**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

**Obinutuzumab for untreated advanced follicular lymphoma [ID1020]**

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Lymphoma Association
   - Roche – comments on the ACD
   - Roche - Supporting Appendix to the ACD Response
   - NHS England

3. **Comments on the Appraisal Consultation Document received through the NICE website**

4. **Evidence Review Group critique of extra information submitted by Roche**
   - 2nd addendum: Critique on the additional evidence submitted in response to the ACD
   - 3rd addendum: Exploratory analyses undertaken by the ERG
   - 4th addendum: Administration costs
   - 5th addendum: Administration costs
   - 6th addendum

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

# Obinutuzumab for untreated advanced follicular lymphoma

**Single Technology Appraisal**

**Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

**Type of stakeholder:**

**Consultees –** Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

**Clinical and patient experts and NHS commissioning experts** – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

**Commentators –** Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

**Public –** Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

**Please note:** Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

| Comment number | Type of stakeholder | Organisation name | Stakeholder comment [sic]<br>Please insert each new comment in a new row | NICE Response<br>Please respond to each comment |
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| 1. | Consultee | Roche Products Ltd | **Revised Base Case Population**<br>The revised base case considers patients at higher risk of progression, as defined by Follicular Lymphoma International Prognostic Index (FLIPI) score of 2 or higher (intermediate and high FLIPI) only.<br><br>The patient population in the company submission (CS) in May 2017 was all symptomatic advanced follicular lymphoma (FL) patients requiring treatment with immunochemotherapy (rituximab or Gazyvaro with chemotherapy) as per the GALLIUM study. This included patients with different risk of relapse according to their FLIPI rating. Evidence in the submission is based on the GALLIUM study in which randomisation was stratified by FLIPI rating. The trial was not designed however to explore differences in outcomes according to FLIPI subgroups, and health economic analyses in the submission were conducted on the FL intention to treat (ITT) group as a whole.<br><br>Subsequently the EMA has required the inclusion of a statement in Section 4.4 of the Gazyvaro Summary of Product Characteristics on the benefit/risk ratio of obinutuzumab in patients with a low FLIPI risk rating (Gazyvaro Summary of Product Characteristics):<br><br>'*Based on a subgroup analysis in previously untreated follicular lymphoma, the efficacy* | The FAD has been amended to consider the higher-risk FLIPI subgroup (see FAD section 3.9) |

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| | | | *in FLIPI low risk (0-1) patients are currently inconclusive (see section 5.1). A therapy choice for these patients should carefully consider the overall safety profile of Gazyvaro plus chemotherapy and the patient-specific situation.'*<br><br>Patients with a low FLIPI score comprised 21% of patients in the GALLIUM ITT population and only 17.8% of the total PFS events. The hazard ratio for G-chemo+G vs R-chemo+R investigator-assessed PFS in this subgroup was 1.11 (95% CI: 0.62-1.99) (September 2016 cut-off date). In view of the uncertainty of benefit in low FLIPI patients and the corresponding statement in the marketing authorisation, Roche believes it would be prudent to consider the eligible patient population for Gazyvaro as first line therapy in FL to be those with intermediate or high FLIPI score (higher risk group). These patients are at greater risk of relapse and have the highest clinical unmet need as patients have a significantly lower duration of response to subsequent treatments and early relapse is associated with a significantly higher mortality. In this group, the benefit of Gazyvaro was clearly demonstrated by superior and consistent PFS over rituximab. This is evidenced by the increased number of events, consistent hazard ratios between the groups and narrower confidence intervals around the estimates. | |
| 2. | Consultee | Roche Products Ltd | **Duration of treatment effect**<br>The committee's preferred assumption of no progression free survival (PFS) treatment effect beyond the GALLIUM study follow up period of 5 years is implausible for anti-CD20 treatments. | The FAD outlines the committee's considerations about duration of treatment effect (see FAD section 3.19) |

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| | | | Due to the indolent nature of FL, long-term follow-up data reaching median PFS is challenging as this is expected to be around 6 years on the current standard of care. For Gazyvaro, data in 1st line FL is limited to the maximum available follow up period of up to 5 years in the GALLIUM study (September 2016 clinical cut-off date). However, based on the experience with Gazyvaro in other settings and the common CD20 target with rituximab there is no evidence in the literature for a finite treatment effect:<br><br>**Evidence for Gazyvaro:** Gazyvaro demonstrates an ongoing effect in GALLIUM after treatment completion (maintenance) as evident from the ongoing separation in the KM curves (see Appendix figure 4). Gazyvaro has also demonstrated longer term treatment effect versus rituximab in the treatment of chronic lymphocytic leukaemia (CLL) as there appears to be an ongoing treatment effect of Gazyvaro over rituximab after 6 months induction therapy in the CLL11 study with median follow up of 43 months, significantly beyond median PFS.<br><br>**Evidence for rituximab:** in addition to the PRIMA study (that investigated R maintenance versus observation only), long-term follow up from R-chemo induction studies in 1st line FL was identified from studies investigating R-chemo versus chemo induction therapy. These studies do not show evidence of a finite duration of treatment effect: Bachy et al. and Herold et al. report long-term follow up in R-chemo induction versus chemo with 8.4 years and up to 8.7 years of median follow up, respectively. These studies indicate that the hazard of progression is lower in the R-chemo arm compared the chemo arm until close to the end of the respective follow up period where estimates become unreliable due to the small numbers at risk (further details on these studies is summarised in the Appendix pp. 10-11). | |

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| | | | **Translation of long-term PFS benefit of R-chemo to G-chemo:** as acknowledged by the committee, Gazyvaro's mechanism of action is similar to that of rituximab in terms of targeting CD20, with Gazyvaro demonstrating enhanced antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis and direct cell death while reducing complement dependent cytotoxicity. Translation of the long-term experience with R-chemo in improving long-term PFS to improved long-term PFS with G-chemo over R-chemo is supported by minimal residual disease (MRD) data after end of induction (EOI) in GALLIUM: MRD response was significantly higher in the G-chemo arm than the R-chemo arm (92% vs 85%; p=0.0041) (Pott C et al., 2016). MRD negativity at EOI was also associated with longer subsequent PFS, with a hazard ratio of 0.35 (95% CI, 0.22, 0.56; p<0.0001) in both treatment arms, indicating that induction treatment contributed to the observed improvement in PFS for G-chemo+G versus R-chemo+R. | |
| 3. | Consultee | Roche Products Ltd | **Non-proportional hazards assumption**<br>Uncertainties on the long-term treatment effect may be addressed using a non-proportional hazards assumption. The GALLIUM trial did not show evidence of a non-proportional hazard over the observation period. Visual inspection of KM curves, especially close to the end of the follow up period, where few patients are at risk, are unreliable to draw these conclusions. The committee also suggested using independent curves for the arms to extrapolate PFS – i.e. assuming a non-proportional hazard. Implementing this approach (see Appendix tables 5 and 6) led to more conservative estimates in terms of PFS gain of G-chemo+G over R-chemo+R than a proportional hazards assumption: the independently fitted models resulted in a long-term decline in | The FAD outlines the committee's considerations about proportional hazards assumptions (see FAD section 3.17) |

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| | | | treatment effect compared to a proportional hazards model. Therefore, instead of using a proportional hazard with an artificial restriction on duration of effect, it seemed more appropriate to use a non-proportional hazard assumption for the long-term extrapolation, fitted to the GALLIUM data and without the need to introduce specific duration of effect assumption. A non-proportional hazard assumption was therefore incorporated in the revised base case. | |
| 4. | Consultee | Roche Products Ltd | **Choice of PFS extrapolation function**<br>The committee's preferred extrapolation of PFS using a Weibull function is implausible as it assumes increasing risk of progression with time spent free of progression.<br>The committee's (and ERG's) preferred PFS extrapolation function was a Weibull function. This approach predicted an increased hazard of progression over time. However, long-term follow up data on R-chemo treated cohorts show in general a long-term decline in the hazard of progression after initial treatment (e.g. in the cohorts of Bachy et al., Herold et al. and the long-term LymphoCare observational cohort in Casulo). This means that patients' risk to progress declines the longer they stay in PFS. Such an assumption was also incorporated in a previous appraisal of rituximab induction therapy, TA226, by extrapolating with Log-normal functions. The Weibull function is therefore implausible and either the Exponential (for proportional hazards) or the Log-Logistic functions (proportional or non-proportional hazards) are more plausible choices. | The FAD outlines the committee's considerations about progression-free survival extrapolations (see FAD section 3.18) |
| 5. | Consultee | Roche Products Ltd | **Time to next anti-lymphoma treatment (TTNALT)**<br>The committee's suggestion that the time to next anti-lymphoma treatment may be a more meaningful endpoint for patients would imply that an economic analysis based on PFS is a conservative approach.<br>Comparing PFS with TTNALT from GALLIUM indicates that: | The FAD outlines the committee's considerations about meaningful outcomes (see FAD section 3.13) |

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| | | | - TTNALT HR of 0.68 (95% CI: 0.52, 0.90, FL ITT) corresponds to the lower PFS-INV HR rather than the numerically higher PFS-IRC, i.e. the treatment effect of G-chemo+G over R-chemo+R by TTNALT is higher than by PFS-IRC (the committee's preference) .<br>- While TTNALT follows progression (PFS) closely for Early PD, treatment seems increasingly delayed for later progression, with a trend of a longer delay in the Gazyvaro arm (see Appendix figure 7).<br>Combining both observations suggests that the difference in mean time to next treatment is larger than the difference in time in PFS alone. This would result in a lower ICER in the economic analysis due to further delaying treatments than predicted by PFS and increasing the time spent treatment free before next treatment as demonstrated in an exploratory analysis (Appendix p. 25, p. 32 table 20). | |
| | Consultee | Roche Products Ltd | **Investigator versus independent review committee (IRC) assessed progression**<br>Although the committee recognised the merits of both, investigator- and IRC- assessed progression, the preferred choice to assess cost effectiveness was IRC as this resulted in a more conservative estimate of treatment effect and cost-effectiveness. On the other hand the committee expressed the view that time to next treatment – TTNALT discussed in 5. [sic.] – may be a more relevant endpoint. As the hazard ratio for TTNALT agrees with the hazard ratio of progressions assessed by the investigator, this would suggest that investigator- assessed PFS is more relevant in determining progression and the need for further treatment. Our revised base case is however based on IRC- assessed PFS and is therefore conservative. | The FAD outlines the committee's considerations about independent versus investigator-led assessment of progression-free survival (see FAD section 3.11) |
| 6. | Consultee | Roche Products Ltd | **Overall survival**<br>The committee raised concerns on the OS predictions of the model based on PFS, as trial based determination of OS benefits of first line treatments in FL is very challenging due to the indolent nature of the disease. | The FAD outlines the committee's considerations about the evidence for overall survival (see FAD |

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| | | | However, the predictions of the model and the trend observed in GALLIUM OS data (HR 0.82, 95% CI: 0.54-1.22, p=0.32) are consistent with the OS benefit of Gazyvaro in the rituximab refractory FL setting and the well-established OS benefit of rituximab in the first line induction setting: According to a meta-analysis of Schulz et al. a PFS HR of 0.58 (95% CI: 0.50-0.68) was associated with an OS HR of 0.63 (95% CI 0.51-0.79) for R-chemo versus chemo induction. More recently, the individual patient data meta-analysis of by Vidal et al. also established the OS benefit of rituximab maintenance after induction over observation in the relapsed setting. | sections 3.12 and 3.20) |
| 7. | Consultee | Roche Products Ltd | **Quality of Life for progressed disease**<br>The committee's preferred utility values for post-progression were based on the observed values in the GALLIUM study. However, EQ-5D data in GALLIUM was collected only during one assessment visit after progression. Therefore, this data cannot be used to represent the overall health related quality of life (HRQoL) of patients in the progression state as it is represented in the model. For example, utility in PFS (after maintenance) was 0.818 and after late progression 0.814 and early progression 0.776. HRQoL after progression (PD) is likely to be lower than the observed values in GALLIUM used as the committee's preferred assumptions as utility post-progression was collected only during one assessment visit after progression. As FL may progress slowly towards symptomatic disease requiring further treatment (see discussion on time-to-next-anti-lymphoma-treatment), utility decline is expected to be delayed. In light of these limitations, we therefore propose to reconsider using lower average values in PD (0.62 for early progression and 0.77 for late progression) as discussed in the Appendix (Section HRQoL). In particular, for patients progressing early where the life expectancy | The FAD outlines the committee's considerations about health related quality of life in the progressed-disease state (see FAD section 3.21) |

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| | | | is considerably lower than for patients progressing late, an associated significant decline in utility is expected.<br><br>In addition to revised PD utility assumptions, GALLIUM utility estimates per arm for PFS were implemented as suggested by the ERG and to be consistent with the implementation of pre- and post-progression mortality rate estimates per arm preferred by the committee. | |
| 8. | Consultee | Roche Products Ltd | **Model structure**<br>Whereas the ERG seemed to find the overall model structure appropriate, the committee expressed concerns that the structure did not accurately reflect the natural history of the disease:<br><br>1) the committee recalled that disease progression is assessed more frequently in clinical trials than in practice;<br>2) the committee was of the impression that the model did not explicitly model response to determine whether people were offered maintenance therapy;<br>3) the model did not account for the time between disease progression and subsequent treatments and<br>4) the model structure may not accurately reflect patients' experience during disease progression.<br><br>However, these points could be addressed within the existing structure:<br>**Timing of clinical assessments:** the model used the costs of follow up visits according to clinical practice, rather than the trial based frequency. To our knowledge there was no | The FAD outlines the committee's considerations about overall model structure and early- and late-progressing disease states (see FAD section 3.16). |

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| | | | systematic way to adjust for any difference in the timing of progression due to different timing of assessments in clinical practice. However, given the indolent nature of the disease it is unlikely to have affected the investigator assessed PFS results compared to clinical practice.<br><br>**Modelling of response:** it was not necessary to model response in the model explicitly as patients in both arms were eligible to receive maintenance if they responded to the respective induction therapy as per study protocol, in agreement with clinical practice. Therefore, the accurate proportion of patients receiving maintenance was given by the time-to-off-treatment observed in GALLIUM. For example, patient who did not receive maintenance would be in the off-treatment health state in PFS (if they had not progressed) or in the Early PD state post-progression.<br><br>**Timing of subsequent treatments:** based on the observed time-to-next-treatment curve (see Appendix figure 7) there appears to be a time delay between progression and next treatment mainly for late progression. However, the difference in the time-to-next-treatment between the arms is larger than the difference in PFS. As the model assumes the same post progression costs, savings in later line treatment costs in the G-chemo+G arm versus the R-chemo+R arms are mainly drivel by the delay in treatment costs. Therefore using PFS to determine timing of next treatment is conservative from the point of the economic analysis.<br><br>**Patients' experience during disease progression:** in the indolent disease setting, there are limited long-term follow up data sets that would allow more accurate modelling, | Comment noted<br><br>Comment noted<br><br>The FAD has been amended to outline the committee's considerations about progression-free survival versus time-to-next-treatment (see FAD section 3.13). The FAD also outlines the committee's considerations about the incorporation of subsequent |

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| | | | especially on HRQoL. Alternative approaches to modelling post-progression costs and outcomes after 1st line treatment include complex patient level simulation. However, this approach also had to rely on literature HRQoL values; requires specific assumptions on a treatment pathway that may not be reflective of actual clinical practice and requires appropriate data for 2nd line treatment outcomes to reflect current clinical practice. | treatment costs (see FAD section 3.26).<br><br>The FAD has been amended to outline the committee's considerations about early and late disease progression states (see FAD sections 3.16 and 3.21) and the incorporation of subsequent treatment costs (see FAD section 3.26). |
| 9. | Consultee | Roche Products Ltd | **Resource use**<br>The committee's comments on the resource use were addressed in the revised economic analysis presented in the Appendix:<br>Vial sharing was implemented, assuming vial sharing for rituximab.<br>Administration costs for IV rituximab and SC rituximab were implemented according to national chemotherapy list administration codes and using respective NHS reference costs – given that rituximab is a well-established standard of care these unit costs should be representative.<br>Further scenario analyses are presented to capture the influence of assumption on subsequent treatment costs on the ICER. In addition TTNALT data suggest the model approach based on PFS is conservative in estimating the reduction in future treatment | The FAD outlines the committee's considerations about vial sharing and administration costs (see FAD sections 3.22 and 3.24). The FAD also outlines considerations about modelling progression-free survival versus time-to-next-treatment (see section 3.13). |

