NICE National Institute for Health and Care Excellence

Cancer Drugs Fund Review

Obinutuzumab with bendamustine for treating follicular lymphoma refractory to rituximab (CDF Review of TA472) [ID1583]

Committee Papers

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CANCER DRUGS FUND REVIEW

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Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from Roche Products

2. **Clarification questions and company responses**
   a. Responses
   b. Responses addendum

3. **Patient group, professional group and NHS organisation submission** from:
   a. Lymphoma Action

4. **Expert personal perspectives** from:
   a. Dr Graham Collins, Consultant Haematologist – clinical expert, nominated by Roche Products

5. **Evidence Review Group report** prepared by School of Health and Related Research (ScHARR)

6. **Evidence Review Group report – factual accuracy check**

7. **Public Health England Study Report**

8. **Technical report**

9. **Technical engagement response from company**

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

Cancer Drugs Fund Review of TA472

Obinutuzumab with bendamustine for treating follicular lymphoma refractory to rituximab [ID1583]

Company evidence submission for committee

November 2019

File name	Version	Contains confidential information	Date
20191106 GADOLIN CDF Review - Company Submission v1.0 [redacted].docx	**1.0**	**Yes**	**06 Nov 2019**

Instructions for companies

This is the template you should use for your evidence submission to the National Institute for Health and Care Excellence (NICE) as part of the Cancer Drugs Fund (CDF) review process. This document will provide the appraisal committee with an overview of the important aspects of your submission for decision-making.

This submission should not be longer than 25 pages, excluding the pages covered by this template. If it is too long it will not be accepted.

Provide supportive and detailed methodological or investigative evidence in an appendix to this submission.

When cross referring to evidence in the original submission or appendices, please use the following format: Document, heading, subheading (page X).

For all figures and tables in this summary that have been replicated, cross refer to the evidence from the main submission or appendices in the caption in the following format: Table/figure name – document, heading, subheading (page X).Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

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Tables and figures

Cancer Drugs Fund review submission

A.1 Background

- Obinutuzumab (Gazyvaro®) in combination with bendamustine (benda) followed by obinutuzumab maintenance (hereby G-benda+G) is recommended for use within the Cancer Drugs Fund (CDF) as an option for treating adults with follicular lymphoma (FL) that did not respond or progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen, only if the conditions in the managed access agreement for obinutuzumab are followed.
- The main source of clinical effectiveness evidence came from the phase III clinical trial GADOLIN. The committee noted that the overall survival (OS) data from the trial were immature and these data were used in the company's cost-effectiveness estimates. It was aware that more mature OS data were likely to be available from the trial by December 2020.
    - **Note:** The original end of study definition for GADOLIN was "when 226 deaths had occurred, which will be approximately 3.5 years after the last patient is enrolled". However, the end of study was later re-defined to when safety follow-up for all patients had been completed (2 years' safety follow-up from last dose). This change was made because the rate of death was much lower than initially projected, meaning the study would end approximately 5.5 years after the last patient enrolled. The last patient last visit occurred on 30 November 2018. See Table 4 for details on different data cuts for the GADOLIN study.
- The committee noted that the cost effectiveness estimates were largely dependent on the duration of the treatment effect on OS, and this was uncertain given the OS data were still immature. The committee considered that it was plausible that the treatment effect was longer than modelled in the company's base case, and agreed that the scenario analysis exploring a different duration of treatment effect on overall survival indicated a plausible potential for G-benda+G to be cost effective (Table 1).
    - **Note:** Table 1 has been updated from that presented in the terms of engagement document to include the updated results for incremental costs and ICERs at CDF entry, which applied an updated PAS.
- The committee considered that the availability of more mature OS data from GADOLIN was likely to resolve the uncertainty around the treatment effect and may give a more robust cost-effectiveness estimate. The committee therefore recommended G-benda+G as an option for use within the CDF as described above.

Table 1: ERG's cost effectiveness results at CDF entry (partitioned survival model only)

			PAS [redacted] (October 2016)		PAS [redacted] (CDF entry)	
Scenario	**Life years gained**	**QALY gained**	**Inc. cost**	**ICER**	**Inc. cost**	**ICER**
Company's base case Partitioned survival approach for overall survival, 5.5 years treatment effect (longest follow-up)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partitioned survival approach for overall survival, 7.0 years treatment effect (sensitivity analysis)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG's preferred estimate Partitioned survival approach for overall survival, 4.0 years treatment effect (last observed event)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partitioned survival approach for overall survival, 25 years treatment effect	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CDF: Cancer Drugs Fund, ERG: Evidence review group, ICER: Incremental cost-effectiveness ratio, QALY: Quality-adjusted life year

Data collection

The data collection agreement specifies the terms of data collection during the period of managed access (1). In summary:

- The magnitude of the OS benefit of G-benda+G compared to benda alone is the main clinical uncertainty.
- To resolve these uncertainties, the primary source of data collection is the ongoing pivotal GADOLIN study. The ongoing OS data collection is expected to reduce the uncertainty around the magnitude of treatment effect i.e. hazard ratio, by increasing the statistical power resulting from additional events and the duration of benefit as a result of the longer follow-up time. In addition, progression-free survival (PFS) assessed by the investigators and next anti-lymphoma treatment will be collected according to trial protocol with the view of updating the economic analysis.
- Observational data will be collected during the period of managed access via the systemic anti-cancer therapy (SACT) dataset to support the data collected in the clinical trial. SACT will collect data on overall survival and duration of therapy. Public Health England will provide a summary of the observational data collected.

A.2 Key committee assumptions

Table 2: Key committee assumptions

Area	Committee preferred assumptions
Population	• Adults with people with FL that are refractory to induction with rituximab in combination with chemotherapy, or who relapse early during rituximab maintenance
Intervention	• Induction with obinutuzumab plus bendamustine followed by maintenance treatment with obinutuzumab alone
Comparators	• Bendamustine
Generalisability	• The committee noted that the evidence base for the marketing authorisation of obinutuzumab was a subgroup from the GADOLIN trial of people with FL (about 81% of the total trial population)
GADOLIN	• The committee noted that G-benda+G resulted in longer PFS than benda induction treatment alone, but the mechanism and reason for this improvement is uncertain • The committee was uncertain whether the observed improvement in PFS was due to induction treatment with obinutuzumab plus benda, or to the additional obinutuzumab maintenance therapy (noting that there was no maintenance therapy in the benda arm)
Overall survival	• The committee noted that the OS data presented by the company were immature ○ The committee considered whether the statistically significant PFS benefit of G-benda+G is likely to translate into improved OS in the longer term • The committee agreed that this data would be helpful to address the uncertainty about the reliability of the limited data on OS for G-benda+G compared with benda • **The committee would like to see updated PFS and OS results form GADOLIN**

Model structure	• After the first committee meeting the committee demonstrated a preference for:
	  ○ using a partitioned survival approach
	  ○ adjusting utility estimates for the effects of aging
	  ○ assuming lower disease progression costs for subsequent treatments
	  ○ using the generic acquisition cost for benda
	  ○ correcting minor programming errors in the model
	  ○ using utility estimates from GADOLIN
	  ○ using alternative drug administration costing assumptions
	• These changes were incorporated into the company's model at the second committee meeting
	• The committee noted that the model population was based on GADOLIN (updated April 2016 data) and combined patients with FL that was refractory to induction treatment with rituximab monotherapy or R-chemotherapy, or was refractory during, or within 6 months of completing maintenance treatment with rituximab monotherapy
	• The committee considered this but concluded that the structure of the company model was acceptable and that it would not limit its consideration to a subgroup with R-chemotherapy refractory disease

	• **The committee expect to see the same model structure in the CDF review**
Duration of treatment effect	• The committee considered several scenarios altering the duration of the expected treatment effect of G-benda+G on OS and noted the ICER was particularly sensitive to this change • In light of the immature survival data the committee noted that G-benda+G may be cost effective if the treatment effect on survival persists for between 7 and 25 years • **The committee expect the company to explore this assumption in scenario analysis** • **The committee noted that because the cost-effectiveness estimates are largely dependent on the duration of the treatment effect on OS, the cost effectiveness estimates should be based on the final analysis of the GADOLIN trial**
Utilities	• Using utility estimates from GADOLIN
End-of-life	• Evidence for the end-of-life criteria was not presented or considered.

Benda: Bendamustine, CDF: Cancer Drugs Fund, FL: Follicular lymphoma, G-benda+G: Obinutuzumab (Gazyvaro) in combination with bendamustine (benda) followed by obinutuzumab maintenance, ICER: Incremental cost-effectiveness ratio, OS: Overall survival, PFS: Progression free survival, R: Rituximab

- Where data collection is anticipated to address the committee's key uncertainties, alternative assumptions should be explored and justified. NICE expects all other committee's preferred assumptions to remain unchanged at the CDF review.

Economic model

The economic model used to achieve the plausible potential was used as the basis for the CDF review. In accordance with the NICE process for the CDF review, the following functionality is available within the model at the CDF review:

- Replication of the key cost-effectiveness results used in committee's decision-making at the point of CDF entry
- Cost-effectiveness results that incorporate data collected during the CDF data collection period, with the assumptions used in committee's decision-making at the point of CDF entry
- Cost-effectiveness results that incorporate data collected during the CDF data collection period plus any associated changes to the company's preferred assumptions
- Capacity to run the key sensitivity and scenario analyses presented in the original company submission

A.3 Other agreed changes

In accordance with the NICE process for CDF review, no additional changes were made or additional evidence included in this submission.

A.4 The technology

Table 3: Technology being reviewed

UK approved name and brand name	Obinutuzumab (Gazyvaro®)
Mechanism of action	Obinutuzumab is a recombinant monoclonal humanised and glycoengineered Type II anti-CD20 IgG1 antibody. It specifically targets the extracellular loop of the CD20 transmembrane antigen on the surface of non-malignant and malignant pre-B and mature B-lymphocytes, but not on haematopoietic stem cells, pro-B-cells, normal plasma cells or other normal tissue (2, 3). Antibodies against CD20 deplete B-cells in lymphoid tissue and as a result, improve response rates, depth of remission, PFS, and OS in FL patients compared with chemotherapy alone (4, 5). Relative to Type I CD20 antibodies, e.g. rituximab, obinutuzumab has demonstrated enhanced antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP) and direct cell death while reducing complement dependent cytotoxicity (CDC) (4, 6). Furthermore, glycoengineering of the fragment crystallisable region of obinutuzumab has resulted in a higher affinity for FcγRIII receptors on immune effector cells such as natural killer cells, macrophages and monocytes as compared to non-glycoengineered antibodies, thereby enhancing ADCC and ADCP (4).
Marketing authorisation/CE mark status	On 16 June 2016, the European Medicines Agency approved obinutuzumab in combination with bendamustine chemotherapy followed by obinutuzumab maintenance in people with follicular lymphoma who did not respond or who progressed during or up to six months after treatment with rituximab or a rituximab-containing regimen
Indications and any restriction(s) as described in the summary of product characteristics	Obinutuzumab currently has additional marketing authorisation for the following therapeutic indications: • In combination with chlorambucil for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and with comorbidities making them unsuitable for full-dose fludarabine based therapy. • In combination with chemotherapy, followed by obinutuzumab maintenance therapy in patients achieving a response, for the treatment of patients with previously untreated advanced follicular lymphoma As noted in the summary of product characteristics, obinutuzumab will only be contraindicated to people who demonstrate hypersensitivity to the medicinal product or any of its excipients (2).
Method of administration and dosage	Obinutuzumab is for intravenous use. It should be given as an intravenous infusion through a dedicated line after dilution. For patients with FL, the recommended dose of obinutuzumab in combination with bendamustine is as follows: ***Induction in combination with bendamustine*** • Cycle 1: 1,000 mg administered on Day 1, Day 8 and Day 15 of the first 28 day treatment cycle

	• Cycles 2–6: 1,000 mg administered on Day 1 of each 28 day treatment cycle. ***Maintenance*** • 1,000 mg, every two months for two years or until disease progression (whichever occurs first)
Additional tests or investigations	n/a
List price and average cost of a course of treatment	**Average length of a course of treatment:** 6 cycles induction followed by up to 12 maintenance doses (i.e. one maintenance dose every 2 months for up to two years or until progression) **Obinutuzumab (list):** • £9,936 cycle 1 • £3,312 per cycle thereafter • £3,312 per maintenance dose With existing (current) PAS: [redacted] **Bendamustine (based on 1.92 m^2 BSA, no vial sharing):** • Per cycle: £68.46 • Total induction (cycles 1–6): £410.76 **Maximum total (based on 6 cycles induction and 2 years maintenance:** List: • £72,038 With existing PAS • [redacted]
Commercial arrangement (if applicable)	A simple patient access scheme (PAS) is in place for obinutuzumab ([redacted] discount from the list price [£3,312.00 per 1,000 mg vial] at [redacted] per 1,000 mg vial).
Date technology was recommended for use in the CDF	July 2017
Data collection end date	June 2019

ADCC: Antibody-dependent cellular cytotoxicity, ADCP: Antibody-dependent cellular phagocytosis, BSA: Body surface area, CDC: Complement dependent cytotoxicity, CLL: Chronic lymphocytic leukaemia, FL: Follicular lymphoma, mg: milligram, OS: Overall survival, PAS: Patient access scheme, PFS: Progression free survival

A.5 Clinical effectiveness evidence

Table 4: Primary source of clinical effectiveness evidence

Study title	GADOLIN (NCT01059630) (7)
Study design	Randomised, open-label Phase III clinical trial
Data cuts	Clinical cut-of-dates (CCODs) • Primary analysis – CCOD September 2014

	• Update 1 – CCOD May 2015 • Update 2 – CCOD April 2016 • Final – CCOD November 2018
Population	Patients with rituximab-refractory FL • History of histologically documented, CD20+, iNHL • Aged ≥18 years • ECOG 0–2 • Previously treated with a maximum of four unique chemotherapy-containing regimens • At least one bi-dimensionally measurable lesion (≥1.5 cm in its largest dimension by CT scan)
Intervention(s)	Obinutuzumab + bendamustine, followed by obinutuzumab maintenance monotherapy (n=164)
Comparator(s)	Bendamustine (n=171)
Outcomes collected that address committee's key uncertainties	• **Progression-free survival (investigator-assessed)** • **Overall survival**
Reference to section in appendix	n/a

CCOD: Clinical cut-off date, CT: Computed tomography, ECOG: Eastern Cooperative Oncology Group (performance status), FL: Follicular lymphoma, iNHL: indolent non-Hodgkins lymphoma

Table 5: Secondary source of clinical effectiveness evidence

Study title	**SACT data cohort study (8)**
Study design	SACT real-world data cohort study
Population	Patients with rituximab-refractory FL (N=92)
Intervention(s)	Obinutuzumab + bendamustine, followed by obinutuzumab maintenance monotherapy
Comparator(s)	Not applicable
Outcomes collected that address committee's key uncertainties	• Treatment duration • Overall survival
Reference to section in appendix	n/a

FL: Follicular lymphoma, SACT: Systemic Anti-Cancer Therapy dataset

The results from the SACT data cohort study support the final analysis of the Phase III GADOLIN study by providing real-world data from the relevant patient population in UK clinical practice. However, data from the SACT data cohort study were not included in the economic model since the final analysis of GADOLIN includes greater patient numbers and follow-up times.

A.6 Key results of the data collection

Primary source of clinical effectiveness evidence: GADOLIN

The efficacy results for the FL population in GADOLIN, at the time of the final clinical cut-off date (CCOD) of 30 November 2018, were consistent with the results of the primary analysis (9, 10). Please refer to the original company submission for full details on the GADOLIN study design.

A.6.1 GADOLIN - progression-free survival (investigator-assessed)

At the time of final analyses (CCOD November 2018), [redacted] of patients in the benda arm and [redacted] of patients in the G-benda+G arm had a PFS event of disease progression as assessed by the investigator, or death.

The INV-PFS in patients with FL (HR 0.51 [95% CI: 0.39; 0.67]) was consistent with that seen from the data cut at the point of CDF entry (CCOD 01 April 2016) (HR 0.52 [0.39, 0.69], p<0.001) (11, 12). The K-M-estimated median INV-PFS in the final analysis was 24.1 months [redacted] in the G-benda+G arm and 13.7 months [redacted] in the benda arm, an absolute increase in median INV-PFS of 10.4 months.

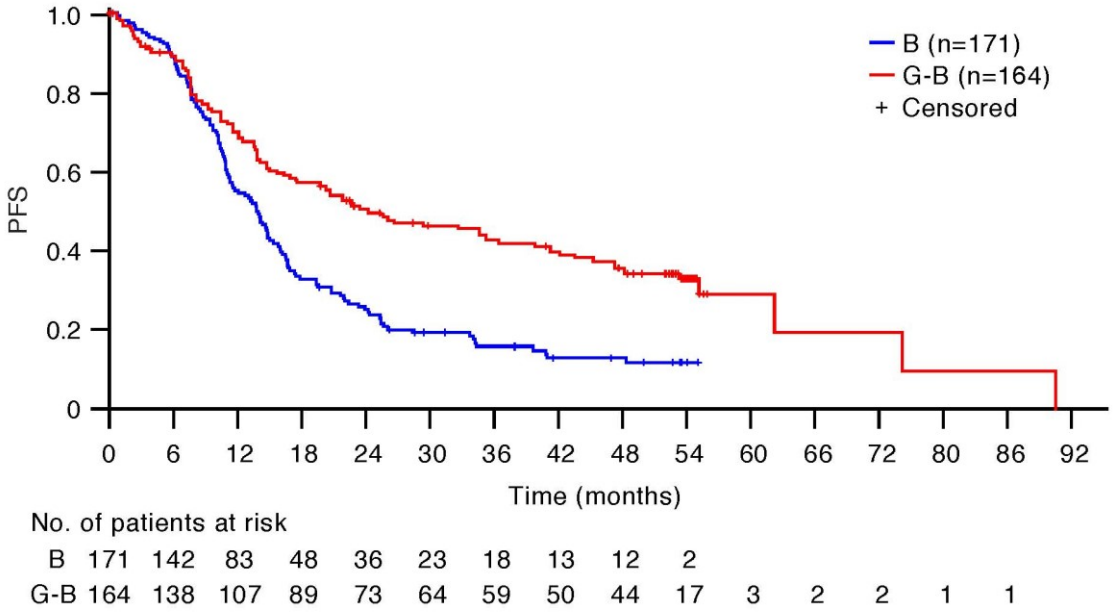
Table 6: Investigator-assessed PFS, FL patients (ITT population)

	Benda n=171	**G-benda+G n=164**
Patients with event, n (%)	[redacted]	[redacted]
Median PFS, months (95% CI)	13.7 [redacted]	24.1 [redacted]
Stratified hazard ratio (95% CI) p value (log-rank)	0.51 (0.39, 0.67) <0.0001	

Benda: Bendamustine, CI: Confidence interval, FL: Follicular lymphoma, G-benda+G: Obinutuzumab (Gazyvaro) in combination with bendamustine (benda) followed by obinutuzumab maintenance, ITT: Intention to treat, PFS: Progression free survival

The K-M plot of INV-PFS in patients with FL shows a clear separation of curves in favour of the G-benda+G arm starting after approximately 6 months in the trial. This corresponds to the time of the first obinutuzumab maintenance dose. The separation is maintained throughout the maintenance/observation period.

Figure 1: KM plot of investigator-assessed PFS, FL patients (ITT population)



B: Bendamustine, FL: Follicular lymphoma, G-B: Obinutuzumab (Gazyvaro) in combination with bendamustine (benda) followed by obinutuzumab maintenance, ITT: Intention to treat, KM: Kaplan-Meier, PFS: Progression free survival

A.6.2 GADOLIN - overall survival

Fewer deaths have occurred in the G-benda+G arm [redacted] compared to the benda arm [redacted]. The HR for risk of death in patients with FL was 0.71 (95%CI: 0.51, 0.98), compared to 0.58 (95% CI: 0.39, 0.86) at the time of the analysis at CDF entry (median OS 53.9 months [95% CI: 40.9, NR] vs. NR [95% CI: NR] in the benda and G-benda+G arms, respectively) (12).

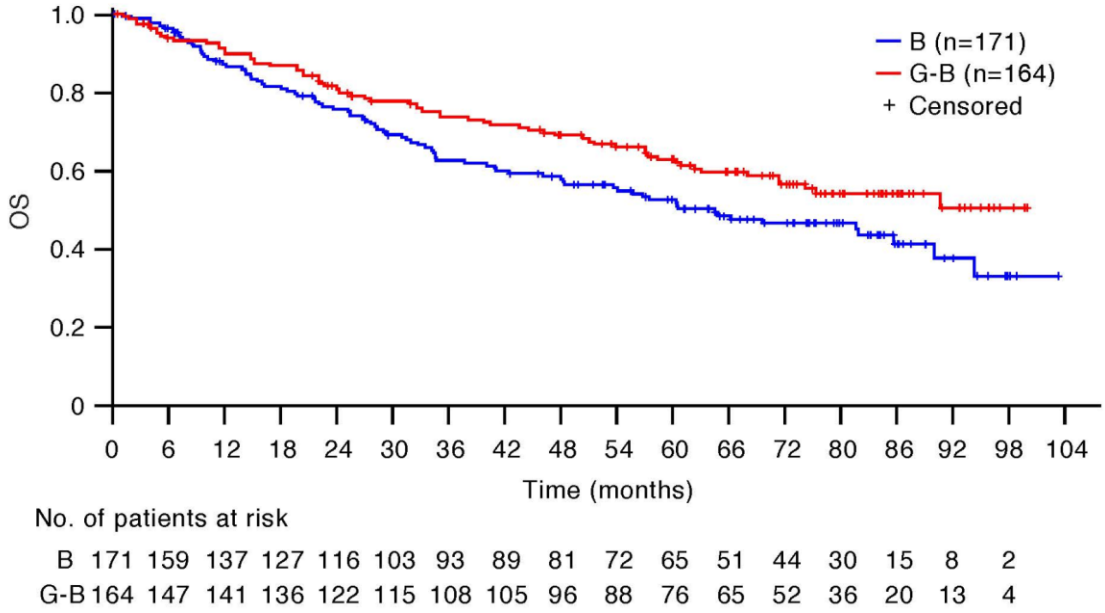
Table 7: Overall survival, FL patients (ITT population)

	Benda n=171	**G-benda+G n=164**
Patients with event, n (%)	[redacted]	[redacted]
Median time to event, months (95% CI)	60.3 [redacted]	NE [redacted]
Stratified hazard ratio (95% CI) p-value (log-rank)	0.71 (0.51, 0.98) p=0.0343	

Benda: Bendamustine, CI: Confidence interval, FL: Follicular lymphoma, G-benda+G: Obinutuzumab (Gazyvaro) in combination with bendamustine (benda) followed by obinutuzumab maintenance, ITT: Intention to treat, NE: Not estimable

Overall survival estimates are robust up to [redacted], at which point [redacted] deaths had occurred, and K-M-estimated event-free rate was [redacted] in the benda arm and [redacted] in the G-benda+G arm. The K-M plot for OS in patients with FL shows a clear separation of curves in favour of the G-benda+G arm from 6 months and beyond.

Figure 2: KM plot of overall survival, FL patients (ITT population)



B: Bendamustine, FL: Follicular lymphoma, G-B: Obinutuzumab (Gazyvaro) in combination with bendamustine (benda) followed by obinutuzumab maintenance, ITT: Intention to treat, KM: Kaplan-Meier

Secondary source of clinical effectiveness evidence: SACT data cohort

Please refer to the NHS England review for full details of the SACT data cohort (8).

Of the 97 new applications for CDF funding for obinutuzumab for rituximab-refractory FL, three patients did not receive treatment and two patients died before treatment. All (92/92) of these applicants for CDF funding have a treatment record in SACT.

Of the 92 patients with CDF applications, 55 (60%) were identified as having completed treatment by 28 February 2019 (latest follow up in SACT dataset). The median treatment duration for all patients was 5.3 months (95% CI: 4.8, 7.8). Forty-six percent of patients were still receiving treatment at 6 months (95% CI: 35, 56), 28% of patients were still receiving treatment at 12 months (95% CI: 18, 40).

A.6.3 SACT cohort – Overall survival (SACT report p.21)

Of the 92 patients with a treatment record in SACT, the minimum follow-up was 4 months from the last CDF application; the median follow-up time in SACT was 12.4 months. The K-M curve for overall survival, censored at 26 June 2019, is provided below. The median survival was not met. Survival at 6 months was 97% (95% CI: 90, 99), 12-month survival was 88% (95% CI: 79, 94).

A.6.4 SACT cohort sensitivity analysis – treatment duration (SACT report p.22)

Sensitivity analyses was carried out on a cohort with at least 6 months' follow-up in SACT. To identify the treatment duration cohort, CDF applications were limited from 26 July 2017 to 28 August 2018 and SACT activity was followed up to the 28 February 2019. Seventy patients

(76%) were included in these analyses. The median follow-up time in SACT was 149.5 days and the median treatment duration for patients in this cohort (N=70) was 4.9 months (95% CI: 4.1, 7.2).

A.6.5 SACT cohort sensitivity analysis – OS with at least 6 months follow up (SACT report p.24)

Sensitivity analyses was also carried out for OS on a cohort with at least 6 months' follow-up in SACT. To identify the cohort, CDF applications were limited from 26 July 2017 to 25 December 2018. Eighty-nine patients (97%) were included in the survival analyses with all patients having a minimum follow-up of 6 months. The median follow-up time in SACT was 12.4 months (377 days); median survival was not met.

A.7 Evidence synthesis

Not applicable for this review.

A.8 Incorporating collected data into the model

Duration of treatment

The duration of treatment, referred to in the original company submission of TA472 (Section 5.2.2, page 115 of 208) as time-to-off-treatment (TTOT), was mature at the time of the original submission and therefore an update was not available nor required, i.e. extrapolation of TTOT was not required as the follow up time reached the maximum time on treatment in both arms.

Safety

The safety profile for G-benda+G at the time of the final data cut (CCOD November 2018) was consistent with the primary analysis (CCOD September 2014) with respect to incidence, type, and severity of AEs. No new safety signals were observed with longer follow-up. Since both the safety results for the FL population, representing 81.1% of the ITT population, were similar to the results for the overall iNHL population, and safety did not represent a key uncertainty in the original appraisal of TA472, safety data were not updated in the current economic model.

Overall survival and progression-free survival

The primary source of clinical data, which formed the update to the economic model, was the GADOLIN study. Data from the final data cut (CCOD November 2018) informed the clinical parameters for PFS and OS in the updated economic model. The partitioned survival model approach, being the committees and ERGs preferred approach to model for OS and PFS, was retained for this updated cost-effectiveness analysis.

At the point of CDF entry, using the previous data cut of the GADOLIN trial (CCOD April 2016), OS was modelled using the observed Kaplan-Meier data applied until the time of the last event

following which survival was modelled using hazards from a dependent survival function (Weibull) fitted to the observed OS data. PFS was modelled only using the independent Weibull functions fitted to the observed PFS data for the entire time horizon, without direct use of the Kaplan-Meier curves.

The last event time and longest follow-up for OS were key data points used in the first economic models for TA472. The last survival event time was used to inform two modelling assumptions: (1) the switch from modelling OS directly using Kaplan-Meier estimates to the parametric extrapolation and (2) the conservative assumption of a limited duration of treatment effect upon OS. Table 8 summarises the changes seen in last event and longest follow-up time points from the April 2016 and November 2018 clinical cut off dates for overall survival.

Table 8: Last survival event and longest follow-up (CCOD April 2016 to CCOD November 2018

Arm:	Benda		G-benda+G	
CCOD:	Apr 2016	Nov 2018	Apr 2016	Nov 2018
Last event Months (years)	53.88 (4.49)	[redacted]	47.44 (3.95)	[redacted]
Longest follow-up Months (years)	65.05 (5.42)	[redacted]	65.91 (5.49)	[redacted]

Benda: Bendamustine, CCOD: Clinical cut-off date, G-benda+G: Obinutuzumab (Gazyvaro) in combination with bendamustine (benda) followed by obinutuzumab maintenance

As PFS and OS results from GADOLIN were extrapolated to the model lifetime time horizon, and lifetime results are not available for patients who participated in this study, guidance from NICE DSU Technical Support Document (TSD) number 14, was considered for survival analysis (13). This informed the choice of appropriate parametric survival models. Specifically, the following points were performed:

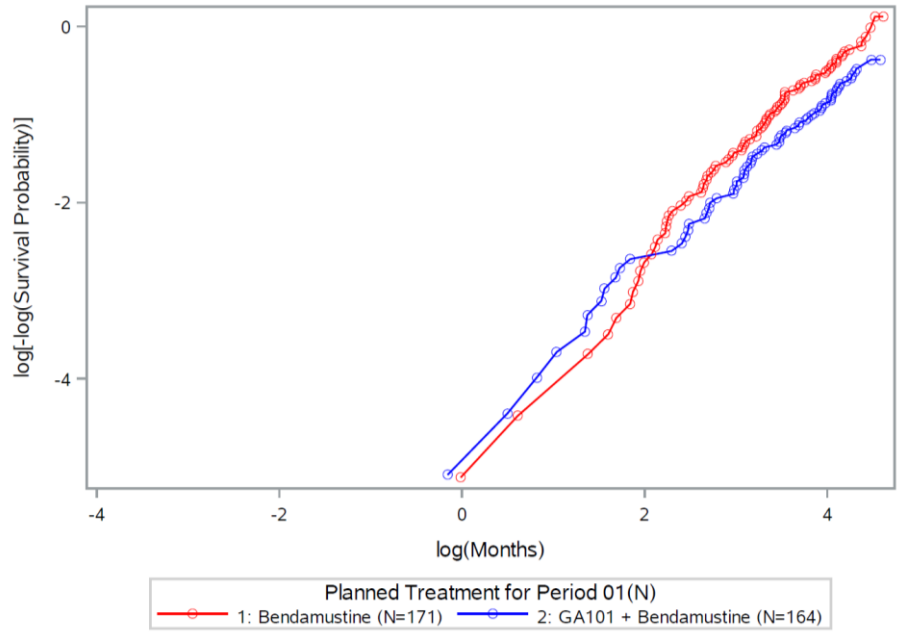
1. Visual inspection of the OS and PFS log-cumulative hazard plots, based on patient level data for the two arms of the GADOLIN trial for patients with FL, to test for the plausibility of the proportional hazards assumption and to examine the hazard of progression or death in each arm over time.
2. The Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) goodness-of-fit statistics were calculated to assess statistical fit of the models to PFS and OS KM data of both arms from the GADOLIN trial.
3. The clinical plausibility of the long-term extrapolations for the base case parametric models were validated by comparing the long-term behaviour of the models with the preferred expectations elicited during the initial STA review of TA472.

Assumptions that were preferred by the ERG and committee during the initial STA review of TA472 were considered when choosing updated survival curves against the observed survival results of the final data cut of the GADOLIN trial (CCOD November 2018).

A.8.1 Overall survival

An updated analysis for OS from the final data cut of GADOLIN (CCOD November 2018) was performed to derive parametric curves and fitting to the latest observed data set given that an area of uncertainty expressed by both the ERG and the committee was OS and the duration of treatment effect upon OS. The updated Kaplan-Meier data and dependent fitted curve parameters were incorporated into the model alongside the previous OS data from the previous data cut (CCOD April 2016).

Figure 3: Log-cumulative hazard plot for overall survival



GA101: Gazyvaro (obinutuzumab)

The proportional hazards (PH) assumption is carried forward from the original submission. Despite the crossing of the curves in Figure 3 early in the treatment phase, the curves appear to remain parallel and tend not to diverge, nor converge, after approximately 4 months. There is no evidence for a decline in treatment effect on OS until the maximum follow up of 98 months. The committees preferred choice of modelling OS, during the review of TA472 in 2016, was to use the Kaplan-Meier data directly to model OS until the last event followed by a parametric extrapolation. This option remains functional within the updated economic model. Since the time at which the last OS event observed is significantly greater than the time of crossing of the curves seen in the log cumulative hazards plot (Figure 3), the dependent parametric model, i.e. PH, remains a plausible and realistic prediction for the updated base case analysis.

To assess the goodness of fit of dependent parametric functions against individual patient level data AIC and BIC statistics are presented for dependent parametric curves, along with curve parameters themselves, in Table 9.

Table 9: AIC/BIC dependent analyses for OS

Distribution	Parameters				Fitting	
	Intercept	Treatment	Scale	Shape	AIC (rank)	BIC (rank)
Pooled						
Exponential	[redacted]	[redacted]	-	-	778.61 (4)	786.24 (1)
Weibull	[redacted]	[redacted]	[redacted]	-	780.61 (5)	792.05 (4)
Log-logistic	[redacted]	[redacted]	[redacted]	-	777.56 (2)	789.00 (3)
Log-normal	[redacted]	[redacted]	[redacted]	-	777.13 (1)	788.57 (2)
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	778.38 (3)	793.63 (6)
Gompertz	[redacted]	[redacted]	[redacted]	-	780.61 (6)	792.05 (5)

AIC: Akaike information criterion, BIC: Bayesian information criterion, OS: Overall survival

Table 10: OS (dependent) Weibull fit parameters and covariance matrices

Deterministic parameter value		Covariance matrix			
			Intercept	Treatment	Scale
Intercept	[redacted]	Intercept	[redacted]	[redacted]	[redacted]
Treatment	[redacted]	Treatment	[redacted]	[redacted]	[redacted]
Scale	[redacted]	Scale	[redacted]	[redacted]	[redacted]

OS: Overall survival

Whilst the dependent log-logistic and log-normal models represent the curve choices that rank in the top 3 best fitting for both AIC and BIC, other parametric functions had similar AIC or BIC values, and all reported within 4 integers of the lowest AIC (14). Therefore, the preferred extrapolation function had to be determined based on the plausible long-term behaviour. Long-term survival estimates at the time of the final data cut (CCOD November 2018) of GADOLIN remained consistent with the survival curves generated against the previous data cut (CCOD April 2016). Here the Weibull curve, also the base-case curve of choice against the previous data cut (CCOD April 2016), remains a conservative curve choice at CDF review (Table 11 and Figure 4). Despite not holding the best statistical fit to the observed data, the dependent Weibull model remained the curve of choice for the updated economic model, consistent with the ERG and committee preferred OS extrapolation in TA472.

A scenario analysis explores the log-normal model to test the impact on the ICER of a curve representing the best statistical fit to the updated observed data (CCOD November 2018).

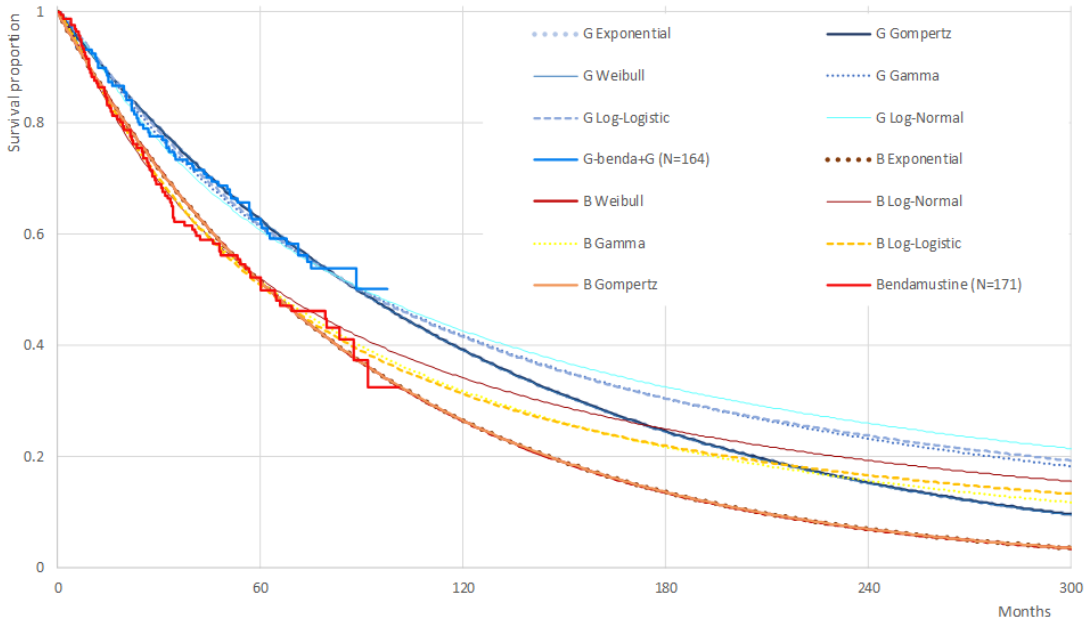
Table 11: 10-year survival estimates from dependent parametric curve extrapolations

Dependent parametric curves	10 year OS (%) extrapolation, April 2016 data cut analysis			10 year OS (%) extrapolation, November 2018 data cut analysis		
	G-benda+G	Benda	Incremental	G-benda+G	Benda	Incremental
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Benda: Bendamustine, G-benda+G: Obinutuzumab (Gazyvaro) in combination with bendamustine (benda) followed by obinutuzumab maintenance, OS: Overall survival

Figure 4: Overall survival plot showing Kaplan-Meier and extrapolated parametric (dependent) functions



G-benda+G: Obinutuzumab (Gazyvaro) in combination with bendamustine (benda) followed by obinutuzumab maintenance, Prefix B: Bendamustine, Prefix G: Obinutuzumab (Gazyvaro) in combination with bendamustine (benda) followed by obinutuzumab maintenance

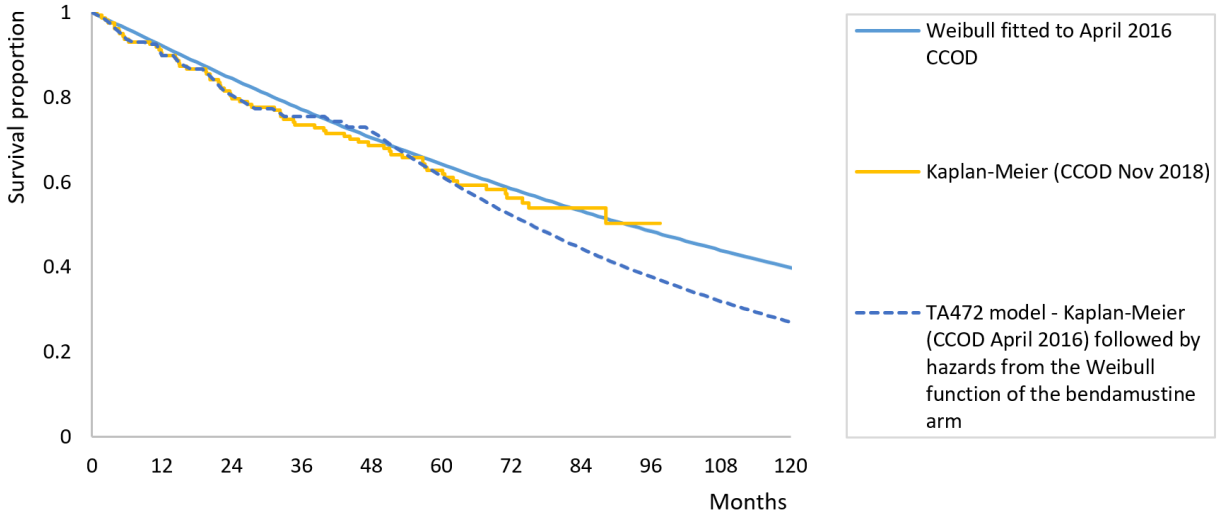
At the conclusion of the original appraisal for TA472, the duration of treatment effect upon overall survival was considered as an area of uncertainty. Meaning, that whilst the duration of treatment itself was already fully mature, there was speculation as to how long beyond the observed follow-up would the OS trend continue the predictions of the dependent parametric models. Figure 5 below depicts three curves:

1. Dependent Weibull curve from the analysis upon the data of the previous data cut (CCOD April 2016)
2. TA472 preferred model assumption for OS being the Kaplan-Meier directly followed by the hazards from the Weibull curve fitted to benda – that is, to infer a cap to the duration of treatment effect, and,
3. The latest Kaplan-Meier survival data from the final data cut of GADOLIN (CCOD November 2018)

Overall, Figure 5 shows that the updated Kaplan-Meier data (CCOD November 2018) follows far more closely the Weibull prediction at CDF entry rather than the previously preferred model assumption by the ERG that used a treatment effect cap of 4.0 years. Using independent parametric models for OS (exploratory) showed no evidence of a declining treatment effect and even increased the mean incremental years gained with G-benda+G versus benda alone. Given

the lack of evidence for a finite duration of treatment effect on OS, no such assumption was used in the base case for the updated economic analysis.

