Cancer Drugs Fund

Managed Access Agreement

Obinutuzumab with bendamustine for treating rituximab-refractory follicular lymphoma

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund – Data Collection Arrangement

Obinutuzumab with bendamustine for treating rituximab-refractory follicular lymphoma [ID841]

Company name: Roche Products Ltd, a company registered in England and Wales with company no: 100674 **(Roche).**

Primary source of data collection: Ongoing clinical study

Date of Agreement	
NICE Agreement Manager	
NHS England Agreement Manager	
Public Health England Agreement Manager	
Roche Agreement Manager	[redacted], Head of HESP

1 Purpose of data collection arrangement

1.1 The purpose of the agreement is to describe the arrangements and responsibilities for further data collection for obinutuzumab with bendamustine for treating rituximab-refractory follicular lymphoma [ID841]. A positive recommendation within the context of a managed access agreement has been provisionally decided by the appraisal committee.

2 Commencement and period of agreement

2.1 This data collection arrangement shall take effect on 30 August 2017. The data collection period is anticipated to conclude with the availability of a final analysis of the GALOLIN study which is currently expected in December 2020 (see section 5.1). The process for exiting the Cancer Drugs Fund will begin at this point and the review of the NICE guidance will start.

2.2 As part of the managed access agreement, the technology will continue to be available via the Cancer Drugs Fund after the data collection period has

ended and while the guidance is being reviewed. This assumes that the data collection period ends as planned and the review of guidance follows the standard timelines described in the addendum to NICE's methods and processes when appraising cancer technologies.

3 Patient eligibility

3.1 The patient population to be treated during the managed access arrangement period are patients 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. This constitutes the entire population covered by the marketing authorisation.

3.2 Obinutuzumab is administered in induction treatment with bendamustine. Patients who respond to induction treatment (i.e. the initial 6 treatment cycles) with obinutuzumab in combination with bendamustine or have stable disease can continue to receive obinutuzumab 1,000 mg as single agent maintenance therapy once every 2 months for two years or until disease progression.

3.3 Approximately 470 patients are expected to be refractory to rituximab, i.e. not respond or progress during or up to 6 months after treatment with rituximab or a rituximab-containing regimen, in England each year. It is expected that up to half of these patients, or approximately 240 per annum, may receive obinutuzumab under the CDF during the managed access arrangement period.

3.4 Obinutuzumab is administered with bendamustine as 6 cycles induction treatment and for patients responding to induction for up to 2 years or until progression as maintenance. The maximum treatment duration is therefore 2.5 years. However, patients discontinue on progression or due to other reasons. In the GADOLIN study the average time on treatment was 1.4 years (Roche Economic Model, Clinical cut-off date 1 April 2016).

4 Area(s) of clinical uncertainty

4.1 An area of clinical uncertainty is the magnitude of the OS benefit of obinutuzumab with bendamustine followed by obinutuzumab compared to bendamustine alone e.g. hazard ratio, and duration of effect.

5 Source(s) of data collection

5.1 The primary source of data collection during the managed access arrangement period will be the final analysis of the ongoing pivotal GADOLIN study, where OS data collection is ongoing. The final analysis is the only remaining pre-planned analysis and would correspond to the longest available follow up time for overall survival (OS). The date of the final analysis of the GADOLIN study is currently assumed to be either (a) event driven by 226 deaths in the intention to treat (ITT) population of 413 patients or (b) following a decision by the study sponsor, F. Hoffman-La Roche Ltd. (**the Sponsor**) (such decision to be duly supported by the US Food & Drug Administration (FDA)). The current estimate for the availability of a final analysis is December 2020 (See Appendix for further details on the GADOLIN study).

5.2 The Systemic Anti-cancer Therapy (SACT) dataset is a mandated dataset as part of the Health and Social Care Information Standards. Data will be collected via SACT dataset alongside the primary source of data collection on anti-lymphoma treatments received prior to treatment with obinutuzumab (rituximab with chemotherapy, rituximab maintenance or rituximab monotherapy), the length of treatment on obinutuzumab and survival in clinical practice. The SACT database routinely reports the data fields needed to collect the data alongside the primary data source, so no additional data items will be collected.