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| | | | costs due to delayed 2nd and higher lines of treatment on G-chemo+G versus R-chemo+R. | |
| 10. | Consultee | Roche Products Ltd | **Biosimilar rituximab comparison**<br>The preferred assumption to base the cost-effectiveness results on a comparison with BS net prices assumes that the displaced technology for IV rituximab is 100% biosimilar. This assumption is unrealistic as data from NHS England shows (https://www.england.nhs.uk/wp-content/uploads/2017/09/biosimilar-medicines-commissioning-framework.pdf), BS uptake only reaches 80% several years after market entry (e.g. infliximab), with shares after 1-2 years below 60% (etanercept). Considering the recent availability of biosimilar rituximab, scenarios considering realistic market shares should be considered for decision making. | The FAD outlines the committee's considerations about the uptake of biosimilar rituximab (see FAD section 3.25) |
| 11. | Consultee | Roche Products Ltd | **Innovation**<br>Whereas the committee considered Gazyvaro not to be innovative, we would like to point out that Gazyvaro is the only new licensed treatment in 1st line follicular lymphoma since the introduction of rituximab in 2006. Furthermore, the need to provide new treatment options in this patient population was recognised by the EMA by granting orphan status to Gazyvaro in FL and the FDA by granting priority review to the 1st line FL indication. | The FAD outlines the committee's considerations about whether obinutuzumab is innovative (see FAD section 3.30) |
| 12. | Consultee | Lymphoma Association | We are concerned that this recommendation will reduce treatment options for a patient population where the length and durability of remission, plus time to next line of | The committee acknowledged the |

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| | | | treatment, and quality of life, are the major considerations. As they have an indolent/chronic and incurable cancer that follows a remitting/relapsing course, follicular lymphoma patients are aware that each period of remission will be shorter than the previous one. Given that one in five patients will face progression of their disease within two years of their first line treatment, then length of remission after first line treatment is an important factor for a significant proportion of patients, if not all of them. | importance of time-to next-treatment for patients (see FAD section 3.13). |
| 13. | Consultee | Lymphoma Association | Regarding side effects, many patients, particularly fitter ones, may prefer the option to balance a limited increase in side effects against a longer period of remission. | The committee considered evidence from the GALLIUM trial about adverse events. The views of clinical experts and patient/carer representatives were considered by the committee when formulating its recommendations. The FAD outlines the committee's considerations about safety results (see FAD section 3.15). |
| 14. | Public | Web comment | The PFS benefit of 30% is significant for all patients as clinically their concern is time to next treatment. This is significant for younger patients who want to delay 2nd treatments as long as possible. NICE has also previously approved single agent rituximab for asymptomatic advanced patients in order to delay time to next treatment based on economic benefit in older patients. This would be in concordance with a benefit in older people having obinutuzumab first line and an additional 30% PFS benefit and having non-lymphoma mortality prior to need for next treatment. | The views of clinical experts and patient/carer representatives were considered by the committee when formulating its recommendations. The committee also considered various estimations of progression-free survival (see section 3.18) and |

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| | | | | the similarities in mechanisms of rituximab and obinutuzumab (see section 3.19). The committee acknowledged the importance of time-to next-treatment for patients (see section 3.13). |
| 15. | Consultee | NHS England | Roche wishes to narrow the use of obinutuzumab in combination with chemotherapy to the subgroup of patients scoring 2 or more using the Follicular Lymphoma International Prognostic Index (FLIPI). The manufacturer states that the trial was not designed to explore differences in outcome according to FLIPI subgroups (albeit a stratified outcome), yet then proceeds to use the subgroup data in this appraisal as a way of seeking an optimised NICE recommendation. A lack of follow-up duration in the trial in the better prognosis FLIPI 0-1 group could easily explain the apparent lack of difference so far between obinutuzumab and rituximab. NHS England is wary of such retrospective analyses being used in this way, just as it would not accept retrospective subgroup analyses which favoured seeking recommendations of obinutuzumab to women (HR 0.49 in the NEJM paper) but not men (HR 0.82) or to those without B symptoms (HR 0.57) but not those with B symptoms (HR 0.86). | The FAD has been amended to consider the higher-risk FLIPI subgroup (see FAD section 3.9) |
| 16. | Consultee | NHS England | NHS England also notes that Roche states in its post-ACD submission that 'FLIPI does not yet have a role in determining treatment selection since no differential benefit for | The FAD has been amended to |

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| | | | currently available therapies has been demonstrated on FLIPI score'. It therefore seems strange for Roche then to retrospectively use a scoring system that is validated for prognosis but not for treatment selection. | consider the higher-risk FLIPI subgroup (see FAD section 3.9) |
| 17. | Consultee | NHS England | NHS England notes that Roche has used incorrect figures for the HRG chemotherapy administration tariffs. Use of the correct figures may not make a large difference to the ICER but would increase the ICER for obinutuzumab. Rituximab infusion times can be shortened very significantly (there is published evidence to shorten the durations of infusion stated in the rituximab SPC) whereas those of obinutuzumab will remain significantly longer and in keeping with the SPC as obinutuzumab causes more infusion reactions and thus infusion times will remain prolonged. The HRG administration cost of R-CVP/R-CHOP for the first cycle would be £449 and for subsequent cycles would be £299. The cost of B-R for the first cycle would be £748 and for subsequent cycles would be £598. The tariff cost of subcutaneous rituximab is £150. The cost of Ob-CVP/Ob-CHOP for the first cycle would be £1047 and then for subsequent cycles would be £449. The tariff cost of B-Ob for the first cycle would be £1352 and for subsequent cycles would be £748. The cost of maintenance Ob would be £449. | The FAD has been amended to consider the change in administration costs (see FAD section 3.24). The committee also heard from the ERG about the implications of updating the administration costs. |
| 18. | Consultee | NHS England | Roche's base case uses the comparator of its own branded rituximab and Roche provides a scenario analysis that it regards as being unlikely in which there is an 80% uptake of biosimilar rituximab which carries a 60% discount. Uptake in NHS England of biosimilar rituximab is currently rapid and faster than anticipated and much faster than previous biosimilars. Use of biosimilar rituximab is subject to a CQUIN. NHS England expects a [redacted] uptake of biosimilar rituximab to be in place by Q3/2018 and [redacted]. | The FAD has been amended to consider the uptake of biosimilars (see FAD section 3.25). The ERG also provided exploratory analyses to inform the committee about the price of available biosimilars. |

**Obinutuzumab for untreated advanced follicular lymphoma [ID1020]**

NICE National Institute for Health and Care Excellence

**Consultation on the appraisal consultation document – deadline for comments** 5pm on 5 October 2017

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| | Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.<br><br>The Appraisal Committee is interested in receiving comments on the following:<br>• has all of the relevant evidence been taken into account?<br>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?<br>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?<br><br>NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:<br>• could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;<br>• could have any adverse impact on people with a particular disability or disabilities.<br><br>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.** |
| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | **Lymphoma Association** |
| **Disclosure**<br>Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | **n/a** |
| **Name of commentator person completing form:** | [redacted] |

| Comment number | Comments |
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# Obinutuzumab for untreated advanced follicular lymphoma [ID1020]

NICE National Institute for Health and Care Excellence

**Consultation on the appraisal consultation document – deadline for comments** 5pm on 5 October 2017

| | Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
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| Example 1 | We are concerned that this recommendation may imply that …….. |
| 1 | We are concerned that this recommendation will reduce treatment options for a patient population where the length and durability of remission, plus time to next line of treatment, and quality of life, are the major considerations. As they have an indolent/chronic and incurable cancer that follows a remitting/relapsing course, follicular lymphoma patients are aware that each period of remission will be shorter than the previous one. Given that one in five patients will face progression of their disease within two years of their first line treatment, then length of remission after first line treatment is an important factor for a significant proportion of patients, if not all of them.<br>. |
| 2 | Regarding side effects, many patients, particularly fitter ones, may prefer the option to balance a limited increase in side effects against a longer period of remission. |
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Insert extra rows as needed

**Checklist for submitting comments**

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

**Note:** We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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

**Obinutuzumab for untreated advanced follicular lymphoma [ID1020]**

NICE National Institute for Health and Care Excellence

**Consultation on the appraisal consultation document – deadline for comments** 5pm on 5 October 2017

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| NICE, its officers or advisory committees. |

**Obinutuzumab for untreated advanced follicular lymphoma [ID1020]**

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| | Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.<br><br>The Appraisal Committee is interested in receiving comments on the following:<br>• has all of the relevant evidence been taken into account?<br>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?<br>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?<br><br>NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:<br>• could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;<br>• could have any adverse impact on people with a particular disability or disabilities.<br><br>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.** |
| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | **Roche Products Ltd** referred to as Roche |
| **Disclosure**<br>Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | N/A |
| **Name of commentator person completing form:** | [redacted] |

| **Comment number** | **Comments** |
|---|---|

# Obinutuzumab for untreated advanced follicular lymphoma [ID1020]

NICE National Institute for Health and Care Excellence

**Consultation on the appraisal consultation document – deadline for comments** 5pm on 5 October 2017

| | Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| | Roche are disappointed with the provisional negative recommendation, although we do recognise the uncertainty presented to the committee through this appraisal due to the indolent nature of follicular lymphoma, where the availability of long-term follow up data presents a challenge.<br><br>Based on our reading of the ACD, the key concerns underpinning the draft negative recommendation are the use of the biosimilar (BS) rituximab net price in the cost-effectiveness analysis and the uncertainty around the following points:<br>• Assumption regarding the duration of treatment effect<br>• Extrapolation of progression free survival<br>• Overall Survival (OS) modelling<br>• Utility assumptions in progressed disease<br>• Model assumptions on subsequent treatment costs<br><br>Our full response is provided below to discuss the points raised in the ACD and we propose alternative assumptions in the revised base case provided as an Appendix (Section Cost-effectiveness).<br>In addition, we propose to consider a revised base case population of patients at higher risk of progression, as defined by Follicular Lymphoma International Prognostic Index (FLIPI) score of 2 or higher (intermediate and high FLIPI) only. Further details are discussed in point 1 below.<br><br>A revised base case is provided in the Appendix (Cost-effectiveness results table 15), demonstrating ICERs in the cost effective range, including in scenarios with biosimilar rituximab pricing and under more realistic biosimilar uptake assumptions. |
| 1 | **Revised Base Case Population**<br>The revised base case considers patients at higher risk of progression, as defined by Follicular Lymphoma International Prognostic Index (FLIPI) score of 2 or higher (intermediate and high FLIPI) only.<br><br>The patient population in the company submission (CS) in May 2017 was all symptomatic advanced follicular lymphoma (FL) patients requiring treatment with immunochemotherapy (rituximab or Gazyvaro with chemotherapy) as per the GALLIUM study. This included patients with different risk of relapse according to their FLIPI rating. Evidence in the submission is based on the GALLIUM study in which randomisation was stratified by FLIPI rating. The trial was not designed however to explore differences in outcomes according to FLIPI subgroups, and health economic analyses in the |

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| | submission were conducted on the FL intention to treat (ITT) group as a whole.<br>Subsequently the EMA has required the inclusion of a statement in Section 4.4 of the Gazyvaro<br><br>Summary of Product Characteristics on the benefit/risk ratio of obinutuzumab in patients with a low FLIPI risk rating (Gazyvaro Summary of Product Characteristics):<br>'Based on a subgroup analysis in previously untreated follicular lymphoma, the efficacy in FLIPI low risk (0-1) patients are currently inconclusive (see section 5.1). A therapy choice for these patients should carefully consider the overall safety profile of Gazyvaro plus chemotherapy and the patient-specific situation.'<br><br>Patients with a low FLIPI score comprised 21% of patients in the GALLIUM ITT population and only 17.8% of the total PFS events. The hazard ratio for G-chemo+G vs R-chemo+R investigator-assessed PFS in this subgroup was 1.11 (95% CI: 0.62-1.99) (September 2016 cut-off date). In view of the uncertainty of benefit in low FLIPI patients and the corresponding statement in the marketing authorisation, Roche believes it would be prudent to consider the eligible patient population for Gazyvaro as first line therapy in FL to be those with intermediate or high FLIPI score (higher risk group). These patients are at greater risk of relapse and have the highest clinical unmet need as patients have a significantly lower duration of response to subsequent treatments (1) and early relapse is associated with a significantly higher mortality (2). In this group, the benefit of Gazyvaro was clearly demonstrated by superior and consistent PFS over rituximab. This is evidenced by the increased number of events, consistent hazard ratios between the groups and narrower confidence intervals around the estimates. |
| 2 | **Duration of treatment effect**<br>The committee's preferred assumption of no progression free survival (PFS) treatment effect beyond the GALLIUM study follow up period of 5 years is implausible for anti-CD20 treatments.<br><br>Due to the indolent nature of FL, long-term follow-up data reaching median PFS is challenging as this is expected to be around 6 years on the current standard of care. For Gazyvaro, data in 1$^{st}$ line FL is limited to the maximum available follow up period of up to 5 years in the GALLIUM study (September 2016 clinical cut-off date). However, based on the experience with Gazyvaro in other settings and the common CD20 target with rituximab there is no evidence in the literature for a finite treatment effect:<br><br>*Evidence for Gazyvaro*: Gazyvaro demonstrates an ongoing effect in GALLIUM after treatment completion (maintenance) as evident from the ongoing separation in the KM curves (see Appendix figure 4). Gazyvaro has also demonstrated longer term treatment effect versus rituximab in the treatment of chronic lymphocytic leukaemia (CLL) as there appears to be an ongoing treatment effect of Gazyvaro over rituximab after 6 months induction therapy in the CLL11 study (3) with median |

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| | follow up of 43 months, significantly beyond median PFS.<br><br>*Evidence for rituximab*: in addition to the PRIMA study (that investigated R maintenance versus observation only), long-term follow up from R-chemo induction studies in 1st line FL was identified from studies investigating R-chemo versus chemo induction therapy. These studies do not show evidence of a finite duration of treatment effect: Bachy et al. (4) and Herold et al. (5) report long-term follow up in R-chemo induction versus chemo with 8.4 years and up to 8.7 years of median follow up, respectively. These studies indicate that the hazard of progression is lower in the R-chemo arm compared the chemo arm until close to the end of the respective follow up period where estimates become unreliable due to the small numbers at risk (further details on these studies is summarised in the Appendix pp. 10-11).<br><br>*Translation of long-term PFS benefit of R-chemo to G-chemo*: as acknowledged by the committee, Gazyvaro's mechanism of action is similar to that of rituximab in terms of targeting CD20, with Gazyvaro demonstrating enhanced antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis and direct cell death while reducing complement dependent cytotoxicity (6, 7). Translation of the long-term experience with R-chemo in improving long-term PFS to improved long-term PFS with G-chemo over R-chemo is supported by minimal residual disease (MRD) data after end of induction (EOI) in GALLIUM: MRD response was significantly higher in the G-chemo arm than the R-chemo arm (92% vs 85%; p=0.0041) (Pott C et al., 2016). MRD negativity at EOI was also associated with longer subsequent PFS, with a hazard ratio of 0.35 (95% CI, 0.22, 0.56; p<0.0001) in both treatment arms, indicating that induction treatment contributed to the observed improvement in PFS for G-chemo+G versus R-chemo+R. |
| 3 | **Non-proportional hazards assumption**<br>Uncertainties on the long-term treatment effect may be addressed using a non-proportional hazards assumption.<br>The GALLIUM trial did not show evidence of a non-proportional hazard over the observation period. Visual inspection of KM curves, especially close to the end of the follow up period, where few patients are at risk, are unreliable to draw these conclusions (8). The committee also suggested using independent curves for the arms to extrapolate PFS – i.e. assuming a non-proportional hazard. Implementing this approach (see Appendix tables 5 and 6) led to more conservative estimates in terms of PFS gain of G-chemo+G over R-chemo+R than a proportional hazards assumption: the independently fitted models resulted in a long-term decline in treatment effect compared to a proportional hazards model. Therefore, instead of using a proportional hazard with an artificial restriction on duration of effect, it seemed more appropriate to use a non-proportional hazard assumption for the long-term extrapolation, fitted to the GALLIUM data and without the need to introduce specific duration of effect assumption. A non-proportional hazard assumption was therefore |