Figure 5: Model comparison – final OS Kaplan Meier for G-benda+G from GADOLIN against two prior modelling assumptions in TA472



CCOD: Clinical cut-off date, G-benda+G: Obinutuzumab (Gazyvaro) in combination with bendamustine (benda) followed by obinutuzumab maintenance, OS: Overall survival

Summary of approach to modelling OS, at CDF entry (CCOD April 2016):

1. Kaplan-Meier data used directly until the time of the last event.
2. After the time of the last event, parametric curves (dependent Weibull functions - fitted to the Kaplan-Meier data) informed the survival for the remainder of the time horizon.
3. Specifically for G-benda+G, the assumption of duration of treatment effect was assumed to cease after the time of the last event. In other words, from the time of the last event, hazards from the parametric fit (Weibull) to the benda arm modelled the OS of G-benda+G.

Updated approach to modelling OS, at CDF-Review (CCOD November 2018):

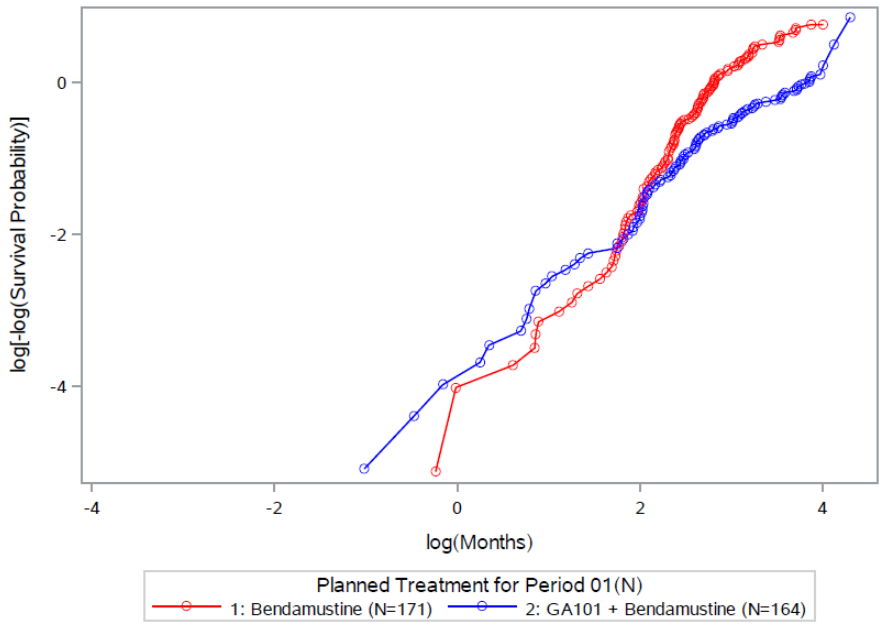
1. Fully fitted dependent Weibull functions against the updated OS data from the final data cut of GADOLIN (CCOD November 2018).
2. Assumption that the Weibull function would, for G-benda+G, be appropriate for the entire time horizon of the analysis, that is, the model does not apply a cap regarding the maximum duration of treatment effect upon OS.

A.8.2 Progression-free survival

An updated analysis for progression free survival (PFS) from the final data cut of GADOLIN (CCOD November 2018) was performed to derive parametric curves and fitting to the latest observed data set. The updated Kaplan-Meier data and independent fitted parameters were incorporated into the economic model. An updated log-cumulative hazard plot for PFS (Figure 6), demonstrates, due to curve crossing, convergence and divergence across time, that

independently fitted parametric models are appropriate given the violation of the PH assumption.

Figure 6: Log-cumulative hazard plot for progression free survival



GA101: Gazyvaro (obinutuzumab)

AIC and BIC statistics are presented separately for G-benda+G and benda to assess the goodness of fit of independent parametric functions against individual patient level data (Table 12).

Table 12: AIC/BIC independent analyses for PFS

Distribution	Parameters			Fitting	
	Intercept	Scale	Shape	**AIC** (rank)	**BIC** (rank)
G-benda+G					
Exponential	[redacted]	-	-	471.21 (4)	474.31 (3)
Weibull	[redacted]	[redacted]	-	472.21 (5)	478.41 (5)
Log-logistic	[redacted]	[redacted]	-	466.72 (1)	473.79 (2)
Log-normal	[redacted]	[redacted]	-	468.55 (3)	472.92 (1)
Gamma	[redacted]	[redacted]	[redacted]	467.59 (2)	477.85 (4)
Gompertz	[redacted]	[redacted]	-	473.21 (6)	479.41 (6)
Benda					
Exponential	[redacted]	-	-	437.13 (5)	440.27 (5)
Weibull	[redacted]	[redacted]	-	430.71 (4)	436.99 (4)
Log-logistic	[redacted]	[redacted]	-	410.52 (2)	409.04 (1)
Log-normal	[redacted]	[redacted]	-	412.5 (3)	416.81 (2)
Gamma	[redacted]	[redacted]	[redacted]	402.76 (1)	421.92 (3)
Gompertz	[redacted]	[redacted]	-	439.13 (6)	445.41 (6)

AIC: Akaike information criterion, Benda: Bendamustine, BIC: Bayesian information criterion, G-benda+G: Obinutuzumab (Gazyvaro) in combination with bendamustine (benda) followed by obinutuzumab maintenance, PFS: Progression free survival

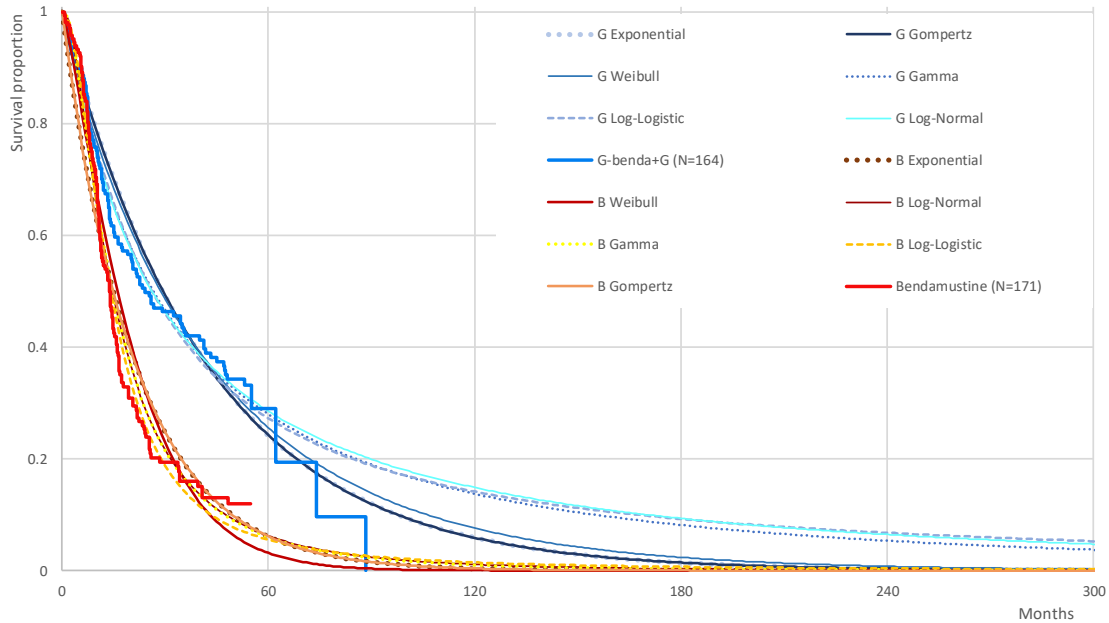
Whilst log-logistic curves represent the best statistically fitting model(s) to the updated observed PFS data, both the Weibull and exponential models represent more conservative longer term choices given the predictions in 10 year PFS seen in Table 13 and Figure 7. Since the Weibull function was the preferred choice of independently modelling PFS across both arms in TA472, this base case assumption remains for this updated cost-effectiveness analysis, with independently fitted log-logistic to both arms as a scenario analysis to explore the impact of choosing the best statistically fitting curve(s).

Table 13: 10-year progression free survival for independent parametric functions

Independent parametric curves	10 year PFS (%) extrapolation, April 2016 data cut analysis			10 year PFS (%) extrapolation, November 2018 data cut analysis		
	G-benda+G	Benda	Incremental	G-benda+G	Benda	Incremental
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Benda: Bendamustine, G-benda+G: Obinutuzumab (Gazyvaro) in combination with bendamustine (benda) followed by obinutuzumab maintenance, PFS: Progression free survival

Figure 7: PFS plot showing Kaplan-Meier and extrapolated parametric (independent) functions



Benda: Bendamustine, G-benda+G: Obinutuzumab (Gazyvaro) in combination with bendamustine (benda) followed by obinutuzumab maintenance, PFS: Progression free survival, Prefix B: Bendamustine, Prefix G: Obinutuzumab (Gazyvaro) in combination with bendamustine (benda) followed by obinutuzumab maintenance

Table 14 and Table 15 show the parameter values for the independent Weibull functions fitted to G-benda+G and benda respectively.

Table 14: PFS Weibull fit parameters and covariance matrix for G-benda+G

Deterministic parameter value		Covariance matrix		
			Intercept	Scale
Intercept	[redacted]	*Intercept*	[redacted]	[redacted]
Scale	[redacted]	*Scale*	[redacted]	[redacted]

G-benda+G: Obinutuzumab (Gazyvaro) in combination with bendamustine (benda) followed by obinutuzumab maintenance, PFS: Progression free survival

Table 15: PFS Weibull fit parameters and covariance matrix for benda

Deterministic parameter value		Covariance matrix		
			Intercept	Scale
Intercept	[redacted]	*Intercept*	[redacted]	[redacted]
Scale	[redacted]	*Scale*	[redacted]	[redacted]

Benda: Bendamustine, PFS: Progression free survival

A.9 Key model assumptions and inputs

The updated economic model structure remained as the partitioned survival approach (preferred by the ERG and the committee). Table O presents details of all other assumptions and inputs changed in base case of the economic model following the CDF data collection period, and the original parameter and/or assumption that contributed to the most conservative cost-effectiveness estimate proposed by the ERG and committee at the time of entry into the CDF (2016). All other parameters and assumptions remain unchanged from the economic model submitted to NICE during TA472.

Table 16: Key model assumptions and inputs

Model input and cross reference	Original parameter /assumption	Updated parameter /assumption	Source/Justification
Data cut			
Clinical Cut-Off Date (CCOD)	CCOD = April 2016 Data available at CDF entry pertaining to time to event outcomes were used to inform occupancy of PFS and OS, and their extrapolations	CCOD = November 2018 Kaplan Meier data and survival curve parameters for OS and PFS from the final data cut of GADOLIN (CCOD November 2018).	Updated Kaplan-Meier data and survival curve parameters taken from the analysis of the final data cut of GADOLIN (CCOD November 2018) are included into the economic model as the OS and PFS data collected during the longer follow-up of GADOLIN was expected to reduce the uncertainty perceived at the original appraisal of TA472. TTOT was mature at the previous data cut (CCOD April 2016) and therefore was not updated.

			The safety profile for G-benda+G at the time of the final data cut (CCOD November 2018) was consistent with the primary analysis and no new safety signals were observed with longer follow-up therefore an update to safety was not required in the updated economic model.
Progression-free survival (PFS)			
PFS extrapolation	Fully fitted Weibull curves, independently for both G-benda+G and benda arms	Curve choice unchanged (fully fitted Weibull curves, independently, for both G-benda+G and the benda arms) yet curve parameters specifically informed from survival analysis of the final data cut (CCOD November 2018).	PFS curve choice remains unchanged in the base case as the Weibull function continued to provide conservative long-term progression-free estimates, comparable to those estimated in TA472 using Weibull as the base case.
		Independent log-logistic curve choice for both arms as a scenario.	*A scenario explores the log-logistic curve independently fitted to each arm as this represents the best statistically fitting curve to the observed data.*
Overall survival (OS)			
Use of OS Kaplan-Meier data	OS was previously modelled using the Kaplan-Meier directly until the time of the last event, which at the time of the previous data cut (CCOD April 2016) was (4.0 years).	Kaplan-Meier not used directly to model OS.	Due to additional survival information obtained from the longer follow-up of the final data cut (CCOD November 2018), fitted survival functions are applied from month 0, i.e. the Kaplan-Meier is not used directly. This avoids potentially appending hazards to the tail of a curve past 7 years where relatively uncertain steps in Kaplan-Meier plots may occur and propagate to produce inaccurate cost-effectiveness estimates.
		An approach (using the Kaplan-Meier directly followed by a parametric extrapolation) is available as a scenario in the updated economic model. The updated value pertaining to the time of the last OS event in the final data cut (CCOD, November 2018), is now [redacted].	*The assumption to use the Kaplan-Meier directly until the time of the last OS event is presented as a scenario.*
Duration of treatment effect on OS	Various scenarios were considered for decision making during the original	Base case updated to assume no cap to the duration of treatment	The updated company preference (base case) to assume no cap to the duration of treatment effect on overall survival. This was informed

	appraisal of TA472 with regards to the duration of treatment effect on overall survival: 1. Time of the last OS event (4.0 years, CCOD April 2016) as the ERG preferred approach 2. Longest follow-up (5.5 years, CCOD April 2016) 3. Model time horizon as per NICE methods guide (25 years)	effect on overall survival: 1. Time of the last OS event ([redacted], CCOD November 2018) 2. Longest follow-up ([redacted], CCOD November 2018) 3. Model time horizon as per NICE methods guide (25 years) as the updated company base case.	due to a lack of observable decline in treatment effect for the longer follow up at the final data cut (CCOD November 2018), despite TTOT already being mature at the previous data cut (CCOD April 2016). The additional Kaplan-Meier data from the final data cut (CCOD November 2018), over and above the previous data cut (CCOD April 2016), showed that OS remained comparable to the parametric extrapolation predicted in 2016 assuming no cap to the duration of treatment effect (Figure 5, Section A.8.1).
OS extrapolation	Fully fitted dependent Weibull curves modelled OS after the time of the last OS event.	Curve choice unchanged (fully fitted Weibull curves, independently, for both G-benda+G and benda arms) yet curve parameters specifically informed from survival analysis of the final data cut (CCOD November 2018).	OS curve choice remains unchanged in the base case as the Weibull function continued to provide conservative long-term progression-free estimates, comparable to those estimated in TA472 using Weibull as the base case.
		Independent log-normal curve choice for both arms used as a scenario.	*This scenario explores the dependent log-normal curves to explore the impact on the ICER of choosing the best statistically fitting curve to the observed data as discussed in Section A.8.1.*
Costs			
Acquisition costs of the intervention and comparator treatments	The acquisition cost of obinutuzumab previously held a discount of [redacted], taking the cost of a vial of Gazyvaro (100 mg) to the NHS, down from a list price of £3,312.00 to [redacted] by use of the PAS effective in 2016. In 2016 the generic acquisition cost of benda was, in absence of eMIT data, estimated to be £27.77 and	The updated (current) PAS brings the acquisition cost of obinutuzumab down to the NHS to [redacted] per vial, and the presence of data available within eMIT brings the cost of benda down to £19.30 and £5.28 for 100 mg and 25 mg vials respectively.	Acquisition costs of medicines are often key drivers in the results seen through cost-effectiveness modelling. To ensure accurate modelling the most recent prices available are used.

	£6.85 respectively for vial sizes of 100 mg and 25 mg respectively (15).		

Benda: Bendamustine, CCOD: Clinical cut-off date, eMIT: Drugs and pharmaceutical electronic market information tool, ERG: Evidence review group, G-benda+G: Obinutuzumab (Gazyvaro) in combination with bendamustine (benda) followed by obinutuzumab maintenance, ICER: Incremental cost-effectiveness ratio, mg: milligram, NHS: National Health Service, OS: Overall survival, PAS: Patient access scheme, PFS: Progression free survival, TTOT: Time to off-treatment

A.10 Cost-effectiveness results (deterministic)

Results from the economic model submitted for the CDF review for the following cost-effectiveness analyses are described in the four cases below (each being a development to the previous case), and presented in Table 17.

(1) Replication of the key cost-effectiveness result(s) considered by committee to demonstrate plausible potential for cost-effectiveness at the time of entry to the CDF;

(2) Cost-effectiveness results that incorporate the data collected during the CDF data collection period, with all other model inputs, parameters, and assumptions unchanged from the cost-effectiveness analysis at CDF entry. These results represent the update to several key data inputs for OS and for PFS:

i) the updated Kaplan-Meier (product limit) data;
ii) the updated survival parameters for curves fitted to the most recent data cut using the same overall parametric curve choices from (1);
iii) the updated time of last OS event (used for duration of direct use of the Kaplan-Meier and also of treatment effect on OS) from 4.0 years (47.4 months) to [redacted];
iv) the updated time of last OS event in the benda arm used to model the Kaplan-Meier for benda OS against the observed data until the time of the last observed event: from 4.5 years (53.9 months) to [redacted].

(3) Cost-effectiveness results that incorporate data collected during the CDF data collection period and any associated changes to the prior preferred assumptions. That is, refined survival-modelling choices for OS to move from the Kaplan-Meier plus parametric extrapolation approach, to a fully parametric approach for the entire time horizon of the analysis. This iteration of the updated cost-effectiveness analysis also assumes no cap to the duration of treatment effect on OS of G-benda+G.

(4) As per (3) with the addition of updates to acquisition costs for obinutuzumab and benda updated to reflect the current PAS and most recent data from eMIT respectively (15).

Table 17: Cost-effectiveness results (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYsG	Inc. QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
Cost-effectiveness analysis 1: Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry								
G-benda+G	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Benda	20,634	5.43	3.62	-	-	-	-	-
Cost-effectiveness analysis 2: Analysis that demonstrated plausible potential for cost-effectiveness at CDF entry – incorporating updated clinical evidence								
G-benda+G	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Benda	21,883	6.02	3.97	-	-	-	-	-
Cost-effectiveness analysis 3: New company base-case								
G-benda+G	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Benda	21,844	5.99	3.96					
Cost-effectiveness analysis 4: New company base-case (updated clinical evidence, curve selections, and intervention and comparator acquisition costs)								
G-benda+G	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,408	[redacted]
Benda	21,687	5.99	3.96					

ICER: incremental cost-effectiveness ratio, Inc: incremental, LYsG: life years gained, QALYs: Quality-adjusted life years

A.11 Probabilistic sensitivity analysis (PSA)

All model variables, which had a distribution assigned, are presented in Table 18. Drug acquisition costs remained fixed. The results of 1,000 (one thousand) iterations of the probabilistic sensitivity analysis are presented in Table 19 and visually depicted in a scatter plot Figure 8 and a cost-effectiveness acceptability curve (Figure 9). In summary, the results of the PSA were consistent with the deterministic ICER and 94% of the iterations fell below the assumed £30,000 per QALY gained threshold.

Table 18: Parameters included in the probabilistic sensitivity analysis

Parameter	Uncertainty	Distribution	Comment
Weibull parameters for PFS G-benda+G arm	Covariance matrix (Table 14)	Multivariate normal	Updated parameters according to survival analysis of the final data cut of GADOLIN (CCOD November 2018)
Weibull parameters for PFS benda arm	Covariance matrix (Table 15)	Multivariate normal	
Weibull parameters for OS	Covariance matrix (Table 10)	Multivariate normal	
Utility PFS	Standard Error	Beta	Not changed from TA472
Utility PD	Standard Error	Beta	Not changed from TA472
Administration costs	25% of mean	Log-normal	Not changed from TA472
Pharmacy costs	25% of mean	Log-normal	Not changed from TA472
Supportive care costs PFS & PD	25% of mean	Log-normal	Not changed from TA472
Adverse event cost	25% of mean	Log-normal	Not changed from TA472
Number of adverse events	Standard deviation	Log-normal	Not changed from TA472

Benda: Bendamustine, G-benda+G: Obinutuzumab (Gazyvaro) in combination with bendamustine (benda) followed by obinutuzumab maintenance, OS: Overall survival, PD: Progressed disease, PFS: Progression free survival

Table 19: Updated base-case results (probabilistic)

Technologies	Total costs (£)	Total LYsG	Total QALYs	Inc. costs (£)	Inc. LYsG	Inc. QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
G-benda+G (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**17,593** (94% of the results of the PSA were below £30,000)	[redacted]
Benda (95% CI)	21,931 (16,140, 28,910)	6.02 (3.79, 8.24)	3.97 (2.63, 5.39)	-	-	-	-	-

Benda: Bendamustine, CI: Confidence interval, G-benda+G: Obinutuzumab (Gazyvaro) in combination with bendamustine (benda) followed by obinutuzumab maintenance, ICER: Incremental cost-effectiveness ratio, LYsG: Life years gained, PSA: Probabilistic sensitivity analysis, QALYs: Quality-adjusted life years

Figure 8: Scatterplot of probabilistic results

Benda: Bendamustine, G-benda+G: Obinutuzumab (Gazyvaro) in combination with bendamustine (benda) followed by obinutuzumab maintenance, QALYs: Quality-adjusted life years, WTP: Willingness to pay

Figure 9: Cost-effectiveness acceptability curve

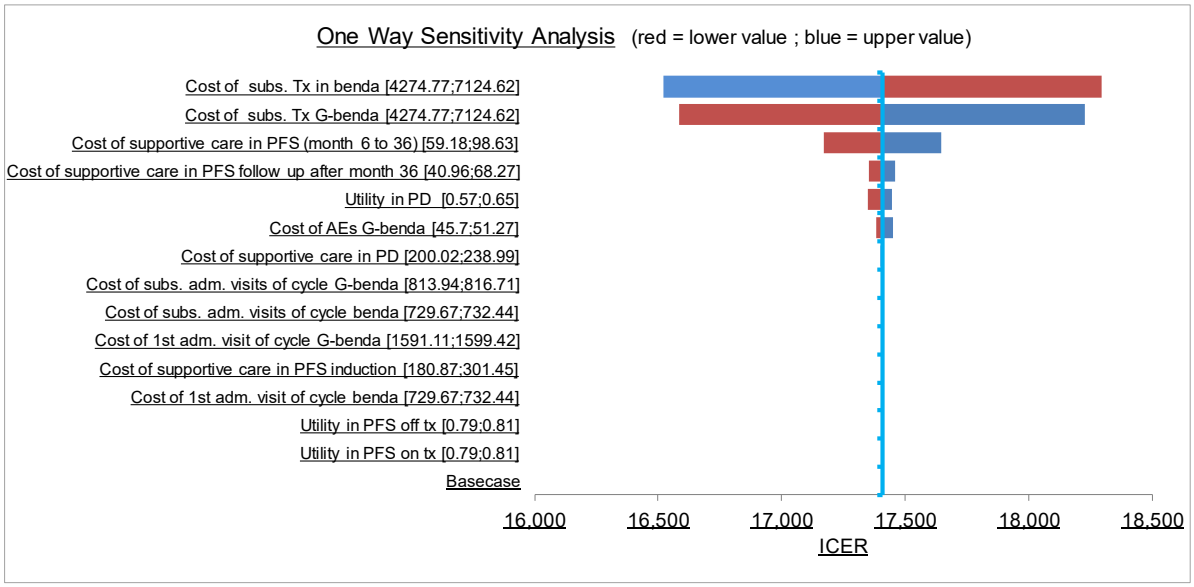
Benda: Bendamustine, QALY: Quality-adjusted life year

As Figure 8 suggests, and Figure 9 confirms, the probability of G-benda+G being the cost-effective choice of therapy at a threshold of £30,000 per QALY is 94%, based on 1000 iterations of the probabilistic model and results.

A.12 Key sensitivity and scenario analyses

The results of a deterministic (one-way) sensitivity analysis, using the same methodology described in the original company submission (Section 5.8.6, page 170 of 208) of TA472, are presented in Figure 10 as a tornado diagram. Scenario analysis for the partitioned survival approach are presented in Table 20.

Figure 10: Tornado diagram – one-way sensitivity analysis



adm: Administration, AEs: Adverse Events, Benda: Bendamustine, G-benda: Obinutuzumab (Gazyvaro) in combination with bendamustine (benda) followed by obinutuzumab maintenance, ICER: Incremental cost-effectiveness ratio, PD: Progressed disease, PFS: Progression free survival, Subs: Subsequent, Tx: Treatment

The largest driver of the differences in cost-effectiveness estimates seen in the tornado diagram are the costs of subsequent treatment in either arm where the highest deterministic ICER falls below £20,000 per QALY gained.

Table 20: Key scenario analyses

Updated base case			**ICER**
Overall survival (OS)	Dependent Weibull curves for the entire model time-horizon		**£17,408**
Duration of treatment effect on OS	No cap on the duration of treatment effect (*i.e.* set to 25 years)		
Progression-free survival (PFS)	Independent Weibull curves for the entire model time horizon		
Acquisition costs for intervention and comparator	Updated PAS ([redacted]% discount) for obinutuzumab and most recent eMIT average costs for benda		
Scenarios	**Scenario detail**	**Brief rationale**	**ICER** (Δ from base case)
[1] Duration of treatment effect on OS lasting until the time of the last OS event.	OS treatment effect until the time of last OS event ([redacted]) from the final data cut of GADOLIN (CCOD November 2018)	ERG preferred base-case (point 1) ERG report section 5.4.	**£21,470** (+£4,062)
[2] Duration of treatment effect assumption extended by [redacted] years in addition to the longest follow-up	The difference between the last OS event and the longest follow-up at the previous data cut (CCOD April 2016) was 1.5 years, this updated value is now [redacted] with the final data cut of GADOLIN (CCOD November 2018). Therefore, the updated duration of treatment effect assumption becomes [redacted].	Duration of treatment effect on OS was a key uncertainty recognised by the ERG and the committee at the point of entry into the CDF. This assumption was a specific scenario (number 2) seen in Table 9 on page 18 of 20 in the appendix to the response to the ACD of TA472.	**£20,327** (+£2,920)
[3] Progression free survival parametric curve choice	The scenario uses independently fitted log-logistic curves for both arms in the analysis.	As per section **A.8.2**, the log-logistic curve represents the best fitting parametric curve choice according AIC/BIC.	**£15,318** (-£2,089)
[4] Overall survival parametric curve choice	The scenario uses dependent log-normal curves for both arms in the analysis.	As per section **A.8.1**, the dependent log-normal curve represents the best fitting parametric curve choice according AIC/BIC.	**£20,206** (+£2,799)
[5] Overall survival modelling method – to use an approach	This scenario used the updated Kaplan-Meier information from the final	This scenario follows the preferred approach to	**£16,629** (-£779)

that refers to the Kaplan-Meier data directly followed by parametric extrapolation	data cut of GADOLIN (CCOD November 2018) directly to model OS until the time of the last event followed by a parametric extrapolation	modelling OS expressed by the ERG and committee during the initial reviews of TA472.	

ACD: Appraisal consultation document, AIC: Akaike information criterion, Benda: Bendamustine, BIC: Bayesian information criterion, CCOD: Clinical cut-off date, CDF: Cancer Drugs Fund, eMIT: Drugs and pharmaceutical electronic market information tool, ERG: Evidence review group, G-benda+G: Obinutuzumab (Gazyvaro) in combination with bendamustine (benda) followed by obinutuzumab maintenance, ICER: Incremental cost-effectiveness ratio, OS: Overall survival, PAS: Patient access scheme, PFS: Progression free survival

A.13 Key issues and conclusions based on the data collected during the CDF review period

The final clinical read out (CCOD November 2018) of the GADOLIN trial represents the key data collected during the CDF review period informing the update to the economic model. At the time of the final analysis, treatment with G-benda+G was associated with clinically meaningful improvement in INV-PFS in patients with FL compared to benda alone (HR 0.51; 95% CI: 0.39; 0.67), with an absolute increase in median PFS of 10.4 months. The final analysis also provides robust overall survival estimates; with up to 54 months follow up, the risk of death with G-benda+G was reduced by 29% compared to the benda arm (HR 0.71; 95% CI: 0.51; 0.98, p=0.0343).

The updated clinical results pertaining to OS and PFS continued to demonstrate the trend the company had expected, and modelled, at prior data cuts, that is, the final data cut of GADOLIN was confirmatory to the clinical information and extrapolations previously presented at the time of the last data cut (CCOD April 2016). The further follow-up also did not provide any evidence for a finite duration of treatment effect on OS. This data instead confirmed that the extrapolation of OS preferred by the ERG at CDF entry underestimated the actual observed OS benefit. The final analysis from GADOLIN (CCOD November 2018) successfully reduced the uncertainty around the average benefits in PFS and OS, and therefore provided robust estimates in terms of both clinical efficacy and QALYs gained within the economic model.

The cost-effectiveness results (ICERs) in the current analysis are considerably less than the results seen at CDF entry (CCOD April 2016). Even without incorporating the updated PAS the ICER of the ERGs preferred scenario fell from [redacted] to [redacted] per QALY gained (Analysis 2 of Table 17), meaning the larger clinical benefits seen at the final data cut (CCOD November 2018) compared to the scenarios used at CDF entry, propagated into reduced ICERs. The current net price for Gazyvaro (obinutuzumab), and choice of modelling OS informed by the new data, brought the ICER down further: the updated base-case returned a deterministic ICER of £17,408 per QALY gained, with a 94% probability of G-benda+G being the cost-effective choice of therapy under a probabilistic analysis, assuming a willingness-to-pay threshold of £30,000 per QALY gained.

The updated base case cost effectiveness analysis, and all scenario analyses, demonstrate that G-benda+G, for the treatment of rituximab-refractory FL, is a cost-effective use of NHS resources and offers a significant extension of PFS and OS for patients in a setting where there are limited treatment options. This final analysis from the GADOLIN trial confirms the company's prediction of long-term clinical and cost effectiveness estimated as the base case option at the time of the original submission and point of CDF entry. Furthermore, the assumption of the effect of G-benda+G treatment stopping at 4 years (at the time of the last OS event) has proven to be inaccurate following the final analysis of the GADOLIN trial. Therefore, G-benda+G for the treatment of rituximab-refractory FL offers a significant extension of PFS and OS for patients in a setting where there are limited treatment options, with the updated base case cost effectiveness analysis (and all scenario analyses) demonstrating that G-benda+G is a cost effective use of NHS resources.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Obinutuzumab in combination with bendamustine for treating rituximab-refractory follicular lymphoma (CDF review TA472) – [ID1583]

Clarification questions

November 2019

File name	Version	Contains confidential information	Date
ID1583 Obinutuzumab - Company CDF-R Clarification Responses v1.0 [redacted]	**1**	**Yes**	**5 December 2019**

Section A: Clarification on effectiveness data

A1. Page 31 of the company's CDF-R submission states that "At the time of the final analysis, treatment with G-benda+G was associated with clinically meaningful improvement in INV-PFS in patients with FL compared to benda alone (HR 0.51; 95% CI: 0.39; 0.67), with an absolute increase in median PFS of 10.4 months"
Please clarify what is regarded as a clinically meaningful benefit in terms of absolute risk, median time to progression-free survival and mean time to progression-free survival.

People with follicular lymphoma (FL) may live for many years after diagnosis. In England and Wales, Cancer Research UK notes that approximately 90% of stage I and stage II patients with FL survive for 5 years or more following diagnosis. The 5-year survival rate declines to approximately 80% in patients with stage III or IV disease (1).

However, data from the US National LymphoCare study has demonstrated that rituximab refractory patients (i.e. patients that had progressed within 2 years of treatment) have a poorer prognosis than responders; 5-year survival among patients with progressive disease was 50% compared with 90% for patients responding to a rituximab containing regimen (2).

Due to a limited number of treatment options available for these patients there is a high unmet need for novel agents which demonstrate good efficacy (e.g. longer duration of response with acceptable safety profiles) for rituximab refractory/ relapsed FL patients.

At the final analysis, treatment of FL patients with G-benda+G resulted in a reduction in the risk of having a PFS event as assessed by the investigator of 49% compared with benda (HR 0.51 [0.39, 0.67], p<0.001) (3), which was consistent with that seen from the data cut at the point of CDF entry (CCOD 01 April 2016) (HR 0.52 [0.39, 0.69], p<0.001) (4, 5). The K-M-estimated median INV-PFS in the final analysis was 24.1 months [redacted] in the G-benda+G arm and 13.7 months

[redacted] in the benda arm, resulting in an absolute increase in median INV-PFS of 10.4 months

In accordance with the unmet need outlined above, we consider these results to be 'clinically meaningful' and this view has been corroborated by the clinical expert opinion (6).

A2. The submission states on page 13, "Overall survival estimates are robust up to [redacted]" What is the relevance of the [redacted] time point and how has 'robust' been determined?

From a statistical perspective, robustness means the time when ≤20% patients are at risk. For the GADOLIN analysis, this rule was not applied and more conservative estimates of robustness were taken, namely when <50% patients were at risk. At the the final analysis, the time point at which the overall rate of patients at risk falls below 50% is from [redacted] onward, therefore OS estimates can be deemed to be robust up to [redacted].

A3. Please provide details of the causes of death in each arm of the GADOLIN trial, and how many were attributable to study drug, using data from the final data cut.

At the time of the final analysis, 184 patients (100/203 [49.3%] in the benda arm; 84/204 [41.2%] in the G-benda+G arm) in the iNHL population had died during the entire study period (an additional 59 patients since the previous updated analysis [1 April 2016]). The major cause of death was disease progression [redacted].

Summary of deaths by phase is provided below.

Table 1: Summary of deaths by phase in GADOLIN (safety evaluable population)

	Benda n=203	G-benda+G n=204
Induction phase		
Subject status, n (%) Alive Dead	[redacted]	[redacted]
Cause of death, n (%) Adverse event Disease progression Other	[redacted]	[redacted]
Follow up after induction phase		

Subject status, n (%) Alive Dead	[redacted]	[redacted]
Cause of death, n (%) Adverse event Disease progression Other	[redacted]	[redacted]
Maintenance treatment phase		
Subject status, n (%) Alive Dead	[redacted]	[redacted]
Cause of death, n (%) Adverse event Disease progression Other	[redacted]	[redacted]
Follow up after maintenance phase		
Subject status, n (%) Alive Dead	[redacted]	[redacted]
Cause of death, n (%) Adverse event Disease progression Other	[redacted]	[redacted]

Source: Final analysis CSR

Table 2: Adverse events leading to death

MedDRA SOC and Preferred Term, n (%)	Benda n=205	G-benda+G n=204
Total number of deaths	[redacted]	[redacted]
Infections and infestations Sepsis Pneumocystis jirovecii pneumonia Escherichia sepsis Fungal sepsis Gastroenteritis Neutropenic sepsis Pneumonia Pseudomonal sepsis Coxsackie myocarditis	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Acute myeloid leukaemia Adenocarcinoma Adenocarcinoma gastric Bladder cancer Colorectal cancer Intestinal adenocarcinoma Leukaemia Malignant melanoma Myelodysplastic syndrome T-cell lymphoma	[redacted]	[redacted]
Nervous system disorders Ischaemic stroke Amyotrophic lateral sclerosis	[redacted]	[redacted]
Blood and lymphatic system disorders Agranulocytosis	[redacted]	[redacted]
Cardiac disorders Myocardial infarction	[redacted]	[redacted]
Immune system disorders Graft versus host disease	[redacted]	[redacted]

Injury, poisoning and procedural complications Vascular pseudoaneurysm	[redacted]	[redacted]
Metabolism and nutrition disorders Tumour lysis syndrome	[redacted]	[redacted]
Renal and urinary disorders End stage renal disease	[redacted]	[redacted]
Vascular disorders Circulatory collapse	[redacted]	[redacted]

*events considered to be related to benda in patients with FL (sepsis, pneumocystis jirovecii pneumonia (x2), acute myeloid leukaemia (x2), leukaemia)
†events considered to be related to G-benda+G in patients with FL (amyotrophic lateral sclerosis, acute myeloid leukaemia, myelodysplastic syndrome, coxsackie myocarditis)
Source: Final CSR

A4. Please provide a table showing how the baseline characteristics in the follicular lymphoma (FL) subgroup of the GADOLIN trial compare with those of patients treated in the systemic anti-cancer therapy (SACT) dataset. Please include data equivalent to that provided in table 4 and table 5 of the SACT report (i.e. age, sex, performance status, timing of progression on rituximab) for the G-benda+G arm of the GADOLIN trial.

Table 3: Patient demographics and baseline characteristics (FL population)

	Benda n=171	**G-benda+G n=164**
Mean age, years (SD)	62.4 (11.0)	61.8 (11.2)
Male, n (%)	98 (57.3)	91 (55.5)
Race, n (%)		
Caucasian	148 (86.5)	144 (87.8)
Black or African American	3 (1.8)	3 (1.8)
Asian	2 (1.2)	4 (2.4)
American Indian or Alaska Native	2 (1.2)	1 (0.6)
Multiple	1 (0.6)	0
Unknown	15 (8.8)	12 (7.3)
Geographic region, n (%)		
Western Europe	79 (46.2)	78 (47.6)
Eastern Europe	18 (10.5)	19 (11.6)
North America	74 (43.3)	67 (40.9)
ECOG PS, n (%)	n=169	n=164
0–1	162 (95.9)	156 (95.1)
2	7 (4.1)	8 (4.9)
Ann Arbor Stage, n (%)	n=170	n=164
I	9 (5.3)	9 (5.5)
II	20 (11.8)	16 (9.8)
III	45 (26.5)	33 (20.1)
IV	86 (50.6)	96 (58.5)
Unknown	10 (5.9)	10 (6.1)

FLIPI, n (%) Low (0,1) Intermediate (2) High (≥3) Unknown	n=170 35 (20.6) 60 (35.3) 69 (40.6) 6 (3.5)	n=164 42 (25.6) 51 (31.1) 64 (39.0) 7 (4.3)
β2 microglobulin, n (%) <3.5 mg/L ≥3.5 mg/L	n=158 123 (77.8) 35 (22.2)	n=158 127 (80.4) 31 (19.6)
Bone marrow involvement at BL, n/patients with data (%)	51/160 (31.9)	45/159 (28.3)
Extranodal involvement, n/patients with data (%)	80/170 (47.1)	87/164 (53.0)
Bulky disease at BL (6 cm threshold), n/patients with data (%)	60/169 (35.5)	53/164 (32.3)
Mean time from diagnosis to randomisation, years (range)	4.25 (0.3–29.9)	4.26 (0.3–32.1)
Refractory to rituximab monotherapy, n (%) PD prior to last rituximab dose Best response of stable disease PD within 6 months of last rituximab dose	42 (24.6) 4 (9.5) 14 (33.3) 24 (57.1)	25 (15.2) 3 (12.0) 5 (20.0) 17 (68.0)
Refractory to rituximab + chemotherapy, n (%) PD prior to last rituximab induction dose Best response of stable disease PD within 6 months after last rituximab induction dose PD during or within 6 months after last rituximab maintenance dose PD within 6 months of last maintenance dose* PD > 6 months after last rituximab dose but within 6 months after best response† Not refractory	129 (75.4) 1 (0.8) 18 (14.0) 46 (35.7) 62 (48.1) 1 (0.8) 1 (0.8) 0	139 (84.8) 4 (2.9) 29 (20.9) 24 (17.3) 76 (54.7) 3 (2.2) 0 (0.0) 3 (2.2)

Benda, bendamustine; BL, baseline; ECOG, Eastern Cooperative Oncology Group performance score; FLIPI, follicular Lymphoma International Prognostic Index; G-benda+G, Gazyvaro + bendamustine followed by Gazyvaro maintenance; iNHL, indolent non-Hodgkin lymphoma; PD, disease progression; SD, standard deviation
*No induction rituximab or last rituximab induction dose unknown
†Considered as refractory for stratification purposes

Table 4: Patient characteristics in the SACT cohort

Characteristic	SACT cohort n=92
Median age, years	65
Age group, n (%)	
<40	1 (1)
40-49	11 (12)
50-59	21 (23)
60-69	25 (27)
70-79	28 (30)
80+	6 (7)
Male, n (%)	54 (59)
ECOG PS, n (%)	
0-1	65 (71)
2	6 (7)
Missing	21 (23)
Failed to respond to or progressed on rituximab induction, n (%)	48 (52)
Progressed on maintenance rituximab or within 6 months of induction, n (%)	44 (48)

Months to progression, n (%)	
≤6 months	26 (59)
>6 months	12 (27)
not captured	6 (14)

A5. Please provide data on reasons for treatment discontinuation for the FL subgroup of the GADOLIN trial (separately by trial arm and using data from the final data cut) for comparison with the data in table 9 of the SACT report. Data similar to that provided in figure 1 of Cheson et al. (2018), but specific to the FL subgroup of the GADOLIN trial would be suitable.

