# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Draft guidance consultation

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using tafasitamab with lenalidomide and rituximab in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

**This document has been prepared for consultation with the stakeholders.** It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

**Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.**

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using tafasitamab with lenalidomide and rituximab in the NHS in England.

For further details, see NICE's technology appraisal and highly specialised technologies guidance manual.

The key dates for this evaluation are:

- Closing date for comments: 17 June 2026
- Second evaluation committee meeting: 07 July 2026
- Details of membership of the evaluation committee are given in section 4

# 1 Recommendations

1.1 Tafasitamab with lenalidomide and rituximab should not be used to treat relapsed or refractory follicular lymphoma (grades 1 to 3a) after 1 or more line of systemic treatment in adults.

1.2 This recommendation is not intended to affect treatment with tafasitamab with lenalidomide and rituximab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

## What this means in practice

These are NICE's draft recommendations. If these recommendations become final, tafasitamab with lenalidomide and rituximab would not be required to be funded and should not be used routinely in the NHS in England for the condition and population in the recommendations.

This is because there is not enough evidence to determine whether tafasitamab with lenalidomide and rituximab is value for money in this population.

### Why the committee made these recommendations

Usual treatment for relapsed or refractory follicular lymphoma after 1 or more lines of systemic treatment is lenalidomide plus rituximab. Other treatments include obinutuzumab plus bendamustine, combinations of chemotherapy plus rituximab-based treatment, and, after 2 or more lines of systemic treatment, epcoritamab.

Clinical trial evidence shows that, compared with lenalidomide plus rituximab alone, tafasitamab plus lenalidomide and rituximab increases how long people have before their condition gets worse. But it is unclear if it increases how long people live.

Tafasitamab plus lenalidomide and rituximab has not been directly compared in a clinical trial with epcoritamab, obinutuzumab with bendamustine or combinations of chemotherapy plus rituximab-based treatment. There are indirect comparisons, but the results are too uncertain to be used.

There are uncertainties in the economic model because it is unclear which approach is most appropriate for modelling differences in how long people live with the different treatments. These uncertainties are increased by assumptions about how well the treatments work in the long term.

Because of the uncertainties in the economic model and clinical evidence, it is not possible to determine the most likely cost-effectiveness estimates for tafasitamab plus lenalidomide and rituximab. So, it should not be used.

# 2 Information about tafasitamab plus lenalidomide and rituximab

## Marketing authorisation indication

2.1 Tafasitamab (Minjuvi, Incyte) 'is indicated in combination with lenalidomide and rituximab for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) (Grade 1 to 3a) after at least one line of systemic therapy'.

## Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for tafasitamab.

## Price

2.3 The list price for tafasitamab is £705 per 200 mg vial (excluding VAT; company submission).

2.4 The company has a commercial arrangement. This makes tafasitamab plus lenalidomide and rituximab available to the NHS with a discount and it would have also applied to this indication if tafasitamab plus



 

lenalidomide and rituximab had been recommended. The size of the discount is commercial in confidence.

### Sustainability

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Incyte will be included here when guidance is published.

# 3 Committee discussion

## The condition

### Follicular lymphoma

3.1 Lymphomas are cancers of the lymphatic system, which is a part of the immune system. Follicular lymphoma is a slow-growing lymphoma that affects B lymphocytes. It is the most common type of low-grade lymphoma. People with this condition typically present with painless lumps (enlarged lymph nodes) in the neck, armpit or groin. Some people may have additional symptoms such as night sweats and recurrent fevers. Some people do not have symptoms so the cancer may have advanced by the time it is diagnosed. Follicular lymphomas are commonly staged from stage 1 (best prognosis) to stage 4 (worst prognosis). The staging depends on how many groups of lymph nodes are affected and where they are in the body, the size of the areas of lymphoma and whether organs outside of the lymphatic system are affected (such as the bone marrow or liver). Follicular lymphomas are also graded from 1 to 3b based on the speed of disease growth. Grades 1 to 3a are considered low grade and represent slow-growing disease, while grade 3b represents high grade disease that grows quickly. Clinical experts noted that there is limited prognostic difference between grades 1 and 3a, so are now grouped under the collective term of 'classical follicular lymphoma'. They noted that grade 3b was excluded from the inMIND trial. In England in 2022 there were 2,404 diagnoses of follicular lymphoma (1,217 in females and 1,187 in males). The 5-year survival rate for people diagnosed with



 

follicular lymphoma is about 85%, and one clinical expert said that the expected survival from diagnosis is more than 18 years. Follicular lymphoma is incurable and has a high risk of relapse or becoming refractory (when the cancer returns or stop responding to treatment). Patient experts explained that the impact of a follicular lymphoma diagnosis has a great physical and emotional burden which should not be underestimated. They also said that the single hardest challenge is the anxiety and fear which pervades every aspect of the lives of people with follicular lymphoma. The fear comes from the uncertainty about the next relapse and what treatment options will be available. The patient experts highlighted that there is no uniform experience of follicular lymphoma and that the condition, and the side effects from managing it, can be life limiting. The committee acknowledged the perspectives shared by patient experts and through submitted statements. It concluded that follicular lymphoma is progressive, incurable and substantially impacts people with the condition.

