Single Technology Appraisal

Tafasitamab with lenalidomide and rituximab for treating relapsed or refractory follicular lymphoma after 1 or more lines of systemic treatment [ID6413]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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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 Incyte Corporation:**
   a. Full submission
   b. Full submission addendum
   c. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**
   a. Response
   b. Addendum

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Lymphoma Action – endorsed by Patient expert, Ms Dallas Pounds

4. **Expert personal perspectives** from:
   a. Professor Andrew Davies, Clinical expert – nominated by Incyte Biosciences UK
   b. Dr Mark Bishton, Clinical expert – nominated by Incyte Biosciences UK
   c. Ms Dallas Pounds, Patient expert – nominated by Lymphoma Action
   d. Dr Zoe Drymoussi, Patient expert – nominated by Follicular Lymphoma Foundation

5. **External Assessment Report** prepared by York Technology Assessment Group, University of York
   a. External Assessment Report
   b. EAG response to company addendum

6. **External Assessment Report – factual accuracy check**
   a. EAG response to FAC check
   b. EAG response to FAC addendum

7. **Managed Access Feasibility Assessment**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Tafasitamab with lenalidomide and rituximab for treating relapsed or refractory follicular lymphoma after 1 or more systemic treatments [ID6413]

Company evidence submission

November 2025

File name	Version	Contains confidential information	Date
ID6413_Tafasitamab RRFL_Evidence Submission [redacted]_241115	1.0	No - redacted	24 November 2025

Contents

Tables and figures

Abbreviations

Abbreviation	Definition
1L	First-line
2L	Second-line
2L+	Second-line and beyond
3L+	Third-line and beyond
ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
AE	Adverse event
AFT	Accelerated failure time
AIC	Akaike information criterion
Allo-SCT	Allogeneic stem cell transplant
ASCT	Autologous stem cell transplant
BIC	Bayesian information criterion
CAR T-cell	Chimeric antigen receptor T-cell
CI	Confidence interval
CMR	Complete metabolic response
CR	Complete response
DLBCL	Diffuse large B-cell lymphoma
DoR	Duration of response
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
eMIT	Electronic market information tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
ESMO	European Society of Medical Oncology
ESS	Effective sample size
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
FAS	Full analysis set
FDG	Fluorodeoxyglucose
FL	Follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GELF	Groupe d'Etude des Lymphomes Folliculaires
HCRU	Healthcare resource utilisation
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRQL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
INV	Investigator assessment
IRC	Independent review committee

Abbreviation	Definition
ITC	Indirect treatment comparison
LDH	Lactate dehydrogenase
MAIC	Matching-adjusted indirect comparison
MZL	Marginal zone lymphoma
NHL	Non-Hodgkin's lymphoma
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
O-B	Obinutuzumab with bendamustine
ONS	Office for National Statistics
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PD	Progressed disease
PET-CR	Positron emission tomography-complete response
PF	Progression-free
PFS	Progression-free survival
PLD	Patient-level data
POD24	Progression of disease within 24 months
PS	Performance status
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life years
Q−Q	Quantile−quantile
QoL	Quality of life
R^2	Lenalidomide and rituximab
R-B	Rituximab with bendamustine
R-CHOP	Rituximab with cyclophosphamide, doxorubicin, vincristine, prednisone
R-CVP	Rituximab with cyclophosphamide, vincristine and prednisolone
RCT	Randomised controlled trial
RDI	Relative dose intensity
R/R	Relapsed or refractory
SAS	Safety Analysis Set
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
STC	Simulated treatment comparison
STM	State transition model
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TLR	Targeted literature review
TRAE	Treatment-related adverse event

Abbreviation	Definition
TSD	Technical Support Document
TTD	Time to treatment discontinuation
TTNT	Time to next treatment
VAS	Visual Analogue Scale

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

- Tafasitamab in combination with lenalidomide and rituximab provides a novel and innovative therapeutic option which offers dual targeting of CD19 and CD20 for the treatment of relapsed or refractory (R/R) follicular lymphoma (FL)
- FL is the second most common type of Non-Hodgkin's lymphoma (NHL) affecting around 20,000 people in the UK
- While FL is a slow-progressing disease, it is life-limiting with a lack of additional therapeutic options as patients progress through the disease
- Prognosis worsens with each subsequent relapse or line of therapy, as the disease becomes increasingly resistant to treatment
- As the disease becomes more difficult to treat, patients experience worsening quality of life and with each subsequent recurrence, FL becomes increasingly difficult to live with
- There is an urgent need for new treatment options in R/R FL that can elicit durable responses to extend the period of progression-free living between treatment lines
- Increasing this progression-free period may reduce the total number of treatments patients will need to manage FL over their lifetime and improves their overall length and quality of life

1.1 Decision problem

The submission covers the full marketing authorisation for tafasitamab plus lenalidomide with rituximab (herein referred to as tafasitamab + R^2) in adults with relapsed or refractory (R/R) follicular lymphoma (FL) after 1 or more systemic treatments.

Relevant comparators for decision making are treatments in the current pathway of care that tafasitamab + R^2 would displace if recommended for use. The introduction of tafasitamab + R^2 would primarily displace current use of lenalidomide with rituximab (R^2), which is considered the current standard of care for R/R FL in the

second-line (2L) or third-line and beyond (3L+) setting. Tafasitamab + R^2 may also displace some use of rituximab with chemotherapy (R-chemotherapy) ± rituximab maintenance in the 2L setting.

Further details are provided in the decision problem summary presented 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 relapsed or refractory follicular lymphoma after 1 or more systemic treatments	Adults with relapsed or refractory follicular lymphoma after 1 or more systemic treatments	No difference
Intervention	Tafasitamab in combination with lenalidomide and rituximab	Tafasitamab in combination with lenalidomide and rituximab	No difference
Comparator(s)	Established clinical management without tafasitamab: Treatment choice will depend on previous treatments, and how effective those treatments were. • Obinutuzumab with bendamustine followed by obinutuzumab maintenance • Lenalidomide with rituximab • Rituximab alone or in combination with chemotherapy • Epcoritamab (subject to NICE evaluation)	Established clinical management without tafasitamab: Treatment choice will depend on previous treatments, and how effective those treatments were. Second-line treatment choices include: • Lenalidomide with rituximab • Rituximab with chemotherapy ± rituximab maintenance Third-line and beyond treatment choices include: • Lenalidomide with rituximab	The decision problem focuses on those treatments tafasitamab would displace. Full details on the current pathway of care and positioning of tafasitamab are provided in Section 1.3.4. Other 'comparator' treatments listed in the final scope issued by NICE would not be displaced with the introduction of tafasitamab + R^2; however, in acknowledgement of their inclusion in scope, the submission appendices provide comparative analyses to additional treatments as follows: Second-line treatment: • Obinutuzumab with bendamustine (O-B) followed by obinutuzumab maintenance O-B followed by obinutuzumab maintenance is restricted to FL that did not respond to or progressed up to 6 months after treatment with rituximab or a rituximab-containing regimen. < 5% of patients are treated with this

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			regimen in clinical practice.[1, 2] Market share data show 0% use of obinutuzumab in the R/R FL setting year to date.[3] Third-line treatment and beyond: • Epcoritamab monotherapy Epcoritamab monotherapy is the subject of an ongoing NICE evaluation. Draft guidance is that epcoritamab should not be used to treat R/R FL in adults after 2 or more lines of treatment.[4] Furthermore, the company are positioning epcoritamab at a later-line of treatment (fourth-line or beyond). The one treatment listed in the NICE scope that is not addressed in the submission or appendices is rituximab monotherapy. Rituximab monotherapy is only used to treat people with stage IIA disease who are asymptomatic (first-line), as maintenance following R-chemotherapy, or potentially as a palliative care alternative so will not be displaced by tafasitamab + R^2. Previous technology appraisal of R^2 concluded that rituximab monotherapy is not a relevant comparator in the R/R FL setting.[5] However, if NICE now

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			believes it is relevant for decision making, comparison to R^2 can act as a conservative proxy as this treatment has proven to be clinically superior to rituximab monotherapy[6] and is more expensive.
Outcomes	The outcome measures to be considered include: • Progression-free survival • Overall survival • Response rates, including time to next treatment and duration of response • Adverse effects of treatment • Health-related quality of life.	The outcome measures to be considered include: • Progression-free survival • Overall survival • Response rates, including time to next treatment and duration of response • Adverse effects of treatment • Health-related quality of life	No difference
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • Type of lymphoma (follicular lymphoma, follicular lymphoma with FDG-avid foci) • Grade of lymphoma • Number of previous treatments	The subgroup to be considered is: • Number of previous treatments	Only the number of previous treatments would potentially have a direct impact on treatment decision-making in clinical practice.
Key: FDG, fluorodeoxyglucose; FL, follicular lymphoma; NICE, National Institute for Health and Care Excellence; O-B, obinutuzumab with bendamustine; R/R, relapsed or refractory; R^2, rituximab + lenalidomide.			

1.2 Description of the technology being evaluated

A description of tafasitamab (MINJUVI®) is presented in Table 2.

The draft Summary of Product Characteristics (SmPC) and the European Public Assessment Report (EPAR) for the R/R FL indication is provided in Appendix A.

Tafasitamab + R^2 is the first and only regimen to offer dual targeting of CD19 and CD20 for the treatment of R/R FL (Table 2).

Anti-CD20 treatments have long been the established standard of care for FL, with high levels of CD20 expression on malignant B-cells making CD20 a good therapeutic target.[7] Rituximab was the first anti-CD20 treatment approved for the treatment of B-cell malignancies in the 1990s and it remains a backbone treatment in the FL clinical pathway of care today (see Section 1.3.4).[7, 8] CD19 has also emerged as a validated and compelling therapeutic target for FL in more recent years, with CD19 shown to be broadly and homogeneously expressed throughout the B-cell differentiation process and thus also highly expressed on malignant B-cells.[8] Tafasitamab offers the opportunity to introduce an anti-CD19 treatment to the FL clinical pathway of care (in the relapsed, refractory setting – see Section 1.3.4).

CD19 serves as a supplementary and complementary target to CD20.[8] Through binding to these antigens, anti-CD19 and anti-CD20 treatments enhance the immune system, triggering antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP), as well as inducing direct cytotoxicity to ultimately cause tumour cell death.[9, 10] Combining tafasitamab (anti-CD19) and rituximab (anti-CD20) was therefore hypothesised to increase tumour cell death compared with their use as monotherapies, and this was subsequently demonstrated in in-vitro and in-vivo models of B-cell lymphomas.[8, 10, 11]

Lenalidomide is an immunomodulatory drug that can further boost the immune system to enhance ADCC and ADCP and induce direct cytotoxicity to cause tumour cell death.[12, 13] Lenalidomide was shown to produce synergistic effects when combined with rituximab in in-vitro and in-vivo models of B-cell lymphomas[12, 13], and has subsequently demonstrated such synergism in clinical studies of R/R FL[6],

resulting in its introduction to the FL clinical pathway of care (in the R/R setting) in 2020 (see Section 1.3.4).[14]

Tafasitamab + R^2 therefore not only provides the first and only regimen to offer dual targeting of CD19 and CD20 for the treatment of R/R FL but also incorporates the synergistic effect of antigen binding and immunomodulatory treatments. Tafasitamab + R^2 has demonstrated enhanced clinical benefit over the current standard of care, R^2, in the pivotal Phase III inMIND study, as evidenced in Section 2 of this submission.

Table 2: Technology being evaluated

UK approved name and brand name	Tafasitamab (MINJUVI®)
Mechanism of action	Tafasitamab is an Fc-enhanced monoclonal antibody that potently binds CD19 antigen expressed on the surface of pre-B and mature B lymphocytes.[8-10] CD19 is broadly and homogeneously expressed across B-cell malignancies, including DLBCL, and FL. On binding to CD19, tafasitamab mediates B-cell lysis through:[8, 9, 15, 16] • Engagement of immune effector cells such as natural killer (NK) cells, gamma-delta (γδ) T cells and phagocytes to help them fight tumour cells • Direct induction of tumour cell death (apoptosis) Tafasitamab is to be administered as an adjunct to R^2 The addition of tafasitamab to R^2 resulting in dual targeting of CD19 and CD20 is a rational approach to improve efficacy and outcomes in patients with lymphoma; the combination of tafasitamab and rituximab improved *in vitro* and *in vivo* efficacy compared with each monotherapy in models of aggressive B-cell lymphoma.[8]
Marketing authorisation	The CHMP adopted a positive opinion on 13 November[17] with EC approval expected by end [redacted]. Submission to the MHRA via the IRP pathway is planned by [redacted]. MHRA approval is anticipated in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The indication of interest to this submission is: *"MINJUVI is indicated in combination with lenalidomide and rituximab for the treatment of adult patients with relapsed or*

	refractory follicular lymphoma (FL) (Grade 1-3a) after at least one line of systemic therapy" Tafasitamab is also indicated in combination with lenalidomide followed by tafasitamab monotherapy for the treatment of adult patients with R/R DLBCL who are not eligible for ASCT. Tafasitamab must be administered by a healthcare professional experienced in the treatment of cancer patients. Premedication to reduce the risk of infusion-related reactions should be administered 30 minutes to 2 hours before tafasitamab infusion. For patients not experiencing IRR during the first three infusions, premedication is optional for subsequent infusions. The premedication may include antipyretics (e.g. paracetamol), histamine H1 receptor blockers (e.g. diphenhydramine), histamine H2 receptor blockers (e.g. cimetidine), or glucocorticosteroids (e.g. methylprednisolone).
Method of administration and dosage	The recommended dose of tafasitamab is 12 mg per kg body weight administered as an intravenous infusion according to the following schedule:[15] • Cycle 1–3: infusion on Day 1, 8, 15 and 22 of each cycle • Cycles 4–12: infusion on Day 1 and 15 of each cycle Each cycle has 28 days. The recommended starting dose of rituximab is 375 mg/m^2 administered as an intravenous infusion according to the following schedule: • Cycle 1: on Days 1, 8, 15, and 22 • Cycles 2–5: on Day 1 of each cycle Each cycle has 28 days. In addition, patients should self-administer lenalidomide capsules at the recommended starting dose of 20 mg daily on Days 1–21 of each 28-day cycle. The starting dose and subsequent dosing may be adjusted according to the lenalidomide SmPC. Tafasitamab in combination with lenalidomide plus rituximab is given for up to twelve cycles for tafasitamab and lenalidomide, and five cycles for rituximab. Treatment with rituximab should be stopped after five cycles of combination therapy. Patients should continue to receive tafasitamab infusions in combination with oral lenalidomide up to Cycle 12. Treatment with tafasitamab + lenalidomide should be stopped after a maximum of twelve cycles.
Additional tests or investigations	No additional tests or investigations are needed beyond those used to diagnose and treat R/R FL in current clinical practice.
List price and average cost of a course of treatment	• List price: £705.00 per 200mg vial • Tafasitamab average cost of treatment course: [redacted] (including RDI) and £108,195 (excluding RDI) • R^2 average cost of treatment course: [redacted] (including RDI) and £9,520 (excluding RDI)

Patient access scheme (if applicable)	[redacted] • PAS price: [redacted] • Tafasitamab average cost of treatment course: [redacted] (including RDI) and [redacted] (excluding RDI)
Key: CHMP, Committee for Medicinal Products for Human Use; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; H1 receptor blockers, histamine H1 receptor blockers; IRP, International Recognition Procedure; IRR, infusion-related reactions; MHRA, Medicines And Healthcare Products Regulatory Agency; NK cells, natural killer cells, RDI, relative dose intensity; R/R, relapsed or refractory; R^2, rituximab + lenalidomide; SmPC, Summary of Product Characteristics. **Source:** MINJUVI SmPC.[15]	

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

1.3.1 Disease overview

FL is the second most common type of NHL – a group of blood cancers that affects white blood cells called lymphocytes.[18] FL develops when the body makes abnormal B lymphocytes and thus is a type of B-cell lymphoma.[18] The abnormal lymphocytes build up in lymph nodes, forming clusters (follicles) that block and prevent the lymphatic system from working properly.[18, 19] In addition to lymph nodes, FL can also form in organs in the lymphatic system such as the thymus and spleen, and in organs outside of the lymphatic system such as the lungs, liver, bone marrow and kidneys.[18, 19] The exact cause of FL is unknown but it mainly affects older adults (median age at diagnosis: 66−68 years) of any gender (sex rate ratio of 1.0).[20-23]

FL is generally considered treatable but incurable and it is characterised by intermittent periods of remission and relapse. While FL is typically responsive to first-line (1L) treatment of anti-CD20 (rituximab or obinutuzumab) with chemotherapy (response rates ≥ 90%), almost all patients eventually relapse and require multiple lines of treatment to manage FL over their lifetime.[24-27] Patients newly diagnosed with FL have a 5-year net survival rate of around 85% and a 5-year overall survival (OS) rate of around 75%.[20, 22, 28] As the disease advances, prognosis worsens, and with each subsequent relapse or line of therapy life expectancy reduces (see Section 1.3.2).[21, 24-27, 29] Patients with R/R FL have a 5-year survival after relapse rate of 33−63% depending on the depth of response to 1L treatment.[30] The relapsing nature

of FL, combined with a lack of curative treatment options, places a significant burden on patients − both physically and emotionally − impacting health-related quality of life (HRQL) across multiple domains, including fatigue, anxiety and uncertainty about disease progression (see Section 1.3.3).

1.3.1.1 Patient numbers

Cancer registration statistics for England recorded 2,404 new cases of FL in 2022.[22] Based on a 10-year prevalence of 27.7 per 100,000 people, the Haematological Malignancy Research Network (HMRN) predicted 18,200 people in the UK would still be alive post-FL diagnosis in 2026.[20] The total number of people living with FL in England and Wales by the end of 2026 is therefore estimated to be around 20,000.

1.3.1.2 Stages, grading and risk stratification

FL is commonly staged from I (best prognosis) to IV (worst prognosis) depending on how many and which groups of lymph nodes are affected, and whether FL has spread to other organs.[18] Stage I/II FL is often referred to as ‘early stage’ or ‘limited stage’ disease with Stage III/IV FL referred to as ‘advanced stage’ disease.[18] Data from the HMRN show that most people with FL in England (up to 70%) have advanced stage disease.[21]

Lymphomas are also grouped by grade and can be low grade or indolent, meaning they grow and spread slowly with symptoms that develop gradually over time; or high grade, meaning they grow faster and more aggressively.[18, 31] FL is categorised as an indolent lymphoma and is further divided into numerical grades (Grade 1−3) with Grade 1, 2 and 3A used to describe low grade/slow growing FL and Grade 3B used to describe high grade/faster growing FL.[18]

Most patients (90−95%[32]) are diagnosed with Grade 1-3A FL denoting ‘slow growing’ disease but once people have experienced multiple relapses, FL is no longer considered slow growing.[4] In reality, the disease course is highly heterogeneous and some patients experience an aggressive disease trajectory (see Section 1.3.2). In addition to rapid relapse, this can also manifest in histological transformation of low grade FL to a more aggressive lymphoma type, such as diffuse large B-cell lymphoma (DLBCL) which has a much lower 5-year net survival rate of around

60%.[18, 33] The rate of histological transformation of FL to DLBCL is around 2−3% per year.[34]

Risk categorisation is also used to support diagnosis of FL to help predict disease course and guide treatment decisions at diagnosis. The most common risk categorisation tool used is the Follicular Lymphoma International Prognostic Index (FLIPI) that assigns a low, intermediate or high-risk categorisation based on the number of risk factors they present with. A detailed overview of staging, grading and risk categorisation tools used to support diagnosis of FL is provided in Appendix K.

1.3.2 Prognosis in relapsed or refractory disease

A published systematic literature review (SLR) designed to identify baseline prognostic factors in patients with R/R FL identified and ranked the following factors in descending order of importance in relation to the impact on prognosis (note, several of these are highly correlated)[35]:

- Progression of disease within 24 months (POD24) of initial treatment
- Disease refractory to immunochemotherapy/chemotherapy
- Disease refractory to last line of therapy
- Number of prior lines of therapy
- Serum lactate dehydrogenase (LDH)
- Eastern Cooperative Oncology Group (ECOG) performance status (PS)
- FLIPI score
- Age at start of line of therapy
- Disease stage
- Disease refractory to rituximab.

The influence of line of therapy, refractory disease and early relapse (POD24) on prognosis is discussed further below.

1.3.2.1 Line of therapy

Although FL is often considered a ‘slow growing’ disease, it remains an incurable malignancy. Most patients require multiple lines of therapy over their lifetime, which are associated with progressively poorer outcomes, as the disease becomes

increasingly resistant to treatment.[25, 26] Multiple real-world datasets demonstrate this worsening prognosis with reduced OS, progression-free survival (PFS) and time to next treatment (TTNT) with each line of therapy, as summarised in Table 3.

Variations in the absolute values reported across these datasets represent the heterogeneity of the FL disease course − there is no ‘average’ time of progression-free living or life expectancy per line of therapy. This warrants caution to be applied when making any ‘naïve’ comparisons across datasets, as further discussed in Section 2.10.

Table 3: Clinical outcomes per line of therapy in real-world datasets

		First-line	Second-line	Third-line	Fourth-line
HMRN dataset	Overall survival				
	Median, years (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
	Progression-free survival				
	Median, years (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
	Time to next line of treatment or death				
	Median, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
MSK study	Overall survival				
	Median, years (95% CI)	NR	11.7 (9.7, NR) N=457	8.8 (6.8, NR) N=299	5.3 (3.5, NR) N=198
	Progression-free survival				
	Median, years (95% CI)	4.7 (3.9, 5.7) N=922	1.5 (1.2, 1.9) N=457	1.1 (0.9, 1.4) N=299	0.9 (0.6, 1.1) N=198
	Event-free survival				
	Median, years (95% CI)	3.9 (3.4, 4.8) N=922	1.0 (0.9, 1.3) N=457	0.7 (0.6, 0.9) N=299	0.6 (0.5, 0.8) N=198
Lympho Care study	Progression-free survival				
	Median, years (95% CI)	6.6 (6.1, 7.2) N=2,429	1.5 (1.4, 1.7) N=889	0.8 (0.7, 1.1) N=438	0.7 (0.5, 1.0) N=172

IDIBAPS study	Overall survival				
	Median, years Decrease in life expectancy, %	NR 17% N=348	7.6 45% N=111	4.8 79% N=41	-
	Progression-free survival				
	Median, years (95% CI)	10.6 (8.0, 13.2) N=348	2.4 (1.2, 3.7) N=111	2.0 (1.4, 2.5) N=41	-

Key: CI, confidence interval; NE, not estimable; OS, overall survival; PFS, progression-free survival; TTNT, time to next treatment.
Source: MSK study − Batlevi et al, 2020[24]; HMRN report (data on file), 2025[21]; LymphoCare study − Link et al. 2019[36]; IDIBAPS study − Rivas-Delgado et al 2019.[27]

1.3.2.2 Primary refractory disease

Prognosis is particularly poor for patients with primary refractory disease (defined as no response or limited response [lasting < 6 months] to first-line treatment) who have an increased risk of histological transformation to a more aggressive lymphoma and face significantly reduced survival expectations. The 5-year survival rate after relapse is approximately halved in patients with primary refractory disease versus those with complete response (CR) to first-line treatment (33% vs 63%).[30]

1.3.2.3 Early relapse (POD24)

Approximately 20% of patients experience POD24 of initial treatment (sometimes measured from diagnosis).[37-41] These patients have a similarly poor prognosis and face significantly reduced survival expectations, with 5-year OS rates more than halved in patients with POD24 disease (26−50% vs 86−94% for patients without POD24 disease).[38, 42, 43]

Data from the HMRN in England report a median life expectancy of [redacted] years for patients with POD24 of initial treatment versus [redacted] years for patients without POD24 of initial treatment.[21] For R/R FL patients with POD24 of initial treatment, the median survival from the start of 2L chemotherapy was [redacted] years and the median survival from the start of 3L chemotherapy was [redacted] years. In comparison, for R/R FL patients

without POD24 of initial treatment, the median survival from the start of 2L chemotherapy was [redacted] years and the median survival from the start of 3L chemotherapy was [redacted] years

Factors that determine early relapse are not fully defined but generally patients who experience POD24 present with more adverse risk profiles at diagnosis compared with non-POD24 patients, including elevated LDH, higher FLIPI scores, more advanced disease stage, higher-grade disease (Grade 3A) and older age.[44] As noted, several of these factors are also independently prognostic.[35]

1.3.3 Burden of disease

1.3.3.1 Clinical burden

Advanced FL imposes a significant clinical burden on patients due to a wide spectrum of symptoms.[45] Fatigue is among the most prevalent and debilitating, often severely diminishing quality of life (QoL).[45] It can hinder essential daily activities such as bathing, using the stairs or preparing meals, while also contributing to a cascade of social and psychological consequences – including reduced capacity to work or care for others; increased irritability, anxiety and depression; and social withdrawal. In older adults, who represent a large proportion of FL patients, fatigue may compound existing age-related challenges such as frailty and isolation.[45] Beyond fatigue, systemic 'B symptoms' associated with all B-cell lymphomas, including night sweats, unexplained fevers and weight loss, are common.[45] FL can also infiltrate bone marrow, leading to anaemia, thrombocytopenia and neutropenia, which worsen symptoms such as fatigue and increase the risks of infection, bruising and bleeding.[45] Disease involvement across various organs may further provoke site-specific symptoms, such as pleural effusions in the lungs causing breathlessness, or gastrointestinal involvement triggering pain, digestive issues or anorexia.[45]

1.3.3.2 Quality of life burden

Despite being classed as 'slow growing', people living with FL report significantly worse QoL and symptom scores than patients with other types of NHL.[46] People often feel isolated by the low grade categorisation of FL and believe it misrepresents the huge emotional burden of having an incurable cancer.[4] This is exacerbated for

people with R/R FL with each relapse and failed treatment making the disease increasingly difficult to live with (see Appendix K) .[46, 47] One of the principal psychological burdens of FL is uncertainty. Those with advanced FL live with a life-threatening condition that may never really go away; the resulting uncertainty can be a constant source of anxiety, and depression is a common problem for people with FL with loss of hope in the future making it difficult for people to enjoy life.[45] Interventions that can extend the period of progression-free living can, therefore, improve QoL.

Patient experts at a recent committee meeting noted how they are constantly living in fear of the cancer returning or transforming into a more aggressive form. This is exacerbated as they run out of treatment options with the disease described as “slow torture because they know treatments will stop working”.[4] The patient experts also talked to the significant impact on carers relating to anxiety, a feeling of helplessness and daily support needs of their loved ones. After hearing their first-hand experiences, the committee concluded that this condition substantially impacts both the people living with FL and their families and carers.[4]

1.3.3.3 Economic burden

The cost of managing FL represents a significant burden to the National Health Service (NHS).[48] This is exacerbated for patients with R/R FL, with each relapse and failed treatment increasing the cost of disease management and placing greater strain on healthcare systems.[49-53] Interventions that delay progression and extend the period between treatment lines can save costs to the NHS.

In a UK-based economic evaluation, patients with FL who were enrolled in the HMRN between 2004 and 2011 and followed through to 2015 demonstrated the considerable economic burden of the disease.[48] The estimated average lifetime cost per patient with FL ranged from £6,165 to £63,864, with cost increasing substantially between 1L and 2L therapy. The total projected cost to the UK healthcare system was between £60 million and £65 million, accounting for approximately 10% of the NHS expenditure on haematological cancers at the time of reporting.

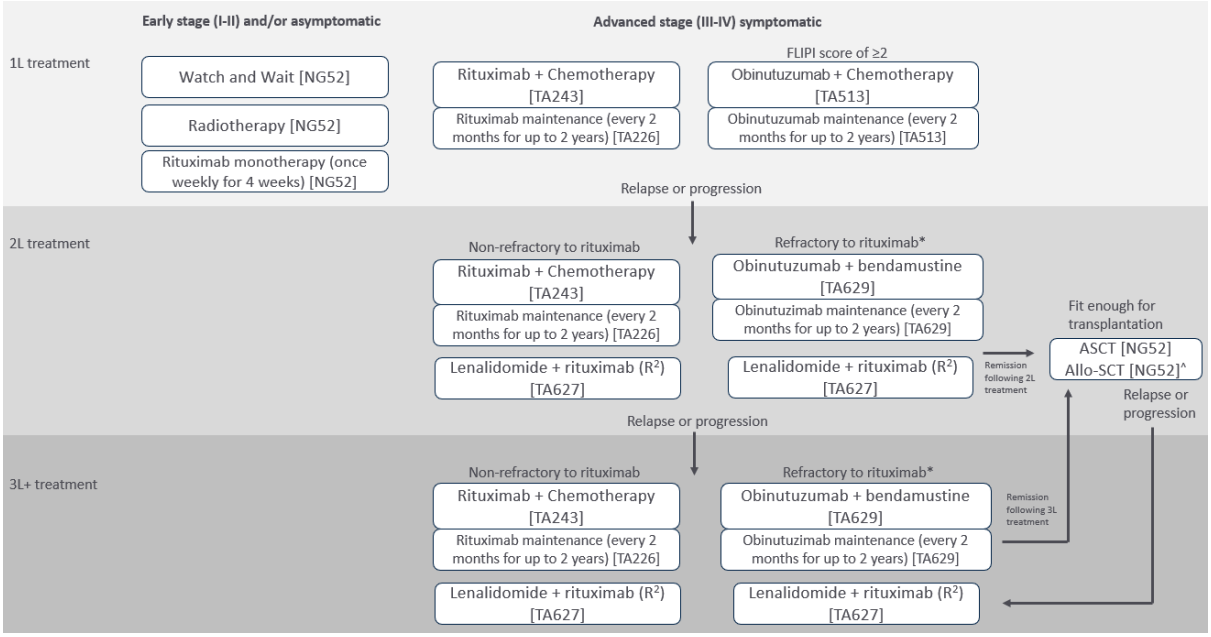
This trend in increasing costs with later lines of treatment is also demonstrated in real-world cost analyses of patients treated in mainland Europe and North America.[49-53] One US study using Medicare and Medicaid fee-for-service data (2011−2020) also reported an increase in healthcare resource use and costs for patients with POD24 or double refractory disease (in which the lymphoma is resistant to an anti-CD20 and an alkylating chemotherapy agent).[49] Additional costs are also associated with histological transformation of FL to DLBCL, as demonstrated in a previous economic model of FL using UK HMRN data.[48] This is due to the more aggressive nature of DLBCL and a need for more intensive and costly care programmes.

1.3.4 Clinical pathway of care

There is no single standard of care or recommended sequence of treatments within the clinical pathway of care for FL – treatment lines are not strictly defined and varied based on previously used treatments.[4]

Treatment options available to patients in England and Wales, in terms of those recommended by the National Institute for Health and Care Excellence (NICE), are depicted in Figure 1.

Figure 1: Treatment options available to FL patients in England and Wales, as recommended by NICE



Key: 1L, first-line; 2L, second-line; 3L, third-line; allo-SCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; FL, follicular lymphoma.
Notes: * FL that did not respond to or progressed up to 6 months after treatment with rituximab or a rituximab-containing regimen.
Source: Adapted from NICE Guidelines and Guidance.[14, 54-58]

In real-world practice, treatment decisions are dependent on multiple disease-specific and patient-specific factors, including disease stage, symptom and tumour burden, patient fitness (age, comorbidities), and in the case of R/R FL, treatment history (type of previous treatment and response to previous treatment).[1, 59] Since R/R FL is incurable, the goal of treatment is to provide the longest disease-free period between treatment lines and preserve patient QoL.[60]

There is no single patient journey through the clinical pathway of care in England and Wales, but the following general treatment approach is adopted based on consultation with eight clinical experts practicing across the UK[1]:

- First-line (1L) treatment:
  - Rituximab monotherapy or 'watch and wait' for patients with asymptomatic FL
  - Anti-CD20 (rituximab or obinutuzumab) with chemotherapy ± anti-CD20 maintenance for patients with symptomatic FL
- Second-line (2L) treatment:
  - Rituximab with chemotherapy (R-chemotherapy) ± rituximab maintenance for patients whose FL responded well to 1L treatment
  - Lenalidomide with rituximab (R^2) for patients whose FL did not respond well to 1L treatment
- Third-line and beyond (3L+) treatment:
  - Lenalidomide with rituximab (R^2) for patients who did not receive R^2 as 2L treatment
  - R-chemotherapy ± rituximab maintenance for patients who received R^2 as 2L treatment (in the absence of any other treatment option)
  - Clinical trial or palliative radiotherapy for patients who have exhausted R^2 and R-chemotherapy options

Although NICE also recommends obinutuzumab with bendamustine (O-B) followed by obinutuzumab maintenance in the 2L+ setting, this is restricted to FL that did not respond to or progressed within 6 months of treatment with rituximab or a rituximab-containing regimen.[58] Fewer than 5% of patients are treated with this regimen in clinical practice according to clinical experts[1, 2] and market share data show 0% use of obinutuzumab in the R/R FL setting year to date (2025).[3]

R^2 is the only treatment option with a different mechanism of action to 1L therapy and, therefore, is considered the current standard of care for R/R FL. It may be reserved for later-line (3L+) use for patients whose FL responded well to 1L treatment, but is also used in the 2L setting for patients whose FL did not respond well to 1L treatment. Market share data support UK clinical expert estimates that 30−40% of patients with R/R FL receiving 2L treatment are treated with R^2 and 60−70% are treated with R-chemotherapy.[1, 3] The most common R-chemotherapy regimens used are:

- R-B – rituximab with bendamustine
- R-CHOP – rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone
- R-CVP – rituximab with cyclophosphamide, vincristine and prednisolone.

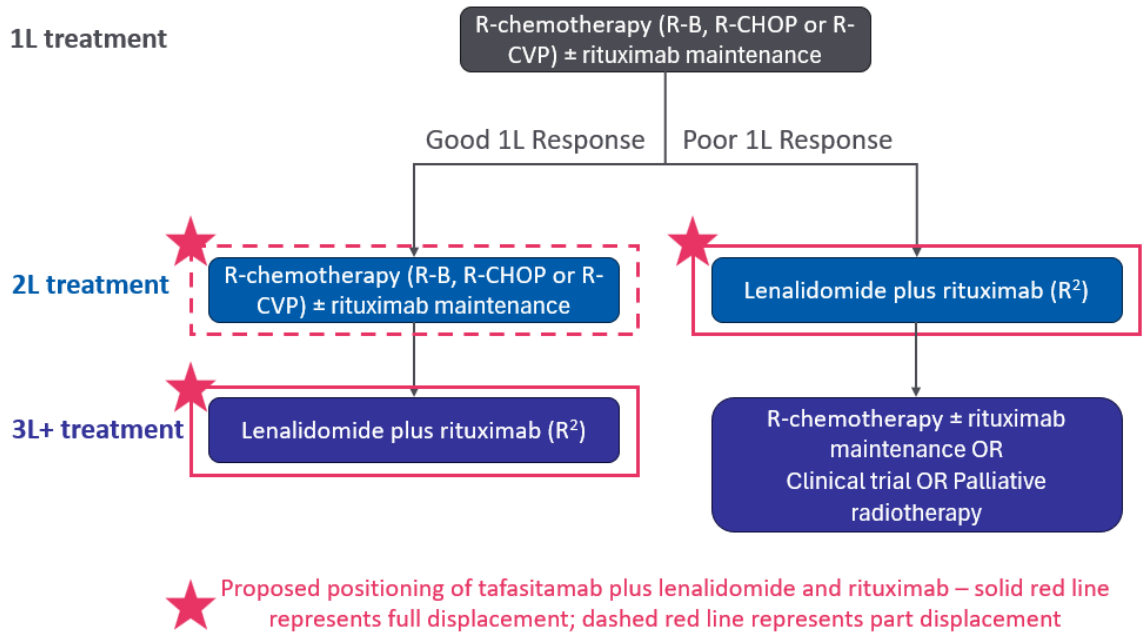
R-maintenance following R-chemotherapy induction is shown to extend response to 1L treatment[61, 62], but its use in clinical practice is varied at the 2L and 3L+ setting. During the COVID-19 era there was an intentional reduction in the use of rituximab as prolonged B-cell depletion resulting from rituximab treatment increases immunosuppression and increases the risk of infections and complications.[1, 60] Consultation with clinical experts suggests up to 30% of patients with R/R FL receive rituximab maintenance treatment in current practice.[1, 2]

All patients who received R-chemotherapy in the 2L setting and require further treatment will receive R^2 (unless contraindicated). Patients who received R^2 in the 2L setting have no treatment options remaining when their disease inevitably progresses. Clinicians may resort to revisiting R-chemotherapy treatment in these patients but only because there are no other options available; R-chemotherapy is not a recommended regimen in the 3L+ setting in clinical guidelines.[59] Alternatively,

clinicians may look for a clinical trial option or treat with palliative radiotherapy. Market share data support clinical expert estimates that 60% of R/R FL patients receiving 3L+ treatment are treated with R^2 and up to 30% are treated with R-chemotherapy in the absence of a better option.[1, 3]

Tafasitamab + R^2 offers a new treatment option to patients with R/R FL and its proposed use is in the 2L+ treatment setting, as depicted in Figure 2. This proposed positioning aligns to European Society for Medical Oncology (ESMO) guidelines in which tafasitamab + R^2 is recommended as a 2L+ treatment option.[59] The introduction of tafasitamab + R^2 would primarily displace current use of R^2 in the clinical pathway of care. However, given the magnitude of improved clinical benefit that can be achieved with tafasitamab + R^2 (see Section 2), it may also displace some use of R-chemotherapy in the 2L setting with the hope that earlier use of a more effective treatment option may prevent or delay the need for subsequent lines of therapy. If a patient does reach the 3L+ treatment setting and R-chemotherapy is being considered, they have either already received R^2 in an earlier line setting or are not suitable for lenalidomide treatment. The same scenario would arise if tafasitamab + R^2 was introduced and therefore tafasitamab + R^2 will not displace any current use of R-chemotherapy in the 3L+ treatment setting. Relevant comparators for tafasitamab + R^2 decision-making are therefore R^2 and R-chemotherapy in the 2L treatment setting and R^2 in the 3L+ treatment setting (Figure 2).

Figure 2: Typical pathway of care for FL patients in England and Wales and proposed positioning for tafasitamab+R²



Key: 1L, first-line; 2L, second-line; 3L, third-line; FL, follicular lymphoma; R², lenalidomide plus rituximab; R-B, rituximab with bendamustine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone.
Source: UK advisory board and clinical validation meetings.[1, 2]

1.3.5 Unmet need

Although FL is often considered a 'slow growing' disease, it remains an incurable malignancy, and patients are never discharged from their treating physicians. The disease course is highly heterogeneous and varying in disease trajectory but almost all patients will experience disease relapse, necessitating multiple lines of therapy. [24, 25] Each subsequent line of therapy is associated with progressively poorer treatment outcomes and premature mortality, with OS, PFS and TTNT times shortening with each line of treatment.[21, 24-27] This results from the disease becoming increasingly resistant to treatment over time, with current 2L and 3L+ treatment options largely replicating 1L treatment options built around the anti-CD20 backbone.[24-27, 29]

Despite their disease being classed as 'slow growing', people living with FL have poorer QoL than patients living with other types of NHL and carry a huge emotional burden of disease.[4, 46] With each subsequent recurrence, FL becomes increasingly

difficult to live with and was recently described as “slow torture” in recognition of the knowledge that treatments will at some point stop working.[4, 45-47] The negative impact of FL on patient QoL can be further exacerbated by adverse effects of treatment and the administration burden of treatment. In NICE technology appraisals in FL over the last 5 years, patient experts have consistently highlighted the unpleasant side effects of chemotherapy and cumulative toxicity, and welcomed any treatment that avoided chemotherapy.[4, 5, 14] Patients may also receive up to 2 years of maintenance treatment following 4−6 months of induction R-chemotherapy treatment, which interrupts their daily schedule and provides a constant reminder of disease, further highlighting the need for more accessible treatments.[4]

There is an urgent need for new treatment options in R/R FL that can elicit durable responses and extend the period of progression-free living between treatment lines, potentially reducing the total number of treatments patients will need to manage FL over their lifetime. The combination of tafasitamab + R^2 addresses this urgent need – offering a novel, chemotherapy-free regimen with a dual targeted anti-CD19 and anti-CD20 mechanism of action.[8, 63] As presented in Section 2, the InMIND Phase III randomised controlled trial (RCT) provides compelling evidence of statistically significant and clinically meaningful improvements in treatment response and PFS outcomes, and early signals of an OS benefit with tafasitamab + R^2 versus current standard of care (R^2), with a medically manageable safety profile (see Section 2.11.6).

1.4 Equality considerations

No equality issues are foreseen.

2 Clinical effectiveness

- The inMIND trial provides high-quality, direct comparative RCT evidence for tafasitamab + R^2 against the current standard of care for people living with R/R FL (R^2)
- Tafasitamab + R^2 demonstrated statistically significant and clinically meaningful improvements in clinical outcomes versus R^2. The addition of tafasitamab to R^2 for a fixed duration of up to one year resulted in:
  - A 57% reduction in risk of progression, relapse or death and extension to the period of progression-free living of over 8 months
  - An absolute increase in complete metabolic response (CMR) rates of ~10% with patients being 1.5 times more likely to achieve a CMR
  - An absolute increase in overall response rate (ORR) of ~11% with patients being twice as likely to achieve a response, and an absolute increase in complete response (CR) of ~11%
  - A 53% reduction in risk of relapse and extension to the period of relapse-free living of over 7.5 months
  - A 55% reduction in the risk of needing a next line of treatment or death and an absolute reduction in the number of patients starting new anti-lymphoma treatment of ~15%.
- Tafasitamab + R^2 shows early signs of a positive benefit on overall survival with a post-futility testing estimate of a 41% reduction in the risk of death
- The addition of tafasitamab to R^2 provided these clinical benefits without negatively impacting on HRQL
- The efficacy of tafasitamab was consistent across prespecified subgroups, including those considered high risk, with poor prognosis
- The addition of tafasitamab does not present any new safety concerns to the established R^2 regimen and offers a favourable safety profile to chemotherapy
- Tafasitamab + R^2 has the potential to address the urgent need for a new treatment option in R/R FL that can provide durable responses to extend the period of progression-free living between treatment lines, reduce the total

number of FL treatments patients will need over their lifetime, and improve overall length and quality of life.

2.1 Identification and selection of relevant studies

The SLR described in Appendix B confirmed the inMIND RCT as the only relevant study of tafasitamab + R^2 to the address the decision problem.

2.2 List of relevant clinical effectiveness evidence

Table 4 summarises the clinical effectiveness evidence from the inMIND study supporting tafasitamab + R^2 for the treatment of adult patients with R/R FL after at least one line of systemic therapy.

Table 4: Clinical effectiveness evidence

Study (NCT)	inMIND (NCT04680052)				
Study design	inMIND is a Phase III double-blind, placebo-controlled, randomised study to compare the efficacy of tafasitamab + R^2 versus the efficacy of placebo + R^2				
Population	Adult patients with R/R FL Grade 1–3A or MZL histological subtypes who had received at least one prior line of systemic therapy. The FL cohort is the focus of this submission				
Intervention(s)	Tafasitamab + R^2				
Comparator(s)	Placebo + R^2				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓
	No			No	
Rationale for use/non-use in the model	inMIND presents the pivotal, regulatory, clinical evidence in support of tafasitamab + R^2 in R/R FL				
Reported outcomes specified in the decision problem	• **Overall survival** • **PFS** • Response rates • DoR • **Adverse effects of treatment** • **HRQL**				
All other reported outcomes	• TTNT • PFS on next treatment • Rate of HT				

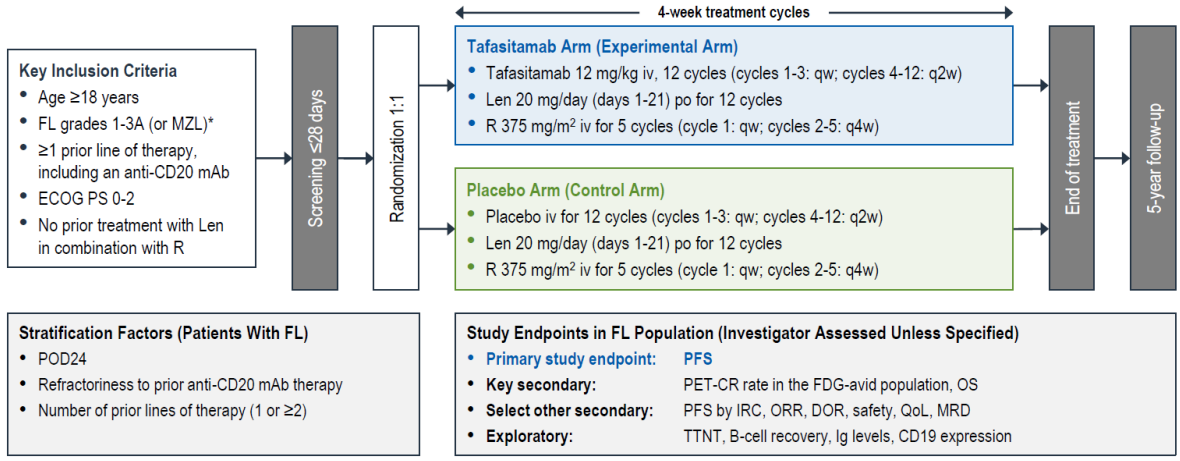
Key: DoR, duration of response; HRQL, health-related quality of life; HT, histological transformation; R/R FL, relapsed or refractory follicular lymphoma; MZL, marginal zone lymphoma; NCT, National Clinical Trial; PFS, progression-free survival; R^2, lenalidomide with rituximab; TTNT, time to next treatment.
Notes: Bolded outcomes are those used in the economic modelling.

2.3 Summary of methodology of the relevant clinical effectiveness evidence

Table 5 provides details of the trial methodology for inMIND. In summary, inMIND is a randomised, placebo-controlled, double-blind Phase III study designed to investigate whether tafasitamab in addition to R^2 provides improved clinical benefits compared with placebo + R^2 in patients with R/R FL of Grade 1–3a or R/R marginal zone lymphoma (MZL).[64] This submission focuses solely on patients with R/R FL after one or more systemic treatments, and the data from this patient group, in line with the marketing authorisation for tafasitamab + R^2 (Table 2).

A total of 654 patients were enrolled in the study and randomised, of which 548 had R/R FL and were included in the full analysis set (FAS) and 546 were included in the Safety Analysis Set (SAS).[64] Two patients randomised to the placebo + R^2 group were not included in the SAS because they did not receive study treatment due to confirmation of rituximab hypersensitivity, and withdrew from the study. Patients proceeded through the study with a fixed treatment schedule of up to 12 cycles with no maintenance, as depicted in Figure 3.

Figure 3: Study scheme for inMIND



Key: DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FDG, fluorodeoxyglucose; FL, follicular lymphoma; IRC, independent review committee; mAb, monoclonal antibody; Len, lenalidomide; MRD, minimal residual disease; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PET-CR, positron emission tomography-complete response; PFS, progression-free survival; po, orally; POD24, progression of disease within 24 months after initial diagnosis (per protocol); q2w, every 2 weeks; QoL, quality of life; qw, once weekly; R, rituximab; R/R, relapsed or refractory; TTNT, time to next treatment.
Notes: Randomisation applies separately for patients with R/R FL and those with R/R MZL.
Source: Sehn et al 2024.[65]

The primary endpoint of the inMIND trial was PFS by investigator (INV) assessment, using the Lugano 2014 criteria, in the FL population.[66] PFS is defined as the time from randomisation to first documented disease progression, or death from any cause, whichever occurs first.

Key secondary endpoints included positron emission tomography-complete response (PET-CR) rate by INV assessment in the fluorodeoxyglucose (FDG)-avid FL population; and OS in the FL population. The (FDG)-avid FL population refers to the tendency of certain types of cells, including cancer cells, to take up the radioactive sugar molecule FDG, which makes them visible on PET scans. Other secondary and exploratory endpoints included: PFS by independent review committee (IRC), minimal residual disease negativity rate, ORR and duration of response (DoR) by INV assessment and IRC, TTNT, histological transformation rates and time to transformation. HRQL was also measured based on the EORTC QLQ-C30, the EQ-5D-5L and FACT-Lym tools in the FL and overall populations. Safety data were analysed descriptively based on the incidence and severity of treatment-emergent adverse events (TEAE) in the FL and overall populations.

Table 5: Summary of inMIND trial methodology

Trial number (acronym)	**NCT04680052 (inMIND)**
Location	A total of 210 locations across Australia, Austria, Belgium, Canada, Czechia, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Japan, South Korea, Netherlands, Norway, Poland, Russia, Spain, Sweden, Switzerland, Taiwan, Turkey, Ukraine, the UK ([redacted] UK sites [also [redacted] in Ireland] and [redacted] patients enrolled in the UK [[redacted] in Ireland] and the US
Trial design	inMIND is a Phase III, randomised, double-blind, placebo-controlled, multicentre study to evaluate the efficacy and safety of tafasitamab + R^2 versus placebo + R^2 in patients with Grade 1–3a R/R FL or R/R MZL A total of 654 patients have been enrolled of which 548 present with R/R FL. Patients are randomised 1:1 to receive either tafasitamab or placebo in addition to R^2

Eligibility criteria	Key inclusion criteria: • Patients aged ≥ 18 years of age who have histologically confirmed Grade 1, 2 or 3a FL (or histologically confirmed nodal MZL, splenic MZL, or extranodal MZL) • Must have been previously treated with at least 1 prior systemic anti-CD20 immunotherapy or chemo-immunotherapy including rituximab monotherapy or chemotherapy plus immunotherapy with rituximab or obinutuzumab, with or without maintenance • Must have documented relapsed[a], refractory[b], or PD[c] after treatment with systemic therapy • Must have at least one measurable disease site defined as at least one nodal lesion > 1.5 cm in longest diameter or at least one extranodal lesion > 1.0 cm in longest diameter • ECOG performance status of 0 to 2 Key exclusion criteria: • Women who are pregnant or breastfeeding • Any histology other than FL and MZL or clinical evidence of transformed lymphoma • Prior non-hematologic malignancy • Congestive heart failure • HCV positivity, chronic HBV infection or history of HIV infection • Active systemic infection • CNS lymphoma involvement • Any systemic anti-lymphoma and/or investigational therapy within 28 days prior to the start of Cycle 1 • Prior use of lenalidomide in combination with rituximab
Settings and locations where data were collected	• Participant data are recorded electronically and each participant will have an eCRF • Participants received tafasitamab/placebo at clinical study sites and under the direct supervision of the clinical study site personnel • Routine laboratory assessments and CT/MRI assessments are conducted regularly throughout the study period • An IDMC monitor data to ensure the safety of the participants enrolled in this study, and evaluate the efficacy of the treatment. The committee have access to unblinded aggregated interim data to make recommendations, suggest clinical study protocol changes, or terminate the study
Intervention	Tafasitamab + R[2] (lenalidomide + rituximab) • Tafasitamab 12 mg/kg by intravenous infusion on days1, 8, 15, and 22 of cycles 1–3 and days 1 and 15 of cycles 4–12

	• Lenalidomide 20 mg/day orally on days 1–21 of cycles 1–12 • Rituximab 375 mg/m^2 by intravenous infusion on 176 days 1, 8, 15, and 22 of cycle 1 and day 1 of cycles 2–5
Comparator	Placebo + R^2 (lenalidomide + rituximab) • Placebo by intravenous infusion on days 1, 8, 15, and 22 of cycles 1–3 and days 1 and 15 of cycles 4–12 • Lenalidomide 20 mg/day orally on days 1–21 of cycles 1–12 • Rituximab 375 mg/m^2 by intravenous infusion on 176 days 1, 8, 15, and 22 of cycle 1 and day 1 of cycles 2–5
Concomitant medications	• Participants may receive concomitant medications that are medically indicated as standard of care for the treatment of symptoms and intercurrent illnesses such as diabetes, hypertension, bronchial asthma, or chronic obstructive pulmonary disease. Participants may also receive therapy to mitigate side effects of the study treatment as clinically indicated, as well as best supportive care as per institutional guidelines Tafasitamab or placebo infusions are to be administered to participants after premedication with oral acetaminophen, an antihistamine such as diphenhydramine hydrochloride, and glucocorticosteroids. The premedication was recommended to be administered approximately 30–60 minutes before starting each infusion[d] • Premedication was mandatory for the first cycle[d] • Prophylaxis of venous thromboembolism was mandatory for all participants due to increased risk of thrombosis in participants treated with lenalidomide without prophylaxis. Choice of prophylaxis is at the investigator's discretion • Participants can be given prophylactic agents for Hepatitis B reactivation and opportunistic infections or growth factors as per institutional guidelines • Precautions should be taken in specific medications administered concomitantly with lenalidomide including digoxin, erythropoietic agents, oestrogen-containing agents, and warfarin • Anticancer therapies including radiotherapy, concurrent antineoplastic therapies as well as live vaccines are not allowed during the trial period
Primary outcomes	PFS by INV assessment in the FL population, using the Lugano 2014 criteria. PFS is defined as the time from randomisation to first documented disease progression, or death from any cause, whichever occurs first
Key secondary outcomes	• PET-CR rate by INV in the FDG-avid FL population, defined as a complete metabolic response at any time after start of treatment • OS in the FL population

Other secondary endpoints	• PFS by IRC in the FL population • ORR by INV in the FL population • DoR by INV in the FL population • HRQL as measured by the EORTC QLQ-C30, the EQ-5D-5L, and FACT-Lym tools in the FL population • Safety based on the incidence and severity of TEAEs in the FL population
Exploratory endpoints	• TTNT by INV assessment in the FL population TTNT is defined as the time from randomisation to start of next anti-lymphoma therapy for any reason or death due to any cause • Rate of and time to histological transformation
Pre-planned subgroups	Efficacy outcome of PFS, PET-CR and OS were assessed based on baseline covariates including demographic characteristics, baseline NKCC, POD24 status, refractoriness to prior anti-CD20 mAb therapy and prior lines of therapy (1or ≥ 2)

Key: CNS, central nervous system; CR, complete response; CT, computed tomography; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; eCRF; electronic case report form; FDG, fluorodeoxyglucose; FL, follicular lymphoma; HBV, hepatitis B; HCV, hepatitis C; HIV, human immunodeficiency virus; HRQL, health-related quality of life; IDMC, Independent Data Monitoring Committee; INV, investigator; IRC, independent review committee; mAb, monoclonal antibody; MRI, magnetic resonance imaging; MZL, marginal zone lymphoma; NCT, National Clinical Trial; NKCC, Natural Killer Cell Count; ORR, overall response rate; PD, progressed disease; PET-CR, positron emission tomography-complete response; PFS, progression-free survival; PR, partial response; R^2, lenalidomide and rituximab; RR, relapsed or refractory; TEAE, treatment-emergent adverse event; TTNT, time to next treatment; SD, standard deviation.
Notes: [a] Relapsed after initial response of CR or PR ≥ 6 months after prior therapy; [b] Achieved less than PR to the last treatment or achieved a CR or PR that lasted less than 6 months; [c] PD after initial response of SD to prior therapy; [d] The premedication timings recommended in the final SmPC are 30 minutes to 2 hours prior to tafasitamab infusion. For patients not experiencing infusion-related reactions during the first 3 infusions, premedication is optional for subsequent infusions.
Source: Incyte Corporation, 2023;[67] Sehn et al, 2024;[65] Incyte Corporation, 2024.[64]

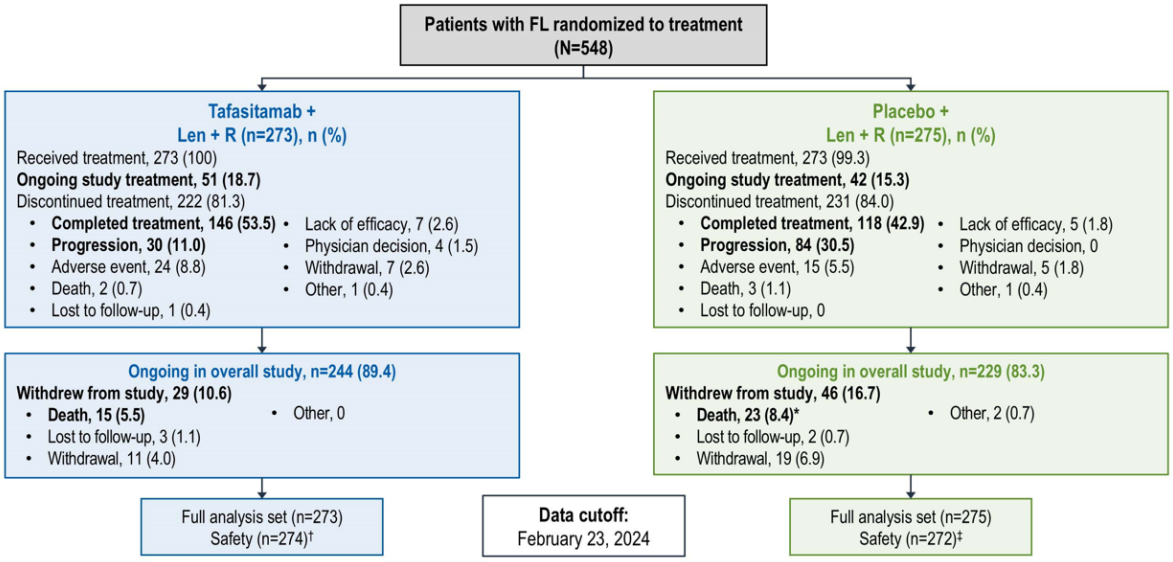
2.3.1 Patient disposition

The FAS included all 548 participants with R/R FL that were randomised, including 273 participants in the tafasitamab + R^2 group and 275 participants in the placebo + R^2 group (Figure 4).

As of the primary data cutoff date (23 February 2024), participants in the tafasitamab + R^2 and placebo + R^2 treatment arms had received a median of 12 and 11 cycles of therapy, respectively.[68] A higher proportion of participants completed the 12 cycles of study treatment in the tafasitamab + R^2 group: 53.5% compared with 42.9% in the placebo + R^2 group. Fifty-one participants (18.7%) in the tafasitamab + R^2 group and

42 participants (15.3%) in the placebo + R^2 group were receiving ongoing treatment; 222 participants (81.3%) and 231 participants (84.0%), respectively, had discontinued treatment, primarily due to therapy completion (54.0% and 43.0%, respectively).[68] A lower proportion of participants discontinued treatment due to progressed disease (PD) in the tafasitamab + R^2 group: 11.0% compared with 30.5% in the placebo + R^2 group.[68] A lower proportion of participants in the tafasitamab + R^2 group withdrew from the study − 10.6% versus 16.7% in the placebo + R^2 group. Reasons for withdrawal were similar across both treatment arms with death being the most common cause − occurring at a higher rate in the placebo + R^2 treatment arm (5.5% with tafasitamab + R^2 and 8.4% with placebo + R^2). [68]

Figure 4: Participant disposition (R/R FL FAS)



Key: FAS, full analysis set; FL, follicular lymphoma; R^2, rituximab with lenalidomide; R/R, relapsed or refractory.
Notes: [a] Two participants randomised to the placebo + R^2 group were not treated due to confirmation of rituximab hypersensitivity and withdrawal by participant. [b] Death for one patient was reported but not recorded in the end-of-study form. [c] One patient randomised to the placebo arm was included in the tafasitamab safety population because the patient erroneously received tafasitamab. [d] Three patients randomised to the placebo arm were not included in the safety population because they erroneously received tafasitamab (n = 1) or did not receive any treatment due to confirmation of R hypersensitivity (n = 1), or the patient withdrew from the study (n = 1).
Source: Trneny et al. 2025.[68]

2.3.2 Patient baseline characteristics

Table 6 provides a summary of baseline characteristics, including demographic and clinical characteristics, for patients with R/R FL included in the inMIND trial. Table 7 presents a summary of prior cancer therapy in the R/R FL population of inMIND. All patients in the inMIND trial documented at least one prior line of therapy including treatments such as rituximab monotherapy or chemotherapy plus immunotherapy with rituximab or obinutuzumab, with or without maintenance (as per inMIND eligibility criteria).

Clinical experts consulted by the Company have confirmed that the baseline characteristics of the R/R FL FAS represent patients presenting in UK practice and are generally consistent with those of patients anticipated to receive tafasitamab + R^2 in UK clinical practice.[1, 2] The median age was 64 years, with a slightly higher proportion of male participants (55%).[68] [redacted].[64]

The demographic and clinical characteristics of patients were generally well balanced across both treatment arms. A large proportion of patients presented with advanced disease based on the Ann Arbor staging (Stage III/IV).[68] More than 50.0% of the patients presented with high-FLIPI scores (that is FLIPI scores ≥ 3), and more than 80.0% of participants presented with high tumour burden based on the GELF criteria.[68]Approximately one-third of the participants documented POD24, more than half of the participants had relapsed, up to 41.0% of participants were refractory to prior therapy and approximately 45.0% of the participants had received at least two prior lines of systemic therapy.[68]

Table 6: Summary of demographic and baseline disease characteristics of R/R FL patients in inMIND (FAS)

Characteristics, n (%)	Tafasitamab + R^2 (n = 273)	Placebo + R^2 (n = 275)	Overall (N = 548)
Region			
North America	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]	[redacted]
Rest of the world	[redacted]	[redacted]	[redacted]

Characteristics, n (%)	Tafasitamab + R^2 (n = 273)	Placebo + R^2 (n = 275)	Overall (N = 548)
Median age, years (range)	64.0 (36-88)	64.0 (31-85)	64.0 (31-88)
≥ 75	54 (20.0)	54 (20.0)	108 (20.0)
Male sex	150 (55.0)	149 (55.0)	299 (55.0)
Ethnicity			
Hispanic or Latino	31 (11.0)	24 (9.0)	55 (10.0)
Not Hispanic or Latino	228 (84.0)	226 (82.0)	454 (83.0)
Not reported	11 (4.0)	23 (8.0)	34 (6.0)
Unknown	3 (1.0)	2 (1.0)	5 (1.0)
Body weight at screening visit (kg), median (range)	[redacted]	[redacted]	[redacted]
Median time since initial FL diagnosis, y (range)	5.2 (0-34)	5.5 (1-33)	5.3 (0-34)
ECOG PS at screening			
0	181 (66.0)	192 (70.0)	373 (68.0)
1	85 (31.0)	75 (27.0)	160 (29.0)
2	7 (3.0)	8 (3.0)	15 (3.0)
Bone marrow involvement			
Yes	88 (32.0)	91 (33.0)	179 (33.0)
No	169 (62.0)	162 (59.0)	331 (60.0)
Unknown	3 (1.0)	13 (5.0)	16 (3.0)
Missing	13 (5.0)	9 (3.0)	22 (4.0)
Ann Arbor stage			
I/II	52 (19.0)	50 (18.0)	102 (10.0)
III/IV	221 (81.0)	225 (82.0)	446 (81.0)
FL grade			
1 or 2	203 (74.0)	203 (74.0)	406 (74.0)
3A	67 (25.0)	71 (26.0)	138 (25.0)
B symptoms, present	63 (23.0)	67 (24.0)	130 (24.0)
FLIPI score			
Low, 0 or 1	57 (21.0)	57 (21.0)	114 (21.0)
Intermediate, 2	79 (29.0)	67 (24.0)	146 (27.0)
High, 3–5	137 (50.0)	150 (55.0)	287 (52.0)
GELF criteria (at least 1 fulfilled criterion)	222 (81.0)	232 (84.0)	454 (83.0)
POD24 of diagnosis[a]	85 (31.0)	88 (32.0)	173 (32.0)

Key: ECOG PS, Eastern Cooperative Oncology Group performance status; FAS, final analysis set; FL, follicular lymphoma, FLIPI, Follicular Lymphoma International Prognostic Index; GELF, Groupe d'Etude des Lymphomes Folliculaires; POD24, progression of disease within 24 months; R^2, lenalidomide and rituximab; R/R, relapsed or refractory.
Notes: [a] Taken from electronic case report form data used for stratification.
Source: Trneny et al. 2025[68]; Incyte Corporation, 2024.[64]

Table 7: Summary of prior cancer therapy of R/R FL patients in inMIND (FAS)

Characteristics, n (%)	Tafasitamab + R^2 (n = 273)	Placebo + R^2 (n = 275)	Overall (n = 548)
Time since last anti-lymphoma therapy and randomisation date, n (%)			
≤ 2 years	147 (54.0)	157 (57.0)	304 (56.0)
> 2 years	126 (46.0)	118 (43.0)	244 (45.0)
Median number of prior lines of therapy (range)	1.0 (1, 7)	1.0 (1, 10)	1.0 (1, 10)
Number of prior lines of therapy, n (%)			
1	147 (54.0)	153 (56.0)	300 (55.0)
2	66 (24.0)	71 (26.0)	137 (25.0)
3	39 (14.0)	30 (11.0)	69 (13.0)
≥ 4	21 (8.0)	21 (8.0)	42 (8.0)
R/R status to last therapy[a] n (%)			
Relapsed	148 (54.0)	164 (60.0)	312 (57.0)
Refractory	112 (41.0)	97 (35.0)	209 (38.0)
Indeterminate[b]	13 (5.0)	14 (5.0)	27 (5.0)
Number of anti-CD20-containing prior therapy lines, n (%)			
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
≥ 4	[redacted]	[redacted]	[redacted]
Refractory to prior anti-CD20 therapy, n (%)	118 (43.2)	115 (41.8)	233 (42.5)

Key: CR, complete response; FAS, final analysis set; FL, follicular lymphoma, PD, progressed disease; PR, partial response; R/R, relapsed or refractory; SD, standard deviation.
Notes: [a] Relapsed lymphoma defined as relapsed after initial response of CR or PR ≥ 6 months after prior therapy. Refractory lymphoma defined as achieved less than PR to the last treatment or achieved a CR or PR that lasted < 6 months. [b] Indeterminate includes participants whose best overall response to prior line of therapy was not evaluated or unknown, and the date of prior progression of disease could not be derived.
Source: Trneny et al. 2025[68]; Incyte Corporation, 2024.[64]

2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Table 8 provides a summary of the statistical analysis and definitions of analysis sets in inMIND.

A total of 654 patients were enrolled in the study, of which 548 had R/R FL.[64, 68] All of these patients were randomised and comprised the FAS which was used to investigate the hypothesis that tafasitamab + R^2 will improve PFS versus placebo + R^2. Randomisation was stratified using an interactive response technology for the following factors[68]:

- POD24 (yes vs no; disease progression within 24 months of initial diagnosis)
- Refractoriness to prior anti-CD20 therapy (yes vs no; refractory defined as not achieving a response or progressing/relapsing during treatment or within 6 months after the last dose of anti-CD20 therapy)
- The number of prior lines of therapy (1 vs ≥ 2)

The primary endpoint and three key secondary endpoints of inMIND are tested by inferential statistics, with the primary endpoint serving as a gatekeeper for study-wise Type I error.[64] The safety population includes 546 participants with R/R FL. Statistical or descriptive analyses were to be conducted at three key points throughout the study[64]:

- The primary analysis was performed after approximately 174 INV-assessed PFS events (including a 5.0% margin to account for loss of events due to censoring of new anti-lymphoma treatment) in the FL FAS to detect a hazard ratio (HR) of 0.65 with 80% power. At the time of the primary PFS analysis, an analysis for futility was also performed for OS using a nonbinding rule with a predefined futility threshold of HR > 1.24
- An interim analysis was performed after 20% of the required PFS events (approximately 35 events) were observed in participants with FL within the FAS population. This interim analysis provided early insights into the study's progress. An independent data monitoring committee was convened after the first 60 patients had completed two cycles of study treatment, and periodically thereafter, to monitor data

and evaluate safety and efficacy based on a preplanned interim futility analysis at an approximate 20.0% information rate

- The final analysis will be conducted at the end of the study, which will occur after the last participant has completed a minimum of 5 years of post-treatment follow-up. This comprehensive analysis will incorporate all available data to draw final conclusions about the study's outcomes

This submission presents data from the primary analysis. Data cutoff was 23 February 2024 and as of this date 206 PFS events and 38 OS events were observed and the median follow-up was 14.1 months for PFS and 15.3 months for OS (in the tafasitamab + R^2 treatment arm).[64]

Table 8: Summary of statistical analyses for inMIND

Hypothesis objective	• H1: Tafasitamab in combination with lenalidomide and rituximab will improve PFS compared with lenalidomide and rituximab alone in participants with R/R FL • The primary endpoint (PFS in the FL population) and the three key secondary endpoints (PFS in the overall population, PET-CR rate in the FL population, and OS in the FL population) will be tested with inferential statistics to control the study-wise Type I error due to the multiple testing of the primary and key secondary endpoints • The primary endpoint analysis of PFS by INV in the FL population will serve as a gatekeeper. If the null hypothesis (of no improvement in PFS with tafasitamab in combination with lenalidomide and rituximab compared with lenalidomide and rituximab) is rejected, the key secondary endpoints can be tested in the following fixed order: 1. PFS by INV in the overall population (FL and MZL) 2. PET-CR rate by INV in FL population 3. OS in FL population • If the null hypothesis is not rejected, the formal sequential testing will be stopped, and the p-values for the remaining key secondary endpoints will be reported for exploratory and illustrative purposes.
Statistical analysis	• The median PFS and OS with 95% CIs were estimated using the Kaplan–Meier method and compared between treatment groups using a stratified log-rank test, with estimation of an HR with 95% CIs using a stratified Cox proportional hazard model • In addition, investigator-assessed PFS event rates at 6, 12, 18, 24, 36, and 48 months will be provided along with the corresponding 2-sided 95% CIs for the estimates • The PET-CR rates, with 95% CIs calculated using the Clopper-Pearson method, were compared between the treatment groups

	using a stratified Cochran-Mantel-Haenszel test, with estimation of an OR with 95% CIs • Hierarchical testing will be implemented for the key secondary endpoints, with the primary endpoint PFS serving as a gatekeeper and will maintain the study-wise Type I error • For the QoL measures, descriptive statistics will be implemented to interpret findings from the EORTC QLQ-C30, ED-5D-5L and FACT-Lym scales • Safety analyses will be conducted for the SAF. No formal statistical testing will be performed. Summary tables may be replaced with listings when appropriate
Key analysis sets	**FAS**: All randomised participants. Treatment groups for this population will be determined according to the treatment they were assigned at the time of randomisation. The FAS will be used for the summary of demographics, baseline characteristics, participant disposition, and analyses of all efficacy data. **Per-Protocol Set**: The subset of the participants in the FAS who are compliant with the requirements of the clinical study protocol with no important protocol deviations. All important protocol deviations or conditions leading to exclusion from the per-protocol set will be detailed in the protocol deviation specifications and identified prior to database lock for the primary analysis. Sensitivity analyses of the primary endpoint may be performed using the per-protocol set. **SAS**: All randomised participants who received at least one dose of tafasitamab/placebo, lenalidomide or rituximab. Treatment groups for this population will be determined according to the actual treatment the participant received regardless of assigned treatment at the time of randomisation. All safety analyses will be conducted using the SAS. **FDG-avid population**: All randomised participants with a PET scan at baseline with a resulting Deauville score of 4 or 5.
Sample size, power calculation	A total number of 174 PFS events in the FL population are required to detect an HR of 0.65 with 80% power at the primary analysis, using a 2-sided, log-rank test at an alpha level of 5% and a 1:1 randomisation ratio between the two treatment groups. Assuming a median PFS of 27.8 months for placebo + R^2, 21 months of enrolment, 12 months of follow-up for PFS, and 15% of dropouts, 528 evaluable FL participants need to be randomised. Overall, 548 participants with R/R FL were included in the FAS, satisfying this requirement
Data management, patient withdrawals	• Data management will be performed in a validated EDC system • Standard censoring methods were applied to TTE analyses for those patients without an event at the time of analysis

Key: CI, confidence interval; EDC, electronic data capture; FAS, final analysis set; FDG, fluorodeoxyglucose; FL, follicular lymphoma; HR, hazard ratio; INV, investigator; MRD, minimal residual disease; MZL, marginal zone lymphoma; NKCC, natural killer cell count; OR, odds ratio; OS, overall survival; PET-CR, positron emission tomography-complete response; PFS, progression-free survival; POD24, progression of disease within 24 months;; QoL, quality of life; RR, relapsed or refractory; SAS, safety analysis set; TTE, time to event.
Source: Trneny et al., 2025[68]; Incyte Corporation, 2024.[64]

2.5 Critical appraisal of the relevant clinical effectiveness evidence

Critical appraisal of inMIND was conducted using the Cochrane Risk of Bias (RoB) checklist, full details of which are provided in Appendix B.

The overall risk of bias is low with inMIND providing high-quality RCT evidence of direct relevance to the decision problem and true double blinding of participants and investigators through placebo administration replicating the infusion requirements of tafasitamab. The population, intervention and comparator investigated in inMIND are directly applicable to how tafasitamab + R^2 is intended to be used in clinical practice, and outcomes are directly reflective of the anticipated outcomes with real world use of tafasitamab + R^2. The slowly progressing nature of FL can make it challenging to demonstrate OS benefits within the timeframe of clinical trials and the incurable nature of FL means the goal of treatment is to provide the longest disease-free period between treatment lines and preserve patient QoL.[60] This highlights the importance of the endpoints of PFS and TTNT to evaluate the clinical impact of R/R FL treatments, which the inMIND trial provides.

There are some minor differences in premedication use in the inMIND trial versus the SmPC recommendations with regard to timings and ongoing use but this has no impact on the applicability of outcomes. There are also some minor differences in the baseline characteristics with patients enrolled to inMIND slightly younger (median age: 64 years[68]) than the median age of patients diagnosed with FL in the UK (median age: 66–68 years[20, 21]) but this is very common in clinical trials and clinical expert consultation confirmed that baseline characteristics of the inMIND population are generally consistent with those of patients anticipated to receive tafasitamab + R^2 in UK clinical practice.[1, 2] Between treatment arms of inMIND, small differences were observed in the proportion of patients refractory to last therapy and proportion of patients who had received at least three prior lines of therapy (Table 7); both were higher in the tafasitamab + R^2 treatment arm so any bias from this difference would be against tafasitamab.

2.6 Clinical effectiveness results of the relevant studies

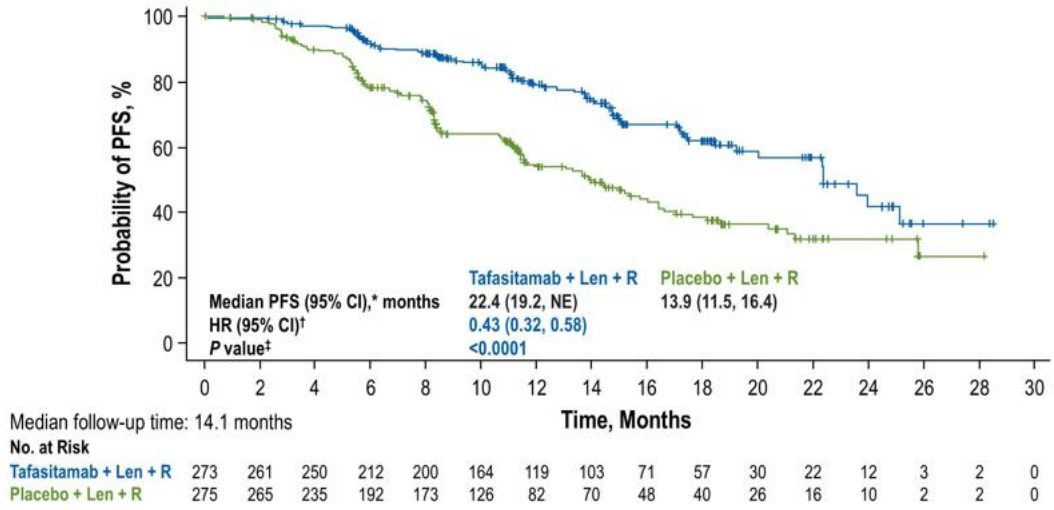
The efficacy results from the inMIND study relevant to the decision problem for this submission are presented in the following subsections. The results start with the primary and secondary endpoints, followed by exploratory outcomes relevant to the decision problem for this submission.

2.6.1 Primary endpoint – PFS by investigator assessment (FL FAS)

After a median follow-up of 14.1 months for PFS, the inMIND study met its primary endpoint of prolonging PFS in R/R FL. The addition of tafasitamab to R^2 resulted in a significant and clinically meaningful improvement in PFS with a 57% reduction in the risk of progression, relapse or death (HR: 0.43; 95% CI: 0.32, 0.58; $p < 0.0001$).[68] The median period of progression-free living was increased by over 8 months versus placebo + R^2 (tafasitamab + R^2: 22.4 months; placebo + R^2: 13.9 months).[68]

The Kaplan−Meier curve demonstrating this significant improvement in PFS by INV assessment is presented in Figure 5. A clear additional treatment effect over placebo + R^2 is evident from 4 months with tafasitamab + R^2 treatment and is maintained for at least 2 years (Figure 5), without the need for maintenance therapy beyond the fixed 1-year treatment period . As shown in the detailed data tables (Appendix L), the estimated PFS rate at 18 months was [redacted] with tafasitamab + R^2 treatment arm compared with [redacted] in participants receiving placebo + R^2.[64]

Figure 5: Kaplan–Meier plot of PFS by INV in the R/R FL population



Key: CI, confidence interval; FL, follicular lymphoma; INV, investigator; Len, lenalidomide; NE, not evaluable; PFS, progression-free survival; R, rituximab; R/R, relapsed or refractory.
Source: Trneny et al. 2025.[68]

2.6.2 Key secondary endpoint – PET-CR by investigator assessment (FDG-avid population)

The addition of tafasitamab to R^2 resulted in a significant and clinically meaningful improvement in complete metabolic response (CMR) rate with patients treated with tafasitamab + R^2 being 1.5 times more likely to achieve a CMR versus placebo + R^2 (p = 0.0286), as summarised in Table 9.[68] The absolute increase in patients achieving a CMR with treatment was ~10% with CMR rates of 49.4% in the tafasitamab + R^2 arm versus 39.8% in the placebo + R^2 treatment arm (Table 9).

Table 9: PET-CRR by INV assessment in the R/R FL population

PET-CR (FDG-avid population)	**Tafasitamab + R^2 (n = 251)**	**Placebo + R^2 (n = 254)**
Patients with post-baseline PET assessments, n (%)[a]	201 (80.1)	205 (80.7)
Best metabolic response based on PET, n (%)[b]		
CMR	124 (49.4)	101 (39.8)
PMR	37 (14.7)	39 (15.4)
NMR/SD	19 (7.6)	12 (4.7)
PMD	19 (7.6)	51 (20.1)
Not assessed	50 (19.9)	46 (19.3)

PET-CR (FDG-avid population)	Tafasitamab + R^2 (n = 251)	Placebo + R^2 (n = 254)
PET-CR rate (95% CI)[c,d]	49.4 (43.1, 55.8)	39.8 (33.7, 46.1)
OR by stratified CMH test (95% CI)[e]	1.5 (1.04, 2.13)	
Stratified CMH test p-value	0.0286	

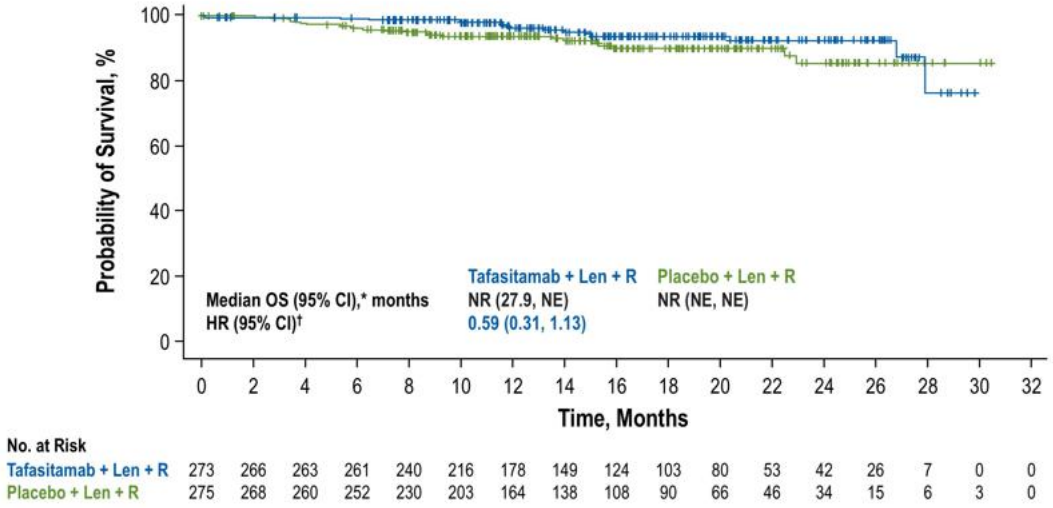
Key: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CMR, complete metabolic response; FDG, fluorodeoxyglucose; FL, follicular lymphoma; ITT, intent to treat; INV, investigator; NMR, no metabolic response; OR, odds ratio; PET-CR, positron emission tomography-complete response; PMD, progressive metabolic disease; PMR, partial metabolic response; R^2, lenalidomide and rituximab; RR, relapsed or refractory; SD, stable disease.
Notes: [a] Calculated based on patients with a positive PET scan at baseline, defined as having a Deauville score of 4 or 5 at baseline. [b] Two patients (0.8%) in both arms had PET after confirmed PD or new anti-lymphoma treatment initiation. [c] The PET-CR rate was defined as the proportion of participants who achieved a CMR at any time after the start of treatment as per Lugano classification among the participants with a positive PET scan at baseline. Participants with no postbaseline assessment by PET or who did not achieve a CMR were classified as non-CR responders. [d] The 95% CIs were calculated using the Clopper-Pearson method. [e] The strata information was based on the data obtained from the IRT that was used for randomisation.
Source: Trneny et al. 2025.[68]

2.6.3 Key secondary endpoint – OS (FL FAS)

At the time of primary analysis, overall survival was assessed against a pre-defined futility threshold. As FL is a slow progressing cancer, OS data were still immature with 38 death events and a median follow-up of 15.3 months, The pre-defined futility threshold was not crossed and an OS trend in favour of tafasitamab + R^2 was observed.[68] Detailed data tables are provided in Appendix L.

The Kaplan−Meier curve for OS is presented in Figure 6. The inMIND trial was not powered to test for OS at the time of primary PFS analysis, but the addition of tafasitamab to R^2 resulted in an estimated 41% reduction in the risk of death (HR: 0.59; 95% CI: 0.31, 1.13; [redacted]).[64, 68] Generally, the shape of the survival curves are representative of the typical ‘slower growing’ disease course with few death events observed within 2 years of treatment, but interpretation of survival curves at later follow-up times must be treated with caution. The apparent ‘drop’ of the tafasitamab + R^2 survival curve below the placebo + R^2 is an artefact of two individual deaths and not representative of the expected longer-term OS to be observed as these data mature (see Section 3).

Figure 6: Kaplan–Meier plot of OS (interim futility analysis) in the R/R FL population



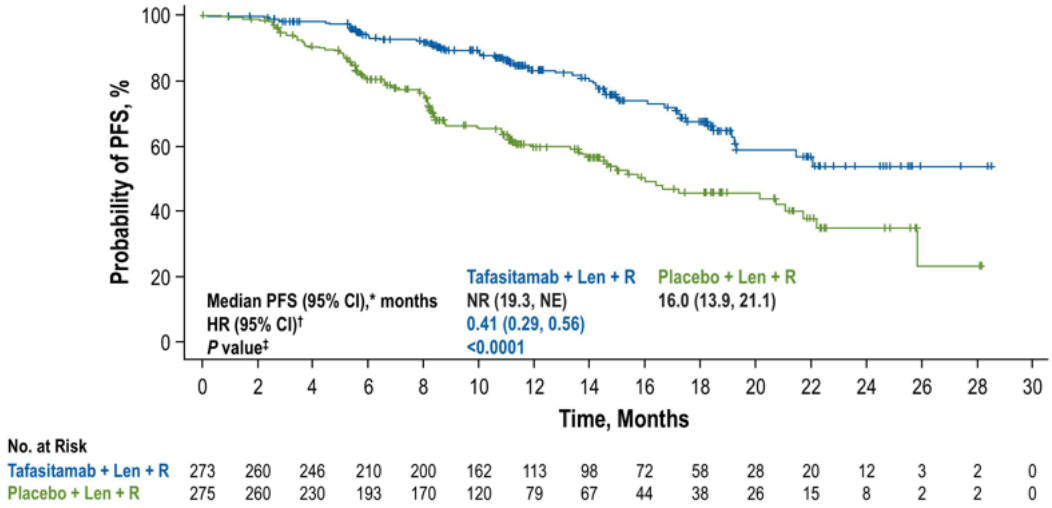
Key: CI, confidence interval; FL, follicular lymphoma; HR, hazard ratio; Len, lenalidomide; NE, not evaluable; OS, overall survival; R, rituximab; R/R, relapsed or refractory.
Source: Trneny et al. 2025.[68]

2.6.4 Secondary endpoint – PFS by independent review committee (FL FAS)

The results for PFS by IRC were consistent with PFS by INV. After a median follow-up of 14.1 months, the addition of tafasitamab to R^2 resulted in a significant and clinically meaningful improvement in PFS with a 59% reduction in the risk of progression, relapse or death (HR: 0.41; 95% CI: 0.29, 0.56; p < 0.0001).[68]

The Kaplan−Meier curve demonstrating this significant improvement in PFS is presented in Figure 7. As was the case with PFS by INV, a clear treatment effect is evident by 4 months of tafasitamab + R^2 treatment and is maintained for at least 2 years (Figure 7).

Figure 7: Kaplan–Meier plot of PFS by IRC in the R/R FL population



Key: CI, confidence interval; FL; follicular lymphoma; HR, hazard ratio; IRC, independent review committee; Len, lenalidomide; NE, not evaluable; PFS, progression-free survival; R, rituximab; R/R, relapsed refractory.
Source: Trneny et al. 2025.[68]

2.6.5 Secondary endpoint – ORR by investigator assessment (FL FAS)

The addition of tafasitamab to R^2 resulted in a significant and clinically meaningful improvement in overall response rate (ORR) with patients treated with tafasitamab + R^2 being twice as likely to achieve a response versus placebo + R^2 ($p = 0.0014$), as summarised in Table 10.[68] The absolute increase in patients achieving a response with treatment was ~11%, with an ORR of 83.5% in the tafasitamab + R^2 arm versus 72.4% in the placebo + R^2 treatment arm (Table 10).

The largest difference between treatment arms in terms of best overall response was the number of patients achieving a CR to treatment, with 45% of participants in the tafasitamab + R^2 treatment arm achieving a CR compared with 34% in the placebo + R^2 arm (Table 10).[68] Additionally, participants receiving tafasitamab + R^2 had lower rates of PD versus participants receiving placebo + R^2. This is important in the incurable disease setting of FL where the goal of treatment is to provide the longest disease-free period between treatment lines.

Table 10: ORR by INV assessment in the R/R FL population

Variable	Tafasitamab + R^2 (n = 273)	Placebo + R^2 (n = 275)
Best overall response based on Lugano classification, n (%)		
CR[a]	124 (45.0)	94 (34.0)
PR	105 (38.0)	105 (38.0)
SD	28 (10.0)	46 (17.0)
PD	7 (3.0)	20 (7.0)
NE	2 (1.0)	0
Not assessed	8 (3.0)	10 (4.0)
ORR, % (95% CI)[b, c]	83.5 (78.6, 87.7)	72.4 (66.7, 77.6)
OR by stratified CMH test (95% CI)[d]	2.0 (1.30, 3.02)	
Stratified CMH test p-value[c]	0.0014	

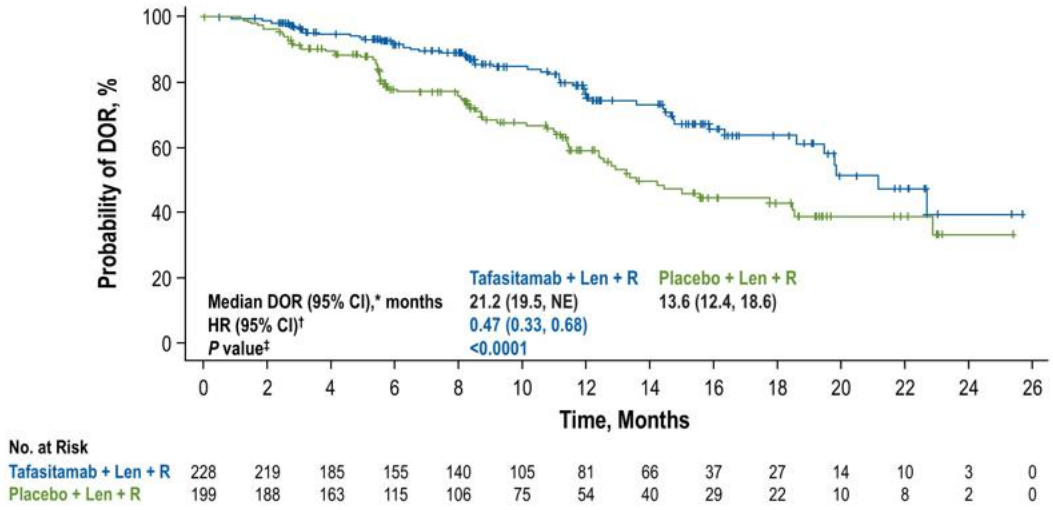
Key: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CR, complete response; FL, follicular lymphoma; INV, investigator; IRT, interactive response technology; ITT, intent to treat; NE, not evaluable; OR, odds ratio; ORR, overall response rate; PD, progressed disease; PMD, progressive metabolic disease; PR, partial response; R^2, lenalidomide and rituximab; R/R, relapsed or refractory; SD, stable disease.
Notes: [a] CR with confirmatory bone marrow response; CR without confirmatory bone marrow response was 52.0% in the tafasitamab + R^2 arm vs 40.7% in the placebo + R^2 arm; [b,] Overall response rate was defined as the proportion of participants who achieved a CR or PR determined as per Lugano classification at any time during the study but before the first PD and before/at the start of a new anti-lymphoma treatment. [c] The 95% CIs were calculated using the Clopper-Pearson method. [d] The strata information was based on the data obtained from the IRT that was used for randomisation.
Source: Trneny et al., 2025.[68]

2.6.6 Secondary endpoint – DoR by investigator assessment (FL FAS)

The addition of tafasitamab to R^2 resulted in a significant and clinically meaningful improvement in DoR with a 53% reduction in risk of relapse (HR: 0.47; 95% CI: 0.33, 0.68; $p < 0.0001$).[68] The combination of tafasitamab + R^2 extended the median period of relapse-free living by over 7.5 months versus placebo + R^2 (tafasitamab + R^2: 21.2 months; placebo + R^2: 13.6 months).

The Kaplan−Meier curve demonstrating this significant improvement in DoR is presented in Figure 8. As observed with PFS, a clear treatment effect became evident at 4 months of treatment and was maintained for at least 2 years.

Figure 8: Kaplan–Meier plot of DoR by INV assessment in the R/R FL population



Key: CI, confidence interval; DoR, duration of response; FL, follicular lymphoma; HR, hazard ratio; INV, investigator; Len, lenalidomide; NE, not evaluable; R, rituximab; R/R, relapsed or refractory.
Source: Trneny et al. 2025.[68]

2.6.7 Secondary endpoint – health-related quality of life (FL FAS population with baseline HRQL assessment)

The in-trial analyses of HRQL show no negative impact on patient HRQL with the addition of tafasitamab to R^2, as measured by no change from baseline in EQ-5D-5L Visual Analogue Scale (VAS) scores, EORTC-QLQ-C30 global health scores or FACT-Lym scores (see Appendix L). Considering one of the key goals of treatment is to preserve patient QoL[60], this is a positive outcome with patients essentially experiencing a significant clinical benefit with no detrimental impact to their HRQL, despite tafasitamab being an 'add on' treatment to the R^2 regimen.

2.6.8 Exploratory endpoint – TTNT by investigator assessment in the R/R FL population (FL FAS)

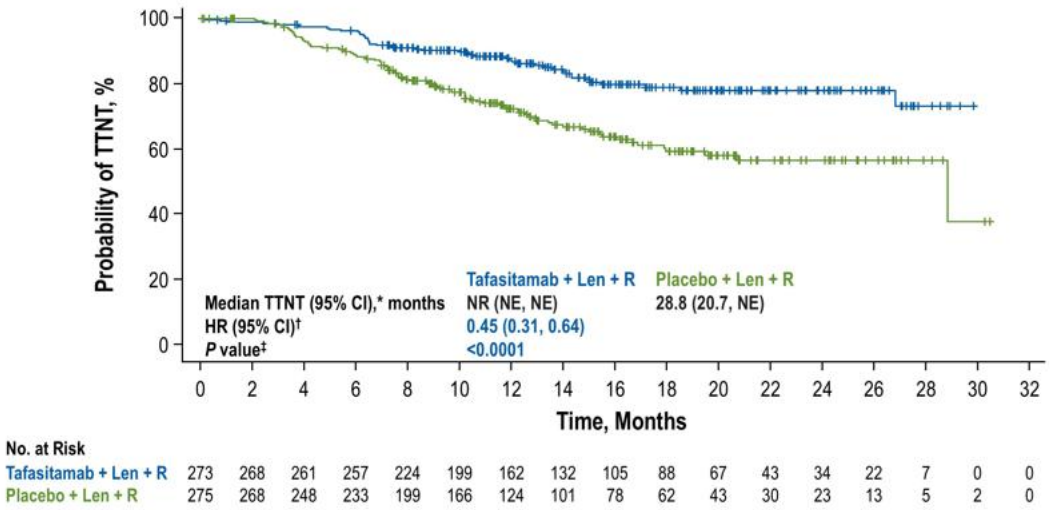
TTNT is increasingly recognised as a clinically meaningful endpoint in R/R FL where the primary goal of treatment is to provide the longest disease-free period between treatment lines (see Section 2.13). The addition of tafasitamab to R^2 resulted in a significant and clinically meaningful improvement in TTNT with a 55% reduction in

the risk of starting another line of treatment or death (HR: 0.45; 95% CI: 0.31, 0.64; p < 0.0001).[68]

The Kaplan−Meier curve demonstrating this significant improvement in TTNT is presented in Figure 9. Median TTNT was 28.8 months in those receiving placebo + R^2 and was not reached for participants receiving tafasitamab + R^2 by the time of the primary analysis. [68]

The absolute reduction in patients who started new anti-lymphoma treatment was ~15%, with 17% of patients in the tafasitamab + R^2 treatment arm needing a next line of treatment versus 32% of patients in the placebo + R^2 treatment arm.[64]

Figure 9: Kaplan–Meier plot of TTNT by INV assessment in the R/R FL population



Key: CI, confidence interval; FL, follicular lymphoma; HR, hazard ratio; INV, investigator; Len, lenalidomide; NE, not evaluable; R, rituximab; R/R, relapsed or refractory; TTNT, time to next treatment.
Source: Trneny et al. 2025[68]

2.6.9 Exploratory endpoint – histological transformation

Although the event numbers are small, a clinically relevant trend in favour of tafasitamab + R^2 was observed in exploratory analyses of histological transformation rates.[69]

As summarised in Table 11, 9 (3.3%) patients in the placebo + R^2 treatment arm had experienced histological transformation of low-grade FL to a more aggressive lymphoma type. In contrast, no patients treated with tafasitamab + R^2 experienced histological transformation. Clinical experts have expressed this is a clinically important observation.[1]

Table 11: Summary of histological transformation and time to transformation of FL to a more aggressive state in the R/R FL population

Variable	Tafasitamab + R^2 (n = 273)	Placebo + R^2 (n = 275)
Participants with transformation into more aggressive histology, n (%)[a]	**0 (0.0)**	**9 (3.3)**
Rate of histological transformation into more aggressive histology, % (95% CI)[b]	0.0 (0.00, 1.3)	3.3 (1.5, 6.1)
OR by stratified CMH test (95% CI)[c]	[redacted]	
Stratified CMH test p-value	[redacted]	
Median time to transformation into more aggressive histology, months (95% CI)[d]	[redacted]	[redacted]

Key: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; IRT, interactive response technology; NE, not evaluable; OR, overall response; R^2, lenalidomide and rituximab; R/R, relapsed or refractory.
Notes: [a] Transformation of FL into more aggressive histology (e.g. DLBCL) was defined as the appearance of diffuse areas of large-cell lymphoma cells within a lymphoma site as proven by a histological examination of a tumour biopsy at the time of disease progression. [b] The 95% CIs were calculated using the Clopper-Pearson method. [c] The strata information was based on the data obtained from the IRT that was used for randomisation. [d] Median time to transformation was estimated using the Kaplan–Meier method.
Source: Sehn et al. 2025[69]; Incyte Corporation, 2024.[64]

2.7 Subsequent treatments used in the relevant studies

Among patients who started post-treatment systemic anti-lymphoma therapy (subsequent treatment), [redacted] had one subsequent treatment, as summarised in Table 12. The most common subsequent treatments were [redacted].[64]

Several of these treatments ([redacted]) are not available to patients in England and Wales (see Section 1.3.4); however, given the immaturity of the OS data at the time of the primary analysis, this is not thought to have introduced bias in

the OS analysis. For the economic modelling, subsequent treatments are reweighted to better reflect the costs of therapies in the care pathway in England and Wales (see Section 3).

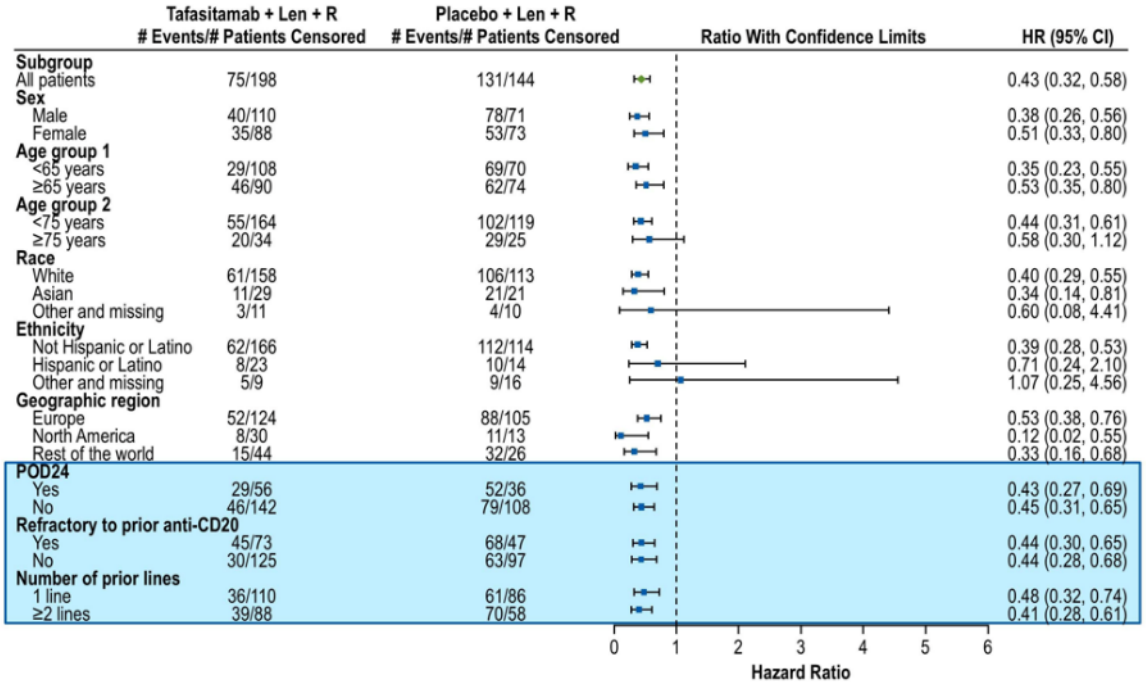
Table 12: Summary of post-treatment systemic anti-lymphoma therapies in the R/R FL population

Variable	**Tafasitamab + R^2 (n = 273)**	**Placebo + R^2 (n = 275)**
Any post-treatment systemic anti-lymphoma therapies, n (%)	[redacted]	[redacted]
Number of post-treatment systemic anti-lymphoma therapies per participant		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Participants with post-treatment systemic anti-lymphoma therapies, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
>3	[redacted]	[redacted]
Most common (≥5% in either arm) post-treatment systemic anti-lymphoma therapy, n (%)		
	Tafasitamab + R^2 [redacted]	**Placebo + R^2** [redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Key: [redacted] CI, confidence interval; [redacted] SD, standard deviation. **Source:** Incyte Corporation, 2024.[64]		

2.8 Subgroup analysis

The PFS benefit from adding tafasitamab to R^2 was observed in all prespecified subgroups, as summarised in Figure 10.[68] Of note, clinical benefit was observed in patients with POD24 of diagnosis, patients refractory to prior anti-CD20 therapies and patients treated with multiple prior lines of therapy – these are difficult-to-treat patients with particularly poor prognosis (see Section 1.3.2).

Figure 10: Forest plot of prespecified subgroup analysis of PFS by INV in the R/R FL population



Key: CI, confidence interval; FL, follicular lymphoma; HR, hazard ratio; INV, investigator; PFS, progression-free survival; POD24, progression of disease within 24 months; R/R, relapsed or refractory.
Source: Trneny et al. 2025[68]

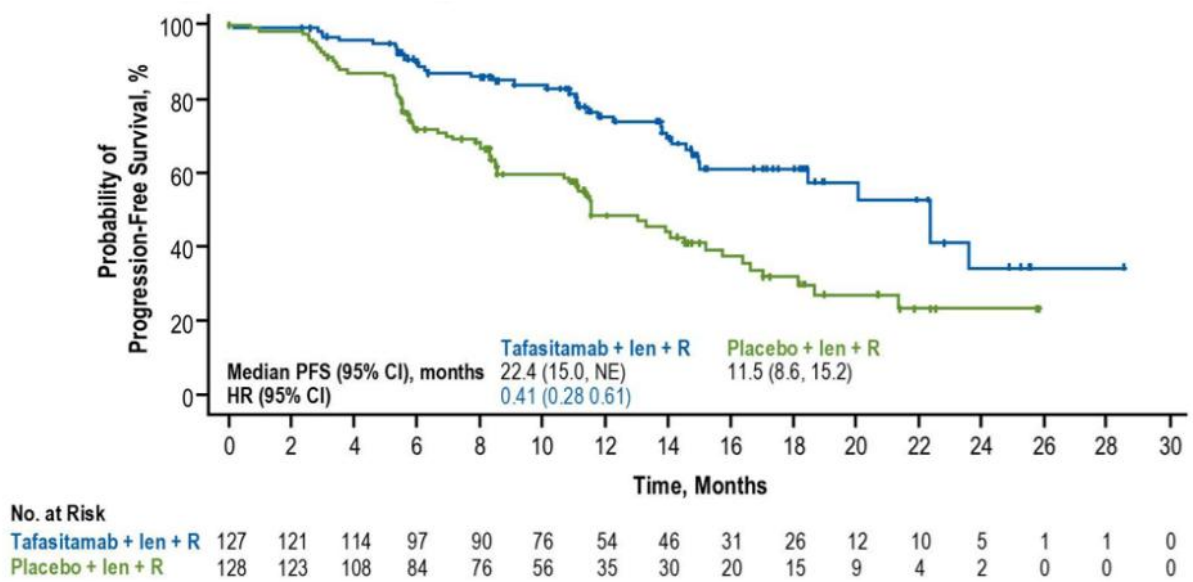
For PFS Kaplan–Meier curves in patients with POD24 of diagnosis and patients refractory to prior anti-CD20 therapy, please see Appendix C. In both of these subgroups, a clear treatment effect is evident at 4 months of tafasitamab + R^2 treatment and is maintained for at least 2 years, aligned with PFS outcomes in the total population.[68]

2.8.1 R/R FL after two or more systemic treatments

The number of previous treatments has a direct impact on treatment decision making in clinical practice. As noted previously, FL becomes more difficult to treat with each subsequent recurrence, as the disease becomes increasingly resistant to treatment.[24-27, 29] R^2 is the only treatment option with a different mechanism of action to 1L therapy so, as noted in the clinical pathway of care section (see Section 1.3.4), it is often reserved for later-line use (3L+) for patients whose FL responded well to 1L treatment and are thus re-treated with R-chemotherapy in the 2L setting.

In patients with R/R FL after two or more systemic treatments, the addition of tafasitamab to R^2 resulted in a clinically meaningful improvement in INV-assessed PFS of an even greater magnitude than observed with tafasitamab + R^2 in the total R/R FL population or the 2L R/R FL population.[68] When used in this 3L+ setting, tafasitamab + R^2 treatment resulted in a 59% reduction in the risk of progression, relapse or death (HR: 0.41; 95% CI: 0.28, 0.61), as depicted in Figure 11.

Figure 11: Kaplan–Meier plot of PFS by INV in patients with R/R FL after 2 or more systemic treatments



Key: CI, confidence interval; FL, follicular lymphoma; HR, hazard ratio; INV, investigator; NE, not estimable; PFS, progression-free survival; R/R, relapsed or refractory.
Source: Trneny et al. 2025.[68]

Further to the clinically meaningful improvement in PFS, the addition of tafasitamab to R^2 also resulted in a clinically meaningful improvement in CR. When used in this 3L+ setting, tafasitamab + R^2 treatment induced a CR in [redacted] of patients, compared with a CR rate of [redacted] in the placebo + R^2 arm and patients treated with tafasitamab + R^2 were [redacted] times more likely to achieve a response versus placebo + R^2 ([redacted]).[70] A positive trend in OS was also observed with use of tafasitamab + R^2 in the 3L+ setting with a [redacted][64]

Key baseline characteristics data for patients with R/R FL after two or more systemic treatments are presented alongside those for the total R/R FL population in Table 13.

There were no unexpected differences in characteristics of patients in the two or more systemic treatments group compared to all R/R FL patients. Differences that are observed − e.g. longer time since diagnosis, shorter time since last treatment and higher rates of rituximab refractoriness − are all hallmarks of their longer treatment history. Importantly, the demographic and clinical characteristics of patients remained generally well balanced across both treatment arms in the 3L+ population and there are no signs that the clinically meaningful improvement in PFS and CR rate, and positive trend in OS with tafasitamab addition to R^2 for these patients are due to differences in prognosis at baseline.

Table 13: Key baseline characteristics of R/R FL patients based on prior lines of treatment in inMIND

	R/R FL patients who had 1 or more prior lines of treatment (2L+ population)			R/R FL patients who had 2 or more prior lines of treatment (3L+ population)		
Characteristics, n (%)	**Tafa + R[2] (n = 273)**	**Placebo + R[2] (n = 275)**	**Overall (N = 548)**	**Tafa + R[2] (n = 126)**	**Placebo + R[2] (n = 122)**	**Overall (N = 248)**
Median age, years (range)	64.0 (36-88)	64.0 (31-85)	64.0 (31-88)	[redacted]	[redacted]	[redacted]
Male sex	150 (54.9)	149 (54.2)	299 (54.6)	[redacted]	[redacted]	[redacted]
Median years since initial FL diagnosis (range)	5.2 (0-34)	5.5 (1-33)	5.3 (0-34)	[redacted]	[redacted]	[redacted]
ECOG PS at screening						
0	181 (66.3)	192 (69.8)	373 (68.1)	[redacted]	[redacted]	[redacted]
1	85 (31.1)	75 (27.3)	160 (29.2)	[redacted]	[redacted]	[redacted]
2	7 (2.6)	8 (2.9)	15 (2.7)	[redacted]	[redacted]	[redacted]
Ann Arbor stage						
I	10 (3.7)	13 (4.7)	23 (4.2)	[redacted]	[redacted]	[redacted]
II	42 (15.4)	37 (13.5)	79 (14.4)	[redacted]	[redacted]	[redacted]
III	72 (26.4)	63 (22.9)	135 (24.6)	[redacted]	[redacted]	[redacted]
IV	149 (54.6)	162 (58.9)	311 (56.8)	[redacted]	[redacted]	[redacted]
FL grade						
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3a	67 (24.5)	71 (25.8)	138 (25.2)	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B symptoms, present	63 (23.1)	67 (24.4)	130 (23.7)	[redacted]	[redacted]	[redacted]
FLIPI score						
Low, 0 or 1	57 (20.9)	57 (20.7)	114 (20.8)	[redacted]	[redacted]	[redacted]

	R/R FL patients who had 1 or more prior lines of treatment (2L+ population)			R/R FL patients who had 2 or more prior lines of treatment (3L+ population)		
Characteristics, n (%)	**Tafa + R^2 (n = 273)**	**Placebo + R^2 (n = 275)**	**Overall (N = 548)**	**Tafa + R^2 (n = 126)**	**Placebo + R^2 (n = 122)**	**Overall (N = 248)**
Intermediate, 2	79 (28.9)	67 (24.4)	146 (26.6)	[redacted]	[redacted]	[redacted]
High, 3–5	137 (50.2)	150 (54.5)	287 (52.4)	[redacted]	[redacted]	[redacted]
GELF criteria (at least 1 fulfilled criterion)	222 (81.3)	232 (84.4)	454 (82.8)	[redacted]	[redacted]	[redacted]
POD24 of diagnosis[a]	85 (31.1)	88 (32.0)	173 (31.6)	[redacted]	[redacted]	[redacted]
Time since last anti-lymphoma therapy and randomisation date, n (%)						
≤ 2 years	147 (53.8)	157 (57.1)	304 (55.5)	[redacted]	[redacted]	[redacted]
> 2 years	126 (46.2)	118 (42.9)	244 (44.5)	[redacted]	[redacted]	[redacted]
Median number of prior lines of therapy (range)	1.0 (1-7)	1.0 (1-10)	1.0 (1-7)	[redacted]	[redacted]	[redacted]
Number of prior lines of therapy, n (%)						
1	147 (53.8)	153 (55.6)	147 (53.8)	[redacted]	[redacted]	[redacted]
2	66 (24.2)	71 (25.8)	66 (24.2)	[redacted]	[redacted]	[redacted]
3	39 (14.3)	30 (10.9)	39 (14.3)	[redacted]	[redacted]	[redacted]
≥ 4	21 (7.7)	21 (7.6)	21 (7.7)	[redacted]	[redacted]	[redacted]
R/R status to last therapy,[a] n (%)						
Relapsed	148 (54.2)	164 (59.6)	312 (56.9)	[redacted]	[redacted]	[redacted]
Refractory	112 (41.0)	97 (35.0)	209 (38.0)	[redacted]	[redacted]	[redacted]
Indeterminate[b]	13 (4.8)	14 (5.1)	27 (4.9)	[redacted]	[redacted]	[redacted]
Number of anti-CD20-containing prior therapy lines, n (%)						

	R/R FL patients who had 1 or more prior lines of treatment (2L+ population)			R/R FL patients who had 2 or more prior lines of treatment (3L+ population)		
Characteristics, n (%)	**Tafa + R^2 (n = 273)**	**Placebo + R^2 (n = 275)**	**Overall (N = 548)**	**Tafa + R^2 (n = 126)**	**Placebo + R^2 (n = 122)**	**Overall (N = 248)**
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rituximab refractory, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ECOG PS, Eastern Cooperative Oncology Group performance status; FAS, final analysis set; FL, follicular lymphoma, FLIPI, Follicular Lymphoma International Prognostic Index; GELF, Groupe d'Etude des Lymphomes Folliculaires; POD24, progression of disease within 24 months; R^2, lenalidomide and rituximab; R/R, relapsed or refractory.
Note: [a] Taken from electronic case report form data used for stratification.
Source: Trneny et al. 2025[68]; Incyte Corporation, 2024.[64]

2.9 Meta-analysis

No additional studies to inMIND provide data for tafasitamab for the treatment of adult patients with R/R FL after at least one line of systemic therapy; therefore, meta-analysis is not applicable.

2.10 Indirect and mixed treatment comparisons

As described in Section 1, relevant comparators for tafasitamab + R^2 decision-making are R^2 and R-chemotherapy in the 2L treatment setting and R^2 in the 3L+ treatment setting. R-chemotherapy regimens used in clinical practice in England and Wales include R-B, R-CHOP and R-CVP (see Section 1.3.4). In the absence of head-to-head data for tafasitamab + R^2 versus R-chemotherapy, the wider evidence base was explored for data to inform potential indirect treatment comparisons (ITC). A summary of this data exploration and subsequent ITC analyses is provided in this section, with full details provided in Appendix B.

It should be noted that O-B and epcoritamab monotherapy are not considered to be relevant comparators for tafasitamab + R^2 for decision-making (see Section 1.3.4). However, as they are included in the NICE scope for this appraisal, the wider evidence base was explored for data to inform potential ITCs of tafasitamab + R^2 versus O-B and versus epcoritamab. The outcomes of this and subsequent ITC analyses are provided in Appendix B. Economic analyses for comparisons of tafasitamab + R^2 versus O-B and versus epcoritamab are provided in Appendix N.

