

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Obinutuzumab with bendamustine for treating follicular lymphoma after rituximab

1 Recommendations

- 1.1 Obinutuzumab with bendamustine followed by obinutuzumab maintenance is recommended, within its marketing authorisation, as an option for treating follicular lymphoma that did not respond or progressed up to 6 months after treatment with rituximab or a rituximab-containing regimen. It is recommended only if the company provides it according to the [commercial arrangement](#).

Why the committee made these recommendations

This appraisal reviews the evidence collected in the Cancer Drugs Fund for obinutuzumab with bendamustine for treating follicular lymphoma that did not respond or progressed with rituximab ([NICE technology appraisal guidance 472](#)).

Evidence from the Cancer Drugs Fund is limited but appears to support the clinical trial evidence. This evidence is in people who had rituximab as first-line treatment. It shows that when follicular lymphoma has not responded well enough (refractory) to rituximab, obinutuzumab with bendamustine improves how long people have before their disease progresses and how long they live compared with bendamustine alone.

Cost-effectiveness estimates for obinutuzumab with bendamustine are in the range usually considered a cost-effective use of NHS resources.

Therefore, it is recommended.

2 Information about obinutuzumab

Marketing authorisation indication

2.1 Obinutuzumab (Gazyvaro, Roche) in combination with bendamustine followed by obinutuzumab maintenance has a marketing authorisation for ‘the treatment of patients with follicular lymphoma who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen’.

Dosage in the marketing authorisation

2.2 Induction treatment:

- Cycle 1: 1,000 mg by intravenous infusion on day 1, day 8 and day 15 of the first 28-day treatment cycle
- Cycles 2 to 6: 1,000 mg by intravenous infusion on day 1 of each 28-day treatment cycle.

2.3 Maintenance treatment:

- 1,000 mg by intravenous infusion every 2 months for 2 years or until disease progression (whichever occurs first).

Price

2.4 £3,312 per 1,000 mg vial (excluding VAT; British national formulary [BNF] edition 71).

2.5 The company has a commercial arrangement (simple discount patient access scheme). This makes obinutuzumab with bendamustine available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company’s responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee ([section 6](#)) considered evidence submitted by Roche, a review of this submission by the evidence review group (ERG), and the technical report developed through engagement with stakeholders. See the [committee papers](#) for full details of the evidence.

The appraisal committee was aware that it had not been possible to fully resolve some key issues during the technical engagement stage.

It recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, table 3, page 31), and took these into account in its decision making. It discussed the following issues (issues 1 and 2), which were outstanding after the technical engagement stage.

Treatment pathway and clinical need

There is an unmet clinical need for people with rituximab-refractory disease

3.1 Follicular lymphoma is the most common type of indolent non-Hodgkin lymphoma and is not considered curable. The aim of treatment is to induce response and control disease progression for as long as possible. The clinical expert explained that treatment is characterised by multiple lines of treatment as the disease responds and relapses. For treatment of advanced (stage 3 or 4) disease that is asymptomatic, [NICE guideline 52](#) on non-Hodgkin lymphoma recommends rituximab monotherapy as a first-line treatment option. For symptomatic advanced follicular lymphoma, [Technology appraisal guidance 243](#) recommends first-line treatment with rituximab and chemotherapy (rituximab–chemotherapy) followed by rituximab maintenance therapy. The committee noted that since the [original appraisal of obinutuzumab with bendamustine](#), NICE has published [technology appraisal guidance 513](#) recommending obinutuzumab with chemotherapy, followed by obinutuzumab maintenance, as a first-line treatment option for advanced follicular lymphoma in adults with a Follicular Lymphoma International Prognostic

Index (FLIPI) score of 2 or more. The clinical expert explained that in clinical practice about half of patients now have obinutuzumab with chemotherapy as first-line treatment, and that second-line treatment depends on the timing of relapse and the chemotherapy agents that were used first line. Disease that relapses after obinutuzumab with chemotherapy may be treated with rituximab–chemotherapy, or with rituximab alone if there is resistance or intolerance to chemotherapy. The clinical expert also explained that when the disease becomes refractory to rituximab the treatment options are limited, and patients have a poor prognosis. Treatment options include chemotherapy (such as cyclophosphamide, fludarabine, bendamustine or chlorambucil) and best supportive care. The committee concluded that there is a high unmet clinical need in patients whose disease is refractory to rituximab.

People with rituximab-refractory follicular lymphoma would welcome another treatment option

3.2 The patient expert explained in their written submission that follicular lymphoma can have a significant effect on the quality of life of patients and their carers. The concern about relapse and the need for repeated courses of treatment is physically and psychologically challenging. People know that they will develop rituximab-refractory disease at some stage, after which the treatment options are limited. It is important for the mental wellbeing of patients to know that new and effective treatment options are available should their disease relapse. New treatments that allow people to live for longer without their disease progressing and with fewer side effects are highly valued by patients. The committee concluded that new treatments for follicular lymphoma that is refractory to rituximab would be welcomed by patients.