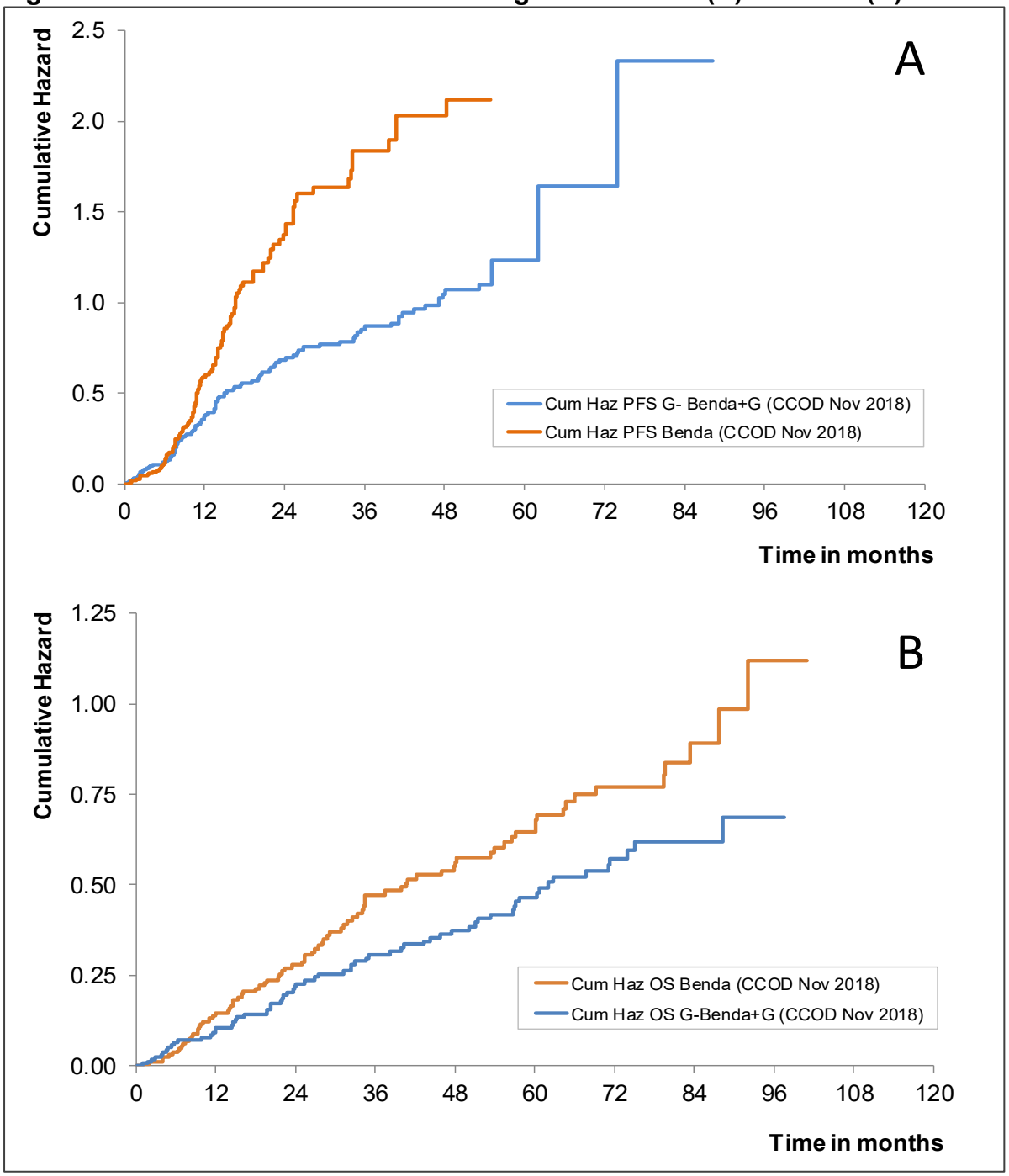
Table 5: Summary of disposition in GADOLIN – FL patients

Status, n (%)	Benda n=171	G-benda+G n=164
Induction started	[redacted]	[redacted]
Ongoing	[redacted]	[redacted]
Completed	[redacted]	[redacted]
Withdrawn	[redacted]	[redacted]
Reasons for withdrawal from induction		
Adverse event	[redacted]	[redacted]
Death	[redacted]	[redacted]
Other	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Withdrawal by subject	[redacted]	[redacted]
Maintenance started	[redacted]	[redacted]
Ongoing	[redacted]	[redacted]
Completed	[redacted]	[redacted]
Withdrawn	[redacted]	[redacted]
Reasons for withdrawal from maintenance		
Adverse event	[redacted]	[redacted]
Death	[redacted]	[redacted]
Other	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Withdrawal by subject	[redacted]	[redacted]
Withdrawn from study	[redacted]	[redacted]
Study terminated by sponsor	[redacted]	[redacted]
Death	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]
Withdrawal by subject	[redacted]	[redacted]

G-B patients can have multiple treatment discontinuation reasons and were counted for each but will be counted only once for the treatment discontinuation total.
The two patients randomised to Benda who crossed over to the G-benda+G arm in maintenance are included in the Benda arm.
Source: Final CSR

A6. PRIORITY Please provide plots of the PFS and OS cumulative hazard functions against time using data from the final data cut.

Figure 1: Cumulative hazard functions against time for (A) PFS and (B) OS



Benda: Bendamustine, CCOD: Clinical cut-off date, Cum Haz: Cumulative Hazards, G-benda+G: Obinutuzumab (Gazyvaro) in combination with bendamustine (benda) followed by obinutuzumab maintenance, OS: Overall survival, PFS: Progression free survival

Section B: Clarification on cost-effectiveness data

B1. PRIORITY Please provide a re-analysis of the progression-free survival data modelling the G-benda+G arm of the GADOLIN study as a change-point model incorporating i) a fixed change-point model at six months and ii) a random change-point, to allow for the change in treatment after six months.

Please refer to the addendum of the company response.

B2. PRIORITY Please provide a re-analysis of the overall survival data allowing for time-varying hazards (either as separate models for each treatment arm or with treatment effects for each parameter in the baseline model). Also, for the G-benda+G arm of the GADOLIN study, model the data using a change-point model incorporating i) a fixed change-point model at six months and ii) a random change-point, to allow for the change in treatment after six months.

The cost-effectiveness model within the company CDF-R submission contains the option to model OS using independent parametric functions. Fitting statistics (AIC and BIC), curve parameters, and undiscounted 10-year survival rates are presented for these independent parametric curves in Table 6.

Table 6: Independent analyses for OS

Distribution	Parameters			Fitting		10-year survival rate
	Intercept	Scale	Shape	AIC (rank)	BIC (rank)	
G-benda+G						
Exponential	[redacted]	-	-	366.67 (1)	369.77 (1)	39.3%
Weibull	[redacted]	[redacted]	-	368.56 (4)	374.76 (4)	40.2%
Log-logistic	[redacted]	[redacted]	-	368.28 (3)	374.22 (2)	45.6%
Log-normal	[redacted]	[redacted]	-	369.69 (6)	374.48 (3)	43.3%
Gamma	[redacted]	[redacted]	[redacted]	368.02 (2)	378.99 (6)	43.3%
Gompertz	[redacted]	[redacted]	-	368.67 (5)	374.87 (5)	39.3%
Benda						
Exponential	[redacted]	-	-	411.94 (4)	415.08 (1)	26.6%
Weibull	[redacted]	[redacted]	-	413.81 (5)	420.10 (5)	25.7%
Log-logistic	[redacted]	[redacted]	-	408.80 (2)	417.00 (4)	31.5%
Log-normal	[redacted]	[redacted]	-	408.80 (1)	415.09 (3)	31.6%
Gamma	[redacted]	[redacted]	[redacted]	410.72 (3)	415.08 (2)	29.8%
Gompertz	[redacted]	[redacted]	-	413.94 (6)	420.22 (6)	26.6%

AIC: Akaike information criterion, Benda: Bendamustine, BIC: Bayesian information criterion, G-benda+G: Obinutuzumab (Gazyvaro) in combination with bendamustine (benda) followed by obinutuzumab maintenance, OS: Overall survival

The ICER decreases from £17,408 per QALY gained to £16,382 per QALY gained when retaining the Weibull function from the company base-case but switching to independent models, driven by an increase in the mean OS difference between G-benda+G and benda. The ICER also decreases marginally when the independent exponential function is used for both arms; the exponential function being the best fitting independent model to G-benda+G across both criterions, and returning the most conservative 10-year survival rate for G-benda+G of the independent distributions.

The above demonstrates that the company base case, which utilises dependent models under the proportional hazards assumption, is a conservative approach to estimating the cost-effectiveness for G-benda+G in this indication.

Please refer to the addendum of the company response regarding the change-point analysis portion of this clarification question.

B3. Please clarify the interpretation of the treatment effect parameter for the models presented in table 9 (page 18 of the company submission).

The values seen within the treatment column of Table 9 (page 18) of the company submission (CDF review) represent the covariate coefficients from the SAS standard output when using the LIFEREG procedure. If there were not to be any covariates in the model, μ would simply be the intercept from the SAS output. For the case in question, the treatment becomes the covariate and $\mu = x'\beta$. In this case, β (the covariate coefficient) is the treatment effect parameter. Supporting documents for the LIFEREG procedure (used in SAS) is available via support.sas.com. Here the parametrisation of distributions used are fully characterised (7).

B4. Please provide information regarding the potential for a differential treatment effect by non-Hodgkin's Lymphoma (NHL) subtype using a single model allowing for interaction with treatment for both PFS and OS outcomes.

The FL population constituted 81.1% of the GADOLIN study population, with the remaining 18.9% constituting other NHL subtypes, namely marginal zone lymphoma (11.4%), small lymphocytic lymphoma (7.3%) and Waldenstrom macroglobulinaemia (0.2%).

The 2008 revision to the World Health Organisation Lymphoma Diagnostic Criteria does not define indolent Non-Hodgkin Lymphoma (iNHL) but individual sub-types, such as FL; therefore, the EMA would only consider licensing in these individual subtypes. As a result, the marketing authorisation granted for G-benda+G was for patients with rituximab-refractory FL, with the scope for the original NICE appraisal also stipulating the population as people with FL that is refractory to rituximab or rituximab-containing regimens.

For completeness, the PFS and OS data for the entire ITT population, i.e. iNHL population is provided below, although data from these subtypes have not been incorporated in the economic analysis due to them not being included within the approved marketing authorisation or scope for this appraisal.

Treatment of patients in the G-benda+G arm of the ITT population of patients with iNHL resulted in a clinically meaningful 43% reduction in the risk of disease progression (as assessed by the investigator) or death, compared with patients in the benda arm (HR 0.57 [95% CI: 0.45, 0.73], stratified analysis). The treatment effect has remained relatively stable since the primary analysis. The K-M-estimated median duration of INV-PFS was 14.1 months [redacted] in the benda arm and 25.8 months [redacted] in the G-benda+G arm, an absolute increase in median PFS of 11.7 months.

Table 7: INV-assessed PFS, iNHL patients (ITT population), stratified analysis

	Benda n=209	**G-benda+G n=204**
Patients with event, n (%)	[redacted]	[redacted]
Median PFS, months (95% CI)	14.1 [redacted]	25.8 [redacted]
Hazard ratio (95% CI)	0.57 (0.45, 0.73)	
p value*	<0.0001	

*log-rank test
Benda, bendamustine; CI, confidence interval; G-benda+G, obinutuzumab (Gazyvaro) + bendamustine followed by obinutuzumab maintenance; NE, not estimated; PFS, progression-free survival

The OS for G-benda+G over benda in the ITT population was stable with longer follow-up; the HR for risk of death in the final analysis was 0.77 (95%CI: 0.57, 1.03) compared to 0.82 (95%CI: 0.52, 1.30) in the primary analysis.

Table 8: Overall survival, iNHL patients (ITT population), stratified analysis

	Benda n=209	G-benda+G n=204
Patients with event, n (%)	100 (47.8)	84 (41.2)
Median time to event, months (95% CI)	65.6 [redacted]	88.3 [redacted]
Hazard ratio (95% CI)	0.77 (0.57, 1.03)	
p value*	0.0810	

*log-rank
Benda, bendamustine; CI, confidence interval; G-benda+G, obinutuzumab (Gazyvaro) + bendamustine followed by obinutuzumab maintenance; NE, not estimated

B5. PRIORITY Please provide a scenario analysis for the economic model including the survival analyses for PFS requested in question B1, making it possible to select these new survival curves as options, as it is currently possible to do for the Weibull, exponential etc.

Please refer to the addendum of the company response.

B6. PRIORITY Please provide a scenario analysis for the economic model including the survival analyses for OS requested in question B2, making it possible to select these new survival curves as options, as it is currently possible to do for the Weibull, exponential etc.

Please refer to the addendum of the company response.

Section C: Textual clarification and additional points

None

References

1. Cancer Research UK. Non-Hodgkin Lymphoma Survival Statistics 2019 [Available from: https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/survival.
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3. F. Hoffmann-La Roche. GADOLIN - Final Clinical Study Report. 2019. Report No.: 1092968.
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5. Cheson BD, Chua N, Mayer J, Dueck G, Trněný M, Bouabdallah K, et al. Overall Survival Benefit in Patients With Rituximab-Refractory Indolent Non-Hodgkin Lymphoma Who Received Obinutuzumab Plus Bendamustine Induction and Obinutuzumab Maintenance in the GADOLIN Study. Journal of Clinical Oncology. 2018;36(22):2259-66.
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7. SAS Institute Inc. SAS/STAT® 13.1 User's Guide: The LIFEREG Procedure 2013 [Available from: https://support.sas.com/documentation/onlinedoc/stat/131/lifereg.pdf.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Obinutuzumab in combination with bendamustine for treating rituximab-refractory follicular lymphoma (CDF review TA472) – [ID1583]

Addendum to

Clarification questions

December 2019

File name	Version	Contains confidential information	Date
ID1583 Obinutuzumab - Company CDF-R Addendum to Clarification Responses v1.0 [redacted]	1	Yes	11 December 2019

Section B: Clarification on cost-effectiveness data

B1. PRIORITY Please provide a re-analysis of the progression-free survival data modelling the G-benda+G arm of the GADOLIN study as a change-point model incorporating i) a fixed change-point model at six months and ii) a random change-point, to allow for the change in treatment after six months.

The segmented Weibull change-point model is described in Coelho-Barros, Achcar et al. (2019). The company estimated parameters for the change point Weibull model by maximising the likelihood function over the observed data. The corresponding Maximum Likelihood Estimator (MLE) corresponds to a Bayesian approach, in which one assumes a uniform likelihood over the parameter space. For the fixed change-point models, only the shapes and scales were estimated whereas the random change point models had an additional parameter to estimate (that is, the change-point itself). Table 1 provides the parameter estimates for PFS as Weibull change point models.

Table 1: PFS analysis – summary of the Weibull change-point model and parameters

Arm	Change-point	Shape α_1	Scale μ_1	Change point (months)	Shape α_2	Scale μ_2	10-year PFS
G-benda+G	Fixed	[redacted]	[redacted]	6.0	[redacted]	[redacted]	8.0%
Benda	Fixed	[redacted]	[redacted]	6.0	[redacted]	[redacted]	0.0%
G-benda+G	Random	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13.7%
Benda	Random	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.4%

Benda: Bendamustine, G-benda+G: Obinutuzumab (Gazyvaro®) in combination with bendamustine (benda) followed by obinutuzumab maintenance, PFS: Progression free survival

Application of the segmented Weibull change-point survival function (equation 1) within the cost-effectiveness model:

$$S(t) = \begin{cases} \exp\left[\left(\frac{t}{\mu_1}\right)^{\alpha_1}\right] & if\ 0 < t < change\ point \\ \exp\left[\left(\frac{t}{\mu_2}\right)^{\alpha_2}\right] & if\ t \geq change\ point \end{cases} \quad (1)$$

A greater mean PFS difference is observed between G-benda+G and Benda over the time horizon ([redacted] months and [redacted] months for the fixed and random change-point Weibull models respectively) when compared to the company base case. That

is, when propagated through the cost-effectiveness model, a reduction in the ICER is expected when change-point models are used to model PFS.

B2. PRIORITY Please provide a re-analysis of the overall survival data allowing for time-varying hazards (either as separate models for each treatment arm or with treatment effects for each parameter in the baseline model). Also, for the G-benda+G arm of the GADOLIN study, model the data using a change-point model incorporating i) a fixed change-point model at six months and ii) a random change-point, to allow for the change in treatment after six months.

Please refer to the company clarification response for the first part of B2. Below seeks to address the change-point analysis part of the question.

Table 2 provides the parameter estimates for OS as Weibull change point models.

Table 2: OS analysis – summary of the Weibull change-point model and parameters

Arm	Change-point	Shape α_1	Scale μ_1	Change point (months)	Shape α_2	Scale μ_2	10-year OS
G-benda+G	Fixed	[redacted]	[redacted]	6.0	[redacted]	[redacted]	41.4%
Benda	Fixed	[redacted]	[redacted]	6.0	[redacted]	[redacted]	25.7%
G-benda+G	Random	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43.2%
Benda	Random	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	28.8%

Benda: Bendamustine, G-benda+G: Obinutuzumab (Gazyvaro®) in combination with bendamustine (benda) followed by obinutuzumab maintenance, OS: Overall survival

A greater mean OS difference is observed between G-benda+G and Benda over the time horizon ([redacted] months and [redacted] months for the fixed and random change-point Weibull models respectively) when compared to the company base case. That is, when propagated through the cost-effectiveness model, a reduction in the ICER is expected when change-point models are used to model OS.

B5. PRIORITY Please provide a scenario analysis for the economic model including the survival analyses for PFS requested in question B1, making it possible to select these new survival curves as options, as it is currently possible to do for the Weibull, exponential etc.

Table 3 provides the cost-effectiveness results of the scenario using change-point Weibull functions to model PFS.

Table 3: Cost-effectiveness results of a scenario using change-point Weibull functions to model PFS

Technologies	Inc. PFS	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Independent segmented Weibull models with a fixed change point at 6.0 months				
G-benda+G versus benda	[redacted]	[redacted]	[redacted]	17,322
Independent segmented Weibull models with a random change points (see Error! Reference source not found.**)**				
G-benda+G versus benda	[redacted]	[redacted]	[redacted]	16,383

Benda: Bendamustine, G-benda+G: Obinutuzumab (Gazyvaro®) in combination with bendamustine (benda) followed by obinutuzumab maintenance, ICER: Incremental cost-effectiveness ratio, PFS: Progression free survival, QALY: Quality-adjusted life year

B6. PRIORITY Please provide a scenario analysis for the economic model including the survival analyses for OS requested in question B2, making it possible to select these new survival curves as options, as it is currently possible to do for the Weibull, exponential etc.

Table 4 provides the cost-effectiveness results of the scenario using change-point Weibull functions to model OS.

Table 4: Cost-effectiveness results of a scenario using change-point Weibull functions to model OS

Technologies	Inc. OS	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Independent segmented Weibull models with a fixed change point at 6.0 months				
G-benda+G versus benda	[redacted]	[redacted]	[redacted]	15,587
Independent segmented Weibull models with a random change points (see Table 2)				
G-benda+G versus benda	[redacted]	[redacted]	[redacted]	15,902

Benda: Bendamustine, G-benda+G: Obinutuzumab (Gazyvaro®) in combination with bendamustine (benda) followed by obinutuzumab maintenance, ICER: Incremental cost-effectiveness ratio, OS: Overall survival, QALY: Quality-adjusted life year

References

Coelho-Barros, E. A., et al. (2019). "Bayesian Inference for the Segmented Weibull Distribution." Revista Colombiana de Estadística **42**(2): 225-243.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Obinutuzumab with bendamustine for treating follicular lymphoma refractory to rituximab [ID1583]

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.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Lymphoma Action
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Lymphoma Action is a national charity, established in 1986, registered in England and Wales and in Scotland. We provide high quality information, advice and support to people affected by lymphoma – the 5th most common cancer in the UK. We also provide education, training and support to healthcare practitioners caring for lymphoma patients. In addition, we engage in policy and lobbying work at government level and within the National Health Service with the aim of improving the patient journey and experience of people affected by lymphoma. We are the only charity in the UK dedicated to lymphoma. Our mission is to make sure no one faces lymphoma alone. Our work is made possible by the generosity, commitment, passion and enthusiasm of all those who support us. In 2018 we raised a total income of £1,432,177 from various fundraising activities. 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. This includes that no more than 20% of our income can come from these companies and there is a cap of £50k per company. Acceptance of donations does not mean that we endorse their products and under no circumstances can these companies influence our strategic direction, activities or the content of the information and support we provide to people affected by lymphoma.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator	Roche - £12,000: support for core activities, information, patient support and education/training Accord Healthcare - NA Actavis - NA Aspen Pharma - NA

products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	Baxter Healthcare - NA Hospira UK - NA Napp Pharmaceuticals - NA Sandoz - NA Sanofi - NA Seacross pharmaceuticals - NA Teva UK - NA Zentiva - NA
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 asked patient contacts who we support to comment. We also had a call-out on our social media channels for patients with a relevant diagnosis to come forward who would like us to consider their views. We sent questionnaires to people who responded, asking about their experience of current treatment and their response to this new technology, with particular emphasis on quality of life. We have used their responses as the basis of this submission. We have also included information based on our prior experience with patients with this condition.
Living with the condition	
6. What is it like to live with the condition? What do carers	Follicular lymphoma is a low-grade lymphoma that is generally treated with the intention of keeping it under control, rather than curing it. People live with the condition for many years. Some people have few

experience when caring for someone with the condition?	symptoms but others might experience a wide variety of signs and symptoms, including enlarged lymph nodes, weight loss, fevers, night sweats, constant itching or fatigue. If follicular lymphoma affects the bone marrow, people can develop neutropenia, anaemia and thrombocytopenia. In some cases, follicular lymphoma can transform into a high-grade lymphoma, which can have serious symptoms requiring urgent treatment. Both the lymphoma and its treatment can significantly affect quality of life. Patients report that they are exhausted, tire easily and are unable to do things they used to. They have to manage time very carefully, refusing things they would otherwise have done and resting frequently. People also report struggling with concentration and memory. This affects their working life, social life and ability to do the things they enjoy. Many people need to take time off work or studies, or even stop work completely. This can be very difficult financially. Some people who have previously been employed find it frustrating to rely on government benefits. The uncertainty of relapse and the need for repeated courses of treatment is also physically and psychologically challenging for patients. Many patients report feeling anxious and find the possibility of relapse frightening. People find it exhausting living with the constant fear of relapse. Caring for someone with follicular lymphoma is challenging emotionally, practically and financially. Carers often provide transport to-and-from hospital appointments and treatment sessions, requiring time off work. They also provide emotional support, whilst trying to deal with an emotionally difficult situation themselves. Several report that carers and family members needing counselling. Some feel that it puts a serious strain on relationships.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Some people do not need treatment initially and enter a period of active monitoring. Patients report finding this psychologically challenging and emotionally draining. One of the main concerns about current treatments is the lack of a durable response and the need for repeated courses of treatment over the years. People worry that there will not be effective treatment

	available if or when they experience relapse. They are also anxious about having to go through the ordeal of treatment again. Although patients are generally grateful for the treatment they have had, many report significant side effects that have impacted their day-to-day life. These include long-term fatigue, persistent nausea and vomiting, cancer-related cognitive impairment and serious infections. Some find it psychologically difficult to lose their hair. People are also concerned about the long-term effects their treatment might have on their health. Many people find going through treatment mentally as well as physically challenging.
8. Is there an unmet need for patients with this condition?	There is a clear unmet need for effective treatments that keep follicular lymphoma in remission for as long as possible, with fewer side effects and late effects.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients feel the availability of an effective treatment for people who have experienced relapse, and particularly for those who have not responded to rituximab, is crucial. Treatments that prolong time in remission are seen as particularly important in an 'incurable' condition. People report finding maintenance therapy much easier to tolerate than repeated courses of chemotherapy and any treatments that 'stave off' the need for chemotherapy are welcomed. One of the patients who responded to our questionnaire had been treated with obinutuzumab. She reported a very rapid response to treatment with rapid tumour shrinkage.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	As with all treatments, patients are concerned about the possibility of side effects. The patient who had experience of obinituzumab experienced side effects of headaches and feeling generally unwell, although these resolved with repeated cycles of treatment. She commented that this was 'a small price to pay' for her response to treatment. The treatment is administered intravenously as an outpatient so travel to and from hospital, and time at the hospital itself, can be demanding. Some people were concerned about the practical issues of transport, time off work, childcare issues, and travel and parking fees during the period of maintenance 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.	

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	
Key messages	

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Follicular lymphoma can have a significant impact on the quality of life of patients and their carers.
- Current treatment options may not produce durable responses and patients are keen for treatments that give them longer remissions. Patients also find the side effects of current treatments difficult.
- There is an unmet need for effective, well tolerated treatment that prolongs time in remission.

- Patients feel obinutuzumab (plus bendamustine) is an important treatment option for people who have not responded or have relapsed after rituximab.
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Obinutuzumab with bendamustine for treating follicular lymphoma refractory to rituximab (CDF Review of TA472) [ID1583]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- 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 13 pages.

About you	
1. Your name	**Dr Graham Collins**
2. Name of organisation	**Oxford Cancer and Haematology Centre, Churchill Hospital, Oxford, UK**

3. Job title or position	**Consultant Haematologist and lymphoma lead for Thames Valley cancer network**
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 this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☒ other (please specify): Member of the NCRI lymphoma clinical study group. I have been nominated by Roche as a clinical expert for this STA.
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 didn't submit one, I don't 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	☐ yes

rest of this form will be deleted after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of treatment in follicular lymphoma is to prolong life. Remission duration and treatment free intervals are also important to patients.
8. 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 prolongation of remission by 2 years would be meaningful and significant. A prolongation of overall survival by any duration would be significant in this setting.
9. In your view, is there an unmet need for patients and	Yes there is. Although many patients with follicular lymphoma have excellent survivals, those that become refractory to rituximab do much less well. This is illustrated by the control arm in the GADOLIN study which demonstrated a median overall survival approximately 4-5 years. Assuming that patients will

healthcare professionals in this condition?	already have had alkylating agent-based therapy (CVP, CHOP), the only other options are bendamustine or fludarabine-based regimens. Based on prior trials, bendamustine would be expected to be the most effective option in this setting. PI3 kinase inhibitors (idelalisib) are licensed in this setting but are not funded in England. Lenalidomide is also commonly used in North America but again is not licensed or funded in this setting in England.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Rituximab refractory follicular lymphoma is treated with chemotherapy. The exact type depends on prior treatment: - Initial bendamustine + rituximab would be treated with CVP or CHOP - Initial CVP or CHOP + rituximab would be treated with bendamustine In younger, fitter patients, many centres would use 2nd line chemotherapy as a bridge to an autologous (or rarely an allogeneic) stem cell transplant. In these cases, chemotherapy known to mobilise stem cells may be used (e.g. ESHAP, ICE). Although patients are rituximab refractory, rituximab is sometimes added into these regimens.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The British Society of Haematology Guidelines are rather out of date, published in 2011. Indeed, bendamustine came under the title 'novel therapy' which is clearly not the case now. The NICE guidelines for non-Hodgkin lymphoma did not cover the situation of rituximab refractory follicular lymphoma. However, they did recommend autologous stem cell transplantation (ASCT) for relapsed follicular lymphoma, based on a cost-effectiveness analysis. They did not specify how best to get patients into remission. The European Society for Medical Oncology (ESMO) guidelines are more recent (2016). They recommend the following in relapsed disease: - Non-cross-reacting chemotherapy (e.g. bendamustine if CHOP or CVP previously used; CHOP or CVP if bendamustine previously used)

	- Using rituximab again if the last antibody-containing regimen achieved a remission duration of 6-12 months or longer. - Mention is made of obinutuzumab although firm recommendations on use are not made. This was before the overall survival data was published.
• 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.)	The pathway in England is not very well defined. Areas of disagreement include: 1. Should ASCT be offered to patients at first relapse? As mentioned above, the NICE guidelines on NHL management recommend ASCT. My impression is that there is more uniformity in offering this to patients who are rituximab refractory as there is an increasing appreciation that this group of patients have a poor outcome generally. 2. Should rituximab be added to chemotherapy in patients relapsing early after a rituximab-containing regimen? The ESMO guidelines only recommend adding in rituximab if the prior remission was 6-12 months or longer. However, centres vary in their approach and some would add in rituximab even if the remission duration was shorter, suggesting that it may synergise with different chemotherapy regimens in different ways. 3. Which upfront chemotherapy regimen to use? This is important as it then affects what chemotherapy at relapse to use. Bendamustine was being increasingly used, but the GALLIUM trial reported increased infectious mortality rates compared with CHOP or CVP. This has led to a drift away from bendamustine, although many centres do use bendamustine in younger patients, with appropriate antimicrobial prophylaxis.
• What impact would the technology have on the current pathway of care?	If a patient has had R-CVP or R-CHOP as frontline treatment and relapses early, the overall survival for Obinutuzumab + bendamustine vs bendamustine alone would argue strongly in favour in using this combination. The availability of this technology MAY increase the selection of R-CVP or R-CHOP as frontline therapy. However, my view is this is unlikely as many centres are using obinutuzumab for FLIPI 2+ (an option according to a recent NICE STA) and those that use bendamustine generally do so as they believe it produces more durable initial remission. I do think it would not be appropriate to restrict the technology to only those patient who have not received bendamustine upfront however. This is because there maybe patients who had initial bendamusinte +

	rituximab, had a long first remission (e.g. 5 years), relapsed and had R-CHOP but then relapse within 6 months. There is no reason to think that re-treatment with bendamustine + obinutuzumab would not provide benefit to these patients. Similarly, with those patients treated with obinutuzumab upfront. If they had long first remission but then a short 2nd remission following, for example, R-CHOP, they would expect to benefit from bendamustine + obinutuzumab in this setting.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology is available through the cancer drugs fund. It would be used in the same way should NICE approve it at this STA.
• How does healthcare resource use differ between the technology and current care?	As stated above, this technology is being used now. Compared with bendamustine alone, there is increased resource associated with obinutuzumab + bendamustine: - Obinutuzuamb is an IV infusion over several hours so dose increase the length of chair time compared with bendamustine alone - In cycle 1, obinutuzumab is given on day 1, 8 and 15 so there are 2 additional visit. For cycles 2-6 there are no additional visits (it is only given on day 1). - Obinutuzumab maintenance adds 12 extra day unit visit (6 per year) compared with chemotherapy alone.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Haematology / oncology day treatment units, secondary or tertiary care.
• What investment is needed to introduce the	Nil as it is being used now.

technology? (For example, for facilities, equipment, or training.)	
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. It is very unusual to see a randomised trial result in an overall advantage in follicular lymphoma. This is because of the usual indolent nature of the disease. However, GADOLIN was tested in a high-risk group, who had become rituximab refractory. Presumably this is why a statistically significant and clinically meaningful difference emerged.
• Do you expect the technology to increase length of life more than current care?	Yes – as evidenced by the improvement in overall survival
• Do you expect the technology to increase health-related quality of life more than current care?	Yes – as remissions are usually associated with better quality of life. Although obinutuzumab does result in more hospital visits, this is modest (once every 2 months during maintenance). Maintenance treatment is associated with adverse events, but these are usually manageable and are not expected to significantly impair quality of life.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The effect is unknown in those patients who have previously been treated with frontline obinutuzumab and / or bendamustine.

The use of the technology	
14. 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.)	It is recommended that for patients who have received bendamustine, and are then receiving maintenance antibody (rituximab or obinutuzumab), prophylactic co-trimoxazole (typically 480-960mg orally, once per day Monday, Wednesday, Friday) should continue for the duration of the induction and maintenance. GCSF may also need to be used for the neutropenia developing during maintenance (which is uncommon but dose occur with any anti-CD20 antibody). As stated above, this technology is being used so there aren't really any other implications.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Progression of disease should lead to the treatment being stopped. It is less clear however when scans should be performed. Pragmatically, my approach is: - Perform a CT or PET after bendamustine + obinutuzumab induction. Proceed with maintenance if a response (PR or CR) is seen.

	- Continue maintenance without additional scanning unless there are clinical reasons to suspect relapse It would also be reasonable to scan after 1-year of maintenance to check there is no evidence of progression although this is not usually my practise.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
17. 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	This is a glycoengineed anti-CD20 antibody and as such is innovative in my view. An improvement in progression free survival, time to next treatment and overall survival represents a significant health-related benefit for this group of patients.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	It is an important advance due to the reported overall survival benefit in addition to the PFS and TTNT benefit.
• Does the use of the technology address any particular unmet need of the patient population?	This is a relatively high-risk follicular lymphoma population. So yes, it does address the relatively poor associated outcomes.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Adverse events are seen with obinutuzumab. There was no excess toxicity seen in the induction phase, presumably as the dose of bendamustine was less in the combination. Maintenance does increase the risk of infections and neutropenia. This may impact a patient's quality of life although oversight by the clinician with timely antibiotic use, GCSF use and if needed treatment cessation would minimise this.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	

• If not, how could the results be extrapolated to the UK setting?	As stated above, practise varies. For those patients receiving R-CVP or R-CHOP frontline, it is straightforward to apply the trial data. For those patients who have had bendamustine and / or obinutuzumab front line it is less clear. However, if very good responses were obtained with these agents upfront but then a much shorter response was obtained after R-CHOP or R-CVP as 2nd line, it would be shame not to be able to offer obintuzumab + bendamustine at this stage as it could deny a treatment that may prolong their life. It is also less clear how to apply this to patients proceeding to ASCT. However, for this group, the better minimal residual rates seen with obinutuzmab + bendamustine may be relevant as ASCT is usually associated with improved outcomes in patients with better remissions prior to transplant. So in my view, intention to proceed to ASCT should not be a restriction to using this technology.
• What, in your view, are the most important outcomes, and were they measured in the trials?	1. Overall survival 2. Time to next treatment 3. Progression free survival Yes – they were used.
• If surrogate outcome measures were used, do they adequately predict	PFS and TTNT are often used as overall survival surrogates. However, as we now have OS data, surrogates are not needed.

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance?	No.
22. How do data on real-world experience compare with the trial data?	I'm not aware of real-world data.

Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
23b. Consider whether these issues are different from issues with current care and why.	
Key messages	
24. In up to 5 bullet points, please summarise the key messages of your statement. • Improved Overall survival • Improved PFS and TTNT • Side effects that are manageable • Would still be relevant to those intended to go to ASCT • Unclear how to apply to those who've had bendamustine and / or obinutuzumab front line but keen not restrict if good remission seen after these agents.	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Obinutuzumab with bendamustine for treating follicular lymphoma refractory to rituximab (TA472): CDF review

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Declared competing interests of the authors

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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 HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

AP critiqued the clinical effectiveness data reported within the company's submission. JWS critiqued the statistical analysis reported within the company's submission. SD critiqued the health economic analysis submitted by the company and conducted the ERG's exploratory analyses. All authors were involved in drafting and commenting on the final report.

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ABBREVIATIONS

AEs	Adverse events
Benda	Bendamustine
BIC	Bayesian Information Criterion
CDF	Cancer Drugs Fund
CDFR-CS	Cancer Drugs Fund Review – Company's submission
CCOD	Clinical cut-off date
CI	Confidence interval
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
eMIT	Electronic market information tool
ERG	Evidence Review Group
FL	Follicular lymphoma
G-benda+G	Obinutuzumab (Gazyvaro®) in combination with bendamustine followed by obinutuzumab maintenance
ICER	Incremental cost-effectiveness ratio
iNHL	Indolent non-Hodgkin's lymphoma
INV-PFS	Investigator assessed progression-free survival
ITT	Intention-to-treat
K-M	Kaplan-Meier
NA	Not applicable
NE	Not estimable
OS	Overall survival
PAS	Patient Access Scheme
PFS	Progression-free survival
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
SACT	Systemic anti-cancer therapy
TSD	Technical Support Document

1 EXECUTIVE SUMMARY

1.1 Critique of the adherence to committee's preferred assumptions from the Terms of Engagement in the company's submission

In general, the company has presented clinical evidence and cost-effectiveness analyses for obinutuzumab (Gazyvaro®) in combination with bendamustine followed by obinutuzumab maintenance (G-benda+G) compared with bendamustine (benda) alone that are consistent with the Terms of Engagement. The only significant deviation from the Terms of Engagement is that the company has amended the approach used to model overall survival (OS) in their preferred base-case scenario, whereas the Terms of Engagement specify that the same model should be used. Although the company have also presented analyses that are consistent with the approach taken to generate the incremental cost-effectiveness ratios (ICERs) in Table 1 of the Terms of Engagement document.[1]

The company's updated base-case uses the parametric survival functions to estimate OS in the economic model for the whole modelled time-horizon and assumes that the treatment effect observed during the trial follow-up persists for the remainder of the patient's lifetime.[2] This differs from the approach taken to generate the ICERs in Table 1 of the Terms of Engagement document whereby Kaplan-Meier (K-M) estimates from the trial were used directly to estimate OS until the time of the last observed event (4.0 years) and parametric survival functions were only used to extrapolate beyond the trial period.[1, 3]

1.2 Summary of the key issues relating to the clinical effectiveness evidence

The updated clinical results pertaining to improvements in OS and investigator assessed progression free survival (INV-PFS) from the GADOLIN trial were sustained over the long-term and reduced the uncertainty perceived during the original appraisal of TA472. In terms of OS, the updated hazard ratio (and its confidence interval [CI]) is shrunk towards the no effect value and suggests a 29% reduction in the risk of death compared to a 38% reduction in the risk of death estimated at the time of the company submission that informed TA472.[2] The data from the systemic anti-cancer therapy (SACT) cohort study are too immature to provide estimates of median survival.[4] Whilst the K-M estimates of OS at 12 months from the SACT cohort[4] and the GADOLIN trial[2] have overlapping CIs, the Evidence Review Group (ERG) notes that any comparison between single arms from separate studies is likely to be subject to bias and should be interpreted with caution.

In addition, the ERG notes that the duration of time spent on treatment appears to be lower in the SACT cohort[4] than in the GADOLIN trial;[5] however, the data from the SACT cohort are immature, hence it is difficult to make meaningful comparisons.

1.3 Summary of the key issues relating to the cost effectiveness evidence

There are two key issues with regards to the cost-effectiveness of G-benda+G compared with bendamustine alone. Firstly, whether the parametric function for OS provides an accurate prediction of OS during the study follow-up period. Secondly, whether it is appropriate to assume a constant treatment effect for the remainder of the patient's lifetime based on the hazard ratio observed during the follow-up period of the GADOLIN trial.

The ERG notes that the cumulative hazard functions for OS suggest that the treatment effect is not constant. In fact, the plot of cumulative hazards suggests that a change in the relative hazards occurs after approximately 6 months and the treatment effect may be increasing over time. Therefore, the ERG prefers to use the Weibull survival functions with a random change-point for PFS and OS as this allows for the treatment effect to vary during the observed follow-up period of GADOLIN. Survival functions incorporating a change-point appear, visually at least, to provide a better representation of the data over both the early and late phases of the GADOLIN trial. Consequently, the ERG considers it reasonable to use these survival functions to extrapolate beyond the trial period.

The ERG also notes that the estimates of cost-effectiveness provided by the model are dependent on the assumption that patients receive a similar duration of treatment in clinical practice to that which occurred in the GADOLIN trial. There is some evidence to suggest that the treatment duration in clinical practice, as measured in the SACT cohort, may be shorter than in the GADOLIN trial, and it is not possible to adjust the estimates of cost-effectiveness to reflect a shorter duration of treatment.