## Clinical management

### Treatment options

3.2 The treatment pathway for follicular lymphoma is broadly organised into lines of treatment based on relapse or progression, with subsequent treatments dictated by those used earlier. For stage 3 or 4 (advanced stage) follicular lymphoma, treatment options at each line include:

- First-line treatment
  - rituximab plus chemotherapy (R+chemo), followed by optional rituximab maintenance monotherapy (see NICE's technology appraisals on rituximab for the first-line treatment of stage III–IV follicular lymphoma [TA243] and rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma [TA226])



 

  - obinutuzumab plus chemotherapy, followed by optional obinutuzumab maintenance monotherapy (see NICE's technology appraisal on obinutuzumab for untreated advanced follicular lymphoma [TA513])
- Second-line treatment (after relapse or progression)
  - lenalidomide plus rituximab ($R^2$; see NICE's technology appraisal on lenalidomide with rituximab for previously treated follicular lymphoma [TA627])
  - R+chemo if the follicular lymphoma responds to rituximab, optionally followed by rituximab maintenance monotherapy
  - obinutuzumab plus bendamustine (O-Benda) for people with rituximab-refractory disease, optionally followed by obinutuzumab maintenance treatment (see NICE's technology appraisal on obinutuzumab with bendamustine for treating follicular lymphoma after rituximab [TA629])
- Third-line treatment (after further relapse or progression)
  - treatments used at second line
  - epcoritamab (see NICE's technology appraisal on epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more lines of systemic treatment [TA1139]).

Clinical experts noted that most people they see have advanced-stage follicular lymphoma. Patient experts highlighted the toxicity and burdensome side effects of treatments including chemotherapy. They said that fatigue and recurrent infections impact their daily life and, in some cases, cause people to stop working or driving. They added that people with follicular lymphoma often prefer to avoid chemotherapy where possible, and clinical experts agreed that chemotherapy-based treatments have significant side effects. Clinical experts highlighted the importance of shared-decision making, particularly given the cumulative toxicity of sequential treatments. They considered tafasitamab plus $R^2$ to be well-tolerated, with a safety profile comparable to $R^2$ alone. The EAG noted that the triple regimen needs additional administrations, which may impact



 

its uptake because of limited NHS chair capacity. The NHS England Cancer Drugs Fund (CDF) lead agreed that capacity is a concern. The company expects that tafasitamab plus $R^2$ will be used at second line, replacing most current $R^2$ use and some R+chemo use. It also noted that there may be overlap in eligibility between epcoritamab and tafasitamab plus $R^2$, and that having multiple treatment options is valued by both healthcare professionals and people with follicular lymphoma. The patient experts agreed, noting that there is no single patient journey. The company said that epcoritamab may be widely used at third-line. But, it is associated with cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) risks, so tafasitamab plus $R^2$ may be more suitable for some people. Clinical experts broadly agreed that the treatment pathway reflects NHS practice, and added that treatments may vary depending on age and fitness. For example, some people may be offered allogenic stem-cell transplantation at second or third line if they are considered fit enough. The committee acknowledged the burden of chemotherapy-based treatments and concluded that there remains a need for more treatment options for this life-long, relapsing condition.

## Comparators

3.3 The committee wanted clarification on which treatment options would be used in the same population as tafasitamab plus $R^2$ and should therefore be considered comparators. At second line, people can currently have O-Benda, $R^2$ or R+chemo. Clinical experts noted that clinical trial evidence for tafasitamab plus $R^2$ showed improved efficacy and no additional toxicity concerns compared with placebo plus $R^2$. So, they expect tafasitamab plus $R^2$ to replace $R^2$ use at second line. They added that, while $R^2$ is a standard of care, treatment choice depends on individual patient history, which may make other options more appropriate. The committee asked how often R+chemo is used. A clinical expert said they are not used often and their use is decreasing. R+chemo treatments (such as rituximab plus bendamustine [R-Benda], rituximab plus