5.3 Blueteq is a system routinely used by NHS England to manage prescribing of CDF funded medicines. Data will be collected via Blueteq alongside the primary source of data collection on anti-lymphoma treatments received prior to treatment with obinutuzumab in clinical practice (rituximab with chemotherapy, rituximab maintenance or rituximab monotherapy). NHS

England is responsible for implementing Blueteq data collection and analysis.

6 Outcome data

6.1 Overall survival is a secondary endpoint in the GADOLIN study. The collection of OS data is ongoing for all patients still in the study until 226 patients in the ITT population have died or the Sponsor decides to terminate the 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 assessed by the investigators (PFS-INV) and next anti lymphoma treatment (NALT) will be collected according to trial protocol with the view of updating the economic analysis.

6.2 OS, PFS-INV and NALT data in the GADOLIN study will be collected in the same way for bendamustine as for the intervention (obinutuzumab with bendamustine followed by obinutuzumab maintenance).

7 Data analysis plan

7.1 The final analysis of the GADOLIN study is triggered by 226 deaths in the ITT population of 413 patients or earlier by Sponsor decision. The final analysis will follow the analysis plan outlined in the trial protocol.

7.2 An annual report detailing updated data collection from GADOLIN in terms of number of recorded events and anticipated date of final analysis will be provided to NICE by Roche. Roche will also communicate any updated information on the timing of final analysis of the GADOLIN trial if such information becomes available in between update reports.

7.3 Analysis of SACT data routinely collected alongside the primary data source is the responsibility of Public Health England (PHE). PHE will provide the results of their analysis in advance of the planned review of this appraisal (to be updated with NICE TA publication number at time of final guidance publication).

8 Ownership of the data

8.1 Data from the GADOLIN study is owned by the Sponsor.

8.2 Data collection will be as per the GADOLIN study protocol.

8.3 SACT data is owned by PHE.

8.4 Blueteq data is owned by NHS England.

9 Publication

9.1 The details/authorship of any proposed publications arising from data collection in the GADOLIN study will be planned with the publication of the final study results by Roche.

9.2 Publication of the analysis results of SACT data collected alongside the primary data source will be planned by PHE. Roche will be given access to the report produced for the review of this appraisal (to be updated with NICE TA publication number at time of final guidance publication).six months before the planned start of the review.

9.3 Publication of the analysis results of Blueteq data collected alongside the primary data source will be planned by NHS England. Roche will be given access to the report produced for the review of this appraisal (to be updated with NICE TA publication number at time of final guidance publication).six months before the planned start of the review.

10 Appendices: List of supporting documents

10.1 GADOLIN Study Data Collection and Final Analysis Date

Appendix I to the data collection arrangement for the single technology appraisal of Obinutuzumab with bendamustine for treating rituximab-refractory follicular lymphoma [ID841]

GADOLIN Study

The GADOLIN study was an open-label, multicentre, randomised, Phase III study to investigate the efficacy and safety of bendamustine (benda) compared with obinutuzumab with bendamustine followed by obinutuzumab maintenance (G-benda+G) in patients with rituximab-refractory, indolent non-Hodgkin lymphoma (iNHL) (1-3).

Study Objectives

The primary objective of this study was to evaluate clinical benefit in terms of progression-free survival (PFS), as assessed by an Independent Radiology Facility (also called independent review committee, IRC), also called PFS-IRC, for obinutuzumab when used in combination with bendamustine compared with bendamustine alone in patients with iNHL refractory to a prior rituximab-containing therapy.

The secondary objectives of this study were as follows:

- To compare PFS as assessed by the investigator (PFS-INV)
- To compare overall survival (OS) between study arms
- To evaluate in each study arm and compare between study arms the following:
    - Overall response rate (ORR) (rate of complete response [CR] + partial response [PR]) and complete response rate (CR) at the study treatment completion/early study treatment termination visit;
    - Best ORR achieved during treatment or within 12 months of the start of treatment;
    - Disease-free survival (DFS) in CR patients;
    - Duration of response in patients with CR and PR
- To compare event-free survival (EFS) between the two study arms
- To evaluate and compare the safety profiles of patients treated with the combination of G-benda+G and benda alone