2.10.1 R-chemotherapy data from published clinical trials

Trials of R-chemotherapy were identified via SLR, detailed in Appendix B. Only one single-arm trial of R-B (the BRB study[71]) met the SLR inclusion criteria. One RCT of R-CHOP versus CHOP reported by Van Oers et al.[72] was identified but did not meet the SLR inclusion criteria. No published studies of R-CVP were identified.

A feasibility assessment was undertaken to assess the comparability of the trials and their populations. This determined that there were several potential sources of heterogeneity between these and the inMIND trial, including study designs, enrolled patients' characteristics, and prior therapies. Notably, the R-chemotherapy trials

were either single-arm or did not have the common comparator arm of R^2 with inMIND.

2.10.2 R-chemotherapy data from HMRN

Due to the limited availability of published clinical trial evidence for R-chemotherapy regimens, real-world data was sought to potentially mitigate this evidence gap.

HMRN is a population-based cohort consisting of around 4 million people, and was established in 2004 to collect patient-level data (PLD) and information on all haematological malignancies in the Yorkshire and Humberside region. The HMRN database comprises laboratory data produced by the Haematological Malignancy Diagnostic Service and patient clinical medical records, and is connected to nationwide information on deaths, cancer registrations, Hospital Episode Statistics (HES), and area-based population data and characteristics sourced from the UK census and the Office for National Statistics (ONS).

This provided real-world outcomes data in R/R FL with R-CHOP, R-CVP, and a combined R-chemotherapy group (R-CHOP, R-CVP); however, the number of patients on each regimen was small ([redacted] R-CHOP patients and [redacted] R-CVP).[21] A feasibility assessment noted heterogeneity in key patient characteristics and definitions of outcomes for the HMRN dataset versus inMIND.

2.10.3 ITC methodology

As the R-chemotherapy trials were either single-arm or did not have the common comparator arm of R^2 with inMIND, and the HMRN provides only observational, uncontrolled data, this precluded the use of network meta-analysis (NMA) or other anchored methods for ITC. Instead, pairwise, population-adjusted ITC techniques that adjust for observed differences in patient baseline characteristics were required. Of the available methods, unanchored Matching Adjusted Indirect Comparisons (MAICs) were deemed most suitable for the time to event data. Given the lack of common comparators, only the tafasitamab + R^2 arm from inMIND could be included in the analyses. Full details of the MAIC methods can be found in the ITC report provided in the reference pack.[73]

A strong assumption of unanchored MAIC is that all prognostic factors and treatment effect modifiers have been adjusted for. A comprehensive assessment was carried out to identify prognostic factors and treatment effect modifiers for inclusion in the MAICs. This included a targeted literature review; consultation with clinical experts; and analyses of PLD from the inMIND trial. Methods and outcomes of each of these investigations are provided in detail in Appendix B.

2.10.4 Results

Table 14 summarises the results from the weighted Cox model with robust standard errors (SE), as well as the effective sample size (ESS) from the MAICs of tafasitamab + R^2 versus R-chemotherapy. Across analyses, there was a general trend in favour of tafasitamab + R^2 with results clearly indicating improved OS, PFS and TTNT but high variability was observed and wide CIs around the point estimates represent uncertainty in the size of benefit.

2.10.5 Uncertainties in the indirect and mixed treatment comparisons

The MAICs could not adjust for most prognostic factors or treatment effect modifiers identified as critical by clinicians. Adjustments that could be made resulted in large losses in the ESS and wide CIs around treatment effect estimates.

Moreover, the MAIC outcomes for PFS and TTNT suggest a lower magnitude of clinical effect for tafasitamab + R^2 versus R-chemotherapy than was observed directly for tafasitamab + R^2 versus R^2 in the inMIND trial. As R^2 was shown to be more effective than R-chemotherapy in the NICE TA627[5], these findings lack face validity. This view has been confirmed by clinical experts. [1, 2]

2.10.6 ITC Conclusion

Given the high levels of uncertainty and lack of face validity for the MAIC results, these are arguably not appropriate to adopt in the cost effectiveness analysis of tafasitamab + R^2 versus R-chemotherapy. A pragmatic approach in which the relative treatment effects for tafasitamab + R^2 versus R^2 from inMIND are assumed to represent the comparison of tafasitamab + R^2 versus R-chemotherapy provides a conservative but arguably more certain estimate of the potential cost-effectiveness of

tafasitamab + R^2 versus R-chemotherapy. However, for completeness, scenario analyses explore the impact of using PFS outcomes from the MAICs versus R-chemotherapy in the economic model (see Section 3).

Table 14: Constant HRs for OS and PFS – tafasitamab + R^2 versus R-chemotherapy

Trial ID	Comparison	Comparator	Tafasitamab + R^2	OS	PFS	TTNT
		N	ESS, n (%[a])	HR (95% CI)[b]	HR (95% CI)[b]	HR (95% CI)[b]
BRB	Tafasitamab + R^2 vs R-B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Van Oers	Tafasitamab + R^2 vs R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HMRN	Tafasitamab + R^2 vs R-chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Tafasitamab + R^2 vs R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Tafasitamab + R^2 vs R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: 2L+, second-line or later; 3L+, third-line or later; ESS, effective sample size; HR, hazard ratio; NR, not applicable; O-B, obinutuzumab with bendamustine; OS, overall survival; PFS, progression-free survival; PH, proportional hazards; R^2, lenalidomide + rituximab; R-BMD, rituximab with bendamustine + mitoxantrone + dexamethasone.
Note: [a] Percent of original sample size; [b] HR (95% CI) from weighted Cox model (robust SE) is presented in this table. Refer to Appendix B for HRs and 95% confidence interval from other derivations.

2.11 Adverse reactions

2.11.1 Treatment-emergent adverse events

For the R/R FL SAS (N = 546), an overall summary of adverse events is presented in Table 15. Numerical differences in reported rates were generally small and do not account for the longer treatment durations in the tafasitamab + R^2 arm arising from its greater efficacy.[64] TEAEs were reported in 542 participants (993%) including 272 participants (993%) receiving tafasitamab + R^2 and 270 (993%) receiving placebo + R^2.[64] There was a slightly higher incidence of serious TEAEs in the tafasitamab + R^2 treatment arm (36%) versus the placebo + R^2 treatment arm (32%), but no increase in the rate of serious treatment-related TEAEs for any of the tafasitamab + R^2 regimen components(Table 15). Tafasitamab and placebo dose interruptions or discontinuations due to TEAEs were similar between treatment arms, as were lenalidomide dose interruptions or discontinuations (Table 15).

Table 15: Overall summary of treatment-emergent- and treatment-related adverse events (R/R FL safety population)

Participants (n [%]) who had at least 1	Tafasitamab + R^2 (n = 274)	Placebo + R^2 (n = 272)	Total (N = 546)
TEAE	272 (993)	270 (993)	542 (993)
Serious TEAE	99 (36)	86 (32)	185 (34)
Grade 3 or 4 TEAE	195 (71)	189 (70)	384 (70)
Fatal TEAE	6 (2)	6 (2)	12 (2)
Tafasitamab/placebo-related TEAE	202 (74)	179 (66)	381 (70)
Serious tafasitamab/placebo-related TEAE	29 (11)	32 (12)	61 (11)
Grade 3 or 4 tafasitamab/placebo-related TEAE	112 (41)	100 (37)	212 (39)
Fatal tafasitamab/placebo-related TEAE	0 (0.	2 (1)	2 (<1)
Lenalidomide-related TEAE	245 (89)	237 (87)	482 (88)
Serious lenalidomide-related TEAE	35 (13)	38 (14)	73 (13)
Grade 3 or 4 lenalidomide-related TEAE	154 (56)	136 (50)	290 (53)
Fatal lenalidomide-related TEAE	0 (0)	2 (1)	2 (<1)
Rituximab-related TEAE	173 (63)	162 (60)	335 (61)
Serious rituximab-related TEAE	17 (6)	24 (9)	41 (8)
Grade 3 or 4 rituximab-related TEAE	72 (26)	69 (25)	141 (26)

Participants (n [%]) who had at least 1	Tafasitamab + R^2 (n = 274)	Placebo + R^2 (n = 272)	Total (N = 546)
Fatal rituximab-related TEAE	0 (0)	1 (<1)	1 (<1)
TEAE leading to permanent discontinuation of tafasitamab/placebo	30 (11)	18 (7)	48 (9)
TEAE leading to permanent discontinuation of lenalidomide	39 (14)	31 (11)	70 (13)
TEAE leading to permanent discontinuation of rituximab	8 (3)	8 (3)	16 (3)
TEAE leading to dose delay or dose interruption of tafasitamab/placebo	203 (74)	190 (70)	393 (72)
TEAE leading to dose reduction, dose missed, or dose interruption of lenalidomide	210 (77)	197 (72)	407 (75)
TEAE leading to dose delay or dose interruption of rituximab	124 (45)	125 (46)	249 (46)

Key: FL, follicular lymphoma; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event; R^2, lenalidomide and rituximab; R/R, relapsed or refractory.
Notes: TEAE is any adverse event either reported for the first time or worsening of a pre-existing event after the first dose of study treatment until 90 days after the last dose of study treatment. Treatment-related TEAEs are TEAEs judged as related by the investigator or with a missing causality. Participants were counted once under each MedDRA system organ class and preferred term. Decimal point approach aligned to publication plan.
Source: Incyte Corporation, 2024.[64]

2.11.2 Common treatment-emergent adverse events

The most frequently occurring TEAEs (≥ 20% incidence) occurring in both treatment arms included neutropenia, diarrhoea, constipation, COVID-19 and rash, as summarised in Table 16.

TEAEs that occurred more frequently (≥ 5% difference) in the tafasitamab + R^2 treatment arm than in the placebo + R^2 arm, respectively, included diarrhoea (37.6% vs 28.3%), COVID-19 (314% vs 23.5%), fatigue (212% vs 15.8%), pruritus (161% vs 103%), back pain (11% vs 6%), oropharyngeal pain (9% vs 4%) and pain in extremity (8% vs 3%).[64, 68] Peripheral oedema occurred more frequently (≥ 5% difference) in the placebo + R^2 arm versus the tafasitamab + R^2 arm (13% vs 7%).[64]

Other clinically noteworthy TEAEs that occurred in more participants in the tafasitamab + R^2 treatment arm compared with the placebo + R^2 treatment arm, respectively, which did not meet the threshold above, included pneumonia ([redacted]

[redacted]), peripheral neuropathy ([redacted]), hypogammaglobulinemia ([redacted]), febrile neutropenia ([redacted]), increased blood alkaline phosphatase ([redacted]), decreased lymphocyte count ([redacted]) and tooth infection ([redacted]).[64]

Table 16: Summary of TEAE in ≥ 5% of participants in any group by MedDRA preferred term (R/R FL safety population)

MedDRA PT, n (%)	**Tafasitamab + R^2 (n = 274)**	**Placebo + R^2 (n = 272)**	**Total (n = 546)**
Participants with any TEAE	272 (993)	270 (993)	542 (993)
Neutropenia	[redacted]	[redacted]	[redacted]
Diarrhoea	103 (37.6)	77 (28.3)	180 (33.0)
COVID-19	86 (31.4)	64 (23.5)	150 (27.5)
Constipation	80 (29.2)	67 (24.6)	147 (26.9)
Rash	60 (21.9)	58 (21.3)	118 (21.6)
Fatigue	58 (21.2)	43 (15.8)	101 (18.5)
Cough	52 (19.0)	47 (17.3)	99 (18.1)
Pyrexia	52 (19.0)	44 (16.2)	96 (17.6)
Muscle spasms	49 (17.9)	49 (18.0)	98 (18.1)
Nausea	49 (17.9)	38 (14.0)	87 (15.9)
Pruritus	44 (16.1)	28 (10.3)	72 (13.2)
Infusion related reaction	43 (15.7)	41 (15.1)	84 (15.4)
Anaemia	[redacted]	[redacted]	[redacted]
Thrombocytopenia	37 (13.5)	42 (15.4)	79 (14.5)
Asthenia	36 (13)	28 (10)	64 (12)
Pneumonia	[redacted]	[redacted]	[redacted]
Back pain	31 (11)	15 (6)	46 (8)
Decreased appetite	[redacted]	[redacted]	[redacted]
Headache	27 (10)	18 (7)	45 (8)
Oropharyngeal pain	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	25 (9)	29 (11)	54 (10)
Neutrophil count decreased	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]
Dizziness	21 (8)	19 (7)	40 (7)
Insomnia	21 (8)	17 (6)	38 (7)
Pain in extremity	21 (8)	7 (3)	28 (5)
Abdominal pain	[redacted]	[redacted]	[redacted]
Oedema peripheral	20 (7)	35 (13)	55 (10)
Urinary tract infection	[redacted]	[redacted]	[redacted]

MedDRA PT, n (%)	**Tafasitamab + R^2 (n = 274)**	**Placebo + R^2 (n = 272)**	**Total (n = 546)**
Arthralgia	19 (7)	21 (8)	40 (7)
Vomiting	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]
Rash maculo-papular	18 (7)	14 (5)	32 (6.)
Respiratory tract infection	18 (7)	24 (9)	42 (8)
Nasopharyngitis	17 (6)	20 (7)	37 (7)
COVID-19 pneumonia	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]
Myalgia	15 (6)	13 (5)	28 (5)
Dyspepsia	14 (5)	12 (4)	26 (5)
Hypotension	[redacted]	[redacted]	[redacted]
Rhinorrhoea	14 (5)	10 (4)	24 (4)
White blood cell count decreased	[redacted]	[redacted]	[redacted]
Weight decreased	13 (5)	14 (5)	27 (5)

Key: FL, follicular lymphoma; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; R^2, lenalidomide and rituximab; R/R, relapsed or refractory; TEAE, treatment-emergent adverse event.
Notes: Participants were counted once under each MedDRA PT. PTs are listed in decreasing order of frequency by the tafasitamab + R^2 group. Decimal point approach aligned to publication plan.
Source: Trneny et al. 2025[68]; Incyte Corporation, 2024.[64]

2.11.3 Grade 3 or 4 treatment-emergent adverse events

There were no marked differences in the overall rates of Grade 3 or 4 TEAEs across treatment arms. A total of 384 participants (70%) in the R/R FL safety population had at least one Grade 3 or 4 TEAE including 195 participants (71%) in the tafasitamab + R^2 treatment arm and 189 (70%) in the placebo + R^2 arm, as summarised in Table 17.[64]

There were also no Grade 3 or 4 TEAEs that occurred more frequently (≥ 5% difference) in either treatment arm. In the tafasitamab + R^2 group, the most frequently occurring Grade 3 or 4 TEAEs (≥ 5% incidence) included neutropenia (39.8%), pneumonia (8.4%), thrombocytopenia (6.2%), and decreased neutrophil count (5.8% each).[68] Similarly, the most frequently occurring Grade 3 or 4 TEAEs (≥ 5% incidence) in participants receiving placebo + R^2 included neutropenia (37.5%),

thrombocytopenia (6.8%), decreased neutrophil count (6.6%), anaemia (5.9%) and pneumonia (5.1%).[68]

It is important to note that the inMIND trial was run during the COVID-19 pandemic, which will have an impact on the adverse reaction rates captured in this trial. This is observed in the rates of Grade 3 or 4 TEAE COVID-19 and COVID-19 pneumonia in the tafasitamab + R^2 treatment arm and the placebo + R^2 arm (5.8% and 4.7% vs 2.2% and 1.1%, respectively).[68]

Table 17: Summary of Grade 3 or 4 TEAE in ≥ 2% of participants in any group by MedDRA preferred term (R/R FL safety population)

MedDRA PT, n (%)	**Tafasitamab + R^2 (n = 274)**	**Placebo + R^2 (n = 272)**	**Total (n = 546)**
Participants with any Grade 3 or 4 TEAE	195 (71)	189 (70)	384 (70)
Neutropenia	109 (39.8)	102 (37.5)	211 (38.6)
Pneumonia	23 (8.4)	14 (5.1)	37 (6.8)
Thrombocytopenia	17 (6.2)	20 (7.4)	37 (6.8)
COVID-19	16 (5.8)	6 (2.2)	22 (4.0)
Neutrophil count decreased	16 (5.8)	18 (6.6)	34 (6.2)
COVID-19 pneumonia	13 (4.7)	3 (1.1)	16 (2.9)
Anaemia	12 (4.4)	16 (5.9)	28 (5.1)
Febrile neutropenia	12 (4)	6 (2)	18 (3)
Acute kidney injury	8 (3)	6 (2)	14 (3)
Pyrexia	4 (2)	6 (2)	10 (2)

Key: FL, follicular lymphoma; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; R^2, lenalidomide and rituximab; R/R, relapsed or refractory; TEAE, treatment-emergent adverse event.
Notes: Participants were counted once under each MedDRA PT. PTs are listed in decreasing order of frequency by the tafasitamab + R^2 group. Decimal point approach aligned to publication plan.
Source: Trneny et al. 2025[68]; Incyte Corporation, 2024.[64]

Grade 3 or above TEAE outcomes in patients with R/R FL after two or more systemic treatments were similar to those in the total population – see Appendix D.

2.11.4 Treatment-related adverse events

A total of 381 participants (70%) in the FL safety population had at least one treatment-related adverse event (TRAE); 202 (74%) in the tafasitamab + R^2 arm and 179 (66%) in the placebo + R^2 arm (Table 18).

The most frequently occurring TRAEs (≥ 10% incidence) were [redacted] and [redacted]. Only [redacted][64]

Table 18: Summary of TRAE in ≥ 5% of participants in any group by MedDRA preferred term (R/R FL safety population)

MedDRA PT, n (%)	**Tafasitamab + R^2 (n = 274)**	**Placebo + R^2 (n = 272)**	**Total (n = 546)**
Participants with any tafasitamab/placebo-related TEAE	202 (74)	179 (66)	381 (70)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Key: FL, follicular lymphoma; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; R^2, lenalidomide and rituximab; R/R, relapsed or refractory; TEAE, treatment-emergent adverse event.
Notes: Participants were counted once under each MedDRA PT. PTs are listed in decreasing order of frequency by the tafasitamab + R^2 group. Decimal point approach aligned to publication plan.
Source: Incyte Corporation, 2024.[64]

2.11.5 Fatal treatment-emergent adverse events

A total of 12 participants (2%) in the R/R FL safety population died due to fatal TEAE; six in each treatment arm. [redacted] (Table 19).[64]

Two deaths in each treatment arm were due to COVID-19-related TEAEs, again showing the impact of the inMIND trial being run during the COVID-19 pandemic; neither were attributed to trial treatment. [64]

Table 19: Summary of TEAE with a fatal outcome by MedDRA SOC and PT (R/R FL safety population)

MedDRA SOC, n (%) PT, n (%)	Tafasitamab + R^2 (n = 274)	Placebo + R^2 (n = 272)	Total (n = 546)
Participants with any fatal TEAE	6 (2)	6 (2)	12 (2)
Cardiac disorders	0 (0.0)	1 (<1.0)	1 (<1.0)
Cardiac failure	0 (0)	1 (<1)	1 (<1)
General disorders and administration site conditions	1 (<1.0)	0 (0.0)	1 (<1.0)
Death	1 (<1)	0 (0)	1 (<1)
Infections and infestations	3 (1)	5 (2)	8 (2)
Bronchopulmonary aspergillosis	0 (0)	1 (<1)	1 (<1)
COVID-19	2 (1)	0 (0)	2 (<1)
COVID-19 pneumonia	0 (0)	2 (1)	2 (<1)
Pneumonia	0 (0)	1 (<1)	1 (<1)
Sepsis	1 (<1)	1 (<1)	2 (<1)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	2 (1)	0 (0)	2 (<1)
Adenocarcinoma gastric	1 (<1)	0 (0)	1 (<1)
Carcinoid tumour in the large intestine	1 (<1)	0 (0)	1 (<1)

Key: FL, follicular lymphoma; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; R^2, lenalidomide and rituximab; R/R, relapsed or refractory; SOC, standard of care; TEAE, treatment-emergent adverse event.
Notes: Participants were counted once under each MedDRA SOC and PT. Red text denotes fatal TEAE deemed related to treatment. Decimal point approach aligned to publication plan.
Source: Incyte Corporation, 2024.[64]

2.11.6 Safety overview

The safety profile of tafasitamab + R^2 was manageable and consistent with expected toxicities of tafasitamab, lenalidomide and rituximab.[68] While nearly all of the study participants observed at least one TEAE (99.3% in both treatment arms), these were comparable and low rates of fatal TEAE and treatment-related TEAEs were reported across both treatment arms.[68] As inMIND was conducted during the COVID-19

pandemic, incidences of COVID-19 infections and COVID-19 pneumonia were recorded (Table 16) and participants in both treatment arms received concomitant COVID-19 vaccines ([redacted] in the tafasitamab + R^2 group and [redacted] in the placebo + R^2 group).[64] Importantly, there were no notable differences in immunoglobulin serum levels at baseline and no meaningful changes during the study (see Appendix D), that would indicate reduced antibody production during treatment. This was reassuring to clinical experts reviewing the safety data for tafasitamab + R^2 from the inMIND trial.[1]

TEAEs that occurred more frequently (≥ 5% difference) in the tafasitamab + R^2 treatment arm compared with the placebo + R^2 arm included diarrhoea, fatigue, pruritus and back pain.[68] These are commonly seen in clinical practice with existing lymphoma treatments, are medically manageable, and did not detrimentally impact on patients' HRQL (see Section 2.6.7). While premedication rules were applied in the inMIND trial, few infusion-related reactions occurred and there was limited need for supportive therapies to mitigate potential administration side effects. This resulted in relaxed premedication rules in the final SmPC (Table 2). The addition of tafasitamab to R^2 for a fixed duration of up to one year offers meaningful clinical benefit with a comparable safety and tolerability profile.

Importantly, some patients in the 2L setting could receive tafasitamab + R^2 in place of R-chemotherapy (see section 1.3.4). [1, 2] In the last 5 years of FL technology appraisals, patient experts have consistently highlighted the unpleasant side effects and cumulative toxicity of chemotherapy, and have spoken of welcoming any treatment that avoids chemotherapy.[4, 5, 14] Tafasitamab + R^2 offers such a non-chemotherapy treatment option.

2.12 Ongoing studies

inMIND is ongoing with final analysis planned after the last participant has completed a minimum of 5 years of post-treatment follow-up. This is anticipated in[redacted].

2.13 Interpretation of clinical effectiveness and safety evidence

2.13.1 Principal findings from the clinical evidence

2.13.1.1 Tafasitamab + R^2 versus R^2

The novel regimen of tafasitamab + R^2 demonstrated statistically significant and clinically meaningful improvements in clinical outcomes versus current standard of care (R^2) that it is primarily anticipated to displace (see Section 1.3.4). More specifically, the addition of tafasitamab to R^2 resulted in[64, 68]:

- A 57% reduction in risk of progression, relapse or death (HR: 0.43; 95% CI: 0.32, 0.58; p < 0.0001), and extension to the period of progression-free living of over 8 months
- An absolute increase in CMR rates of ~10% with patients being 1.5 times more likely to achieve a CMR (odds ratio [OR]: 1.5; 95% CI: 1.04, 2.13; p = 0.0286)
- An absolute increase in ORR of ~11% with patients being twice as likely to achieve a response (OR: 2.0; 95% CI: 1.30, 3.02; p = 0.0014), and an absolute increase in CR of ~11%
- A 53% reduction in risk of relapse and extension to the period of relapse-free living of over 7.5 months (HR: 0.47; 95% CI: 0.33, 0.68; p < 0.0001)
- A 55% reduction in the risk of needing a next line of treatment or death (HR: 0.45; 95% CI: 0.31, 0.64; p < 0.0001), and an absolute reduction in the number of patients starting new anti-lymphoma treatment of ~15%

The addition of tafasitamab to R^2 elicited durable responses, extended the period of progression-free living between treatment lines and reduced the need for a next line of treatment, therefore addressing the urgent unmet need in R/R FL (see Section 1.3.5). Patients report worsening QoL with active relapsed disease and, with each failed treatment, that FL becomes increasingly difficult to live with. [46, 47] In the real-world setting, treatments that extend the period of relapse- and progression-free living, as demonstrated by tafasitamab + R^2, are therefore expected to have a positive impact on patients' lives. In addition, exploratory analyses showed no patients in the tafasitamab + R^2 arm experienced histological transformation of FL

(vs 3% of patients in the placebo + R^2 arm), which is clinically relevant considering the much worse prognosis for patients when FL transforms to a more aggressive lymphoma type (see Section 1.3.1).

The consistency of improvements across clinical outcomes highlights the robustness of data from the inMIND trial and supports the early indications that tafasitamab + R^2 will also improve OS for people living with R/R FL. While the inMIND trial was designed around the hypothesis that tafasitamab + R^2 will improve PFS versus placebo + R^2, early data show the addition of tafasitamab to R^2 also resulted in an estimated 41% reduction in the risk of death (HR: 0.59; 95% CI: 0.31, 1.13; p = 0.1061).[64] Current data are maturing and OS will be assessed at the future 5-year analysis.

Immaturity of OS data is a common challenge in the incurable FL setting, where the primary goal of treatment is to provide the longest disease-free period between treatment lines. Other FL therapies (O-B and R^2) have been recommended in previous NICE TAs when clinical evidence showed a statistically significant slowing of disease progression and a non-statistically significant OS benefit.[5] Longer-term follow-up of their trials (GADOLIN trial of O-B in rituximab refractory patients, and AUGMENT trial of R^2 in non-refractory patients) have subsequently demonstrated a statistically significant OS benefit at 5 years.[74, 75] It is therefore plausible that the clear statistically significant improvements in PFS, and the early indications of a OS benefit, observed with tafasitamab + R^2 in the inMIND trial will translate into a long-term OS benefit (see section 3.2.2.2 for further discussion).

The clinical benefit of adding tafasitamab to R^2 was observed in all prespecified subgroups, including patients with POD24, patients refractory to prior anti-CD20 therapies and patients treated with multiple prior lines of therapy – these are difficult-to-treat patients with particularly poor prognosis (see Section 1.3.2). In patients with R/R FL after two or more systemic treatments, the addition of tafasitamab to R^2 resulted in a clinically meaningful improvement in INV-assessed PFS of an even greater magnitude than observed with tafasitamab + R^2 in the total R/R FL population or the 2L R/R FL population.[68] This is of notable importance given the particularly high unmet needs in this patient group.

The safety profile of tafasitamab + R^2 was manageable and consistent with expected toxicities of tafasitamab, lenalidomide and rituximab.[68] The addition of tafasitamab does not present any new safety concerns to the established R^2 regimen, and clinical experts confirm they have no concerns with managing potential toxicities.[1] Importantly, the addition of tafasitamab to R^2 had no detrimental impact on patients' HRQL.[60, 68] It provided the clinical benefits observed with a fixed duration of treatment up to 1 year with no maintenance period following this term.

2.13.1.2 Tafasitamab + R^2 versus R-chemotherapy

Although the introduction of tafasitamab + R^2 would primarily displace use of R^2 in the clinical pathway of care, given the magnitude of improved clinical benefit that can be achieved with this regimen it may also displace some use of R-chemotherapy in the 2L setting (see Section 1.3.4).

In the absence of direct comparative data, unanchored MAICs were conducted to attempt to estimate the relative efficacy of tafasitamab + R^2 versus R-chemotherapy. Across analyses, there was a general trend in favour of tafasitamab + R^2 but due to substantial limitations in the evidence available for the comparators (see Section 2.10) they only offer exploratory comparative insights, rather than robust comparisons. Even under a highly conservative assumption that R-chemotherapy has similar effectiveness to R^2, tafasitamab + R^2 would provide a clinically meaningful PFS and OS benefit over R-chemotherapy.

2.13.2 Strengths and limitations of the clinical evidence base

2.13.2.1 Key strengths

The inMIND trial is the first large-scale placebo-controlled study designed to validate the approach of combining two monoclonal antibodies (anti-CD19 with anti-CD20) for the treatment of FL. It provides high-quality RCT evidence, which is powered to test the clinical outcomes of most relevance to patients, carers and healthcare providers. The primary endpoint of PFS by INV is more clinically meaningful than OS in the FL setting, given the treatable but incurable nature of this disease, and reflects how the disease is managed in clinical practice. Indeed, the primary goal of treatment is to provide the longest disease-free period between treatment lines. To this point,

inMIND also provides TTNT data – TTNT is increasingly recognised as a clinically meaningful endpoint in R/R FL as it captures both disease progression and treatment decisions, reflecting real-world disease management and impact on HRQL.

The population, intervention and comparator investigated in inMIND are directly applicable to how tafasitamab + R^2 is anticipated to be used in clinical practice, and outcomes are directly reflective of the anticipated outcomes with real world use of tafasitamab + R^2. It should be noted that the outcomes of the R^2 arm of inMIND differ from outcomes of the R^2 arm of AUGMENT – the pivotal trial for R^2 that informed its NICE TA (TA627).[14] This is due to marked differences in the baseline prognosis of enrolled patients, with the inMIND trial population representing a patient cohort with a much worse prognosis than the AUGMENT population. Whilst the AUGMENT trial excluded patients who were refractory to prior anti-CD20 therapy, and only 17% of patients randomised to R^2 were refractory to their last therapy, 42% of patients randomised to R^2 in inMIND had disease that was refractory to prior anti-CD20 therapy, and 35% were refractory to their last therapy. There were also more patients with high tumour burden in the inMIND R^2 treatment arm than in the AUGMENT R^2 treatment arm (84% vs 54%) (Table 6). Consequently, outcomes from these two studies should not be compared.

Clinical experts consulted by Incyte have confirmed that the R^2 results observed in inMIND are more reflective of clinical experience than the R^2 results observed in AUGMENT.[1] They further confirmed they have no concerns with the applicability of outcomes from the inMIND trial to the intended target population, and would welcome the availability of tafasitamab + R^2 given its added value and potential to address the longstanding unmet need for additional novel treatment options for people living with FL.[1, 2]

2.13.2.2 Key limitations

The inMIND trial was not powered to test for OS at the time of primary PFS analysis, and event numbers are low at this time. This is positive for patients and not unexpected given the typically slower growing disease course in early stages of treatment, even the R/R setting. However, it does mean there is unavoidable

uncertainty around the magnitude of OS benefit tafasitamab + R^2 will provide. In recognition of this uncertainty, Incyte have included a proposal for managed access (see Section 3.8) that would accommodate early access to tafasitamab + R^2, while data collection is ongoing.

There are some differences in the subsequent treatments received in inMIND and treatments available in NHS England, most notably use of [redacted] patients in tafasitamab + R^2 arm and [redacted] patients in R^2 arm). This does not impact analyses of the primary endpoint of PFS and given the early nature of OS analyses is unlikely to have had any impact on this outcome either. It does however warrant a different approach to allocation and costing of subsequent therapies in the economic analyses, which is discussed and explored in more detail in Section 3.5.4.1.

Further uncertainty is associated with the paucity of evidence for R-chemotherapy, which precludes robust indirect comparisons. Whilst there may be some displacement of R-chemotherapy, the introduction of tafasitamab + R^2 will primarily displace R^2, for which robust, direct comparative data are available. As R^2 has already demonstrated clinical and cost-effectiveness versus R-chemotherapy, relative treatment effects for tafasitamab + R^2 versus R^2 can also be applied to R-chemotherapy in a pragmatic and highly conservative proxy approach.

3 Cost-effectiveness

- A primary base case partitioned survival model was developed to compare tafasitamab + R^2 in its anticipated 2L+ relapsed or refractory FL licensed indication against R^2, which, as the current standard of care therapy, is the most relevant comparator
- Direct comparative data for tafasitamab + R^2 and R^2 were taken from the inMIND trial. Although inMIND demonstrated a clear statistically significant improvement in PFS and an early indication of a clinically meaningful improvement in OS for tafasitamab + R^2, the current OS data are immature. A conservative approach was taken to modelling long-term outcomes, to reflect uncertainty in the magnitude of the long-term OS benefit
- In the primary base case analysis versus R^2, tafasitamab + R^2 generated an additional [redacted] LYs and [redacted] QALYs, with incremental lifetime costs of [redacted], resulting in an ICER of £32,672 per QALY gained
- While the magnitude of the OS benefit with tafasitamab + R^2 is a key area of uncertainty, scenario analyses exploring plausible alternative OS modelling assumptions yielded relatively stable ICER estimates
- An analysis exploring state transition modelling to generate OS from PFS and post-progression survival (PPS), rather than extrapolating the OS data directly from the trial, yielded an ICER for tafasitamab + R^2 of £27,101 per QALY gained compared with R^2
- Secondary analyses comparing tafasitamab + R^2 versus R-B, R-CVP, and R-CHOP in the 2L setting, by conservatively assuming the relative treatment effects from the inMIND trial, gave ICERs of £29,029, £28,723 and £30,982 per QALY gained, respectively
- In the key 3L+ subgroup analysis versus R^2, tafasitamab + R^2 generated an additional [redacted] LYs and [redacted] QALYs, with incremental lifetime costs of [redacted], resulting in an ICER of £27,377 per QALY gained
- Collectively, the primary base case and an extensive range of secondary, subgroup and scenario analysis demonstrate the significant benefits to patients offered by tafasitamab + R^2 and its plausible potential to be cost effective

- In recognition of the uncertainty in the long-term outcomes related to OS, a proposal for managed access is included in this submission.
  - This would accommodate early access to this innovative treatment for patients who have an unmet medical need with limited treatment options, while data collection is ongoing

3.1 Published cost-effectiveness studies

An SLR was conducted to identify any published literature on relevant economic analyses of treatments for patients with R/R FL. The SLR was initially conducted on 18 March 2024 and was updated on 22 April 2025. Full details of the SLR search strategy, study selection process and results can be found in Appendix E. Among the 19 economic evaluations of treatments for people with R/R FL, 13 included a partitioned survival model structure based around three health states: progression-free (PF), PD and death. A search of previous NICE submissions in FL was also conducted (see Appendix E). All submissions similarly used this three-state partitioned survival modelling approach as the base case. More details of how these evaluations have informed the de novo analysis are discussed in Appendix E.

3.2 Economic analysis

3.2.1 Patient population

Tafasitamab + R^2 is proposed as a treatment option for R/R FL in the 2L+ setting. In line with the proposed licenced indication for tafasitamab + R^2, the base case of the cost-effectiveness model evaluates tafasitamab + R^2 versus R^2 using data from the FL FAS population from inMIND. This trial population consists of patients with Grade 1−3A FL who present with R/R disease after receiving at least one systemic anti-CD20 immunotherapy or chemo-immunotherapy as 1L therapy (i.e. 2L+ setting).[64]

The inMIND trial included a large subgroup of patients with FL who had experienced multiple relapses or were refractory to 2L treatment, representing a 3L+ population.[64] This 3L+ subgroup has particular relevance due to the following factors:

- The number of prior treatments directly influences treatment decisions in clinical practice
- FL becomes increasingly difficult to treat with each relapse, as the disease develops greater resistance to therapy
- R² is currently the only available treatment option with a mechanism of action distinct from that used in 1L therapy[76]
- Consequently, R² is often reserved for 3L+ use, particularly for patients who responded well to 1L treatment and were subsequently retreated with R-chemotherapy in the 2L setting

Cost effectiveness results for this subgroup are presented in Section 3.12.

3.2.2 Model structure

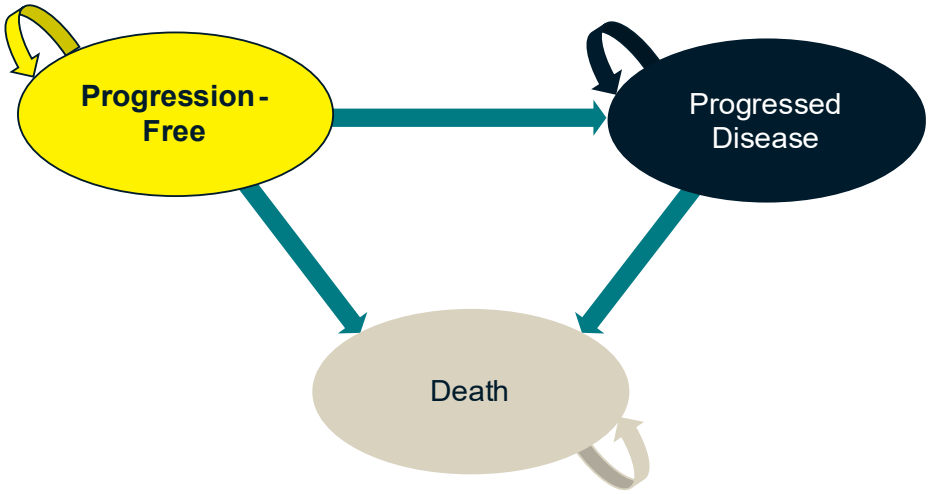
3.2.2.1 Partitioned survival model (base case)

A standard three-state partitioned survival modelling approach is adopted for the base case model (Figure 12). Consistent with best practice guidance on developing cost-effectiveness models, including NICE Decision Support Unit (DSU) Technical Support Documents (TSDs) 13[77], 14[78], 19[79] and 21[80], the partitioned survival modelling framework was selected after reviewing the literature and considering each of the following factors:

- Partitioned survival models are widely used in oncology modelling. Most economic evaluations identified in the economic SLR also employed this approach (Appendix E). The most recent NICE appraisals in FL[5, 58, 81, 82] have also employed partitioned survival models to estimate clinical benefits in terms of delaying disease progression, delaying TTNT, and improvement in OS (Appendix E)
- Partitioned survival models allow the proportion of patients in each health state to be defined directly by the individual survival curves (OS, PFS and time to treatment discontinuation [TTD]) extrapolated from the trial data
- Partitioned survival models allow for considerable flexibility in incorporating long-term extrapolations of efficacy outcomes, and for performing scenario analysis to address uncertainty

- Partitioned survival models also allow HRs derived from an ITC to weight reference curves, which allows multiple comparators to be considered consistently and relatively simply in the model

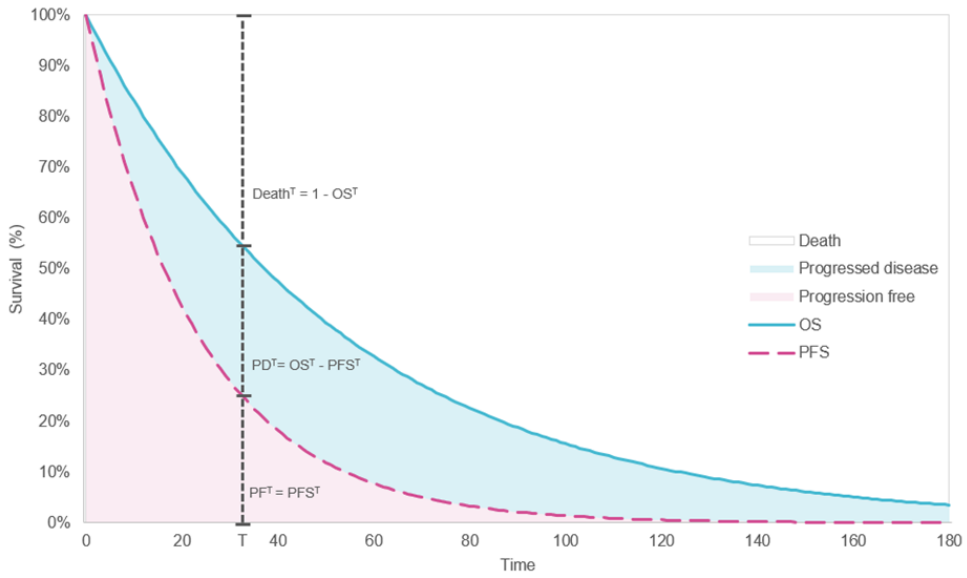
Figure 12: Model diagram



All patients enter the model in the PF health state, where it is assumed that they receive tafasitamab + R^2 or the comparator. During each cycle, patients may remain in the PF state, progress or die. Patients who have progressed may remain alive within the PD state and receive subsequent treatment, or die, with death being the absorbing state. In both the PF and PD states, patients may also be either on or off treatment. All health states in the model are mutually exclusive, and patients can only occupy one of the states at any given time.

This partitioned survival analysis uses fitted PFS and OS curves to calculate a health state's occupancy at a given time using the area under the curve approach (Figure 13). The proportion of patients in the PF state is estimated directly from the area under the extrapolated PFS curve over time, while the proportion in the death state is estimated directly as 1−OS curve over time. The proportion of patients in the PD state is estimated as the difference between the extrapolated PFS and OS curves.

Figure 13: Health state occupancy at time T



Key: PD, progressed disease, PFS, progression-free survival; OS, overall survival.

In addition, the following adjustments are applied to maintain logical consistency in the patient flow of the model:

- The mortality risk at each model cycle is capped by age-matched general population mortality, sourced from the latest available ONS Life Tables
- A limit is built into the model to ensure that PFS cannot exceed OS

3.2.2.2 State transition model (scenario analysis)

At the request of the EAG during the decision-problem meeting, an exploratory state transition model has been developed as a scenario analysis to complement the base case partitioned survival model. In a state transition model, rather than extrapolating OS data directly from a trial, long-term OS is effectively constructed via a structural assumption that OS = PFS + PPS. The treatment effect on OS is therefore determined by the combined effect of this structural assumption and the treatment effect on PFS and PPS. Data on PFS and PPS and their relationship to OS in R/R FL are therefore required to construct and appropriately parameterise the state transition model.

The structural relationship between PFS and OS events in FL is somewhat nuanced. A systematic review of studies in patients with FL, published in 2024, found that PFS

is only a weak surrogate for OS (correlation coefficient; 0.383, $p < 0.001$)[83], which suggests that gains in PFS may not always translate into clear OS benefits.[83] Yet, during the validation interviews undertaken for this submission, clinical experts had mixed opinions on the relationship between PFS and OS, and acknowledged it may differ across different patient cohorts.[2] For patients with a slow progressing cancer, that continues to respond well to multiple lines of rituximab-based therapies and who are unlikely to die soon following relapse, the relationship between PFS and OS is thought to be limited. In contrast, for patients with a more aggressive disease course that does not respond well to rituximab-based therapies and who are likely to die close to relapse, the relationship between PFS and OS is thought to be strong.[84]

While the inMIND trial provides robust PFS evidence, the limitations in the analysis of OS data extend to analysis of PPS. Given this, and the mixed and nuanced views of clinicians on the relationship between PFS and OS, it was necessary to look to external data sources to inform the expected relationship between PFS, PPS and OS, and to estimate the expected PPS for tafasitamab + R^2 and R^2 in the 2L+ inMIND population of interest.

Clinicians indicated that the relationship between PFS and OS may be influenced by rituximab refractory status.[2] The inMIND trial population includes a mix of patients by rituximab refractory status (see Table 7); it was therefore concluded that external sources to inform PPS in the state transition model should ideally include rituximab refractory and non-refractory patients. Additionally, as PPS data are rarely published, they should provide sufficient data from which the relationship between PFS and long-term OS could be explored, and to allow PPS to be estimated.

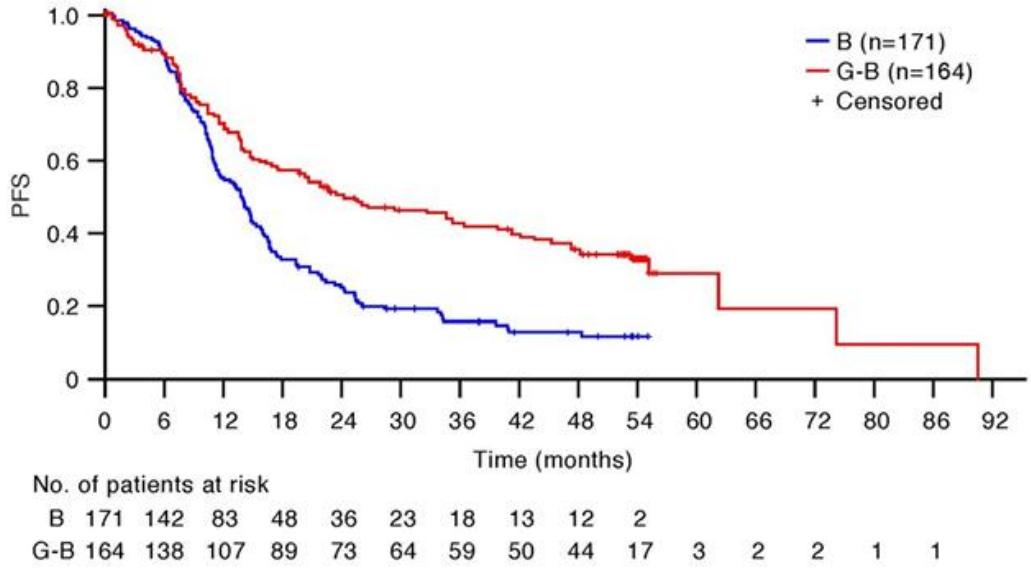
The only RCTs of therapies for relapsed or refractory FL with long-term OS follow-up are the AUGMENT trial of R^2, conducted in non-rituximab refractory patients,[74] and the GADOLIN trial of O-B, conducted in rituximab refractory patients.[75] These demonstrated that statistically significant improvements in PFS can translate into long-term OS benefits in rituximab refractory and non-refractory patients.

The AUGMENT trial, at a median follow-up of 28.3 months, showed a significant benefit in PFS for R^2 versus placebo + rituximab in the R/R FL population (median PFS 39.4 moths vs 13.8 months; HR: 0.40 [95% CI 0.29, 0.55]; $p < 0.0001$).[6, 85] Over

a longer-term follow-up of 66.1 months, efficacy was sustained and a significant OS benefit was reported for R^2; 5-year OS rates were 85.9% versus 77.0%; HR: 0.49 (0.28, 0.85).[85] However, as median OS had not been reached in either treatment arm, it is not possible to infer from these data whether the observed OS benefit was due to improvement in both PFS and PPS, or was due to improvement in PFS alone.

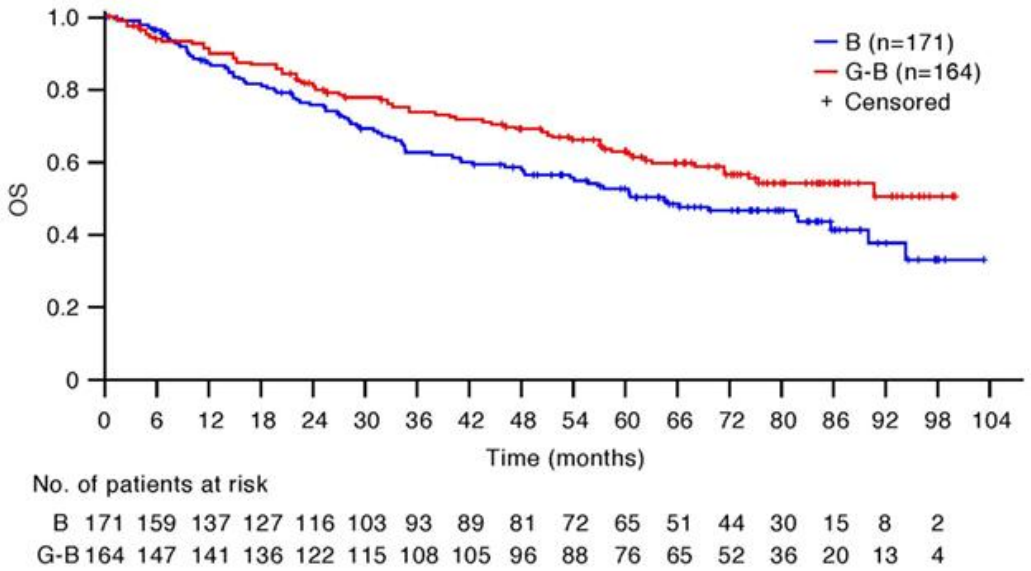
The final analysis of the GADOLIN trial, with a maximum OS follow-up time in excess of 98 months, showed a significant benefit for O-B versus placebo + bendamustine in both PFS (median PFS 24.1 months vs 13.7 months; HR: 0.51 [95% CI 0.39, 0.67]; p < 0.0001) (Figure 15) and OS (median OS not reached vs 60.3 months; HR: 0.71 [95% CI 0.51, 0.98]; p = 0.0343) (Figure 15).[75] Based on pragmatic consideration of these median PFS and OS data, the median OS in the O-B arm if there was no effect of treatment on PPS would be expected to be close to 70.7 months (i.e. 60.3 months + [24.1 months – 13.7 months]). However, after over 98 months of follow-up, median OS was still not reached in the O-B arm. Conservatively assuming a median OS for O-B of 98 months, the median PPS with O-B would necessarily be 73.9 months (i.e. 98 months – 24.1 months), compared with 46.6 months (i.e. 60.3 months – 13.7 months) for placebo + bendamustine. These data therefore indicate that the OS benefit with O-B in this rituximab refractory population was due to improvements in both PFS and PPS.

Figure 14: GADOLIN Kaplan–Meier plot of investigator-assessed PFS, patients with FL (ITT population)



Key: B, bendamustine; FL, follicular lymphoma; G-B, obinutuzumab in combination with bandamustine followed by obinutuzumab maintenance; ITT, intention-to-treat; PFS, progression-free survival. **Source:** Sehn et al. 2019.[75]

Figure 15: GADOLIN Kaplan–Meier plot of overall survival, patients with FL (ITT population)



Key: B, bendamustine; FL, follicular lymphoma; G-B, obinutuzumab in combination with bandamustine followed by obinutuzumab maintenance; ITT, intention-to-treat; PFS, progression-free survival. **Source:** Sehn et al. 2019.[75]

Based on the GADOLIN trial data, a state transition model (STM) with a beneficial treatment effect on both PFS and PPS informing OS may be appropriate for a rituximab refractory population. For a non-rituximab refractory population, the AUGMENT trial was unable to provide sufficient insights on the relationship between PFS, PPS and OS. However, prespecified subgroup analysis of the inMIND trial indicates there are no differences in PFS treatment effects for tafasitamab + R^2 versus R^2 in rituximab refractory and non-refractory patients (see Figure 10). In the absence of evidence or a biological rationale for the improvement observed in PFS to be accompanied by a reduction in PPS following treatment with tafasitamab + R^2, it is plausibly conservative to assume that PPS would be unaffected by treatment in non-rituximab refractory patients. For non-rituximab refractory patients, a state transition model with only beneficial effects on PFS informing OS (i.e. assuming no differences in PPS between treatment arms) may therefore be appropriate.

Based on these data, the following state transition model-based scenarios are explored:

- STM 1: A model in which OS benefit is determined only by PFS benefit:
  - A conservative scenario that assumes the same PPS for both tafasitamab + R^2 and R^2, where OS differences are driven by PFS differences alone. In the absence of PPS data from AUGMENT or another exclusively non-rituximab refractory population, PPS has been estimated from the OS and PFS data from the UK HMRN real-world dataset described in Section 2.10 and Appendix B
- STM 2: A model in which OS benefit is determined by benefit in both PFS and PPS:
  - A scenario assuming a beneficial treatment effect on both PFS and PPS. Treatment-specific PPS data are derived for tafasitamab + R^2 and R^2 based on the relationship between PFS and OS observed in the long-term follow-up of the GADOLIN trial

Given that the inMIND trial population includes both rituximab refractory and non-refractory patients, STM 1, (assuming no beneficial impact on PPS) is likely to

significantly underestimate the relationship between PFS and OS across the inMIND trial population, based on the findings from the GADOLIN trial in rituximab refractory patients. In contrast, STM 2 (assuming both a PFS and a PPS benefit) is likely to overestimate the relationship between PFS and OS across the inMIND trial population. Therefore, a third scenario (STM 3) that weights the relationship between PFS and OS based on the proportion of rituximab refractory and non-refractory patients in the inMIND trial is conducted to provide the most plausible state transition modelled estimate of the expected cost-effectiveness of tafasitamab +R^2 versus R^2 in the licensed population.

Further details of the implementation and parameterisation of the state transition model scenarios are provided in Section 3.3.3.1.3.

3.2.2.3 Perspective

In line with NICE guidance, the base case considers a payer perspective. Direct costs faced by the NHS and Personal Social Services (PSS) are captured and all costs are expressed in pounds sterling (£). The cost year is 2023/24. Where costs are inflated to the year 2023/24, NHS Cost Inflation Index (after 2015) and Health and Community Health Services (before 2015) indices are used.[86]

3.2.2.4 Time horizon and cycle length

The model time horizon represents the patient's lifetime up to a maximum age of 100 years. The base case starting age is 64.2 years, aligned to the inMIND trial population (Table 6). Therefore, the maximum effective time horizon will be 36 years.

The model cycle length is fixed at 7 days (1 week). This cycle length is considered sufficiently short to accurately capture key clinical outcomes, as well as allowing precise calculation of drug acquisition and administration costs over time. In the base case, half-cycle correction is not applied due to the short model cycle length.

3.2.2.5 Discounting

All outcomes (costs, quality-adjusted life years [QALYs] and life years [LYs]) are discounted at 3.5% per annum in the model, based on the NICE reference case.[87] Scenario analysis included outcomes discounted at 1.5% per annum.

3.2.3 Intervention technology and comparators

3.2.3.1 Intervention

The intervention investigated within this model is tafasitamab + R^2, which is administered in line with the inMIND trial and licensed dosing schedule. Patients receive tafasitamab 12 mg/kg intravenously on Days 1, 8, 15 and 22 (i.e. every week) for the first three treatment cycles and 12 mg/kg intravenously on Days 1 and 15 (i.e. every 2 weeks) from treatment cycle 4 onwards, up to a maximum of 12 treatment cycles. Each treatment cycle is defined as 28 days. In addition, patients in the tafasitamab + R^2 arm receive lenalidomide at 20 mg every day on Days 1–21 for up to 12 cycles, and rituximab 375 mg/m^2 intravenously on Days 1, 8, 15 and 22 of Cycle 1, and Day 1 of Cycles 2–5. Further information is provided in Table 20.

Table 20: Dosage, route and administration frequency of intervention

Drug	Dose	Route	Frequency
Tafasitamab	12 mg/kg	IV	Days 1, 8, 15, and 22 of Cycles 1–3, and Days 1 and 15 of Cycles 4–12
Lenalidomide	20 mg	PO	Every day on Days 1–21 of Cycles 1–12
Rituximab	375 mg/m^2	IV	Days 1, 8, 15, and 22 of Cycle 1, and Day 1 of Cycles 2–5
Key: IV, intravenous, PO, per oral.			

3.2.3.2 Comparators

The current standard of care treatment in the UK for R/R FL is R^2, as recommended by NICE and used as the comparator in the inMIND trial (see Section 1.3.4). As confirmed by clinical experts, R^2 is the primary comparator to tafasitamab + R^2 in the 2L+ treatment setting.[1, 2] The dosing of the R^2 components (lenalidomide and

rituximab) follows the same schedule as that for patients receiving tafasitamab + R^2, as shown in Table 20.

Another relevant comparator for the economic evaluation is R-chemotherapy, as there may be some displacement of R-chemotherapy use in the 2L setting, with the hope that earlier use of a more effective treatment option (tafasitamab + R^2) will prevent or delay progression of FL and the need for subsequent lines of therapy (see Section 1.3.4).

As discussed in Section 1.3.4, the most common R-chemotherapy regimens used in the UK are:

- R-B – rituximab with bendamustine
- R-CHOP – rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone
- R-CVP – rituximab with cyclophosphamide, vincristine and prednisolone

Dosing information for R-chemotherapy was derived from corresponding SmPCs. Rituximab maintenance in the R-B, R-CHOP and R-CVP regimens can be administered by intravenous infusion (375 mg/m^2) or subcutaneous injection (1,400 mg). Both options are administered on Day 1 of each 3-monthly cycle for up to 2 years. As UK standard clinical practice is to administer rituximab subcutaneously during the maintenance phase,[1, 2] the model base case assumes the use of subcutaneous rituximab, while the impact of assuming intravenous rituximab is tested in a scenario analysis (see Section 3.11.3).

Table 21: Secondary model comparators with dosing schedules

Comparator	Treatment	Phase	Dose	Route	Frequency
R-B*	Rituximab	Induction	375 mg/m^2	IV	Day 1 of Cycles 1–6
	Bendamustine		90 mg/m^2	IV	Days 1 and 2 of Cycles 1–6
	Rituximab	Maintenance	SC: 1,400 mg IV: 375 mg/m^2	SC or IV	Day 1 of each 3-monthly

Comparator	Treatment	Phase	Dose	Route	Frequency
					cycle, up to 2 years
R-CHOP*	Rituximab	Induction	375 mg/m^2 on Day 1	IV	Day 1 of Cycles 1–6
	Doxorubicin		50 mg/m^2 on Day 1	IV	Day 1 of Cycles 1–6
	Vincristine		1 mg/m^2 on Day 1	IV	Day 1 of Cycles 1–6
	Cyclophosphamide		750 mg/m^2 on Day 1	IV	Day 1 of Cycles 1–6
	Prednisolone		40 mg/m^2 on Days 1–5	PO	Days 1–5 of Cycles 1–6
	Rituximab	Maintenance	SC: 1,400 mg IV: 375 mg/m^2	SC or IV	Day 1, of each 3-monthly cycle, up to 2 years
R-CVP*	Rituximab	Induction	375 mg/m^2	IV	Day 1 of Cycles 1–8**
	Cyclophosphamide		750 mg/m^2	IV	Day 1 of Cycles 1–8**
	Vincristine		1 mg/m^2	IV	Day 1 of Cycles 1–8**
	Prednisolone		40 mg/m^2	PO	Days 1–6 of Cycles 1–8**
	Rituximab	Maintenance	SC: 1,400 mg IV: 375 mg/m^2	SC or IV	Day 1, of each 3-monthly cycle, up to 2 years

Key: IV, intravenous; PO, per oral; R-B, rituximab with bendamustine; R-CHOP, rituximab + doxorubicin + vincristine + cyclophosphamide + prednisolone; R-CVP, rituximab + cyclophosphamide + vincristine + prednisolone; SC, subcutaneous.

Note: * R-chemotherapy is comprised of these separate rituximab-based regimens; ** R-CVP can be given for Cycles 6–8 and a maximum of eight cycles was assumed.

3.3 Clinical parameters and variables

3.3.1 Overview of survival modelling process

The primary source of clinical data for the base case partitioned survival model is inMIND, as it provides direct evidence for tafasitamab + R^2 versus the most relevant comparator, R^2, in the population of interest. The key endpoints used to inform the base case partitioned survival model are PFS, OS and TTD. HRQL and adverse events observed in inMIND were also incorporated into the model.

Efficacy outcomes (OS, PFS and TTD) for tafasitamab + R^2 and R^2 were modelled using PLD for the FAS FL population from inMIND. The proportional hazards assumption was assessed for OS and PFS to determine if proportional hazards models would be appropriate. This assessment used visual inspection of the observed Kaplan−Meier curves, Schoenfeld residuals and log-cumulative hazard plots.

Extrapolation of outcomes beyond the trial period is required to assess the cost-effectiveness of tafasitamab + R^2 over a lifetime time horizon. Parametric survival curves were fitted to OS and PFS outcomes from inMIND (both separately and jointly) to inform efficacy in the tafasitamab + R^2 and R^2 arms of the economic model. Standard parametric survival curves (exponential, Weibull, log-normal, log-logistic, Gompertz, gamma and generalised gamma) were considered based on guidance from NICE TSD 14.[78]

For the model base case, curve selection was informed by following the systematic process below:

- Assessment of proportional hazards assumption using log-cumulative hazard plots, Schoenfeld residual plots and quantile−quantile plots
- Consistency and alignment of the different joint and separately fitted parametric PFS and OS curves with the observed PFS and OS data
- Visual fit to the observed Kaplan−Meier data within the inMIND trial period
- Within-trial goodness-of-fit statistics per the Akaike information criterion (AIC) and Bayesian information criterion (BIC)

- Clinical plausibility of long-term survival extrapolations informed by UK clinical experts[2]
- Clinical plausibility of long-term extrapolations of the hazards informed by UK clinical experts[2]
- Clinical plausibility of long-term extrapolations of the hazards informed by RWE (HMRN datasets described in Section 2.10.2)
- Consistency with Committees' preferred assumptions in previous NICE appraisals[14]

Outputs of the above curve selection process were validated by two independent health economists during submission preparation. The most appropriate and plausible models for OS and PFS were then used to inform the model base case, with alternative plausible models tested in various scenario analyses.

In the absence of direct comparative data, the comparative effectiveness of R-chemotherapy (R-CHOP, R-CVP, and R-B) should be informed by robust ITCs. However, as discussed in Section 2.10, due to limitations with the publicly available R-chemotherapy trial and registry data, there were challenges in conducting robust MAICs to estimate the comparative effectiveness of tafasitamab + R^2 versus R-chemotherapy, and the results lacked face validity.

Therefore, a pragmatic approach has been adopted using inMIND RCT data on tafasitamab + R^2 versus R^2 to represent the comparative effectiveness of tafasitamab + R^2 versus R-chemotherapy. Given that NICE TA627[14] and clinical experts indicate that R^2 would be expected to be meaningfully more effective than R-chemotherapy, this is a highly conservative assumption. Furthermore, this assumption enables the conduct of fully incremental analyses; without it, only pairwise comparisons would be possible against each R-chemotherapy regimen, as each MAIC would yield different PFS and OS curves for the tafasitamab + R^2 arm, resulting in varying total costs, LYs, and QALYs for the intervention depending on the comparator used in the cost-effectiveness analysis.

3.3.2 Progression-free survival modelling

3.3.2.1 Tafasitamab + R^2 versus R^2: PFS

3.3.2.1.1 PFS curve selection

Table 22 provides a summary of the determination of the most appropriate curves for modelling PFS, based on the comprehensive, systematic process outlined above. Full details of the completion of all steps in the process are provided in Appendix L.

The jointly fitted generalised gamma and log-logistic curves were considered the most clinically and statistically plausible to model long-term PFS. Generalised gamma is applied in the base case as it yields landmark survival values slightly closer to those suggested by the clinicians during the validation process, and log-logistic is explored in scenario analysis.

Table 22: Summary of the considered PFS curves based on each criterion

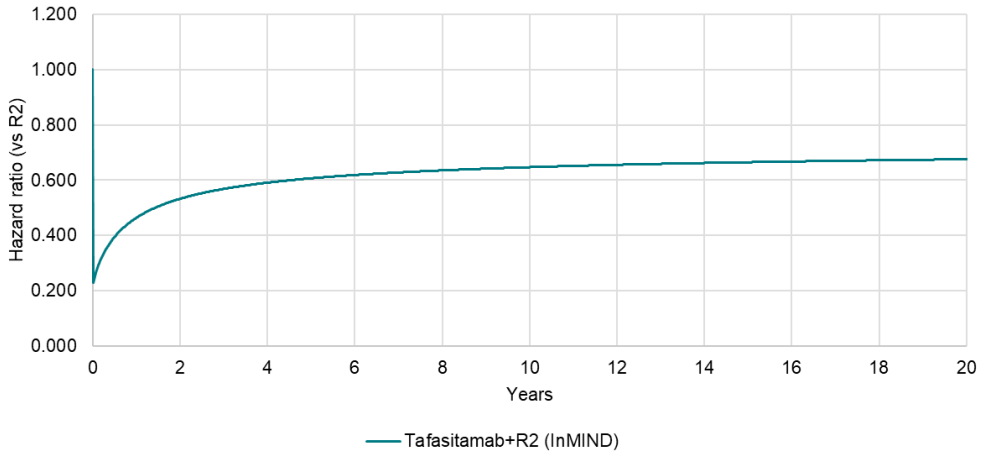
Criterion assessed	Inference for appropriate curves	Justification
PH assessment: Log-cumulative hazard plot and Schoenfeld residual plot	Separately fitted non-AFT models	Significant p-value in the Schoenfeld Individual Test
AFT assessment: Quantile−quantile plot	Jointly fitted AFT models	Linearity in the quantile–quantile plot
Plausibility of OS long-term extrapolations	Jointly fitted models; only jointly fitted models were considered following this assessment	Consistency with extrapolations aligned with clinical validation of OS: tafasitamab + R^2 should have longer OS than R^2 if the same parametric curve is selected for both arms
Visual fit and within-trial goodness-of-fit	Jointly fitted generalised gamma, gamma and log-logistic	Models within 5 points of the best fitting model based on AIC and BIC
Plausibility of long-term extrapolations	Jointly fitted generalised gamma and log-logistic	Extrapolations most aligned with clinical validation
Plausibility of long-term hazards	Jointly fitted generalised gamma, log-logistic and log-normal	Extrapolations most aligned with clinical validation and RWE from HMRN: decreasing hazards after the initial months
Conclusion on PFS curve selection	Jointly fitted generalised gamma in base case	Closest to clinician expectations on PFS over time. Log logistic (next closest) explored in scenario analysis

Key: AIC, Akaike information criterion; AFT, accelerated failure time; BIC, Bayesian information criterion; OS, overall survival.

3.3.2.1.2 PFS treatment effect waning

Figure 16 shows that the PFS HR converges to approximately 0.65 at 20 years using the base case extrapolation. As noted by clinicians during validation, it is unlikely that the tafasitamab + R^2 treatment effect versus R^2 persists for 20 years or more.[2] Therefore, a treatment-waning effect was considered to reflect a plausible treatment effect over time.

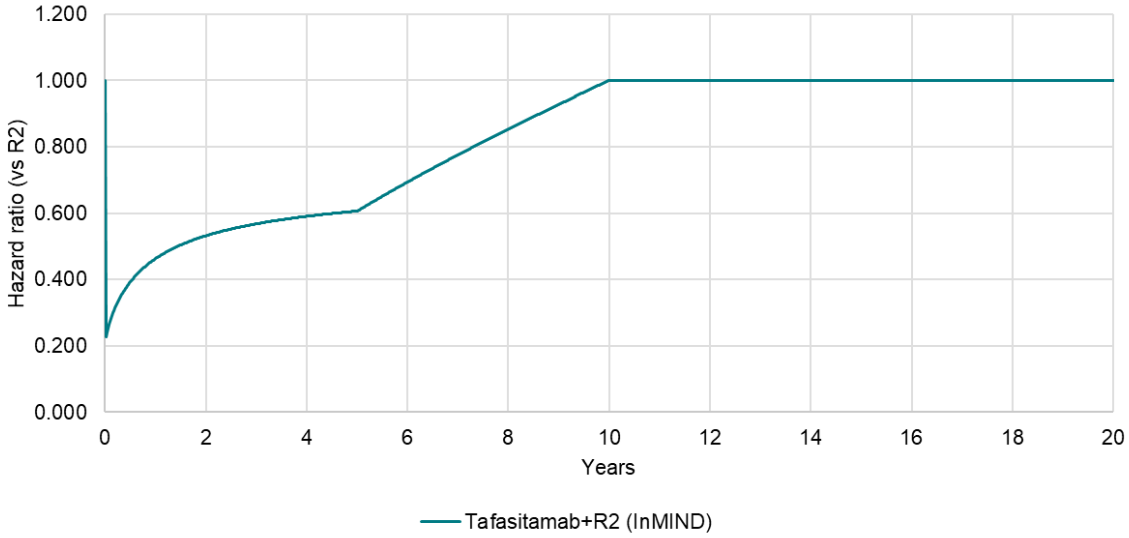
Figure 16: PFS long-term hazard ratio (no waning)



Key: PFS, progression-free survival; R^2, rituximab with lenalidomide.

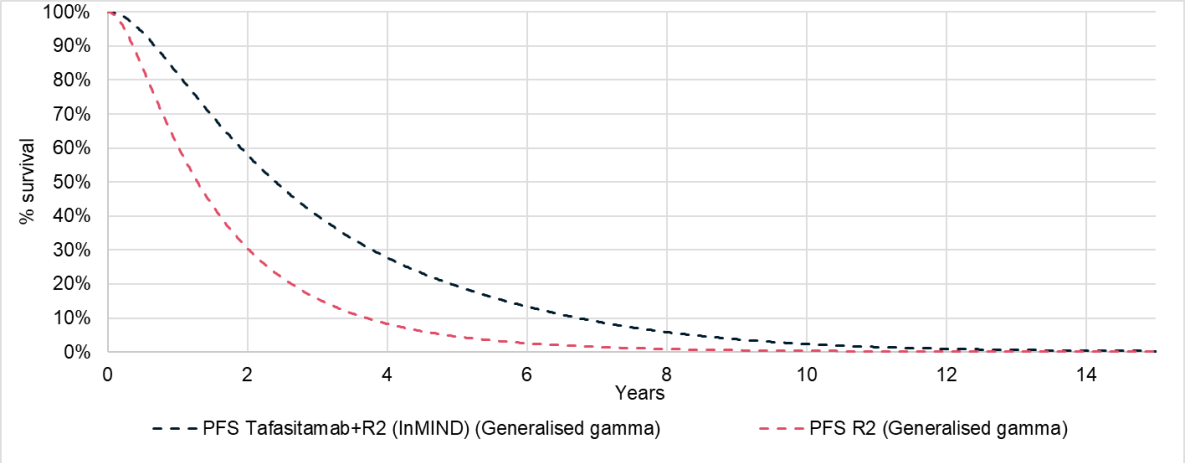
In NICE TA627, the Committee considered it plausible that treatment waning would start between 5 and 10 years and selected a 5-year starting point as the base case.[14] During clinical validation for this submission, clinicians agreed that the hazards could start to converge after 5 years.[2] However, in NICE TA627, an instantaneous waning effect was applied at 5 years.[14] An instantaneous waning effect would lead to an implausible instant change in the hazard ratio. Therefore, the base case assumes waning occurs over a period of 5 years. This assumption, in combination with waning starting at 5 years, leads to a gradual convergence of the hazard ratio to 1 between 5 and 10 years (Figure 17). The survival curves after the waning effect is applied (Figure 18) are consistent with the clinical expectations for PFS described previously. These extrapolations represent a more conservative interpretation of the plausible range considered by the Committee during TA627.

Figure 17: PFS long-term hazard ratio (waning starting at 5 years with a duration of 5 years)



Key: PFS, progression-free survival; R^2, rituximab with lenalidomide.

Figure 18: Tafasitamab + R^2 and R^2 PFS extrapolations with treatment waning effect



Key: PFS, progression-free survival; R^2, rituximab with lenalidomide.

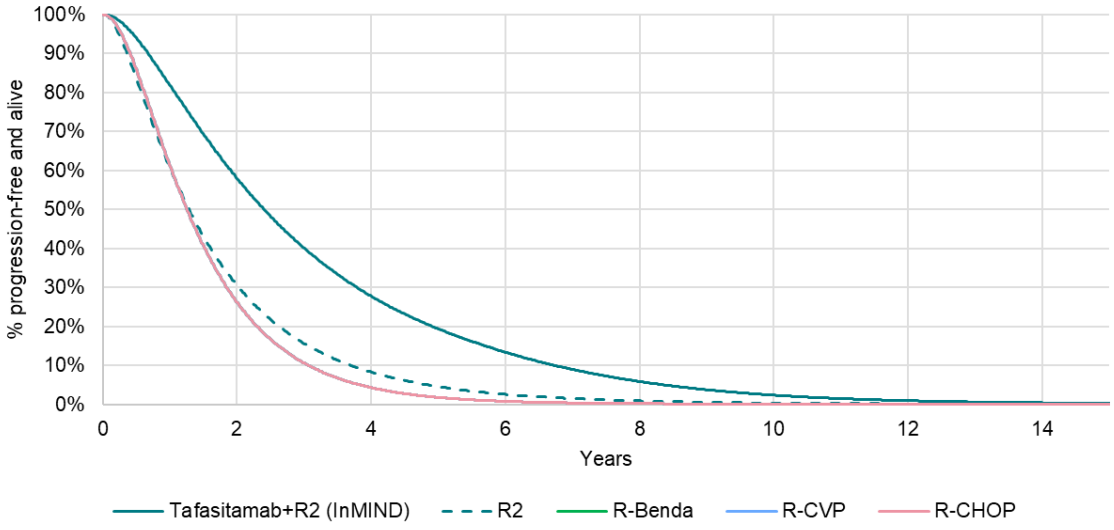
Alternative treatment waning effect assumptions were tested in the scenario analysis, including different starting points and durations of the waning effect, such as a 10-year waning duration, which resulted in a smoother convergence of the hazard ratio to 1. When isolating the waning effect on the PFS curves, the scenario

analysis shows that the impact on the ICER is limited (due to relatively small utility decrement after progression, see Section 3.4).

3.3.2.2 Tafasitamab + R^2 versus R-chemotherapy: PFS

As noted in Sections 2.10 and 3.3.1, the MAIC results lack face validity. Consequently, the model takes a conservative approach by assuming that the relative treatment effects for tafasitamab + R^2 versus R^2 represent the relative treatment effects for tafasitamab + R^2 versus R-chemotherapy regimens (R-B, R-CVP, and R-CHOP). This is implemented by applying the same PFS hazard ratio for tafasitamab + R^2 versus R^2 (HR: 0.41; see Section 2.6.4) to the tafasitamab + R^2 extrapolated PFS curves to derive the R-chemotherapy survival curves, rather than directly using the R^2 PFS curve. This approach results in some minor differences between the R^2 and the R-chemotherapy PFS curves (Figure 19). These differences have a negligible impact on the respective ICERs, given the small utility decrement and the additional healthcare resource utilisation (HCRU) costs after progression.

Figure 19: R-B, R-CHOP and R-CVP long-term PFS extrapolations



Key: PFS, progression-free survival; R^2, rituximab with lenalidomide; R-B, rituximab with bendamustine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; R-CVP, rituximab with cyclophosphamide, vincristine and prednisolone.

3.3.3 Overall survival modelling

3.3.3.1 Tafasitamab + R^2 versus R^2: OS

3.3.3.1.1 OS curve selection

OS curve selection followed same comprehensive, systematic process used for PFS and outlined in Section 3.3.1.

Table 23 provides a summary of the determination of the most appropriate OS. Full details of the completion of all steps in the process are provided in Appendix L.

Despite clear OS data challenges, the selection process indicates that jointly fitted generalised gamma and log-logistic are the most clinically and statistically plausible parametric curves for modelling OS in the long term. The generalised gamma curve is applied in the base case as it most closely reflects the expected OS rates over time expressed by clinicians during the validation process. Log-logistic, as the next most plausible model, is explored in scenario analysis.

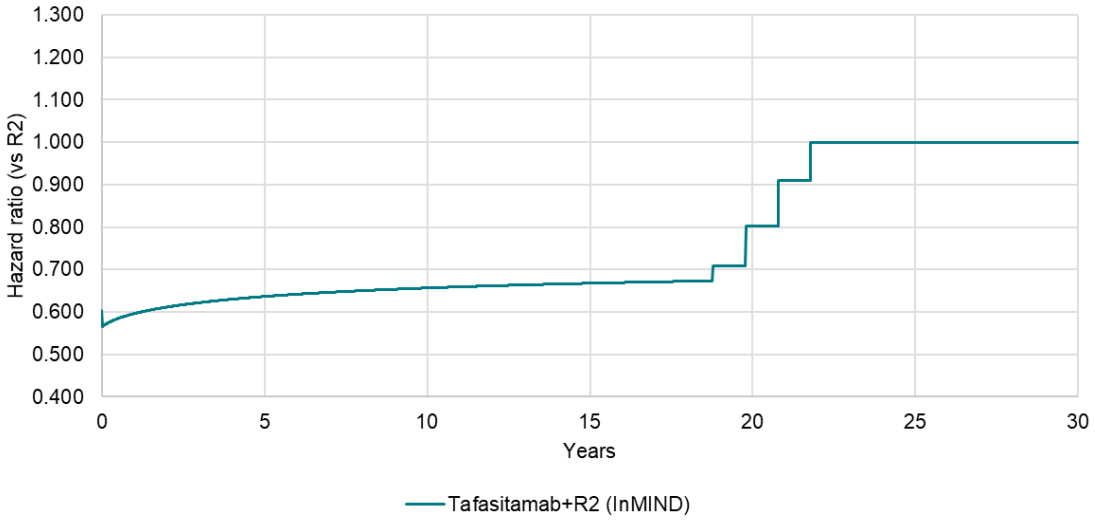
Table 23: Summary of the considered OS curves based on each criterion

Criterion assessed	Inference for appropriate curves	Justification
PH assessment: Log-cumulative hazard plot and Schoenfeld residual plot	Jointly fitted non-AFT models	Non-significant p-value in the Schoenfeld Individual Test
AFT assessment: Quantile−quantile plot	Not informative	OS data limited
Plausibility of OS long-term extrapolations	Jointly fitted models; only jointly fitted models were considered following this assessment	Extrapolations aligned with clinical validation: tafasitamab + R^2 should have longer OS than R^2 if the same parametric curve is selected for both arms
Visual fit and within-trial goodness-of-fit	All jointly fitted curves	Models within 5 points of the best fitting model based on AIC and BIC
Plausibility of long-term extrapolations	Jointly fitted generalised gamma and log-logistic	Extrapolations aligned with clinical validation
Plausibility of long-term hazards	Jointly fitted exponential and generalised gamma	Extrapolations aligned with clinical validation and RWE from HMRN: fluctuating hazards without a clear trend, which on average are assumed to remain constant in the long term
Conclusion on OS curve selection	Jointly fitted generalised gamma in base case	Closest to clinician expectations on PFS over time. Log logistic (next closest) explored in scenario analysis
Key: AFT, accelerated failure time; OS, overall survival.		

3.3.3.1.2 OS treatment effect waning

Figure 20 shows that, using the base case extrapolation, the OS hazard ratio converges to approximately 0.7 over 18 years, and only then begins to approach 1, driven by background mortality. Since the tafasitamab + R^2 treatment effect on OS is unlikely to persist this long, treatment effect waning was incorporated into the base case.

Figure 20: OS long-term hazard ratio (no waning)



Key: OS, overall survival; R^2, rituximab with lenalidomide.

Due to the limited follow-up in inMIND, there is uncertainty on the treatment effect duration. Assumptions in previous appraisals (TA627) and alignment with the medium-term survival gains reported in relapsed or refractory FL trials were considered to select the base case waning assumptions. During TA627[14], the Committee deemed it plausible to start the waning effect between Years 5 and 10, and it selected 5 years in the model base case. A waning effect starting at 5 years and with a 5-year duration was initially selected and explored for plausibility.

Table 24 presents the base case extrapolated OS landmarks for tafasitamab + R^2 and R^2 with this waning assumption applied, and the OS landmarks estimated from the published long-term OS Kaplan–Meier curves from the GADOLIN[75] and AUGMENT[74] trials. Assuming that the OS benefit observed across the GADOLIN[75] and AUGMENT[74] trials provides a plausible range of OS benefit to be expected over time following a clear PFS benefit, the observed OS benefit with tafasitamab + R^2 over time with a waning effect starting at 5 years and with a 5-year duration appears to be plausible and was therefore adopted for the base case.

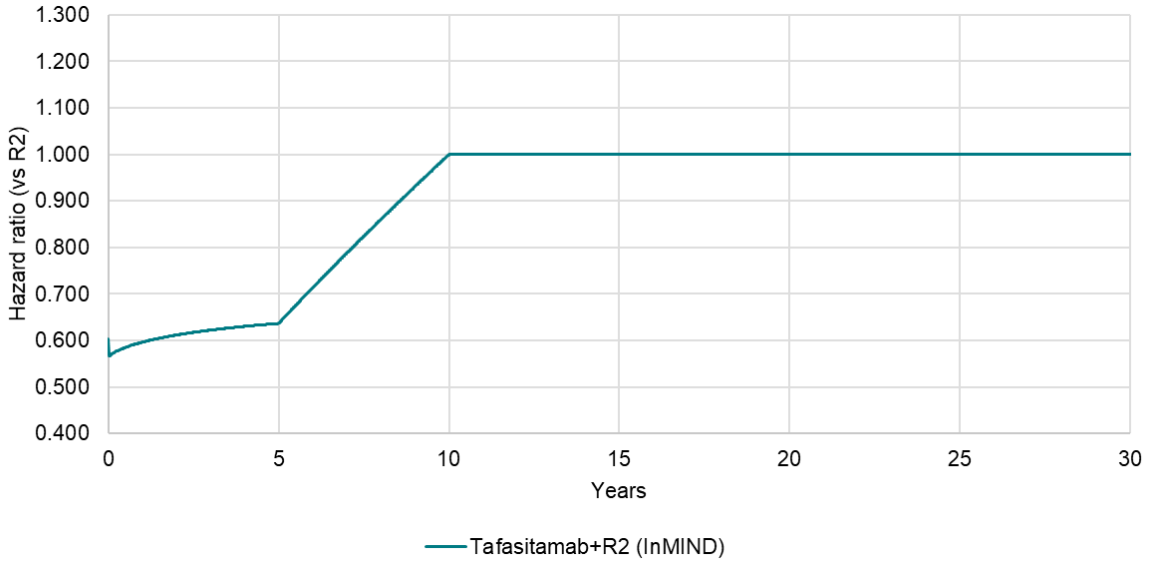
Table 24: Tafasitamab + R^2 and R^2 base case landmarks (with waning effect) compared to GADOLIN and AUGMENT OS Kaplan–Meier curves

Extrapolations	OS landmarks							
	1 year	**3 years**	**4 years**	**5 years**	**6 years**	**7 years**	**11 years**	**15 years**
inMIND (jointly fitted generalised gamma curves); HR: 0.59 (95% CI 0.31, 1.13)								
Tafasitamab + R^2	96.4%	86.2%	81.1%	76.1%	70.9%	65.6%	44.9%	29.7%
R^2	93.9%	78.3%	70.9%	64.1%	57.8%	52.1%	34.5%	22.8%
Difference	2.5%	7.9%	10.2%	12.0%	13.1%	13.5%	10.4%	6.9%
GADOLIN KM curves; HR: 0.71 (95% CI 0.51, 0.98)								
O-Benda	91.2%	74.3%	70.3%	64.2%	59.5%	54.7%	N/A	N/A
Benda	87.8%	62.8%	58.8%	53.4%	47.3%	43.9%	N/A	N/A
Difference	3.4%	11.5%	11.5%	10.8%	12.2%	10.8%	N/A	N/A
AUGMENT KM curves; HR: 0.59 (95% CI 0.37, 0.95)[a]								
R^2	95.6%	87.3%	86.7%	83.1%	82.3%	82.3%	N/A	N/A
Rituximab monotherapy	96.6%	83.7%	81.9%	77.1%	69.3%	67.1%	N/A	N/A
Difference	-1.0%	3.6%	4.8%	6.0%	13.0%	15.2%	N/A	N/A

Key: HR, hazard ratio; KM, Kaplan–Meier; N/A, not applicable; NHL, non-Hodgkins lymphoma; OS, overall survival; R^2, rituximab + lenalidomide.
Note: [a] This KM curve relates to the overall indolent NHL population enrolled in AUGMENT in the absence of a long-term FL KM curve.

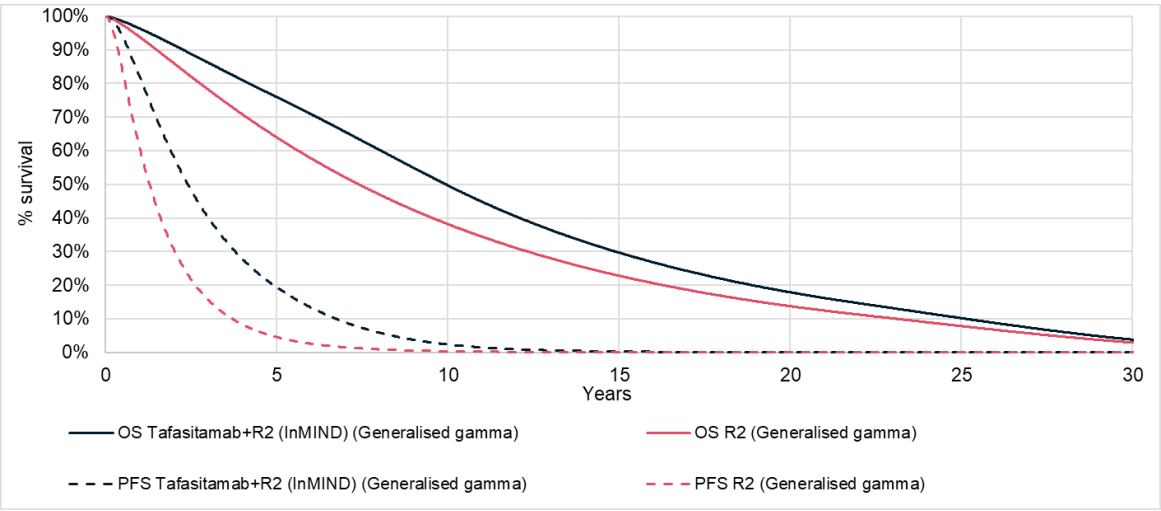
The resulting hazard ratio over time incorporating the treatment effect waning is presented in Figure 21. The OS curves after treatment effect waning and background mortality adjustment are displayed in Figure 22. Table 25 presents the OS landmarks at specific timepoints. The base case waning assumption is potentially conservative, since a longer treatment waning duration was also considered plausible (i.e. 10-year duration) in NICE TA627.[14] Alternative treatment waning effect assumptions, such as 10-year duration, were therefore tested in scenario analyses (see Section 3.11.3).

Figure 21: OS long-term hazard ratio (waning starting at 5 years with a duration of 5 years)



Key: OS, overall survival; R^2, rituximab with lenalidomide.

Figure 22: Tafasitamab + R^2 and R^2 OS extrapolations with treatment waning effect



Key: OS, overall survival; R^2, rituximab with lenalidomide.

Table 25: Base case OS landmarks with waning effect

Treatment	OS landmarks					
	2 years	5 years	10 years	20 years	30 years	35 years
Tafasitamab + R^2	91.4%	76.1%	49.8%	17.9%	3.8%	0.7%
R^2	86.1%	64.1%	38.2%	13.7%	2.9%	0.5%
Key: OS, overall survival; R^2, rituximab with lenalidomide.						

3.3.3.1.3 State transition modelling approach (scenario analysis)

A state transition modelling approach was explored in the scenario analysis to the base case to estimate long-term OS based on PFS and PPS, rather than extrapolating the direct OS data from inMIND. This is similar to the approach taken in NICE TA1103.[88]

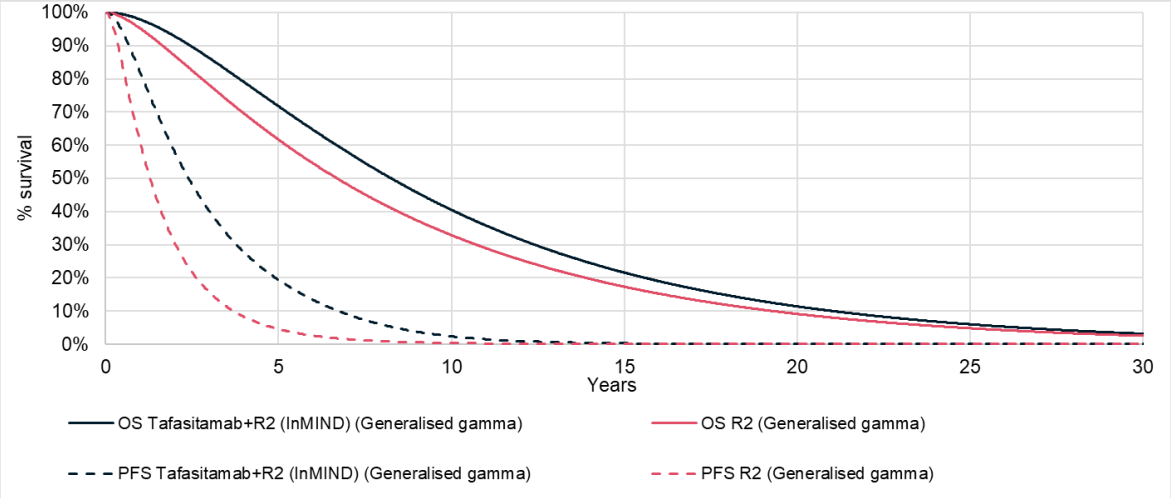
The STM analyses were implemented by extrapolating PFS by IRC data from inMIND using parametric curves, as in the standard partitioned survival modelling approach. The probability of patients moving to the progressed health state was estimated based on the PFS extrapolations and the proportion of PFS events that were deaths. PPS rates were derived externally, and OS was determined by the relationship: OS = PFS + PPS. Beyond this, the STM used the same inputs or assumptions as those used in the base case PSM.

As discussed in the Model Structure Section (Section 3.2.2.2), a beneficial treatment effect on OS can be achieved via either a beneficial effect on PFS alone (i.e. assuming no benefit on PPS following a PFS benefit, a scenario referred to as 'STM 1') or a beneficial effect on both PFS and PPS (a scenario referred to as 'STM 2'). For STM 1 and STM 2, treatment-specific PFS data for tafasitamab + R^2 and R^2 are available from the inMIND trial, but PPS data need to be estimated from external sources. An additional scenario that combines the approaches used in STM 1 and STM 2 to produce a more plausible analysis that is more applicable to the anticipated licensed population for tafasitamab + R^2 is also provided (referred to as 'STM 3').

STM 1 modelling

For STM 1, in the absence of sufficient alternative data sources, treatment-independent PPS is estimated using the HMRN database (described in Section 2.10). Based on the HMRN data, a median PPS of 64.7 months is estimated from the median PFS and OS observed for R-chemotherapy regimens (Table 28). This is applied to both the tafasitamab + R^2 and the R^2 arms of the STM 1 model. The resulting long-term OS extrapolations and landmarks based on this PPS estimate are presented in Figure 23 and Table 26.

Figure 23: STM 1 model survival curves (PPS derived from HMRN data)



Key: OS, overall survival; PPS, post-progression survival; R^2, rituximab with lenalidomide; STM, state transition model.

Table 26: STM 1 model OS landmarks (PPS derived from HMRN data)

Treatment	OS landmarks					
	2 years	5 years	10 years	20 years	30 years	35 years
Tafasitamab + R^2	92.9%	71.9%	40.6%	11.4%	3.1%	1.7%
R^2	87.0%	61.8%	32.9%	9.1%	2.5%	1.3%

Key: OS, overall survival; PPS, post-progression survival; R^2, rituximab with lenalidomide; STM, state transition model.

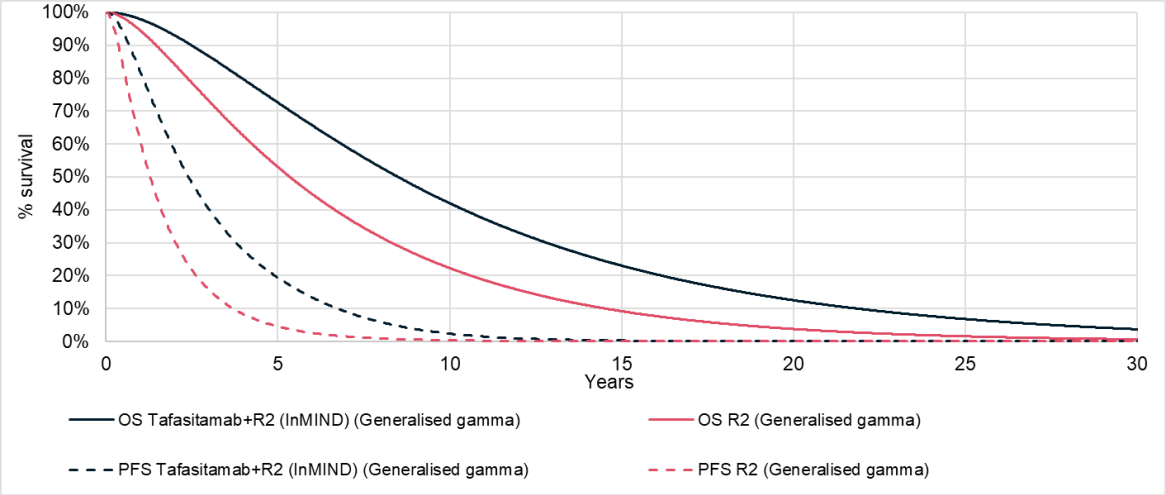
This simplistic approach to estimating treatment-independent PPS for STM 1 generates slightly lower OS estimates for both tafasitamab + R^2 and R^2 compared to the base case partitioned survival model (see Table 25 and Table 26). As the

inMIND trial includes a proportion of patients (41%) who are rituximab refractory, and the GADOLIN trial demonstrates that, in such patients, OS benefit would be achieved via gains in both PFS and PPS, the assumption of no PPS benefit is likely to underestimate the relationship between PFS and OS. STM 1 is therefore likely to lead to a highly conservative ICER estimate for tafasitamab + R^2 versus R^2.

STM 2 modelling

As detailed in Section 3.2.2.2, the AUGMENT trial of R^2 (conducted in non-rituximab refractory patients[74]) and the GADOLIN trial of O-B (conducted in rituximab refractory patients[75]) demonstrated that statistically significant improvements in PFS can translate into long-term OS benefits in rituximab refractory and non-refractory patients. However, only the GADOLIN trial provided sufficient long-term data with which to estimate PPS. Median PFS is 13.7 months in the placebo + bendamustine arm and 24.1 months in the O-B arm. Median OS is 60.3 months in the placebo + bendamustine arm was not reached in the O-B arm. To estimate the median PPS for the O-B arm, the median OS was conservatively assumed to be 90 months, as the OS curve nearly reaches 50% at that time point and no additional events are observed due to heavy censoring. Based on the previously reported median values and assumptions, the median PPS was estimated to be 67.9 months for the O-B arm and 46.6 months for the placebo + bendamustine arm (Table 28), indicating that the long-term OS benefit observed in the GADOLIN trial was achieved via a beneficial effect on both PFS and PPS. The GADOLIN trial, therefore, provides estimates of PPS for STM 2; the estimated PPS for the O-B arm is assumed to reflect the PPS for tafasitamab + R^2, and the estimated PPS for the placebo + bendamustine arm is assumed to reflect PPS for R^2 (and R-chemotherapy regimens). Figure 24 and Table 27 present the resulting long-term OS extrapolations and landmarks for STM 2.

Figure 24: STM 2 model survival curves (PPS derived from GADOLIN)



Key: OS, overall survival; PPS, post-progression survival; R^2, rituximab with lenalidomide; STM, state transition model.

Table 27: STM 2 model OS landmarks (PPS derived from GADOLIN)

Treatment	OS landmarks					
	2 years	5 years	10 years	20 years	30 years	35 years
Tafasitamab + R^2	93.1%	72.7%	42.1%	12.5%	3.7%	2.0%
R^2	84.3%	53.2%	22.3%	3.8%	0.6%	0.3%

Key: OS, overall survival; PPS, post-progression survival; R^2, rituximab with lenalidomide; STM, state transition model.

This simplistic approach to estimating treatment-specific PPS for STM 2 generates very similar long-term OS estimates to the base case partitioned survival model for the tafasitamab + R^2 arm; however, OS estimates for the R^2 arm are notably more pessimistic: 64.1% versus 53.2% at 5 years, 38.2% versus 22.3% at 10 years and 13.7% versus 3.8% at 20 years (see Table 25 and Table 27). OS for the R^2 arm is likely underestimated as it is based on the PPS of the placebo + bendamustine arm in rituximab refractory patients, which have a poorer prognosis than the overall population of the inMIND trial. STM 2 may therefore underestimate the ICER for tafasitamab + R^2 versus R^2, but provides a lower bound for the likely ICER estimate.

STM 3 modelling: most plausible and reflective of the licensed indication

The STM 1 and STM 2 modelling approaches are simplistic in their estimation of PPS and OS, and are likely to lead to overestimation and underestimation of the

ICER for tafasitamab + R^2 versus the comparator. Nonetheless, they provide an ICER range within which the true ICER is likely to sit.

STM 3 adopts a more robust approach to the estimation of PPS, which is also weighted to reflect the proportion of patients in the inMIND trial that will achieve both a PFS and a PPS benefit, and the proportion who will achieve only a PFS benefit. The resulting ICER is therefore more reflective of the true cost-effectiveness of tafasitamab + R^2 in its anticipated licensed indication.

As demonstrated in Section 3.2.2.2, in the GADOLIN trial, which was conducted exclusively in rituximab refractory patients, the OS benefit with O-B was achieved via benefit in both PFS and PPS. As shown in Table 28, the ratio of estimated PPS:PFS is aligned across the O-B and comparator arms. In the inMIND trial, 41% of patients were refractory to rituximab. Therefore, a treatment-specific PPS for the 41% of rituximab refractory patients in the inMIND trial can be estimated by applying the GADOLIN PPS:PFS ratio to the median PFS observed with tafasitamab + R^2 and R^2 in the inMIND trial. As median PFS by IRC had not been reached in the tafasitamab + R^2 arm, the median PFS by INV was pragmatically adopted.

Furthermore, as noted in Section 3.2.2.2, it is plausibly conservative to assume that PPS would be unaffected by treatment in non-rituximab refractory patients. For the 59% of patients in the inMIND trial who were not refractory to rituximab, it is therefore conservatively assumed that OS benefit would be driven by PFS benefit alone, and a common, treatment-independent PPS should be applied to both arms of the model. In the absence of a source of PPS data exclusively for non-rituximab refractory patients, this PPS estimate is taken from the HMRN database. Table 29 provides a summary of the median PPS values estimated for the 41% of rituximab refractory and 59% of non-refractory patients in the inMIND trial. The weighed approach resulted in a median PPS of 66.7 months for the tafasitamab + R^2 arm and 55.9 months for the R^2 arm.

Table 28: Median PFS, OS and PPS in the GADOLIN trial

Trial/Study	Treatment	Median PFS (months)	Median OS (months)	Median PPS (months)	Ratio Median PPS / Median PFS
GADOLIN	O-Benda	24.1	92	67.9	2.8
	Benda	13.7	60.3	46.6	3.4
HMRN	R-Chemo	35.1	99.8	64.7	not used

Key: HMRN, Haematological Malignancy Research Network; O-benda, obinutuzumab + bendamustine; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; R^2, rituximab + lenalidomide.

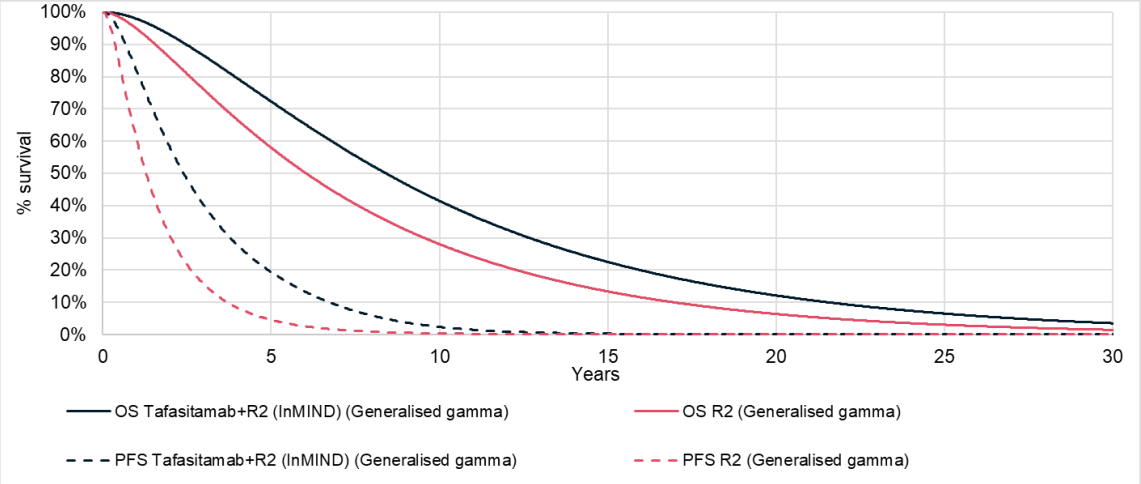
Table 29: Median PPS values used in each scenario

Approach	Treatment	PPS (months)	Notes
HMRN median values (non-rituximab refractory)	Tafasitamab + R^2	64.7	See Table 28
	R^2	64.7	See Table 28
GADOLIN median values (rituximab refractory)	Tafasitamab + R^2	67.9	See Table 28
	R^2	46.6	See Table 28
Weighted approach	Tafasitamab + R^2	66.7	41%*(22.4*3.1) + 59%*64.7
	R^2	55.9	41%*(13.9*3.1) + 59%*64.7

Key: HMRN, Haematological Malignancy Research Network; PPS, post-progression survival; R^2, rituximab with lenalidomide.

Figure 25 and Table 30 present the long-term OS extrapolations and landmarks based on the STM 3 weighted approach compared to the base case partitioned survival model extrapolations.

Figure 25: STM 3 model survival curves (based on the weighted approach)



Key: OS, overall survival; PPS, post-progression survival; R^2, rituximab with lenalidomide; STM, state transition model.

Table 30: STM3 model OS landmarks (based on the weighted approach)

Approach	Treatment	OS landmarks					
		2 years	**5 years**	**10 years**	**20 years**	**30 years**	**35 years**
Weighted approach	Tafasitamab + R^2	93.0%	72.4%	41.5%	12.1%	3.5%	1.9%
	R^2	85.9%	58.1%	28.1%	6.4%	1.4%	0.7%
PSM approach	Tafasitamab + R^2	91.4%	76.1%	49.8%	17.9%	3.8%	0.7%
	R^2	86.1%	64.1%	38.2%	13.7%	2.9%	0.5%

Key: OS, overall survival; PPS, post-progression survival; PSM, partitioned survival model; R^2, rituximab with lenalidomide; STM, state transition model.

STM model extrapolations versus base case PSM extrapolations

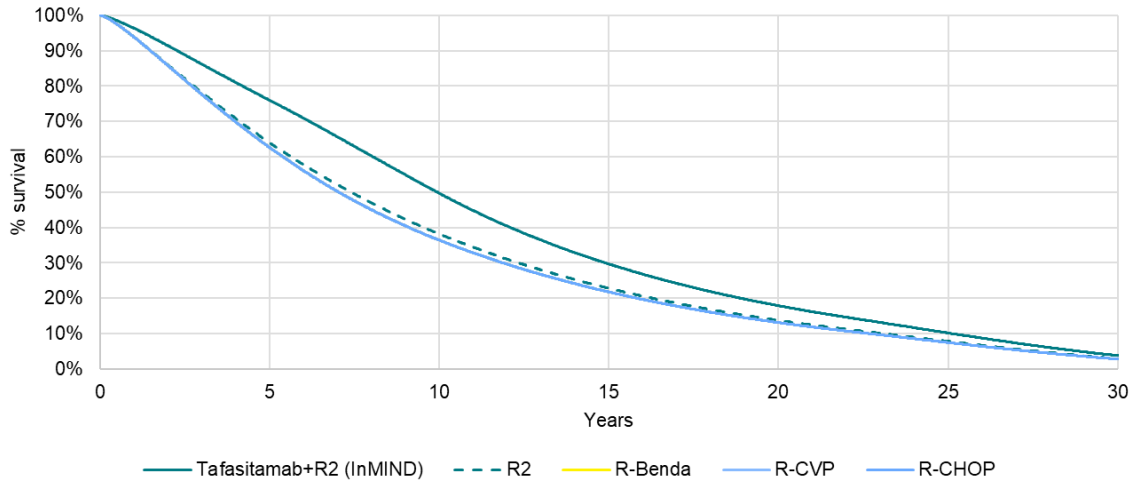
As expected, the state transition models provide different survival estimates for both arms of the model compared with the base case partitioned survival model. This is influenced by the assumed structural link between PFS and OS events, the source of data for estimating PPS, and the method of implementation of PPS in the state transition models. It should be noted that, whilst the OS data in the base case partitioned survival model are subject to uncertainty due to the limited follow-up time in the inMIND trial, clinicians have informed and validated the OS extrapolations in the base case partitioned survival model.

Implementation of the state transition models has required a range of assumptions and use of external data sources, which are also subject to uncertainty. The extent to which the state transition models can inform the plausibility of the base case partitioned survival model extrapolations is, therefore, unclear. However, the survival extrapolations for R^2 in STM 3 align with clinicians' expectations and, based on the methodology adopted, it is reasonable to conclude that the STM 3 model (weighted to the inMIND trial population) provides more plausible estimates of the long-term benefit of treatment on OS and provides estimates of the cost-effectiveness of tafasitamab + R^2 that are more aligned with expectations in the anticipated licensed population than either STM 1 or STM 2. Cost-effectiveness results for these STM-based scenarios are presented in Table 59.

3.3.3.2 Tafasitamab + R^2 versus R-chemotherapy: OS

As noted for PFS (Section 3.3.2.2), the model takes a conservative approach by assuming that the relative treatment effect for tafasitamab + R^2 versus R^2 observed in the inMIND trial reflects the relative treatment effect for tafasitamab + R^2 versus R-chemotherapy (R-B, R-CVP, and R-CHOP). This is implemented in the model by applying the same hazard ratio for tafasitamab + R^2 versus R^2 (HR: 0.59; see Section 2.6.3) to the tafasitamab + R^2 extrapolations to derive the R-chemotherapy survival curves. Figure 26 shows the OS extrapolations for R-B, R-CHOP and R-CVP compared to R^2 and tafasitamab + R^2. As seen in the figure, the OS curves of the R-chemotherapies are similar to that of R^2.

Figure 26: R-B, R-CHOP and R-CVP long-term OS extrapolations



Key: OS, overall survival; R^2, rituximab with lenalidomide; R-B, rituximab with bendamustine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; R-CVP, rituximab with cyclophosphamide, vincristine and prednisolone.

3.3.4 Time to treatment discontinuation

In the economic model, TTD is used to estimate the proportion of patients who are on or off treatment in each model cycle. TTD is defined as the time from the date of the first dose until the date of the last exposure to treatment. The Kaplan–Meier curve for both arms is presented in Figure 27. There is a notable drop in both curves, reflecting treatment-stopping rules in line with the administration of tafasitamab + R^2 in inMIND. In brief, tafasitamab and lenalidomide are administered for a maximum of 12 cycles and, therefore, all patients in both arms were assumed to have discontinued treatment from Cycle 12 onwards. However, rituximab is discontinued after five cycles (Table 20) and, therefore, rituximab-specific costs are not applied from Cycle 5 onwards.

Figure 27: Observed Kaplan−Meier curve of TTD (tafasitamab + R^2 versus R^2)

Key: KM, Kaplan–Meier; R^2, rituximab with lenalidomide; TTD, time to treatment discontinuation.

As the Kaplan–Meier curve is available up to the end of the treatment period (i.e. twelve 28-day cycles) for both arms, the Kaplan–Meier estimates from the trial are used directly to inform the duration of treatment in the model. Figure 28 displays tafasitamab + R^2 and R^2 TTD curves alongside the extrapolated PFS curves.

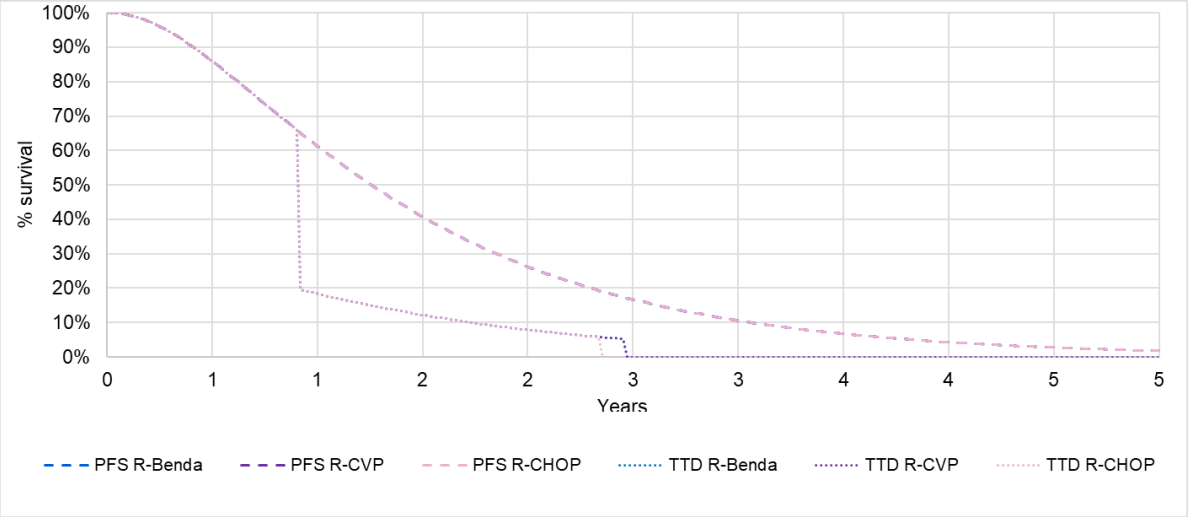
Figure 28: Tafasitamab + R^2 and R^2 TTD curves compared to PFS curves

Key: R^2, rituximab with lenalidomide; PFS, progression-free survival; TTD, time to treatment discontinuation.

Given the lack of data to inform the TTD curves for the R-chemotherapy comparators, and based on the clinical expectation that R-CVP and R-CHOP would have lower discontinuation than R^2 (as they are lower-intensity regimens), it was

assumed that the HR of TTD versus PFS is equal to 1 (i.e. the discontinuation rate for R-chemotherapy is equal to the progression rate).[2] Not all patients receive rituximab maintenance; based on the clinical validation exercise, the model assumes that 30% of patients who complete the induction phase receive rituximab maintenance.[2] The same HR of TTD versus PFS was assumed during the maintenance phase. Time-on-treatment was capped based on the SmPC maximum number of cycles (see Table 21).

Figure 29: R-B, R-CHOP and R-CVP TTD curves compared to PFS curves



Key: R[2], rituximab with lenalidomide; R-B, rituximab with bendamustine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; R-CVP, rituximab with cyclophosphamide, vincristine and prednisolone; PFS, progression-free survival; TTD, time to treatment discontinuation.

3.3.5 Safety

Adverse events (AEs) (Grade 3+) that occurred in at least 2% of patients in either arm of inMIND were included in the model for tafasitamab + R[2] and R[2], in accordance with other FL appraisals.[14, 81, 82, 89] AE frequencies for R-chemotherapy were retrieved from their respective trials (R-B from the BRB study[71]; R-CHOP from the Van Oers study[72]). The frequencies of all AEs included in the model are presented in Table 31. For R-CVP, no data were available; therefore, the frequency of AEs was assumed to be the same as R-CHOP.[72]

As inMIND was conducted during the COVID-19 pandemic, incidences of COVID-19 infection (tafasitamab + R^2, 5.8%; placebo + R^2, 2.2%) and COVID-19 pneumonia (tafasitamab + R^2, 4.7%; placebo + R^2, 1.1%) were recorded.[68] In the base case, these COVID-19-related AEs are excluded from the analysis to align with the R-chemotherapies, which do not include COVID-19 AEs. The impact of including these AEs is explored in the scenario analysis.

Table 31: Grade 3+ AE proportions that occurred in at least 2% of patients

Adverse event	Tafasitamab + R² N = 274 (%)	R² N = 272 (%)	R-B N = 52 (%)	R-CVP N = 324 (%)	R-CHOP N = 324 (%)
Acute kidney injury	8 (3%)	6 (2%)	0 (0.0%)	NR	NR
Anaemia	12 (4.4%)	16 (5.9%)	1 (1.9%)	8 (3.4%)	8 (3.4%)
COVID-19	16 (5.8%)	6 (2.2%)	0 (0.0%)	NR	NR
COVID-19 pneumonia	13 (4.7%)	3 (1.1%)	0 (0.0%)	NR	NR
Febrile neutropenia	12 (4%)	6 (2%)	0 (0.0%)	NR	NR
Leukopenia	[redacted]	[redacted]	22 (42.3%)	NR	NR
Neutropenia	109 (39.8%)	102 (37.5%)	21 (40.4%)	128 (54.7%)	128 (54.7%)
Neutrophil count decreased	16 (5.8%)	18 (6.6%)	0 (0.0%)	NR	NR
Pneumonia	23 (8.4%)	14 (5.1%)	0 (0.0%)	NR	NR
Pruritus	1 (<1%)	0 (0%)	NR	31 (13.2%)	31 (13.2%)
Pyrexia	4 (2%)	6 (2%)	0 (0.0%)	NR	NR
Thrombocytopenia	17 (6.2%)	20 (7.4%)	0 (0.0%)	NR	NR
Hypogammaglobulinaemia	[redacted]	[redacted]	NR	12 (5.1%)	12 (5.1%)

Key: AE, adverse event; N, number; NR, not reported; R², rituximab with lenalidomide; R-B, rituximab with bendamustine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; R-CVP, rituximab with cyclophosphamide, vincristine and prednisolone.
Note: Decimal point approach aligned to source/publication plan.
Source: Trneny et al. 2025[68]; Incyte Corporation, 2024[64]; Matsumoto et al. 2015[71]; van Oers et al. 2006.[72]

The impact of AEs on HRQL is accounted for in the model by using the incidences of treatment-related AEs reported in Table 31, with application of appropriate utility decrements (Section 3.4.4 and 3.5.3).