 

cyclophosphamide, doxorubicin, vincristine and prednisolone [R-CHOP] or rituximab plus cyclophosphamide, vincristine and prednisolone [R-CVP]) would not be used at second line if it had already been used at first line. O-Benda is also limited to people with rituximab-refractory follicular lymphoma, a smaller subgroup than those with rituximab non-refractory disease. The company and EAG thought that O-Benda was not relevant due to limited use in NHS practice. The CDF lead, citing Blueteq data, reported that 85% of people starting second-line treatment in the last 12 months had $R^2$ and 15% had O-Benda, but data for R+chemo was not provided. Clinical experts agreed that the availability of epcoritamab at third line, and the need for effective subsequent treatments, means that tafasitamab plus $R^2$ would be prioritised at second line and used less at third line. It would mainly be used at third line in people who did not have $R^2$ at second line, including a small population who would not be offered epcoritamab because of CRS or ICANS risks. The committee was uncertain if retreatment with $R^2$ at third line was done in practice, but concluded that the most relevant comparator for tafasitamab plus $R^2$ is $R^2$ at both second and third line. Tafasitamab plus $R^2$ may displace some use of R+chemo and O-Benda, but these chemotherapy-based treatments are used infrequently and are declining. The committee noted that epcoritamab is expected to be used at third line after treatment with tafasitamab plus $R^2$ at second line. It added that, where tafasitamab plus $R^2$ would be used at third line, it is following second-line R+chemo or O-Benda, or when epcoritamab is unsuitable. So, the committee concluded epcoritamab to be of limited relevance as a comparator. But it noted that this would depend on whether there was any retreatment with $R^2$ in NHS practice, and requested further clinical input on this. The committee noted that there was some use of O-Benda which may be replaced by tafasitamab plus $R^2$ if recommended. It concluded that O-Benda is a relevant comparator, but because of lower uptake it was less relevant for decision making.

# Clinical effectiveness

## inMIND trial

3.4 inMIND is a phase 3, double-blind, placebo-controlled randomised trial comparing tafasitamab plus R$^2$ with placebo plus R$^2$ in adults with relapsed or refractory grade 1 to 3a follicular lymphoma after 1 or more lines of systematic treatment. 548 people were enrolled across 210 locations globally, including several centres in the UK (exact numbers are considered confidential by the company and cannot be reported here). People were randomised 1 to 1 to the tafasitamab or placebo arm, with treatments given in 28-day cycles. In the tafasitamab arm, people had 12 mg/kg of tafasitamab by intravenous infusion weekly for cycles 1 to 3, then every 2 weeks for cycles 4 to 12. People in the placebo arm had placebo intravenous infusions matching the same schedule. Both arms received:

- 20 mg/day of lenalidomide orally on days 1 to 21 for 12 cycles
- 375 mg/m$^2$ of rituximab by intravenous infusion weekly for the first cycle, then once per cycle for cycles 2 to 5.

The primary endpoint of inMIND was progression-free survival (PFS), assessed by investigators using the Lugano 2014 criteria. Key secondary endpoints included overall survival (OS), PFS assessed by an independent review committee, overall response rate, duration of response, adverse events and health-related quality of life. The full analysis set at the February 2024 data cut-off included 273 participants in the tafasitamab plus R$^2$ arm and 275 in the placebo plus R$^2$ arm. Median follow-up was 14.1 months for PFS and 15.3 months for OS. The results showed a statistically significant improvement in PFS when taking tafasitamab plus R$^2$ compared with placebo plus R$^2$.

- Investigator assessed PFS
  - tafasitamab plus R$^2$ median = 22.4 months (95% confidence interval [CI] 19.2 months to not estimable)



 

  - placebo plus $R^2$ median = 13.9 months (95% CI 11.5 to 16.4 months)
  - hazard ratio (HR) = 0.43 (95% CI 0.32 to 0.58)
- Independent review committee assessed PFS
  - tafasitamab plus $R^2$ median = not reached (95% CI 19.3 months to not estimable)
  - placebo plus $R^2$ median = 16.0 months (95% CI 13.9 to 21.1 months)
  - HR = 0.41 (95% CI 0.29 to 0.56)

The clinical experts highlighted that inMIND clearly showed a strong PFS benefit for tafasitamab plus $R^2$ over $R^2$ alone. They also noted that remaining progression-free is a key aim of treatment. OS results showed a numerical, but not a statistically significant, reduction in the risk of death when taking tafasitamab plus $R^2$ compared with placebo plus $R^2$. Median OS was not reached in either arm. The company said that inMIND was not powered to assess OS at the February 2024 data cut-off. It added that the data's immaturity with few death events is typical of slow-growing follicular lymphoma. The committee recalled that people may live for more than 18 years from diagnosis (see section 3.1). It noted that the slow-progressing nature of follicular lymphoma makes it difficult to determine any OS benefit with a median follow-up of only 15.3 months. The committee welcomed the inMIND trial data, noting the importance of the head-to-head comparison with a standard NHS treatment. It concluded that tafasitamab plus $R^2$ increases the time people remain progression-free compared with $R^2$ alone. But the committee considered the OS results to be very immature, and noted that further evidence (such as longer follow-up or data collected through a possible CDF entry) would be needed to determine if tafasitamab plus $R^2$ offers any additional OS benefit (see section 3.18).