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| | incorporated in the revised base case. |
| 4 | **Choice of PFS extrapolation function**<br>The committee's preferred extrapolation of PFS using a Weibull function is implausible as it assumes increasing risk of progression with time spent free of progression.<br>The committee's (and ERG's) preferred PFS extrapolation function was a Weibull function. This approach predicted an increased hazard of progression over time. However, long-term follow up data on R-chemo treated cohorts show in general a long-term decline in the hazard of progression after initial treatment (e.g. in the cohorts of Bachy et al. (2), Herold et al. (3) and the long-term LymphoCare observational cohort in Casulo (2)). This means that patients' risk to progress declines the longer they stay in PFS. Such an assumption was also incorporated in a previous appraisal of rituximab induction therapy, TA226, by extrapolating with Log-normal functions (9). The Weibull function is therefore implausible and either the Exponential (for proportional hazards) or the Log-Logistic functions (proportional or non-proportional hazards) are more plausible choices. |
| 5 | **Time to next anti-lymphoma treatment (TTNALT)**<br>The committee's suggestion that the time to next anti-lymphoma treatment may be a more meaningful endpoint for patients would imply that an economic analysis based on PFS is a conservative approach.<br>Comparing PFS with TTNALT from GALLIUM indicates that:<br>- TTNALT HR of 0.68 (95% CI: 0.52, 0.90, FL ITT) corresponds to the lower PFS-INV HR rather than the numerically higher PFS-IRC, i.e. the treatment effect of G-chemo+G over R-chemo+R by TTNALT is higher than by PFS-IRC (the committee's preference) .<br>- While TTNALT follows progression (PFS) closely for Early PD, treatment seems increasingly delayed for later progression, with a trend of a longer delay in the Gazyvaro arm (see Appendix figure 7).<br>Combining both observations suggests that the difference in mean time to next treatment is larger than the difference in time in PFS alone. This would result in a lower ICER in the economic analysis due to further delaying treatments than predicted by PFS and increasing the time spent treatment free before next treatment as demonstrated in an exploratory analysis (Appendix p. 25, p. 32 table 20). |
| 6 | **Investigator versus independent review committee (IRC) assessed progression**<br>Although the committee recognised the merits of both, investigator- and IRC- assessed progression, the preferred choice to assess cost effectiveness was IRC as this resulted in a more conservative estimate of treatment effect and cost-effectiveness. On the other hand the committee expressed the view that time to next treatment – TTNALT discussed in 5. – may be a more relevant endpoint. As the hazard ratio for TTNALT agrees with the hazard ratio of progressions assessed by the investigator, this would suggest that investigator- assessed PFS is more relevant in determining progression and the need for further treatment. Our revised base case is however based on IRC- assessed PFS and |

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| | is therefore conservative. |
| 7 | **Overall survival**<br>The committee raised concerns on the OS predictions of the model based on PFS, as trial based determination of OS benefits of first line treatments in FL is very challenging due to the indolent nature of the disease.<br>However, the predictions of the model and the trend observed in GALLIUM OS data (HR 0.82, 95% CI: 0.54-1.22, p=0.32) are consistent with the OS benefit of Gazyvaro in the rituximab refractory FL setting (9) and the well-established OS benefit of rituximab in the first line induction setting: According to a meta-analysis of Schulz et al. (10) a PFS HR of 0.58 (95% CI: 0.50-0.68) was associated with an OS HR of 0.63 (95% CI 0.51-0.79) for R-chemo versus chemo induction. More recently, the individual patient data meta-analysis of by Vidal et al. (11) also established the OS benefit of rituximab maintenance after induction over observation in the relapsed setting. |
| 8 | **Quality of Life for progressed disease**<br>The committee's preferred utility values for post-progression were based on the observed values in the GALLIUM study. However, EQ-5D data in GALLIUM was collected only during one assessment visit after progression. Therefore, this data cannot be used to represent the overall health related quality of life (HRQoL) of patients in the progression state as it is represented in the model. For example, utility in PFS (after maintenance) was 0.818 and after late progression 0.814 and early progression 0.776. HRQoL after progression (PD) is likely to be lower than the observed values in GALLIUM used as the committee's preferred assumptions as utility post-progression was collected only during one assessment visit after progression. As FL may progress slowly towards symptomatic disease requiring further treatment (see discussion on time-to-next-anti-lymphoma-treatment), utility decline is expected to be delayed. In light of these limitations, we therefore propose to reconsider using lower average values in PD (0.62 for early progression and 0.77 for late progression) as discussed in the Appendix (Section HRQoL). In particular, for patients progressing early where the life expectancy is considerably lower than for patients progressing late, an associated significant decline in utility is expected.<br><br>In addition to revised PD utility assumptions, GALLIUM utility estimates per arm for PFS were implemented as suggested by the ERG and to be consistent with the implementation of pre- and post-progression mortality rate estimates per arm preferred by the committee. |
| 9 | **Model structure**<br>Whereas the ERG seemed to find the overall model structure appropriate, the committee expressed concerns that the structure did not accurately reflect the natural history of the disease:<br><br>1. the committee recalled that disease progression is assessed more frequently in clinical trials |

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| | than in practice;<br>2. the committee was of the impression that the model did not explicitly model response to determine whether people were offered maintenance therapy;<br>3. the model did not account for the time between disease progression and subsequent treatments and<br>4. the model structure may not accurately reflect patients' experience during disease progression.<br><br>However, these points could be addressed within the existing structure:<br>1. Timing of clinical assessments: the model used the costs of follow up visits according to clinical practice, rather than the trial based frequency. To our knowledge there was no systematic way to adjust for any difference in the timing of progression due to different timing of assessments in clinical practice. However, given the indolent nature of the disease it is unlikely to have affected the investigator assessed PFS results compared to clinical practice.<br>2. Modelling of response: it was not necessary to model response in the model explicitly as patients in both arms were eligible to receive maintenance if they responded to the respective induction therapy as per study protocol, in agreement with clinical practice. Therefore, the accurate proportion of patients receiving maintenance was given by the time-to-off-treatment observed in GALLIUM. For example, patient who did not receive maintenance would be in the off-treatment health state in PFS (if they had not progressed) or in the Early PD state post-progression.<br>3. Timing of subsequent treatments: based on the observed time-to-next-treatment curve (see Appendix figure 7) there appears to be a time delay between progression and next treatment mainly for late progression. However, the difference in the time-to-next-treatment between the arms is larger than the difference in PFS. As the model assumes the same post progression costs, savings in later line treatment costs in the G-chemo+G arm versus the R-chemo+R arms are mainly drivel by the delay in treatment costs. Therefore using PFS to determine timing of next treatment is conservative from the point of the economic analysis.<br>4. Patients' experience during disease progression: in the indolent disease setting, there are limited long-term follow up data sets that would allow more accurate modelling, especially on HRQoL. Alternative approaches to modelling post-progression costs and outcomes after 1st line treatment include complex patient level (7) simulation. However, this approach also had to rely on literature HRQoL values; requires specific assumptions on a treatment pathway that may not be reflective of actual clinical practice and requires appropriate data for 2nd line treatment outcomes to reflect current clinical practice. |
| 10 | **Resource use**<br>The committee's comments on the resource use were addressed in the revised economic analysis |

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| | presented in the Appendix:<br>1. Vial sharing was implemented, assuming vial sharing for rituximab.<br>2. Administration costs for IV rituximab and SC rituximab were implemented according to national chemotherapy list administration codes and using respective NHS reference costs – given that rituximab is a well-established standard of care these unit costs should be representative.<br>Further scenario analyses are presented to capture the influence of assumption on subsequent treatment costs on the ICER. In addition TTNALT data suggest the model approach based on PFS is conservative in estimating the reduction in future treatment costs due to delayed 2nd and higher lines of treatment on G-chemo+G versus R-chemo+R. |
| 11 | **Biosimilar rituximab comparison**<br>The preferred assumption to base the cost-effectiveness results on a comparison with BS net prices assumes that the displaced technology for IV rituximab is 100% biosimilar. This assumption is unrealistic as data from NHS England shows (https://www.england.nhs.uk/wp-content/uploads/2017/09/biosimilar-medicines-commissioning-framework.pdf), BS uptake only reaches 80% several years after market entry (e.g. infliximab), with shares after 1-2 years below 60% (etanercept). Considering the recent availability of biosimilar rituximab, scenarios considering realistic market shares should be considered for decision making. |
| 12 | **Innovation**<br>Whereas the committee considered Gazyvaro not to be innovative, we would like to point out that Gazyvaro is the only new licensed treatment in 1st line follicular lymphoma since the introduction of rituximab in 2006. Furthermore, the need to provide new treatment options in this patient population was recognised by the EMA by granting orphan status to Gazyvaro in FL and the FDA by granting priority review to the 1st line FL indication. |

Insert extra rows as needed

**Checklist for submitting comments**

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- Complete the disclosure about links with, or funding from, the tobacco industry.
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# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single technology appraisal

# Gazyvaro▼ (obinutuzumab) in combination with chemotherapy for the first-line treatment of patients with advanced follicular lymphoma

## Supporting Appendix to the

## ACD Response

## Roche Product Limited

**October 2017**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| ID1020 – Appendix to Roche ACD response [CIC] | 1.1 Errata p 31 in PAS results corrected | Yes | 10th October 2017 |

# Table of contents

# Clinical effectiveness

## *Patient population for Gazyvaro in first-line FL*

The patient population in the company submission in May 2017 was all symptomatic advanced follicular lymphoma (FL) patients requiring treatment with immunochemotherapy as per the GALLIUM study. This included patients with different risk of relapse according to their Follicular Lymphoma International Prognostic Index (FLIPI) rating. Evidence in the submission is based on the GALLIUM study in which randomisation was stratified by FLIPI rating. The trial was not powered however to explore differences in outcomes according to FLIPI subgroups, and health economic analyses in the submission were conducted on the FL ITT group as a whole.

Subsequently, the EMA has required the inclusion of a statement in Section 4.4 of the Gazyvaro Summary of Product Characteristics on the benefit/risk ratio of obinutuzumab in patients with a low FLIPI risk rating:

*'Based on a subgroup analysis in previously untreated follicular lymphoma, the efficacy in FLIPI low risk (0-1) patients is currently inconclusive (see section 5.1). A therapy choice for these patients should carefully consider the overall safety profile of Gazyvaro plus chemotherapy and the patient-specific situation.'*

Patients with a low FLIPI score comprised 21% of patients in the GALLIUM ITT population. The hazard ratio for G-chemo+G vs R-chemo+R investigator-assessed PFS in this subgroup was 1.11 (95% CI: 0.62-1.99) (September 2016 cut-off date) (Figure 1). This was supported by the independent review committee (IRC)-assessed PFS analysis (HR 1.17 [0.60, 2.31]) (Figure 2). A summary of the investigator- and IRC-assessed PFS hazard ratios by FLIPI subgroup is presented in Table 1.

**Figure 1: Investigator-assessed PFS by FLIPI (September 2016 data cut-off)**

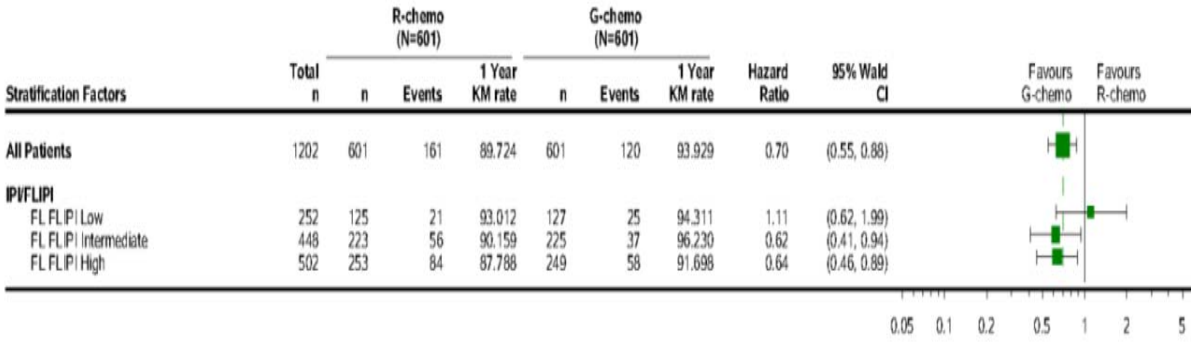
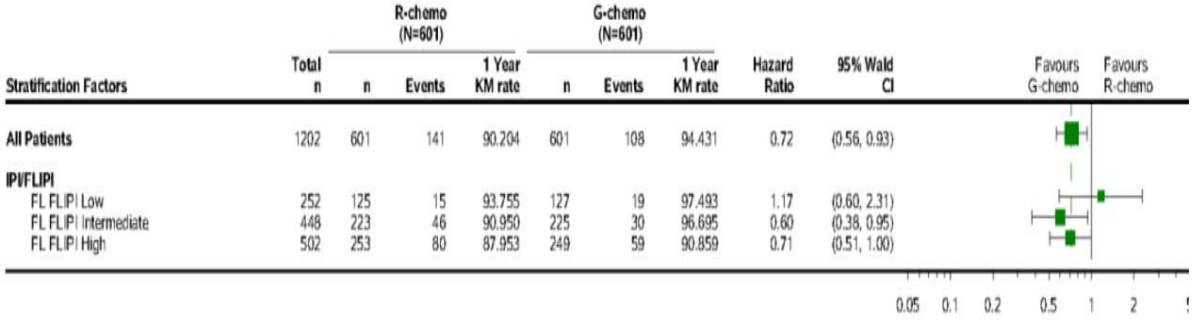


**Figure 2: IRC-assessed PFS by FLIPI**




As expected, the number of PFS events recorded in patients at lower risk of relapse over the GALLIUM follow up period was small, comprising only 17.8% of the total PFS events. The difference in events was therefore more susceptible to chance differences in baseline characteristics, and the study was not powered to compare outcomes according to FLIPI subgroup.

In view of the uncertainty of benefit in low FLIPI patients and the corresponding statement in the marketing authorisation, Roche believes it would be prudent to consider the eligible patient population for Gazyvaro as first-line therapy in FL to be those with intermediate or high FLIPI score. These patients are at greater risk of relapse and have the highest clinical unmet need. Choice of first treatment is important, particularly in higher risk patients, as response to subsequent treatments is reduced both in quality and duration, even in the rituximab era (Alperovich A et al., 2016). In this higher risk group, the benefit of Gazyvaro was clearly demonstrated by superior and consistent PFS over rituximab. This is evidenced by the increased number of events, consistent hazard ratios between the groups and narrower confidence intervals around the estimates. This is irrespective of whether investigator-assessed or independent review committee-assessed PFS is taken as the endpoint (Table 1).

**Table 1: Summary of PFS by FLIPI subgroups**

| FLIPI, HR (95% CI) | Investigator-assessed PFS | IRC-assessed PFS |
|---|---|---|
| Low | 1.11<br>(0.62, 1.99) | 1.17<br>(0.60, 2.31) |
| Intermediate | 0.62<br>(0.41, 0.94) | 0.60<br>(0.38, 0.95) |
| High | 0.64<br>(0.46, 0.89) | 0.71<br>(0.51, 1.00) |

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| Higher risk (intermediate + high) | 0.62 (0.47, 0.80) | 0.67 (0.51, 0.88) |

FLIPI low, n=252; FLIPI intermediate, n=448; FLIPI high, n=50

A revised economic analysis based on the group of patients with intermediate or high risk FLIPI (excluding the low risk population) is presented below. Although the trial was not powered for these subgroups individually, excluding the low FLIPI group from the analysis resulted in sufficient PFS events to allow analysis for modelling purposes, such as PFS extrapolation and analysis of utilities with similar statistical uncertainty to the analyses presented based on the ITT population. The patient characteristics of this group are summarised in Table 2.