3.4 Measurement and valuation of health effects

3.4.1 HRQL data from clinical trials

The base case utilities were estimated from the five-level EQ-5D® (EQ-5D-5L) data collected in the inMIND clinical trial. The EQ-5D-5L questionnaire was administered to patients at the following timepoints:

- Baseline: Day 1 of Cycle 1
- During treatment: Day 1 of each cycle, ± 2 days
- Post-treatment: At the end of the treatment ± 2 days and at efficacy follow-up for patients who discontinue study treatment for reasons other than disease progression, until disease progression, initiation of new anticancer therapy, lost to follow-up, withdrawal of consent, or death

The mean change from baseline in EQ-5D-5L VAS scores over time following treatment with tafasitamab + R^2 or placebo + R^2 shows no difference across treatments (Appendix L), which suggests that adding tafasitamab to current standard of care, R^2, has a limited impact on HRQL, partly due to the similar AE profile. Additionally, in the mixed-effects regression model, treatment assignment was not found to be a significant predictor in the best-fitted model (see further detail in the following paragraphs). Consequently, EQ-5D questionnaire values were pooled across both treatment groups for the analysis, assuming health state utilities independent from treatment in the cost-effectiveness model. This assumption is aligned with previous NICE appraisals in FL.[14, 81, 82, 89]

Only patients with a baseline and at least one post-baseline EQ-5D questionnaire observation were included in the final analysis. To align with the structure of the cost-effectiveness model, all post-baseline EQ-5D questionnaire observations were further categorised to the following:

- PF: observations before the date of progression of disease
- Progressed: observations on and after the date of progression of disease

The number of patients and observations included in the utility analysis by progression status is shown in Table 32.

Table 32: Number of patients and observations included in the utility analysis

Source	Progression-free		Progressed	
	Number of patients	Number of observations	Number of patients	Number of observations
inMIND	518	5,027	83	108

A mixed-effects regression model was developed to estimate health-state-based (i.e. PF or progressed) utility values using the 'nlme' package in R, adjusting for prognostic factors. The model included a random effect parameter for each patient to adjust for correlation between multiple observations from the same patient. Stepwise covariate selection was used to pragmatically identify covariates to be included in the final model. Conditional AIC values were used to compare the fits of various models, where a lower conditional AIC score indicates better model fit. The final chosen, best-fitted model included the following covariates: progression status, baseline utility, number of prior lines of therapy and time since prior cancer therapy. Notably, treatment assignment was not found to be a significant predictor in this best-fitted model. Further details of this can be found in the utility regression analysis report provided in the reference pack.[90]

3.4.2 Mapping

The EQ-5D-5L questionnaire descriptive scores were mapped to the EQ-5D-3L questionnaire using the Hernández Alava method[91] according to NICE guidance, with UK-specific EQ-5D questionnaire index scores calculated using the UK EQ-5D-3L questionnaire value set (Dolan 1997).[92] The 'emmeans' R package was used to calculate the marginal mean estimates from the respective fitted linear mixed models. The utility values used in the model, stratified by progression status, are presented in Table 33.

Table 33: Observed EQ-5D-5L questionnaire values from inMIND, mapped to EQ-5D-3L using the Hernandez Alava algorithm

Health state	Utility (95% CI)
Progression-free	0.842 (0.794, 0.890)
Post-progression	0.805 (0.752, 0.858)
Key: CI, confidence interval; EQ-5D-5L, EuroQol 5-dimension 5-level. **Note:** Marginal mean health state utility estimates and 95% CIs estimated using the 'emmeans' R package.	

3.4.3 Health-related quality of life studies

An initial SLR was conducted on 18 March 2024 to identify humanistic outcomes, including HRQL and utility values, in patients with R/R FL. An update of the SLR was conducted on 22 April 2025. Full details of the SLR search strategies, study selection processes and results can be found in Appendix F. In total, nine publications met the inclusion criteria and were included in the review (Appendix F). Out of these, eight focused on R/R FL, with the remaining study focusing on a combined R/R FL and MZL population. Most utility or HRQL studies were multinational studies using EQ-5D-3L or EQ-5D-5L instruments. There were no studies conducted exclusively in the UK, nor examined using a non-specific value set. Utility values were variably reported and often limited to change-from-baseline analyses or EQ-VAS scores. Additionally, utility values from previous TAs in FL were considered, which included direct utility values reported in the AUGMENT, GADOLIN, and GO29781 trials, as well as from Wild et al., a study that included 222 patients aged 18 years and over with histologically confirmed FL and an ECOG performance status of 0–2 (summarised in Table 34). These values were explored in the model as a scenario analysis (Section 3.11.3).

Table 34: Alternative utility values from previous NICE TAs

Study	Patient population	Treatment	Utility instrument	Utility values
TA627[14] / AUGMENT[6]	Adult patients with previously treated FL	R[2] versus rituximab monotherapy	EQ-5D-3L	Progression-free: 0.867 Progressed (on treatment): 0.841

Study	Patient population	Treatment	Utility instrument	Utility values
				Progressed (off treatment): 0.806
TA629[58] / GADOLIN[93]	Adults with FL who did not respond to or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen	Obinutuzumab with bendamustine versus bendamustine	Unspecified	Progression-free (on treatment): 0.822 Progression-free (off treatment): 0.807 Progressed: 0.758
TA892[82]/ GO29781[94]	Adults with R/R FL who had two or more previous lines of systemic therapy	Mosunetuzumab versus R^2, rituximab with bendamustine, and obinutuzumab with bendamustine	EQ-5D-5L, mapped to EQ-5D-3L	Progression-free: 0.804 Progressed: 0.750
Wild et al. 2006[95]	Adults with FL	N/A	N/A	Progression-free: 0.805 Progressed (on treatment): 0.736 Progressed (off treatment): 0.618

Key: EQ-5D-3L, EuroQol 5-dimension 3-level; EQ-5D-5L, EuroQol 5-dimension 5-level; FL, follicular lymphoma; N/A, not applicable; R^2, rituximab with lenalidomide; R/R, relapsed or refractory; TA, technology appraisal.

3.4.4 Adverse reactions

The corresponding disutility value, as well as the duration of each AE, were derived from the literature and are presented in Table 35. For each AE, a QALY decrement was calculated by multiplying the incidence rate, disutility, and duration. The QALY decrements were then summed across all AEs and applied as a one-off decrement

in the first cycle, based on a simplifying assumption that AEs occur immediately after the treatment and would only require acute care to resolve them.

Table 35: Disutility and duration of adverse events

Adverse event	Event utility decrement	Source (decrement)	Event duration (days)	Source (duration)
Acute kidney injury	-0.0380	TA306[96]	29.75	Assumption, same as renal injury, TA306[96]
Allergic reaction	-0.0980	Hannouf et al. (2012)[97]	24.36	Assumed maximum of all Grade 3/4 AEs
Anaemia	-0.1190	Swinburn et al. (2010)[98]	16.07	TA306[96]
COVID-19	-0.0610	Halpin et al. (2020).[99] Values used in the SCHARR MTA and TA900 were derived from non-COVID population	6.50	Halpin et al. (2020)[99]
COVID-19 pneumonia	-0.1550	Halpin et al. (2020)[99]	12.00	Halpin et al. (2020)[99]
Febrile neutropenia	-0.1500	Lloyd et al. (2006)[100]	5.90	inMIND
Infusion related reaction	-0.1950	Tolley et al. (2013)[101]	7.00	Assumption
Leukopenia	-0.1190	TA513[57] (assumed to be the same as anaemia)	14.00	TA306[96]
Lymphopenia	-0.1000	Stein et al. (2018)[102]	14.00	Assumption, same as leukopenia, TA306[96]
Neutropenia	-0.0900	Nafees et al. (2008)[103]	13.40	inMIND
Neutrophil count decreased	-0.1000	Stein et al. (2018)[102]	13.40	inMIND, assumed to be equal to neutropenia
Pneumonia	-0.1900	TA171[104], TA897[105] TA974[106]	13.50	inMIND

Adverse event	Event utility decrement	Source (decrement)	Event duration (days)	Source (duration)
Pruritus	-0.0070	Matza et al. (2019)[107]	24.36	Assumed maximum of all Grade 3/4 AEs
Pyrexia	-0.1100	TA872[108]	2.00	TA872[108]
Sepsis	-0.2670	Hannouf et al. (2012)[97]	25.25	inMIND
Thrombocytopenia	-0.3100	TA897[105]	21.40	inMIND
Urinary tract infection	-0.0700	Armstrong et al. (2009)[109]	16.00	inMIND
Vomiting	-0.0760	Nafees et al. (2008)[103]	10.50	NICE ERG report on pre-chemo enzalutamide TA377[110]; also reported in NICE ERG report on post-chemo abiraterone TA259[111]
Hypogammaglobulinaemia	0.0000	Assumption	0.00	Assumption

Key: AE, adverse event; ERG, Evidence Review Group; MTA Multiple Technology Appraisal, NICE, National Institute for Health and Care Excellence; SCHARR, Sheffield Centre for Health and Related Research; TA, technology appraisal.

AE disutilities could be double-counted if it is considered that they are already accounted for in the utility regression analysis. The base case assumes that the utility regression analysis does not account for AE disutilities to avoid double counting. Scenario analysis tests the assumption that AE disutilities are reflected in the utility analysis (see Section 3.11.3).

3.4.5 HRQL data used in the cost-effectiveness analysis

Given that the PF utility values were higher than those of the age- and sex-matched general population utility from Hernández Alava et al.[91], the utility value for the age- and sex-matched general population was used as the PF utility value in the base case. A proportional decrement based on the difference of the mapped PF and progressed utility values from inMIND was applied to the PF utility value to obtain the utility value for the progressed state, similar to the approach used in TA627.[14] The

final health state-based utility values used in the base case is presented in Table 36. The absolute decrement approach is tested in the scenario analysis.

Table 36: Health state based utility values applied in the base case

Health state	Utility
Progression-free	0.824
Post-progression	0.788

3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted to identify relevant cost and HCRU evidence for patients with R/R FL. The SLR was initially conducted on 18 March 2024 and was updated on 22 April 2025. Full details of the SLR search strategy, study selection process and results can be found in Appendix G. Given that no studies reported costs or healthcare resource use in the UK setting, HCRU inputs were based on previous NICE appraisals for FL.

The following direct medical costs are included in the economic analysis:

- Drug acquisition and administration costs for intervention, comparators, and subsequent therapy
- Healthcare resource utilisation, by health states
- End of life costs
- AEs

All costs are inflated to 2023/2024 values using inflation indices published by the Personal Social Services Research Unit (PSSRU).[86]

3.5.1 Intervention and comparators' costs and resource use

3.5.1.1 Drug acquisition and administration costs

Drug acquisition and administration costs for tafasitamab + R^2 and R^2 are calculated for patients who were on treatment in each arm of the model. These costs were

calculated per component based on the TTD observed in inMIND, the planned dosing and administration regimen, and acquisition cost. The dosing schedules implemented for each treatment are outlined in Table 20 and Table 21.

Due to the lack of available data, the average relative dose intensity (RDI) of rituximab in the inMIND tafasitamab + R^2 arm during Cycles 2–5 (94.18%) was used for the rituximab component of the R-chemotherapy regimens. The average RDI of tafasitamab + R^2 (85.90%) was assumed for components of the R-chemotherapy regimens other than rituximab. Despite the uncertainty on the RDI for the R-chemotherapy components other than rituximab, the impact on the total acquisition costs is small due to their low acquisition costs per cycle (Table 38).

In addition, all patients were assumed to receive allopurinol 100 mg once daily as prophylaxis for tumour lysis syndrome during the first week of the cycle, in accordance with the SmPC for lenalidomide and assumptions used in TA627.[14] All unit costs were sourced from either the Monthly Index of Medical Specialties (MIMS)[112] or the electronic market information tool (eMIT)[113], as summarised in Table 37.

If available, prices from eMIT were used as they represent the real average price paid by the NHS for the drug over a 12-month period (until end of June 2024). Prices from MIMS represent the drug list price. [redacted] discount for tafasitamab was included in the base case analysis. No other discounts were included in the base case.

Table 37: Drug unit costs

Drug name	Drug form	Available unit amounts	Units in packet	Price (£)	Source
Tafasitamab	40 mg/mL (vial)	5 mL	1	705.00 (list price) [redacted] (PAS price)	MIMS Incyte
Lenalidomide	Tablet	2.5 mg	21	26.23	eMIT
		5 mg	21	31.48	
		10 mg	21	27.55	
		20 mg	21	43.27	
Rituximab		10 mL	3	471.50	MIMS

Drug name	Drug form	Available unit amounts	Units in packet	Price (£)	Source
	10 mg/mL (vial)	50 mL	2	1,517.67	
Allopurinol	Tablet	100 mg	28	0.91	eMIT
Bendamustine	100 mg/mL (vial)	1 mL	5	£127.14	eMIT
	25 mg/mL (vial)	1 mL	5	£41.86	eMIT
Rituximab	10 mg/mL (vial)	10 mL	3	£471.50	MIMS
	10 mg/mL (vial)	50 mL	2	£1,517.67	MIMS
Rituximab (SC)	119.66 mg/mL (vial)	12 mL	1	£1,344.65	MIMS
Cyclophosphamide	2,000 mg/mL (vial)	1 mL	1	£27.50	eMIT
	1,000 mg/mL (vial)	1 mL	1	£13.11	eMIT
	500 mg/mL (vial)	1 mL	1	£11.18	eMIT
Doxorubicin	2 mg/mL (vial)	100 mL	1	£17.67	eMIT
	2 mg/mL (vial)	25 mL	1	£10.06	eMIT
Vincristine	1 mg/mL (vial)	1 mL	5	£30.08	eMIT
	1 mg/mL (vial)	2 mL	5	£38.42	eMIT
Prednisolone	Tablet	25 mg	56	£12.78	eMIT
	Tablet	5 mg	27	£0.91	eMIT

Key: eMIT, electronic market information tool; MIMS, Monthly Index of Medical Specialties.
Note: All comparator drugs are list prices.
Source: eMIT 2025[113]; MIMS 2023.[112]

In the modelled base case, the company assumes drug wastage for drugs administered intravenously, meaning that a full vial would be used when opened, without considering vial sharing. This applies to all injection-based treatments used in the model in the base case. For drugs with either body surface area (BSA) or

weight-based dosing, the method of moments technique was used to estimate the average number of vials required per dose. For lenalidomide, the 20 mg pack was considered the most efficient based on cost per tablet and dose schedule. This allowed for the cost of a full pack of lenalidomide (21 tablets) to be incurred per cycle, thereby eliminating any potential wastage.

A per-cycle RDI value (observed in inMIND) is applied to all patients in the model, as not all patients receiving treatment will receive the full course of therapy because of missed doses or dose reductions. Table 38 presents the acquisition cost for each regimen's component per model cycle before and after applying RDIs.

Table 38: Drug acquisition costs per component per model cycle (with PAS)

Regimen	Component	Period	Dose	Drug acquisition cost per treatment cycle	Average acquisition cost per model cycle	RDI	Average acquisition cost per model cycle after applying RDI
Tafasitamab + R[2]	Tafasitamab	Cycles 1–3 (28 days)	12 mg/kg on Days 1, 8, 15, 22	[redacted]	[redacted]	[redacted]	[redacted]
		Cycles 4–12 (28 days)	12 mg/kg on Days 1, 15	[redacted]	[redacted]	[redacted]	[redacted]
	Lenalidomide	Cycles 1–12 (28 days)	20 mg QD on Days 1–21	£43.27	£10.82	[redacted]	[redacted]
	Rituximab	Cycle 1 (28 days)	375 mg/m^2 on Days 1, 8, 15, 22	£4,500.43	£1,125.11	[redacted]	[redacted]
		Cycles 2–5 (28 days)	375 mg/m^2 on Day 1	£1,125.11	£281.28	[redacted]	[redacted]
R[2]	Lenalidomide	Cycles 1–12 (28 days)	20 mg QD on Days 1–21	£43.27	£10.82	[redacted]	[redacted]
	Rituximab	Cycle 1 (28 days)	375 mg/m^2 on Days 1, 8, 15, 22	£4,500.43	£1,125.11	[redacted]	[redacted]
		Cycles 2–5 (28 days)	375 mg/m^2 on Day 1	£1,125.11	£281.28	[redacted]	[redacted]
R-B	Rituximab (induction)	Cycles 1–6 (28 days)	375 mg/m^2 QD on Day 1	£1,125.11	£281.28	[redacted]	[redacted]

Regimen	Component	Period	Dose	Drug acquisition cost per treatment cycle	Average acquisition cost per model cycle	RDI	Average acquisition cost per model cycle after applying RDI
	Bendamustine (induction)	Cycles 1–6 (28 days)	90 mg/m^2 QD on Days 1 and 2	£108.39	£31.13	[redacted]	[redacted]
	Rituximab (maintenance)	2 years after six induction cycles (90 days)	1,400 mg QD on Day 1	£1,344.63	£103.08	[redacted]	[redacted]
R-CHOP	Rituximab (induction)	Cycles 1–6 (21 days)	375 mg/m^2 QD on Day 1	£1,125.11	£375.04	[redacted]	[redacted]
	Doxorubicin (induction)	Cycles 1–6 (21 days)	50 mg/m^2 QD on Day 1	£8.23	£5.89	[redacted]	[redacted]
	Vincristine (induction)	Cycles 1–6 (21 days)	1 mg/m^2 QD on Day 1, max dose of 2 mg	£10.02	£5.02	[redacted]	[redacted]
	Cyclophosphamide (induction)	Cycles 1–6 (21 days)	750 mg/m^2 QD on Day 1	£24.64	£8.21	[redacted]	[redacted]
	Prednisolone (induction)	Cycles 1–6 (21 days)	40 mg/m^2 QD on Day 1 to 5	£2.42	£0.81	[redacted]	[redacted]
	Rituximab (maintenance)	2 years after six induction cycles (90 days)	1,400 mg QD on Day 1	£1,344.63	£103.08	[redacted]	[redacted]

Regimen	Component	Period	Dose	Drug acquisition cost per treatment cycle	Average acquisition cost per model cycle	RDI	Average acquisition cost per model cycle after applying RDI
R-CVP	Rituximab (induction)	Cycles 1–8 (21 days)	375 mg/m^2 QD on Day 1	£1,125.11	£375.04	[redacted]	[redacted]
	Cyclophosphamide (induction)	Cycles 1–8 (21 days)	750 mg/m^2 QD on Day 1	£23.30	£8.21	[redacted]	[redacted]
	Vincristine (induction)	Cycles 1–8 (21 days)	1 mg/m^2 QD on Day 1	£10.02	£5.02	[redacted]	[redacted]
	Prednisolone (induction)	Cycles 1–8 (21 days)	40 mg/m^2 QD on Days 1–5	£2.42	£0.81	[redacted]	[redacted]
	Rituximab (maintenance)	2 years after eight induction cycles (90 days)	1,400 mg QD on Day 1	£1,344.63	£103.08	[redacted]	[redacted]

Key: QD, once per day; R-B, rituximab with bendamustine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; R-CVP, rituximab with cyclophosphamide, vincristine and prednisolone; RDI, relative dose intensity.

Administration costs were applied dependent on whether the drug is administered intravenously (as a simple or complex procedure), subcutaneously, or orally, as summarised in Table 39. All intravenous administrations were assumed to be performed in an outpatient setting. A cost of £0 was assumed for subcutaneous administration. All unit costs were sourced from NHS Reference Costs 2023/24.[114]

Table 39: Administration type and associated costs

Treatment	Administration cost (£)	Reference
Oral	0.00	Assumption
Subcutaneous administration	0.00	Assumption
Intravenous chemotherapy, first administration, simple regimen	528.11	NHS Reference Costs 2023/24. Daycase. SB13Z: Deliver more Complex Parenteral Chemotherapy at First Attendance
Intravenous chemotherapy, first administration, complex regimen	570.43	NHS Reference Costs 2023/24. Daycase. SB14Z Daycase: Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance
Intravenous chemotherapy, subsequent administration	426.15	NHS Reference Costs 2023/24. Daycase. SB15Z. Deliver Subsequent Elements of a Chemotherapy Cycle
Key: NHS, National Health Service. **Source:** NHS Reference Costs 2023/24.[114]		

The drug administration costs per treatment component and model cycle are found in Table 40. For tafasitamab + R^2, a cost of £570.43 (SB14Z – deliver complex chemotherapy, including prolonged infusional treatment, at first attendance) was applied for the first administration of each cycle, and a cost of £426.15 (SB15Z – deliver subsequent elements of a chemotherapy cycle) was applied for each subsequent administration per cycle. For R^2, a cost of £528.11 (SB13Z – deliver more complex parenteral chemotherapy at first attendance) was applied for the first administration of each cycle and £426.15 (SB15Z – deliver subsequent elements of a chemotherapy cycle) was applied for subsequent administrations, in accordance with TA627.[14] Following clinical practice, and as described in Section 3.2.3.2, it is

assumed that rituximab maintenance therapy is administered subcutaneously.[1, 2] A scenario analysis tests intravenous administration for rituximab maintenance.

When multiple drugs are administered on the same day, it is assumed that only one administration cost is incurred. Co-administrations are implemented in the model by multiplying the unadjusted administration cost per cycle by one minus the percentage of administrations that are co-administered. Table 40 provides the number of coadministrations observed during the period and percentage that it represents. For example, during Cycles 1–3, tafasitamab is co-administered six times with rituximab on Days 1, 8, 15, and 22 of Cycle 1 and Day 1 of Cycles 2 and 3. Given that the total number of administrations required for tafasitamab for Cycles 1–3 is 12, tafasitamab is co-administered 50% of the time with rituximab. Therefore, adjusting the total costs of tafasitamab by this proportion will prevent double counting costs that have been accounted for in the administration of rituximab.

Table 40: Drug administration costs per component per model cycle

Regimen	Component	Period	Dosing description	Number of coadministration	Coadministration description	Coadministration (%)	Average admin cost per cycle (£)
Tafasitamab + R^2	Tafasitamab	Cycles 1–3 (28 days)	Days 1, 8, 15 and 22 for Cycles 1–3, Days 1 and 5 for Cycles 4–12	6	With rituximab. Cycle 1: Days 1, 8, 15, and 22. Cycle 2-3: Day 1	50	231.11
		Cycles 4–12 (28 days)		2	With rituximab. Cycle 4-5: Day 1	11	221.46
	Lenalidomide	Cycles 1–12 (28 days)	QD on Days 1–21, for up to 12 cycles	N/A	N/A	0	0.00
	Rituximab	Cycle 1 (28 days)	Days 1, 8, 15, and 22 for Cycle 1, Day 1 for Cycles 2–5	N/A	N/A	0	451.64
		Cycles 2–5 (28 days)		N/A	N/A	0	132.03
R^2	Lenalidomide	Cycles 1–12 (28 days)	QD on Days 1–21 for up to 12 cycles	N/A	N/A	0	0.00
	Rituximab	Cycle 1 (28 days)	Days 1, 8, 15, and 22 for Cycle 1, Day 1 for Cycles 2–5	N/A	N/A	0	451.64
		Cycles 2–5 (28 days)		N/A	N/A	0	132.03

Regimen	Component	Period	Dosing description	Number of coadministration	Coadministration description	Coadministration (%)	Average admin cost per cycle (£)
R-B	Rituximab (induction)	Cycles 1–6 (28 days)	375 mg/m^2 QD on Day 1	N/A	N/A	0	132.03
	Bendamustine (induction)	Cycles 1–6 (28 days)	90 mg/m^2 QD on Days 1 and 2	N/A	6	50	124.57
	Rituximab (maintenance)	2 years after six induction cycles (90 days)	1,400 mg QD on Day 1	N/A	N/A	0	0.00
R-CHOP	Rituximab	Cycles 1–6 (21 days)	Day 1 of each chemotherapy cycle	6	With Cyclophosphamide. Cycle 1-8: Days 1	100	0.00
	Rituximab (SC)	2 years after six induction cycles (90 days)	Day 1 of each cycle	N/A	N/A	0	0.00
	Doxorubicin	Cycles 1–6 (21 days)	Day 1 of each chemotherapy cycle	6	With Cyclophosphamide. Cycle 1-8: Days 1	100	0.00
	Vincristine	Cycles 1–6 (21 days)	Day 1 of each chemotherapy cycle	6	With Cyclophosphamide. Cycle 1-8: Days 1	100	0.00

Regimen	Component	Period	Dosing description	Number of coadministration	Coadministration description	Coadministration (%)	Average admin cost per cycle (£)
	Cyclophosphamide (IV)	Cycles 1–6 (21 days)	Max dose 2 mg	N/A	N/A	0	190.14
	Prednisolone	Cycles 1–6 (21 days)	Day 1 of each chemotherapy cycle	N/A	N/A	0	0.00
R-CVP	Rituximab (induction)	Cycles 1–8 (21 days)	375 mg/m^2 QD on Day 1	8	With Vincristine. Cycle 1-8: Days 1	100	0.00
	Rituximab (maintenance)	2 years after eight induction cycles (90 days)	1,400 mg QD on Day 1	N/A	N/A	0	0.00
	Cyclophosphamide (induction)	Cycles 1–8 (21 days)	750 mg/m^2 QD on Day 1	8	With Vincristine. Cycle 1-8: Days 1	100	0.00
	Vincristine (induction)	Cycles 1–8 (21 days)	1 mg/m^2 QD on Day 1	N/A	N/A	0	190.14
	Prednisolone (induction)	Cycles 1–8 (21 days)	40 mg/m^2 QD on Days 1–5	N/A	N/A	0	0.00

Key: N/A, not applicable; QD, once per day; R^2, rituximab with lenalidomide; R-B, rituximab with bendamustine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; R-CVP, rituximab with cyclophosphamide, vincristine and prednisolone.

3.5.2 Health-state unit costs and resource use (HCRU)

Costs associated with disease management and monitoring were considered and included in the economic model, in line with the NICE reference case.[87] Healthcare resource use was assumed to be different between the PFS and PD states, as resource utilisation is likely to differ upon disease progression. In the base case, resource use reported in NICE TA627[14] were used, where disease monitoring resource use costs were assumed to be similar to those presented in previous FL NICE submissions and ESMO guidelines (Table 41). Resource use in the PFS state was further divided into resource use during the induction phase, during the maintenance phase, or during follow-up, and are applied weekly as follows:

- PFS (induction) resource use is applied to the proportion of patients in the PFS state receiving induction therapy
- PFS (maintenance) resource use is applied to the proportion of patients in the PFS state receiving maintenance therapy (R-chemotherapy)
- PFS (follow-up) resource use is applied to proportion of patients remaining in the PFS state who have completed induction or maintenance therapy

Table 41: Healthcare resource utilisation frequency by progression status

Healthcare resource	Frequency, per month			
	PFS (Induction)	PFS (Maintenance)	PFS (Follow-up)	PD
Outpatient visits: Haematology led	1.00	0.33	0.25	1.00
Diagnostic tests: FBC	1.00	0.33	0.25	1.00
Diagnostic tests: Patient history/physical exam	1.00	0.33	0.25	1.00
Diagnostic tests: Full profile (U&E, LFT, Calcium)	1.00	0.33	0.25	1.00
Diagnostic tests: Serum IgG, IgA, IgM, and electrophoresis	1.00	0.33	0.25	1.00

Healthcare resource	Frequency, per month			
	PFS (Induction)	PFS (Maintenance)	PFS (Follow-up)	PD
Diagnostic tests: LDH test	1.00	0.33	0.25	1.00
CT scans	0.17	0.04	0.00	0.00

Key: CT, computed tomography; FBC, full blood count; Ig, immunoglobulin; LDH, lactate dehydrogenase; LFT, live function tests; PD, progressed disease; PFS, progression-free survival; U&E, urea and electrolytes.
Source: NICE TA627.[14]

The frequency for each of the healthcare resource is first converted to a frequency per model cycle length and then multiplied by unit costs based on NHS reference costs[114] or costs reported in TA627[14] (which themselves were taken from TA243[55]) inflated to 2024 costs, as summarised in Table 42.

Table 42: Resource use unit costs, for TA627 resource use

Component	Cost (£)	Source
Outpatient visits: Haematology led	205.00	NHS Reference Costs 2022/23: Consultant Led. 303 - Clinical Haematology Service. WF01A Non-Admitted Face-to-Face Attendance, Follow-up[114]
Diagnostic tests: FBC	7.55	NICE TA627 (from TA243)[14]
Diagnostic tests: Patient history/ physical exam	7.47	NICE TA627 (from TA243)[14]
Diagnostic tests: Full profile (U&E, LFT, Calcium)	20.56	NICE TA627 (from TA243)[14]
Diagnostic tests: Serum IgG, IgA, IgM, and electrophoresis	30.17	NICE TA627 (from TA243)[14]
Diagnostic tests: LDH test	15.25	NICE TA627 (from TA243)[14]
CT scans	136.00	NHS Reference Costs 2023/24: Total HRGs. RD27Z Computerised Tomography Scan of more than Three Areas[114]

Key: CT, computed tomography; FBC, full blood count; HRG, healthcare resource group; Ig, immunoglobulin; LDH, lactate dehydrogenase; LFT, live function tests; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; TA, technology appraisal; U&E, urea and electrolytes.

3.5.3 Adverse reaction unit costs and resource use

In the base case analysis, Grade 3–5 drug-related AEs that occurred in at least 2% of patients in either treatment arm of inMIND were included (Table 31). The impact of less severe AEs and AEs occurring in fewer than 2% of patients on cost-effectiveness results is expected to be negligible.

AE unit costs are presented in Table 43; these are applied to the reported AE rate in the first cycle of the model as one-off costs. AE costs have been informed by previous NICE submissions and NHS reference costs.

Table 43: Adverse event costs

Adverse event	Cost per event (£)	Description
Acute kidney injury	4,184.64	Non-Elective Inpatient – Long Stay. Weighted average of LA07H to LA07P
Allergic reaction	£547.19	NHS reference costs 2023/24: DC, NES, NEL. Weighted average of WH05Z
Anaemia	5,280.57	Non-Elective Inpatient - Long Stay. Weighted average of SA03G to SA03H
COVID-19	2,261.62	Non-Elective Inpatient - Long Stay, Non-Elective Inpatient - Short Stay. Weighted average of DX21A - COVID-19 Infection, 19 years and over
COVID-19 pneumonia	12,155.97	Assume to be equal to pneumonia
Febrile neutropenia	4,125.77	Non-Elective Inpatient - Long Stay. Weighted average of SA35A to SA35E
Infusion related reaction	750.00	Non-Elective Inpatient - Short Stay. SA31E
Leukopenia	750.00	Non-Elective Inpatient - Long Stay. SA31E
Lymphopenia	4,292.71	Non-Elective Inpatient - Long Stay. Weighted average of SA08G to SA08J - Other Haematological or Splenic Disorders
Neutropenia	4,292.71	Non-Elective Inpatient - Long Stay. Weighted average of SA08G to SA08J - Other Haematological or Splenic Disorders
Neutrophil count decreased	560.71	Non-Elective Inpatient – Short Stay. Weighted average of SA08G to SA08J - Other Haematological or Splenic Disorders
Pneumonia	12,155.97	Non-Elective Inpatient - Long Stay. Weighted average of DZ11K to DZ11V - Lobar, Atypical or Viral Pneumonia, with Multiple Interventions
Pruritus	170.00	NHS reference costs 2023/24: Service code: 300, General Medicine, Outpatient Attendance
Pyrexia	1,362.47	Non-Elective Inpatient - Long Stay, Non-Elective Inpatient - Short Stay. Weighted average of WJ07A

Adverse event	Cost per event (£)	Description
		to WJ07D - Fever of Unknown Origin with Interventions
Sepsis	4,831.09	Non-Elective Inpatient - Long Stay. Weighted average of WJ06A to WJ06J
Thrombocytopenia	4,595.08	Non-Elective Inpatient - Long Stay. Weighted average of SA12G to SA12K -Thrombocytopenia
Urinary tract infection	4,092.41	Non-Elective Inpatient - Long Stay: weighted average of LA04H, LA04J, LA04K, LA04L, LA04M, LA04N, LA04P, LA04Q, LA04R, LA04S
Vomiting	750.00	Non-Elective Inpatient - Short Stay SA31E
Hypogammaglobulinaemia	0.00	Assumption
Key: NHS, National Health Service. **Source:** NHS Reference Costs 2023/24.[114]		

3.5.4 Miscellaneous unit costs and resource use

3.5.4.1 Subsequent treatment costs

While subsequent treatment data from inMIND are available (Table 12), it was observed that some options available during the trial are not in routine use in the UK and hence may not be representative of current UK practice. However, these treatments are not expected to have a different effect on OS compared with those available in the UK and, therefore, do not affect the generalisability of the trial results to UK clinical practice.

As the inMIND distribution was not considered appropriate, values from the clinical advisory board were used to reflect current real-world distributions, where clinicians suggested that a proportion of patients are still likely to receive R-chemotherapy again after disease progression, which includes R-B, R-CHOP, R-CVP, and rituximab monotherapy.[1] Additionally, a small group of patients may go on to receive stem cell transplant (SCT). Based on clinical validation, tafasitamab + R^2 and R^2 are expected to have a near-identical distribution of subsequent treatments. Clinical experts expected that patients who had progressed after R-chemotherapy (R-B, R-CHOP and R-CVP) would most likely receive R^2 or another R-chemotherapy. These assumptions were validated during the clinical interviews. The subsequent treatment distributions were reweighted to total 100%; the distributions provided by clinicians did not total 100% as they accounted for no treatment (which is already reflected in the model). The final distributions used in the economic analyses are presented in Table 44.

Table 44: Distribution of subsequent treatments used in base case analysis

Subsequent treatment	2L treatment				
	Tafasitamab + R^2	R^2	R-B	R-CVP	R-CHOP
R-B	23.12%	23.12%	0.00%	0.00%	0.00%
R-CHOP	34.68%	34.68%	0.00%	0.00%	0.00%
R-CVP	23.12%	23.12%	0.00%	0.00%	0.00%
R^2	0.00%	0.00%	100.00%	100.00%	100.00%
Rituximab monotherapy	11.56%	11.56%	0.00%	0.00%	0.00%
Allo-SCT	1.73%	1.73%	0.00%	0.00%	0.00%
Auto-SCT	5.78%	5.78%	0.00%	0.00%	0.00%

Key: 2L, second-line; allo-SCT, allogeneic stem cell transplant; auto-SCT, autologous stem cell transplant; R^2; lenalidomide with rituximab; R-B, rituximab with bendamustine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; R-CVP, rituximab with cyclophosphamide, vincristine and prednisolone.

The distribution from inMIND was explored as a scenario analysis (Table 45), first by removing all treatments that are not currently in use in the UK, and thereafter by re-weighting the remaining treatments. For R-chemotherapy regimens, the distributions for scenario analysis were assumed to be equivalent to R^2.

Table 45: inMIND distribution of subsequent treatments used in the scenario analysis

Subsequent treatment	2L treatment	
	Tafasitamab + R^2	R^2
O-B	[redacted]	[redacted]
R-B	[redacted]	[redacted]
R-CHOP	[redacted]	[redacted]
R-GemOx	[redacted]	[redacted]
R-GDP	[redacted]	[redacted]
Allo-SCT	[redacted]	[redacted]
Auto-SCT	[redacted]	[redacted]
Rituximab monotherapy	[redacted]	[redacted]
R-ESHAP	[redacted]	[redacted]

Key: 2L, second-line; allo-SCT, allogeneic stem cell transplant; auto-SCT, autologous stem cell transplant; R^2; lenalidomide with rituximab; O-B, obinutuzumab with bendamustine; R-B, rituximab with bendamustine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; R-ESHAP, rituximab with etoposide, methylprednisolone, cytarabine and cisplatin; R-GDP, rituximab with gemcitabine, dexamethasone and cisplatin; R-GemOx, rituximab with gemcitabine and oxaliplatin.

In the model, the distribution of subsequent treatments only affects costs and does not factor in any adjustments to efficacy. No long-term OS adjustments are required, as the curve selection is based on UK clinical expectations. The same clinicians who validated the OS extrapolations also validated the subsequent treatment distribution. Therefore, their long-term OS estimates already account for the UK-specific treatment sequence. The inMIND distribution is similar across arms (Table 45). The most relevant difference is the [redacted] of patients that received allogeneic stem cell transplant (allo-SCT) in the tafasitamab + R^2 arm, compared with [redacted] in the R^2 arm. Considering the inMIND follow-up time, this difference is not expected to have impacted OS. Even if the OS Kaplan–Meier data had accounted for the survival benefit associated with allo-SCT, the treatment waning effect has been selected and validated to reflect the expected OS based on the PFS benefit and the current distribution of subsequent treatments according to UK practice. Hence, the impact of subsequent treatments is implicitly accounted for in the long-term modelling of OS for tafasitamab + R^2 and R^2.

Costs associated with subsequent treatments were included as a per-cycle cost applied to newly progressed patients (i.e. patients that did not die before progression). The average cost per patient was based on the proportion of patients receiving each subsequent

treatment, the percentage of PFS events that were deaths, and costs associated with drug acquisition and administration. The proportion of patients who receive subsequent treatments was informed by clinical expert opinion.[1, 2] It was assumed that 86.5% of patients will proceed to receive subsequent treatments; the same proportion was assumed for all treatments.

PFS events include both progression and death events. The inMIND data show that some patients died before progression.[64] Therefore, the company applied the percentage of PFS events that are death events to account for these patients, who will not receive subsequent treatments. As it is not expected in practice that the tafasitamab + R^2 arm would have more death events before progression ([redacted]) than R^2 ([redacted]) for the same patient profile, the average is applied to both arms ([redacted]) (Table 46). This average is also applied to R-chemotherapy.

Table 46: Percentage of PFS events that are death events

Population	Death events	PFS events	Percentage	Source
Tafasitamab + R^2	[redacted]	[redacted]	[redacted]	inMIND 2L+ population
R^2	[redacted]	[redacted]	[redacted]	inMIND 2L+ population
Overall	[redacted]	[redacted]	[redacted]	Calculation
Key: R^2, rituximab with lenalidomide.				

Informed by the UK advisory board, a mean duration of treatment of 24 weeks was assumed for all treatments.[1] Where applicable, the mean time on treatment for subsequent treatments accounts for the induction and maintenance phase.

All drug unit costs were sourced from the latest available data from MIMS[112] or the eMIT.[113] Drug unit cost and dosing schedules are described in Table 21 and Table 37. The unit cost and dosing schedules of the subsequent treatments that are not considered to be relevant comparators in the model are provided in Appendix I. The total acquisition and administration cost for each regimen is provided in Table 47.

Table 47: Subsequent therapy costs

Subsequent treatment	Total acquisition cost (£)	Total administration cost (£)
O-B	[redacted]	£12,605.86
R-B	[redacted]	£6,158.43

Subsequent treatment	Total acquisition cost (£)	Total administration cost (£)
R-CHOP	[redacted]	£3,422.59
R-GemOx	£9,491.23	£7,972.66
R-GDP	£8,143.68	£10,237.65
Rituximab monotherapy	£6,203.15	£0.00
R-ESHAP	£8,673.40	£14,261.98
R^2	[redacted]	£3,919.02
R-CVP	[redacted]	£4,563.45

Key: O-B, obinutuzumab with bendamustine; R^2; lenalidomide with rituximab; R-B, rituximab with bendamustine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; R-CVP, rituximab with cyclophosphamide, vincristine and prednisolone.
Source: eMIT 2025[113]; MIMS 2023.[112]

For the small proportion of patients going on to receive SCT, they may receive either autologous stem cell transplant (ASCT) or allo-SCT. Unit costs for ASCT and allo-SCT were obtained from NHS Reference Costs[114], and these costs are shown in Table 48.

Table 48: Breakdown of costs for stem cell transplant and radiotherapy

Therapy	Components	Cost (£)	Source
ASCT	Stem cell collection	5,674.22	NHS Reference Costs 2023/24: Elective Inpatient. SA18 - Bone Marrow Harvest
	ASCT	34,000.00	NICE NG52: NHL Diagnosis and Management. Appendix A, uplifted to 2023/24 values
Allo-SCT	Allo-SCT	49,986.30	NHS Reference Cost 2023/24: Elective Inpatient. Weighted average of SA38A, SA39A, SA40Z - Peripheral Blood Stem Cell Transplant, Allogeneic

Key: allo-SCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; HRG, healthcare resource group; NHL, Non-Hodgkin's lymphoma; NHS, National Health Service.
Source: NHS reference costs.[114]

In addition, prior to ASCT, patients will also require conditioning with high-dose chemotherapy. In the model, it is assumed that the BEAM (carmustine, etoposide, cytarabine, and melphalan) regimen is used. Unit costs were obtained from eMIT[113], and administration costs were assumed to be covered by the ASCT procedure, in line with TA895[115] and TA1048[89] and as summarised in Table 49.

Table 49: High dose chemotherapy costs

Drug	Dosing regimen	Drug acquisition cost per regimen (£)	Drug acquisition cost source	Administration cost per regimen (£)	Administration details	Total regimen cost (£)	Proportion receiving
BEAM							
Carmustine	300 mg/m^2 on Day 1	2,577.40	eMIT	0.00	Assumed to be covered by ASCT procedure, in line with TA1048 and TA895	2,577.40	100% (Assumption)
Etoposide	200 mg/m^2 on Day 2 to 5		eMIT				
Cytarabine	200 mg/m^2 on Day 2 to 5		eMIT				
Melphalan	140 mg/m^2 on Day 6		eMIT				

Key: allo-SCT, allogeneic stem cell transplant; BEAM, carmustine + etoposide + cytarabine + melphalan; eMIT, electronic market information tool; HDCT, high-dose chemotherapy; TA, technology appraisal.
Source: eMIT 2025.[113]

The final acquisition and administration costs associated with the subsequent therapies for the intervention and comparator arms are summarised in Table 50. For tafasitamab + R^2 and R^2, higher administration costs are driven by SCT costs, which are included as administration costs.

Table 50: Total subsequent therapy cost per treatment arm

Regimen	Sub treatment acquisition costs (£)	Sub treatment administration costs (£)
Tafasitamab + R^2	[redacted]	£6,479.50
R^2	[redacted]	£6,479.50
R-B	[redacted]	£3,389.96
R-CVP	[redacted]	£3,389.96
R-CHOP	[redacted]	£3,389.96
Key: O-B, obinutuzumab with bendamustine; R^2, lenalidomide with rituximab; R-B, rituximab with bendamustine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; R-CVP, rituximab with cyclophosphamide, vincristine and prednisolone.		

3.5.4.2 End-of-life costs

A one-off end-of-life cost was applied to patients at the point of dying to reflect the cost of terminal care, sourced from the PSSRU Unit Costs of Health and Social Care 2024 at £12,038 in 2023/2024 value.[86] This cost was based on research carried out by the Nuffield Trust in 2012, which examined the health and social care service use patterns across seven local authorities for a cohort of 73,243 people who died.[86] The estimated average cost of care services required by patients in their final year of life were collated, and reported by diagnostic group. These services include direct medical costs, such as inpatient admissions, outpatient visits, and A&E visits, as well as indirect costs such as residential, nursing, and home care. The cost of care for cancer patients was used to inform the base case analysis, as it included a comprehensive list of healthcare resource reflective of real-world practice in a population representative of that of the final scope.

3.6 Severity

To estimate the absolute and proportional severity modifiers, the QALY shortfall calculator (developed by the University of York, the Sheffield Centre for Health and Related Research [SCHARR] and Lumanity) was used: QALY Shortfall Calculator.

The quality-adjusted life expectancy for the general population was calculated in line with methods from NICE TSD 23[116] (informed by the baseline age and gender composition from inMIND [Table 51]), and adjusted using UK population norm values for EQ-5D, as reported by Hernández Alava et al.[91]

Table 51: Summary features of QALY shortfall analysis

Factor	Value	Reference to section in the submission
Proportion female	45.4%	Table 6
Starting age	64.2	Table 6
Key: QALY, quality-adjusted life year.		

The total QALYs for patients receiving standard of care (i.e. R^2) in UK clinical practice (and based on the final scope) was informed by the results of the base case economic analysis, which was then compared against the total expected QALY gains of the general population (without FL) to generate a would-be difference due to the disease (Section 3.10.1). Depending on the absolute and/or proportional shortfall estimated, appropriate QALY weights may be applied in accordance with NICE DSU TSD 23.[116]

The result of the QALY shortfall analysis is shown in Table 52. Based on the analysis, the expected absolute and proportional shortfalls are 4.96 QALYs and 45.9%, respectively, which are lower than that required for a multiplier to be applicable (12 and 85%, respectively). Therefore, a QALY weight of 1 is assumed in the model.

Table 52: Summary of QALY shortfall analysis

Remaining QALYs for general population	Expected QALYs for patients with FL on current treatment	Absolute shortfall	Proportional shortfall	QALY weight
10.81	5.85	4.96	45.9%	×1
Key: FL, follicular lymphoma; QALY, quality-adjusted life year.				

3.7 Uncertainty

Despite best efforts in considering all available evidence for this economic evaluation, there remain some areas of uncertainty, which the Company has sought to address through extensive clinical and economic validation, exploring different structural assumptions, evaluating joint parameter uncertainty, and conducting various scenario analysis. These areas of uncertainty are as follows:

- Extrapolation of long-term outcomes (PFS and OS) based on relatively short-term clinical trial data is a common challenge for most oncology products undergoing NICE appraisal.[117, 118] Due to the short trial follow-up, the survival extrapolations required to estimate long-term treatment efficacy may be subject to uncertainty. The model was therefore designed to include the flexibility to explore various survival modelling approaches to extrapolate beyond the observed duration of the clinical trial. As discussed in Section 3.3, selection and validation of curves to best represent long-term clinical trajectory were conducted according to the NICE reference case, followed by input from clinical experts and health economists. Where possible, findings from HMRN data were also used to confirm selection of survival extrapolations
- The occurrence of treatment waning could not be fully explored given the relatively short-term trial data from inMIND. Clinical experts were of the view that treatment waning is likely to occur in line with other fixed dose regimens when being assessed in economic analysis. Discussions around the treatment waning effect are a recurrent topic for discussion in NICE appraisals. As in previous appraisals in FL, the company has explicitly incorporated a waning effect in the model. The treatment waning effect in the base case analysis was conservatively assumed to start at Year 5, with a duration of 5 years (Sections 3.3.2 and 3.3.3), based on the clinical plausibility of the OS gain given the PFS benefit. Due to the uncertainty in the structural assumption, alternative values are explored in scenario analyses (see Section 3.11.3)
- In the absence of direct comparative evidence between tafasitamab + R^2 against R-chemotherapy comparators, ITCs in the form of unanchored MAICs were conducted, but with a high level of uncertainty due to deficiencies in the publicly available data for the comparators (see Section 2.10). The MAIC results were shared

with the clinicians during the validation process, and they agreed that the MAICs lacked face validity because the results were not aligned with clinical expectations. Consequently, the model takes a conservative approach by assuming the relative treatment effect of tafasitamab + R^2 versus R-chemotherapy (R-B, R-CVP, and R-CHOP) is the same as that of tafasitamab + R^2 versus R^2.

3.8 Managed access proposal

Based on currently available evidence, the company believes that tafasitamab offers a clinically effective and cost-effective treatment option to the NHS and, thus, recommendation for routine commissioning is supported. However, if the Committee concludes that data uncertainties warrant further data collection, the Company would support the option of a recommendation with managed access. A proposal for managed access is therefore included as part of the company submission.

As a cancer drug, tafasitamab is eligible for consideration within the Cancer Drugs Fund (CDF). Incyte acknowledges that there are uncertainties in long term OS (see Section 2.6.3), treatment waning (see Section 3.3.3) and TTNT (see Section 2.6.8), and therefore, has developed a proposal to address these uncertainties. The inMIND trial is ongoing, with final analysis planned after the last participant has completed a minimum of 5 years of post-treatment follow-up. This is anticipated in [redacted]. This final analysis will be performed on OS and TTNT data which will be at least 4 years more mature than the current data and will therefore provide greater certainty on the impact of tafasitamab + R^2 on these outcomes. Early access to tafasitamab + R^2 via the CDF will also allow real-world outcomes, with its use to be collected through the Systemic Anti-Cancer Therapy (SACT) registry. This proposal for data collection is summarised in Table 53; the anticipated timeframe of data collection is up to [redacted], aligning with the anticipated availability of the final OS analysis of the inMIND trial.

The Company believes the proposal for managed access would be feasible to implement as it uses established mechanisms (ongoing clinical trial and SACT) to collect longer-term data. This approach has been successfully used for other R/R FL treatments with uncertainty around longer-term benefit at the time of evidence submission (e.g. obinutuzumab with bendamustine). Of note, in addition to the proposed sources for clinical outcome data, Blueteq will be set up to collect data on

the real-world patient demographics and clinical characteristics for whom tafasitamab + R^2 is prescribed in practice. This will include ECOG PS, POD24, refractory status, line of therapy and time since last treatment.

Table 53: Overview of proposal for data collection

Source	inMIND trial	SACT
Source description	Phase III double-blind, placebo-controlled, randomised study	Mandated dataset as part of the Health and Social Care Information Standards
Population	Adult patients with R/R FL Grade 1–3A after one or more systemic treatments	All patients who use systemic anti-cancer therapies across all NHS England trusts
Intervention(s)	Tafasitamab + R^2	Tafasitamab + R^2
Comparator(s)	R^2	N/A
Outcomes	**Overall survival** Progression-free survival **Time to next treatment**	**Overall survival** Progression-free survival **Time to next treatment**
Data analysis	The final analysis will be conducted after the last participant has completed a minimum of 5 years of post-treatment follow-up	The company will not have access to the NHS Digital patient data, but will receive de-personalised summary data
Governance	Incyte own the inMIND dataset, and will conduct analyses based on prespecified study assessments and procedures	All necessary governance arrangements through SACT, and other datasets brought together by NHS Digital, have been established with NHS trusts and NHSE&I
Study used in the NICE economic model	Yes	No
Trial start date	Patients were enrolled between 16 April 2021 and 10 August 2023	Start of CDF
Data cut submitted to NICE	Primary analysis - data cutoff date 23 February 2024	N/A
Anticipated data cut after a period of managed access	Final analysis – anticipated data availability [redacted]	[redacted]
Registry previously used within a NICE MAA	N/A	Yes

Key: CDF, Cancer Drugs Fund; FL, follicular lymphoma; MAA, managed access agreement; N/A, not applicable; R^2; lenalidomide with rituximab; R/R, relapsed or refractory; SACT, systemic anti-cancer therapy.
Note: Bold text highlights primary sources of data to address key uncertainties in the existing clinical evidence base.

3.9 Summary of base-case analysis inputs and assumptions

3.9.1 Summary of base-case analysis inputs

A summary of the variables applied in the economic analysis are presented in Table 54.

Table 54: Summary of variables applied in the economic model

Variable	Value	SE	Within PSA varied by	Reference to section in submission
Settings				
Time horizon	40	-	Not varied	Section 3.2.2.4
Age (years)	64.20	-	Not varied	Section 3.2.2.4
BSA (mg/m^2)	1.86	0.25	Normal	Section 2.3.2
Weight (kg)	76.93	18.56	Normal	Section 2.3.2
Discount rate costs and outcomes	3.5%	-	Not varied	Section 3.2.2.5
Clinical outcomes				
PFS (tafasitamab + R^2)	Generalised gamma, jointly fitted	Specific variance-covariance matrix	Based on the inverse of the normal cumulative distribution for the specified mean and variance-covariance matrix	Section 3.3.2
PFS (R^2)				
OS (tafasitamab + R^2)	Generalised gamma, jointly fitted	Specific variance-covariance matrix		Section 3.3.3
OS (R^2)				
TTD (tafasitamab + R^2)	Direct Kaplan–Meier	-	Not varied	Section 3.3.4
TTD (R^2)				
Treatment waning	At 5 years, over 5 years	-	Not varied	Section 3.3
MAIC HRs. Assumed equivalent HR to tafasitamab + R^2 versus R^2			Gamma	Section 2.10
Acquisition cost inputs				
Drug cost per pack. See detailed list in Table 37		-	Not varied	Section 3.5.1
Relative dose intensity. See detailed list in Table 38		NR	Beta	

Variable	Value	SE	Within PSA varied by	Reference to section in submission
Administration costs (£)				
Oral	0.00	NR	Normal	Section 3.5.1
IV complex/simple (first administration)	570.43	NR	Normal	
IV complex/simple (subsequent administration)	426.15	NR	Normal	
IV simple (first administration)	528.11	NR	Normal	
Inpatient administration	559.86	NR	Normal	
Subcutaneous	0.00	NR	Normal	
ICU	252.98	NR	Normal	
Resource use costs (£)				
Haematologist led	205.00	NR	Normal	Section 3.5.2
FBC (Diagnostic tests)	6.28	NR	Normal	
Patient history/physical exam (Diagnostic tests)	6.21	NR	Normal	
Full profile (U&E, LFT, calcium) (Diagnostic tests)	17.10	NR	Normal	
Serum IgG, IgA, IgM and electrophoresis (Diagnostic tests)	25.10	NR	Normal	
LDH test (Diagnostic tests)	12.69	NR	Normal	
CT scans	136.00	NR	Normal	
Resource use frequency				
See detailed list in		NR	Normal	Section 3.5.2
Adverse event probability				
See detailed list in		NR	Beta	Section 3.4.4
Adverse event costs				
See detailed list in		NR	Normal	Section 3.5.3
Utility inputs				
Progression-free	0.824	0.025	Beta	Section 3.4.5
Progressed disease	0.788	0.027	Beta	
Adverse event disutility inputs				

Variable	Value	SE	Within PSA varied by	Reference to section in submission
See detailed list in		NR	Beta	Section 3.4.4

Key: BSA, body surface area; CT, computed tomography; FBC, full blood count; ICU, intensive care unit; Ig, immunoglobulin; IV, intravenous; LDH, lactate dehydrogenase; LFT, live function tests; NR, not reported; OS, overall survival; PFS, progression-free survival; PSA, probabilistic sensitivity analysis; R^2, rituximab with lenalidomide; SE, standard error; TTD, time to discontinuation; U&E, urea and electrolytes.

3.9.2 Assumptions

Table 55 contains the key assumptions for the de novo economic model.

Table 55: Summary of assumptions of the base case economic analysis

Category	Assumption	Justification
Population	Adult patients with R/R FL with relapsed or refractory disease after receiving at least one systemic anti-CD20 immunotherapy or chemo-immunotherapy as first line treatment therapy	Aligned with the decision problem of this appraisal
Comparator	R^2 (primary) R-chemotherapy (secondary)	Aligned with the decision problem of this appraisal and confirmed by clinical experts
Model settings and structure	Baseline characteristics in line with inMIND	Confirmed by clinical experts to be reflective of UK clinical practice
	3-state partitioned survival model	Established model structure to assess cost-effectiveness of oncology therapies, which is also used in other NICE appraisals in FL. Reflects the natural progression of patients with R/R FL who had failed one prior line of therapy
	Lifetime horizon	In line with NICE reference case
	UK NHS and PSS perspective	In line with NICE reference case
Clinical effectiveness	Efficacy data sourced from inMIND for tafasitamab + R^2 and R^2	In line with NICE reference case; inMIND presents direct trial data to examine comparative efficacy between the intervention and the comparator

Category	Assumption	Justification
	Assume equivalence between R^2, R-B, R-CHOP and R-CVP	Due to the lack of face validity of the MAIC results, the model takes a conservative approach by assuming that the efficacy of R-B, R-CVP, and R-CHOP is equivalent to that of R^2. The same hazard ratio for tafasitamab + R^2 versus R^2 was applied to the tafasitamab + R^2 extrapolations to derive the R-chemotherapies survival curves
	Jointly fitted generalised gamma curves assumed to be base case for PFS and OS	Selection of curves were made in line with guidance from NICE DSU TSD 14
	Treatment waning starting at 5 years with a 5-year duration	Based on the plausibility of OS long-term extrapolations in the tafasitamab + R^2 arm
Quality of life inputs	EQ-5D utilities based on inMIND, mapped to EQ-5D-3L using UK value set	Direct utility values elicited from the population of interest, in line with NICE guidance
	PF utilities capped to the general population utility. PD derived using the proportional decrement after progression in the inMIND utilities	Utilities capped to prevent patients with R/R from having a higher utility than the healthy general population
	AEs utility decrement applied during the first cycle of the model time horizon	AEs likely to occur upon treatment and are thus considered to be once-off
Cost and resource inputs	Dosing of tafasitamab + R^2 and R^2 based on administration in inMIND	Based on proposed marketing authorisation
	Healthcare resource use dependent on health states, based on TA627	Accepted for use in TA627, deemed to be reflective of clinical practice

Key: AE, adverse event; CD20, cluster of differentiation 20; DSU, Decision Support Unit; EQ-5D, EuroQoL-5 dimensions; EQ-5D-3L, EuroQoL-5 dimensions-3 levels; FL, follicular lymphoma; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PD, progressed disease; PFS, progression-free survival; PSS, Personal Social Services; R^2, lenalidomide + rituximab; R/R, relapsed or refractory; TA, technology appraisal; TSD, Technical Support Document.

3.10 Base-case results

3.10.1 Base-case incremental cost-effectiveness analysis results

Table 56 shows the base incremental analysis and the ICER results for tafasitamab + R^2 versus R^2 with a [redacted].

Tafasitamab + R^2 is estimated to offer greater health benefits compared to R^2, with an additional [redacted] and [redacted] gained per patient lifetime. Tafasitamab + R^2 is associated with incremental costs of [redacted], resulting in an ICER of £32,672 per QALY gained.

Against all R-chemotherapy regimens, use of tafasitamab + R^2 was associated with higher health benefits, with an additional [redacted] and [redacted] LYs and QALYs gained. Additional costs versus R-B were [redacted] across a lifetime horizon, resulting in an ICER of £29,029 per QALY gained. When compared with R-CVP, use of tafasitamab + R^2 was associated with additional lifetime costs of [redacted], resulting in an ICER of £28,723 per QALY gained. Similar results were generated when compared with R-CHOP, with additional lifetime cost of [redacted], resulting in an ICER is £30,982 per QALY gained.

The fully incremental analysis in Table 56 shows that R-Benda and R-CVP are strictly dominated by R^2 as they yield higher costs and lower QALYs. Compared with R-CHOP, R^2 results in [redacted] additional costs, [redacted] additional life years and [redacted] additional QALYs, resulting in an ICER of £17,888 per QALY gained.

Table 57 presents the net health benefit at £20,000 and £30,000 for each pairwise comparison.

Table 56: Base case fully incremental analysis (with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)	Fully incremental ICER (£/QALY)
R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,982	-
R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,029	Strictly Dominated
R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,672	£17,888
R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,723	Strictly Dominated
Tafasitamab + R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	£32,672
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.								

Table 57: Base case Net Health Benefit (with PAS)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000/QALY	NHB at £30,000/QALY
Tafasitamab + R^2	[redacted]	[redacted]	[redacted]	[redacted]	-	-
R^2	[redacted]	[redacted]	[redacted]	[redacted]	-0.67	-0.09
R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	-0.54	0.04
R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	-0.52	0.05
R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-0.65	-0.04
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALY, quality-adjusted life year.						

3.11 Exploring uncertainty

3.11.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was performed on key model inputs, involving the sampling of values from the uncertainty distribution of each input across numerous iterations. The normal distribution was applied for costs and resource use. For utilities and probabilities, the beta distribution was utilised, as it generates values ranging between 0 and 1. A gamma distribution was used for PFS and OS HRs for tafasitamab + R^2 versus R-chemotherapy. Full details on the distributions used for key inputs can be found in Section 3.8.

The results of the PSA based on 1,000 iterations are presented in Table 58. Compared with R^2, tafasitamab + R^2 was associated with [redacted] incremental costs and [redacted] incremental QALYs, corresponding to an ICER of £38,225 per QALY gained. The probabilistic results show lower life years and QALYs than the deterministic results (see Figure 30). This asymmetry in the probabilistic results is caused by the combination of the high uncertainty in the OS extrapolations (captured by the variance-covariance matrix) and the treatment waning effect. Some iterations will generate a significantly higher survival for tafasitamab + R^2 than for R^2. In these iterations, the survival gain will be capped in the long term by the imposition of the treatment waning effect. However, in the iterations where tafasitamab + R^2 OS is similar to R^2 OS, the treatment waning will have a minimal impact, as the hazards will be similar. In summary, whilst it is important to capture joint parameter uncertainty via PSA, the PSA provides an artificially high estimate of the probabilistic ICER.

Figure 31 shows the cost-effectiveness acceptability curve that demonstrates the probability that tafasitamab + R^2 will be cost-effective against R^2 at a number of willingness-to-pay thresholds. At £30,000 per QALY gained, the probability that tafasitamab + R^2 is cost-effective is 32.3%; however, due to the reasons noted above, this is likely to be an artificially low estimate of the probability. Figure 30 presents the cost-effectiveness plane for tafasitamab + R^2, which plots the mean incremental costs and QALYs of the PSA. Most of the points lie within the northeast

quadrant of the plane, indicating that tafasitamab + R^2 is more costly and more effective than R^2.

Figure 32 shows the PSA convergence plot. At approximately 100 iterations, the ICER becomes relatively stable.

Table 58: Mean probabilistic base case results

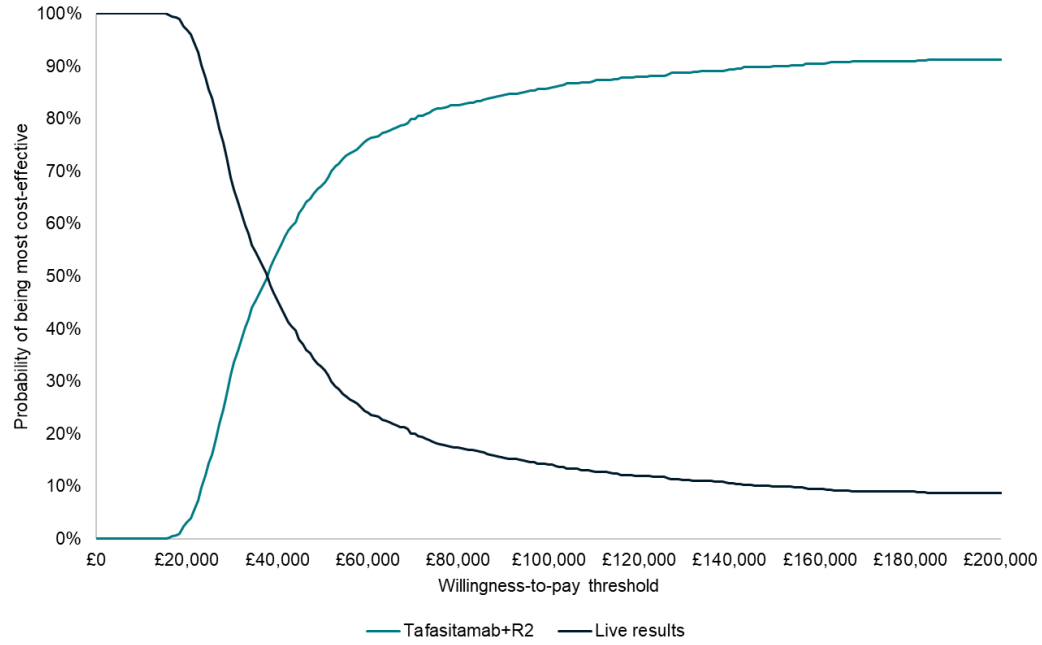
	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ QALY)
R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Tafasitamab + R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,225

Key: ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life years gained; QALY, quality-adjusted life year; R^2; lenalidomide with rituximab.

Figure 30: Cost-effectiveness plane

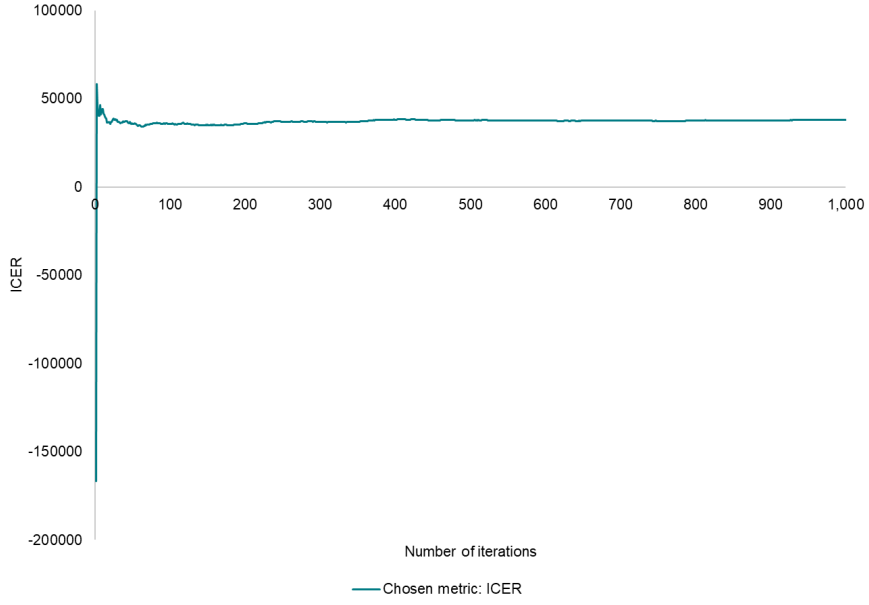
Key: QALY, quality-adjusted life year; R^2; lenalidomide with rituximab; WTP, willingness-to-pay.

Figure 31: Cost-effectiveness acceptability curve



Key: R^2; lenalidomide with rituximab.

Figure 32: PSA convergence plots



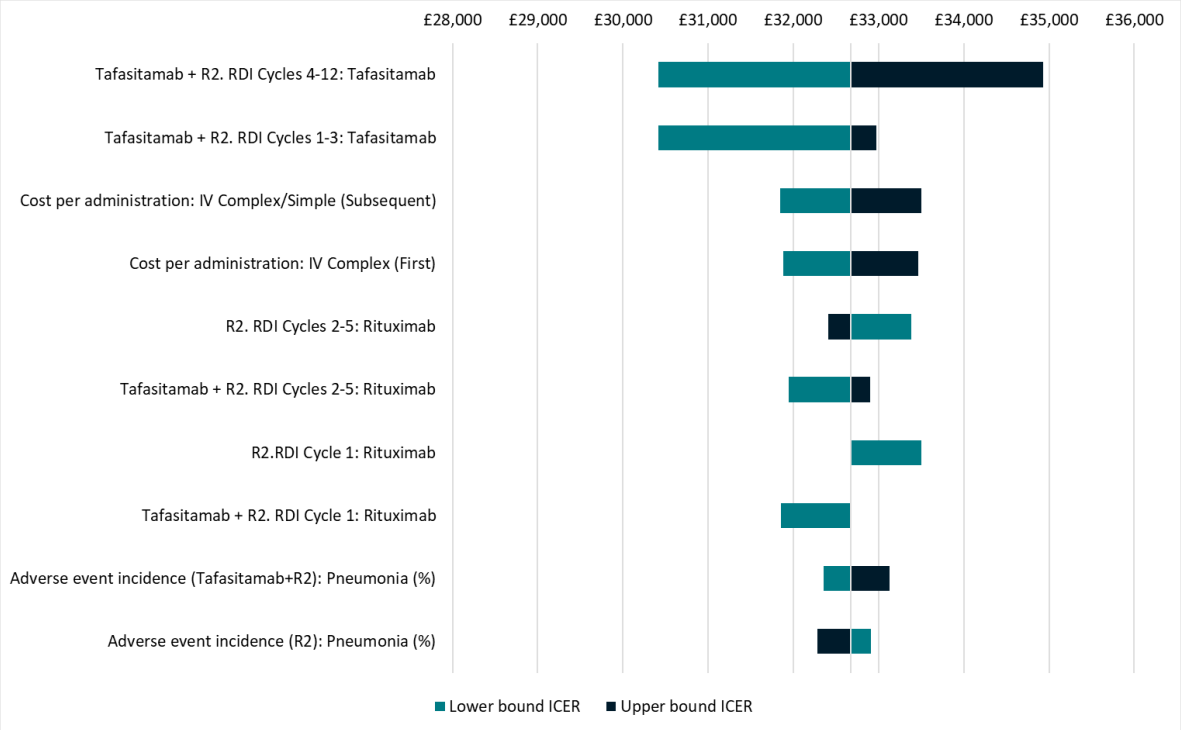
Key: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis.

Results versus R-B, R-CHOP and R-CVP and presented in Appendix H.

3.11.2 One-way sensitivity analysis

One-way sensitivity analysis was conducted by varying key model parameters within its upper and lower confidence limit, or by +/- 10% of its standard error when the limits are not available. The resultant ICERs were tabulated and ranked according to their highest deviation from the base case ICER. Figure 33 shows the 10 parameters which have the greatest influence on the ICER for tafasitamab + R^2 versus R^2. The key drivers of the model results include RDI for tafasitamab (which in the model relates to its acquisition costs), followed by the assumed costs of intravenous administration.

Figure 33: Tornado diagram showing results from one-way sensitivity analysis



Key: ICER, incremental cost-effectiveness ratio; IV, intravenous; R^2; lenalidomide with rituximab.

Results versus R-B, R-CHOP and R-CVP and presented in Appendix H.

3.11.3 Scenario analysis

To further explore structural uncertainty and assumptions within the model, scenario analyses were performed to analyse the effect of varying a specific model parameter on the base-case results. These scenarios included curve selections, source of inputs, and modelling options, and are listed in Table 59. The ICERs from the scenario analysis ranged from £20,465 to £48,748 per QALY gained. However, the scenarios leading to ICERs that are materially greater than the base case are of questionable plausibility. The most influential scenario explored was the use of a 10-year time horizon, as it reflects the intervention's higher upfront costs. However, a 10-year time horizon is insufficient to capture the relevant differences in long-term outcomes as all the costs are accrued early but the benefits are extended over the long term (tafasitamab + R^2 OS at 10 years 49.8% vs 38.2% in the R^2 arm). When a more appropriate longer time horizon is considered (see 20-year time horizon and the base case lifetime time horizon), the ICER decreases, as the incremental costs remain similar, but the incremental QALYs increase as it takes into consideration the improved OS during a longer period. Similarly, due to tafasitamab upfront costs during the first year of the model, a lower discount rate increases the value of future incremental QALYs while the incremental costs are constant, and consequently, the ICER decreases.

Treatment waning also has a notable effect on the ICER. As discussed in Section 3.3.3.1.2, in TA627, the Committee considered a waning effect beginning between 5 and 10 years to be plausible. The base case model conservatively assumes waning starts at 5 years and lasts for 5 years. Extending the waning duration to a plausible 10 years decreases the ICER to £28,676 per QALY gained.

Alternative extrapolations for OS and PFS using clinically and statistically plausible parametric models have a limited impact on the base-case ICER, supporting the robustness of the results. For example, applying log-logistic curves for OS and PFS lowers the ICER to £31,784, indicating that the base-case estimate may be conservative. While OS remains a key area of uncertainty, long-term projections based on a range of plausible model assumptions consistently demonstrate stable ICER estimates.

Using PFS by INV rather than PFS by IRC also has a limited effect on the ICER (£33,762), as the decrease in HRQL after progression is small and HCRU costs in the PD state are similar to those in the PF state. Alternative health state utility values, including those from the GADOLIN and AUGMENT studies, had minimal effect on the ICER, indicating that the base case utility values from the inMIND trial are likely to be reasonable.

While adoption of the inMIND distribution of subsequent treatments increased the ICER slightly to £34,876/QALY, this is not reflective of UK clinical practice; the base case distribution is therefore more applicable to the decision problem. Other scenario analyses – such as including COVID-related AEs, removing AE disutilities, or assuming intravenous administration for rituximab maintenance in R-chemotherapy regimens – had minimal impact on the ICER.

As the lenalidomide patent has expired, an alternative scenario was conducted to assess the impact of a 30% reduction in its price. Since tafasitamab + R^2 is an add-on to R^2, the price reduction similarly affects both treatment arms' acquisition costs, resulting in negligible change in incremental costs and the ICER.

The state transition modelling approach explores the impact of generating long-term OS from PFS and PPS, rather than extrapolating the (limited) OS data directly from the trial. Distinctly different ICER estimates are generated depending on the assumptions made around the relationship between PFS, PPS and OS. When assuming that the treatment provides a benefit only on the probability of progression – by applying the median PPS observed in the 2L+ R-chemotherapy arm from the HMRN across all treatments (scenario STM 1) – the ICER increases from £32,627 to £42,121 per QALY gained. Conversely, when assuming a treatment benefit on both the PFS and PPS, as suggested by the GADOLIN PFS and OS Kaplan–Meier curves (scenario STM 2), the ICER decreases from £32,627 to £17,090 per QALY gained. As detailed in Section 3.3.3.1.3, these two scenarios are likely to over- and underestimate the ICER for tafasitamab + R^2 versus R^2. A more plausible state transition-based model scenario (STM 3) that weights the previous two scenarios to reflect the inMIND trial population, and generates survival extrapolations that

generally align with clinical expectations, produces an ICER estimate of £27,101 per QALY gained.

Scenario analyses versus R-chemotherapy are presented in Appendix H.

Table 59: Results from scenario analysis versus R[2]

#	Scenario Name	Inc. Costs	Inc. LYs	Inc. QALYs	ICER	ICER vs base case	ICER vs base case (%)
-	Base case	[redacted]	[redacted]	[redacted]	£32,672	-	-
1	time_horizon_10_years	[redacted]	[redacted]	[redacted]	£48,748	16,076	49.2
2	State_transition_GADOLIN (STM 2)	[redacted]	[redacted]	[redacted]	£20,465	-12,207	-37.4%
3	State_transition_HMRN (STM 1)	[redacted]	[redacted]	[redacted]	£42,121	9,449	28.9%
4	State_transition_weighted (STM 3)	[redacted]	[redacted]	[redacted]	£27,101	-5,571	-17.1%
5	discounting_1.5%	[redacted]	[redacted]	[redacted]	£28,149	-4,523	-13.8
6	OS_PFS_waning_7_years_5Ydur	[redacted]	[redacted]	[redacted]	£28,670	-4,002	-12.2
7	OS_PFS_waning_5_years_10Ydur	[redacted]	[redacted]	[redacted]	£28,676	-3,996	-12.2
8	OS_PFS_waning_5_years_3Ydur	[redacted]	[redacted]	[redacted]	£35,391	2,719	8.3
9	Wastage_No	[redacted]	[redacted]	[redacted]	£30,432	-2,240	-6.9
10	SubTx_dist_inMIND	[redacted]	[redacted]	[redacted]	£34,876	2,204	6.7
11	time_horizon_20_years	[redacted]	[redacted]	[redacted]	£34,672	2,000	6.1
12	OS_PFS_waning_5_years_7Ydur	[redacted]	[redacted]	[redacted]	£30,723	-1,949	-6.0
13	PFS_IA	[redacted]	[redacted]	[redacted]	£33,762	1,090	3.3
14	util_wild	[redacted]	[redacted]	[redacted]	£33,761	1,089	3.3
15	OS_PFS_joint_log-logistic	[redacted]	[redacted]	[redacted]	£31,784	-888	-2.7
16	util_TA898	[redacted]	[redacted]	[redacted]	£33,502	830	2.5
17	COVID_include	[redacted]	[redacted]	[redacted]	£33,179	507	1.6
18	PFS_joint_log-logistic	[redacted]	[redacted]	[redacted]	£32,176	-496	-1.5
19	OS_joint_log-logistic	[redacted]	[redacted]	[redacted]	£32,272	-401	-1.2
20	R_maintenance_IV	[redacted]	[redacted]	[redacted]	£32,976	303	0.9
21	util_GADOLIN	[redacted]	[redacted]	[redacted]	£32,793	121	0.4
22	util_AUGMENT	[redacted]	[redacted]	[redacted]	£32,717	45	0.1
23	lenalidomide_30%_discount	[redacted]	[redacted]	[redacted]	£32,670	-2	0.0

#	Scenario Name	Inc. Costs	Inc. LYs	Inc. QALYs	ICER	ICER vs base case	ICER vs base case (%)
24	AE_utility_exclude	[redacted]	[redacted]	[redacted]	£32,670	-2	0.0
Key: ICER, incremental cost-effectiveness ratio; inc., incremental; LY, life year; QALY, quality-adjusted life year.							

3.12 Subgroup analysis

As introduced in Section 3.2.1, the inMIND trial included a subgroup of patients with FL who have experienced multiple relapses or were refractory to 2L treatment, and who were also randomised to receive either tafasitamab + R^2 or R^2, representing a 3L+ population.

The 3L+ subgroup analysis employs the same approach and assumptions as the base case analysis in the overall inMIND FL population, including the PFS and OS curve selection for extrapolation. However, only R^2 is a relevant comparator. In this subgroup of patients with particularly high unmet needs, tafasitamab + R^2 has an ICER of £27,377 per QALY gained (Table 60). Full results are presented in Appendix M.

Table 60: Cost-effectiveness results of tafasitamab + R^2 versus R^2 in the 3L+ population

	Total costs (£)	Total LYG	Total QALY	Inc. costs (£)	Inc. LYG	Inc. QALY	ICER (£/ QALY)	NHB at £20 K	NHB at £30 K
R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Tafa + R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	27,377	-0.44	0.11
Key: ICER, incremental cost-effectiveness ratio; inc., incremental; LYG, life years gained; NHB, net health benefit; QALY, quality-adjusted life year; R^2; lenalidomide with rituximab; tafa, tafasitamab.									

3.13 Benefits not captured in the QALY calculation

It is accepted that FL has a substantial impact on not only the people living with FL, but also their families and carers.[4] However, this is currently understudied in a quantitative way and has not been formally considered in the economic analysis.

As tafasitamab + R^2 has been shown to improve LYs and QALYs for people living with FL in this analysis, it is anticipated that its use may also provide QoL benefits to their families and carers. Indeed, the hope that tafasitamab + R^2 offers people living with FL is likely to provide positive value independent of the survival and HRQL benefits captured in the QALY calculation.

3.14 Validation

3.14.1 Internal validity

The de novo economic model was validated extensively by an independent health economist, with coding and calculations reviewed for accuracy and inconsistencies. A checklist, developed using publicly available checklists as a guide, was used in the validation exercise.[119-121]

3.14.2 External validity

3.14.2.1 Clinical and economic validation

Individual interviews were conducted with four clinical oncologists and two independent health economists from the UK to obtain insights to address key areas of uncertainty.[2, 122] The first round of interviews was conducted between 16 July 2025 and 30 July 2025, lasting 1–1.5 hours each. A second interview was conducted on 22 October with two clinicians to obtain final validation of the model base case, lasting 1.5 hours. The main points discussed during the validation meetings and the areas in which these were incorporated in the submission are the following:

- Confirmation that the trial population was reflective of the 2L+ R/R FL population in UK, in line with the final scope
- Discussion on the treatment pathway of patients with FL who had progressed after first line therapy in the UK, including the agents typically used in the UK across 1L,

2L, and 3L settings. This also involved extensive validation of the composition of likely subsequent treatment following disease progression with various 2L agents. Findings were incorporated into Section 3.5.4.1

- Validation and discussion of long-term PFS and OS projections, including landmark values, curve selections, likely hazards profile, and treatment waning. Results were first fed into selection of the most appropriate family of curves, followed by the final base case model, as evidence in Sections 3.3.2, 3.3.3, and 3.3.4
- Agreement on the use of trial-based utility values, where all clinicians confirmed applicability, and that the relative differences between PF and PD states were largely consistently with other trials (Sections 3.4.1 and 3.4.5)
- Discussion on the methodology and results of the ITCs

3.14.2.2 External data sources

As described in Section 3.3.3.1.1, the GADOLIN and AUGMENT OS Kaplan–Meier curves were used to assess the plausibility of the medium-term survival benefit derived from the inMIND OS extrapolations. The difference in the medium-term survival estimates between tafasitamab + R^2 and R^2 predicted by the model was compared to the difference observed in the trials between the intervention arm and the comparator arm. Additionally, both trials were used to justify the partitioned survival model over the state transition model, as explained in Section 3.2.2. Median PFS and OS values from GADOLIN and AUGMENT were considered to derive PPS rates for the state transition model presented in the scenario analysis (see Section 3.3.3.1.3).

To support the understanding of real-world clinical trajectory of patients with FL and to guide selection of curve extrapolations, real-world data from the HMRN were used.[21] Key clinical outcomes relevant to this section included real world OS and PFS. Both OS and PFS were described using the Kaplan–Meier curves, and used to inform the base case OS and PFS curves by selecting parametric curves that resembled the HMRN smoothed hazards plots. The scenario analysis using the state transition model was also informed by the post-progression survival observed in the HMRN data.

3.15 Interpretation and conclusions of economic evidence

In the primary base case analysis using the standard partitioned survival modelling approach, tafasitamab + R^2 in its licensed indication of 2L+ R/R FL had an ICER of £32,672 per QALY gained compared with the current standard care therapy, R^2.

In secondary comparisons versus relevant R-chemotherapy regimens in the 2L setting (R-B, R-CVP, and R-CHOP), tafasitamab + R^2 had ICERs of £29,029, £28,723, and £30,982 per QALY gained, respectively. In a subgroup analysis in the 3L+ R/R FL setting, in which patients have a particularly high unmet need, tafasitamab + R^2 had an ICER versus R^2 of £27,377 per QALY gained.

The partitioned survival model was developed and parameterised using the most robust comparative data available to date from the inMIND trial. As reported in Section 2.6, this robust Phase III trial demonstrated a clear statistically significant and clinically meaningful improvement in PFS (PFS by IRC HR: 0.41; 95% CI: 0.29, 0.56; $p < 0.0001$), and early indications of a clinically meaningful improvement in OS (HR: 0.59; 95% CI: 0.31, 1.13; [redacted]) for tafasitamab + R^2 versus R^2; however, current OS data are immature.[64, 68] Although there is evidence from the long-term follow-up of the GADOLIN[75] and AUGMENT[74] trials that clear improvements in PFS can translate into long-term improvements in OS, there is currently uncertainty in the magnitude of the long-term OS benefit with tafasitamab + R^2.

The modelling of OS (and PFS) therefore followed a comprehensive and systematic approach using best practice methods for extrapolation. Extensive validation with clinical and health economic experts, and against external trial and real-world evidence sources, was undertaken. This ensured that the most statistically appropriate and clinically plausible OS curves were used in the base case model.

A broad range of scenario analyses were conducted to explore the impact of key structural assumptions, and particularly to explore the OS modelling assumptions. Alternative extrapolations for OS using clinically and statistically plausible parametric models had a limited impact on the base-case ICER; applying the next most plausible parametric model to extrapolate OS (log-logistic) marginally lowered the

base case ICER to £32,272 per QALY gained. OS treatment effect waning had a notable effect on the ICER, but alternative waning scenarios indicate that the base case waning assumption could be conservative. At the request of the EAG, state transition modelling was also undertaken to explore the impact of generating long-term OS from PFS and PPS, rather than extrapolating the (limited) OS data directly from the inMIND trial. In the most plausible of three state transition-based model scenarios that were explored (STM 3), which was aligned with the inMIND trial population and generated survival extrapolations that aligned with clinical expectations, the ICER versus R^2 was £27,101 per QALY gained. So, while the magnitude of the OS benefit with tafasitamab + R^2 is a key area of uncertainty, plausible alternative OS modelling assumptions have yielded relatively stable ICER estimates.

Collectively, the primary base case analysis versus R^2 in the licensed indication of 2L+ R/R FL, the secondary analyses versus R-chemotherapy in the 2L setting, the subgroup analysis versus R^2 in the 3L+ R/R FL setting, and the extensive range of scenario analyses, demonstrate the significant benefits to patients offered by tafasitamab + R^2, and its plausible potential to be cost-effective. In recognition of the uncertainty in the long-term outcomes, a proposal for managed access is included in this submission. This would accommodate early access to this innovative treatment for patients who have an unmet medical need with limited treatment options, while data collection is ongoing.

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5 Appendices

Appendix A: Summary of product characteristics (SmPC) and UK public assessment report

Appendix B: Identification, selection and synthesis of clinical evidence

Appendix C: Subgroup analysis

Appendix D: Adverse reactions

Appendix E: Published cost-effectiveness studies

Appendix F: Health-related quality of life studies

Appendix G: Cost and healthcare resource identification, measurement and valuation

Appendix H: Clinical outcomes and disaggregated results from the model

Appendix I: Price details of treatments included in the submission

Appendix J: Checklist of confidential information

Appendix K: Additional background information

Appendix L: Additional inMIND data and survival analysis

Appendix M: R/R FL after two or more systemic treatments (3L+) survival and economic analyses

Appendix N: O-Bendamustine and Epcoritamab comparisons

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Tafasitamab with lenalidomide and rituximab for treating relapsed or refractory follicular lymphoma after 1 or more systemic treatments [ID6413]

Company evidence addendum

April 2026

File name	Version	Contains confidential information	Date
ID6413_Tafasitamab RRFL_Evidence Addendum [redacted]_100426_Incyte	1.0	redacted	10 April 2026

1 Addendum Summary

- Epcoritamab for treating relapsed or refractory (R/R) follicular lymphoma (FL) after 2 or more lines of systemic treatment (3L+) is now recommended and is set to become a new standard of care, as supported by clinical opinion
  - Comparison of tafasitamab + R^2 versus epcoritamab is thus now highly relevant in this setting
- Tafasitamab + R^2 offers a clinically effective treatment option compared with epcoritamab in the 3L+ FL population as demonstrated in matching adjusted indirect treatment comparison (MAIC)
  - Estimated [redacted] reduction in the risk of progression, relapse or death (hazard ratio [HR]: [redacted]; 95% confidence interval [CI]: [redacted])
  - Estimated [redacted] reduction in the risk of death (HR: [redacted]; 95% CI: [redacted])
- Tafasitamab + R^2 also offers a cost-effective treatment option compared with epcoritamab in the 3L+ FL population as demonstrated in economic modelling
- When adopting the TA1139 committee preferred assumptions in the modelling approach, tafasitamab + R^2 dominates epcoritamab, with life year (LY) gains consistent with evidence and expectations from the MAIC analyses
  - The same outcome is observed when applying the ID6413 company base case, which takes a slightly more conservative approach to the TA1139 committee preferred assumptions despite a more robust evidence base
- While tafasitamab + R^2 remains a cost-effective treatment option when the ID6413 EAG preferred assumptions are applied, it is estimated to be marginally less effective, with LY gains no longer consistent with evidence and expectations from the MAIC analyses
  - There is a clear dissonance between appraisal approaches with an overly conservative approach adopted by the ID6413 EAG that lacks face validity
- We understand some of the dissonance and preference to conservatism is explained by the uncertainty, driven by limited long term outcomes data from in the inMIND trial. This is why a proposal for managed access is retained in this submission

  - This would accommodate early access to tafasitamab + R^2 for patients who continue to have an unmet medical need despite the recommendation of epcoritamab monotherapy, while data collection is ongoing
- We also acknowledge that an optimised recommendation in the 3L+ setting may represent a pragmatic approach, consistent with the EAG's observation that cost-effectiveness is more favourable in later lines of therapy.
- While we remain open to an optimised 3L+ recommendation, we believe that the evidence base and modelling approach may also support consideration of tafasitamab + R^2 in the full licensed 2L+ population, subject to the Committee's judgement on uncertainty.

2 Background

Two contemporaneous NICE appraisals in relapsed/refractory (R/R) follicular lymphoma (FL); epcoritamab (TA1139) and tafasitamab plus lenalidomide with rituximab (tafasitamab + R^2) (ID6413) have been conducted within a similar timeframe. However, they have adopted materially different approaches across several key methodological domains, including comparator selection, evidence generation, model structure, and treatment-effect assumptions. While such differences may be justified by the specific evidence base available for each technology, they have the potential to materially influence the efficiency frontier and the resulting cost-effectiveness conclusions within the same treatment pathway.

These differences may be individually justifiable; however, taken together, they may lead to divergent conclusions that do not appear consistent within a fully incremental cost-effectiveness framework and may therefore lack face validity. This is particularly pertinent in the 3L+ setting, where both technologies are relevant within the same clinical pathway. Given the proximity of these appraisals and their overlap in the treatment pathway, it is important to consider whether these methodological differences may also influence the consistency of decision-making and the interpretation of value across technologies. A summary of the evidence base and assumptions adopted is provided in Table 1 with further details provided in the Addendum Appendix.

Table 1: Evidence base and assumptions adopted in TA1139 and impact on this appraisal (ID6413)

	Evidence base and assumptions adopted in TA1139	Evidence base and assumptions adopted in ID6413	Impact on this appraisal (ID6413)
Intervention data	• Single-arm Phase II trial data (N=128) • Unclear period of follow-up for OS (data cut and follow-up data redacted) • Unclear OS estimates (data redacted) but OS at 18 months presented at CM suggesting follow-up no more than 2 years	• Randomised, controlled trial (RCT) - Phase III data (N=548) • Median follow-up of 15.3 months for OS • Early signals of OS benefit with HR vs R^2: 0.59; 95% CI: 0.31, 1.13)	• Robust RCT data should reduce the quantification of uncertainty applied via model assumptions • Differences in trial follow-up / data maturity do not seem to adequately justify differences in preferred approaches
Key comparator data	• HMRN data used to estimate comparator effect • 'Basket' comparator combined R-chemotherapy, chemotherapy, R^2, O-B and other therapies despite proven differences in their effect – As demonstrated in RCT data, for example, GADOLIN[1], AUGMENT[2] and Van Oers[3] which all showed chemotherapy is less effective than R^2, R-chemotherapy and O-B • Unclear OS estimate for 'basket' comparator in 3L+ FL in the HMRN data (data redacted) but assuming similar to Wasterlid 2024[4] – 2-year OS ~50%; 5-year OS ~35%	• RCT Phase III data for R^2 used in base case – R2 already accepted to be more effective than R-chemotherapy in TA627[5] – Tafasitamab + R^2 vs R^2 OS HR: 0.59 (95% CI: 0.31, 1.13) • HMRN data for R-CVP, R-CHOP and the two combined for R-chemotherapy used in scenario analyses – Tafasitamab + R^2 vs R-chemotherapy OS HR: [redacted] • OS estimates from 'basket' of HMRN treatment data range: [redacted] with typically longer estimates for R-chemotherapy / immune-chemotherapy treatments	• Head-to-head RCT data for the primary comparator (R^2) should reduce the quantification of uncertainty applied via model assumptions • Should we have applied HMRN OS HR rather than head-to-head RCT data outcomes would be more favourable to tafasitamab + R^2 • HMRN data used for additional comparison to individual R-chemotherapy treatments (R-CHOP, R-CVP, R-B) should reduce uncertainty • Should we have applied a 'basket' comparator from HMRN data, outcomes would be more favourable to tafasitamab + R^2

Model structure	• PSM model structure applied as observed in all previous NICE appraisals for FL treatments • The PSM model structure is acknowledged to have the direct advantage of using observed trial data • The company were asked to consider a STM but did not provide and were not challenged on this point	• PSM model structure applied in company base case • STM model structure explored in scenario analyses at the request of the EAG	• Further support for company base case approach (PSM) that: – Provides a consistent framework for decision making in FL – Supports a flexible framework for quantifying uncertainty of alternative survival assumptions – Enables direct incorporation of observed data
PPS benefit	• Unclear what PPS benefit is modelled as outcomes are redacted but some PPS benefit looks to be assumed • Plausibility of PPS benefit was not identified as a key issue and did not impact decision making	• Some PPS benefit assumed in company base case aligned with existing evidence: – Early signals of OS and PPS benefit from robust RCT data for tafasitamab + R[2] (inMIND[6]) – Significant OS benefit observed in robust RCT data for comparator treatments in FL with longer follow-up (GADOLIN[1] and AUGMENT[2]) demonstrating plausibility of PFS benefits leading to longer term OS benefits – PPS benefit observed in robust RCT data for O-B in FL with estimated 27.3 months gain in PPS vs control arm (GADOLIN[1]) – Clinical validation of an expected PPS benefit in at least a proportion of patients, including R-refractory patients	• Further support for company base case approach that: – Provides a consistent PPS assumption for decision making in FL – Maximises use of available evidence to validate assumptions

		– Biological rationale for a PPS benefit when introducing a new treatment class to the FL care pathway • EAG preferred an assumption of no PPS benefit but provided no new evidence to support this assumption	
Waning assumptions	• No treatment waning applied despite a stopping rule at 3 years adopted for epcoritamab treatment • Clinical experts noted that treatment waning would be expected but it is difficult to estimate • Consideration of treatment waning was not identified as a key issue and did not impact decision making	• Gradual treatment waning at 5 years for 5 years assumed in company base case aligned with previous appraisal assumptions (TA627[7]) and validated by clinicians[8] • EAG explored less conservative scenarios of instantaneous treatment waning at 5 years or gradual treatment waning at 2 years for 3 years • Company updated base case to the mid-point assumption of instantaneous treatment waning at 5 years	• Further support for conservatism of updated company base case approach that assumes treatment waning from 5 years • More aggressive treatment waning assumptions are unjustified when none are being applied in TA1139
COVID-19 adjustment	• Adjustment for COVID-19 deaths in PFS and OS considered appropriate	• No adjustment for COVID-19 deaths in PFS and OS in the PSM company base case as conservative approach • Simple adjustment for COVID-19 deaths in the STM company scenario, considering: – The higher proportion of death events related to COVID-19 in the tafasitamab + R^2 arm ([redacted] vs [redacted])	• Further support for company base case approach that: – Provides a consistent assumption for decision making in FL – Maximises use of available evidence to validate assumptions

		– The associated higher proportion of PFS events that are death in the tafasitamab + R^2 arm ([redacted] vs [redacted]) – The more comparable proportion of PFS events that are death post-adjustment ([redacted] vs [redacted]) • No adjustment for COVID-19 deaths in the EAG STM base case – Combined with an assumption of equal PPS across treatments, a LY loss is estimated for tafasitamab + R^2 vs R^2 in the progressed health state; this lacks face validity vs observed data	
Key: 3L+, third- or later-line; FL, follicular lymphoma; O-B, obinutuzumab with bendamustine; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; R^2, lenalidomide with rituximab; R-B, rituximab with bendamustine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP, rituximab with cyclophosphamide, vincristine and prednisolone; RCT, randomised controlled trial; STM, state transition model.			

3 Comparison to epcoritamab in 3L+

At the time of the company evidence submission for tafasitamab + R^2, epcoritamab was not recommended and therefore a comparison to epcoritamab was not presented in full within the main submission.

Analyses were provided in the company appendices (Appendix B and Appendix N), and we thank the NICE team for allowing us to submit this company evidence addendum to present a comparison to epcoritamab and consider the wider impact of the epcoritamab appraisal on the tafasitamab + R^2 appraisal.

The clinical community would welcome the introduction of two innovative treatment options into the FL care pathway, where no single patient journey exists. Tafasitamab + R^2 would provide a clinically effective (see Section 3.1) and cost-effective (see Section 3.2) alternative to epcoritamab in the 3L+ setting.

Tafasitamab + R^2 offers a differentiated adverse event (AE) profile to epcoritamab, characterised by the absence of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, which are associated with bispecific antibodies[9], alongside a shorter, time-limited treatment duration, which may be better suited to some patients.

3.1 Indirect treatment comparison

In the absence of head-to-head data for tafasitamab + R^2 versus epcoritamab, the wider evidence base was explored for data to inform a potential indirect treatment comparison (ITC). Trials of epcoritamab were identified via a systematic literature review (SLR), previously detailed in Appendix B of the company submission.

The EPCORE NHL-1 Phase II trial, which formed the basis of the evidence submission for TA1139 was the only trial identified for epcoritamab.[10] A comparative summary of the trial characteristics, key patient characteristics and definitions of outcomes for the inMIND and EPCORE NHL-1 trials can be found in Appendix B.1.4.1.3 of the company submission.

Generally, the trial population of EPCORE NHL-1 had poorer prognosis at baseline. When comparing baseline characteristics of the 3L+ populations of both trials:

- More patients in EPCORE NHL-1 had high risk FLIPI score (61% vs [redacted])
- More patients in EPCORE NHL-1 had an Eastern Cooperative Oncology Group (ECOG) performance score of 1 or 2 (45% vs [redacted])
- More patients in EPCORE NHL-1 had disease refractory to the last prior regimen (69% vs [redacted])

These characteristics were therefore adjusted for in a matching adjusted indirect treatment comparison (MAIC) along with age and Ann Arbor disease stage.[11] A high proportion of patients in EPCORE NHL-1 also had double refractory disease (70%) or progression of disease within 24 months (POD24) of first-line chemotherapy (42%). Equivalent data were not available for inMIND and therefore these characteristics could not be adjusted for in the MAIC. Patient characteristics before and after weighting are presented in Appendix B.1.4.3.2 of the company submission (Table 30).

The effective sample size (ESS) for tafasitamab + R^2 after weighting was [redacted] which is [redacted] of the original sample size in the 3L+ population in inMIND.[11] Across progression-free survival (PFS) and overall survival (OS) analyses, results trended in favour of tafasitamab + R^2, as summarised in Table 2. These results indicate improved PFS and OS with tafasitamab + R^2 versus epcoritamab, however, wide confidence intervals (CI) around the point estimates represent uncertainty in the size of benefit.

Table 2: Constant hazard ratios for OS and PFS – 3L+ FL population

Trial ID	Comparison	Tafa + R^2, N / ESS	Comparator, N	OS HR (95% CI)	PFS HR (95% CI)
inMIND vs EPCORE NHL-1	Tafa + R^2 vs epcoritamab	[redacted]	128	[redacted]	[redacted]
Key: CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; R^2, lenalidomide with rituximab.					

3.2 Economic analysis

Due to differences in the preferred assumptions / settings applied to economic analysis in TA1139 and ID6413, we have provided three economic analyses for the comparison of tafasitamab + R^2 versus epcoritamab in the 3L+ FL population.

Table 3 summarises the key assumptions applied in each analysis and Table 4, Table 5 and Table 6 presents the resulting outcomes. All comparisons use the list price for epcoritamab and [redacted].

Table 3. Key assumptions applied in the economic analysis scenarios

	TA1139 committee's preferred assumptions	**ID6413 EAG base case**	**ID6413 company base case (updated during clarification)**
Model structure	PSM	STM (median PPS: 64.7m)	PSM
PPS benefit	Yes	No	Yes
Waning assumptions	No waning	Waning starting at: 2 years Waning duration: 3 years	Waning starting at: 5 years Waning duration: 0 years
COVID-19 adjustment	Yes	No	Yes
PFS extrapolations	Singley fitted Weibull to HMRN data for comparator Inverse HR applied to above for intervention	Independently fitted gamma to RCT data for intervention and comparator	Independently fitted log-logistic to RCT data for intervention and comparator

Key: COVID-19, Coronavirus 2019; EAG, Evidence Assessment Group; HR, hazard ratio; m, months; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; PSM, partitioned survival model; STM, state-transition model; TA, Technology Appraisal.

When the TA1139 committee's preferred assumptions are applied to the tafasitamab + R^2 pairwise comparison versus epcoritamab, tafasitamab + R^2 dominates epcoritamab (Table 4), and the highest incremental life years (LY) and quality-adjusted life years (QALY) gains are observed. The key driver of this is the lack of treatment waning assumption applied in TA1139 (Table 3).

Conversely, under the ID6413 EAG base case assumptions, the pairwise comparison shows that tafasitamab + R^2 is associated with marginally lower LYs and QALYs compared with epcoritamab, but at a lower cost. This reflects a south-west quadrant outcome that implies epcoritamab would not be cost-effective versus tafasitamab + R^2 (Table 5). Key drivers to the lower LY and QALY estimates are the early treatment waning assumption that dilutes the estimated PFS benefit of tafasitamab + R^2 (Table 2), and the combined effect of the state transition model (STM) structure and lack of COVID-19 adjustment to the proportion of PFS events that are deaths that reverse the OS benefit of tafasitamab + R^2 (Table 2). Under the EAG base case assumptions, patients who have not progressed have a higher probability of death on tafasitamab + R^2 than on epcoritamab, with no treatment-difference in the probability of death for patients who have progressed. Considering the MAIC outcomes which estimate a [redacted] reduction in risk of death (HR: [redacted]; 95% CI:[redacted]) with tafasitamab + R^2 versus epcoritamab, the economic analysis using the ID6413 EAG base case settings lack face validity.

Outcomes using the TA1139 preferred assumptions versus ID6413 base case assumptions show a clear dissonance between appraisal approaches, with an overly conservative approach adopted by the ID6413 EAG that lacks face validity. We understand some of the dissonance and preference to conservatism is explained by the uncertainty, driven by limited long term outcomes data from in the inMIND trial. However, we believe our company base case settings, that when applied to the tafasitamab + R^2 pairwise comparison versus epcoritamab estimate LY and QALY gains that fall between those estimated with the prior two scenarios, strikes the right balance of conservatism to quantify this uncertainty.

Importantly, irrespective of the assumptions applied, tafasitamab + R^2 is shown to be cost-effective in the 3L+ setting and we remain open to an optimised 3L+ recommendation. However, we believe the evidence base and modelling outcomes may also support consideration of tafasitamab + R^2 in the fully licensed 2L+ population, subject to the Committee's judgement on uncertainty.

Table 4: Committee's preferred assumptions in TA1139 base case results of tafasitamab + R^2 vs epcoritamab – 3L+ FL

Treatment	Total costs (£)	Total LYs	PP LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Inc. QALYs	ICER
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Tafasitamab + R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Tafasitamab + R^2 dominates

Key: 3L+, third- or later-line; FL, follicular lymphoma; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALYs, quality-adjusted life years; PP, post-progression; R^2; rituximab with lenalidomide.

Table 5: ID6413 EAG base case results of tafasitamab + R^2 vs epcoritamab – 3L+ FL

Treatment	Total costs (£)	Total LYs	PP LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Inc. QALYs	ICER
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Tafasitamab + R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Tafasitamab + R^2 is less costly, and less effective

Key: 3L+, third- or later-line; FL, follicular lymphoma; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALYs, quality-adjusted life years; PP, post-progression; R^2; rituximab with lenalidomide.

Table 6: ID6413 Company base case (updated during clarification) results of tafasitamab + R^2 vs epcoritamab – 3L+ FL

Treatment	Total costs (£)	Total LYs	PP LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Inc. QALYs	ICER
Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]				-
Tafasitamab + R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Tafasitamab + R^2 dominates

Key: 3L+, third- or later-line; FL, follicular lymphoma; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALYs, quality-adjusted life years; PP, post-progression; R2; rituximab with lenalidomide.

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Addendum Appendix

Trial follow-up time

All appraisal assumptions should be considered in the context of the trial follow-up. Mature data will allow a partitioned survival model (PSM) to better reflect the PFS, OS and post-progression survival (PPS) observed within the trial follow-up. In addition, more mature data will capture the patterns in the observe hazards, which will factor into the waning assumptions.

In TA1139, the length of follow-up for the EPCORE NHL-1 dose expansion phase was redacted and was 5.7 months for the dose optimisation phase.[12] The median follow-up for the earlier April 2023 published data cut was 17.4 months and 5.7 months for the expansion phase and optimisation phase, respectively.[10] Based on observed OS at 18 month data being presented at the TA1139 committee meeting, and landmark OS estimates being presented for validation at 2, 4, 5 and 10 years, the total follow-up time is estimated to be approximately 2 years.

Model structure

In TA1139, the company provided a PSM in line with previous R/R FL appraisals.[12] They further explained that the three-state PSM structure was selected because it offers a data-driven, flexible approach that is well-established in economic modelling of oncological diseases, particularly in R/R FL. Additionally, they argued that PSMs have the advantage of directly incorporating observed survival data (such as PFS and OS), which reduces the uncertainty that can arise when estimating separate transition probabilities required in an STM.

The EAG for TA1139 explained that PSMs are widely used in oncology trials to model clinically important endpoints such as OS and PFS and it was suitable for use in the appraisal.[12] However, it also added that despite the company's justifications for using a PSM appearing reasonable, the EAG believed the company should have considered an STM.

In ID6413 (Tafasitamab + R^2 appraisal), the company adopted a three-health state PSM for the base case model based on the extent of its use in oncology, and on the

its recent use in NICE appraisals in FL[5, 13-15]. In addition, at the request of the EAG during the decision-problem meeting, an exploratory state transition model was developed as a scenario analysis to complement the base case PSM. The company explained that the structural relationship between PFS and OS events in FL is somewhat nuanced. Longer-term follow up of the AUGMENT and GADOLIN studies have shown the significant PFS benefit translating to a significant OS benefit. [1, 2] Five-year results from AUGMENT showed updated results for OS consistent with the improvement of PFS; while the median OS was not reached for either group, there was a significant improvement in OS for R^2 versus control (HR: 0.59; 95% CI: 0.37, 0.95; p=0.0285).[2] Final results of the GADOLIN study showed a sustained and clinically relevant OS benefit in patients treated with O-B versus control (HR, 0.71; 95% CI: 0.51, 0.98; p=0.0343).[1] During the validation interviews undertaken for this submission, clinical experts had mixed opinions on the relationship between PFS and OS, and acknowledged it may differ across different patient cohorts.[8] For patients with a slow progressing cancer, that continues to respond well to multiple lines of rituximab-based therapies and who are unlikely to die soon following relapse, the relationship between PFS and OS is thought to be more limited.

The EAG considered the appropriateness of the company's PSM to be largely dependent on the maturity of the observed data informing survival outcomes, particularly OS, and believed that the extrapolations based on the relatively immature inMIND data are subject to extensive uncertainty, making it exceptionally difficult to judge whether predicted survival gains are reasonable. The EAG acknowledge that the evidence in support of a surrogate relationship between PFS and OS in FL is mixed. Despite the limitations of the STM and the limited evidence in support of a surrogate relationship between PFS and OS, the EAG considered the STM approach to be more appropriate than the PSM in the present context, as it more transparently reflects the assumptions required to estimate long-term survival outcomes.

The differences between the two EAG preferred approaches in TA1139 and ID6413 are not adequately justified by differences in trial follow-up duration. In addition, the surrogacy between PFS and OS endpoints, and the plausibility and generalisability of any PPS benefit, were not assessed sufficiently by the ID6413 EAG; these

considerations are fundamental to the specification of an STM structure. Given the recent use of the PSM in NICE appraisals in FL[5, 13-15] —including the recent appraisal of epcoritamab in relapsed or refractory follicular lymphoma after 2 or more lines of systemic treatment (TA1139)[12]—the company considers the PSM to be the most appropriate approach, as it enables direct incorporation of observed survival data and supports a flexible framework for evaluating alternative survival assumptions.

Post-progression survival benefit

In TA1139, despite the EAG stating that the company should have considered an STM, the surrogacy between PFS and OS was not discussed, and neither was the within trial PPS.[12]

In the EAG report for TA1139, the EAG flagged that the mean post-progression survival for epcoritamab is "far in excess" of the equivalent time for current 4L+ care. Under the EAG's preferred approach to modelling, the epcoritamab PPS time is "less than the pre-progression survival time, and more similar to the comparator".[12] When assessing the impact of subsequent CAR-T cell therapy, the EAG stated that the company did not provide PPS-specific Kaplan-Meier curves or hazard estimates. Despite the company not providing the PPS-specific Kaplan-Meier curves or any evidence on the PPS benefit, the EAG did not list PPS as a key issue for the committee's discussion.

In ID6413 (tafasitamab + R^2), the company explained that for patients with a more aggressive disease course that does not respond well to rituximab-based therapies and who are likely to die close to relapse, the relationship between PFS and OS is thought to be strong.[16] In the inMIND trial population, [redacted] of the 2L+ cohort had rituximab-refractory disease and [redacted] of the 3L+ cohort had rituximab-refractory disease.[17] Based on pragmatic consideration of the median PFS and OS data from the final analysis of the GADOLIN trial, the median PPS with O-B would be 73.9 months, compared with 46.6 months for placebo + bendamustine.[1] This indicates the OS benefit with O-B in the GADOLIN population was due to improvements in both PFS and PPS. During the clarification stage, at the request of the EAG, the company

provided the PPS survival landmark estimates from inMIND, showing an early advantage in PPS.

The EAG considered that the PPS landmarks were difficult to interpret without an appropriate statistical analysis, and that the biological rationale for a PPS benefit based on the GADOLIN data is unclear because the PPS benefits observed in GADOLIN (which evaluated O-B in rituximab-refractory patients) do not imply that rituximab-refractory patients would respond similarly to tafasitamab + R². Given the considered uncertainty and the lack of clear biological rationale, the EAG preferred to adopt a “more conservative” assumption of no PPS benefit in the STM, as explicitly stated in the EAG report. Rather than conservative, this is considered a pessimistic assumption given the evidence available.

The company considers that the PPS benefit was addressed differently by the two EAGs. In the tafasitamab + R^2 appraisal, the company included an STM in response to an EAG request made at the decision-problem meeting. As a result, the ID6413 EAG focused on the PPS assumptions and the estimated mean life years accrued in the progressed disease state. In contrast, this assumption and its implications were not discussed during the epcoritamab appraisal as the company did not provide the STM scenario.[12]

Treatment waning effect

Treatment waning was not applied in the epcoritamab company’s base case analysis or explored in scenario analysis.[12] The EAG’s clinical experts’ opinion was that treatment waning would occur and applying treatment waning in the economic model was reasonable assumption. However, EAG was unable to incorporate any treatment waning scenarios at the time of report submission as it awaited further input on clinically plausible treatment waning assumptions to explore. In both committee meetings, waning was not included as a key issue for discussion.

The company acknowledges that the impact of the treatment waning assumptions is conditioned on the maturity of the data and the follow-up time. If the data is mature enough, the extrapolations could potentially account for the increasing hazards (treatment waning effect) and an explicit waning assumption would not be required.

The Kaplan-Meier curves and the survival extrapolations for epcoritamab are redacted. Therefore, it is not possible to assess if the hazards are converging, which would indicate suitability of an explicit waning assumption.

In TA1139, the committee preferred to use the HMRN data as the reference curve and applied the inverse HR.[12] The EAG report for epcoritamab provides the OS extrapolations of the HMRN data for the 4L+ population (Figure 1). As seen in Figure 1, the expected survival in the 4L+ population is approximately 20% at 2.7 years (1,000 days), and 16% at 5.4 years (2,000 days) in most curves, which is aligned with Wasterlid (2024)[4] as presented in the ACM2 committee slides (Figure 2 and Figure 3). If we assume similar landmarks to Wasterlid (2024) in the HMRN 3L+ population based on the similarities between HMRN 4L+ and Wasterlid (2024), the expected OS would be 52% at 2 years, and 37% at 5 years. Given that the epcoritamab survival is derived by applying the inverse hazard ratio to the HMRN arm, the OS will be higher than the HMRN estimates at the previous time points. Despite having a relatively high survival at 2 and 5 years, and a treatment stopping rule for epcoritamab at 3 years, the lack of a treatment waning assumption was not presented by the EAG as a key issue. Thus, the committee's base case included a constant hazard ratio (inverse hazard ratio) to the derive the long-term survival.