Clinical evidence

Obinutuzumab with bendamustine improves progression-free survival and overall survival compared with bendamustine alone

3.3 The clinical effectiveness evidence came from GADOLIN, an open-label randomised controlled trial. It compared obinutuzumab with bendamustine induction treatment followed by obinutuzumab maintenance, against bendamustine induction therapy alone. The intention-to-treat population in GADOLIN was people with indolent non-Hodgkin lymphoma, of whom about 81% had follicular lymphoma. Patients were included in the trial if their disease was refractory to induction treatment with rituximab monotherapy, refractory to induction treatment with rituximab–chemotherapy, or relapsed during or within 6 months of completing 2-year maintenance treatment with rituximab monotherapy. The main clinical uncertainty identified by the committee in the [original appraisal of obinutuzumab with bendamustine](#) was the amount of survival benefit for obinutuzumab with bendamustine. It had concluded that more mature overall-survival data from GADOLIN would be likely to resolve uncertainty around the treatment effect of obinutuzumab with bendamustine, and allow more reliable cost-effectiveness estimates. The current appraisal reviewed the most recent data from GADOLIN. This showed statistically significant improvements in progression-free survival and overall survival, which is consistent with the primary analysis. Median overall survival was not reached in the obinutuzumab with bendamustine group and was 60.3 months in the bendamustine group (hazard ratio 0.71, 95% confidence interval 0.51 to 0.98, $p=0.0343$). This suggests a 29% reduction in the risk of death with obinutuzumab with bendamustine. The committee concluded that mature data from GADOLIN show that obinutuzumab with bendamustine improves progression-free survival and overall survival compared with bendamustine induction treatment alone.

The systemic anti-cancer therapy (SACT) data are not robust enough to use in the economic model

3.4 Observational data for patients in the Cancer Drugs Fund obtained from the SACT dataset was presented by the company, but was not included in its economic analysis. The length of follow-up for overall survival in SACT ranged from 4 months to 23 months, and the median follow-up was 12.4 months. This limited length of follow up was the result of the company providing further GADOLIN data earlier than intended. It means that an estimate of median survival cannot be provided by the SACT data because they are too immature. The committee acknowledged that the Kaplan–Meier estimates of overall survival at 12 months were similar from the SACT data and GADOLIN, and had overlapping confidence intervals. However it noted the ERG’s comment that any comparison between single groups from separate studies is subject to bias and should be interpreted with caution. The ERG also highlighted that time on treatment appears to be lower in SACT than in GADOLIN. The committee accepted the comments from the Cancer Drugs Fund clinical lead that SACT included a higher proportion of people with multiple-relapsed disease, who therefore had a poorer prognosis compared with the trial population. It also accepted that the immaturity of the SACT data made it difficult to make meaningful comparisons. The committee concluded that the SACT data provide a useful insight into the use of obinutuzumab with bendamustine in clinical practice and early real-world evidence, but are not robust enough to be used in economic modelling.

Generalisability of GADOLIN results to NHS clinical practice

GADOLIN data are generalisable to people whose disease responded satisfactorily to first-line treatment with obinutuzumab and/or bendamustine

3.5 The clinical expert explained that the survival benefit for obinutuzumab with bendamustine has only been demonstrated for people who had rituximab–chemotherapy as first-line treatment. People who had bendamustine or obinutuzumab with chemotherapy first line were not

included in GADOLIN, and the effect of further obinutuzumab with bendamustine is not known in this population. The committee recalled that about half of the clinical population eligible for obinutuzumab with bendamustine will have had obinutuzumab with chemotherapy first-line, following publication of [technology appraisal guidance 513](#) (see section 3.1). It therefore considered whether the results from GADOLIN were generalisable to these patients. The clinical expert explained that there is no reason to expect that retreatment with obinutuzumab and bendamustine would not benefit people with disease that had responded to these treatments earlier in the treatment pathway, and that had not relapsed early after stopping treatment. He noted that some people have a very good response to first-line treatment with bendamustine or obinutuzumab with chemotherapy and remain disease free for a long period. It would be reasonable to assume that retreatment with obinutuzumab with bendamustine could offer further benefit when disease relapses after rituximab-chemotherapy. However, retreatment would not be expected to be beneficial if there had not been a good response, or early relapse, with first-line treatment with obinutuzumab and chemotherapy. The committee concluded that the results from GADOLIN are generalisable to people with rituximab-refractory disease that responded to treatment with obinutuzumab with chemotherapy earlier in the treatment pathway.

Obinutuzumab with bendamustine is suitable for patients for whom a stem cell transplant is intended

- 3.6 The clinical expert highlighted that second-line chemotherapy may be used as a bridge to a stem cell transplant in younger and fitter patients in clinical practice in the NHS. The committee noted that 11 patients in SACT had an autologous stem cell transplant instead of maintenance therapy with obinutuzumab. In GADOLIN 10% of people went on to have an autologous or allogenic stem cell transplant, and this was reflected in the economic model. The clinical expert explained that obinutuzumab with bendamustine would be a suitable option in people for whom a stem cell

transplant is an option because it is associated with better minimal residual rates, which improve the outcome of a stem cell transplant. The committee concluded that obinutuzumab with bendamustine is suitable for patients for whom a stem cell transplant is intended.