1.4 Summary of ERG's preferred assumptions and resulting ICER

The ERG's preferred assumptions, used to generate the results in Table 1, were as follows:

- Use the Weibull survival functions with random change-points for PFS and OS
- Apply latest costs for bendamustine from the electronic market information tool (eMIT) database

The ICER for the ERG's preferred base-case is £15,045 per QALY gained; this is based on the deterministic model which uses point estimates of parameters. The ERG notes that the company's implementation of the Weibull functions with change-points within the economic model does not incorporate any uncertainty associated with the Weibull functions for PFS and OS. Therefore, the ERG believes that the uncertainty around the ERG's preferred base-case ICER is likely to have been underestimated in the probabilistic sensitivity analysis (PSA).

Table 1: ICER resulting from ERG's preferred assumptions

Option	Total costs	Total QALYs	Δ costs	Δ QALYs	ICER £/QALY
G-benda+G	[redacted]	[redacted]	[redacted]	[redacted]	£15,045
Benda	[redacted]	[redacted]			

QALY, quality-adjusted life-year

The ERG notes that the key factors which have resulted in the change to the ICERs since the analyses for TA472 are;

1. the updated OS data from GADOLIN
2. the company's assumption of a lifetime treatment effect beyond the observed data from GADOLIN
3. the use of a Weibull change-point function for the hazard function which allows the hazard function to change during the period observed in GADOLIN
4. the company's updated PAS.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

In August 2017, NICE published guidance on the use of obinutuzumab (Gazyvaro®) with bendamustine for treating follicular lymphoma (FL) refractory to rituximab (TA472).[3]

Obinutuzumab in combination with bendamustine (benda) followed by obinutuzumab maintenance (hereby, G-benda+G) was recommended by NICE for use within the Cancer Drugs Fund (CDF) as an option for treating adults with FL that did not respond or progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen, only if the conditions in the managed access agreement for obinutuzumab are followed (TA472).[3]

The purpose of this CDF review is to determine whether or not obinutuzumab with bendamustine can now be recommended for routine use for the treatment of FL.[6]

2.2 Background

In TA472, the main source of clinical effectiveness evidence came from the Phase III clinical trial GADOLIN. The committee noted that the overall survival (OS) data from the trial were immature and these data were used in the company's cost-effectiveness estimates. It was aware that more mature OS data were likely to be available from the trial by December 2020.[1] The committee also noted that the cost-effectiveness estimates were largely dependent on the duration of treatment effect assumed when extrapolating the overall survival data.[1] The committee also noted that the availability of more mature survival data from GADOLIN would be likely to resolve the uncertainty around the duration of treatment effect and would therefore be expected to significantly reduce the uncertainty around the cost-effectiveness of obinutuzumab.[1]

As part of the CDF review process, NICE provided the manufacturer of Gazyvaro® (Roche Products Ltd, hereby referred to as "the company") with a "Terms of Engagement" document which sets out NICE's expectation for the company's CDF review submission (hereafter referred to as the CDFR-CS).[1] This specifies the committee's preferred assumptions for economic modelling and the cost-effectiveness analyses that should be provided in the CDFR-CS.

In November 2019, the company submitted updated clinical and cost-effectiveness evidence informed by the final data cut of the GADOLIN trial (clinical cut-off date [CCOD] of November 2018).[2] In addition, the company provided some additional data and analyses in response to the clarification request on 5th December 2019 and further additional analyses, on the 12th of December 2019, in an addendum to their response to the clarification request.[7, 8] The purpose of this report is to critique the

evidence provided by the company in terms of both its scientific robustness and its compliance with the Terms of Engagement provided by NICE.

2.3 Critique of company's adherence to committee's preferred assumptions from the Terms of Engagement

A summary of the company's adherence to the committee's preferred assumptions, as specified in the Terms of Engagement, is provided in Table 2.

The main area of deviation from the Terms of Engagement is that the company have moved away from modelling OS using the K-M estimate up to the time of the last event, followed by parametric extrapolation. Instead, they have used the parametric survival function to model OS throughout the time horizon. In addition, the Terms of Engagement document specified that the company explore a range of assumptions for duration of treatment effect as the committee previously considered scenarios ranging from the time of the last event (4 years), to lifetime (25 years). A range of scenarios has been explored by the company; the company's preferred scenario includes a lifetime treatment effect.

Table 2: Preferred assumption from Terms of Engagement

Assumption	Terms of engagement	Deviations and company rationale	ERG comment on any deviations
Population	Adults with FL that are refractory to induction with rituximab in combination with chemotherapy, or who relapse early during rituximab maintenance	No deviation	NA
Intervention	Induction with obinutuzumab plus bendamustine followed by maintenance treatment with obinutuzumab alone (G-benda+G)	No deviation	NA
Comparators	Bendamustine (benda)	No deviation	NA
Progression free and overall survival	The committee would like to see updated PFS and OS results from GADOLIN	No deviation	NA
Economic model structure	After the first committee meeting the committee demonstrated a preference for: • using a partitioned survival approach to estimate overall survival • adjusting utility estimates for the effects of aging • assuming lower disease progression costs for subsequent treatments • using the generic acquisition cost for bendamustine • correcting minor programming errors in the model • using utility estimates from GADOLIN • using alternative drug administration costing assumptions The committee expected to see the same model structure in the CDF review	The company's updated base-case analysis uses parametric functions to model survival for the whole time horizon, whereas previously the K-M estimate was used up to the time of the last observed OS event. However, a company scenario analysis is provided (company scenario 5) in which the K-M estimate was used up to the time of the last observed OS event. Otherwise, the model structure and assumptions are consistent with the Terms of Engagement (excepted where described as differing in the rows below)	The ERG does not believe that the single Weibull parametric survival functions used in the company's updated base-case accurately capture the cross-over of the OS curves in the first year of the GADOLIN trial.

Duration of treatment effect	The committee noted that G–Benda+G may be cost effective if the treatment effect on survival persists for between 7 and 25 years and expect the company to explore this assumption which should be based on the final analysis of the GADOLIN trial.	The company's updated base-case scenario assumes a lifetime treatment effect but scenarios exploring shorter durations of treatment effect ([redacted]) are provided (company scenarios 1 and 2). The company states that the updated results are consistent with a constant proportional hazard and therefore the estimates of OS from the parametric survival functions are applied throughout the patient's lifetime in the model in the company's updated base-case.	The ERG does not agree that the updated data from GADOLIN support an assumption of constant treatment effects. ERG prefers to use the Weibull survival functions with a random change-point for PFS and OS as this allows for the treatment effect to vary during the observed follow-up period of GADOLIN
Utilities	Utility estimates from GADOLIN	No deviation	NA
Duration of time on treatment	Assumption not specified in Terms of Engagement	The model provided with the CDFR-CS uses time-to-off-treatment (TTOT) data from the April 2016 data cut on the basis that the TTOT data were mature at the time of TA472 and therefore an update was not required.	The ERG notes that the median duration of maintenance treatment was [redacted] months ([redacted] days) in the CSR for the latest data cut (CCOD Nov 2018)[9] whereas the median duration of maintenance treatment was 18 months (521 days) based on the April 2016 data cut[5].
Resource use and costs	Assumption not specified in Terms of Engagement and therefore no change expected	Company has provided analyses with an updated Patient Access Scheme (PAS) and updated costs for generic bendamustine.	Updating of drug costs is considered reasonable by the ERG. The ERG notes that a more recent price for bendamustine is now available but the ERG's exploratory analyses show that incorporating this has little impact on the ICERs.
Adverse events (AEs)	Assumption not specified in Terms of Engagement and therefore no change expected	No deviation	NA

Abbreviations: AEs, adverse events; benda, bendamustine alone; CDF, cancer drugs fund; ERG, Evidence Review Group; FL, follicular lymphoma; G-benda+G, obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance therapy; K-M, Kaplan-Meier; NA, not applicable; OS, overall survival; PAS, patient access scheme; PFS, progression free survival

3 CLINICAL EFFECTIVENESS

3.1 Critique of new clinical evidence

The CDFR-CS submitted two new sources of clinical effectiveness evidence.[2] The key evidence was obtained from the GADOLIN trial and included unpublished extended follow-up data for overall survival (OS) and investigator assessed progression-free survival (INV-PFS). Additional observational evidence (real world data) was collected during the period of managed access from the systemic anti-cancer therapy [SACT] dataset. These data are described in a report by Public Health England (hereby referred to as the SACT report), which included data on OS and duration of therapy.[4] The ERG has no major concerns about the new OS and PFS data. A brief summary of the submitted data is provided below.

- **GADOLIN Trial**

The efficacy results for the FL population in the GADOLIN trial, at the time of the final clinical cut-off date (CCOD) of 30 November 2018, were broadly consistent with the results of the primary analysis (CCOD September 2014).[9, 10] A summary of the investigator assessed PFS and OS results are provided in Table 3 and Figure 1 and Figure **2**. In terms of OS, the updated hazard ratio (and its CI) is shrunk towards the no effect value and suggests a 29% reduction in the risk of death compared to a 38% reduction in the risk of death estimated at the time of the company submission for TA472 (CCOD 1st May 2015).

In addition, the CDFR-CS states that the "*safety profile for G-benda+G at the time of the final data cut (CCOD November 2018) was consistent with the primary analysis (CCOD September 2014) with respect to incidence, type, and severity of AEs. No new safety signals were observed with longer follow-up*."

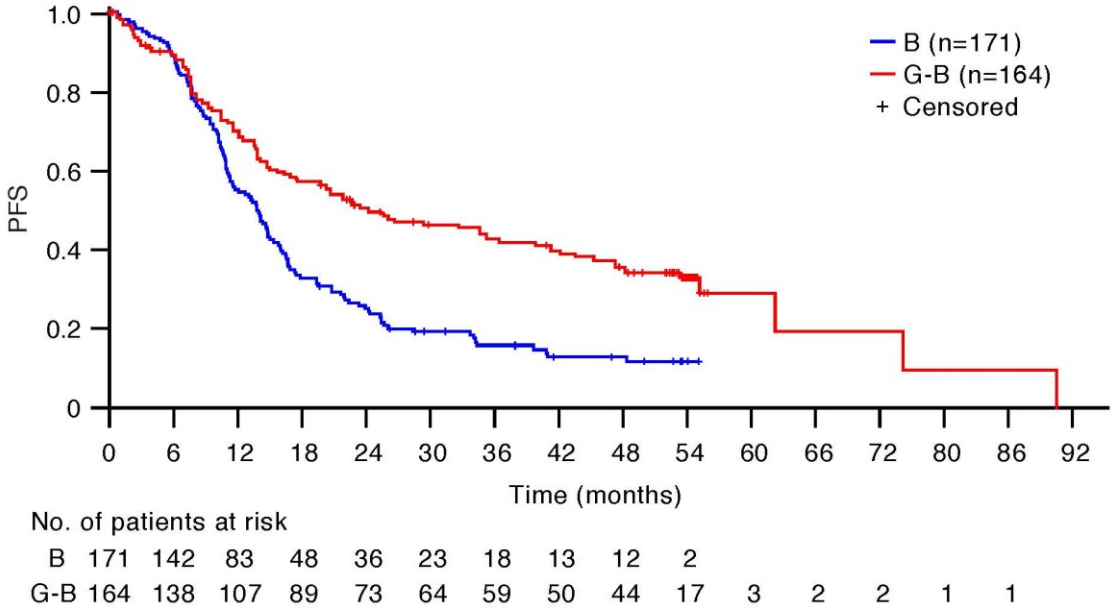
Table 3: Investigator-assessed PFS and OS in FL patients from the GADOLIN trial, stratified analysis (adaptation of Table 6 and 7, ERG report for TA472, [11] pg. 54-55, and CDFR-CS,[2] pg. 12-13)

	Primary efficacy analysis		Updated analysis		New updated analysis	
	Cut-off date: 1st September 2014		Cut-off date: 1st May 2015		Cut-off date: 30 November 2018	
	Arm A: G-benda+G	Arm B: benda only	Arm A: G-benda+G	Arm B: benda only	Arm A: G-benda+G	Arm B: benda only
	n=155	n=166	n=164	n=171	n=164	n=171
Investigator-assessed PFS						
Patients with event, n	54 (34.8%)	90 (54.2%)	67 (40.9%)	108 (63.2%)	[redacted]	[redacted]
Median PFS, months (95% CI)	NE (22.5, NE)	13.8 (11.4, 16.2)	29.2 (20.5, NE)	13.8 (11.5, 15.8)	24.1 [redacted]	13.7 [redacted]
Difference in PFS, months	-		15.4		10.4	
Hazard ratio (95% CI)	0.48 (0.34, 0.68)		0.47 (0.34, 0.64) [a]		0.51 (0.39, 0.67)	
p-value [b]	<0.0001		<0.0001		<0.0001	
Overall survival						
Patients with event, n	25 (16.1%)	36 (21.7%)	30 (18.3%)	48 (28.1%)	[redacted]	[redacted]
Median time to event, months (95% CI)	NE (NE, NE)	NE (39.8, NE)	NE (NE, NE)	NE (42.2, NE)	NE [redacted]	60.3 [redacted]
Hazard ratio (95% CI)	0.71 (0.43, 1.19)		0.62 (0.39, 0.98)		0.71 (0.51, 0.98)	
p-value [b]	0.1976		0.0379		0.0343	

benda, bendamustine only; CI, confidence interval; G-benda+G, obinutuzumab + bendamustine followed by obinutuzumab maintenance; NE, not estimated; OS, overall survival; PFS, progression-free survival

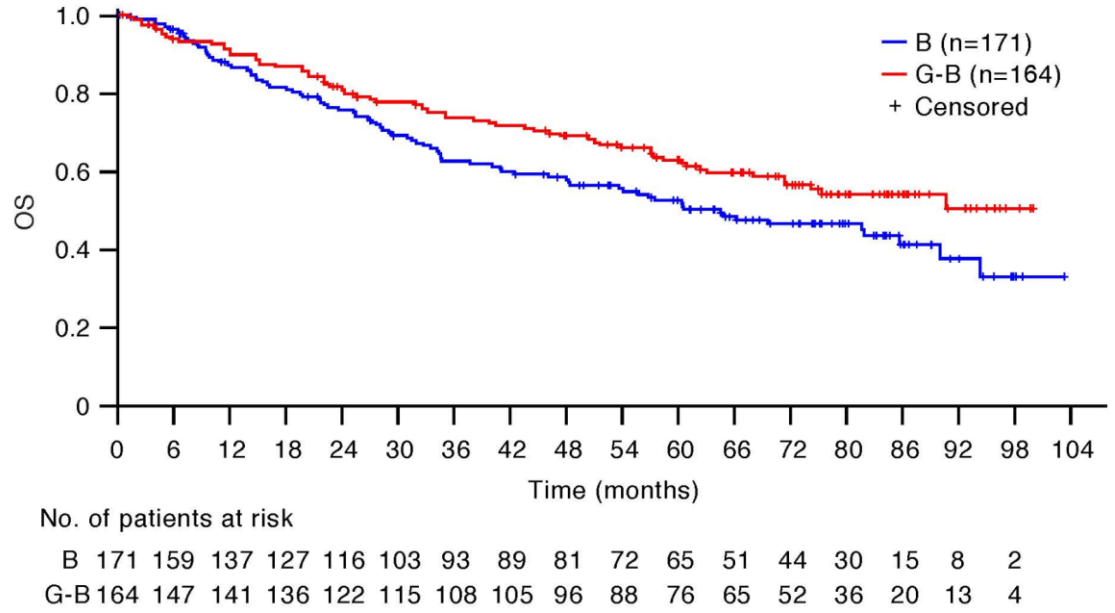
[a] Unstratified analysis results: hazard ratio, 0.48; 95% CI: 0.35, 0.65; p-value <0.0001

[b] Log-rank test, stratified analysis



B: Bendamustine, FL: Follicular lymphoma, G-B: Obinutuzumab (Gazyvaro) in combination with bendamustine (benda) followed by obinutuzumab maintenance, ITT: Intention to treat, KM: Kaplan-Meier, PFS: Progression free survival

Figure 1: KM plot of investigator-assessed PFS from final data cut (CCOD Nov 2018), FL patients - (ITT population) (reproduction of Figure 1, CDFR-CS,[2] pg. 13)



B: Bendamustine, FL: Follicular lymphoma, G-B: Obinutuzumab (Gazyvaro) in combination with bendamustine (benda) followed by obinutuzumab maintenance, ITT: Intention to treat, KM: Kaplan-Meier

Figure 2: KM plot of overall survival from final data cut (CCOD Nov 2018), FL patients - (ITT population) (reproduction of Figure 2, CDFR-CS,[2] pg. 14)

- **SACT data cohort**

During the period of managed access, data on OS and duration of therapy were collected for individuals included in the SACT cohort up to 28th February 2019 (92 eligible CDF applications).[4] The median treatment duration for all patients in the SACT cohort was 5.3 months (95% CI: 4.8 to 7.8 months).[4] Forty-six percent of patients were still receiving treatment at 6 months (95% CI: 35 to 56 months), 28% of patients were still receiving treatment at 12 months (95% CI: 18 to 40 months).[4] Although the FL population in the SACT cohort and GADOLIN trial appeared similar in terms of median age and gender, 71% of the SACT cohort had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 compared with approximately 95% in the GADOLIN trial.[4,7]

The ERG notes that the duration of treatment in SACT is substantially different to that observed in the GADOLIN trial. In GADOLIN, 81.9% of patients randomised to G-Benda+G received the full 6 does of induction therapy and the median duration of exposure to obinutuzumab in the maintenance phase was 521 days (i.e. 17 months of a maximum of 2 years maintenance therapy) (Cheson 2018, supplementary data).[5] Table 8 of the SACT report shows that in the 55 patients who had stopped treatment during follow-up, only 9 of these stopped after 6 months.[4] Table 9 of the SACT report shows that 29 of the 55 patients who had stopped treatment during follow-up were recorded as having completed treatment as prescribed.[4] This suggests that many of those who had stopped were prescribed obinutuzumab as an induction therapy (i.e. G-benda) and were not subsequently prescribed obinutuzumab as a maintenance therapy (i.e. G-benda+G) as per the GADOLIN trial. Eleven patients in the SACT dataset went on to have stem cell treatment which could explain why they did not go on to have maintenance therapy.[4] However, the sensitivity analysis excluding these patients found a median treatment duration of 7.2 months, with 44 of the 81 patients in this cohort having stopped treatment during follow-up and 35 of these having stopped before 6 months (Table 18 of SACT report).[4] The data from SACT suggest that obinutuzumab may be being prescribed as an induction therapy without being followed by a maintenance period (i.e. G-benda instead of G-benda+G). Although, it is possible that this is due to the manner in which the reason for stopping is reported in the database, or due to patients having maintenance therapy being more likely to be censored before stopping treatment due to the limited duration of follow-up in SACT where the median duration of follow-up for time on treatment was only 148 days (i.e. 4.9 months).[4] However, the K-M estimate of the time on treatment in the SACT cohort show a steady reduction in the probability of remaining on treatment between 3 and 12 months (see Figure 3 reproduced from Figure 9 of the SACT report).[4] For comparison, the proportion remaining on treatment at 12 months based on the K-M estimate from the GADOLIN trial was [redacted] (extracted from the company's Excel model by the ERG).[2]

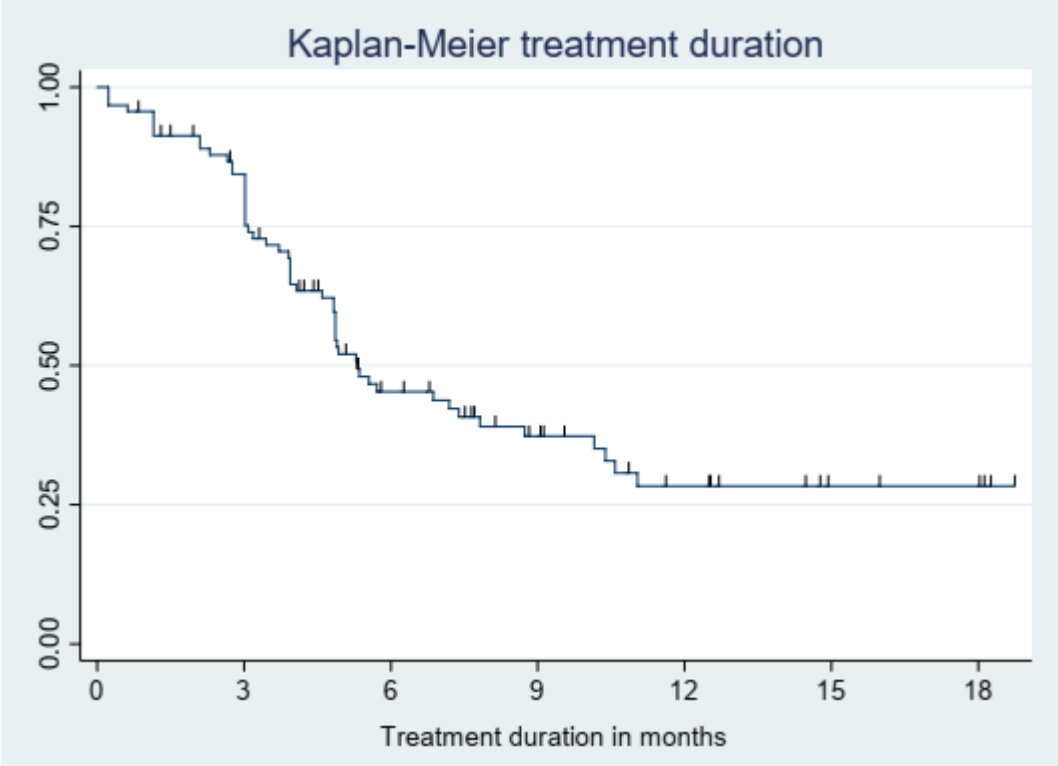


Figure 3: Kaplan-Meier plot for treatment duration in the 92 patients included in the SACT cohort [reproduced from Figure 9 of the SACT report][4]

Patients included in the SACT cohort were traced for their vital status up to 26th June 2019.[4] The duration of follow-up for OS in the SACT cohort ranged from 4 months to 23 months and the median follow-up time for OS was 12.4 months.[4] The limited duration of follow-up in the SACT cohort means that an estimate of median OS cannot be provided as the data are too immature. The K-M estimate of OS at 12 months was 88% (95% CI 79% to 94%) based on the SACT cohort.[4] The K-M estimate of OS at 12 months from the final data cut (CCOD November 2018) of GADOLIN (extracted from the company's Excel model by the ERG) was [redacted] Although these two estimates suggest some degree of consistency, they are both uncertain and the ERG notes that comparisons of single arms from different cohorts are open to bias, particularly if no adjustment is made for differences in relevant prognostic factors and treatment effect modifiers. Therefore, any comparison of survival rates between these two cohorts should be interpreted with caution.

3.2 Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness was undertaken by the ERG.

3.3 Conclusions of the clinical effectiveness section

The updated clinical results pertaining to improvements in OS and INV-PFS from the GADOLIN trial were sustained over the long term and reduced the uncertainty perceived at the time of TA472. In terms of OS, the updated hazard ratio (and its CI) is shrunk towards the no effect value and suggests a 29% reduction in the risk of death compared to a 38% reduction in the risk of death estimated at the time of the company submission for TA472 (May 2015 CCOD).[2] The data from the SACT cohort are too immature to provide estimates of median survival.[4] Whilst the K-M estimates of OS at 12 months from the SACT cohort and the GADOLIN trial have overlapping CIs, the ERG notes that any comparison between single arms from separate studies is likely to be subject to bias. In addition, the ERG notes that the duration of time spent on treatment appears to be lower in the SACT cohort than in the GADOLIN trial, although again, the data from the SACT cohort are immature, hence it is difficult to make meaningful comparisons.[4, 5]

4 COST EFFECTIVENESS

4.1 Summary and critique of the company's submitted economic evaluation by the ERG

4.1.1 Model structure

The model structure is identical to that used in TA472 and is therefore consistent with that specified by NICE in the Terms of Engagement.[1, 2]

4.1.2 Population

The population modelled is adults with FL that are refractory to induction with rituximab in combination with chemotherapy, or who relapse early during rituximab maintenance.[2] This is consistent with the Terms of Engagement.[1]

The PFS and OS data used in the model are based on the subgroup of patients with FL from the GADOLIN trial. This is consistent with the Terms of Engagement document which states, "*The committee noted that the evidence base for the marketing authorisation of obinutuzumab was a subgroup from the GADOLIN trial of people with FL (about 81% of the total trial population)"*[1]

4.1.3 Interventions and comparators

The intervention is induction with obinutuzumab plus bendamustine followed by maintenance treatment with obinutuzumab alone (G-bend+G).[2] The comparator is induction therapy with bendamustine with no subsequent maintenance therapy (benda). These are consistent with the interventions and comparators specified in the Terms of Engagement document. [1]

4.1.4 Perspective, time horizon and discounting

No changes have been made to the perspective, time horizon or discounting since the analyses for TA472.[2]

4.1.5 Treatment effectiveness and extrapolation

The key areas updated by the company, since the analyses that informed TA472, are the parameter estimates for the survival functions associated with PFS and OS.[2] This is in line with the Terms of Engagement document, which stated that the committee would like to see updated PFS and OS results from GADOLIN.[1] The parameter estimates for PFS and OS used in TA472 were informed by the April 2016 data cut[a] from the GADOLIN trial and are therefore affected by the incorporation of additional evidence from the final data cut (CCOD November 2018).

[a] It should be noted that the company's original submission for TA472 included data from the 1st May 2015 data cut, but data from the April 2016 data cut were later provided in response to the ACD and were incorporated in the economic analyses that informed the committee's final decision and the ICERs reported in Table 1 of the Terms of Engagement document.

For PFS, the company has fitted the same set of parametric distributions to the PFS data from the final data cut (CCOD November 2018) as were fitted to the previous data cut. Within the CDFR-CS model, the Weibull survival function was chosen by the company on the basis that *"the Weibull function continued to provide conservative long-term progression-free estimates, comparable to those estimated in TA472 using Weibull as the base case."* Therefore, the company employs the same parametric distribution for PFS as used in the analyses that informed TA472, but the new Weibull survival function applied in the CDFR-CS has updated parameters because it has been fitted to the final data cut (CCOD November 2018) from GADOLIN rather than the April 2016 data cut. The ERG notes that the Weibull distribution was not the parametric model with the best fit to the observed data according to the Bayesian Information Criterion (BIC), although it accepts that goodness-of-fit criteria associated with the observed data is not the only criterion on which an OS function should be chosen. The company claims that the log-logistic survival function was the best fitting survival function to the observed PFS data.[2] The CDFR-CS provides a scenario analysis using the log-logistic parametric function but uses the Weibull in the company's updated base-case.[2]

For OS, the company again fitted the same set of parametric distributions to the OS data from the final data cut (CCOD November 2018) as previously fitted to the data from the April 2016 data cut.[2] The company chose to use the Weibull survival function in its updated base-case, which was consistent with the choice of model incorporated previously for TA472. The ERG notes that the Weibull distribution was not the model with the best fit to the observed data according to the BIC, although it accepts that goodness-of-fit criteria associated with the observed data is not the only criterion on which an overall survival function should be chosen. The company claims that the log-normal survival function was the best fitting function to the observed OS data.[2] The CDFR-CS provides a scenario analysis using the log-normal distribution but uses the Weibull distribution in the company's updated base-case.[2]

In the modelling for TA472, the parametric OS survival functions were not used throughout the time horizon of the model. Instead, a number of different approaches were taken during several time periods as follows;

1. The K-M survival functions were used directly until the time of the last OS event (47.44 months for G-benda+G and 53.88 months for bendamustine based on the April 2016 data cut).
2. After the time of the last event, parametric survival functions (dependent Weibull functions [i.e. assuming proportional hazards] fitted to the data) informed the survival for the remainder of the time horizon.
3. Specifically for G-benda+G, the assumption of duration of treatment effect was assumed to cease after the time of the last event (4.0 years in the April 2016 data cut). In other words,

from the time of the last event, hazards from the Weibull distribution fitted to the benda arm were used to model the OS of the G-benda+G arm.

In the CDFR-CS, the company's approach to modelling overall survival in their updated base-case has changed to the following;

1. Dependent Weibull distributions (i.e. assuming proportional hazards) fitted to the updated OS data from the final data cut of GADOLIN (CCOD November 2018) have been applied throughout the whole modelled time horizon

2. Assumption that the Weibull survival function would for G-benda+G, be appropriate for the entire time horizon of the analysis i.e. the model does not apply a cap regarding the maximum duration of treatment effect upon OS.

The ERG notes that there are several settings that need to be selected to move between the cost-effectiveness analyses that informed TA472 and the company's updated base-case for this CDF review. These involve;

- Selecting whether OS is based on the K-M survival function from the GADOLIN trial or the parametric survival function in the period of trial follow-up.
- Selecting the time-point that is used to switch from the K-M survival function to the parametric survival function.
- Selecting the time-point at which the treatment effect is assumed to cease and further changes in OS are predicted from the bendamustine OS survival function rather than the G+benda+G OS survival function.

When providing scenario analyses using the K-M survival functions from the final data cut (CCOD November 2018), the company has applied the last event time in the final data cut which was [redacted] months for G-benda+G and [redacted] for benda, when using the final data cut (CCOD November 2018).

The ERG notes that Table 16 of the CDFR-CS states that the company has used Weibull survival functions fitted independently to each of the GADOLIN trial arms for extrapolating OS.[2] However, the ERG notes that the ICERs provided in the CDFR-CS are generated when selecting the "dependent" survival functions (i.e. assuming proportional hazards) option for OS which is consistent with the text describing the approach to modelling OS (CDFR-CS, p20) and the presentation of the survival candidate survival functions (CDFR-CS, Tables 9, 10, 11, and Figure 4). Therefore, the ERG believes that it was the company's intention to use the dependent survival functions (i.e. assuming proportional hazards for the Weibull function in the company's updated base-case), which was

consistent with the approach at the time of TA472, and the statement regarding the use of independently fitted models in Table 16 is an error.

The OS and PFS survival predictions used in the model for the key company cost-effectiveness analyses (i.e. those presented in Table 6) and for the two company scenario analyses using alternative parametric functions (company scenario analyses 4 and 5 in Table 7) are provided in Appendix 1 and 2 for reference.

In response to the clarification request (responses to questions B1, B2), the company provided a re-analysis of the PFS and OS survival data modelling using a segmented Weibull change-point model.[8] For both OS and PFS, the company estimated the survival functions when making two different assumptions about the timing of the change-point. Firstly, they assumed that the change point occurred at exactly 6 months (referred to as the fixed change-point model), and secondly, they included the time of the change point as an uncertain parameter within the model, allowing the change point to be estimated from the data to obtain the best fit (referred to as the random change-point model).

The results of the Weibull change-point analyses for OS and PFS are provided in Table 4 and Table 5 respectively. Plots of survival functions for OS and PFS when using the fixed change-point models are provided in Figure 4 and plots of survival functions for OS and PFS when using the random change-point models are provided in Figure 5.

Table 4: Summary of Weibull change-point model for PFS [reproduced from Table 1 of the company's response to clarification question B1][8]

Arm	Change-point	Shape α_1	Scale μ_1	Change point (months)	Shape α_2	Scale μ_2	10-year PFS
G-benda+G	Fixed	[redacted]	[redacted]	6.0	[redacted]	[redacted]	8.0%
Benda	Fixed	[redacted]	[redacted]	6.0	[redacted]	[redacted]	0.0%
G-benda+G	Random	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13.7%
Benda	Random	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.4%

Table 5: **Summary of Weibull change-point model for OS [reproduced from Table 2 of the company's response to clarification question B2][8]**

Arm	Change-point	Shape α_1	Scale μ_1	Change point (months)	Shape α_2	Scale μ_2	10-year OS
G-benda+G	Fixed	[redacted]	[redacted]	6.0	[redacted]	[redacted]	41.4%
Benda	Fixed	[redacted]	[redacted]	6.0	[redacted]	[redacted]	25.7%
G-benda+G	Random	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43.2%
Benda	Random	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	28.8%

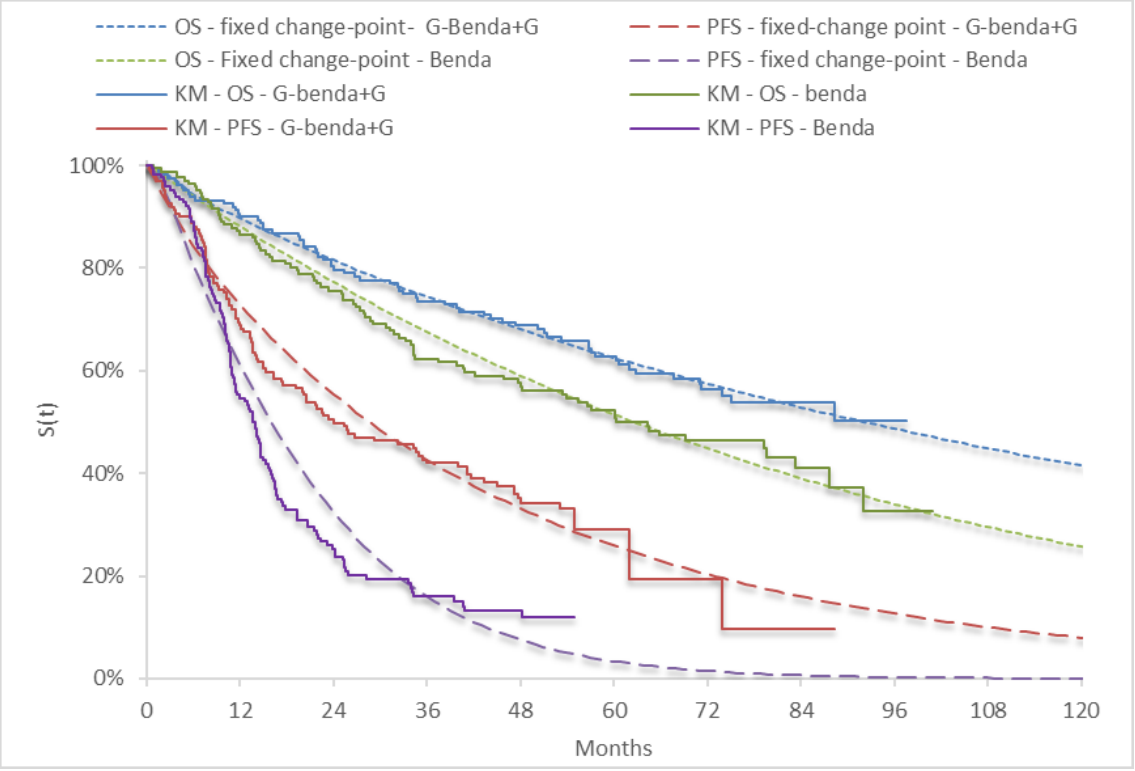


Figure 4: [redacted][8]

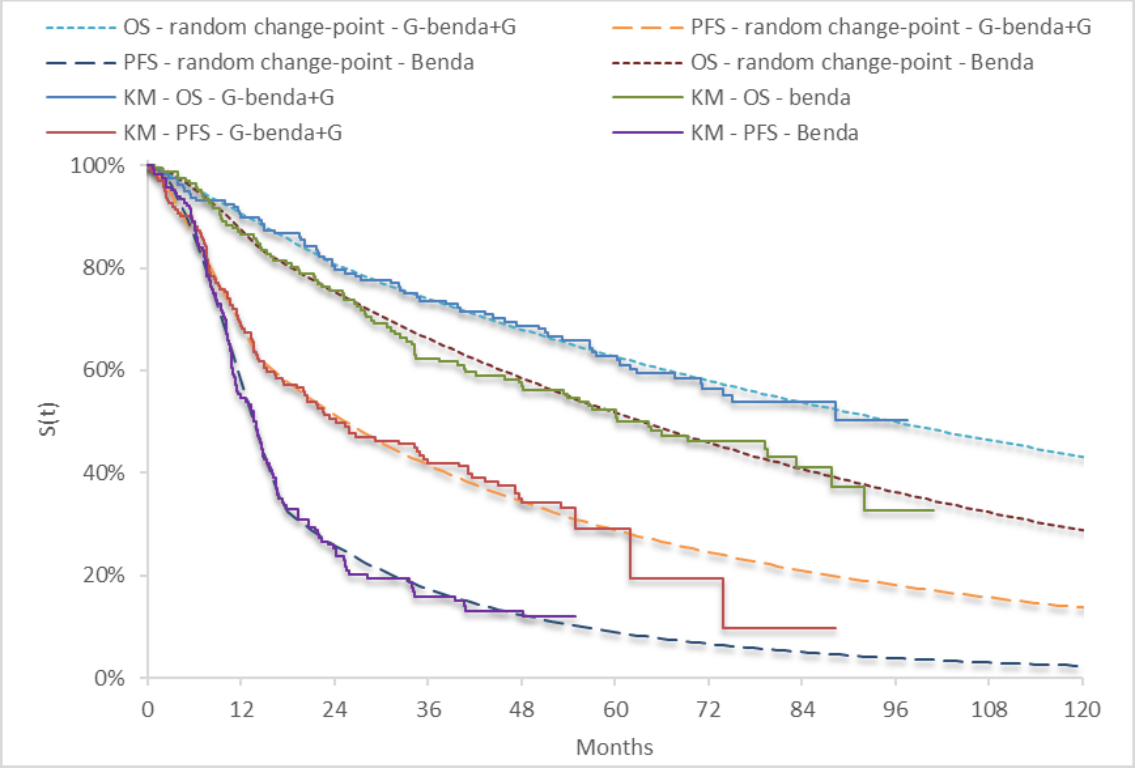


Figure 5: [redacted][8]

ERG critique of the treatment effectiveness and extrapolation

Overall Survival

The ERG has some concerns with the choice of models used to represent OS. In Section A.6.2 of the CDFR-CS, the company notes that "*The K-M plot for OS in patients with FL shows a clear separation of curves in favour of the G-benda+G arm from 6 months and beyond*" corresponding to the time of the first obinutuzumab maintenance dose.[2] It is plausible that a single hazard function over the lifetime of patients for patients treated with G-benda+G does not provide a realistic model for the data and a model that allows for a change-point in the hazard function would be more realistic.

In spite of the ERG's concern that a different model form for the G-benda+G arm may be appropriate, the company assessed whether it was reasonable to assume proportional hazards using a log cumulative hazard plot against log of time as per the guidance provided by NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14. In fact, an assessment of proportional hazards should be of the log cumulative hazard functions against time,[12] and a plot against log time was rightly criticised because the long-term difference is compressed on the log time scale.[13] The company provided plots against time, in response to clarification question A6 which suggests that a

proportional hazards assumption is not appropriate and that a change in the relative hazards occurs after approximately 6 months (Figures 6A and 6B).[7] Furthermore, the ERG disagrees with the company that a proportional hazards assumption is realistic other than as a convenient modelling assumption that implies that the treatment effect is constant over the time horizon of the economic model. In fact, Figure 6A suggest that the treatment effect may be increasing over time.

The ERG is unclear what parameterisations are used to model the different treatment arms for the models described in Table 9 of the CDFR-CS and what the treatment parameter represents (e.g. log hazard ratios or acceleration factors) except for the simplest models. Furthermore, although the company has suggested that a proportional hazards assumption is plausible and realistic, the ERG notes that not all models are proportional hazards models; for example, a log-logistic model is an accelerated failure time or proportional odds model and a lognormal model is an accelerated failure time model.

The ERG prefers to use BIC as a basis for model comparison, and notes that a difference in BIC between models of up to two is barely worth a mention. Thus, Table 9 of the CDFR-CS suggests that the exponential distribution provides the best fit of the models fitted by the company to the sample data, although the ERG accepts that the best fitting model to the sample data may not represent the most plausible model overall. However, the ERG notes that none of the proposed models, including the assumption made by the company of a constant treatment effect, may actually represent the true underlying data generation process for the reasons described above.

In response to clarification question B2, the company provided results of Weibull fixed and random change-point models (see Figure 4 and Figure 5). The fixed change-point was at six months corresponding to the time of the first obinutuzumab maintenance dose. The company did not provide estimates of uncertainty associated with the model parameters, did not assess the relative goodness-of-fit of the change-point models with the original models and did not consider alternative distributions for the data. Nevertheless, the ERG considers a change-point model to better represent the data generation process and, visually at least, the survival functions incorporating a change-point appear to provide a better representation of the observed data over both the early and late phase of the GADOLIN trial and is the model preferred by the ERG.

