]	[redacted]	25,867
PFS distribution (most conservative analysis): • Zanubrutinib: Exponential** HMRN registry basket: Log-normal*	[redacted]	[redacted]	29,228
PFS distribution (statistical fit zanubrutinib): • Zanubrutinib: Exponential** HMRN registry basket: Exponential**	[redacted]	[redacted]	26,040
OS distribution (statistical fit zanubrutinib): • Zanubrutinib: Exponential[β] HMRN registry basket: Exponential[β]**	[redacted]	[redacted]	22,792
OS distribution (most conservative analysis): • Zanubrutinib: Weibull** HMRN registry basket: log-normal*	[redacted]	[redacted]	27,170
TTD distribution: Zanubrutinib: Exponential	[redacted]	[redacted]	18,935
Treatment specific utilities	[redacted]	[redacted]	23,063
NICE TA627 Company utilities	[redacted]	[redacted]	23,590
NICE TA627 EAG utilities	[redacted]	[redacted]	25,069

Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER/QALY (£)
Exclude age adjustment	[redacted]	[redacted]	24,910
Exclude restrict of MAGNOLIA PF utility by age-sex matched general population	[redacted]	[redacted]	24,100
Wastage not applied	[redacted]	[redacted]	26,075
AEs not applied (costs and QALYs)	[redacted]	[redacted]	26,227

Source: CS Section B.3.11.3, Table 86, p.169[4]
Abbreviations: AE = adverse event; CS = company submission; HMRN = Haematological Malignancy Research Network; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence; OS = overall survival; PF = progression-free; PFS = progression-free survival; QALY = quality-adjusted life year; SMR = standardised mortality rate; TTD = time to discontinuation

Table 5.7: Scenario analysis provided by the company (probabilistic)

Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER/QALY (£)
Base-case	[redacted]	[redacted]	26,775
No discounting	[redacted]	[redacted]	25,587
High discount rates (6%)	[redacted]	[redacted]	27,484
Time horizon: 20 years	[redacted]	[redacted]	27,883
MAGNOLIA, weighted to HMRN N=[redacted] dataset	[redacted]	[redacted]	29,043
MAGNOLIA-003, weighted to HMRN N=[redacted] dataset	[redacted]	[redacted]	27,861
Adjusted (by SMR=1.41) age-gender matched background mortality restriction applied	[redacted]	[redacted]	29,601
PFS distribution (statistical fit HMRN): • Zanubrutinib: Weibull¥ HMRN registry basket: Weibull¥	[redacted]	[redacted]	26,660
PFS distribution (most conservative analysis): • Zanubrutinib: Exponential** HMRN registry basket: Log-normal*	[redacted]	[redacted]	30,152

Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER/QALY (£)
PFS distribution (statistical fit zanubrutinib): • Zanubrutinib: Exponential** HMRN registry basket: Exponential**	[redacted]	[redacted]	25,253
OS distribution (statistical fit zanubrutinib): • Zanubrutinib: Exponential$^{\beta}$ HMRN registry basket: Exponential$^{\beta}$**	[redacted]	[redacted]	23,233
OS distribution (most conservative analysis): • Zanubrutinib: Weibull** HMRN registry basket: log-normal*	[redacted]	[redacted]	27,578
TTD distribution: Zanubrutinib: Exponential	[redacted]	[redacted]	20,767
Treatment specific utilities	[redacted]	[redacted]	23,899
NICE TA627 Company utilities	[redacted]	[redacted]	24,714
NICE TA627 EAG utilities	[redacted]	[redacted]	26,382
Exclude age adjustment	[redacted]	[redacted]	25,449
Exclude restrict of MAGNOLIA PF utility by age-sex matched general population	[redacted]	[redacted]	25,047
Wastage not applied	[redacted]	[redacted]	26,589
AEs not applied (costs and QALYs)	[redacted]	[redacted]	26,454

Source: CS Section B.3.11.3, Table 87, p.170[4]

Abbreviations: AE = adverse event; CS = company submission; HMRN = Haematological Malignancy Research Network; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence; OS = overall survival; PF = progression-free; PFS = progression-free survival; QALY = quality-adjusted life year; SMR = ; TTD = time to discontinuation

As shown in Table 5.6 and Table 5.7, the majority of the scenario analyses had a minimal impact on the estimated ICER. The three scenarios which increased the ICER by the most were:

- the use of the MAGNOLIA trial data only for zanubrutinib rather than the pooled MAGNOLIA-003 dataset;
- the inclusion of age-sex matched background mortality restriction; and
- implementing the most conservative parametric survival curves for PFS.

In relation to these scenarios, the EAG note that given the differences between the MAGNOLIA and AU-003 trials (for instance the proportion of high functioning patients as measured by the ECOG) and the limited number of covariates included in the MAIC, it is unsurprising that there is a relatively large change in the ICER due to the use of the MAGNOLIA trial data only rather than the pooled MAGNOLIA-003 dataset. As noted in Section 4.2.6, the EAG are satisfied with the exclusion of the adjusted age-gender matched background mortality restriction based on the SMR. As further noted in Section 4.2.6, the EAG has some concerns regarding the uncertainty related to the long-term extrapolations from the parametric survival modelling. An additional exploratory analysis has been undertaken by the EAG in Section 6.1.2.

Table 5.8 presents the additional sensitivity analyses that were provided by the company in response to the PfCs (PfC, questions B2, B5c, B6-B9, B11a, B13d, B15b, B17b).[8]

Table 5.8: Additional sensitivity analysis provided by the company

Clarification Question	Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER/QALY (£)
B2	Updated economic analysis using CHRONOS-3 trial data	[redacted]	[redacted]	25,906
B5c	Different length of treatment waning – [redacted]	[redacted]	[redacted]	32,362
B5c	Different length of treatment waning – 5 years	[redacted]	[redacted]	28,144
B5c	Different length of treatment waning – [redacted]	[redacted]	[redacted]	26,347
B6-B9	Updated medication costs	[redacted]	[redacted]	26,341
B11a	Resource use- Patient History/Physical Exam - in PF health state Lower value: 0.149	[redacted]	[redacted]	25,865
B11a	Resource use - Patient History/Physical Exam- in PF health state Lower value: 0.329	[redacted]	[redacted]	26,601

Clarification Question	Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER/QALY (£)
B11a	Resource use- Haematologist Visits - in PF health state Lower value: 0.149	[redacted]	[redacted]	25,883
B11a	Resource use - Haematologist Visits - in PF health state Lower value: 0.329	[redacted]	[redacted]	26,579
B13d	Relaxing of the assumption of a one-off subsequent treatment cost from both arms	[redacted]	[redacted]	26,275
B13d	Relaxing of the assumption of a one-off subsequent treatment cost from zanubrutinib arm	[redacted]	[redacted]	25,626
B13d	Relaxing of the assumption of a one-off subsequent treatment cost from the comparator arm (HMRN basket)	[redacted]	[redacted]	26,846
B15b	Utility values for the PF health state from Major[53] Utility value=0.71	[redacted]	[redacted]	28,572
B15b	Utility values for the PF health state from Major[53] Utility value= 0.66	[redacted]	[redacted]	30,844
B15b	Utility values for the PF health state from Major[53] Utility value= 0.72	[redacted]	[redacted]	28,158
B15b	Utility values for the PF health state from Major[53] Utility value = 0.69	[redacted]	[redacted]	29,439

Clarification Question	Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER/QALY (£)
B17b	AE specific disutility and duration estimates	[redacted]	[redacted]	26,197

Source: Produced by EAG, based on company response to PfC questions B2, B5c, B6-B9, B11a, B13d, B15b, B17b[8]
Abbreviations:, AE = adverse event; ICER = incremental cost-effectiveness ratio; PF = progression-free; QALY = quality-adjusted life year

As shown in Table 5.8, the majority of the additional scenario analyses undertaken by the company in response to the PfCs had a minimal impact on the estimated ICER. The two sets of scenarios which increased the ICER by the most were:

- Different lengths of treatment waning; and
- Alternative values for the PF health state from Major.[53]

In relation to the set of scenarios related to treatment waning, the EAG note that although assuming a treatment waning length of [redacted] increases the ICER considerably, this can be considered a highly conservative assumption, and that the company in their response to the PfCs noted that this scenario was "*clinically implausible*", as it assumes that 50% of patients would continue to receive treatment without gaining any benefit from zanubrutinib. In relation to the set of scenarios related to the PF utility values from Major[53], the EAG note that although the scenario assuming a utility value of 0.66 increases the estimated ICER to above the £30,000 per QALY threshold, this can be considered a particularly conservative assumption. Furthermore, as noted by the company, given the nature of the Major study[53] it is unclear how relevant the PF utility values are for use in the CEM. Overall, the EAG is satisfied with the exploration of uncertainty in model parameters undertaken by the company in the CS and in response to the PfCs.

5.2.3.1 The company's exploratory economic analysis comparing zanubrutinib with rituximab monotherapy using CHRONOS-3 trial data

As discussed in Section 3.3.2.3, as part of the response to the PfC the company conducted an updated MAIC between MAGNOLIA-003 and CHRONOS-3 (PfC, question A10).[8] In the company's response to clarification question B2, the company provided details of an updated economic analysis using this exploratory comparison. As shown in Table 5.9, a number of changes were made to the economic model settings for this exploratory comparison.

Table 5.9: Changes to data inputs and model settings for exploratory cost-effectiveness analysis

Parameter(s)	Changes from company base-case
MAGNOLIA-003 survival extrapolations	Weighted MAGNOLIA-003 to CHRONOS-3 population
Comparator survival extrapolations	Rituximab monotherapy survival extrapolations for PFS, OS and TTD sourced from CHRONOS-3 population
Baseline characteristics	Mean age: [redacted] years Proportion female: [redacted] BSA: [redacted] m^2
Time horizon	[redacted] years

Parameter(s)	Changes from company base-case
Comparator arm treatment costs	100% rituximab monotherapy
PFS distribution choice	Log-normal for both treatment arms
OS curves	Log-normal for both treatment arms
TTD curves	Log-normal for zanubrutinib. Assumed equal to PFS for rituximab monotherapy
Subsequent treatment basket	Exclude rituximab monotherapy retreatment for rituximab monotherapy arm
Safety profile	Model only AEs from rituximab monotherapy only for comparator arm.

Source: Table 15 and Table 16 from the company's response to PfC question B2 [8]
Abbreviations: AE = adverse event; BSA = body surface area; OS = overall survival; PFS = progression free survival; TTD = time to discontinuation

Goodness of fit statistics and extrapolated parametric survival curves for the updated survival analyses are shown in Appendix 2. The EAG note that the inherent uncertainty related to the choice of parametric survival curve for the PFS and OS parameters (as discussed in Section 4.2.6) is also present in the updated exploratory analysis. Overall, the EAG are satisfied that this exploratory analysis has been conducted appropriately. As acknowledged by the company in the response to the PfCs (question A10)[8] the updated MAIC should be considered exploratory only and the results should be interpreted with caution due to the small sample sizes, the enrolment of relapsed patients only in CHRONOS-3 and the differences between CHRONOS-3 and patients receiving rituximab monotherapy in UK clinical practice. This caution should also be applied to the exploratory economic analysis.

5.3 Benefits not captured in the QALY calculation

The company stated that there are several benefits of zanubrutinib not captured in the QALY calculation. The company stated that the potential improved safety profile of zanubrutinib was not captured in the QALY calculation due to the lack of data on AEs. The EAG agree that the data available on AEs is limited but note that the improved safety profile of zanubrutinib is captured as part of the AEs, which are directly involved in the QALY calculations. As noted in Section 4.2.8.1, the EAG has concerns regarding how the AEs were handled in the CS, specifically regarding the simplifying assumption surrounding the disutility values and durations, as well as the fact that AEs were only incorporated into the economic model at one time-point. Including the AEs in the economic model for more than one time-point may give a fairer reflection of the overall impact of the AEs over the model time horizon.

The company also state that there may be benefits related to the fact that a simple oral regimen administered at home means that there may be cost savings from an NHS resource perspective. The EAG agrees with the company that the assumption of the same NHS resource use across zanubrutinib and the HMRN registry basket may be conservative in nature.

The company also state that there may be benefits for caregivers or family members due to the predicted improvement in PFS and OS, though also note that this is not included in the perspective recommended by NICE or used in their analysis. The EAG agree that, whilst these factors are important, these associated costs fall outside the perspective recommended by NICE.

5.4 Budget Impact

Alongside the CEM, the company provided a budget impact analysis (BIA) over a five-year time horizon.[62] The BIA contained two potential scenarios; one where zanubrutinib is introduced onto the market and another scenario with the current treatment landscape (Rituximab +/- chemotherapy or Chemotherapy alone). Estimates of population size and populational growth were gathered from the Office of National Statistics (ONS),[63,64] and estimates of the incidence and prevalence of R/R MZL were gathered from the HMRN.[65,66] The EAG are satisfied that these are the most appropriate sources for these data.

Annual per patient costs for both zanubrutinib and the comparator over time were derived from the CEM. EAG comment on these costs is provided in Section 4.2.10. Projections for the market share in the scenario where zanubrutinib is introduced onto the market were informed by off-label ibrutinib usage in the HMRN registry report[67] and BeiGene market uptake predictions over 5 years, with the company stating that "*in year 1 zanubrutinib will displace off-label use of ibrutinib ([redacted]%), as a licensed BTKi, and reach at maximum market share of [redacted]% by year 5*". During the clarification process (PfC, question B20),[8] the EAG asked the company to provide further justification for the assumptions regarding their estimates of market share. The company responded by reiterating that the estimates were based on confidential BeiGene market research, and further noted that [redacted] The NHS Budget Impact Test threshold is regarded as exceeded if the budget impact shows potential to be greater than £20 million in any of the first 3 years of a technology's use in the NHS.[68] The EAG note that there is inherent uncertainty in relation to the potential market share of zanubrutinib, however are satisfied that given the rarity of R/R MZL, the cumulative additional cost of zanubrutinib over a three year time horizon are unlikely to exceed the impact test threshold. Overall, the EAG is satisfied that the BIA has been conducted appropriately.