Figure 1: TA1139 EAG analysis. OS extrapolations fitted to HMRN data

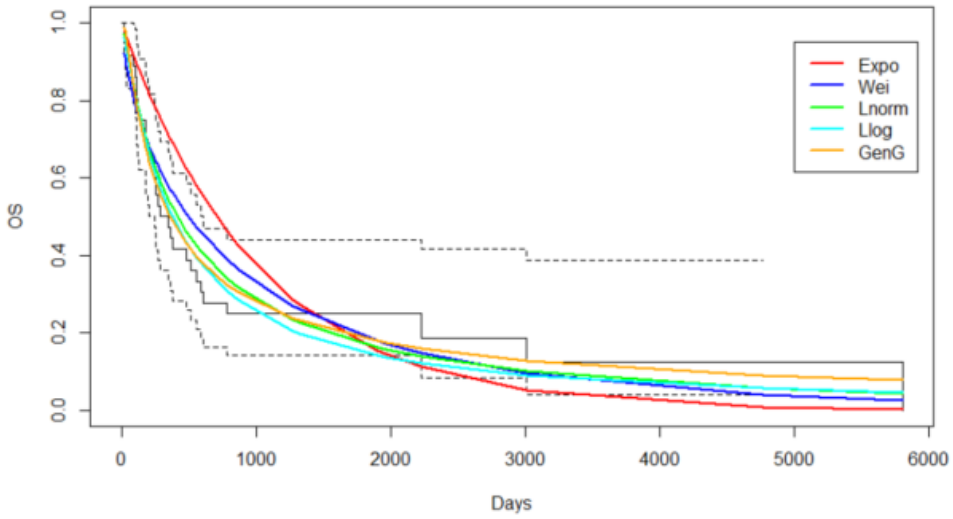

Figure 6: Overall survival extrapolations fitted to HMRN data

Figure 2: ACM2 Committee Public Slides. Wasterlid (2024) OS landmarks

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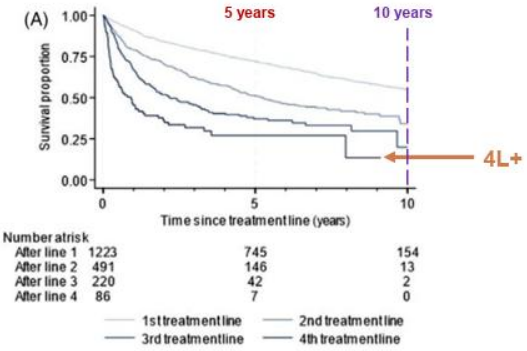
4L+ HMRN data and Wasterlid (2024) OS

HMRN OS from start of 4L+, months

[redacted]

From company submission

Wasterlid (2024) OS, years



NICE Abbreviations: 4L, fourth line; HMRN, Haematological Malignancy Research Network; OS, overall survival. 34

Figure 3: ACM2 Committee Public Slides. OS landmarks by source

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Approximate OS landmarks by source

Source	HMRN	Wasterlid 2024	LEO CReWE Casulo 2022	ReCORD-FL Salles 2022	Chihara 2025
Location	Yorkshire & Humber	Sweden	US	7 countries including Europe	US
Dates	[redacted]	2007-2014	2002 - 2018	1998 - 2019	2000 - 2017
EAG critique	UK registry, small study, limited reporting of baseline characteristics	Large study, generalisable to NHS but no baseline characteristics	US based, heterogeneous treatments (inc. experimental); 94% at 3L	No PFS data (but EFS as proxy); 80% at 3L; excluded ECOG >1	-
3L+ OS: 2 years	[redacted]	52%	90% approx.	85% approx.	59%
3L+ OS: 5 years	[redacted]	37%	75%	68% approx.	33%
3L+ OS: 10 years	[redacted]	NR	63% approx.	52% approx.	15% approx.
4L+ OS: 2 years	[redacted]	36%	N/A	75% approx.	52%
4L+ OS: 5 years	[redacted]	27%	N/A	55% approx.	26%
4L+ OS: 10 years	[redacted]	NR	N/A	40% approx.	12% approx.

NICE Abbreviations: OS, overall survival; HMRN, Haematological Malignancy Research Network; LEO, Lymphoma Epidemiology Outcomes; CReWE, Consortium for Real World Evidence; EAG, external assessment group; PFS, progression-free survival; EFS, event-free survival; ECOG, Eastern Cooperative Oncology Group; 3L/4L, third-/fourth-line; NR, not reported. 35

In ID6413 (tafasitamab + R^2), the company applied a gradual waning starting at 5 years with a duration of 5 years following the assumptions in NICE TA627, in which the Committee considered it was plausible that treatment waning would start

between 5 and 10 years and selected a 5-year starting point as the base case.[7] Additionally, during the clinical validation for ID6413, clinicians agreed that the hazards could start to converge after 5 years.[8]

The EAG believed there was considerable uncertainty around both the duration over which a full treatment effect should be assumed and the period over which any subsequent attenuation should occur. The EAG noted that the assumptions previously accepted in TA627 appear largely arbitrary and are not clearly linked to either the mechanism of action of R² or the underlying disease biology. It explored two scenarios: instantaneous waning applied at 5 years, and gradual waning applied at two years with a three-years duration. The EAG selected as the base case the most conservative of the two explored scenarios, with the waning effect starting at two years with a duration of three years.

As with the PPS benefit and the incremental LYs accrued in the progressed disease health state, treatment waning was not discussed during the epcoritamab appraisal.[8] In NICE TA627, the Committee considered it plausible that treatment waning would begin between 5 and 10 years and selected a 5-year start point for the base case. Although a waning effect starting at 5 years was explored in the EAG scenario analyses, the ID6413 EAG considered that this assumption was insufficiently justified. Instead, they adopted waning starting at 2 years with a 3-year duration as the base case assumption, resulting in more conservative estimates of incremental QALYs for tafasitamab + R^2.

Adjustments for COVID-19 deaths

The EPCORE NHL-1 trial started in June 2020 and was impacted by the COVID-19 pandemic. In TA1139, the committee concluded that IPCW adjustment of EPCORE NHL-1 was appropriate to account for the COVID-19 deaths in the 3L+ population.[12] They also concluded that full censoring of COVID-19 deaths in the HMRN dataset was appropriate.

In ID6413 (tafasitamab + R^2), the company did not adjust the OS extrapolations despite the higher proportion of COVID-related death events in the tafasitamab + R^2 arm [[redacted] out of [redacted] death events ([redacted]) in the tafasitamab + R^2 arm compared to [redacted] out

of [redacted] death events ([redacted]) in the R2 arm)]. In the STM, the company used the pooled proportion of PFS events that were deaths ([redacted]). At the clarification stage, as the EAG request for treatment specific proportion of PFS events that were deaths, in addition to the treatment-specific proportions, the company provided the adjusted proportions by excluding the COVID-related deaths ([redacted]% in the tafasitamab + R^2 arm compared to [redacted] in the R^2 arm). However, the EAG considered for the base case the unadjusted proportions ([redacted] in the tafasitamab + R^2 arm compared to [redacted] in the R^2 arm.

The TA1139 EAG considered it appropriate to adjust OS and PFS extrapolations to account for COVID-related death events, whereas the ID6413 EAG considered it inappropriate to adjust the proportion of PFS events that were deaths. Under the assumption of a common PPS across treatments, and given a higher proportion of PFS events classified as deaths in the tafasitamab + R^2 arm, the model estimated negative incremental LYs accrued in the progressed disease health state for tafasitamab + R^2.

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's a plain English summary of their submission written for patients participating in the evaluation. It's 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's 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.

Notes for authors: Please complete the template using plain language, taking time to explain all scientific terminology. As you draft your response, please do not delete the intro text included in each section. It might be a useful reference for patient reviewers.

However, any text preceded by the words '**Notes for authors**' simply contains additional prompts for the company to advise them on the type of information that may be most relevant, and the level of detail they need to include. **You may delete this text where indicated.**

Section 1: submission summary

1a) Name of the medicine

Both generic and brand name.

Generic name: Tafasitamab Brand name: Minjuvi®   Tafasitamab is given in combination with two other cancer medicines: lenalidomide and rituximab (see Section 3)

1b) Population this treatment will be used by

Please outline the main patient population that is being appraised by NICE:

Adults with follicular lymphoma (FL) that has come back (relapsed) or did not respond to treatment (refractory), following at least one prior therapy.

1c) Authorisation

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Marketing authorisation is pending – please see Section 1.2 of the company submission for anticipated dates of approval.

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:

Nominal general grants have been provided to: Lymphoma Action, Blood Cancer UK, Blood Cancer Alliance, Cancer52, The Leukaemia Care, and Maggie's Centres

Section 2: current landscape

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.

FL is the second most common type of non-Hodgkin's lymphoma (NHL) – a group of blood cancers that affects white blood cells called lymphocytes.[1] FL develops when lymphocytes change, grow uncontrollably, and cluster together to form lumps in the lymph nodes and surrounding organs.[1] These 'lumps' stop the lymphatic system, which is a crucial part of the body's immune system, from working properly.[1]

About 2,400 people are diagnosed with FL every year in the UK.[2] The exact cause of FL is unknown, but it mainly affects older adults (with half the patients over the age of 67 years) of any gender.[3] FL is typically considered a slow-growing cancer that is treatable but incurable. The life expectancy of people who are newly diagnosed with FL is relatively good, with most people (85%) expected to be alive for at least five years post-diagnosis.[1] However, FL does become life-limiting over time.[4, 5]

Following initial treatment, people with FL can remain cancer-free for many years, but the cancer nearly always comes back; this is called a relapse.[1, 4, 5] Relapse is common, and as a result, people normally receive many subsequent lines of treatment to manage FL over their lifetime.[4, 5] With each relapse and next line of therapy, life expectancy reduces as a result of the FL becoming less responsive to treatment options which work in a similar way to those they have already received.[4, 5] Some people with FL have cancer that is resistant to treatment; this is known as being refractory.

FL can cause a range of physical symptoms that may seriously affect peoples' quality of life. One of the most common symptoms of FL is fatigue (feeling very tired), which can be overwhelming and make everyday tasks like washing, climbing stairs or cooking difficult.[1, 6] Other physical symptoms can include swelling around the neck, armpit and groin, night sweats, unexplained fevers and weight loss.[1] FL can also affect the bone marrow, leading to an increased risk of anaemia, bruising and bleeding.[1] If the disease spreads to other organs, it can cause additional problems such as breathlessness or digestive issues, depending on the organ affected.[6]

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?

The main test to diagnose FL is a lymph node biopsy.[1] This involves taking a sample of one or more of the swollen lymph nodes and looking at it under the microscope for abnormal cells. Microscopic imaging can also inform how fast-growing the FL is – this is reflected in an FL 'grading'. Grades 1, 2 and 3A are low grade, which means slow-growing; Grade 3B is high grade, which means fast-growing.[1]

Additional tests are conducted to assess the stage of FL – this information helps healthcare professionals understand what parts of the body have been affected by the lymphoma.[1] There are four stages of FL – Stages I and II are considered early or limited stage, with FL localised to one side of the diaphragm, while Stages III and IV are referred to as advanced stage, with FL spreading to both sides of the diaphragm (Stage III) and to the bone marrow and other organs (Stage IV).[1] Most people diagnosed with FL in England – around 70% – have advanced stage disease.[3]

Although FL often starts as a low grade, slow-growing lymphoma, it can become more aggressive over time, especially after it has returned more than once. In some cases, it can change into a faster-growing type of lymphoma such as diffuse large B-cell lymphoma (DLBCL), which requires more urgent medical attention and has a lower survival rate.[1, 7] Healthcare professionals call this 'transformation'.

Further to diagnosis, staging and grading, people with FL are also assessed for risk factors that can help predict the likely course of disease and inform treatment decisions. The Follicular Lymphoma International Prognostic Index (FLIPI) is the most common scoring system used. It considers specific characteristics of people with FL and the disease to give a low, mediate or high risk categorisation.[1, 8, 9] Other clinical characteristics associated with a poorer outlook include high number of previous therapies, early relapse, and disease that is refractory to treatment.[10]

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.

FL is a slow-growing blood cancer that often returns after treatment. There is no fixed treatment pathway for relapsed or refractory FL (R/R FL), and care is tailored to each person based on factors like disease stage, symptoms, overall health, and how well previous treatments worked.[11-13] Since FL is incurable, the goal is to provide the longest disease-free period between treatments and preserve quality of life.[14]

The following general treatment approach is adopted in the UK[13]:

- First-line (1L):
  - Rituximab monotherapy or monitoring only, known as 'watch and wait', for patients with asymptomatic FL
  - Anti-CD20 treatments (rituximab or obinutuzumab) with chemotherapy ± anti-CD20 for up to 2 years after the main treatment has finished for patients with symptomatic FL
- Second-line (2L):
  - Lenalidomide with rituximab (R^2) for patients whose FL did not respond well to 1L treatment – R^2 is considered standard of care
  - Rituximab with chemotherapy (R-chemotherapy) ± rituximab for up to 2 years after the main treatment has finished for patients whose FL responded well to 1L treatment
- Third-line and beyond (3L+):
  - Lenalidomide with rituximab (R^2) for patients who did not receive R^2 as 2L treatment – R^2 is considered standard of care
  - R-chemotherapy ± rituximab for up to 2 years after the main treatment has finished for patients who received R^2 as 2L treatment (in the absence of any other treatment option)
  - Clinical trial or palliative radiotherapy (used to relieve symptoms) for patients who have exhausted R^2 and R-chemotherapy options

Obinutuzumab with bendamustine followed by obinutuzumab after the main treatment has finished is also a treatment option for people with FL that did not respond to or progressed within 6 months after treatment with rituximab or a

rituximab-containing regimen. However, a low percentage of patients are treated with this regimen in clinical practice.[13]

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.

Although FL is considered a slow-growing cancer, many people living with it experience a substantial emotional and physical burden. Patients often report worse quality of life and more severe symptoms than those with other types of NHL.[15] The label 'low grade' can feel misleading, as it doesn't reflect the reality of living with an incurable cancer.[11] One of the principal emotional burdens of FL is uncertainty. Many people with FL experience ongoing anxiety, and it's common to feel depressed or to lose hope; these emotional challenges can make it hard to enjoy everyday life, even when physical symptoms are managed.[6] This is worse for people with R/R FL with each time the cancer returns (relapse) and failed treatment making the cancer increasingly difficult to live with.[15, 16]

Patient experts have described the experience as *"slow torture"*, knowing that treatments will eventually stop working.[11] This emotional toll also affects carers, who often feel helpless and anxious while providing daily support.[11] Research from a UK-based study involving 222 patients across eight treatment centres confirmed that quality of life worsens with disease relapse[16], highlighting the importance of therapies that can extend the time between relapses and help people live more comfortably for longer. A selection of patient testimonies highlighting the substantial burden of people living with FL are provided below:

"Tiredness, as most people reading this will know, can be just as debilitating as pain"[17]

[paraphrased] *"My cancer has relapsed 3 times since diagnosis in 2015. I have received several treatments but am anxious I will eventually run out of*

treatments…there is a profound psychological impact of experiencing repeated relapses"[11]

"At the moment I struggle with feeling anxious a lot of the time. My fear is that the lymphoma will come back. I know there is nothing I can do about this, but it is challenging."[18]

"Unfortunately, despite how intense the treatment was, it didn't completely clear the cancer at my halfway scan. There was still a small amount left, which meant I had to continue with more chemotherapy. In the end, I went through a total of six rounds of chemo. It was exhausting and incredibly challenging..."[18]

Section 3: the treatment

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.

Tafasitamab is a type of targeted cancer treatment known as a monoclonal antibody.[19]
Tafasitamab works by attaching to the CD19 protein on the surface of cancer cells. When attached to CD19, this activates the immune system to attack and kill the cancer cells, which can slow down and shrink the lymphoma.[19]

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.

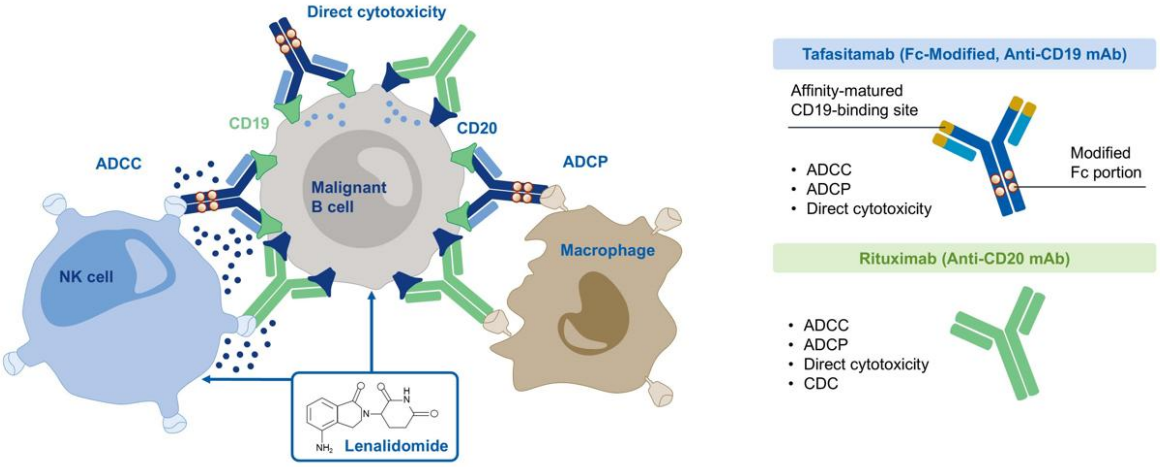
If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

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.

Tafasitamab is designed to be used in combination with two other cancer medicines: lenalidomide and rituximab – these medicines are already used in combination with one another in a treatment regime called R^2 which is considered current standard of care for R/R FL.[13]

The tafasitamab plus R^2 combination is the first regimen to target two different proteins found on the cancer cells involved in FL (CD19 and CD20), making it a powerful approach to treating R/R FL. A visual summary of tafasitamab plus R^2 working together is provided in Figure 1.

Figure 1: Tafasitamab plus R^2 targeting of CD19 and CD20 plus lenalidomide immunomodulation



Key: ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CDC, complement-dependent cytotoxicity; mAB, monoclonal antibody; NK, natural killer.

Source: Trneny et al. 2025.[20]

Research has shown that the addition of tafasitamab to R^2 improves clinical benefit without increasing the risk of side effects, as described in Section 3e–3g.

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?

A doctor experienced in treating cancer will supervise the treatment.

Tafasitamab is given as a slow injection into a vein, known as an intravenous (IV) infusion, which is a drip into the vein given at a dose tailored to each person's weight (12 mg per kilogram of body weight).[19] It is administered in 28 day cycles according to the following schedule:

Cycle 1–3: infusion on Days 1, 8, 15, and 22

Cycle 4–12: infusion on Days 1 and 15

The first infusion of tafasitamab will take up to 2.5 hours; each subsequent infusion of tafasitamab will take up to 2 hours.

Rituximab is also given by IV infusion at a dose tailored to each person's weight (375 mg per square meter of body surface area). It is administered in 28 day cycles according to the following schedule:

Cycle 1: infusion on Days 1, 8, 15, and 22

Cycle 2–5: infusion on Day 1

On days where both tafasitamab and rituximab are being given, only one appointment will be scheduled, at which both treatments will be infused one after the other.

Lenalidomide is prescribed as a capsule to be taken orally on Days 1 to 21 of each 28 day cycle. The recommended starting dose is 20 mg per day, but this may be adjusted depending on individual needs.

After a maximum of five cycles of tafasitamab plus R^2 therapy, treatment with rituximab is stopped. Treatment cycles of tafasitamab and lenalidomide are then continued for up to twelve cycles. This is equivalent to a maximum treatment period of approximately 1 year.

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.

The main clinical trial providing evidence for the use of tafasitamab + R^2 compared to R^2 is the inMIND trial (NCT04680052).

inMIND was designed to find out how well tafasitamab works compared with placebo (a replica solution with no active medicine) when added to the R^2 regimen, and how safe it is.[19]

The trial is ongoing, with a final analysis planned after all participants have been monitored for at least 5 years following treatment.[20] Primary analysis of data from inMIND was carried out in February 2024 when participants had been monitored for around 15 months on average; these data are presented below.

inMIND took place across multiple treatment centres, including sites in the UK and Ireland. Both patients and researchers were 'blinded' to treatment, meaning they did not know which patients had been assigned to receive tafasitamab or placebo in addition to R^2.[19] In total, 548 people with R/R FL were randomised in a 1:1 ratio to receive tafasitamab + R^2 or placebo + R^2.[20]

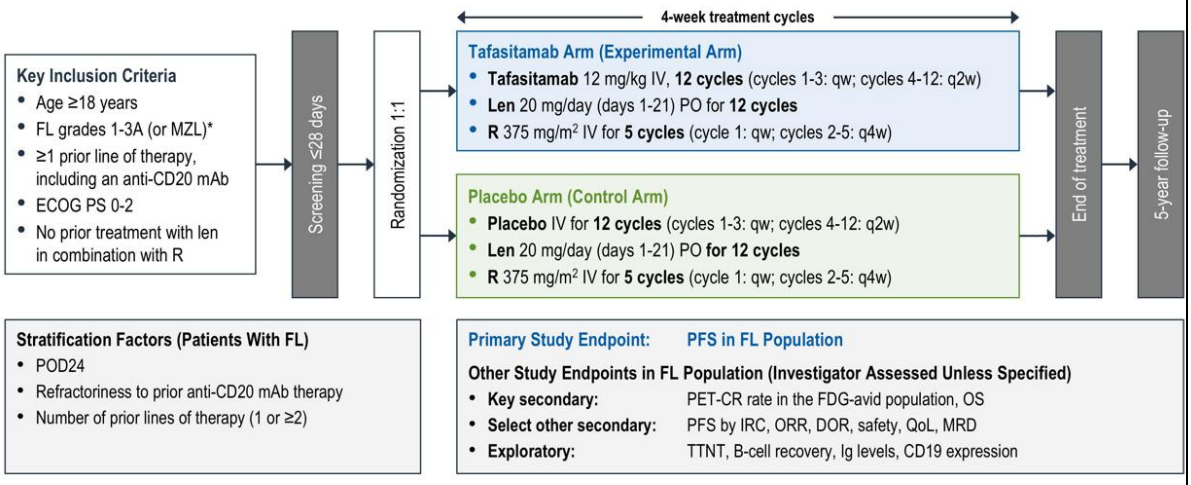
To be included, patients had to[20]:

- Be over 18 years old
- Have confirmed Grade 1–3A FL
- Been previously treated with rituximab (or other anti-CD20) based therapy
- Have documented relapsed, refractory or progressive disease

Patients who had previously been treated with R^2 or had received any treatment for R/R FL within 28 days of trial treatment were excluded.

An overview of the inMIND study design is depicted in Figure 2.

Figure 2: Study design of inMIND



Key: DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; FDG, fluorodeoxyglucose; FL, follicular lymphoma; IRC, independent review committee; mAb, monoclonal antibody; MRD, minimal residual disease; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PET-CR, positron

emission tomography – complete response; PFS, progression-free survival; po, orally; POD24, progression of disease within 24 months of diagnosis; q2w, every 2 weeks; QoL, quality of life; qw, once weekly; R/R, relapsed or refractory; TTNT, time to next treatment.
Source: Trneny et al. 2025.[20]

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.

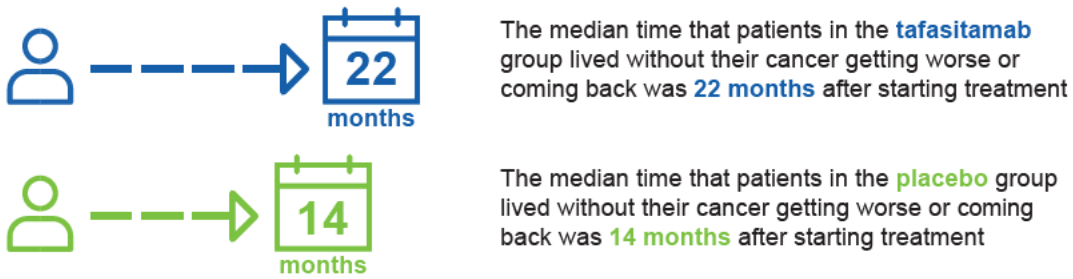
- Are any of the outcomes more important to patients than others and why?
- Are there any limitations to the data which may affect how to interpret the results?

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.

Primary endpoint: Progression-free survival
The primary aim of inMIND was to find out how long people with FL could live without their cancer getting worse or coming back – this is called progression-free survival (PFS).[19]

The trial showed that the addition of tafasitamab to R^2 significantly improved PFS in people whose FL had returned or stopped responding to treatment.[20] People receiving tafasitamab + R^2 lived without disease progression for a median of 22.4 months, compared with 13.9 months for those receiving placebo + R^2 – an improvement of over 8 months.

Figure 3: Median time of PFS in inMIND



Key: PFS, progression-free survival.
Source: Sehn et al. 2024.[19]

The addition of tafasitimab to R^2 reduced the risk of the cancer worsening, coming back, or the patient dying by 57%. Importantly, benefits of tafasitamab + R^2 were seen as early as 4 months into treatment, and lasted for at least 2 years, without needing ongoing maintenance therapy.[20]

Different subgroups of patients were also looked at, based on disease characteristics such as number of previous therapies at the beginning of the study. The addition of tafasitamab to R^2 reduced the risk of the cancer worsening and relapse in groups including:[20]:

- People who had received two or more previous therapies
- People who had early relapse, measured as progression of disease within 24 months (POD24) of initial diagnosis
- People who had disease that was refractory to rituximab (or other anti-CD20 treatment)

Key secondary endpoint: Complete metabolic response

One of the key secondary aims of inMIND was to measure how many people with FL could achieve a complete metabolic response (CMR) to treatment, which means no signs of active disease on a positron emission tomography (PET) scan.[20]

The trial showed that the addition of tafasitamab to R^2 significantly improved the CMR rate in people whose FL had returned or stopped responding to treatment. [20] People receiving tafasitamab + R^2 were 1.5 times more likely to achieve a CMR compared to those receiving placebo + R^2. Overall, 49% of people treated with tafasitamab + R^2 group achieved CMR, compared with 40% of people treated with placebo + R^2.

Secondary endpoint: Overall response and duration of response

The inMIND trial showed that the addition of tafasitamab to R^2 also significantly improved the overall response rate (ORR) in people whose FL had returned or stopped responding to treatment.[20] The absolute increase in patients achieving a response with treatment was ~11%, with an ORR of 84% in the tafasitamab + R^2 group, compared with 72% in the placebo + R^2 group. Additionally, people receiving tafasitamab + R^2 were twice as likely to achieve a response to treatment compared with those receiving placebo + R^2.

Importantly, the response to treatment was durable, with people receiving tafasitamab + R^2 living without relapse for a median of 21.2 months, compared with 13.6 months for those receiving placebo + R^2 – an improvement of over 7.5

months.[20] The addition of tafasitamab to R^2 reduced the risk of relapsing or dying by 53%.

Key secondary outcome: Overall survival

Researchers are still observing patients in the inMIND trial to measure how long they live – this is called overall survival (OS).[19] Early results show that people treated with tafasitamab + R^2 may live longer, with an estimated 41% reduced risk of dying compared with people treated with R^2 alone.[20]

Exploratory endpoint: Time to next treatment

Time to next treatment (TTNT) is a clinically meaningful endpoint in R/R FL where the primary goal of treatment is to provide the longest disease-free period between treatment lines. TTNT measures both disease progression and treatment decisions, reflecting real-world patient management.

inMIND showed that the addition of tafasitamab to R^2 significantly improved TTNT in people whose FL had returned or stopped responding to treatment.[20] The proportion of people who needed another line of treatment after tafasitamab + R^2 was 17%, compared with 32% of people needing another line of treatment after placebo + R^2. Furthermore, the addition of tafasitamab to R^2 reduced the risk of needing another line of treatment or dying by 55%.

Exploratory endpoint: Transformation of FL

No one in the tafasitamab + R^2 arm of inMIND has experienced transformation to a faster-growing type of lymphoma to date, compared with nine people in the placebo + R^2 arm.[21] Although these numbers are small, they are clinically relevant, considering the dismal outlook for people whose lymphoma transforms to DLBCL or other more aggressive lymphoma type (compared to FL).[1, 7]

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.

Health-related quality of life (HRQL) was measured in the inMIND trial using three validated questionnaires[22]:

- EuroQol-5 Dimension (EQ-5D): a common general health assessment tool that measures five key dimensions of daily living/activities
- European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30): a common tool for people with cancer that measures functioning, symptoms and general health
- Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym): a common tool for people with lymphoma that measures general well-being as well as lymphoma-specific symptoms

The addition of tafasitamab to R^2 had no negative impact on patient HRQL.[22] This is a positive outcome for patients with R/R FL, for whom the goal of treatment is to preserve quality of life while providing the longest disease-free period between treatment lines.[14]

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.

Like all medicines, tafasitamab can cause side effects, although most are considered mild in nature and medically manageable. Possible side effects of tafasitamab include:

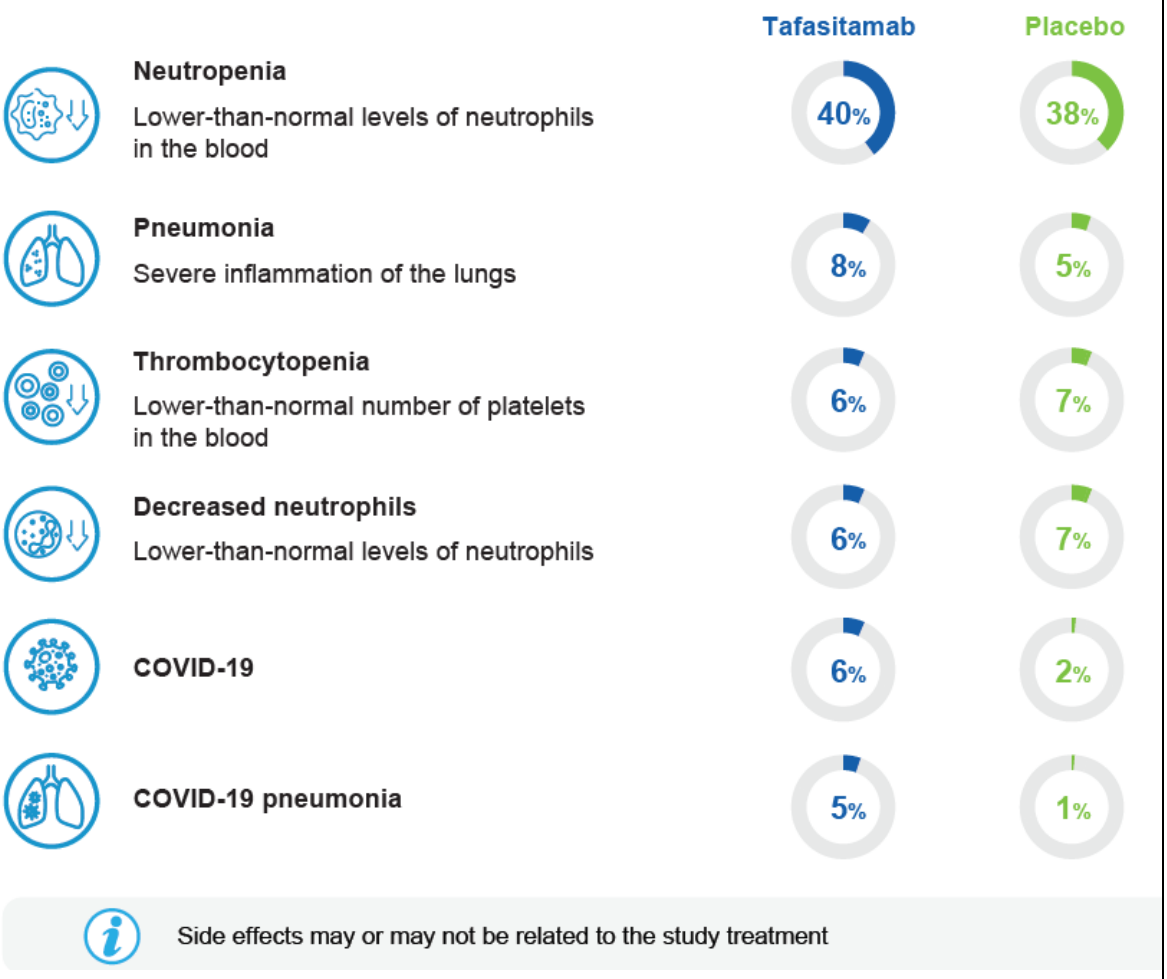
- Reduction in number of blood cells, which increases risk of infection, bleeding, tiredness and/or shortness of breath
- Low blood potassium which can lead to muscle cramps or swelling

- Bacterial, viral or fungal infections
- Fever or rash
- Pain (particularly in the back or stomach), weakness or tiredness
- Diarrhoea, constipation, nausea or vomiting
- Cough or shortness of breath
- Decreased appetite

In the inMIND trial, the safety of tafasitamab + R^2 was measured by recording the number and type of treatment-emergent adverse events (TEAEs), defined as any undesirable experience that occurs after a patient is given a treatment.[19] Almost all patients in both groups (99%) experienced at least one TEAE; of these, approximately 70% were considered to be medically significant (Grade 3 or 4).

The most common medically significant (Grade 3 or 4) TEAEs were similar in both groups, as summarised in Figure 4.

Figure 4: Medically significant (Grade 3 or 4) TEAES in inMIND



Key: TEAE, treatment-emergent adverse event.

Source: Sehn et al. 2024.[19]

A total of 30 people (11%) had to discontinue tafasitamab treatment due to side effects, compared with 18 people (7%) who had to discontinue placebo treatment.[19] A total of six people (2%) in each treatment group died due to side effects. Importantly, none of the deaths in the tafasitamab + R^2 arm were thought to be directly related to tafasitamab treatment.[20]

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

- Tafasitamab + R^2 is the first and only regimen to offer dual targeting of CD19 and CD20, potentially enhancing anti-tumour activity beyond CD20-only regimens.
- High quality scientific research has proven that the addition of tafasitamab to the current standard of care for R/R FL, which is R^2, results in[20]:
  - A 57% reduction in risk of cancer worsening, relapse, or death and extension to the period of disease-free living of over 8 months
  - An absolute increase in CMR rates of ~10%, with patients being 1.5 times more likely to achieve a CMR
  - An absolute increase in ORR of ~11%, with patients being twice as likely to achieve a response, and an absolute increase in complete response of ~11%
  - A 53% reduction in risk of relapsing or death and extension to the period of relapse-free living of over 7.5 months
  - A 55% reduction in the risk of needing another line of treatment or death and an absolute reduction in the number of patients needing another line of treatment of ~15%
- Early signals suggest the addition of tafasitamab to R^2 also reduces the risk of lymphoma transformation and improves life expectancy[20, 21]
- Tafasitamab + R^2 had a positive clinical benefit in all groups of patients, including those with clinical characteristics associated with a poorer outlook[20]

- The addition of tafasitamab to R^2 extended the period of disease-free living between treatment lines with no negative impact on patient HRQL[22], thus meeting the goal of treatment for R/R FL[14]
- The addition of tafasitamab to R^2 presented no new safety concerns, with common side effects typical of most lymphoma treatments and medically manageable[19]
- Tafasitamab + R^2 has a fixed duration of treatment up to 1 year with no extended treatment period after the main treatment has finished – this limits the administration burden of treatment

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

- Tafasitamab is an 'add on' treatment to current standard of care (R^2) and thus increases administration burden during the treatment term – this is limited and counterbalanced by the extended period of disease-free living between treatment lines after the tafasitamab + R^2 treatment term
- Like all medicines, tafasitamab can cause side effects but, as noted above, common side effects are typical of most lymphoma treatments and medically manageable[19] – importantly, the side effects did not negatively impact patient HRQL in the inMIND study[22]

3j) 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.

A cost-effectiveness model has been developed to help determine whether the addition of tafasitamab to R^2 provides value for money to the National Health Service (NHS). The model design is a simplified representation of the patient experience and a common design used in cancer modelling, including previous cost-effectiveness models in the FL space.

In simplified terms, costs and quality of life estimates are assigned based on three potential health states – progression-free, progressed disease and death. People with R/R FL enter the model in the progression-free health state and are assumed to receive tafasitamab + R^2 or R^2 treatment. The cost-effectiveness model then predicts the likelihood of patients to remain progression-free or move to the progressed disease or death health state in 7 day cycles. Within the progressed disease health state, additional lines of treatment are received and the overall cost of disease management increases, reflecting real-world practice.

Although tafasitamab + R^2 has an additional upfront cost, its increased effectiveness (which for the cost-effectiveness model is measured in terms of quality-adjusted life years [QALYs]) balances this cost. More specifically, the addition of tafasitamab to R^2 extends the time people spend in the progression-free health state, resulting in an overall increase in QALYs over a patient's lifetime and an offset of upfront costs.

The cost-effectiveness model does rely on some key assumptions when data are not available, including conservative longer term overall life expectancy assumptions, as the OS data from inMIND are not yet fully mature.

3k) 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)

People with R/R FL currently have a substantial unmet medical need, as current treatments rely on anti-CD20 therapies, which become less effective over time.[4, 5] Tafasitamab + R^2 is the first and only regimen to offer dual targeting of CD19 and CD20 and therefore is innovative, with the potential to represent a 'step change' in treatment and become the new standard of care for people with R/R FL.

While the QALY benefits capture the main clinical effects of the addition of tafasitamab to R^2, they do not adequately capture the value of hope that a novel treatment option can offer to patients and their loved ones, for whom the fear of relapse and running out of treatment options has a marked negative impact on quality of life.[11, 17]

3l) 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

No equality issues are foreseen.

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. 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.

Tafasitamab Patient Information Leaflet: https://www.medicines.org.uk/emc/files/pil.13003.pdf

inMIND Plan Language Summary:

inMIND Trial Publication – Efficacy and Safety: TAFASITAMAB (TAFA) PLUS LENALIDOMIDE (LEN) AND RITUXIMAB (R) FOR... - Trneny M - EHA-5680 - Jun 14 2025

inMND Trial Publication – Quality of Life: IBCL-625: Quality of Life (QoL) Outcomes With Tafasitamab Plus Lenalidomide and Rituximab for Relapsed or Refractory Follicular Lymphoma (R/R FL): Results From a Phase 3, Double-Blind, Randomized, Placebo-Controlled, International, Multicenter Study (inMIND) - ScienceDirect

inMIND Clinical Trials Record: https://clinicaltrials.gov/search?term=NCT04680052

Further information on NICE and the role of patients:

- Public Involvement at NICE
- NICE's guides and templates for patient involvement in HTAs
- EUPATI guidance on patient involvement in NICE
- EFPIA – Working together with patient groups
- National Health Council Value Initiative

- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe

4b) Glossary of terms

Anaemia: a condition where people have low red blood cells or haemoglobin (a protein found in red blood cells) in the blood that results in tiredness and pale skin

CD19 and CD20: proteins found on cancer cells involved in FL

Clinically meaningful: when a treatment makes a real, noticeable difference to a person's health or quality of life. This could be feeling better, being able to do everyday activities more easily, or having fewer symptoms or side effects

Complete response: when doctors can no longer detect cancer in the body after treatment. This is a very positive result, but it doesn't always mean all cancer cells have been killed—there may still be some cancer present that could grow and spread again over time

Cost-effectiveness: evaluation of the relative costs and benefits of treatment options that help make informed decisions on the best value for money health care options for the NHS

Diffuse large B-cell lymphoma: is a fast-growing, aggressive type of blood cancer that affects immune cells called B cells and usually needs urgent medical attention

Follicular lymphoma: the second most common form of NHL that affects a specific type of white blood cell called B-lymphocytes which are crucial to the adaptive immune system

Health-related quality of life: formal measure of an individual's or group's perception of physical and mental health at specific points in time

Incremental cost-effectiveness ratio: key metric used to evaluate the cost-effectiveness of a new healthcare technology compared to an alternative technology. Calculated by dividing the difference in total costs by the difference in total health benefits

Intravenous (IV) infusion: a way of administering a drug or other substance into the bloodstream through a needle or tube inserted into a vein

Lymphocytes: specialised white blood cells that are part of your immune system; the cells that become cancerous in lymphoma

Medically significant side effect: a side effect that limits daily activities such as bathing and dressing, is disabling, or could be life-threatening, need hospital care,

or cause lasting problems; referred to as a **Grade 3 or 4 treatment emergent adverse event** in the inMIND trial

Monoclonal antibody: laboratory-made proteins that mimic the immune system's ability to fight off harmful pathogens that don't belong in your body, including cancer cells

Non-Hodgkin's lymphoma (NHL): a group of blood cancers that affect white blood cells called lymphocytes

Overall response rate: the proportion of people whose cancer either shrinks or disappears after treatment. It includes both complete responses (no signs of cancer) and partial responses (cancer gets smaller but doesn't fully go away)

Overall survival: the length of time people stay alive after starting treatment or being diagnosed with cancer (depending on when you start to measure it from)

Palliative therapy: treatment used to relieve symptoms of a condition that does not treat the underlying condition

Positron-emission tomography (PET) scan: a medical imaging technique that uses a radioactive tracer to visualise metabolic processes in the body; used to look at how active cancer cells are

Quality-adjusted life year: a measurement that shows how many additional months or years of life of a reasonable quality a patient may gain due to treatment

Quality of life: an individual's perception that encompasses various aspects of day-to-day life, including health, well-being, and social conditions

Refractory: cancer that does not respond to treatment at all or when the response to treatment does not last very long (less than 6 months)

Relapse: when cancer reappears or grows again after a period of remission or stable disease

Side effect: any undesirable experience that occurs after a patient is given a treatment that may or may not be caused by the drug or medical treatment; referred to as a **treatment emergent adverse event** in the inMIND trial

Significant clinical effect: a statistically significant outcome measure used to determine whether observed results are likely due to chance or reflect a true effect

Standard of care: the accepted way a condition is treated in clinical practice

4c) References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Tafasitamab with lenalidomide and rituximab for treating relapsed or refractory follicular lymphoma after 1 or more systemic treatments [ID6413]

Clarification questions

January 2025

File name	Version	Contains confidential information	Date
ID6413 Tafasitamab clarification letter_23012026 [redacted]	3.0	redacted	23/01/2025

Section A: Clarification on effectiveness data

inMIND trial design

A1. Priority question: The current data cut for inMIND is 23 February 2024. Is another data cut available? If so, please provide updated analyses for all protocol specified outcomes. If not, please clarify when analyses at the next data cut will be available.

As per the statistical analysis plan, the next data cut will be the final analysis which is planned after the last participant has completed a minimum of 5 years of post-treatment follow-up. This is anticipated in [redacted]. At this time there is no additional analysis planned from the InMIND trial.

A2. Please provide the statistical analysis plan for inMIND.

The statistical analysis plan is provided alongside this response document.

A3. Clinical study report (CSR) Table 3 presents the timing of response assessment but does not clarify whether these were made by investigator (INV) as well as independent review committee (IRC). Given that IRC response assessment was added as a secondary endpoint in protocol Amendment 7, please clarify whether response was assessed by INV and IRC in the follicular lymphoma (FL) full analysis set (FAS) at all efficacy assessments. Please discuss any limitations of the response assessments by INV and by IRC in inMIND.

Table 3 in the protocol, as opposed to the CSR, contains the schedule for bone marrow sampling and radiologic scans. It also denotes the schedule of response assessments based on the results from these procedures/scans. Response was assessed by investigators on an ongoing basis according to the schedule in Table 3 of the protocol.

For the FL full analysis set, there were procedures in place to ensure that response was assessed by the IRC, at all of the timepoints at which response was assessed by investigators. The results from the local bone marrow sampling and radiologic scans were made available for retrospective central assessments of response. In addition, subject-level dossiers, containing additional relevant clinical data, were also

made available to the central review body, on an ongoing basis. The vendor and study team actively monitored and reconciled the availability of results from bone marrow sampling, radiologic scans, and subject-level dossiers, to facilitate comprehensive central assessments of response (IRC).

There were limited instances in which bone marrow results, scans, or subject-level dossiers were not available for central review and the strong concordance between the INV and IRC assessments ([redacted] and [redacted], respectively[1]) suggests these procedures were effective and resulted in accurate and complete assessments of response by INV and by IRC.

Response assessments by INV are intended to replicate assessments as they are conducted in clinical practice but are subject to a higher level of subjectivity than response assessments by IRC. The more objective response assessments by IRC are considered more appropriate for economic modelling purposes given they are less prone to assessor bias. This approach aligns with that adopted in the majority of previous technology appraisals in the FL space (TA604, TA627, TA892, TA894).[2-5]

inMIND subgroup analyses

A4. Priority question: Please provide full results, including Kaplan–Meier (KM) curves and tables, of analyses comparing tafasitamab + lenalidomide with rituximab (R^2) with placebo + R^2 for DoR (IRC) and time to next treatment (TTNT) in the FL FAS at the latest available data cut, separately for patients on their second-line (2L) and on their third or later line (3L+)

Kaplan–Meier curves are not available but summary data tables for the results requested are provided in Table 1 and Table 2.

The addition of tafasitamab to R^2 resulted in a significant and clinically meaningful improvement in duration of response (DOR) and time to next treatment (TTNT) when used as a 2L or 3L+ treatment. This significant and clinically meaningful clinical benefit is aligned with that observed in the FAS population (2L+) and supports the conclusion that tafasitamab + R^2 is an effective treatment option across treatment lines. As described in the company submission (see Section 1.3.4) there is no single patient journey through the clinical pathway of care in England and Wales and new

treatment options are needed for use at varying points of the care pathway for people with R/R FL. Tafasitamab + R^2 reimbursement aligned with the FAS population (2L+) of the inMIND trial would meet this unmet need.

Table 1: Duration of response by independent review committee (FL FAS)

	Patients on 2L therapy		**Patients on 3L+ therapy**	
Variable	**Tafa + R²** **(N = 147)**	**PBO + R²** **(N = 153)**	**Tafa + R²** **(N = 126)**	**PBO + R²** **(N = 122)**
Number of responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]
Censored participants, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
No post-baseline assessment	[redacted]	[redacted]	[redacted]	[redacted]
Ongoing	[redacted]	[redacted]	[redacted]	[redacted]
Study discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Start of new anti-lymphoma therapy	[redacted]	[redacted]	[redacted]	[redacted]
Death or PD after ≥ 2 missed assessments	[redacted]	[redacted]	[redacted]	[redacted]
Median DOR, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier estimates (95% CI) of DOR rate				
6 months	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]
2 years	[redacted]	[redacted]	[redacted]	[redacted]
Stratified log-rank test p-value	[redacted]		[redacted]	
HR (95% CI)	[redacted]		[redacted]	

Key: 2L, second-line; 3L+, third or later line; CI, confidence interval; DOR, duration of response; FAS, Full Analysis Set; FL, follicular lymphoma; HR, hazard ratio; NE, not estimable; PD, progressive disease; R^2, lenalidomide with rituximab.
Source: Incyte Corporation, 2025.[6]

Table 2: Summary of time to next treatment (FL FAS)

	Patients on 2L therapy		Patients on 3L+ therapy	
Variable	**Tafa + R² (N = 147)**	**PBO + R² (N = 153)**	**Tafa + R² (N = 126)**	**PBO + R² (N = 122)**
Number of events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Start of new anti-lymphoma therapy	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]
Censored participants, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
No start of new anti-lymphoma therapy	[redacted]	[redacted]	[redacted]	[redacted]
Median TTNT, months (95% CI)	NE (26.8, NE)	28.8 (20.7, NE)	NE (NE, NE)	NE (14.0, NE)
Kaplan–Meier estimates (95% CI) of TTNT rate				
6 months	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]
2 years	[redacted]	[redacted]	[redacted]	[redacted]
Stratified log-rank test p-value	[redacted]		[redacted]	
HR (95% CI)	[redacted]		[redacted]	

Key: 2L, second-line; 3L+, third or later line; CI, confidence interval; DOR, duration of response; FAS, Full Analysis Set; FL, follicular lymphoma; HR, hazard ratio; NE, not estimable; PD, progressive disease; R², lenalidomide with rituximab; TTNT, time to next treatment
Source: Incyte Corporation, 2025.[6]

A5. Please provide subgroup analyses for PFS (by INV and by IRC) in the FL FAS population according to subgroups specified in the NICE final scope, i.e. type of lymphoma (follicular lymphoma, follicular lymphoma with FDG-avid foci), and grade of lymphoma. Please present the results of subgroup analyses of PFS by IRC in the FL FAS population, as per CS Figure 10.

Subgroup analyses for PFS by type of lymphoma and grade of lymphoma were not pre-planned within the inMIND trial. The distribution of patients with FDG-avid foci FL and FL Grade 1 or 2 versus 3A was even across treatment arms, and no concerns were raised by clinical experts on the generalisability of these characteristics to real-

world patients. Such post hoc analyses would thus not provide statistically or clinically meaningful results that would usefully contribute to decision making and therefore have not been conducted due to time constraints.

Results of post hoc subgroup analyses of PFS by IRC in the FAS population are presented in Table 3. The PFS benefit of adding tafasitamab to R^2 was observed in all pre-specified subgroups including patients with POD24 at diagnosis, patients refractory to prior anti-CD20 therapies and patients treated with multiple prior lines of therapy – these are difficult-to-treat patients with particularly poor prognosis.

Table 3: Post hoc subgroup analysis of PFS by IRC (FL FAS)

Subgroup	Tafasitamab + R^2		Placebo + R^2		HR (95% CI)
	# events / # patients	Median PFS (95% CI)	# events / # patients	Median PFS (95% CI)	
Sex					
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age group 1					
< 65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age group 2					
< 75 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 75 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race					
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other and missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity					
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other and missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographic region					
Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
North America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rest of the world	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
POD24					
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Subgroup	Tafasitamab + R^2		Placebo + R^2		HR (95% CI)
	# events / # patients	Median PFS (95% CI)	# events / # patients	Median PFS (95% CI)	
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refractory to prior anti-CD20					
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior lines					
1 line	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥2 lines	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; FL, follicular lymphoma; HR, hazard ratio; IRC, independent review committee; PFS, progression-free survival; POD24, progression of disease within 24 months; R^2, lenalidomide with rituximab; R/R, relapsed or refractory.
Source: Incyte Corporation, 2025.[6]

inMIND post-progression outcomes and subsequent therapies

A6. Priority question: CSR Table 2.3.2.1, and CSR Figure 4.7.1 show PFS2 (i.e. progression on subsequent treatment) results in FL FAS.

a) **If a more recent data cut is available, please provide an updated table and KM curves.**

These data are not available.

b) **Please clarify what the therapies received on next treatment were for each arm in this analysis.**

Please see details of therapies received on next treatment by PFS status in Table 4. As further discussed in response to A6 c) below, subsequent treatment data from the inMIND trial are too immature to draw any meaningful conclusions from these data.

Table 4: Summary of PFS status on next treatment (FL FAS)

PFS status on next treatment / next treatment regimen	**Treatment group**	
	[redacted]	[redacted]
Alive with no PD after next anti-lymphoma treatment	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

PFS status on next treatment / next treatment regimen	Treatment group	
Disease progression on next anti-lymphoma treatment		

PFS status on next treatment / next treatment regimen	Treatment group	
	[redacted]	[redacted]
Start of a subsequent anti-lymphoma treatment	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Key: FAS, full analysis set; FL, follicular lymphoma; PD, progressive disease; PFS, progression-free survival; R^2, lenalidomide with rituximab.
Source: Incyte Corporation, 2025.[6]

c) Please discuss the effect of tafasitamab on post-progression survival outcomes, accounting for the potential confounding effect of subsequent therapies.

The positive impact of extending time to progression on post-progression survival (PPS) is described in detail in the response to B2a. In summary, tafasitamab + R2 provides prolonged disease control through a novel dual targeting of CD19 and CD20 that could result in a lower tumour burden and a less aggressive disease phenotype at relapse with lower likelihood of emergence of treatment-resistant cells. The engineering of the fc part of tafasitamab was designed to enhance immune-mediated cytotoxicity and is expected to improve the depth of malignant B-cell depletion, which may support prolonged disease control. This should create better conditions for subsequent therapies, both in terms of tolerance and potential for durable response. Data from the inMIND trial are too immature to show any differences in subsequent therapy use or response with tafasitamab use and therefore such a benefit is not factored into the economic modelling but may be observed with longer-term follow-up.

A7. Priority question: CS Table 12 presents information on subsequent therapies received in each arm. Please provide further details in a new table that includes a breakdown of therapies received in each subsequent line of therapy, by treatment arm.

Please find the summary of therapies received in each subsequent line of therapy by treatment arm in Table 5. Subsequent treatment data from the inMIND trial are too immature to draw any meaningful conclusions from these data. In real-world practice, clinical experts expected the subsequent treatment use to be near-identical after progression on tafasitamab + R^2 or R^2 alone.[7]

Table 5: Summary of most common (≥5% in either arm) post-treatment systemic anti-lymphoma therapies by line of therapy per treatment arm, R/R FL population

	Tafasitamab + R² (n = [redacted])					Placebo + R² (n = [redacted])				
	Line 1	Line 2	Line 3	Line 4	Line 5+	Line 1	Line 2	Line 3	Line 4	Line 5+
[redacted]										

R^2 and R-chemotherapy

A8. Priority question: Please supply further evidence to support the claim that it is both reasonable and "conservative" (CS p64) to assume equivalent efficacy of R^2 (from inMIND) and R-Chemotherapy. This could include:

a) **KM plots of PFS, OS, and TTND comparing unadjusted or adjusted R2 (from inMIND) to R-chemotherapy from other sources**

b) **Unanchored MAIC analyses comparing R2 (from inMIND) to R-chemotherapy, in 2L and 3L+.**

c) **Further examination of data and analyses from the original trials and assessments of R2, such as data and analyses from TA627.**

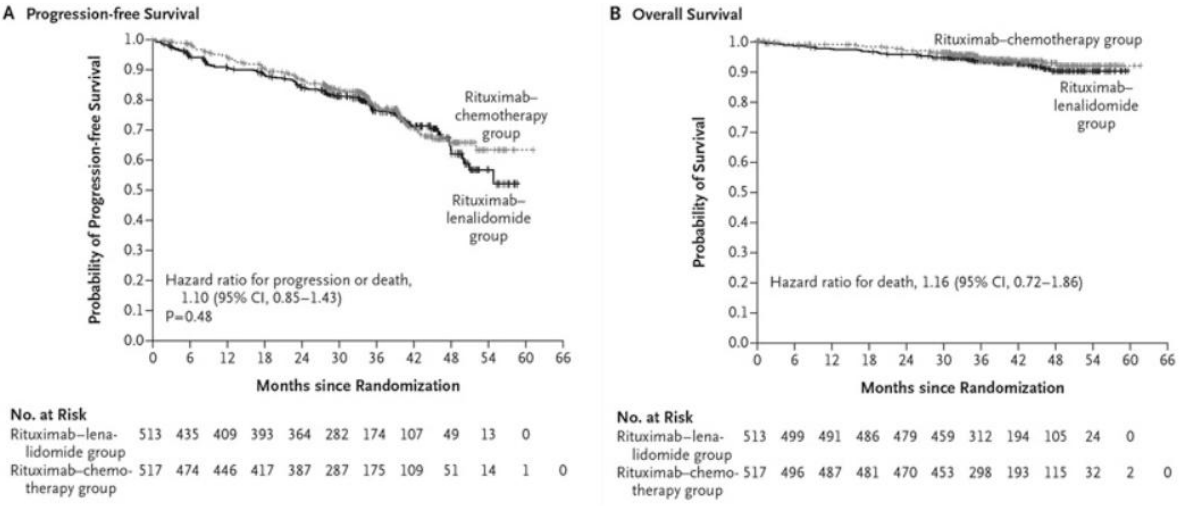
As discussed in the company submission there is a challenging data gap in the availability of evidence for the treatment of R/R FL with R-chemotherapy. Those studies that were identified all had several potential sources of heterogeneity compared with the inMIND trial (see company submission Section 2.10 and Appendix B and addendum ITC report). In summary, there are no suitable sources of data for R-chemotherapy that would allow informative comparison of unadjusted or adjusted R^2 data from inMIND with R-chemotherapy.

The limitations and lack of face validity of the unanchored MAICs for tafasitamab + R^2 versus R-chemotherapy presented in the company submission and addendum ITC report would equally apply to such analyses using R^2 from inMIND when compared with data from Van Oers or HMRN. Comparator datasets lacked several baseline characteristics deemed crucial by clinical experts, and differences in definitions further reduced comparability. Adjustments in the tafasitamab + R^2 MAICs led to large losses in ESS ([redacted]%), with some analyses based on very small patient numbers, contributing to wide 95% CIs and high uncertainty. Additional challenges included low event counts for OS and differences in endpoint definitions across RCT and real-world sources. The same issues would arise in proposed R^2 vs R-chemotherapy MAICs, resulting in similarly high uncertainty and lack of face validity, making such results inappropriate to inform decision making.

What is available is a previous robust technology appraisal [TA627] that concluded R^2 is a clinically- and cost-effective treatment compared with R-chemotherapy.[8] It is specifically noted in the FAD for TA627 that: "*clinical experts said that it was clinically implausible for the average progression-free survival of lenalidomide with rituximab to be worse than the average progression-free survival of R-CHOP and R-CVP*". Furthermore, although the data and analyses from TA627 cannot be further examined as they are redacted, given these clinician views, the positive ICERs presented in the FAD to TA627 must arise from positive incremental costs and positive incremental benefits of R^2 vs R-chemotherapy. The conclusions from TA627 therefore clearly indicate that R^2 is accepted by the clinical community and by the NICE committee to be more effective than R-chemotherapy. Such a conclusion is also indicated in the Scottish Medicines Consortium (SMC) accepting R^2 for use within NHS Scotland.[9] Our base case modelling approach in this appraisal, assuming that R-chemotherapy is equivalent to R^2 is therefore reasonable (in the absence of robust data with which to conduct confirmatory analyses) and conservative (in that it effectively biases any comparison of tafasitamab + R^2 vs R-chemotherapy in favour of R-chemotherapy).

In the absence of any robust data in the R/R FL setting, we refer the EAG to the RELEVANCE trial which is a Phase III RCT investigating the efficacy and safety of R^2 versus R-chemotherapy of people with previously untreated FL. [10] In this trial, efficacy results were similar with R^2 and R-chemotherapy with no significant differences observed in PFS or OS, as shown in the Kaplan–Meier curves presented in Figure 1. We may expect a difference in efficacy in the R/R FL setting that we do not see in the 1L FL setting given R-chemotherapy would be a retreatment approach in this setting and thus unlikely to be as successful.

Figure 1: Progression-free survival (A) and overall survival (B) in the RELEVANCE trial comparing R^2 and R-chemotherapy (ITT)



Key: CI, confidence interval; ITT, intention-to-treat; R^2, lenalidomide and rituximab.
Source: Morschhauser et al. 2018.[10]

Health-related quality of life

A9. Health-related quality of life (HRQL) results are presented in a conference poster.[11] Please provide any linked published or unpublished reports where available.

No linked published or unpublished reports are available beyond those provided in the previous reference packs, which included:

- Strati et al. 2025. Quality of life outcomes with tafasitamab plus lenalidomide and rituximab for relapsed or refractory follicular lymphoma: Results from a Phase 3, double-blind, randomized, placebo-controlled, international, multicentre study (inMIND). Presented at 13th Annual Meeting of the SOHO – reference 38 of the appendices reference pack

- Incyte Corporation. A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicentre Study to Evaluate the Efficacy and Safety of Tafasitamab Plus Lenalidomide in Addition to Rituximab Versus Lenalidomide in Addition to Rituximab in Patients With Relapsed/Refractory (R/R) Follicular Lymphoma Grade 1 to 3a or R/R Marginal Zone Lymphoma. (Clinical Study Report)– reference 64 of the CS reference pack

- Incyte Corporation. Patient-Reported Outcome Analysis for Tafasitamab in Relapsed / Refractory Follicular Lymphoma: Final Technical Report. (PRJ003554) – reference 90 of the CS reference pack

Indirect treatment comparisons

A10. Priority question: Please provide full details of the matching-adjusted indirect comparison (MAIC) methods and analyses comparing inMIND with Haematological Malignancy Research Network (HMRN) data and with Van Oers data, in line with the material presented in the original indirect treatment comparisons (ITCs) in the CS Appendix and associated report.[12] Please ensure this includes an assessment of the proportional hazard (PH) assumption, tabulated results for all outcomes, and all KM curves or data sourced from Van Oers and HMRN reports.

Please see the provided addendum technical report for the MAICs based on HMRN and Van Oers, which includes full details of the data sources and results. As outlined in the company submission and report addendum, there are several limitations of the comparator evidence base which restricted the ability to conduct robust indirect treatment comparisons. Notably, despite extensive efforts to account for confounding characteristics, several clinically important variables identified for matching were not mutually available between inMIND and the comparator studies, and therefore could not be included in the adjustment, such as ECOG PS, duration of previous response/remission, double refractory status, POD24 , response to last therapy, number of lymph nodes involved and tumour bulk. Therefore, there is high potential for unmeasured confounding and bias in the relative treatment effect estimates. As such, the MAIC results are deemed unreliable and inappropriate for decision making. Instead, the use of randomised data from inMIND and the conservative assumption that R-chemo and R2 are equivalent (see response to A8), as used in the company submission, is considered the most robust approach based on the evidence available.

A11. Priority question: CS Appendix Table 13 lists the characteristics of the HMRN participants broken down by whether they were in 2L or 3L setting, but this is not presented for inMIND. Please update this table to include a similar

breakdown for patients in 2L and 3L in inMIND, to allow for a more granular assessment of the comparability of patients between these two evidence sources.

Table 6 provides the tafasitamab + R2 patient characteristics for 2L and 3L patients. As noted in the response to A10, several clinically relevant characteristics – including ECOG PS, duration of previous response/remission, double refractory status, POD24, response to last therapy, number of lymph nodes involved, and tumour bulk – were not consistently available across studies, limiting the ability to determine comparability between inMIND and HMRN populations. These data gaps undermine the robustness of any MAIC analyses and contribute to the uncertainty in the ITCs, reinforcing the rationale for relying on randomised data from inMIND and the conservative assumption of equivalent efficacy between R-chemo and R2 (see response to A8) in the company submission.

Table 6: Patient characteristics by 2L and 3L

Characteristics	inMIND – 2L	HMRN – 2L		inMIND – 3L	HMRN – 3L	
	Tafasitamab + R^2 (N = 147)	R-CHOP (N = 78)	R-CVP (N = 54)	Tafasitamab + R^2 (N = 66)	R-CHOP (N = 14)	R-CVP (N = 6)
Age, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS, n (%)						
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ann Arbor stage at diagnosis, n (%)						
Stage I or II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage III or IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FL histology grade at study entry, n (%)						
1 or 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FLIPI risk score at diagnosis, n (%)						
Low (0–1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intermediate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High (≥ 3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Characteristics	inMIND – 2L	HMRN – 2L		inMIND – 3L	HMRN – 3L	
	Tafasitamab + R^2 (N = 147)	R-CHOP (N = 78)	R-CVP (N = 54)	Tafasitamab + R^2 (N = 66)	R-CHOP (N = 14)	R-CVP (N = 6)
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B symptoms present, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression of disease within 24 months of treatment, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression of disease within 24 months of initial diagnosis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time since diagnosis, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior lines of therapy, n (%)						
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior ASCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refractory to rituximab, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refractory to last prior regimen, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: 1L, first-line; 2L, second-line; 3L, third-line; ASCT, autologous stem cell transplant; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; HMRN, Haematological Malignancy Research Network; NR, not reported; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP, rituximab plus cyclophosphamide, vincristine, and prednisone; R^2, lenalidomide plus rituximab; SD, standard deviation.

Notes: ** A patient is considered as POD24 if they have had documented progression within 24 months of the start of the first-line of systemic therapy (1L) - POD24 is also estimated for patients that have had documented progression within 24 months of the start of the second-line (2L) and third-line (3L) of systemic therapy.

A12. Priority question: Please provide a MAIC comparing Tafasitamab+R^2 from inMIND against R-chemotherapy in the 2L setting only. Please ensure the methodology and reporting are consistent with the ITC report.[12].

Please see the provided addendum technical report for the MAICs based on HMRN and Van Oers, which includes results of MAICs for tafasitamab + R^2 versus R-chemotherapy in 2L using data from inMIND and HMRN. As mentioned in response to A10, there are several limitations with the MAICs, meaning they are unreliable and not suitable for decision making, and the use of randomised data from inMIND in the Company Submission is preferred.

A13. The definition of PFS differs between the studies included in the ITC (as shown in Appendix B, Table 9 and 18). Please discuss whether and to what extent differences in PFS definitions between studies may affect the results of the ITCs, including a discussion of potential magnitude and direction of bias in relative estimates.

Table 7 shows the PFS definitions across studies in the evidence base, including differences in assessor type, start times, and response criteria. To minimise bias in the ITCs, the type of PFS assessment in inMIND was matched to that reported in each comparator trial where possible (e.g. where comparator trials reported PFS by INV, PFS INV from inMIND was used). Van Oers and HMRN did not report whether PFS was assessed by INV or IRC; for these, PFS IRC was used from inMIND, as IRC assessment is generally thought to be less prone to bias. In terms of start times, BRB, HMRN, and EPCORE NHL1 measured PFS from the first day of treatment, whereas inMIND measured from randomisation; the median time from randomisation to treatment start in inMIND was ≤ 3 days, so any bias from this difference was considered minimal and no adjustment was made.

Differences in response criteria present greater potential for bias: inMIND and EPCORE NHL1 used Lugano 2014 (PET/CT-based, metabolic response, stricter progression rules), BRB used IWG 1999 (CT-based, bidimensional), Van Oers used LEXCOR (CT-based, unidimensional), and GADOLIN used Cheson 2007 (PET for aggressive lymphomas, CT primary for indolent). For HMRN, as a real-world dataset, the method used to assess progression is unclear and may have varied between patients, further increasing uncertainty. PET based criteria can confirm progression

earlier than CT based criteria, whereas older CT only methods may delay progression classification. This means trials using Lugano 2014 (inMIND, EPCORE NHL1) could appear to have shorter PFS than CT based trials (BRB, Van Oers, GADOLIN), even if true efficacy is equivalent. Such differences may bias relative estimates in the ITCs, with the likely direction being underestimation of PFS for Lugano based trials compared with older CT based criteria.

-Although steps were taken in the MAICs to minimise bias from differences in PFS assessment, it was not possible to eliminate the risk of unmeasured confounding, particularly given the heterogeneity in criteria and uncertainty around progression assessment in HMRN. These factors add to the overall limitations of the evidence base and reduce confidence in the relative PFS estimates from the ITCs. Consequently, the MAIC results were not considered sufficiently robust to inform decision making, and the approach taken in the company submission – using randomised data from inMIND and the conservative assumption that R-chemo and R2 have equivalent efficacy – was preferred based on the available evidence.

Table 7: Comparison of PFS definitions across studies in the evidence base

Study ID	Intervention	PFS assessor	PFS definition and criteria
inMIND	Tafasitamab + R^2	IA and IRC available	The time from randomisation to first documented disease progression, or death from any cause, whichever comes first. Disease response (including PD) was assessed via CT or MRI according to the Lugano 2014 criteria
BRB	R-B	IA	The time from the first dose of trial drug to the first documentation of disease progression or death Disease response (including PD) was assessed via enhanced CT or MRI according to International Working Group Response Criteria for NHL
Van Oers	R-CHOP	NR	No PFS definition reported for the induction phase, but the maintenance phase definition was defined as interval between the date of second randomisation and date of first relapse, progression, or death Disease response (including PD) was assessed via CT according to LEXCOR criteria

Study ID	Intervention	PFS assessor	PFS definition and criteria
HMRN	R-chemotherapy	NR	Defined as time from treatment initiation to disease progression (including transformation to diffuse large B-cell lymphoma) or death due to any cause. Response criteria not reported
GADOLIN	O-B	IA*	Time from randomisation to the earliest of progression, relapse, or death as a result of any cause Tumour response was assessed according to the Cheson revised response criteria for non-Hodgkin lymphoma (2007)
EPCORE NHL-1	Epcoritamab	IA	Time from Day 1 of Cycle 1 to first documented PD or death due to any cause Tumour response was assessed according to the Lugano criteria (2014)

Key: CT, computed tomography; HMRN, Haematological Malignancy Research Network; IA, investigator assessment; IRC, independent review committee; MRI, magnetic resonance imaging; NHL, non-Hodgkin lymphoma; NR, not reported; O-B, obinutuzumab + bendamustine; PD, progressive disease; PFS, progression-free survival; R-B, rituximab + bendamustine; R-CHOP, rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; R-chemotherapy, rituximab + chemotherapy.

Notes: * Although IRC-assessed PFS was available from earlier data cuts in GADOLIN, the published data with the longest follow-up was used in the MAICs, which was PFS per IA.

A14. The weighted Cox model is an extension of Cox PH model. Considering this, please explain what the HR weighted Cox model (PFS and OS) in Appendix B signifies. If the weighted Cox model is used, please confirm which weighing technique was employed for the MAICs, and confirm whether it accounted for the potential violation of the PH assumption. If feasible, please provide a time-varying hazard ratio, wherever the PH assumption is violated in the ITCs (as shown in Table 105 of the ITC report).[12]

The term “HR from weighted Cox model” in Appendix B refers to constant HRs from weighted Cox PH models. These constant HRs were estimated from (weighted) Cox PH models that included a single covariate for treatment arm. MAIC weights were derived using the method of moments approach described in NICE DSU TSD 18 to match key baseline characteristics of the tafasitamab + R² population to those reported for the comparator trial, with all comparator arm patients assigned a weight of 1. Robust SEs were calculated using a sandwich estimator for the primary analysis, and bootstrapping was explored in sensitivity analyses. The models assumed PH and did not incorporate adjustments for potential violations. While time-

varying HRs could theoretically be estimated where PH is violated, the MAIC results are highly uncertain and have limited face validity, meaning such estimates would be similarly unreliable and unlikely to be informative for decision making. As an alternative measure of relative treatment effect that does not rely on the PH assumption, differences in RMST are provided in the response to Question A15.

A15. Follow-up duration varied between the studies included in the ITC. Please clarify whether any statistical methods were considered to account for this (e.g. Restricted Mean Survival Time, which is especially appropriate when the PH assumption is violated).

No adjustments were made in the MAIC analyses to account for differences in follow-up time between studies. As an alternative to constant HRs, Table 8 presents the difference in RMST from the MAIC analyses, which provides a measure of average survival time up to a specified point and is appropriate when the PH assumption may not hold. For each MAIC, the RMST time point was set to the smaller of the maximum observed time in the weighted tafasitamab + R^2 arm or the comparator arm, ensuring both arms were compared over an identical period of follow-up. A difference in RMST > 0 indicates that tafasitamab + R^2 provides longer mean survival than the comparator within the chosen time window. Note that the standard errors for RMST and its differences did not account for variation in the MAIC weights, which may lead to underestimation of the uncertainty in the 95% CIs. Nevertheless, 95% CIs for all analyses were wide and overlapped 0. The point estimates suggest improved OS and PFS for tafasitamab + R^2 versus R-chemotherapy in all analyses except for PFS versus R-CVP. Given that tafasitamab + R^2 has been shown to improve PFS versus R^2 in inMIND, and R^2 is considered more efficacious than R-chemotherapy, this result lacks face validity. As with all other MAIC analyses, these RMST results share the same limitations and should therefore be interpreted with caution.

Table 8: MAIC results – difference in RMST

Comparator study	Treatment arm	LOT	N/ESS (% of original sample size)	HR (95% CI; robust SE)	RMST time point	RMST (95% CI; months)	Difference in RMST (95% CI; months)
OS							
BRB	R-B	2L+	[redacted]	Reference	NA	NR	Reference
	Tafasitamab + R^2		[redacted]	NR	NA	NR	NR
Van Oers	R-CHOP	2L–3L	[redacted]	Reference	[redacted]	[redacted]	Reference
	Tafasitamab + R^2		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HMRN	R-chemotherapy	2L–3L	[redacted]	Reference	[redacted]	[redacted]	Reference
	Tafasitamab + R^2		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HMRN	R-CHOP	2L–3L	[redacted]	Reference	[redacted]	[redacted]	Reference
	Tafasitamab + R^2		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HMRN	R-CVP	2L–3L	[redacted]	Reference	[redacted]	[redacted]	Reference
	Tafasitamab + R^2		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GADOLIN	O-B	2L+	[redacted]	Reference	[redacted]	[redacted]	Reference
	Tafasitamab + R^2		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EPCORE NHL-1	Epcoritamab	3L+	[redacted]	Reference	[redacted]	[redacted]	Reference
	Tafasitamab + R^2		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS							
BRB	R-B	2L+	[redacted]	Reference	[redacted]	[redacted]	Reference
	Tafasitamab + R^2		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Van Oers	R-CHOP	2L–3L	[redacted]	Reference	[redacted]	[redacted]	Reference
	Tafasitamab + R^2		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HMRN	R-chemotherapy	2L–3L	[redacted]	Reference	[redacted]	[redacted]	Reference
	Tafasitamab + R^2		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HMRN	R-CHOP	2L–3L	[redacted]	Reference	[redacted]	[redacted]	Reference

Comparator study	Treatment arm	LOT	N/ESS (% of original sample size)	HR (95% CI; robust SE)	RMST time point	RMST (95% CI; months)	Difference in RMST (95% CI; months)
	Tafasitamab + R^2		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HMRN	R-CVP	2L–3L	[redacted]	Reference	[redacted]	[redacted]	Reference
	Tafasitamab + R^2		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GADOLIN	O-B	2L+	[redacted]	Reference	[redacted]	[redacted]	Reference
	Tafasitamab + R^2		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EPCORE NHL-1	Epcoritamab	3L+	[redacted]	Reference	[redacted]	[redacted]	Reference
	Tafasitamab + R^2		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; ESS, effective sample size; HR, hazard ratio; NA, not applicable; NR, not reported; OS, overall survival; PFS, progression-free survival; PH, proportional hazards; R^2, lenalidomide + rituximab; R-B, rituximab + bendamustine; R-CHOP, rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; R-CVP, rituximab + cyclophosphamide + vincristine + prednisone; RMST, restricted mean survival time.
Notes: *Evidence that the PH assumption is violated.
Difference in RMST > 0 indicates that tafasitamab + R^2 provides longer mean survival than the comparator, up to the given time point. The standard error calculated for the RMST and therefore difference in RMST does not account for variation in the weights and may be an underestimate of the true uncertainty; 95% CIs for the difference in RMST should be interpreted with caution.

A16. CS Appendix Table 12 (Summary of key inclusion criteria) states that age and performance status are not reported for HMRN. Please clarify. Does this mean that these variables were not accounted for when selecting data from HMRN, and if so, why?

The HMRN study did not explicitly define an age inclusion or exclusion criterion; however, baseline characteristics indicate that all patients were ≥ 18 years, aligning with inMIND. ECOG PS was not part of the formal eligibility criteria for HMRN, likely due to lack of data availability. InMIND included patients with ECOG PS 0–2, but it is unclear whether the HMRN population was aligned with this criterion. In the MAICs, age was included as a matching variable in all analyses, but ECOG PS could not be matched because data were missing for the comparator. As the distribution of ECOG PS in the HMRN population is unknown, comparability of the matched populations cannot be assessed, introducing the potential for unmeasured confounding. This limitation increases the overall uncertainty of the MAICs and reinforces that the results should not be used to inform decision making, further supporting the approach taken in the company submission.

Section B: Clarification on cost-effectiveness data

Model structure

B1. Priority question: A key feature of a partitioned survival model (PSM) is that OS is modelled directly. However, in this appraisal, the OS data are very immature, with limited follow-up. In addition, OS outcomes in the inMIND trial may be confounded by the use of subsequent treatments not available in the NHS. The EAG is therefore concerned that parametric extrapolation of the inMIND OS data cannot generate reliable long-term estimates of treatment benefit. Given these limitations, the EAG has substantive concerns regarding the appropriateness of a PSM structure.

a) **Please provide further justification for adopting a PSM, explaining why a state-transition model (STM) is considered less appropriate for the current decision problem.**

As discussed in the Evidence Submission Section 3.2.2.2, the exploratory state transition approach was developed as a scenario analysis to complement the base case partitioned survival model at the request of the EAG during the decision problem meeting (18th Sept 2025).

The main limitation of the STM is the underlying structural assumption in the context of FL. As described in NICE TSD 19, “In the PartSA approach, each endpoint (e.g. PFS, OS) is modelled independently of the other endpoints included within the model, whereas in state transition models clinical events are explicitly related”. The structural relationship between PFS and OS events in FL is somewhat nuanced with mixed evidence and opinion on the strength and linearity of the relationship as previously described in Section 3.2.2.2 of the company submission. In reality, this reflects the heterogeneity of the FL disease course with some patients experiencing a slow growing disease trajectory and others experiencing an aggressive disease trajectory. The relationship is further impacted by treatment effect with new treatment classes observed to re-establish disease control that facilitates longer PPS (see response to B2d).

The PSM approach better accommodates the different structural relationship between PFS and OS for different patient types through its direct use of trial outcomes from inMIND that enrolled a broad patient population. As outlined in the company submission (Section 3.2.2.1), prior NICE appraisals in FL have used a PSM, and these were considered appropriate to inform decision making. In particular, for the appraisal of R^2 (the primary comparator for this submission), the committee “concluded that a partitioned survival model was appropriate, and that a state transition model was not needed on this occasion”. In contrast, the STM approach required a three-step process using rituximab refractory status-based patient groups as proxies for diverse disease trajectory cohorts to allow the different structural relations between PFS and OS to be factored into the economic analyses.

Additionally, the state-transition model does not eliminate the need to extrapolate data. Extrapolating more immature data, such as post-progression survival, produces more uncertain estimates for those specific transitions probabilities and hence creating more uncertainty in the projected overall survival outcomes. As the EAG acknowledges, the inMIND OS data are immature, with only 38 deaths observed, corresponding to less than 8% of the trial population. As such, there are insufficient evidence to reliably estimate separate rates of mortality by progression status, as would be required for a state transition model. Given the immature PPS from inMIND, the STM uses median overall survival results from the GADOLIN study, which are based on a small number of patients still being followed at the midpoint of survival (and on the restricted mean survival estimates following Clarification Question B2c). Ideally, extrapolation should be based on more mature data on time from progression to death, using the best fitting parametric survival curve for those data.

As described in the Evidence Submission Section 3.7, extrapolation of long-term outcomes based on relatively short-term clinical trial data is a common challenge for most oncology products undergoing NICE appraisal.[13, 14] Following NICE TSD19 and EAG recommendations during the Decision Problem meeting, the company has provided a STM alongside the PSM with different specifications to explore various survival modelling approaches to extrapolate beyond the observed duration of the clinical trial. The company recognises that all modelling methods have limitations.

Although both PSM and STM approaches were considered, the company believes the PSM is more suitable for decision making because it uses the trial results more directly.

Even so, both models produced reasonable long-term survival estimates for all treatments, as described in Section 3.3.3.1.3 of the Evidence Submission. The models were tested in scenario analyses, and the resulting ICERs were within the cost-effectiveness range accepted by NICE. For this reason, the company considers that the STM supports the long-term results from the PSM and helps reduce uncertainty about the cost-effectiveness of tafasitamab + R^2.

b) Please clarify the assumptions made within each approach, specifically highlighting the methodological differences between a partitioned survival model and pseudo state transition model (see NICE DSU TSD 19 for reference). Please complete the summary table below, outlining the relevant attributes of the two approaches.

The following assumptions about the state transition model relate to the specific transitions used in the company's cost-effectiveness model for this appraisal. Unlike the current state transition model, other models can use constant transition probabilities for PFS.

	Partitioned survival analysis	**State transition model**
How state is membership estimated	Includes three mutually exclusive health states: progression-free, progressed and death. Separate survival functions are estimated from the inMIND trial (for tafasitamab + R^2 and R^2) and the MAIC HRs (for R-chemotherapies). At each time point t, the proportion of the cohort in each state is derived algebraically from the survival curves. Parametric models are fitted to the inMIND data to derive the extrapolated PFS and OS. PFS represents patients who are alive and have not progressed. OS represents all patients who are alive. The patients who are alive and have progressed are derived as $OS_t - PFS_t$	Includes three mutually exclusive health states: progression-free, progressed and death. Therefore, the model accounts for three possible transitions: PF → PD, PF → death and PD → death. PF → PD Separate survival functions for PFS are estimated from the inMIND trial (for tafasitamab + R^2 and R^2) and the MAIC HR (for R-chemotherapies). At each time point t, the proportion of the cohort in each the progression-free health state is derived algebraically from the survival curve. PF → Death The extrapolated PFS curve includes progression events and death events. The proportion of PFS events that are death observed in the inMIND trial is applied to the patients leaving the PF health state (PFS_t - PFS_{t-1}) to derive the patients transitioning from PF to death. PD → Death A PPS rate is applied to the patients who are alive and have progressed. Survival rates are derived based on median PPS.

	Partitioned survival analysis	State transition model
		Median PPS is derived as median OS minus median PFS. PPS rate is estimated as *-LN(0.5) / median PPS*. Alternatively, based on CQ B5c, the restricted mean survival time is used instead of median values.
Data inputs	inMIND PFS and OS KM curves	PF → PD inMIND PFS KM curves for each arm and inMIND proportion of PFS events that are death for each arm and inMIND PFS KM curves. PF → Death inMIND PFS KM curves for each arm and inMIND proportion of PFS events that are death for each arm and inMIND PFS KM curves. PD → Death O-B and bendamustine median PFS and OS in the GADOLIN trial (the restricted mean survival time is also used as requested by the EAG in CQ B5c) R^2 and rituximab monotherapy median PFS and OS in the AUGMENT trial (the restricted mean survival time is also used as requested by the EAG in CQ B5c)

	Partitioned survival analysis	**State transition model**
Methods for reflecting time-dependency in event risks	Survival curves for OS and PFS are estimated using parametric models whose hazards change over time. PFS is capped by OS and OS and PFS endpoints are conditioned on general population mortality.	PF → PD Survival curves for PFS are estimated using parametric models whose hazards change over time. PF → Death The transitions from PF to death are based on the PFS curve, which allows for time-dependent transitions. PD → Death The post-progression mortality rate is constant across time and does not reflect time-dependency in death event in patients who are alive and have progressed. The use of constant rates is limited by the availability of PPS data. Additionally, applying time-varying mortality rates post-progression would require complex calculations as the model would need to track the exact cycle in which in patient has progressed.
How extrapolation of overall survival is performed	Beyond the observed OS, extrapolations are determined by parametric models. The curve selection is discussed in Appendix L.2.3. OS adjusted for background mortality	PFS extrapolated by fitted parametric models. Patients entering the progressed health state are derived by applying the proportion of PFS events that are death to ΔPFS_t. A constant survival rate is applied to the patients in the progressed health state.

	Partitioned survival analysis	**State transition model**
How extrapolation of treatment effects on overall survival is performed	Extrapolation of treatment effects on OS is performed by fitting and extending survival models beyond the observed trial period, which results in different patterns of the treatment effect (hazard ratio) over time.	Treatment effect on OS is composed of two elements - A treatment effect on PFS: Extrapolation of treatment effects on PFS is performed by fitting and extending survival models beyond the observed trial period, which results in different patterns of the treatment effect (hazard ratio) over time. - A treatment effect of PPS: The estimation of the PPS is based on the median PPS (or RMS) transformed to a constant survival rate. As discuss in the Evidence Submission Section 3.3.3.1.3, the treatment effect (i.e. a treatment-specific PPS rate) is based on the beneficial effect on PPS of delaying progression in those patients that experienced an early relapse (rituximab-refractor or POD24) in the previous line of therapy.
Risks to validity of extrapolation of OS	Due to the limited follow-up time in the FL context, OS extrapolations are based on a reduced number of death events, which is reflected in the difference in survival estimates across the standard parametric curves.	The STM underlying assumptions and data requirements are different from the STM. The limitations of the STM are detailed in CQ B1a.

	Partitioned survival analysis	State transition model
	The base case curves have been validated during clinical interviews and are align with UK clinical practice (see Appendix L.2.3)	However, the scenario based on the STM3 results in OS extrapolations that align with UK clinical practice (see Appendix L.2.3).
Consideration for use within decision making process	Extrapolation of long-term outcomes based on relatively short-term clinical trial data is a common challenge for most oncology products undergoing NICE appraisal.[13, 14] The company considered the results of the cost-effectiveness analysis are robust as the base case curves have been validated during clinical interviews and are align with UK clinical practice (see Appendix L.2.3). Uncertainty has been appropriately explored, particularly via alternative structural assumptions (STM) and parametric curves.	As described in CQ B1a, the STM is subject to its own limitations. The company considered the results of the cost-effectiveness scenario analysis are robust as the scenario based on the STM3 results in OS extrapolations align with UK clinical practice (see Appendix L.2.3). Uncertainty has been appropriately explored, particularly via alternative structural assumptions (PSM) and different assumptions of the PPS survival benefit (STM1-3).

c) **Please incorporate additional functionality into the STM to allow the proportion of PFS events classified as death events to be modelled separately for each treatment arm, rather than assuming a common proportion as currently implemented.**

The company has updated the model to allow the proportion of PFS events classified as death events to be modelled separately for each treatment arm.

In the Tafasitamab + R^2 arm, [redacted] out of [redacted] death events are related to COVID 19 or unexpected death, while [redacted] out of [redacted] death events are related to COVID 19 in the R^2 arm (Table 9). These are not considered to be attributable to treatment. If the proportion of PFS events that are death is derived excluding these events, the difference between the proportions is reduced ([redacted], Table 10). Given the limited follow-up and the similarities between treatment arms after adjusting for COVID 19 death events, the company believes that pooling both arms to derive the proportion of PFS events that are death is the most appropriate approach.

Table 9. List of reasons for death for patients with PFS events that are death

Tafasitamab + R^2	R^2
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	

Key: PFS, progression free survival; R^2, lenalidomide with rituximab.

Table 10. Percentage of PFS events that are death excluding events not attributable to follicular lymphoma or treatment-emergent adverse events

Scenario	Population	Death events	PFS events	Percentage
All PFS events that are death included	Tafasitamab + R^2	[redacted]	[redacted]	[redacted]
	R^2	[redacted]	[redacted]	[redacted]
PFS events not attributable to follicular lymphoma or treatment-emergent adverse events excluded	Tafasitamab + R^2	[redacted]	[redacted]	[redacted]
	R^2	[redacted]	[redacted]	[redacted]

Key: PFS, progression free survival; R^2, lenalidomide with rituximab.

B2. Priority question: The CS describes three alternative STM parameterisations that differ in assumptions regarding post-progression survival (PPS). The company suggests that extending the time to progression could influence PPS.

a) Please comment on the biological mechanism that could plausibly underpin such a relationship, and how this relates to mechanism(s) of action of tafasitamab + R^2.

Extending time to progression can positively influence post-progression survival (PPS). Prolonged disease control may contribute to a more favourable disease state at relapse, characterised by lower tumour burden and reduced clinical aggressiveness. In turn, this may support improved outcomes to subsequent lines of therapy. This relationship of improved prognosis with extended PFS is well established in FL with POD24 and primary refractory disease proven prognostic factors (see Sections 1.3.2.2 and 1.3.2.3 of the company submission).

Tafasitamab + R^2 provides prolonged disease control through its novel dual targeting of CD19 and CD20 which reduces the likelihood of clonal evolution and potentially prevents the emergence of treatment-resistant cells as part of its effective suppression of malignant B-cell proliferation. Introducing a treatment with a novel mechanism of action helps prevent the progressively poorer outcomes observed with each line of therapy as the disease becomes increasingly resistant to treatment (see

Section 1.3.2.1 of the company submission). This is particularly impactful for patients who have rituximab refractory disease for whom a new treatment target can help re-establish disease control. The enhanced PPS benefit of a new treatment class in rituximab refractory disease is observed in longer-term data from the GADOLIN trial as discussed in response to part d) of this question supporting clinical plausibility of this assumption.

b) Please provide an analysis of PPS using data from the inMIND trial. Your analysis should include a presentation of KM curves and appropriate statistical evaluation to assess the evidence for a post-progression survival benefit.

As shown in Table 11, patients in the inMIND trial who received tafasitamab + R^2 had higher post-progression survival at 6, 12, and 18 months. However, these results should be interpreted with caution because there were few events in the tafasitamab + R^2 arm and the follow-up period was limited.

Table 11. KM estimates of post-progression survival for patients with disease progression

	Treatment Group	
	Tafasitamab + Rituximab + Lenalidomide (N=67)	**Placebo + Rituximab + Lenalidomide (N=124)**
Number (%) of participants with death		
Death	[redacted]	[redacted]
Censored	[redacted]	[redacted]
Last known alive	[redacted]	[redacted]
Study discontinuation	[redacted]	[redacted]
Kaplan–Meier estimates (95% CI) of post-progression survival rate at		
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
2 years	[redacted]	[redacted]

Key: CI, confidence interval; KM, Kaplan–Meier.

c) The company's interpretation of the PFS and OS data from the HMRN database and GADOLIN trial relies on subtracting median OS and PFS which may be misleading. Please reconduct these comparisons comparing restricted mean survival time.

Median survival and restricted mean survival time are summary measures used to describe time-to-event outcomes. They are based on different methods, which can result in differences in how the results are interpreted.

Median OS and median PFS correspond to observable, clinically meaningful milestones. Median PFS corresponds to the time by which half the population has progressed, while median OS corresponds to the time by which half the population has died. Subtracting them approximates the typical interval between progression and death for the median patient. Even though this is not a formal statistical identity, it reflects the central tendency of disease course, and it aligns with how clinicians conceptualize PPS in practice. By contrast, the RMST is the average survival time up to a pre-specified time horizon (τ), equal to the area under the survival curve from 0 to τ, and the RMST subtraction does not correspond to any clinical milestone.

For the specific implementation of the state transition, the RMST is less appropriate than the median values to derive PPS due to the sensitivity of RMST(OS) to late follow-up and censoring, truncation time sensitivity of RMST-based differences, the confounding effect of subsequent therapies on RMST and the asymmetric impact of follow-up duration and censoring on RMST in cross-trial OS comparisons.

1. Sensitivity of RMST(OS) to late follow-up and censoring
    - RMST (OS) integrates the survival function over the entire interval $[0, \tau]$. As a result, survival probabilities near the truncation time contribute disproportionately to the estimate, making RMST(OS) highly sensitive to late follow-up behaviour.
    - When censoring is substantial near τ, the variance of RMST(OS) increases markedly. Small, random fluctuations in the KM curve at late times—where few patients remain at risk—can lead to large changes in RMST(OS).
    - In settings with immature OS follow-up, the tail of the Kaplan–Meier curve is estimated from very few patients and is dominated by censoring rather than events. Consequently, RMST(OS) increasingly reflects uncertain extrapolation of tail behaviour rather than observed survival experience.
    - Median overall survival is an event-driven, locally defined measure corresponding to the time at which the survival function reaches 50%. It

depends only on the behaviour of the survival curve around the median and does not rely on assumptions about survival beyond that point.

- Once the median OS is observed, additional follow-up does not affect its estimation. Late censoring and instability in the survival tail have no impact, making median-based estimates structurally more stable than RMST when OS data are incomplete.

2. Truncation time sensitivity of RMST-based differences

   - The difference between RMST(OS) and RMST(PFS) is intrinsically sensitive to the choice of truncation time τ. Because $\tau$is often determined by administrative follow-up rather than clinical relevance, small changes in τcan materially alter the magnitude—and potentially the direction—of the estimated difference.

   - This sensitivity is asymmetric, as RMST(PFS) is usually far less affected by τdue to earlier event accrual and more mature data. As a result, RMST-based estimates of post-progression survival can be unstable when OS follow-up is limited.

   - In contrast, median OS minus median PFS does not depend on truncation assumptions and remains invariant to follow-up length once both medians are reached, providing a more interpretable and robust summary in the presence of heterogeneous or incomplete follow-up.

3. Confounding effect of subsequent therapies on RMST

   - Because RMST averages overall survival over the entire follow-up, RMST can be heavily influenced by late survival gains from post protocol or later line therapies, making it more sensitive to differences in treatment availability, sequencing, or effectiveness across trials.

   - In comparison, median OS is determined around the point when half the patients have had events, so it largely reflects the early post-progression interval and is less affected by late survival from salvage therapies — making it more robust to confounding from subsequent treatments.

4. Asymmetric impact of follow-up duration and censoring on RMST in cross-trial OS comparisons

- In cross-trial comparisons, restricted mean survival time for overall survival (RMST(OS)) is intrinsically sensitive to differences in maximum follow-up duration. Trials with longer observation accumulate more area under the survival curve, whereas trials with shorter follow-up systematically underestimate RMST(OS), even when underlying survival patterns are similar.
- Even when a common truncation time is applied, RMST(OS) estimates can remain unstable because the amount and quality of information near the truncation point vary across studies. As follow-up diverges, RMST increasingly depends on sparse, heavily censored tail data, causing the difference between RMST(OS) and RMST(PFS) to reflect trial design and censoring patterns rather than true post-progression survival, whereas median-based summaries remain stable once the median is observed.

Additionally, the approach using median values has recently been accepted by the EAG in NICE TA1103 for estimating PPS from external sources.[15]

Despite company considers RMST an unsuitable method for deriving PPS, the model has been updated to allow PPS to be derived using RMST (Table 12 reports RMST (OS), RMST (PFS), and the difference RMST (OS) – RMST (PFS), alongside the median values used as the base case in STM3. Relative to PPS estimates derived from median values, using RMST results in lower PPS across all treatment arms. In addition, RMST produces a higher PPS for the O-B arm compared with bendamustine, which is inconsistent with clinical expectations.

Table 13 presents the PPS analysis based on RMST. A key limitation of this method is that it requires an estimate of PFS to be multiplied by the PPS/PFS ratio. RMST for PFS cannot be used for this purpose, as it is truncated by the inMIND follow-up period and therefore does not reflect average survival. Median PFS values remain usable; however, RMST (PFS) values are higher than the median (see Table 12). Combining median values with RMSTs produces results that are difficult to interpret and limits the ability to draw meaningful conclusions.

Table 14 shows incremental results of tafasitamab + R^2 vs R^2 of the scenario analysis using the RMST for the STM3 approach. The ICER versus R^2 increases from £27,101 to £29,033.

Table 12: PFS, OS and PPS in the GADOLIN trial using the RMST

Trial/Study	Treatment	Median PFS (months)	Median OS (months)	Median PPS (months)	Ratio Median PPS / Median PFS	RMS PFS (months)	RMS OS (months)	RMS PPS (months)	Ratio RMS PPS / RMS PFS
GADOLIN	O-Benda	24.1	92	67.9	2.8	35.38	69.93	34.55	0.98
	Benda	13.7	60.3	46.6	3.4	23.07	60.23	37.16	1.61
HMRN	R-Chemo	35.1	99.8	64.7	not used	84.68	108.28	23.6	not used

Key: HMRN, Haematological Malignancy Research Network; O-benda, obinutuzumab + bendamustine; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; R^2, rituximab + lenalidomide; RMS, restricted mean survival.

Table 13: PPS values used in each scenario using the RMST

Approach	Treatment	PPS (months) – Median values	PPS (months) – RMST	Notes
HMRN median values (non-rituximab refractory)	Tafasitamab + R^2	64.7	23.6	
	R^2	64.7	23.6	
GADOLIN median values (rituximab refractory)	Tafasitamab + R^2	67.9	34.55	
	R^2	46.6	37.16	

Approach	Treatment	PPS (months) – Median values	PPS (months) – RMST	Notes
Weighted approach	Tafasitamab + R^2	66.7	25.8	41%*(22.4*1.29) + 59%*23.6
	R^2	55.9	21.3	41%*(13.9*1.29) + 59%*23.6
Key: HMRN, Haematological Malignancy Research Network; PPS, post-progression survival; R², rituximab with lenalidomide; RMST, restricted mean survival time.				

Table 14. Scenario analysis using the RMST (Tafasitamab + R2 vs R^2)

Scenario Name	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Difference to base case	% Difference to base case
STM3	[redacted]	[redacted]	[redacted]	£27,101		
STM3 using RMST	[redacted]	[redacted]	[redacted]	£29,033	£1,932	7.1%
Key: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year; R², rituximab with lenalidomide; RMST, restricted mean survival time.						

d) Considering the evidence from the HMRN database and the GADOLIN trial, please discuss why a post-progression survival benefit was observed in the GADOLIN trial but not in the HMRN dataset. In your response, make specific reference to the characteristics of the populations enrolled in each dataset, as well as the mechanisms of action of the treatment regimens under consideration.

The relationship between PFS and OS is complicated in FL. Two key factors have a major impact on this relationship but both are closely correlated:

1. The natural disease course with some patients experiencing a slow growing disease trajectory and unlikely to die soon after relapse and others experiencing a faster growing disease trajectory and likely to die early post relapse.

2. Treatment response with prolonged disease control may typically result in a lower tumour burden at relapse and thus improved outcomes post relapse – this is more likely with different treatment classes across lines of therapy.

Both of these factors are in play in the HMRN database versus the GADOLIN trial. The HMRN dataset reflects a patient group who are generally experiencing a slower growing disease trajectory and responding well to R-chemotherapy based treatment, whereas the GADOLIN trial reflects those experiencing an aggressive disease trajectory and not responding well to R-chemotherapy based treatment. This is reflected in the characteristics of the populations enrolled in each dataset, particularly the 100% rituximab refractory, 94% refractory to last therapy and 76% double refractory status of the GADOLIN trial (O-B arm) versus 20% rituximab refractory and 24% refractory to last therapy status of the HMRN dataset as shown in **Table 15**.

Obinutuzumab is a second-generation anti-CD20 antibody providing enhanced B-cell depletion effect over rituximab. The use of obinutuzumab in rituximab refractory disease serves to provide prolonged disease control in a patient group experiencing faster growing disease and likely to die post relapse if they continued on the natural

disease course. Obinutuzumab re-established disease control and thus we not only see a direct PFS benefit but also an enhanced PPS benefit, as observed in the GADOLIN trial (and in the inMIND trial – see response to B2a).

Table 15: Comparability of patient characteristics between GADOLIN and HMRN data

Characteristics	**GADOLIN – 2L+**		**HMRN – 2L**		**HMRN – 3L**	
	O-bendamustine (N=164)	Bendamustine (N=)	[redacted]	[redacted]	[redacted]	[redacted]
Age, mean (SD)	Median (range): 63 (34−87)		[redacted]	[redacted]	[redacted]	[redacted]
Male, n (%)	91 (56)		[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS, n (%)	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]
Ann Arbor stage at diagnosis, n (%)						
Stage I or II	-	-	[redacted]	[redacted]	[redacted]	[redacted]
Stage III or IV	-	-	[redacted]	[redacted]	[redacted]	[redacted]
Missing	-	-	[redacted]	[redacted]	[redacted]	[redacted]
FL histology grade at study entry, n (%)						
1 or 2	130 (79)		[redacted]	[redacted]	[redacted]	[redacted]
3a	26 (16)		[redacted]	[redacted]	[redacted]	[redacted]
Other	8 (5)		[redacted]	[redacted]	[redacted]	[redacted]
Missing	-		[redacted]	[redacted]	[redacted]	[redacted]
FLIPI risk score at diagnosis, n (%)						
Low (0–1)	42 (26)		[redacted]	[redacted]	[redacted]	[redacted]
Intermediate	5 (31)		[redacted]	[redacted]	[redacted]	[redacted]
High (≥ 3)	64 (39)		[redacted]	[redacted]	[redacted]	[redacted]
POD24[a]	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]

Characteristics	GADOLIN – 2L+		HMRN – 2L		HMRN – 3L	
	O-bendamustine (N=164)	Bendamustine (N=)	[redacted]	[redacted]	[redacted]	[redacted]
Time since diagnosis, mean (SD)	4.3 years (range:0.3–32.1)		[redacted]	[redacted]	[redacted]	[redacted]
Prior lines of therapy, median (range)	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]
Prior lines of therapy, n (%)						
1	84 (51)		[redacted]	[redacted]	[redacted]	[redacted]
2	50 (31)		[redacted]	[redacted]	[redacted]	[redacted]
3	22 (13)		[redacted]	[redacted]	[redacted]	[redacted]
4	4 (2)		[redacted]	[redacted]	[redacted]	[redacted]
≥5	4 (2)		[redacted]	[redacted]	[redacted]	[redacted]
Refractory to rituximab, n (%)	164 (100)		[redacted]	[redacted]	[redacted]	[redacted]
Refractory to last prior regimen, n (%)	154 (94)		[redacted]	[redacted]	[redacted]	[redacted]
Double refractory, n (%)	147 (76)		[redacted]	[redacted]	[redacted]	[redacted]

Key: 2L, second-line; 2L+, second-line or later; 3L, third-line; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; NR, not reported; O, obinutuzumab; PS, Performance Status; R-CHOP, rituximab + cyclophosphamide + doxorubicin + vincristine + prednisolone; R-CVP, rituximab + cyclophosphamide + vincristine + prednisolone; SD, standard deviation.
Notes: [a]In the HMRN database, a patient is considered as POD24 if they have had documented progression within 24 months of the start of the first-line of systemic therapy (1L) - POD24 is also estimated for patients that have had documented progression within 24 months of the start of the second-line (2L) and third-line (3L) of systemic therapy.

B3. Priority question: The company's base case analysis predicts a post-progression survival (PPS) advantage of [redacted] life years, whereas the company's preferred parameterisation of the state-transition model (STM 3) predicts a PPS advantage of [redacted] life years. Please justify this discrepancy.

Due to the immaturity of the survival data, alternative approaches to survival extrapolation may result in different estimates of PPS. The base case PSM approach makes full use of the inMIND data and provides survival extrapolations that align with clinical expectations and is the company's preferred approach to support decision making.

As outlined in response to CQ B2 Table 11, tafasitamab + R^2 provides a PPS benefit when compared to R^2. In the company's base case, a PSM is used where the benefit in the PPS health state is estimated as the difference between life years in progressed disease, derived by subtracting PFS from OS extrapolations. As described in the Evidence Submission Section 3.3.3.1.3, the state transition model (STM 3) explicitly models the PPS benefit (i.e. treatment-specific PPS rates) based on proportion of patients that are rituximab refractory from inMIND as rituximab refractory FL often behaves more aggressively and responds less well to other antibody-based regimens, which results in a poorer OS prognosis. These differences in the structural assumptions can lead to differences in the progressed life years.

While the STM life years in the progressed disease health state in each treatment are not sensitive to the curve choice for PFS, the PSM life years in the progressed health state depend on the curve choice for the PFS as the health state occupancy in the progressed disease is derived as OS minus PFS. Therefore, changes to the PFS curves will alter the life years in the progressed disease state. For example, using separately fitted curves (as discussed in CQ B7b), will lead to a [redacted] benefit in the PD state.

In the base case PSM, the [redacted] life year benefit on the progressed disease health state represents a 1.91% increment compared to R^2 (1.49% increase compared to R^2 total life years). For example, using separately fitted curves results in [redacted] incremental life years – 4.96% increment compared to R^2 (3.66% increase compared to R^2 total life years). Based on the duration of FU in inMIND, this could be considered a conservative approach of calculating total LYs according to available

clinical validation. On the other hand, the STM3 approach results in [redacted] additional life years in the progressed state, which represents a 9.79% increment (7.26% increase compared to R^2 total life years). Although progressed disease life years are around 4 times lower in the base case PSM than in STM3, the PPS benefit estimated with the STM remains reasonable given the clinical benefit seen in patients with early progression on prior treatment, and the increment relative to R^2 total life years (7.26%) is within a plausible range. The two STMs that incorporate a PPS benefit led to lower ICERs than the PSM (reductions of 17.1% to 37.4%), while use of separately fitted curves (as discussed in CQ B7b) led to a [redacted] benefit in the PD state. Therefore, the current base case analysis is potentially conservative with regards to PPS.

Therefore, the company believes that the differences in life years are within the range of plausible benefit in PPS. Additionally, the company is aware of these differences and selected the most conservative approach within the plausible approaches (i.e. the company preferred the PSM over the STM3).

Extrapolation of survival data

B4. Priority question: The company uses jointly fitted parametric AFT models (with shared shape/scale parameters) for extrapolation of PFS and OS.

a) **Please provide further clarification on the rationale for this approach, given that independent fitting is typically preferred unless identical shape parameters are strongly justified.**

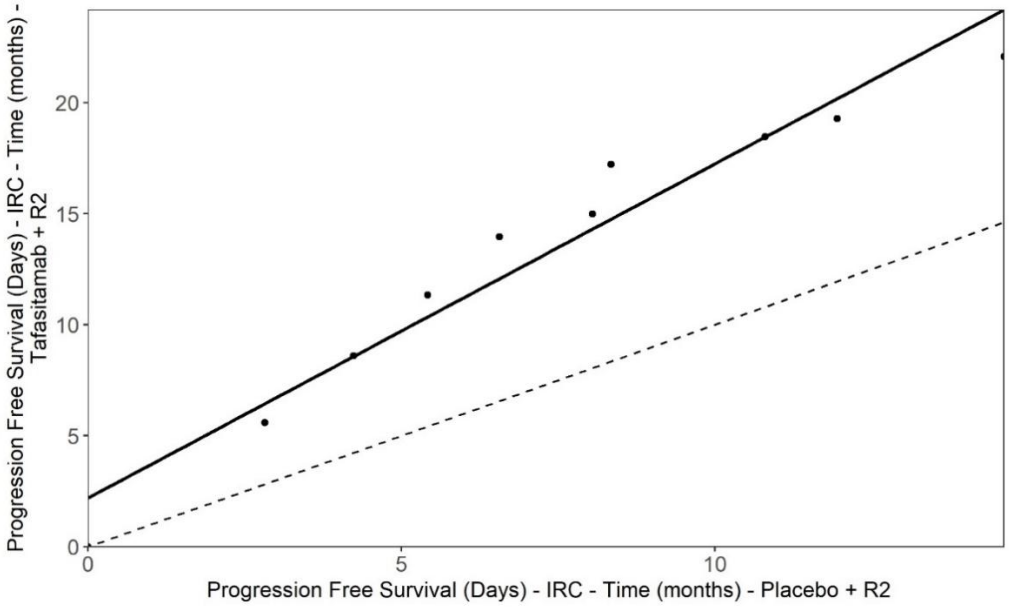
Jointly fitted models imply that both arms share the same underlying shape of the hazard function. The difference between arms is captured by one parameter that results in: a constant multiplier to the hazards of one arm (HR) or an acceleration factor (time ratio) in an accelerated failure time (AFT) framework.

Where one HR is applied to the entire modelled period, the proportional hazards assumption must be made – that is, the treatment effect is proportional over time and the survival curves fitted to each treatment group have a similar shape. The approach can be used within proportional hazards models such as the exponential, Gompertz or Gamma. On the other hand, models such as log-logistic and Log-

normal models are accelerated failure time models and do not produce a single HR, and thus the proportional hazards assumption does not hold with these models. When a treatment group is used as a covariate in these models, the treatment effect is measured as an 'acceleration factor' rather than a HR. Weibull and generalised gamma are accelerated failure time models that in special cases can be simplified to PH models: the Weibull curve can be simplified to an exponential and the generalised gamma to a gamma.

As described in NICE TSD 14, "generally, when patient-level data are available, it is unnecessary to rely upon the proportional hazards assumption and apply a proportional hazards modelling approach – the assumption should be tested which will indicate whether it may be preferable to separately fit parametric models to each treatment arm, or to allow for time-varying hazard ratios". The company tested the PH assumption and concluded it was not appropriate to use jointly fitted curves for PFS IRC (see Appendix L2 Figures 21 and 22). The accelerated time factor assumption was also tested in Appendix L2 Figure 23 through the quantile–quantile plot. The quantile–quantile plots in the x axis the empirical quantiles of survival times in the baseline group (R^2) and in the y axis the corresponding empirical quantiles of survival times in the comparison group (tafasitamab + R^2). If the points lie in a straight line, the accelerated failure time assumption is seemingly not violated. As seen in Appendix L2 Figure 23 (Figure 2 in the CQ), the points lie on a straight line and therefore, AFT models were considered appropriate to model PFS extrapolations beyond the clinical data.

Figure 2: Quantile–quantile plot (progression-free survival, independent review committee [PFS IRC]) – tafasitamab + R^2 versus R^2



Key: IRC, independent review committee; R^2, lenalidomide with rituximab.
Notes: Dotted black line indicates reference line (acceleration factor of 1).

Additionally, NICE TSD 14 indicates, “While fitting separate parametric models to individual treatment arms may be justified, it is important to note that fitting different types of parametric model to different treatment arms would require substantial justification, as different models allow very different shaped distributions. Hence if the proportional hazards assumption does not seem appropriate it is likely to be most sensible to fit separate parametric models of the same type, allowing a two-dimensional treatment effect on both the shape and scale parameters of the parametric distribution”. Therefore, in response to CQ B7b, independently fitted models for PFS using the same parametric model were also explored.

Tafasitamab + R^2 provides clinically meaningful improvements in both OS and PFS, along with statistically significant improvements in several supportive clinical outcomes. Hence it is important that the survival benefits observed in inMIND for tafasitamab + R^2 are reflected in the modelled extrapolations. As described in CQ B4b, for OS, the only separately fitted models for which the hazard function was always lower for tafasitamab + R^2 (compared to R^2) are the exponential (for which

the independent and jointly fitted models are identical) and Log-normal. However, both result in implausible survival estimates at 20 and 30 years for tafasitamab + R^2.

For PFS, both external evidence and clinical input suggested that the long-term hazard function would be decreasing; of the separately fitted models the Log-normal and log-logistic were the only models to satisfy this property in both arms (see Figure 30 in Appendix L.2). However, as described in CQ B7b, only the log-logistic provided plausible extrapolations.

b) Please outline the assumptions and implications associated with jointly fitted and independently fitted models.

The assumptions and implications associated with jointly fitted and independently fitted models are described in CQ B4a. CQ B7a outlines the potential inconsistencies associated with using separate independent curves to model PFS while using joint curves for OS. CQ B7b describes the clinical plausibility of using independently fitted models for the PFS assessment.

Appendix L.2.3 describes the OS assessment. As seen in Appendix L.2.3 Figure 45, using separately fitted OS results in crossing hazards for all the parametric curves except for exponential and Log-normal. Both curves result in implausible survival estimates at 20 and 30 years for tafasitamab + R^2: for the exponential the model results in 43.3% at 20 years and 28.5% at 30 years; for the Log-normal the model results in 56.4% at 20 years and 47.7% at 30 years (unadjusted by background mortality). As discussed in Appendix L.2.3, clinicians expected that approximately 60% of patients will remain alive at 10 years, and between 15% and 25% at 20 years for the R^2 arm, with moderately higher survival for the tafasitamab + R^2 arm at 10 and 20 years.

B5. Priority question: In CS section 3.3.3.1.1, justification for the OS extrapolations adopted in the model is provided by comparing landmark OS predicted by the model with data from the GADOLIN and AUGMENT.

a) **Please comment on the comparability of these trial populations to inMIND and their relevance to the current decision problem.**

Neither of the trial populations of GADOLIN or AUGMENT are directly comparable to the inMIND trial population. However, in the absence of any more comparable longer-term datasets, they are both used alongside RWE from the HMRN and clinical expert opinion to validate the OS extrapolations.

The major differences between trial populations are related to eligibility criteria regarding rituximab refractory status which is an established prognostic factor.[16] The GADOLIN trial only enrolled patients with rituximab refractory disease whereas the AUGMENT trial only enrolled patients with non-rituximab refractory disease and the inMIND trial enrolled a mixed patient population with regard to refractory status. On this characteristic alone and in very naïve terms, we would therefore expect patients enrolled to GADOLIN to have the shortest survival, patients from the AUGMENT trial to have the longest survival and patients from the inMIND trial to have survival that sits somewhere between these survival times. This is what is observed when comparing OS landmarks, as presented in Table 24 of the company submission.

A more detailed overview of the baseline characteristics of the inMIND and GADOLIN trial populations of the intervention arms, as presented in Table 16, show that other differences include:

- A higher proportion of patients with FL histology Grade 3 disease, representing a more aggressive tumour phenotype in the inMIND trial
- A higher proportion of patients with FLIPI risk score >3, representing high risk disease in the inMIND trial
- A longer time since diagnosis in the inMIND trial – this characteristic is not directly related to poorer prognosis and is likely to be an artefact of the broader patient population than the rituximab refractory patients enrolled to GADOLIN

Table 16. inMIND and GADOLIN baseline characteristics

Characteristic	Tafasitamab + R^2	O-B (FL)	O-B (ITT)
	(N = 273)	(N = 164)	(N = 194)
Median age, years	64.0	63.0	63.0
Age < 63 years	41%	50%	NR
Male	55%	56%	57%
ECOG PS			
0	66%	NR	95%
1	31%	NR	
2	3%	NR	5%
Ann Arbor stage			
Stage I	4%	NR	NR
Stage II	15%	NR	NR
Stage III	26%	NR	NR
Stage IV	55%	NR	NR
FL histology grade			
1 or 2	74%	79%	82%
3a	25%	16%	16%
Other	1%	5%	2%
FLIPI risk score			
Low (0–1)	21%	27%	28%
Intermediate	29%	32%	32%
High (≥ 3)	50%	41%	40%
B symptoms present	23%	NR	
Time since diagnosis (years), mean	6.7	4.3	4.2
Prior lines of therapy			
1	54%	51%	47%
2	24%	30%	32%
≥ 3	22%	19%	21%
Refractory to rituximab	41%	100%	100%
Refractory to last prior regimen	41%	94%	92%

Key: FL, follicular lymphoma; FLIPI, follicular lymphoma international prognostic index; ITT, intention-to-treat; NR, not reported; O-B, obinutuzumab + bendamustine; R^2, rituximab + lenalidomide.