## Generalisability of inMIND to the NHS

3.5 The EAG considered the inMIND trial to be broadly generalisable to the NHS. But it noted that the trial population may be younger than people starting second-line treatment for follicular lymphoma. The EAG also thought that the proportion of people in inMIND with progression of disease within 24 months (POD24) of diagnosis may have been lower than in NHS practice, and the proportion who were rituximab-refractory may have been higher. The company stated that the full inMIND population reflects the NHS population who would be expected to have tafasitamab plus $R^2$ at second line or later. The company submission stated that the trial included chimeric antigen receptor T-cell (CAR-T) therapy as a subsequent treatment which is not available in the NHS. It stated that subsequent CAR-T use would have limited impact because of immature OS data, and that subsequent treatments were reweighted to exclude costs not relevant to the NHS. The clinical experts considered the inMIND population to be generalisable to the population seen in NHS practice. The committee concluded that inMIND was broadly generalisable to the population who would have tafasitamab plus $R^2$ at second line or later.

## Indirect and mixed treatment comparisons for R+chemo and O-Benda

3.6 The company did matching-adjusted indirect comparisons (MAIC) to compare tafasitamab plus $R^2$ with R+chemo and O-Benda. It noted several limitations, including:

- limited adjustment for prognostic factors and potential treatment effect modifiers
- small effective sample sizes
- wide confidence intervals
- face validity concerns (for example, results suggesting worse PFS with $R^2$ than R+chemo).



 

The company did not consider the MAICs to be reliable and instead assumed that R+chemo would have the same efficacy outcomes as $R^2$ in the model. It said this assumption was conservative because $R^2$ was likely to be superior to R+chemo. The EAG agreed with the limitations of the MAICs against all comparators and thought that the assumption of clinical equivalence was appropriate but was uncertain whether it was conservative. Both the company and EAG assumed clinical equivalence between R+chemo and $R^2$ in their base cases. The committee recalled that the clinical experts said the use of R+chemo at 2 or more lines of systemic treatment was low and declining, limiting its relevance as a comparator and that there was limited use of O-Benda (see section 3.4). It concluded that it was acceptable to assume equivalent efficacy between R+chemo and $R^2$, although this introduced some uncertainty. It also concluded that comparisons with R+chemo and O-Benda were limited by the available evidence, noting that these comparators were less relevant for decision making.

## Indirect treatment comparison for epcoritamab

3.7 After epcoritamab was recommended in TA1139, it became a relevant comparator for tafasitamab plus $R^2$ at third line in relapsed or refractory follicular lymphoma for people who had not had $R^2$ at second line. After the submission of the EAG report, but before the appraisal committee meeting, the company submitted an addendum detailing its comparison with epcoritamab at third line. The committee appreciated the company's effort to prepare an addendum at this stage. This unanchored MAIC compared tafasitamab plus $R^2$ with epcoritamab using EPCORE NHL-1, the main evidence from TA1139. The company noted that the EPCORE NHL-1 population had a poorer prognosis at baseline than the third line or later population in inMIND. The EPCORE NHL-1 population included a higher proportion of people with high-risk Follicular Lymphoma International Prognostic Index (FLIPI) scores, Eastern Cooperative Oncology Group (ECOG) performance scores of 1 or 2, and follicular lymphoma refractory to prior treatment (exact numbers are considered



 

confidential by company and cannot be reported here). Clinical experts agreed that there was a poorer prognosis in the EPCORE NHL-1 population, with one expert noting that the poorer prognosis was, in part, because the trial spanned peak-COVID periods. When the committee asked how survival outcomes compared between inMIND and EPCORE NHL-1, the clinical expert noted that comparisons were difficult because EPCORE NHL-1 is a single-arm trial and inMIND is a randomised control trial (RCT). The HR results for PFS and OS from the MAIC favoured tafasitamab plus $R^2$, but the confidence intervals were wide (the results are considered confidential by the company so cannot be reported here). The EAG noted that the effective sample size after adjustment (considered confidential by the company and not reported here) indicated moderate overlap between studies. But, as with the MAICs for R+chemo, this analysis could not adjust for key covariates (such as, double refractory status and POD24) and relied on an unanchored comparison. The EAG also did unadjusted Cox models, based on digitised Kaplan-Meier (KM) curves. But the EAG emphasised that this analysis was exploratory, does not account for trial differences and should not be used to compare tafasitamab plus $R^2$ with epcoritamab. It advised that, given the limited time it had to critique the epcoritamab addendum, results should be interpreted with caution. The committee noted the limitations of the MAIC and the uncertainty around the HR estimates. It also recalled that epcoritamab was only a relevant comparator for a small proportion of the population, and that there may be limited additional evidence to compare tafasitamab plus $R^2$ with epcoritamab. The committee welcomed additional evidence and requested a full critique of the modelling to reduce uncertainty in this comparison.