5.5 Validation

The company stated that, on completion of the model programming, a comprehensive quality check of the model was conducted by an internal health economist not involved with the original programming to ensure the model contained no errors and worked as intended. The company stated that this model validation process uncovered minimal discrepancies and no impactful model calculation errors, with the refined model used in the final analysis. The EAG found some minor discrepancies in the CEM and requested that the company provide an updated model with no such discrepancies as part of the clarification process (PfC, questions B6-B9).[8] In response, the company explained that these minor discrepancies were due to rounding. The EAG are satisfied with this response.

The EAG requested that the company provide a completed copy of the Assessment of the Validation Status of Health Economic Decision Models (AdViSHE)[69] tool as part of the clarification process (PfC, question B19).[8] In response, the company stated that there was insufficient time to complete the AdViSHE, and instead provided more assurances over the rigour of the model in terms of conception, input data validation, validation of the computerised model and operational validation. The company also provided additional technical quality checks. The company reiterated that the model structure, assumptions, model inputs and outputs were validated by UK clinical experts, economic and statistical experts at an advisory board organised by the company, with the feedback from the experts incorporated into the submission. The EAG note that the company did not report any external validation with external datasets or cross-validation with previously conducted technology appraisals. However, the EAG appreciate that, due to the very limited research in this specific clinical area, this may not have been

possible. Overall, the EAG was satisfied with the steps taken by the company to externally validate the economic model.

6 EVIDENCE ASSESSMENT GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Based on the considerations in the preceding sections of this EAG report, the EAG defined an EAG base-case. This EAG base-case included several adjustments to the company base-case presented in Section 5. These adjustments have been subdivided into three categories (derived from Kaltenthaler 2016).[70]

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model where the EAG considers that reasonable alternative assumptions are preferred)

6.1.1 EAG base-case

Adjustments made by the EAG to derive the EAG base-case (using the CS base-case as starting point) are listed below.

Fixing errors

In the CS base-case, some of the health care costs were not inflated to a 2022/23 cost year. While the company retain the original costs in their base-case due to the minor impact on the ICER, the EAG have included these updated costs in the EAG base-case.

Fixing violations

No violations were identified by the EAG.

Matters of judgement

1. In the company base-case, AE disutilities and durations were assumed to be the same for all AEs. While the company retain the original values in their base-case due to the minor impact on the ICER, the EAG have included the updated disutilities and durations.

2. In the company base-case, some of the drug acquisition costs from the BNF were out of date. The EAG would like to emphasise that this was not an error on the part of the company, as the BNF seems to have updated their list of cost and suppliers since the CS was submitted. While the company retain the original costs in their base-case due to the minor impact on the ICER, the EAG have included these updated costs in the EAG base-case.

3. At the request of NICE, the EAG updated the costs for several drugs based on prices from the drugs and pharmaceutical electronic market information tool (eMIT),[60] rather than the BNF.[59]

4. In the company base-case, the utility value for the PF health state was sourced from MAGNOLIA (capped by general population utility) and the utility value for the PD state was sourced from CADTH pCODR. In the EAG base-case, the utility value for the PF health state has been retained but the utility value for the PD health state has been adjusted to account for the utility decrement (0.056) from the PF health state to the PD health state used in TA627 (0.716).[55] To estimate an SE for this updated utility value, the EAG assumed that the PD health

state utility state utility value was equally as uncertain as the PF utility value (2.72% of mean). The SE estimate in the EAG base-case is therefore 0.019.

6.1.2 EAG exploratory scenario analyses

The EAG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the EAG base-case.

- Use the parametric survival curves with the lowest AIC in all cases.
- Use the parametric survival curves with the lowest BIC in all cases.
- Use the most pessimistic parametric survival curves in all cases.

6.1.3 EAG subgroup analyses

No subgroup analyses were performed by the EAG.

6.2 Impact on the ICER of additional analyses undertaken by the EAG

6.2.1 The EAG base-case, scenario and sensitivity analyses

The EAG base-case was presented in Section 6.1.1. In this Section, Table 6.1 shows how individual adjustments impact the results, plus the combined effect of all above mentioned adjustments simultaneously, resulting in the EAG base-case. Table 6.2 presents the results of the company's deterministic sensitivity analysis conditional on the EAG base-case. Table 6.3 presents the results of the company's scenario analysis conditional on the EAG base-case. Table 6.4 presents the results of the company's additional scenario analysis (in response to the PfCs) conditional on the EAG base-case. Table 6.5 presents the EAG's exploratory scenario analysis conditional on the EAG base-case. The submitted model file contains the details of the analyses conducted by the EAG (the 'EAG Changes' sheet provides an overview of the cells that were altered for each adjustment).

Table 6.1: Deterministic/probabilistic EAG base-case

Technologies	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base-case (deterministic)	[redacted]	[redacted]	26,197
Company base-case (probabilistic – 1000 replications)	[redacted]	[redacted]	26,775
Company base-case (probabilistic – 5000 replications)	[redacted]	[redacted]	26,814
Fixing error: prices inflated to 2022/23 price year (deterministic)	[redacted]	[redacted]	26,239
Matter of judgement: AE disutilities and lengths sourced from the wider literature (deterministic)	[redacted]	[redacted]	26,198
Matter of judgement: updated costs from the BNF (deterministic)	[redacted]	[redacted]	26,341
Matter of judgement: updated drug prices from eMIT (deterministic)	[redacted]	[redacted]	26,391

Technologies	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Matter of judgement: updated utility value for PD health state (deterministic)	[redacted]	[redacted]	26,374
EAG base-case: combination of all changes made by the EAG (deterministic)	[redacted]	[redacted]	26,612
EAG base-case: combination of all changes made by the EAG (probabilistic – 1000 replications)	[redacted]	[redacted]	27,141
EAG base-case: combination of all changes made by the EAG (probabilistic – 5000 replications)	[redacted]	[redacted]	27,238

Source: Produced by EAG
Abbreviations: AE = adverse event; BNF = British National Formulary; EAG = Evidence Assessment Group; eMIT = electronic market information tool; ICER = incremental cost-effectiveness ratio; PD = progressed disease; QALY = quality-adjusted life year

Table 6.2: Company's deterministic sensitivity analysis (conditional on EAG base-case)

Parameter	Lower bound ICER (£)	Upper bound ICER (£)
Utility: PFS	25,245	28,240
HRU: patient history/physical exam	26,268	27,029
HRU: haematologist visit	26,287	27,006
Diagnostic cost: patient history/physical exam	26,335	26,948
Cost: haematologist visit	26,350	26,929
Cost: terminal care	26,469	26,730
BSA	26,522	26,698
Subsequent treatment use: single agent rituximab	26,524	26,693
Subsequent treatment use: bendamustine-rituximab	26,529	26,685
HRU: patient history/physical exam	26,530	26,679

Source: Produced by EAG
Abbreviations: BSA = body surface area; EAG = Evidence Assessment Group; HRU = healthcare resource use; ICER = incremental cost-effectiveness ratio; PFS = progression-free survival

Table 6.3: Company's scenario analyses (conditional on EAG base-case)

Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
No discounting	[redacted]	[redacted]	25,467
High discount rates (6%)	[redacted]	[redacted]	27,452
Time horizon: 20 years	[redacted]	[redacted]	26,803

Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
MAGNOLIA, weighted to HMRN N=[redacted] dataset	[redacted]	[redacted]	29,450
MAGNOLIA-003, weighted to HMRN N=[redacted] dataset	[redacted]	[redacted]	26,811
Adjusted (by SMR = 1.41) age-gender matched background mortality restriction applied	[redacted]	[redacted]	28,598
PFS distribution (statistical fit HMRN distribution) Zanubrutinib: Weibull Rituximab +/- chemotherapy, chemotherapy alone: Weibull	[redacted]	[redacted]	26,384
PFS distribution (most conservative analysis) Zanubrutinib: exponential Rituximab +/- chemotherapy, Chemotherapy alone: Log-normal	[redacted]	[redacted]	28,786
PFS distribution (statistical fit zanubrutinib) Zanubrutinib: exponential Rituximab +/- chemotherapy, chemotherapy alone: exponential	[redacted]	[redacted]	26,481
OS distribution (most conservative analysis) Zanubrutinib: exponential Rituximab +/- chemotherapy, chemotherapy alone: exponential	[redacted]	[redacted]	22,598
OS distribution (most conservative analysis) Zanubrutinib: Weibull Rituximab +/- chemotherapy, chemotherapy alone: Log-normal	[redacted]	[redacted]	27,867
TTD distribution (exponential)	[redacted]	[redacted]	19,300
Treatment specific utilities	Not applicable with EAG base-case		
NICE TA627 company utilities	Not applicable with EAG base-case		
NICE TA627 EAG utilities	Not applicable due to EAG base-case		
Exclude age adjustment	[redacted]	[redacted]	25,298
Exclude the restriction of MAGNOLIA PF utility by age-sex matched general population	[redacted]	[redacted]	24,468
Wastage not applied	[redacted]	[redacted]	26,450
AEs not applied (costs and QALYs)	[redacted]	[redacted]	26,640

Source: Produced by EAG
Abbreviations: AE = adverse event; EAG = Evidence Assessment Group; HMRN = Haematological Malignancy Research Network; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence; OS = overall survival; PF = progression-free; PFS = progression-free survival; QALY = quality-adjusted life year; SMR = standardised mortality ratio; TTD = time to discontinuation

Table 6.4: Company's additional scenario analyses (conditional on EAG base-case)

Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Updated economic analysis using CHRONOS-3 trial data	[redacted]	[redacted]	29,501
Different length of treatment waning – [redacted]	[redacted]	[redacted]	34,898
Different length of treatment waning – 5 years	[redacted]	[redacted]	29,121
Different length of treatment waning – [redacted]	[redacted]	[redacted]	26,802
Updated medication costs	Part of EAG base-case		
Patient history/physical exam in PF health state: 0.149	[redacted]	[redacted]	26,269
Patient history/physical exam in PF health state: 0.329	[redacted]	[redacted]	27,031
Haematologist visits in PF health state: 0.149	[redacted]	[redacted]	26,287
Haematologist visits in PF health state: 0.329	[redacted]	[redacted]	27,008
Relaxing of the assumption of a one-off subsequent treatment cost (zanubrutinib and HMRN basket)	[redacted]	[redacted]	26,684
Relaxing of the assumption of a one-off subsequent treatment cost (zanubrutinib)	[redacted]	[redacted]	26,077
Relaxing of the assumption of a one-off subsequent treatment cost (HMRN basket)	[redacted]	[redacted]	27,219
Alternative value for the PF health state from Major (2021): 0.71[53]	Not applicable with EAG base-case		
Alternative value for the PF health state from Major (2021): 0.66[53]	Not applicable with EAG base-case		
Alternative value for the PF health state from Major (2021): 0.72[53]	Not applicable with EAG base-case		
Alternative value for the PF health state from Major (2021): 0.69[53]	Not applicable with EAG base-case		
AE specific disutility and duration estimates	Part of EAG base-case		

Source: Produced by EAG
Abbreviations: AE = adverse event; EAG = Evidence Assessment Group; HMRN = Haematological Malignancy Research Network; ICER = incremental cost-effectiveness ratio; PF = progression-free; PFS = progression-free survival; QALY = quality-adjusted life year

Table 6.5: EAG's exploratory scenario analyses (conditional on EAG base-case)

Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Parametric survival analysis – all curves chosen on the basis of the lowest AIC: • PFS HMRN registry basket: Weibull • PFS zanubrutinib: Exponential	[redacted]	[redacted]	18,232

Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
• OS HMRN registry basket: Gamma • OS zanubrutinib: Exponential • TTD zanubrutinib: Exponential			
Parametric survival analysis – all curves chosen on the basis of the lowest BIC: • PFS HMRN registry basket: Exponential • PFS zanubrutinib: Exponential • OS HMRN registry basket: Gamma • OS zanubrutinib: Exponential • TTD zanubrutinib: Exponential	[redacted]	[redacted]	17,676
Parametric survival analysis – most pessimistic survival curve chosen for every parameter: • PFS HMRN registry basket: Log-normal • PFS zanubrutinib: Exponential • OS HMRN registry basket: Log-normal • OS zanubrutinib: Weibull • TTD zanubrutinib: Gompertz	[redacted]	[redacted]	31,957
Source: Produced by EAG Abbreviations: AIC = Akaike's Information Criterion; BIC = Bayesian Information Criterion; EAG = Evidence Assessment Group; HMRN = Haematological Malignancy Research Network; ICER = incremental cost-effectiveness ratio; OS = overall survival; PFS = progression free survival; QALY = quality adjusted life year; TTD = time to discontinuation			

6.3 EAG's preferred assumptions

The estimated EAG preferred (deterministic) base-case ICER, based on the EAG preferred assumptions highlighted in Section 6.1.1, was £26,612 per QALY gained for zanubrutinib compared to treatments from the HMRN registry basket. The probabilistic EAG base-case analyses using 1000 replications was £27,141 and indicated cost effectiveness probabilities of [redacted] and [redacted] at willingness to pay thresholds of £20,000 and £30,000 per QALY gained, respectively. The probabilistic EAG base-case analyses using 5000 replications was £27,238 and indicated cost-effectiveness probabilities of [redacted] and [redacted] at willingness to pay thresholds of £20,000 and £30,000 per QALY gained, respectively.