A more detailed overview of the baseline characteristics of the inMIND and AUGMENT trial populations of the R^2 treatment arm, as presented in Table 17, show that other differences include:

- A higher proportion of patients at least 70 years of age, representing an older patient population in the inMIND trial

- A higher proportion of patients with Ann Arbor Stage III/IV, representing advanced stage disease in the inMIND trial
- A higher proportion of patients with FL histology Grade 3 disease, representing a more aggressive tumour phenotype in the inMIND trial
- A higher proportion of patients with FLIPI risk score >3, representing high risk disease in the inMIND trial
- A higher proportion of patients with disease refractory to last prior therapy, representing poorer prognosis in the inMIND trial
- A higher proportion of patients with B symptoms present and elevated LDH, representing more aggressive or metabolically active disease in the inMIND trial
- A higher proportion of patients with high tumour burden in the inMIND trial

As noted in section 2.13.2.1 of the Evidence Submission, " *the outcomes of the R2 arm of inMIND differ from outcomes of the R2 arm of AUGMENT – the pivotal trial for R2 that informed its NICE TA (TA627).14 This is due to marked differences in the baseline prognosis of enrolled patients, with the inMIND trial population representing a patient cohort with a much worse prognosis than the AUGMENT populatio**n".***

Table 17. inMIND and AUGMENT baseline characteristics

Characteristic	**inMIND R^2**	**AUGMENT R^2**
	(N = 275)	**(N = 147)**
Age ≥ 70 years	36%	23%
Male	55%	42%
ECOG PS		
0	70%	67%
1 or 2	30%	33%
Ann Arbor stage III/IV	82%	37%
FL histology grade		
1 or 2	74%	85%
3a	26%	15%
FLIPI high risk	55%	37%
Refractory to anti-CD20	42%	0%
Refractory to last prior regimen	35%	18%
B symptoms present	24%	8%

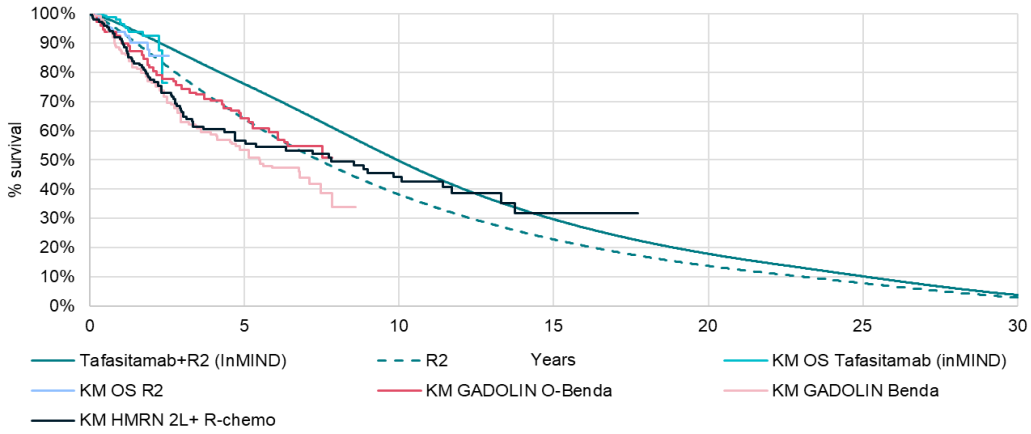
LDH elevated	33%	23%
High tumour burden per GELF	84%	52%
Key: ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; GELF, Groupe d'Etude des Lymphomes Folliculaires; LDH, lactate dehydrogenase; R^2, rituximab + lenalidomide.		

b) Please repeat this validation process using HMRN as the external data source. This should ideally attempt to reflect the line of therapy rather than considering mixed line of therapy populations.

Section 3.3.1.1 of the Company Submission compares the survival differences predicted by the inMIND (Tafasitamab + R^2 vs R^2) extrapolations with those observed in the GADOLIN (O-B vs B) and AUGMENT (R^2 vs R monotherapy) trials at specific timepoints. However, a similar comparison using the HMRN data is not possible because the data only includes information on one treatment arm (R-chemotherapy).

Figure 3 presents a naïve comparison between the inMIND OS extrapolations and 2L+ R-chemotherapy outcomes from HMRN. In this comparison, the KM curve for R-chemotherapy has not been adjusted for prognostic factors or treatment effect modifiers. As a result, the magnitude of the survival estimates cannot be meaningfully compared to real world evidence (RWE). As noted in Section 2.10.5 of the Company Submission, the MAICs were unable to account for most prognostic factors or treatment effect modifiers considered critical by clinicians. This limitation reduces the face validity of the findings.

Figure 3. inMIND OS extrapolations naïve comparison versus 2L+ R-chemotherapy from HRMN



Key: 2L+, second-line plus; HRMN, Haematological Malignancy Research Network; KM, Kaplan–Meier; O-Benda, obinutuzumab with bendamustine; OS, overall survival; R2, lenalidomide with rituximab

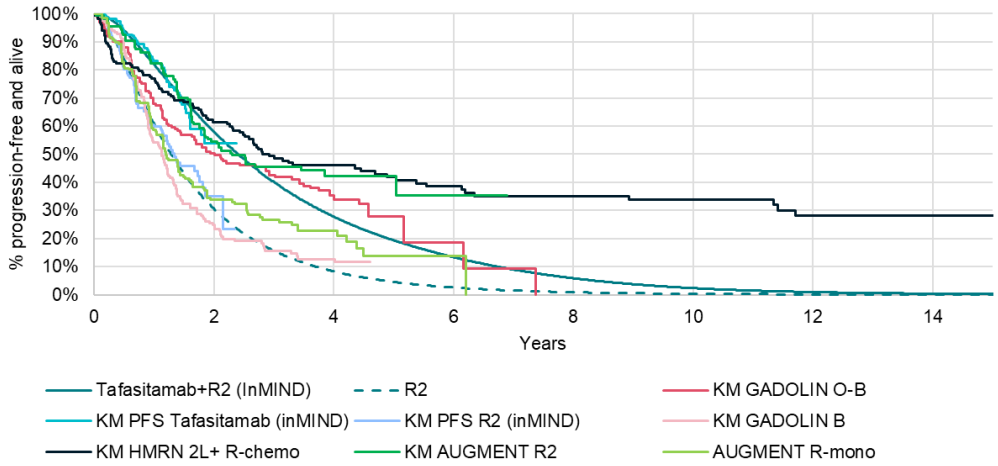
c) Please also complete this validation process for PFS using all relevant sources.

Figure 4 shows the PFS KM curves from GADOLIN, AUGMENT, and HMRN, alongside the inMIND PFS extrapolations. As outlined in CQ B5a, the R² arm from AUGMENT represents a population having a better prognosis than those patients in inMIND, which may explain why the inMIND R² extrapolations are lower than the AUGMENT R² KM curve.

After trial follow-up, the extrapolated PFS for tafasitamab + R² was slightly below the OB PFS KM from GADOLIN. While this naïve comparison cannot support firm conclusions, the magnitude of tafasitamab + R² PFS estimates is broadly consistent with the OB arm. Although the generalised gamma model provided the best fit for PFS, it may underestimate survival. Clinicians involved in validation expected 5year survival for tafasitamab + R² to be between 20–30%, but the model predicts 19.5%.

The unadjusted KM curve for 2L+ R-chemo lacks face validity, as R² has been shown to be more effective than R-chemo (NICE TA627[8]). As noted in CQ B5b, MAICs could not adjust for most prognostic factors or treatment effect modifiers identified as critical by clinicians. Therefore, the findings lack face validity, and comparison with HMRN was not considered appropriate.

Figure 4. inMIND PFS extrapolations naïve comparison versus 2L+ R-chemotherapy from HRMN, GADOLIN and AUGMENT



Key: 2L+, second-line plus; HRMN, Haematological Malignancy Research Network; KM, Kaplan–Meier; R2, lenalidomide with rituximab

B6. Please justify why the efficacy of non-R^2 comparators was modelled using a hazard ratio, given that this approach assumes proportional hazards, which has been explicitly rejected by the company's analysis of Schoenfeld plots. Please justify why the R2 curve from inMIND was not used instead.

The model was originally designed to derive the relative efficacy of non-trial comparators from the MAIC hazard ratio versus tafasitamab + R^2, and not versus R^2. To simplify the calculations, to assume the same efficacy as R^2 for the non-trial comparators (R-chemotherapies), the model used the HR of tafasitamab + R^2 versus R^2 applied to those comparators.

The company acknowledge the limitations with this approach in the Evidence Submission Section 3.3.2.2 and 3.3.3.2. However, the company agrees with the EAG that the approach might not be the optimal approach based on the Schoenfeld plots. Therefore, the company has updated the model to assume the same survival curves as the R^2 arm, rather than applying the observed hazard ratio of tafasitamab + R^2 versus R^2 from the inMIND trial. As previously described in the company submission (Section 3.3.2.2 and 3.3.3.2), the assumption that R-chemotherapy regimens have the same efficacy as R2 can be considered conservative.

Table 18, Table 19 and Table 20 provide the incremental results of tafasitamab + R^2 vs R-chemotherapy regimens of the scenario the analysis using the updated efficacy assumptions. The ICER increases approximately 13% versus the R-chemotherapy regimens.

Table 18. Scenario analysis using the updated efficacy assumptions (Tafasitamab + R^2 vs R-Benda)

Scenario Name	Increment-al Costs	Increment-al LYs	Increment-al QALYs	ICER	Differ-ence to base case	% Differ-ence to base case
Base case	[redacted]	[redacted]	[redacted]	£29,029		
Updated efficacy assumpt-ions	[redacted]	[redacted]	[redacted]	£32,906	£3,877	13.4%

Key: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year; R-Benda, bendamustine plus rituximab.

Table 19. Scenario analysis using the updated efficacy assumptions (Tafasitamab + R^2 vs R-CVP)

Scenario Name	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Difference to base case	% Difference to base case
Base case	[redacted]	[redacted]	[redacted]	£28,723		
Updated efficacy assumptions	[redacted]	[redacted]	[redacted]	£32,567	£3,844	13.4%

Key: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year; R-CVP, rituximab plus cyclophosphamide, vincristine, and prednisone.

Table 20. Scenario analysis using the updated efficacy assumptions (Tafasitamab + R^2 vs R-CHOP)

Scenario Name	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Difference to base case	% Difference to base case
Base case	[redacted]	[redacted]	[redacted]	£30,982		
Updated efficacy assumptions	[redacted]	[redacted]	[redacted]	£35,070	£4,088	13.2%

Key: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

B7. In Appendix L (page 121) the company outlines the motivation for using a jointly fitted PFS, which appears to be largely motivated by the desire to maintain consistency with the approach for OS.

a) Please outline the potential drawbacks or inconsistencies associated with using separate independent curves to model PFS while using joint curves for OS.

Using separate independent curves to model PFS while using joint curves for OS can lead to implausible relationships between PFS and OS curves (e.g. OS hazards improving while PFS hazard worsens, or vice versa) and there is a disconnect between the timing and magnitude of treatment effects across outcomes. Joint OS models implicitly assume shared treatment effects across arms, whereas

independently fitted PFS curves do not, potentially leading to inconsistent disease progression patterns caused by different hazard dynamics per arm. This is reflected in a mismatch of the PFS and OS hazards evolution (e.g. declining PFS hazard but rising OS hazard). As OS shares events with PFS, it is important that these two endpoints are analysed in a consistent manner.

b) Putting aside any consistency issues, please explore which approach to modelling (separate or joint) is most appropriate for PFS.

The jointly fitted model used in the base case meets the clinical expectations as described in Appendix L.2.1.

Table 21 and Table 22 display the inMIND PFS extrapolations using independently fitted curves. For tafasitamab + R^2, two parametric models result in extrapolations partially aligned with clinical expectation. At 5 years the exponential predicted 33.5% and the log-logistic 17.5% (compared to 20-30% from expert opinion). At 10 years the exponential predicted 11.2% and the log-logistic 5.2% (compared to 5% from expert opinion).

For R^2, at 3 years the exponential predicted 23.6% and the log-logistic 18.7% (compared to 15% from expert opinion). At 5 years the exponential predicted 9.0% and the log-logistic 8.7% (compared to 5-10% from expert opinion). As an independently fitted exponential model is the same as a jointly fitted exponential model, the log-logistic is considered further. It is noted that the survival estimates from the independently fitted and jointly fitted log-logistic models are very similar; with absolute differences less than 3.3% and 1.3% over time for tafasitamab + R^2 and R^2, respectively.

Table 21. Tafasitamab + R^2 independently fitted PFS IRC extrapolations

	Expon-ential	Gamma	General-ised gamma	Gomp-ertz	Log-logistic	Log-normal	Weibull
1 years	80.4%	82.6%	83.2%	84.1%	82.6%	81.6%	83.1%
2 years	64.6%	55.5%	53.5%	51.5%	55.5%	60.7%	53.7%
3 years	51.9%	33.8%	27.4%	12.8%	36.3%	46.1%	28.3%
5 years	33.5%	10.8%	3.7%	0.0%	17.5%	28.8%	4.6%
7 years	21.6%	3.1%	0.2%	0.0%	9.9%	19.3%	0.4%
10 years	11.2%	0.4%	0.0%	0.0%	5.2%	11.7%	0.0%

Key: IRC, independent review committee; PFS, progression-free survival; R^2, lenalidomide with rituximab.

Table 22. R^2 independently fitted PFS IRC extrapolations

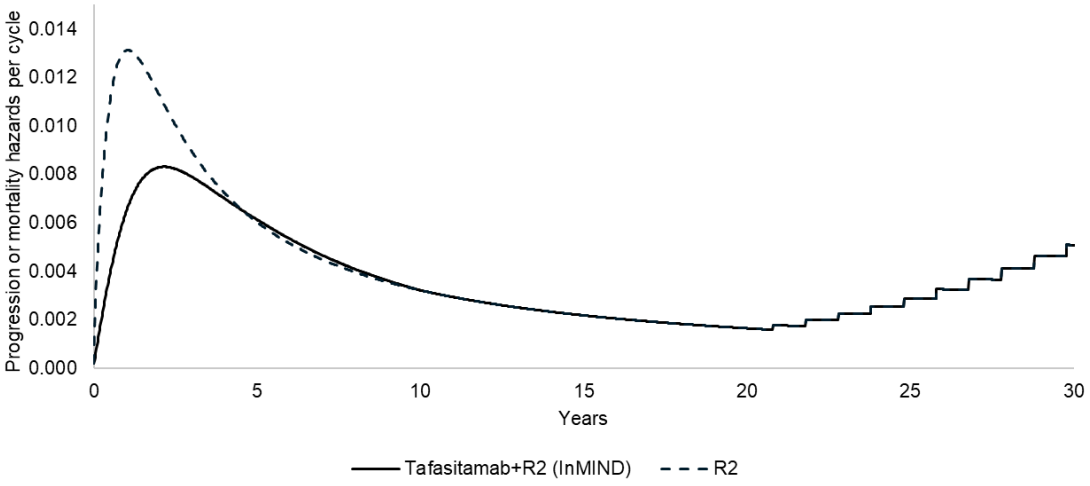
	Exponential	Gamma	Generalised gamma	Gompertz	Log-logistic	Log-normal	Weibull
1 years	61.8%	62.0%	60.3%	63.2%	60.4%	60.4%	62.7%
2 years	38.1%	29.1%	34.8%	30.6%	31.6%	33.8%	28.9%
3 years	23.6%	12.4%	22.3%	9.8%	18.7%	20.7%	11.1%
5 years	9.0%	2.0%	11.1%	0.1%	8.7%	9.4%	1.1%
7 years	3.4%	0.3%	6.5%	0.0%	5.1%	4.9%	0.1%
10 years	0.8%	0.0%	3.4%	0.0%	2.8%	2.3%	0.0%

Key: IRC, independent review committee; PFS, progression-free survival; R^2, lenalidomide with rituximab.

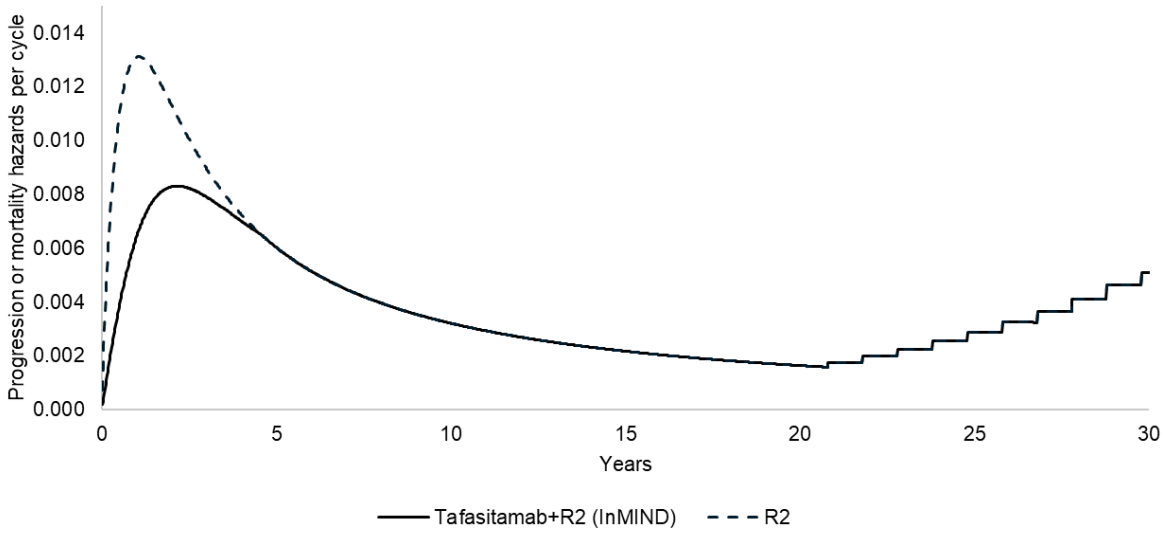
Figure 5 presents tafasitamab + R^2 and R^2 PFS hazards using log-logistic. Figure 5a shows the unadjusted hazards. Figure 5b includes a cap to prevent tafasitamab + R^2 hazards being higher than R^2 hazards. The hazards based on the log-logistic curve are increasing during the first years and decreasing over the time horizon until the background mortality starts to affect the hazards. This pattern is aligned with the feedback provided during the clinical validation and with the R-chemotherapies hazards from the HMRN database (see Appendix L.2.1 Figure 28). Although treatment waning is applied, the effect is not visible as the log-logistic curves result in a convergence of the hazards without having to apply a treatment waning effect in the model (see Figure 6). The PFS extrapolations after adjusting tafasitamab + R^2 hazards are presented in Figure 7.

Figure 5. Tafasitamab + R^2 and R^2 PFS hazards using log-logistic

a) Tafasitamab + R^2 hazards not capped

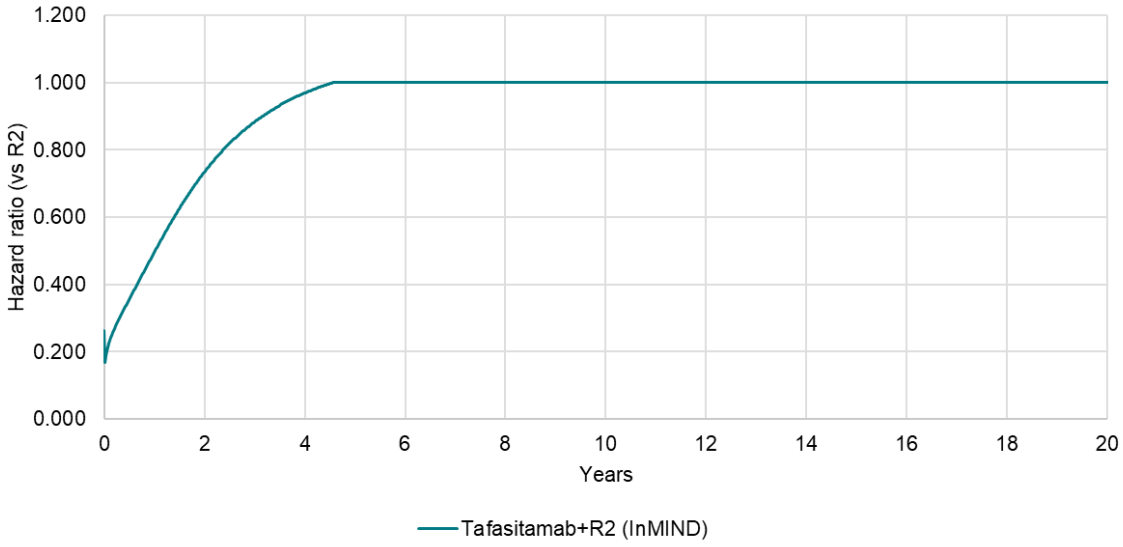


b) Tafasitamab + R^2 hazards capped to R^2 hazards



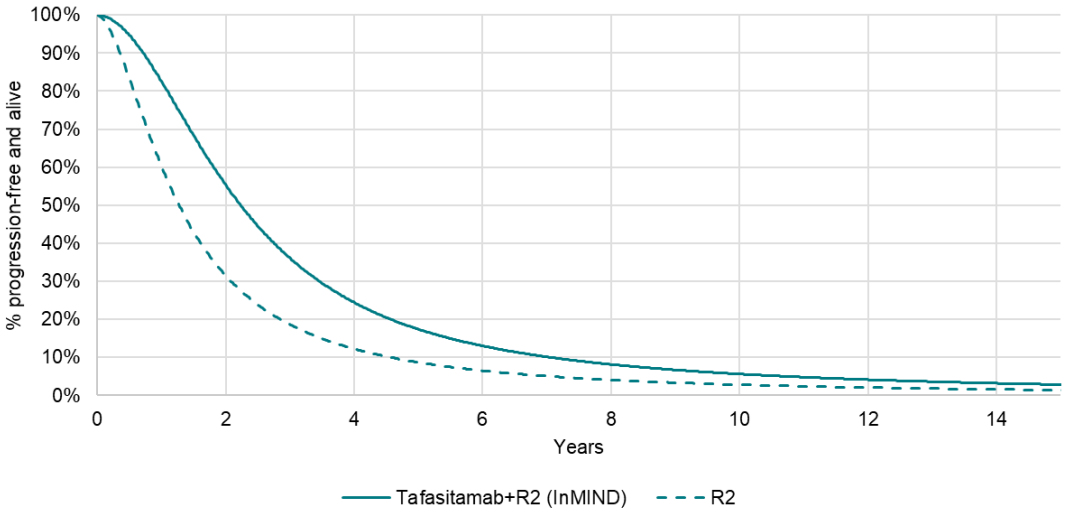
Key: PFS, progression-free survival; R^2, lenalidomide with rituximab.

Figure 6. Tafasitamab + R^2 versus R^2 PFS hazard ratio



Key: PFS, progression-free survival; R^2, lenalidomide with rituximab.

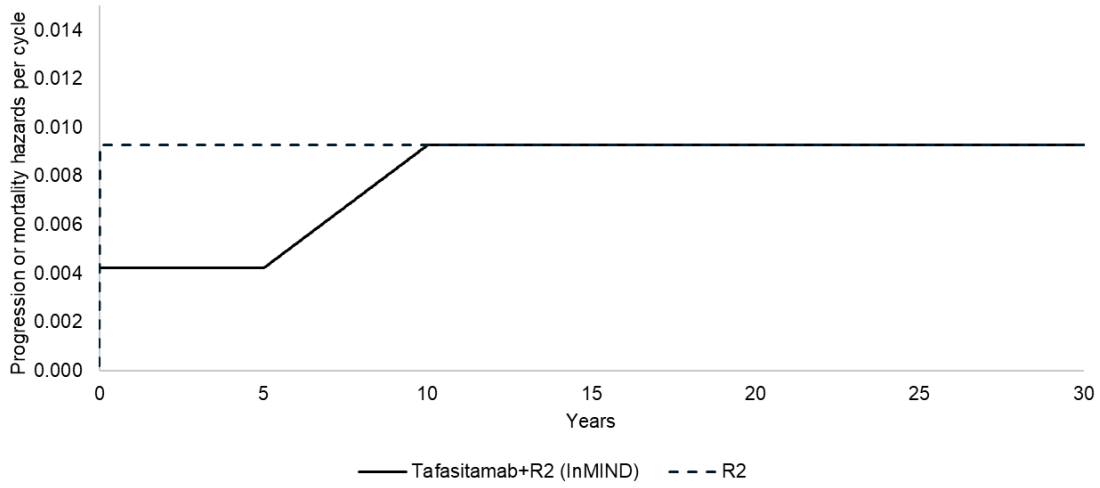
Figure 7. Tafasitamab + R^2 and R^2 PFS extrapolations using log-logistic



Key: PFS, progression-free survival; R^2, lenalidomide with rituximab.

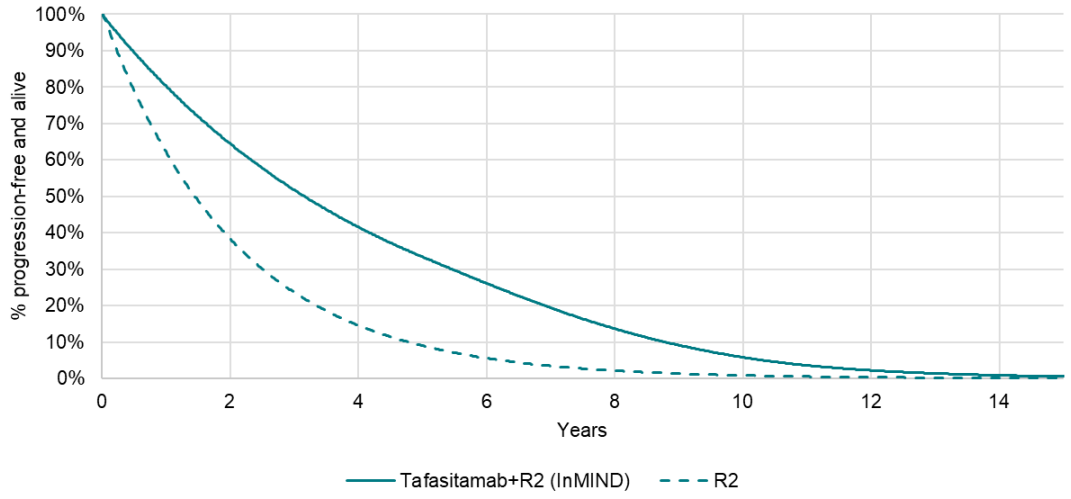
Figure 8 presents tafasitamab + R^2 and R^2 PFS hazards using an exponential curve. The hazards based on the exponential curve are constant across time, which is not aligned with the feedback provided during the clinical validation and with the R-chemotherapies hazards from the HMRN database (see Appendix L.2.1 Figure 28). The PFS extrapolations are presented in Figure 9.

Figure 8. Tafasitamab + R^2 and R^2 PFS hazards using exponential



Key: PFS, progression-free survival; R^2, lenalidomide with rituximab.

Figure 9. Tafasitamab + R^2 and R^2 PFS extrapolations using exponential



Key: PFS, progression-free survival; R^2, lenalidomide with rituximab.

Additionally, the exponential curve is the worst fitting curve in both arms and its more than 5 points from the best fitting curve. The log-logistic curve is within 5 points of the best fitting curve and within the 3 best fitting curves in both arms (see Table 23 and Table 24.

Table 23. Tafasitamab + R^2 AIC and BIC

Model	AIC	BIC	Rank AIC	Rank BIC
Exponential	592.210	595.820	7	7
Gamma	573.890	581.108	3	3
Gen. Gamma	575.095	585.923	4	5
Gompertz	576.486	583.705	5	4
Log-Logistic	573.405	580.624	2	2
Log-Normal	583.126	590.344	6	6
Weibull (AFT)	573.111	580.330	1	1

Key: AFT, accelerated failure time; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; R^2, lenalidomide with rituximab.

Table 24. R^2 AIC and BIC

Model	AIC	BIC	Rank AIC	Rank BIC
Exponential	936.944	940.561	7	6
Gamma	919.349	926.582	4	4
Gen. Gamma	914.483	925.333	2	3
Gompertz	933.536	940.769	6	7
Log-Logistic	916.374	923.608	3	2
Log-Normal	912.665	919.899	1	1
Weibull (AFT)	922.661	929.895	5	5

Key: AFT, accelerated failure time; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; R^2, lenalidomide with rituximab.

The jointly fitted generalised gamma curves are more aligned with clinical expectation than independently fitted log-logistic curves. In the tafasitamab + R^2 arm, at 5 years the jointly fitted generalised gamma predicts 19.5% survival, while the separately fitted log-logistic predicts 17.5% (compared to 20-30% from expert opinion). In the R^2 arm, the jointly fitted generalised gamma predicts 4.6% survival, while the separately fitted log-logistic 8.7% (compared 5% from expert opinion). Therefore, the company believes that the jointly fitted generalised gamma curves are more appropriate to model the long-term OS benefit and should be used for decision making. However, independently fitted log-logistic and the jointly fitted log-logistic curves (as described in the scenario analyses in Section 3.11 of the Evidence Submission) are presented in the scenario analysis for completeness (Table 25). The impact on the ICER is minimal, increasing to £33,391 (+2.2%) when using separately fitted log-logistics curves and decreasing to £32,174 (-1.5%) when using jointly fitted log-logistics curves.

Table 25. Scenario analysis using alternative extrapolations for PFS (Tafasitamab + R^2 vs R^2)

Scenario Name	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Difference to base case	% Difference to base case
Base case	[redacted]	[redacted]	[redacted]	£32,672		
Separately fitted log-logistic PFS curves	[redacted]	[redacted]	[redacted]	£33,391	£719	2.2%
Jointly fitted log-logistic PFS curves	[redacted]	[redacted]	[redacted]	£32,174	-£498	-1.5%

Key: ICER, incremental cost-effectiveness ratio; LY, life year; PFS, progression-free survival; QALY, quality-adjusted life year; R^2, lenalidomide with rituximab.

B8. Priority question: Please integrate the results of the MAIC requested in question A12 into scenario analysis?

As discussed in the limitations to the MAIC requested in A12, these analyses are not considered suitable for decision making, and as such have not been added to the economic model. As previously considered for the 2L+ and 3L+ population, the model conservatively assumes the same efficacy for the R-chemotherapy regimens and R2 in the 2L population.

Population

B9. Priority question: The executable model allows the separate consideration of the 3L+ population, but not the 2L-only group. Please provide a subgroup analysis of the 2L-only population.

Incyte has provided the requested 2L-only ICERs but emphasise that these results should be interpreted with caution and treated as exploratory rather than decision-relevant. The 2L-only subgroup is based on smaller patient numbers and fewer outcome events, leading to imprecise incremental QALY estimates, wide uncertainty,

and ICERs that are highly sensitive to survival extrapolation and subsequent-treatment assumptions

In contrast, the 2L+ population (including 3L+) aligns with the decision problem and expected NHS use and is supported by a larger, more stable evidence base, providing a more reliable assessment of cost-effectiveness. Accordingly, while 2L-only results are presented transparently in response to the committee's request, the 2L+ analysis should carry greater weight in informing the committee's conclusions.

The data below represent the 2L-only subgroup survival analysis from the inMIND study, including the OS, PFS IRC, and TTD endpoints. For OS and PFS, results are provided using both jointly fitted and separately fitted assessments. As previously described, the 2L-subgroup analysis was not pre-specified in the clinical trial SAP and was conducted solely to address the EAG Clarification Questions.

A detailed PFS and OS analysis including the log-cumulative hazards, QQ plots, Schoenfeld residuals, fit statistics, visual fit assessments, long-term extrapolations, survival landmarks, smoothed hazard plots and hazard extrapolations is provided in the Clarification questions Addendum.

Table 26: Progression-free Survival – Summary

Treatment	Subjects	Events	Censors	Median (months; 95% CI)	Restricted mean survival (months; SE)	Hazard Ratio (95% CI)
Placebo + R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tafasitamab + R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 10: Progression-free Survival - Kaplan-Meier

Table 27:Overall Survival - Summary

Treatment	Subjects	Events	Censors	Median (months; 95% CI)	Restricted mean survival (months; SE)	Hazard Ratio (95% CI)
Placebo + R2						
Tafasitamab + R2						

Figure 11: Overall Survival - Kaplan-Meier

Table 28: Time to treatment discontinuation - Summary

Treatment	Subjects	Events	Censors	Median (years; 95% CI)	Restricted mean survival (years; SE)	Hazard Ratio (95% CI)
Placebo + R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tafasitamab + R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 12: Time to treatment discontinuation - Kaplan-Meier

Following the survival estimates provided by clinicians for the 2L+ validation process, we identified the Weibull and gamma models as the most suitable for extrapolating 2L OS, while the generalised gamma, log-normal, and log-logistic models were selected as the most appropriate for extrapolating PFS. All models are based on the jointly fitted assessment.

Table 29 presents the scenario analysis for the 2L population, based on the most plausible parametric models. Across all scenarios, the ICERs are consistently around £50,000.

Table 29. 2L scenario analysis of tafasitamab + R^2 against R^2 using jointly fitted curves

Base case	Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER
OS: Weibull PFS: Generalised gamma	R^2	[redacted]	[redacted]	[redacted]				
	Tafasitamab+R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,581
OS: Weibull PFS: Log-normal	R^2	[redacted]	[redacted]	[redacted]				
	Tafasitamab+R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,635
OS: Weibull PFS: Log-logistic	R^2	[redacted]	[redacted]	[redacted]				
	Tafasitamab+R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,121
OS: Gamma PFS: Generalised gamma	R^2	[redacted]	[redacted]	[redacted]				
	Tafasitamab+R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£49,703
OS: Gamma PFS: Log-normal	R^2	[redacted]	[redacted]	[redacted]				
	Tafasitamab+R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£49,756
OS: Gamma	R^2	[redacted]	[redacted]	[redacted]				

PFS: Log-logistic	Tafasitamab+R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,228

HRQL

B10. Priority question: The EAG notes that the relatively high utilities observed in the inMIND trial and is concerned that this may reflect substantial attrition in the HRQL dataset.

a) **Please report the number of missing HRQL observations at each time point and describe how missingness was handled in the regression analysis (e.g. complete case analysis vs multiple imputation).**

Missingness of utility observations (derived from EQ-5D-5L questionnaire responses) by scheduled study visit, are provided in table 30 below for the FL FAS analysis set. Of note 30 of the 548 patients did not complete any EQ-5D-5L questionnaires throughout the study and hence contributed no utility observations.

Several intercurrent events were considered, after which visits were no longer considered scheduled and hence were omitted from the denominator of the missingness percentage:

I. Death – no subsequent regular visits or end of treatment visits were considered missing

II. Treatment discontinuation – no subsequent regular visits (i.e. Cycle 1, Day 1 [C1D1], C2D1, C3D1, ... C12D1) were considered missing, but an end of treatment visit was scheduled for the day the decision to cease treatment was made. Efficacy follow-up visits (i.e. Month 16 [M16], M18, M20, M24, M28) were also applicable depending on the reason for treatment discontinuation.

III. Efficacy follow-up visits were not scheduled if treatment discontinuation was due to disease progression, hence efficacy follow-up visits for patients who discontinued due to disease progression were not considered missing.

Table 30: EQ-5D-5L UK utility observation missingness by visit: FAS

Study visit	Tafasitamab + R²			Placebo + R²			Total		
	Observations, n (% of FAS)	Missing, n (%)	Observation not scheduled, n	Observations, n (% of FAS)	Missing, n (%)	Observation not scheduled, n	Observations, n (% of FAS)	Missing, n (%)	Observation not scheduled, n
BASELINE	253 (92)	22 (8)	0	250 (92)	22 (8)	0	503 (92)	44 (8)	0
CYCLE 2 DAY 1	226 (82)	40 (15)	9	229 (84)	41 (15)	2	455 (83)	81 (15)	11
CYCLE 3 DAY 1	222 (81)	42 (16)	11	229 (84)	34 (13)	9	451 (82)	76 (14)	20
CYCLE 4 DAY 1	214 (78)	46 (18)	15	207 (76)	49 (19)	16	421 (77)	95 (18)	31
CYCLE 5 DAY 1	210 (76)	41 (16)	24	204 (75)	39 (16)	29	414 (76)	80 (16)	53
CYCLE 6 DAY 1	205 (75)	44 (18)	26	198 (73)	35 (15)	39	403 (74)	79 (16)	65
CYCLE 7 DAY 1	201 (73)	44 (18)	30	177 (65)	41 (19)	54	378 (69)	85 (18)	84
CYCLE 8 DAY 1	183 (67)	50 (21)	42	174 (64)	33 (16)	65	357 (65)	83 (19)	107
CYCLE 9 DAY 1	181 (66)	45 (20)	49	156 (57)	42 (21)	74	337 (62)	87 (21)	123
CYCLE 10 DAY 1	165 (60)	56 (25)	54	141 (52)	46 (25)	85	306 (56)	102 (25)	139
CYCLE 11 DAY 1	145 (53)	71 (33)	59	132 (49)	45 (25)	95	277 (51)	116 (30)	154
CYCLE 12 DAY 1	135 (49)	72 (35)	68	127 (47)	45 (26)	100	262 (48)	117 (31)	168
END OF TREATMENT	176 (64)	90 (34)	9	177 (65)	84 (32)	11	353 (65)	174 (33)	20
FOLLOW-UP (MONTH 16)	43 (16)	159 (79)	73	25 (9)	138 (85)	109	68 (12)	297 (81)	182
FOLLOW-UP (MONTH 18)	39 (14)	161 (80)	75	34 (12)	131 (79)	107	73 (13)	292 (80)	182
FOLLOW-UP (MONTH 20)	23 (8)	177 (88)	75	19 (7)	142 (88)	111	42 (8)	319 (88)	186
FOLLOW-UP (MONTH 24)	15 (5)	183 (92)	77	14 (5)	147 (91)	111	29 (5)	330 (92)	188

Study visit	Tafasitamab + R²			Placebo + R²			Total		
	Observations, n (% of FAS)	Missing, n (%)	Observation not scheduled, n	Observations, n (% of FAS)	Missing, n (%)	Observation not scheduled, n	Observations, n (% of FAS)	Missing, n (%)	Observation not scheduled, n
FOLLOW-UP (MONTH 28)	2 (1)	196 (99)	77	3 (1)	158 (98)	111	5 (1)	354 (99)	188
All Scheduled Visits	2638 (63)	1539 (37)	-	2496 (66)	1272 (34)	-	5134 (65)	2811 (35)	-

Key: FAS, full analysis set; R², lenalidomide with rituximab.

A linear mixed model was used for the utility regression analyses, assuming utility observations were missing at random. No explicit imputation of the missing utility observations (by multiple imputation or otherwise) was performed, rather the linear mixed modelling method handled missing data implicitly under a missing at random (MAR) assumption.

Missing data was low (<5%) among covariates considered for inclusion in modelling (baseline utility, and baseline patient characteristics), as such a complete cases approach was used for missingness of covariate data. The analysis dataset used made the following restrictions:

- Patients without a baseline (C1D1) and at least one post-baseline utility observation were omitted (97 observations omitted for 15 unique patients)
- Patients with missing baseline characteristics data for included covariates (Race and BMI) were omitted (228 observations for 23 unique patients)

b) Please provide evidence that patients experiencing adverse events continued to contribute HRQL data.

Table 31 below shows the number of EQ-5D-5L questionnaire responses in the FL FAS population that occurred during a severe (grade >=3) adverse event. Approximately 42% of EQ-5D-5L questionnaire responses coincided with a severe adverse event. A response was deemed to coincide with a severe AE if the questionnaire evaluation date fell between the recorded start and end date of the adverse event. “Ongoing” adverse events end dates were imputed as the patients study end date, or where patients had not yet exited the study, the study data cut date ("2024-02-23").

Table 31: EQ-5D-5L questionnaire responses during severe, grade >=3 adverse events in FL FAS population

Questionnaire dimension	Total responses, n	Response during severe AE?	
		No, n	Yes, n
Mobility	5140	2969	2171
Self-care	5140	2969	2171

Questionnaire dimension	Total responses, n	Response during severe AE?	
		No, n	Yes, n
Unusual activities	5138	2968	2170
Pain/discomfort	5139	2970	2169
Anxiety/depression	5137	2968	2169
Visual analogue scale	5125	2958	2167

Key: AE, adverse event; FL, add details; FAS, full analysis set.

B11. Priority question: In the company's base case analysis, it is assumed that patients in the pre-progression health state have a quality of life equivalent to the general population. This is at odds with early statements made in the CS, which emphasise the burden on patients. Please comment on the clinical plausibility of the modelled pre-progression utility values.

Quality of life modelling is based on EQ-5D data collected in the inMIND trial and therefore is a simplified assessment of quality of life in a selected population. It is very common to see trial-based utilities that are higher than we might expect in the real-world population, particularly in a disease like FL where a lot of the burden is related to fear and uncertainty that are not adequately captured by the EQ-5D tool, but may also be positively impacted by enrolment to a trial.

In the FL space it is common to see trial-based utilities higher than not only the real-world population but actually of the general population, and clinical experts would relate this to the selected population nature of all trial populations. The approach where we therefore assume equivalent quality of life in the pre-progression state to the general population is aligned to previous technology appraisals, including TA627, where such an approach was deemed appropriate.[3]

In the scenario analyses in Section 3.11 of the Evidence Submission, lower utility values than those of the general population were tested using data from the GADOLIN and GO29781 trials. These alternative values had a minimal effect on the ICER.

B12. Due to the design of the inMIND trial, limited HRQL data were collected in patients following disease progression.

a) Please comment on the adequacy of the inMIND trial to reflect the HRQL in patients with progressed disease.

There were limited post-progression utility observations in the FL FAS population of the inMIND study. Only 108 EQ-5D-5L observations were observed post-progression compared with 5027 pre-progression observations. The EQ-5D-5L questionnaire visit schedule was the primary reason for the limited number of post-progression observations. EQ-5D-5L questionnaire visits were scheduled on Day 1 of each treatment cycle until treatment discontinuation or completion of the 12 x 28-day cycle treatment regimen. Patients who demonstrated radiologic or metabolic progression of disease per the Lugano criteria discontinued treatment. A single end of treatment visit was scheduled on the day of treatment discontinuation or treatment completion. EQ-5D-5L questionnaire follow-up visits were scheduled only for patients who did not discontinue treatment due to disease progression and continued until disease progression, initiation of new anti-cancer therapy, lost to follow-up, withdrawal of consent, or death. Only 191 patients in the FL FAS population progressed during the study, and not all had either an end of treatment or final follow-up EQ-5D-5L questionnaire visit, hence the relatively small number of post-progression utility observations. These post-progression EQ-5D-5L observations are also understood to have been taken soon after progression occurs.

Clinical expert feedback did note that the absolute progression-free utility estimate (0.842) was higher than expected for R/R FL patients in clinical practice but the utility reduction (-0.037) on progression is broadly in line with expectations. The clinical expert noted that HRQL decline in patients with R/R FL is less than what can be expected for newly diagnosed patients. No major step-change reductions are expected to occur as patients have already lived with and been treated for FL for an extended period of time. Patients generally continue to work and are “coping with the disease”. The HRQL change in patients with R/R FL is instead expected to be a gradual decline.

We note that given this clinical expert input, although the utility decrement estimated for progression (-0.037) was broadly in line with expectations, it potentially underestimates the true progression decrement as the post-progression utility observations were observed only shortly after progression had occurred and hence may not capture a continued “gradual decline” in HRQL experienced by patients post-progression. This is particularly pertinent given the known decline in HRQL preceding death for patients with cancer.[17, 18] Hence the benefit of delayed disease progression for tafasitamab + R^2 may not be fully captured in the economic evaluation

b) Please present an additional regression analysis considering HRQL by line of therapy.

The regression analysis submitted included a model covariate for number of prior anti-lymphoma treatments (i.e. prior lines of therapy). Please see reference 90 from the company submission.

Costs and resource use

B13. Priority question: The EAG notes that NHS reference costs have been published for the latest financial year (2024/25). Please update sourced unit costs to use the most recent cost data.

The company has updated all the NHS costs to the latest financial year (2024/25). The updated administration costs are presented in Table 32.

Table 32. Updated administration costs

Administration type	Cost per administration (NHS 2023/24)	Cost per administration (NHS 2024/25)	Source	Cost per administration (NHS 2024/25) + preparation time
IV Complex/Simple (Subsequent)	£426.15	£438.41	Daycase. SB15Z	£452.66
IV Complex (First)	£570.43	£571.26	Daycase. SB14Z	£585.51
IV Simple (First)	£528.11	£553.43	Daycase. SB13Z	£567.68
Subcutaneous	Assumed £0	£435.51	Daycase. SB12Z	£449.76
Infusion preparation time	Not used	£14.25	Per hour cost for hospital-based scientific and professional staff (Band 6) from Personal Social Services Research Unit (PSSRU)	NA

Key: IV, intravenous; NA, not applicable.

The updated AEs costs are presented in Table 33.

Table 33. Updated adverse event costs

Department Code	Currency Code	Currency Description	Episodes (NHS 2023/24)	Unit cost (NHS 2023/24)	Episodes (NHS 2024/25)	Unit cost (NHS 2024/25)
NEL	SA03G	Haemolytic Anaemia with CC Score 3+	990	£5,497.00	982	£5,200.81
NEL	SA03H	Haemolytic Anaemia with CC Score 0-2	146	£3,813.00	189	£3,408.95
NEL	DZ11K	Lobar, Atypical or Viral Pneumonia, with Multiple Interventions, with CC Score 14+	*	*	5548	£9,880.88
NEL	DZ11L	Lobar, Atypical or Viral Pneumonia, with Multiple Interventions, with CC Score 9-13	*	*	3102	£8,074.60
NEL	DZ11N	Lobar, Atypical or Viral Pneumonia, with Single Intervention, with CC Score 13+	*	*	15358	£6,982.30
NEL	DZ11P	Lobar, Atypical or Viral Pneumonia, with Single Intervention, with CC Score 8-12	*	*	9760	£5,312.15
NEL	DZ11R	Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 14+	51	£10,446.00	85108	£5,191.51
NEL	DZ11S	Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 10-13	58	£14,543.00	91331	£4,027.17
NEL	DZ11T	Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 7-9	24	£10,021.00	53771	£3,219.23
NEL	DZ11U	Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 4-6	*	*	37638	£2,768.82
NEL	DZ11V	Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 0-3	*	*	22176	£2,306.23
DC	SA08G	Other Haematological or Splenic Disorders, with CC Score 6+	513	406	724	£519.31
DC	SA08H	Other Haematological or Splenic Disorders, with CC Score 3-5	697	399	767	£430.31

Department Code	Currency Code	Currency Description	Episodes (NHS 2023/24)	Unit cost (NHS 2023/24)	Episodes (NHS 2024/25)	Unit cost (NHS 2024/25)
DC	SA08J	Other Haematological or Splenic Disorders, with CC Score 0-2	1314	420	1540	£422.69
NEL	SA12G	Thrombocytopenia with CC Score 8+	1094	5909	1288	£5,807.86
NEL	SA12H	Thrombocytopenia with CC Score 5-7	496	3975	496	£4,013.87
NEL	SA12J	Thrombocytopenia with CC Score 2-4	535	3336	546	£3,764.19
NEL	SA12K	Thrombocytopenia with CC Score 0-1	250	2770	268	£2,635.32
DC	KC05H	Fluid or Electrolyte Disorders, with Interventions, with CC Score 0-4	*	*	*	*
DC	KC05J	Fluid or Electrolyte Disorders, without Interventions, with CC Score 10+	1775	461	*	*
DC	KC05K	Fluid or Electrolyte Disorders, without Interventions, with CC Score 7-9	3048	445	2383	£527.09
DC	KC05L	Fluid or Electrolyte Disorders, without Interventions, with CC Score 4-6	6358	458	4194	£452.20
DC	KC05M	Fluid or Electrolyte Disorders, without Interventions, with CC Score 2-3	5094	490	7891	£507.54
DC	KC05N	Fluid or Electrolyte Disorders, without Interventions, with CC Score 0-1	3354	427	5620	£444.20
NEL	DZ09J	Pulmonary Embolus with Interventions, with CC Score 9+	1616	7050	3222	£409.44
NEL	DZ09K	Pulmonary Embolus with Interventions, with CC Score 0-8	543	4369	503	£4,662.42
NEL	DZ09L	Pulmonary Embolus without Interventions, with CC Score 12+	6908	4909	7287	£4,932.67
NEL	DZ09M	Pulmonary Embolus without Interventions, with CC Score 9-11	4839	3658	4893	£3,776.52
NEL	DZ09N	Pulmonary Embolus without Interventions, with CC Score 6-8	5237	2982	4977	£3,115.37
NEL	DZ09P	Pulmonary Embolus without Interventions, with CC Score 3-5	4918	2553	4468	£2,623.47
NEL	DZ09Q	Pulmonary Embolus without Interventions, with CC Score 0-2	2181	2222	1872	£2,297.54
DC	DZ09L	Pulmonary Embolus without Interventions, with CC Score 12+	28	886	56	£951.78

Department Code	Currency Code	Currency Description	Episodes (NHS 2023/24)	Unit cost (NHS 2023/24)	Episodes (NHS 2024/25)	Unit cost (NHS 2024/25)
DC	DZ09M	Pulmonary Embolus without Interventions, with CC Score 9-11	63	825	121	£810.64
DC	DZ09N	Pulmonary Embolus without Interventions, with CC Score 6-8	194	661	287	£718.58
DC	DZ09P	Pulmonary Embolus without Interventions, with CC Score 3-5	444	544	516	£596.63
DC	DZ09Q	Pulmonary Embolus without Interventions, with CC Score 0-2	505	438	552	£481.26
DC	WH05Z	Allergy or Adverse Allergic Reaction	4424	345.35	4271	£431.33
NEL	WH05Z	Allergy or Adverse Allergic Reaction	790	2280.48	703	£2,703.04
NES	WH05Z	Allergy or Adverse Allergic Reaction	4115	431.42	4842	£478.72
DC	WH07A	Infections or Other Complications of Procedures, with Multiple Interventions, with CC Score 2+	*	*	*	*
DC	WH07B	Infections or Other Complications of Procedures, with Multiple Interventions, with CC Score 0-1	*	*	*	*
DC	WH07C	Infections or Other Complications of Procedures, with Single Intervention, with CC Score 2+	*	*	*	*
DC	WH07D	Infections or Other Complications of Procedures, with Single Intervention, with CC Score 0-1	37	579	21	£1,019.80
DC	WH07E	Infections or Other Complications of Procedures, without Interventions, with CC Score 4+	31	524	81	£460.73
DC	WH07F	Infections or Other Complications of Procedures, without Interventions, with CC Score 2-3	424	467	743	£448.52
DC	WH07G	Infections or Other Complications of Procedures, without Interventions, with CC Score 0-1	3115	420	3937	£453.12
NEL	WH07A	Infections or Other Complications of Procedures, with Multiple Interventions, with CC Score 2+	1634	12712	1821	£13,533.61
NEL	WH07B	Infections or Other Complications of Procedures, with Multiple Interventions, with CC Score 0-1	1481	7352	1593	£7,926.52
NEL	WH07C	Infections or Other Complications of Procedures, with Single Intervention, with CC Score 2+	1690	7291	1922	£7,765.32

Department Code	Currency Code	Currency Description	Episodes (NHS 2023/24)	Unit cost (NHS 2023/24)	Episodes (NHS 2024/25)	Unit cost (NHS 2024/25)
NEL	WH07D	Infections or Other Complications of Procedures, with Single Intervention, with CC Score 0-1	2783	4907	3030	£5,034.26
NEL	WH07E	Infections or Other Complications of Procedures, without Interventions, with CC Score 4+	1618	6077	1965	£6,322.85
NEL	WH07F	Infections or Other Complications of Procedures, without Interventions, with CC Score 2-3	4104	4353	4644	£4,408.20
NEL	WH07G	Infections or Other Complications of Procedures, without Interventions, with CC Score 0-1	10823	3084	11112	£3,219.95
NES	WH07A	Infections or Other Complications of Procedures, with Multiple Interventions, with CC Score 2+	37	985	58	£2,686.77
NES	WH07B	Infections or Other Complications of Procedures, with Multiple Interventions, with CC Score 0-1	92	1973	69	£1,383.01
NES	WH07C	Infections or Other Complications of Procedures, with Single Intervention, with CC Score 2+	219	1159	119	£1,761.49
NES	WH07D	Infections or Other Complications of Procedures, with Single Intervention, with CC Score 0-1	319	1167	301	£1,251.63
NES	WH07E	Infections or Other Complications of Procedures, without Interventions, with CC Score 4+	655	864	816	£888.76
NES	WH07F	Infections or Other Complications of Procedures, without Interventions, with CC Score 2-3	3999	650	4836	£678.71
NES	WH07G	Infections or Other Complications of Procedures, without Interventions, with CC Score 0-1	32576	516	34046	£541.72
NEL	WJ06A	Sepsis with Multiple Interventions, with CC Score 9+	3909	11830	4092	£11,604.51
NEL	WJ06B	Sepsis with Multiple Interventions, with CC Score 5-8	2409	9980	2312	£10,049.50
NEL	WJ06C	Sepsis with Multiple Interventions, with CC Score 0-4	718	7910	722	£7,917.80
NEL	WJ06D	Sepsis with Single Intervention, with CC Score 9+	6672	7704	6811	£7,720.45

Department Code	Currency Code	Currency Description	Episodes (NHS 2023/24)	Unit cost (NHS 2023/24)	Episodes (NHS 2024/25)	Unit cost (NHS 2024/25)
NEL	WJ06E	Sepsis with Single Intervention, with CC Score 5-8	6252	6318	5916	£6,751.49
NEL	WJ06F	Sepsis with Single Intervention, with CC Score 0-4	2392	5419	2082	£5,853.20
NEL	WJ06G	Sepsis without Interventions, with CC Score 9+	34590	5068	36237	£5,244.23
NEL	WJ06H	Sepsis without Interventions, with CC Score 5-8	49064	4100	46373	£4,250.16
NEL	WJ06J	Sepsis without Interventions, with CC Score 0-4	27812	3243	23628	£3,430.68
DC	FD05A	Abdominal Pain with Interventions	10	1432	*	*
DC	FD05B	Abdominal Pain without Interventions	7535	421	8775	£478.17
NEL	FD05A	Abdominal Pain with Interventions	3181	3787	3099	£4,165.23
NEL	FD05B	Abdominal Pain without Interventions	25398	2411	23725	£2,625.06
NES	FD05A	Abdominal Pain with Interventions	79	1229	64	£1,114.14
NES	FD05B	Abdominal Pain without Interventions	173908	437	178954	£447.81
NEL	LA07H	Acute Kidney Injury with Interventions, with CC Score 11+	3442	8064	3608	£8,472.02
NEL	LA07J	Acute Kidney Injury with Interventions, with CC Score 6-10	3590	6326	3711	£6,551.89
NEL	LA07K	Acute Kidney Injury with Interventions, with CC Score 0-5	2271	5006	2237	£5,319.35
NEL	LA07L	Acute Kidney Injury without Interventions, with CC Score 12+	10109	4896	10197	£5,131.22
NEL	LA07M	Acute Kidney Injury without Interventions, with CC Score 8-11	13847	3960	14414	£4,273.80
NEL	LA07N	Acute Kidney Injury without Interventions, with CC Score 4-7	17003	3278	16604	£3,497.91
NEL	LA07P	Acute Kidney Injury without Interventions, with CC Score 0-3	7916	2723	7240	£2,913.64
NEL	SA35A	Agranulocytosis with CC Score 13+	440	6288	412	£5,715.41
NEL	SA35B	Agranulocytosis with CC Score 9-12	458	4256	538	£4,865.01
NEL	SA35C	Agranulocytosis with CC Score 5-8	739	3729	709	£3,935.84
NEL	SA35D	Agranulocytosis with CC Score 2-4	551	3121	569	£3,398.74
NEL	SA35E	Agranulocytosis with CC Score 0-1	140	2953	146	£2,720.57
NEL	KC05J	Fluid or Electrolyte Disorders, without Interventions, with CC Score 10+	25760	4210	27946	£4,335.49

Department Code	Currency Code	Currency Description	Episodes (NHS 2023/24)	Unit cost (NHS 2023/24)	Episodes (NHS 2024/25)	Unit cost (NHS 2024/25)
NEL	KC05K	Fluid or Electrolyte Disorders, without Interventions, with CC Score 7-9	12972	3151	12860	£3,303.35
NEL	KC05L	Fluid or Electrolyte Disorders, without Interventions, with CC Score 4-6	10505	2640	9643	£2,823.74
NEL	KC05M	Fluid or Electrolyte Disorders, without Interventions, with CC Score 2-3	3551	2312	3075	£2,378.11
NEL	KC05N	Fluid or Electrolyte Disorders, without Interventions, with CC Score 0-1	1016	2066	888	£2,193.89
NES	KC05J	Fluid or Electrolyte Disorders, without Interventions, with CC Score 10+	17799	691	21021	£730.86
NES	KC05K	Fluid or Electrolyte Disorders, without Interventions, with CC Score 7-9	16278	627	17359	£662.29
NES	KC05L	Fluid or Electrolyte Disorders, without Interventions, with CC Score 4-6	21106	566	21315	£595.11
NES	KC05M	Fluid or Electrolyte Disorders, without Interventions, with CC Score 2-3	12255	487	11849	£520.11
NES	KC05N	Fluid or Electrolyte Disorders, without Interventions, with CC Score 0-1	6425	418	6315	£431.32
NEL	DZ23L	Bronchopneumonia without Interventions, with CC Score 11+	3484	4763	3161	£4,701.31
NEL	DZ23M	Bronchopneumonia without Interventions, with CC Score 6-10	1784	3307	1516	£3,368.57
NEL	DZ23N	Bronchopneumonia without Interventions, with CC Score 0-5	810	2593	614	£2,489.44
NES	DZ23L	Bronchopneumonia without Interventions, with CC Score 11+	1851	797	1859	£808.92
NES	DZ23M	Bronchopneumonia without Interventions, with CC Score 6-10	1670	716	1626	£727.13
NES	DZ23N	Bronchopneumonia without Interventions, with CC Score 0-5	1335	594	1207	£657.00
NEL	SA01G	Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC Score 8+	1906	5686	1852	£5,219.47
NEL	SA01H	Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC Score 5-7	489	3955	439	£4,370.51

Department Code	Currency Code	Currency Description	Episodes (NHS 2023/24)	Unit cost (NHS 2023/24)	Episodes (NHS 2024/25)	Unit cost (NHS 2024/25)
NEL	SA01J	Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC Score 2-4	295	3637	294	£3,924.91
NEL	SA01K	Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC Score 0-1	65	2608	86	£3,666.03
NES	SA01G	Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC Score 8+	1015	820	1116	£843.80
NES	SA01H	Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC Score 5-7	516	736	509	£794.02
NES	SA01J	Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC Score 2-4	442	692	482	£785.25
NES	SA01K	Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC Score 0-1	185	739	184	£694.42
NEL	DX21A	COVID-19 Infection, 19 years and over	17457	3901	13532	£4,130.33
NES	DX21A	COVID-19 Infection, 19 years and over	17813	655	13691	£697.90
NEL	DX11A	COVID-19 Infection, with Pneumonia, 19 years and over	9666	4200	5992	£4,248.10
NES	DX11A	COVID-19 Infection, with Pneumonia, 19 years and over	5417	743	3645	£738.36
NEL	WJ07A	Fever of Unknown Origin with Interventions, with CC Score 4+	189	7819	202	£8,016.17
NEL	WJ07B	Fever of Unknown Origin with Interventions, with CC Score 0-3	238	4400	203	£4,578.02
NEL	WJ07C	Fever of Unknown Origin without Interventions, with CC Score 4+	2099	3204	2003	£3,477.63
NEL	WJ07D	Fever of Unknown Origin without Interventions, with CC Score 0-3	2668	2529	2437	£2,852.95
NES	WJ07A	Fever of Unknown Origin with Interventions, with CC Score 4+	9	542	16	£1,385.17
NES	WJ07B	Fever of Unknown Origin with Interventions, with CC Score 0-3	14	674	*	*

Department Code	Currency Code	Currency Description	Episodes (NHS 2023/24)	Unit cost (NHS 2023/24)	Episodes (NHS 2024/25)	Unit cost (NHS 2024/25)
NES	WJ07C	Fever of Unknown Origin without Interventions, with CC Score 4+	2904	634	3275	£679.36
NES	WJ07D	Fever of Unknown Origin without Interventions, with CC Score 0-3	8294	544	8882	£571.12
NEL	SA08G	Other Haematological or Splenic Disorders, with CC Score 6+	1275	4886	1411	£4,851.47
NEL	SA08H	Other Haematological or Splenic Disorders, with CC Score 3-5	370	3268	388	£3,341.55
NEL	SA08J	Other Haematological or Splenic Disorders, with CC Score 0-2	365	3259	289	£3,256.68
NES	SA08G	Other Haematological or Splenic Disorders, with CC Score 6+	865	666	1026	£725.62
NES	SA08H	Other Haematological or Splenic Disorders, with CC Score 3-5	763	603	756	£608.03
NES	SA08J	Other Haematological or Splenic Disorders, with CC Score 0-2	1375	471	1241	£496.23
NES	HC32G	Low Back Pain with Interventions	17	1053	*	*
NES	HC32H	Low Back Pain without Interventions, with CC Score 6+	2110	682	2459	£664.26
NES	HC32J	Low Back Pain without Interventions, with CC Score 3-5	4170	595	4451	£613.59
NES	HC32K	Low Back Pain without Interventions, with CC Score 0-2	14834	507	16211	£477.50
RP	FD10J	Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 11+	27	72	*	*
RP	FD10K	Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 6-10	29	287	128	£228.55
RP	FD10L	Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 3-5	326	196	166	£412.71
RP	FD10M	Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2	587	216	482	£224.08
CL	WF01A	Outpatient Attendances (GENERAL INTERNAL MEDICINE SERVICE - 300)	1067792	170	250624	£193.09

Department Code	Currency Code	Currency Description	Episodes (NHS 2023/24)	Unit cost (NHS 2023/24)	Episodes (NHS 2024/25)	Unit cost (NHS 2024/25)
NES	AA31C	Headache, Migraine or Cerebrospinal Fluid Leak, with CC Score 11+	5414	628	6654	£654.39
NES	AA31D	Headache, Migraine or Cerebrospinal Fluid Leak, with CC Score 7-10	10650	561	12091	£584.94
NES	AA31E	Headache, Migraine or Cerebrospinal Fluid Leak, with CC Score 0-6	64237	448	64758	£454.85
RP	WJ03E	Standard Infectious Diseases without Interventions, with CC Score 4-6	27	212	44	£343.52
RP	WJ03F	Standard Infectious Diseases without Interventions, with CC Score 2-3	34	247	74	£334.68
RP	WJ03G	Standard Infectious Diseases without Interventions, with CC Score 0-1	136	128	116	£268.26
RP	HD21D	Soft Tissue Disorders with CC Score 12+	38	201	40	£88.71
RP	HD21E	Soft Tissue Disorders with CC Score 9-11	42	127	55	£141.46
RP	HD21F	Soft Tissue Disorders with CC Score 6-8	99	144	143	£191.96
RP	HD21G	Soft Tissue Disorders with CC Score 3-5	173	158	211	£189.60
RP	HD21H	Soft Tissue Disorders with CC Score 0-2	322	121	314	£120.50
NES	CB02A	Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, with Interventions, with CC Score 5+	554	945	519	£1,095.56
NES	CB02B	Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, with Interventions, with CC Score 1-4	611	1026	547	£1,251.52
NES	CB02C	Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, with Interventions, with CC Score 0	365	1019	277	£1,186.99
NES	CB02D	Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, without Interventions, with CC Score 5+	45503	582	49221	£605.41
NES	CB02E	Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, without Interventions, with CC Score 1-4	54181	495	54180	£482.90

Department Code	Currency Code	Currency Description	Episodes (NHS 2023/24)	Unit cost (NHS 2023/24)	Episodes (NHS 2024/25)	Unit cost (NHS 2024/25)
NES	CB02F	Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, without Interventions, with CC Score 0	33016	450	31598	£424.45
NEL	LA04H	Kidney or Urinary Tract Infections, with Interventions, with CC Score 12+	4047	8582	4068	£8,811.56
NEL	LA04J	Kidney or Urinary Tract Infections, with Interventions, with CC Score 9-11	3459	6481	3449	£6,811.00
NEL	LA04K	Kidney or Urinary Tract Infections, with Interventions, with CC Score 6-8	4029	5343	3893	£5,724.76
NEL	LA04L	Kidney or Urinary Tract Infections, with Interventions, with CC Score 3-5	3203	4463	3035	£4,799.03
NEL	LA04M	Kidney or Urinary Tract Infections, with Interventions, with CC Score 0-2	1638	3973	1622	£4,085.68
NEL	LA04N	Kidney or Urinary Tract Infections, without Interventions, with CC Score 13+	11562	5572	11815	£5,723.07
NEL	LA04P	Kidney or Urinary Tract Infections, without Interventions, with CC Score 8-12	30902	4339	30685	£4,503.06
NEL	LA04Q	Kidney or Urinary Tract Infections, without Interventions, with CC Score 4-7	35677	3434	33688	£3,619.95
NEL	LA04R	Kidney or Urinary Tract Infections, without Interventions, with CC Score 2-3	13973	2712	12486	£2,894.96
NEL	LA04S	Kidney or Urinary Tract Infections, without Interventions, with CC Score 0-1	8548	2274	7660	£2,400.44
NEL	FD01J	Gastrointestinal Infections without Interventions, with CC Score 0-1	12811	2254	13596	£2,417.94
CC	XC01Z	Adult Critical Care, 6 or more Organs Supported	*	*	87	£306,501.48
CC	XC02Z	Adult Critical Care, 5 Organs Supported	34	3537	242	£778,336.77

Department Code	Currency Code	Currency Description	Episodes (NHS 2023/24)	Unit cost (NHS 2023/24)	Episodes (NHS 2024/25)	Unit cost (NHS 2024/25)
CC	XC03Z	Adult Critical Care, 4 Organs Supported	744	3156	594	£1,943,743.85
CC	XC04Z	Adult Critical Care, 3 Organs Supported	2849	2363	2349	£6,292,699.67
CC	XC05Z	Adult Critical Care, 2 Organs Supported	10019	1706	6277	£10,812,185.34
CC	XC06Z	Adult Critical Care, 1 Organ Supported	46252	972	30621	£29,623,153.11
CC	XC07Z	Adult Critical Care, 0 Organs Supported	14647	1187	7052	£13,321,512.53
NES	SA31E	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC Score 2-3	529	749.9988014	520	£795.36
NES	DZ38Z	Oxygen Assessment and Monitoring	46	309.0514975	11	£482.48
NES	AA22C	Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 14+	1491	890.4275259	1977	£1,066.65
NES	AA22D	Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 11-13	1366	820.2995246	1489	£902.05
NES	AA22E	Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 8-10	1774	836.1734364	1847	£862.14
NES	AA22F	Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 5-7	2096	818.4138887	2272	£786.97
NES	AA22G	Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 0-4	3714	639.5356637	3671	£682.82
NEL	EB08A	Syncope or Collapse, with CC Score 13+	14390	4513.166932	15868	£4,670.76
NEL	EB08B	Syncope or Collapse, with CC Score 10-12	10144	3342.977735	10070	£3,544.71

Department Code	Currency Code	Currency Description	Episodes (NHS 2023/24)	Unit cost (NHS 2023/24)	Episodes (NHS 2024/25)	Unit cost (NHS 2024/25)
NEL	EB08C	Syncope or Collapse, with CC Score 7-9	8568	2733.43519	8189	£2,959.09
NEL	EB08D	Syncope or Collapse, with CC Score 4-6	6091	2342.826347	5597	£2,503.93
NEL	EB08E	Syncope or Collapse, with CC Score 0-3	3272	2083.364832	3057	£2,287.75
NEL	DZ16H	Pleural Effusion with Multiple Interventions, with CC Score 11+	1086	8870.0193	1205	£9,360.15
NEL	DZ16J	Pleural Effusion with Multiple Interventions, with CC Score 6-10	737	5868.44067	762	£6,578.21
NEL	DZ16K	Pleural Effusion with Multiple Interventions, with CC Score 0-5	357	4738.839397	316	£4,685.12
NEL	DZ16L	Pleural Effusion with Single Intervention, with CC Score 11+	2684	5544.251396	2868	£5,729.41
NEL	DZ16M	Pleural Effusion with Single Intervention, with CC Score 6-10	2592	3919.137359	2566	£4,275.01
NEL	DZ16N	Pleural Effusion with Single Intervention, with CC Score 0-5	1506	3293.731835	1464	£3,515.60
NEL	DZ16P	Pleural Effusion without Interventions, with CC Score 11+	4619	4045.05777	5131	£4,297.66
NEL	DZ16Q	Pleural Effusion without Interventions, with CC Score 6-10	3958	3007.901016	4016	£3,222.70
NEL	DZ16R	Pleural Effusion without Interventions, with CC Score 0-5	2119	2431.965649	2077	£2,722.14

The updated HCRU costs are presented in Table 34.

Table 34. Updated HCRU costs

Department Code	Department Description	Currency Code	Currency Description	Unit cost (NHS 2023/24)	Unit cost (NHS 2024/25)
CL	Consultant Led	WF01A	Non-Admitted Face-to-Face Attendance, Follow-up (GENERAL INTERNAL MEDICINE SERVICE - 300)	£205.00	£209.77
Total HRG	HRG cost	RD27Z	Computerised Tomography Scan of more than Three Areas	£136.00	£160.82

Key: HCRU, health care resource utilisation.

Table 35 provides the incremental results of tafasitamab + R^2 vs R^2 of the scenario analysis using the updated NHS costs. The ICER versus R^2 decreases by £92.

Table 35. Scenario analysis using the updated NHS costs (Tafasitamab + R^2 vs R^2)

Scenario Name	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Difference to base case	% Difference to base case
Base case	[redacted]	[redacted]	[redacted]	£32,672		
Updated NHS costs	[redacted]	[redacted]	[redacted]	£32,580	-£92	-0.3%

Key: ICER, incremental cost-effectiveness ratio, LY, life year; QALY, quality-adjusted life year; R^2, lenalidomide with rituximab.

B14. The EAG notes that the electronic Market Information Tool (eMIT) has been updated with data from the 12 months to the end of June 2025. Please update cost and resource use data to use the most recent eMIT costs.

As discussed in the NICE clarification call, this question is being resolved concurrently.

B15. Priority question: CS section 3.5.1.1 details the relative dose intensity used for components of R-chemotherapy regimens in the model.

a) **Please confirm what proportion of the reduction in RDI is attributable to missed doses versus dose reductions, and how treatment interruptions were factored into these estimates.**

Relative dose intensity (RDI) was calculated for each participant by averaging dose / planned dose x delivered volume / start volume. Treatment interruptions would be factored into these estimates if they resulted in under delivery of the planned dose; an interruption that is subsequently completed would not change the RDI.

Exact details on the proportion of the reduction in RDI attributable to missed doses versus dose reductions is not available. However, as per protocol, dose reduction was not permitted for tafasitamab/placebo or rituximab so we can assume any reduction in RDI is attributed to missed doses or under delivery of the planned dose.

The CSR exposure tables [Table 12, Table 14, Table 16] do provide data on the number of patients who experienced a dose interruption, dose delay or missed dose.

b) **The CS states "The average RDI of tafasitamab + R2 ([redacted]) was assumed for components of the R-chemotherapy regimens other than rituximab". Please specify where this average RDI value was obtained (e.g., the CSR section/table, or another source).**

The average RDI of tafasitamab + R^2 refers specifically to the average RDI of the tafasitamab component in the tafasitamab + R^2 arm from cycle 1 to cycle 12. These values are provided in Table 3.1.5.1 from the CSR. While reviewing the inputs, the company has found a minor error in the calculations and updated the value: from

0.859 to 0.8503. The individual values used for the average are provided in Table 36.

Table 36. Tafasitamab RDI (Cycles 1-12)

Cycle	RDI
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Key: RDI, relative dose intensity

The updated RDI value does not impact the comparison versus R^2. Table 37, Table 38 and Table 39 provide the incremental results of tafasitamab + R^2 vs R-chemotherapy regimens of the scenario analysis using the updated RDI. The scenario has no impact on the ICER due to the small change on the RDI and the low cost of the non-rituximab components of the R-chemotherapy regimens.

Table 37. Scenario analysis using the updated RDI (Tafasitamab + R^2 vs R-Benda)

Scenario Name	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Difference to base case	% Difference to base case
Base case	[redacted]	[redacted]	[redacted]	£29,029		
Updated RDI	[redacted]	[redacted]	[redacted]	£29,032	£3	0.0%

Table 38. Scenario analysis using the updated RDI (Tafasitamab + R^2 vs R-CVP)

Scenario Name	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Difference to base case	% Difference to base case
Base case	[redacted]	[redacted]	[redacted]	£28,723		
Updated RDI	[redacted]	[redacted]	[redacted]	£28,723	£0	0.0%

Table 39. Scenario analysis using the updated RDI (Tafasitamab + R^2 vs R-CHOP)

Scenario Name	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Difference to base case	% Difference to base case
Base case	[redacted]	[redacted]	[redacted]	£30,982		
Updated RDI	[redacted]	[redacted]	[redacted]	£30,982	£0	0.0%

B16. Administration costs are presented in CS section 3.5.1.1 and Table 39, with costs applied in accordance with TA627.

a) A cost of £0 was assumed for subcutaneous administration of Rituximab during the maintenance phase. This differs from the assumption in TA627, which modelled a cost for rituximab maintenance at first subcutaneous administration. Please justify why a zero cost has been applied.

The model used a zero cost for subcutaneous administration based on the approach of TA907, which was used as it represents a more recent source. Following the EAG comment, the company has updated its base case to include the administration cost of rituximab during the maintenance phase. The updated base case uses the same source and code as in TA627: SB12Z: Deliver Simple Parenteral Chemotherapy at First Attendance (Daycase)

The updated RDI value does not impact the comparison versus R^2. Table 40, Table 41 and Table 42 provide the incremental results of tafasitamab + R^2 vs R-chemotherapy regimens of the scenario analysis using the updated subcutaneous administration costs. The scenario reduces the ICER approximately by £1,200 compared to all R-chemotherapies as it increases the administration costs of rituximab maintenance.

Table 40. Scenario analysis using the updated subcutaneous administration cost (Tafasitamab + R^2 vs R-Benda)

Scenario Name	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Difference to base case	% Difference to base case
Base case	[redacted]	[redacted]	[redacted]	£29,029		
Updated SC costs	[redacted]	[redacted]	[redacted]	£27,849	-£1,180	-4.1%

Table 41. Scenario analysis using the updated subcutaneous administration cost (Tafasitamab + R^2 vs R-CVP)

Scenario Name	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Difference to base case	% Difference to base case
Base case	[redacted]	[redacted]	[redacted]	£28,723		
Updated SC costs	[redacted]	[redacted]	[redacted]	£27,542	-£1,181	-4.1%

Table 42. Scenario analysis using the updated subcutaneous administration cost versus (Tafasitamab + R^2 vs R-CHOP)

Scenario Name	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Difference to base case	% Difference to base case
Base case	[redacted]	[redacted]	[redacted]	£30,982		
Updated SC costs	[redacted]	[redacted]	[redacted]	£29,809	-£1,173	-3.8%

b) Pharmacy preparation costs were also applied for all infusion treatments in TA627, assuming a 15-minute infusion preparation time. Please explain why this cost was not modelled.

Whilst there may be an argument that the costs of this preparation time would already be included in the reference costs, the company has updated its base case to align with TA627 and includes a 15-minute infusion preparation time. As in TA627, it used the per hour cost for hospital-based scientific and professional staff (Band 6) from Personal Social Services Research Unit (PSSRU) costs (£57). The preparation time cost is included in the administration cost of all infusion treatments. Table 43 presents the updated administration costs based on NHS 2024/25 reference costs, and the unit cost per administration including the preparation time.

Table 43. Updated administration costs

Administration type	Cost per administration (NHS 2023/24)	Cost per administration (NHS 2024/25)	Source	Cost per administration (NHS 2024/25) + preparation time
IV Complex/Simple (Subsequent)	£426.15	£438.41	Daycase. SB15Z	£452.66
IV Complex (First)	£570.43	£571.26	Daycase. SB14Z	£585.51
IV Simple (First)	£528.11	£553.43	Daycase. SB13Z	£567.68
Subcutaneous	Assumed £0	£435.51	Daycase. SB12Z	£449.76
Infusion preparation time	Not used	£14.25	Per hour cost for hospital-based scientific and professional staff (Band 6) from Personal Social Services Research Unit (PSSRU)	NA

Table 44 provides the incremental analysis of tafasitamab + R^2 vs R^2 using the infusion preparation time costs versus R^2. The ICER increases from £32,672 to £32,914 (0.7%).

Table 44. Scenario analysis using the infusion preparation time costs (Tafasitamab + R^2 vs R^2)

Scenario Name	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Difference to base case	% Difference to base case
Base case	[redacted]	[redacted]	[redacted]	£32,672		
Updated infusion preparation time	[redacted]	[redacted]	[redacted]	£32,914	£242	0.7%

B17. CS Section 3.5.4.1 explains how the distributions of subsequent treatments shown in Table 44 were derived. A distribution from inMIND displayed in Table 45 was used in a scenario analysis. Please justify why the proportions of patients receiving allogeneic stem cell transplant (allo-SCT) as subsequent treatment in Tafasitamab + R^2 and R^2 are assumed to be equal in the base case, despite the inMIND distribution indicating a notable difference ([redacted] of patients in the tafasitamab + R^2 arm compared with [redacted] in the R^2 arm). The EAG acknowledges the company's statement that this difference is unlikely to have impacted OS; however, there are cost implications.

Distributions of subsequent treatments were informed by clinical expert opinion for the base case analysis as the inMIND trial data were not considered representative of UK clinical practice. The difference in allo-SCT use observed at the time of data cutoff in the inMIND trial was not aligned with clinical expert opinion that there would be no difference in the use of allo-SCT between treatment arms.

The scenario analysis applying the inMIND distribution of subsequent treatment explores the cost implication of this difference and does report a small increase to the ICER (+6.7%).

Section C: Textual clarification and additional points

Systematic review searches: clinical effectiveness

C1. Please clarify how non-randomised studies and systematic reviews were identified in the original searches[19] and the update searches in CS Appendix B.

Original SLR (January 2024)

The clinical SLR search strategy was designed to capture all eligible study designs specified in the PICOS, including RCTs, single-arm studies, and other non-randomised interventional studies, as well as relevant published SLRs for cross-referencing. Non-randomised evidence was restricted to interventional designs. Observational studies were excluded from the clinical SLR but were considered within the economic and humanistic evidence review, as pre-specified.

Published SLRs were retained at title and abstract screening for citation chasing only to identify additional eligible primary studies and were not used as direct evidence sources.

SLR Update (April 2025)

The update used the same overall approach as the original clinical SLR, and expanded the PICOS to include three additional interventions, epcoritamab, odronextamab, and lisocabtagene maraleucel. To ensure these newly added treatments were fully incorporated into the evidence base, the search strategies for these interventions were run from database inception, rather than being limited to the incremental update period only.

As in the original review, published SLRs were screened for citation chasing only to identify additional eligible primary studies and were not included as direct outcome evidence. For SLR publications considered relevant at title and abstract screening, the full texts were obtained and reviewed specifically to support structured reference-mining. We checked the reference lists of these published SLRs to identify any additional eligible primary interventional studies that were not retrieved by the database searches. Any primary studies identified through this process were then screened against the clinical SLR eligibility criteria.

C2. Please provide the search strategies used to identify evidence for the ITC report.[12]

The evidence base for the indirect treatment comparison (ITC) was sourced from the clinical SLR (original search – 12 Jan 2024; update search – 16 Apr 2025). The inMIND trial patient-level data (including OS, PFS, and TTNT outcomes) used in the ITC were provided directly by Incyte Corporation as part of the company evidence submission. These data originated from the Phase III inMIND study (randomised, double-blind, placebo-controlled) and were supplied as confidential for use in population-adjusted indirect comparisons.

As no suitable studies with R-CHOP or R-CVP were identified in the SLR, alternative sources of comparator evidence were required to enable a comparison to R-CHOP and R-CVP. The Van Oers study, a Phase III, open-label, multicentre RCT, was identified post hoc to support comparisons with R-CHOP, as this study was used to inform ITCs presented in TA627. Note that Van Oers was identified in the SLR but excluded as patients were not required to be treated with prior anti-CD20 therapy and had no prior exposure to an anti-CD20. An additional study based on real-world data from the Haematological Malignancy Research Network (HMRN) was commissioned by Incyte to support the NICE submission. The HMRN study is a population-based cohort study using real-world R-CVP and R-CHOP data from a UK-based registry that started in 2004.

C3. Please supply the name of the interface/provider that was used to search Embase and the Cochrane Library for both the original systematic review (Appendix A, 11.1.1, p261 Embase and 11.1.3, p263 Cochrane)[19] and the updated systematic review (CS Appendix B, table 1, p9-10 Embase and table 3, p12-13 Cochrane).

For both the original and the updated SLRs, Embase was searched using the Embase.com interface (Elsevier), with strategies executed directly in Embase rather than through an intermediary platform such as Ovid.

For both the original and the updated SLRs, the Cochrane Library was searched using the Cochrane Library interface on Wiley's platform (CochraneLibrary.com). We ran the strategies directly in the Cochrane Library using the Advanced Search, and

limited retrieval to CDSR and CENTRAL. No intermediary search service was used. Running the strategies in the native interface supported use of Cochrane-specific search functions, including proximity operators and built-in limits.

C4. Please clarify which fields were searched in the following search lines:

Appendix A of report by Avalere Health[19]

- 11.1.1 (p261-262) Embase search strategy – lines 16-20
- 11.1.2 (p262-263) PubMed search strategy – lines 16, 18-20
- 11.1.3 (p263-264) Cochrane search strategy – lines 19, 27-29

CS Appendix B

- Table 1 (p9) Embase search strategy (SLR update) – lines 16-20
- Table 2 (p11) MEDLINE search strategy (SLR update) – lines 16-20
- Table 3 (p12-13) Cochrane search strategy (SLR update) – lines 1, 6, 11-14, 19, 21

Original SLR (January 2024)

Embase (Appendix A 11.1.1, p. 261–262), lines 16-20

- Line 16 (interventions): This line defines the intervention concept for the search. Using OR between terms, it retrieves any record that mentions at least one of the listed treatments or treatment classes, including named agents (for example, tafasitamab, rituximab, obinutuzumab, mosunetuzumab, idelalisib, duvelisib, tazemetostat, zanubrutinib, ibrutinib, ibritumomab tiuxetan), CAR-T products (axicabtagene ciloleucel, tisagenlecleucel), chemotherapy-related terms (including bendamustine and the truncated term chemotherap*), immunotherapy-related terms (immunotherap*), and transplant concepts (stem cell transplant, autologous, allogeneic). The truncation (*) broadens retrieval to word variants (for example, chemotherapy or chemotherapeutic, immunotherapy or immunotherapeutic). The line is written without field tags such as ti,ab (title or abstract) and without Emtree explode commands such as exp, which keeps the search broad by allowing Embase to apply its default searching and term mapping across multiple record fields and indexing.

- Lines 17 to 20 (study design): These lines form the study design filter for interventional evidence, and they are intentionally broad. Line 17 uses Emtree controlled vocabulary with explode (for example, 'clinical trial'/exp) plus several publication or indexing “topic” terms (for example, “randomi?ed controlled trial (topic)”, “phase 1 to 4 clinical trial (topic)”, “multicenter study (topic)”) to capture records indexed as clinical trials across trial phases and formats. Line 18 adds a wide free-text set of trial descriptors (for example, RCT, random allocation, randomi?, blinding terms, placebo, crossover, prospective study) to pick up trials described in the record text and keywords. Line 19 applies a proximity clause linking placebo or randomisation wording to generic study terms (NEAR/3), which increases capture of trial reports where the design language appears in narrative form. Line 20 adds proximity blinding terminology (for example, singl*, doubl*, tripl* NEAR/1 blind*, dumm*, mask*) to further retrieve blinded studies. Although these lines do not include explicit field tags, Embase applies default searching and term mapping across multiple record fields and indexing. This keeps the design filter inclusive, with specificity handled later during screening.

MEDLINE (Appendix A 11.1.2, p. 262–263), lines 16, 18-20

- Line 16 (interventions): This line functions as an intervention keyword set. Because no field tags were added (for example, [tiab]), Medline treats the terms as an All Fields search and applies Automatic Term Mapping for unquoted terms, so Medline searches across the record fields it indexes (for example, title, abstract, MeSH terms, substance names, and other indexed fields). This keeps retrieval broad and increases the chance of capturing records even when a treatment is indexed rather than stated prominently in the title or abstract.

- Lines 18 to 20 (study design): Lines 18 to 20 act as a broad study design filter. Line 18 lists common trial descriptors and related terms (RCT, random allocation, randomiz*/randomis*, blinding terms, placebo*, crossover, prospective study, phase 1 to 4, multicenter) so records describing interventional designs are retrieved even when authors use different wording. Line 19 combines placebo or randomisation wording with generic research

terms (study, trial*, data, evidence, analysis) to capture records where design details appear in narrative form. Line 20 targets blinded studies by combining single or double or triple with blind, dummy, or mask terms. Because no field tags (for example, [tiab]) were used, Medline runs these as untagged searches across its default set of fields rather than restricting to title and abstract, which keeps retrieval broad.

Cochrane (Appendix A 11.1.2, p. 263–264), lines 19, 27-29

- Line 19 (interventions): Lists intervention terms (for example, tafasitamab, rituximab, obinutuzumab, bendamustine, mosunetuzumab, CAR-T terms, stem cell transplant, autologous, allogeneic, immunotherapy*).This line is entered without field tags (no ti,ab,kw), so the strategy does not restrict the search to specific fields. The Cochrane platform applies its default search fields for free-text terms when no field tags are specified.

- Lines 27–29 (study design): These lines capture interventional trial designs using free-text terminology covering trial type and phases, randomisation and placebo wording, co-occurrence logic linking these concepts with study or trial terms, and blinding or masking terms. These lines are not set combinations. Because no field tags are shown (for example, :ti,ab,kw), they are not field-restricted and use the Cochrane platform's default search fields for free-text terms. Cochrane then combines results using OR, so the set includes any record mentioning at least one listed drug, treatment class, or transplant term. "All text" searching does not include reference lists.

SLR update (April 2025)

Embase (CS Appendix B, Table 1, p. 9), lines 16 to 20

- Line 16 (intervention): We searched for the intervention names using the same approach as the original SLR, using quotation marks for multi-word treatment names to ensure phrase searching. The newly added interventions were included as separate terms and searched from database inception (see line 28).
- Lines 17 to 20 (study design): We searched for the study design using the same approach as the original SLR.

MEDLINE (CS Appendix B, Table 2, p. 11), lines 16 to 20

- Line 16 (intervention): We searched for the intervention names using the same approach as the original SLR, using quotation marks for multi-word treatment names to ensure phrase searching. The newly added interventions were included as separate terms and searched from database inception (see line 26).
- Lines 17 to 20 (study design): We searched for the study design using the same approach as the original SLR.

Cochrane Library (CS Appendix B, Table 3, p. 12 to 13), lines 1, 6, 11 to 14, 19, and 21

- Lines 1 and 6 (disease): These lines searched the disease concepts using MeSH descriptors for “Lymphoma, Follicular” (line 1) and “Lymphoma, B-Cell, Marginal Zone” (line 6), consistent with the original review.
- Lines 11 to 14 (relapse and refractory): These lines searched relapsed and refractory concepts using MeSH descriptors, consistent with the original review.
- Line 19 (intervention): This line searched the intervention terms as in the original review. Because no field tags were specified, the Cochrane platform applied its default fields for free-text searching.
- Line 21 (newly added interventions): Newly added intervention terms were included and searched from database inception to ensure full capture within the review scope.

C5. Please provide the keywords and number of hits retrieved for the update searches of:

- EHA and ASH conferences
- HTA agency websites
- ClinicalTrials.gov
- WHO International Clinical Trials Registry Platform (ICTRP)

listed on page 13, CS Appendix B.

For the SLR update, we hand searched supplementary sources, including the EHA and ASH conference websites, HTA agency websites, ClinicalTrials.gov, and WHO ICTRP. We used the same keywords as the original SLR to keep the update

consistent with the original methods. The sources searched, keywords used, and results are summarised below.

EHA and ASH conference search results

Research meeting	Search terms	Update SLR Hits (2024-April 2025)	Update SLR Inclusions
ASH	Follicular	494	7
	“Marginal zone”	113	
	MZL	67	
EHA 2024-2025	Follicular	57	5
	“Marginal zone”	6	
	MZL	2	
Total		**739**	**12**

HTA search results

HTA agency	Search terms	Update SLR Hits (2024-April 2025)	Update SLR Inclusions
National Health for Health and Care Excellence (NICE)	Follicular	6	1
	“Marginal zone”	2	0
	MZL	0	0
Institute for Clinical and Economic Review (ICER)	Follicular	0	0
	“Marginal zone”	0	0
	MZL	0	0
Canadian Agency for Drugs and Technologies in Health (CADTH)	Follicular	6	0
	“Marginal zone”	0	0
	MZL	0	0
Scottish Medicines Consortium (SMC)	Follicular	22	0
	“Marginal zone”	1	1
	MZL	1	0
All Wales Medicines Strategy Group (AWMSG)	Follicular	12	0
	“Marginal zone”	3	0
	MZL	0	0
Total		**53**	**2**

Clinical trial search results

Registry searches	Search terms	Update SLR Hits (2024-April 2025)	Update SLR Inclusions
Clinicaltrials.gov	Relapsed/Refractory Follicular Lymphoma; Relapsed Follicular Lymphoma	31	0
	Relapsed/Refractory Marginal Zone Lymphoma; Relapsed Marginal Zone Lymphoma	6	0
International Clinical Trials Registry Platform (ICTRP)	Follicular	95	0
	"Marginal Zone"	30	0
Total		**162**	**0**

Summary of company changes to base case and scenarios

The company has updated its base case to

- Use R2 inMIND extrapolations to inform the R-chemotherapies survival (CQ B6)
- Use the 2024/2025 NHS costs (CQ B13)
- Use the corrected RDI value for non-rituximab components (CQ B15)
- Use the updated subcutaneous administrations costs (CQ B16a)
- Use the updated infusion preparation time costs (CQ B16b)

Table 45 presents the ICER of tafasitamab + R^2 against R^2. Table 46, Table 47 and Table 48 show the ICER of tafasitamab + R^2 against the R-chemotherapy regimens.

Table 45. Updated base-case results of tafasitamab + R^2 against R^2

Base case	Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER
Original company base case	R^2	[redacted]	[redacted]	[redacted]				
	Tafasitamab+R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,672

Updated company base case	R^2	[redacted]	[redacted]	[redacted]				
	Tafasitamab+R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,821

Table 46. Updated base-case results of tafasitamab + R^2 against R-Benda

Base case	Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER
Original company base case	R-Benda	[redacted]	[redacted]	[redacted]				
	Tafasitamab+R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,029
Updated company base case	R-Benda	[redacted]	[redacted]	[redacted]				
	Tafasitamab+R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,285

Table 47. Updated base-case results of tafasitamab + R2 against R-CVP

Base case	Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER

Original company base case	R-CVP	[redacted]	[redacted]	[redacted]				
	Tafasitamab+R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,723
Updated company base case	R-CVP	[redacted]	[redacted]	[redacted]				
	Tafasitamab+R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,154

Table 48. Updated base-case results of tafasitamab + R2 against R-CHOP

Base case	**Treatment**	**Total costs (£)**	**Total LYs**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYs**	**Incremental QALYs**	**ICER**
Original company base case	R-CHOP	[redacted]	[redacted]	[redacted]				
	Tafasitamab+R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,982
Updated company base case	R-CHOP	[redacted]	[redacted]	[redacted]				
	Tafasitamab+R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,707

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Tafasitamab with lenalidomide and rituximab for treating relapsed or refractory follicular lymphoma after 1 or more systemic treatments [ID6413]

Clarification questions addendum

January 2025

File name	Version	Contains confidential information	Date
ID6413 Tafasitamab clarification letter Addendum_22012026 [redacted]	1.0	Yes	22/01/2025

B9. Priority question: The executable model allows the separate consideration of the 3L+ population, but not the 2L-only group. Please provide a subgroup analysis of the 2L-only population.

As described in the clarification letter, this section provides a detailed PFS and OS analysis including the log-cumulative hazards, QQ plots, Schoenfeld residuals, fit statistics, visual fit assessments, long-term extrapolations, survival landmarks, smoothed hazard plots and hazard extrapolations.

Figure 1: Progression-free Survival - Log-cumulative Hazard

Figure 2: Progression-free Survival - QQ plot

Figure 3: Progression-free Survival - Schoenfeld residuals

Table 1: Fit statistics of progression-free survival extrapolation (jointly fitted PFS-IRC)

Distribution	AIC	AIC rank	BIC	BIC rank

Exponential	776.3	7	783.7	7
Gamma	752.7	4	763.8	3
Gen. Gamma	751.7	2	766.6	5
Gompertz	764.7	6	775.8	6
Log-Logistic	751.9	3	763.0	2
Log-Normal	749.7	1	760.9	1
Weibull	755.2	5	766.3	4

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; Gen. Gamma, generalised gamma; IRC, independent review committee.
Note: Green shade represents the models within 5 points of the model with the best fit.

Figure 1. R^2 jointly fitted PFS IRC parametric fitting (short term)

Figure 2. R^2 jointly fitted PFS IRC parametric fitting (long term)

Figure 3. Tafasitamab + R^2 jointly fitted PFS IRC parametric fitting (short term)

Figure 4. Tafasitamab + R^2 jointly fitted PFS IRC parametric fitting (long term)

Figure 5.Tafasitamab + R^2 vs R^2 jointly fitted PFS IRC parametric fitting (long term)

Table 2. R^2 jointly fitted PFS-IRC long term modelled landmarks

	Exponential	Gamma	Generalised gamma	Gompertz	Log-logistic	Log-normal	Weibull
1 years							
2 years							
3 years							
5 years							
7 years							
10 years							

Table 3. Tafasitamab + R^2 jointly fitted PFS-IRC long term modelled landmarks

	Exponential	Gamma	Generalised gamma	Gompertz	Log-logistic	Log-normal	Weibull
1 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 6. Tafasitamab + R^2 vs R^2 PFS IRC smoothed hazard plots and hazard extrapolations

Table 4: Tafasitamab + R^2 fit statistics of progression-free survival extrapolation (separately fitted PFS-IRC)

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	307.2	7	310.2	7
Gamma	295.6	2	301.5	2
Gen. Gamma	297.5	5	306.5	6
Gompertz	299.3	6	305.3	5
Log-Logistic	295.5	1	301.5	1
Log-Normal	296.1	4	302.1	4
Weibull	295.8	3	301.8	3

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; Gen. Gamma, generalised gamma; IRC, independent review committee.
Note: Green shade represents the models within 5 points of the model with the best fit.

Table 5: R^2 fit statistics of progression-free survival extrapolation (separately fitted PFS-IRC)

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	469.1	7	472.1	6
Gamma	458.5	4	464.6	3
Gen. Gamma	457.4	2	466.5	5
Gompertz	466.1	6	472.1	7
Log-Logistic	457.8	3	463.9	2
Log-Normal	455.6	1	461.7	1
Weibull	460.1	5	466.2	4

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; Gen. Gamma, generalised gamma; IRC, independent review committee.
Note: Green shade represents the models within 5 points of the model with the best fit.

Figure 7. R^2 separately fitted PFS IRC parametric fitting (short term)

Figure 8. R^2 separately fitted PFS IRC parametric fitting (long term)

Figure 9. Tafasitamab + R^2 separately fitted PFS IRC parametric fitting (short term)

Figure 10.Tafasitamab + R^2 separately fitted PFS IRC parametric fitting (long term)

Figure 11.Tafasitamab + R^2 vs R^2 separately fitted PFS IRC parametric fitting (long term)

Table 6. R^2 separately fitted PFS-IRC long term modelled landmarks

	Exponential	Gamma	Generalised gamma	Gompertz	Log-logistic	Log-normal	Weibull
1 years							
2 years							
3 years							
5 years							
7 years							
10 years							

Table 7. Tafasitamab + R^2 separately fitted PFS-IRC long term modelled landmarks

	Exponential	Gamma	Generalised gamma	Gompertz	Log-logistic	Log-normal	Weibull
1 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 12. Tafasitamab + R^2 vs R^2 PFS IRC smoothed hazard plots and hazard extrapolations

Figure 4: Overall Survival - Log-cumulative Hazard

Figure 5: Overall Survival - QQ plot

Figure 6: Overall Survival - Schoenfeld residuals

Table 8: Fit statistics of overall survival extrapolation (jointly fitted)

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	170.7	2	178.1	1
Gamma	171.5	4	182.7	3
Gen. Gamma	169.4	1	184.2	7
Gompertz	171.9	7	183.0	6
Log-Logistic	171.6	5	182.7	4
Log-Normal	171.0	3	182.1	2
Weibull	171.6	6	182.7	5

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; Gen. Gamma, generalised gamma
Note: Green shade represents the models within 5 points of the model with the best fit.

Figure 13. R^2 jointly fitted OS parametric fitting (short term)

Figure 14. R^2 jointly fitted OS parametric fitting (long term)

Figure 15. Tafasitamab + R^2 jointly fitted OS parametric fitting (short term)

Figure 16. Tafasitamab + R^2 jointly fitted OS parametric fitting (long term)

Figure 17. Tafasitamab + R^2 vs R^2 jointly fitted OS parametric fitting (long term)

Table 9. R^2 jointly fitted OS long term modelled landmarks

	Exponential	Gamma	Generalised gamma	Gompertz	Log-logistic	Log-normal	Weibull
2 years							
5 years							
10 years							
20 years							
30 years							
35 years							

Table 10. Tafasitamab + R^2 jointly fitted OS long term modelled landmarks

	Exponential	Gamma	Generalised gamma	Gompertz	Log-logistic	Log-normal	Weibull
2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
35 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 18. Tafasitamab + R^2 vs R^2 OS smoothed hazard plots and hazard extrapolations

[redacted]

Table 11: Tafasitamab + R^2 fit statistics of overall survival extrapolation (separately fitted)

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	73.5	6	76.5	1
Gamma	72.7	2	78.7	3
Gen. Gamma	74.0	7	82.9	7
Gompertz	73.4	5	79.4	6
Log-Logistic	72.8	4	78.8	5
Log-Normal	72.5	1	78.5	2
Weibull	72.8	3	78.8	4

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; Gen. Gamma, generalised gamma.
Note: Green shade represents the models within 5 points of the model with the best fit.

Table 12: R^2 fit statistics of progression-free survival extrapolation (separately fitted)

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	97.2	2	100	2
Gamma	99.2	5	105	5
Gen. Gamma	52.8	1	62	1
Gompertz	99.2	7	105	7
Log-Logistic	99.2	4	105	4
Log-Normal	98.7	3	105	3
Weibull	99.2	6	105	6

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; Gen. Gamma, generalised gamma.
Note: Green shade represents the models within 5 points of the model with the best fit.

Figure 19. R^2 separately fitted OS parametric fitting (short term)

Figure 20. R^2 separately fitted OS parametric fitting (long term)

Figure 21. Tafasitamab + R^2 separately fitted OS parametric fitting (short term)

Figure 22. Tafasitamab + R^2 separately fitted OS parametric fitting (long term)

Figure 23. Tafasitamab + R^2 vs R^2 separately fitted OS parametric fitting (long term)

Table 13. R^2 separately fitted OS long term modelled landmarks

	Exponential	Gamma	Generalised gamma	Gompertz	Log-logistic	Log-normal	Weibull
2 years							
5 years							
10 years							
20 years							
30 years							
35 years							

Notes: The generalised gamma does not converge

Table 14. Tafasitamab + R^2 separately fitted OS long term modelled landmarks

	Exponential	Gamma	Generalised gamma	Gompertz	Log-logistic	Log-normal	Weibull
2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
35 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 24. Tafasitamab + R^2 vs R^2 OS smoothed hazard plots and hazard extrapolations

[redacted]

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Tafasitamab with lenalidomide and rituximab for treating relapsed or refractory follicular lymphoma after 1 or more systemic treatments [ID6413]

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. 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.**	• Incyte Biosciences UK - £10,000 in 2024 towards our information provision • Abbvie - £15,000 in 2025 towards information provision, helpline and workshops and £25,000 in 2024 towards our preparing for treatment project, helpline and information provision • Bristol Myers Squibb - £10,000 in 2025 towards our mission and objectives and £8,000 in 2024 towards support groups • Pfizer - £4,000 in 2025 towards sponsorship of our lymphoma information days • Roche - £25,000 in 2025 towards information, peer support services and sponsorship of our lymphoma management courses, and £20,000 in 2024 towards our helpline, information provision and preparing for treatment project
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
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 follicular lymphoma. We combined the information gathered with our experiences of working with these patients and their carers.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Lymphoma is a type of blood cancer where white blood cells known as lymphocytes grow out of control. It is the 5th most common type of cancer in the UK. There are two main types of lymphoma: non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). NHL is the most prevalent, with around 14,200 people diagnosed each year in the UK. There are many different types of NHL which can be classified in two main ways. Firstly, they can be grouped into low-grade and high-grade based on how fast they grow. Secondly, they can be grouped depending on the type of lymphocyte they developed from: B cells or T cells. Follicular lymphoma (FL) is the most common type of NHL with 2,300 people being diagnosed every year in the UK. It is a low-grade lymphoma developing from B cells. The B cells usually develop in clumps called follicles within the lymph nodes. FL can occur at any age but tends to be a lymphoma of older age with most cases occurring in people over the age of 60. These people are usually still fit and healthy when they develop FL, often with grandchildren that they want to spend time with and thinking towards retirement. The diagnosis can be devastating and bring a blow to their future plans as described here: *"The worst part is the uncertainty … not knowing when it will return."* Most people with FL develop lumps, usually in their neck, armpits or groin. These are swollen lymph nodes. People can also experience weight loss, fevers, sweats, frequent infections and fatigue. As FL is a low-grade lymphoma these symptoms tend to develop gradually and it can often take a long time, and many appointments before a patient is diagnosed as described by this patient: *"… taking in my case several years to diagnose, and not knowing why I was becoming so incapacitated."* Fatigue tends to be a particularly disabling symptom, and one which our patients find has a huge impact on their lives.

	"Symptoms of fatigue, weight loss and loss of muscle mass with resulting physical weakness were severe enough to impact daily life." In some people FL has no symptoms and the diagnosis is picked up incidentally when having investigations for something else. As well as the physical impact, FL can have a less obvious impact on a patient's emotional and mental wellbeing. It can be a very anxious time when adjusting to the new diagnosis, as well as waiting for the treatment and hoping that it will work. This psychological impact should not be underestimated. FL can be both staged, which indicates how advanced it is, and graded, which indicates how many large lymphocytes can be seen under a microscope. Grades 1,2 and 3A are all slow growing and are treated in a different way to grade 3B which is fast growing. Our patients reflected that low grade is often viewed as less serious because treatment may not be immediately required, and survival is better. However, by doing this people forget about the emotional burden that having an incurable cancer is. When a person is diagnosed with follicular lymphoma this diagnosis does not just have an impact on them, but also the people around them. Family and friends often have to make changes to their lives taking on more caring and financial responsibilities. *"During Covid my partner and I ended up having to shield for 3 years, which put an end not only to attending social events, but greatly affected my ability to maintain friendships. I lost 90% of my friendships during that time, and feel more isolated today. I was advised by my hospital to shield for 2 years, then I relapsed, hence the extended isolation time. It was also extremely difficult to see 2 of my 3 children as they lived 200 miles away and could not take extended breaks off work."* *"My partner: at her worst, she could do very little [dog walks, shopping, housework, cooking, gardening]. Huge emotional burden."*

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	If a person is diagnosed with early-stage FL, which is about 1 in 5 people, they may not need to be started on treatment straightaway. People can go years like this in what is known as 'active surveillance', or 'watch and wait'. Whilst people avoid the symptoms of active treatment it is still a very difficult time and can be referred to by patients as 'worry and wait'. If treatment is required in early-stage disease this may be radiotherapy or rituximab antibody treatment. Most people at diagnosis have advanced stage disease. Despite this if they do not have troublesome symptoms, they may be treated the same as early-stage disease. If treatment is required, this is usually in the form of chemotherapy combined with antibody therapy. Chemoimmunotherapy, although often successful, can be very intense, requiring multiple visits to the hospital. It can also cause a number of short and long-term side effects including fatigue, sickness, diarrhoea, hair loss and recurrent infections. Here are some examples of the impact these side effects can have: *"I had bad brain fog for 7 years following RCHOP…It was very frustrating as I could no longer keep a lot of information in my head at one time, and to this day I forget things that people have told me about themselves that I really should remember."* *"Permanently depressed immune system: I don't use buses in winter due to the risk of picking up bugs, as I cannot shake them off and frequently end up with chest infections which wipe me out for 3-4 weeks each time. I sometimes have to decline social invitations at short notice if someone I am meeting has a bad cold, because each time I catch a virus I end up coughing and being awake at night for 3-4 weeks."* *"Peripheral neuropathy from RCHOP meant I had to stop driving, so I am now reliant on my partner, and not independent."* *"The chemo fatigue was challenging. I managed to get fit enough to walk our dogs, but for most of the 7 years following RCHOP I was unable to pull my weight with housework, or do any significant gardening. This is frustrating and I am so fortunate that my partner is really understanding."*

	If a patient responds well to chemoimmunotherapy they will usually be offered maintenance treatment. This involves having an injection of the antibody used in the chemoimmunotherapy every 2-3 months for up to 2 years. The aim of this is to keep the FL under control and make the remission period last as long as possible. This is because FL is unfortunately not curable, and almost everyone will relapse at some stage. Knowing that their disease is likely to come back whilst struggling with the side effects from treatment can be incredibly tough. *"There is an emotional impact both from dealing with these symptoms and their impact but also dealing with the knowledge that my type of lymphoma is currently incurable and carries a risk of transformation to a more aggressive form of lymphoma."* The treatment for relapsed disease depends on a number of things such as previous treatment used, the side-effects and impact of this treatment and how quickly the disease relapsed. Options for treatment are the same chemoimmunotherapy regimen, a different chemoimmunotherapy regimen, radiotherapy, obinutuzumab with bendamustine, or rituximab with lenalidomide. If there is a good response to treatment, a course of higher dose chemotherapy with a stem cell transplant may be offered. Unfortunately, none of these treatments, even the most intense, will cure FL and relapse is likely to happen at some point. This knowledge can have a profound impact on the mental wellbeing of the patient and their loved ones. *"Once you finish a treatment, not knowing what your next treatment will be. I was told to expect a stem cell transplant following RCVP, but at the end of treatment review I was told I'd be going on Rituximab maintenance instead. I was truly terrified of the idea of a stem cell transplant, and obsessed about it all through chemo."*

8. Is there an unmet need for patients with this condition?	Yes, patients strongly feel that there is an unmet need for a less toxic treatment with the potential for a good response which will provide another option for treatment and remove the uncertainty that patients with FL have to live with. *"I definitely benefitted from both chemos: if I had no had RCHOP in 2012 I would have been dead early in 2013. The side effects have been challenging, but I have learned to adapt, and not all are permanent. However chemo has some major side effects, and it also is not suitable for everyone [eg those with heart / liver/ kidney problems, and the elderly]. Having less toxic treatments like monoclonal antibodies would be fabulous if they were as effective at putting us into remission."*

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The main advantage that patients could identify was the option of a treatment with less short and long term side effects when compared to chemoimmunotherapy. Also, an option which may require less time in hospital was seen as a potential advantage. *"Yes, a less toxic treatment would mean that we had a much better quality of life. We would have less extreme problems during chemo, and would be less likely I think to struggle with chemo brain, we'd be fitter and therefore healthier and happier. Less need for isolation due to risks of picking up bugs would make the whole treatment more bearable. Not everyone gets through chemo without long term problems; a significant number develop health issues due to the toxicity of the drugs used. This further limits our treatment options when we relapse."* *"Anything less toxic and with fewer side effects would make life so much more bearable, and we'd hopefully be isolated from the world for a shorter time. My kids clearly struggled to see me very ill. I feel it was hard on them to see me struggle to get through each day. Even today I eventually run out of energy when caring for my grandkids, and I'm shattered after every visit".* *"If it's an infusion, it would surely be shorter than having a cocktail of chemo meds."*

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Our patients could not identify any possible disadvantages of this treatment.

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.	*"I'd imagine that less physically fit people and the really elderly may be able to tolerate it better than regular chemo, because I found Rituximab so easy to tolerate."*

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Our patients could not think of any potential equality issues.

Other issues

13. Are there any other issues that you would like the committee to consider?	*"For me, the most important criterion is, which drug is safest, and is likely to give me a good remission?"*
14. What current treatments are available (and are therefore relevant comparators for the technology) for people who have already had: • **1 systemic treatment** • **2 or more systemic treatments?**	

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission.	• Follicular lymphoma is the most common type of non-Hodgkin lymphoma • It is currently incurable and all patient's have to live with the prospect of relapse after each treatment • Current treatment options have a number of short- and long-term side-effects which can be debilitating • There is a need for more treatment options with less side effects and better response rates • Tafasitamab with lenalidomide and rituximab gives another non-chemotherapy based treatment option for patients, which can hopefully improve outcomes and quality of life.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Single Technology Appraisal

Tafasitamab with lenalidomide and rituximab for treating relapsed or refractory follicular lymphoma after 1 or more systemic treatments [ID6413]

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.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

NICE National Institute for Health and Care Excellence

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 10th April.** 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 follicular 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	Andrew DAVIES
2. Name of organisation	University Hospitals Southampton and University of Southampton UK Blood Cancer Research Network
3. Job title or position	Professor of Haematological Oncology
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 follicular lymphoma? ☐ A specialist in the clinical evidence base for follicular 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.	Nil
8. What is the main aim of treatment for follicular lymphoma?	Follicular lymphoma (FL) is a prototypical indolent B-cell non-Hodgkin lymphoma characterised by a relapsing–remitting clinical course with substantial clinical and

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	biological heterogeneity. Most patients present with advanced-stage disease, often with widespread lymphadenopathy and bone marrow involvement, yet may remain asymptomatic for prolonged periods. The clinical history is often marked by a variable need for treatment at presentation or progression, with initial management not infrequently involving active surveillance in selected patients. A small number of patients will have localised disease that can be managed with involved field radiotherapy. Systemic therapy is required in patients who have disease attributable symptoms, organ comprise or bulky/ rapidly progressing disease. Despite high initial response rates to immunochemotherapy, FL is generally considered incurable with standard approaches, as successive relapses are common and remissions tend to shorten over time. The concept of 'functional cure' in the era of modern therapies has been discussed in the clinical community, but this remains achievable in only a subset of patients. The clinical trajectory of FL is further complicated by the risk of histologic transformation to a more aggressive lymphoma phenotype, most commonly diffuse large B-cell lymphoma. This has a significant impact upon outcomes. Prognostic indices such as FLIPI and FLIPI2, along with emerging molecular markers, help stratify risk and may guide management decisions. Progression of disease within 24 months (POD24) refers to the occurrence of relapse or progression within two years of initiating first-line immunochemotherapy. It has emerged as a robust early clinical endpoint that identifies a subgroup of patients with markedly inferior outcomes compared with those experiencing later relapse. In recent years, therapeutic advances have begun to reshape outcomes, particularly in the relapsed and refractory setting. Nonetheless, optimising long-term disease control while minimizing treatment-related toxicity remains a central challenge in the management of this chronic malignancy. The overarching aim of treatment in follicular lymphoma (FL) is to achieve maximal durable disease control while preserving quality of life, recognising that for most patients the disease remains incurable with standard approaches. In this context,

	prolongation of progression-free survival (PFS) and delaying the need for subsequent lines of therapy are key therapeutic goals, particularly given the relapsing–remitting nature of FL. Equally important is minimising treatment-related toxicity, as many patients will require multiple lines of therapy over time; thus, balancing efficacy with tolerability is central to treatment selection. Beyond traditional clinical trial endpoints, patient centred outcomes, including quality of life, convenience and ease of administration, have to be key factors in clinical decision making. Consequently, shared decision-making has become a cornerstone of FL management, incorporating patient values, lifestyle considerations, and risk tolerance alongside disease-specific factors. This individualised approach ensures that treatment strategies align not only with prognostic and biological features but also with patient preferences, supporting optimal long-term care.
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)	A clinically meaningful treatment response reflects both depth and durability of remission alongside patient centred benefit. Achieving prolonged progression-free survival is a key therapeutic objective whilst maintaining functional status delivered in the context of low toxicity with high convenience.
10. In your view, is there an unmet need for patients and healthcare professionals in follicular lymphoma?	Within the current NHS landscape there are clear unmet needs in FL. From a disease perspective, there remain heterogeneity of outcomes and suboptimal durability of response particularly after successive therapies. With progressive lines of therapies, remission durations are shorter. There is also a continued need for therapies with improved toxicity profiles, given the cumulative burden of treatment over a patient's lifetime. There is however a particularly pronounced unmet need in the relapsed and refractory setting in the current NHS framework. It is well recognised that in the UK patients with FL have fewer accessible options compared with other countries. It is clear that we need equitable and timely access to innovative therapeutics for FL within the NHS.