**Table 2: Summary of patient characteristics the higher risk(FL intermediate/high FLIPI) and ITT group**

| | **Higher risk FLIPI** | | **ITT population** | |
|---|---|---|---|---|
| | **R-chemo n=476** | **G-chemo n=474** | **R-chemo n=601** | **G-chemo n=601** |
| Mean age, years (SD) | 59.4 (12.4) | 59.9 (11.4) | 57.7 (12.2) | 58.2 (11.5) |
| Male, n (%) | 207 (43.5) | 219 (46.2) | 280 (46.6) | 283 (47.1) |
| Mean height, cm (SD) | 167.6 (9.5) | 167.6 (9.7) | 168.4 (10.1) | 168.3 (10.0) |
| Mean weight, kg (SD) | 74.1 (16.6) | 75.5 (17.0) | 75.2 (17.0) | 76.3 (17.9) |
| Mean body surface area, $m^2$ (SD) | 1.83 (0.2) | 1.84 (0.2) | 1.84 (0.2) | 1.86 (0.2) |
| Mean BMI, $kg/m^2$ (SD) | 26.2 (4.8) | 26.7 (4.9) | 26.4 (5.9) | 26.8 (5.3) |
| Race, n (%) | | | | |
| Caucasian | 377 (79.2) | 389 (82.1) | 481 (80.0) | 487 (81.0) |
| Black or African American | 0 | 1 (0.2) | 1 (0.2) | 3 (0.5) |
| Asian | 79 (16.6) | 75 (15.8) | 98 (16.3) | 100 (16.6) |
| American Indian or Alaska Native | 1 (0.2) | 0 | 1 (0.2) | 0 |
| Native Hawaiian/ Pacific islander | 0 | 1 (0.2) | 0 | 1 (0.2) |
| Multiple | 3 (0.6) | 0 | 3 (0.5) | 0 |
| Other | 16 (3.4) | 8 (1.7) | 17 (2.8) | 10 (1.7) |
| ECOG PS, n (%) | n=475 | n=473 | n=599 | n=600 |
| 0–1 | 453 (95.4) | 459 (97.0) | 576 (96.2) | 585 (97.5) |
| 2 | 22 (4.6) | 14 (3.0) | 23 (3.8) | 15 (2.5) |
| Ann Arbor Stage, n (%) | n=475 | n=471 | n=597 | n=598 |
| I | 7 (1.5) | 4 (0.8) | 8 (1.3) | 10 (1.7) |
| II | 20 (4.2) | 7 (1.5) | 44 (7.4) | 41 (6.9) |
| III | 168 (35.4) | 171 (36.3) | 209 (35.0) | 208 (34.8) |
| IV | 280 (58.9) | 289 (61.4) | 336 (56.3) | 339 (56.7) |
| Bone marrow involvement at BL, n/patients with data (%) | 259/473 (54.8) | 272/467 (58.2) | 295/598 (49.3) | 318/592 (53.7) |
| Extranodal involvement, n/patients with data (%) | 326/476 (68.5) | 329/474 (69.4) | 396/601 (65.9) | 392/601 (65.2) |
| Bulky disease at BL (6 cm threshold), n/patients with data (%) | 218/475 (45.9) | 192/473 (40.6) | 271/600 (45.2) | 255/600 (42.5) |
| Mean time from diagnosis to randomisation, months (range) | 7.89 (0.0–168.1) | 6.21 (0.2–121.6) | 7.28 (0.0–168.1) | 6.25 (0.1–121.6) |

A summary of GALLIUM efficacy in intermediate or high FLIPI patients in first-line FL patients is presented in Table 3 below.

**Table 3: Summary of key outcome results in higher risk FL patients (intermediate/high FLIPI)**

| **CCOD 10 September 2016** | | |
|---|---|---|
| **Efficacy Outcomes** | **R–chemo n=476** | **G–chemo n=474** |
| **PFS (Investigator-assessed) (primary efficacy endpoint as specified in the protocol)** | | |
| HR (95% CI); stratified p-value | 0.62 (0.47,0.80); p=0.0003 | |
| Event-free proportion at 3 years, % (95% CI) | 72.46 % (67.91, 76.48) | 81.71 % (77.64, 85.10) |
| Event-free proportion at 2 years, % (95% CI) | 79.22 % (75.18, 82.68) | 87.47 % (84.03, 90.21) |
| **PFS (IRC-assessed)** | | |
| HR (95% CI); stratified p-value* | 0.67(0.51, 0.88); p=0.0034 | |
| Event-free proportion at 3 years, % (95% CI) | 75.95 % (71.60, 79.73) | 83.20 % (79.23, 86.48) |
| Event-free proportion at 2 years, % (95% CI) | 79.79 % (75.77, 83.22) | 88.15 % (84.77, 90.82) |
| **End-of Induction Response (Investigator-assessed) - without PET** | | |
| Overall Response (CR/PR), n (%), | 407 (85.7%) | 416 (87.8%) |
| % difference (Δ) (95% CI)†; p-value‡ | 2.08 (-2.35, 6.51); p=0.2954 | |
| Complete Response (CR), n (%), | 109 (22.9%) | 88 (18.6%) |
| % difference (95% CI)†; p-value‡ | -4.38 (-9.65, 0.88); p= 0.1012 | |
| **OS** | | |
| Patients with event | 48 (10.1%) | 37 (7.8%) |
| HR (95% CI); stratified p-value | 0.76 (0.49-1.16); p=0.2022 | |
| **Duration of Response (Investigator-assessed)** | | |
| Patients with event | 122/448 (24.1%) | 82/445 (18.4%) |
| HR (95% CI) | 0.61 (0.46, 0.81) | |
| **TTNALT (Investigator-assessed)** | | |
| Patients with event | 104 (21.8%) | 67 (14.1%) |
| HR (95% CI); stratified | 0.61(0.45, 0.83); p=0.0017 | |

HR, Hazard ratio; PET, positron emission tomography; TTNALT, time to next anti-lymphoma treatment
*log-rank test; stratification factors were chemotherapy regimen (CHOP, CVP, or bendamustine) and FLIPI risk group (low, intermediate, high).
†Hauck-Anderson test
‡Chi-square test.

## *Use of the FLIPI score in clinical practice*

In patients with newly-diagnosed FL FLIPI is the most widely used clinical prognostic index (Casulo et al., 2017). Clinical practice guidelines for follicular lymphoma support the use of FLIPI as a prognostic tool and recommend that FLIPI should be recorded at diagnosis (Dreyling et al., 2016, McNamara et al., 2012). FLIPI does not yet have a role in determining treatment selection, since no differential benefit for currently available therapies has been demonstrated based on FLIPI score. Results of a sub-analysis of the GALLIUM trial support a new potential role for FLIPI to select higher risk patients for G-chemo+G therapy.

Choice of first treatment is important, particularly in higher risk patients, as response to subsequent treatments is reduced both in quality and duration. This has recently been confirmed in the era of rituximab therapy; median PFS for first, second- and third-line treatments have been reported as 4.8, 1.6, and 1 year respectively (Alperovich A et al., 2016).

The information on which FLIPI scoring is based is routinely collected in clinical practice and would not require additional tests to be performed.

**Table 4: FLIPI assessment criteria**

| **FLIPI** | | | | |
|---|---|---|---|---|
| **5 factors** | Age | <60 years vs ≥60 years | | |
| | Haemoglobin | ≥12g/dL vs <12g/dL | | |
| | Serum LDH | ≤ULN vs >ULN | | |
| | Ann-Arbor stage | I-II vs III-IV | | |
| | No. of nodal sites | ≤4 vs >4 | | |
| | | | | |
| **Risk group** | **No. of FLIPI factors** | **5-yr overall survival (%)** | **10-yr overall survival (%)** | **Relative risk** |
| Low/Good | 0–1 | 91 | 71 | 1 |
| Intermediate | 2 | 78 | 51 | 2.3 |
| High/Poor | ≥3 | 53 | 36 | 4.3 |

# Cost-effectiveness

To address uncertainties raised in the ACD, additional evidence and analysis based on a revised model was undertaken. The revised model inputs and assumptions were related to PFS extrapolation, validation of OS predictions, utilities and cost inputs.

## *Model structure*

No revision of the model structure (Figure 22 in the company submission) was undertaken. Whereas the ERG seemed to find the overall model structure appropriate, the committee expressed concerns that the structure did not accurately reflect the natural history of the disease:

1. The committee recalled that disease progression is assessed more frequently in clinical trials than in practice;
2. The committee was of the impression that the model did not explicitly model response to determine whether people were offered maintenance therapy;
3. The model did not account for the time between disease progression and subsequent treatments;
4. The model structure may not accurately reflect patients' experience during disease progression.

However, these points could be addressed within the existing structure:

1. **Timing of clinical assessments:** the model used the costs of follow up visits according to clinical practice, rather than the trial based frequency. To our knowledge there was no systematic way to adjust for any difference in the timing of progression due to different timing of assessments in clinical practice. However, given the indolent nature of the disease it is unlikely to have affected the investigator assessed PFS results compared to clinical practice.
2. **Modelling of response:** it was not necessary to explicitly model response as patients in both arms were eligible to receive maintenance if they responded to the respective induction therapy as per study protocol, in agreement with clinical practice. Therefore, the accurate proportion of patients receiving maintenance was given by the time-to-off-treatment observed in GALLIUM. For example, patient who did not receive maintenance would be in the off-treatment health state in PFS (if they progressed) or in the Early PD state post-progression.
3. **Timing of subsequent treatments:** based on the observed time-to-next-treatment curve (Figure 7) there appears to be a time delay between progression and next treatment mainly for late progression. However, the difference in the time-to-next-

treatment between the arms is larger than the difference in PFS. As the model assumes the same post progression costs, savings in later line treatment costs in the G-chemo+G arm versus the R-chemo+R arms are mainly driven by the delay in treatment costs. Therefore, using PFS to determine timing of next treatment is conservative from the point of the economic analysis.

4. **Patients experience during disease progression:** in the indolent disease setting, there are limited long-term follow up data sets that would allow more accurate modelling, especially on HRQoL. Alternative approaches to modelling post-progression costs and outcomes after first-line treatment include complex patient level simulation (Papaioannou et al., 2012). However, this approach also had to rely on literature HRQoL values, required specific assumptions on a treatment pathway that may not be reflective of actual clinical practice and requires data for second line treatment outcomes that reflects current clinical practice[1].

Due to this limitation in available data to populate a more detailed, post-progression pathway, the existing model structure was maintained. However, the current model incorporates the key model assumption common to approaches in the first-line setting that the treatment pathway (and therefore costs and outcomes) are the same in the intervention and control arm and do not depend on the type of anti-CD20 treatment received prior to progression. Time in post-progression can therefore be estimated with post-progression mortality data, either from the GALLIUM trial for early PD or from a representative R-chemo+R cohort from the PRIMA study. Uncertainties in post-progression utilities and cost can be addressed with scenario analysis as discussed below.

## *Extrapolation of PFS and duration of treatment effect*

To provide revised assumptions on the future PFS benefit of G-chemo+G versus R-chemo+R in the model, further evidence for long-term treatment effect of the anti-CD20 treatments Gazyvaro and rituximab were investigated. In addition, non-proportional hazard parametric functions which fitted individually to the treatment arms, as alternative to the proportional hazards approach, were explored.

[1] For example, the relapsed/refractory trial data used from van Oers et al. (van Oers et al., 2010) was based on a patient cohort where the majority had progressed early and included patients that had been treated with chemotherapy only in 1st line.

## *Duration of treatment effect for anti-CD20 treatments*

Due to the indolent nature of FL, long-term follow-up data reaching median PFS is challenging as this is expected to be around 6 years on the current standard-of-care. For Gazyvaro, data in first-line FL are limited to the maximum available follow up period of up to 5 years in the GALLIUM study (September 2016 clinical cut-off date). However, the committee's preferred assumption of no treatment effect post follow up is implausible based on the experience with Gazyvaro in other settings and the common CD20 target with rituximab.

For example, Gazyvaro has demonstrated a longer term treatment effect versus rituximab in the treatment of chronic lymphocytic leukaemia (CLL). There appears to be no evidence of a finite duration of treatment effect in the CLL11 study (Goede et al., 2015) which compared G-chlorambucil versus R-chlorambucil with follow up significantly beyond the initial induction treatment phase and median PFS.

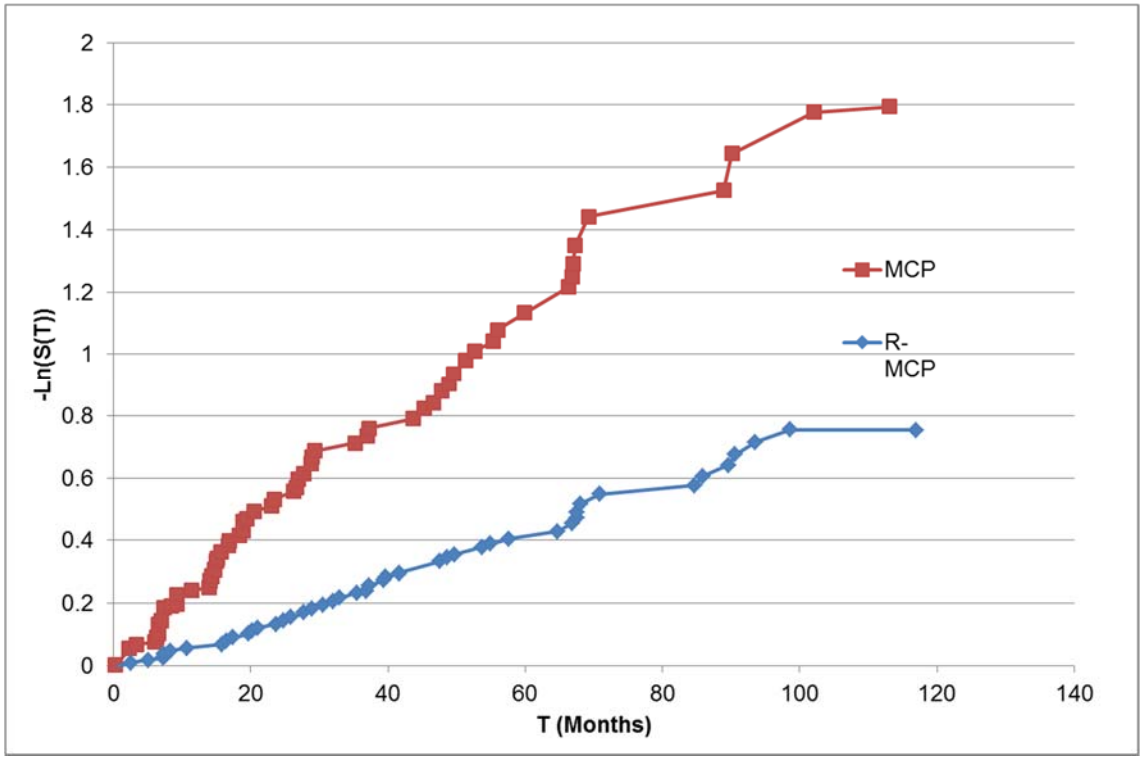
As acknowledged by the committee, the mechanism of action of Gazyvaro is similar to that of rituximab in terms of targeting CD20, with Gazyvaro demonstrating enhanced antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP) and direct cell death while reducing complement dependent cytotoxicity (CDC) (Golay et al., 2013, Mossner et al., 2010). Therefore, the long-term experience with rituximab based regimens with regards to the duration of treatment effect on PFS is expected to apply to Gazyvaro. In addition to the PRIMA study (that investigated R maintenance versus observation), long-term follow up from R-chemo induction studies in first-line FL was identified from first-line studies of R-chemo induction therapy. These studies do not show evidence of a finite duration of treatment effect:

Bachy et al. report results from the FL2000 study comparing cyclophosphamide, Adriamycin, etoposide and prednisolone plus interferon-α2a (CHVP-I) versus rituximab-CHVP-I (R-CHVP-I) with 8.4 years of median follow up (Bachy et al., 2013). The authors calculated hazard functions for both arms. These indicate a reduced hazard of progression on R-chemo induction versus chemo alone for up to 7 years; close the end of the follow up period where the number at risk becomes low and confidence intervals around hazard estimates increase significantly.