The most influential adjustment in the EAG base-case was the use of the updated drug prices from the eMIT.[60] In the company's scenario analysis (Table 6.3), the scenario which increased the ICER the most was the use of the MAGNOLIA trial data alone weighted to the HMRN basket, rather than the use of both the MAGNOLIA and AU-003 trials weighted to the HMRN basket as in the company base-case. In the company's additional scenario analysis in response to the PfCs[8] (Table 6.4), the scenario that increased the ICER the most was an extreme assumption related to the treatment waning. The scenario that increased the ICER the second most was the company's exploratory comparison of zanubrutinib versus rituximab monotherapy using CHRONOS-3 trial data. The EAG exploratory scenario analyses

(Table 6.5) produced ICERs far removed from both the company and EAG base-case. However, the EAG acknowledge that these are based on assumptions that can be considered extreme.

6.4 Conclusions of the cost-effectiveness section

The EAG consider that the company complied with the NICE reference case. An SLR was conducted to identify relevant cost-effectiveness studies for the treatment of adults with R/R MZL. One cost utility analysis from a UK perspective was identified,[55] however this study was only indirectly relevant to the decision problem. The company's modelling approach consisted of a PSM with a lifetime time horizon. Zanubrutinib was considered within the economic evaluation for the treatment of patients with R/R MZL who have received at least one prior anti-CD20-based therapy. The comparators considered in the CEM were rituximab with or without chemotherapy and chemotherapy alone. To populate the PSM, data on PFS and OS were derived from pooling the MAGNOLIA and AU-003 trials for zanubrutinib. Due to MAGNOLIA and AU-003 being single-arm trials, data were taken from the HMRN registry basket for the comparator arm. An unanchored MAIC analysis was used to adjust the zanubrutinib dataset to the HMRN registry basket. Parametric survival analysis was used to extrapolate the patient level data on PFS, OS, and TTD over a lifetime time horizon. HRQoL data for the PF health state was taken from MAGNOLIA, while an SLR was conducted to identify data for the PD health state.

There are several issues related to the cost-effectiveness analysis in this submission. Firstly, the company chose to use a PSM as their modelling framework. Although the EAG acknowledge that PSMs are commonly used in advanced or metastatic cancers and have been accepted by NICE in several previous health technology appraisal submissions, PSMs have a key methodological limitation in that health state occupancy is based on a set of non-mutually exclusive survival curves. Although the EAG note that the population of an alternative model (such as an STM) has its own limitations, the EAG consider this to be the most appropriate modelling framework for the decision problem.

A second issue is the immaturity of the available survival data for zanubrutinib, with only a small number of PFS and OS events having occurred in the two key clinical trials. Although this is expected given the indolent nature of MZL, given that the PSM framework relies on long-term estimates of PFS and OS, this introduces a substantial level of uncertainty into the long-term survival extrapolations from the parametric survival modelling. This is exemplified with the significant heterogeneity in the predictions from different parametric survival curves with almost identical statistical fit for zanubrutinib.

A third issue is that there is uncertainty relating to the utility values for the PFS and PD health states. The utility value for the PFS state was estimated from the MAGNOLIA trial. This utility value lacked face validity, therefore the company capped this value at the age and gender matched general population level. This unusually high value for PFS is a source of uncertainty. The utility value for the PD health state was taken from the CADTH pCODR submission for bendamustine for NHL. This utility value is uncertain as the study it is taken from is a different clinical condition and from a Canadian population; it is therefore not aligned to the decision problem. An alternative utility value for the PD health state was included in the EAG base-case.

The EAG also identified several minor issues, including issues related to the disutility values used by the company in the CEM and some of the health care unit costs. Changes to the disutility values and unit costs were incorporated into the EAG base-case. Furthermore, as discussed in the conclusion on the clinical effectiveness (Section 3.4), the use of an unanchored MAIC is a further source of uncertainty related to the matching of the data from the MAGNOLIA and AU-003 trials to the data from the HMRN

registry. Given these various issues, the EAG consider the cost-effectiveness results to be subject to considerable uncertainty.

In the company (deterministic) base-case, the model results amount to £26,197 per QALY when compared to the HMRN registry basket. The EAG considers that there remains substantial uncertainty regarding the cost-effectiveness results presented by the company. The company undertook several scenario analyses to explore the potential uncertainty in their base-case results. The scenarios that increased in the ICER the most were:

- the use of the MAGNOLIA trial data only for zanubrutinib treatment effectiveness rather than the pooled MAGNOLIA-003 dataset;
- the inclusion of age-sex matched background mortality restriction; and
- implementing the most conservative parametric survival curves for PFS.

The individual adjustments to the model by the EAG had a relatively minor impact on the ICER. The estimated EAG (deterministic) base-case was £26,612 per QALY. The EAG undertook several exploratory scenario analyses which greatly impacted the ICER, although these were based on extreme assumptions and should therefore be interpreted with caution.

It is worth emphasising that, for many of the key potential biases identified by the EAG in both the clinical and cost-effectiveness sections, including the use of an unanchored MAIC, the immaturity of the data, and the impact of the company's choice of modelling framework, the EAG were unable to fully explore these issues as part of this report. Overall, the EAG is of the opinion that the ICERs reported by the company are subject to substantial uncertainty.

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Appendix 1: Additional diagnostic plots provided by the company

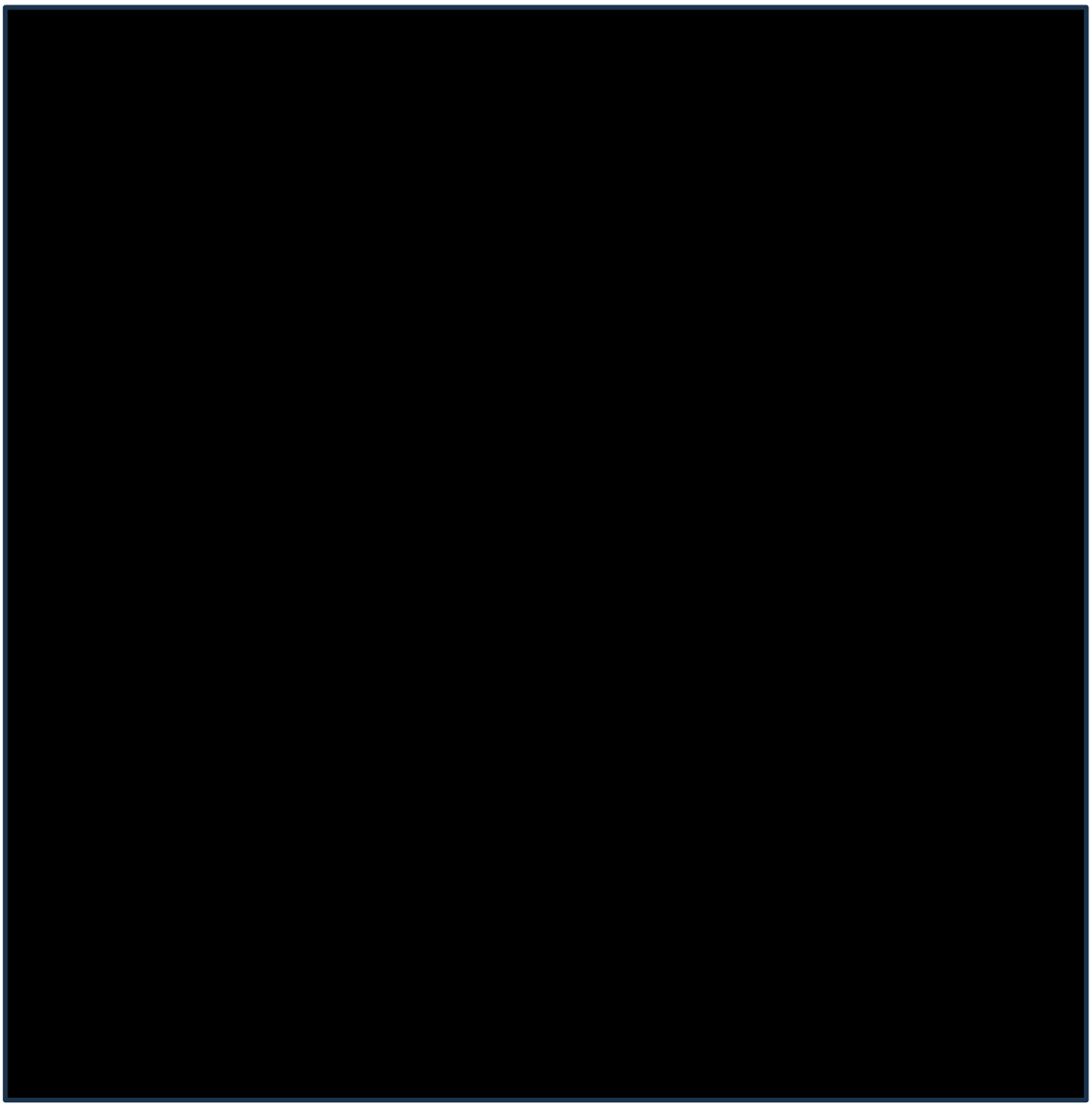
Source: company response to PfC, question 3b, Figure 6[8]
Abbreviations: PfC = points for clarification

Source: company response to PfC, question 3b, Figure 10[8]
Abbreviations: PfC = points for clarification

Source: company response to PfC, question 3b, Figure 14[8]
Abbreviations: PfC = points for clarification

Source: company response to PfC, question 3b, Figure 4[8]
Abbreviations: PfC = points for clarification

Source: company response to PfC, question 3b, Figure 8[8]
Abbreviations: PfC = points for clarification



Source: company response to PfC, question 3b, Figure 12[8]
Abbreviations: PfC = points for clarification

OS: HMRN registry data

Source: company response to PdC, question 3b, Figure 5[8]
Abbreviations: PfC = points for clarification

Source: company response to PfC, question 3b, Figure 9[8]
Abbreviations: PfC = points for clarification

Source: company response to PfC, question 3b, Figure 13[8]
Abbreviations: PfC = points for clarification

OS: zanubrutinib

Source: company response to PfC, question 3b, Figure 3[8]
Abbreviations: PfC = points for clarification

Source: company response to PfC, question 3b, Figure 7[8]
Abbreviations: PfC = points for clarification

Source: company response to PfC, question 3b, Figure 11[8]
Abbreviations: PfC = points for clarification

Appendix 2: Updated goodness of fit statistics and extrapolations for exploratory scenario analysis

Table A1: Goodness of fit statistics for PFS in exploratory scenario analysis

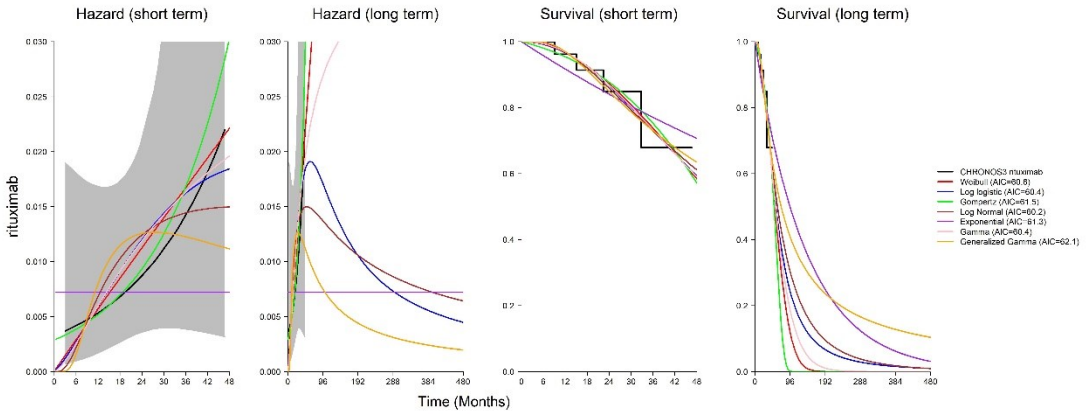
Distribution		
	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

Source: Produced by EAG, based on additional material supplied to the EAG by the company in response to PfC question B2[8]
Abbreviations: AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria
Bold indicates the distribution with the best statistical fit.

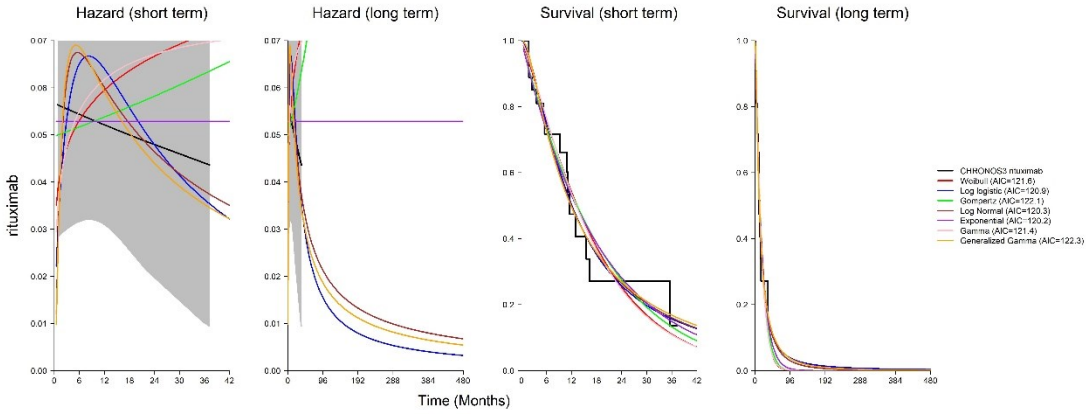
Table A2: Goodness of fit statistics for OS in exploratory scenario analysis

Distribution		
	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

Source: Produced by EAG, based on additional material supplied to the EAG by the company in response to PfC question B2[8]
Abbreviations: AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria
Bold indicates the distribution with the best statistical fit.