## Economic model

### Model structures

3.8 The company built a partitioned survival model (PSM) with 1-week cycles over a 36-year time horizon. It has 3 health states: progression-free,



 

progressed disease and death. The occupation of the health states is determined by extrapolated survival curves. The inMIND PFS and OS KM curves inform the company's base-case analysis comparing tafasitamab plus $R^2$ with $R^2$. The same data informs the comparison with R+chemo, assuming equivalent clinical efficacy with $R^2$ (see section 3.6), but uses costs associated with the respective R+chemo combinations. Health state utility values were mapped to EQ-5D-3L from EQ-5D-5L data collected during inMIND. The model adopts an NHS and Personal Social Services perspective, with a 3.5% annual discount rate for costs and QALYs. The company also developed a state transition model (STM) using the same health states as the PSM. Similarly to the PSM, the PFS KM curves from inMIND inform PFS. But the OS KM curves are not used in the STM. Instead, OS is modelled indirectly as the sum of PFS and post-progression survival (PPS). PPS is modelled by applying a PPS rate which determines the number of people who transition from the progressed disease state to death in each cycle. So, the treatment effect on OS reflects the PFS benefit observed in inMIND plus any PPS benefit. In the STM, OS is determined by 3 transition probabilities:

- Probability of progression: from extrapolated inMIND PFS curves and dictates movements between progression-free (PF) and progressed disease (PD) health states
- Probability of death in PF health state: fixed proportion of PFS events represent deaths in each cycle (derived from inMIND data)
- Probability of death in PD health state: derived from external sources with 3 scenarios exploring different PPS approaches

The company proposed 3 STM approaches based on clinical advice suggesting that refractory status may impact PPS:

- STM approach 1 (STM1) relies on PFS only for OS benefit, using HMRN data in non-rituximab-refractory follicular lymphoma to model a common PPS across treatment arms

- STM approach 2 (STM2) has treatment-specific PPS based on the GADOLIN RCT (comparing O-Benda with bendamustine in rituximab-refractory follicular lymphoma) which, with PFS, determines OS
- STM approach 3 (STM3) uses a weighted combination of approaches 1 and 2, based on the proportion of the inMIND population that is rituximab-refractory.

### Appropriateness of the model approach with immature OS data

3.9 The company maintained that the PSM was more appropriate, with it being widely used across oncology. It said that, unlike some forms of the STM, the PSM structure does not rely on the surrogacy of PFS to OS. The company cited Milrod et al. (2024), a systematic review and meta-analysis, which found a weak correlation of 0.383 ($p<0.001$) between PFS and OS in follicular lymphoma. One clinical expert explained that historically there was thought to be a poor link between PFS and OS because of its slow-growing nature. But they added that GADOLIN and RELEVANCE (which compared $R^2$ with R+chemo in untreated follicular lymphoma) trials, with longer follow-up, suggest the link may be stronger in relapsed disease. The EAG agreed that some trials suggest weak surrogacy between PFS and OS but noted some limitations in this evidence. It said the STM has the advantage of allowing the more mature inMIND PFS data to be the primary driver of benefits in the model. The committee noted that the appropriateness of either model depends on other uncertainties, including PFS and OS extrapolations, PPS approach, treatment effect waning, and the proportion of PFS events that are deaths (see section 3.13). The company considered STM3 (see section 3.8) to be the most plausible STM approach because it reflects the inMIND population that would achieve a PPS benefit based on refractory status. It considered STM1 to underestimate, and STM2 to overestimate, the PPS benefit. The EAG used STM1 in its base case and noted that there was not a clear biological rationale for a PPS benefit in favour of tafasitamab plus $R^2$ (like there might be for shrinkage of solid tumours). It also highlighted that the PPS benefit in STM2 and STM3 were based on



 