Herold et al. report results from the OSHO#39 study comparing first-line mitoxantrone, chlorambucil, prednisolone (MCP) versus R-MCP with median follow up of 87 months (7.3 years) and 104 months (8.7 years), respectively (Herold et al., 2015). The authors report KM PFS plots in Figure 2 of the publication. Plotting the digitized KM PFS data from Herold et al.

as log-cumulative hazard (Figure 3), it is apparent that the curves continue to move apart for the entire duration of follow up period, i.e., the hazard of progression remains lower in the R-chemo group compared to chemotherapy alone.

**Figure 3: Log-cumulative hazard plot of digitised KM data from Herold et al. 2015**

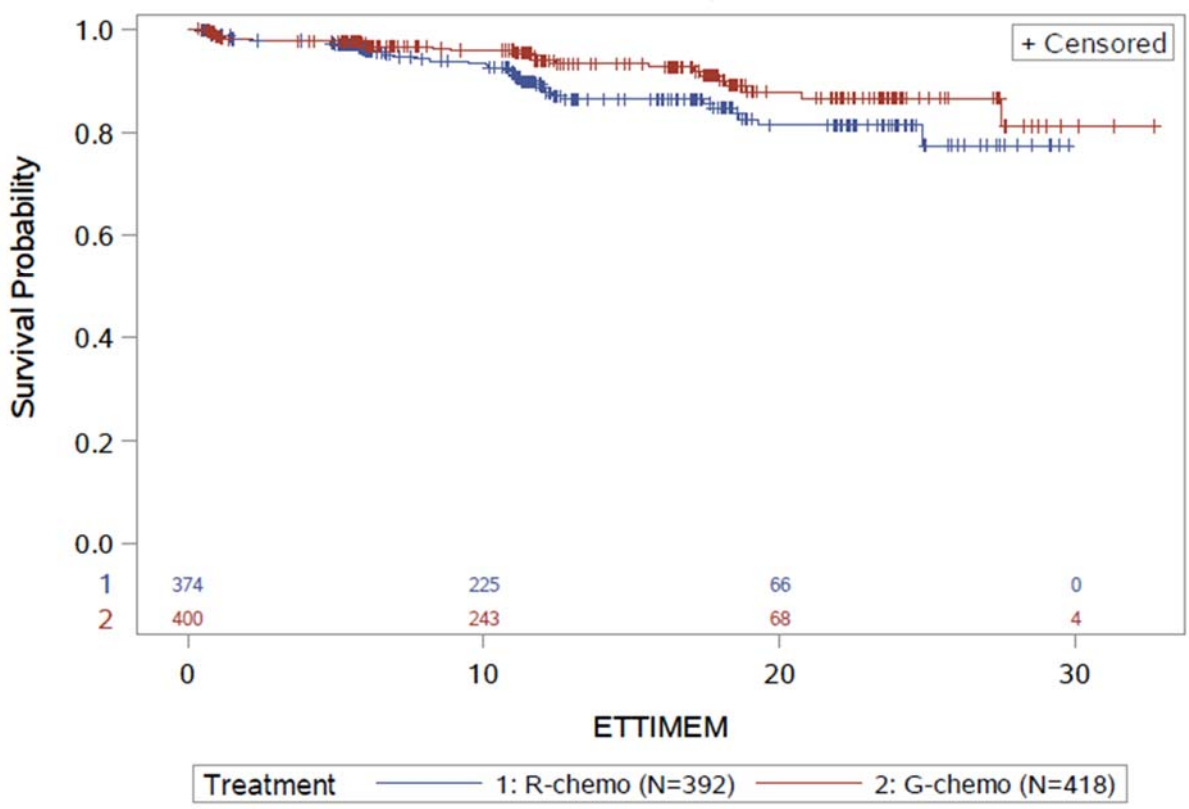



In conclusion, no evidence for a finite duration of treatment effect – or duration of effect significantly shorter than median PFS - was identified in studies of anti-CD20 treatments where long-term randomised follow up data was available.

## *Treatment effect in GALLIUM and non-proportional hazards approach*

In the GALLIUM study, the ongoing treatment effect of Gazyvaro over rituximab can be seen in the KM PFS curves for patients who completed treatment i.e., post maintenance, in Figure 4. The curves show a continued trend to separate.

**Figure 4 PFS per treatment arm in GALLIUM post maintenance (in follow up, FL ITT)**




A further indication for the ongoing duration of treatment effect of Gazyvaro in first-line FL comes from the minimal residual disease (MRD) data after end of induction (EOI) in GALLIUM: MRD negativity was significantly higher in the G-chemo arm than the R-chemo arm (92% vs 85%; p=0.0041) (Pott C et al., 2016). MRD negativity at EOI was associated with longer subsequent PFS, with a hazard ratio of 0.35 (95% CI, 0.22, 0.56; p<0.0001) in both treatment arms, indicating that induction treatment contributed to the observed improvement in PFS for G-chemo+G versus R-chemo+R over the follow up period – extending significantly beyond the initial induction period.

As proposed in the ACD, PFS functions were also fitted independently to the PFS KM curves in the G-chemo+G and the R-chemo+R arm. This approach is normally recommended if there is evidence for a non-proportional hazard (Latimer, 2013). The results of the AIC/BIC fit statistics are shown in Table 5 below per arm and for the different PFS endpoints.

**Table 5: AIC/BIC fit statistics for independent (non-proportional hazard) models**

| Subgroup | Treatment | Endpoint - def | Distribution | AIC (Rank) | BIC (Rank) | log_likelihood |
|---|---|---|---|---|---|---|
| All FL population | G-Chemo | Investigator | EXPONENTIAL | 790.20 (5) | 794.60 (1) | -394.10 |
| All FL population | G-Chemo | Investigator | WEIBULL | 786.46 (2) | 795.26 (3) | -391.23 |
| All FL population | G-Chemo | Investigator | LLOGISTIC | 786.48 (3) | 795.28 (4) | -391.24 |
| All FL population | G-Chemo | Investigator | LNORMAL | 786.29 (1) | 795.09 (2) | -391.15 |
| All FL population | G-Chemo | Investigator | GAMMA | 787.69 (4) | 800.88 (5) | -390.84 |
| All FL population | R-Chemo | Investigator | EXPONENTIAL | 995.68 (4) | 1000.08 (2) | -496.84 |
| All FL population | R-Chemo | Investigator | WEIBULL | 996.43 (5) | 1005.22 (5) | -496.21 |
| All FL population | R-Chemo | Investigator | LLOGISTIC | 994.48 (3) | 1003.28 (3) | -495.24 |
| All FL population | R-Chemo | Investigator | LNORMAL | 990.00 (1) | 998.80 (1) | -493.00 |
| All FL population | R-Chemo | Investigator | GAMMA | 991.94 (2) | 1005.14 (4) | -492.97 |
| High and intermediate | G-Chemo | Investigator | EXPONENTIAL | 624.36 (5) | 628.52 (1) | -311.18 |
| High and intermediate | G-Chemo | Investigator | WEIBULL | 621.71 (2) | 630.03 (3) | -308.86 |
| High and intermediate | G-Chemo | Investigator | LLOGISTIC | 621.91 (3) | 630.23 (4) | -308.95 |
| High and intermediate | G-Chemo | Investigator | LNORMAL | 621.30 (1) | 629.63 (2) | -308.65 |
| High and intermediate | G-Chemo | Investigator | GAMMA | 623.06 (4) | 635.55 (5) | -308.53 |
| High and intermediate | R-Chemo | Investigator | EXPONENTIAL | 842.31 (4) | 846.47 (2) | -420.15 |
| High and intermediate | R-Chemo | Investigator | WEIBULL | 843.39 (5) | 851.72 (4) | -419.70 |
| High and intermediate | R-Chemo | Investigator | LLOGISTIC | 841.40 (3) | 849.73 (3) | -418.70 |
| High and intermediate | R-Chemo | Investigator | LNORMAL | 837.78 (1) | 846.11 (1) | -416.89 |
| High and intermediate | R-Chemo | Investigator | GAMMA | 839.76 (2) | 852.26 (5) | -416.88 |
| All FL population | G-Chemo | IRC | EXPONENTIAL | 741.84 (4) | 746.24 (2) | -369.92 |
| All FL population | G-Chemo | IRC | WEIBULL | 740.47 (3) | 749.27 (4) | -368.23 |
| All FL population | G-Chemo | IRC | LLOGISTIC | 740.01 (2) | 748.81 (3) | -368.00 |

| | | | | | | |
|---|---|---|---|---|---|---|
| All FL population | G-Chemo | IRC | LNORMAL | 737.06 (1) | 745.86 (1) | -366.53 |
| All FL population | G-Chemo | IRC | GAMMA | 743.13 (5) | 756.32 (5) | -368.56 |
| All FL population | R-Chemo | IRC | EXPONENTIAL | 916.98 (4) | 921.38 (2) | -457.49 |
| All FL population | R-Chemo | IRC | WEIBULL | 918.40 (5) | 927.19 (5) | -457.20 |
| All FL population | R-Chemo | IRC | LLOGISTIC | 916.59 (3) | 925.39 (4) | -456.30 |
| All FL population | R-Chemo | IRC | LNORMAL | 910.00 (1) | 918.80 (1) | -453.00 |
| All FL population | R-Chemo | IRC | GAMMA | 910.78 (2) | 923.98 (3) | -452.39 |
| High and intermediate | G-Chemo | IRC | EXPONENTIAL | 605.21 (4) | 609.37 (1) | -301.60 |
| High and intermediate | G-Chemo | IRC | WEIBULL | 604.72 (2) | 613.04 (3) | -300.36 |
| High and intermediate | G-Chemo | IRC | LLOGISTIC | 605.17 (3) | 613.49 (4) | -300.59 |
| High and intermediate | G-Chemo | IRC | LNORMAL | 604.29 (1) | 612.62 (2) | -300.15 |
| High and intermediate | G-Chemo | IRC | GAMMA | 606.21 (5) | 618.69 (5) | -300.10 |
| High and intermediate | R-Chemo | IRC | EXPONENTIAL | 791.97 (4) | 796.14 (2) | -394.99 |
| High and intermediate | R-Chemo | IRC | WEIBULL | 793.57 (5) | 801.91 (5) | -394.79 |
| High and intermediate | R-Chemo | IRC | LLOGISTIC | 791.67 (3) | 800.00 (4) | -393.84 |
| High and intermediate | R-Chemo | IRC | LNORMAL | 786.16 (1) | 794.49 (1) | -391.08 |
| High and intermediate | R-Chemo | IRC | GAMMA | 787.41 (2) | 799.90 (3) | -390.70 |

As with the original analysis of the submission, all functions presented plausible fits to the observed data and in most situations the Log-normal function presented the numerically best fit. However, as the AIC/BIC statistics was not indicative of the accuracy of the future prediction, selection of a suitable function for long-term extrapolation had to be based on the plausible long-term behaviour based on external data.

To assess the difference between the proportional hazard and independent functions differences in predicted median PFS and mean PFS were assessed under the assumption of a cap on the maximal duration of effect of 9 years. The results shown in Table 6 for PFS-IRC indicate that non-proportional hazard models resulted in a more conservative estimate of the median and mean PFS gain, this was also the case for investigator assed PFS.

**Table 6: PFS extrapolation results in higher risk FL patients (intermediate/high FLIPI, PFS-IRC)**

| Model | Time in PFS | Incremental LY in PFS (undiscounted) G-Chemo+G vs. R-Chemo+R | |
|---|---|---|---|
| | | Proportional Hazards | Non-proportional Hazards (independent) |
| Weibull | Mean | 1.95 | 1.56 |
| | Median | 2.75 | 2.08 |
| Exponential | Mean | 2.12 | 2.12 |
| | Median | 3.00 | 3.00 |
| Log-Logistic | Mean | 2.25 | 1.88 |
| | Median | 3.17 | 2.67 |
| Log-Normal | Mean | 2.17 | 2.18 |
| | Median | 3.75 | 3.75 |
| Gamma | Mean | 2.09 | 2.09 |
| | Median | 4.08 | 4.08 |

## *Choice of the revised base-case extrapolation function*

In addition to the external validity of the PFS extrapolation function discussed in the submission, the plausibility of different functional forms was revisited based on the long-term follow up data from R-chemo induction studies discussed above (Bachy et al., 2013, Herold et al., 2015). Bachy et al. investigate the hazard of progression over time after R-chemo induction therapy and find that in the long-term, the hazard of progression declines in both arms. This is also consistent with the Log-cumulative hazard plot of the Herold PFS data in Figure 3 which appears to be consistent with a constant or declining hazard. A decreasing

hazard of progression after about 12 month from initial R-chemo treatment was also observed in observational cohorts (Casulo et al., 2015). Therefore, the use of the Weibull function in the extrapolation, which predicts an increasing hazard of progression over time in both arms, does not seem plausible.

As there was no indication for a finite duration of effect of anti-CD20 treatments in the literature, the committee's preferred assumption of no effect after the observation period in GALLIUM (5 years) was implausible. Based on the results in Table 6, using a non-proportional hazards model was the more appropriate approach to incorporate a potential decline in treatment effect in the long-term PFS extrapolation that did not require assumptions on a specific duration of effect and was based on fitting the actually observed GALLIUM data. To present external validity with a constant or decreasing hazard of progression, the Log-Logistic function was deemed more plausible than the Weibull function. The Log-Logistic function was also seen as plausible by clinical experts as discussed in the company submission.

Compared to the original submission, PFS-IRC was used. Although PFS-INV was more realistic and comparable to clinical practice, as acknowledged by the committee, using PFS-IRC provided a more conservative approach as it resulted in a numerically smaller treatment effect compared to the primary endpoint of investigator assessed PFS. Use of PFS-INV and alternative extrapolation functions were investigated in scenario analyses.

## *Model predictions for PFS and OS*

In agreement with the ERGs and the committee's preference to implement analyses by treatment arm, mortality in PFS and PD were treated independently in the revised base case, although differences did not reach statistical significance with values presented in Table 7.

**Table 7: Model mortality per health state (GALLIUM September 2016 cut-off date)**

| | **Higher risk FL (intermediate/high FLIPI)** | **FL ITT** |
|---|---|---|
| PFS (Pre-progression) – Monthly rate | | |
| R-chemo+R | 0.09% (0.06%-0.16%) | 0.08% (0.05%-0.13%) |
| G-chemo+G | 0.12% (0.08%-0.19%) | 0.11% (0.08%-0.17%) |
| Pooled | 0.11% (0.08%-0.15%) | 0.10% (0.07%-0.13%) |
| Early PD (PPS) – hazard (per month) – PD based on IRC | | |

| | | |
|---|---|---|
| R-chemo+R | 1.81% | 1.70% |
| G-chemo+G | 1.44% | 1.25% |
| Pooled | 1.67% | 1.61% |
| Late PD (PPS) | | |
| R-chemo+R and G-chemo+G | 0.58% | 0.58% |

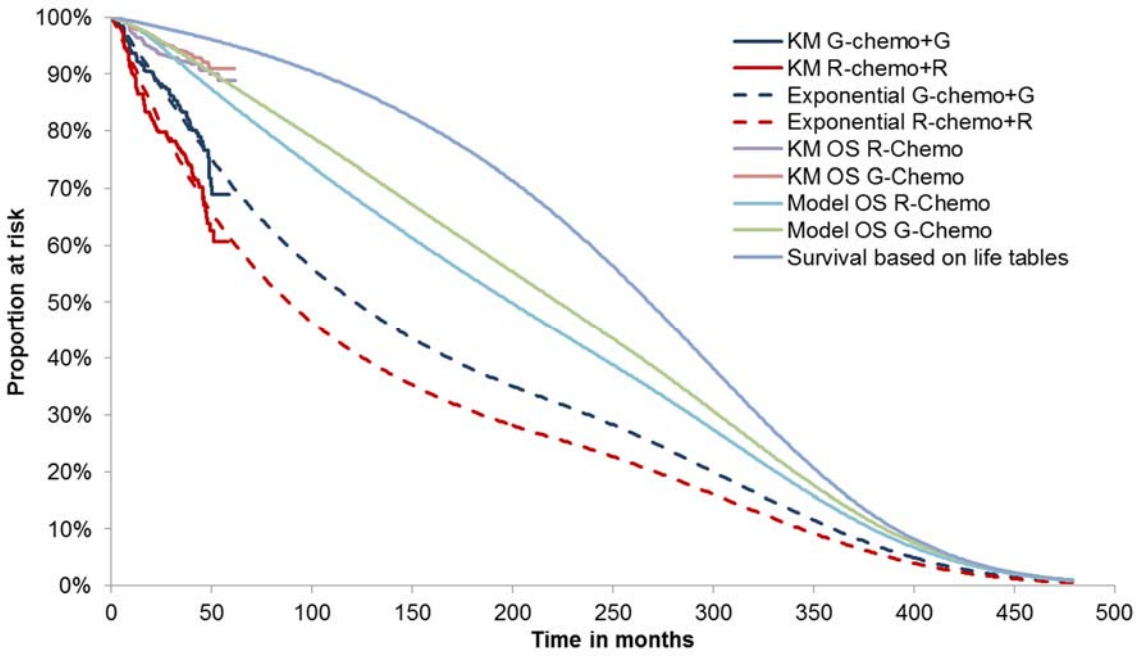
Table 8 presents a summary of the revised base-case clinical input assumptions.