	The need for more tolerable, outpatient-friendly therapies which that allow patients to maintain normal functioning is clear. The psychological burden of repeated relapse and uncertainty is important for patients with FL. Patients wish to enjoy as much time as possible in remission and well before disease recurrence. This reinforces the unmet need for treatments that provide longer-lasting remission and reduce the cyclical nature of care .
11. How is follicular 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?	Follicular lymphoma (FL) in England is primarily managed according to national and international guidance, and selection is much informed by assessments from National Institute for Health and Care Excellence (NICE). The British Society for Haematology follicular lymphoma guidelines from 2020 are no longer considered contemporaneous. The most widely used international framework in the UK comes from the European Society for Medical Oncology [Eyre et al 2025]. NICE technology appraisals are strongly influential in determining which therapies are routinely available within the NHS, while the guidelines provide detailed recommendations on diagnosis, risk stratification, and management. First-line treatment is stratified by tumour burden and symptoms. Patients with asymptomatic, low–tumour burden disease are typically managed with active surveillance (“watch and wait”). For those requiring treatment, standard frontline therapy consists of anti-CD20–based immunochemotherapy (e.g., rituximab with bendamustine, CHOP, or CVP), followed in some cases by maintenance rituximab to prolong progression free survival. A small number of patients with localised presentation (rare) will be managed with radiotherapy alone. In the relapsed setting, options include re-treatment with immunochemotherapy, rituximab–lenalidomide (R^2) and for patients with high-risk features high-dose chemotherapy and peripheral blood progenitor rescue may be offered to younger and fitter patients when remission has been achieved. More recently the bispecific

	antibody epcoritamab has been approved in the third line + setting [TA1139]. There is a limited role for allogeneic transplantation. There are variations in practice • **Choice of frontline regimen** (e.g., bendamustine-rituximab vs R-CHOP), often influenced by patient fitness, clinician preference, risk profile and loal practice. • **Use and duration of maintenance rituximab**, which may differ based on interpretation of benefit vs infection risk • **Management at relapse**, particularly timing of treatment and sequencing of therapies Shared decision-making plays a major role. If adopted within the NHS, tafasitamab, lenalidomide and rituximab would most likely be positioned as an alternative to or replacement for R² in patients after at least one prior line of therapy. The regimen could be used at second line or third-line plus. The impact of introduction would • **Shift standard of care**: It could become a preferred option over R² alone, based on improved progression-free survival. • **Delay of subsequent therapies**: By improving durability of response, it may postpone the need for more treatments

	• **Increased treatment complexity**: The addition of a third agent would increases treatment burden compared with R². This will have an impact on day case capacity and patient convenience • **Patient selection refinement**: Clinicians may preferentially use the tafasitamab, R^2 regimen in patients at higher risk of early progression of disease (eg POD24) as a chemotherapy free approach. This would be particularly advantageous to older patients or those with co-morbidities
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? • 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)	Tafa-R² would be used broadly in a similar clinical context to rituximab–lenalidomide (R²), primarily in the relapsed/refractory setting after at least one prior or more lines of therapy. Like R², it is a time-limited, outpatient-delivered regimen, and would fit within existing pathways. The addition of tafasitamab introduces a more intensive early treatment phase compared with R² where rituximab dosing is less frequent after induction. There will be more resource use in deliver than R2. This includes infusions capacity and pharmacy work load. Monitoring would be similar to R2 and given the broadly comparable toxicity profile, so no major additional burden in adverse event management is anticipated. Improved progression-free survival may conversely reduce downstream resource use, including fewer relapses and delayed need for subsequent therapies therefore reducing hospitalisations and need for subsequent therapy related to progressive disease. The regimen would be delivered exclusively in secondary care within haematology and oncology day care settings.

	Introducing Tafa-R² into the NHS would not require major new infrastructure and would be a relatively straightforward addition to existing lymphoma services. Adoption would involve service adaptation, including: • Additional chair time and staffing in chemotherapy/day units, particularly in the early cycles • Staff education on tafasitamab administration, scheduling, and toxicity management but this is in line with other therapeutic monoclonal antibodies • Some adjustments to clinic flow to accommodate more frequent early visits Overall, Tafa-R² would be used in a similar line of therapy and setting as current care, but with some greater upfront resource use due to increased infusion requirements. It has the potential to offer system-level benefits if improved disease control reduces the need for treatments. In the EPCORE NHL-1 study, the basis for TA1139, epcoritamab monotherapy delivered after two or more prior lines of therapy, a complete response rate of 62.5% The inMIND data in the ≥2 prior lines subgroup showed tafa-R^2 benefit was consistent with the overall trial outcomes (HR ~0.41) although in the third line + setting there it is not possible to be too granular with the data presented. In the third line plus setting there may be shift from epcoritamab to tafa-R^2 depending on individual patient factors/selection. These are outlined below.
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?	To date there is no demonstration that the tafasitamab + R2 regiment prolongs overall survival compared to R2 + placebo. This is because follow-up was short, just 15 months. The secondary endpoint of time to next treatment was longer with tafasitamab + R2 (not reached vs 29.8 months). This is clinically meaningful for patients as it represents time not on therapy. At the time of the primary report of the study 83%

	of patient receiving tafasitamab had not started an additional therapy, whilst 66% of the R2+placebo patients had required an additional treatment. Quality of life was measured in the inMIND study by validated questionnaires. The results were similar. It is a reasonable assumption that with prolong follow-up, those in continued remission will enjoy a better quality of life than those patients with relapsed disease.
14. For how long might you expect the full treatment effect of tafasitamab with lenalidomide and rituximab to be durable? • Do you expect the treatment effect to wane over time? • Would you be able to estimate, or point to evidence supporting, how long the full effect of treatment would last?	The inMIND study demonstrated a substantial improvement in progression-free survival with tafasitamab added to R². The median was 22.4 months compared to 13.9 months for R^2. The hazard ratio was 0.43, ie a 57% risk reduction. Prolongation of PFS was regardless of POD24 status. There is no expectation that there would be a waning in the effect size over time and this appears apparent from the Kaple-Meier curves presented, although follow-up is short.
15. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
16. 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? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Additional burden of delivery outlined above in section 12. There will be no additional requirement for supportive care, adverse event management or monitoring.
17. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Initiation of Tafa-R^2 would follow established principles for FL

	• Clinical indication for therapy (e.g., symptomatic or high–tumour burden disease, GELF criteria) • Use in the relapsed/refractory setting • Fitness for treatment, • Adequate haematological and organ function • Patient meets any required NICE appraisal guidance Clinicians may prioritise patients at higher risk of poor outcomes (e.g., early relapse/POD24) Stopping rules are usually clearly defined and include: • Disease progression • Unacceptable toxicity (including persistent cytopenias or serious infection) • Completion of planned treatment duration • Patient choice Treatment continuation is guided by regular evaluation. This comprises clinical review and blood monitoring (e.g., neutropenia, thrombocytopenia). Imaging (typically CT or PET-CT) will be performed at defined intervals to assess response along with ongoing assessment of symptoms and quality of life. Monitoring would be no different to those receiving R^2. There is no additional biomarker testing required.
18. 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	There may be a number of aspects that are not captured by conventional instrument including • The clear psychological benefits of durable remissions. Avoiding relapse carries substantial benefit including reduced anxiety, greater future planning and a sense of more time living normally. These are not well captured by conventional utility measures.

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	• Longer progression-free intervals mean fewer repeated treatment episodes, clinic visits, and transitions between therapies. • Postponing or avoiding my intensive therapy with higher toxicities. • Reducing therapy exposure will reduce cumulative toxicities. • Reduced impact of relapse on the burden caregivers.
19. 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?	As a novel targeting antibody based regimen, Tafa-R² can reasonably be considered innovative within the current FL landscape. It is perhaps best characterised as an incremental but meaningful advance rather than a true step-change. Its innovation lies in combining dual antibody targeting(CD20 via rituximab and CD19 via tafasitamab with an immunomodulatory backbone (lenalidomide), thereby enhancing immune-mediated tumour clearance without introducing chemotherapy. The improvement in progression-free survival seen in the inMIND study suggests a clear advance over the current R² standard. It is pragmatic innovation, delivering enhanced efficacy using a regimen that is feasible within standard NHS outpatient infrastructure. The regimen addresses several well-recognised unmet needs in FL by improving durability of response in relapsed disease. A central challenge in FL is progressively shorter remissions with each line of therapy. It provide an options for patients at higher risk (e.g., POD24). A more effective second-line therapy may be particularly valuable for patients with early relapse, who have poorer outcomes with standard approaches. It offers a way to enhance efficacy without reverting to cytotoxic chemotherapy, which is important for patients with comorbidities or cumulative toxicities and may delay the need for more intensive therapies in some.
20. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	In the phase III inMIND study, the addition of tafasitamab to lenalidomide and rituximab did not result in a clinically meaningful increase in overall toxicity compared with the control arm of R², with broadly comparable safety profiles

	between groups. No excess in treatment-related mortality was observed with the triplet. From a qualitative standpoint, the toxicity spectrum of tafasitamab–lenalidomide–rituximab largely mirrored that of R² alone, with cytopenias (particularly neutropenia), fatigue, and gastrointestinal effects such as diarrhoea representing the most common adverse events across both arms. Serious adverse events were not disproportionately increased relative to the control group. The efficacy gains observed with tafasitamab are achieved without a trade-off in tolerability. Considering a choice between epcoritamab and tafa-R^2 in the third line + setting, the former has some specific toxicities which may guide treatment choices 1. Cytokine release syndrome (CRS). CRS occurred in 65% of patients in the EPCORE pivotal cohort, with 2% reaching grade 3. Even with the optimised cycle 1 regimen, CRS occurred in 49%. This requires step-up dosing, and in the pivotal cohort hospitalisation after the first full dose. For patients with significant comorbidities or who live far from a specialist centre this toxicity profile may be a meaningful barrier. Tafa-R^2 has no CRS signal given that is is a non-T-cell-engaging antibody 2. Immune effector cell-associated neurotoxicity syndrome (ICANS). ICANS occurred in 6% of the EPCORE pivotal cohort. While grades were low (4% grade 1, 2% grade 2) and all resolved, for patients with pre-existing neurological conditions or in whom neurotoxicity monitoring is difficult, this is a relevant consideration. 3. Infections. Epcoritamab is a T-cell-engaging bispecific that continuously redirects and activates T-cells, combined with its B-cell depleting effect, creating profound immunosuppression. Pneumonia occurred in meaningful numbers in the EPCORE pivotal study, and infections were the leading cause of treatment discontinuation with 13% of patients discontinued due to infection. With tafa-R^2 serious pneumonia occurred in

	8% with tafasitamab versus 5% with placebo. Although both regimens carry meaningful infection risk, as expected in this patient population receiving B-cell depleting therapies, the infection burden appears heavier with epcoritamab. For older patients, those with pre-existing pulmonary disease, or immunocompromised individuals, this distinction is clinically meaningful.
21. 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?	The phase III inMIND trial broadly reflects key elements of UK NHS practice, but with important limitations. The study population aligns well with the population treated with R² in England and consistent with NHS commissioning. It included UK centres The trial captured the key efficacy outcomes relevant to NHS decision-making, although OS data remain immature. PFS is a validated and widely accepted surrogate endpoint in FL, particularly in the relapsed setting. It correlates with duration of remission, time off treatment and benefits to patients of disease control
22. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
23. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA137, TA627, TA629 or TA1139?	No
24. How do data on real-world experience compare with the trial data?	No robust real-world datasets yet exist for the tafasitamab–lenalidomide–rituximab triplet in FL.

25. If tafasitamab with lenalidomide and rituximab was recommended, would it displace any use of epcoritamab (see TA1139) at third-line or later? • Would tafasitamab with lenalidomide and rituximab be used in the same population that epcoritamab is used? • Why might people be offered one treatment but not the other?	Tafasitamab + R^2 (rituximab and lenalidomide) has a distinct mechanism of action to epcoritamab. It would not displace the latter as third-line therapy. It is likely that tafasitamab + R^2 would be used as a second-line therapy. In the third line setting there are circumstances where Tafa-R^2 may displace epcoritamab. 1. Refractory to CD20 therapies, 43% of the inMIND population were refractory to CD20 therapies. Tafa-R^2 showed consistent benefit regardless of anti-CD20 refractory status. The CD19 targeting of tafasitamab provides an independent mechanism. 2. Cytokine release syndrome risk with epcoritamab: Concerns in those with co-morbidities or frailty. 3. ICANS concerns eg patients with neurological co-morbidity 4. Access and administration setting. Epcoritamab, while subcutaneous, requires the infrastructure for CRS monitoring, step-up dosing protocols, and ready access to tocilizumab. This may be a practical limiting factor. 5. Preference for fixed-duration therapy. Tafa-R2 is a 12-cycle fixed-duration regimen. Epcoritamab is treat-to-progression. For logistical or psychological reasons, patient may prefer a mixed duration therapy.
26. 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 belief, sex, and sexual orientation or people with any other shared characteristics.	Not to my knowledge

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:

- Tafa-R^2 provides a statistically significant and clinically meaningful improvement in progression-free survival across a high-risk population. This is important for patients.
- Readily deliverable within current NHS infrastructure
- A favourable and manageable safety profile that does not compromise treatment delivery. No additional demand on NHS systems from increased burden of adverse events
- Durable responses result in delayed time to next treatment, reducing downstream treatment burden and toxicities
- Innovation. The first validated approach combining two unconjugated monoclonal antibodies targeting different B-cell antigens, establishing a new clinical paradigm.

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.

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Single Technology Appraisal

Tafasitamab with lenalidomide and rituximab for treating relapsed or refractory follicular lymphoma after 1 or more systemic treatments [ID6413]

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.

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NICE National Institute for Health and Care Excellence

Part 1: Treating follicular 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	Mark Bishton
2. Name of organisation	University of Nottingham; Nottingham University Hospitals NHS Trust
3. Job title or position	Associate Professor and Honorary 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 follicular lymphoma? ☒ A specialist in the clinical evidence base for follicular 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.	N/A
8. What is the main aim of treatment for follicular lymphoma?	Most patients have incurable, advanced stage disease that has a long natural history. A small number of asymptomatic patients never need treatment and approximately 30-50% of patients able to receive standard treatment never need

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	further treatment. Those patients who do progress, tend to have a long relapsing/remitting course despite multiple lines of therapy. The primary treatment aim for all lines of therapy when needed is to keep the disease at bay (progression free survival) whilst maintaining quality of life.
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)	Complete metabolic remission (by CT-PET imaging)
10. In your view, is there an unmet need for patients and healthcare professionals in follicular lymphoma?	Yes. Patients with relapsed follicular lymphoma classically follow a long relapsing/remitting course with progressively shorter remissions despite multiple lines of therapy. This paradigm is being altered by newer therapies – epcoritamab has just been commissioned by NICE for third line treatment. There is early progression and poor survival in 20-25% of patients treated with first line immuno-chemotherapy These patients suffer cumulative complications or treatment resistance and pass through multiple lines of therapy quickly. There is no single, standard treatment pathway, and limited outcome data for immuno-chemotherapy in R/R FL. There is a need to focus on improving/maintaining quality of life for patients who require multiple lines of therapy.
11. How is follicular lymphoma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which?	There is no single standard treatment pathway, and for relapsed disease no randomised trials comparing experimental with immuno-chemotherapy. There is limited outcome data from immuno-chemotherapy in rrFL.

• 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?	There are British Committee for standards in haematology (BCSH) guidelines for follicular lymphoma which encompass first and later lines of therapy. The relapsed section is outdated as it does not consider rituximab-lenalidomide (R2) as a 2L+ option or epcoritamab as 3l+ option and discusses non-commissioned/withdrawn treatment options (radioimmunotherapy, idelalisib). For first line treatment, there are two chemotherapy options CHOP/CVP and Bendamustine, and each can be combined with either Rituximab or Obinutuzumab monoclonal antibody for first line treatment. Antibody maintenance can be used for responders for up to 2 years although use of maintenance varies significantly. From second line onwards R2 is commissioned and is probably the most common regimen although was never compared to immuno-chemotherapy In this setting, and immuno-chemotherapy with rituximab can also be used. Therapies are sequenced at the physician's discretion and so 2nd line+ therapies vary significantly. Dependant on the age and fitness of the patient, autologous stem cell transplantation, and those patients who did not receive maintenance antibody after first line immuno-chemotherapy may receive following second (or third) line therapy. Epcoritamab is now commissioned for 3L+ treatment unless patients have already received bispecific antibodies as part of a clinical trial or compassionate access scheme and will be used for nearly all patients in this setting. R2-tafasitamab would be preferentially used for 2L treatment and would mean that immuno-chemotherapy would likely only be used for the rare 4L+ patients.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	R2-tafasitamab would be given in Daycase of level 2+ centres in secondary 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)	Tafasitamab is a naked antibody and there is no concern regarding administration so no extra equipment, or training is required. There are 30 infusions of tafasitamab and whilst rituximab infusions are given on days 1, 8, 15, and 22 of cycle 1 and day 1 of cycles 2–5, there would be 22 extra visits, as well as extra chair time (1.5-2 hours per infusion) as otherwise patients would be on oral lenalidomide monotherapy.
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?	Based on phase 3 randomised controlled trial data: Improvements in progression free survival should be seen compared to R2. Quality of life studies were reported (but not presented) as being the same when compared to R2. No overall survival benefit was seen compared to R2 but follow up is short and so this is expected.
14. For how long might you expect the full treatment effect of tafasitamab with lenalidomide and rituximab to be durable? • Do you expect the treatment effect to wane over time? • Would you be able to estimate, or point to evidence supporting, how long the full effect of treatment would last?	It is very hard to know if the treatment effect will wane over time in part as in the follow up remains short and for the R2 group the median PFS was <12 months and the R2-tafa group was still receiving 2 weekly infusions up to this point. There is no reason to think the effect will be lost however as the 'gap between the curves' seems to remain consistent.
15. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No

16. 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? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Other than extra treatments in haematology day cases as outlined above, I do not think there will be any new practical implications. The RCT reported were no notable differences in immunoglobulin levels at baseline or during the study among patients receiving tafasitamab or placebo. IVIG was used in 37/274 (14%) patients receiving tafasitamab and 23/272 (8%) receiving placebo based on investigator's site practice.
17. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Only patients who require treatment 2L+ will receive treatment. R2-tafa is a time limited treatment which would finish after 12 cycles unless there is disease progression or toxicity. The median number of cycles of R2-tafa received in the study was 12
18. 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	Quality of life in the RCT was measured by the EQ-5D-5L scale, the EORTC QLQ-C30 scale, and the five FACT-Lym subscales and three composite scores were similar for R2 and R2-tafa. I cannot think of other relevant substantial health benefits.
19. 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?	The inMIND study was the first phase III RCT to show improvement in progression free survival compared to an accepted standard of care in relapsed FL for over 15 years. There was no patient sub-group which didn't benefit from the addition of tafasitamab to R2.

20. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The addition of tafasitamab to R2 did not alter the incidence of either Gr1-2 or 3-4 adverse events – even though the study was conducted during the Covid-19 pandemic.
21. 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?	The RCT compared R2-tafasitamab, and R2 is considered one of the standards of care for RR FL in the UK. There was improvement in the PFS which I consider to be the most important outcome for this disease and there was no detriment to measured quality of life which is also very important. No surrogate outcome measures were used I am not aware of any adverse effects not apparent in clinical trials which have come to light subsequently.
22. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
23. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA137, TA627, TA629 or TA1139?	Another RCT has also used R2 as the comparator arm and outcomes appear similar to the inMIND study: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(25)02360-8/fulltext
24. How do data on real-world experience compare with the trial data?	There is limited real world evidence for R2. I am only aware of a single centre study conducted by a very large cancer centre (MSKCC) which reported on 69 pts with relapsed FL. Outcomes appear somehwta better than the R2 arm in inMIND but there is significant bias. https://haematologica.org/article/view/haematol.2024.285600

25. If tafasitamab with lenalidomide and rituximab was recommended, would it displace any use of epcoritamab (see TA1139) at third-line or later? • Would tafasitamab with lenalidomide and rituximab be used in the same population that epcoritamab is used? • Why might people be offered one treatment but not the other?	I think if approved, patients will receive R2-tafa at 2L and 3L+ epcoritamab. Epcoritamab will not be displaced. Most patients who will have epcoritamab in the coming 12-24 months will have already received R2 and will not be eligible for R2-tafa. If R2-tafa is approved then outside of clinical trials, this regimen would have the most evidence in the 2L setting and would be used preferentially.
26. 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 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	There are no equality concerns. Ethnicity data is reported in the RCT.

• 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:

R2-tafasitamab has shown progression free survival benefits compared to R2 in the context of an RCT.

R2-tafasitamab is well tolerated does not show increased toxicity when compared to R2.

R2-tafasitamab requires 30 extra infusions to deliver.

Click or tap here to enter text.

Click or tap here to enter text.

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Single Technology Appraisal

Tafasitamab with lenalidomide and rituximab for treating relapsed or refractory follicular lymphoma after 1 or more systemic treatments [ID6413]

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 follicular lymphoma or caring for a patient with follicular 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).

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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.

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Your response should not be longer than 15 pages.

The deadline for your response is **12pm** on **Wednesday 29 April 2026.** 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, 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.

Patient expert statement

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NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with follicular lymphoma

Table 1 About you, follicular lymphoma, current treatments and equality

1. Your name	Dallas Pounds
2. Are you (please tick all that apply)	☐ A patient with follicular lymphoma? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with follicular 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 not completed part 2 of the statement

6. What is your experience of living with follicular lymphoma? **If you are a carer (for someone with follicular lymphoma) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for follicular 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?**	
8. If there are disadvantages for patients of current NHS treatments for follicular lymphoma (for example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of tafasitamab with lenalidomide and rituximab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your 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 tafasitamab with lenalidomide and rituximab 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 tafasitamab with lenalidomide and rituximab over current treatments on the NHS please describe these.	

For example, are there any risks with tafasitamab with lenalidomide and rituximab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from tafasitamab with lenalidomide and rituximab 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	
12. Are there any potential equality issues that should be taken into account when considering follicular lymphoma and tafasitamab with lenalidomide and rituximab? 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 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?	

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:

- 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.

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Friday 10 April 2026.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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2. Are you (please tick all that apply)	☐ A patient with follicular lymphoma? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with follicular lymphoma? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	The Follicular Lymphoma Foundation
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 not completed part 2 of the statement

6. What is your experience of living with follicular lymphoma? **If you are a carer (for someone with follicular lymphoma) please share your experience of caring for them**	As a patient organisation, we are in touch with a large patient base, with whom we have regular contact. I personally do not have a lived experience of FL or any of the relevant treatments. However, I am representing the feelings and experience of our patient community. There is a range of patient experiences from very low to very high tumour burden; from those who are on watch and wait to those who are waiting for their 6th line of treatment for example. Living with FL is often described by patients as living with a constant sense of uncertainty and unpredictability. Our patient insights have shown a wide range of experiences, from those on watch and wait with minimal symptoms to others undergoing their sixth line of treatment. The most common fear is that FL will return or transform into a more aggressive form. Fewer patients worry about rapid progression or treatment side effects, but many express concern about running out of treatment options and affording care. Our surveys have revealed that nearly half of patients find coping with uncertainty about the future to be the hardest challenge. Other major difficulties include balancing emotional wellbeing with physical symptoms, and feeling isolated or misunderstood. Constant anxiety, worrying that every new symptom is FL-related, is a common theme. Carers often share these emotional burdens. We hear that carers play a crucial role in daily life and treatment decisions, and they too struggle with anxiety, helplessness, and the need for their own support.
7a. What do you think of the current treatments and care available for follicular lymphoma on the NHS?	The current treatments available for R/R FL patients are very limited, unless they transform to DLBCL, where CAR-T is already approved.

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	Our patient insights have shown that in general people are aware that innovative treatments exist but there are major knowledge gaps and concerns around accessibility.
8. If there are disadvantages for patients of current NHS treatments for follicular lymphoma (for example, how they are given or taken, side effects of treatment, and any others) please describe these	There are very few options for R/R FL patients on the NHS, and chemotherapy is still widely used. The side-effect profile, and cumulative toxicity experienced by patients affects every part of their lives – with chronic fatigue, immunosuppression, brain fog, neuropathy, nausea, and over well-known side-effects. These can significantly impact on patients' daily lives and ability to work.
9a. If there are advantages of tafasitamab with lenalidomide and rituximab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your 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 tafasitamab with lenalidomide and rituximab 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**	A randomized trial showed the marked prolongation of progression-free-survival with this combination compared to no tafasitamab, meaning patients lived longer without the disease being active. This treatment combination also being a chemo-free regimen provides several advantages – one of the most significant being avoiding the chemo-related side effects. We consider living free-of-disease for a significantly longer time is the most important. Additionally, with the intended use in earlier stages of relapse, it gives a new option for patients who may be fitter, younger and with less aggressive FL biology.
10. If there are disadvantages of tafasitamab with lenalidomide and rituximab over current treatments on the NHS please describe these. For example, are there any risks with tafasitamab with lenalidomide and rituximab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	We do not see any particular disadvantages of this combination compared with lenalidomide-rituximab based on the randomized InMIND trial, or with other regimens approved for later line therapy of follicular lymphoma.

11. Are there any groups of patients who might benefit more from tafasitamab with lenalidomide and rituximab 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	The other immunotherapeutic option in this patient population is epcoritamab, which has a different side-effect and risk profile, and can be limited to administration in tertiary care centers. Also, most patients eventually relapse after either of these treatments. So, having both regimens will provide 2 sequential treatment options to many patients to prolong their disease-free, and likely overall, survival. Further, the tafasitamab regimen may well be more available outside major centers, enhancing accessibility to new treatments.
12. Are there any potential equality issues that should be taken into account when considering follicular lymphoma and tafasitamab with lenalidomide and rituximab? 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 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?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Patients are very excited and hopeful for a new option for R/R FL, in a space where there is very little available.
- Tafasitamab +R2 has shown some excellent response in FL patients, and so it would be hugely significant should it be approved.
- There is always anxiety over the expected side-effects and cumulative toxicity, and patients will want reassurance over that.
- The trials supporting this appraisal look promising in terms of increasing the PFS without significant difference in side effect profile.
- It would be a significant advantage to have a chemo-free treatment regimen option for R/R FL patients, affecting patients' quality of life.

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EXTERNAL ASSESSMENT GROUP REPORT

Tafasitamab with lenalinomide and rituximab for treating relapsed or refractory follicular lymphoma after 1 or more systemic treatments [ID6413]

Produced by

York Technology Assessment Group, University of York, Heslington, York, YO10 5DD

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Date completed	16/02/2026

Declared competing interests of the authors

None

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

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Contributions of authors

AL co-wrote Sections 1 and 3.3, wrote sections 2.2, 3.4. 3.5 and 3.7 and contributed to the write-up of all clinical sections (Sections 2 and 3).

DC performed the critical review of the economic analyses and contributed to the writing of section 4 and Section 5 of the report.

CUC co-wrote Section 3.3 and wrote Sections 2.3 and 3.1.

JD performed the critical review of the economic analyses and contributed to the writing of section 4 and Section 5 of the report.

JB wrote Sections 2.1 and 3.3.2.10.

MH provided information support for the project and wrote Section 3.1.1.

MS wrote Section 3.6, oversaw all clinical parts of this report (Sections 2 and 3), and takes joint responsibility for the report.

RH contributed to the writing of sections 1, 4 and 5, oversaw the critical review of the economic analyses, and takes joint responsibility for the report.

Note on the text

All commercial-in-confidence (CON) data have been highlighted in blue and underlined.

Table of Contents

List of Tables

List of Figures

List of abbreviations

1L	First-line
2L	Second-line
2L+	Second-line and beyond
3L+	Third-line and beyond
AESI	Adverse events of special interest
ASCT	Autologous Stem Cell Transplant
CAR-T	Chimeric antigen receptor T-cell therapy
CDF	Cancer Drugs Fund
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIC	Commercial in confidence
CMH	Cochran-Mantel-Haenszel
CMR	Complete metabolic response
CQ	Clarification question
CS	Company submission
CSP	Clinical study protocol
DoR	Duration of response
EAG	External assessment group
FAS	Full analysis set
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FL	Follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRQL	Health related quality of life
HT	Histological transformation
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
INAHTA	International Health Technology Assessment database
iNHL	Indolent non-Hodgkin's lymphoma
INV	Investigator
IRC	Independent Review Committee
IRT	Interactive Response Technology
ITC	Indirect treatment comparison
KM	Kaplan-Meier
LCH	Log cumulative hazard
LDH	Lactate dehydrogenase
LOT	Lines of treatment
mAb	Monoclonal antibody
MAIC	Matching-adjusted indirect comparisons
MHRA	Medicines and Healthcare products Regulatory Agency
MLZ	Marginal zone lymphomas
NA	Not applicable
NE	Not estimable

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NKCC	Natural Killer Cell Count
O-B	Obinutuzumab + bendamustine
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PET-CR	Positron Emission Tomography - Complete Response
PFS	Progression-free survival
PLB	Placebo
POD24	Progression of disease within 24 months
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
QALY	Quality-adjusted life year
QoL	Quality of life
QWiC	Institute of Quality and Efficiency in Health Care
R/R	Relapsed or refractory
R^2	Placebo + rituximab and lenalinomide
R-B	Rituximab + bendamustine
R-Chemo	Rituximab-based chemotherapy
R-CHOP	Rituximab with cyclophosphamide, doxorubicin, vincristine, prednisone
RCT	Randomised controlled trial
R-CVP	Rituximab with cyclophosphamide, vincristine and prednisolone
R-ESHAP	Rituximab, etoposide, methylprednisolone, cytarabine, cisplatin
R-GDP	Rituximab, gemcitabine, dexamethasone, cisplatin
R-GEMOX	Rituximab, gemcitabine, oxaliplatin
ROB 2.0	Cochrane risk of bias tool
SACT	Systemic anti-cancer therapy
SAP	Statistical analysis plan
SD	Standard deviation
SLR	Systematic literature review
SoC	Standard of care
STA	Single technology assessment
$T+R^2$	Tafasitamab + rituximab and lenalidomide
TEAE	Treatment-emergent adverse event
TRAE	Treatment-related adverse event
TTNT	Time to next treatment
UK	United Kingdom
US	United States
VAS	Visual Analogue Scale

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 explains the key issues in more detail. Secondary issues and modelling errors identified by the EAG are explored in sections 1.4 and 1.5. Background information on the condition, technology and evidence, and non-key issues are presented in later sections of the EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1 Summary of key issues

ID 6413	Summary of issue	Impact on results	Report sections
1	The overal survival benefit of tafasitamab is highly uncertain: inMIND OS results are very immature, and it is uncertain whether PFS benefits compared with R^2 will translate into OS improvements.	Large	3.3.2, 4.2.5.2
2	The relative effectiveness of tafasitamab + R^2 against most comparators is highly uncertain: Most of the effectiveness evidence is informed by unanchored matching-adjusted indirect comparisons with significant limitations	Unknown	3.4, 3.5, 4.2.5.1
3	Appropriate model structure and surrogacy assumptions: A state-transition model may offer a more appropriate approach given the limited overall survival (OS) data, but it relies on the assumption that improvements in progression-free survival (PFS) will lead to commensurate improvements in OS.	Large	4.2.2
4	Extrapolation of progression free survival: The extrapolation of PFS is based on a joint modelling approach, which is not clearly justified. The EAG considers that separately fitted curves may provide a superior fit to the observed data.	Small	4.2.5.3
5	Post progression survival (PPS) benefit for Tafasitamab Plus R^2: In a scenario analysis using a state-transition model, the company assumes a post-progression survival (PPS) benefit that is not clearly justified.	Large	4.2.5.5
6	Waning assumptions: In modelling PFS and OS, a full treatment effect is assumed for five years, followed by five years of waning. The empirical support for this is, however, weak and lacks a clear clinical rationale.	Large	4.2.5.4

ID 6413	Summary of issue	Impact on results	Report sections
7	Joint modelling of 2L and 3L+ populations: The cost-effectiveness of Tafasitamab plus R^2 appears to differ substantially depending on whether a 2L or 3L+ setting is considered.	Large	4.2.3

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- The company's preferred model structure uses a partition survival model (PSM) approach; the EAG prefers to use a state transition model (STM).
- When using an STM approach, the company prefers to use a weighted approach combining data from the Haematological Malignancy Research Network (HMRN) database and the GADOLIN trial. The EAG prefers to use data from the HMRN database alone.
- The company prefers to use a jointly fitted generalised gamma model to extrapolate progression free survival (PFS); the EAG prefers to use a separately fitted log logistic.
- The company prefers to apply waning of the treatment effect, assuming 5 years full effect followed by 5 years waning. The EAG prefers to apply 2 years of full effect followed by 3 years waning.
- The EAG prefers not to pool data on the proportion of events that are death events
- The EAG prefers to apply relative dose intensity (RDI) adjustment on a per-cycle basis.
- When comparing to R-chemotherapy regimens, the EAG prefers to assume time to treatment discontinuation (TTD) is the same as R^2.

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 ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing progression-free survival
- Increasing overall survival

Overall, the technology is modelled to affect costs by:

- Its higher acquisition costs
- Its higher administration costs

The modelling assumptions that have the greatest effect on the ICER are:

- The size of the overall survival benefit for tafasitamab plus R^2 (Extrapolation of OS)
- The model structure adopted PSM vs STM and in the context of the size of the post-progression survival benefit for tafasitamab plus R^2 (extrapolation of post-progression survival)
- Treatment waning
- How relative dose intensity is applied in the economic model

1.3 EAG's key issues

Issue 1 The overall survival benefit of tafasitamab is highly uncertain.

Report section	3.3.2
Description of issue and why the EAG has identified it as important	The clinical evidence for tafasitamab plus rituximab and lenalinomide (tafasitamab plus R^2) is based on the interim results of inMIND trial, an ongoing, phase 3 RCT comparing tafasitamab plus R^2 with placebo plus rituximab and lenalinomide (R^2), that included 548 patients with relapsed or refractory (R/R) follicular lymphoma (FL). At the February 2024 data cut, with a median follow-up of 15.3 months, only 38 death events were observed and median overall survival (OS) was not reached in either arm. While there was some evidence of improved OS with tafasitamab plus R^2 when compared to placebo plus R^2 it was not statistically significant. Data are limited by significant immaturity, which preclude any meaningful interpretation. It is uncertain whether progression-free survival (PFS) benefits will translate into a longer-term OS benefit for tafasitamab plus R^2. Evidence from trials in FL indicates that PFS may only be a weak surrogate predictor of OS, although this evidence has limitations.
What alternative approach has the EAG suggested?	The EAG presents several analyses to explore the uncertainty in OS. These include an alternative model structure (see Issue 3) and scenario analyses exploring cases where no OS benefit is modelled.
What is the expected effect on the cost-effectiveness estimates?	In a scenario analysis where no OS benefit is modelled, the ICER increases from £32,821 to £682,597 per QALY
Could any additional evidence or analyses be provided to resolve this key issue?	Substantially more mature data from inMIND is required to show that tafasitamab plus R^2 leads to clinically significant improvements in OS compared with R^2. The next inMIND data cut will be the final analysis and is anticipated in [redacted]. Observational data through managed access (Cancer Drugs Fund-CDF) may be beneficial provided it is collected over a sufficiently long period. Although non-randomised, this data may not be subject to some of the potential limitations from inMIND, notably: the applicability of the trial population (see secondary issue 1), and confounding from subsequent therapies not available for routine practice (notably Chimeric Antigen Receptor [CAR] T-cell therapy).

Issue 2 The relative effectiveness of tafasitamab + R^2 against most comparators is highly uncertain

Report section	3.4, 3.5
Description of issue and why the EAG has identified it as important	inMIND only included comparator evidence for R^2. No randomised comparisons were available between tafasitamab + R^2 and all other comparators relevant to the decision problem, notably rituximab+chemotherapy (R-chemotherapy) regimens. Due to the limited evidence, all indirect comparisons were informed by unanchored matching-adjusted indirect comparisons (MAICs) for OS, PFS and time-to-next treatment (TTNT). All MAICs have significant limitations and may not provide reliable estimates of relative effectiveness. None of the MAICs could account for all relevant prognostic factors and treatment effect modifiers, and therefore failed to meet a key assumption. All studies were unblinded and had design limitations. Substantial differences in trial design and populations limited their comparability. OS data was based on few events and was generally immature, and OS results were potentially confounded by subsequent therapies that may not reflect NHS practice. Some MAIC results may lack face validity, when compared to previous STAs. The direction and magnitude of bias due to these limitations is highly uncertain. The company model makes the "conservative" assumption that all R-chemotherapy options have the same effectiveness and safety as R^2 on the basis that R-chemotherapy is expected, based on past assessments, to be worse than R^2. Both EAG and company clinical advisers consider this assumption to have some problems; it does not fully concur with the findings of adjusted and unadjusted indirect comparisons.
What alternative approach has the EAG suggested?	The lack of suitable data prevents a meaningful exploration of the relative efficacy of R-chemotherapy.
What is the expected effect on the cost-effectiveness estimates?	Unknown
Could any additional evidence or analyses be provided to resolve this key issue?	Sufficiently longer-term OS evidence would address the issue of OS immaturity, and Cancer Drugs Fund (CDF) data would potentially address confounding due to subsequent non-routine therapies (see Issue 1); however, future evidence would be unlikely to address most of the limitations inherent to the indirect comparisons.

Issue 3: Most appropriate model structure and surrogacy assumptions

Report section	4.2.2
Description of issue and why the EAG has identified it as important	The company's base-case analysis uses a partitioned survival model (PSM) in which the magnitude of modelled overall survival benefits is derived directly from extrapolated OS data from the inMIND trial. As discussed in Issue 1, however, the OS data available to inform the economic analysis are very limited, and the resulting extrapolations are highly uncertain. Given these limitations, the EAG considers it inappropriate to directly infer the magnitude of OS benefit from the available data. Instead, the EAG prefers a state-transition model (STM) structure in which progression-free survival PFS serves as the primary driver of modelled survival benefits. This approach provides a more structured framework for estimating OS benefits and makes the assumptions underlying the PSM, specifically the implied surrogate relationship between PFS and OS, more explicit. The EAG notes, however, that evidence supporting PFS as a surrogate for OS is generally weak and associated with substantial uncertainty. Therefore, the EAG's preference for an STM approach is contingent on the assumption that some OS benefit exists, which, as highlighted in Issue 1, remains highly uncertain based on the current evidence.

What alternative approach has the EAG suggested?	The EAG preference is to use an STM model in place of the company's preferred PSM structure.
What is the expected effect on the cost-effectiveness estimates?	In scenario analysis using an STM approach and assuming no post-progression survival benefit, the ICER increases from £32,821 to £42,277 per QALY.
Could any additional evidence or analyses be provided to resolve this key issue?	Longer-term OS evidence is necessary to establish the magnitude of any OS benefit, and would also support assumptions relating to the predictive value of PFS benefits already observed.

Issue 4: PFS extrapolation

Report section	4.2.5.3
Description of issue and why the EAG has identified it as important	The company used a joint modelling approach to extrapolate PFS, estimating a single set of baseline survival parameters across treatment arms rather than fitting separate models to each arm. The company's preferred PFS extrapolation is the generalised gamma distribution. The EAG considers the company's overall approach to selecting an appropriate parametric extrapolation to be broadly valid and consistent with best practice, but notes that, while joint modelling is methodologically acceptable, the rationale for its use appears to be driven more by concerns regarding OS extrapolations than by the PFS data itself. The EAG therefore considers it appropriate to also explore a range of separately fitted parametric functions. Among these, the separately fitted log-logistic is preferred. This model demonstrates good statistical fit in both treatment arms, with no alternative providing a clearly superior fit. It also shows a modestly improved visual fit to the observed Kaplan–Meier data compared with the company's jointly fitted models, which tend to overestimate PFS relative to the observed data, particularly for tafasitamab plus R^2.
What alternative approach has the EAG suggested?	The EAG preference is to use a separately fitted log-logistic model to extrapolate PFS. Amongst the jointly fitted models, the EAG agrees that the company's preferred jointly fitted generalised gamma is the most appropriate.
What is the expected effect on the cost-effectiveness estimates?	In scenario analysis where a separately fitted gamma model is fitted to PFS the ICER increases from £32,821 to £34,156 per QALY.
Could any additional evidence or analyses be provided to resolve this key issue?	Longer-term PFS may help better inform decisions about the most appropriate PFS extrapolation.

Issue 5: PPS assumptions

Report section	4.2.5.5
Description of issue and why the EAG has identified it as important	In the company's scenario analysis using a STM structure, several alternative approaches to modelling PPS are explored. These approaches consider different assumptions regarding the potential for tafasitamab plus R² to provide additional benefits after progression, drawing on data from the HMRN and GADOLIN trials. The company's preferred approach is based on a weighted analysis of both trials and models a PPS survival benefit in rituximab-refractory patients. The EAG has several concerns regarding the company's preferred approach. These include questions about its consistency with the current OS data and the rationale for using an STM framework, the lack of direct evidence supporting PPS benefits, and the absence of a clear biological justification. The EAG is particularly concerned that the company's preferred approach assumes PPS benefits observed in the GADOLIN trial can be applied to the current context, which lacks a clear clinical rationale. The EAG is also concerned that the company's method for estimating PPS survival based on subtracting median OS from median PFS may misrepresent mean survival and time-dependent risks, making it an imprecise and potentially misleading method for modelling transitions.
What alternative approach has the EAG suggested?	The EAG preference is to use data from the HMRN database to model PPS and to assume no PPS benefit.
What is the expected effect on the cost-effectiveness estimates?	In scenario analysis using an STM approach and assuming no post-progression survival benefit, the ICER increases from £32,821 to £42,277 per QALY.
Could any additional evidence or analyses be provided to resolve this key issue?	Further exploration of the clinical rationale for PPS could be valuable, as could a more in-depth analysis of PPS using data from the inMIND trial. However, the current uncertainty in PPS assumptions largely reflects the lack of mature OS data from inMIND. Additional follow-up of this data will therefore be necessary to meaningfully inform and update the current assumptions.

Issue 6: Waning assumptions

Report section	4.2.5.4
Description of issue and why the EAG has identified it as important	The company applies waning assumptions to both PFS and OS, assuming a five-year period of full treatment effect followed by a five-year gradual waning of the effect. These assumptions are informed by those used in TA627, which assumed a five-year full treatment effect followed by instantaneous waning, along with clinical expert opinion. The EAG agrees with the company that waning of PFS and OS treatment effects is appropriate and that gradual waning is more clinically plausible than an instantaneous loss. The EAG is, however, concerned about both the duration of the full treatment effect period and the length of the waning period. The company base-case assumptions imply some partial treatment effect for a total of ten years, which is well beyond the maximum follow-up of the trial (approximately 2.5 years). The EAG also notes that analysis of hazard trends for both PFS and OS does not indicate a clear continuation of treatment effect beyond two years, supporting the use of more conservative assumptions regarding the duration of the treatment effect.
What alternative approach has the EAG suggested?	In the absence of clear evidence to the contary the EAG prefers to assume a full treatment effect of 2 years followed by 3 years waning.
What is the expected effect on the cost-effectiveness estimates?	In scenario analysis, assuming 2 years full effect followed by 3 years waning, the ICER increases from £32,821 to £57,565 per QALY.
Could any additional evidence or analyses be provided to resolve this key issue?	Further exploration of the biological rationale for a longer treatment effect duration may be helpful. Further, data collection for both OS and PFS would also help better guide the most appropriate waning assumptions.

Issue 7: Joint modelling of 2L and 3L+

Report section	4.2.3
Description of issue and why the EAG has identified it as important	Aligning with the marketing authorisation, the company's base-case analysis considers the combined 2L+ population. While the EAG considers this approach reasonable, it notes that aggregating across lines of therapy may obscure important differences in the cost-effectiveness of tafasitamab plus R^2. Cost-effectiveness is likely to vary by line of therapy because of differences in treatment effect, prognosis, and the relevance of comparators. Subgroup analyses from inMIND suggest a slightly greater relative treatment effect in 3L+ patients; however, confidence intervals overlap and the trial was not powered to support formal comparisons between subgroups. Patients treated in the 3L+ setting also have a poorer prognosis, as evidenced by higher rates of POD-24, longer time since diagnosis, and greater rituximab refractoriness. Comparator relevance may also differ by line of therapy: both R^2 and R-chemotherapy are relevant in 2L, whereas R^2 alone is more appropriate in 3L+, introducing additional heterogeneity in cost-effectiveness.
What alternative approach has the EAG suggested?	The substantial difference in estimated cost-effectiveness suggests that an optimised recommendation may warrant consideration.
What is the expected effect on the cost-effectiveness estimates?	In Scenario analysis, considering the 2L and 3L+ populations separately, the ICER for each subgroup is respectively £50,635 and £27,377 per QALY.
Could any additional evidence or analyses be provided to resolve this key issue?	Additional evidence or analyses is unlikely to help resolve this issue.

1.4 Secondary issues identified by the EAG

Issue 8: The applicability of the inMIND population to clinical practice is uncertain

Report section	3.3.1 and 4.2.3
Description of issue and why the EAG has identified it as important	inMIND includes a population that is likely to be younger on average than in NHS practice. It is unclear whether the proportion of patients with POD24 in inMIND reflects NHS evidence for R/R FL patients. The proportion of patients who are refractory to rituximab is substantially higher in inMIND than in the HMRN database, although the extent to which the HMRN data provided by the company reflects the entire NHS population of R/R FL who would be eligible for tafasitamab plus R^2 is uncertain.
What alternative approach has the EAG suggested?	The EAG is satisfied with the company's base assumptions.
What is the expected effect on the cost-effectiveness estimates?	In Scearnio analysis using an average starting age of 68 (based on HMRN data), the ICER increases from £32,821 to £34,032 per QALY.
Could any additional evidence or analyses be provided to resolve this issue?	CDF data for tafasitamab plus R^2, and NHS England data on the characteristics of the population receiving comparator therapies relevant to the decision problem would allow for a more complete assessment of the applicability of the inMIND population to NHS practice.

Issue 9: Calculation of the proportion of PFS events that are deaths

Report section	4.2.5.5
Description of issue and why the EAG has identified it as important	The company assumes that the proportion of death events is the same for patients receiving tafasitamab plus R² and those receiving R² alone, and therefore pools data across treatment arms in the inMIND trial to estimate this parameter. The EAG considers this approach inappropriate, as it is inconsistent with the observed trial data, which show a higher proportion of PFS events resulting in death in the tafasitamab plus R² arm ([redacted] compared with R² alone ([redacted]). Pooling across arms therefore, masks an observed imbalance and misrepresents the inMIND results. Moreover, given the additional toxicity associated with the triplet regimen, a higher risk of death prior to progression with tafasitamab plus R² is clinically plausible and cannot be ruled out.
What alternative approach has the EAG suggested?	The EAG therefore prefers to use arm-specific rates based on the observed data, which more accurately reflect the trial outcomes and associated mortality risks.
What is the expected effect on the cost-effectiveness estimates?	In scenario analysis, where specific death proportions are used, the ICER decreases from £32,821 to £32,219 per QALY.
Could any additional evidence or analyses be provided to resolve this issue?	Further PFS evidence will help refine estimates of the proportion of death events.

Issue 10: Relative dose intensity and chair capacity

Report section	4.2.7.1
Description of issue and why the EAG has identified it as important	Delivery of tafasitamab plus R² raises important NHS capacity concerns. Compared with R², the regimen requires seven additional cycles of IV infusion, longer infusion times, and greater transfusion use, placing additional pressure on day-unit services. The company's clinical advisory board, along with the EAG's clinical advisor, were particularly concerned that this may impact the uptake of tafasitamab plus R². The EAG also notes that the observed RDI for tafasitamab in the inMIND trial in later treatment cycles, indicates that an increasing proportion of patients do not receive all scheduled infusions as treatment progresses. This is consistent with a higher incidence of treatment-emergent adverse events (TEAEs) with tafasitamab plus R^2 compared with R^2 alone, and may suggest that the observed RDI pattern is driven by cumulative toxicity and an increasing burden of adverse events over time. In terms of the model, the primary concern is that the application of a single, constant average RDI to adjust costs does not reflect this time-dependent decline in drug administration. In practice, early cycles appear to be delivered at close to full intensity, whereas later cycles involve materially fewer administered doses. As a result, this approach may underestimate both drug acquisition and administration costs.
What alternative approach has the EAG suggested?	Capacity concerns may impact the evaluation of the company's managed access proposal as implementation in the NHS may require further investment in NHS capacity. The EAG prefers to apply treatment cycle-specific RDI to more accurately account for the resource implications of missed doses.
What is the expected effect on the cost-effectiveness estimates?	Where cycle-specific RDI is used in the model, the ICER decreases from £32,821 to £31,946 per QALY.
Could any additional evidence or analyses be provided to resolve this issue?	Input from NHS England on day case capacity may be informative to address capacity concerns.

1.5 Company's modelling errors identified by the EAG

The company updated its model to clarify and correct a minor error in the calculation of subsequent treatment costs. No further errors were identified.

1.6 Summary of EAG's preferred assumptions and resulting ICER

Table 2 presents the results of the EAG's pairwise analysis vs $R^{2,}$ and

Table 3 presents fully incremental results considering all potential comparators.

Table 2 EAG Exploratory Pairwise scenario analyses (deterministic)

Scenario		Technology	Total		Incremental		Pairwise ICER
			Costs	QALYs	Costs	QALYs	
Company base case		R^2	[redacted]	[redacted]			
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£32,821
1a	**Model Structure (STM with PPS benefit from HMRN)**	R^2	[redacted]	[redacted]			
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£42,277
1b	**Model Structure (STM with PPS benefit from GADOLIN)**	R^2	[redacted]	[redacted]			
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£20,605
1c	**Model Structure (STM with PPS benefit Weighted)**	R^2	[redacted]	[redacted]			
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£27,246
2	**PSM, OS Joint with no tx effect covariate**	R^2	[redacted]	[redacted]			
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£682,597
3	**PFS Extrapolation: Separately fitted log-logistic**	R^2	[redacted]	[redacted]			
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£33,559
4	**PFS Extrapolation: Separately fitted gamma**	R^2	[redacted]	[redacted]			
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£34,156
5	**OS Extrapolation: Separately fitted log logistic**	R^2	[redacted]	[redacted]			
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£137,930
6a	**Waning of OS and PFS: 5 yrs full & 0 yrs waning**	R^2	[redacted]	[redacted]			
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£42,402
6b	**Waning of OS and PFS: 2 yrs full & 3 yrs waning**	R^2	[redacted]	[redacted]			
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£57,565
7	**TTD for R-Chemo is equal to R2**	R^2	Tafa +Applies only to the fully incremental				
		Tafa +R^2					
8	**Proportion of deaths in PFS events is tx arm-specific (inMIND)**	R^2	[redacted]	[redacted]			
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£32,219
9	**Starting age, 68.0 yrs based on HRRN 2L R-CVP**	R^2	[redacted]	[redacted]	[redacted]	[redacted]	£34,032
		Tafa +R^2	[redacted]	[redacted]			
10	**RDI applied per tx cycle (Tafa)**	R^2	[redacted]	[redacted]	[redacted]	[redacted]	£31,946
		Tafa +R^2	[redacted]	[redacted]			
		R^2	[redacted]	[redacted]			

EAG base case (deterministic)	Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£71,172
EAG base case (probabilistic)	R^2	[redacted]	[redacted]			
	Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£69,587
Abbreviations: ICER, incremental cost effectiveness ratio; LYs, life-years; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; QALY, quality-adjusted life-years; R^2, lenalidomide and rituximab; R-B, rituximab with bendamustine, R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP, Rituximab with cyclophosphamide, vincristine and prednisolone; RDI, relative dose intensity; STM, state transition model; Tafa, Tafasitamab; Tx, treatment.						

Table 3 EAG Exploratory fully incremental scenario analyses (deterministic)

Scenario		**Technology**	**Total**		**Incremental**		**Fully incremental ICER**
			Costs	**QALYs**	**Costs**	**QALYs**	
Company base case		R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
		R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£33,707
1a	**Model Structure (STM with PPS benefit from HMRN)**	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
		R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£43,478
1b	**Model Structure (STM with PPS benefit from GADOLIN)**	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
		R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£21,096
1c	**Model Structure (STM with PPS benefit Weighted)**	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
		R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£27,949
2	**PSM, OS Joint with no tx effect covariate**	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
		R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£728,075
3	**PFS Extrapolation: Separately fitted log-logistic**	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
		R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£34,471
4		R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-

	PFS Extrapolation: Separately fitted gamma	R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£35,105
5	**OS Extrapolation: Separately fitted log logistic**	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
		R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£142,860
6a	**Waning of OS and PFS: 5 yrs full & 0 yrs waning**	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
		R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£43,595
6b	**Waning of OS and PFS: 2 yrs full & 3 yrs waning**	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
		R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£59,245
7	**TTD for R-Chemo is equal to R2**	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
		R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£35,602
8	**Proportion of deaths in PFS events is tx arm-specific (inMIND)**	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
		R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£33,132
9	**Starting age, 68.0 yrs based on HRRN 2L R-CVP**	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
		R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£34,955
10	**RDI applied per tx cycle (Tafa)**	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
		R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£32,722
EAG base case (deterministic)		R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
		R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated

	R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
	R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
	Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£73,312

Abbreviations: ICER, incremental cost effectiveness ratio; LYs, life-years; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; QALY, quality-adjusted life-years; R^2, lenalidomide and rituximab; R-B, rituximab with bendamustine, R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP, Rituximab with cyclophosphamide, vincristine and prednisolone; RDI, relative dose intensity; STM, state transition model; Tafa, Tafasitamab; Tx, treatment.

1.7 Outline of confidential comparator or subsequent treatment prices

The confidential appendix to the EAR includes analyses using confidential pricing arrangements for lenalidomide, rituximab, rituximab (subcutaneous injection), and gemcitabine. This includes the results of the company base-case analysis, sensitivity and scenario analyses and the results of exploratory analyses conducted by the EAG, with results reflecting the application of confidential pricing arrangements.

2 BACKGROUND

This report presents a critique of the company submission (CS) to NICE from Incyte Pharmaceuticals on the clinical effectiveness and cost-effectiveness of tafasitamab (MINJUVI®) in combination with lenalidomide and rituximab (R^2) for the treatment of relapsed or refractory (R/R) follicular lymphoma (FL) in adults (aged ≥18 years) after one or more prior systemic therapies.

At the time of submission, tafasitamab has not yet received marketing authorisation for the FL indication. The European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion in November 2025, with European Commission approval received in January 2026. At the time of the CS, approval from the Medicines and Healthcare products Regulatory Agency (MHRA) was anticipated in [redacted].

2.1 Critique of the company's description of underlying health problem

2.1.1 Follicular lymphoma

The company's description of FL is presented in CS Section 1.3.1 and is broadly appropriate, accurate, and relevant to the decision problem.

Follicular lymphoma is an indolent but incurable B-cell non-Hodgkin lymphoma, characterised by repeated cycles of remission and relapse over a prolonged disease course. The disease arises from malignant B lymphocytes that accumulate in lymph nodes to form follicular structures, though involvement may also occur in extranodal sites such as the bone marrow, spleen, liver, and lungs.[1, 2]It predominantly affects older adults, with a median age at diagnosis of approximately 66–68 years in England, and occurs with similar frequency in males and females (sex rate ratio of 1.0).[3-6]

Cancer registration statistics recorded 2,404 new cases of FL in England in 2022, and approximately 20,000 people are estimated to be living with the condition across England and Wales.[3, 5] During the 2023–24 period, FL accounted for 21,798 consultant episodes and 20,960 admissions, resulting in 19,514 day cases and 11,954 bed days.[5]

Follicular lymphoma is staged from Stage I to Stage IV based on the extent of nodal and extranodal involvement, with advanced-stage disease (Stage III/IV) indicating more widespread disease across multiple lymph node regions and/or involvement of extranodal sites.[1, 8] The majority of patients (up to 70%) present with advanced-stage disease at diagnosis.[4] In addition to staging, FL is classified by histological grade, which reflects the tumour growth rate and biological behaviour. Approximately 90–95% of patients are diagnosed with low-grade disease (Grade 1–3A), which is generally considered indolent or slow growing at presentation.[7] However, despite this initial classification,

disease behaviour can vary considerably between patients and may become more aggressive over time, particularly following multiple relapses.[7]

2.1.2 Prognosis in relapsed or refractory disease

In clinical practice, relapsed and refractory disease represent distinct but overlapping concepts. Refractory disease generally refers to failure to respond to treatment, including progression during or shortly after therapy, whereas relapsed disease refers to recurrence following an initial response, often at new anatomical sites. In FL, partial responses may be clinically acceptable where symptoms resolve or disease burden substantially reduces, and treatment may be discontinued despite residual disease.

While FL is commonly described as "slow growing", disease behaviour is highly heterogeneous. With successive relapses, the disease often becomes more aggressive and increasingly resistant to treatment.[9] The risk of histological transformation to more aggressive lymphoma, most commonly diffuse large B-cell lymphoma, is approximately 2–3% per year.[10] Most patients with FL require multiple lines of systemic therapy over their lifetime. Prognosis worsens with each subsequent relapse or line of therapy as the disease becomes increasingly resistant to treatment.[11, 12]

Real-world evidence summarised in CS Table 3 demonstrates a marked decline in clinical outcomes with successive lines of therapy. Across multiple datasets, median overall survival, progression-free survival, and time to next treatment decrease substantially with later-line treatment. Although these trends are consistent, absolute estimates vary across evidence sources, likely reflecting differences including study populations, treatment eras, and definitions of lines of therapy.

Early relapse represents a particularly poor prognostic variable. Approximately 20% of patients experience progression of disease within 24 months (POD24) of initial treatment.[13-17] Patients with POD24 have substantially worse outcomes, with 5-year overall survival rates of 26–50%, compared with 86–94% in patients without POD24.[14, 18, 19]

The EAG agrees with the company that patients who experience POD24 tend to present with more adverse risk profiles at diagnosis compared with non-POD24 patients, including elevated LDH, higher Follicular Lymphoma International Prognostic Index (FLIPI) scores, more advanced disease stage, higher-grade disease and older age, although predictive variables of early relapse are not fully defined, and clinical factors alone only have limited positive predictive value.[18]

The company appropriately emphasises the heterogeneity of the FL disease course, which is supported by clinical advice to the EAG. Importantly, there is no reliable objective method at disease onset to predict individual patterns of response, remission durability, or disease progression, and average survival estimates should therefore be interpreted with caution.

2.1.3 Burden of disease

The company's description of the burden of disease and health-related quality of life (QoL) in FL is presented in CS Section 1.3.3. Overall, the EAG considers this description to be broadly appropriate and relevant to the decision problem, although some aspects warrant further contextualisation.

Follicular lymphoma imposes a substantial and multifaceted burden on patients, encompassing physical symptoms, psychological distress, and impacts on daily functioning.[20] Specifically, fatigue is identified as one of the most common and debilitating symptoms and is frequently reported across the disease course.[20] However, clinical advice to the EAG indicates that fatigue can be difficult to disentangle from treatment-related effects, particularly in patients receiving systemic therapies, and its severity and persistence vary considerably between individuals.

Health-related QoL worsens as patients progress through successive lines of therapy, with QoL often relatively well preserved during first-line (1L) and second-line (2L) treatment, but tends to deteriorate more noticeably in later lines of therapy (third-line and beyond [3L+]), where treatment options become more limited and disease control more difficult.[21, 22] This pattern reflects both increasing disease burden and cumulative treatment-related toxicity.

Advanced FL is associated with a broad symptom burden, including fatigue, systemic 'B symptoms', and complications of bone marrow involvement such as anaemia and increased susceptibility to infection.[20] Distinguishing the relative contribution of disease and treatment to these symptoms is often challenging, which is particularly relevant when interpreting comparative QoL outcomes between treatment strategies.

Clinical advice to the EAG highlights that side effects and treatment tolerability vary substantially between patients, influenced by age, comorbidities, disease characteristics, and prior treatment exposure. In general, chemotherapy-based regimens are associated with a greater negative impact on quality of life, largely due to immunosuppression and the associated risks of infection and treatment-related adverse effects. Once patients exhaust available treatment options, health-related quality of life often declines markedly toward the end of life, typically in the final three to six months, driven by progressive disease, increasing symptom burden, and limited scope for further disease-modifying therapy.

UK population-based modelling found marked variation in progression and survival outcomes across the disease course, and lifetime QALY varying substantially according to age, treatment pathways, relapse history, and transformation to aggressive lymphoma.[23] This highlights that late-line disease and end-of-life care may contribute disproportionately to morbidity and healthcare utilisation.

2.1.4 Tafasitamab

The EAG considers the company's description of the technology to be clear, accurate, and appropriate.

Tafasitamab (MINJUVI®) is an Fc-enhanced humanised monoclonal antibody (IgG1) that targets the CD19 antigen, which is broadly and homogeneously expressed on malignant B cells in FL.[24-26] Binding of tafasitamab to CD19 results in tumour cell death through immune-mediated mechanisms, including antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis, as well as through direct induction of apoptosis.[24, 25, 27, 28] In the proposed regimen, tafasitamab is administered in combination with lenalidomide and rituximab, providing dual targeting of CD19 and CD20.

The recommended dose of tafasitamab is 12 mg per kg body weight, administered as an intravenous infusion.[27] Tafasitamab is given on Days 1, 8, 15 and 22 of Cycles 1 to 3, and on Days 1 and 15 of Cycles 4 to 12, with each cycle lasting 28 days.[27] Tafasitamab is administered in combination with R^2 for a fixed duration of up to 12 cycles, in accordance with the draft Summary of Product Characteristics. Premedication to reduce the risk of infusion-related reactions is recommended prior to administration, particularly during the initial infusions.[29]

2.2 Critique of the company's overview of current service provision

2.2.1 Clinical pathway

The clinical pathway for FL is presented in CS Section 1.3.4. and is broadly reflective of practice. The EAG agrees with the company that there is no single standard of care or recommended sequence of treatments, and that treatments lines are not strictly defined. The EAG clinical adviser noted that treatment sequences vary widely across patients in FL. Treatment decisions are informed by disease burden (including disease characteristics and stage), patient characteristics (age, frailty and comorbidities), biological and genetic factors (including histological grade and transformation risk), and treatment history (including time to relapse and prior exposure) in the R/R setting. Patient and clinician preferences also contribute to variations in practice. There is currently no objective way to assess at onset how quickly patients will respond and progress, or how aggressive the disease may become over time.

CS Figure 1 presents a summary of treatment options available to FL patients based on NICE recommendations. Clinical advice to the EAG confirmed that this was broadly reflective of practice in England and Wales.

In the 1L setting, the treatment goal is to achieve a long-lasting remission. For patients with asymptomatic, low-burden, advanced disease, the standard of care is watch and wait ('active monitoring'), whilst rituximab monotherapy is also an option for patients with low-burden disease. For symptomatic and fit patients, rituximab plus bendamustine (R-B) is the most frequently prescribed chemoimmunotherapy.[30] Alternative rituximab or obinutuzumab-based chemotherapy (R/O-Chemo) may be considered. This includes a combination of rituximab, cyclophosphamide, doxorubicin, oncovin (vincristine), and prednisone (R-CHOP), which is typically reserved for patients where high-grade transformation is confirmed or suspected. Chlorambucil or cyclophosphamide, vincristine and prednisone (CVP), with rituximab or obinutuzumab, is favoured in patients for whom the toxicities of bendamustine are thought to be too high.[31] Clinical advice to the EAG indicated rituximab-based therapies were generally preferred as more familiar, and although obinutuzumab-based immunochemotherapy and maintenance therapy has been reported to result in longer progression-free survival than rituximab-based therapy, high-grade adverse events are more common with obinutuzumab-based chemotherapy; predominantly infusion-related reactions, but also a small increase in the rate of severe neutropenia and severe infections. [32] Maintenance therapy can be considered for those who respond to 1L induction.

In 2L, the choice of therapy is notably influenced by the patient's POD24 status. Following relapse on 1L treatment, R^2 is a standard of care option (TA627).[33] R-chemotherapy may be alternatively offered to patients who are non-refractory to rituximab. [34] This includes R-B if not previously received, while younger, fitter patients may receive R-CHOP (followed by Auto-SCT in a subset of eligible patients); R-CVP may be preferred in older, frailer patients. Obinutuzumab plus bendamustine (O-B) is recommended for patients who are refractory to rituximab or who progressed within six months of rituximab therapy (NICE TA629),[35] although market share data clinical advice to the company and the EAG indicates this is rarely used in practice. [30, 34] Autologous Stem Cell Transplant (ASCT) may be considered for a subset of young and fit patients with poor response to initial therapy.

In the 3L+ setting, patients who received R-chemotherapy will most commonly receive R^2.[30] R-chemotherapies may be repeated due to lack of alternative options, although ESMO guidelines do not recommend R-chemotherapy in 3L+.[36] NICE guidance for epcoritamab for R/R FL after 2 or more systemic treatments is under development at the time of writing this report; the draft guidance recommends that epcoritamab should not be used in adults with R/R FL after two or more lines of therapy.[9] There is no established treatment for R/R FL following three or more systemic treatments. Patients who have exhausted other options may repeat treatments, receive an investigational treatment as part of a clinical trial, or undergo palliative radiotherapy. CAR-T therapy (axicabtagene ciloleucel) is not recommended for R/R FL after 3 or more prior systemic therapies.[37]

2.2.2 Intended positioning of tafasitamab within the clinical pathway

CS Figure 2 presents the company's intended positioning of tafasitamab plus R^2 in the clinical pathway. The company considers that tafasitamab plus R^2 would primarily displace R^2, and that may also partially displace some use of R-chemotherapy in the 2L. The company therefore considers that relevant comparators in this appraisal are R^2 and R-chemotherapy in the 2L treatment setting and R^2 in 3L+. The EAG clinical adviser considered the company's positioning to be broadly reasonable and noted that tafasitamab plus R^2 has the potential to displace a significant proportion of R-Chemotherapy in the treatment pathway; for instance, tafasitamab plus R^2 could be a suitable alternative for patients who might not tolerate R-Chemotherapy. The EAG clinical adviser also indicated that R-chemotherapy could be a relevant comparator in the 3L setting.

2.3 Critique of company's definition of decision problem

CS Table 1 presents a description of the NICE final scope, the decision problem addressed within the CS and the rationale for any differences between the two. This information, along with the EAG comments, is presented in Table 4.

2.3.1 Population

The population addressed in the company decision problem is in line with NICE's final scope. The inMIND trial included adults with R/R FL after one or more systemic treatments.

2.3.2 Intervention

The intervention, tafasitamab (12 mg per kg body weight administered intravenously) in combination with lenalidomide (20 mg daily self-administered orally) and rituximab (375 mg/m^2 administered intravenously), is in line with the NICE final scope and licensed indication.

2.3.3 Comparators

The company evaluated evidence for all comparators listed in the NICE final scope, except for rituximab monotherapy. Overall, the EAG considers that this approach is appropriate. The EAG clinical adviser agreed with the company's justification that rituximab monotherapy may only be used as a palliative option in the R/R FL setting and is therefore not a relevant comparator. The company's decision problem focused on therapies that tafasitamab plus R^2 would displace such as R^2 and rituximab with chemotherapy (including R-B, R-CHOP and R-CVP) ± rituximab maintenance as second line, and R^2 as 3L treatment. O-B was also included, although the company noted that its use is very limited in practice. Although the final NICE guidance on epcoritamab as not yet been issued at the time of writing this report, the EAG considers the company's decision to include it in the decision problem to be appropriate.

2.3.4 Outcomes

The company reported all the outcomes listed in the NICE's final scope: progression-free survival (PFS), overall survival (OS), response rates (RR), time to next treatment (TTNT), duration of response (DOR), adverse effects of the treatments and health related quality of life (HRQL). The company also reported additional outcomes including PFS on next treatment and rate of histological transformation.

Table 4 Summary of decision problem

-	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with relapsed or refractory follicular lymphoma after 1 or more systemic treatments	Adults with relapsed or refractory follicular lymphoma after 1 or more systemic treatments	No difference	No concerns.
Intervention	Tafasitamab in combination with lenalidomide and rituximab (tafasitamab plus R^2)	Tafasitamab plus R^2	No difference	No concerns.
Comparator(s)	Established clinical management without tafasitamab: Treatment choice will depend on previous treatments, and how effective those treatments were. • Obinutuzumab with bendamustine followed by obinutuzumab maintenance • Lenalidomide with rituximab • Rituximab alone or in combination with chemotherapy Epcoritamab (subject to NICE evaluation)	Established clinical management without tafasitamab: Treatment choice will depend on previous treatments, and how effective those treatments were. Second-line treatment choices include: • Lenalidomide with rituximab • Rituximab with chemotherapy ± rituximab maintenance Third line and beyond treatment choices include: Lenalidomide with rituximab	The decision problem focuses on those treatments tafasitamab would displace. Full details on the current pathway of care and positioning of tafasitamab are provided in CS Section 1.3.4. Other 'comparator' treatments listed in the final scope issued by NICE would not be displaced with the introduction of tafasitamab plus R^2; however, in acknowledgement of their inclusion in scope, the submission appendices provide comparative analyses to additional treatments as follows: Second-line treatment: • Obinutuzumab with bendamustine (O-B) followed by obinutuzumab maintenance O-B followed by obinutuzumab maintenance is restricted to FL that did not respond to or progressed up to 6 months after treatment with rituximab or a rituximab-containing regimen. < 5% of patients are treated with this regimen in clinical practice.[38, 39] Market share data show 0% use of obinutuzumab in the R/R FL setting year to date.[40]	No concerns. The EAG clinical adviser confirmed that rituximab montherapy is not a relevant comparator where tafasitamab plus R^2 would be expected to be positioned in the clinical pathway. The company evaluated evidence for all other comparators listed in the NICE final scope.

-	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			Third-line treatment and beyond: • Epcoritamab monotherapy Epcoritamab monotherapy is the subject of an ongoing NICE evaluation. Draft guidance is that epcoritamab should not be used to treat R/R FL in adults after 2 or more lines of treatment.[41] Furthermore, the company are positioning epcoritamab at a later-line of treatment (fourth-line or beyond). The one treatment listed in the NICE scope that is not addressed in the submission or appendices is rituximab monotherapy. Rituximab monotherapy is only used to treat people with stage IIA disease who are asymptomatic (1L), as maintenance following R-chemotherapy, or potentially as a palliative care alternative so will not be displaced by tafasitamab + R^2. Previous technology appraisal of R^2 concluded that rituximab monotherapy is not a relevant comparator in the R/R FL setting.[42] However, if NICE now believes it is relevant for decision making, comparison to R^2 can act as a conservative proxy as this treatment has proven to be clinically superior to rituximab monotherapy[43] and is more expensive.	
Outcomes	The outcome measures to be considered include: • Progression-free survival • Overall survival	The outcome measures to be considered include: • Progression-free survival • Overall survival	No difference	The outcomes reported in the CS are in line with the NICE's final scope.

-	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• Response rates, including time to next treatment and duration of response • Adverse effects of treatment • Health-related quality of life.	• Response rates, including time to next treatment and duration of response • Adverse effects of treatment Health-related quality of life		
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • Type of lymphoma (follicular lymphoma, follicular lymphoma with FDG-avid foci) • Grade of lymphoma Number of previous treatments	The subgroup to be considered is: • Number of previous treatments	Only the number of previous treatments would potentially have a direct impact on treatment decision-making in clinical practice.	The company did not provide subgroup analyses for type and grade of lymphoma following a request from the EAG. The EAG considers the company's justification for not providing these results to be insufficient. This is further discussed in Section 3.3.2.1.
Economic analysis	Adults with relapsed or refractory follicular lymphoma after 1 or more systemic treatments	Adults with relapsed or refractory follicular lymphoma after 1 or more systemic treatments	n/a	The economic analysis aligns with the NICE scope and NICE reference case. The EAG considers the 2L-only and 3L+ subgroups separately.
Abbreviations: FDG, fluorodeoxyglucose; FL, follicular lymphoma; NICE, National Institute for Health and Care Excellence; O-B, obinutuzumab with bendamustine; R/R, relapsed or refractory; R^2, rituximab + lenalidomide.				

3 CLINICAL EFFECTIVENESS

3.1 Critique of the review methods

3.1.1 Search strategies

Searches for the original SLR undertaken in January 2024, were located in a separate report by Avalere Health included with the CS.[44] The original searches were updated in April 2025, with the search strategies provided in CS Appendix B. The search results were also used to inform the company ITC.

The EAG found that the searches for RCTs of tafasitamab or comparators specified in the NICE scope for relapsed or refractory FL/MLZ were adequate in general, however noted that retrieval from some databases was limited to trials published in English. The search for non-randomised interventional studies, single arm studies and systematic reviews in PubMed and Embase were found to be inadequate due to missing terms for these study types within the database search strategies. In addition, databases containing non-Cochrane systematic reviews were not searched. Due to the limitations found by the EAG in the company searches it is possible that some non-English language studies, non-randomised interventional studies, single arm studies and systematic reviews of tafasitamab or relevant comparators may have been missed. The EAG appraisal of the searches is presented in Table 5.

Table 5 EAG appraisal of evidence identification

Topic	EAG response	Note
Is the report of the search clear and comprehensive?	PARTLY	It was unclear which fields and subject headings had been searched for some search lines of the PubMed, Embase and Cochrane Library search strategies. The response to clarification questions C4 and C5 provided an explanation for this. This was verified by the EAG for PubMed and the Cochrane Library but not for Embase.com as we do not have access to this version of Embase.
Were appropriate sources searched?	PARTLY	Embase, PubMed, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials were searched along with searches of relevant conference proceedings, trial registers, Health Technology Assessment (HTA) agency websites and reference checking of relevant systematic reviews. Missing sources: KSR Evidence, Epistemonikos, Database of Abstracts of Reviews of Effects, and the International Health Technology Assessment database (INAHTA).
Was the timespan of the searches appropriate?	YES	Databases: inception to April 2025 Manual conference abstract searches: January 2021 to April 2025 HTA agency website searches: January 2021 to April 2025
Were appropriate parts of the PICOS included in the search strategies?	PARTLY	*Original SLR* Population: Relapsed or refractory FL/MZL AND (Intervention: tafasitamab OR comparators, as per table 2, page 37 of the SLR report by Avalere Health[44]) AND Study design: RCTs *SLR update* Population: Relapsed or refractory FL/MZL AND (Intervention: tafasitamab OR comparators: as per original SLR above plus 3 additional comparators epcoritamab, odronextamab and lisocabtagene maraleucel) AND Study design: RCTs The above search structures do not include study designs that were mentioned in the inclusion criteria: non-randomised studies, single-arm studies, and systematic reviews.
Were appropriate search terms used?	PARTLY	Search terms (both text word and subject headings) for non-randomised studies, single-arm studies and systematic reviews were missing from the search strategies for PubMed and Embase.
Were any search restrictions applied appropriate?	NO	Bias could have been introduced into the review by the application of a limit to studies in English and the exclusion of letters and case reports from the search results.
Were any search filters used validated and referenced?	NO	Externally validated search filters to limit to particular study designs (RCTs, SRs) are available but were not used and therefore not referenced.

Abbreviations: SLR: systematic literature review; FL: follicular lymphoma; RCT: randomised controlled trial; SR: systematic review. EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

3.1.2 Study selection

The EAG considers the study selection process to be generally appropriate. The company followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [45] principles.

The company's selection criteria are reported in the company's Clinical SLR report. [44] Randomised controlled trials (RCTs), non-randomised studies and single arm trials were included in the selection criteria. The EAG noted that epcoritamab was not included in the original SLR selection criteria (Table 2), but it was added to the updated SLR.

The EAG also noted that adverse events were not included as part of the outcomes on Table 2 and safety parameters were excluded from the eligibility criteria. Therefore, relevant safety data may have been missed. Evidence for HRQL (or QoL) was identified through a separate SLR. The EAG considered the method used to be appropriate.

Screening and selection of articles were carried out by two independent researchers and discrepancies were resolved via discussion or by a third researcher. The EAG considers the screening and selection of articles included in the SLR to be appropriate.

3.1.3 Data extraction and quality assessment

Data was extracted by one researcher and validated by another researcher. The EAG considers the data extraction process to be broadly appropriate.

The company used the Cochrane risk of bias (ROB 2.0) tool to assess RCTs and the Cochrane ROBINs-1 tool to assess the quality of non-randomised trials. Results from the quality assessment were reported graphically and narratively. Individual Cochrane RoB assessments of randomised and non-randomised studies included in the submission were not accessible in the SLR report. The company did not report how many researchers performed the quality check and how discrepancies were resolved if there were any discrepancies.

3.1.4 Evidence synthesis

Evidence extracted in the SLR was synthesised narratively and quantitatively using matching-adjusted indirect comparisons (MAICs). A critique of the MAICs is presented in Section 3.5.

3.2 Critique of the methods of the trials of the technology of interest

This section provides an overview of the methodology of inMIND.[46, 47] Section 3.2.1 to 3.2.5 describe the design of the inMIND trial in more detail, and section 3.3 describes inMIND in the context of current NHS practice.

Table 6 Clinical effectiveness study of technology of interest

	inMIND[46]
Role in this evaluation	Evidence of the clinical effectivenness and safety of therapies evaluated in the trial were used to inform the economic model.
Study type	Ongoing, phase 3, randomised, double-blind, placebo-controlled, multicentre study. No longer recruiting.
Period of recruitment	16th April 2021 to 10th August 2023
Location	210 locations across 28 countries: Australia, Austria, Belgium, Canada, Czechia, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Japan, South Korea, Netherlands, Norway, Poland, Russia, Spain, Sweden, Switzerland, Taiwan, Turkey, Ukraine, the UK, and the US
Exclusion criteria	histology other than FL and MZL or clinical evidence of transformed lymphoma, congestive heart failure, any systemic anti-lymphoma and / or investigational therapy with 28 days prior to the start of Cycle 1 and prior use of lenalidomide in combination with rituximab. See CS Table 5 for further details.
Patient group	Adults patients (Age ≥18 years) with R/R FL grade 1 – 3A or MZL histological subtypes who had recevived at least one prior line of systemic treatment.
Subgroups	Refractoriness to prior anti-CD20 mAb therapy, number of previous treatments (1 or ≥ 2), baseline NKCC, and POD24 status. Further subgroups analyses were reported by the company by sex, age, ethnicity, and races amongst others.
Intervention	Tafasitamab (12mg/kg, administered intravenously on Days 1, 8, 15 and 22 of Cylces 1 to 3 and on Days 1 and 15 of cycles 4 to 12. Each Cycle has 28 days) with lenalidomide (20mg/day, administered orally on Days 1 to 21 of Cycles 1 to 12) and rituximab (375 mg/m^2, administered intravenously, on Days 1, 8, 15, and 22 of Cycle 1 and on Day 1 of Cycles 2 to 5).
Comparator	Placebo (0.9% saline solution IV administered intravenously on Days 1, 8, 15 and 22 of Cylces 1 to 3 and on Days 1 and 15 of cycles 4 to 12. Each Cycle has 28 days) with lenalidomide (20mg/day, administered orally on Days 1 to 21 of Cycles 1 to 12) and rituximab (375 mg/m^2, administered intravenously, on Days 1, 8, 15, and 22 of Cycle 1 and on Day 1 of Cycles 2 to 5).
Primary outcome	PFS by INV assessment in the FL population, using the Lugano 2014 criteria.[48]
Secondary outcomes	• PET-CR rate by investigator assessment in the FDG-avid FL population, defined as a complete metabolic response at any time after start of treatment. • OS in the FL Population. • PFS by investigator assessment in the overall population (FL and MZL).
Duration of study	Median OS: 15.3 months; median PFS: 14.1 months at the 23 February 2024 data cut in the tafasitamab plus R^2 arm

Abbreviations: FL, follicular lymphoma; FDG, fluorodeoxyglucose; MZL, marginal zone lymphoma; mAb, monoclonal antibody; NKCC, Natural Killer Cell Count; POD24, progression of disease within 24 months; OS, Overall survival; UK United Kingdom; US, United States.

3.2.1 Participant eligibility criteria

Participant eligibility criteria for inMIND are summarised in the CS Section 2.3. inMIND recruited adults' patients (age ≥ 18 years) who have histologically confirmed Grade 1, 2 or 3a FL (or histologically confirmed nodal MZL, splenic MZL, or extranodal MZL). However, this submission focused on the FL cohort only. Participants recruited into the inMIND trial must have had one or more prior line of therapy(s) including an anti-CD20 mAb, documented relapsed, refractory or PD after

treatment with systemic therapy. They must also have an ECOG performance score of 0 to 2, and no prior treatment with lenalidomide in combination with rituximab.

The EAG considers the eligibility criteria for participant recruited into inMIND to be appropriate and reflect the current NHS practice.

3.2.2 Comparator

The EAG and EAG's clinical adviser consider the main comparator (R^2) evaluated in the inMIND trial to be appropriate as it is the most used therapy in the NHS practice given a relapse or refractory following the first line of therapy.

3.2.3 Randomisation and allocation concealment

Information on the randomisation of participants was reported in the CS (Section 2.4), CSR, and publication of the inMIND study.[47]

Participants were randomised in a 1:1 ratio to tafasitamab plus R^2 or placebo plus R^2 centrally using an Interactive Response Technology (IRT) system. The clinical study report specified that FL and MZL groups were to be randomised separately. In the FL group, randomisation was stratified by the number of prior lines of therapy (<2 vs ≥ 2), progression of disease within 24 months (POD24) and refractories to prior anti-CD20 therapy.

The EAG noted that there was generally balanced distribution of participant characteristics between the two treatments groups (CS Table 6 and Table 7). The EAG considers the randomisation and allocation concealment methods for FL participants to be appropriate.

3.2.4 Blinding

Blinding methods are reported in the trial publication and the CSP. The inMIND study is a double-blinded study and the company stated that the participants, investigators and study team members were blinded to the treatment assignment until the time of primary analysis. The IRT approach used in the randomisation process aided in the concealment of the treatment assignment to the participants. Furthermore, the infusion bag and lines were covered to block the solution colour during infusion.

The EAG considers the blinding methods to be appropriate and limit the risk of bias due to deviations from the intended interventions.

3.2.5 Trial outcomes

The primary, secondary and exploratory outcomes are listed on Table 5 in the CS, and the results are presented in CS Section 2.6.

The primary endpoint is the progression free survival (PFS) by investigator (INV) assessment using the Lugano 2014 criteria [48]. The secondary outcomes are PET-CR rate by INV in the FDG-avid FL population, overall survival and PFS by Independent Review Committee (IRC) in the FL population, ORR by INV, DoR by INV, HRQL and safety outcomes (based on the incidence and severity of TEAE). Exploratory endpoints include time to next treatment (TTNT) by INV and rate of and time of histological transformation. The company added PFS by IRC as a secondary endpoint on Amendment 7 of the protocol. However, the company noted that procedures were in place to estimate the PFS by IRC using the full analysis set of FL (FL FAS) at the same timepoints as the PFS by INV was assessed (CQ A3).

The EAG noted that in response to CQ A3, the company's used the PFS by IRC in its economic modelling in place of the PFS by INV used in the original submission. The aim was to remove investigator's subjective bias and to ensure that the company's modelling approach aligns with majority of the previous technology appraisal for FL.

The EAG considers this approach to be appropriate as the PFS by IRC is a more objective endpoint

3.2.6 Statistical analysis

A summary of the statistical analysis method is presented in CS, with further details in the CSR and the statistical analysis plan (SAP) which was submitted following an EAG request (CQ, A2). The EAG considers that the statistical methods used by the company to analyse the primary and secondary endpoints to be appropriate.

The full analysis set (FAS) which included all randomised participants with FL was used to evaluate the PFS by INV (primary endpoint), overall survival, PFS by IRC, ORR by INV, DoR by INV, DoR by IRC, HRQL, TTNT and histological transformation. PET-CR endpoint was evaluated using the FDG-avid population which included all randomised participants with a PET scan at baseline with a resulting Deauville score of 4 or 5. Safety outcomes were measured using the SAS population, which included all randomised participants who received at least one dose of therapies evaluated.

Kaplan-Meier curves were used to estimate the hazard ratios (HR) primary endpoint - PFS by INV, and some secondary endpoints, PFS by IRC, OS, DoR by INV, DoR by IRC, and TTNT. Censoring rules for the primary outcome followed the FDA guidance and sensitivity analyses with alternative censoring rules were conducted. For OS outcome, participants who were still alive were censored at last known alive date, regardless of new anti-lymphoma therapy. The EAG considers the approach of censoring rules to be broadly appropriate. The company performed sensitivity analyses using alternative censoring rules to estimate the PFS by INV in the FL FAS and FL per-protocol set (PPS) populations. The estimates obtained were consistent with the main analysis.

The stratified Cochran-Mantel-Haenszel (CMH) method was used to calculate odd ratios (OR) relating to some secondary outcomes including the PET-CR, ORR by INV, and histological transformation. HRQL was measured using the changes from baseline in EQ-5D-5L Visual Analogue Scale (VAS) scores EORTC-QLQ-C30 global health scores or FACT-Lym scores. All estimates from the statistical analysis of the primary and secondary endpoints were presented alongside the 95% CI and p-values.

3.3 Critique of the results of the trials of the technology of interest

3.3.1 Participant characteristics and applicability of the inMIND trial

A summary of the key baseline characteristics of FL patients inMIND are presented in CS Tables 6 and 7. Following an EAG request, the company provided a breakdown of baseline characteristics by lines of treatment (CQ, A11).

The median age of patients in inMIND was 64.0 (31-88). This is younger than NHS England data for FL patients initiating 2L treatment in the NHS (68.0 years [57-75][49], although it is uncertain whether this population is fully reflective of patients who would be eligible for tafasitamab plus R^2. The reported mean age of inMIND patients was [redacted] The rate of patients who were refractory to rituximab was [redacted] The proportion of POD24 from diagnosis was 32.0%, which may be lower than NHS England data.[49] The EAG's clinical adviser noted that other baseline patient characteristics in inMIND were broadly reflective of the people who would be eligible for tafasitamab plus R^2 in NHS practice.

There was no notable imbalance in the baseline characteristics distribution of participants between the tafasitamab arm and placebo arm including when stratified by line of therapy (CQ, A11, Table 6). The absolute percentage differences of participants' distribution at the baseline between both arms ranged from 0% to 8%.

3.3.2 Results of the inMIND trial

This section provides a critique of the clinical effectiveness results of inMIND from the primary analysis (data cut 23 February 2024) in the FAS FL population presented in CS Section 2.6.

3.3.2.1 Progression-free survival

Median follow-up for PFS (INV) (primary outcome) was 14.1 months. Median PFS was reached at 22.4 months in the tafasitamab plus R^2 arm, and 13.9 months in the placebo plus R^2 arm. There was a statistically significant reduction in the risk of PFS (INV) for tafasitamab plus R^2 compared with

placebo plus R^2 (HR: 0.43; 95% CI: 0.32, 0.58). CS Figure 5 showed a clear separation of Kaplan-Meier curves from approximately 4 months.

PFS (IRC) results (secondary endpoint) were similar (HR: 0.41; 95% CI: 0.29, 0.56), with the corresponding CS Figure 7 showing a similar trend. Concordance rates between the INV and IRC assessments ([redacted]% and [redacted]%, respectively) were relatively [redacted] overall. Although there was no evidence of systematic differences between PFS (IRC) and PFS (INV), the EAG agrees with the company that PFS (IRC) is more objective and less prone to assessor bias than PFS (INV), and that PFS (IRC) should be preferred for economic modelling.

The company stated that these PFS results were clinically significant, although they recognised that PFS may only be a weak surrogate marker of OS in R/R FL. This key issue is further discussed in Section 4.2.5.2, following a discussion of the OS evidence.

Subgroup analyses

Results of inMIND pre-specified subgroup analyses for PFS (INV) are presented in CS Section 2.8 and CS Appendix C. These showed no evidence of differences in relative effectiveness between the trial arms according to POD24 status, refractory status to prior anti-CD20 therapies, and prior lines of therapy (1L vs. ≥2L). Two subgroup analyses stratified by age group were conducted (<65 and ≥65 years; <75 and ≥75 years). These showed that relative to placebo plus R^2, tafasitamab plus R^2 was numerically more beneficial in younger patients (<65 years: HR 0.35 [95% CI 0.23 to 0.55] vs. ≥65 years: HR 0.53 [95% CI 0.35 to 0.80]; <75 years: HR 0.44 [95% CI 0.31 to 0.61] vs. ≥75 years: HR 0.58 [95% CI 0.30 to 1.12]). Between-group differences were not statistically significant as confidence intervals overlapped in each of the two age group analyses. Post-hoc subgroup analyses for PFS (IRC) were provided following a request from the EAG (CQ A5) and showed broadly similar results.

Subgroups according to type and grade of lymphoma were specified in the final NICE scope but were not presented. In response to a request from the EAG to provide these analyses, the company replied that these were not conducted due to time constraints (CQ A5). The company also considered that variables for lymphoma type (FDG-avid foci FL) and grade (FL Grade 1 or 2 versus 3A) were evenly balanced between trial arms and did not raise concerns about applicability to practice, and that post-hoc subgroup analyses would be unlikely to provide statistically or clinically meaningful results. Although the EAG agrees with most of these points, it considers that the lack of time is an insufficient justification for not providing results for subgroups listed in the NICE scope, and that the lack of "statistically or clinically meaningful results" still needs to be evidenced.

3.3.2.2 Overall survival

Median follow-up for OS was 15.3 months for the tafasitamab plus R^2 treatment arm. At the February 2024 data cut, 38 death events were observed, and median OS was not reached in either arm. The point estimate favoured tafasitamab plus R^2 when compared to placebo plus R^2 (HR: 0.59; 95% CI: 0.31, 1.13) but it was not statistically significant. This result should be interpreted with caution, as OS data are significantly immature and the inMIND trial was not powered to test for OS at the time of this analysis.

CS Figure 6 shows Kaplan-Meier curves for OS. Data are limited by significant censoring and insufficient follow-up, which preclude any meaningful interpretation. Although the EAG agrees with the company that the observed drop in OS in the tafasitamab plus R^2 and crossing of the survival curves at approximately 28 months may be due a statistical artefact caused by two death events and limited number of patients at risk, significantly more mature evidence is required to show whether tafasitamab plus R^2 improves OS compared with R^2. In response to a clarification request from the EAG, the company confirmed that, as per the SAP, the next data cut will be the final analysis and is planned after the last participant has completed a minimum of 5 years of follow-up. This is anticipated in [redacted].

3.3.2.3 PFS as a predictor of OS: critique of the evidence from the Milrod (2024) review

Given the immaturity of OS data, the predictive relationship between PFS and longer-term OS is essential to the decision problem and is a key driver of the company's model (see Section 4.2.5.2). The company acknowledged that PFS is only a weak surrogate for OS in FL, suggesting that PFS gains with tafasitamab may not always translate into clear OS benefits compared with SoC (CS Section 3.2.2.2). This statement is based on the results of a review published in 2024 by Milrod et al.[50] The rest of this subsection provides a critique of this review.

Milrod (2024) aimed to conduct a review and pooled analysis to evaluate the strength of surrogacy relationship between PFS and OS in FL. The Clinicaltrials.gov database was searched for all phase III randomized clinical trials investigating FL from up to December 2023. Published trials of pharmacological and/or non-pharmacological interventions that investigated FL and reported results for PFS and OS in first and subsequently LOT were included. Unadjusted linear regression analysis weighted by sample size was performed to calculate Pearson correlation coefficients (r) and a coefficient of determination (R-squared) between PFS and OS. Strength of surrogacy was assessed following the Institute of Quality and Efficiency in Health Care (QWiG) criteria: weak ($r \leq 0.7$), medium ($r > 0.7$ to $r < 0.85$), and strong ($r \geq 0.85$).[51]

Twenty trials (10,724 patients) were included, with a median follow-up of 50.5 months. Ten trials were conducted in the 1L setting and ten were in R/R FL. Fourteen interventional arms (63.6%)

showed a PFS benefit, and 2 (9.1%) found a PFS and OS benefit. The correlation coefficient between PFS and OS was 0.383 ($p<0.001$) across all LOT. Correlation coefficients by LOT were similar in first line compared with the R/R setting: r=0.503 in LOT1, r=0.438 in R/R FL ($p<0.001$ for both). The coefficient of determination was 0.15 (95% CI 0.002 to 0.35), indicating that, across all LOTs, approximately 15% of the variance in OS may be explained by changes in PFS.

To the EAG's knowledge, Milrod (2024) is the most up to date evidence review on the surrogacy relationship between PFS and OS in FL. However, it has several limitations. No databases other than clinicaltrials.gov were searched, and only published studies were included. Several trials included non-FL indolent lymphomas. Studies were pooled using weighted, unadjusted regression analyses rather than formal meta-analytic methods. Analyses did not account for uncertainty in both PFS and OS HR. Potential sources of heterogeneity, including variation in participant characteristics and interventions, PFS outcome definitions, follow-up duration were not accounted for. Analyses ignored effects from cross-over designs and from subsequent therapies (notably CAR-T, SACT and bispecifics such as epcoritamab and mosunetuzumab). R/R setting analyses combined 2L and subsequent LOT, thereby masking possible differences in OS as post-progression survival reduces significantly after each subsequent LOT.

Although Milrod (2024) suggests that the correlation between PFS and OS in the R/R FL setting is weak, the EAG considers that this evidence has significant limitations. In particular, the review does not account for patient and disease course heterogeneity. Clinical advisers to the company noted that the surrogacy relationship may differ across different patient cohort. For instance, the correlation between PFS and OS is likely to be weak for patients with slow-progressing disease who respond well to multiple lines of R-based therapies, whereas PFS may be a stronger surrogate marker in those with more aggressive disease and poor response to R-based treatment. Clinical advice to the company and to the EAG also indicated that PFS could be a stronger predictor of OS in later LOT (3+). Although these statements are clinically plausible, the company were not able to support these empirically due to the lack of evidence.

3.3.2.4 Response rates

Complete metabolic response (CMR) rate (PET-CR) was higher in the tafasitamab plus R^2 arm compared with placebo plus R^2 (49.4% vs. 39.8%) and the difference was statistically significant (OR 1.5 [95% CI 1.04 to 2.13]).

Overall response rates (ORR), which included complete response (CR) and partial response (PR) by INV are summarised in CS Table 10. The ORR was 83.5% in the tafasitamab plus R^2 arm versus 72.4% in the placebo plus R^2 treatment arm; the difference was statistically significant (OR 2.0 [95% CI 1.30, 3.02]). CR rates were numerically higher in the tafasitamab plus R^2 arm (45.0%) compared to

placebo plus R^2 (34.0%). ORR by IRC is reported in CSR Section 9.3.6.2 and were broadly comparable.

3.3.2.5 Duration of response

Median DOR (INV) was reached at 21.2 months in the tafasitamab plus R^2 arm, and 13.6 months in the placebo plus R^2 arm. There was a statistically significant difference in DOR favouring tafasitamab plus R^2 compared with placebo plus R^2 (HR: 0.47; 95% CI: 0.33, 0.68). CS Figure 8 showed a clear separation of Kaplan-Meier curves from approximately 4 to 6 months. The EAG considers that the crossing of the survival curves observed at approximately 23 months may be an artefact from the limited number of patients at risk at that timepoint. Median DOR (IRC) was [redacted] in the tafasitamab plus R^2 arm and [redacted] months in the placebo arm (HR [redacted]; 95% CI [redacted] to [redacted]).

In response to a request from the EAG, the company provided separate analyses for patients on their 2L and on their 3L+ (CQ A4, Table 1). These showed [redacted].

3.3.2.6 Time to next treatment

Median TTNT was not reached for participants receiving tafasitamab plus R^2 and was 28.8 months in the placebo plus R^{2}group. The difference between study arms was statistically significant (HR 0.45, 95% CI 0.31 to 0.64). In response to a request from the EAG, separate analyses by LOT were provided for TTNT (CQ A4, Table 2). The [redacted].

Although these results are promising, the EAG considers TTNT to be a weaker trial endpoint, as the criteria for the next treatment were not specified in the trial protocol, and thresholds for treatment are subjective and will likely vary by clinician.

3.3.2.7 Subsequent therapies

CS Section 2.7 summarises data on subsequent systemic anti-lymphoma therapies. In the tafasitamab plus R^2 arm, [redacted] ([redacted]%) received at least one subsequent treatment, compared with [redacted] ([redacted]%) in the placebo plus R^2 arm. Among the [redacted] patients who started post-treatment therapy across both arms, [redacted] had one subsequent treatment. Table 7 shows that the most common subsequent treatments were [redacted] Several of these treatments, most notably [redacted], are not available in routine NHS practice, which limits the applicability of the trial evidence.

Given the immaturity of the OS data, the company argued that the OS results from the primary analysis are unlikely to be significantly biased by these non-routine therapies. The EAG considers that

the immaturity of the OS data means that there is insufficient evidence to assess the magnitude of potential bias from non-routine and routine subsequent therapies on OS. Given the [redacted] proportion of patients receiving subsequent therapies in the comparator arm and the distribution of subsequent therapies by arm, the EAG agrees that any bias on OS would be unlikely to favour tafasitamab plus R^2 over placebo plus R^2.

Table 7 Most common (>5% in either arm) post-treatment systemic anti-lymphoma therapy, n (%)

	Tafasitamab + R^2 [redacted]	Placebo + R^2 [redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: adapted from CS Table 12
Key: [redacted] CI, confidence interval; [redacted] SD, standard deviation.

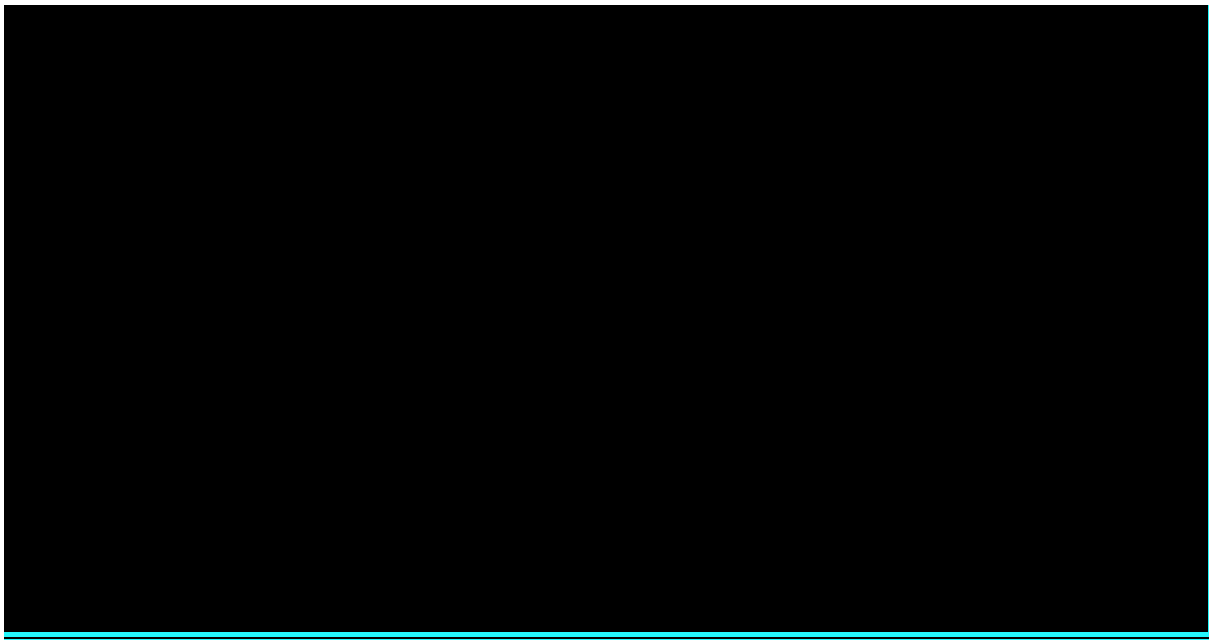
3.3.2.8 Progression-free survival on next treatment (PFS2)

Data on PFS2 was reported in CSR Section 9.4.2. The Kaplan-Meier curves are reproduced in Figure 1. The estimated median PFS on next anti-lymphoma treatment was [redacted]. PFS2 was [redacted]

In response to a request from the EAG, the company presented a summary of therapies received on next treatment per arm (CQ A6, Table 4). As per Table 7 above, several of these treatments were not available in routine NHS practice, which limits the applicability of the PFS2 data. In the tafasitamab plus R^2 arm, [redacted] ([redacted] of those receiving subsequent treatment) were alive with no PD after their next anti-lymphoma treatment, compared with [redacted] in the placebo plus R^2 arm.

The company consider that the efficacy of subsequent therapies was maintained after previous treatment with tafasitamab plus R^2. The EAG consider that, although there is no evidence to suggest otherwise, the evidence is too limited to confirm this: the PFS2 analyses are exploratory by nature and included limited numbers of patients, and the OS data is limited by its immaturity.

Figure 1 Kaplan-Meier estimates of progression-free survival on next treatment (FL FAS)



Source: inMIND CSR Figure 4.7.1

Key: Tafa=tafasitamab + R^2; Pbo=placebo + R^2; NE: not estimable

3.3.2.9 Histologic transformation

Nine (3.3%) patients in the placebo plus R^2 experienced histological transformation, compared with none in the tafasitamab plus R^2 group (see further details in CS Table 11). Whilst the transformation rate observed in the placebo plus R^2 arm is within the expected range,[10] clinical experts to the company considered the conversion rate in the tafasitamab plus R^2 group to be clinically important, as histological transformation is considered a key driver of FL-related mortality.[52] However, the estimated median time to histological transformation into more aggressive histology was not reached in either treatment group. Although these results are promising, the EAG consider that the exploratory nature of this analysis and data immaturity mean that the true magnitude of effect of tafasitamab on post-progression histological transformation is uncertain.

3.3.2.10 Adverse effects of treatment

A summary of adverse events is presented in CS Section 2.11, with additional details provided in the inMIND trial clinical study report (CSR). Overall, the EAG considers the reporting of safety outcomes to be generally clear and comprehensive, and the key findings are summarised below.

In the inMIND trial safety population (N = 546), almost all participants in both treatment arms experienced at least one treatment-emergent adverse event (TEAE) (99.3% in both the tafasitamab plus R^2 arm and the placebo plus R^2 arm). Serious TEAEs were reported in 36% of participants receiving tafasitamab plus R^2 and 32% receiving placebo plus R^2. Grade 3 or 4 TEAEs occurred in 71% and 70% of participants, respectively. Fatal TEAEs were reported in 2% of participants in each arm (six deaths per arm). Treatment-emergent adverse events leading to permanent discontinuation of tafasitamab or placebo occurred in 11% of participants in the tafasitamab plus R^2 arm and 7% in the placebo plus R^2 arm.[46]

The company states that numerical differences in reported adverse event rates were generally small and did not account for the longer treatment duration in the tafasitamab plus R^2 arm arising from its greater efficacy (CS Section 2.11). Treatment exposure was reported as similar between groups, with a median of 12 cycles (range 1–12) in the tafasitamab arm and 11 cycles (range 1–12) in the placebo arm; exposure to lenalidomide and rituximab was also similar between groups. However, CSR Table 12 indicates that [redacted] This suggests that, despite similar median treatment duration, tafasitamab plus R^2 was associated with more frequent interruptions or omissions of scheduled infusions.

The most frequently occurring TEAEs (≥20% incidence) in both treatment arms included neutropenia, diarrhoea, constipation, COVID-19 and rash. TEAEs that occurred more frequently (≥5% absolute difference) in the tafasitamab plus R^2 arm included diarrhoea (37.6% vs 28.3%), COVID-19 (31.4% vs 23.5%), fatigue (21.2% vs 15.8%), pruritus (16.1% vs 10.3%), back pain (11.0% vs 6.0%), oropharyngeal pain (9.1% vs 3.7%) and pain in extremity (8.0% vs 3.0%). Peripheral oedema occurred more frequently with placebo plus R^2 than with tafasitamab plus R^2 (13% vs 7%, respectively).

There were no marked differences in the overall rates of Grade 3 or 4 TEAEs across treatment arms. The most frequently occurring Grade 3 or 4 TEAEs (≥5% incidence) in the tafasitamab plus R^2 arm were neutropenia (39.8%), pneumonia (8.4%), thrombocytopenia (6.2%) and decreased neutrophil count (5.8%). In the placebo plus R^2 arm, the most frequent Grade 3 or 4 TEAEs were neutropenia (37.5%), thrombocytopenia (7.4%), decreased neutrophil count (6.6%), anaemia (5.9%) and pneumonia (5.1%). The inMIND trial was conducted during the COVID-19 pandemic, which likely influenced adverse event reporting; Grade 3 or 4 COVID-19 and COVID-19 pneumonia events were more frequent in the tafasitamab plus R^2 arm than in the placebo plus R^2 arm (5.8% vs 2.2% and 4.7% vs 1.1%, respectively).

Treatment-related adverse events (TRAEs) were reported in 74% of participants in the tafasitamab plus R^2 arm and 66% in the placebo plus R^2 arm. The most frequent TRAEs were [redacted] and [redacted], with [redacted] occurring more frequently in the tafasitamab plus R^2 arm ([redacted]). Infusion-related reactions occurred in [redacted] of participants receiving tafasitamab plus R^2 and [redacted] receiving placebo plus R^2.

Twelve participants (2%) died due to fatal TEAEs (six in each treatment arm). None of the deaths in the tafasitamab plus R^2 arm were considered treatment-related. In the placebo plus R^2 arm, two deaths (cardiac failure and sepsis) were attributed to treatment. Two deaths in each arm were due to COVID-19-related TEAEs, none of which were attributed to trial treatment.

Adverse events of special interest (AESIs) were uncommon and occurred at similar overall rates between treatment arms. Any treatment-emergent AESI was reported in [redacted]% of participants receiving tafasitamab plus R^2 ([redacted]) and [redacted]% receiving placebo plus R^2 ([redacted]) (CSR Table 3.2.31.1). Events captured as AESIs included cytokine release syndrome ([redacted]% vs [redacted]%), infusion-related reactions ([redacted]% vs [redacted]%), tumour lysis syndrome ([redacted]% vs [redacted]%), and secondary primary malignancy ([redacted]% vs [redacted]%) in the tafasitamab plus R^2 vs placebo plus R^2 arms, respectively.

Treatment-relatedness of adverse events was assessed by site investigators rather than by an independent adjudication committee, although the EAG notes that blinding methods (as discussed in Section 3.2) reduced the risk of detection bias in adverse event reporting.

Overall, the company concludes that tafasitamab plus R^2 has a manageable and acceptable safety profile (CS Section 2.11.6). The EAG broadly agrees, noting that no new or unexpected safety signals were identified. However, the sample size and duration of follow-up limit the ability to detect rare adverse events and longer-term safety outcomes.

3.3.2.11 Health-related quality of life

Health-related quality of life (HRQL) results were reported in Appendix L1. These included mean changes from baseline in EQ-5D-5L, global health status EORTC-QLQ-C30 and FACT-Lym scores over time from baseline up to the end of treatment. Further details are presented in the CSR and a separate conference poster.[46, 53] The company confirmed that no other published or unpublished HRQL sources were available (CQ A9).

Completion rates (defined as the proportion of patients who received ≥1 study drug at the visit, or who had a record of a visit at EOT that also had ≥1 QoL assessment at that time point) ranged from 87% to 98% over time. Overall, HRQL outcomes were similar over time between the tafasitamab plus R^2 and placebo plus R^2 groups; they remained stable and below minimally important differences threshold across all 3 questionnaires (EORTC QLQ-C30, FACT-Lym, and EQ-5D-5L). The EAG

agrees with the company that this suggests a limited impact of tafasitamab on HRQL, and that the magnitude of change observed over time is unlikely to be clinically meaningful.[53]

3.4 Critique of studies identified and included in the indirect treatment comparison or multiple treatment comparison

In the absence of head-to-head data for tafasitamab plus R^2 versus R-chemotherapy, further evidence was sourced by the company to inform potential indirect treatment comparisons. Methods for identifying relevant studies are described in CS Appendix B, with further details reported in a technical report.[54] Trials were identified via a SLR. Overall, the EAG found that the study identification process was reasonably well reported. Comprehensive bibliographic searches were conducted up to April 2025. The searches and selection criteria of the company's SLR included a wider range of interventions than the NICE final scope, although the ITC presented in the CS only included interventions within the NICE scope. Eligible population included adults with R/R follicular lymphoma (Grade 1–3a) or R/R marginal zone lymphoma (≥ 1 prior anti-CD20 therapy), although it appears that only FL population were included in the ITCs. All NICE specified scope outcomes were included, with the exception of safety. The inclusion of observational, "real-world" unpublished evidence was justified in the absence of suitable published evidence for some R-chemotherapy options, although it does not appear to have been identified through a systematic review process, and it is unclear if other relevant unpublished sources might have been missed.

Five trials (inMIND, BRB study, GADOLIN and EPCORE NHL-1, Van Oers) .[46, 55-58] and one observational dataset from the HMRN[4] were included. All five trials were identified by the company's SLR. One RCT of R-CHOP versus CHOP reported by Van Oers (2006) did not meet the SLR inclusion criteria, as it included patients without prior rituximab-based therapy. Despite this limitation, given the absence of other RCT evidence on R-CHOP, the EAG considers that the decision to include this trial in the ITCs was appropriate. The inclusion of HMRN, an NHS-specific evidence source, is also justified in the absence of published studies of R-CVP and is in line with previous TAs.[37] The company did not discuss whether other non-UK "real-world" evidence sources were considered (e.g. Flatiron, ReCORD-FL, Lymphoma Epidemiology of Outcomes Consortium for Real World Evidence [LEO CReWE] and SCHOLAR-5). AUGMENT, an RCT comparing R^2 with rituximab monotherapy,[59] was included in the company SLR but excluded from the ITCs, although the R^2 arm of AUGMENT was compared with the R^2 arm of inMIND in an exploratory analysis. The EAG considers the exclusion of AUGMENT from the ITC to be justified; the relative efficacy of R^2 vs tafasitamab plus R^2 is better informed by randomised, head-to-head evidence from inMIND, and the exclusion of rituximab monotherapy from the ITC is in line with the decision problem (see Section 2.3). A summary of studies included in the MAICs is provided in Table 8.

Table 8 Design and methods of studies included in the ITCs

	Treatment arm included in ITC	Design	Location	Enrolled population	FL N *	Start year
inMIND	T+R^2	RCT, double blind, phase III	Multinational	FL and MZL (2L+)	273	2021
BRB study	R-B	Single arm trial, open label, phase II	Japan	iNHL (2L+)	40	2011
Van Oers	R-CHOP	RCT, open label, phase III	Multinational	FL (2L+)	234	1998
HMRN database	R-CHOP R-CVP	Observational, retrospective	Yorkshire and Humber	FL (2L/3L)	[redacted] (total) [redacted] (R-CHOP) [redacted] (R-CVP)	2005
GADOLIN	O-B	RCT, open label, phase III	Multinational	iNHL (2L+)	164	2010
EPCORE NHL-1	Epcoritamab	Single arm trial, open label, phase II	Multinational	FL (2L+)	128	2018

Source: CS Appendix Tables 6, 11 and 15

Abbreviations: 2L, second-line; 2L+, second-line or later; 3L+, third-line or later; FL, follicular lymphoma; iNHL, indolent non-Hodgkin's lymphoma; ITT, intention to treat; MZL, marginal zone lymphoma; N, sample size; NA, not applicable; R-B, rituximab with bendamustine, R-CHOP, rituximab + doxorubicin + vincristine + cyclophosphamide + prednisolone; R-CVP, rituximab + cyclophosphamide + vincristine + prednisolone; RCT, randomised controlled trial; O-B; obinutuzumab with bendamustine; R^2, rituximab with lenalidomide
*Number of participants in treatment arm included in the ITC

The company's feasibility assessment identified several sources of heterogeneity between the inMIND trial and comparator trials, including study designs, patient characteristics and prior therapies.