Progression-Free Survival

The ERG has some concerns with the choice of models used to represent PFS. In Sections A.6.1 of the CDFR-CS, the company notes that "*The K-M plot of INV-PFS in patients with FL shows a clear separation of curves in favour of the G-benda+G arm starting after approximately 6 months in the trial. This corresponds to the time of the first obinutuzumab maintenance dose.*"[2] It is plausible that a

single hazard function over the lifetime of patients for patients treated with G-benda+G does not provide a realistic model for the data and a model that allows for a change-point in the hazard function would be more realistic.

As with OS, the company follows the guidance of NICE DSU TSD 14 by plotting the log of the cumulative hazard functions against log time rather than against time.[14] Nevertheless, unlike with OS, the company concludes that there is reason to believe that hazards are not proportional, which is supported by Figure 6A

The company modelled the PFS data using independent Weibull distributions on the basis that this was the preferred approach in TA472 and because it generated conservative estimates of the 10-year PFS rates.[2] The ERG suggests that assuming a single Weibull model over the horizon of the economic model may not represent the underlying data generation process, and that Figure 6A suggests that the assumption may under-estimate the benefit of G-benda+G on PFS.

In response to clarification question B1, the company provided results of Weibull fixed and random change-point models. The fixed change-point was at six months corresponding to the time of the first obinutuzumab maintenance dose. The company did not provide estimates of uncertainty associated with the model parameters, did not assess the relative goodness-of-fit of the change-point models with the original models and did not consider alternative distributions for the data. Nevertheless, the ERG considers a change-point model to better represent the data generation process and, visually at least, the survival functions incorporating a change-point appear to provide a better representation of the observed data over both the early and late phase of the GADOLIN trial and is the model preferred by the ERG.

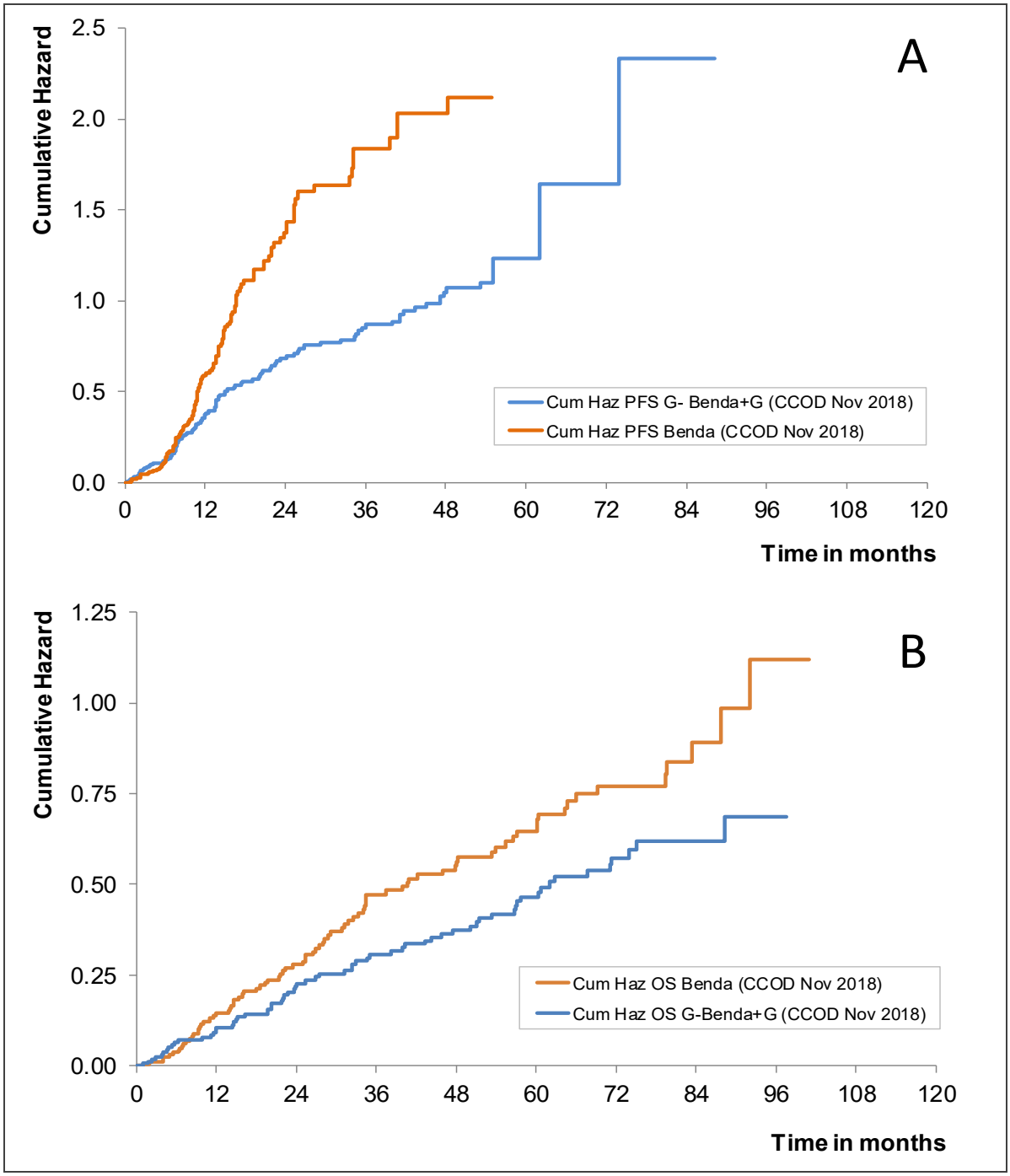


Figure 6: Cumulative hazard functions against time for (A) PFS and (B) OS [reproduced from Figure 1 of the company's response to the clarification request][7]

4.1.6 Time on treatment

The company states that the time-to-off treatment (TTOT) data were mature at the time of the April 2016 data cut used in the economic analyses that informed TA472 and therefore these data have not been updated to reflect data from the final data cut (CCOD November 2018).[2] The ERG notes that whilst the full pattern of discontinuation was observed at the time of the April 2016 data-cut, with the proportion of patients in the FL patients remaining on G-benda+G treatment recorded [redacted] patients in the FL subgroup randomised to G-

benda+G were censored before completing treatment (data extracted from the model provided with the CDFR-CS). The ERG has compared the data on treatment exposure reported by Cheson et al., which was based on the April 2016 data cut, with that reported in the CSR for the final data cut (CCOD Nov 2018).[5, 9] The ERG notes that the median duration of maintenance therapy with obinutuzumab was 521 days (17 months) based on the April 2016 data cut and [redacted] days [redacted] months) based on the final CSR (CCOD Nov 2018).[5, 9] In addition, the median numbers of maintenance doses received were 9 and [redacted] for the April 2016 and November 2018 data cuts respectively. Therefore, it is possible that incorporating updated data on TTOT from the November 2018 data cut would have a marginal impact on the costs of G-benda+G in the economic analysis, despite the data being relatively mature at the time of the TA472.

The ERG also notes the earlier discussion regarding the shorter median duration of treatment in the SACT cohort compared with the median duration of treatment in the GADOLIN trial. The ERG notes that, as the estimates of PFS and OS in the economic model are based directly on the data from the GADOLIN trial, they cannot be adjusted to account for a different duration of treatment as there is no connection in the model between time on treatment and the clinical outcomes of PFS and OS which determine the QALYs gained. Therefore, it is not possible to use the company's model to estimate the cost-effectiveness of G-benda+G when assuming a shorter duration of treatment.

4.1.7 Adverse events

The company states that the "*safety profile for G-benda+G at the time of the final data cut (CCOD November 2018) was consistent with the primary analysis and no new safety signals were observed with longer follow-up therefore an update to safety was not required in the updated economic model*."[2] The ERG notes that AEs were not a significant driver of cost-effectiveness in the analyses that informed TA472. Therefore, any possible bias introduced by not incorporating updated evidence on AEs was considered likely to be small by the ERG. For this reason, no further consideration was given to the updated AE data.

4.1.8 Health-related quality of life

No changes have been made to the utility data applied in the model since the analyses for TA472 and therefore this is consistent with what was specified in the Terms of Engagement.[1, 2]

4.1.9 Resources and costs

The company have applied an updated cost for bendamustine, to reflect changes in the costs recorded in the eMIT database, and a revised PAS for obinutuzumab in their preferred base-case scenario.[2] The updated PAS is a simple discount of [redacted], which is greater than the PAS discount applied at CDF entry of [redacted] and the PAS applied to generate the ICERs in Table 1 of the Terms of Engagement document, which was [redacted] The cost of bendamustine applied previously was £27.77 and £6.85 for

vial sizes of 100mg and 25mg respectively. The company's updated base-case applies costs of £19.30 and £5.28 for 100mg and 25mg vials respectively. No further changes have been made to the resource use and cost data applied in the model since the analyses for TA472, and therefore the analyses submitted are otherwise consistent with what was specified in the Terms of Engagement.

The ERG considers that the updating of costs for bendamustine and the application of the new PAS are appropriate. However, the ERG was unable to check the updated cost of bendamustine in the eMIT database at the time of the CDFR-CS as the eMIT database was updated on the 15th November 2019 after the company finalised their submission and archived versions are not available online. The ERG notes that the cost of bendamustine has reduced further in the 15th November 2019 version of the eMIT database to £11.39 for 100mg (£56.96 for 5 vials of 100mg) and £3.07 for 25mg (in this case the price per single vial is lower than for 5 vials).[15]

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The CDFR-CS presents a number of cost-effectiveness analyses in which incremental changes are made between the approach used in TA472 and their current preferred base-case.[2] The ERG has summarised the results of these analyses alongside the various changes made to parameters and assumptions in Table 6 (NB: these analyses use point parameter estimates, i.e. deterministic). Cost-effectiveness analysis 4 is referred to by the company as its 'updated base-case' (CDFR-CS, page 32) and in this analysis G-benda+G has an incremental cost of [redacted], an incremental QALY gain of [redacted] QALYs and an ICER of £17,408 per QALY gained, compared with bendamustine alone.

The results of the probabilistic sensitivity analysis (PSA) for the company's updated base-case were reasonably consistent with an ICER of £17,593 from the PSA compared with an ICER of £17,408 based on the deterministic analysis. The company reports that 94% of the PSA runs provided an ICER below £30,000 per QALY. The ERG notes that the proportion of PSA runs with an ICER under £20,000 per QALY is [redacted] (Figure 8 of CDF-CS).[2]

It can be seen that each of the changes introduced by the company lowers the incremental costs and increase the QALYs gained with the exception of the updated prices which [redacted] but did not affect the QALYs gained.

5.2 Company's sensitivity analyses

In addition, the company presents a number of scenario analyses exploring the impact of using alternative data and/or assumptions.[2] These are summarised in Table 7. It can be seen that limiting the duration of treatment effect to the last OS event observed in the intervention arm of the GADOLIN trial increases the ICER to £21,470 per QALY gained. Switching from the Weibull survival function to the log-logistic function for PFS decreased the ICER to £15,318. This is mainly because the additional time spent in the PFS state for G-benda+G compared to bendamustine alone is [redacted] when using the log-logistic function for PFS than when using the Weibull function for PFS (see CDFR-CS, Table 13), and this increases the incremental QALYs gained.[2] However, switching to the log-normal survival function for OS increased the ICER, mainly because of a reduction in the incremental QALYs gained. This is because although the log-normal survival function predicts [redacted] between the two arms for the log-normal parametric function than for the Weibull parametric function (see CDFR-CS, Table 11).[2] In the company's scenario analysis 5, the K-M survival functions were used up to the time of the last OS event but the parametric survival functions, assuming a lifetime persistence of treatment effect, were used thereafter. This decreased the ICER to £16,626 per QALY gained,

because in this scenario, the size of the gap between the OS functions going forwards is dependent on the K-M estimate at the time of the last observed OS event.

The company also provided cost-effectiveness results in response to clarification questions B5 and B6 in which they implemented the Weibull change-point survival models for PFS and OS respectively.[8] These are summarised in Table 8. It can be seen that the ICER is lower in each of the four scenarios presented in Table 8 than in the company's updated base-case. In scenarios 6 and 7, the use of either a fixed or random change-point for PFS results in an increase in the additional time spent in PFS, and therefore an increase in QALYs, compared with the base-case which used a single Weibull function. The increase is larger when using the random change-point for PFS than when using the fixed change-point for PFS ([redacted] versus [redacted] additional QALYs). In scenarios 8 and 9, the use of a fixed or random change-point for OS results in an increase in the additional life-years (LYs) gained compared with the use of a single Weibull survival function, but the increase is larger for the fixed change-point at 6 months compared to the random change-point ([redacted] versus [redacted] additional LYs gained).

Table 6: Cost-effectiveness results (deterministic) presented in the CDFR-CS (adapted from Table 17 of the CDFR-CS)[2]

Scenario	Data cut used for K-M and parametric survival function estimation	Use of K-M survival function for OS	Switch to parametric OS for G-Benda+G	Switch to parametric OS for benda	End of treatment effectiveness	Drug acquisition costs	Incr Costs	Incr QALYs	ICER
Company Cost-effectiveness analysis 1	April 2016	Yes	47.44 months	53.88 months	4.0 years	CDF PAS and 2016 cost for generic benda	[redacted]	[redacted]	[redacted]
Company Cost-effectiveness analysis 2	November 2018	Yes	[redacted] months	[redacted] months	4.0 years		[redacted]	[redacted]	[redacted]
Company Cost-effectiveness analysis 3	November 2018	No	NA	NA	25 years (i.e. lifetime)		[redacted]	[redacted]	[redacted]
Company Cost-effectiveness analysis 4 – **company's updated base-case**	November 2018	No	NA	NA	25 years (i.e. lifetime)	Updated PAS and 2019 cost for generic benda	[redacted]	[redacted]	**£17,408**

Table 7: Company's scenario analyses (adapted from Table 20 of the CDFR-CS)[2]

Scenario	Data cut used for K-M and parametric survival function estimation	Use of K-M survival function for OS	Switch to parametric OS for G-Benda+G	Switch to parametric OS for benda	End of treatment effectiveness	Drug acquisition costs	Incr Costs	Incr QALYs	ICER
Company scenario 1	November 2018	No	NA	NA	[redacted] ([redacted] months) (last OS event)	Updated PAS and 2019 costs for generic benda	[redacted]	[redacted]	£21,470
Company scenario 2	November 2018	No	NA	NA	[redacted] years	Updated PAS and 2019 costs for generic benda	[redacted]	[redacted]	£20,327
Company scenario 3 – as per base-case with log-logistic survival function for PFS	November 2018	No	NA	NA	25 years (i.e. lifetime)	Updated PAS and 2019 costs for generic benda	[redacted]	[redacted]	£15,318
Company scenario 4 – as per base-case with lognormal survival function for OS	November 2018	No	NA	NA	25 years (i.e. lifetime)	Updated PAS and 2019 costs for generic benda	[redacted]	[redacted]	£20,206
Company scenario 5 – new clinical data and acquisition cost with K-M survival function until last OS event followed by parametric extrapolation	November 2018	Yes	[redacted] months	[redacted] months	25 years (i.e. lifetime)	Updated PAS and 2019 costs for generic benda	[redacted]	[redacted]	£16,629

Table 8: Company's scenario analyses incorporating change-point models (adapted from Tables 3 and 4 of company response to clarification questions B5 and B6)[8]

Scenario	Additional years spent in PFS state	Incr LYs	Incr Costs	Incr QALYs	ICER
Company updated base-case	[redacted]	[redacted]	[redacted]	[redacted]	**£17,408**
Company scenario 6 – Weibull model with change-point at 6 months for PFS	[redacted]	[redacted]	[redacted]	[redacted]	£17,322
Company scenario 7 – Weibull model with random change-point for PFS	[redacted]	[redacted]	[redacted]	[redacted]	£16,383
Company scenario 8 – Weibull model with change-point at 6 months for OS	[redacted]	[redacted]	[redacted]	[redacted]	£15,587
Company scenario 9 – Weibull model with random change-point for OS	[redacted]	[redacted]	[redacted]	[redacted]	£15,902

5.3 Model validation and face validity check

The ERG was able to use the company's model to reproduce all of the ICERs presented in the CDFR-CS. The ERG noted that the company's model employed a different time for the switch from the K-M survival function to extrapolation using the parametric survival function in the G-benda+G and benda arms. The ERG was uncertain if this had been agreed as being appropriate at the time of TA472, but it noted that the company's model generated the ICERs reported in Table 1 of the Terms of Engagement document when using this approach and implementing the PAS in place prior to CDF negotiations (i.e. [redacted]). Therefore, the ERG considered the company's approach to be consistent with the Terms of Engagement.[1]

The ERG also compared the company's model to the ERG model from TA472 dated 5th October 2016. The ERG was able to reproduce the ICERs reported in Table 1 of the Terms of Engagement document using the ERG model dated 5th October 2016 when incorporating the differential times for switching from the K-M survival functions to the parametric survival functions used to extrapolate OS for the two arms. Therefore, the ERG believes that the company's model is consistent with the models used in TA472, at least for those scenarios presented in Table 1 of the Terms of Engagement.

The ERG then implemented each of the changes described in Table 6 starting from the model dated 5th October 2016 and was able to reproduce all of the ICERs in Table 6. Therefore, the ERG is satisfied that no changes have been made to the model by the company, other than those described in the CDFR-CS.

The ERG also re-ran the PSA for the company's updated base-case using 1000 simulations and obtained an ICER of £17,681 per QALY gained, which the ERG considered to be sufficiently consistent with the ICER for the PSA reported by the company of £17,593.

The ERG also validated the ICERs provided in response to clarification questions B5 and B6,[8] which included Weibull change-point models for PFS and OS respectively, and was satisfied that these had been incorporated appropriately in the model submitted by the company on the 12th of December 2019.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

The ERG combined two of the company's scenario analyses to create ERG scenario analysis 1, which included:

- the use of the K-M survival functions to directly estimate OS up to the last OS event in both arms
- followed by an assumption of no treatment effect beyond the last OS event.

However, in this scenario analysis, the gap between the two OS functions is heavily dependent on the position of the last OS event in the K-M survival function and the ERG was not confident that this scenario had face validity based on a visual inspection of the survival functions (see Figure 7).

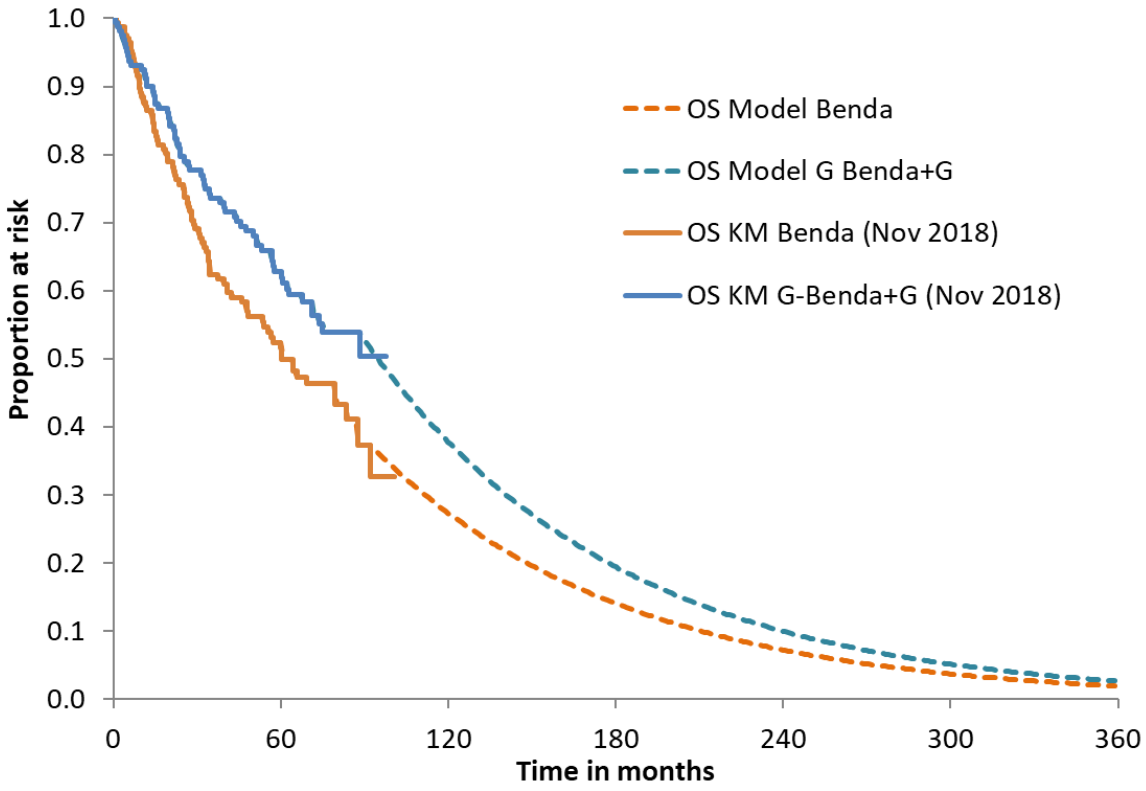


Figure 7: OS survival functions for ERG scenario 1 in which the K-M survival functions are used to last OS event ([redacted] months/[redacted] years), and parametric OS survival functions applied thereafter with no treatment effect assumed beyond the last OS event

To address this, the ERG conducted ERG scenario analysis 2 in which;

- the K-M survival functions were used up to [redacted] months
- the parametric survival functions for OS were used to extrapolate from this event to the last OS event ([redacted] months/[redacted] years)

- an assumption of no treatment effect was made thereafter by applying the hazards from the comparator group to both treatment arms.

The ERG considered that this had more face validity than scenario analysis 1 based on a visual inspection of the OS survival functions (see Figure 8).

The time point of [redacted] months was selected as the CDF-CS states that *"overall survival estimates are robust up to [redacted] months, at which point [redacted] deaths had occurred, and K-M-estimated event-free rate was [redacted] in the benda arm and [redacted] in the G-benda+G arm."*[2] It therefore seemed reasonable to choose this point to switch from the K-M survival functions to the parametric functions for OS, as this avoids placing undue emphasis on the data points at the end of the K-M survival functions, which are more subject to uncertainty.

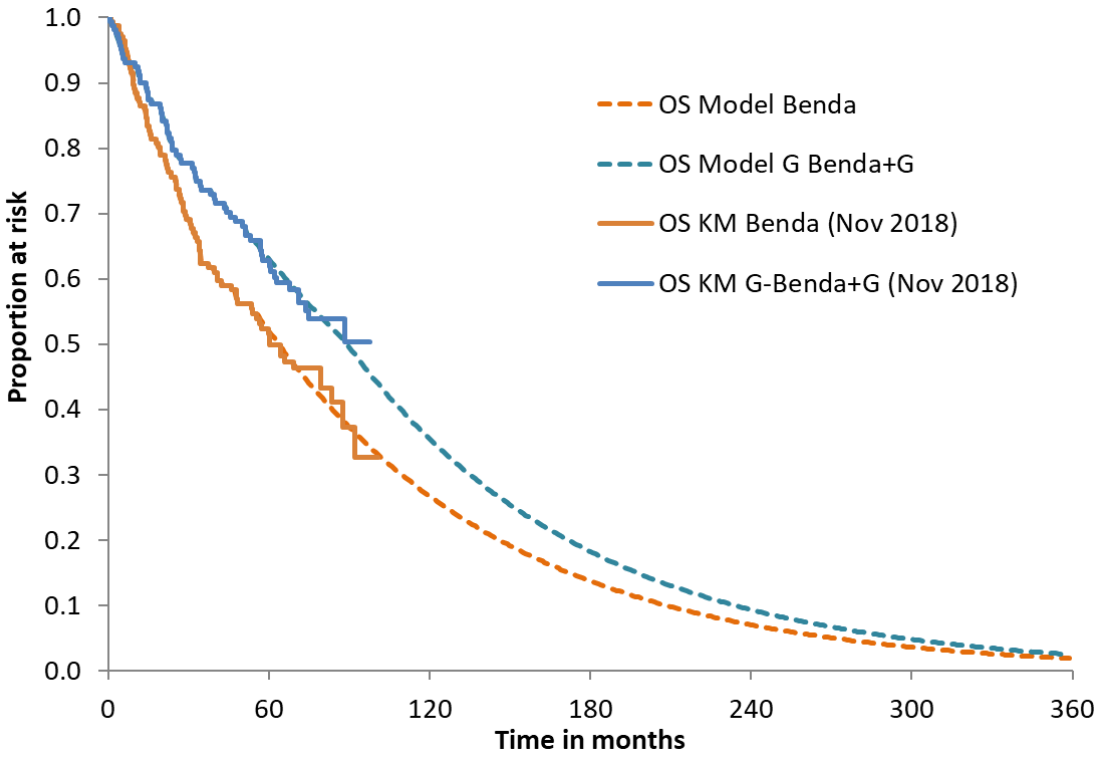


Figure 8: OS survival functions for ERG scenario 2 in which the K-M survival functions are used to [redacted] months followed by parametric OS survival functions with treatment effect assumed to end at [redacted] months / [redacted] years

Following the receipt of the later clarification response to questions B1, B2, B5 and B6,[8] the ERG conducted ERG scenario analysis 3, which included the Weibull survival function with random change-point for both PFS and OS (i.e. combination of company scenario analyses 7 and 9).

In addition, the ERG wished to explore whether the small change in the price of bendamustine between the time of the CDF-CS and the time of writing of the ERG report was likely to have a small or large impact on the ICERs. Therefore, scenario analysis 4 was conducted in which the latest price for bendamustine from the eMIT database was applied in conjunction with the approach used in ERG scenario analysis 3.

In an attempt to assess the potential size of any bias introduced by the company using the TTOT data from the April 2016 CCOD instead of updated TTOT data from the November 2018 CCOD, the ERG adjusted the incremental costs from scenario 4 to account for one additional dose of obinutuzumab in year 3 of the model. The ERG notes that this scenario analysis does not accurately capture the potential impact of incorporating an updated K-M curve for TTOT because it does not capture the exact timing of any additional doses received, which will affect the discounting rate applied. However, this exploratory analysis, reported as ERG scenario 5, provides an indication of the likely size and direction of any potential bias.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The impact on the ICER of the assumptions made in the ERG's five scenario analyses is provided in Table 9.

It can be seen by comparing ERG scenario analysis 1 (see, Table 9) to company scenario 5 (see, Table 7) that the model is still somewhat sensitive to the assumption regarding the duration of treatment effect, with the ICER increasing from £16,629 to £20,472 per QALY gained when limiting the duration of treatment effect to the time of the last OS event observed in GADOLIN ([redacted] years/[redacted] months). However, the ERG notes that the uncertainty related to this factor is much smaller than at the time of TA472. This is because in the April 2016 data cut that informed TA472, the time of the last OS event was 4.0 years and, in the analyses that informed TA472, there was a substantial increase in the ICER when extending the duration of treatment effect from 4.0 years to 7.0 years (see CDFR-CS, Table 1).[2]

It can also be seen, by comparing ERG scenario analysis 2 with ERG scenario analysis 1, that when using the K-M survival functions to model OS in the early stages, the model is somewhat sensitive to the timing of the switch from using the K-M survival functions to using the parametric survival functions to extrapolate OS. This is because the parametric survival functions are 'tacked on' to the last K-M estimate and therefore the absolute difference in OS predicted in the model is heavily dependent on the OS estimates at the time at which the switch is made.

ERG scenario analysis 3 demonstrates that the combined impact of using Weibull distributions with random change-points for both PFS and OS is to further lower the ICER than when implementing the random change-point Weibull for either PFS or OS individually.

A comparison of ERG scenario 3 with ERG scenario 4 shows that the cost-effectiveness estimates are not particularly sensitive to the small change in the cost of generic bendamustine since the time of the CDFR-CS.

ERG scenario 5 demonstrates that the impact of increasing the incremental costs to include acquisition and administration costs for one additional dose of obinutuzumab received in the third year of the model (i.e. increased incremental cost of [redacted]) is to increase the ICER to [redacted] per QALY. However, as discussed above this only provides an indication of the likely size and direction of any potential bias as it does not accurately capture the timing of any additional doses.

6.3 ERG's preferred assumptions

Of the models fitted, the ERG prefers to use the Weibull survival functions with random change-points for PFS and OS because the change-point models provide a more plausible representation of the data generation process. However, because no other distributions were considered by the company, the ERG is unable to confirm whether the Weibull change-point models provide the most plausible survival functions. The ERG also prefers to use the most up-to-date costs from the eMIT database for bendamustine, although this is noted to have a small impact on the ICER. Therefore, the ERG's preferred ICER is £15,045 per QALY gained.

The ERG notes that the company should have incorporated uncertainty associated with the parameters of the Weibull survival functions and the change-points in the economic model. However, the company has not included any measure of uncertainty associated with the Weibull change-point survival functions within the economic model provided. This is a significant limitation, particularly, as these survival functions are applied for the whole time horizon in the ERG's preferred base-case and therefore this scenario effectively incorporates no uncertainty with regards to time spent in the PFS and OS states. Despite this limitation, the ERG ran the probabilistic version of the model for their preferred base-case and obtained an ICER of £15,035 per QALY gained with all of the 1000 PSA samples providing an ICER under £20,000. However, the ERG notes that this should not be taken as an accurate estimate of the uncertainty around the mean ICER because the model no longer incorporates any uncertainty around the PFS and OS survival functions. It is possible that including this uncertainty would not have a large impact on the mean costs and QALYs obtained from the PSA, as in the company's base-case, there is good agreement between the deterministic ICER and the

probabilistic ICER, but it is expected to have a large impact on the uncertainty around the ICER estimated by the PSA.

The ERG notes that the results for ERG scenario 4 are not only affected by the updated data from GADOLIN and the incorporation of the Weibull change-point models for OS and PFS, but they are also significantly affected by the updated PAS provided by the manufacturer, which has had a large impact on the ICERs compared with the analyses that informed TA472. For example, the ICERs presented in Table 1 of the Terms of Engagement document were based on a PAS discount of [redacted][1] Using this earlier PAS discount rate would have generated an ICER for ERG scenario 4 of [redacted] per QALY gained, which is substantially higher than the ICER of £15,045 per QALY gained based on the current PAS, which includes a discount of [redacted].[2] Therefore, the updated PAS has also had a significant impact on the decision uncertainty.

Table 9: ERG scenario analyses

Scenario	Data cut used for K-M and survival functions	Use of K-M survival function for OS	Switch to parametric OS survival functions for G-Benda+G	Switch to parametric OS survival function for benda	End of treatment effectiveness	Drug acquisition costs	Incr Costs	Incr QALYs	ICER
Company cost-effectiveness analysis 4 – company's updated base-case	November 2018	No	NA	NA	25 years (i.e. lifetime)	Updated PAS and 2019 costs for generic benda	[redacted]	[redacted]	£17,408
ERG scenario 1 – use K-M estimates until last event and assume no treatment effect after last event	November 2018	Yes	[redacted] months	[redacted] months	[redacted] years ([redacted] months) (last OS event)	Updated PAS and 2019 costs for generic benda	[redacted]	[redacted]	£20,472
ERG scenario 2 – use K-M estimates until [redacted] months and assume no treatment effect after last event	November 2018	Yes	[redacted]	[redacted]	[redacted] years ([redacted] months) (last OS event)	Updated PAS and 2019 costs for generic benda	[redacted]	[redacted]	£21,301
ERG scenario 3 – Weibull survival functions with random change-points for PFS and OS	November 2018	No	NA	NA	25 years (i.e. lifetime)	Updated PAS and 2019 costs for generic benda	[redacted]	[redacted]	£15,020
ERG scenario 4 – ERG scenario 3 with latest eMIT price for bendamustine **– ERG preferred base-case**	November 2018	No	NA	NA	25 years (i.e. lifetime)	Updated PAS and 2019 costs for generic benda	[redacted]	[redacted]	**£15,045**
ERG scenario 5 – ERG scenario 4 with incremental costs adjusted to include one additional dose of obinutuzumab in the 3rd year of the model.	November 2018	No	NA	NA	25 years (i.e. lifetime)	Updated PAS and 2019 costs for generic benda	[redacted]	[redacted]	[redacted]

6.4 Conclusions of the cost effectiveness section

The company's preferred ICER is substantially lower than the ICERs in Table 1 of the Terms of Engagement document. The main factors that have resulted in this change to the ICERs are;

- the updated OS data from GADOLIN
- the allowance in the change-points models for the hazard function to change during the period observed in GADOLIN
- the company's assumption of a life-time treatment effect beyond the observed data from GADOLIN
- the company's updated PAS.

The ERG's preferred ICER is lower than that derived from the company's preferred assumptions. This is mainly because of the inclusion of the Weibull survival functions with random change-points for both PFS and OS. The ERG considers that using this model is preferable to using a single Weibull function for each treatment arm because it better represents the way each treatment strategy was administered and the consequent data generation process. Furthermore, empirical evidence provided by plots of the cumulative hazard functions against time for PFS and OS suggest that the hazards diverge after the initial 6 month treatment period. In addition, the survival functions incorporating a change-point appear to provide a better representation of the observed data over both the early and late phase of the GADOLIN trial. Consequently, the ERG considers it reasonable to use these survival functions as the basis for extrapolation beyond the trial period.

There is one remaining area of uncertainty which could have a substantial impact on the ICERs. The data from the SACT cohort suggest that many patients are being recorded as having completed treatment even though the median treatment duration is under 6 months, which may suggest that obinutuzumab is being used in clinical practice as an induction treatment without a maintenance phase (i.e. G-benda instead of G-benda+G). It is difficult to predict what the cost-effectiveness of obinutuzumab would be if it were to be used only as an induction therapy because the model is based on PFS and OS outcomes from the GADOLIN trial and therefore the model assumes the exact same treatment duration as observed in GAOLIN. Therefore, it is important to remember, that the cost-effectiveness estimates presented here are only applicable to the use of G-benda+G in a manner consistent with how it was used in the GADOLIN trial.

7 END OF LIFE

End of life considerations were judged to be not applicable at the time of TA472 and no evidence has been presented to suggest that this judgement should be reconsidered.

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Appendix 1: OS plots for key company cost-effectiveness analyses and scenario analyses

NB: All plots in appendix 1 have been extracted from the company's economic model by the ERG.

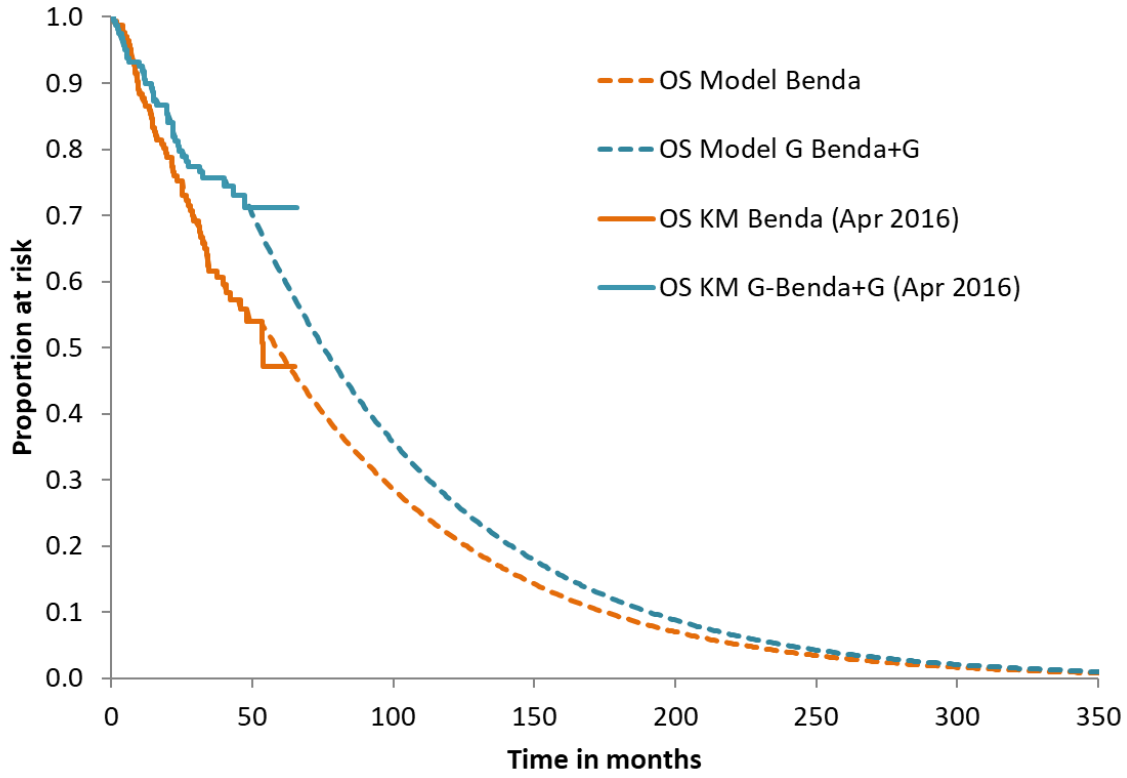

Figure 9: OS for Company cost-effectiveness analysis 1 (ICER = [redacted])

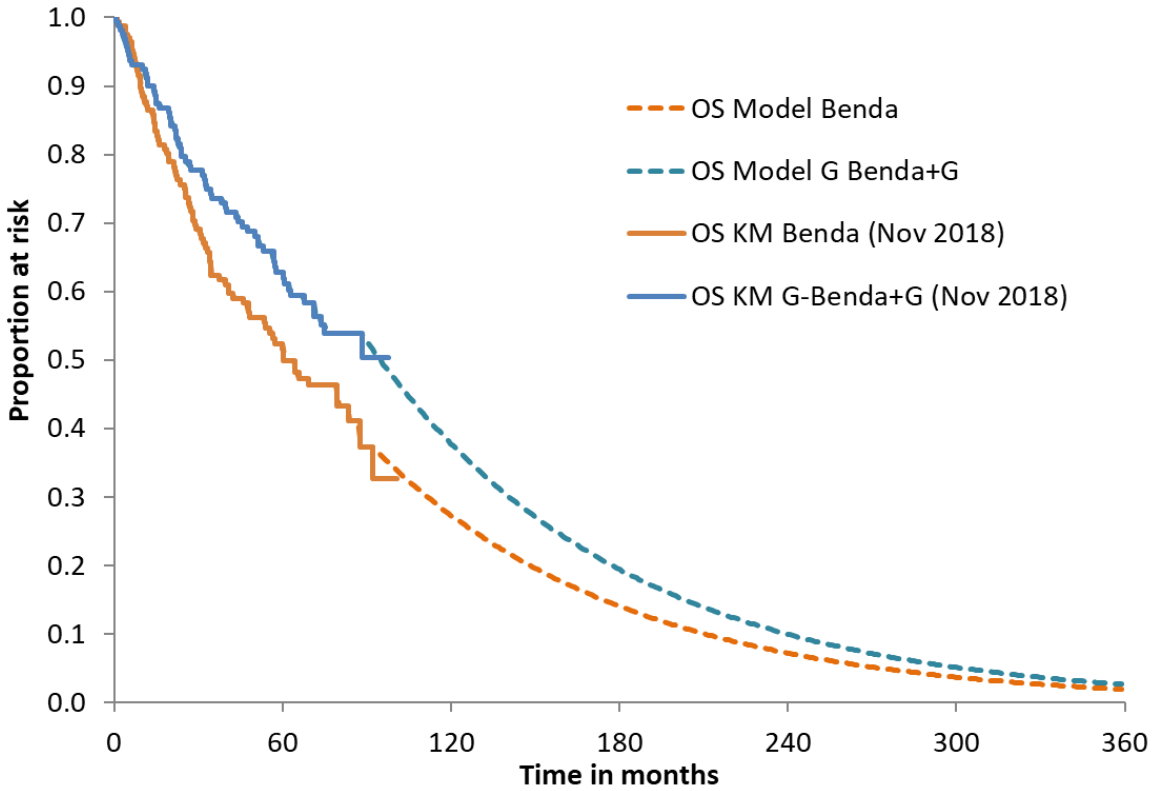

Figure 10: OS for Company cost-effectiveness analysis 2 (ICER = [redacted])

)

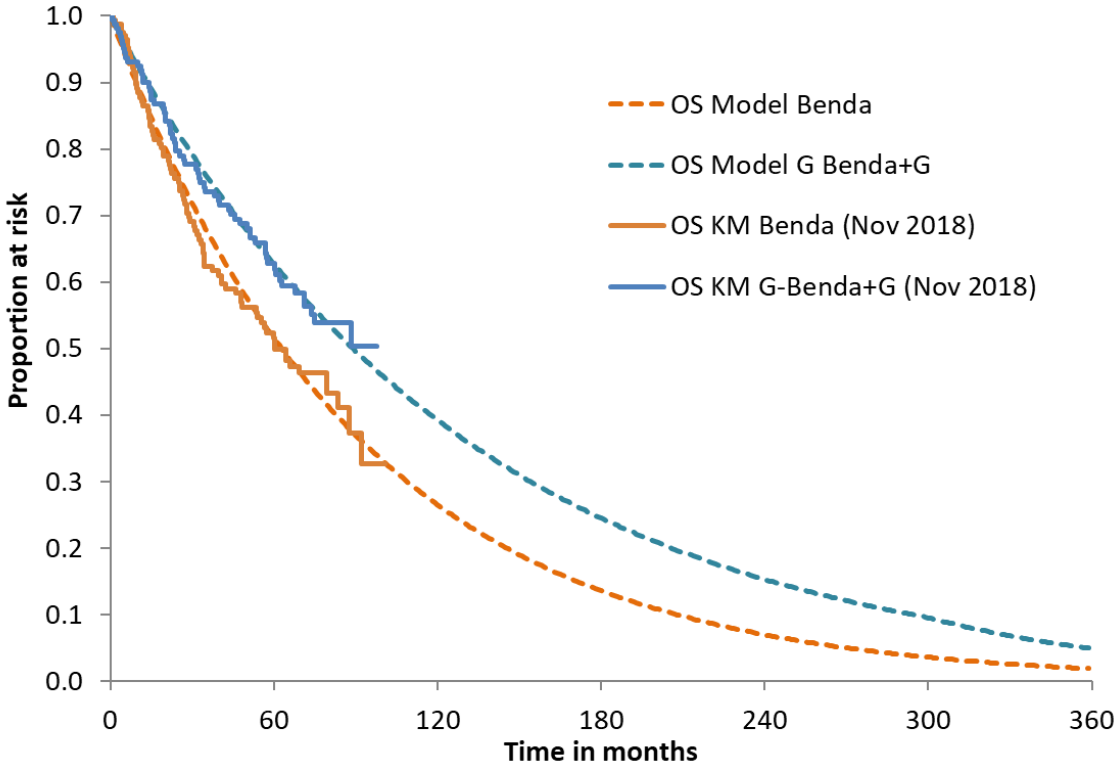

Figure 11: OS for Company cost-effectiveness analyses 3 and 4 (ICERs = [redacted] and [redacted] respectively)

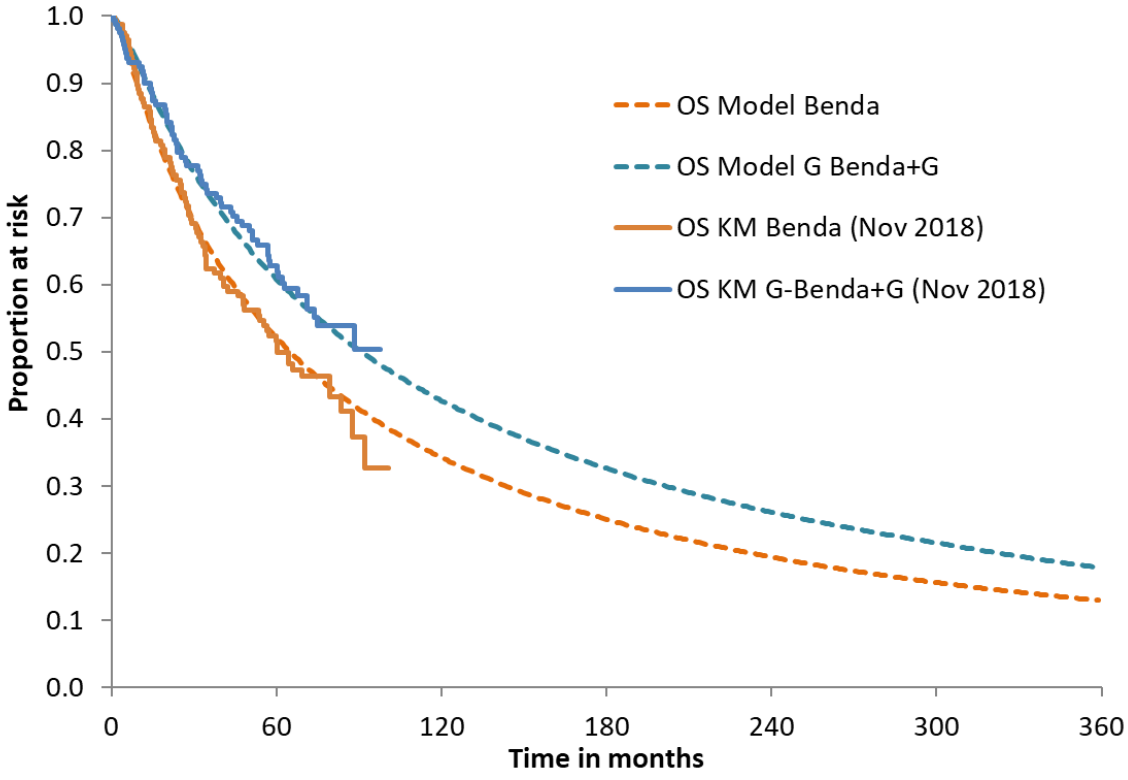

Figure 12: OS for Company scenario analysis 4 using log-normal parametric survival function (ICER [redacted])

Appendix 2: PFS plots when using April 2016 and November 2018 Data cuts

NB: All plots in appendix 2 have been extracted from the company's economic model by the ERG.