**Table 8: Revised base case clinical input assumptions (higher risk & ITT FL)**

| Parameter | Revised base case | Justification |
|---|---|---|
| PFS source | IRC (secondary endpoint) | ERG preferred, more conservative compared to INV |
| PFS extrapolation function | Log-Logistic | Increased hazard of progression with time implausible based on rituximab data. Log-logistic can be implemented as non-proportional hazard (see below) and was originally considered plausible by external experts |
| Duration of treatment effect | Non-proportional hazards assumption. | 'No effect post observation' assumption implausible<br>Non-proportional hazard scenarios using function fitted to individual arms from GALLIUM result in a declined hazard ratio over time |
| PFS and PD mortality | Per treatment arm. | Preferred by ERG/committee assumption |

Model based results for PFS and OS are shown in Figure 5 and key results in Table 9. PFS fitted the observed KM curves well to about 50 months, where only small numbers (< 10%) were at risk in both arms and the KM estimates unreliable. As discussed above, the predicted long-term decrease in the hazard of progression was plausible based on published long-term follow up data. Furthermore, the Log-Logistic model also resulted in plausible long-term PFS prediction at 10 years where clinical experts estimated PFS to be around 30-40% with a prediction based on investigator assessed PFS for the FL IT population of 40.1%.

**Figure 5: Revised base case PFS and OS in FL higher risk (intermediate/high FLIPI; PFS IRC)**




The key model predictions for the base case are summarised in Table 9.

**Table 9: Revised base case model PFS and OS outcomes (undiscounted)**

| | G-chemo+G | R-chemo+R | Difference |
|---|---|---|---|
| ***Higher risk FL patients (intermediate/high FLIPI)*** | | | |
| **Mean LY in PFS** | 13.36 | 11.48 | 1.88 |
| **Median PFS** | 10.00 | 7.33 | 2.67 |
| **Total Mean LY (OS)** | 18.44 | 17.21 | 1.24 |
| **Median OS** | 18.50 | 16.58 | 1.92 |
| ***FL ITT*** | | | |
| **Mean LY in PFS** | 13.65 | 12.32 | 1.33 |
| **Median PFS** | 10.33 | 8.33 | 2.00 |
| **Total Mean LY (OS)** | 18.72 | 17.78 | 0.94 |
| **Median OS** | 18.83 | 17.42 | 1.42 |

FLIPI,

Overall, the predicted OS behaviour seemed conservative in comparison with the GALLIUM observation as the model seemed to reproduce the observed OS curve in the G-chemo+G arm of GALLIUM but appeared to overestimate (until about median follow up of 41 months) OS in the R-chemo+R comparator arm. This is further illustrated in Table 10 when calculating this predicted risk ratio of death at 12, 24, 48 and 60 months, respectively; the ratio is in agreement with the OS HR 0.76 (95% CI, 0.49-1.16, p=0.20) in the higher risk patients and the OS HR 0.82 (95% CI: 0.54-1.22, p=0.32) in the FL ITT population.

**Table 10: Model survival predictions**

| Months | Survival G-chemo+G | Survival R-chemo+R | Difference | *Model Mortality risk ratio* |
|---|---|---|---|---|
| ***Higher risk FL patients (intermediate/high FLIPI)*** | | | | |
| 12 | 98.3% | 98.2% | 0.1% | *0.78* |
| 24 | 96.0% | 95.0% | 1.0% | *0.70* |
| 48 | 90.7% | 87.8% | 2.8% | *0.76* |
| 60 | 88.0% | 84.5% | 3.5% | *0.78* |
| ***FL ITT*** | | | | |
| 12 | 98.5% | 98.5% | 0.0% | *0.82* |
| 24 | 96.4% | 95.8% | 0.6% | *0.73* |
| 48 | 91.6% | 89.5% | 2.1% | *0.78* |
| 60 | 89.0% | 86.4% | 2.6% | *0.80* |

Due to the indolent nature of the disease, accurate determination of trial-based OS benefits of first-line treatments in FL is very challenging. However, the predictions of the model and the trend observed in GALLIUM are consistent with the OS benefit of Gazyvaro in the rituximab-refractory FL setting and the well-established OS benefit of rituximab in the first-line induction setting. According to a meta-analysis of Schulz et al. (Schulz et al., 2007) a PFS HR of 0.58 (95% CI: 0.50-0.68) was associated with an OS HR of 0.63 (95% CI 0.51-0.79) for R-chemo versus chemo induction. More recently, the individual patient data meta-analysis of by Vidal et al. (Vidal et al., 2017) also established the OS benefit of rituximab maintenance after induction over observation in the relapsed setting.

Furthermore, in the rituximab-refractory setting, Gazyvaro with bendamustine followed by Gazyvaro maintenance showed a statistically significant improvement in OS versus bendamustine alone (OS HR 0.58, 95% CI: 0.39-0.86 and PFS HR 0.57, 95% CI 0.44-0.73); the prognosis for patients in this group was poor and consequently a larger number of OS events was available at follow up (Cheson BD et al., 2016). A continued trend to OS benefit of Gazyvaro over rituximab was also observed in CLL (CLL11 study with 43 months median follow up; median PFS 16 months (Goede et al., 2015)), despite the significantly older population and high incidence of non-disease related deaths.

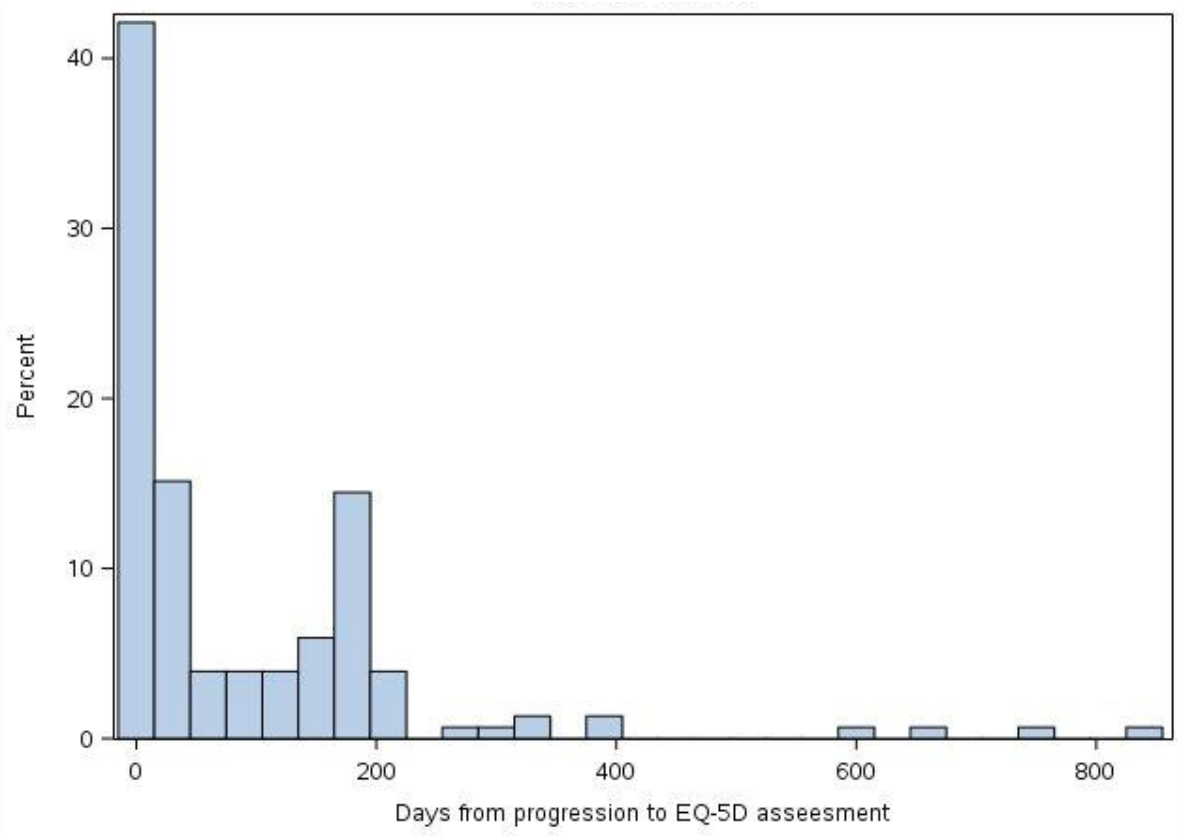
OS predictions are also consistent with different model approaches using patient level simulation with a complex pathway for rituximab in first line induction therapy (TA226). Papaioannou et al. predicted a 2.97 year PFS gain of R-CVP versus CVP alone and a 1.64

year mean OS gain based on Log-normal extrapolation of PFS data (Papaioannou et al., 2012). In their base-case therefore, 55% of PFS gain translated into OS gain. Using the Log-normal extrapolation in the current model scenario resulted in a mean PFS gain of 2.59 years and OS gain of 1.39 years, i.e. 54% in line with Papaioannou et al.; using the base-case Log-logistic function resulted in 2.04 years PFS gain and 1.27 years OS gain, i.e. a ratio of 62%. As the example demonstrates, translation ratios depend on various assumptions made in the model and the range of the current model is consistent with other modelling approaches.

### *HRQoL*

There is uncertainty over the exact course of the utility profile over time for patients progressing after first-line treatment as to our knowledge there is no longitudinal data source that would allow a detailed determination of the course. As discussed in the submission, utility at early or late progression was collected in GALLIUM only during one assessment visit after progression. The timing of the assessment in relation to progression is shown in Figure 6 and indicates that the majority of assessments in PD followed within 1–2 months. However, disease progression is likely to be slow, especially in the late PD patient group and symptoms that lead to a reduction in quality of life may develop delayed as indicated by time to next anti-lymphoma treatment (TTNALT) discussed below.

**Figure 6: HRQoL assessment in relation to progression (GALLIUM FL ITT)**




Therefore, assuming PD utilities from GALLIUM at progression throughout the health state is not informative of further disease related decline in HRQoL.

PD utility values from the Wild et al. (Wild D et al., 2006) used in the submission were derived in an Oxford Outcomes Study in 2005 (Wild D, 2005). In addition to the PD state utility derived in the study, the report investigated additional health state utilities as shown in Table 11.

**Table 11: FL utility values per Oxford Outcomes study**

| State | N | Mean (SD)/[SE] |
|---|---|---|
| Active disease – Newly diagnosed | 50 | 0.83 (0.22)[0.03] |
| Active disease – Relapsed | 33 | 0.62 (0.32)[0.06] |
| Partial response to therapy | 39 | 0.77 (0.21)[0.03] |
| Remission/Full response to therapy | 66 | 0.79 (0.23)[0.03] |
| Disease free | 27 | 0.88 (0.15)[0.03] |

| Aggregate states | | |
|---|---|---|
| PD (post-progression) | 33 | 0.62 [0.06] |
| Pre-Progression | 132 | 0.805 [0.018] |

Although the study included patients with serval treatment cycles, it did not report on early and late progression separately. The committee noted patient HRQoL may improve or decrease depending on progression and subsequent remission cycles. However, patients in early PD have a significantly reduced life expectancy, with a median of around 5 years overall survival (Casulo et al., 2015) that is closer to an aggressive disease. Furthermore, outcomes of subsequent chemotherapy for progression on rituximab show <10 months median PFS (Kahl et al., 2010), indicating that subsequent remissions in the early progression group are likely to be short. Therefore, decline in utility for early progression is expected to be faster, with less time spend in subsequent remissions. The revised base case therefore assumes PD utilities (0.62) from Wild for the early PD patient group to reflect this.

For the late PD patient group (the majority of patients), patients may spend more time in subsequent remissions, although a recent observational cohort reported significantly shorter 2nd remissions (Alperovich A et al., 2016). One potential approach to account for this is to use an average weighted utility from the cross-sectional Oxford Outcomes study data: weighting the utilities in 'active disease – relapsed', 'partial response to therapy', 'remission/full response to therapy' and 'disease free' by the number of observations results in an average utility of 0.766. This value was applied for the late PD state in the revised model.

In the revised model, utility values from GALLIUM were also implemented per treatment arm as preferred by the ERG and consistent with the revised implementation of PFS and PD mortality rates per treatment arm based on data from the GALLIUM study. Although there was no statistically significant difference between the arms (as for mortality in PFS and PPS), there was numerically higher utility value (as mirrored by Fact-Lym values) for the G-chemo+G arm in PFS maintenance/follow up (on or off treatment). As this trend was not present in induction it is unlikely that this was caused by a bias introduced by the open label design in GALLIUM. It is plausible that, on average, patients in the G-chemo-G arm in PFS (on maintenance or follow up) had a higher quality of life due the improved disease control versus R-chemo+R, as indicated by the deeper response in induction according to MRD and the lower risk progression.

## *Costs*

### Administration costs

Administration costs were revised in line with the latest National Chemotherapy List delivery codes (April 2017, accessed at TRUD, https://isd.digital.nhs.uk/trud3/user/guest/group/0/home in September 2017). As rituximab (in combination with chemotherapy) is a well-established standard-of-care, the respective unit costs from the national schedule are expected to be representative for the average administration costs. Administration costs are summarised in Table 12 below.

**Table 12 NHS national regimen codes and unit costs**

| Regimen/Cycle | Delivery code | Reference, comment | Unit cost (£)* |
|---|---|---|---|
| Bendamustine+Rituximab (1st Course) | SB14Z | National Chemotherapy List | 407 |
| Bendamustine+Rituximab (Sub Courses) | SB13Z | National Chemotherapy List | 337 |
| R-CVP or R-CHOP; all cycles | SB13Z | National Chemotherapy List | 337 |
| Rituximab (INTRAVENOUS Maintenance) | SB13Z | National Chemotherapy List | 337 |
| Rituximab (SUBCUTANEOUS Maintenance) | SB12Z | National Chemotherapy List | 199 |
| G-chemo induction (first visit each cycle) | SB14Z | National Chemotherapy List – assumed to be the same as obinutuzumab + chlorambucil | 407 |
| G-chemo induction – subsequent visits (day 8 + 15) in first cycle | SB15Z | National schedule of reference costs: Deliver subsequent elements of a chemotherapy cycle | 361 |
| G maintenance | SB13Z | Assumed to be the same as R IV maintenance | 337 |

*Day case preferred assumption in TA472 (majority of cases in the national schedule are day cases), lower outpatient costs assumed for Subcutaneous administration

This resulted in the revised administration cost per cycle as summarised in Table 13 below.