- To characterise the pharmacokinetics of G-benda and evaluate for drug-drug interactions by comparing the pharmacokinetics of the combination with those of bendamustine alone
- To analyse pharmacoeconomics (medical resource utilisation) in both arms of the study
- To assess patient-reported outcomes (PROs) in both treatment arms

Trial Period

The first patient entered the study 15 April 2010; the study reached its primary endpoint at the third pre-planned interim analysis (clinical cut-off date 01 September 2014). The study is ongoing and the final analysis will be triggered by 226 death events in the ITT (iNHL) population or on upon decision by the sponsor. The estimated of timing of the final analysis is discussed below.

Available Analyses

The GADOLIN study met its primary endpoint at the time of the third pre-planned interim analysis (clinical cut-off date 1 September 2014). The study was unblinded to the sponsor and the results of the primary analysis published (3). Data collection continued as per protocol.

A further data cut (1 May 2015) was conducted as part of a 90 day FDA safety update. This data cut showed a trend towards an OS benefit of G-benda+G versus benda (2)

An exploratory analysis was agreed with investigators and conducted to analyse the OS benefit and submit the results to the American Society of Hematology Conference in 2016 (clinical cut-off data 1 April 2016) (4). However, while the secondary endpoints of OS and PFS-INV were collected, the assessment of progression by the independent review committee assessment of PFS (PFS-IRC) had stopped.

Data cuts with maturity of OS data and median follow up are summarised in **Table 1** below.

Table 1 Analyses and OS events in the GADOLIN study

Analysis	Clinical cut-off date	Deaths (ITT population) N (%)			Median follow up (ITT, months)	
		G-benda+G	benda	Total	G-benda+G	benda
Primary analysis (pre-planned third interim analysis)	01/09/2014	34 (17.5)	41 (20.3)	75	21.9	20.3
90 FDA day safety (Updated analysis)	01/05/2015	42 (20.6)	56 (26.8)	98	25.3	24.5
Exploratory OS analysis	01/04/2016	52 (25.5)	73 (34.9)	125	34.0	30.0

ITT, Intention to Treat; OS, Overall Survival; G-benda+G, obinutuzumab with bendamustine followed by obinutuzumab; benda, bendamustine.

Ongoing Data Collection

Although independent, blinded assessment of PFS-IRC (primary endpoint) was stopped, the secondary endpoints PFS-INV and OS are being collected as described below.

Follow-up in response until progression: patients are initially assessed every 2 months (physical examination) and with CT every 3 months until disease progression, patient discontinuation from the study, or until 2 years from the last study treatment in Cycle 6 (whichever comes first). Patients who continue to demonstrate a response to treatment at the final follow-up visit (i.e., FU16 ± 28 days, approximately 25 months from Cycle 6, Day 1) will continue to be assessed every 6 months for an additional 2 years or until disease progression (whichever occurs first). Patients who complete all response follow-up will continue to be followed for OS twice annually until approximately 226 deaths have occurred.

Follow-up post-progression: patients will be followed for OS twice per year until approximately 226 deaths have occurred for the following:

- New anti-lymphoma therapy
- Survival.