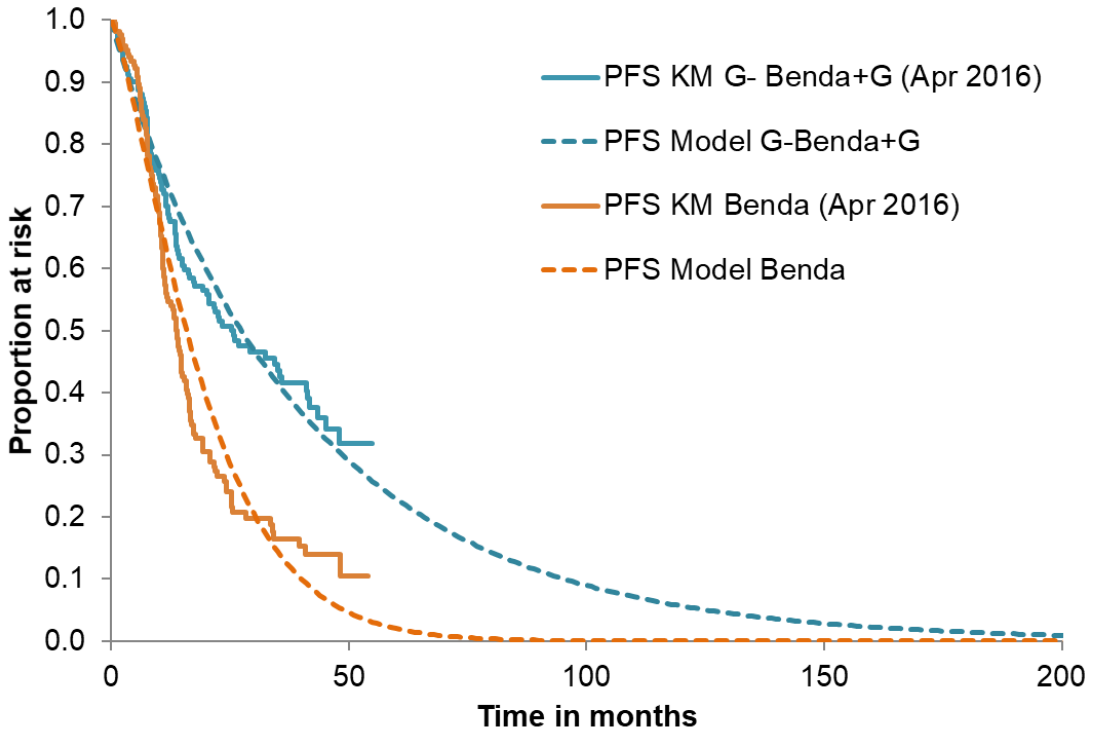

Figure 13: PFS when using April 2016 data cut (company cost-effectiveness analysis 1)

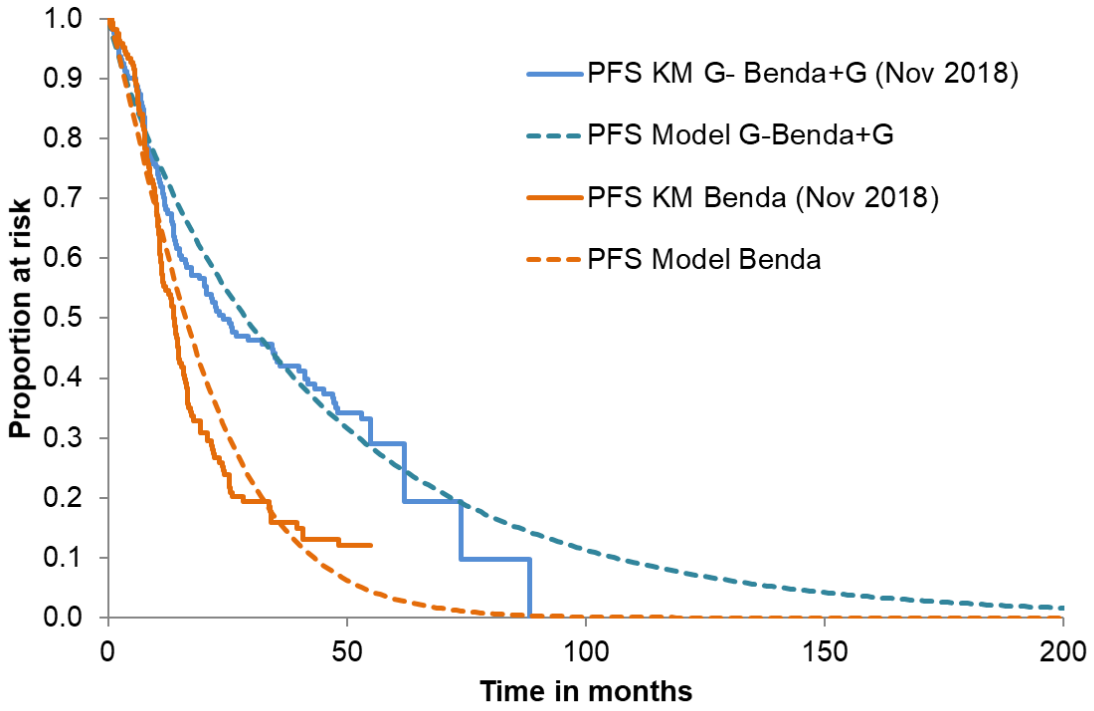

Figure 14: PFS when using Nov 2018 data cut (company cost-effectiveness analyses 2 to 4)

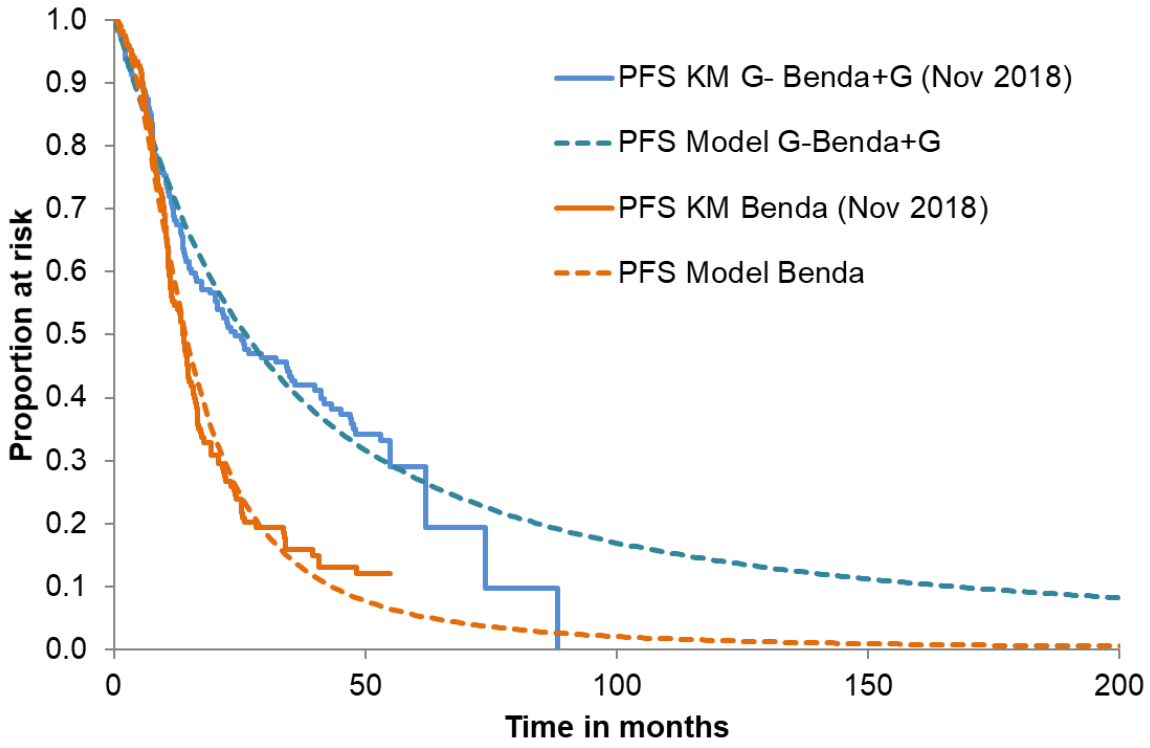

Figure 15: **PFS when using log-logistic fitted to November 2018 data cut (company scenario analysis 3)**

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Obinutuzumab with bendamustine for treating follicular lymphoma refractory to rituximab (CDF Review of TA472) [ID1583]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on Tuesday 7 January 2020** 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.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Adherence to Terms of Engagement

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The Company acknowledges that, within the Terms of Engagement document the "*committee expected to see the same model structure in the CDF review*". The Company believes the ERG's statement, *"…significant deviation from the Terms of Engagement is that the company has amended the approach used to model overall survival (OS) in their preferred base-case scenario...."* repeated within the ERG report (pages 6, 10, and 11), to be inaccurate.	The Company asks for a clear acknowledgment that the requirements within the Terms of Engagement document were adhered to.	For the following reasons the Company believes the ERG's statement, to be inaccurate: (1) The aforementioned requirement within the Terms of Engagement document does not set out a granular necessity for the company to retain all elements of the previous model structure for the updated base-case specifically. (2) In full transparency, the Company retained the detailed structure and functionality within the model available at the time of CDF entry and presented (scenario) results transparently as such. (3) The Company considers that the broader modelling structure were retained in the updated analysis since in the original appraisal of TA472 both a Markov modelling approach was used to model PFS and inform OS and later an area-under-the-curve modelling approach used (preferred by the ERG and the committee).	It is the ERG's opinion that the test of whether the company's submission is consistent with the terms of engagement should be applied to the company's revised base-case analysis as it is not possible to apply a single test of consistency to all of the multiple scenarios presented. This is why the ERG highlighted the discrepancy between the method used to model OS in the company's preferred base-case and the method used in the scenarios that are presented in Table 1 of the Terms of Engagement document. However, the ERG report clearly states, on page 6, that *"the company have also presented analyses that are consistent with the approach taken to generate the incremental cost-effectiveness ratios (ICERs) in Table 1 of the Terms of Engagement document".* The ERG does not therefore believe that the report is factually inaccurate when the quoted sentence is read within context.

Public Health England

Protecting and improving the nation's health

Obinutuzumab with bendamustine for treating rituximab-refractory follicular non-Hodgkin's lymphoma

Data review

Commissioned by NHS England and NHS Improvement

About Public Health England

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Contents

Executive summary

The National Institute for Health and Care Excellence (NICE) appraised the clinical and cost effectiveness of obinutuzumab for the treatment of patients diagnosed with follicular non-Hodgkin's lymphoma (NHL). The appraisal committee highlighted clinical uncertainty around estimates of treatment duration and overall survival (OS) in the evidence submission. As a result, they recommended commissioning of obinutuzumab through the Cancer Drugs Fund (CDF) to allow a period of managed access, supported by additional data collection to answer the clinical uncertainty.

NHS England and NHS Improvement commissioned Public Health England (PHE) to evaluate the real-world treatment effectiveness of obinutuzumab in the CDF population during the managed access period. This report presents the results of the use of obinutuzumab, in clinical practice, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

This report, and the data presented, demonstrate the potential within the English health system to collect real-world data to inform decision-making about patient access to cancer treatments via the CDF. The opportunity to collect real-world data enables patients to get access to promising new treatments much earlier than might otherwise be the case, whilst further evidence is collected to address clinical uncertainty.

The NHS England and NHS Improvement and PHE partnership for collecting and following up real-world SACT data in the CDF in England has resulted in analysis of data for the full patient population, with 100% of patients and 98% of patient outcomes reported in the SACT dataset. PHE and NHS England and NHS Improvement are committed to providing world first high-quality real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

Methods

NHS England and NHS Improvements Blueteq® system was used to provide a reference list of all patients with an application for obinutuzumab for rituximab-refractory follicular NHL in the CDF. Patient NHS numbers were used to link Blueteq applications to PHE's routinely collected SACT data to provide SACT treatment history.

Between 26 July 2017 and 25 January 2019, 101 applications for obinutuzumab were identified in the NHS England and NHS Improvement's Blueteq system. Following appropriate exclusions (see Figures 1 and 2), 92 unique patients who received

treatment were included in these analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS)[1].

Results

All 92 (100%) unique patients with CDF applications were reported in the SACT dataset.

Median treatment duration for the analysis cohort was 5.3 months (161 days) [95% CI: 4.8, 7.8]. 46% [95% CI: 35%,56%], of patients were receiving treatment at 6 months and 28% [95% CI: 18%, 40%] of patients were receiving treatment at 12 months.

At data cut off, 60% (N=55) of patients were identified as no longer being on treatment; 53% (N=29) of patients had stopped treatment as prescribed.18% (N=10) of patients stopped treatment due to progression, 18% (N=10) of patients stopped treatment due to acute toxicity, 5% (N=3) of patients chose to end their treatment and 4% (N=2) of patients died not on treatment. One patient had a missing outcome, this was not submitted by the treating trust, this patient was identified as completing treatment as they had not received treatment in at least 3 months.

The median OS was not met. OS at 6 months was 97% [95% CI: 90%, 99%], OS at 12 months was 88% [95% CI: 79%, 94%].

Sensitivity analysis was conducted for a cohort with at least 6 months' data follow-up in the SACT dataset, results showed a slight difference in treatment duration when compared to the full analysis cohort. A second sensitivity analysis was carried out to evaluate treatment duration when excluding patients who received a stem cell transplant following obinutuzumab, results showed the median treatment duration was longer than the full analysis cohort.

Introduction

Follicular lymphoma is a low-grade non-Hodgkin lymphoma (NHL) and is the most common type of low-grade lymphoma accounting for around 18% of all NHL diagnoses. In 2017, 2,168 patients were diagnosed with follicular lymphoma, (1,095 males, 1,073 females)[2].

Patients diagnosed with stage 3 or stage 4 disease may be offered rituximab induction therapy as a first line therapy.

Obinutuzumab is recommended as a treatment option for treating rituximab-refractory follicular lymphoma amongst patients who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab containing regimen[3].

Background to this report

The Public Health England and NHS England and NHS Improvement partnership on cancer data – using routinely collected data to support effective patient care

High quality and timely cancer data underpin NHS England NHS Improvement and Public Health England's (PHE's) ambitions of monitoring cancer care and outcomes across the patient pathway. The objective of the PHE and NHS England and NHS Improvement partnership on cancer data is to address mutually beneficial questions using Systemic Anti-Cancer Therapy (SACT) data collected by PHE. This includes NHS England and NHS Improvement commissioning PHE to produce routine outcome reports on patients receiving treatments funded through the Cancer Drugs Fund (CDF) during a period of managed access.

The CDF is a source of funding for cancer drugs in England[4]. From the 29 July 2016 NHS England implemented a new approach to the appraisal of drugs funded by the CDF. The new CDF operates as a managed access scheme that provides patients with earlier access to new and promising treatments where there is uncertainty as to their clinical and cost effectiveness. During this period of managed access, ongoing data collection is used to answer the uncertainties raised by the NICE committee and inform drug reappraisal at the end of the CDF funding period[5].

PHE will analyse data derived from patient-level information collected in the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the National Cancer Registration and Analysis Service, which is part of PHE.

NICE Appraisal Committee appraisal of obinutuzumab treating rituximab-refractory follicular lymphoma [TA472]

The NICE Appraisal Committee reviewed the evidence for the clinical and cost effectiveness of obinutuzumab in treating rituximab-refractory follicular lymphoma [TA472] and NICE published the guidance for this indication in August 2017[6].

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended commissioning of obinutuzumab through the CDF for a period of 41 months, from July 2017 to December 2020.

During the CDF funding period, results from ongoing clinical trials evaluating obinutuzumab in the licensed indication are likely to answer the main clinical uncertainties raised by the NICE committee. The ongoing trials that will support the

evaluation of obinutuzumab is the GADOLIN clinical trial. Data collected from the GADOLIN clinical trial will be the primary source of data collection.

Analysis of the SACT dataset will provide information on real-world treatment patterns and outcomes for obinutuzumab use in rituximab-refractory follicular lymphoma in England, during the CDF funding period. This will act as a secondary source of information alongside the results of the GADOLIN[7].

The key areas of uncertainty identified by the committee for re-appraisal at the end of the CDF data collection are:

- treatment duration for the use of obinutuzumab
- overall survival (OS) from the start of a patient's first treatment with obinutuzumab

Approach

Upon entry to the CDF, representatives from NHS England and NHS Improvement, NICE, PHE and the company (Roche) formed a working group to agree the Data Collection Agreement (DCA). The DCA set out the real-world data to be collected and analysed to support the NICE re-appraisal of obinutuzumab. It also detailed the eligibility criteria for patient access to obinutuzumab through the CDF and CDF entry and exit dates.

This report includes patients with approved CDF applications (via Blueteq®) for obinutuzumab, followed-up in the SACT dataset collected by PHE.

Methods

CDF applications – identification of the cohorts of interest

NHS England and NHS Improvement collects applications for CDF treatments through their online prior approval system (Blueteq®). The Blueteq application form captures essential baseline demographic and clinical characteristics of patients, needed for CDF evaluation purposes. Where appropriate, Blueteq data are included in this report.

Consultants must complete a Blueteq application form for every patient receiving CDF funded treatment. As part of the application form, consultants must confirm that a patient satisfies all clinical eligibility criteria to commence treatment. NHS England and NHS Improvement shares an extract from the Blueteq database with PHE monthly. This extract contains NHS numbers, primary diagnosis and drug information of all patients with an approved CDF application (which therefore met the treatment eligibility criteria). The data exchange is governed by a data sharing agreement between NHS England and NHS Improvement and PHE.

PHE collates data on all SACT prescribed drugs by NHS organisations in England, irrespective of the funding mechanism. The Blueteq extract is therefore essential to identify the cohort of patients whose treatment was funded by the CDF.

Obinutuzumab clinical treatment criteria.

The criteria for patient access to obinutuzumab are:

- patient with follicular lymphoma (FL) who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen
- Obinutuzumab administered with bendamustine as 6 cycles induction treatment
- patients who respond, or have stable disease, following induction treatment with obinutuzumab and bendamustine (i.e. the initial 6 cycles of treatment) can continue to receive obinutuzumab 1,000 mg as single agent maintenance therapy once every 2 months for up to 2 years or until disease progression

CDF applications - de-duplication criteria

Before conducting any analysis on CDF treatments, the Blueteq data is examined to identify duplicate applications. De-duplication rules are applied which are:

- if 2 trusts apply for obinutuzumab for the treatment of rituximab-refractory follicular lymphoma for the same patient (identified using the patient's NHS number), and

both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected
- if 2 trusts apply for obinutuzumab for the treatment of rituximab-refractory follicular lymphoma for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF trust did not match the SACT treating trust
- if 2 applications are submitted for obinutuzumab for the treatment of rituximab-refractory follicular lymphoma and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected.

Initial CDF cohorts

The analysis cohort is limited to the date obinutuzumab entered the CDF for this indication, onwards. Any treatments delivered before the CDF entry date are excluded as they are likely to be patients receiving treatment via an Early Access to Medicines Scheme (EAMS) or a compassionate access scheme run by the pharmaceutical company. These schemes may have different eligibility criteria compared to the clinical treatment criteria detailed in the CDF managed access agreement for this indication.

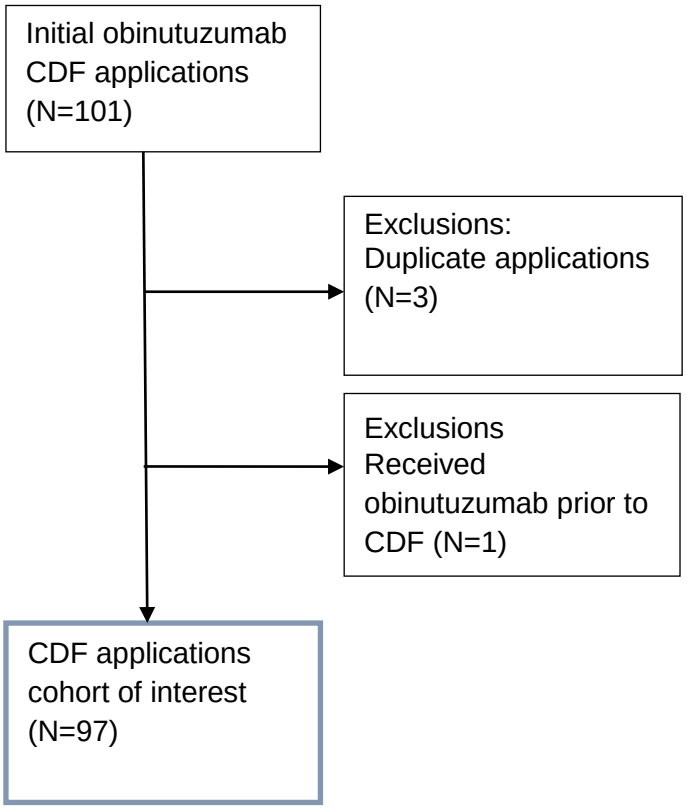
The CDF applications included in these analyses are from 26 July 2017 to 25 January 2019.

A snapshot of SACT data was taken on 1 June 2019 and made available for analysis on the 7 June 2019. The snapshot includes SACT activity up to the 28 February 2019. Tracing the patients' vital status was carried out on 26 June 2019 using the personal demographics service (PDS)[1].

There were 101 applications for CDF funding for obinutuzumab for treating rituximab-refractory follicular lymphoma between 26 July 2017 and 25 January 2019 in the NHS England and NHS Improvement Blueteq database. Following de-duplication this relates to 98 unique patients.

An additional patient was excluded from these analyses as they appeared to have received obinutuzumab prior to the drug being available through the CDF.

Figure 1: Derivation of the cohort of interest from the initial CDF applications made for obinutuzumab for rituximab-refractory follicular lymphoma between 26 July 2017 and 25 January 2019.



Linking CDF cohort to SACT

NHS numbers were used to link SACT records to CDF applications for obinutuzumab in NHS England and NHS Improvement's Blueteq system. Information on treatments in SACT were examined to ensure the correct SACT treatment records were matched to the CDF application, this includes information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes in SACT.

Addressing clinical uncertainties

Treatment duration

Treatment duration is calculated from the start of a patient's treatment to their last known treatment date in SACT.

Treatment start date is defined as the date the patient started their CDF treatment. This date is identified as the patient's earliest treatment date in the SACT dataset for the treatment of interest.

Data items used to determine a patient's earliest treatment date are:

- start date of regimen – SACT data item #22
- start date of cycle – SACT data item #27
- administration date – SACT data item #34

The earliest of these dates is used as the treatment start date.

The same SACT data items (#22, #27, #34) are used to identify a patient's final treatment date. The latest of these 3 dates are used as the patient's final treatment date. Additional explanation of these dates is provided below:

Start date of regimen
A regimen defines the drugs used, their dosage and frequency of treatment. A regimen may contain many cycles. This date is generally only used if cycle or administration dates are missing.

Start date of cycle
A cycle is a period of time over which treatment is delivered. A cycle may contain several administrations of treatment, after each treatment administration, separated by an appropriate time delay. For example; a patient may be on a 3-weekly cycle with treatment being administered on the 1st and 8th day, but nothing on days 2 to 7 and days 9 to 20. The 1st day would be recorded as the "start day of cycle". The patient's next cycle would start on the 21st day.

Administration date
An administration is the date a patient is administered the treatment, which should coincide with when they receive treatment. Using the above example, the administrations for a single 3-week cycle would be on the 1st and 8th day. The next administration would be on the 21st day, which would be the start of their next cycle.

The interval between treatment start date and final treatment date is the patient's time on treatment.

All patients are then allocated a 'prescription length' which is a set number of days added to the final treatment date to allow for the fact that they are effectively still 'on treatment' between administrations. The prescription length should correspond to the typical interval between treatment administrations.

If a patient dies between administrations, then their censor date is their date of death and these patients are deemed to have died on treatment unless an outcome summary is submitted to the SACT database confirming that the patient ended treatment due to disease progression or toxicity before death.

Obinutuzumab is administered intra-venously. As such, treatment is generally administered in a healthcare facility and healthcare professionals are able to confirm that treatment administration has taken place on a specified date. A duration of 7-days, 13-days or 27-days has been added to final treatment date for all patients, this represents the duration from a patient's last cycle to their next[8]. Obinutuzumab is a 28-day cycle consisting of 3 administrations. Obinutuzumab is administered on day 1, 8 and 15 of a 28-day cycle.

If a patient's last treatment administration is day 1 of the cycle: 7 days are added the treatment duration (to cover effective treatment to day 8).

If the last treatment administrations are day 1 and 8 of the cycle: 7 days are added the treatment duration (to cover effective treatment to day 15).

If the last treatment administrations are day 1, 8 and 15 of the cycle: 13 days are added the treatment duration (to cover effective treatment to day 27).

Treatment duration is calculated for each patient as:

Treatment duration (days) = (Final treatment date – Treatment start date) + prescription length (days).

Once a patient's treatment duration has been calculated, the patient's treatment status is identified as one of the following.

No longer receiving treatment (event), if:

- the patient has died
- the outcome summary (SACT data item #41) detailing the reason for stopping treatment has been completed
- there is no further SACT records for the patient following a 3 -month period

If none of the above apply, the patient is assumed to still be on treatment and is censored.

Overall survival (OS)

OS is calculated from the CDF treatment start date, not the date of a patient's cancer diagnosis. Survival from the treatment start date is calculated using the patient's earliest treatment date, as described above, and the patient's date of death or the date the patient was traced for their vital status.

All patients in the cohort of interest are submitted to the PDS to check their vital status (dead/alive). Patients are traced before any analysis takes place. The date of tracing is used as the date of follow-up (censoring) for patients who have not died.

OS is calculated for each patient as the interval between the earliest treatment date where a specific drug was given to the date of death or date of follow-up (censoring).

OS (days) = Date of death (or follow up) – treatment start date

The patient is flagged as either:

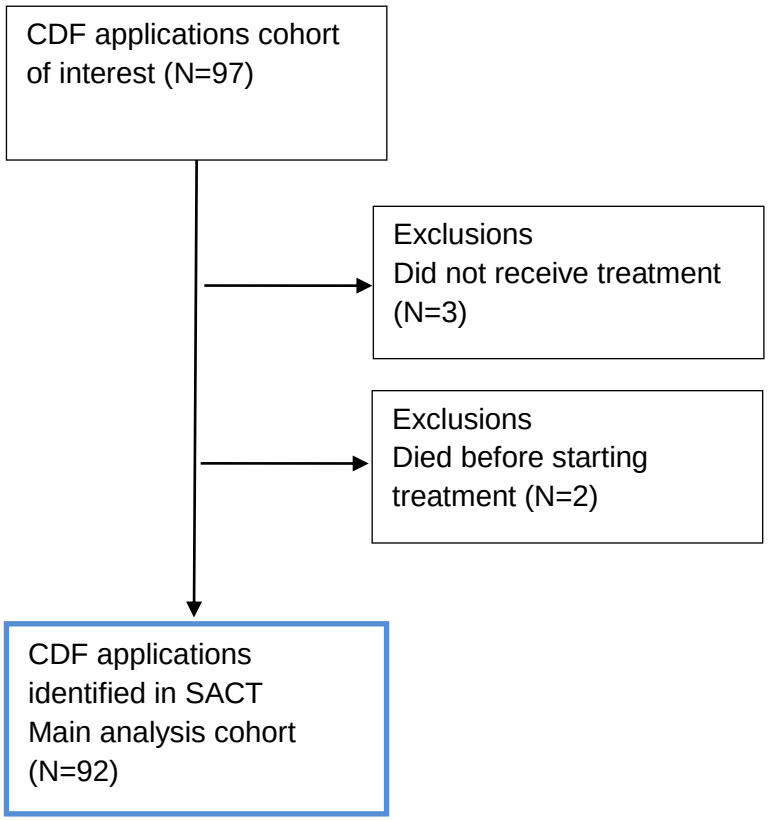
- dead (event) – at the date of death recorded on the PDS
- alive (censored) – at the date patients were traced for their vital status as patients are confirmed as alive on this date

Results

Cohort of interest

Of the 97 new applications for CDF funding for obinutuzumab for rituximab-refractory follicular lymphoma, three patients did not receive treatment and two patients died before treatment[1] (see Figure 2).

Figure 2: Matched cohort - SACT data to CDF (Blueteq®) applications for obinutuzumab for rituximab-refractory follicular lymphoma between 26 July 2017 and 25 January 2019



A maximum of 92 obinutuzumab records are expected in SACT for patients who were alive, eligible and confirmed to have commenced treatment (Figure 2). 100% (92/92) of these applicants for CDF funding have a treatment record in SACT.

[1] The three patients that did not receive treatment and two that died before treatment were confirmed with the relevant trusts by the PHE data liaison team.[2] Figures may not sum to 100% due to rounding.

Completeness of SACT key variables

Table 1 presents the completeness of key data items required from SACT. Completeness is >76% for all key items and 100% for primary diagnosis, date of birth, gender and treatment dates.

Table 1: Completeness of key SACT data items for the obinutuzumab cohort (N=92)

Variable	Completeness (%)
Primary diagnosis	100%
Date of birth (used to calculate age)	100%
Sex	100%
Start date of regimen	100%
Start date of cycle	100%
Administration date	100%
Performance status at start of regimen	77%

Table 2 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment. Therefore, the percentage completeness provided for outcome summary is for records where we assume treatment has stopped and an outcome is expected. Outcomes are expected if a patient has died or has not received treatment with obinutuzumab in at least three months. These criteria are designed to identify all cases where a patient is likely to have finished treatment. Based on these criteria, outcomes are expected for 55 patients. Of these, 54 have an outcome summary recorded in the SACT dataset 98% (54/55).

Table 2: Completeness of outcome summary for patients that have ended treatment (N=55)

Variable	Completeness (%)
Outcome summary of why treatment was stopped	98 %

Completeness of Blueteq key variables

Table 3 and 4 presents the completeness of key data items required from Blueteq. Completeness of rituximab progression phase is 100% and the number of months from rituximab to progression (maintenance rituximab only) is 86% complete.

Table 3: Completeness of rituximab progression phase in Blueteq (N=92)

Variable	Completeness (%)
Rituximab progression phase	100%

Table 4: Completeness of months to progression (maintenance rituximab) in Blueteq (N=44)

Variable	Completeness (%)
Number of months from maintenance rituximab to progression	86%

Patient characteristics

The median age of the 92 patients receiving obinutuzumab for rituximab-refractory follicular lymphoma was 65 years. The median age in males and females was 65 and 67 years respectively.

Table 5: Patient characteristics (N=92)

Patient characteristics[2]		Frequency (N)	Percentage (%)
Sex	Male	54	59%
	Female	38	41%
Age	<40	1	1%
	40-49	11	12%
	50-59	21	23%
	60-69	25	27%
	70-79	28	30%
	80+	6	7%
Performance status	0	34	37%
	1	31	34%
	2	6	7%
	3	0	0%
	4	0	0%
	Missing	21	23%

Rituximab progression

The phase of progression and months from rituximab to progression is shown in table 6. Obinutuzumab is only accessible to patients who showed no response to rituximab or progressed during or within 6 months of treatment (induction or maintenance phase). 59%(N=26) of patients progressed within 6 months on maintenance phase, 27% (N=12) of patients progressed >6 months of their maintenance phase.

[2] Figures may not sum to 100% due to rounding.

Table 6: Disease progression: treatment phase and months from rituximab treatment to progression in Blueteq (N=92)[3]

				Months to progression		
Treatment phase	**Response**	**Frequency (N)**	**Percentage (%)**	**≤6 months**	**>6 months**	**not captured**
Induction rituximab	Failed to respond or progressed on induction rituximab	48	52%			
Maintenance rituximab	Progressed on or within 6 months of maintenance rituximab	44	48%	59% (N=26)	27% (N=12)	14% (N=6)

Treatment duration

Of the 92 patients with CDF applications, 55 (60%) were identified as having completed treatment by 28 February 2019 (latest follow up in SACT dataset). Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or they have not received treatment with obinutuzumab in at least 3 months (see Table 7). The median follow-up time in SACT was 148 days.

Presently, 60% of trusts submit their SACT return to the submission portal two months after the month's treatment activity has ended, this provides a maximum follow-up period of 19 months. 40% of trusts submit their SACT return to the submission portal one month after the month's treatment activity has ended, this would provide the maximum follow-up period of 20 months. SACT follow-up ends 28 February 2019.

Table 7: Breakdown by patients' treatment status[4,5,6]

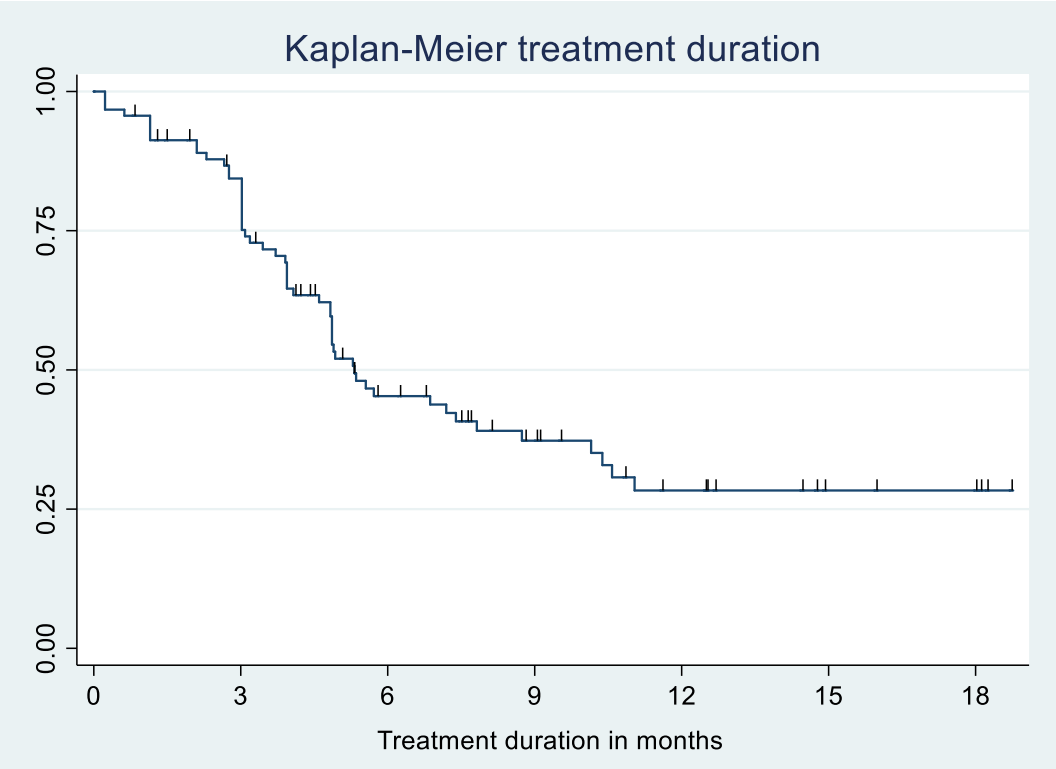
Patient status	**Frequency (N)**	**Percentage (%)**
Patient died - not on treatment	13	14%
Treatment stopped	42	46%
Treatment ongoing	37	40%
Total	**92**	**100%**

The Kaplan-Meier curve for ongoing treatment is shown in figure 3. The median treatment duration for all patients was 5.3 months (161 days) [95% CI: 4.8, 7.8] (N=92).