Source: Additional material supplied to the EAG by the company in response to PfC question B2[8]



Source: Additional material supplied to the EAG by the company in response to PfC question B2[8]

Zanubrutinib for treating relapsed or refractory marginal zone lymphoma [ID5085]

Addendum

Produced by Newcastle University

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Date completed 18th April 2024

Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Any de-personalised data are highlighted in pink throughout the report.

Additional Results Requested by NICE

Following the Pre-Meeting Briefing (17th April 2024), NICE requested that the EAG provide two additional scenario analyses:

- EAG base case with the most conservative distributions for PFS and OS (Additional Scenario 1)
- EAG base case with the most conservative distributions for PFS and OS, using the company's exploratory analysis comparing zanubrutinib with rituximab monotherapy using the CHRONOS-3 trial (Additional Scenario 2)

Both additional scenarios are presented deterministically and probabilistically (with 1,000 replications).

Table 1: Additional Scenario Analysis Requested by NICE

Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
EAG Base Case (Deterministic)	[redacted]	[redacted]	26,612
EAG Base Case (Probabilistic - 1,000 replications)	[redacted]	[redacted]	26,775
Additional Scenario 1 (Deterministic) PFS Zanubrutinib: Exponential PFS HMRN registry basket: Log-normal OS Zanubrutinib: Weibull OS HMRN registry basket: Log-normal	[redacted]	[redacted]	30,210
Additional Scenario 1 (Probabilistic) PFS Zanubrutinib: Exponential PFS HMRN registry basket: Log-normal OS Zanubrutinib: Weibull OS HMRN registry basket: Log-normal	[redacted]	[redacted]	28,109
Additional Scenario 2 (Deterministic) – using CHRONOS trial data (rituximab monotherapy, n=29) PFS Zanubrutinib: Exponential PFS CHRONOS: Log-logistic OS Zanubrutinib: Gompertz OS CHRONOS: Exponential	[redacted]	[redacted]	Dominated
Additional Scenario 2 (Probabilistic) – using CHRONOS trial data (rituximab monotherapy, n=29) PFS Zanubrutinib: Exponential PFS CHRONOS: Log-logistic OS Zanubrutinib: Gompertz OS CHRONOS: Exponential	[redacted]	[redacted]	Dominated

Source: Produced by EAG
Abbreviations: EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

The EAG note that in both additional scenarios the TTD distribution is unchanged from the EAG base-case. The EAG further note that for Additional Scenario 2, the use of the most conservative PFS and OS distributions using the company's exploratory analysis (comparing zanubrutinib with rituximab monotherapy using data from the CHRONOS-3 trial) results in the OS curve for zanubrutinib crossing below the OS curve for the comparator after approximately 5 years, with this reflected in the extreme results. Accordingly, these results should be treated with extreme caution.

Single Technology Appraisal

Zanubrutinib for treating relapsed or refractory marginal zone lymphoma [ID5085]

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 23 February 2024** 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 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Abbreviations

AE	Adverse event
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
BNF	British National Formulary
BR	Bendamustine-rituximab
BSH	British Society for Haematology
CADTH	Canadian Agency for Drugs and Technology in Health
CASP	Critical Appraisal Skills Programme
CLL	Chronic lymphocytic leukaemia
CS	Company submission
DCO	Data cut off
DoF	Data of file
EAG	External Assessment Group
eMIT	Drugs and pharmaceutical electronic market information tool
ERG	Evidence review group
ESS	Effective sample size
HMRN	Haematological Malignancy Research Network
HRQoL	Health-related quality-of-life
HTA	Health Technology Appraisal
ICER	Incremental cost-effectiveness ratio
LTE	Long term extension
LYG	Life-year gained
MAIC	Matching adjusted indirect comparison
MZL	Marginal zone lymphoma
NHL	Non-Hodgkin’s lymphoma
NICE	National Institute for Health and Care Excellence

ORR	Overall response rate
OS	Overall survival
PD	Progressed disease
PF	Progression-free
PfC	Point of clarification
PFS	Progression-free survival
PPS	Post-progression survival
PSM	Partitioned survival model
QALY	Quality-adjusted life-year
RCT	Randomised controlled trial
STM	State-transition model
TEAE	Treatment emergent adverse event
TTD	Time to treatment discontinuation
TTDeath	Time to pre-progression death
TTP	Time to pre-progression

Issue 1: Clinical evidence issues

Description of problem	Description of proposed amendment	Justification for amendment	Response from EAG
Uncertainty in the clinical evidence The EAG report raises concerns about the level of uncertainty in the clinical evidence presented in the CS which relate to the • Key issue 1: Lack of RCT evidence • Key issue 2: Uncertainty in the results of the MAIC It is important to note that until the marketing authorisation of zanubrutinib, no licensed treatment options existed for patients with R/R MZL. Both the BSH and EMSO treatment guidelines recommend the use of chemotherapy/immunotherapy regimens based on their effectiveness in other indolent cancers.[1,2] When coupled with the rarity of disease, the lack of licensed treatment options makes it increasingly challenging for an RCT to be conducted. Whilst the Company does not dispute the presence of uncertainty associated with the MAIC analysis conducted in the absence of an RCT, the Company believes the wording around the existence of uncertainty should be softened from a 'key issue', to a 'concern'. This is primarily as many technologies have been recommended by NICE based on MAIC analysis in the absence of a direct comparative effectiveness evidence, this includes a number of blood cancers. [3-5] Additionally the EAG appear to be satisfied with how the MAIC was conducted, suggesting the MAIC methodology is robust and that there are no additional analyses which could be conducted to reduce uncertainty. In tying the clinical evidence to the cost-effectiveness analysis, the extensive sensitivity analyses presented on the MAIC as part of the CS and in response to the EAG clarification question, demonstrate that the ICER is not sensitive to assumptions in the MAIC analysis, providing further certainty in the clinical evidence. In light of these points, the Company believe the wording around the existence of uncertainty should be softened from a 'key issue' to a 'concern'. Further details are provided in the rows below.			
Key Issue 1: Lack of RCT evidence			

Section 3.2, p.29: "Single-arm trials are useful to obtain preliminary evidence of the efficacy of the treatment and to collect safety data but are generally not used as confirmation of efficacy. In certain rare diseases, including rare cancers, it is not unusual for clinical data from such trials to be used as pivotal evidence in marketing authorisation applications or health technology assessments. Single-arm trials such as MAGNOLIA and AU-003 are however subject to methodological limitations which necessitate comparison with other data to demonstrate treatment benefit."	The Company requests the text is amended to: "In certain rare diseases, including rare cancers, it is not unusual for clinical data from such trials to be used as pivotal evidence in marketing authorisation applications or health technology assessments. **Additionally, the company provided a quality assessment of the MAGNOLIA and AU-003 studies 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 (details found in Section B.2a.5 and B.2b.5, respectively).** [6,7] **The assessments indicated that both trials were well-designed single-arm trials, with the appropriate steps taken to minimise bias where possible.** ~~Single-arm trials such as MAGNOLIA and AU-003 are h~~ **H**owever**, they are** subject to methodological limitations which necessitate comparison with other data to demonstrate treatment benefit."	The Company acknowledges that single-arm trials are subject to methodological limitations and that the lack of an RCT has methodological implications for the MAIC. However, it should be highlighted that both MAGNOLIA and AU-003 were assessed 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. [6,7] The assessment indicated that both studies are well-designed, with the appropriate steps taken to minimise bias where possible. In addition, experts in attendance the advisory board agreed that the evidence from the trials were compelling, and that the patient populations could be	A modified version of the proposed amendment text has been added: "In certain rare diseases, including rare cancers, it is not unusual for clinical data from such trials to be used as pivotal evidence in marketing authorisation applications or health technology assessments. The company provided quality assessments of the MAGNOLIA and AU-003 studies 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 (details found in Section B.2a.5 and B.2b.5, respectively). The assessments, which the EAG were satisfied with, indicated that both trials were well-designed, with the appropriate steps taken to minimise bias. However, single-arm trials

		considered generalisable to patients in the UK.[8]	such as MAGNOLIA and AU-003 are subject to methodological limitations which necessitate comparison with other data to demonstrate treatment benefit.”
Section 3.2, p. 29: “[redacted]”[8]	The Company request the text is amended to: “[redacted]”[8]	Clarification of statement made during the advisory board.	The EAG has made the suggested change, with the full wording taken directly from the HTA advisory board reference: [redacted]”[8]
Section 3.4, p.49: "The MAGNOLIA and AU-003 studies used in the CS comprise populations which are considered generalisable to that seen in NHS clinical practice. Whilst not uncommon in rare diseases, including rare cancers, single-arm trials are subject to	The Company request the text is amended to: "The MAGNOLIA and AU-003 studies used in the CS comprise populations which are considered generalisable to that seen in NHS clinical practice. Whilst not uncommon in rare diseases, including rare cancers **and although the company provided evidence that the studies were well-designed to minimise bias**	As discussed in the row above, the company acknowledges that single-arm trials are subject to methodological limitations and that the lack of an RCT has methodological implications for the MAIC. However, both studies were assessed and determined to be well-	The EAG has made the change, using slightly modified wording. “The MAGNOLIA and AU-003 studies used in the CS comprise populations which are considered generalisable to that seen in NHS clinical practice. Whilst not

methodological limitations which necessitates the comparison with other data to demonstrate the benefit of treatment. The evidence from the trials is compared with a historical control (subset of the HMRN registry) to facilitate comparability of survival and other outcome measures with patients not treated with zanubrutinib."	**where possible,** single-arm trials are subject to methodological limitations which necessitates the comparison with other data to demonstrate the benefit of treatment. The evidence from the trials is compared with a historical control (subset of the HMRN registry) to facilitate comparability of survival and other outcome measures with patients not treated with zanubrutinib."	designed, with the appropriate steps taken to minimise bias where possible.	uncommon in rare diseases, including rare cancers, single-arm trials are subject to methodological limitations. Although, the EAG are satisfied with the conduct of the trials, and the evidence the company provided to minimise bias, uncertainty is inherently introduced when using an external control group to assess effectiveness The evidence from MAGNOLIA and AU-003 is compared a historical control (subset of the HMRN registry) to facilitate comparability of survival and other outcome measures with patients not treated with zanubrutinib.”
Section 3.4, p.50: "However, the implication of using single-arm trials to determine the clinical effectiveness of zanubrutinib in R/R MZL patients is compromised compared to using an RCT. Whilst single-arm studies	The Company request the text is amended to: "However, the implication of using single-arm trials to determine the clinical effectiveness of zanubrutinib in R/R MZL patients is compromised compared to using an RCT. Whilst single-arm studies are not uncommon in trials for rare diseases and cancers	As discussed in the row above, the Company acknowledge that single-arm trials are subject to methodological limitations and that the lack of an RCT has methodological implications for the MAIC. However, both studies	The EAG has made the suggested change.

are not uncommon in trials for rare diseases and cancers, there is inherent uncertainty associated with the resultant need to use an unanchored MAIC to facilitate comparison with other treatments for R/R MZL."	**and the company provided evidence that the studies were well-designed which minimised bias where possible**, there is inherent uncertainty associated with the resultant need to use an unanchored MAIC to facilitate comparison with other treatments for R/R MZL."	were assessed and determined to be well-designed, with the appropriate steps taken to minimise bias where possible.	
Key issue 2: Uncertainty in the results of the MAIC			
Section 1.3, Table 1.3, p.14: "3.) Only five covariates were included within the MAIC model due to the lack of available baseline data from the HMRN registry."	Suggest remove this text under the Key issue 2.	The covariates included within the MAIC model were validated during an advisory board of UK experts (11th October 2023).[8] Given that upon weighting the MAGNOLIA-003 trial population to the HMRN population there was an ESS of [redacted], less than [redacted] of the total unweighted MAGNOLIA-003 population, the Company maintain that including more covariates into the MAIC analysis would have decreased	The EAG appreciate that the reason five covariates were included in the MAIC is because these were the only variables available from the HMRN registry. The EAG also acknowledges that these covariates were validated at the company's board of UK experts. As such, the EAG have added the following to Section 3.3.4 of the Report (p.48): "The covariates included in the MAIC were validated during an advisory board of

		the ESS further, raising uncertainty in the analyses. Furthermore, a 'leave one out' sensitivity analyses demonstrated that the removal of covariates from the MAIC did not impact the conclusions from the MAIC analyses.	UK experts on 11 October 2023.[8]" However, as noted in NICE Decision Support Unit Technical Document 18: "*However, small effective sample sizes are an indication that the weights are highly variable due to a lack of population overlap, and that the estimate may be unstable*" (p.27). [9] The substantial decrease in ESS for the weighted MAGNOLIA-003 population suggested that there is an overall lack of overlap between MAGNOLIA-003 and the HMRN registry basket, which increases the uncertainty in the MAIC results.
Section 3.1.3, p.29: "As detailed in the Cochrane Handbook,[10] contacting study authors to obtain or confirm data	The Company request the text is amended to: "As detailed in the Cochrane Handbook,[10] contacting study authors to obtain or confirm data makes the	The Company acknowledge that if available additional unpublished evidence from the authors could have been used in a	The EAG has made the suggested change.

makes the review more complete, potentially enhances precision and reduces the impact of reporting biases. In response to the points for clarification (PfC),[11] the company stated that the authors of the identified trials were not asked for additional data regarding the MZL participants (Question A9). This has important implications as to whether all relevant data were extracted and subsequently included in the MAIC, which is discussed further in Section **Error! Reference source not found.**."	review more complete, potentially enhances precision and reduces the impact of reporting biases. In response to the points for clarification (PfC),[11] the company stated that the authors of the identified trials were not asked for additional data regarding the MZL participants**. The company's justification is that it would have taken too long for the data from the authors to be populated into the CS and that timely patient access was prioritised** (Question A9). This has important implications as to whether all relevant data were extracted and subsequently included in the MAIC, which is discussed further in Section **Error! Reference source not found.**."	MAIC. However, the Company deemed that it would have taken too long for the data from the authors to be received, assessed, analysed and populated into the CS, assuming they would be willing to share such information. Furthermore, the Company's primary focus during the development of the submission was timely patient access given the high unmet for innovative treatments in MZL.	
Section 3.2.2, Table 3.8, p.38: Summary of the EAG's critique on the design, conduct and analysis of the AU-003 trial: *Statistical analysis*	Suggest amending the EAG's assessment of the robustness of methods from 'Some concerns' to 'Appropriate'.	As the EAG found the approach to determine the AU-003 sample size, "acceptable" and were "satisfied that the correct datasets were used for the respective analyses". The EAG's conclusion of	The EAG have made the suggested change.