GADOLIN treatments (O-Benda and bendamustine) and not inMIND treatments. The company highlighted that other trials, including GADOLIN and AUGMENT, suggested a clear PPS benefit. The committee asked the clinical experts if there was a biological rationale for a PPS benefit for tafasitamab plus $R^2$ compared with $R^2$. One clinical expert explained that effective treatment returns enlarged lymph nodes to normal size, which is captured as a complete response, but this would occur before disease progression. The clinical expert said there may be an immunological priming effect of treatment creating a more active immunological environment after disease progression, but this was uncertain. The company said there is early trial data which may support a PPS benefit and also noted lower rates of histological transformation with tafasitamab plus $R^2$ compared with $R^2$ in inMIND. The committee noted this but thought that, whilst plausible, a PPS benefit was not supported by the evidence submitted. The committee considered that both PSM and STM structures could be appropriate and welcomed the company's efforts in preparing multiple model structures. Particularly, it noted that the company's submission was in line with recommendations in the NICE Decision Support Unit's Technical Support Document 19, which suggests using PSM alongside STM. But it considered that exploration of OS extrapolation in the PSM was limited, particularly the choice of distributions. The committee suggested that separately fitted models, which may already accommodate an implicit treatment effect waning (see section 3.11), should be explored further. It also thought that alternative distributions may produce PPS estimates between those in STM1 and STM3 and would like to see this explored. Overall, the committee requested further exploration of model structure alongside other modelling assumptions (see section 3.13).

## Extrapolation of progression-free survival

3.10 The company and EAG chose different parametric curves to extrapolate long-term PFS. In its base case, the company used jointly fitted generalised gamma curves. It said that the quantile-quantile plots and



 

consistency with the jointly fitted OS extrapolations supported this approach with accelerated failure time models. The company selected generalised gamma based on having one of the best statistical fits and matching its clinical experts' expectations. It considered the jointly fitted log-logistic to be a reasonable approach also. The EAG argued that the joint or independent fitting of PFS curves should rely on the PFS data and not those selected for OS. It said that the company's jointly fitted generalised gamma curves overestimated PFS across both arms, particularly for tafasitamab plus $R^2$. The EAG fit PFS curves independently and selected the log-logistic for both arms based on having one of the best statistical fits and matching the company's clinical experts' expectations. It noted that, when using the PSM model, the difference between PFS extrapolations had a small impact on the cost effectiveness results. The committee noted that, unlike OS, which was immature, the inMIND PFS data showed a considerable benefit in favour of tafasitamab plus $R^2$ (see section 3.4). The company noted that one of the limitations of independently fitting PFS was that it may double count treatment effect waning if waning was also explicitly modelled. This is because separately fitted curves allow the implied HR to converge more freely than jointly fitted curves. The committee considered this when it discussed treatment effect waning (see section 3.11). It requested to see the implied PFS HRs under different extrapolations alongside the PFS HR over time from inMIND. It thought that both company and EAG approaches to modelling PFS were plausible but concluded that the most appropriate would depend on other modelling assumptions (see section 3.13).

## Treatment effect waning

3.11 Tafasitamab plus $R^2$ is a fixed-duration treatment which can be administered for up to 48 weeks. Both the company and EAG agree that over time, without active treatment or fundamental alteration of disease biology, the incremental treatment benefit would wane. The company base case (which used the PSM, see section 3.9) assumed a full treatment effect for 5 years, followed by 5 years of gradual waning, after



 

which PFS and OS hazards were equalised between arms. Clinical expert advice and conclusions from the R$^2$ technology appraisal (TA627) informed the duration of full treatment effect and waning. The company argued that no treatment effect waning had been applied in the epcoritamab technology appraisal (TA1139), so any waning in the third-line comparison would disadvantage tafasitamab plus R$^2$. The EAG agreed that gradual waning was appropriate, but argued that the TA627 treatment effect waning did not seem to be linked to a mechanism of action or disease biology. Citing the PFS log-cumulative hazard and Schoenfeld residual plots, the EAG thought that some convergence of effectiveness occurred during the trial duration and doubted if a long period of full effect was warranted. In its base case, it used a full treatment effect for 2 years followed by 3 years of gradual waning. As the EAG base case used STM1 with no PPS benefit, treatment effect waning was only applied to PFS. The company felt there was double counting of treatment effect waning in the EAG's STM model with independently fitted PFS curves. It cited the implied PFS HRs of different model approaches. Compared with the company base case, the implied PFS HRs in the EAG's base case approached 1 quite quickly, even before the explicit treatment effect waning period started at 2 years. The EAG acknowledged that starting at 2 years for treatment effect waning on PFS was possibly conservative. The committee thought it was likely that the separately fitted log-logistic PFS curves already implicitly accounted for some treatment effect waning. But it did not consider this to be double counting, noting that applying the explicit treatment effect waning modelling approach had a limited impact on cost-effectiveness estimates when added to the separately fitted log-logistic curves and used with STM1. The committee concluded that the issues of model structure selection (see section 3.9), PFS extrapolation (see section 3.10), and treatment effect waning were all linked (see section 3.13).