Final Analysis Date

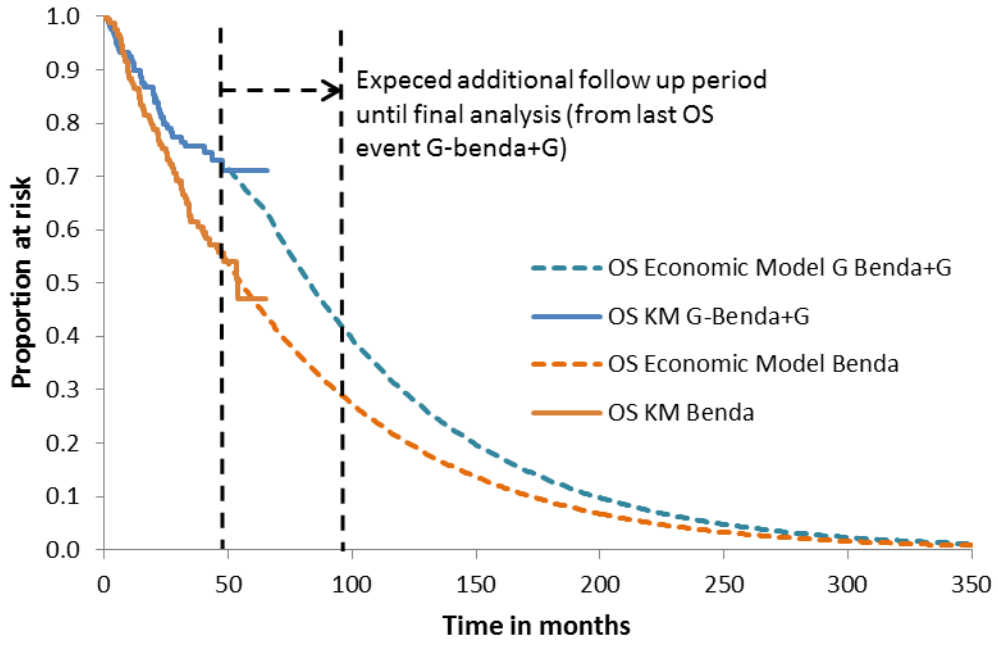
The latest version of the protocol includes an event driven end date when 226 deaths have occurred or the option for the sponsor (F Hoffmann-La Roche Ltd.) to decide to terminate the study. In the ITT population of 413 patients, 226 death events would correspond to approximately reaching median OS in the G-benda+G arm. At the time of the protocol update (version 8) on 24 October 2013, after the interim futility analysis, final analysis was predicted to occur approximately 96 months after first patient enrolment (i.e. by mid-2018). However, predictions were based on a model of the future survival in the arms; the increased and maintained OS effect observed in the latest exploratory analysis (exploratory OS analysis; 1 April 2016 cut-off date) was not predicted. The latest prediction for the 226th event to occur is by [redacted] and therefore a final analysis is expected to be available by end-2020.

OS Observation for Decision Making

As outlined in our response to the ACD, the ICER in the revised economic model that incorporated the ERGs preferred assumptions was most sensitive to the duration of the treatment effect on OS, i.e. for how long the observed OS hazard ratio was applied after the current observation period going forward. However, it was difficult to estimate the duration of effect in the relapsed/refractory FL setting as no evidence from other studies on a typical duration of OS effect was available. Therefore, our base-case and the ERGs analysis had to rely on the conservative assumptions that there was no treatment effect beyond the longest observation period of 5.5 years (G-benda+G arm) or beyond the time of the last OS event at 4.0 years, respectively. The estimate of life years (LY) and QALYs gained was therefore sensitive to the length of observation time and the resulting observed minimum duration of effect.

At the projected final analysis date, the observation time would have increased by approximately 4 years as shown in Figure 1. Therefore, a maximum follow up time until the final analysis may seem appropriate and would result in the best estimate for LYs and QALYs gained.

Figure 1 GADOLIN OS data (1 April 2016, FL Population) extrapolation and additional follow up expected at final analysis.



Benda, bendamustine; G-benda+G, obinutuzumab with bendamustine followed by obinutuzumab ; KM, Kaplan-Meier.

References

1. Clinical study report, GAO4753g/GO01297 primary analysis; report number 1051204. 2015 July. Report No.
2. Clinical study report, GAO4753g/GO01297 updated analysis; report number 1067639. 2015 2015. Report No.
3. Sehn LH, Chua N, Mayer J, Dueck G, Trneny M, Bouabdallah K, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. Lancet Oncol. 2016;17(8):1081-93.
4. Cheson BD, Trněný M, Bouabdallah K, Dueck G, Gribben J, Lugtenburg JP, et al. Obinutuzumab plus Bendamustine Followed by Obinutuzumab Maintenance Prolongs Overall Survival Compared with Bendamustine Alone in Patients with Rituximab-Refractory Indolent Non-Hodgkin Lymphoma: Updated Results of the GADOLIN Study. ASH; San Diego2016.

Commercial Access Agreement

Obinutuzumab with bendamustine for treating rituximab-refractory follicular lymphoma

The contents of this document have been redacted as they are confidential