**Table 13: Revised administration costs per cycle**

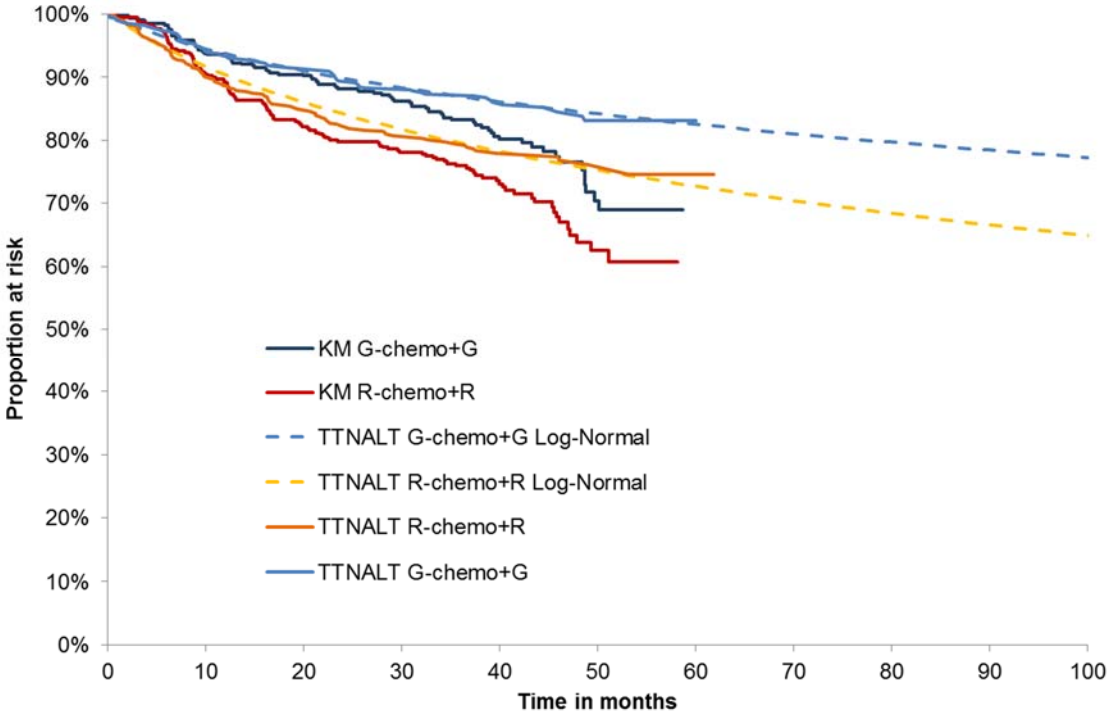
| Scenario | Tariff | Pharmacy | Transport | Total |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 1st Cycle G-chemo | £1129.00 | £34.50 | £35.31 | £1198.81 |
| Subsequent cycle G-chemo | £407 | £11.50 | £11.77 | £430.27 |
| 1st Cycle R-benda | £407 | £11.50 | £11.77 | £430.27 |
| 1st Cycle R-CVP or R-CHOP | £337 | £11.50 | £11.77 | £360.27 |
| Subsequent cycles R-chemo | £337 | £11.50 | £11.77 | £360.27 |
| G or R IV maintenance cycle | £337 | £11.50 | £11.77 | £360.27 |
| R SC maintenance cycle | £199 | - | £11.77 | £210.77 |

### Subsequent treatment costs

To investigate model assumptions on the costs of subsequent lines of treatment, time to next anti-lymphoma treatment (TTNALT) KM data was compared to PFS from GALLIUM in Figure 7. For early progression next anti-lymphoma treatment (NALT) appears to follow with or shortly after progression and seems to be increasingly delayed for later progression, with a trend of a longer delay in the Gazyvaro arm. This is also evident from the TTNALT HR of 0.68 (95% CI: 0.52, 0.90, FL ITT) that corresponds to the PFS-INV HR rather than the numerically higher PFS-IRC.

**Figure 7: Time-to-next-treatment, extrapolation and PFS-IRC (intermediate/high FLIPI)**




Therefore, implementing TTNALT into the timing of treatment costs would favour the Gazyvaro arm: even under the assumption of equal costs of a subsequent treatment, this would be deferred further or more patients would die of other caused before requiring subsequent treatment. The current model assumption of including costs of subsequent treatment lines at first progression is therefore conservative as demonstrated in an exploratory scenario analysis that used TTNALT to determine the probability of receiving a subsequent treatment based on the TTNALT. This analysis used the costs for one immunochemotherapy treatment episode of £12,228 (based on Papaioannou et al.). This resulted in a decreased ICER versus applying higher costs (including discounted costs of further lines based on Papaioannou et al.) at progression alone due to increased saving in further treatment costs of -£3,400 versus -£2,193 estimated for the base case.

Further cost assumption scenarios were investigated in scenario analyses. All scenarios assumed that once treatment was required, i.e. after progression, the same costs would apply to both arms.

Further implementing TTNALT as the main driver of the Markov model may decrease the ICER due to the fact that the mean gain in treatment free time on Gazyvaro is higher than the mean time gained in PFS; 1. the TTNALT HR is smaller than PFS-IRC HR; 2. TTNALT shows a decreasing hazard of subsequent treatment with time. Extrapolation is therefore likely to result in a higher mean gain in treatment free time than the mean time gained in PFS.

### Biosimilar (BS) rituximab costing scenarios

The preferred assumption to base the cost-effectiveness results on a comparison with BS net prices in essence assumes that the displaced technology for IV rituximab is 100% biosimilar. This assumption is unrealistic. As data from NHS England shows (https://www.england.nhs.uk/wp-content/uploads/2017/09/biosimilar-medicines-commissioning-framework.pdf), BS uptake only reaches 80% several years after market entry (e.g. infliximab), with shares after 1-2 years below 60% (etanercept). Considering the recent availability of biosimilar rituximab, MabThera IV constitutes currently the majority of IV rituximab used. While the base case results presented are based on MabThera IV net prices, BS price and market share scenarios are presented as scenario analysis with up to 60% discount and 80% uptake.

## *Summary of revised model inputs*

A summary of the revised base-case model parameters is provided **Table 14** below.

**Table 14: Summary of variables applied in the economic model (intermediate/high FLIPI)**

| Variable | Value | Source/Comment |
|---|---|---|
| Age | 62.6 | NICE preferred assumption |
| Weight | 75.7 | GALLIUM trial |
| Height | 168.3 | GALLIUM trial |
| Time horizon | 50 years | NICE preferred assumption |
| Discount rate for costs and outcomes | 3.50% | NICE reference case |
| Monthly probability of death from PFS R-chemo+R | 0.09% | GALLIUM trial |
| Monthly probability of death from PFS G-chemo+G | 0.12% | GALLIUM trial |
| PFS source | IRC | NICE preferred assumption |
| PFS extrapolation function | Log-logistic | This appendix |
| Proportional hazard model | No | This appendix |
| PFS duration of effect | Not limited | This appendix, Non-proportional hazard assumption |
| PPS | Per arm | Committee preferred assumpion |
| Early PPS Lambda (λ) R-chemo+R | 1.81% | GALLIUM trial |
| Early PPS Lambda (λ) G-chemo+G | 1.44% | GALLIUM trial |
| Late PPS Lambda (λ) | 0.56% | PRIMA trial |
| Utility | Per arm | ERG preference |
| PFS off txt – induction G-chemo | 0.765 | GALLIUM trial EQ5-D |
| PFS off txt – induction R-chemo | 0.779 | GALLIUM trial EQ5-D |
| PFS off txt – maint. & follow up G | 0.826 | GALLIUM trial EQ5-D |
| PFS off txt – maint. & follow up R | 0.810 | GALLIUM trial EQ5-D |
| PFS on txt – induction G-chemo | 0.823 | GALLIUM trial EQ5-D |
| PFS on txt – induction R-chemo | 0.824 | GALLIUM trial EQ5-D |

| | | |
|---|---|---|
| PFS on txt – maint. G | 0.834 | GALLIUM trial EQ5-D |
| PFS on txt – maint. R | 0.828 | GALLIUM trial EQ5-D |
| Early PD G-chemo+G | 0.620 | Wild et al. 2006 |
| Early PD R-chemo+R | 0.620 | Wild et al. 2006 |
| Late PD G-chemo+G | 0.766 | Based on Wild et al. 2005 |
| Late PD R-chemo+R | 0.766 | Based on Wild et al. 2005 |
| 1st administration in cycle G-chemo, R-bend | £407 | SB14Z (NHS reference costs 2015-16) |
| Subsequent administrations in cycle | £361 | SB15Z (NHS reference costs 2015-16) |
| Maintenance administration (IV), Administration R-CHOP, R-CVP | £337 | SB13Z (NHS reference costs 2015-16) |
| Maintenance administration (SC) | £199 | SB12Z (NHS reference costs 2015-16) |
| Pharmacy cost | £11.50 | 15 min PSSRU 2016 |
| Patient transport costs | £11.77 | Papaioannou et al. 2012 |
| Proportion receiving SC as maintenance | [redacted]% | Roche data on file |
| Chemotherapy market share | UK market research | NICE preferred assumption |
| Gazyvaro 1,000 mg* | £3,312.00 | BNF 2017 |
| MabThera IV 100 mg* | £174.63 | BNF 2017 |
| MabThera IV 500 mg* | £873.15 | BNF 2017 |
| MabThera SC 1400 mg* | £1344.65 | MIMS 2017 |
| BS rituximab IV 100 mg* | £157.17 | MIMS 2017 |
| BS rituximab IV 500 mg* | £785.84 | MIMS 2017 |
| Bendamustine 25 mg | £6.85 | BNF 2017 |
| Bendamustine 100 mg | £27.77 | BNF 2017 |
| Cyclophosphamide 500 mg | £7.84 | EMIT 2016 |
| Cyclophosphamide 1000 mg | £8.87 | EMIT 2016 |
| Doxorubicin 50 mg | £4.04 | EMIT 2016 |
| Vincristine 1 mg | £3.14 | EMIT 2016 |
| Prednisolone, 30 5 mg tablets | £0.93 | EMIT 2016 |
| Haematologist visit | £166 | NHS reference costs 2015-16 Code: 303 |
| Diagnostic tests/examinations | £65.27 | Papaioannou D 2012 |
| CT scan | £132 | NHS reference cost 2015-16 (RD27Z) |
| Aggregate subsequent treatments | £13,427 | Papaioannou D 2012 |
| Anaemia (3) | £3,021 | NHS Reference Costs SA03G (NL) |
| Febrile Neutropenia (3) | £6226.29 | NICE CG NHL, 2016 |
| Dyspnoea (3) | £0.00 | Not costed |
| Infusion related reaction (3) | £600.65 | NHS Reference Costs SA31E (NS) |
| Infusion related reaction (4) | £600.65 | NHS Reference Costs SA31E (NS) |
| Neutropenia (3) | £867.00 | LRiG estimate rev. TA162, TA175 |
| Neutropenia (4) | £867.00 | LRiG estimate rev. TA162, TA175 |
| Pneumonia (3) | £4154.97 | NHS Reference Costs DZ11P (NL) |
| Leukopenia (3) | £3236.25 | NHS Reference Costs SA31E (NL) |
| Leukopenia (4) | £3236.25 | NHS Reference Costs SA31E (NL) |
| Vial sharing | Yes | |

*List prices, confidential net prices applied as per original submission.

## *Results*

### Base case for higher risk FL patients

The cost-effectiveness results are presented for the higher risk FL group in Table 15 below based on the Gazyvaro net price of [redacted], MabThera IV net price of [redacted] per 100 mg vial, [redacted] per 500 mg vial and MabThera SC net price of [redacted] per 1400mg. Biosimilar pricing assumptions are presented in a scenario analysis.

**Table 15: Deterministic base case results (intermediate/high FLIPI)**

| Technologies | Total Costs (£) | Total LYG | Total QALYs | Inc Costs (£) | Inc LYG | Inc QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| G-chemo+G | [redacted] | 12.90 | 9.83 | | | | |
| R-chemo+R | [redacted] | 12.14 | 9.08 | [redacted] | 0.76 | 0.75 | [redacted] |

Values in the table are discounted and half cycle corrected

Disaggregated QALYs per health state are summarised in **Table 16**.

**Table 16: Summary of QALY gain by health state (intermediate/high FLIPI)**

| | G-chemo+G | R-chemo+R | Difference | Absolute | % of absolute |
|---|---|---|---|---|---|
| **Health state** | | | | | |
| Progression free survival | 7.68 | 6.53 | 1.15 | 1.15 | 74% |
| Progression < 2 yrs | 0.25 | 0.37 | -0.12 | 0.12 | 8% |
| Progression > 2 yrs | 1.91 | 2.18 | -0.27 | 0.27 | 18% |
| Total | 9.84 | 9.08 | 0.75 | 1.55 | 100% |

Values in the table are discounted and half cycle corrected

Disaggregated costs per health state and cost items are summarised in **Table 17** below.

**Table 17: Summary of predicted resource use by category of cost (intermediate/high FLIPI)**

| State | Cost (G-chemo) | Cost (R-chemo) | Cost difference | Absolute difference | % of absolute |
|---|---|---|---|---|---|
| **PFS** | | | | | |
| Gazyvaro | [redacted] | 0 | [redacted] | [redacted] | [redacted] |
| MabThera | 0 | [redacted] | [redacted] | [redacted] | [redacted] |
| Chemotherapy | 296 | 295 | 1 | 1 | [redacted] |
| Drug Administration | 6,561 | 4,467 | 2,094 | 2,094 | [redacted] |
| Adverse Events | 1,182 | 977 | 205 | 205 | [redacted] |
| Supportive Care | 8,468 | 7,493 | 975 | 975 | [redacted] |
| *PFS Total* | [redacted] | [redacted] | [redacted] | | |

| **Progressive disease** | | | | | |
|---|---|---|---|---|---|
| Supportive care and subsequent treatment costs | 7,416 | 9,609 | -2,193 | 2,193 | [redacted] |
| **Total PD & PFS** | [redacted] | [redacted] | [redacted] | [redacted] | 100% |

Values in the table are discounted and half cycle corrected

## Sensitivity analysis

**Table 18: Deterministic sensitivity analysis FL higher risk (intermediate/high FLIPI)**

| Parameter modified | Base value | High Value* | Low Value* | ICER High | ICER low |
|---|---|---|---|---|---|
| **Utilities*** | | | | | # |
| PFS induction on treatment | 0.823 | 0.829 | 0.823 | [redacted] | [redacted] |
| PFS induction on treatment off treatment | 0.765 | 0.770 | 0.765 | [redacted] | [redacted] |
| PFS maintenance on tx. | 0.834 | 0.841 | 0.835 | [redacted] | [redacted] |
| PFS maintenance/follow up off tx. | 0.826 | 0.833 | 0.827 | [redacted] | [redacted] |
| Early PD | 0.618 | 0.689 | 0.542 | [redacted] | [redacted] |
| Late PD | 0.766 | 0.789 | 0.741 | [redacted] | [redacted] |
| **Costs** | | | | | |
| 1st administration G-chemo | 430 | 530 | 344 | [redacted] | [redacted] |
| 1st administration R-chemo | 360 | 474 | 274 | [redacted] | [redacted] |
| Administration G-chemo (subsequent) | 384 | 485 | 312 | [redacted] | [redacted] |
| Administration R-chemo (subsequent) | 384 | 475 | 313 | [redacted] | [redacted] |
| Administration maintenance G | 360 | 454 | 289 | [redacted] | [redacted] |
| Administration maintenance R | 265 | 335 | 214 | [redacted] | [redacted] |
| Supportive care PFS induction | 253 | 293 | 224 | [redacted] | [redacted] |
| Supportive care PFS maintenance | 83 | 95 | 72 | [redacted] | [redacted] |

| | | | | | |
|---|---|---|---|---|---|
| Supportive care PFS follow up | 58 | 67 | 50 | [redacted] | [redacted] |
| AEs - G-chemo+G | 54 | 58 | 51 | [redacted] | [redacted] |
| AEs - R-chemo+R | 46 | 50 | 43 | [redacted] | [redacted] |
| Supportive care early PD | 231 | 270 | 199 | [redacted] | [redacted] |
| Supportive care late PD | 58 | 67 | 50 | [redacted] | [redacted] |
| Subsequent treatment early PD | 13,427 | 17,452 | 10,358 | [redacted] | [redacted] |
| Subsequent treatment late PD | 13,427 | 17,312 | 10,212 | [redacted] | [redacted] |

*Only G-Chemo+G arm utilities shown for simplicity, R-chemo+R result in similar variations.