		‘some concerns’ is not aligned with the above findings.	
Section 3.3, Table 3.11, p.42: Summary of the methodology of the company’s MAIC and EAG comments: *Statistical methods*	Suggest amending the EAG’ assessment from ‘Key issue 2’ to ‘Some concern’.	The EAG state that the unanchored MAICs approach “was appropriate due to the lack of comparative data available” (EAG report p.42), which is not aligned with the EAG’s final conclusion in Table 3.11.	Though the EAG appreciate that the use of the unanchored MAIC was unavoidable and appropriate due to only having data available from single-arm studies, this does not diminish the inherent uncertainty that the use of an unanchored MAIC brings to the overall results. Combined with other methodological limitations surrounding the MAIC (including the lack of covariates included within the model and lack of participant characteristics from the HMRN registry basket; see EAG Report Table 1.3, p.13-14), the EAG believes that the MAIC is open to a large amount of uncertainty and remains a key issue for decision-making.

Section 3.3, Table 3.11, p.43: Summary of the methodology of the company's MAIC and EAG comments: *Study characteristics and demographics*	Suggest amending the EAG's assessment from 'Key issue 2' to 'Some concern'.	The EAG state that there was 'little the Company could have done to resolve this issue' and have suggested no additional analyses for exploration. As such this does not align with the conclusion of 'key issue'. Identification of the HMRN registry cohort was performed to align with the eligibility criteria of the MAGNOLIA and AU-003 trials, and was validated as appropriate by experts in attendance at the UK advisory board. [8] Extensive sensitivity analyses were also performed by the Company which covered alternative HMRN cohorts (N=[redacted], N=[redacted]), matching to MAGNOLIA only and a 'leave one out' sensitivity analyses. Across all analyses the results were consistent,	As noted in EAG Report Table 1.3 (p.14), the EAG appreciate that it is difficult to resolve the issue surrounding the lack of demographic data available from the HMRN registry basket. However, despite the EAG acknowledging that this is an unresolvable issue, it does not diminish the uncertainties that arise from a lack of demographic data to match to MAGNOLIA-003. Combined with other methodological limitations surrounding the MAIC (including the lack of covariates included within the model and the use of an unanchored MAIC; see EAG Report Table 1.3, p.13-14), the EAG believes that the MAIC is open to a large amount of uncertainty and remains a key issue for decision-making.

		demonstrating the robustness in the selection of patients from the HMRN registry, the clinical data for zanubrutinib and the MAIC methodology.	
Section 3.3, Table 3.11, p.43: Summary of the methodology of the company's MAIC and EAG comments: *Covariates included in the MAIC*	Suggest amending the EAG' assessment from 'Key issue 2' to 'Some concern'.	As described above, the covariates included within the MAIC model were validated as appropriate during an advisory board of UK experts (11th October 2023). [8] Given that upon weighting the MAGNOLIA-003 trial population to the HMRN population there was an ESS of [redacted], less than [redacted] of the total unweighted MAGNOLIA-003 population, the Company maintain that including more covariates in the MAIC analysis would have decreased the ESS further, raising uncertainty in the analyses. Extensive	The EAG appreciate that the reason five covariates were included in the MAIC is because these were the only variables available from the HMRN registry. The EAG also appreciate that these covariates were validated at the company's board of UK experts. As such, the EAG have added the following to Section 3.3.4 of the Report (p.48): "The covariates included in the MAIC were validated during an advisory board of UK experts on 11 October 2023.[8]" However, as noted in NICE Decision Support Unit Technical Document 18:

		scenario analyses were conducted for the MAIC, including a 'covariate leave one out' which demonstrated that the results were robust to changes in matching variables.	"*However, small effective sample sizes are an indication that the weights are highly variable due to a lack of population overlap, and that the estimate may be unstable*" (p.27). [9] The substantial decrease in ESS for the weighted MAGNOLIA-003 population suggested that there is an overall lack of overlap between MAGNOLIA-003 and the HMRN registry basket, which increases the uncertainty in the MAIC results.
Section 3.3.2, p.44: "The company responded that they did not approach study authors for additional information regarding the five trials, stating that they prioritised engagement with the HMRN registry as it was considered a more reliable data source by UK clinical experts in consultation with the company."	The Company request the text is amended to: "The company responded that they did not approach study authors for additional information regarding the five trials, stating **it would have taken too long for data from the authors to be received, assessed, analysed and populated into the CS, assuming they would be willing to share such information. Instead,** ~~that~~ they prioritised	As described above and also noted in response to the EAG clarification questions, the Company deemed that it would have taken too long for the data from the authors to be received, assessed, analysed and populated into the CS, assuming they would be willing to share such information. Furthermore, the	The EAG have changed the statement to the following: "The company responded that they did not approach study authors for additional information regarding the five trials, stating that it would have taken too long for data from the authors to be received, assessed, analysed and populated into the CS,

	engagement with the HMRN registry as it was considered a more reliable data source by UK clinical experts in consultation with the company. **Please refer to Section B.2.9.1.1 of the CS for further details."**	Company's primary focus during the development of the submission was timely patient access given the high unmet for innovative treatments in MZL.	assuming they would be willing to share such information. Instead, they prioritised engagement with the HMRN registry as it was considered a more reliable data source by UK clinical experts in consultation with the company (see CS Section B.2.9.1.1 for further details)."
Section 3.3.2.3, p. 48: "As this exploratory MAIC followed the same methodology as in the CS, it is unanchored and therefore open to considerable uncertainty. However, the EAG acknowledge that the company described the MAIC comparing MAGNOLIA-003 with CHRONOS-3 to be exploratory."	The Company request the text is amended to: "As this exploratory MAIC followed the same methodology as in the CS, it is unanchored and therefore open to considerable uncertainty. However, the EAG acknowledge that the company described the MAIC comparing MAGNOLIA-003 with CHRONOS-3 to be exploratory **and that an unanchored MAIC is appropriate given the lack of available comparative data and the single-arm nature of the zanubrutinib trials.**"	As described above, given that the EAG believe the unanchored MAICs approach "was appropriate due to the lack of comparative data available" (p.42).	The EAG appreciate the company's comments and have amended the statement to the following: "As this exploratory MAIC followed the same methodology as in the CS, which is appropriate given the lack of available comparative data and the single-arm nature of the MAGNOLIA and AU-003 trials, it is unanchored and therefore open to considerable uncertainty."

Section 3.3.4, p.48: "Clinical advice to the EAG noted that TP53 mutation may also have been a relevant prognostic variable for MZL, which could not be included within the MAIC due to the lack of data available from the HMRN registry."	The Company request the text is amended to: "Clinical advice to the EAG noted that TP53 mutation may also have been a relevant prognostic variable for MZL, which could not be included within the MAIC due to the lack of data available from the HMRN registry. **However, the UK clinical experts in attendance at the advisory board for zanubrutinib did not highlight the presence of a TP53 mutation as a key covariate to include.**"	As described above, the covariates included within the MAIC model were approved by an advisory board of UK clinicians (11th October 2023).[8]	The EAG have added the following statement: "However, UK clinical experts in attendance at an advisory board for zanubrutnib did not highlight the presence of TP53 mutation as a key covariate.[8]"

Issue 2: Cost-effectiveness issues

Description of problem	Description of proposed amendment	Justification for amendment	Response from EAG
Uncertainty in the cost-effectiveness analysis The EAG report raises concerns about the level of uncertainty in the cost-effectiveness analysis, particularly around: • Key issue 3: the choice of a PSM • Key issue 4: the selection of PFS and OS predictions • Key issue 5: the selection of curves for extrapolation • Key issue 6: PD and PF utilities.			

Whilst the Company does not dispute the presence of uncertainty in the cost-effectiveness analysis, the wording around the existence of uncertainty should be softened to clarify that they are only 'concerns'.

Regarding 'Key issue 3: the choice of a PSM', the Company would like to highlight that the recommendations outlined in the NICE DSU TSD 19 for use of PSM were followed, [12] these include:

- Recommendation 1: The model conceptualisation process should be routinely reported and the rationale for the chosen modelling approach explicitly justified on the basis of theoretical and practical considerations (see CS B.3.2.5, p.113)
- Recommendation 2: Consistent and appropriate terminology should be applied in future appraisals when describing the PSM approach (e.g. use of the term "Partitioned survival analysis") (throughout the CS and clarification response).
- Recommendation 3: A summary of the main structural assumptions should be routinely reported and justified as required by the NICE guide to the methods of technology appraisal (see CS B.3.9.2, Table 80, p.160-162).
- Recommendation 4: All stakeholders should recognise the specific limitations of PSM approach for the purposes of extrapolation (see CS B.3.15.2, p.176-177).
- Recommendation 5: Modelling choices that influence outcomes in the extrapolation period should reflect all relevant evidence.
    - For this recommendation all treatment effects over time were reported (see CS B.3.3.7, p.130-131) and treatment waning options were provided (see clarification response B5, p.48-53). Specific assumptions around time in each health state could not be explored through changes to individual probabilities but the time in each health state was assessed for clinical plausibility (e.g. no large post-progression survival benefit in the base case). Furthermore, extensive scenario analyses were conducted on the choice of PFS and OS curve to explore the uncertainty in the proportion of patients estimated across the health states.
- Recommendation 6: Within-trial survival curves corresponding to individual clinical events should be supplied alongside partition survival analyses models.
    - For this recommendation specific KMs for time to progression and post-progression survival could be generated for each data set (MAGNOLIA-003 and HMRN), if required. However, this is typically used to support a modelled post-progression survival benefit (as described by Soares, 2020) [13] which is not relevant in this case.

The Company also conducted extensive sensitivity analyses as part of the CS, which the EAG replicated with their preferred base case, and across all scenario analyses the ICER does not diverge substantially from the base-case ICER. Furthermore, for the probabilistic sensitivity analysis, deterministic sensitivity analysis and the majority of scenario analyses, zanubrutinib remains cost-effective at the £30,000 threshold. This suggests that the results obtained are robust regardless of the uncertainty.

Figure 1 shows the results from all scenario analyses conducted using the EAG's base case. The only two scenarios that lead to ICERs above the £30,000 threshold were:

A. The scenario where treatment waning is implemented at [redacted] (which the EAG noted was a highly conservative scenario, based on extreme assumptions and hence should be interpreted with caution) lead to an ICER of £34,898; and
B. The extremely conservative scenario where most pessimistic survival curve was chosen for zanubrutinib and the most optimistic curves were chosen for the HMRN registry basket, which lead to an ICER of £31,957. The survival curves selected were:
    - PFS HMRN registry basket: Log-normal,
    - PFS zanubrutinib: Exponential,
    - OS HMRN registry basket: Log-normal,
    - OS zanubrutinib: Weibull; and
    - TTD zanubrutinib: Gompertz.

Figure 1: Scatterplot of scenario analysis using the EAG and Company revised base case

Abbreviations: EAG – external assessment group; QALY – quality-adjusted life-year.