Cost effectiveness

The company's updated model used the committee's preferred assumptions

3.7 The committee considered the preferred committee assumptions from the original appraisal of obinutuzumab with bendamustine. It recalled that variation in the cost-effectiveness estimates was largely dependent on the extrapolation of overall survival, which was uncertain because the trial data were immature. The committee had concluded that there was a plausible potential for obinutuzumab with bendamustine to be cost effective, and that updated survival data could reduce the uncertainty and produce more reliable cost-effectiveness estimates using the original economic model. The ERG explained that the company had largely adhered to the preferred committee assumptions, with some exceptions (see sections 3.8. and 3.9). The committee concluded that the company had satisfactorily acknowledged the preferred assumptions from the original appraisal of obinutuzumab with bendamustine.

A random change-point model is appropriate for estimating overall survival

3.8 The company presented its original model with updated survival data. The updated base case used dependent Weibull functions assuming proportional hazards, fitted to overall-survival data from the most recent data cut of GADOLIN throughout the time horizon of the model. The committee noted that this approach differed from that used in the original appraisal, in which overall survival was modelled using Kaplan–Meier data up to the time of the last observed event in the trial followed by parametric extrapolation. The new approach no longer applied a cap on the maximum duration of treatment effect for obinutuzumab with bendamustine because the company considered that the updated

GADOLIN data did not support a declining treatment effect over time. The ERG explained that the company had acknowledged that the Kaplan–Meier survival data from GADOLIN shows ‘a clear separation of curves in favour of the obinutuzumab with bendamustine arm from 6 months and beyond’, corresponding to the time of switching from induction to maintenance treatment. Therefore, the company’s approach of using a single hazard function over the lifetime of patients in the model is not appropriate. This is also supported by log cumulative hazard plots against time showing that the proportional hazards assumption does not hold and that a change in the relative hazards occurs after about 6 months. The ERG considered that using a random change-point model, which allows the hazard function to change during the observed period in GADOLIN, provides a better visual representation of the observed overall-survival data over the early and late phase of GADOLIN and it used this in its preferred base-case analysis. The company also provided a fixed change-point model with a fixed change-point at exactly 6 months, corresponding to the time of the first obinutuzumab maintenance dose. The ERG preferred the random change-point model because there is uncertainty about the precise timing of a change in the hazard function. The company accepted the ERG’s approach after technical engagement. The committee also agreed with the ERG’s comments about the modelling approach. It concluded that a random change-point model was appropriate for estimating overall survival.

A single Weibull function over the horizon of the model may underestimate the progression-free survival benefit of obinutuzumab with bendamustine

3.9 The company fitted independent parametric models to the updated progression-free survival data from GADOLIN because the proportional hazards’ assumption did not hold and it was the preferred approach in the original appraisal. The ERG considered that the models used by the company in its base case did not provide a realistic model for the GADOLIN data. Log cumulative hazard functions against time showed that a single Weibull function to predict progression-free survival over a

patient's lifetime may underestimate the benefit of obinutuzumab with bendamustine on progression-free survival, and that an analysis which incorporates a change-point in the hazard function may be more appropriate. The company accepted the ERG's approach after technical engagement. The committee agreed with the ERG's comments, and it concluded that a random change-point model was appropriate for estimating progression-free survival.

Cost-effectiveness results

The estimates are within the range considered a cost-effective use of NHS resources

3.10 The company's incremental cost-effectiveness ratios (ICERs) estimated using the Weibull survival functions with fixed or random change-points preferred by the committee (see sections 3.8 and 3.9) ranged from £15,587 per quality-adjusted life year (QALY) gained to £17,322 per QALY gained. Using the ERG's preferred random change-point models for both progression-free survival and overall survival, with an updated price for bendamustine, the ICER was £15,045 per QALY gained. These ICERs are within the range normally considered to be a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). The committee concluded that obinutuzumab with bendamustine could be recommended for routine commissioning for treating follicular lymphoma that is refractory to rituximab or a rituximab-containing regimen.

4 Implementation

4.1 [Section 7\(6\) of the National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

- 4.2 [Chapter 2 of Appraisal and funding of cancer drugs from July 2016 \(including the new Cancer Drugs Fund\) – A new deal for patients, taxpayers and industry](#) states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The [NHS England and NHS Improvement Cancer Drugs Fund list](#) provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.
- 4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 4.4 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has follicular lymphoma that is refractory to rituximab and the doctor responsible for their care thinks that obinutuzumab with bendamustine followed by obinutuzumab maintenance is the right treatment, it should be available for use, in line with NICE’s recommendations.

5 Review of guidance

- 5.1 The guidance on this technology will be considered for review 3 years after publication. The guidance executive will decide whether the

technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Jane Adam
Chair, appraisal committee
March 2020

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee A](#).

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

The [minutes of each appraisal committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

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

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