[3] months to progression was not required for the induction rituximab treatment phase
[4] Figures may not sum to 100% due to rounding.
[5] Table 10 presents the outcome summary data reported by trusts. This includes patients from Table 7 that 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[6] Deaths on treatment and deaths not on treatment are explained in the methodology paper available on the SACT website: http://www.chemodataset.nhs.uk/nhse_partnership/

46% of patients were still receiving treatment at 6 months [95% CI: 35%,56%], 28% of patients were still receiving treatment at 12 months [95% CI: 18%, 40%].

Figure 3: Kaplan-Meier treatment duration (N=92)



Tables 8 and 9 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 19 months (577 days).

Table 8: Number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0 - 18	3 - 18	6 - 18	9 - 18	12 - 18	15-18	18
Number at risk	92	73	32	20	11	5	3

Table 9 shows that for all patients who received treatment, 37 were still on treatment (censored) at the date of follow-up and 55 had ended treatment (events).

Table 9: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored).

Time intervals (months)	0 - 18	3 - 18	6 - 18	9 - 18	12 - 18	15-18	18
Censored	37	32	23	16	11	5	3
Events	55	41	9	4	0	0	0

Table 10 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 60% (N=55) of patients had ended treatment at 28 February 2019.

Table 10: Treatment outcomes for patients that have ended treatment (N=55)[7,8,9]

Outcome	Frequency (N)	Percentage (%)
Stopped treatment – progression of disease	10	18%
Stopped treatment – acute chemotherapy toxicity	10	18%
Stopped treatment – patient choice	3	5%
Treatment completed as prescribed[10]	29	53%
Stopped treatment – died not on treatment	2	4%
Stopped treatment – no treatment in at least 3 months	1	2%
Total	**55**	**100%**

Table 11: Treatment outcomes and treatment status for patients that have ended treatment (N=55)

Outcome[11]	Patient died [12] not on treatment	Treatment stopped
Stopped treatment – progression of disease	7	3
Stopped treatment – acute chemotherapy toxicity	2	8
Stopped treatment – patient choice	1	2
Treatment completed as prescribed	1	28
Stopped treatment – died not on treatment	2	
Stopped treatment – no treatment in at least 3 months		1
Total	**13**	**42**

[7] Figures may not sum to 100% due to rounding.
[8] Table 10 presents the outcome summary data reported by trusts. This includes patients from Table 7 that 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[9] One patient has been identified as completing treatment as no treatment record has been submitted to SACT in at least 3 months.
[10] 11 patients were identified in HES as receiving a SCT following obinutuzumab
[11] Relates to outcomes submitted by the trust in table 10.
[12] Relates to treatment status in table 7 for those that have ended treatment.

Overall survival

Of the 92 patients with a treatment record in SACT, the minimum follow-up was 4 months (121 days) from the last CDF application. Patients were traced for their vital status on 26 June 2019, this date was used as the follow-up date (censored date) if a patient is still alive. The median follow-up time in SACT was 12.4 months (377 days).

Figure 4 provides the Kaplan-Meier curve for overall survival, censored at 26 June 2019. The median survival was not met. Survival at 6 months was 97% [95% CI: 90%, 99%], 12 months survival was 88% [95% CI: 79%, 94%].

Figure 4: Kaplan-Meier survival plot (N=92)

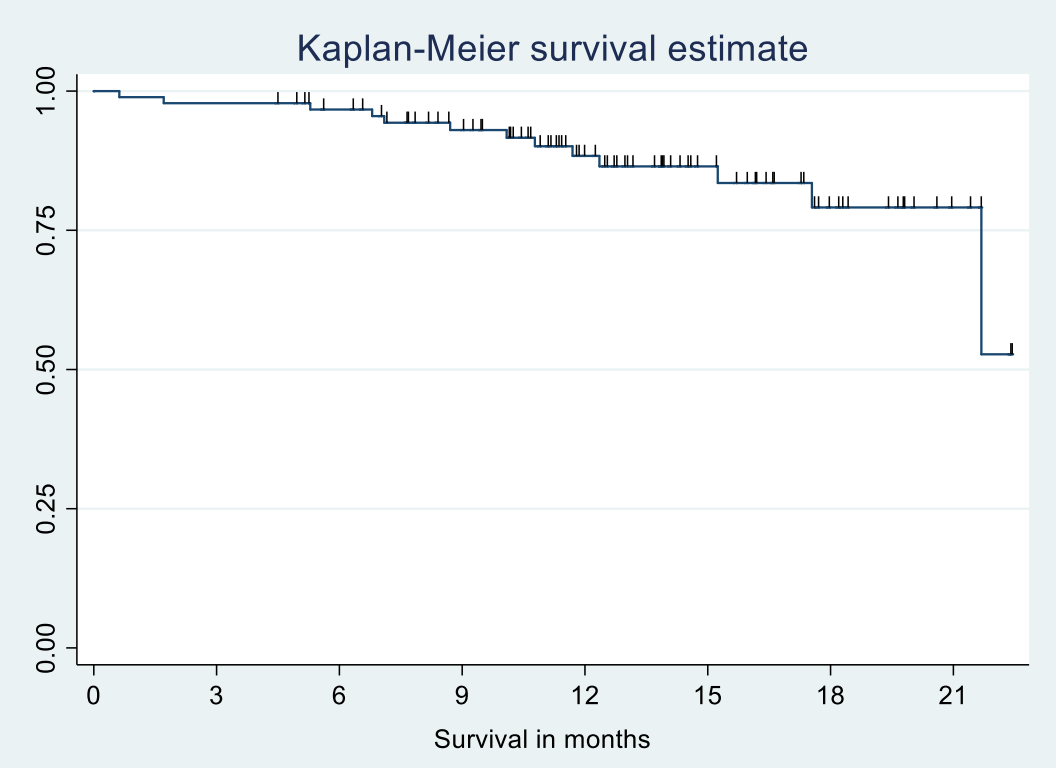


Table 12 and 13 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 23 months (699 days), all patients were traced on 26 June 2019.

Table 12: Includes the number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0-21	3-21	6-21	9-21	12-21	15-21	18-21	21
Number at risk	92	90	84	70	48	30	15	5

Table 13 shows that for all patients who received treatment, 79 were still alive (censored) at the date of follow-up and 13 had died (events).

Table 13: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints.

Time intervals (months)	0-21	3-21	6-21	9-21	12-21	15-21	18-21	21
Censored	79	79	74	63	44	27	14	4
Events	13	11	10	7	4	3	1	1

Sensitivity analyses

Cohort 1: 6-month SACT follow up

Treatment duration

Sensitivity analyses was carried out on a cohort with at least 6 months' follow-up in SACT. To identify the treatment duration cohort, CDF applications were limited from 26 July 2017 to 28 August 2018 and SACT activity was followed up to the 28 February 2019. 70 patients (76%) were included in these analyses. The median follow-up time in SACT was 149.5 days.

The Kaplan-Meier curve for ongoing treatment is shown in figure 5. The median treatment duration for patients in this cohort was 4.9 months (149 days) [95% CI: 4.1, 7.2] (N=70).

Figure 5: Kaplan-Meier treatment duration (N=70)

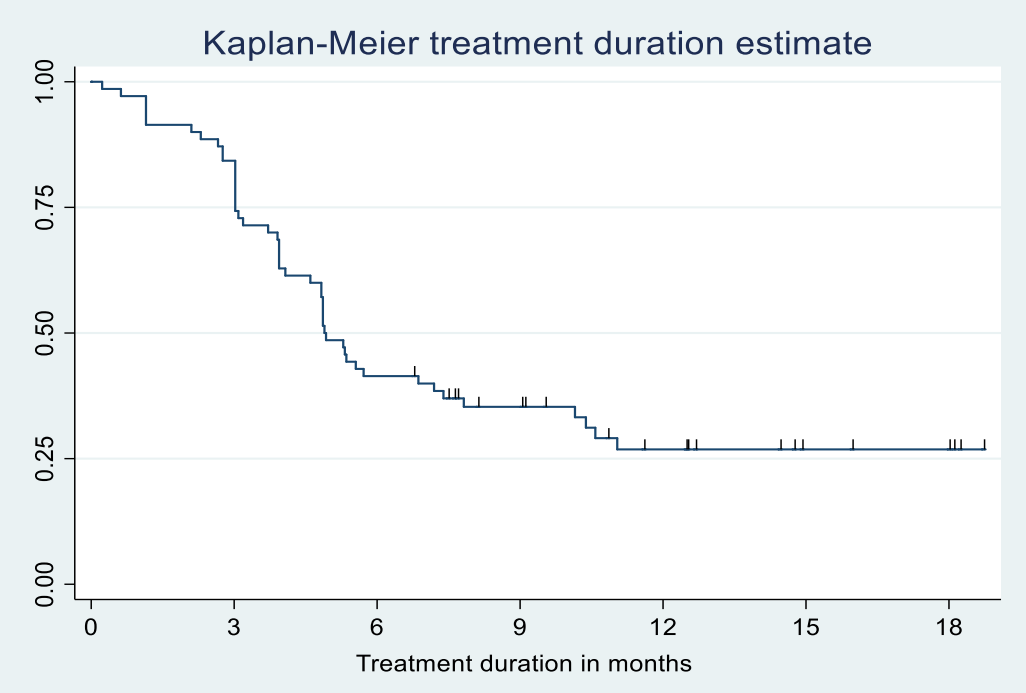


Table 14 and 15 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for treatment duration was 19 months. The minimum follow-up was 6 months.

Table 14: Number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0 - 18	3 - 18	6 - 18	9 - 18	12 - 18	15-18	18
Number at risk	70	59	29	20	11	5	3

Table 15 shows that for all patients who received treatment, 21 were still on treatment (censored) at the date of follow-up and 49 had ended treatment (events).

Table 15: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored).

Time intervals (months)	0 - 18	3 - 18	6 - 18	9 - 18	12 - 18	15-18	18
Censored	21	21	21	16	11	5	3
Events	49	38	8	4	0	0	0

Overall survival

Sensitivity analyses was also carried out for OS on a cohort with at least 6 months' follow-up in SACT. To identify the cohort, CDF applications were limited from 26 July 2017 to 25 December 2018. 89 patients (97%) were included in the survival analyses with all patients having a minimum follow-up of 6 months. Follow up continued from treatment start date to date of tracing for vital status (26 June 2019). The median follow-up time in SACT was 12.4 months (377 days).

Figure 6 provides the Kaplan-Meier curve for overall survival, censored at 26 June 2019. The median survival was not met.

Figure 6: Kaplan-Meier survival plot (N=89)

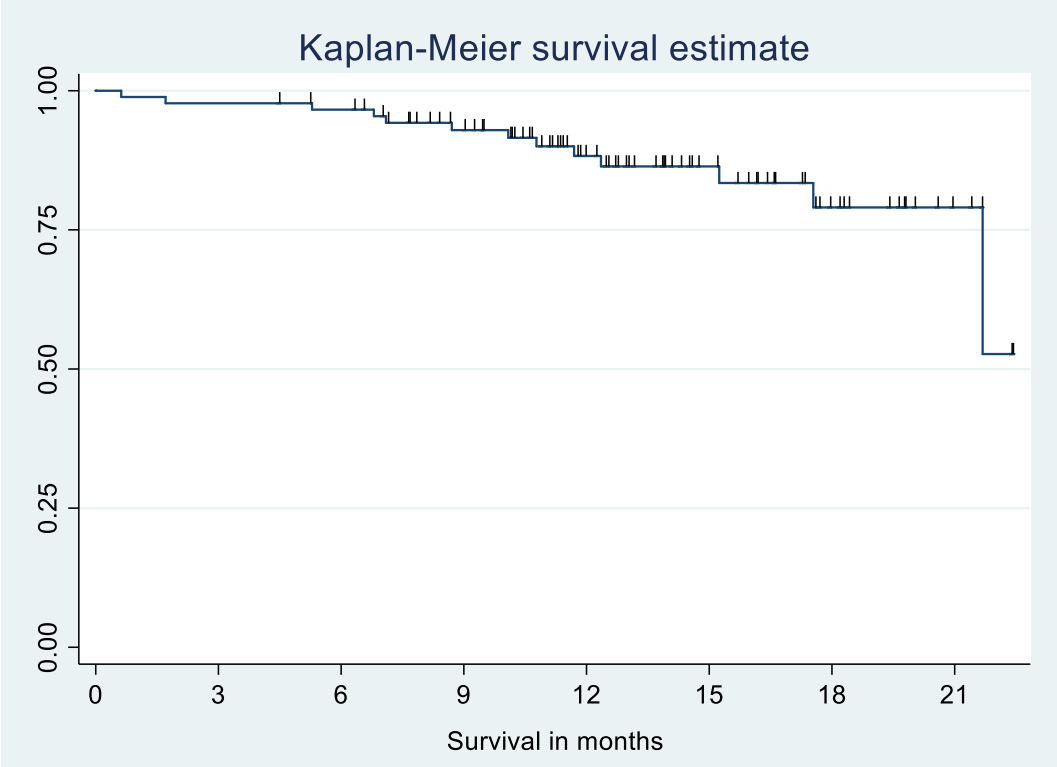


Table 16 and 17 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 23 months (699 days), all patients were traced on 26 June 2019.

Table 16: Includes the number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0-21	3-21	6 -21	9-21	12-21	15-21	18-21	21
Number at risk	89	87	84	70	48	30	15	5

Table 17 shows that for all patients who received treatment, 76 were still alive (censored) at the date of follow-up and 13 had died (events).

Table 17: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints.

Time intervals (months)	0-21	3-21	6 -21	9-21	12-21	15-21	18-21	21
Censored	76	76	74	63	44	27	14	4
Events	13	11	10	7	4	3	1	1

Cohort 2: Stem cell transplant exclusions

Treatment duration

Eleven patients were identified in the Hospital Episodes Statistics (HES)[9] admitted patient care dataset as having received a stem cell transplant (SCT) after their last obinutuzumab treatment date in SACT. A secondary analysis was carried out excluding these SCT patients from the cohort. The median follow-up time in SACT for the ex-SCT cohort was 150 days.

The Kaplan-Meier curve for ongoing treatment is shown in figure 7. The median treatment duration for patients in this cohort was 7.2 months (219 days) [95% CI: 4.9, 10.6] (N=81).

Figure 7: Kaplan-Meier survival plot (N=81)

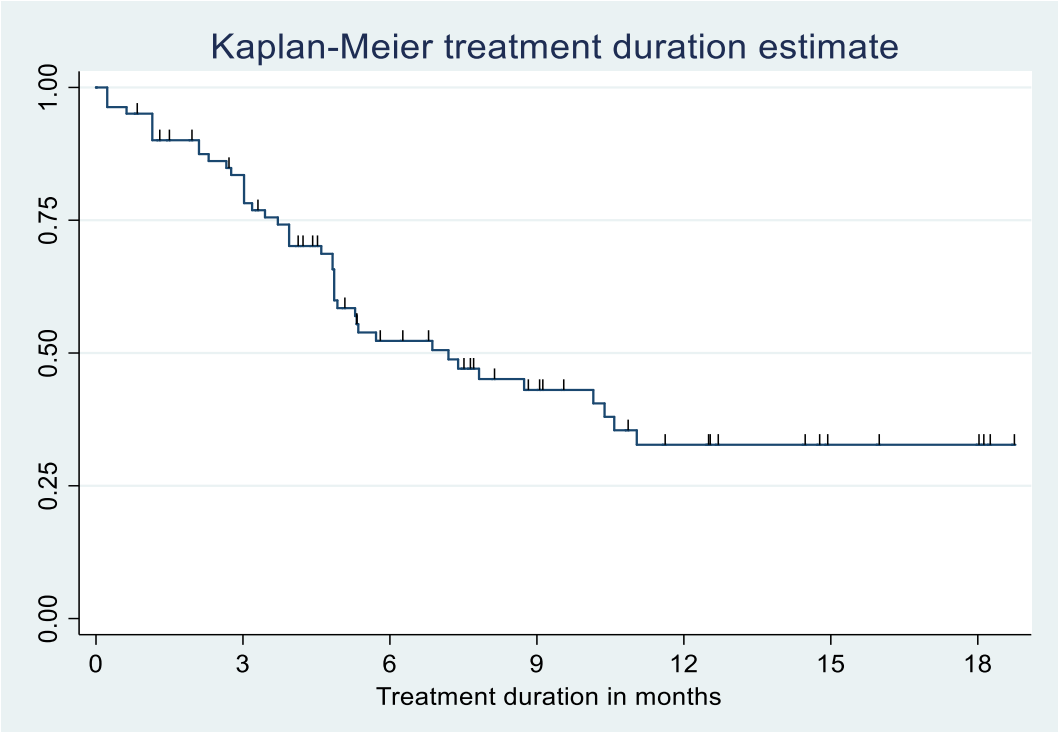


Table 18: Includes the number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0 - 18	3 - 18	6 - 18	9 - 18	12 - 18	15-18	18
Number at risk	81	63	32	20	11	5	3

Table 19: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored).

Time intervals (months)	0 - 18	3 - 18	6 - 18	9 - 18	12 - 18	15-18	18
Censored	37	32	23	16	11	5	3
Events	44	31	9	4	0	0	0

Table 20: Median treatment duration, full cohort and sensitivity analysis.

Metric	Standard analysis: Full cohort	Sensitivity analysis: 6 months follow-up cohort	Sensitivity analysis: Excluding transplant patients
N	92	70 (treatment duration) 89 (OS)	81
Median treatment duration	5.3 months (161 days) [95% CI: 4.8, 7.8]	4.9 months (149 days) [95% CI: 4.1, 7.2]	7.2 months (219 days) [95% CI: 4.9, 10.6]
OS	Not met	Not met	

Conclusions

92 patients received obinutuzumab for the treatment of rituximab-refractory follicular lymphoma [TA472] through the CDF in the reporting period (26 July 2017 and 25 January 2019). All patients were reported to the SACT dataset. An additional 5 patients with a CDF application, did not receive treatment or died before treatment. This was confirmed with the trust responsible for the CDF application by the team at PHE. All 92 patients receiving treatment in the approved indication were reported in the SACT dataset, giving a SACT ascertainment of 100%.

Patient characteristics from the SACT dataset show that proportionally more males received obinutuzumab treatment compared to females (59% male, 41% female). Most of the cohort was aged between 50 and 79 years (80%) and 77% of patients had a performance status between 0 and 2 at the start of their regimen.

At the end of the data collection period, 60% (N=55) of patients were identified as no longer being on treatment. Of these, 98% (N=54) of patients had an outcome submitted by the treating trust to the SACT dataset which detailed the reason why a patient ended their treatment. 53% (N=29) of patients had stopped treatment as prescribed. 18% (N=10) of patients stopped treatment due to progression, 18% (N=10) of patients stopped treatment due to acute toxicity, 5% (N=3) of patients chose to end their treatment and 4% (N=2) of patients died not on treatment. One patient had a missing outcome, this patient was identified as completing treatment as no treatment record had been submitted to SACT by the treating trust in at least 3 months.

The median treatment duration was 5.3 months (161 days) [95% CI: 4.8, 7.8]. The median follow-up was 148 days and the maximum follow-up was 19 months (577 days).

The median overall survival was not met. The minimum follow-up was 4 months (121 days), the maximum follow-up was 23 months (699 days).

Sensitivity analyses were carried out to evaluate a cohort for which all patients had a minimum follow-up of 6 months. Results for this cohort showed a slight difference in treatment duration (full cohort = 5.3 months; sensitivity analysis cohort = 4.9 months), this difference was not statistically significant. There was no difference in overall survival, the median survival was not met.

A second sensitivity analysis was carried out to evaluate treatment duration when excluding patients who received a stem cell transplant following obinutuzumab. The median treatment duration for this cohort was longer than the main analysis cohort, 7.2 months (219 days) [95% CI: 4.9, 10.6].

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Obinutuzumab with bendamustine for treating follicular lymphoma refractory to rituximab

This appraisal is a Cancer Drugs Fund (CDF) review of TA472. This recommended obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance for use within the CDF as an option for treating adults with follicular lymphoma that did not respond or progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.

This document is the draft technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee. The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting. The technical report should be read with the full supporting documents for this appraisal.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

Issue date: January 2020

1. Topic background

1.1 Disease background: Follicular Lymphoma

- Non-Hodgkin's lymphoma (NHL) is a type of cancer that develops in the lymphatic system. It includes several different conditions, which may be classified based on their grade, or type. Low-grade, or 'indolent' NHL is slow growing, and often has long survival times but low cure rates.

- Follicular lymphoma (FL) is one of the most common types of indolent NHL. It is an incurable disease that develops when the body makes abnormal B lymphocytes that collect in lymph nodes or other body organs as follicles (clumps).

- About 1900 people are diagnosed with FL annually in the UK with median age at diagnosis of 60-65 years. Most people have advanced FL at diagnosis and treatment is dependent on whether the lymphoma is symptomatic. Approximately 87% of people with FL survive for 5 years or more.

1.2 Treatment pathway

- The aim of treatment for FL is to induce response and control disease progression for as long as possible. Some people initially have asymptomatic slowly progressing disease and will be on a 'watch and wait' policy until treatment becomes necessary.

- Once the condition has progressed to the extent that people need treatment, first-line induction with rituximab in combination with chemotherapy (R-chemotherapy) is initial treatment that induces a response in most people. This is followed by rituximab maintenance therapy.

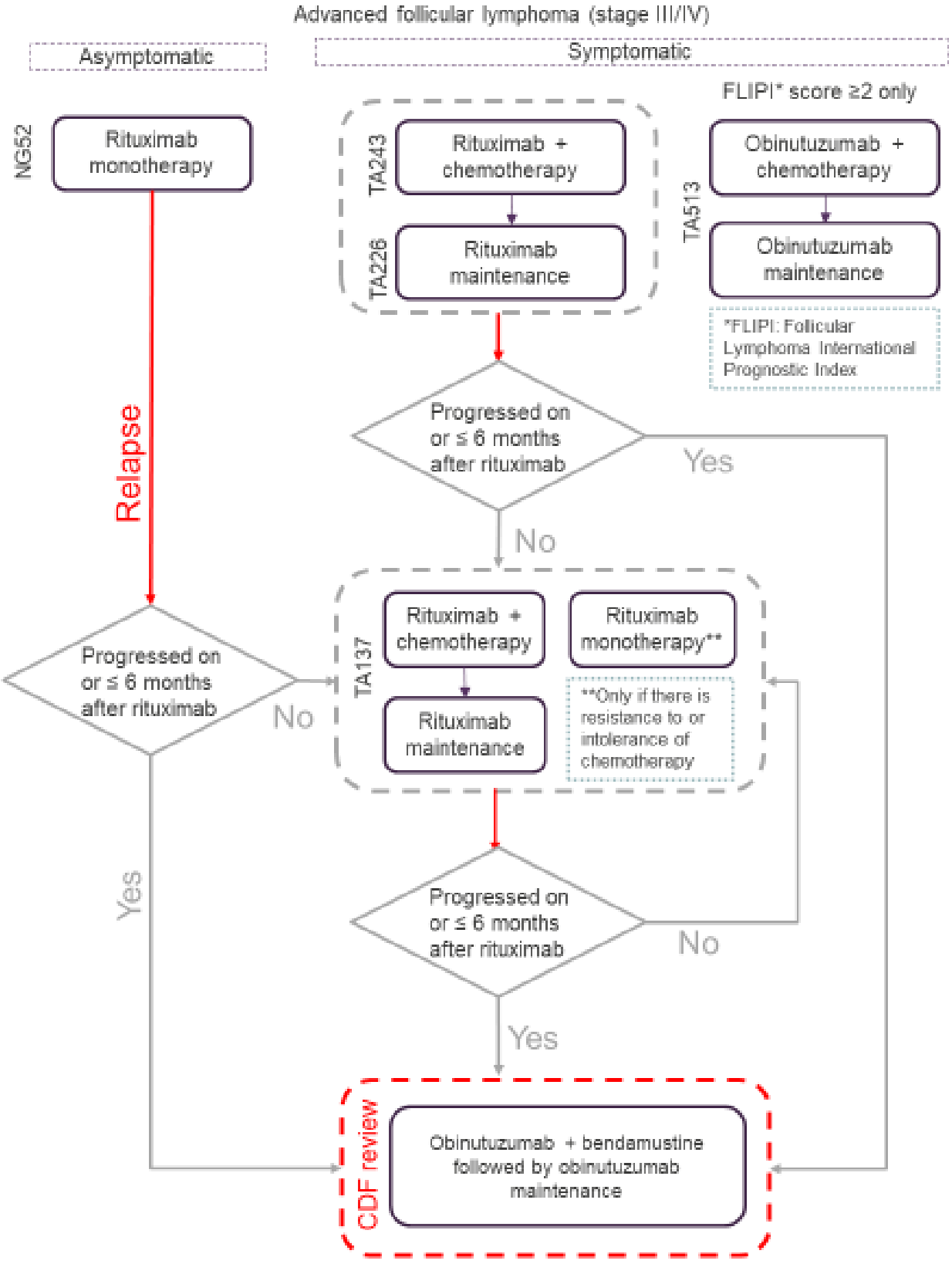
- NICE guideline 52 (NG52) on non-Hodgkin's lymphoma recommends rituximab monotherapy as an option for stage III or IV disease which is still asymptomatic although rituximab does not have a marketing authorisation in the UK for this indication.

- Most people relapse after the initial response, and second-line treatment depends on the timing of relapse following first-line treatment and the chemotherapy agents used first line. It is often characterised by multiple lines of treatment as the disease responds and relapses. Cancers that do not respond to rituximab or relapse soon after finishing treatment are termed ‘rituximab refractory’.

- People that do not respond to induction treatment with R-chemotherapy are considered to have uncontrolled disease, and the worst prognosis. These people are considered to have disease that is the most refractory to rituximab, and in clinical practice they may be offered bendamustine monotherapy. Bendamustine monotherapy is not recommended by NICE.

- Treatment options for rituximab-refractory FL include single- or multi-agent chemotherapy (for example, including cyclophosphamide, fludarabine, bendamustine or chlorambucil) and best supportive care.

Treatment pathway



Issue date: January 2020

1.3 Technology being considered for CDF review

Marketing authorisation	Obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance is indicated 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
Mechanism of action	Type 2 glycoengineered antibody that binds to the CD20 protein present on B cells, except stem or plasma cells, and causes cell death.
Administration and dose	Obinutuzumab is given by intravenous infusion. **Induction:** • Cycle 1: 1,000 mg on Day 1, Day 8 and Day 15 of the first 28- day treatment cycle • Cycles 2–6: 1,000 mg on Day 1 of each 28-day treatment cycle. **Maintenance** • 1,000 mg every 2 months for 2 years or until disease progression (whichever occurs first).
List price	£3,312 per 1,000-mg vial (excluding VAT; British national formulary [BNF] edition 71). A confidential discount on the price has been agreed.

1.4 Clinical evidence

- The primary source of clinical effectiveness evidence was the GADOLIN trial.

Study design	Phase III, open label, randomised, multicentre
Location	International: 82 sites & 14 countries; 5 sites in UK
Population	Adults with indolent NHL (**n=413**). 81.1% with FL (**n=335**) Only population with follicular lymphoma (81.1% of trial population) considered: People with follicular lymphoma who are refractory to induction with rituximab in combination with chemotherapy or who relapsed during or within 6 months of maintenance with rituximab monotherapy.
Intervention(s)	Obinutuzumab in combination with bendamustine induction followed by obinutuzumab maintenance monotherapy (**n=164**)
Comparator(s)	Induction with bendamustine (n=171)
Outcomes	• Investigator assessed progression-free survival– primary outcome • Overall survival (OS) • Event-free survival • Duration of response • Adverse effects of treatment • Health-related quality of life

1.5 Key committee conclusions from TA472:

- The magnitude of the overall survival (OS) benefit of obinutuzumab with bendamustine, compared with bendamustine alone, was the main clinical uncertainty. The committee considered that availability of more mature OS data from the GADOLIN trial was likely to resolve uncertainty around treatment effect and may produce more robust cost-effectiveness estimates.

- Cost effectiveness estimates were largely dependent on the duration of treatment effect assumed when extrapolating the overall survival data, and this was uncertain due to the immaturity of the OS data. The committee considered it plausible that treatment effect was longer than modelled in the company's base case and agreed that the scenario analysis exploring a different duration of treatment effect on OS indicated a plausible potential for obinutuzumab with bendamustine to be cost effective.

- The data collection agreement specified the terms of data collection during the managed access period:

    - The primary source of data collection was the GADOLIN trial. The ongoing OS data collection was expected to reduce the uncertainty around the magnitude of treatment effect by increasing statistical power resulting from additional events and the duration of benefit through longer follow-up time. In addition, investigator assessed progression-free survival (PFS) and next anti-lymphoma treatment were collected to update the economic analysis

    - Observational data via the systemic anti-cancer therapy (SACT) dataset supports the data collected in GADOLIN. This includes data on OS and duration of therapy.

1.6 **Preferred committee assumptions from Terms of Engagement:**

- As part of the CDF review process, a “Terms of Engagement” document was developed which specified the committee’s preferred assumptions for economic modelling and the cost-effectiveness analyses that should be provided by the company:

Area	Committee preferred assumptions	ERG comment on any deviation
Population	People with FL who are refractory to induction with rituximab in combination with chemotherapy, or who relapse early during rituximab maintenance	• No deviation
Intervention	Obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance	• No deviation
Comparators	Bendamustine	• No deviation
Generalisability	The evidence base for the marketing authorisation of obinutuzumab was a subgroup from GADOLIN of people with FL (81% of the trial population)	• NA
Progression-free and overall survival	**Committee would like to see** updated **PFS and OS data from trial**	• No deviation
Model structure and assumptions	At the 1st committee meeting, the committee preferred: • a partitioned survival approach • adjusting utility estimates for the effects of ageing • assuming lower disease progression costs for subsequent treatments • using the generic acquisition cost for bendamustine • correcting minor programming errors in the model • using utility estimates from GADOLIN • using alternative drug administration costing	• Model structure and assumptions mostly consistent except the company's updated base-case analysis uses parametric functions to model overall survival for the whole time-horizon. • In the original appraisal KM estimates were used up to the time of the last observed OS event. Scenario analyses are provided by which KM estimates are used up to the time of the last OS observed event (scenario 5). • ERG does not think that the parametric survival functions accurately capture the cross-over of the OS curves in the first year of the GADOLIN trial.

Area	Committee preferred assumptions	ERG comment on any deviation
Duration of treatment effect	Cost-effectiveness estimates were largely dependent on the duration of the treatment effect on OS. Sensitivity analyses showed that obinutuzumab with bendamustine may be cost effective if the treatment effect on survival persists for between 7-25 years. This assumption should be explored in scenario analyses and based on the final analysis of GADOLIN.	• Company's base-case assumes a lifetime treatment effect as the company considers that the updated results are consistent with a constant proportional hazard. Scenarios exploring shorter durations of treatment effect ([redacted] are provided (company scenarios 1 and 2). • The ERG considers that the updated data from GADOLIN does not support an assumption of constant treatment effects.a • ERG prefers Weibull survival functions with a random change-point for PFS and OS. This allows for the treatment effect to vary during the observed follow-up period of GADOLIN
Utilities	Using utility estimates from GADOLIN	• No deviation
Duration of time on treatment	Assumption not specified in Terms of Engagement, therefore no change expected. The company uses time-to-off-treatment (TTOT) data from the April 2016 data cut in the model on the basis that the TTOT data were mature at the time of TA472 and therefore an update was not required.	• ERG notes that median duration of maintenance treatment was 17 months for April 2016 and [redacted] for Nov 2018 data-cut. Median numbers of maintenance doses received were 9 and [redacted] for the 2016 and 2018 data cuts respectively. It is possible that incorporating updated data on TTOT from the Nov 2018 data cut would have a marginal impact on the costs of obinutuzumab with bendamustine followed by obinutuzumab maintenance in the economic analysis, despite the data being relatively mature at the time of the TA472.

Area	Committee preferred assumptions	ERG comment on any deviation
Resource use and costs	Assumption not specified in Terms of Engagement and therefore no change expected. Analyses with updated Patient Access Scheme (PAS) and updated costs for generic bendamustine provided by company.	• ERG considers updating drug costs is reasonable. ERG analyses include a more recent price for bendamustine but this has little impact on the ICERs.
Adverse events (AEs)	Assumption not specified in Terms of Engagement and therefore no change expected	• No deviation
End-of-life	Evidence for the end-of-life criteria was not presented or considered.	• NA

Source: Adapted from table 2 (page 6) of company submission and table 2 (page 15) of ERG report

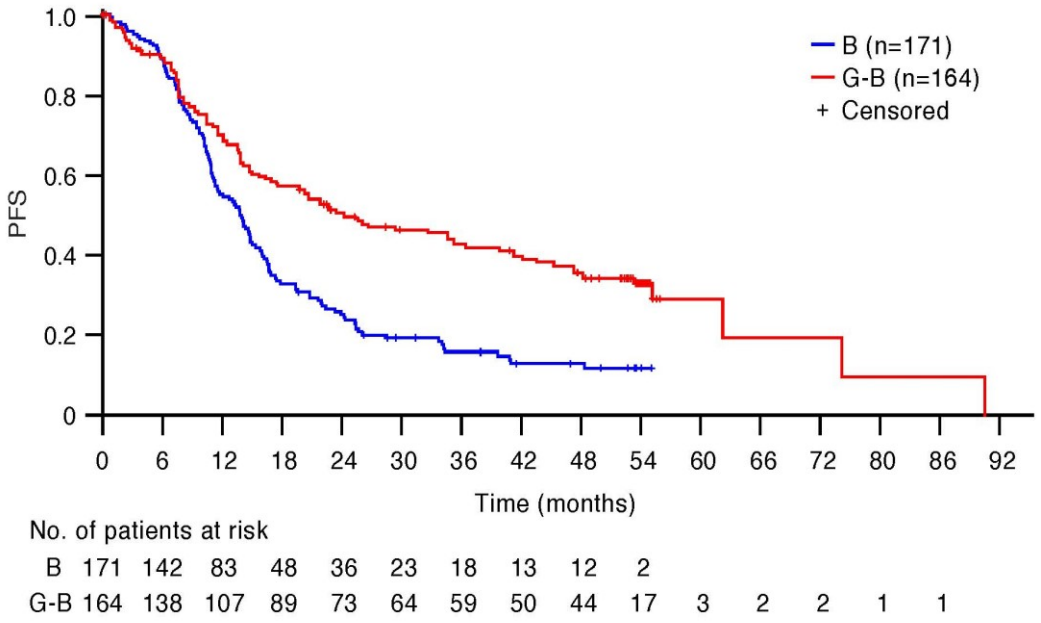
1.7 Updated clinical effectiveness results from GADOLIN after managed access period (clinical cut-off date, November 2018)

Investigator-assessed PFS, FL patients (ITT population)

	Bendamustine arm n=171	Obinutuzumab with bendamustine arm n=164
Patients with event, n (%)	[redacted]	[redacted]
Median PFS, months (95% CI)	13.7 [redacted]	24.1 [redacted]
Stratified hazard ratio (95% CI) p value (log-rank)	0.51 (0.39, 0.67) <0.0001	

- The results are consistent with those at the time of the analysis at CDF entry (April 2016) (HR 0.52 [0.39, 0.69], p<0.001).

Kaplan-Meier (KM) plot of investigator-assessed PFS, FL patients (ITT population)



- The company reports that the KM plot for investigator-assessed PFS shows separation of curves in favour of the obinutuzumab arm starting after approximately 6 months in the trial. This corresponds to the time of the first obinutuzumab maintenance dose. The separation is maintained throughout the maintenance/observation period.

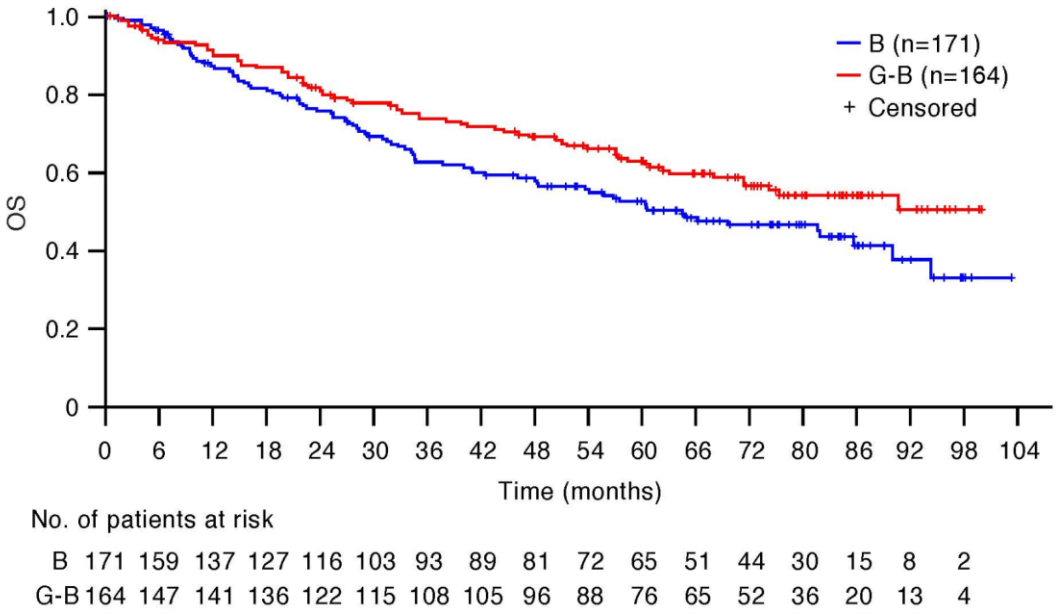
Overall survival, FL patients (ITT population)

	Bendamustine arm n=171	Obinutuzumab with bendamustine arm n=164
Patients with event, n (%)	[redacted]	[redacted]
Median time to event, months (95% CI)	60.3 [redacted]	NE [redacted]
Stratified hazard ratio (95% CI) p-value (log-rank)	0.71 (0.51, 0.98) p=0.0343	

- At the time of the analysis at CDF entry in April 2016, the hazard ratio for OS was 0.58 (95% CI: 0.39, 0.86). Median OS in the bendamustine arm was 53.9 months [95% CI: 40.9, NR] but was not reached in the

obinutuzumab with bendamustine arm. The ERG states that the final data suggests a 29% reduction in the risk of death in the obinutuzumab with bendamustine arm, compared with a 38% reduction estimated at the time of the company submission for TA472 (cut-off date 1st May 2015).

KM plot of overall survival (ITT population)



- The company reports that the OS estimates are robust up to [redacted], at which point [redacted] deaths had occurred. Separation of curves in favour of the obinutuzumab arm from 6 months and beyond can be seen.

1.8 Secondary source of clinical effectiveness evidence: SACT data

- There were 97 new applications for CDF funding for obinutuzumab for rituximab-refractory FL, 5 of whom did not receive treatment. Of the 92 patients with a treatment record, 55 (60%) were identified as having completed treatment by 28 February 2019 (latest follow up in SACT dataset).

- Median treatment duration for all patients was 5.3 months (95% CI: 4.8 to 7.8). Forty-six percent of patients were still receiving treatment at 6 months (95% CI: 35 to 56) and 28% were still receiving treatment at 12 months (95% CI: 18 to 40). A sensitivity analysis excluding the 11 patients who went on to have stem cell therapy found a median treatment duration of 7.2 months, with 44 of the 81 patients in this cohort having stopped treatment during follow-up and 35 of these having stopped before 6 months. The ERG highlights that the duration of time spent on treatment appears to be substantially lower in the SACT cohort than in GADOLIN where 81.9% of patients randomised to obinutuzumab with bendamustine had the full 6 doses of induction therapy and the median duration of exposure to obinutuzumab in the maintenance phase was 17 months. However, the ERG acknowledges that the data from SACT are immature, and that this makes it difficult to make meaningful comparisons with GADOLIN.