Key issue 3: the choice of a partitioned survival model

Description of problem	Description of proposed amendment	Justification for amendment	Response from EAG
Sections 1.4 and 4.2.2.1: The EAG state that a STM is a more appropriate approach to	The text should be amended throughout the EAG report to clarify that given the data available, a PSM, not a STM, is the appropriate	The company outlined a number of key justifications for use of a PSM over STM in the CS and	The EAG acknowledge that data limitations may inhibit the

the zanubrutinib cost-effectiveness analysis within the decision problem. However as stated by the company in the Clarification response, an STM is not feasible given the available data.	approach to the cost-effectiveness analysis.	the clarification response, including: • Greater data requirements in an STM compared to a PSM (as also acknowledged by the EAG within their report). • Precedence of PSM approaches being accepted by NICE committee in previous lymphoma and zanubrutinib NICE health technology assessment submissions (TA627, TA649, TA833 and TA933).[3,14-16] The Company maintain that it would not be possible to conduct a cost-effectiveness analysis using an STM approach, particularly as an STM relies on the availability of data to calculate transition probabilities which split PFS and OS into TTDeath, TTP and PPS. For zanubrutinib, given that few	parametrisation of a STM in this context. The EAG has made some minor changes to the text throughout the EAG report to emphasise this: • Table 1.4 (Page 14) • Section 4.4.2.1 (Pages 54-55) • Section 6.4 (Page 101) The specific wording is detailed in the relevant rows below.

		deaths occurred over the course of the trial, reflective of the indolent nature MZL as a slow growing form of NHL, estimates of TTDeath and PPS probabilities would be based on very few transitions and as such transitions would be more uncertain than estimates of PFS and OS. Furthermore, the HMRN registry did not provide data that would allow transition probabilities to be calculated, meaning that an STM approach would be infeasible for the comparator arm of the model. The EAG noted that a key reason the STM approach should be used over the PSM was that PFS and OS were independently modelled which, as explained in NICE TSD 19, [12] means that model may estimate large post-progression survival benefit. Whilst this may present an issue, in the CS base case this does not appear to be true as post-progression survival in the zanubrutinib arm is smaller	

		than in the HMRN basket arm in both absolute terms ([redacted] versus [redacted] LYG, respectively) and relative terms (19.4% versus 37.4% of total LYG for their respective treatment arm) suggesting that the Company's estimates are conservative. Given the issues with data availability and the conservative estimates of post-progression survival, a PSM is the only robust approach to modelling zanubrutinib for the decision problem.	
Section 1.4, Table 1.4, p.14: "However, PSMs have a key methodological limitation in that in these models, health state occupancy is based on a set of non-mutually exclusive survival curves. This has a number of implications, principally that the extrapolations produced from these survival curves may not be appropriate."	Given the Company's EAG Clarification response and the above discussion of STMs and PSMs, please specify the implications, their significance and, where applicable, what the Company has done to mitigate their impact.	The Company has provided extensive reasoning as to why the use of a STM is neither appropriate nor feasible for modelling the cost-effectiveness of zanubrutinib.	No change – not a mistake or factual error.

Section 1.4, Table 1.4, p.15: "A STM presented alongside the existing PSM would resolve the uncertainty related to the model structure."	The Company request the text to be amended to: "A STM presented alongside the existing PSM ~~would~~ **could** resolve the uncertainty related to the model structure**, however, given the limited data available to inform transitions in the STM, this is both infeasible and unlikely**."	As discussed above, the estimation of TTDeath and PPS probabilities required to inform a STM would be uncertain given the low of number of death events observed in the zanubrutinib trials. Therefore, a STM is unlikely to relieve any uncertainty associated with a PSM. Furthermore, it is not feasible to estimate the transition probabilities required for a STM from the HMRN data, further prohibiting the feasibility of building a STM.	The EAG has made the suggested change with a modification to the company's suggested wording: "A STM presented alongside the existing PSM could resolve the uncertainty related to the model structure. The EAG acknowledge that data limitations may inhibit the parametrisation of such a model in this specific context".
Section 4.2.2.1, p.54: 	The Company request the text to be amended to: 	The Company has demonstrated that PPS is unlikely to have been overestimated for zanubrutinib, as discussed above, and this should be reflected in the EAG report.	No change – not a mistake or factual error.

	However, PPS estimates in the company's submission are conservative with zanubrutinib having a lower absolute and relative PPS benefit compared with the HMRN registry basket."		
Section 4.2.2.1, p.54: "The EAG is of the opinion that, given a sufficient evidence base, an STM would give more accurate cost-effectiveness results than a PSM."	The Company request the text to be amended to: "The EAG is of the opinion that, given a sufficient evidence base, an STM would give more accurate cost-effectiveness results than a PSM. **However, with limited data available to inform transitions, an STM approach is both infeasible and unlikely to address the uncertainties.**"	The wording should reflect the high level of uncertainty that would be present if a STM approach was adopted, as discussed above.	The EAG has made the suggested change with a modification to the company's suggested wording: "The EAG is of the opinion that, given a sufficient evidence base, an STM could give more accurate cost-effectiveness results than a PSM. The EAG acknowledge that data limitations may inhibit the parametrisation of such a model in this specific context".

Section 1.4, Table 1.5, p.15: "The small numbers of patients to have progressed or died by the end of the MAGNOLIA and AU-003 clinical trials are a cause of inherent uncertainty in the cost effectiveness analysis, as it makes long term predictions very difficult."	The Company request additional text is added: "The small numbers of patients to have progressed or died by the end of the MAGNOLIA and AU-003 clinical trials are a cause of inherent uncertainty in the cost effectiveness analysis, as it makes long term predictions very difficult. **This also demonstrates the difficulty in obtaining robust results from a STM approach, as there would be few events to inform transition probabilities.**"	The wording should also highlight the difficulty of estimating transition probabilities and therefore implementing a STM approach, as discussed above.	No change – not a mistake or factual error.
Key issue 4: Uncertain PFS and OS predictions for zanubrutinib **Key issue 5: Uncertainty in the choice of parametric survival curve**			
Section 1.4, Table 1.6, p.15-16: "As a consequence of this, the extrapolations for these outcomes are also extremely uncertain, with significant heterogeneity in the predictions from different parametric survival curves with almost identical statistical fit."	The Company request the text is amended to: "As a consequence of this, the extrapolations for these outcomes are ~~also extremely~~ uncertain, ~~with significant heterogeneity in the predictions from different parametric survival curves with almost identical statistical fit.~~ **however, sensitivity analyses demonstrate the limited**	The Company's extensive sensitivity analyses have explored the uncertainty associated with the long term PFS and OS estimates and demonstrate that choice of curves has little impact on the cost-effectiveness of zanubrutinib. Therefore, the Company does not consider this	No change – not a mistake or factual error.

	impact of curve selection on the ICER."	a key issue for a decision making.	
Section 1.4, Table 1.6, p.16: "Furthermore, there is a lack of concurrence between the estimates from the various parametric survival curves and clinical expert opinion gathered by both the company and the EAG."	The Company request the text is amended to: "Furthermore, there is a lack of concurrence between the estimates from the various parametric survival curves and clinical expert opinion gathered by both the company and the EAG. **However, extensive sensitivity analyses, including best- and worst-case scenarios, demonstrated that the base-case estimates are robust, and curve selection has little impact on the ICER, with estimates consistently cost-effective at the £30,000 per QALY ICER threshold.**"	The Company's sensitivity analyses demonstrate that the choice of survival curve for PFS and OS has little impact on the cost-effectiveness of zanubrutinib. Therefore, the Company does not consider this a key issue for a decision making.	No change – not a mistake or factual error.
Section 4.2.7.1, p.57: "Given the lack of concurrence between the OS rates estimated by the clinical experts and the KM data, the EAG consider the choice of parametric survival function to	The Company request the text is amended to: "Given the lack of concurrence between the OS rates estimated by the clinical experts and the KM data, the EAG consider the choice of parametric survival function to be subject to ~~considerable~~ uncertainty. **However, sensitivity analyses**	The Company's sensitivity analyses demonstrate that the choice of survival curve for PFS and OS has little impact on the cost-effectiveness of zanubrutinib. Therefore, the Company does not consider this a key issue for a decision making.	No change – not a mistake or factual error.

be subject to considerable uncertainty."	**conducted suggest the impact of such uncertainty on results is limited.**"		
Section 4.2.7.1, p.57: "…the EAG consider the reasoning for choosing the log-logistic curve over the log-normal curve to be questionable. However, given this inherent uncertainty, the EAG consider the company choice of curve in the base case to be satisfactory."	The Company request the text is amended to: "…the EAG consider the reasoning for choosing the log-logistic curve over the log-normal curve to be questionable. However, **as the company conducted extensive sensitivity analyses, including best- and worst-case scenarios, that demonstrated that the base-case estimates are robust, with consistent cost-effectiveness and little variation in the ICER,** ~~given this inherent uncertainty,~~ the EAG consider the company choice of curve in the base case to be satisfactory."	The Company's sensitivity analyses demonstrate that the choice of survival curve for PFS and OS has little impact on the cost-effectiveness of zanubrutinib. Therefore, the Company does not consider this a key issue for a decision making.	No change – not a mistake or factual error.
Section 4.2.7.2, p.59: "The EAG consider the choice of curve to be subject to considerable uncertainty. However, given this inherent uncertainty, the EAG consider the company choice of curve in	The Company request the text is amended to: "The EAG consider the choice of curve to be subject to ~~considerable~~ uncertainty. However, **as the company conducted extensive sensitivity analyses, including best- and worst-case scenarios,**	The Company's sensitivity analyses demonstrate that the choice of survival curve for PFS and OS has little impact on the cost-effectiveness of zanubrutinib. Therefore, the Company does not consider this	No change – not a mistake or factual error.

the base case to be satisfactory.”	**that demonstrated that the base-case estimates are robust, with consistent cost-effectiveness and little variation in the ICER,** ~~given this inherent uncertainty,~~ the EAG consider the company choice of curve in the base case to be satisfactory.”	a key issue for a decision making.	
Section 4.2.7.3, p.60: “Given the lack of concurrence between the OS rates estimated by the clinical experts and the KM data, the EAG consider the choice of parametric survival function to be subject to considerable uncertainty.”	The Company request the text is amended to: “Given the lack of concurrence between the OS rates estimated by the clinical experts and the KM data, the EAG consider the choice of parametric survival function to be subject to considerable uncertainty. **However, sensitivity analyses conducted suggest the impact of the uncertainty on cost-effectiveness results is minimal.**”	The Company’s sensitivity analyses demonstrate that the choice of survival curve for PFS and OS has little impact on the cost-effectiveness of zanubrutinib. Therefore, the Company does not consider this a key issue for a decision making.	No change – not a mistake or factual error.
Section 4.2.7.3, p.60: “…the EAG consider the reasoning for choosing the log-logistic curve over the log-normal curve to be questionable. However, given this inherent uncertainty, the EAG consider the company	The Company request the text is amended to: “…the EAG consider the reasoning for choosing the log-logistic curve over the log-normal curve to be questionable. However, **as the company conducted extensive sensitivity analyses, including**	The Company’s sensitivity analyses demonstrate that the choice of survival curve for PFS and OS has little impact on the cost-effectiveness of zanubrutinib. Therefore, the Company does not consider this	No change – not a mistake or factual error.

choice of curve in the base case to be satisfactory."	**best- and worst-case scenarios, that demonstrated that the base-case estimates are robust, with consistent cost-effectiveness and little variation in the ICER,** ~~given this inherent uncertainty,~~ the EAG consider the company choice of curve in the base case to be satisfactory."	a key issue for a decision making.	
Section 4.2.7.4, p.62: "The EAG consider the choice of curve to be subject to considerable uncertainty. However, given this inherent uncertainty the EAG consider the company choice of curve in the base case to be satisfactory."	The Company request the text is amended to: "The EAG consider the choice of curve to be subject to ~~considerable~~ some uncertainty. However, **as the company conducted extensive sensitivity analyses, including best- and worst-case scenarios, that demonstrated that the base-case estimates are robust, with consistent cost-effectiveness and little variation in the ICER,** ~~given this inherent uncertainty,~~ the EAG consider the company choice of curve in the base case to be satisfactory."	The Company's sensitivity analyses demonstrate that the choice of survival curve for PFS and OS has little impact on the cost-effectiveness of zanubrutinib. Therefore, the Company does not consider this a key issue for a decision making.	No change – not a mistake or factual error.
Section 4.2.7.5, p.64: "The EAG consider the choice of curve to be subject to considerable uncertainty.	The Company request the text is amended to: "The EAG consider the choice of curve to be subject to ~~considerable~~	The Company's sensitivity analyses demonstrate that the choice of survival curve for PFS and OS has little impact on the	No change – not a mistake or factual error.

However, given this inherent uncertainty the EAG consider the company choice of curve in the base case to be satisfactory.”	some uncertainty. However, **the company conducted extensive sensitivity analyses, including best- and worst-case scenarios, that demonstrated that the base-case estimates are robust, with consistent cost-effectiveness and little variation in the ICER** ~~given this inherent uncertainty,~~, the EAG consider the company choice of curve in the base case to be satisfactory.”	cost-effectiveness of zanubrutinib. Therefore, the Company does not consider this a key issue for a decision making.	
Section 4.2.7.7, p.67: “The EAG considers the extrapolations of the data from the MAGNOLIA and AU-003 trials to be subject to considerable uncertainty.”	The Company request the text is amended to: “The EAG considers the extrapolations of the data from the MAGNOLIA and AU-003 trials to be subject to ~~considerable~~ **some** uncertainty. **However, the company conducted extensive sensitivity analyses, including best- and worst-case scenarios, to assess the impact of the different extrapolations on the ICER. These analyses demonstrated that the base-case estimates are robust, as there was little variation in the ICER, and estimates consistently**	The Company’s sensitivity analyses demonstrate that the choice of survival curve for PFS and OS has little impact on the cost-effectiveness of zanubrutinib. Therefore, the Company does not consider this a key issue for a decision making.	No change – not a mistake or factual error. .

	cost-effective at the £30,000 per QALY ICER threshold."		
Key issue 6: uncertainty in the utility values for the PFS and PD health states			
Section 1.4, Table 1.7, p.16: "Although scenario analyses were undertaken to address the uncertainty around both values, these utility values are a source of uncertainty."	The Company request the text is amended to: "Although scenario analyses ~~were~~ undertaken **demonstrated the limited impact on cost-effectiveness** ~~to address the uncertainty around both values~~, these utility values are a source of uncertainty."	Scenario analyses demonstrate that the utility values do not substantially impact the cost-effectiveness of zanubrutinib. Therefore, the Company does not consider this a key issue for a decision making.	No change – not a mistake or factual error.
Section 1.4, Table 1.7, p.16: "The EAG has explored alternative HRQoL utility values in the EAG base case and EAG scenario analyses."	The Company request the text is amended to: "The EAG has explored alternative HRQoL utility values**, based on a fixed decrement of 0.056 following progression,** in the EAG base case and EAG scenario analyses."	The utility approach should be introduced to clarify why the ICER increased with the EAG preferred utility.	No change – not a mistake or factual error.
Section 4.2.9.4, p.75: "The EAG acknowledge that the utility values from TA627 were deemed to be too high by the EAG for that submission."	The Company request the text is amended to: "The EAG acknowledge that the utility values from TA627 were deemed to be too high by the EAG for that submission **and they *[the TA627***	In the EAG report for TA627, the following is statement is included "*the ERG judges that a larger utility difference between PF and PD health states would be more plausible*".[14] Given this,	No change – not a mistake or factual error.