## Proportion of progression-free survival events that are deaths

3.12 In inMIND, a proportion of PFS events were deaths, and this is factored into the different model approaches. In the PSM, this proportion only impacts on the ICER through the number of people who have subsequent treatments, but OS is modelled using extrapolated inMIND OS KM data. The company's base case uses pooled data from both treatment arms. In the STM, this proportion drives part of the OS in each treatment arm. The EAG's base case uses treatment arm-specific proportions. The proportion in the tafasitamab plus $R^2$ arm was higher than in the $R^2$ arm (considered confidential by the company and cannot be reported here). This difference had a small impact on the PSM incremental cost effectiveness ratios (ICERs), a moderate impact on ICERs for STM2 and STM3, and a large impact on ICERs for STM1. The company stated that there was no reason to expect tafasitamab plus $R^2$ would lead to more deaths than $R^2$ alone before disease progression. The EAG said that the pooled proportion masked differences between treatment arms and that a higher mortality risk is plausible with the triple regimen. It also preferred the model to reflect the trial data. The company argued that it was inconsistent to consider the inMIND OS data too immature to model OS whilst noting a treatment benefit for $R^2$ in pre-progression deaths. It also added that if tafasitamab plus $R^2$ is associated with a higher proportion of pre-progression deaths, then this effect should be subject to the same treatment effect waning applied to PFS, and the proportions should equalise between treatment arms over time. The committee noted that this assumption was more important when PFS was the main driver of the model (as in STM1) and less important when a PPS benefit was modelled. It requested further data and clinical rationale on whether it was more plausible that there might be more deaths in the PF health state for tafasitamab plus $R^2$ compared with $R^2$ alone. The committee also concluded that, if the EAG scenario was used, then any treatment effect waning applied to PFS should also be applied to differences in the proportions of PFS events that are deaths.



 

## Committee conclusions on model structure

3.13 The committee recalled that several structural choices were interlinked and that selecting one parameter might affect the appropriateness of another. For example, when using STM1, the choice of PFS distribution might affect whether an explicit treatment effect waning mechanism is appropriate. It concluded that it would like to see:

- Detailed exploration of the implied PFS HRs under the different distributions and treatment effect waning choices, and a direct comparison to the HR from inMIND (see sections 3.10 and 3.11).
- Detailed exploration of the implied OS HRs under the various model structures and a direct comparison to the HR from inMIND (noting data is immature; see section 3.4).
- Further exploration of OS extrapolations including separately fitted curves presented alongside inMIND KM data and comparison of the implied HRs with other modelling choices and with the HR from inMIND.
- Further exploration of the plausibility of treatment-specific proportions of PFS events that are deaths and their impact, particularly for STM approaches (see section 3.12)
- Clinical rationale and justification to help determine the most plausible combination of modelling assumptions.

## Per-cycle relative dose intensity approach over time

3.14 The EAG noted that the inMIND data appears to show fewer full doses of tafasitamab plus $R^2$ over time. So, it argued that the relative dose intensity (RDI) used in the company base case, and calculated from inMIND, overestimates the average doses received in later model cycles. The EAG used a per-cycle RDI which reduces over time which slightly reduced the ICER. The company considered a uniform RDI across model cycles to be appropriate, but considered the EAG approach reasonable also. The committee concluded that a per-cycle RDI that reduced over time was consistent with inMIND and should be used.



 

### Modelling of populations by treatment line

3.15 The full marketing authorisation for tafasitamab includes relapsed or refractory follicular lymphoma at second-line or later. The company and EAG modelled the whole population in their base cases, but the EAG noted that inMIND data includes both second line and third line or later subgroups. It did scenario analyses, varying the baseline characteristics, comparators, and treatment effects associated with each treatment line subgroup. For example, the PFS HR for tafasitamab plus $R^2$ compared with $R^2$ alone was 0.48 (95% CI 0.32 to 0.74) compared to 0.41 (0.28 to 0.61). Tafasitamab plus $R^2$ had a greater relative effect at third-line or later than in the second line only subgroup. Similarly, the EAG scenarios estimated that tafasitamab plus $R^2$ was more cost effective in the third-line or later subgroup. The company noted that second line or later reflects the full marketing authorisation for tafasitamab. It argued that inMIND was not powered for the second line only subgroup analyses, which had a smaller sample size and fewer outcome events. So, the company considered the analyses by treatment line to be exploratory and not relevant for decision making. The committee concluded that modelling the whole population across treatment lines was appropriate. This makes use of the larger sample size of inMIND and the more certain estimates of treatment effect. The committee acknowledged the EAG's point that there may be additional benefit with tafasitamab plus $R^2$ compared with $R^2$ alone in third-line or later treatment. However, it recalled that clinical experts expect tafasitamab plus $R^2$ to be used mainly at second line.