- For OS, minimum follow-up was 4 months from the last CDF application and median follow-up time was 12.4 months. The data are too immature to provide estimates of median survival. Survival at 6 months was 97% (95% CI: 90 to 99), 12-month survival was 88% (95% CI: 79 to 94). The ERG highlights that this is consistent with the KM estimate for OS at 12 months from the final data cut of GADOLIN of 90% (95% CI 85 to 95) but that comparisons between single arms from separate studies are likely to be subject to bias

- The SACT data were not included in the company's model because the final analysis of GADOLIN includes greater patient numbers and follow up times.

1.9 Updated model: changes to model parameters since TA472

Model input	Original parameter /assumption	Updated parameter /assumption	Company's source /justification
Data cut			
Clinical Cut-Off Date	April 2016	November 2018	KM data and survival curve parameters for PFS and OS from the final data cut of GADOLIN used to reduce uncertainty. Duration of treatment was mature at previous data cut-off so not updated. Safety data consistent with earlier data so not updated.
Progression-free survival (PFS)			
PFS extrapolation	Fully fitted Weibull curves, independently for both treatment arms. Weibull functions fitted to observed PFS data for entire time horizon, without direct use of the KM curves.	Curve choice unchanged but curve parameters fitted to the final data cut from GADOLIN rather than April 2016 data cut.	Weibull function continues to provide conservative long-term PFS estimates, comparable to those estimated in TA472 using Weibull as the base case.
		Independent log-logistic curve choice for both arms as a scenario.	*A scenario explores the log-logistic curve independently fitted to each arm as this represents the best statistically fitting curve to the observed data.*
Overall survival (OS)			
Use of OS Kaplan-Meier data	OS modelled using KM data until the time of the last event (4.0 years in April 2016 data cut), followed by parametric extrapolation.	KM data not used directly to model OS - company has moved away from modelling OS using KM data up to the time of the last event, and instead use the parametric survival function to model OS throughout the time horizon.	Due to additional survival data, fitted survival functions are applied from month 0 to avoid potentially appending hazards to the tail of a curve past 7 years where relatively uncertain steps in KM plots may occur and propagate to produce inaccurate cost-effectiveness estimates.

Model input	Original parameter /assumption	Updated parameter /assumption	Company's source /justification
		An approach using KM followed by a parametric extrapolation is available as a scenario analysis. The time of the last OS event in final data cut is [redacted].	
Duration of treatment effect on OS	Various assumptions were considered in the decision making: 1. Time of the last death (4.0 years for April 2016 data cut, ERG's preferred approach) 2. Longest follow-up (5.5 years) 3. Lifetime (Model time horizon 25 years).	Base case updated to assume no cap to the duration of treatment effect on OS. A range of scenarios considered: 1. Time of last OS event ([redacted],) 2. Longest follow-up ([redacted],) 3. Lifetime (25 years, new base case).	Assumption of lifetime treatment effect was informed by updated trial data which showed no observable decline in treatment effect with longer follow up. Extrapolation of time on treatment was not required as follow-up time reached maximum time on treatment in both arms of trial. The additional KM data from the final data cut showed that OS remained comparable to the parametric extrapolation predicted in 2016 in TA472 assuming no cap to the duration of treatment effect.
OS extrapolation	Fully fitted dependent Weibull curves from time of last OS event informed the survival for the remainder of the time horizon.	Same as previous model but curve parameters updated from survival analysis of final data cut.	Weibull function continued to provide conservative long-term OS estimates, comparable to those estimated in TA472 using Weibull as the base case.
		Independent log-normal curve choice for both arms used as a scenario.	*Log-normal is statistically the best fitting function.*

Model input	Original parameter /assumption	Updated parameter /assumption	Company's source /justification
Costs			
Acquisition costs of the intervention and comparator treatments	Agreed PAS for obinutuzumab. Acquisition cost of bendamustine estimated to be £27.77 (100 mg) and £6.85 (25 mg).	PAS updated. eMIT data reduces cost of bendamustine to £19.30 (100 mg) and £5.28 (25 mg). No other changes to resource use/cost data.	Most recent prices are used.

Adapted from table 16 (page 23) of the company submission

2. Summary of the draft technical report

2.1 In summary, the technical team considered the following:

Issue 1 Overall survival modelling approach

Issue 2 Progression free survival modelling approach

2.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- Data from the SACT cohort are too immature to provide reliable estimates of OS. The duration of follow-up for OS in the SACT cohort ranged from 4 to 23 months and the median follow-up time for OS was 12.4 months.
- The estimates of cost-effectiveness are dependent on the assumption that patients have a similar duration of treatment in clinical practice to in the GADOLIN trial. There is some evidence to suggest that the treatment duration in clinical practice, as measured in the SACT cohort, may be shorter than in the GADOLIN trial, and it is not possible to adjust the estimates of cost-effectiveness in the model to reflect a shorter duration of treatment.

2.3 The cost-effectiveness results include an updated commercial arrangement (patient access scheme) for obinutuzumab with bendamustine.

2.4 Taking these aspects into account, the ERG's preferred assumptions result in an incremental cost-effectiveness ratio (ICER) of 15,045 per QALY gained (see table 2)

2.5 The End of life Criteria do not apply to this technology

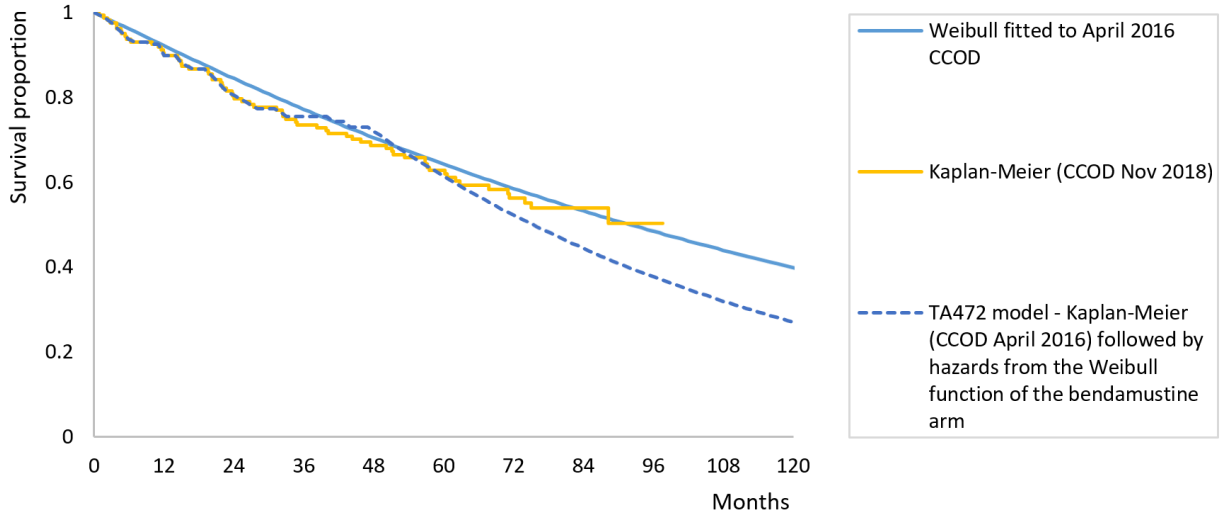
2.6 No equality issues were identified.

3. Key issues for consideration

Issue 1– Overall survival modelling approach

Background/description of issue	The **company's** updated base case uses dependent Weibull functions assuming proportional hazards, fitted to updated OS data from the latest data cut of GADOLIN throughout the time horizon of the model. This is different from the committee's preferred modelling approach in TA427 in which KM survival functions were used directly until the time of the last death (47.44 months for obinutuzumab with bendamustine followed by obinutuzumab maintenance and 53.88 months for bendamustine) then parametric survival functions (dependent Weibull functions assuming proportional hazard fitted to the data) informed the survival for the remainder of the time horizon. The duration of treatment effect was assumed to cease after the time of the last event (4.0 years in the April 2016 data cut) for obinutuzumab with bendamustine. From the time of the last event, hazards from the Weibull distribution fitted to the bendamustine arm were used to model the OS of the obinutuzumab with bendamustine arm. The **company** has moved away from modelling OS in its base case using KM data up to the time of the last observed event followed by parametric extrapolation, although it does include this as a scenario analysis, which reduces the ICER slightly. The new modelling approach for OS also no longer applies a cap on the maximum duration of treatment effect on OS for treatment with obinutuzumab with bendamustine. The **company** considers that the updated KM data more closely follow the Weibull prediction at CDF entry rather than the previously preferred model assumption by the **ERG** that used a treatment effect cap of 4.0 years (see Figure 1). Furthermore, using independent parametric models for OS showed no evidence of a declining treatment effect and even increased the mean incremental years gained for the obinutuzumab with bendamustine arm. Therefore, given the lack of evidence for a finite duration of treatment effect on OS, a treatment effect cap was not applied in the **company** base case. However, the company tests alternative assumptions for treatment effect duration in scenario analyses. For example, scenario analysis 1 in which treatment effect is not extrapolated beyond the period observed in the trial (i.e. beyond the last death at [redacted] years), increases the ICER by £4,062.

Figure 1: Model comparison – final OS Kaplan Meier for obinutuzumab with bendamustine followed by obinutuzumab maintenance from GADOLIN against two prior modelling assumptions in TA472



CCOD: Clinical cut-off date

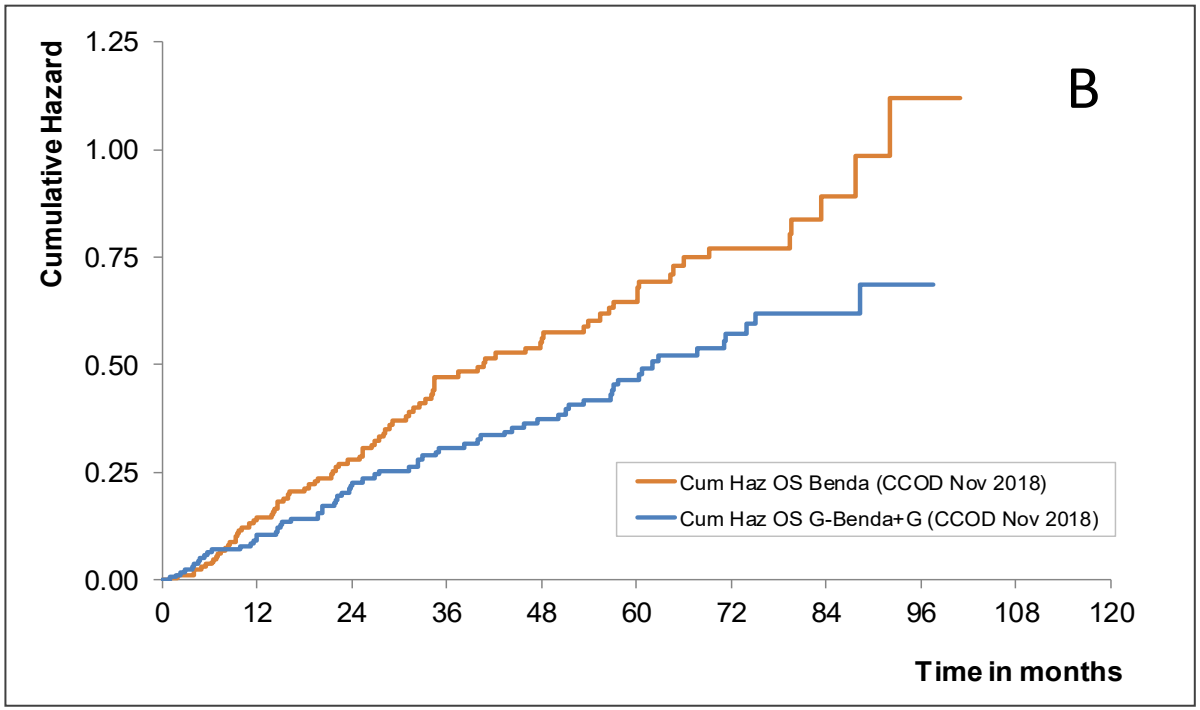
Source: Figure 5 (page 20 of company submission)

Although the Weibull function was used in the base case, the company reported that the log-normal function was the best fitting function to the observed OS data and provided a scenario analysis 4 using this, which increased the base case ICER by £2,799.

The **ERG** noted that the choice of models used to represent OS by the **company** may not provide a realistic model for the data from GADOLIN. They noted that the **company** states in their own submission that '*The KM plot for OS in patients with FL shows a clear separation of curves in favour of the obinutuzumab with bendamustine followed by obinutuzumab maintenance arm from 6 months*

	and beyond" corresponding to the time of the first obinutuzumab maintenance dose. This suggests that a single hazard function over the lifetime of patients treated with obinutuzumab with bendamustine followed by obinutuzumab maintenance may not be realistic and a model that allows for a change point in the hazard function would provide a better prediction of OS. Log cumulative hazard plots against time also suggest that a proportional hazards assumption is not appropriate and that a change in the relative hazards occurs after approximately 6 months.

Figure 2: OS log cumulative hazard functions against time

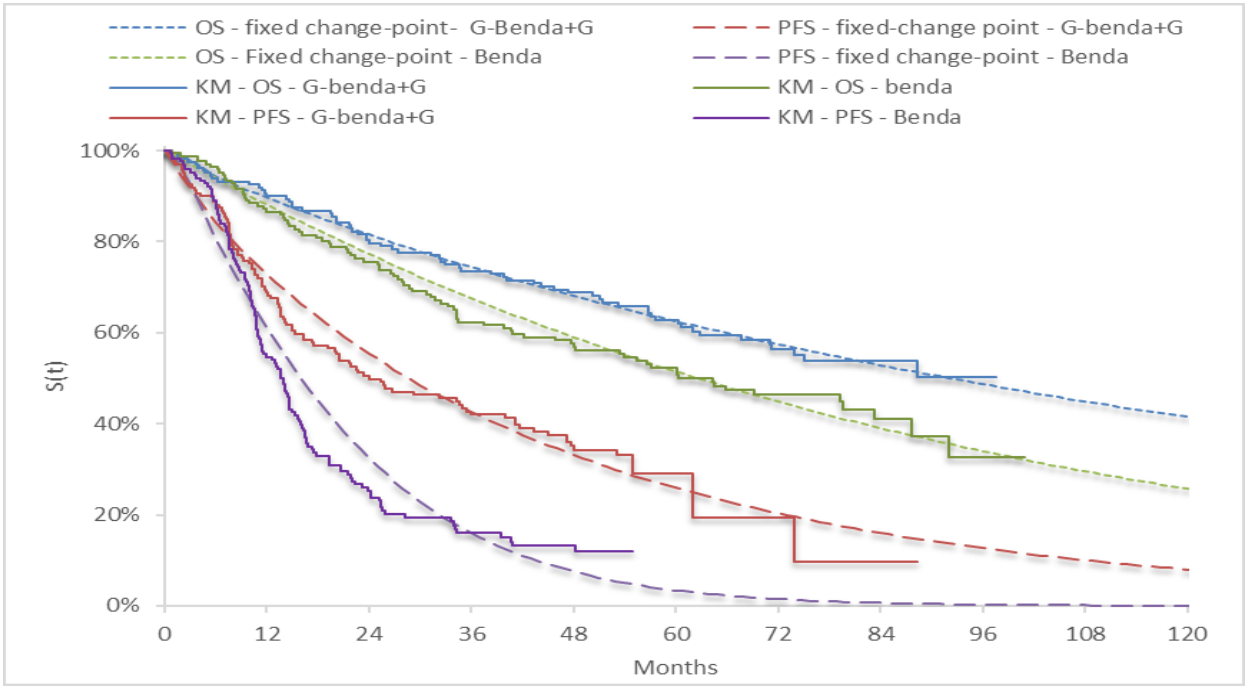


Source: Figure 4 (page 25 of ERG report)

The **ERG** did not think that the use of a single Weibull function accurately captures the cross-over of the OS estimates in the first year of GADOLIN. In response to the ERG's clarification request (questions B1 and B2), the company provided a re-analysis of PFS and OS survival data modelling using a segmented Weibull change-point model. The company estimated survival functions for both PFS and OS when making two different assumptions about the timing of the change-point. Firstly, it assumed that the change point occurred at exactly 6 months (referred to as the fixed change-point model), and secondly, it included the time of the change point as an uncertain parameter within the

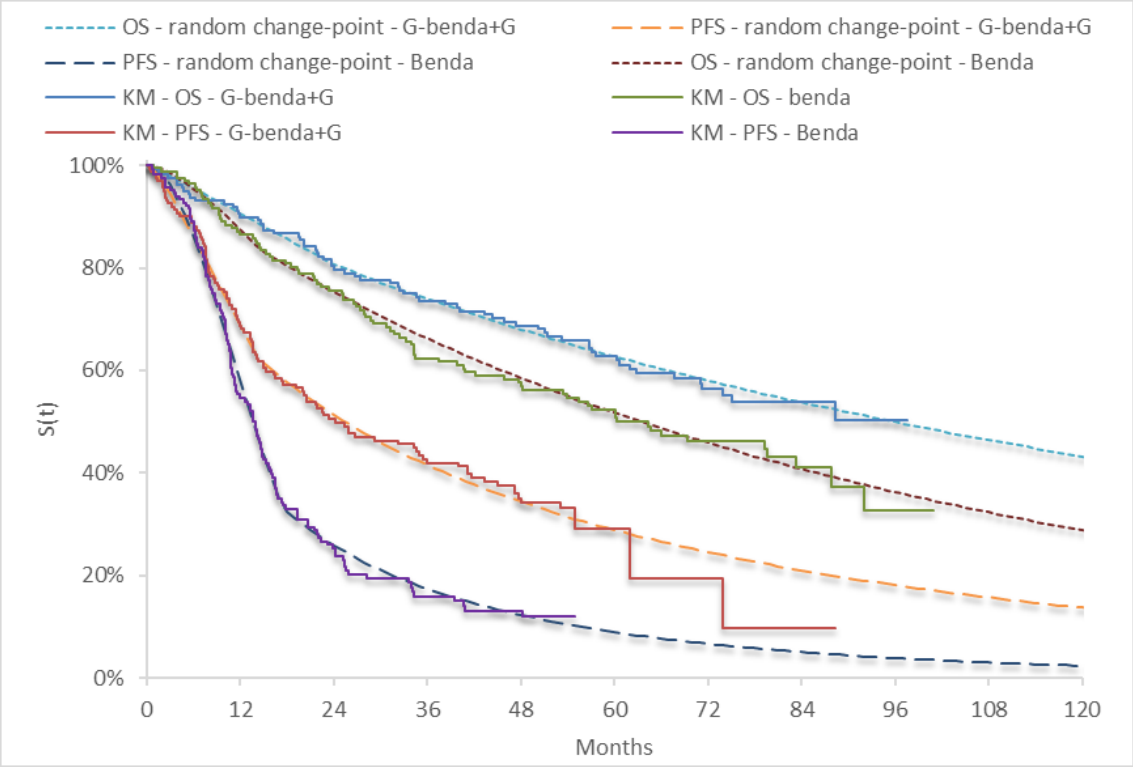
model, allowing the change point to be estimated from the data to obtain the best fit (referred to as the random change-point model).

Figure 3: OS and PFS survival curves for Weibull with fixed change-point at 6 months (extracted by ERG from company model submitted in response to clarification questions B5 and B6)



Source: Figure 4 (page 29) of ERG report

Figure 4: OS and PFS survival curves for Weibull with random change-point (extracted by the ERG from company model submitted in response to clarification questions B5 and B6)

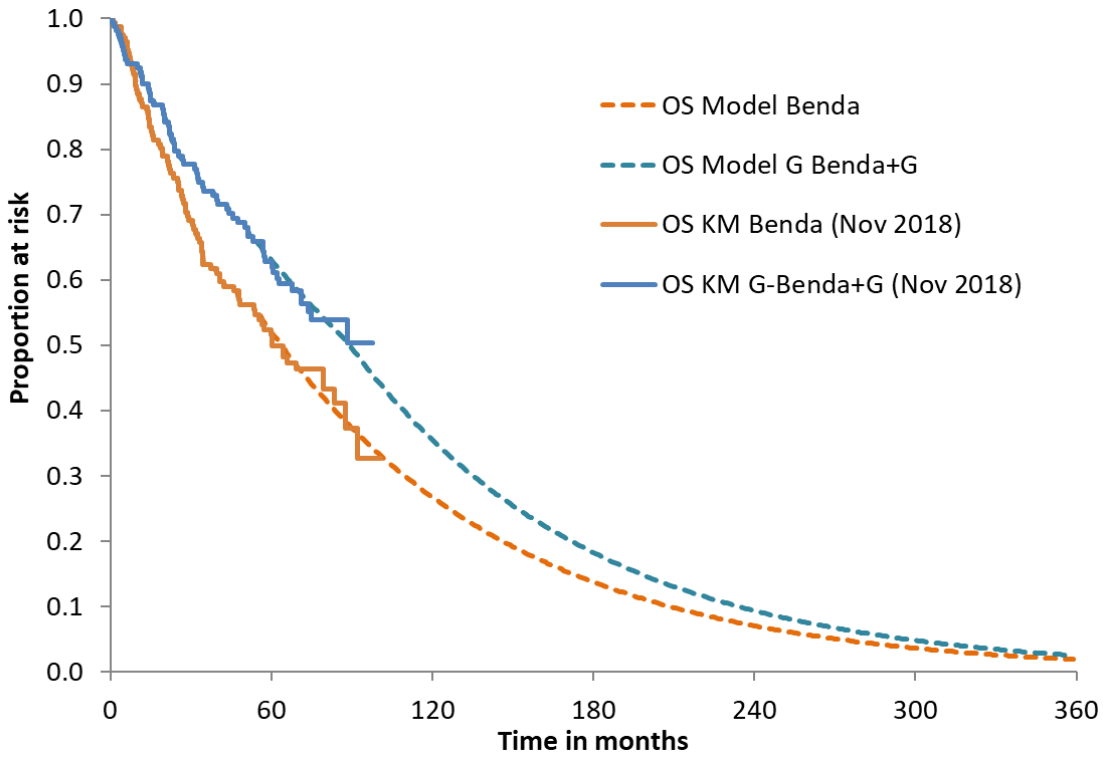


Source: Figure 5 (page 30) of ERG report

The fixed change-point at 6 months corresponded to the time of the first obinutuzumab maintenance dose. The ERG noted that the company did not provide estimates of uncertainty associated with the

	model parameters, did not assess the relative goodness-of-fit of the change-point models with the original models and did not consider alternative distributions for the data. Despite this, the ERG considers a change-point model using Weibull survival functions to better represent the data generation process. The survival functions incorporating a change-point appear to provide a better representation visually of the observed data over the early and late phase of the GADOLIN trial and is the model preferred by the ERG. It notes, however, that because no other distributions were considered by the company, it is unable to confirm whether the Weibull change-point models provide the most plausible survival functions. In addition, the absence of any measures of uncertainty associated with the Weibull functions for PFS and OS is a significant limitation, particularly, as these survival functions are applied for the whole time-horizon in the ERG's preferred base-case. The ERG base case therefore incorporates no uncertainty with regards to time spent in the PFS and OS states. The ERG believes that it is possible that including this uncertainty would not have a large impact on the mean costs and QALYs obtained from the probabilistic sensitivity analyses (PSA), as in the company's base-case, there is good agreement between the deterministic ICER and the probabilistic ICER, but it is expected to have a large impact on the uncertainty around the ICER estimated by the PSA. The ERG prefers the random change-point model as this allows for the treatment effect to vary during the observed follow-up period of GADOLIN and uses this in its preferred base case analysis. Alternative modelling approaches to modelling OS were explored in scenario analyses by both the company and ERG. For example, in scenario analysis 2, the ERG explored using KM data directly up to the point at which OS data is robust ([redacted]) in both arms. A Weibull survival function is then used to extrapolate until the time of the last OS event ([redacted]) based on the assumption that there is no treatment effect beyond the last event thereafter. The time point of [redacted] was selected as the company states that "*overall survival estimates are robust up to* [redacted]*, at which point* [redacted] *deaths had occurre*d". The ERG's scenario analysis 2 increases the ICER to £21,301 from the company's base case estimate of £17,408. This analysis is not the ERG's preferred base case but shows how using KM directly and not extrapolating the treatment effect beyond the period observed in the trial affects the ICER.

Figure 5: OS survival functions for ERG scenario 2: KM survival functions till [redacted] months followed by parametric OS survival functions with treatment effect assumed to end at [redacted] years



Source: Figure 8 (page 44 of the ERG report)

Abbreviation: Benda: bendamustine, G Benda+ G: obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance

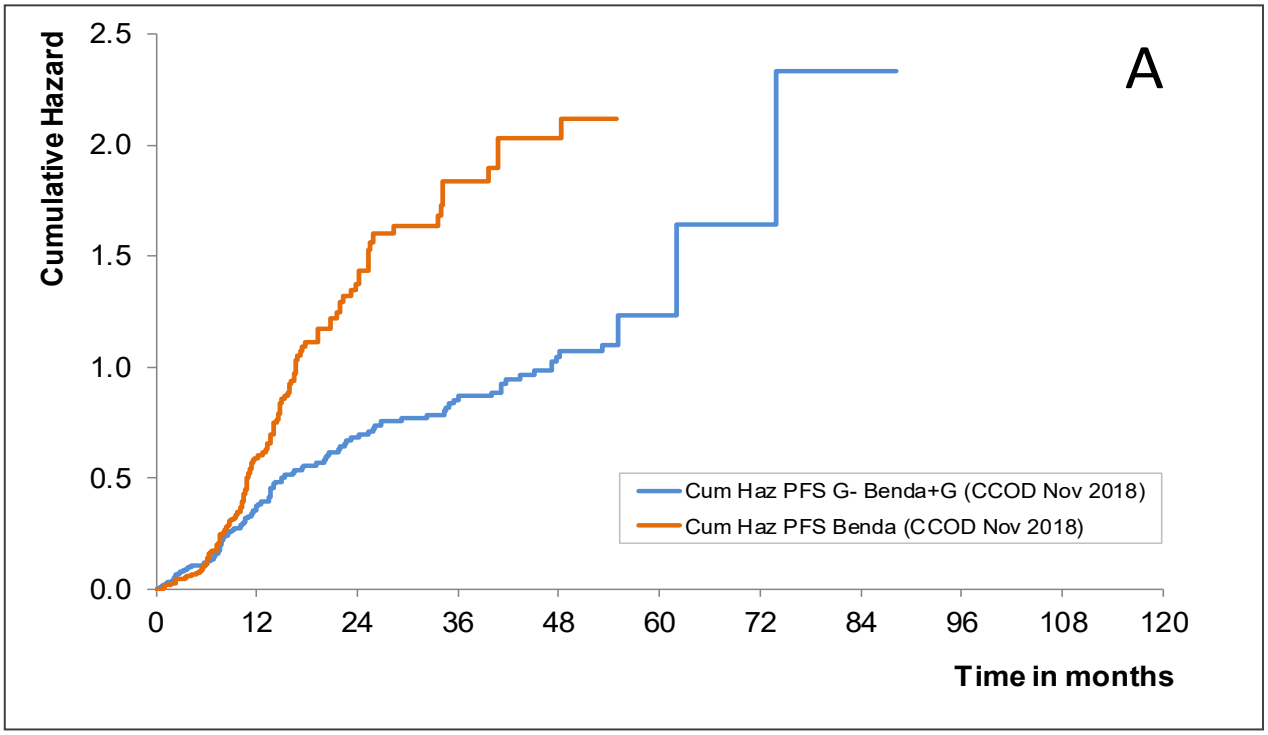
Why this issue is important	The log cumulative hazard functions against time for OS suggest that using a single parametric function to predict OS over the whole of the patient's life-time may not be accurate and that an analysis which incorporates a change-point in the hazard function may provide a better prediction of OS. The ERG's preferred model incorporates the Weibull change-point for the hazard function which allows the hazard function to change during the period observed in GADOLIN (the random change-point model). This reduces the base case ICER from the company's estimate of £17,408 to 15,045 per QALY gained.
Technical team preliminary judgement and rationale	A single hazard function over the lifetime of patients treated with obinutuzumab with bendamustine may not be accurate. A model that allows for a change point in the hazard function appears to provide a better prediction of OS, although the absence of any measure of uncertainty associated with the Weibull change-point survival functions within the model is a limitation of the analysis.
Questions for engagement	a) Does the updated data from GADOLIN support an assumption of constant treatment effects for the remainder of the patient's lifetime, as in the company's approach? b) Does the company's use of a single parametric Weilbull function for OS provide an accurate prediction of OS during the study follow-up period and does it accurately capture the cross-over of the OS estimates in the early phase of the trial? Or does the ERG's preference for an analysis which incorporates a change-point in the hazard function predict more plausible OS estimates?

Issue 2 – Progression free survival modelling approach

Background/description of issue	For PFS, the company fitted the same parametric distributions to the PFS data from the final data cut (Nov 2018) as were fitted to the previous data cut. The **company** considered that the proportional hazards assumption did not hold due to curve crossing, convergence and divergence across time when considering the log-cumulative hazard plot for PFS (see Figure 5). Therefore, independently fitted parametric models were fitted to the updated PFS data from GADOLIN. PFS data were modelled using the independent Weibull distributions on the basis that this was the preferred approach in TA472 and because it generated conservative estimates of the 10-year PFS rates. The company also provided a scenario analysis 3 using the log-

logistic parametric function, reporting that this was the best fit to the observed PFS data. Switching from the Weibull survival function to the log-logistic function for PFS decreased the ICER by £2,089.

Figure 5: PFS log cumulative hazard functions against time



Source: Figure 4 (page 25 of ERG report)

The **ERG** considered that the choice of models used to represent PFS by the **company** may not provide a realistic model for the data from GADOLIN. They noted that the **company** states in their

	own submission that '*The KM plot of INV-PFS in patients with FL shows a clear separation of curves in favour of the obinutuzumab with bendamustine followed by obinutuzumab maintenance arm starting after approximately 6 months in the trial. This corresponds to the time of the first obinutuzumab maintenance dose'*. This suggests that a single hazard function over the lifetime of patients treated with obinutuzumab with bendamustine followed by obinutuzumab maintenance may not be plausible and a model that allows for a change point in the hazard function would be more realistic. The ERG suggests that assuming a single Weibull model over the horizon of the model may underestimate the benefit of obinutuzumab with bendamustine on PFS. In response to clarification, the company provided results of Weibull fixed and random change-point models for both PFS and OS (see figures 3 and 4). Please see issue 1 for a full discussion of the ERG critique of these models and impact on ICER. The ERG's preferred modelling approach for PFS included using the change-point model as these appeared a better representation of the observed data over both the early and late phase of the GADOLIN trial.
Why this issue is important	The log cumulative hazard functions against time for PFS suggest that using a single parametric function to predict PFS over the whole of the patient's life-time may not be accurate and that an analysis which incorporates a change-point in the hazard function may provide a better prediction of PFS. Log cumulative hazard plot for PFS suggests that the company's approach may underestimates the benefit of obinutuzumab with bendamustine followed by obinutuzumab maintenance.
Technical team preliminary judgement and rationale	Assuming a single Weibull model over the horizon of the model may underestimate the benefit of obinutuzumab with bendamustine on PFS; a model that allows for a change point in the hazard function appears to provide a better prediction of PFS.
Questions for engagement	a) Is the **company's** approach assuming a single parametric function to predict PFS over the life-time of a patient, appropriate, or does the ERG's preference for an analysis which incorporates a change-point in the hazard function predict more plausible PFS estimates?

4. Issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 1: Company's scenario analyses incorporating change-point models

Scenario	Incr LYs	Incr Costs	Incr QALYs	ICER
Company updated base-case	[redacted]	[redacted]	[redacted]	**£17,408**
Company scenario 6 – Weibull model with change-point at 6 months for PFS	[redacted]	[redacted]	[redacted]	£17,322
Company scenario 7 – Weibull model with random change-point for PFS	[redacted]	[redacted]	[redacted]	£16,383
Company scenario 8 – Weibull model with change-point at 6 months for OS	[redacted]	[redacted]	[redacted]	£15,587
Company scenario 9 – Weibull model with random change-point for OS	[redacted]	[redacted]	[redacted]	£15,902

Table 2: ERG's preferred assumptions and impact on the cost-effectiveness estimate

Scenario	Incremental costs	Incremental QALY's	ICER	Change from base case
Company base case			**£17,408**	
ERG scenario 1: using KM estimates until last event ([redacted]) and assuming no treatment effect after last event	[redacted]	[redacted]	£20,472	+£3,424
4ERG scenario 2: using KM estimates until [redacted] and assuming no treatment effect after last event	[redacted]	[redacted]	£21,301	+£3,893
ERG scenario 3: Weibull survival functions with random change-points for PFS and OS	[redacted]	[redacted]	£15,020	-£2,388
ERG scenario 4: ERG scenario 3 with latest eMIT price for bendamustine **ERG preferred base-case**	[redacted]	[redacted]	**£15,045**	**-£2,003**
ERG scenario 5: ERG scenario 4 with incremental costs adjusted to include one additional dose of obinutuzumab in the 3rd year of the model.	[redacted]	[redacted]	[redacted]	[redacted]

Table 3: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Immature secondary clinical effectiveness evidence from SACT cohort	Data from the SACT cohort are too immature to provide reliable estimates of median OS. The duration of follow-up for OS in the SACT cohort ranged from 4 to 23 months and the median follow-up time for OS was 12.4 months. The limited duration of follow-up in the SACT cohort means that an estimate of median OS cannot be provided as the data are too immature.	Unknown
Duration of treatment	The estimates of cost-effectiveness are dependent on the assumption that patients have a similar duration of treatment in clinical practice to in the GADOLIN trial. There is some evidence to suggest that the treatment duration in clinical practice, as measured in the SACT cohort, may be shorter than in the GADOLIN trial, and it is not possible to adjust the estimates of cost-effectiveness to reflect a shorter duration of treatment.	Difficult to predict because the model is based on PFS and OS outcomes from the GADOLIN trial and therefore the model assumes the exact same treatment duration as observed in GADOLIN.

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Technical engagement response form

Obinutuzumab with bendamustine for treating follicular lymphoma refractory to rituximab (CDF Review of TA472) [ID1583]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **Tuesday 4 February 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text:

'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, 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 during engagement 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.

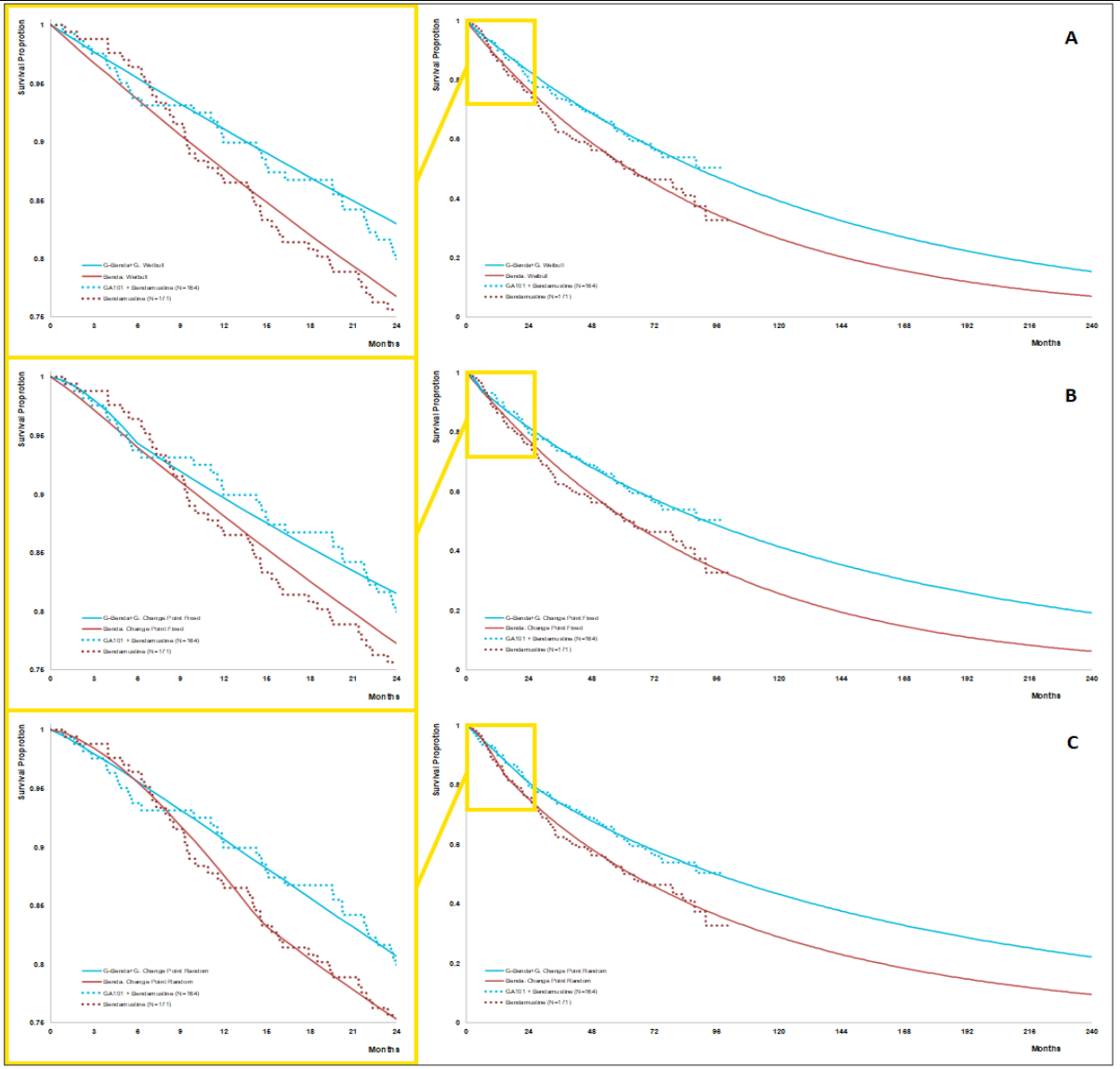
About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Roche Products Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Overall survival modelling approach	
Does the updated data from GADOLIN support an assumption of constant treatment effects for the remainder of the patient's lifetime, as in the company's approach?	A constant treatment effect of G-benda+G for the remainder of the patient's lifetime is supported by the OS data demonstrated in the final data cut of the GADOLIN trial (CCOD Nov 2018). In particular, there is no indication of a declining treatment effect over time. The company also recognises that the assumption used by the ERG reflects the observed data more accurately; that is, the plot of cumulative hazards suggests the treatment effect may even be increasing over time.
Does the company's use of a single parametric Weilbull function for OS provide an accurate prediction of OS during the study follow-up period and does it accurately capture the cross-over of the OS estimates in the early phase of the trial? Or does the ERG's preference for an analysis which incorporates a change-point in the hazard function predict more plausible OS estimates?	At the time of submission, the company believed the single parametric Weibull function was the most reasonable approach, and a conservative one, to modelling overall survival. The company believes the ERG's approach, which incorporates a change-point in the hazard function, models overall survival more accurately during the first 24 months of the observed period due to the introduction of additional parameters and predicts plausible OS estimates. Figure 1

	shows the comparison of these models overlaid to Kaplan-Meier plots from the final data cut of the GADOLIN trial (CCOD November 2018). Whilst a better fit does not necessarily lead to more plausible long-term extrapolations, both extrapolation methods (Weibull with and without change points) provide plausible long-term extrapolations with similar predictions on long-term OS due to the maturity of the data set. **Figure 1. Observed and modelled overall survival from GADOLIN (CCOD Nov 2018), A: Standard Weibull, B: Fixed change-point Weibull, C: Random change-point Weibull**


A
B
C
Survival Proportion
Months

	As demonstrated in Figure 1(c), the random change-point Weibull model more accurately captures the cross-over of the OS estimates in the early phase of the trial when compared to 1(a) or 1(b), albeit the crossing of the curves is also uncertain itself due to low event rates early in the observed period.
Issue 2: Progression free survival modelling approach	
Is the company's approach assuming a single parametric function to predict PFS over the life- time of a patient, appropriate, or does the ERG's preference for an analysis which incorporates a change-point in the hazard function predict more plausible PFS estimates?	The company believes that whilst both approaches produce reasonable and plausible estimates of PFS, the ERG's approach more accurately models PFS during the first 24 months of follow up data from the GADOLIN trial.