3.4.1 Study designs and methods of studies included in the MAICs

A critique of the study designs and their comparability is presented in CS Appendix 1.4.1. The EAG considers the company's critique to be generally balanced and fair.

All studies of R-chemotherapy were open-label, therefore adherence to treatment protocols may have been less strict than in inMIND, and differences in investigator assessed outcomes may have occurred for PFS and TTNT, which include a subjective element. The EAG agrees with the company that the magnitude and direction of bias from the use of open-label arms are difficult to predict.

The R-chemotherapy studies were initiated 10 to 23 years before the initiation of inMIND (except for EPCORE NHL-1, which started in 2018). The potential bias introduced by differences in study periods across studies is difficult to assess. Van Oers was conducted before the establishment of R-chemotherapy in the 1L setting. The EAG agrees with the company that this may have introduced bias favouring R-CHOP in the 2L setting in the ITC between inMIND and Van Oers, as response rates

reduce with repeat exposure to rituximab. All other studies included patients who were R/R following an anti-CD20 antibody-based regimens. BRB was conducted exclusively in Japan, which further limits its comparability. The retrospective nature of the HMRN study means that data collection standard may not have been as stringent as in a trial context, with higher risk of selection bias, and missing and inconsistent data.

Follow-up times for OS differed across trials with shorter median follow-up for inMIND (15.3 months), the BRB study (14.0 months), EPCORE NHL-1 (17.4 months) than in the Van Oers study (39.4 months) and GADOLIN (57.5 months). HMRN also covered a significantly longer period (from 2005 to 2023, median follow-up NR) than inMIND. Response assessment criteria differed across trials: inMIND and EPCORE used Lugano 2014,[48] BRB applied the IWWM criteria, [60] Van Oers used the LEXCOR criteria[61] and GADOLIN employed the criteria by Cheson (2007)[62] Formal response assessment criteria were not applied in HMRN. Among comparator studies, only GADOLIN had PFS assessed by IRC; all other comparator studies had response assessed by unblinded investigators, making them at high risk of assessor bias. Overall, PFS definitions across nearly all comparators studies were not aligned with inMIND; the resulting magnitude and direction of bias is difficult to assess.

3.4.2 Population characteristics of studies included in the MAICs

All studies included adults with ECOG 0 to 2 (where ECOG status was recorded). GADOLIN and BRB enrolled a broader population of people with indolent NHL, including FL and non-FL patients; only results for subgroups of FL patients were included in the ITC. EPCORE NHL-1 included patients with a least two prior therapies (3L+); all other ITC studies included patients with at least one prior therapy. GADOLIN only included patients who were refractory to prior rituximab; this limits the comparability of O-B patients compared with tafasitamab plus R^2. Van Oers was conducted prior to the era of rituximab, which, as discussed above, limits its comparability to inMIND. All other studies included a mix of refractory and non-refractory patients to rituximab.

Patient characteristics of studies included in the ITC are presented in CS Appendix B 1.4.3.2. The EAG broadly agrees with the company's assessment of comparability in population characteristics across studies. Heterogeneity in study population characteristics was observed, including for age, sex, ECOG status, disease stage, FL histology grade, FLIPI risk score, presence of B symptoms, time since diagnosis, prior lines of therapy and refractory status. Data were not reported for clinically important characteristics; this limited assessments of comparability and the extent to which study population differences could be adjusted for in the ITCs.

3.5 Critique of the indirect comparison or multiple treatment comparison

With the exception of inMIND, all trials included in the ITCs were either single-arm or did not have the common comparator arm of R^2 with inMIND. Network meta-analysis or other anchored methods were therefore not possible, and unanchored matching-adjusted indirect comparisons (MAICs) were used to estimate relative effects between interventions. Due to the lack of common comparators, only the tafasitamab plus R^2 arm from inMIND was included in the analysis.

3.5.1 Selection of covariates for adjustment

To identify potential prognostic factors and treatment effect modifiers for adjustment, the company conducted a targeted literature review, which was supplemented by consultation with four clinical experts and patient-level data analyses of the inMIND trial. Overall, the EAG considers that the covariate selection process was well reported.

Results of the targeted review are presented in CS Appendix B.1.4.3.1 with further details in a separate report.[63] For OS, age and FLIPI scores were the most consistently reported relevant covariates, and no treatment effect modifiers were identified. For PFS, favourable tumour characteristics, and earlier stage disease were commonly reported. There was only partial overlap between relevant prognostic factors for OS and PFS.

Patient-level data exploratory analyses of inMIND were conducted to identify prognostic factors using univariate regression models to FL population of inMIND across both study arms. Treatment effects modifiers were identified by fitting regression models that accounted for treatment interaction. For OS, ECOG PS, elevated LDH levels, histology grade and FLIPI risk score at baseline were found to be prognostic, and race was identified as a treatment effect modifier. For PFS, the following variables were identified as prognostic: ECOG PS, FLIPI score, histology grade, LDH levels, high tumour burden, time since diagnosis, prior lines of therapy, rituximab-refractory, refractory to last prior therapy and POD24; age, region and Ann Arbor staging were found to be treatment effect modifying.

Following clinical consultation, prognostic factors and treatment effect modifiers were scored and ranked in order of importance, to identify characteristics for potential adjustment in PFS and OS MAICs. CS Appendix Table 20 lists 14 variables. Duration of previous response/remission was consistently ranked of highest importance, followed by refractory status to last therapy. POD24, double refractory status (to CD20 + anthracycline) and number of prior lines of therapy were also ranked as high overall. It is unclear whether these variables were ranked and considered equally important for PFS and OS. Given the evidence identified in the company's targeted review for PFS and OS prognostic factors, and the limited correlation between PFS and OS (see Section 3.3.2.2), the

EAG considers that separate covariate rankings for PFS, OS and TTNT would have been preferable. The ranking exercise only included 14 covariates, and excluded some prognostic factors identified as relevant in the targeted review (e.g. Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria, bone marrow involvement and blood markers, or geographic region). Reasons for these exclusions were not reported, although the EAG clinical adviser considered that the company's list included all key known prognostic factors/treatment effect modifiers and that the rankings were broadly appropriate. Unavoidably, many of these variables are correlated (e.g. duration of previous response/remission and POD24 status, refractory and double refractory status, FLIPI composite score and several individual components).

CS Appendix Table 21 summarises the 20 prognostic factors and treatment effect modifiers identified for potential adjustment in the MAICs from the targeted review, clinical expert consultations and/or analyses of inMIND. This shows that the covariates considered relevant varied by source and by outcome (PFS and OS).

Of those characteristics, sex, race, histology grade at trial entry and B symptoms at baseline were excluded from the MAIC as they were not considered relevant by clinical experts or in exploratory analyses of inMIND. Tumour bulk/ bulky disease, double-refractory status, duration of previous response/remission and response to last prior therapy were not available for inMIND, and several covariates including Ann Arbor Staging and number of nodal sites were not reported by any comparator trial. Therefore, these covariates were also excluded from the MAICs. As the definition of POD24 differed between inMIND and the comparator trials, the company chose to exclude this covariate from the MAICs. The EAG checked the definitions of POD24 in each of the studies included in the MAICs and agreed that this exclusion was appropriately justified, although this is a significant limitation of the MAICs given the likely relevance of this variable as a predictor of OS (see Section 2.2). The covariates included in each of the MAICs are presented in CS Appendix Tables 22 and 23. These show that further potentially relevant covariates were excluded from individual MAICs due to lack of reporting in comparator trials.

3.5.2 Calculation of propensity scores

The methods used to derive MAIC weights are presented in a separate technical report.[54] Briefly, weights for the MAICs were derived using a propensity score logistic regression model. As IPD was available for inMIND, and only published aggregate data was available for the comparator studies, the method of moments was utilized to run the propensity score logistic regression. Weights were calculated and histograms generated to explore whether any patients were either over or underrepresented in the MAICs. Effective sample sizes (ESS, the number of independent non-weighted individuals that are required to give an estimate with the same precision as the weighted

sample estimate) were calculated using standard methods.[64] Given the limitations of the evidence, the EAG considers the methods used to estimate the propensity scores to be appropriate.

3.5.3 Assessment of overlap between studies included in the ITCs

Demographic and disease characteristics with and without weighting are presented in Appendix B, Tables 24 to 30.

Compared with tafasitamab plus R^2 (inMIND), there were notable differences in age prior to weighting in three comparator studies: more patients receiving R-CHOP in van Oers were younger than 54 years, and evidence for O-B (GADOLIN) included more patients younger than 63 years; conversely, patients receiving R-CVP were older on average. Reported age characteristics were otherwise broadly comparable. ECOG status differed in one study (patients receiving R-B were somewhat fitter), and FLIPI scores varied (more high-risk scores with R-CVP, and fewer high scores for patients receiving R-B, R-CHOP [Van Oers] and O-B). The distribution of Ann Arbour stage classification was somewhat less favourable to patients receiving R-CHOP (van Oers) compared with tafasitamab plus R^2. Patients on tafasitamab plus R^2 tended to be more heavily pre-treated than those on R-CHOP (Van Oers and HMRN) and R-CVP. Compared with tafasitamab plus R^2, patients on R-CVP and R-CHOP (HMRN) were less likely to be refractory to rituximab/their last prior regimen, whereas those receiving O-B and epcoritamab had a substantially higher rate of refractory status. In response to a clarification request from the EAG, the company provided further details on the characteristics of the inMIND and HMRN populations by LOT (2L and 3L) (CQ A11). The [redacted] number of patients included in HMRN at 3L (N=[redacted]) limits any comparison by LOT. No other notable differences were identified by the EAG, although the limited reporting of patient and disease characteristics hindered the extent to which inMIND could be compared with the other studies included in the MAIC.

Histograms of the raw and rescaled weights were presented in the ITC technical report for R-B, O-B and epcoritamab. The distribution of rescaled weights indicated that a large proportion of patients had weights between 0 and 2, with only a small number of patients having weights greater than 4. There was no evidence of extreme weighting that may further bias the MAIC results.

ESS ranged from [redacted] across the MAICs. For the MAIC comparing tafasitamab plus R^2 with epcoritamab, the ESS after weighting was [redacted] of the tafasitamab plus R^2 subpopulation, indicating some overlap for the covariates that were measured in both trials. In all other MAICs, the overlap between the tafasitamab plus R^2 arm and the comparator trials was more limited, as reflected by the ESS, which ranged from [redacted] of the unweighted sample size of the tafasitamab plus R^2 arm in all but one MAIC. Overall, except for the MAIC comparing tafasitamab plus R^2 vs. epcoritamab, the size of these ESS relative to the original sample size indicate that the MAIC estimates may be

unstable. [64] However, ESS estimates are limited by the lack of reporting of key covariates in the studies included in the MAICs. This significantly limits the extent to which the inMIND population can be formally compared with other comparator studies.

3.5.4 Analytical methods

Statistical methods for deriving weighted time to event estimates were reported in the ITC report, with further details following a request from the EAG (CQ A14). Constant HRs were estimated from weighted Cox proportional hazard (PH) models that included a single covariate for treatment arm. Robust standard errors were derived using a sandwich estimator for the primary analysis, and sensitivity analyses were conducted using bootstrapping. An assessment of the PH assumption was performed using appropriate methods, including an analysis of log-cumulative hazard (LCH) plots, Schoenfeld residual plots and the Schoenfeld Individual test. The models assumed PH and did not adjust for potential violations. In response to a clarification request from the EAG, the company confirmed that no adjustments were made in the MAICs to account for differences in follow-up time between studies (CQ15), and conducted Restricted Mean Survival Time (RMST) analyses, which is appropriate notably when the PH assumption may be violated.

3.5.5 Results

Results of the main MAIC analyses are summarised in Table 9. For analyses of OS, tafasitamab plus R^2 was [redacted], where data were not available for a comparison. Hazard ratios ranged from [redacted]

For analyses of PFS tafasitamab plus R^2 was [redacted].

TTNT analyses showed that tafasitamab plus R^2 was [redacted].

3.5.5.1 Violation of the proportional hazards assumption and Restricted Mean Survival Time analyses

There was evidence of [redacted] In response to a clarification request from the EAG (CQ A14), the company stated that while time-varying HRs could theoretically be estimated where PH is violated, the uncertainty and lack of face validity of the MAIC meant that time-varying

estimates would be similarly unreliable and unlikely to be informative. As an alternative measure of relative treatment effect that does not rely on the PH assumption, differences in RMST were provided.

Results of the RMST analyses are presented in the Company's response to CQ 15, Table 8. Point estimates suggested improved OS duration compared with all other comparators. PFS was numerically favourable to tafasitamab plus R^2 compared with BRB, R-CHOP and epcoritamab, but not compared with O-B and R-CVP. The EAG agrees with the company that as the standard errors for RMST analyses did not account for variation in the MAIC weights, the width of the 95% CIs may have been underestimated.

Table 9 MAIC results: constant HRs for OS, PFS and TTNT

Trial ID	Comparison	Population	Comparator	T + R^2	OS	PFS	TTNT
			N	ESS, n (%[a])	HR (95% CI)[b]	HR (95% CI)[b]	HR (95% CI)[b]
BRB	T + R^2 vs R-B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Van Oers	T + R^2 vs R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HMRN	T + R^2 vs R-chemo (R-CHOP and R-CVP pooled)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	T + R^2 vs R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	T + R^2 vs R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GADOLIN	T + R^2 vs O-B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EPCORE NHL-1	T + R^2 vs Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Sources: CS Table 14, with further details Appendix B 1.4.4.1, the Technical Report, and following a clarification request from the EAG (CQ A12), from a Technical Report Addendum.
[a] Percent of original sample size; [b] HR (95% CI) from weighted Cox model (robust SE). Results for other derivations are reported in Appendix B. [c] Evidence of potential violation of the proportional hazards assumption
Abbreviations: T + R^2: tafasitamab + rituximab with lenalidomide; R-B: rituximab with bendamustine; R-chemo: R-chemotherapy; R-CHOP, rituximab + doxorubicin + vincristine + cyclophosphamide + prednisolone; R-CVP, rituximab + cyclophosphamide + vincristine + prednisolone; R^2, 2L+, second-line or later; 3L+, third-line or later; ESS, effective sample size; HR, hazard ratio; NR, not applicable; O-B, obinutuzumab with bendamustine; OS, overall survival; PFS, progression-free survival; PH, proportional hazards; R^2, lenalidomide + rituximab

3.5.5.2 Results stratified by line of therapy

As tafasitamab plus R^2 is anticipated to partially displace R-Chemotherapy in the 2L setting, the EAG requested from the company that they provide additional analyses comparing tafasitamab plus R^2 against R-chemotherapy in the 2L setting only (CQ A12). Methods and results were presented in an addendum report.[65] The methods were generally consistent with the main MAICs and results were reported comprehensively. Van Oers did not report sufficient information to allow MAICs by LOT. Results for MAICs in the 2L and 3L setting were reported for comparisons between inMIND and HMRN.

Results in the 2L setting are summarised in Table 10. OS results were [redacted] PFS results showed [redacted] TTNT was [redacted] Results from the sensitivity analyses using bootstrapping were [redacted]. There was evidence of [redacted].

Results for the 3L setting were also reported in the MAIC addendum. Analyses in this setting [redacted].

Table 10 MAIC results: tafasitamab + R^2 vs. R-CHOP and R-CVP (inMIND vs. HMRN) in the 2nd line setting

Study ID	Comparison	Population	Comparator	Tafasitamab + R^2	OS	PFS (IA)	TTNT
			N	ESS, N (%[a])	HR (95% CI)[a]	HR (95% CI)[a]	HR (95% CI)[a]
HMRN	Tafasitamab + R^2 vs R-chemotherapy (R-CHOP and R-CVP pooled)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Tafasitamab + R^2 vs R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Tafasitamab + R^2 vs R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Technical Report Addendum
Abbreviations: OS: overall survival; PFS: progression-free survival; IA: investigator assessed; TTNT: time-to-next treatment; ESS: effective sample size; SE: standard error[a] Hazard ratios (95% CI) from weighted Cox model (robust SE); [b] evidence of potential violation of the PH assumption; [c] evidence of clear violation of the PH assumption

3.5.5.3 Face validity

The company stated that the MAIC outcomes for PFS and TTNT suggest a lower magnitude of clinical benefit for tafasitamab plus R^2 versus R-chemotherapy than what was observed directly for tafasitamab plus R^2 versus R^2 in the inMIND trial (CS Section 2.10.5). The company considered this was unexpected and may lack face validity, as a previous indirect comparison between AUGMENT and HMRN data found R^2 to be more effective than R-chemotherapy.[NICE TA627] The EAG agrees that the MAIC informing TA627 found that R^2 was associated with longer PFS and OS compared with R-chemotherapy in 2L, although could not check numerical results as they were redacted. The EAG notes that the MAIC comparing R^2 with R-chemotherapy informing TA627 is also subject to limitations, notably because it is unanchored and could not match for all relevant prognostic and treatment effect modifiers.[TA627] As noted by clinical advisers to the EAG, the company, and to NICE (TA627), combining R-CVP and R-CHOP as a single R-chemotherapy comparator may not be appropriate as it masks potential differences between these treatments, which may have distinct effectiveness and safety profiles. The EAG clinical adviser considered that, compared with R-CVP, R-CHOP may have superior PFS and worse toxicity, and is therefore likelier to be used in younger, fitter patients. The EAG agrees with the company that the fact that PFS was more favourable to R-CVP than to R-CHOP in the company's MAICs lacks face validity. Overall, due to the lack of robust evidence comparing these treatments, the EAG concludes that the relative benefits of tafasitamab plus R^2 over R-chemotherapy regimens remain uncertain.

3.5.6 Summary of MAIC critique

EAG considers that the company's assessment of the limitations of the MAICs to be generally fair. The EAG agrees that the MAICs have important limitations and may not provide reliable estimates of relative effectiveness between tafasitamab plus R^2 and comparator therapies. Unlike inMIND, all studies included in the MAICs were open-label. The lack of available data for anchored comparisons is a significant limitation of the ITCs. None of the comparisons could account for all relevant prognostic factors and treatment effect modifiers and therefore failed to meet a key assumption of unanchored MAICs. Clinically important variables including duration of previous response/remission/POD24, double refractory status, response to last therapy, number of lymph nodes involved and tumour bulk could not be accounted for, therefore the MAIC results are at high risk of bias due to unmeasured confounding. The overlap between patient characteristics measured in inMIND and the comparator studies was limited in all MAICs; follow-up duration and PFS definitions differed between the studies, further limiting their comparability. OS data was based on few events and generally immature, and OS results were potentially confounded by subsequent therapies that may not reflect NHS practice. Due to a lack of evidence, the relative OS benefit of tafasitamab plus R^2 against R-Benda is unknown. The precision of relative effect estimates was limited by the limited number of events, particularly for OS and in the 3L setting. Some results potentially lacked face validity, notably comparisons between tafasitamab plus R^2 and R-CVP. There was evidence suggesting that the proportional hazard assumption was violated in several comparisons, most notably for PFS. RMST analyses helped to address concerns regarding the violation of the PH assumption and differences in follow-up duration between studies. However, as the company noted, they share most of the same limitations as the other MAICs analyses. The direction and magnitude of bias due to the cumulative limitations of the MAICs results is highly uncertain.

3.6 Additional work on clinical effectiveness done by the EAG

To supplement the critique of the indirect comparisons presented in Section 3.5 and to further examine claims made by the company that assuming equivalence in efficacy between R^2 and R-chemotherapy is a "conservative" assumption (CS Table 1 and CS Sections 2.10.6 and 2.13), the EAG has further examined PFS and OS data across different treatment regimens.

The EAG digitally extracted data from supplied PFS and OS Kaplan-Meier curves for all eligible interventions, drawn from the main CS, the ITC documentation supplied by the company and the HMRN report.[4, 54] Data were reconstructed for analysis using the "reconstructKM" package in R. Data were analysed using Kaplan-Meir curves, Cox proportional hazards models and Weibull models. The EAG notes that as data are reconstructed, they may not exactly match the original trial data. Only unweighted curves were extracted, and all analyses are unadjusted for any confounding factors and so may not match results from adjusted comparisons such as MAICs.

Data were extracted for the following treatments, and trials:

- Tafasitamab plus R^2, inMIND
- R^2, inMIND
- R-B, BRB and HMRN
- R-CHOP, HMRN and van Oers
- R-CVP, HMRN
- O-B, GADOLIN

For data extracted from HMRN sources, only data on 2L therapy given small numbers in 3L+.

Figure 2 shows the reconstructed survival curves for PFS, and Figure 3 similarly for OS. Table 11 summarises results of Cox proportional hazard models of naïve, unweighted and unadjusted analyses comparing R^2 to other treatments. The results highlight the difficulty in making indirect comparisons across treatments. OS survival rates appear broadly similar across treatments. Hazard ratios are close to one when comparing most treatments to R^2. This supports the company position of assuming equivalence in OS for R^2 and other R-chemotherapy regimens. While tafasitamab shows the best overall survival, it is not statistically significant superior to any treatment (results not shown).

For PFS there is considerably more variation across treatments. R^2 has superior PFS when compared to data drawn from the HMRN for R-B, R-CHOP and R-CVP, but markedly inferior PFS when compared to O-B from the GADOLIN trial. The data also highlights considerable differences across data sources, with PFS on R-CHOP and R-B being much higher in the van Oers trial and the BRB trial respectively than in the HMRN data. When comparing tafasitamab plus R^2 to other treatments, tafasitamab was not statistically superior to R-B from the BRB trial, O-B from the GADOLIN trial or R-CHOP from the van Oers trial.

In summary, while these simple, naive indirect comparisons go some way to supporting the company's assumption that R^2 is equivalent to R-CHOP or R-CVP, it does not support the assumption that R^2 is equivalent to R-B or O-B. There is also no clear evidence that tafasitamab plus R^2 is more effective than R-B or O-B. The EAG notes that these are unadjusted analyses and so should be considered as illustrative and exploratory, alongside the more formal MAICs conducted by the company (see Section 3.5). They also highlight concerns with linking PFS and OS data: these trials showed very considerable differences in PFS curves, but this did not translate into substantial differences in OS.

Figure 2 Comparison of PFS across multiple treatments

Abbreviations*:* R-B, rituximab with bendamustine, R-CHOP, rituximab + doxorubicin + vincristine + cyclophosphamide + prednisolone; R-CVP, rituximab + cyclophosphamide + vincristine + prednisolone; O-B; obinutuzumab with bendamustine; R2: lenalinomide with rituximab; CS: company submission

Figure 3 Comparison of OS across multiple treatments

Abbreviations: R-B, rituximab with bendamustine, R-CHOP, rituximab + doxorubicin + vincristine + cyclophosphamide + prednisolone; R-CVP, rituximab + cyclophosphamide + vincristine + prednisolone; O-B; obinutuzumab with bendamustine; R2: lenalinomide with rituximab; CS: company submission

Table 11 Results of Cox models comparing R^2 to other treatments

Outcome	Treatment - source	Hazard ratio (vs R^2)	95% CI		P-value
OS	O-B - ITC-GADOLIN	1.03	0.63	1.7	0.898
	R-B - HMRN 2L	0.97	0.5	1.86	0.923
	R-CHOP - HMRN 2L	0.97	0.55	1.7	0.918
	R-CHOP - van Oers	0.81	0.5	1.34	0.415
	R-CVP - HMRN 2L	1.11	0.62	1.99	0.725
	Tafasitamab - CS	0.62	0.34	1.14	0.123
PFS	O-B - ITC-GADOLIN	0.53	0.4	0.7	<0.001
	R-B - HMRN 2L	4.71	2.99	7.42	<0.001
	R-B - ITC-BRB	0.7	0.45	1.09	0.117
	R-CHOP - HMRN 2L	3.33	2.33	4.78	<0.001
	R-CHOP - van Oers	0.41	0.32	0.54	<0.001
	R-CVP - HMRN 2L	3.36	2.28	4.94	<0.001
	Tafasitamab - CS	0.48	0.36	0.63	<0.001

Abbreviations: OS: overall survival; PFS: progression-free survival; 2L, second-line; ITC: indirect treatment comparison; R-B, rituximab with bendamustine, R-CHOP, rituximab + doxorubicin + vincristine + cyclophosphamide + prednisolone; R-CVP, rituximab + cyclophosphamide + vincristine + prednisolone; O-B; obinutuzumab with bendamustine
* HR>1 favours R^2;HR<1 favours named comparator

3.7 Conclusions of the clinical effectiveness section

The EAG considers that the company decision problem is generally in line with the NICE scope, and considers that the exclusion of the comparator R-monotherapy from the decision problem is justified.

The primary evidence on tafasitamab plus R^2 comes from the inMIND trial. The EAG considers this to be a generally well-conducted trial at low risk of bias. The interim results from the trial show evidence that tafasitamab plus R^2 leads to a statistically and clinically meaningful improvement in PFS compared to placebo plus R^2. While there was numerical evidence of improved OS with tafasitamab plus R^2, results were not statistically significant. OS data are limited by significant immaturity, which preclude any meaningful interpretation. It is uncertain whether the relative PFS benefits of tafasitamab plus R^2 compared with R^2 may translate into improved OS. A review of trials in FL indicates that PFS may only be a weak surrogate predictor of OS, although this evidence has limitations.

Comparisons between tafasitamab plus R^2 and R-B, O-B, R-CHOP, R-CVP, and epcoritamab could only be conducted indirectly via unanchored MAIC analyses. The indirect comparisons of OS suggested that [redacted]. OS data were [redacted]. For analyses of PFS, tafasitamab plus R^2 was [redacted]. The direction and magnitude of bias due to the cumulative limitations of the MAICs is highly uncertain, therefore these findings may not be reliable.

In conclusion, the EAG considers that the clinical evidence suggests that tafasitamab plus R^2 could reasonably replace R^2 in R/R FL. However, the long-term survival benefits remain uncertain. Limitations of the indirect comparisons make the relative benefits and harms of tafasitamab plus R^2 compared with R-B, O-B, R-CHOP, R-CVP, and epcoritamab highly uncertain.

Substantially more mature data from inMIND is required to demonstrate that tafasitamab plus R^2 leads to clinically significant improvements in OS compared with relevant comparators. CDF data collected over a sufficiently long period would potentially address confounding of OS outcomes for tafasitamab plus R^2 due to subsequent non-routine therapies; however, any future evidence would be unlikely to address most of the limitations inherent to the indirect comparisons.

4 COST-EFFECTIVENESS

This section presents a summary and critique of the cost-effectiveness evidence included in the company's submission. Section 4.1 focuses on the company's review of the cost-effectiveness evidence and section 4.2 covers the company's economic evaluation.

4.1 Critique of the review of cost-effectiveness evidence

The company conducted an SLR to identify relevant published economic analyses for patients with R/R FL. The full SLR search strategy, study selection process and results are detailed in an SLR report of HRQL and economic evidence.[66] The company also presents summary results of a search of previous NICE submissions in FL in Appendix E of the CS. Searches were undertaken on 18th March 2024 and later updated on 22nd April 2025. A critique of the searches carried out in relation to the HRQL and economic evidence is reported in Appendix 1 and Appendix 2 respectively.

4.1.1 Study selection

Studies including adults with R/R FL (Grade 1-3a) or R/R MZL with at least one prior anti-CD20 therapy were eligible for inclusion. Double-blind screening was conducted at both the title/abstract and full-text levels, with discrepancies either resolved through discussion between the two reviewers or by a third independent reviewer. Data extraction from included full-text studies was performed by one researcher using a Microsoft Excel®-based template and independently reviewed by a second researcher. Study selection was restricted to English language studies only. Despite this restriction, the EAG believes that the study selection process was appropriate.

4.1.2 Inclusion/exclusion criteria

The inclusion criteria followed a Population, Intervention, Comparator, Outcomes, Study design, and Timeframe (PICOST) framework and were generally appropriate. The population was restricted to adults diagnosed for R/R FL (Grade 1-3a) or R/R MZL with at least one prior anti-CD20. No restrictions were placed on interventions and comparators. Outcomes informing HRQL were restricted to: EQ-5D (EQ-5D-3L/EQ-5D-5L), EORTC QLQ-C30, FACT-Lym, disease-related PROs, generic PROs, disease-related utilities, and generic utilities. Eligible study designs included: observational studies, relevant published SLRs, economic evaluations, and HTA reports of specific interventions. The company performed quality appraisal using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement 2022, for which the results were embedded in Appendix E of the SLR report as links.[66]However, the links are inactive and not accessible to the EAG.

The EAG considers the eligibility criteria for both the HRQL and economic evidence sufficient for the company to fulfil its objective to identify cost-effectiveness studies.

4.1.3 Identified studies

4.1.3.1 HRQL review

Based on the company's SLR report, a total of six studies met the eligibility criteria for inclusion for HRQL in the original search and five relevant HTA submissions were identified through *ad hoc* searches. Of these, eight studies focused on R/R FL; these consisted of three clinical trials, and the five HTA submissions. Two studies focused on a mixed population, one of which reported subgroup analyses specific to R/R FL. The remaining study focused exclusively on R/R MZL. In the updated search, six unique studies from nine reports were identified, of which five studies reported HRQL outcomes for R/R FL and one study reported outcomes for a mixed population including R/R FL. This included two newly identified trials, and new evidence from two previously included trials. Two observational studies were also identified, but the FL grade distribution or prior anti-CD20 treatment was not specified in the studies.

The results of the searches were presented separately based on disease population including, R/R FL (grade 1–3a) and R/R FL MZL (mixed population), and therapies of focus; CAR-T cell therapy (lisocabtagene maraleucel and tisagenlecleucel), immunochemotherapy (O-B compared to bendamustine monotherapy), targeted therapy (zanubrutinib plus obinutuzumab compared to obinutuzumab monotherapy), immunotherapy (odronextamab and epcoritamab), and other treatment options. The identified HTAs were from the CADTH and SMC and assessed the following interventions: idelalisib, O-B, tisagenlecleucel, and mosunetuzumab. None of these studies were UK specific, with majority being multinational studies. Of the included studies, five studies, including those with new evidence from trials included in the original search, reported EQ-5D-3L/5L scores, and eight studies reported EQ-VAS scores.

Details of all included studies were reported in Table 4 to Table 6 of the SLR report.[66]

Points for Critique

The CS states that a total of nine publications met the inclusion criteria, this is inconsistent with the number of included studies detailed in the SLR report (Sections 1.4.1 and 4.1, and the Excel file of included studies provided by the company). Notably, an observational study by Johnson et at., (2024)[21] evaluating QoL in patients with FL in Europe and the United States was an included study in the SLR report but listed in the company's Excel file of excluded studies.

Evidence from the SLR was not used to inform utility values in the decision model. However, utility values were considered from previous NICE TAs which included direct utility values from the

AUGMENT (TA627)[67], GADOLIN (TA629)[35] and GO29781 (TA892)[68] trials and a utility elicitation study in FL patients by Wild et al., 2006.[69] Results from these studies are presented in Table 34 of CS and were explored in scenario analysis (Section 3.11.3 of CS). These sources, including studies reporting on the AUGMENT and GO29781 trials, did not make up the studies included in the HRQL searches.

4.1.3.2 Economic evidence review

In the economic evidence review, a total of 38 references met the eligibility criteria in the original search. Of these, 35 assessed R/R FL only, two reported separate outcomes for both FL and MZL, and one reported outcomes for R/R MZL only. The updated search identified 19 unique studies from 21 reports. Results were organised by disease population—R/R FL (grade 1–3a) or R/R MZL—and by treatment type: immunotherapy, CAR-T cell therapy, immunochemotherapy, targeted therapy, transplantation, and any treatment.

The full search yielded 35 economic model-based analyses, including cost-effectiveness, cost-minimisation, cost-utility, and budget impact studies. In addition, a cost-consequence model analysis, a burden of illness study, and three micro-costing exercises were included. The remaining studies did not specify the type of economic analysis. Model designs comprised twelve PSMs, three Markov models, and one decision-analytic model (based on the overview of included studies provided in Table 13 of the SLR report). The remaining studies either relied on alternative analyses, such as area under the curve or per-patient total cost of therapy modelling or did not report the model design.

The majority of economic analyses (18 studies) were conducted from a US perspective, with the remaining studies from Canada (two), Italy (two), Ireland, the Netherlands, Norway, Sweden, China, and one multinational study.

The company also searched previous NICE submissions in FL, summarised in Appendix E of the CS. The interventions assessed included rituximab (TA137)[70], idelalisib (TA604)[71], R2 (TA627)[67], O-B (TA629)[35], mosunetuzumab (TA892)[68], and axicabtagene ciloleucel (TA894).[37] All six submissions considered a 3-state partition survival model (PSM), with one submission (TA604)[71] additionally using cohort STMs for three separate comparisons.

An overview of the included economic studies was reported in Table 13 of the SLR report.[66]

4.1.3.3 Interpretation of the cost-effectiveness review

None of the studies identified in the HRQL or economic evidence reviews were UK-specific, and the company did not directly use findings from these SLRs to inform the model beyond its structural framework. Instead, HRQL values from previous NICE appraisals were applied in scenario analyses, and prior data were used to inform HCRU values in the base-case analysis.

In an informal search, the EAG identified additional UK-based evidence that could have supplemented the company's model. Wang et al., (2018) reported a discrete event simulation model for FL using population-based HMRN data (n = 740 patients diagnosed between September 2004 and August 2011).[23] The model captured patient pathways, including second-line and later symptomatic treatments, with costs evaluated from an NHS perspective. Treatment costs were derived from the HMRN cohort and corresponding resource use. Lifetime costs per patient receiving second-line treatment including SCT were £60,261, with 12.15 QALYs, whereas for patients not receiving SCT, costs were £36,000 with 8.34 QALYs. The EAG also identified a UK utility elicitation study by Wang et al. (2017), though only the abstract was available.[72] This study used HMRN data for 181 newly diagnosed FL patients between 2012 and 2016, who completed EQ-5D-5L questionnaires at six months and then at 12-month intervals. Utilities were aggregated by disease state—watch-and-wait, treatment, and remission. Neither of these studies was included in the company's SLR, yet they represent relevant UK-specific evidence that could have informed the model and strengthened the assessment.

4.2 Critique of the submitted economic evaluation

4.2.1 NICE reference case checklist

Table 12 summarises the EAG's assessment of whether the company's economic evaluation meets the NICE reference case and other methodological recommendations.

Table 12 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	QALY benefits to treated individuals were considered.
Perspective on costs	NHS and Personal Social Services	NHS and PSS costs have been considered.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	A cost-utility analysis was implemented.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The economic model uses a 36-year time horizon. This is sufficient given the disease area.
Synthesis of evidence on health effects	Based on systematic review	The company initiated a systematic review to identify relevant sources of data.
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.	EQ-5D-5L data was collected in the inMIND trial. These values were cross-walked to EQ-5D-3L values using the Hernandez *et al.* mapping function. [73]
Source of data for measurement of health-related quality of life	Reported directly by patients, carers or both	Derived from EQ-5D data directly obtained from patients in the inMIND trial.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes

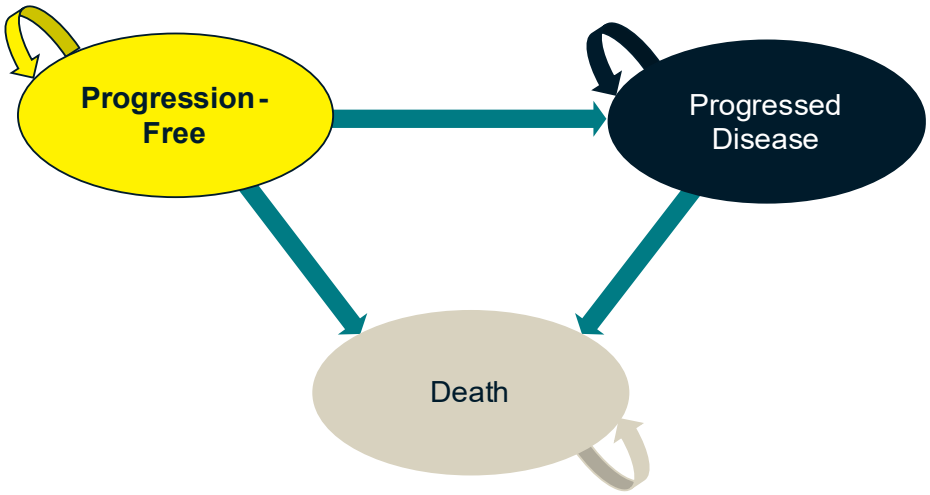
Element of health technology assessment	Reference case	EAG comment on company's submission
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the people having the health benefit, except in specific circumstances	Yes.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Costs were based on UK sources, including the eMIT and NHS reference costs.[74, 75] Resource use rates were based on values used in TA 627.[67]
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Costs and benefits have been discounted at 3.5% per annum.

4.2.2 Model structure

The company submitted a PSM to estimate the lifetime cost-effectiveness of tafasitamab plus R^2 with either R^2 or one of four alternative R-chemotherapy combinations. The PSM comprised three mutually exclusive health states: progression-free survival (PFS), progressed disease (PD), and Death. The model uses a cycle length of one week, and no half-cycle correction is applied (due to the short cycle length). The modelled time horizon is 36 years, and costs and benefits are discounted at 3.5% in line with the reference case.

The cohort enters the model in the PFS health state, and in each weekly cycle, patients can remain in this state, progress into PD, or progress to Death. Patients are not allowed to return to the PFS state once in the PD state. The transitions from the PFS state to PD, or death states are defined by the time-dependent PFS and OS curves from the inMIND trial and extrapolated beyond the available data using parametric models over a lifetime horizon (Section 4.2.5). The proportion of patients alive over time is estimated directly from the OS curve, with the hazard of death constrained to be at or above the corresponding age- and gender-matched all-cause general population risk of death by age. OS is partitioned into the proportion of patients who are alive with PD (OS minus PFS) and the proportion of patients who are alive without having progressed (PFS). Figure 4, illustrates the PSM structure for the three health states in the model.

Figure 4 Model structure



Source: CS Figure 12

In addition to the PSM structure described above, the company also presents a scenario analysis using a STM approach. This alternative approach uses the same three health states as the PSM, but transitions are modelled differently. Specifically, transition probabilities between health states are explicitly modelled and define the proportion of patients moving to each health state within a given model cycle. Health state occupancy is therefore the product of three transition probabilities: i) the probability of progression, ii) the probability of death in the PF health state, and iii) the probability of death from the PD health state.

In the STM, OS is determined by all three transition probabilities and depends on the time spent in the PFS and PD health states. As in the PSM, transitions from PFS to PD are modelled as time-dependent, based on the PFS curve from the inMIND trial extrapolated over the model's time horizon. Transitions from PFS to death are also derived from the inMIND trial, assuming a constant proportion of PFS events represent deaths. In contrast to the PSM, transitions from PD to death are not informed by inMIND trial data; instead, they are informed by external sources, including the HRMN database, the GADOLIN trial, or a weighted combination of both. Accordingly, the company presents three alternative STM model versions to explore different assumptions regarding the duration of post-progression survival (PPS) and the magnitude of any PPS benefits (see Section 4.2.5.5 for a detailed discussion).

Points for critique

Appropriateness of the PSM model structure

PSMs and STMs are widely accepted approaches to oncology modelling, and both have been accepted in previous NICE TAs. In the present context, the EAG considers the appropriateness of the company's PSM to be largely dependent on the maturity of the observed data informing survival outcomes, particularly OS. The extrapolation of outcomes over a lifetime horizon (see Section

4.2.5.2) is critical, as uncertainty in long-term OS directly leads to uncertainty in cost-effectiveness estimates. As acknowledged by the company, the OS data from inMIND are immature, with only 15 death events in the tafasitamab plus R^2 arm and 23 in the R^2 arm, and a median follow-up of 15.3 months. Extrapolations based on these data are therefore subject to extensive uncertainty, making it exceptionally difficult to judge whether predicted survival gains are reasonable. Further, reported differences in OS are not statistically significant; it is therefore unclear whether it is appropriate to model any survival gain. The OS data are also potentially confounded, as subsequent therapies received following progression were not fully reflective of the NHS pathway, see Section 3.5.

A STM may at least partially overcome the disadvantages associated with the PSM approach, as it places greater emphasis on PFS, which is substantially more mature and not subject to confounding biases from subsequent treatment. An STM also allows for alternative data, including non-randomised or real-world evidence more representative of the NHS treatment pathway, to be incorporated, and can therefore better reflect current NHS practice regarding subsequent treatment options. The main disadvantage of the STM approach is that it assumes a structural dependency between PFS and OS outcomes. Furthermore, where external data is used to model transitions from progressed disease to death, it results in estimates of OS that are no longer based on a randomised comparison.

The implied dependency between PFS and OS in a state-transition model is central to the STM approach and provides a means with which to inform estimates of OS in the absence of direct evidence. This approach, however, requires a surrogacy assumption, whereby PFS benefits are assumed to translate into proportional OS benefits. Assessment of this assumption is consequently crucial to the viability of this approach as emphasised in the NICE methods guide, which states: *"When the use of 'final' clinical endpoints is not possible and 'surrogate' data on other outcomes are used to infer the effect of treatment on mortality and health-related quality of life, evidence in support of the surrogate-to-final end point outcome relationship must be provided together with an explanation of how the relationship is quantified for use in modelling."* [76]

Evidence in support of a surrogate relationship between PFS and OS in FL is, however, mixed. As discussed in Section 3.3.2.3, the most up-to-date evidence suggests that the relationship between PFS and OS is weak, with PFS explaining only a small proportion of the observed variation in OS across lines of therapy. While clinical opinion indicates that PFS may be a stronger predictor of OS in later lines of therapy, this hypothesis is currently unsupported by published empirical evidence. Consequently, any STM approach that relies on PFS to inform long-term OS necessarily rests on a weak and uncertain surrogacy assumption, introducing additional structural uncertainty and limiting confidence in the modelled OS gains.

Despite these limitations of the STM and the weak evidence in support of a surrogate relationship between PFS and OS, the EAG considers that the STM approach still has value for the following reasons. First, the company's base-case analysis predicts a sizable OS benefit. However, the observed OS data do not support the magnitude of these modelled benefits, and therefore the PSM implicitly assumes that the statistically significant improvements observed in PFS translate into gains in OS. The STM approach simply makes this assumption explicit rather than implicit, providing a more transparent and structured framework for decision-making. Second, the immaturity of the OS data from inMIND is such that extrapolation of OS directly from the trial data is associated with extreme uncertainty, to the extent that it is not possible to estimate the magnitude of any OS benefit with confidence. While the STM does not resolve this uncertainty, it provides a structured approach to estimating relative OS outcomes in a setting where direct evidence is lacking. Therefore, subject to acceptance that some OS benefit exists, and acknowledging the uncertainty inherent in the surrogate relationship between PFS and OS, the EAG considers the STM approach to be more appropriate than the PSM in the present context, as it more transparently reflects the assumptions required to estimate long-term survival outcomes.

4.2.3 Population

The population considered in the company's base-case analysis comprised adults with relapsed or refractory follicular lymphoma (FL; grade 1–3a) who had received at least one prior line of systemic therapy. This population is consistent with the anticipated MHRA approval, proposed licensed indication and marketing authorisation for tafasitamab in combination with R² (lenalidomide and rituximab) in the UK, and aligns with the NICE final scope (CS, p.15).

The cost-effectiveness model is informed by data from the inMIND trial, specifically the FL FAS (n = 548). This population includes patients with grade 1–3a FL who experienced R/R disease following at least one prior line of systemic anti-CD20 immunotherapy or chemo-immunotherapy, corresponding to treatment in the second- and third-line settings. The company's base-case (2L+) and subgroup (3L+) analyses compare tafasitamab plus R² (the inMIND intervention arm) with R² alone (the comparator arm), using progression-free survival and overall survival outcomes within a partitioned survival modelling framework.

The company reports that clinical expert validation was undertaken to confirm that the inMIND trial population is representative of patients with R/R FL eligible for treatment in the UK and is consistent with the final scope.

The model incorporates a limited set of baseline population characteristics—age, sex, mean body weight and mean body surface area (BSA), see Table 13.

Table 13 Baseline patient characteristics of the modelled population

Characteristic	Modelled population
Age	64.20 years
Sex	54.6 % male
Weight	76.93 kg
Mean BSA (mg/m^2)	1.86
Source: Company model **Key:** BSA, body surface area; kg, kilograms; m^2, meters squared; mg, milligrams	

Age and sex were also used to determine background mortality, and age/sex-related adjustments were applied to utility values. The company state that baseline characteristics of the inMIND population are generally consistent with those of patients anticipated to receive tafasitamab plus R^2 in UK clinical practice. [34, 77]

Points for critique

Generalisability of inMIND trial

As discussed in Section 3.3.1, the EAG considers the inMIND modelled population to be broadly appliable to patients with grade 1–3a follicular lymphoma treated in NHS clinical practice, albeit with some notable differences. Compared with patients typically treated with R-Chemotherapy in the NHS, trial participants may be younger, have longer times to diagnosis and remission, higher rates of rituximab-refractory disease, and more favourable POD24 status.[3, 4] In addition, a small proportion of patients in inMIND (8.0%) had received four or more prior lines of therapy; according to a clinician consulted during the company's clinical validation meeting, [34] such patients would be more likely to receive epcoritamab in NHS practice, if it becomes available. Taken together, the extent to which the inMIND FL participants truly reflects the population who would be receiving tafasitamab plus R^2 in practice is uncertain.

Of particular relevance to the economic model is the age distribution of the inMIND population, which is modestly younger than would be expected in NHS practice. The median age in inMIND was 64 years [78]) which is [redacted] than patients initiating R-CHOP (median [redacted] years), but [redacted] than patients receiving R-CVP (median [redacted]) and FL patients initiating 2L treatment in the NHS (68.0 years [57-75][49], although it is uncertain whether this population is fully reflective of patients who would be eligible for tafasitamab plus R^2.

Although neither dataset may be fully representative of all patients treated in the NHS, the observed age difference is potentially relevant given considerations around treatment tolerability. As highlighted during the Advisory Board meeting [77], older and frailer patients may have greater difficulty tolerating lenalidomide. In addition, eligibility for tafasitamab plus R^2 requires patients to be sufficiently fit to receive up to 28 tafasitamab infusions over a 12-month period. Consequently, patients considered suitable for tafasitamab plus R^2 in clinical practice may, on average, be younger

and fitter than the broader relapsed or refractory follicular lymphoma population and may therefore experience comparatively better outcomes on lenalidomide-containing regimens. To explore the impact of this uncertainty, the EAG considers a scenario analysis in which an older starting age, informed by the HMRN population, is applied in the model. This analysis is intended to explore the uncertainty associated with the starting age at treatment initiation (see Section 5.2.2), which is an important driver of cost-effectiveness in the modelling of FL because a substantial proportion of deaths are attributable to background mortality rather than disease progression.

2L vs 3L+ subgroup

The company's base-case analysis reflects the proposed marketing authorisation and therefore pools patients treated in the second line (2L) and third line or later (3L+) settings. The EAG has concerns that combining these populations may mask meaningful heterogeneity in cost-effectiveness across lines of therapy and considers that separate consideration of these groups may be appropriate. Cost-effectiveness may plausibly differ by line of treatment for several reasons, including variation in treatment effect, differences in underlying prognosis, and differences in the relevant comparator treatments across treatment lines.

Subgroup analyses from the inMIND trial indicate a modest difference in the hazard ratio (HR) for progression-free survival (PFS), with an HR of 0.48 (95% CI 0.32 to 0.74) in 2L patients compared with 0.41 (95% CI 0.28 to 0.61) in 3L+ patients, suggesting a slightly greater relative treatment effect in the later-line population. However, these findings should be interpreted cautiously, as the confidence intervals overlap substantially and the trial was not powered to formally assess differences in treatment effect by line of therapy.

Notwithstanding this, patients treated in the 3L+ setting would be expected to have a materially poorer prognosis than those treated in 2L, reflecting more refractory, advanced or aggressive disease. This is supported by baseline characteristics reported in Table 6 of the company's clarification response, where the proportion of patients with POD-24 is higher in the 3L+ population than in the 2L population (35% versus 27%), time since diagnosis is longer ([redacted] years versus [redacted] years), and a greater proportion of patients who are refractory to rituximab ([redacted] versus [redacted]). The EAG's clinical adviser also emphasised that line of therapy is an important prognostic factor. Taken together, the EAG considers that heterogeneity in ICERs across lines of therapy cannot be ruled out.

In addition, as discussed in Section 4.2.4, the relevance of R-chemotherapy regimens as comparators is less clear in the 3L+ setting. The appropriate comparator set may therefore differ by line of therapy, with both R² and R-chemotherapy relevant in the 2L setting, but R² alone more likely to be relevant in the 3L+ setting. Given the differences in acquisition and administration costs between R² and R-

chemotherapy regimens, this may introduce further heterogeneity into estimates of cost-effectiveness across treatment lines.

In light of these concerns, the EAG requested at clarification that the company provide a subgroup analysis restricted to the 2L-only population (B9); a scenario considering the 3L+ population only had already been included in the CS. The clarification response indicated that the ICER for the 2L-only population was substantially higher, at approximately £50,000 per QALY gained, and was broadly consistent across the OS extrapolations considered. This contrasts with an ICER of £27,377 per QALY gained in the 3L+ setting. Given this marked difference in cost-effectiveness across subgroups, the NICE committee may wish to consider an optimised recommendation focused on the 3L+ population.

4.2.4 Interventions and comparators

The company's economic model compared tafasitamab plus R^2 with R^2 alone and rituximab-based chemotherapy regimens, namely R-B, R-CHOP and R-CVP. The company stated that tafasitamab plus R^2 is expected to displace R^2 in the current treatment pathway and, therefore, considered R^2 to be the primary comparator for the appraisal. The company also indicated that some displacement of R-chemotherapy is anticipated in the 2L setting. All treatments were modelled using a 28-day cycle, with individual regimen components administered on specified days within each cycle. Autologous or allogeneic SCT was not included as a comparator, nor was obinutuzumab plus bendamustine, which is currently a NICE recommended treatment option. Epcoritamab was also excluded from the analysis; epcoritamab is currently under NICE evaluation in the 3L+ setting.

Dosing of tafasitamab plus R^2 was consistent with the inMIND trial and the marketing authorisation. Tafasitamab was administered intravenously (IV) at a weight-based dose of 12 mg/kg on Days 1, 8, 15 and 22 for the first three treatment cycles, followed by 12 mg/kg on Days 1 and 15 (i.e. every two weeks) from Cycle 4 onwards, for up to 12 cycles in total. Lenalidomide was administered at a fixed oral dose of 20 mg daily on Days 1–21 of each cycle, for up to 12 cycles. Rituximab was administered IV at a BSA based dose of 375 mg/m² on Days 1, 8, 15 and 22 of Cycle 1, and on Day 1 of Cycles 2–5. In the R^2 comparator arm, dosing schedules and treatment frequencies matched those used in the tafasitamab plus R^2 regimen, excluding tafasitamab.

The economic model also included three rituximab-based chemotherapy comparators: R-B, R-CHOP and R-CVP. Induction treatment for all R-chemotherapy regimens was modelled using 28-day cycles, followed by rituximab maintenance where applicable. Dosing information for the R-chemotherapy comparators was derived from the corresponding SmPCs.

During induction, rituximab was administered IV at a dose of 375 mg/m² in combination with regimen-specific chemotherapy agents. In the R-B regimen, rituximab was administered on Day 1 of 6 cycles alongside bendamustine administered IV at 90 mg/m² on Days 1 and 2, also for 6 cycles. In the R-CHOP regimen, rituximab was administered on Day 1 of 6 cycles in combination with doxorubicin (50 mg/m² IV on Day 1), vincristine (1 mg/m² IV on Day 1), cyclophosphamide (750 mg/m² IV on Day 1), and oral prednisolone (40 mg/m² on Days 1–5). In the R-CVP regimen, rituximab was administered on Day 1 of 8 cycles in combination with cyclophosphamide (750 mg/m² IV on Day 1), vincristine (1 mg/m² IV on Day 1), and oral prednisolone (40 mg/m² on Days 1–6.

Following induction, rituximab maintenance was modelled for all R-chemotherapy regimens. Maintenance treatment was administered either subcutaneously (SC) at a fixed dose of 1,400 mg or IV at 375 mg/m² on Day 1 of each 3-monthly cycle, for a period of up to 2 years. In the company's base case analysis, all patients were assumed to receive SC rituximab, with scenario analysis exploring the impact of assuming IV rituximab administration.

Subsequent treatments were modelled to be received by 86.8% of patients who progressed and included R-chemotherapy regimens (R-B, R-CHOP and R-CVP), rituximab monotherapy, and both allogeneic and autologous SCT. The distribution of subsequent treatments was based on proportions elicited from a clinical advisory board, with the same distribution applied irrespective of whether subsequent therapy represented third- or fourth-line treatment. The company noted that, although data on subsequent treatments were available from the inMIND trial, it did not consider it appropriate to model these distributions because several therapies used in the trial are not available in the NHS.

Points for critique

Role of R-Chemotherapy

The EAG agrees with the company that tafasitamab plus R² would be expected to replace R² in the current treatment pathway and therefore represents a key comparator in the appraisal. The EAG also considers that tafasitamab plus R² may displace some use of R-chemotherapy regimens, particularly in the 2L setting, although the extent of any such displacement is uncertain.

Clinical advice to the EAG indicated that R-chemotherapy is currently used in the 2L setting primarily in patients with high-risk disease (for example, those with POD24), high tumour burden, a perceived risk of histological transformation, or in younger, fitter patients who are better able to tolerate chemotherapy toxicity, particularly bendamustine- or CHOP-based regimens.[31] Use of R-chemotherapy in this setting therefore reflects a balanced clinical judgement between the need for rapid and durable disease control and the desire to avoid chemotherapy-related toxicity, with treatment selection being highly individualised rather than protocol-driven. Clinical advice also

indicated that treatment decisions vary between centres, resulting in substantial heterogeneity in current NHS practice and the national guidelines state that, as with front-line therapy, the optimal chemotherapy regimen at the point of relapse has not been determined.

On this basis, tafasitamab plus R² is unlikely to replace R-chemotherapy in all patients with aggressive or high-burden relapsed follicular lymphoma, for whom chemo-immunotherapy is likely to remain the preferred option. However, the EAG notes that clinical trial evidence suggests benefits of tafasitamab plus R² across a range of patient subgroups, including those with POD24, which may support broader applicability in selected patients. Further, in situations where current clinical decision-making is finely balanced, there may be a shift from R-chemotherapy towards tafasitamab plus R², reflecting the greater efficacy of the triplet regimen compared with R² alone. The extent of any displacement of R-chemotherapy will therefore depend on evolving clinical experience with tafasitamab plus R² and its demonstrated efficacy and tolerability in real-world practice.

The EAG therefore considers R-chemotherapy to be a relevant comparator to tafasitamab plus R² in the 2L setting. In contrast, in the 3L+ setting, clinical advice to the EAG indicated that treatment decisions are mostly driven by prior therapies received, with use of R-chemotherapy typically reserved for patients who have previously received R². Patients would therefore not typically be retreated with tafasitamab plus R² if they had previously received R² in the 2L setting. This would indicate that R-chemotherapy is less relevant as a comparator in the 3L + setting. However, the heterogeneous nature of the pathway and individualised selection of treatments means that R-chemotherapy can't be ruled out as a comparator in the 3L+ setting and clinical advice indicated an expectation that some R-chemotherapy would be displaced in the 3L+ setting.

Role of obinutuzumab plus bendamustine and epcoritamab

The EAG agrees that obinutuzumab plus bendamustine is not a relevant comparator in the present appraisal. Clinical advice to the EAG indicated that this regimen is rarely, if ever, used in current NHS practice in relapsed or refractory follicular lymphoma. This view is consistent with advice obtained through the company's advisory board and aligns with the opinion of the NHS England Cancer Lead provided as part of TA892 (mosunetuzumab for treating relapsed or refractory follicular lymphoma),[68] in which obinutuzumab plus bendamustine was not considered a relevant comparator in the 3L+ setting. On this basis, the EAG considers its exclusion from the analysis to be appropriate.

The EAG also agrees, in principle, with the exclusion of epcoritamab as a comparator. Clinical advice to the EAG indicated that, although epcoritamab is currently under consideration by NICE for use from the 3L setting onwards and could therefore represent a potentially relevant comparator to tafasitamab plus R. However, the EAG understands that, within ID6338, the company is positioning

epcoritamab for use in the fourth-line (4L) setting and beyond. On this basis, epcoritamab is unlikely to represent a relevant comparator to tafasitamab plus R² in the 3L setting. However, the EAG notes that this positioning remains subject to change, and the relevance of epcoritamab will ultimately need to be considered by the committee at the point of decision-making, in light of any recommendations arising from the parallel appraisal. It may also be the case that epcoritamab becomes a relevant subsequent treatment and, as such becomes part of the mix of subsequent treatments received by patients.

4.2.5 Treatment effectiveness and extrapolation

As discussed in detail in Section 4.2.2, the company used a PSM consisting of three health states: PFS, PD, and death. Consistent with this model structure, OS and PFS survival curves were used to calculate the health state membership based on observed OS and PFS data from the inMIND trial using data from the latest data cut (23rd February 2024). Due to a lack of appropriate data on the relative efficacy of R-chemotherapy regimens, the analysis assumes that R-chemotherapy and R² have equivalent efficacy.

To inform the model health state transitions, and cost and resource use, it was necessary to extrapolate the available PFS, OS, and TTD data observed in the trial. This was achieved using parametric models. The procedure for each extrapolation was similar for all three outcomes. The extrapolated survival curves inform patient membership of model health states, where membership of the Death and PFS states is informed by the survival curves themselves, and PD state membership is calculated as the difference between the proportion of patients in the PFS state and the Death state.

4.2.5.1 Clinical equivalence of R² and R-chemotherapy regimens

As described in Section 3.4, there is no head-to-head evidence comparing R-chemotherapy regimens with either tafasitamab plus R² or R² alone. Similarly, there is no direct randomised evidence in the relapsed or refractory setting comparing alternative R-chemotherapy regimens with each other. In an attempt to generate estimates of relative effectiveness, the company conducted MAICs using single-arm data from relevant randomised controlled trials, supplemented with evidence from the HMRN.

However, the company concluded that the results of these analyses were not sufficiently reliable for inclusion in the economic model. In particular, the MAICs suggested that PFS associated with R-chemotherapy regimens may be superior to that observed with R², which the company considered to lack face validity and to be inconsistent with previous NICE guidance, specifically TA627, which evaluated R² for the treatment of relapsed or refractory follicular lymphoma.

Given these limitations in the available evidence, the company instead adopted the simplifying assumption that R-chemotherapy is equivalent to R² in terms of efficacy. The company considered

this assumption to be conservative and likely to favour R-chemotherapy. In the original base case, this assumption was implemented by applying the hazard ratios, estimating the relative effectiveness of tafasitamab plus R² versus R² to the PFS and OS curves for tafasitamab plus R² in order to generate predicted PFS and OS outcomes for R-chemotherapy. Following clarification questions and at the suggestion of the EAG, the company subsequently simplified its approach by directly using the extrapolated PFS and OS curves for R² to represent outcomes for R-chemotherapy.

Points for critique

The EAG considers the company's assumption of equivalent efficacy between R² and R-chemotherapy to introduce significant uncertainty into the model. Firstly, the assumption appears to imply that all R-chemotherapy regimens have equivalent efficacy, which is highly uncertain. Clinical evidence and expert opinion suggest differences between commonly used R-chemotherapy regimens. In previously treated FL, R-CHOP is generally regarded as more effective than R-CVP, and R-CVP is often used in older or less fit patients because of its lower toxicity profile, rather than equivalent efficacy to R-CHOP. This interpretation was reflected in TA627,[67] where the committee and clinical experts noted clinically meaningful differences between R-CHOP and R-CVP, even though the economic model assumed equivalence for practical reasons.

There is also evidence from retrospective and observational studies that R-B may provide similar or longer progression-free survival than R-CHOP, although this does not clearly translate into an overall survival advantage. For example, some retrospective data have suggested longer PFS with R-B versus R-CHOP, albeit without a demonstrated OS benefit.[79]

Secondly, the EAG does not consider there to be sufficient evidence to support the company's assertion that R² and R-chemotherapy are equivalent in efficacy and certainly not enough to conclude that this assumption is conservative. Randomised evidence from the RELEVANCE trial[80] in the frontline setting showed similar outcomes between R² and R-chemotherapy in previously untreated patients but did not demonstrate superiority of R²; this evidence primarily reflects first-line therapy rather than the relapsed setting. Furthermore, the MAICs provided by the company do not robustly support equivalence, and the EAG highlights that R-chemotherapy is often selected for patients with prior chemo-sensitive disease or disease perceived to be at higher risk of transformation, which may imply systematic differences in outcomes that are not captured by simple equivalence assumptions.

The EAG therefore advises that the company's assumption of equivalent efficacy should be viewed with considerable caution. Although the MAIC estimates may not be reliable (see Section 3.5), these scenarios reflect alternative plausible assumptions regarding relative efficacy in the absence of direct evidence.

4.2.5.2 Overall survival (OS) extrapolation

The observed OS data from the inMIND trial was obtained from the latest data cut for a median follow-up of 15.8 months in the tafasitamab plus R^2 arm and 14.6 months in the R^2 arm. Data was immature with on 15/273 events in the tafasitamab plus R^2 months and 23/275 in the R^2 arm.

To extrapolate available OS data, the company fitted parametric survival model jointly to both arms using AFT models for consistency with the extrapolation approach for PFS. The company noted that the use of independent models indicated that tafasitamab plus R^2 offers inferior survival which the company considered inconsistent with the demonstrated benefit on PFS.

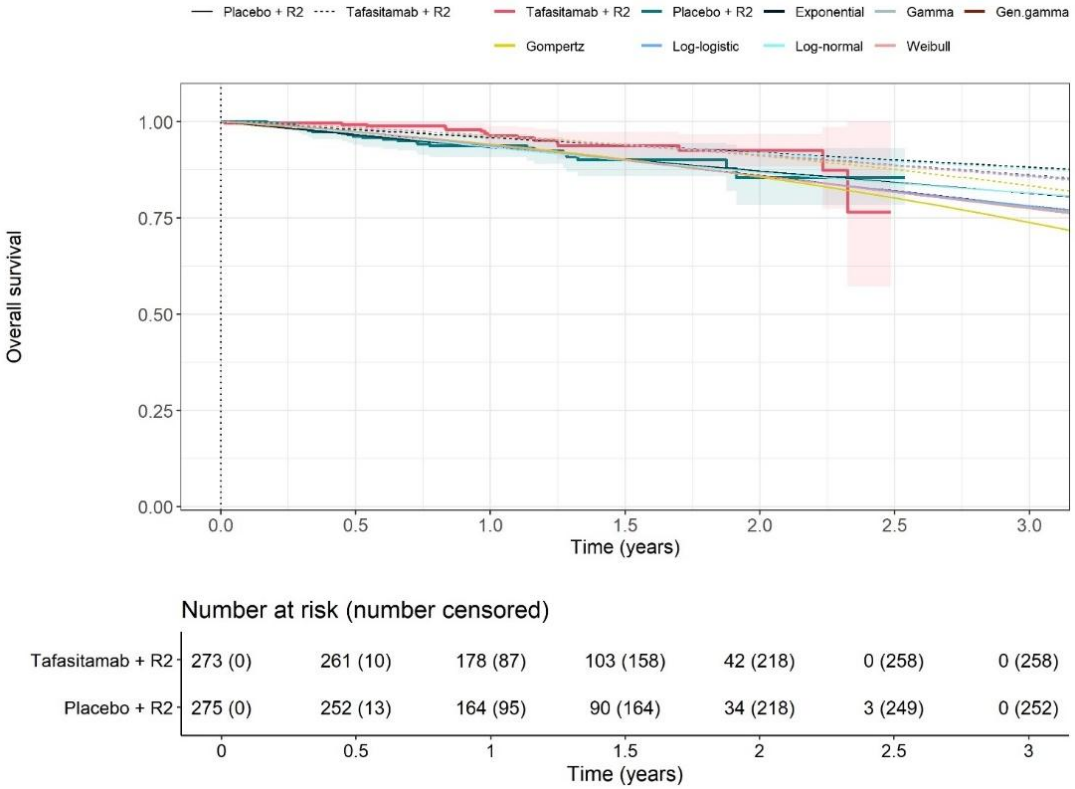
The AIC and BIC for each of the models fitted to inMIND KM curves for OS are presented in Table 14. A comparison of each model against the underlying KM curve can be seen in Figure 5 and Figure 6.

Table 14 Goodness of fit (AIC + BIC) of parametric distributions for OS

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	487.4	5	496.0	1
Gamma	486.7	2	499.6	3
Gen. Gamma	488.6	7	505.9	7
Gompertz	487.0	4	499.9	5
Log-Logistic	486.6	1	499.5	2
Log-Normal	488.5	6	501.4	6
Weibull	486.7	3	499.6	4

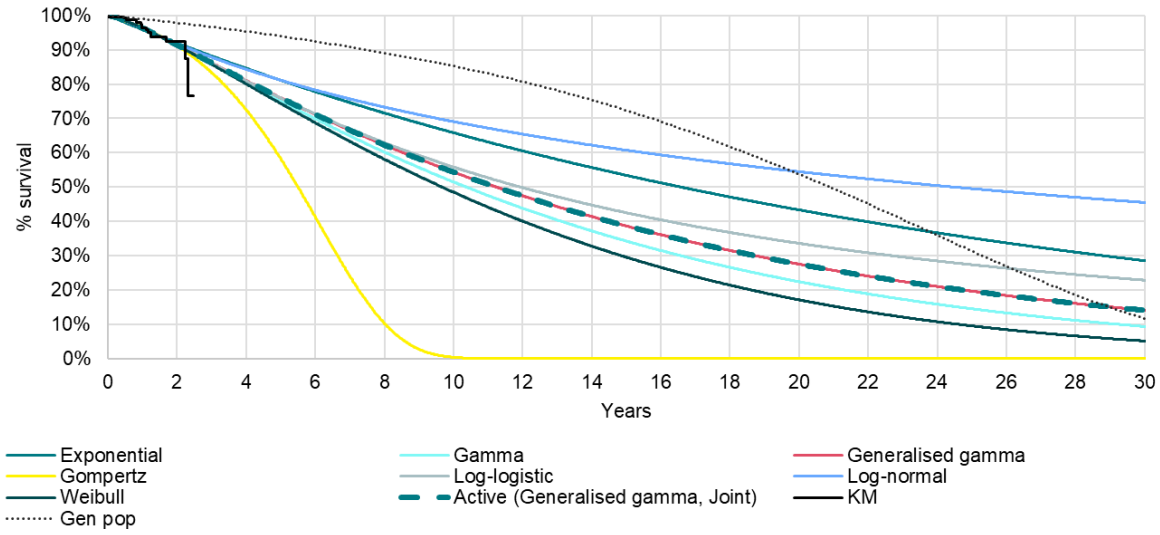
Source: CS Appendix L, Table 105
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; Gen. gamma; generalised gamma.
Notes: Green shade represents the models within 5 points of the model with the best fit.

Figure 5 OS parametric extrapolations short term



Source: CS Appendix L, Figure 39

Figure 6 OS parametric extrapolations long term



Source: CS Appendix L, Figure 40

The company selected the generalised gamma distribution for the base-case analysis. Scenario analysis was also presented using the log-logistic distribution (considered the 2nd choice curve by the company). Selection of the most appropriate OS extrapolation was conducted through structured

clinical expert elicitation, using the observed KM data alongside alternative parametric fits to assess the plausibility of long-term survival patterns given the immaturity of the OS data. Clinician feedback was used to judge whether modelled survival at key long-term time points (10, 20 and 30 years) was clinically credible and consistent with external evidence. This process informed the choice of a base-case extrapolation that balanced fit to the observed data with realistic long-term survival expectations, while alternative parametric forms were retained for sensitivity analyses. The selection of the generalised gamma was considered to be the most consistent with clinical expectations and was selected over the log-logistic as it predicted lower survival at 30 years, which was considered more consistent with clinical expectations.

In addition to clinical plausibility, the plausibility of long-term hazard trends was considered when selecting an appropriate parametric extrapolation. This included examination of smoothed hazard plots; however, these did not indicate a consistent pattern, with tafasitamab plus R^2 showing increasing hazards after approximately 2 years and R^2 showing decreasing hazards. The company attributed this apparent inconsistency to the small number of events and limited follow-up in the inMIND trial and therefore sought to inform expectations regarding long-term hazard behaviour using external HRMN data.

Smoothed hazard plots derived from HRMN suggested a complex pattern, with increasing hazards up to around 2 years, decreasing hazards between years 2 and 6, and increasing hazards thereafter. However, inspection of the hazards implied by the jointly fitted parametric models based on inMIND showed that none reproduced this pattern, which the company considered unsurprising given the limited trial follow-up. In the absence of a clear or stable hazard trend in the inMIND data, the company assumed that hazards would, on average, remain approximately constant over the long term. On this basis, the company considered the exponential and generalised gamma models to be appropriate, with the generalised gamma preferred as it was judged to be consistent with clinical expectations while allowing for broadly constant hazards over time.

Points for critique

Immaturity of OS data

As discussed in Section 4.2.2, and as acknowledged by the company, the OS data from the inMIND trial remain immature, with limited follow-up and a small number of observed events. These limitations are central to the interpretation of the model outputs, as the company's base-case analysis relies on extrapolating this limited OS evidence to estimate the survival benefit associated with tafasitamab plus R^2, which is the primary driver of incremental QALYs.

As noted briefly in Section 4.2.2, the EAG considers the current OS data too immature to support reliable inferences regarding the magnitude, or indeed the existence, of any OS benefit. This

uncertainty is evident in the company's parametric extrapolations. When separate parametric models are fitted to the observed OS data, several parametric extrapolations suggest superior survival for R^2 compared with tafasitamab plus R^2, a finding the company considers clinically implausible and which the EAG agrees is unlikely, given the observed PFS benefit and trend in OS. Although joint modelling resolves this internal inconsistency, it does not address the underlying immaturity of the OS data. As shown in Figure 5 and Figure 6, the resulting long-term survival projections vary substantially, with several predicting survival hazards below those of the general population within a relatively short time horizon.

The EAG therefore does not consider extrapolation of the currently available OS data to be a sufficiently robust basis for decision-making and instead proposes two alternative approaches. The first is to adopt a STM framework (primarily) informed by the more mature PFS data, using the magnitude of the PFS benefit to inform any subsequent OS benefit. As outlined in Section 4.2.2, this approach requires the assumption of a surrogate relationship between PFS and OS, which represents a strong assumption in FL, where the supporting evidence is mixed. The second approach is to retain the PSM structure used in the company's base case, but to make the potentially conservative assumption that tafasitamab plus R^2 confers no OS benefit relative to R^2.

The EAG considers these alternatives to provide a more structured and transparent basis for decision-making, as they better bound the uncertainty associated with OS outcomes, rather than relying on selection among OS extrapolations derived from very limited and immature evidence.

Extrapolation of OS

Notwithstanding the EAG's view that extrapolation of the current OS data is not an appropriate basis for decision-making, a brief assessment of the company's OS extrapolations is presented below to illustrate the extent of uncertainty associated with the available evidence.

In this context, the EAG notes that the company's rejection of joint modelling appears to be driven primarily by concerns regarding the clinical plausibility of the resulting OS extrapolations rather than statistical considerations. While the EAG acknowledges that some independently fitted parametric models generate clinically implausible predictions, with large OS benefits in favour of R^2, the EAG does not consider this, in itself, a sufficient reason to dismiss joint modelling. Among the independently fitted models, the Weibull and Gamma distributions generate more clinically reasonable OS projections, albeit with substantially more conservative estimates of survival benefit than the company's preferred extrapolation. However, comparison of the Weibull extrapolation with OS landmark estimates elicited by the company from its clinical advisory board suggests that this may be overly pessimistic, and the Gamma distribution therefore appears to represent the most reasonable separately fitted curve.

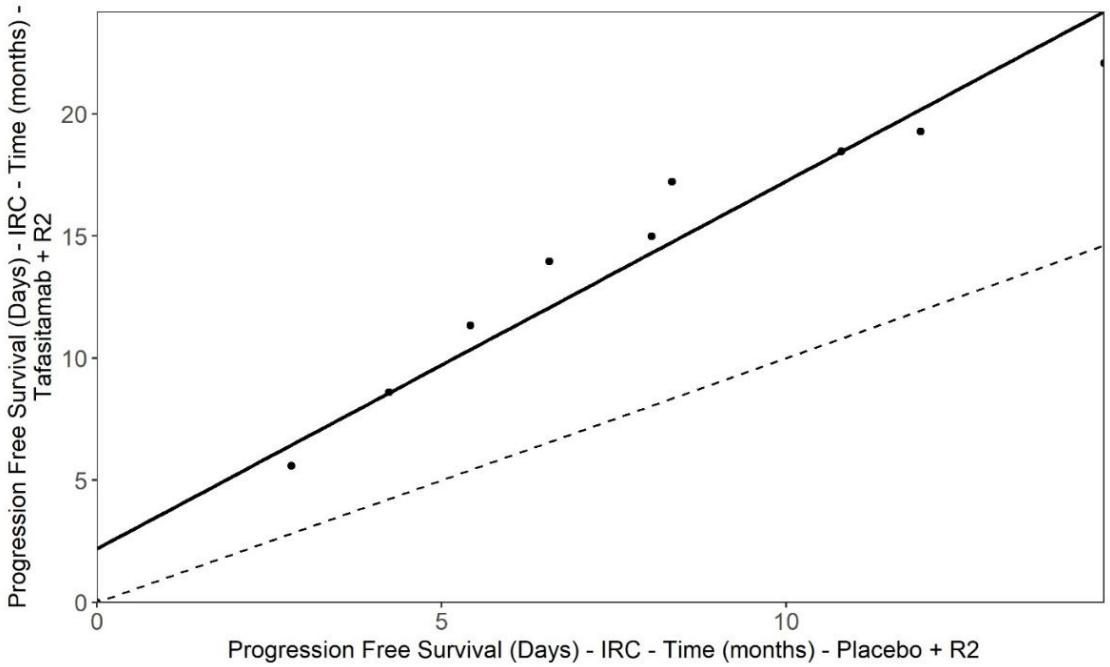
Among the jointly fitted models, the EAG considers the overall logic of the company's model selection process to be broadly reasonable and notes that several alternatives to the company's preferred generalised gamma model (including the Gamma, log-logistic and Weibull distributions) produce similar ICER estimates. Of the remaining candidate models (exponential, log-normal and Gompertz), none generate OS projections that are considered clinically plausible. Comparison of the company's preferred generalised gamma model with the independently fitted Gamma model shows very similar OS landmark estimates at 5, 10 and 20 years. On this basis, the EAG considers these two extrapolations to be broadly comparable in terms of clinical plausibility, should the committee prefer to engage with OS extrapolation within the PSM framework despite the immaturity of the underlying data.

4.2.5.3 Progression-free survival (PFS) extrapolation

In line with the PSM adopted in the company's base case, occupancy of the progression-free health state was determined by the PFS curve and was informed by extrapolating observed PFS data from the inMIND trial.

The company's process for fitting survival models was to test for proportional hazards using log-cumulative hazards plots and Grambsch-Therneau correlation tests between Schoenfield residuals, see Figures 21 and 22 of Appendix L of the CS. In their interpretation of this evaluation of the proportional hazards assumption, the company noted that the log-cumulative hazard plots were relatively parallel between arms across the entire follow-up period, suggesting that the assumption of proportional hazards might hold. However, they also noted that Schoenfeld residual test indicated that the proportional hazards assumption is violated. On this basis, the company considered that modelling approaches based on the assumption of proportional hazards are less suitable and alternatively considered joint modelling of PFS outcomes using accelerated failure time (AFT) models such as log-logistic, log-normal and generalised gamma. To evaluate the suitability of joint modelling using an AFT model, the company assessed quantile−quantile (Q−Q) plots, see Figure 7. Specifically, these plots compare the survival time quantiles between treatment arms to determine if the treatment effect acts as a constant time-scaling factor. A linear relationship between the quantiles indicates that the survival distributions are proportionally related, providing graphical evidence that the AFT assumption is appropriate. Based on quantile–quantile (Q–Q) plot assessment, the AFT assumption was considered plausible. Jointly fitted AFT models were therefore retained for further analysis. Separately fitted AFT and non-AFT models were not considered further because they produced OS predictions that the company considered implausible (see previous discussion). Therefore, only jointly fitted models were retained for the company's base-case PFS analysis.

Figure 7: Quantile-quantile plot (progression free survival)



Source: CS Appendix L, Figure 23
Key: IRC, independent review committee; R^2, lenalidomide with rituximab.

Notes: Dotted black line indicates reference line (acceleration factor of 1).

The statistical fit of the alternative jointly fitted model is reported in Table 15. Based on statistical fit, AFT models generally had lower AIC and BIC values than alternative specifications. The log-logistic model had the lowest AIC and BIC, with the gamma model within five points on both criteria, and the generalised gamma model within five points on AIC only. On this basis, the log-logistic, gamma and generalised gamma models were considered broadly comparable in terms of statistical fit and evaluated for clinical plausibility. Clinical plausibility was assessed through structured expert elicitation, using the KM data alongside the parametric fits. Clinicians were asked to judge the likelihood of patients remaining progression-free at key time points (3, 5 and 10 years). Both generalised gamma and log-logistic distributions were considered plausible; R^2 PFS was expected to be approximately 5–15% at 5 years and 1–10% at 10 years, while tafasitamab plus R^2 was expected to be 20–30% at 5 years and around 5% at 10 years.

Table 15: Fit statistics of progression-free survival extrapolation (jointly fitted PFS-IRC)

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	1529.2	7	1537.8	7
Gamma	1492.1	3	1505.0	2
Gen. Gamma	1491.6	2	1508.9	4
Gompertz	1511.7	6	1524.6	6
Log-Logistic	1488.5	1	1501.5	1
Log-Normal	1494.2	4	1507.2	3
Weibull	1496.3	5	1509.2	5

Source: CS Appendix L, Table 101
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; Gen. Gamma, generalised gamma; IRC, independent review committee.

Long-term hazard trends were examined using smoothed hazard plots, see Figure 27 of the CS Appendix L. Hazards observed in the inMIND trial were inconclusive beyond approximately two years due to the small number of patients at risk. External data from the HMRN dataset was therefore considered. This indicated an initial increase in hazards followed by a subsequent decline, a pattern consistent with the log-logistic and generalised gamma models. Based on these considerations, the generalised gamma distribution was used in the base case as it produced landmark survival estimates closest to clinician expectations, with the log-logistic included in scenario analyses.

Points for critique

Joint modelling of PFS

A key feature of the company's approach to extrapolating PFS is the use of a joint model across both treatment arms rather than fitting separate models to each arm. Joint modelling estimates a single set of parameters for the baseline survival distribution and incorporates the treatment arm through an explicit effect, whereas separate modelling estimates an independent set of parameters for each arm, such that the scale and shape of the time-to-event distribution are estimated separately. Joint modelling is often regarded as methodologically purer because it enforces a coherent comparison across arms, whereas separate models allow differences to arise through extrapolation rather than being directly informed by the observed treatment effect. In practice, however, independent arm-based modelling is commonly adopted in NICE appraisals, with greater emphasis placed on the clinical plausibility of extrapolations and visual and statistical goodness of fit than on the theoretical advantages of joint modelling.

In assessing the appropriateness of a joint modelling approach for PFS, the EAG agrees with the company that a proportional hazards assumption is unlikely to be reasonable and concurs with the interpretation of the Q–Q plots, which do not indicate clear violations that would preclude joint modelling. However, the EAG notes that the company's rationale for adopting a joint model for PFS

appears to be driven primarily by concerns regarding the plausibility of OS extrapolations and a rejection of independent OS models, rather than by statistical considerations arising from the observed PFS data. As discussed above, the EAG does not consider the company's OS extrapolation approach to be sufficiently supported by the available data, given that current OS follow-up is limited and does not reliably inform the magnitude of any treatment effect. The EAG therefore considers either a state-transition modelling framework, in which OS is primarily determined by PFS, or a partitioned survival approach assuming no OS benefit to be more appropriate. Under both approaches, joint modelling of OS is not relevant. Given the loss of this justification, the EAG considers that it is reasonable to also consider independent, separate modelling of PFS data, as well as joint models.

Preferred extrapolation of PFS

The EAG considers the company's overall approach to selecting an appropriate PFS extrapolation to be broadly appropriate and consistent with best practice. In relation to joint modelling, the EAG agrees with the company that the generalised gamma and log-logistic provide reasonable extrapolations of PFS. However, as noted above, the EAG considers it appropriate to also examine independently fitted alternatives. Among these, the EAG considers the independently fitted log-logistic to represent the most appropriate option once statistical fit, visual fit, and clinical plausibility are considered jointly.

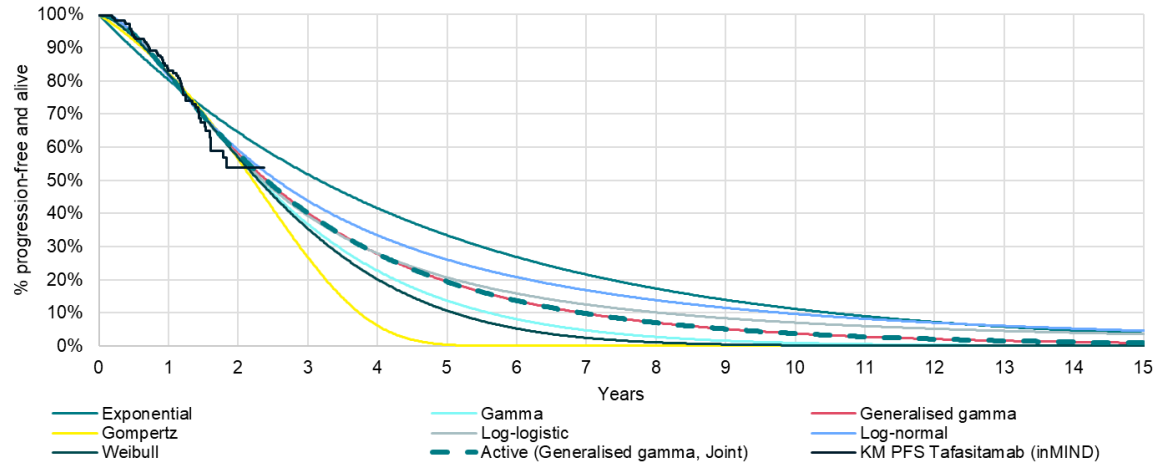
The separately fitted log-logistic demonstrates good statistical fit in both treatment arms, with no alternative providing a clearly superior fit (see Table 16). It also shows a modestly improved visual fit to the observed KM data; the jointly fitted models tend to overestimate PFS relative to the observed data, particularly in the tafasitamab plus R^2, resulting in more optimistic long-term survival than is supported by the available evidence. See Figures 8 to 11.

Table 16: Fit statistics of progression-free survival extrapolation (separately fitted PFS-IRC)

	Tafasitamab plus R²				R²			
Distribution	**AIC**	**AIC rank**	**BIC**	**BIC rank**	**AIC**	**AIC rank**	**BIC**	**BIC rank**
Exponential	592.210	7	595.820	7	936.944	7	940.561	6
Gamma	573.890	3	581.108	3	919.349	4	926.582	4
Gen. Gamma	575.095	4	585.923	5	914.483	2	925.333	3
Gompertz	576.486	5	583.705	4	933.536	6	940.769	7
Log-Logistic	573.405	2	580.624	2	916.374	3	923.608	2
Log-Normal	583.126	6	590.344	6	912.665	1	919.899	1
Weibull	573.111	1	580.330	1	922.661	5	929.895	5

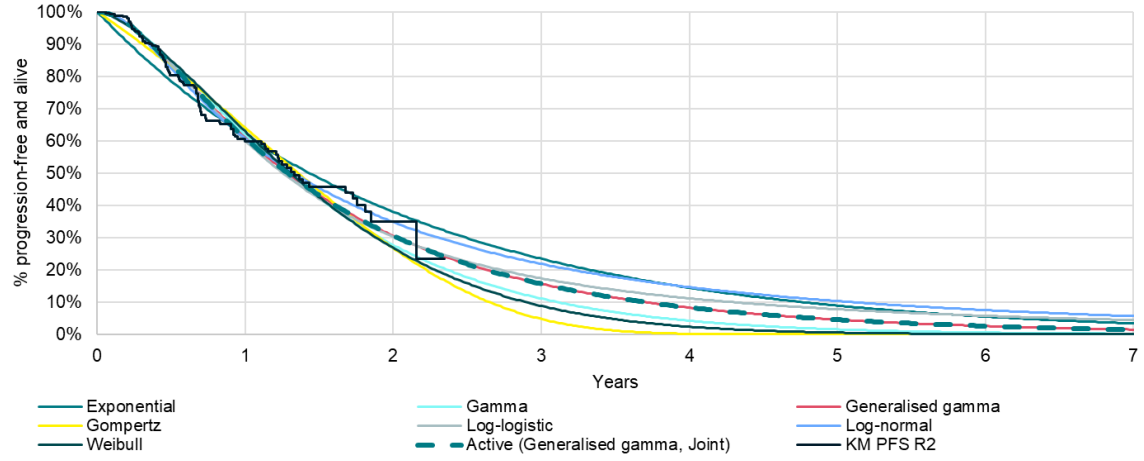
Source: Company model
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; Gen. Gamma, generalised gamma; IRC, independent review committee.

Figure 8 Jointly fitted PFS parametric extrapolations - tafasitamab plus R²



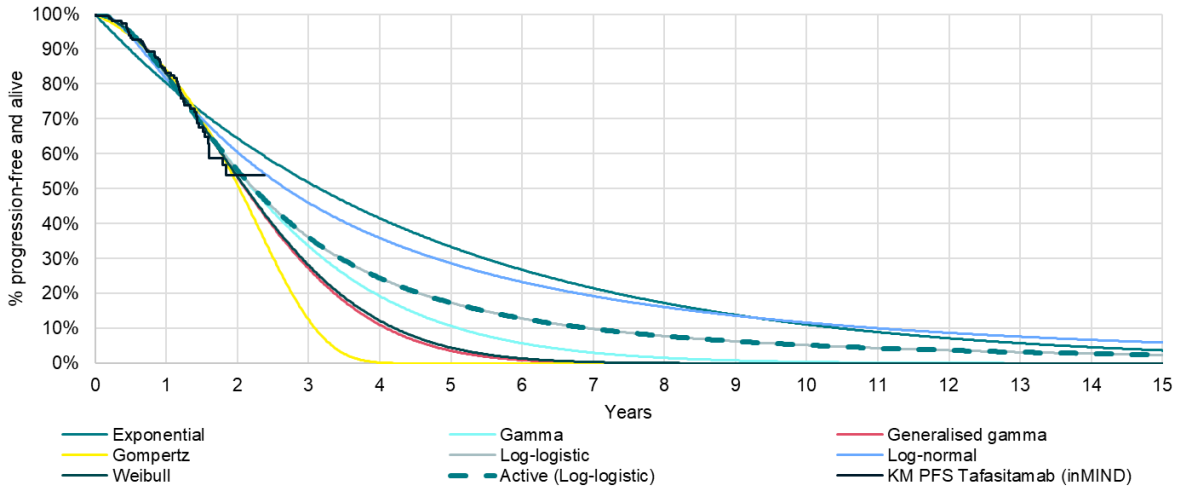
Source: CS Appendix L, Figure 25

Figure 9 Jointly fitted PFS parametric extrapolations - R²



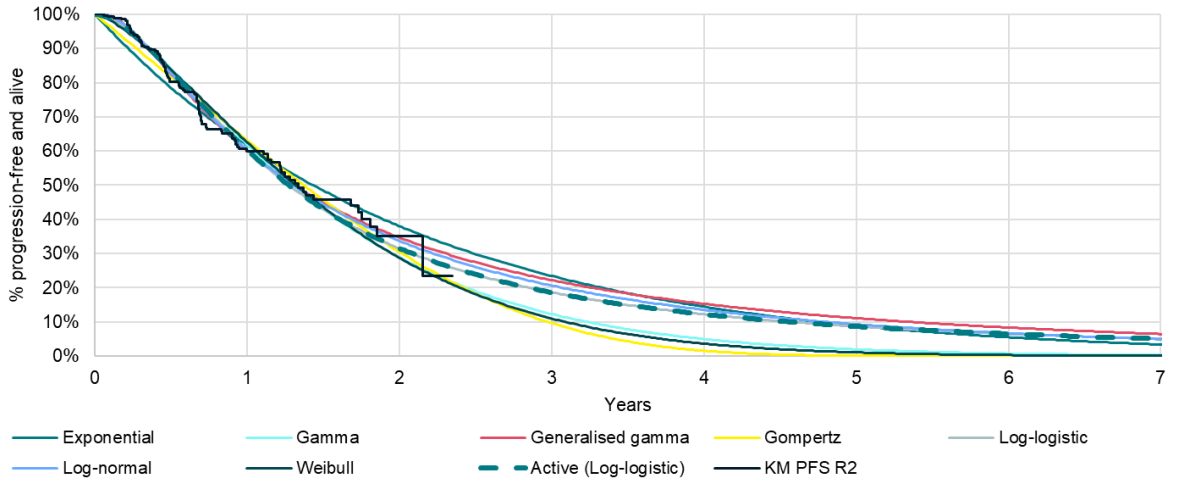
Source: CS Appendix L, Figure 26

Figure 10 Separately fitted PFS parametric extrapolations - tafasitamab plus R²



Source: Company model

Figure 11 Separately fitted PFS parametric extrapolations - R²



Source: Company model

The landmark survival estimates also more closely match the ranges reported in the company's clinical elicitation exercise, particularly in the R² arm. For tafasitamab plus R², clinicians anticipated 20–30% progression-free survival at 5 years and approximately 5% at 10 years. The independently fitted log-logistic predicts 17.5% at 5 years and 5.2% at 10 years, compared with 19.5% and 3.7%, respectively, under the jointly fitted generalised gamma. For R², clinical expectations ranged from 5 to 10% at 5 years and 1 to 4% at 10 years. The independently fitted log-logistic predicts 8.7% at 5 years and 2.8% at 10 years, whereas the jointly fitted generalised gamma predicts 4.6% and 0.3% at 5 and 10 years, respectively.

Overall, the EAG considers that the independently fitted log-logistic provides the more clinically plausible extrapolation when assessed across both treatment arms simultaneously, as it avoids

overestimation of survival in the tail of the observed KM data, and sits more comfortably within the clinically elicited ranges.

4.2.5.4 Duration of treatment effect

For both PFS and OS the company assumed a 5-year full treatment effect followed by a 5-year waning period over which hazards were assumed to converge. These assumptions were informed by clinical expert opinion, which agreed that the hazards could start to converge after and assumptions accepted in NICE TA627, [67] where a 5-year full treatment followed by instantaneous waning was accepted for decision-making.

Points for critique

The EAG notes that the company's extrapolation approach is based on the joint fitting of parametric models to PFS and OS, which implicitly imposes a permanent treatment effect through an acceleration factor. However, there is no clear biological rationale to support the assumption that tafasitamab plus R² would confer such a lasting effect. While tafasitamab plus R² improves disease control via ongoing biological and immune-mediated mechanisms and may result in deep and durable remissions in a subset of patients, residual disease is likely to remain. In the absence of a mechanism that fundamentally alters the underlying disease biology, it is therefore biologically likely that the relative treatment effect will attenuate over time, particularly given that treatment is time-limited. The EAG therefore agrees with the company that a permanent treatment effect is not justified and that treatment effect waning should be explored in the extrapolation.

Regarding the form of waning, the EAG agrees that a gradual attenuation of treatment effect is more clinically plausible than an abrupt loss of effect, as modelled in TA627.[67] In FL, relapse risk would typically be expected to increase progressively over time as residual disease re-emerges, rather than returning suddenly, which is more consistent with a gradual reduction in treatment effect. However, there is considerable uncertainty around both the duration over which a full treatment effect should be assumed and the period over which any subsequent attenuation should occur. The EAG notes that the assumptions previously accepted in TA627 [67] appear largely arbitrary and are not clearly linked to either the mechanism of action of R² or the underlying disease biology.

Exploratory analyses of the trial data, including log–cumulative hazard plots and Schoenfeld residuals, also raise questions about the appropriateness of assuming a prolonged period of full treatment effect. These analyses suggest convergence of treatment effects for PFS between 6 months and one year. After one year, the PFS hazards start to diverge between treatment arms. Similarly for OS convergence of treatment effects for is observed between one year and 2 years, after which hazards diverge. s. As such, the assumption of a full treatment effect persisting for five years, as applied in the company's base case, is difficult to reconcile with the observed data. While these

analyses cannot determine the long-term pattern of waning, they do provide limited empirical support for exploring earlier and potentially less gradual attenuation than assumed by the company. The EAG therefore explores a range of alternative waning scenarios in Section 5.2.

4.2.5.5 Post progression survival and STM

In the company's base-case model, state occupancy is derived directly from the extrapolated PFS and OS survival curves, consistent with a PSM structure. In addition to the base case, the company presents a scenario analysis using a STM structure, in which transitions between health states are modelled explicitly. Within this three-state model, individuals in the progression-free state may remain progression-free, transition to progressed disease, or transition to death; individuals in the progressed-disease state may remain in that state or transition to death; and the death state is absorbing.

Transitions from the PF state to progressed disease or death are informed by extrapolated PFS data from the inMIND trial, with a fixed proportion of PFS events assumed to represent death. Consequently, occupancy of the progression-free state and transitions to progressed disease are handled analogously to the PSM approach. The company assumes that the proportion of death events is the same for patients receiving tafasitamab plus R^2 and those receiving R^2 alone. Although the inMIND trial observed a higher proportion of PFS events resulting in death for tafasitamab plus R^2 ([redacted]) than for R^2 ([redacted]), the company applies a common fixed rate of [redacted], estimated by pooling data across both trial arms. to explore this uncertainty, the company presented a scenario during clarification that showed the treatment-specific proportion of PFS events. However, this scenario excluded COVID-related and other unexpected deaths, which the company noted resulted in a more comparable proportion of deaths between groups, at [redacted] for tafasitamab plus R^2 and [redacted] for R^2.

Transitions from progressed disease to death are informed by extrapolated post-progression survival (PPS) data, which were not derived from the inMIND trial but estimated using external sources, namely the HMRN database and the GADOLIN trial. These sources allowed the company to explore different assumptions regarding any PPS benefit associated with tafasitamab plus R^2, resulting in three distinct STM scenarios.

Across all STM analyses, PFS by IRC was extrapolated using parametric curves consistent with the base-case PSM, while PPS rates were derived from external data. In line with the STM structure, OS was calculated as the sum of PFS and PPS. Aside from these differences in PPS and OS modelling, the STM used the same inputs and assumptions as the base-case model.

In **STM 1**, it was assumed that any treatment effect on OS is achieved solely through a benefit in PFS, with no additional PPS benefit. In this scenario, PPS was assumed to be treatment independent and

was estimated using HMRN data for non-rituximab-refractory patients. Median PPS was 64.7 months and was applied to both the tafasitamab plus R^2 and R^2 arms.

In **STM 2**, it was assumed that a treatment effect on OS is achieved through benefits in both PFS and PPS. PPS was estimated separately for each treatment arm using data from the GADOLIN trial, which was conducted in rituximab-refractory patients. Median PPS was estimated as 67.9 months for the tafasitamab plus R^2 arm and 46.6 months for the R^2 arm, calculated as the difference between median OS and PFS. As median OS was not reached in the O-B arm, it was assumed to be 90 months, corresponding to the point at which the OS curve approached 50%.

In **STM 3**, the approaches used in STM 1 and STM 2 were combined to reflect the anticipated licensed population in the inMIND trial. In inMIND, 41% of patients were rituximab-refractory, and 59% were non-refractory. For the refractory subgroup, treatment-specific PPS was estimated by applying the PPS:PFS ratio observed in the GADOLIN trial to the median PFS observed with tafasitamab plus R^2 and R^2 in inMIND. As median PFS by IRC had not been reached in the tafasitamab plus R^2 arm, median PFS by investigator assessment was used. For the non-refractory subgroup, PPS was assumed to be treatment independent and based on the HMRN estimate of 64.7 months for both arms. Applying a weighted average based on the proportion of refractory and non-refractory patients resulted in median PPS estimates of 66.7 months for the tafasitamab plus R^2 arm and 55.9 months for the R^2 arm.

Points for critique

Proportion of death events

The EAG has concerns regarding the company's approach of pooling the proportion of death events across both arms. While the EAG recognises that there may be limited clinical rationale for a difference between arms, this approach diverges from the observed data and therefore misrepresents the inMIND trial results. Moreover, the addition of tafasitamab and the increased toxicity of the triplet regimen could plausibly increase the proportion of PFS events that are deaths; thus, a difference in the proportion of death events before progression cannot be ruled out. The EAG therefore prefers to use arm-specific rates based on the observed data, which more accurately reflect the trial outcomes and associated mortality risks.

PPS benefit

The EAG considers there to be substantial uncertainty regarding PPS and any assumption that tafasitamab plus R^2 continues to prolong survival after progression.

First, the primary rationale for adopting a STM is that the observed OS benefit does not strongly indicate an OS advantage for tafasitamab plus R^2. As outlined in Section 4.2.2, the STM leverages

observed PFS to estimate the potential magnitude of a PPS benefit. Any assumed PPS effect, therefore, dilutes the main strength of this approach and introduces unsupported assumptions about additional OS benefits beyond those related to delayed progression.

Second, the company's preferred extrapolation of PFS and OS data from inMIND, as used in the PSM, implies minimal PPS benefit. This contrasts with the company's preferred assumptions and highlights the lack of direct evidence from inMIND supporting a PPS effect. During the clarification step, the EAG requested supporting evidence from inMIND, including KM survival curves and appropriate statistical analyses, to substantiate the PPS assumption. The company's response was partial, providing only landmark PPS estimates. These suggest a numerical advantage for tafasitamab plus R², but without appropriate statistical analyses, full interpretation is difficult. Provision of the requested KM curves would have enabled a more nuanced comparison and potentially allowed further validation of assumptions adopted in the alternative STM analyses.

Third, the biological rationale for a PPS benefit is unclear. Unlike solid tumours, there is no primary tumour shrinkage that might suggest such an effect. Moreover, the assumed benefits based on GADOLIN lack clear clinical justification. PPS benefits observed in GADOLIN (which evaluated O-B in rituximab-refractory patients) do not imply that rituximab-refractory patients would respond similarly to tafasitamab plus R². Notably, tafasitamab plus R² includes rituximab, whereas O-B does not, highlighting differences in regimen and mechanism. The EAG notes that a reduced rate of histological transformation was observed for tafasitamab plus R² compared with R² alone (0% versus 3.3%), which may indicator a possible mechanism for a PPS benefit. However, as discussed in Section 3.3.2.9, this analysis was exploratory and based on immature data. Consequently, the true magnitude of any effect of tafasitamab on post-progression histological transformation remains uncertain.

Given this uncertainty and lack of clear biological rationale, the EAG prefers to adopt a more conservative assumption of no PPS benefit.

Estimation approach

While the EAG acknowledges that the available data to support PPS extrapolations is limited and the company are reliant on the outcomes data reported in the respective publications, the EAG is concerned that company's approach to estimating PPS relies on several strong assumptions.

Firstly, using median survival times to estimate post-progression survival by simple subtraction has important mathematical limitations. Subtracting median survival times to estimate post-progression survival is limited because medians do not capture the shape of the survival curve, censoring, or variability in patient outcomes. This approach can misrepresent mean survival and time-dependent

risks, making it an imprecise method for modelling transitions. A more mathematically consistent approach would be to use restricted mean survival time (RMST) because it uses the full survival curve up to a specified time horizon, rather than focusing on a single point like the median. This allows it to account for the timing and distribution of all events, as well as censoring, providing a more accurate estimate of the average survival experience.

At the clarification stage, the EAG asked the company to justify its use of median-based estimates to derive post-progression survival in the STM, rather than using RMST. In response, the company argued that RMST is less appropriate in this context due to its sensitivity to late follow-up and censoring, truncation time, confounding from subsequent therapies, and asymmetry in cross-trial comparisons. The company noted that median overall survival is event-driven and locally defined, making it structurally more stable and interpretable when OS data are immature or follow-up is heterogeneous.

The EAG acknowledges the company's rationale and agrees that median-based estimates may be more robust in the presence of immature OS data and censoring. However, the EAG also notes that median subtraction does not capture the full survival distribution and may overlook variability in post-progression outcomes. Given the limitations of both approaches, the EAG considers it prudent to explore both median- and RMST-based methods in sensitivity analyses to assess the robustness of post-progression survival estimates and their impact on cost-effectiveness results. Results presented as part of the clarification response, however, demonstrate that this has only a limited impact on the ICER (increase of <£2000 per QALY).

Secondly, STM 3 relies on the assumption that the ratio of PFS to PPS observed in one trial can be used to estimate PPS benefits in a completely different setting. This is a particularly strong assumption because it implicitly assumes that the relationship between PFS and PPS is treatment-independent and population-independent. In reality, PPS is influenced by the mechanism of action of the therapy, prior treatment history, and patient characteristics, none of which are necessarily consistent across trials. The source trial used to derive the PFS:PPS ratio compared O-B with bendamustine monotherapy in a rituximab-refractory population. Extrapolating this ratio to estimate PPS for tafasitamab plus R^2 versus R^2 alone assumes that rituximab-refractory patients would respond in the same way to a fundamentally different regimen that contains rituximab, a major mechanistic difference. Therefore, this approach is highly speculative, and there is no compelling evidence that it provides a valid estimate of PPS in the target comparison. The EAG consequently does not consider STM3 valid for decision-making.

4.2.5.6 Time to treatment discontinuation

Time to discontinuation for tafasitamab plus R² and R² was informed by KM data from the inMIND trial. As this data was available up to and beyond the end of the treatment period, it was not necessary to extrapolate this data, and it was therefore incorporated into the model directly. To reflect the posology of both regimens, it was assumed that rituximab treatment ended in cycle 5. For the R-chemotherapy regimens, it was assumed that the PFS survival curve represented time to discontinuation. The company justified this approach, stating that R-chemotherapy is a less intense regimen than R² and, as such, would have lower discontinuation.

Points for critique

The EAG considers the company's approach to modelling time on treatment appropriate for tafasitamab plus R² and for R² alone. The EAG, however, does not agree with the company's approach to modelling time on treatment for the R-chemotherapy regimens. The company's suggestion that R-chemotherapy is less intensive than R² does not align with conventional clinical consensus or the published evidence. R-chemotherapy regimens such as R-CHOP and R-CVP are multi-agent immunochemotherapy approaches and are generally associated with higher acute toxicity than R², which is a chemotherapy-free regimen that is typically considered less intensive, albeit with a distinct toxicity profile. Although direct head-to-head comparisons of toxicity across all R-chemotherapy regimens and R² are limited, evidence from the RELEVANCE trial and other analyses suggests that chemotherapy-containing regimens have different, but not clearly more favourable, safety profiles, with higher rates of grade 3/4 neutropenia and related complications reported in patients treated with R-chemotherapy compared with R². In the absence of robust evidence to inform the duration of R-chemotherapy treatment, the EAG therefore prefers an approach in which time on treatment for R-chemotherapy is assumed to be equivalent to that for R², aligning with the company's base assumptions regarding efficacy.

4.2.6 Health related quality of life

The CS considers HRQL associated with (i) the PF and PD health states and (ii) disutilities related to AEs. A description of the systematic searches for HRQL evidence (referred to as *humanistic evidence reviews*) is provided in Appendix F. This appendix primarily links to a company-sponsored report [81] based on a SLR with searches conducted on the 9th of February 2024 and updated on the 22nd of April 2025. The CS reports that nine publications met the inclusion criteria. As discussed in Section 4.1, the SLR didn't identify any studies that were exclusively conducted in the UK. However, the EAG identified a paper based on HMRN data,[23] that may be of relevance. Utility values explored in scenario analyses were identified from previous TAs in FL.

Health-state utility values for PF and PD in the company's base case are derived from EQ-5D-5L data collected in the inMIND trial and mapped to EQ-5D-3L using the Hernández-Alava algorithm.[73]) The data were analysed using a mixed-effects regression model to estimate health-state-based utility values. The final model, selected using stepwise covariate selection, included progression status, baseline utility, number of prior lines of therapy, and time since prior cancer therapy. Treatment assignment was not included as a covariate as it was not a statistically significant predictor in the best-fitting model. Predicted health-state utilities from this analysis are reported in Table 17.

Table 17 Health state based utility values based on mapped observed EQ5D inMIND data and applied decrements to form the base case values

Health State	inMIND (95% CI)	Base case
Progression -free	0.842 (0.794, 0.890)	0.824
Post-progression	0.805 (0.752, 0.858)	0.788
Source: CS, Table 33 and 36		

Utility values for the PF health state estimated from the inMIND trial exceeded general population norms, which the company considered clinically implausible. PF utilities were therefore modelled using age- and sex-matched general population values reported in Hernández Alava et al.[73] To estimate the impact of disease progression, the company applied a proportional decrement of 4.4%, derived from the proportional difference between the PF and PD utility values estimated in the mixed-effects regression analysis of the inMIND trial data. This approach is similar to that adopted in TA627. [67] An absolute (rather than proportional) progression-related decrement was explored in a scenario analysis but was found to have minimal impact on the ICER.

Alternative health state utility values from Wild et al.[69], TA892[68]/GO29751[82], TA629[35]/GADOLIN[56] and TA627[67]/ AUGMENT[59] were tested in scenario analyses (Table 18) with a maximum ICER difference of <£1,000 per QALY gained relative to the company base-case.

Table 18 Summary of utility values for cost-effectiveness analysis

Health state	InMIND	TA892[68] - GO29781	Wild 2006[69]	TA627[67] - AUGMENT	TA627[67]- GADOLIN
Progression-free (on treatment)	0.842	0.804	0.805	0.867	0.822
Progression-free (off treatment)					0.807
Progressed (on treatment) (decrement compared to PF)	0.805 (-0.037)	0.750 (-0.054)	0.736 (-0.069)	0.841 (-0.026)	0.758 (-0.064)
Progressed (off treatment) (decrement compared to PF)			0.618 (-0.187)	0.806 (-0.061)	0.758 (-0.049)
Source: Adapted from Figure 14[34] **Key:** PF; Progression free					

4.2.6.1 Adverse effects utility decrements

Utility decrements and durations of 19 AEs are presented in the CS, based on grade 3/4 events occurring in ≥2% of patients by line of therapy (LoT) for the intervention and comparators considered. The loss of QALYs per AE was calculated by multiplying the incidence rate, disutility, and duration. Within the model, the company applied a one-off AE disutility in the first cycle. The company's base case assumes that the utility regression analysis does not account for AE disutilities. A scenario analysis tested the assumption that AE disutilities are reflected in the utility analysis and found very little impact on the ICER (-£2).

Points for critique

Appropriateness of PF health state values

The EAG agrees that health state utility values should not exceed those of the general population. However, the burden of disease described in the CS (pp. 24–25) and the Patient Organisation Submission from Lymphoma Action suggests that HRQL in patients with FL may be below that of healthy individuals and therefore below the values used in the model. The company also noted in its clarification response (B11) that aspects of fear and uncertainty may not be fully captured by the EQ-5D. The model is, however, relatively insensitive to the specific PF values selected assumption, and the EAG acknowledges that similar approaches have been accepted in TA627.[67] On this basis, the EAG considers the company's approach of capping PF utility values at general population levels to be reasonable in the absence of a superior alternative.

Appropriateness of PD health state values

The company states that a proportional decrement approach was used in TA627. However, the EAG was unable to access the relevant information in TA627, as the methodology was provided in an appendix not available to the EAG. Nonetheless, TA627 committee papers suggest that these values are based on the AUGMENT trial. In the CEM for this appraisal, the proportionate decrement is 4.4% [(0.805/0.842)-1], and the absolute decrement is 0.037 (0.842-0.805), which was derived from the mixed-effects regression model [81]. These decrements were then subtracted from the general population utility of 0.824 for a population aged 64 years. The EAG accepts the rationale and methodological validity behind the decrement calculation.

The EAG considers the collection and mapping of EQ-5D data for the PF health state in the inMIND study to be appropriate. However, there are concerns regarding the suitability of the trial data used to inform the PD health state utility values. The number of observations in the PD health state is small, raising questions about whether the resulting estimates are sufficiently robust for decision-making. In the tafasitamab plus R^2 arm, the PD utility value is based on 33 observations from 28 patients (Table 7, [81]), compared with 4,307 post-baseline complete observations from 467 patients overall. In its PfC

response (B12), the company explained that only 191 patients in the FL FAS population progressed during the study, and not all of these patients completed an EQ-5D-5L questionnaire at the end of treatment or at final follow-up, resulting in the limited number of post-progression utility observations. The company also noted that post-progression EQ-5D-5L data were generally collected soon after progression, which may not fully capture the more gradual decline in HRQL typically observed following disease progression.

The regression model does, however, include prior LoTs, which provides limited support for a decrease in utility values with increasing LoT, reflected by negative coefficient estimates, albeit not statistically significant. The direction of effect is consistent with external evidence; for example, Johnson et al. (2024)[21] reported that patients with FL in later LoTs experienced significantly worse quality-of-life outcomes across most domains compared with those at earlier LoTs.

However, as the PD utility value is not a key driver of the model results, the EAG does not explore this issue further.

4.2.6.2 Effect of adverse effects on HRQL

The model included grade 3/4 AEs occurring in ≥2% of patients for each treatment, by LoT, using data from a range of trial sources. For the 19 AEs listed in the CS, the EAG noted a few minor points regarding the sourcing of values; these are summarised in Appendix 3Appendix Table 3 for completeness.

Using a one-off disutility is a conventional method to capture the impact of AEs on HRQL in the model. While this approach may not capture all aspects of patient experience, it is considered reasonable in the absence of a more detailed alternative.

4.2.6.3 EAG preferred utility values

Notwithstanding the issues outlined above the, the EAG considers EQ-5D data from the inMIND trial to be the most appropriate available source for health state utility values. The EAG accepts the company's values in the 2L+ population and has used these values for each subgroup (2L-only and 3L+). Table 19 is the EAG preferred utility values per patient population, noting that the model is not substantively sensitive to alternative utility values.

Table 19 EAG preferred utility values related to patient population

Health state	2L+	2L-only Subgroup	3L+ Subgroup
Progression-free	0.824	0.824	0.824
Progressed	0.788	0.788	0.788
Key: 2L; Second line; 3L: Third line			

4.2.7 Resources and costs

The company's model includes costs relating to drug acquisition and administration, healthcare resource use by health states, end of life costs and management of adverse events.

The company conducted an SLR to identify relevant cost and HCRU evidence for patients with R/R FL. Full details of the search strategy, study selection and results are provided in an SLR report of HRQL and economic evidence.[66] None of the studies reported costs or healthcare use in the UK setting and were therefore considered of limited relevance to the decision problem. The company based HCRU used in their *de novo* analysis on inputs from previous NICE appraisals for FL. A summary of these appraisals is presented in Appendix E of CS, Table 66.

4.2.7.1 Drug acquisition and administration costs

Table 20 summarises the drug acquisition costs applied in the model. Drug costs were calculated at the component level, with treatment duration informed by time-to-discontinuation data from inMIND, planned dosing according to the dosing schedule and administration regimen (see Section 4.2.4), and drug acquisition costs. Unit costs were sourced from the Monthly Index of Medical Specialties (MIMS) or the electronic Market Information Tool (eMIT).[74, 83]

Average RDI for R-chemotherapy regimens was derived from the tafasitamab plus R^2 arm of inMIND. For rituximab, the mean RDI across cycles 2–5 was applied to the rituximab component, while the average RDI from the tafasitamab plus R^2 arm was applied to the remaining components of R-chemotherapy. Per-cycle RDIs were applied uniformly to all patients to capture dose reductions and missed doses.

All patients were assumed to receive allopurinol once daily during the first week of each cycle as concomitant therapy.