## Cost-effectiveness estimates

### The committee's preferred assumptions

3.16 The committee noted its preferred assumptions, which included:

- $R^2$ is the most important comparator for this appraisal across treatment lines (see section 3.3),



 

- R+chemo and O-Benda are comparators for a small number of people for tafasitamab plus $R^2$ at second line but are likely to be of limited relevance (see section 3.3),
- epcoritamab is a relevant comparator for tafasitamab plus $R^2$ at third line for people who did not have $R^2$ at second line, but is likely to be of limited relevance (see section 3.3),
- using the efficacy of $R^2$ from inMIND for R+chemo in its comparison with tafasitamab plus $R^2$ because of limited evidence and MAICs (see section 3.6),
- per-cycle RDI should vary over time to reflect inMIND and the fewer full doses of tafasitamab plus $R^2$ taken at later time points (see section 3.14).

The committee also noted the high level of uncertainty, specifically that:

- Long-term modelling of OS when used in the PSM is uncertain (see section 3.4).
- It was unclear whether a PSM or STM approach should be used and if an STM is appropriate, which approach should be used to model PPS (see section 3.9).
- How long the relative treatment effect of tafasitamab plus $R^2$ is considered durable and at what point treatment effect waning should start and end (see section 3.11).
- Whether pooled or treatment-specific proportions of PFS events that are deaths are appropriate, particularly for the STM (see section 3.12).

The committee would like to see the following analyses and additional evidence to help it decide on the cost effectiveness of tafasitamab plus $R^2$:

- evidence and clinical justification to understand whether retreatment with $R^2$ at third line occurs in practice (see section 3.3),
- any additional evidence to understand whether a tafasitamab plus $R^2$ OS benefit is applicable (see section 3.4),



 

- any additional evidence for comparators with limited uptake, if feasible (see section 3.6),
- any additional evidence for the comparison with epcoritamab and full critique by the EAG (see section 3.7),
- comparison of modelled OS from the different PSM and STM approaches with the inMIND data (see section 3.9),
- further exploration of the appropriateness of parametric curves for PFS (and OS if PSM is appropriate; see section 3.10),
- evidence and clinical justification to inform treatment effect waning (see section 3.11),
- further exploration of the appropriateness of pooled or treatment-specific proportions of PFS events that are deaths (see section 3.12)
- exploration of the interlinked modelling issues (see section 3.13).

## Acceptable ICER

3.17 NICE's technology appraisal and highly specialised technologies guidance manual notes that, above a most plausible ICER of £25,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits (see section 3.20). The committee noted the high level of uncertainty (see section 3.16). It considered that the analyses covered the range of uncertainty, but this was above the range to be considered an acceptable ICER. The committee noted that additional analyses could reduce the range of ICERs. It concluded that the ICER range would be reconsidered at the second committee meeting, taking into account any new analyses presented.

## Managed access

3.18 The committee noted that several uncertainties could be mitigated by a managed access period. This would provide longer-term OS data, as well as providing information on implementation considerations such as uptake and any impact on chair capacity. The NICE managed access team said that tafasitamab plus $R^2$ was a suitable candidate for CDF entry to collect data to resolve uncertainties. The CDF lead agreed that this could resolve key uncertainties. The committee concluded that although the company had produced an acceptable managed access proposal, tafasitamab plus $R^2$ could not be recommended for use in managed access because it did not have plausible potential to be cost effective at the currently agreed price.

## Other factors

### Equality

3.19 The committee did not identify any equality issues.

### Uncaptured benefits

3.20 The committee considered whether there were any uncaptured benefits of tafasitamab plus $R^2$. It noted that tafasitamab plus $R^2$ may have an effect on histological transformation compared with $R^2$ alone, as suggested by the inMIND data, but this was uncertain. The committee concluded that tafasitamab plus $R^2$ may have a preferable rate of histological transformation. But, it noted this could be accounted for in the modelling through a PPS benefit.

## Conclusion

### Recommendation

3.21 The committee recalled the uncertainties with some of the clinical and the economic evidence. It highlighted the significant uncertainty around an OS treatment benefit, which increased when considering model structure, long-term extrapolations of PFS and OS, the proportion of PFS events



 

that are death, the presence of any PPS benefit and treatment effect waning together. The committee noted that it could not determine the most plausible ICER. So, it did not recommend tafasitamab plus $R^2$ for treating relapsed or refractory follicular lymphoma after 1 or more lines of systemic treatment.

# 4 Evaluation committee members and NICE project team

## Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

## Chair

**James Fotheringham**

Chair, technology appraisal committee C

## NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager, and an associate director or principal technical adviser.

**Sammy Shaw**

Technical lead

**Samuel Slayen**

Technical adviser

**Leena Issa**

Project manager

**Adam Brooke**

Principal technical adviser

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