	***EAG]* stated that "a larger utility difference between PF and PD health states would be more plausible" than the difference present.**"	the EAG's report should be amended to accurately represent the EAG's view in TA627.	
Section 4.2.9.4, p.75: "Although the company have conducted a range of scenario analyses around these values, an alternative value for the PD health state is included in the EAG base case, presented in Section 6.1.1."	The Company requests the text is amended to: "~~Although~~ The company have conducted a range of scenario **and sensitivity** analyses around these values, **which demonstrate that the results are robust and are consistently cost-effective at a £30,000 per QALY threshold. Despite this,** an alternative value for the PD health state is included in the EAG base case, presented in Section 6.1.1."	The Company's sensitivity analyses demonstrate that PD utility has little impact on the cost-effectiveness of zanubrutinib. Therefore, the Company does not consider this a key issue for a decision making.	No change – not a mistake or factual error.

Issue 3: Updates to the Company's base-case cost-effectiveness analysis

Description of change	Description of proposed amendment	Justification for amendment	Response from EAG
As detailed in the rows below the Company accept all the changes made by the EAG in their base case. As such, the company and EAG base case is aligned, at £26,612 per QALY gained (as per Table 6.1 of the EAG report). Importantly, across all scenarios analysis conducted by the EAG and the Company the ICER remained bellowed £30,000 per QALY gained, with the			

exception for two scenarios (which were deemed **highly conservative and to be interpreted with caution** by the EAG, given that they were based on **extreme assumptions, see Section 5.2.3, p.90**) where the ICER remained below £35,000.			
In the CS base-case AE disutilities were assumed to be the same for all AEs. The EAG updated AE disutilities with values from the literature in their base case.	The Company accept the EAG's change.	N/A	N/A
In the updated company base-case drug acquisition costs have been updated to reflect the latest available BNF prices as per the EAGs base-case.	The Company accept the EAG's change.	N/A	N/A
In the updated company base case several drug acquisition costs have been updated based on the latest available prices from eMIT, as per the EAG base case.	The Company accept the EAG's change.	N/A	N/A
In the company base case, the PD health state utility was sourced from	In the interest of cooperation, with the priority of timely	The Company maintain that the PD utility applied in the original CS is a more appropriate utility to capture the HRQoL	N/A

CADTH pCODR, however in the EAG base case the PD utility has updated it to reflect the utility decrement (0.056) presented in the submission TA627.	patient access, the Company accepts the EAG's change.	of patients with disease progression. The EAG's base-case utility decrement of 0.056 following disease progression fails to capture the increased disease burden on patients and is much lower than the decrement accepted in previous NICE appraisals for relevant blood cancers.[3,16] Furthermore, in TA627, the EAG appraising the technology argued that the utilities presented in the submission were unreasonable, so using their submission values to determine the decrement would be inappropriate.[14] Specifically commenting on the decrement, stating "*the ERG judges that a larger utility difference between PF and PD health states would be more plausible*".[14] The Company believe there is a duty to follow precedence set by NICE. However, as changing the PD utility to the EAGs preferred value has a minimal impact on the ICER and in the interest of cooperation and timely patient access, the Company accept the EAG's change.	

Issue 4: Mistakes and factual errors – clinical

Description of problem	Description of proposed amendment	Justification for amendment	Response from EAG
Section 2, Table 2.1, p.19: "Clinical advice to the EAG, and the updated guidance[1] has highlighted rituximab may have only limited use in this patient population."	The Company requests the text is amended to: "Clinical advice to the EAG~~, and the updated guidance~~[1] has highlighted rituximab may have only limited use in this patient population. **However, the updated BSH guidance suggests that rituximab monotherapy is a suitable option for a broader patient population.[1]**"	In Section 2.1, EAG states that, according to the BSH, rituximab monotherapy is an "*option for patients with symptomatic relapsed splenic MZL and extranodal MZL/mucosa-associated lymphoid who have previously achieved a durable response to rituximab monotherapy*" (p. 16).[1] Patients with extranodal and splenic MZL represent 60% and 20% of patients with MZL, respectively. This indicates that rituximab monotherapy is an appropriate treatment option for the majority of MZL patients.	The EAG have reworded the text to make it clear where clinical advice has been given, and where the BSH guidance is used (full details of the BSH guidance is provided in Section 2.1 of the EAG report): "The comparators are largely in line with the NICE scope. Clinical advice to the EAG has highlighted rituximab may have only limited use in this patient population. The updated BSH guidance states the specific circumstances that the use of single agent rituximab and splenectomy might be considered relevant.[1] "

Section 3.1, Table 3.1, p.25: "An important aspect of collating data for inclusion in the SLR is seeking out key unpublished information that is missing from reports of included studies. This was not undertaken and is further described in Section **Error! Reference source not found.**."	The Company request the text is amended to: "An important aspect of collating data for inclusion in the SLR is seeking out key unpublished information that is missing from reports of included studies. This was not undertaken **and was justified by the company as** ~~and~~ is further described in Section **Error! Reference source not found.**."	The Company have provided justifications in the clarification response on why requesting additional unpublished evidence from the authors was not prioritised and undertaken.	The EAG has made the following change: "An important aspect of collating data for inclusion in the SLR is seeking out key unpublished information that is missing from reports of included studies. This was not undertaken, and was justified by the company. This is further described in Section **Error! Reference source not found.**."
Section 3.1.2, Table 3.2, p.28: "Source: Table 9, Document B"	Update source from "Document B" to "Appendix D".	Typographical error.	The EAG has made the suggested change.
Section 3.2.1, Table 3.3, p.29-30: "Whilst the patient flow seems appropriate, and the extension or 'roll-over' of	"Whilst the patient flow seems appropriate, and the extension or 'roll-over' of patients participating in MAGNOLIA to the LTE study is typical of early phase oncology trials, the EAG	The Company acknowledge while the LTE studies could reduce uncertainty on the long term PFS and OS extrapolations. However, the	No change – not a mistake or factual error.

patients participating in MAGNOLIA to the LTE study is typical of early phase oncology trials, the EAG cannot be sure of the impact or results of the LTE study. It is likely however, that the extension trial would provide valuable patient data over the coming years."	cannot be sure of the impact or results of the LTE study. **The company maintains that the data presented in the CS is sufficient for decision making.** It is likely however, that the extension trial would provide valuable patient data over the coming years."	data is not expected to be available until 2025, preventing the data informing the decision making for this appraisal. Additionally, the Company does not expect the additional data to impact the overall conclusions of the clinical evidence and that the data currently presented in the CS are sufficient for decision making.	
Section 3.2.1, Table 3.3, p.30-31: *Baseline characteristics - Section in CS where methods are reported: "B.2a.3.4, Table 10, p.33 - 35"*	Update page number from "35" to "36".	Typographical error.	The EAG has made the suggested change.
Section 3.2.1, Table 3.3, p.31: Subgroup analyses: "Whilst most of the confidence intervals overlap, there appears to be a difference in response between sexes. It is unclear to the EAG what	The Company request the text is amended to: "Whilst most of the confidence intervals overlap, there appears to be a difference in response between sexes. **However, it is important to note that the confidence intervals overlap indicating no statistically significant**	The Company acknowledge that while the difference between the ORR for males and females is large, the confidence intervals do overlap, indicating no statistically significant	The EAG has made the following change: "Whilst all the confidence intervals overlap, indicating no statistically significant

may have caused the difference. Further real-world evidence may help understand any differential treatment effect by subgroups.”	**difference in outcomes**. It is unclear to the EAG what may have caused the difference. Further real-world evidence may help understand any differential treatment effect by subgroups.	difference between the two patient groups.	difference in outcomes, there is tentative evidence of a possible difference in response between sexes (males: 83.3, 95% CI 67.19, 93.63; females: 50.0, 95% CI 31.30, 68.70). It is unclear to the EAG what may have caused the difference. Further real-world evidence may help understand any differential treatment effect by subgroups.”
Section 3.2.1, Table 3.3, p. 31: *Results - Section in CS where methods are reported: “B.2a.6, p.41/42”*	Update page number from “41/42” to “41 - 50"	Typographical error.	The EAG has made the suggested change.
Section 3.2.1, Table 3.3, p. 31: “The company reported subgroup analysis included: age, sex, ECOG PS, prior line of systemic therapy (< 3 versus ≥ 3), disease status,	The Company request the text is amended to: “The company reported subgroup analysis included: age, sex, ECOG PS, prior line of systemic therapy (< 3 versus ≥ 3), **years since last anti-lymphoma therapy (≤ 2 versus > 2),**	Typographical error	The EAG has made the suggested change.

prior treatment (R-CVP versus R-CHOP versus BR versus all others), disease stage (stage I versus II, III and IV), MZL subtype (extranodal versus nodal versus splenic), baseline extranodal disease, baseline LDH"	disease status, prior treatment (R-CVP versus R-CHOP versus BR versus all others), **bulky disease (longest diameter ≤ 5 cm versus > 5 cm and ≤ 10 cm versus > 10 cm), bone marrow involvement,** disease stage (stage I versus II, III and IV), MZL subtype (extranodal versus nodal versus splenic), baseline extranodal disease, baseline LDH"		
Section 3.2.1.1, p.32: "The CS report that an integrated interim safety report is expected in December 2024.[17] Adverse events, alongside PFS, DOR and OS (time frame, up to five years) will be collated during this trial. Although no further DCOs are planned in MAGNOLIA, the LTE study offers an opportunity to collate further efficacy and safety outcomes and reduce uncertainty, particularly concerning survival in the medium to long term."	The Company request the text is amended to: "The CS report that an integrated interim safety report is expected in December 2024 **and so will not be ready for this submission**.[17] Adverse events, alongside PFS, DOR and OS (time frame, up to five years) will be collated during this trial. Although no further DCOs are planned in MAGNOLIA, the LTE study offers an opportunity to collate further efficacy and safety outcomes and reduce uncertainty, particularly concerning survival in the medium to long term. **However, it should be noted that the company maintains that the data**	The Company acknowledge while the LTE studies could reduce uncertainty on the long term PFS and OS extrapolations. However, the data is not expected to be available until December 2024, preventing the data informing the decision making for this appraisal. Additionally, the Company does not expect the additional data to impact the overall conclusions of the clinical evidence and that the data currently presented in the CS are sufficient for decision making.	The EAG has made the following change: "The LTE study (BGB-3111; NCT04170283), is a single group assignment, non-randomised, open label study with an estimated study completion of December 2028. The CS report that an integrated interim safety report is expected in December 2024,[18] and therefore not ready for this submission."

	currently in the submission is sufficient for decision making."		The EAG has omitted the last sentence as it is a matter of judgement.
Section 3.2.1.2, Table 3.5, p.33: "Source: CS Document B, Table 12"	Update table number from "12" to "14".	Typographical error.	The EAG has made the suggested change.
Section 3.2.1.2, Table 3.6, p.34: "Source: CS Document B, Table 12"	Update table number from "12" to "45".	Typographical error.	The EAG has made the suggested change.
Section 3.2.1.2, Table 3.7, p.35: "Source: CS Document B, Table 12"	Update table number from "12" to "46".	Typographical error.	The EAG has made the suggested change.
Section 3.2.1.3, p.35 - 36: "Notably, female patients appear have considerably worse ORR compared to males (ORR 83.3, 95% CI 67.19 to 93.63, n = 30 and ORR 50.0, 95% CI 31.30 to 68.70, n = 15 for males and females, respectively). It is	The Company request the text is amended to: "Notably, female patients appear have considerably worse ORR compared to males (ORR 83.3, 95% CI 67.19 to 93.63, n = 30 and ORR 50.0, 95% CI 31.30 to 68.70, n = 15 for males and females, respectively). It is unclear to the EAG what may have caused the	The Company acknowledge that while the difference between the ORR for males and females is large, the confidence intervals do overlap, indicating no statistically significant difference between the two patient groups.	The EAG has made the suggested change.

unclear to the EAG what may have caused the differences. Further real-world evidence may help understand any differential treatment effect by subgroups."	differences **however, it is important to note that the confidence intervals overlap indicating no statistically significant difference in outcomes**. Further real-world evidence may help understand any differential treatment effect by subgroups."		
Section 3.2.1.3, p.36: "Source: CS, Table 8;[17] MAGNOLIA CSR[19]"	Update from "Table" to "Figure".	Typographical error.	The EAG has made the suggested change.
Section 3.2.2, Table 3.8, p.37: "The EAG note that out of the 385 participants enrolled in the study"	Update the value of participants enrolled in the study from "385" to "380".	Typographical error.	The EAG has made the suggested change.
Section 3.2.2, Table 3.8, p.37: *Section in CS where methods are reported: Baseline characteristics*	Section in CS where methods are reported is missing for baseline characteristics. Add "B.2b.3.4, Table 28, p.56/57"	Typographical error.	The EAG has made the suggested change.
Section 3.2.2, Table 3.8, p.38, Section in CS where methods are reported: Statistical analyses:	Update from "59/59" to "58/59"	Typographical error.	The EAG has made the suggested change.