Table 20 Drug acquisition costs with tafasitamab PAS

Regimen	Component	Period	Dose	Drug acquisition cost per treatment cycle	Average acquisition cost per model cycle	RDI	Average acquisition cost per model cycle after applying RDI
Tafasitamab + R^2	Tafasitamab	Cycles 1–3 (28 days)	12 mg/kg on Days 1, 8, 15, 22	[redacted]	[redacted]	[redacted]	[redacted]
		Cycles 4–12 (28 days)	12 mg/kg on Days 1, 15	[redacted]	[redacted]	[redacted]	[redacted]
	Lenalidomide	Cycles 1–12 (28 days)	20 mg QD on Days 1–21	£43.27	£10.82	[redacted]	[redacted]

Regimen	Component	Period	Dose	Drug acquisition cost per treatment cycle	Average acquisition cost per model cycle	RDI	Average acquisition cost per model cycle after applying RDI
	Rituximab	Cycle 1 (28 days)	375 mg/m^2 on Days 1, 8, 15, 22	£4,500.43	£1,125.11	[redacted]	[redacted]
		Cycles 2–5 (28 days)	375 mg/m^2 on Day 1	£1,125.11	£281.28	[redacted]	[redacted]
R^2	Lenalidomide	Cycles 1–12 (28 days)	20 mg QD on Days 1–21	£43.27	£10.82	[redacted]	[redacted]
	Rituximab	Cycle 1 (28 days)	375 mg/m^2 on Days 1, 8, 15, 22	£4,500.43	£1,125.11	[redacted]	[redacted]
		Cycles 2–5 (28 days)	375 mg/m^2 on Day 1	£1,125.11	£281.28	[redacted]	[redacted]
R-B	Rituximab (induction)	Cycles 1–6 (28 days)	375 mg/m^2 QD on Day 1	£1,125.11	£281.28	[redacted]	[redacted]
	Bendamustine (induction)	Cycles 1–6 (28 days)	90 mg/m^2 QD on Days 1 and 2	£108.39	£31.13	[redacted]	[redacted]
	Rituximab (maintenance)	2 years after six induction cycles (90 days)	1,400 mg QD on Day 1	£1,344.63	£103.08	[redacted]	[redacted]
R-CHOP	Rituximab (induction)	Cycles 1–6 (21 days)	375 mg/m^2 QD on Day 1	£1,125.11	£375.04	[redacted]	[redacted]
	Doxorubicin (induction)	Cycles 1–6 (21 days)	50 mg/m^2 QD on Day 1	£8.23	£5.89	[redacted]	[redacted]
	Vincristine (induction)	Cycles 1–6 (21 days)	1 mg/m^2 QD on Day 1, max dose of 2 mg	£10.02	£5.02	[redacted]	[redacted]
	Cyclophosphamide (induction)	Cycles 1–6 (21 days)	750 mg/m^2 QD on Day 1	£24.64	£8.21	[redacted]	[redacted]
	Prednisolone (induction)	Cycles 1–6 (21 days)	40 mg/m^2 QD on Day 1 to 5	£2.42	£0.81	[redacted]	[redacted]
	Rituximab (maintenance)	2 years after six induction cycles (90 days)	1,400 mg QD on Day 1	£1,344.63	£103.08	[redacted]	[redacted]
R-CVP	Rituximab (induction)	Cycles 1–8 (21 days)	375 mg/m^2 QD on Day 1	£1,125.11	£375.04	[redacted]	[redacted]
	Cyclophosphamide (induction)	Cycles 1–8 (21 days)	750 mg/m^2 QD on Day 1	£23.30	£8.21	[redacted]	[redacted]
	Vincristine (induction)	Cycles 1–8 (21 days)	1 mg/m^2 QD on Day 1	£10.02	£5.02	[redacted]	[redacted]
	Prednisolone (induction)	Cycles 1–8 (21 days)	40 mg/m^2 QD on Days 1–5	£2.42	£0.81	[redacted]	[redacted]

Regimen	Component	Period	Dose	Drug acquisition cost per treatment cycle	Average acquisition cost per model cycle	RDI	Average acquisition cost per model cycle after applying RDI
	Rituximab (maintenance)	2 years after eight induction cycles (90 days)	1,400 mg QD on Day 1	£1,344.63	£103.08	[redacted]	[redacted]

Source: CS Table 38
Key: QD, once per day; R-B, rituximab with bendamustine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; R-CVP, rituximab with cyclophosphamide, vincristine and prednisolone; RDI, relative dose intensity.

Drug wastage was assumed for drugs administered IV. The methods of moments technique was used to estimate the average number of vials per dose for BSA or weight-based dosing.

Administration costs were dependent on whether the mode of administration was IV (simple or complex regimen), SC, or oral. IV administration was assumed to be administered in an outpatient setting. No administration cost was assumed for SC administration in the original company base case. The model incorporates co-administration by adjusting administration costs where multiple drugs are administered on the same day.

All unit costs were sourced from NHS reference costs[75] and updated to the latest values following PfCs. As the CS states that costs for subsequent administrations were in accordance with TA627, the company also updated its base case in response to PfCs, to include a cost for rituximab maintenance at first SC administration to align with TA627. These costs are detailed in Table 21 below.

Table 21. Updated administration costs

Administration type	Cost per administration (NHS 2023/24)	Cost per administration (NHS 2024/25)	Source	Cost per administration (NHS 2024/25) + preparation time

IV Complex/Simple (Subsequent)	£426.15	£438.41	Daycase. SB15Z	£452.66
IV Complex (First)	£570.43	£571.26	Daycase. SB14Z	£585.51
IV Simple (First)	£528.11	£553.43	Daycase. SB13Z	£567.68
Subcutaneous	Assumed £0	£435.51	Daycase. SB12Z	£449.76
Infusion preparation time	Not used	£14.25	Per hour cost for hospital-based scientific and professional staff (Band 6) from Personal Social Services Research Unit (PSSRU)	NA
Source: PfC response Table 39				

Points for critique

Hospital chair time and RDI costs adjustments

Delivery of tafasitamab plus R² raises important NHS capacity concerns. Compared with R², the regimen requires seven additional cycles of IV infusion, longer infusion times, and greater use of transfusions, placing additional pressure on day-unit services. The company's clinical advisory board highlighted the additional resource use and cost pressures associated with delivering tafasitamab plus R², noting that IV infusion times vary across centres but typically exceed 90 minutes. By contrast, rituximab can be administered SC, including at home, from cycle 2 onwards. Both the company's clinical advisory board and the EAG's clinical adviser expressed concern that these factors may adversely affect the uptake of tafasitamab plus R² within existing NHS capacity constraints.

The EAG also notes that the observed RDI for tafasitamab in the inMIND trial declines in later treatment cycles, indicating that an increasing proportion of patients do not receive all scheduled infusions as treatment progresses. Consistent with this pattern, Table 15 of the CS reports a higher incidence of TEAEs with tafasitamab plus R² than with R² alone, both overall (36% vs 32%) and for events leading to treatment discontinuation (11% vs 7%) or dose interruption (74% vs 70%). Taken together, these data may suggest that declining RDI over time is driven by cumulative toxicity and an increasing burden of adverse events.

The EAG's primary modelling concern is that the application of a single, constant average RDI to adjust costs does not reflect the observed time-dependent decline in drug administration. Evidence from inMIND suggests that early cycles are delivered at close to full dose intensity, while later cycles involve materially fewer administered doses. See clarification response Table 32. Applying a constant average RDI across all cycles may therefore misrepresent drug acquisition and administration costs.

A secondary implication relates to NHS capacity and resource use. While reduced dosing in later cycles may decrease chair time and nursing requirements during those periods, the model does not explicitly capture this effect. In particular, the analysis does not distinguish between planned and actual administrations, nor does it account for additional or unscheduled visits associated with dose interruptions or adverse event management. The EAG considers that a more appropriate approach would be to model RDI at the cycle level and apply it directly to the number of administrations, rather than adjusting administration costs using a single average RDI. This is explored in EAG additional analyses presented in Section 5.2.

4.2.7.2 Health-state unit costs and resource use (HCRU)

HCRU was defined based on PFS and PD states to capture differences in resource utilisation upon disease progression, as presented in Table 41 of CS. This included haematology visits, diagnostic tests and a CT scan, and was based on resource use reported in NICE TA627.[67] Resource use in the PFS state also differs by treatment phase (induction, maintenance, and follow-up). Unit costs are either based on NHS reference costs[75] or those reported in TA627[67], as detailed in Table 42 of CS.

The EAG is satisfied with this application.

4.2.7.3 Adverse events (AEs)

AEs are modelled for grade 3+ drug-related AEs that occurred in at least 2% of patients in inMIND (Table 31 of CS, with unit costs presented in Table 43 of CS). AE costs are applied in the first cycle of the model as one-off costs. Costs are sourced from NHS reference costs.[75]

The EAG notes that the cost formula for AEs only draws from either AE costs for tafasitamab plus R^2 or R^2, meaning that changes to AE costs for R-chemotherapy are not reflected in the results. Additionally, Table 31 of CS reports anaemia events (3.4%) for R-CVP and R-CHOP, which were not included in the model.

4.2.7.4 Subsequent treatment costs

The inMIND trial reported subsequent treatment use (Table 12 of the CS); however, several of the treatments included are not routinely used in UK clinical practice. Consequently, the company based the distribution of subsequent therapies on input from its clinical advisory board. The advisers suggested that, following disease progression, a proportion of patients would still be expected to receive R-chemotherapy (R-B, R-CHOP, R-CVP, or rituximab). The resulting base-case distribution of subsequent treatments is presented in Table 44 of the CS, with identical distributions assumed for the tafasitamab plus R^2 and R^2 arms.

While the clinical experts anticipated that subsequent therapy after R-chemotherapy would include either R^2 or alternative R-chemotherapy regimens, the economic analysis assigns 100% of these

patients to subsequent treatment with R². The EAG notes that this simplifying assumption may not fully reflect expected clinical practice.

As a scenario analysis, the company explored the distribution of subsequent treatments observed in inMIND (Table 45 of the CS), reweighted after excluding treatments not currently used in the UK. In this analysis, distributions following R-chemotherapy were assumed to be equivalent to those following R².

The model assumes that 86.5% of patients proceed to receive subsequent treatment, with costs applied on a per-cycle basis to newly progressed patients. This assumption was informed by company-sponsored clinical expert opinion. Total acquisition and administration costs for each subsequent therapy are reported in Table 47 of the CS. To account for deaths occurring prior to progression in inMIND, the average proportion of PFS events that were deaths was applied across all treatment arms.

As part of subsequent treatment, a small proportion of patients were assumed to undergo SCT, including autologous SCT or allogeneic SCT. SCT costs, sourced from NHS reference costs[75] and NICE guideline NG52 on the diagnosis and management of non-Hodgkin's lymphoma[84], are presented in Table 48 of the CS. Conditioning with high-dose chemotherapy prior to ASCT was modelled using the carmustine, etoposide, cytarabine, and melphalan (BEAM) regimen. Drug acquisition costs for BEAM were sourced from eMIT[74], with administration costs assumed to be captured within the ASCT procedure in line with NICE TA1048 and TA895.[85, 86] These costs are reported in Table 49 of the CS.

The EAG is satisfied with the company's approach to modelling subsequent treatment.

4.2.7.5 End-of-life costs

The cost of care for cancer patients sourced from the PSSRU was used to inform a one-off end-of-life cost applied to reflect the cost of terminal care. These costs represent the cost of care in the last twelve months of life based on service user patterns for a cohort of 73,243 people who died.[87]

The EAG is satisfied with the end-of-life costs and the application in the model.

4.2.7.6 Confidential pricing arrangements

The treatment acquisition costs in the company's analyses (CS and Section 5 of the EAG report) reflect only the confidential pricing agreement for tafasitamab, which is currently a [redacted] discount to the list price. The EAG notes that additional confidential prices and discounts apply to other components of both the intervention and comparator regimens. Table 22 summarises the components for which confidential prices differ from the publicly available list prices used to generate the results presented in this report. These confidential prices were provided to the EAG and used to replicate all

analyses for consideration by the Appraisal Committee; the corresponding results are reported in the confidential appendix.

Table 22 Source of the confidential prices used in the confidential appendix.

Treatment	Source of price/type of confidential arrangement
Lenalidomide	Medicines procurement and supply chain price
Rituximab	Medicines procurement and supply chain price
Rituximab (SC)	Medicines procurement and supply chain price
Gemcitabine (2000 mg vial size)	Medicines procurement and supply chain price

5 COST-EFFECTIVENESS RESULTS

Section 5.1 summarises the company's cost-effectiveness results, section 5.2 presents the EAG's additional work and preferred assumptions, and section 5.3 explores decision modifiers including the company's and EAG's preferred QALY weighting for severity.

5.1 Company's cost effectiveness results

5.1.1 Company's base case

The results of the company's revised base case following the clarification response are summarised in this section. The cost-effectiveness results presented in the following sections are inclusive of a confidential PAS discount for tafasitamab with [redacted]. No other discounts are included in the company's base case.

The company presented the updated base-case as pairwise results for tafasitamab plus R^2 compared to R^2 and R-chemotherapy regimens (R-CHOP, R-B, R-CVP). The deterministic results are presented in Table 23 below as fully incremental analyses. A severity modifier of 1 was applied in the company model.

Table 23 Company's updated deterministic base-case cost-effectiveness results without severity weighting

-	Total costs	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	Pairwise ICER (£/QALY)	Fully incremental ICER (£/QALY)
R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,707	-
R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,821	Strictly Dominated
R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,285	Strictly Dominated
R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,154	Strictly Dominated
Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		£33,707

Abbreviations: R^2, lenalidomide and rituximab;. R-Benda, rituximab with bendamustine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; R-CVP, rituximab with cyclophosphamide, vincristine and prednisolone

The EAG conducted a probabilistic sensitivity analysis (PSA) on the updated base case, running 1,000 iterations, consistent with the original company base case. Probabilistic results in the company model are generated pairwise for tafasitamab plus R^2 versus R^2, and these results are presented in Table 24. Compared with R^2, tafasitamab plus R^2 was associated with incremental costs of [redacted] and incremental QALYs of [redacted], corresponding to an ICER of £39,669 per QALY gained.

The results of the PSA show lower QALYs compared with the deterministic company base case. The company suggested that this reflects the high uncertainty associated with the OS extrapolations

combined with the treatment waning effect. In iterations where tafasitamab plus R^2 generates higher survival than R^2, the survival gain is limited by the treatment waning effect. Conversely, where OS is similar between the two treatments, the impact of treatment waning is minimal.

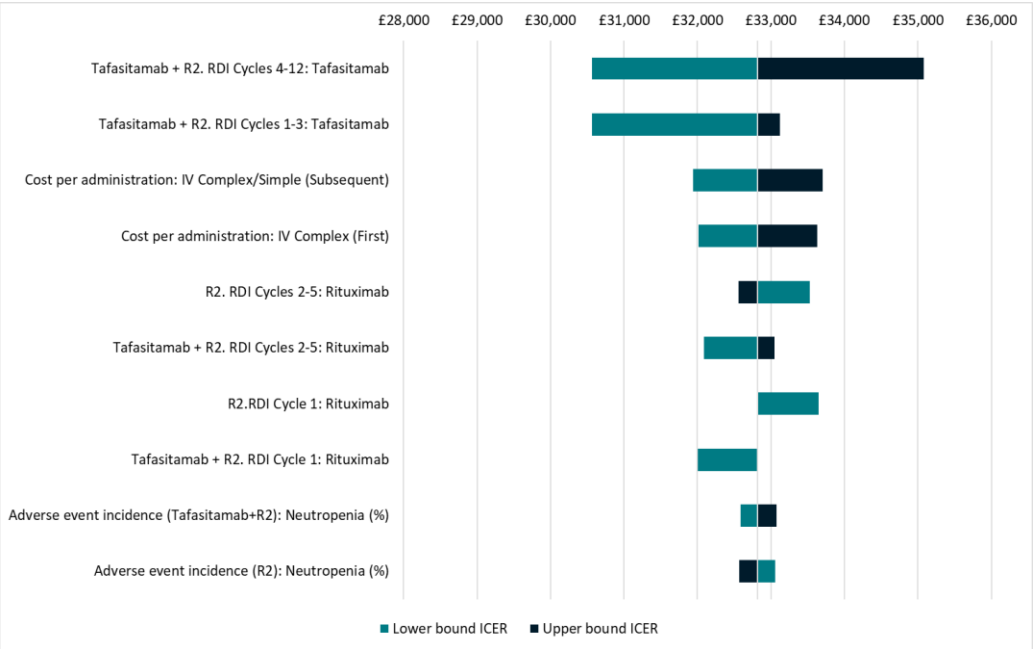
Table 24 Company's updated probabilistic base-case cost-effectiveness results without severity weighting

-	Total costs	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Tafa + R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,669
Abbreviations: R^2, lenalidomide and rituximab.							

5.1.2 Company's sensitivity and scenario analyses

The company conducted one-way sensitivity analysis to identify the parameters with the greatest influence on the ICER for tafasitamab plus R^2 versus R^2. The EAG performed this analysis on the company's updated base-case, which is presented in Figure 12. The results suggest that RDI for tafasitamab, followed by costs for IV administration, were the most influential parameters on the ICER.

Figure 12 Tornado diagram



Source: Updated company model

The company presented results of the deterministic scenario analyses for tafasitamab plus R^2 versus R^2 in Section 3.11.3 of the CS. The EAG conducted these scenario analyses using the company's updated base case. Additional scenario analyses were presented at the clarification stage in response to EAG

queries. Results from both sets of analyses are shown in Table 25. Note that the results presented at the clarification stage were based on the original company base case. Scenarios 26, 29, 30, 31, and 32 in Table 25 constituted the updated base case.

The EAG was unable to replicate scenario 29, which updated NHS costs, although the difference from the company's reported ICER was relatively minor (+£9).

Table 25 Company's additional scenario analysis (deterministic tafasitamab + R^2 versus R^2)

#	Scenario	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
-	Base case	[redacted]	[redacted]	[redacted]	£32,821
1	time_horizon_10_years	[redacted]	[redacted]	[redacted]	£48,826
2	State_transition_GADOLIN (STM 2)	[redacted]	[redacted]	[redacted]	£20,605
3	State_transition_HMRN (STM 1)	[redacted]	[redacted]	[redacted]	£42,277
4	State_transition_weighted (STM 3)	[redacted]	[redacted]	[redacted]	£27,246
5	discounting_1.5%	[redacted]	[redacted]	[redacted]	£28,315
6	OS_PFS_waning_7_years_5Ydur	[redacted]	[redacted]	[redacted]	£28,813
7	OS_PFS_waning_5_years_10Ydur	[redacted]	[redacted]	[redacted]	£28,820
8	OS_PFS_waning_5_years_3Ydur	[redacted]	[redacted]	[redacted]	£35,545
9	Wastage_No	[redacted]	[redacted]	[redacted]	£30,581
10	SubTx_dist_inMIND	[redacted]	[redacted]	[redacted]	£35,309
11	time_horizon_20_years	[redacted]	[redacted]	[redacted]	£34,809
12	OS_PFS_waning_5_years_7Ydur	[redacted]	[redacted]	[redacted]	£30,869
13	PFS_IA	[redacted]	[redacted]	[redacted]	£33,939
14	util_wild	[redacted]	[redacted]	[redacted]	£33,915
15	OS_PFS_joint_log-logistic	[redacted]	[redacted]	[redacted]	£31,919
16	util_TA898	[redacted]	[redacted]	[redacted]	£33,655
17	COVID_include	[redacted]	[redacted]	[redacted]	£33,059
18	PFS_joint_log-logistic	[redacted]	[redacted]	[redacted]	£32,310
19	OS_joint_log-logistic	[redacted]	[redacted]	[redacted]	£32,421
20	R_maintenance_IV	[redacted]	[redacted]	[redacted]	£33,138
21	util_GADOLIN	[redacted]	[redacted]	[redacted]	£32,943
22	util_AUGMENT	[redacted]	[redacted]	[redacted]	£32,867
23	lenalidomide_30%_discount	[redacted]	[redacted]	[redacted]	£32,819
24	AE_utility_exclude	[redacted]	[redacted]	[redacted]	£32,820
Scenarios in company clarification response (based on original base-case)					

#	Scenario	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
25	Restricted mean survival time (CQ B2c)	[redacted]	[redacted]	[redacted]	£29,033
26	Updated efficacy assumptions (CQ B6) a) Tafa + R^2 vs R-Benda	[redacted]	[redacted]	[redacted]	£32,906
	b) Tafa + R^2 vs R-CVP	[redacted]	[redacted]	[redacted]	£32,567
	c) Tafa + R^2 vs R-CHOP	[redacted]	[redacted]	[redacted]	£35,070
27	Alternative PFS extrapolations (CQ B7) a) Separately fitted log-logistic PFS curves	[redacted]	[redacted]	[redacted]	£33,391
	b) Jointly fitted log-logistic PFS curves	[redacted]	[redacted]	[redacted]	£32,174
28	2L using jointly fitted curves (CQ B9) a) OS: Weibull, PFS: Generalised gamma	[redacted]	[redacted]	[redacted]	£50,581
	b) OS: Weibull, PFS: Log-normal	[redacted]	[redacted]	[redacted]	£50,635
	c) OS: Weibull, PFS: Log-logistic	[redacted]	[redacted]	[redacted]	£51,121
	d) OS: Gamma, PFS: Generalised gamma	[redacted]	[redacted]	[redacted]	£49,703
	e) OS: Gamma, PFS: Log-normal	[redacted]	[redacted]	[redacted]	£49,756
	f) OS: Gamma, PFS: Log-logistic	[redacted]	[redacted]	[redacted]	£50,228
29	Updated NHS costs (CQ B13)	[redacted]	[redacted]	[redacted]	£32,589
30	Corrected average RDI for tafasitamab (CQ B15 b) a) Tafa + R^2 vs R-Benda	[redacted]	[redacted]	[redacted]	£29,032
	b) Tafa + R^2 vs R-CVP	[redacted]	[redacted]	[redacted]	£28,723
	c) Tafa + R^2 vs R-CHOP	[redacted]	[redacted]	[redacted]	£30,982
31	Updated subcutaneous administration costs (CQ B16) g) Tafasitamab + R^2 vs R-Benda	[redacted]	[redacted]	[redacted]	£27,849
	h) Tafa + R^2 vs R-CVP	[redacted]	[redacted]	[redacted]	£27,542
	i) Tafa + R^2 vs R-CHOP	[redacted]	[redacted]	[redacted]	£29,809
32	Including infusion preparation time costs (CQ B16b)	[redacted]	[redacted]	[redacted]	£32,914

Abbreviations: CQ, clarification question; ICER, incremental cost effectiveness ratio; LYs, life-years; NHS, national health service; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-years; R^2, lenalidomide and rituximab; R-B, rituximab with bendamustine, R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP, Rituximab with cyclophosphamide, vincristine and prednisolone; STM, state transition model

5.2 EAG's additional analyses

5.2.1 Model validation and face validity check

The EAG reviewed the company's base-case and sensitivity analyses, including the use of a structured checklist to conduct a series of black-box tests to assess the internal validity of the model. These tests examined the internal logic of the model and the predictive validity of key parameter inputs (for

example, whether increasing treatment effectiveness resulted in improved cost-effectiveness). In addition, the model code was examined for potential errors, including tracing the flow of parameters through the model and reviewing the main calculation sheets to understand how costs and QALYs were accrued.

At the clarification stage, the company updated the economic model to correct a minor calculation error in the application of subsequent treatment costs, resulting in a small change to the base-case ICER. No further errors were identified during the EAG's validation of the model.

5.2.2 EAG's exploratory analyses using company's base case

Table 26 is the summary of EAG's exploratory analyses using the company's base case.

Table 26 Summary of EAG's exploratory analyses using company's base case Summary of EAG's exploratory analyses using company's base case

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
1a	PSM structure, jointly fitted OS extrapolation including treatment effect covariate.	STM model structure, PPS benefit based on HRMN	As described in Section 4.2.2, the company's preferred partitioned survival model (PSM) relies on extrapolation of highly immature overall survival (OS) data. The EAG therefore prefers a state transition model (STM) structure, in which the more mature progression-free survival (PFS) evidence serves as the primary driver of modelled survival benefits. The EAG's base-case analysis adopts an STM with post-progression survival (PPS) informed by HMRN data (Scenario 1a). In addition, the EAG presents alternative STM-based scenarios using PPS informed by GADOLIN (Scenario 1b) and by a weighted average of HMRN and GADOLIN (Scenario 1c).	4.2.2
1b	PSM structure, jointly fitted OS extrapolation including treatment effect covariate.	STM model structure, PPS benefit based on the GADOLIN trial		
1c	PSM structure, jointly fitted OS extrapolation including treatment effect covariate.	STM model structure, PPS benefit based on the weighted average of HRMN and GADOLIN trial		
2	PSM structure, jointly fitted OS extrapolation including treatment effect covariate.	PSM model structure, OS extrapolation jointly fitted with no-treatment-effect.	To explore the uncertainty surrounding overall survival (OS) benefits, and to reflect the lack of a statistically significant difference in observed OS, the EAG presents a scenario in which no OS benefit is conferred by tafasitamab.	4.2.5.2
3	PSM structure, jointly fitted OS extrapolation including treatment effect covariate.	PFS extrapolation: Separately fitted log-logistic	The EAG considers that there is a weak rationale for preferring jointly fitted survival models and therefore explores several plausible alternative extrapolations for both PFS and OS.	4.2.5.3
4	PFS extrapolation jointly fitted generalised gamma	PFS extrapolation separately fitted gamma		
5	OS extrapolation jointly fitted generalised gamma	OS extrapolation: Separately fitted log-logistic		
6a	Waning of OS and PFS, full effect for 5 years, followed by 5 years of waning.	Waning of OS and PFS, full effect for 5 years, followed by 0 years of waning.	The EAG considers there to be significant uncertainty regarding the duration of tafasitamab treatment effect and therefore explores two alternative scenarios that are more	4.2.5.4

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
6b	Waning of OS and PFS, full effect for 5 years, followed by 5 years of waning.	Waning of OS and PFS, full effect for 2 years, followed by 3 years of waning.	consistent with precedent and the available survival data. Scenario 6a aligns with the assumptions accepted in TA627, while Scenario 6b adopts a more conservative waning assumption, aligned with observed hazard trends and the duration of follow-up.	
7	Time to discontinuation for R-chemotherapy is based on PFS	Time to discontinuation for R-chemotherapy is based on R^2 time to discontinuation curve.	The EAG disagrees with the company's assertion that the R-chemotherapy regimens are less intensive. Consistent with the assumption of equivalence between R^2 and R-chemotherapy, the EAG assumes that time to treatment discontinuation for R-chemotherapy is the same as for R^2. This scenario applies only to the fully incremental analysis.	4.2.5.6
8	The proportion of PFS events that are deaths is common to both, based on pooled data from inMIND	The proportion of PFS events that are deaths is arm-specific based on inMIND	The EAG considers it appropriate to model separately the proportion of progression-free survival (PFS) events that are deaths, in order to align with the differences observed in the inMIND trial.	4.2.5.5
9	Starting age (64) based on inMIND trial	Starting age (68.0yrs) based on HRMN data set	There is some evidence from the HRMN database that the average age of eligible patients may be higher than that of patients recruited to inMIND.	4.2.3
10	Average RDI applied thoughout time on treatment	Per treatment cycle, RDI applied	The EAG noted that the RDI varies considerable across the the treatmenht period and therefore explores a scenario in which RDI varies by treatment cycle.	4.2.7

The results of the scenario analyses described in Table 26 are presented in Table 27 as a pairwise comparison vs R^2 and fully incrementally in Table 28 considering all comparators. These results include the PAS discount for tafasitamab only. Results inclusive of all available PAS discounts and other commercial arrangements, are provided in the confidential appendix to this report.

Table 27 EAG Exploratory Pairwise scenario analyses (deterministic)

Scenario		Technology	Total		Incremental		Pairwise ICER
			Costs	QALYs	Costs	QALYs	
Company base case		R^2	[redacted]	[redacted]			
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£32,821
1a	**Model Structure (STM with PPS benefit from HMRN)**	R^2	[redacted]	[redacted]			
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£42,277
1b	**Model Structure (STM with PPS benefit from GADOLIN)**	R^2	[redacted]	[redacted]			
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£20,605
1c	**Model Structure (STM with PPS benefit Weighted)**	R^2	[redacted]	[redacted]			
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£27,246
2	**PSM, OS Joint with no tx effect covariate**	R^2	[redacted]	[redacted]			
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£682,597
3	**PFS Extrapolation: Separately fitted log-logistic**	R^2	[redacted]	[redacted]			
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£33,559
4	**PFS Extrapolation: Separately fitted gamma**	R^2	[redacted]	[redacted]			
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£34,156
5	**OS Extrapolation: Separately fitted log logistic**	R^2	[redacted]	[redacted]			
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£137,930
6a	**Waning of OS and PFS: 5 yrs full & 0 yrs waning**	R^2	[redacted]	[redacted]			
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£42,402
6b	**Waning of OS and PFS: 2 yrs full & 3 yrs waning**	R^2	[redacted]	[redacted]			
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£57,565
7	**TTD for R-Chemo is equal to R2**	R^2	Tafa +Applies only to the fully incremental				
		Tafa +R^2					
8	**Proportion of deaths in PFS events is tx arm-specific (inMIND)**	R^2	[redacted]	[redacted]			
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£32,219
9	**Starting age, 68.0 yrs based on HRRN 2L R-CVP**	R^2	[redacted]	[redacted]	[redacted]	[redacted]	£34,032
		Tafa +R^2	[redacted]	[redacted]			
10	**RDI applied per tx cycle (Tafa)**	R^2	[redacted]	[redacted]	[redacted]	[redacted]	£31,946
		Tafa +R^2	[redacted]	[redacted]			

Abbreviations: ICER, incremental cost effectiveness ratio; LYs, life-years; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; QALY, quality-adjusted life-years; R^2, lenalidomide and rituximab; R-B, rituximab with bendamustine, R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP, Rituximab with cyclophosphamide, vincristine and prednisolone; RDI, relative dose intensity; STM, state transition model; Tafa, Tafasitamab; Tx, treatment.

Table 28 EAG Exploratory fully incremental scenario analyses (deterministic)

Scenario		Technology	Total		Incremental		Fully incremental ICER
			Costs	QALYs	Costs	QALYs	
Company base case		R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
		R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£33,707
1a	Model Structure (STM with PPS benefit from HMRN)	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
		R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£43,478
1b	Model Structure (STM with PPS benefit from GADOLIN)	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
		R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£21,096
1c	Model Structure (STM with PPS benefit Weighted)	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
		R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£27,949
2	PSM, OS Joint with no tx effect covariate	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
		R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£728,075
3	PFS Extrapolation: Separately fitted log-logistic	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
		R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£34,471
4	PFS Extrapolation: Separately fitted gamma	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
		R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£35,105
5	OS Extrapolation: Separately fitted log logistic	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
		R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated

		R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£142,860
6a	**Waning of OS and PFS: 5 yrs full & 0 yrs waning**	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
		R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£43,595
6b	**Waning of OS and PFS: 2 yrs full & 3 yrs waning**	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
		R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£59,245
7	**TTD for R-Chemo is equal to R2**	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
		R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£35,602
8	**Proportion of deaths in PFS events is tx arm-specific (inMIND)**	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
		R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£33,132
9	**Starting age, 68.0 yrs based on HRRN 2L R-CVP**	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
		R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£34,955
10	**RDI applied per tx cycle (Tafa)**	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
		R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
		Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£32,722

Abbreviations: ICER, incremental cost effectiveness ratio; LYs, life-years; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; QALY, quality-adjusted life-years; R^2, lenalidomide and rituximab; R-B, rituximab with bendamustine, R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP, Rituximab with cyclophosphamide, vincristine and prednisolone; RDI, relative dose intensity; STM, state transition model; Tafa, Tafasitamab; Tx, treatment.

5.2.3 EAG's preferred assumptions

The cumulative impact of the EAG's preferred assumptions is presented in Table 29 below as a pairwise comparison to R^2 and as a full incremental analysis in Table 30, including all comparators. The EAG's preferred base case is primarily driven by model structure, duration of treatment effect and waning assumptions. Given the high of level of uncertainty around a number of the key efficacy parameters in the model, the EAG's preferred base case represents a plausible but reasonably optimistic set of assumptions.

The EAG base case adopts the following scenarios described in Section 5.2.2:

- Scenario 1a: STM with PPS benefit from HMRN
- Scenario 3: PFS Extrapolation with separately fitted log-logistic
- Scenario 6b: Waning of OS and PFS: 2 years full & 3 years waning
- Scenario 8: Proportion of deaths in PFS events is treatment-specific (inMIND)
- Scenario 10: RDI applied per treatment cycle (Tafa)

Table 29 EAG's preferred model assumptions pairwise analysis (Deterministic)

Technology	Total		Incremental		Pairwise ICER
	Costs	QALYs	Costs	QALYs	
R^2	[redacted]	[redacted]	[redacted]		
Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: EAG, evidence assessment group, ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-years; R^2, lenalidomide and rituximab; Tafa, Tafasitamab.					

Table 30 EAG's preferred model assumptions fully incremental analysis (Deterministic)

Technology	Total		Incremental		Fully incremental ICER
	Costs	QALYs	Costs	QALYs	
R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£116,598
Abbreviations: EAG, evidence assessment group, ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-years; R^2, lenalidomide and rituximab; Tafa, Tafasitamab.					

Probabilistic results for the EAG's alternative base case are presented in Table 31 below as a pairwise comparison to R^2. Unfortunately, the PSA function in the company's model did not permit a full incremental analysis in including all comparators. The model was set to the EAG's preferred assumptions and run with 1,000 iterations. In the probabilistic EAG base case, Tafasitamab plus R^2 had a ~[redacted] probability of being the most cost-effective option at a willingness-to-pay threshold of £30,000.

Table 31 EAG's base case analysis results pairwise analysis (probabilistic)

Technology	Total		Incremental		ICER (£ per QALY)
	Costs	QALYs	Costs	QALYs	
R^2	[redacted]	[redacted]			
Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£69,587
Abbreviations: EAG, evidence assessment group, ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-years; R^2, lenalidomide and rituximab; Tafa, Tafasitamab.					

5.2.4 Scenario analyses using EAG's preferred assumptions

Table 32 presents the EAG preferred base case for the 3L+ subgroup. This is the only subgroup that the company produced in their original CS. R-Chemo is not considered as a comparator in the 3L+ subgroup setting.

Table 32 EAG's preferred model assumptions for the 3L+ subgroup (Deterministic)

Technology	Total		Incremental		ICER (£ per QALY)
	Costs	QALYs	Costs	QALYs	
R^2	[redacted]	[redacted]			
Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£110,316
Abbreviations: EAG, evidence assessment group, ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-years; R^2, lenalidomide and rituximab; Tafa, Tafasitamab.					

At clarification upon EAG request, the company produced the 2L-only subgroup. Table 33 presents the EAG preferred base case for the 2L-only subgroup in the pairwise analysis and Table 34 for the fully incremental analysis.

Table 33 EAG's preferred model assumptions for the 2L-only subgroup (Deterministic)

Technology	Total		Incremental		ICER (£ per QALY)
	Costs	QALYs	Costs	QALYs	
R^2	[redacted]	[redacted]			
Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£176,105
Abbreviations: EAG, evidence assessment group, ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-years; R^2, lenalidomide and rituximab; Tafa, Tafasitamab.					

Table 34 EAG's preferred model assumptions for the 2L-only subgroup (Deterministic)

Technology	Total		Incremental		Fully incremental ICER
	Costs	QALYs	Costs	QALYs	
R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, evidence assessment group, ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-years; R^2, lenalidomide and rituximab; Tafa, Tafasitamab.

5.3 Decision modifiers

This analysis was undertaken using the QALY Shortfall Calculator in R developed by the University of York (https://shiny.york.ac.uk/shortfall/). Inputs were said to be aligned with the modelled population in the base case, reflecting a mean age of 64.2 years and 45.4% proportion female Table 35 presents a summary of the QALY shortfall analysis.

Table 35 Summary of QALY shortfall analysis

	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY Shortfall
Company base case (per model)				
R-CHOP	10.81	[redacted]	[redacted]	[redacted]
R^2	10.81	[redacted]	[redacted]	[redacted]
R-Benda	10.81	[redacted]	[redacted]	[redacted]
R-CVP	10.81	[redacted]	[redacted]	[redacted]
Company base case (Using QALY shortfall calculator)				
R-CHOP	11.30	[redacted]	[redacted]	[redacted]
R^2	11.30	[redacted]	[redacted]	[redacted]
R-Benda	11.30	[redacted]	[redacted]	[redacted]
R-CVP	11.30	[redacted]	[redacted]	[redacted]
EAG base-case (Using QALY shortfall calculator)				
R-CHOP	11.30	[redacted]	[redacted]	[redacted]
R^2	11.30	[redacted]	[redacted]	[redacted]
R-Benda	11.30	[redacted]	[redacted]	[redacted]
R-CVP	11.30	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; QALY, Quality Adjusted Life Years; R^2, lenalidomide and rituximab; Tafa, Tafasitamab.

5.3.1 QALY weighting for severity

The EAG preferred assumptions for the general population QALY shortfall estimates are detailed in Table 36. These are based on the baseline characteristics of the R/R FL FAS population from the inMIND trial.

Table 36 Summary of company's or EAG's preferred assumptions for general population QALY shortfall estimates

Factor	Value or source (reference to appropriate table or figure in submission)	Reference to section in submission or rationale
Sex distribution	45.4% Female; 55.6% Males	Demographic and baseline disease characteristics of R/R FL patients in inMIND; Table 6 and Table 51.
Starting age	64.2 years	Demographic and baseline disease characteristics of R/R FL patients in inMIND; Table 6 and Table 51.
Expected years of life	11.30	Reference case: MVH value set + HSE 2014 ALDVMM model (Hernandez Alava et al. 2022 [73]) This is the quality-adjusted life expectancy (QALE) value.
Quality of life by age	Yes applied.	As per company base case analysis in worksheet <Utilities> using HSE 2014 dataset
Discount rate	3.5%	NICE reference case[76]
Abbreviations: ALDVMM, Adjusted limited dependent variable mixture model; CS, Company submission; EAG, External Assessment Group; HSE, Health Survey for England; MVH, Measurement and valuation group; NICE, National Institute for Health and Care Excellence; Y, yes.		

Table 37 is a summary of the QALY shortfall analyses and preferred QALY weighting for the company's and EAG's base case.

Table 37 Summary of company's and EAG's base-case QALY shortfall analyses and preferred QALY weighting

-	Expected total QALYs for the general population	Expected total QALYs for people living with a condition on current treatment	Absolute QALY shortfall	Proportional QALY shortfall	Preferred QALY weight
Company's base case	10.81	[redacted]	[redacted]	[redacted]	None
EAG's base case	11.30	[redacted]	[redacted]	[redacted]	None
Abbreviations: EAG, External Assessment Group; QALY, Quality Adjusted Life Years;					

5.3.2 Uncaptured benefits

In the CS, the company presented (in Section 3.13; CS, pp 166) one short paragraph outlining potential benefits of tafasitamab plus R^2 that they considered not to be captured in the QALY

calculation. The company referred to (i) QoL benefits to their families and carers, and (ii) the hope that the intervention offers people living with FL. The EAG has no issues with these purported uncaptured benefits.

The EAG considers the value of hope and option value to be subjective and difficult to quantify, whilst outside the NICE reference case. The costs of informal care and impact on caregivers and family members could be a significant benefit that is not captured in the QALY calculations; however, the company have not presented any quantitative evidence to show that FL associated with a substantial effect on carer's HRQL and how the availability of tafasitamab plus R^2 benefits carers. The EAG also notes that the HRQL of R/R FL appears to be relatively small and therefore it is unclear if there would be a significant impact on carers.

5.3.3 Health inequalities

No health inequalities are foreseen.

5.4 Conclusions of the cost-effectiveness section

The company submitted a PSM to estimate the cost-effectiveness of tafasitamab plus R² compared with R² alone and with three alternative R-chemotherapy combinations. The EAG considers R² to be the principal comparator for this appraisal; however, some displacement of R-chemotherapy is likely, particularly in the 2L setting.

The EAG considers that the company's economic analysis broadly reflects the decision problem and is consistent with the NICE reference case. The key uncertainties in this appraisal primarily relate to the immaturity of the survival data, particularly overall survival (OS). As acknowledged by the company, the OS data from inMIND are immature, with only 15 death events in the tafasitamab plus R² arm and 23 in the R² arm, and a median follow-up of 15.3 months. This limitation in the available evidence is central to the interpretation of the model results, as the company's base-case analysis relies on extrapolating these limited OS data to estimate the survival benefit associated with tafasitamab plus R², which is the primary driver of incremental QALYs.

The EAG considers the current OS data too immature to support reliable inferences regarding either the magnitude or the existence of any OS benefit. Consequently, the EAG does not consider the company's PSM structure to be appropriate for decision-making in its current form. Instead, the EAG sought to characterise the uncertainty associated with OS by exploring two alternative approaches. The first adopts a STM framework, primarily informed by the more mature PFS data, with the magnitude of the PFS benefit used to inform any subsequent OS benefit. The second retains the PSM structure used in the company's base case but applies the conservative assumption that tafasitamab plus R² confers no OS benefit relative to R². The EAG considers that these approaches provide a

structured and transparent basis for decision-making and bound the plausible range of OS outcomes. However, the STM approach necessarily assumes a surrogate relationship between PFS and OS, for which the available literature provides only limited supporting evidence.

Beyond model structure, substantial uncertainty also relates to survival extrapolation, treatment effect waning and the modelling of PPS. Extrapolation is central to both modelling frameworks: PFS extrapolation is particularly influential within the STM, while OS extrapolation is critical within the PSM. In both cases, the EAG prefers separately fitted parametric models rather than the company's jointly fitted approaches and proposes alternative extrapolations on this basis. The EAG notes that the model is highly sensitive to the choice of OS curve, with its preferred extrapolations resulting in materially higher ICERs. Given the small number of observed OS events, long-term survival projections are driven predominantly by structural and distributional assumptions rather than robust empirical data.

The EAG also considers the company's assumptions regarding treatment effect waning and PPS to be key structural drivers of the results. The company assumes a 5-year period of full treatment effect followed by a further 5-year period of gradual waning for both PFS and OS. While the EAG agrees that a permanent treatment effect is not biologically plausible and that gradual waning is more clinically reasonable than an abrupt loss of effect, the empirical basis for a 5+5-year structure is weak and largely precedent-based. Given the time-limited nature of treatment and the absence of mature long-term data, the EAG considers a shorter duration of full treatment effect (2 years) followed by 3 years of waning to be more conservative and more consistent with the underlying disease biology.

Within the STM framework, assumptions regarding PPS are also critical in determining the magnitude of any OS benefit. The company's preferred STM incorporates a treatment-specific PPS benefit derived by weighting evidence from the HMRN database and the GADOLIN trial. The EAG considers this approach to rely on strong and unvalidated assumptions, including the transferability of PPS:PFS relationships across trials, populations and regimens with differing mechanisms of action. In the absence of robust evidence from inMIND demonstrating a treatment-specific PPS advantage and given the lack of a clear biological rationale for such an effect, the EAG prefers to assume no PPS benefit.

Overall, the cost-effectiveness estimates are highly sensitive to assumptions regarding how OS benefits are estimated. Further follow-up from inMIND, with a substantially greater number of OS events, is therefore likely to be critical in reducing structural uncertainty and enabling more reliable estimation of the long-term survival benefit associated with tafasitamab plus R².

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APPENDICES

APPENDIX 1. SYSTEMATIC LITERATURE REVIEW –HRQL

A search for studies on the HRQL (humanistic burden) of patients with R/R FL/MZL was carried out in 2024 and updated in April 2025. The search strategies were located in Appendix B of a separate report by Avalere Health and Lumanity included with the CS. [66]

Overall, the searches were good quality with a range of both published and unpublished sources of evidence searched. A few more minor issues are noted in the EAG appraisal of the searches in Table 1 below.

Appendix Table 1 EAG appraisal of evidence identification for SLR of HRQL

Topic	EAG response	Note
Is the report of the search clear and comprehensive?	YES	
Were appropriate sources searched?	PARTLY	Major databases were searched (PubMed, Embase, EconLit and the NHS Economic Evaluations Database (NHS EED)) with additional searches of conference proceedings and selected HTA agencies. **Relevant sources not searched:** - INAHTA and the HTA database - reference checking of included studies and reviews
Was the timespan of the searches appropriate?	YES	Databases: inception to 9 April 2025 Conference proceedings: 2021-2024 HTA agencies: 2021- 22 April 2025
Were appropriate parts of the PICOS included in the search strategies?	YES	**PubMed and Embase** Population: R/R FL/MZL AND HRQL (humanistic outcomes) **EconLit, NHS EED, conference proceedings and HTA agencies** Population: R/R FL/MZL
Were appropriate search terms used?	PARTLY	Search terms for NHS EED and EconLit were simplified to just 2 search terms for the population, although both databases allow more complex searching.
Were any search restrictions applied appropriate?	PARTLY	Search was limited to English language articles only.
Were any search filters used validated and referenced?	NO	Search filters were not used. The searches of PubMed and Embase were limited to HRQL (humanistic outcomes) using a comprehensive set of terms (text word and subject headings) to represent this concept.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

APPENDIX 2. SYSTEMATIC LITERATURE REVIEW – COST EFFECTIVENESS AND HCRU

A combined search for studies on the cost-effectiveness of treatments for R/R FL/MZL and studies relating to the healthcare costs and resource use of patients with R/R FL/MZL were carried out in 2024 and updated in April 2025. The search strategies were located in Appendix D of a separate report by Avalere Health and Lumanity included with the CS. [66]

Overall, the searches were good quality with a range of both published and unpublished sources of evidence searched. A few more minor issues are noted in the EAG appraisal of the searches in Table 2 below.

Appendix Table 2 EAG appraisal of evidence identification for SLRs of cost-effectiveness and HCRU

Topic	EAG response	Note
Is the report of the search clear and comprehensive?	YES	A minor error was found – the search strategies were found in Appendix D rather than Appendix C as reported on page 30, Section 3.2.1.1
Were appropriate sources searched?	PARTLY	Major databases were searched (PubMed, Embase, EconLit and the NHS Economic Evaluations Database (NHS EED)) with additional searches of conference proceedings and selected HTA agencies. **Relevant sources not searched:** - INAHTA and the HTA database - reference checking of included studies and reviews
Was the timespan of the searches appropriate?	YES	Databases: inception to 9th April 2025 Conference proceedings: 2021-2024 HTA agencies: 2021- 22 April 2025
Were appropriate parts of the PICOS included in the search strategies?	YES	**PubMed and Embase** Population: R/R FL/MZL AND (economic evaluations OR HCRU studies) **EconLit, NHS EED, conference proceedings and HTA agencies** Population: R/R FL/MZL
Were appropriate search terms used?	PARTLY	Search terms for NHS EED and EconLit were simplified to just 2 search terms for the population, although both databases allow more complex searching.
Were any search restrictions applied appropriate?	PARTLY	- Retrieval was restricted to English language studies only, therefore language bias is possible. - Conference abstracts were removed from the search results from Embase, so the search for conference abstracts was focussed on a more limited set of 5 different conference proceedings.
Were any search filters used validated and referenced?	NO	Search filters were not used. The searches of PubMed and Embase were limited to economic evaluations and HCRU studies using a comprehensive set

		of terms (text word and subject headings) to represent economic evaluations and HCRU studies.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

APPENDIX 3. DISCREPANCIES IDENTIFIED IN THE AES VALUES

Appendix Table 3 Discrepancies identified in the Adverse Events (AEs) values

Issue	Adverse event	Type	Description
1	Acute kidney injury	Inconsistent source reference	The event utility source is listed as TA306[88] in the CS but in the model, it is TA942
2	Allergic reaction	Incorrect source	The event utility source is listed as Hannouf et al. (2012) [89] this is a 21-gene recurrence score assay in breast cancer). In TA627 – the Hannouf et al. 2012[90] is in head and neck cancer. The decrement value for allergy or anaphylaxis is -15% of base case value (0.65) which gives -0.098.
3	Allergic reaction	Value of duration	Assumed maximum of all Grade 3/4 AEs was used for duration of pruritis. The value of 24.36 was used and comes from the model. However, this is based on 29 AEs in the company model that come from a variety of sources.
4	COVID-19	Incorrect Source	Halpin et al. (2020) [91] reference is a letter to the editor. Neither disutility nor duration mentioned in letter.
5	COVID-19 pneumonia	Incorrect Source	Halpin et al. (2020) [91] reference is a letter to the editor. Neither disutility nor duration mentioned in letter.
6	Pruritis	Value of duration	Assumed maximum of all Grade 3/4 AEs was used for duration of pruritis. The value of 24.36 was used and comes from the model. However, this is based on 29 AEs in the company model that come from a variety of sources.
7	Pyrexia	Inconsistent source reference	The event utility source and duration source is listed as TA872[92] but in the model it is TA559. The values are found in TA872.
8	Sepsis	Incorrect source	The event utility source is listed as Hannouf et al. (2012)[89]- this is a 21-gene recurrence score assay in breast cancer). In TA627 – the Hannouf et al. 2012[90] is in head and neck cancer. The decrement value for sepsis is -41% of base case value (0.65) which gives -0.267. The duration is lifetime.
9	Sepsis	Incorrect transcription	The duration value should be 13.2 days. The value 25.25 refers to the standard deviation. Source Table 81[46]
10	Sepsis	Value of duration	Assumed maximum of all Grade 3/4 AEs was used for duration of pruritis. The value of 24.36 was used and comes from the model. However, this is based on 29 AEs in the company model that come from a variety of sources.
11	Urinary tract infection	Provenance of data	Calculation found (1.00 -0.93 = 0.07) in Armstrong et al. (2009)[93]. Original Source: Ackerman 2000[94]which is based on n=13 (weighed average used)
12	Vomiting	Value incorrect	In Nafees et al. (2008) [95] Table 2: Nausea & vomiting = -0.04802 (not -0.0760). Duration of event in model uses reference 121 but should be 111.

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EAG ADDENDUM

Review of the company's addendum on epcoritamab:

Tafasitamab with lenalinomide and rituximab for treating relapsed or refractory follicular lymphoma after 1 or more systemic treatments [ID6413]

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None

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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1 OVERVIEW

This addendum to the External Assessment Report (EAR) report presents the External Assessment Group's (EAG) critique of the additional evidence provided by the company in their addendum. The company addendum compared tafasitamab + R^2 to the recently approved epcoritamab in third-line and later therapy (3L+). The addendum included a matched adjusted indirect comparison (MAIC) analysis to compare the clinical effectiveness of tafasitamab + R^2 and epcoritamab, and updated economic analyses comparing the cost-effectiveness of the two interventions. These are briefly critiqued by the EAG in this document.

The company addendum also presents a discussion of differences between this assessment of tafasitamab (ID6413) and the STA process for epcoritamab (TA1139) in their Table 1. The EAG acknowledges some of the concerns raised by the company. The EAG notes that epcoritamab was approved based on a single-arm Phase II trial, with comparisons to other therapies coming from limited MAIC analyses using HMRN data only. By contrast, the company submission and EAG report for tafasitamab are based on an RCT compared to R^2, with comparisons with other therapies being either direct (for R^2) or through MAICs based on original trial data for other comparators.

However, we consider it inappropriate for us to further examine the issues raised by the company in their Table 1 as we were not party to the work of the other EAG or to any committee discussion around epcoritamab. Also, much of the critical information required to make a fair comparison of the two STAs is currently redacted.

2 DESCRIPTION AND CRITIQUE OF ADDITIONAL EVIDENCE

The company addendum supplied a MAIC comparing tafasitamab + R^2 to epcoritamab in 3L+ patients. This MAIC was included in the original company submission as part of the wider indirect comparisons of tafasitamab with other therapies, but was not considered by the EAG at the time as epcoritamab was not in scope.

As this MAIC was part of the company submission the EAG's original critique of the MAICs in general also applies to this (see EAG Report Sections 3.5), and so is not repeated in detail here. Overall, the EAG agrees with the company that EPCORE NHL-1 patients had worse prognosis compared with inMIND overall, which limits their comparability. The effective sample size (ESS) of [redacted] of the total sample size indicated moderate overlap, although several key covariates (notably double refractory status and POD24, as acknowledged by the company) could not be adjusted for as were not reported in both trials. The lack of control group in the epcoritamab trial meant that the MAIC was unanchored and relied on the strong assumption that all prognostic factors and treatment

effect modifiers were accounted for, which was not met. The magnitude and direction of potential bias due to these limitations is difficult to predict.

For comparison, the EAG have extended the additional work in EAG Report Section 3.6 to extract and reconstruct data from survival curves for 3L+ patients including tafasitamab + R^2 and R^2 (from iMIND), epcoritamab (from EPCORE NHL-1), R-CHOP and R-B (from HMRN). No data on R-CVP was available for 3L+ patients, and OS data was not available for R^2. The reconstructed survival curves for PFS are given in Figure 1, for OS in Figure 2. The EAG's unadjusted Cox models are compared to the company MAIC in Table 1.

The survival curves show that tafasitamab + R^2 appears to be [redacted] epcoritamab for both PFS and OS. [redacted]. Both tafasitamab + R^2 and epcoritamab [redacted] to R-B and R-CHOP, but R^2 is [redacted] to both R-B and R-CHOP for PFS. Both unadjusted Cox models and MAICs show evidence [redacted], although the MAIC gives [redacted]. As discussed in EAG report Section 3.6, these illustrative and exploratory analyses should be interpreted alongside the more formal MAICs conducted by the company. Given the limited comparability between trial populations and the worse prognosis of EPCORE NHL-1 participants, and despite the limitations of the MAIC discussed above and in the EAG report, the EAG considers that the company's more conservative MAICs results should be preferred for decision making.

Table 1 Cox models and MAICs comparing tafasitamab+R^2 to epcoritamab in 3L+

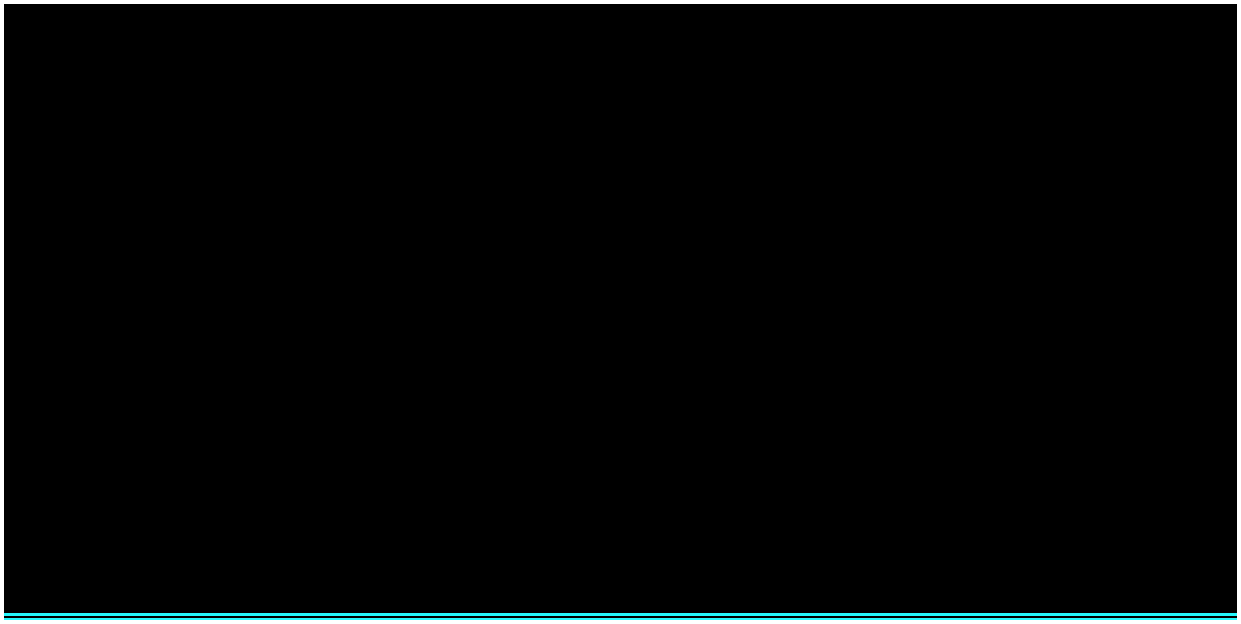
	Hazard ratios for tafasitamab+R^2 vs epcoritamab*	
	PFS (95% CI)	**OS (95% CI)**
EAG unadjusted Cox model	[redacted]	[redacted]
Company MAIC	[redacted]	[redacted]

Abbreviations: OS: overall survival; PFS: progression-free survival; 3L+, third and subsequent lines of therapy; MAIC: matching-adjusted indirect comparison.
* HR<1 favours tafasitamab+R^2

Figure 1 PFS for therapies in 3L+ patients

Abbreviations: R-B, rituximab with bendamustine, R-CHOP, rituximab + doxorubicin + vincristine + cyclophosphamide + prednisolone; R2: lenalinomide with rituximab

Figure 2 OS for therapies in 3L+ patients



Abbreviations: R-B, rituximab with bendamustine, R-CHOP, rituximab + doxorubicin + vincristine + cyclophosphamide + prednisolone

3 DESCRIPTION AND CRITIQUE OF ECONOMIC MODELLING

The External Assessment Group (EAG) was requested by NICE to undertake validity checks on the additional evidence submitted in the company's addendum, which incorporates epcoritamab as a comparator. Given the limited health economics resources available to the EAG, and the breadth of the company's response, the work undertaken does not constitute a full critique of the addendum. Instead, the EAG presents a high-level summary based on a limited inspection of the economic model and accompanying documentation.

The company has incorporated the MAIC results (Table 1) into the economic analysis by applying the estimated hazard ratios for progression-free survival (PFS) and overall survival (OS) to the relevant survival curves for tafasitamab + R². This approach follows the partitioned survival model (PSM) used in the company's base case and assumes proportional hazards (which is not tested). Consistent with the company's base case, treatment-effect waning is retained and modelled as an instantaneous loss of treatment effect at 5 years. Drug acquisition and administration costs for epcoritamab are based on the list price and assume costs associated with a simple intravenous infusion. Treatment duration is capped at 3 years, consistent with the NICE recommendation.

The EAG is broadly satisfied with the company's approach to incorporating evidence from the MAIC, notwithstanding the limitations of this analysis highlighted above. However, it has not been possible to undertake a comprehensive validation of the company's analysis. The EAG therefore makes no assurance as to the validity of the results presented. The EAG also makes the following observations:

- The life-year (LY) and quality-adjusted life-year (QALY) gains associated with epcoritamab appear to differ substantially from those reported in TA1139. Even when the model is calibrated to adopt the preferred assumptions in TA1139, the LY gains predicted by the company's analysis, 7.72 (undiscounted) differ materially from the 12.63 LYs reported in TA1139. This represents a marked difference in predicted survival benefit and suggests that the underlying model behaviour differs materially between the analyses. A more detailed examination of the modelling approaches adopted in TA1139 and in the company's addendum would be required to explain this discrepancy.

- The committee's decision in TA1139 appears to have been informed by a very large estimated QALY gain in favour of epcoritamab (over 4 QALYs compared with standard care). While the company do not present a fully incremental analysis including both epcoritamab and standard of care regimens, a comparison across pairwise analyses in the 3L+ population indicates that the model predicts R^2 to be superior to epcoritamab. The EAG acknowledges that the comparator structures differ between the analyses, with TA1139

modelling a basket of treatments as standard care rather than specific regimens. However, the magnitude of the difference in predicted outcomes again suggests important differences in the modelling approach that would require further explanation.

- The company suggests that their analysis based on the EAG's base-case lacks face validity because tafasitamab + R² is predicted to be less costly and less effective to epcoritamab. However, this result appears to be primarily driven by the model structure adopted and the assumptions regarding post-progression survival (PPS). The scenario presented by the company does not align with the EAG's preferred state transition model structure, because this structure is applied only to the tafasitamab + R² arm, while the epcoritamab arm retains the company's preferred PSM structure. An important implication of this is that, although PFS is shorter for epcoritamab, PPS is longer, resulting in a small net LY gain in favour of epcoritamab.

- The EAG emphasises that, given the limited follow-up and substantial uncertainty in the OS data, predictions regarding OS benefits should be structurally linked to PFS gains, and the same model structure should be applied across all treatment arms. The EAG therefore favours assumptions under which no additional PPS benefit is assumed for epcoritamab. While the EAG has not been able to implement this analysis due to resource constraints, the longer PFS for tafasitamab + R² would be expected to result in LY and QALY gains in favour of tafasitamab + R², consistent with the company's base-case analysis. The EAG does not consider the company's characterisation of the EAG base case to accurately reflect the EAG's preferred assumptions.

Overall, while the company has attempted to incorporate epcoritamab into the economic analysis using the available MAIC evidence, the EAG considers that the results presented in the addendum should be interpreted with caution. The EAG's review has been limited to high-level validity checks and has not included a full technical critique of the model or its implementation. In addition, the differences identified between the outcomes predicted in the company's analysis and those reported in TA1139, together with the structural issues noted above, indicate that further clarification of the modelling approach would be required before robust conclusions could be drawn regarding the relative cost-effectiveness of epcoritamab and tafasitamab + R².

3.1 Results

The EAG has re-analysed the company base case and selected scenario analyses as produced in Section 3.2 of the company evidence addendum and has incorporated patient access scheme (PAS) discounts for tafasitamab and epcoritamab, and available medicines procurement and supply chain (MPSC) prices.

As these results include confidential discounts, they are supplied in an appendix to this document.

Single Technology Appraisal

Tafasitamab with lenalidomide and rituximab for treating relapsed or refractory follicular lymphoma after 1 or more systemic treatments [ID6413]

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 Monday 23 February 2026** 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.

Issue 1 Duration of treatment effect

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Potentially misleading statement: EAG report page 91 *"These analyses suggest convergence of treatment effects for both PFS and OS from approximately two years onwards."* AND *"As such, the assumption of a full treatment effect persisting for five years, as applied in the company's base case, is difficult to reconcile with the observed data. While these analyses cannot determine the long-term pattern of waning, they do provide empirical support for exploring earlier and potentially less gradual attenuation than assumed by the company."*	Reword to reflect the unknown pattern of the observed hazards *"These analyses suggest convergence of treatment effects for PFS between 6 months and one year. After one year, the PFS hazards start to diverge between treatment arms. Conclusions from the OS hazard should be judged uncertain due to the number of events."* AND *"As such, the assumption of a full treatment effect persisting for five years, as applied in the company's base case, is unknown and no robust conclusion can be made on the gradual attenuation."*	The observed data does not provide enough evidence for a convergence of the hazards, specifically for the PFS hazards. In the company submission appendix (Appendix L.2.1. Progression-free survival), Figure 27 presents the inMIND PFS smoothed hazard plots. The hazards diverge during the first 6 months. They then become more similar, as noted by the EAG, but only for the next 6 months. At the 1-year mark (with 113 patients at risk in the tafasitamab plus R^2 arm and 79 in the R^2 arm), the hazards diverge again, with no sign of returning to similar levels.	We have updated the text to better reflect the observed hazard trends. As already acknowledged these data do not provide information on long-term hazard trends but provide some suggestion that convergence may take place prior to five years.

Issue 2 Proportion of PFS events that are death

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Incomplete statement EAG report page 92 *"Transitions from the PF state to progressed disease or death are informed by extrapolated PFS data from the inMIND trial, with a fixed proportion of PFS events assumed to represent death. Consequently, occupancy of the progression-free state and transitions to progressed disease are handled analogously to the PSM approach. The company assumes that the proportion of death events is the same for patients receiving tafasitamab plus R² and those receiving R² alone. Although the inMIND trial observed a higher proportion of PFS events resulting in death for tafasitamab plus R² ([redacted]%) than for R² ([redacted]%), the company applies a common fixed rate of [redacted]%, estimated by pooling data across both trial arms."*	To avoid misleading the committee, add a statement to reflect the alternative scenario provided by the company during the Clarification Questions stage. *"… the company applies a common fixed rate of [redacted]%, estimated by pooling data across both trial arms.* *At the clarification stage, the company presented a scenario, as requested by the EAG, showing the treatment-specific proportion of PFS events that were deaths, adjusted for COVID-related mortality. After excluding COVID-related deaths and other unexpected deaths, the proportions became more similar: [redacted] for tafasitamab plus R² and [redacted] for R²."*	The EAG report does not reflect that the company explained in the Clarification Response B1c that the observed differences across treatment arms are driven by COVID-related deaths, and the company provided an alternative scenario for treatment-specific proportions of PFS events that are deaths.	We have edited the text to acknowledge the scenario provided at clarification.

Issue 3 Post progression survival benefit

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 5.2.3 of the EAR, the EAG present their preferred base case, which should "represent use a plausible but reasonably optimistic set of assumptions". The EAG base case: • Uses HMRN data as the input for post-progression survival for both R2 plus chemotherapy and tafasitamab plus R2, which results in no PPS benefit for tafasitamab plus R2 • Estimates OS that does not align with the KM data for inMIND. These limitations have either not been considered	Within Section 5.2.3, a short paragraph on limitations of the preferred EAG assumptions should be provided.	The company's base case for modelling of PPS benefit for tafasitamab is based on: • inMIND early PPS data (Table 11 in the company response to EAG clarification questions) • A reduced histological transformation for tafasitmab patients (Section 2.6.9; Table 11, company submission, 0% vs 3.3% for tafasitamab plus R2 versus R2, respectively) • The dual-target mechanism for tafasitamab plus R2 (Section 1.2, company submission) • Mature 2L+ data from GADOLIN demonstrate that substantial PFS effects can translate into OS benefit with longer follow-up. (Section	The EAG explains in Section 4.2.5.5 why it does not consider a PPS benefit appropriate, noting the limited overall survival data, which show no statistically significant benefit, the substantial uncertainty associated with transposing PPS treatment effects observed in GADOLIN, and the limited evidence submitted on relative PPS benefits from inMIND. We have however edited section 4.2.5.5 to note the reduced transformation rate.

and/or are not highlighted in the report.		2.13.1.1, company submission) The EAG's base case does not consider these data/mechanisms of action reflecting a conservative approach when considering the benefits for tafasitamab plus R2	

Issue 4 Description of the expected PFS by the clinicians

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Error in the expected progression-free expected survival reported by the EAG EAG report page 90 *"For R^2, clinical expectations ranged from 5 to 15% at 5 years and 1 to 10% at 10 years."*	Amend the expected survival to reflect the clinical validation exercise performed by the company. *"For R^2, clinical expectations ranged from 5 to 10% at 5 years and 1 to 4% at 10 years."*	The values reported by the EAG do not match the values provided by the company in the company appendix (Appendix L.2.1. Progression-free survival - Page 128).	Edited as suggested

Issue 5 Description of extrapolated PFS curves

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Incomplete information EAG report page 90 *"The independently fitted log-logistic predicts 17.5% at 5 years and 5.2% at 10 years, compared with 19.5% and 3.7%, respectively, under the jointly fitted generalised gamma."* AND *"The independently fitted log-logistic predicts 8.7% at 5 years and 2.8% at 10 years, whereas the jointly fitted generalised gamma predicts 4.6% and 0.3% at 5 and 10 years, respectively."*	Add description of the features of the gamma curve as it is selected in the EAG base case. *"The independently fitted log-logistic predicts 17.5% at 5 years and 5.2% at 10 years, compared with 19.5% and 3.7%, respectively, under the jointly fitted generalised gamma, and 10.8% and 0.4% respectively based on the independently fitted gamma curve."* AND *"The independently fitted log-logistic predicts 8.7% at 5 years and 2.8% at 10 years, whereas the jointly fitted generalised gamma predicts 4.6% and 0.3% at 5 and 10 years, respectively. The independently fitted gamma curve results in a survival of 2.0% at 5 years, and 0.0% at 10 years."*	The EAG report does not describe the features of the independently fitted PFS gamma curve, which is selected as the EAG base case.	We have not edited this text as loglogistic rather than gamma function should have been included in the EAG base case. Results and text in section 5 have been updated accordingly. We apologise for this oversight.

Issue 6 The relative effectiveness of tafasitamab plus R^2 against relevant comparators

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report page 15 Issue 2 description and conclusion	To avoid misleading the committee, revise description and conclusion to more accurately represent the EAG analyses and discussion of this issue including: - Reference to the positive signals of an OS benefit for tafasitamab versus R-chemotherapy - Reference to the superior PFS benefit of R^2 vs R-chemotherapy as well as prior conclusions of TA627 supporting the conservative base case assumption of equivalence	Current conclusion does not include a summary of results as described in detail in Section 3.5.5. Without this inclusion, there is a possibility of misleading the reader.	Not a factual inaccuracy. The issue tables summarise key concerns the EAG has with the submission. They are not a summary of the evidence and should not be read independently of the report sections listed in the tables.

Issue 7 Misrepresentation of company conclusions on HRQL impact

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report page 49 *"The EAG agrees with the company that this suggests a limited impact of tafasitamab on HRQL, and that the magnitude of change observed over time is unlikely to be clinically meaningful."*	Revise paragraph to more accurately represent company conclusions in the main submission and clarification query responses. Suggested change: *"The EAG agrees with the company that this suggests a limited impact of tafasitamab on HRQL, and that the magnitude of change observed over time for progression-free patients is unlikely to be clinically meaningful."*	Current phrasing is a misinterpretation of company conclusions. While the impact is described as 'limited' in Section 3.4.1, this is taken out of context when described as the company conclusions on tafasitamab's impact on HRQL. In Section 2.6.7 the company conclusion is that in-trial HRQL analyses show no negative impact on patient HRQL which is a positive outcome with patients experiencing a significant clinical benefit with no detrimental impact to their HRQL. As discussed in Section 2.13.1.1, tafasitamab is expected to have a clinically meaningful benefit on patient HRQL due to its extension of progression-free living times. This is unlikely to be fully captured in the economic evaluation as discussed in the company	Not a factual inaccuracy. The wording of the sentence in EAG report page 49 closely reflects the conclusions of the most complete report of the HRQL results provided by the company, which includes several co-authors affiliated with the company (Strati et al. 2025). The reference has been added to the sentence to avoid any possible confusion.

		response to clarification question B12 a).	

Issue 8 Minor typographical / content errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report page 24 *"…with European Commission approval anticipated by end of"*	Amend sentence to reflect current status: *"…with European Commission approval received in January 2026"*	Incomplete and out of date sentence	This has been corrected.
EAG report page 24 *"The majority of patients (up to 70%) present with advanced-stage disease (Stage III/IV), while approximately 90–95% are diagnosed with low-grade disease (Grade 1–3A)."*	Remove sentence	Data repeated in subsequent (more detailed) paragraph.	Sentence removed.
EAG report page 25 *"While FL is commonly described as "slow growing", disease behaviour is highly heterogeneous. With*	Remove one of the two sentences highlighted in green.	Duplication of sentence in current paragraph.	Second sentence removed.

successive relapses, the disease often becomes more aggressive and increasingly resistant to treatment. The risk of histological transformation to more aggressive lymphoma, most commonly diffuse large B-cell lymphoma, is approximately 2–3% per year. Most patients with FL require multiple lines of systemic therapy over their lifetime. Prognosis worsens with each subsequent relapse or line of therapy as the disease becomes increasingly resistant to treatment. The rate of histological transformation to more aggressive lymphoma, most commonly diffuse large B-cell lymphoma, is estimated to be 2–3% annually."			
EAG report page 26 *… and clinical factors alone only have limited positive*	Rerun reference management software.	Unformatted references.	To check

predictive value {Jurinovic, 2016 #5;Merryman, 2025 #6}			
EAG report page 37, Table 6 *"…who had received at least prior line of systemic treatment"*	Update sentence as follows: *"…who had received at least one prior line of systemic treatment"*	Missing word in sentence	This has been corrected.
EAG report page 47 *"Peripheral oedema occurred more frequently with placebo plus R^2 than with tafasitamab plus R^2 (7% vs 13%, respectively)."*	Reorder data in line with sentence message: *"Peripheral oedema occurred more frequently with placebo plus R^2 than with tafasitamab plus R^2 (13% vs 7%, respectively)."*	Risk of misinterpretation	This has been corrected.
EAG report page 48 *"Events captured as AESIs included cytokine release syndrome ([redacted] vs [redacted]), infusion-related reactions ([redacted] vs [redacted]), tumour lysis syndrome ([redacted] vs [redacted]), and secondary primary malignancy ([redacted] vs [redacted])."*	Clarify order of data presented as follows: *"Events captured as AESIs included cytokine release syndrome ([redacted] vs [redacted]), infusion-related reactions ([redacted] vs [redacted]), tumour lysis syndrome ([redacted] vs [redacted]), and secondary primary malignancy ([redacted] vs [redacted]) in the tafasitamab plus R^2 vs placebo plus R^2 arms, respectively."*	Risk of misinterpretation	Edited as suggested.
EAG report page 48	Remove paragraph.	Duplication of text / data (more detailed) included in	Paragraph deleted.

"The company states that numerical differences in adverse event rates were small and did not account for longer treatment duration in the tafasitamab plus R^2 arm . In the inMIND publication, treatment exposure was similar between groups, with a median of 12 cycles (range 1–12) in the tafasitamab arm and 11 cycles (range 1–12) in the placebo arm."		paragraph 2 on previous page (page 47).	
EAG report page 51 *"Follow-up times differed across trials with shorter median follow-up…"*	Add clarification on follow-up time as follows: *"Follow-up times for OS differed across trials with shorter median follow-up…"*	Risk of misinterpretation	Clarification added.

Issue 9 Data / cross-reference errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report page 37, Table 6 Period of recruitment: 16th April to 23rd February 2024	Correct dates as follows: Period of recruitment: 16th April to 10th August 2023	Data error 23rd February 2024 is the primary analysis data cut off date	Thank you, this has been corrected.
EAG report page 40 *"The reported mean age of inMIND patients was [redacted]"*	Correct data as follows: *"The reported mean age of inMIND patients was [redacted]"*	Data error Current data are for the 2L/3L cohort of patients randomised to tafasitamab (n = [redacted]) and not the full trial population	Corrected.
EAG report page 40 *"…HMRN patients receiving R-CHOP in 2L ([redacted]) and 3L ([redacted])"*	Correct data as follows: *"…HMRN patients receiving R-CHOP in 2L ([redacted]) and 3L ([redacted])"*	Data error	Corrected.
EAG report 43 *"… r=0.483 in R/R FL (p<0.001 for both)."*	Correct data as follows: *"… r=0.438 in R/R FL (p<0.001 for both)."*	Data error	Corrected.
EAG report 44	Correct cross-reference as follows: *"Table 7 shows that the most common subsequent treatments were…"*	Cross-reference error	Corrected.

"Table 4 shows that the most common subsequent reatments were…"			
EAG report page 51 *"HMRN also covered a significantly longer period (from 2005 to 2023) than inMIND (median follow-up NR)"*	Correct data as follows: *"HMRN also covered a significantly longer period (from 2005 to 2023) than inMIND (median follow-up: 15.3 months)"*	Data error	The sentence was meant to state that the median follow-up duration is unknown for HMRN. This has been clarified to avoid confusion.
EAG report page 65, Table 9 GADOLIN MAIC results for TTNT presented in table	GADOLIN MAIC results for TTNT are not available. Results presented are unweighted MAIC results for PFS and need replacing with 'NA'	Data error	Not a factual inaccuracy: these results were extracted from the company's submitted ITC report, Table 28.
EAG report page 106 *"Table 23: Tafa + R^2 Incremental costs (£) equal [redacted]"*	Correct data as follows: "[redacted]	Data error	We have checked this scenario, and the results appear to be correct. When generating these results we have used Use R2 inMIND extrapolations for R-chemotherapies as we understood this reflected the company's base case following clarification.

Issue 10 Incorrect / updated confidential marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
EAG report page 45, Table 7 Table legend	Treatment details in legend key also need marking up as confidential	**Key:** [redacted]; CI, confidence interval; [redacted]; SD, standard deviation.	Corrected.
EAG report page 55 Treatment-related adverse event (TRAE) data	Some TRAE data unpublished with no known plans to publish so need marking up as confidential	The most frequent TRAEs were [redacted] and [redacted], with [redacted] occurring more frequently in the tafasitamab plus R^2 arm ([redacted]). Infusion-related reactions occurred in [redacted] of participants receiving tafasitamab plus R^2 and [redacted] receiving placebo plus R^2.	Corrected.
EAG report pages 54-55 Estimated sample size (ESS) data	ESS data unpublished with no know plans to publish so need marking up as confidential	ESS ranged from [redacted] across the MAICs. For the MAIC comparing tafasitamab plus R^2 with epcoritamab, the ESS after weighting was [redacted] of the tafasitamab plus R^2 subpopulation, indicating some overlap for the covariates that were measured in both trials. In all other MAICs, the overlap between the tafasitamab plus R^2 arm	Corrected.

		and the comparator trials was more limited, as reflected by the ESS, which ranged from [redacted] of the unweighted sample size of the tafasitamab plus R^2 arm in all but one MAIC.	
EAG report, Section 3.6 Additional work on clinical effectiveness done by the EAG	Work conducted on unpublished clinical data with no known plans to publish so need marking up as confidential	Figure 2, Figure 3 and Table 11 content all need marking up	We note it is not clear whether material here is confidential as it is an EAG analysis and not derived from the company submission. We have marked Figures 2 and 3 as confidential as a precaution. Table 11 is purely an EAG analysis, so is not confidential.
EAG report, Pages 72, 81 & 120 OS follow-up and event numbers	Data now published with inMIND final manuscript published in the Lancet journal so confidential marking can be removed.	Page 72: As acknowledged by the company, the OS data from inMIND are immature, with only 15 death events in the tafasitamab plus R^2 arm and 23 in the R^2 arm, and a median follow-up of 15.3 months. Page 81: The observed OS data from the inMIND trial was obtained from the latest data cut for a median follow-up of 15.8 months in the tafasitamab plus R^2 arm and 14.6 months in the R^2 arm. Data was immature with on 15/273 events in the	Corrected.

		tafasitamab plus R^2 months and 23/275 in the R^2 arm. Page 120: As acknowledged by the company, the OS data from inMIND are immature, with only 15 death events in the tafasitamab plus R^2 arm and 23 in the R^2 arm, and a median follow-up of 15.3 months.	

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EAG ADDENDUM
Update to FAC results:

Tafasitamab with lenalinomide and rituximab for treating relapsed or refractory follicular lymphoma after 1 or more systemic treatments [ID6413]

Produced by
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Declared competing interests of the authors

None

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.

Note on the text

All commercial-in-confidence (CON) data have been highlighted in blue and underlined.

Copyright statement

Table of Contents

1 OVERVIEW

This addendum to the External Assessment Report (EAR) report presents the updated results that were inadvertently not updated at the time of the Factual Accuracy Check (FAC). This omission was also identified by the company prior to NICE committee meeting. The EAG has also updated Tables based on the decision modifiers (Section 5.3 in the EAG report).

2 DESCRIPTION AND RESULTS

The EAG has re-analysed all EAG exploratory analyses, the EAG base case and subgroup analyses (3L+ subgroup and 2L-only subgroup) and provides updated Tables, as needed, in Section 2.1 below.

The equivalent results with confidential patient access scheme (PAS) discounts for tafasitamab, and available medicines procurement and supply chain (MPSC) prices are presented in a confidential appendix to this addendum.

2.1 Updated Tables

The updated tables are based on the EAG base case and subgroup analyses (3L+ subgroup and 2L-only subgroup) using the separately fitted *log-logistic* distribution for progression free survival (PFS) curves. These results also impact the decision modifier Tables. These are also supplied here for completeness.

Please note that these Tables are numbered here using the same numbers as in the EAG report (Dated: 16/02/2026) to aid comparison.

Table 30 EAG's preferred model assumptions fully incremental analysis (Deterministic)

Technology	Total		Incremental		Fully incremental ICER
	Costs	QALYs	Costs	QALYs	
R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£73,312

Abbreviations: EAG, evidence assessment group, ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-years; R^2, lenalidomide and rituximab; Tafa, Tafasitamab.

Table 32 EAG's preferred model assumptions for the 3L+ subgroup (Deterministic)

Technology	Total		Incremental		ICER (£ per QALY)
	Costs	QALYs	Costs	QALYs	
R^2	[redacted]	[redacted]			
Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£58,883

Abbreviations: EAG, evidence assessment group, ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-years; R^2, lenalidomide and rituximab; Tafa, Tafasitamab.

Table 33 EAG's preferred model assumptions for the 2L-only subgroup (Deterministic)

Technology	Total		Incremental		ICER (£ per QALY)
	Costs	QALYs	Costs	QALYs	
R^2	[redacted]	[redacted]			
Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£109,646

Abbreviations: EAG, evidence assessment group, ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-years; R^2, lenalidomide and rituximab; Tafa, Tafasitamab.

Table 34 EAG's preferred model assumptions for the 2L-only subgroup (Deterministic)

Technology	Total		Incremental		Fully incremental ICER
	Costs	QALYs	Costs	QALYs	
R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	-
R^2	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
Tafa +R^2	[redacted]	[redacted]	[redacted]	[redacted]	£111,741

Abbreviations: EAG, evidence assessment group, ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-years; R^2, lenalidomide and rituximab; Tafa, Tafasitamab.

Table 35 Summary of QALY shortfall analysis

	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY Shortfall
Company base case (per model)				
R-CHOP	10.81	[redacted]	[redacted]	[redacted]
R^2	10.81	[redacted]	[redacted]	[redacted]
R-Benda	10.81	[redacted]	[redacted]	[redacted]
R-CVP	10.81	[redacted]	[redacted]	[redacted]
Company base case (Using QALY shortfall calculator)				
R-CHOP	11.30	[redacted]	[redacted]	[redacted]
R^2	11.30	[redacted]	[redacted]	[redacted]
R-Benda	11.30	[redacted]	[redacted]	[redacted]
R-CVP	11.30	[redacted]	[redacted]	[redacted]
EAG base-case (Using QALY shortfall calculator)				
R-CHOP	11.30	[redacted]	[redacted]	[redacted]
R^2	11.30	[redacted]	[redacted]	[redacted]
R-Benda	11.30	[redacted]	[redacted]	[redacted]
R-CVP	11.30	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; QALY, Quality Adjusted Life Years; R^2, lenalidomide and rituximab; Tafa, Tafasitamab.

Table 37 Summary of company's and EAG's base-case QALY shortfall analyses and preferred QALY weighting

-	Expected total QALYs for the general population	Expected total QALYs for people living with a condition on current treatment	Absolute QALY shortfall	Proportional QALY shortfall	Preferred QALY weight
Company's base case	10.81	[redacted]	[redacted]	[redacted]	None
EAG's base case	11.30	[redacted]	[redacted]	[redacted]	None

Abbreviations: EAG, External Assessment Group; QALY, Quality Adjusted Life Years;

Committee Briefing

Explanation

This page details the Managed Access Team's overall assessment on whether a medicine could be suitable for Managed Access and if data collection is feasible. The feasibility assessment does not provide any guidance on whether a medicine is a cost-effective, or plausibly cost-effective, use of NHS resources. This document should be read alongside other key documents, particularly the company's evidence submission and External Assessment Group (EAG) Report. Further detail for each consideration is available within the separate tabs.

The feasibility assessment indicates whether the Managed Access Team have scheduled to update this document, primarily based on whether it is undertaking actions to explore outstanding issues. There may be other circumstance when an update is required, for example when the expected key uncertainties change or a managed access proposal is substantially amended. In these cases an updated feasibility assessment should be requested from the Managed Access Team.

Topic name: **Tafasitamab with lenalidomide and rituximab for treating relapsed or refrac**
Topic ID: **6413**
Managed Access Lead: **Sarika Paul**
Date of assessment(s): **12/03/2026**

Feasibility of successful managed access	Comments / Rationale	
Yes	Rationale for rating	There is a managed access proposal that seems well place to collect appropriate data to help resolve the evidence uncertainties.
	Previous ratings and rationale for change	

Managed Access Proposal	Yes	
Managed Access Team input at Committee meeting	High	As there is a managed access proposal an analyst will be present at the meeting and available to answer questions

Area	Rating	Comments / Rationale
Is the technology considered a potential candidate for managed access?	Yes	As a cancer drug, this technology is eligible for reimbursement through the CDF, and a proposal has been made to enable this
Are there outstanding uncertainties that could be resolved with further data collection?	High	Many of the identified uncertainties relate to the immaturity of the OS data from the inMIND trial. Further data collection from this trial, and addittional data from SACT and Blueteq will help resolve these evidence uncertainties.
Can data collection from ongoing clinical trials and RWE sources resolve relevant uncertainties?	Yes	The ongoing inMIND trial will be able to provide data that is at least 4 years more mature than the data cut in the submission. The company also propose up to 4 years of SACT data collection which will provide RWE on overall survival, and blueteq critieria will provide information on patient demographics and clinical characteristics.
Are there any other points to note that suggest RWE data collection may be beneficial or challenging in resolving uncertainties?	High	Yes, the company propose using SACT and blueteq data to help redce uncertainty during a period of managed access
Are there any other substantive issues (excluding price) that are a barrier to a MAA?	No	None identified

Key questions for committee if Managed Access is considered	
1	
2	
3	

4	
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6	

Highlighted uncertainties, other issues or ongoing Managed Access Team actions	
1	
2	
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Commissioner Ops Briefing

Explanation

This page guides the discussion between the Managed Access Team and partner organisations at Managed Access Operational meetings. It provides a summary of the MAT's overall assessment on whether a medicine could be suitable for Managed Access and if data collection is feasible. It is updated with key issues raised by either MAT or the other participants in those meetings. This page is not aimed at the Committee or other readers, and may make points that seem irrelevant outside of the target audience, but should contain no confidential information. As with the overall feasibility assessment, it does not provide any guidance on whether a medicine is a cost-effective, or plausibly cost-effective, or use of NHS resources. This document should be read alongside other key documents, particularly the company's evidence submission and External Assessment Group (EAG) Report. Further detail for each consideration is available within the separate tabs.

Whilst a rationale is provided, in general the ratings for each area:
Green - No key issues identified
Amber - Either outstanding issues that the Managed Access team are working to resolve, or subjective judgements are required from committee / stakeholders (see key questions)
Red - The managed access team does not consider this topic suitable for a managed access recommendation.

The Managed Access Team may not assess other areas where its work has indicated that topic is not suitable for a managed access recommendation.

Topic name:	**Tafasitamab with lenalidomide and rituximab for treating relapsed or refract**
Topic ID:	**6413**
Managed Access Lead:	**Sarika Paul**
Date of assessment(s):	**17/02/2026**

Feasibility of successful managed access	Comments / Rationale	
Yes	Rationale for rating	There is a managed access proposal that seems well place to collect appropriate data to help resolve the evidence uncertainties.
	Previous ratings and rationale for change	

Managed Access Proposal	Yes	
Managed Access Team input at Committee meeting	High	As there is a managed access proposal an analyst will be present at the meeting and available to answer questions

Area	Rating	Comments / Rationale
Is this technology eligible for managed access through the CDF or IMF?	Yes	As a cancer drug, this technology is eligible for reimbursement through the CDF, and a proposal has been made to enable this
What is the likelihood that further data collection could sufficiently resolve key uncertainties?	High	Many of the identified uncertainties relate to the immaturity of the OS data from the inMIND trial. Further data collection from this trial, and addittional data from SACT and Blueteq will help resolve these evidence uncertainties.
Are data sources are available for data collection during a managed access period? Will these sources feasibly resolve the key uncertainties?	Yes	The ongoing inMIND trial will be able to provide data that is at least 4 years more mature than the data cut in the submission. The company also propose up to 4 years of SACT data collection which will provide RWE on overall survival, and blueteq critieria will provide information on patient demographics and clinical characteristics.
Is RWE data collection within managed access feasible?	High	Yes, the company propose using SACT and blueteq data to help redce uncertainty during a period of managed access
Are there any other substantive issues (excluding price) that are a barrier to a MAA?	No	None identified

Points raised by MAT	
1	Do NHSE colleagues have any information or thoughts on the addittional capacity required for tafasitmab infusions compared to rituximab + lenolidomide? Is this a barrier to use?
2	Do NHSE colleagues have thoughts on if SACT data would be useful to identify differences in efficacy between 2L and 3L treatment?
3	
4	

5	
6	

Points raised by managed access Ops Group	
1	The addittional infusion time would be 1.5-2 hours on top, and so NHSE colleagues do not consider this a barrier to use
2	NHSE colleagues note that blueteq criteria can record what line of treatment it is prescribed as, and then patients can be linked to SACT.
3	
4	
5	
6	

Early Identification for Managed Access

Explanation on criteria
These criteria should be met before a technology can be recommended into managed access through the CDF or IMF. To give a 'high' rating, the Managed Access Team should be satisfied that it can be argued that the technology meets the criteria. Companies interested in managed access must engage early with NICE and demonstrate that their technology is suitable for managed access.

Date agreed with NHSE	02/03/2026

Is this technology eligible for managed access through the CDF or IMF?	
Rating	**Rationale**
Yes	As a cancer drug, this technology is eligible for reimbursement through the CDF, and a proposal has been made to enable this

Uncertainties

Explanation

This page details the Managed Access Team's assessment on whether data collection could sufficiently resolve key uncertainties through further data collection within managed access. The overall assessment is the key judgement from the Managed Access Team.

The Managed Access Team will justify its decision, but broadly it is a matter of judgement on whether the further data collection could lead to a positive NICE decision at the point the technology exits managed access. For this reason individual uncertainties that have a higher impact on the ICER have a greater impact on the overall rating.

Further detail is available on each uncertainty identified primarily informed from a company's managed access proposal, the External Assessment Group (EAG) report, judgements from the NICE Managed Access Team, and where available directly from NICE committee deliberations. The likelihood that data could sufficiently resolve each specific outcome is informed both by the expected primary data source in general (as detailed in the separate tab) and specifically whether the data collected is expected to sufficiently resolve that uncertainty.

What is the likelihood that further data collection could sufficiently resolve key uncertainties?	
Rating	**Rationale**
High	Many of the identified uncertainties relate to the immaturity of the OS data from the inMIND trial. Further data collection from this trial, and addittional data from SACT and Blueteq will help resolve these evidence uncertainties.

Key Uncertainties

Number	Title	Summary of issue	Impact on ICER	Data available to resolve uncertainty	Data collection in company proposal	Resolvable with managed access	Managed Access Team view on feasibility
EAG1	The overall survival benefit of tafasitamab is highly uncertain.	The clinical evidence for tafasitamab plus rituximab and lenalinomide (R2) is based on the interim results of inMIND trial, an ongoing, phase 3 RCT comparing tafasitamab plus R2 with placebo plus rituximab and lenalinomide (R2), that included 548 patients with relapsed or refractory (R/R) follicular lymphoma (FL). At the February 2024 data cut, with a median follow-up of 15.3 months, only 38 death events were observed and median overall survival (OS) was not reached in either arm. While there was some evidence of improved OS with tafasitamab plus R2 when compared to placebo plus R2 it was not statistically significant. Data are limited by significant immaturity, which preclude any meaningful interpretation. It is uncertain whether progression-free survival (PFS) benefits will translate into a longer-term OS benefit for tafasitamab plus R2. Evidence from trials in FL indicates that PFS may only be a weak surrogate predictor of OS, although this evidence has limitations.	In a scenario analysis where no OS benefit is modelled, the ICER increases substantially and would impact decision making.	Substantially more mature data from inMIND is required to show that tafasitamab plus R2 leads to clinically significant improvements in OS compared with R2. Additional data from SACT may be beneficial to help generalisability and to validate the trial, if it is collected over a long enough period.	Yes - there is further data from the inMIND trial, and the company propose up to 4 years of SACT data collection including OS	High	There is a managed access proposal to allow data collection to help resolve this uncertainty.
EAG2	The relative effectiveness of tafasitamab + R2 against most comparators is highly uncertain	inMIND only included comparator evidence for lenalidomide + rituximab (R2). No randomised comparisons were available between tafasitamab + R2 and all other comparators relevant to the decision problem, notably rituximab+chemotherapy (R-chemotherapy) regimens. Due to the limited evidence, all indirect comparisons were informed by unanchored matching-adjusted indirect comparisons (MAICs) for OS, PFS and time-to-next treatment (TTNT). All MAICs have significant limitations and may not provide reliable estimates of relative effectiveness. None of the MAICs could account for all relevant prognostic factors and treatment effect modifiers, and therefore failed to meet a key assumption. All studies were unblinded and had design limitations. Substantial differences in trial design and populations limited their comparability. OS data was based on few events and was generally immature, and OS results were potentially confounded by subsequent therapies that may not reflect NHS practice. Some MAIC results may lack face validity, when compared to previous STAs. The direction and magnitude of bias due to these limitations is highly uncertain. The company model makes the “conservative” assumption that all R-chemotherapy options have the same effectiveness and safety as R2 on the basis that R-chemotherapy is expected, based on past assessments, to be worse than R2. Both EAG and company clinical advisers consider this assumption to have some problems; it does not fully concur with the findings of adjusted and unadjusted indirect comparisons.	Not quantified	Sufficiently longer-term OS evidence would address the issue of OS immaturity, and Cancer Drugs Fund (CDF) data would potentially address confounding due to subsequent non-routine therapies; however, future evidence would be unlikely to address most of the limitations inherent to the indirect comparisons.	Yes - there is further data from the inMIND trial, and the company propose up to 4 years of SACT data collection including OS	Medium	Data collection in managed access could partially resolve this uncertainty. in regard to the OS benefit of tafasitamab + R2, but it would not help with the uncertainty around the indirect comparisons.

EAG3	Most appropriate model structure and surrogacy assumptions	The company's base-case analysis uses a partitioned survival model (PSM) in which the magnitude of modelled overall survival benefits is derived directly from extrapolated OS data from the inMIND trial. However the EAG considers it inappropriate to directly infer the magnitude of OS benefit from the available data. Instead, the EAG prefers a state-transition model (STM) structure in which progression-free survival PFS serves as the primary driver of modelled survival benefits. This approach provides a more structured framework for estimating OS benefits and makes the assumptions underlying the PSM, specifically the implied surrogate relationship between PFS and OS, more explicit. The EAG notes, however, that evidence supporting PFS as a surrogate for OS is generally weak and associated with substantial uncertainty. Therefore, the EAG's preference for an STM approach is contingent on the assumption that some OS benefit exists.	This would increase the ICER and would impact decision making	Longer-term OS evidence is necessary to establish the magnitude of any OS benefit, and would also support assumptions relating to the predictive value of PFS benefits already observed.	Yes - there is further data from the inMIND trial, including both OS and PFS. The company also propose up to 4 years of SACT data collection including OS, however PFS is not collected in SACT.	Medium	Data collection in managed access could partially resolve this uncertainty by providing further OS data from the trial and SACT, and PFS data from the trial. This would help select the most appropriate modelling approach upon exiting managed access. However committee discussion will be needed to determine the appropriate model structure in this appraisal.
EAG4	Progression free survival extrapolation	The company used a joint modelling approach to extrapolate PFS, estimating a single set of baseline survival parameters across treatment arms rather than fitting separate models to each arm. The company's preferred PFS extrapolation is the generalised gamma distribution. The EAG considers the company's overall approach to selecting an appropriate parametric extrapolation to be broadly valid and consistent with best practice, but notes that, while joint modelling is methodologically acceptable, the rationale for its use appears to be driven more by concerns regarding OS extrapolations than by the PFS data itself. The EAG therefore considers it appropriate to also explore a range of separately fitted parametric functions. The EAG preference is to use a separately fitted log-logistic model to extrapolate PFS. Amongst the jointly fitted models, the EAG agrees that the company's preferred jointly fitted generalised gamma is the most appropriate.	This would increase the ICER but would not impact decision making	Longer-term PFS may help better inform decisions about the most appropriate PFS extrapolation.	Yes - there is further data from the inMIND trial, including PFS.	High	While further data would help inform decisions about the most appropriate PFS extrapolation, committee discussion can also be used to determine the most appropriate modelling approach with the data currently available.
EAG5	Post progression survival assumptions	In the company's scenario analysis, several alternative approaches to modelling PPS are explored, drawing on data from the Haematological Malignancy Research Network (HMRN) and GADOLIN trials. The company's preferred approach is based on a weighted analysis of both trials and models a PPS survival benefit in rituximab-refractory patients. The EAG has several concerns regarding the company's preferred approach. These include questions about its consistency with the current OS data and the rationale for using an STM framework, the lack of direct evidence supporting PPS benefits, and the absence of a clear biological justification. The EAG is particularly concerned that the company's preferred approach assumes PPS benefits observed in the GADOLIN trial can be applied to the current context, which lacks a clear clinical rationale. The EAG is also concerned that the company's method for estimating PPS survival based on subtracting median OS from median PFS may misrepresent mean survival and time-dependent risks, making it an imprecise and potentially misleading method for modelling transitions. The EAG preference is to use data from the HMRN database to model PPS and to assume no PPS benefit.	This would increase the ICER and would impact decision making	The current uncertainty in PPS assumptions largely reflects the lack of mature OS data from inMIND. Additional follow-up of this data will therefore be necessary to meaningfully inform and update the current assumptions.	Yes - there is further data from the inMIND trial, and the company propose up to 4 years of SACT data collection including OS	High	Data collection in managed access could help resolve this uncertainty by providing further OS data from the trial and SACT.
EAG6	Waning assumptions	The company applies waning assumptions to both PFS and OS, assuming a five-year period of full treatment effect followed by a five-year gradual waning of the effect. These assumptions are informed by those used in TA627, which assumed a five-year full treatment effect followed by instantaneous waning, along with clinical expert opinion. The EAG agrees with the company that waning of PFS and OS treatment effects is appropriate and that gradual waning is more clinically plausible than an instantaneous loss. The EAG is, however, concerned about both the duration of the full treatment effect period and the length of the waning period. The company base-case assumptions imply some partial treatment effect for a total of ten years, which is well beyond the maximum follow-up of the trial (approximately 2.5 years).	In scenario analysis, assuming 2 years full effect followed by 3 years waning, there is a large increase in the ICER which would impact decision making	Further, data collection for both OS and PFS would also help better guide the most appropriate waning assumptions.	Yes - there is further data from the inMIND trial, including both OS and PFS. The company also propose up to 4 years of SACT data collection including OS, however PFS is not collected in SACT.	Medium	Data collection in managed access could help resolve this uncertainty by providing further OS data from the trial and SACT. A normal MAA is up to 5y long but can be longer if necessary, with strong justification. Within the normal MAA period of 5 y, further data would help but not fully resolve uncertainty.
EAG7	Joint modelling of 2L and 3L+	Aligning with the marketing authorisation, the company's base-case analysis considers the combined 2L+ population. While the EAG considers this approach reasonable, it notes that aggregating across lines of therapy may obscure important differences in the cost-effectiveness of tafasitamab plus R2. Cost-effectiveness is likely to vary by line of therapy because of differences in treatment effect, prognosis, and the relevance of comparators. The EAG suggest that the substantial difference in estimated cost-effectiveness suggests that an optimised recommendation may warrant consideration.	In Scenario analysis, considering the 2L and 3L+ populations separately, the ICER for each subgroup is substatially different.	Additional evidence or analyses is unlikely to help resolve this issue.	This is not mentioned in the managed access proposal, however clarification with NHSE colleagues states that it is possible to use blueteq criteria to record line of treatment, which could be linked with SACT outcomes for patients.	Medium	Blue teq criteria, linked with SACT data, may help identify which line of therapy people recieve the therapy as, and some clinical outcomes.
EAG8	The applicability of the inMIND population to clinical practice is uncertain	inMIND includes a population that is likely to be younger on average than in NHS practice. It is unclear whether the proportion of patients with POD24 in inMIND reflects NHS evidence for R/R FL patients. The proportion of patients who are refractory to rituximab is substantially higher in inMIND than in the HMRN database, although the extent to which the HMRN data provided by the company reflects the entire NHS population of R/R FL who would be eligible for tafasitamab plus R2 is uncertain.	This causes a small increase in the ICER, but is unlikely to impact decision making.	CDF data for tafasitamab plus R2, and NHS England data on the characteristics of the population receiving comparator therapies relevant to the decision problem would allow for a more complete assessment of the applicability of the inMIND population to NHS practice.	Yes - the managed access proposal includes collection of NHSE patient characteristics and demographics using blueteq criteria	High	

EAG9	Calculation of the proportion of PFS events that are deaths	The company assumes that the proportion of death events is the same for patients receiving tafasitamab plus R^2 and those receiving R^2 alone, and therefore pools data across treatment arms in the inMIND trial to estimate this parameter. The EAG considers this approach inappropriate, as it is inconsistent with the observed trial data, which show a higher proportion of PFS events resulting in death in the tafasitamab plus R^2 arm. Moreover, given the additional toxicity associated with the triplet regimen, a higher risk of death prior to progression with tafasitamab plus R^2 is clinically plausible and cannot be ruled out. The EAG therefore prefers to use arm-specific rates based on the observed data, which more accurately reflect the trial outcomes and associated mortality risks.	This causes a small reduction in the ICER, but is unlikely to impact decision making.	Further PFS evidence would help refine estimates of proportion of death events	Yes - there is further data from the inMIND trial, including both OS and PFS. The company also propose up to 4 years of SACT data collection including OS, however PFS is not collected in SACT.	High	
EAG10	Relative dose intensity and chair capacity	Delivery of tafasitamab plus R^2 raises important capacity concerns. The regimen requires seven additional cycles of IV infusion, longer infusion times, and greater transfusion use, placing additional pressure on day-unit services. This may impact the uptake of tafasitamab plus R^2. Addittional the EAG note that the observed RDI for tafasitamab indiactes that an increasing proportion of patients do not receive all scheduled infusions as treatment progresses. In terms of the model, the primary concern is that the application of a single, constant average RDI to adjust costs does not reflect this time-dependent decline in drug administration. In practice, early cycles appear to be delivered at close to full intensity, whereas later cycles involve materially fewer administered doses. As a result, this approach may underestimate both drug acquisition and administration costs. The EAG prefers to apply treatment cycle-specific RDI to more accurately account for the resource implications of missed doses.	This causes a small reduction in the ICER, but is unlikely to impact decision making.	Input from NHS England on day case capacity may be informative to address capacity concerns.	This is not mention in the managed access proposal, and further data collection is unlikely to help resolve the uncertainty.	Low	The NICE managed access team asked NHSE this question, they considered it would be an addittional 1-2 hours infusion time.

Data Collection

Explanation

This tab collects information on the data sources that could be available for further data collection during a period of managed access, including any ongoing clinical trials, NHS registry data sets, and non-registry data sets. Analysts should assess the availability of this data to answer key uncertainties.

Are data sources are available for data collection during a managed access period? Will these sources feasibly resolve the key uncertainties?	
Rating	**Rationale**
Yes	The ongoing inMIND trial will be able to provide data that is at least 4 years more mature than the data cut in the submission. The company also propose up to 4 years of SACT data collection which will provide RWE on overall survival, and blueteq critieria will provide information on patient demographics and clinical characteristics.

Existing or proposed clinical trials	
Name and registry ID of trial	A Phase 3 Study to Assess Efficacy and Safety of Tafasitamab Plus Lenalidomide and Rituximab Compared to Placebo Plus Lenalidomide and Rituximab in Patients With Relapsed/Refractory (R/R) Follicular Lymphoma or Marginal Zone Lymphoma. (InMIND) ClinicalTrials.gov ID NCT04680052
Is trial proposed for managed access?	Yes
Link to clinicaltrial.gov	https://www.clinicaltrials.gov/study/NCT04680052
Start date	Apr-21
Anticipated completion date	Aug-28
Data cut presented to committee	Feb-24
Data collection timeline	Final analysis will be conducted when the data is at least 4 years more mature than the data cut submitted to the committe. All participants will have a minimum of 5 years follow-up.
Description of trial	A total of 654 patients were enrolled in the study and randomised, of which 548 had R/R FL and were included in the full analysis set (FAS) and 546 were included in the Safety Analysis Set (SAS). The primary endpoint of the inMIND trial was PFS by investigator (INV) assessment, in the FL population. PFS is defined as the time from randomisation to first documented disease progression, or death from any cause, whichever occurs first. Key secondary endpoints included positron emission tomography-complete response (PET-CR) rate by INV assessment in the fluorodeoxyglucose (FDG)-avid FL population; and OS in the FL population. After a median follow-up of 14.1 months for PFS, the inMIND study met its primary endpoint of prolonging PFS in R/R FL. The addition of tafasitamab to R2 resulted in a significant and clinically meaningful improvement in PFS with a 57% reduction in the risk of progression, relapse or death (HR: 0.43; 95% CI: 0.32, 0.58; p < 0.0001). The median period of progression-free living was increased by over 8 months versus placebo + R2 (tafasitamab + R2: 22.4 months; placebo + R2: 13.9 months). At the time of primary analysis, overall survival was assessed against a pre-defined futility threshold. As FL is a slow progressing cancer, OS data were still immature with 38 death events and a median follow-up of 15.3 months,
Link(s) to published data	

NHS registry data	
Name of registry	SACT
Is registry proposed for managed access?	Yes
Mandated data collection?	Yes
Available to use?	Yes
Data items already collected	Yes - the principle data field from SACT necessary to resolve uncertainty will be OS.
Issues raised by committee or stakeholders	
Data collection timeline	The company proposal suggests up to 4 years of SACT data collection.

Data collected in clinical practice

SACT

Explanation on criteria

This tab collects more detailed information on the data within registries, and on the registries themselves. It will only be important to fill these firelds in if a managed access agreement is likely to happen.

Is RWE data collection within managed access feasible?		
Overall Rating	**Rationale/comments**	
High		Yes, the company propose using SACT and blueteq data to help redce uncertainty during a period of managed access

Data Source		
Relevance to managed access		
Existing, adapted, or new data collection	Existing	NHS England's SACT dataset is an established mandatory dataset
Prior experience with managed access	High	NHS England's SACT Team have extensive experience with managed access in the Cancer Drugs Fund
Relevance of existing data items	High	0
If required, ease that new data items can be created / modified	Not applicable	No additional data items to be included
How quickly could the data collection be implemented	Normal timelines	SACT is an existing mandatory dataset. No additional time is required to implement data collection in clinical practice
Data quality		
Population coverage	High	SACT is an existing mandatory dataset that will capture the entire population treated with the medicine in clinical practice
Data completeness	High	NHS England's SACT Team have established processes in place to ensure high data completeness. Cohort of interest is identified by Blueteq records and NHS Digital follow-up with trusts where data is missing
Data accuracy	High	SACT is an established mandatory dataset and there is a good understanding of using SACT in clinical practice. NHS England's SACT Teaml have a dedicated help desk and follow-up with trusts where data submitted is ambiguous or lacks face validity
Data timeliness	High	Trusts submit records to the SACT dataset monthly
Quality assurance processes	Yes	Dedicated SACT data liaison officers and SACT helpdesk. Established process to ensure data quality available at: http://www.chemodataset.nhs.uk

Data availability lag	Low	Four months are required from data collection to allow for data to be uploaded to SACT, follow-up of missing data, and analysis and production of NHS England's SACT Team's report
Data sharing / linkage		
New data sharing arrangements required?	No	Data sharing agreements between NHSE, SACT, blueteq and Personal Demographics Service (vital status) have been previously established
New data linkages required?	No	Data linkage has been previously established to allow NHSD to link blueteq applications to SACT activity to identify the cohort of interest.
If yes, has the governance of data sharing been established	Not applicable	0
Analyses		
How easily could collected data be incorporated into an economic model	High	0
Existing methodology to analyse data	Yes	Established methodology available here: http://www.chemodataset.nhs.uk
If no, is there a clear process to develop the statistical analysis plan	Not applicable	0
Existing analytical capacity	High	Established analytical capacity
Governance		
Lawful basis for data collection	Yes	6(1)e of the United Kingdom General Data Protection Regulations (UK GDPR). Statutory authority to process confidential patient information (without prior patient consent) afforded through the National Disease Registries (NDRS) Directions 2021
Privacy notice & data subject rights	Not applicable	Mandated dataset as part of the Health and Social Care Information Standards
Territory of processing	Yes	UK
Data protection registration	Yes	0
Security assurance	Yes	0
Existing relevant ethics/research approvals	Not applicable	0
Patient consent	Yes	No prior patient consent required
Funding		
Existing funding	Yes	Established partnership between NHS Englands CDF team and SACT team (part of NDRS)
Additional funding required for MA	No	0
If yes, has additional funding been agreed in principle	Not applicable	0
Service evaluation checklist - registry specific questions		
HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
Does data collection through registry require any change from normal treatment or service standards?	No	Established mandatory dataset. No additional data items created

Are any of the clinical assessments not validated for use or accepted clinical practice	No	See above
HRA question 3. Is the study designed to produce generalisable or transferable findings?		
Would the data generated for the purpose of managed access be expected to be used to make decisions for a wider patient population than covered by the marketing authorisation / NICE recommendation	No	Data collection mandated by a Data Collection Agreement would be used for the purpose of the NICE guidance update
Additional considerations for managed access		
Are the clinical assessments and data collection comparable to current clinical practice data collection?	Yes	Established mandatory dataset. No additional data items created
Burden		
Additional patient burden	No	Existing mandated data set. No additional burden of data collection within managed access
Additional clinical burden	No	Existing mandated data set. No additional burden of data collection within managed access
Other additional burden	No	0

Other issues	SACT

Explanation

This page details the Managed Access Team's assessment on whether there are any potential barriers to agreeing a managed access agreement and that any potential managed access agreement operates according to the policy framework developed for the Cancer Drugs Fund and Innovative Medicines Fund.

The items included are informed by the relevant policy documentation, expert input from stakeholders including the Health Research Authority, and the Managed Access team's experience with developing, agreeing and operating managed access agreements. Additions or amendments may be made to these considerations as further experience is gained from Managed Access.

Are there any substantive issues (excluding price) that are a barrier to a MAA	
Overall rating	**Rationale/comments**
No	None identified

		Rating	Rationale / comments
Burden	Expected overall additional patient burden from data collection?	Low	Data collection in clinical practice through existing mandated data set. No additional burden of data collection within managed access
	Expected overall additional system burden from data collection?	Low	As above
	Do stakeholders consider any additional burden to be acceptable	Yes	0
	Would additional burden need to be formally assessed, and any mitigation actions agreed, as part of a recommendation with managed access	No	0

		Rating	Rationale / comments
Patient Safety	Have patient safety concerns been identified during the evaluation?	No	No additional patient safety concerns identified
	Is there a clear plan to monitor patient safety within a MA?	Yes	No additional patient safety concerns identified
	Are additional patient safety monitoring processes required	No	No additional patient safety concerns identified

		Rating	Rationale / comments
Patient access after MAA	Are there are any potential barriers to the agreed exit strategy for managed access, that in the event of negative NICE guidance update people already having treatment may continue at the company's cost	Yes	It the event of negative NICE guidance at the end of managed access it is expected, in line with principles of the Innovative Medicines Fund and Cancer Drugs Fund, that patients will continue to be able to receive the treatment until such time that the patient and the treating clinician determines it is no longer clinically appropriate.
	If yes, have NHS England and the company agreed in principle to the exit strategy	Yes	0

		Rating	Rationale / comments
Service implementation	Is the technology disruptive to the service	No	0
	Will implementation subject the NHS to irrecoverable costs?	No	0
	Is there an existing service specification which will cover the new treatment?	Yes	0

		Rating	Rationale / comments
Patient eligibility	Are there specific eligibility criteria proposed to manage clinical uncertainty	No	It is expected that the entire eligible patient population, as recommended by NICE, will be able to access the medicine. Detailed blueteq criteria will be developed by NHSE prior publication of any positive draft final NICE guidance
	If yes, are these different to what would be used if the technology had been recommended for routine use?	Not applicable	-

		Rating	Rationale / comments

Service evaluation checklist	HRA question 1. Are the participants in your study randomised to different groups?		
	Will the technology be available to the whole recommended population that meet the eligibility criteria?	Yes	As above
	HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
	Will the technology be used differently to how it would be if it had been recommended for use?	No	0
	Any issues from registry specific questions	No	0
	HRA question 3. Is the study designed to produce generalisable or transferable findings?		
	Any issues from registry specific questions	No	0
	Additional considerations for managed access		
	Is it likely that this technology would be recommended for routine commissioning disregarding the cost of the technology?	Yes	0
	Any issues from registry specific questions	No	0

		Rating	Rationale / comments
Equality	Are there any equality issues with a recommendation with managed access	No	There are not expected to be any equality issues from a recommendation for use with managed access compared to a recommendation for routine use.

		Rating	Rationale / comments
Timings	Likelihood that a Data Collection Agreement can be agreed within normal FAD development timelines	Yes	It is expected that a data collection agreement could be agreed within normal FAD development timelines (35 days) if committee make a recommendation for use in managed access