"B.2b.4, p.59/59."			
Section 3.2.2, Table 3.8, p.39, Section in CS where methods are reported: Results: *"B.2b.6, Tables 33-27, Figure 13; B.2b.10, Tables 48-50"*	Update from "B.2b.6, Tables 33-27, Figure 13; B.2b.10, Tables 48-50" to "B.2b.6, p.61-68"	Typographical error.	The EAG has made the following change: B.2b.6, Tables 33-37, Figure 13; B.2b.10, p.61-69.
Section 3.2.2, Table 3.8, p.39, Section in CS where methods are reported: Subgroup analyses: *"B.2b.3, Table 25."*	Missing page number. Add "p.52/53"	Typographical error.	The EAG has made the suggested change.
Section 3.2.2, Table 3.8, p.39: "The primary endpoint, ORR, was met. However, from the perspective of survival outcomes (PFS, OS), the datasets may be considered relatively immature."	The Company request the text is amended to: "The primary endpoint, ORR, was met. However, from the perspective of survival outcomes (PFS, OS), the datasets may be considered relatively immature. **This reflects the prognostic nature of MZL as a slow growing form of NHL. The company has taken measures to explore and overcome the uncertainty associated with the extrapolating**	Whilst the Company acknowledges that data is relatively immature, this is to be expected given the indolent nature of MZL. Furthermore, the Company conducted extensive scenario analyses and compared landmark extrapolations to expert clinical opinion to explore and account for this uncertainty. The text should reflect this approach.	The EAG have made the following change: "The primary endpoint, ORR, was met. However, from the perspective of survival outcomes (PFS, OS), the datasets may be considered relatively immature. This in part, reflects the prognostic nature of MZL as a slow growing form of non-

	PFS and OS through extensive scenario analyses."		Hodgkin lymphoma (NHL)." The EAG consider the last few sentences which the company have proposed as a matter of judgement and have therefore made no change.
Section 3.2.2.1, p.40: "Over [redacted] remained on study treatment in the LTE study. This expansion trial encompasses participants with B-cell malignancies who currently participated or are participating in a BeiGene parent study. [18] In the CS, it is stated that an interim safety report for the LTE study is expected in December 2024.[17] It is unclear to the EAG whether results from the LTE will be reported for MZL patients	The Company request the text is amended to: "Over [redacted] remained on study treatment in the LTE study. This expansion trial encompasses participants with B-cell malignancies who currently participated or are participating in a BeiGene parent study.[18] In the CS, it is stated that an interim safety report for the LTE study is expected in December 2024 **and so will not be available to inform decision making in this appraisal**. [17] It is unclear to the EAG whether results from the LTE will be reported for MZL patients specifically, or grouped with other B-	The Company acknowledge while the LTE studies could reduce uncertainty on the long term PFS and OS extrapolations. However, the data is not expected to be available until December 2024, preventing the data informing the decision making for this appraisal. Additionally, the Company does not expect the additional data to impact the overall conclusions of the clinical evidence and that the data currently presented in	The EAG has amended the text to the following: "Over [redacted] remained on study treatment in the LTE study. This expansion trial encompasses participants with B-cell malignancies who currently participated or are participating in a BeiGene parent study.[18] In the CS, it is stated that an interim safety report for the LTE study

specifically, or grouped with other B-cell malignancies."	cell malignancies. **However, it should be noted that the company maintains that the data currently in the submission is sufficient for decision making."**	the CS are sufficient for decision making.	is expected in December 2024, and therefore not ready for this submission. [17] It is unclear to the EAG whether results from the LTE will be reported for MZL patients specifically, or grouped with other B-cell malignancies." The EAG has omitted the last sentence the company proposed as it is a matter of judgement.
Section 3.3, Table 3.11, p.42, CS section: Pooling of the MAGNOLIA and AU-003 trial data: *"B.2.9.1, p.76-81; PfC question A7"*	Update "A7" to "A8".	Typographical error.	The EAG has made the suggested change.
Section 3.3.2, p.44: "In response, the company maintained that additional MAICs with these trials were not feasible or appropriate."	The Company request the text is amended to: "In response, **the company conducted an exploratory MAIC analysis comparing against**	Correction to reflect the additional MAIC versus CHRONOS-3 that was presented in the clarification response.	The EAG has made the suggested change.

	CHRONOS-03. However, the company maintained that additional MAICs with these trials were not feasible or appropriate.”		
Section 3.3.2.3, p.46: *“HMRN registry basket (PfC, question A10, Table 10).”*	Remove mention of Table 10.	Typographical error.	The EAG has made the suggested change.
Section 3.3.3.1, p.46: "The company also noted that the registry had not yet been processed and that it is expected that these patients will not have reached second-line therapy."	The Company request that the text is amended to: The company also noted that the registry “**have not processed patients diagnosed post-2021 onwards yet, however it is expected that many of these patients still would not have reached second-line therapy***.”*	The Company believe that the sentence is difficult to understand without clarification.	The EAG has made the suggested change with a slight modification to the company’s suggested wording: “The company also noted that the registry have not yet processed patients diagnosed post-2021, though it is expected that many of these patients would still not have reached second-line therapy”.

Issue 5: Mistakes and factual errors – cost-effectiveness

Description of problem	Description of proposed amendment	Justification for amendment	Response from EAG
Section 4.2.2.1, Figure 4.1, p.53: Source: CS Section B.3.2.2, Figure 18, p.10	Update the source page number from "p.109" to "p.110".	Typographical error.	The EAG has made the suggested change.
Section 4.2.2.1, Figure 4.2, p.54: Source: CS Section B.3.2.4, Figure 18, p.112	Update the source figure number from "18" to "19".	Typographical error.	The EAG has made the suggested change.
Section 4.2.7.1, p.57: "log-logistic was chosen over log-normal due to its lower combined AIC and BIC;"	The Company request that the text is amended to: "log-logistic was chosen over log-normal due to its lower ~~combined~~ AIC and BIC **scores, both individuals and combined**;"	The decision informed by the AIC and BIC scores was not solely made on the combined score as implied in the report. The decision also considered the individual AIC and BIC scores, clinical plausible and visual fit.	The EAG has made the suggested change.
Section 4.2.7.1, p.57: [redacted]	Provide more detail on the clinical expert's views or replace quote of "about right" with wording such as "the estimate of 20% was deemed reasonable".	The expert opinion gathered by the EAG on the expected 10-year PFS for the HMRN registry arm is presented ambiguously, as it does not	No change – not a mistake or factual error.

[redacted][8] Clinical expert opinion gathered by the EAG suggested that this estimate of 20% was "*about right*"."	It should also be clarified that the advisory board conducted by the Company is a more robust form of eliciting clinical expert opinion, as there was more than one clinician present. The Company request that the text is amended to: [redacted] Clinical expert opinion gathered by the EAG suggested that this estimate of 20% was "*about right*", **assuming OS was** [redacted]."	suggest if the clinical expert's opinion was with the assumption that the OS rate was around 40% at 10 years or if this estimate of 20% was specifically correct, an underestimate or an overestimate. If OS was around 20% (the lowest estimate provided by clinical experts at the advisory board)[8], a prediction of 20% for PFS would be infeasible. Therefore, a caveat should be added to the EAG's claim that PFS was underestimated for the HMRN registry arm.	
Section 4.2.7.3, p.60: "Due to the immaturity of the data, the EAG consider it extremely difficult to assess the curve choice through visual fit."	The Company request that the text is amended to: "Due to **prognostic nature of MZL, as a slow growing form of NHL, relative** immaturity **is a feature** of the data. **As a result,** the EAG consider it ~~extremely~~ difficult to assess the curve choice through visual fit **alone**."	Whilst the Company acknowledge that data is relatively immature, this is to be expected given the indolent nature of MZL. Therefore, the language should be softened to reflect this.	No change – not a mistake or factual error.

Section 4.2.7.5, p.64: "Goodness-of-fit statistics for landmark TTD rates and the parametric survival extrapolations for zanubrutinib are shown in Table 4.12 and Figure 4.7."	The Company requests that the text is amended to: "Goodness-of-fit statistics ~~for~~**,** landmark TTD rates and the parametric survival extrapolations for zanubrutinib are shown in Table 4.12**, Table 4.13** and Figure 4.7". Table 4.13 should be created in this section from CS Section B.3.3.6 Table 64, p.129, showing the landmark survival TTD estimates.	This section is inconsistent with the rest of the extrapolation sections as it does not present the landmark estimates for TTD.	The EAG has made the suggested change.
Section 4.2.7.5, p.65: The source for Figure 4.7 is incorrect.	Update the source figure number from "24" to "25".	Typographical error.	The EAG has made the suggested change.
Section 4.2.8.2, p.71: "Although this is a strong assumption, as noted in Section 4.2.7.1, given the minor impact on the cost-effectiveness results the EAG are satisfied with this assumption."	The Company request that the text is amended to: "Although this is a strong assumption, as noted in Section 4.2.7.1, given **that it is commonly accepted in previous NICE submissions**[3,16] **and** the minor impact on the cost-effectiveness results the EAG are satisfied with this assumption."	This assumption follows the precedent set in NICE submissions and is in line with what has previously been accepted in TA833[3] and TA931[16], and whilst the EAG deems it to be a "strong assumption" it is consistent with previous submissions.	No change – not a mistake or factual error.

Section 4.2.8.2, p.71: "During the clarification process, the company provided inflated costs to the EAG (PfC, question B12).[11]"	The Company request that a statement is added: " During the clarification process, the company provided inflated costs to the EAG (PfC, question B12).[11] **Inflating costs to the latest cost year had a limited impact on the ICER.**"	This will help the reader understand that corrections to the 'cost inflation' has limited impact on the cost-effectiveness of zanubrutinib.	No change – not a mistake or factual error.
Section 4.2.9.4, Table 4.19, p.74: The wrong page number is reported.	Update the source page number from "p.137" to "p.138".	Typographical error.	The EAG has made the suggested change.
Section 4.2.9.4, Table 4.20, p.75: The wrong page number is reported.	Update the source page number from "p.143" to "p.145".	Typographical error.	The EAG has made the suggested change.
Section 4.2.9.4, p.75: "Although the company have conducted a range of scenario analyses around these values, an alternative value for the PD health state is included in the EAG base-case, presented in Section 6.1.1."	The Company request that the text is amended to: "Although the company have conducted a range of scenario analyses around these values **which demonstrate that the results are robust and are consistently cost-effective at a £30,000 per QALY threshold**, an alternative value for the	The report does not comment on the significance of using an alternative utility value for PD to the ICER. Adding this will help the committee understand that this is not an influential factor in the cost-effectiveness of zanubrutinib.	No change – not a mistake or factual error.

	PD health state is included in the EAG base-case, presented in Section 6.1.1."		
Section 4.2.10.3, p.79: "The company indicated that there are no specific recommendations on the management of R/R MZL with respect to healthcare resource use…"	The Company request that the text is amended to: "The company indicated that ~~there are~~ **the BSH guidelines make** no specific recommendations on the management of R/R MZL with respect to healthcare resource use…".	This clarifies that the Company is referring to the BSH guidelines specifically when stating there are no recommendations on health resource use.	The EAG has made the suggested change.
Section 5.2.1, Table 5.4, p.82: The wrong page number is reported.	Update the source page number from "p.164" to "p.165".	Typographical error.	The EAG has made the suggested change.
Section 5.2.1, Figure 5.1, p.83: The wrong page number is reported.	Update the source page number from "p.164" to "p.165".	Typographical error.	The EAG has made the suggested change.
Section 5.2.1, Figure 5.2, p.83: The wrong page number is reported.	Update the source page number from "p.165" to "p.166".	Typographical error.	The EAG has made the suggested change.
Section 5.2.1, p.83-84:	The Company request that a statement is added:	The report does not compare the results from the 5,000	The EAG has made the suggested change with

"The EAG ran the company model with 5000 simulations (the maximum permittable in the CEM), where the ICER changed to £26,814 per QALY for zanubrutinib when compared to the HMRN registry basket."	"The EAG ran the company model with 5000 simulations (the maximum permittable in the CEM), where the ICER changed to £26,814 per QALY for zanubrutinib when compared to the HMRN registry basket. **This represents a relatively small increase in the ICER of £39 compared to the ICER estimated with 1000 simulations in the CS.**"	simulations ran by the EAG and the 1,000 ran by the company in the submission. Adding this will help the reader understand the robustness of the ICER estimate.	a slight modification to the company's suggested wording: "This represents an increase in the ICER of £39 compared to the ICER estimated with 1000 simulations in the CS"
Section 5.2.2, Table 5.5, p.84: The wrong page number is reported.	Update the source page number from "p.165" to "p.166".	Typographical error.	The EAG has made the suggested change.
Section 5.2.2, Figure 5.3, p.85: The wrong page number is reported.	Update the source page number from "p.166" to "p.167".	Typographical error.	The EAG has made the suggested change.
Section 5.2.3, Table 5.6, p.86: The wrong page number is reported.	Update the source page number from "p.168" to "p.169".	Typographical error.	The EAG has made the suggested change.

Section 5.2.3, p.90: "In relation to the set of scenarios related to treatment waning, the EAG note that although assuming a treatment waning length of [redacted] years increases the ICER considerably…"	The Company request that the text is amended to: "In relation to the set of scenarios related to treatment waning, the EAG note that although assuming a treatment waning length of [redacted] years **(equivalent to median TTD of zanubrutinib)** increases the ICER considerably…"	This change provides context on why this value was chosen for a scenario.	The EAG has made the suggested change.
Section 4.2.8, Table 4.14, p.69: Values in the row 'Basket proportion' require redaction	Please redact data presented as it is considered commercial in confidence by the company.	[redacted]	The EAG has made the suggested change.

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