**Figure 8: Tornado diagram for base case (intermediate/high FLIPI)**

[FIGURE REDACTED]

A 1,000 iteration probabilistic sensitivity analysis was conducted in order to determine the uncertainty surrounding the base-case ICERs. The scatter plot and the corresponding cost-effectiveness acceptability curve are shown in Figure 9 and Figure 10 respectively.

**Figure 9: Incremental cost and QALY PSA base case results (intermediate/high FLIPI)(Corrected)**

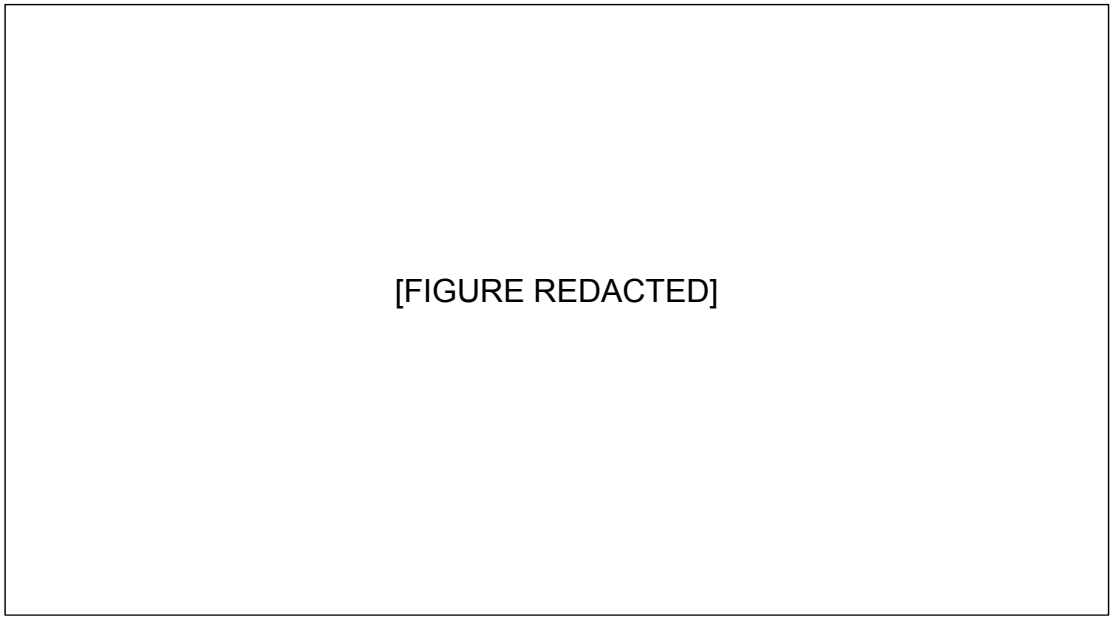
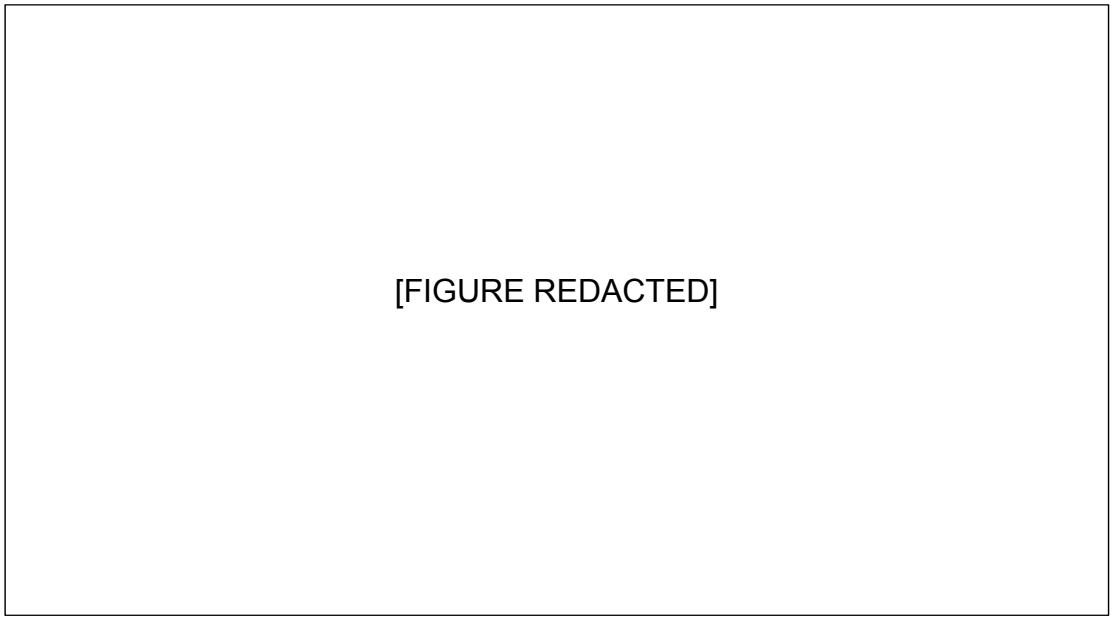



**Figure 10: Cost-effectiveness acceptability curve (intermediate/high FLIPI)(Corrected)**




This analysis indicated that G-chemo+G was more cost-effective than R-chemo+R in [redacted]% of simulations at a threshold of £30,000/QALY gained. The probabilistic base-case ICER was £[redacted]QALY.

### Scenario analysis

Sensitivity of the results to key inputs and to the choice of different PFS extrapolation functions was further investigated in a range of scenarios summarised in **Table 19** below.

**Table 19: Scenario analysis for revised base case (intermediate/high FLIPI)**

| Scenario | Inc. Cost | Inc. LY | Inc. QALYs | ICER |
|---|---|---|---|---|
| **Base-case** | [redacted] | 0.76 | 0.75 | [redacted] |
| Utility PFS: GALLIUM – pooled values | [redacted] | 0.76 | 0.63 | [redacted] |
| Utility PD: GALLIUM by arm | [redacted] | 0.76 | 0.72 | [redacted] |
| Utility PFS/PD: GALLIUM pooled | [redacted] | 0.76 | 0.58 | [redacted] |
| Utility Late PD/ Early PD: Wild et al. 0.62 | [redacted] | 0.76 | 0.80 | [redacted] |
| **PFS Extrapolation** | | | | |
| PFS-IRC Weibull (NPH) | [redacted] | 0.752 | 0.721 | [redacted] |
| PFS-IRC Log-Normal (NPH) | [redacted] | 0.826 | 0.818 | [redacted] |
| PFS-IRC Generalised Gamma (NPH) | [redacted] | 0.799 | 0.798 | [redacted] |
| PFS-INV Weibull (NPH) | [redacted] | 0.798 | 0.759 | [redacted] |
| PFS-INV Log-Normal (NPH) | [redacted] | 0.884 | 0.871 | [redacted] |
| PFS-INV Generalised Gamma (NPH) | [redacted] | 0.930 | 0.911 | [redacted] |
| PFS-INV Log-Logistic (NPH) | [redacted] | 0.813 | 0.797 | [redacted] |
| PFS-IRC Exponential (PH + 9 year maximum duration) | [redacted] | 0.797 | 0.761 | [redacted] |
| PFS-IRC Weibull (PH + 9 year maximum duration) | [redacted] | 0.780 | 0.736 | [redacted] |
| PFS-IRC Log-Normal (PH + 9 year maximum duration) | [redacted] | 0.789 | 0.782 | [redacted] |
| PFS-IRC Generalised Gamma (PH + 9 year maximum duration) | [redacted] | 0.772 | 0.772 | [redacted] |
| PFS-IRC Log-Logistic (PH + 9 year maximum duration) | [redacted] | 0.796 | 0.777 | [redacted] |
| PFS-INV Exponential (PH + 9 year maximum duration) | [redacted] | 0.883 | 0.835 | [redacted] |
| PFS-INV Weibull (PH + 9 year maximum duration) | [redacted] | 0.854 | 0.796 | [redacted] |
| PFS-INV Log-Normal (PH + 9 year maximum duration) | [redacted] | 0.885 | 0.867 | [redacted] |
| PFS-INV Generalised Gamma (PH + 9 year maximum duration) | [redacted] | 0.887 | 0.867 | [redacted] |
| PFS-INV Log-Logistic (PH + 9 year maximum duration) | [redacted] | 0.874 | 0.846 | [redacted] |
| PFS-IRC Log-Logistic (NPH + 9 year maximum duration) | [redacted] | 0.748 | 0.737 | [redacted] |
| **Mortality** | | | | |
| PFS mortality & PPS pooled | [redacted] | 0.78 | 0.79 | [redacted] |
| **NALT Costs** | | | | |
| NALT Costs (immunochemotherapy £12,228) applied with TTNALT | [redacted] | 0.76 | 0.75 | [redacted] |
| Early PD from GALLIUM (£5,438); Late PD literature (£13,427) applied with PFS | [redacted] | 0.76 | 0.75 | [redacted] |
| Early PD & Late PD from GALLIUM (£5,438) applied with PFS | [redacted] | 0.76 | 0.75 | [redacted] |
| Early PD from literature; Late PD 2 X literature (26,854) applied with PFS | [redacted] | 0.76 | 0.75 | [redacted] |
| Early PD from 2X literature (26,854); Late PD literature, applied with PFS | [redacted] | 0.76 | 0.75 | [redacted] |

NPH= Non-proportional hazard;

Sensitivity and scenario analyses confirmed that the ICERs were sensitive to the same inputs identified in the original submission. These were the choice of PFS extrapolation and utilities in PD. ICERs were relatively insensitive to assumptions on NALT costs – however the scenario using TTNALT indicates that the base case approach is conservative in estimating cost offsets in later lines of therapy.

**Biosimilar (BS) rituximab share and net price scenarios**

Table 20 presents the base case ICERs depending on BS net price – expressed as % reduction versus the MabThera list price – and market share of IV rituximab use.

**Table 20: Base case ICERs under different BS discount and share scenarios (intermediate/high FLIPI)**

| | | **BS market share** | | | |
|---|---|---|---|---|---|
| | | 20% | 40% | 60% | 80% |
| **BS net price (reduction from MabThera IV list)** | -20% | [redacted] | [redacted] | [redacted] | [redacted] |
| | -30% | [redacted] | [redacted] | [redacted] | [redacted] |
| | -40% | [redacted] | [redacted] | [redacted] | [redacted] |
| | -50% | [redacted] | [redacted] | [redacted] | [redacted] |
| | -60% | [redacted] | [redacted] | [redacted] | [redacted] |

**Results in the FL ITT group**

Results for the revised model assumptions for the entire GALLIUM FL ITT population (low, intermediate and high) FLIPI are summarized in **Table 21**. Disaggregated QALYs gained are presented in **Table 22** and disaggregated costs are summarized in **Table 23**, respectively.

**Table 21: Deterministic base case results (FL ITT)**

| Technologies | Total Costs (£) | Total LYG | Total QALYs | Inc Costs (£) | Inc LYG | Inc QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| G-chemo+G | [redacted] | 13.06 | 9.95 | | | | |
| R-chemo+R | [redacted] | 12.49 | 9.36 | [redacted] | 0.57 | 0.59 | [redacted] |

Values in the table are discounted and half cycle corrected

**Table 22: Summary of QALY gain by health state (FL ITT)**

| | G-chemo+G | R-chemo+R | Difference | Absolute | % of absolute |
|---|---|---|---|---|---|
| **Health state** | | | | | |
| Progression free survival | 7.76 | 6.94 | 0.82 | 0.82 | 78% |
| Progression < 2 yrs | 0.27 | 0.35 | -0.08 | 0.08 | 8% |
| Progression > 2 yrs | 1.93 | 2.08 | -0.15 | 0.15 | 14% |
| Total | 9.95 | 9.36 | 0.59 | 1.05 | 100% |

Values in the table are discounted and half cycle corrected

**Table 23: Summary of predicted resource use by category of cost (FL ITT)**

| State | Cost (G-chemo) | Cost (R-chemo) | Cost difference | Absolute difference | % of absolute |
|---|---|---|---|---|---|
| **PFS** | | | | | |
| Gazyvaro | [redacted] | 0 | [redacted] | [redacted] | [redacted] |
| MabThera | 0 | [redacted] | [redacted] | [redacted] | [redacted] |
| Chemotherapy | 298 | 295 | 3 | 3 | [redacted] |
| Drug Administration | 6,666 | 4,500 | 2,167 | 2,167 | [redacted] |
| Adverse Events | 1,210 | 988 | 222 | 222 | [redacted] |
| Supportive Care | 8,538 | 7,879 | 659 | 659 | [redacted] |
| *PFS Total* | 44,621 | 29,973 | 14,649 | | |
| | | | | | |
| Supportive care and subsequent treatment costs | 7,507 | 8,992 | -1,485 | 1,485 | [redacted] |
| **Total PD & PFS** | [redacted] | [redacted] | [redacted] | [redacted] | 100% |

Values in the table are discounted and half cycle corrected

## References


ALPEROVICH A, BATLEVI C, SMITH K, YING Z, SOUMERAI J, COPELAND A, JOFFE E, CARON P & P, D. 2016. Benchmark of Progression Free Survival for Multiple Lines of Therapy in Follicular Lymphoma Treated in the Rituximab Era. *Blood,* 128**,** 2955.

BACHY, E., HOUOT, R., MORSCHHAUSER, F., SONET, A., BRICE, P., BELHADJ, K., CARTRON, G., AUDHUY, B., FERME, C., FEUGIER, P., SEBBAN, C., DELWAIL, V., MAISONNEUVE, H., LE GOUILL, S., LEFORT, S., BROUSSE, N., FOUSSARD, C., SALLES, G. & GROUPE D'ETUDE DES LYMPHOMES DE, L. A. 2013. Long-term follow up of the FL2000 study comparing CHVP-interferon to CHVP-interferon plus rituximab in follicular lymphoma. *Haematologica,* 98**,** 1107-14.

CASULO, C., BYRTEK, M., DAWSON, K. L., ZHOU, X., FARBER, C. M., FLOWERS, C. R., HAINSWORTH, J. D., MAURER, M. J., CERHAN, J. R., LINK, B. K., ZELENETZ, A. D. & FRIEDBERG, J. W. 2015. Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study. *J Clin Oncol,* 33**,** 2516-22.

CASULO, C., NASTOUPIL, L., FOWLER, N. H., FRIEDBERG, J. W. & FLOWERS, C. R. 2017. Unmet needs in the first-line treatment of follicular lymphoma. *Ann Oncol,* 28**,** 2094-2106.

CHESON BD, TRNĚNÝ M, BOUABDALLAH K, DUECK G, GRIBBEN J, LUGTENBURG JP, PRESS O, SALLES GA, FINGERLE-ROWSON G, MATTIELLO F, WASSNER-FRITSCH E & SEHN LH 2016. 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 Diego.

DREYLING, M., GHIELMINI, M., RULE, S., SALLES, G., VITOLO, U. & LADETTO, M. 2016. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol,* 27**,** v83-v90.

GOEDE, V., FISCHER, K., BOSCH, F., FOLLOWS, G., FREDERIKSEN, H., CUNEO, A., LUDWIG, H., CROMPTON, N., MAURER, J., UGUEN, M., FINGERLE-ROWSON, G. & HALLEK, M. 2015. Updated survival analysis from the CLL11 study: Obinutuzumab versus rituximab in chemoimmunotherapy-treated patients with chronic lymphocytic leukemia. *Blood,* 126**,** 1733.

GOLAY, J., DA ROIT, F., BOLOGNA, L., FERRARA, C., LEUSEN, J. H., RAMBALDI, A., KLEIN, C. & INTRONA, M. 2013. Glycoengineered CD20 antibody obinutuzumab activates neutrophils and mediates phagocytosis through CD16B more efficiently than rituximab. *Blood,* 122**,** 3482-91.

HEROLD, M., SCHOLZ, C. W., ROTHMANN, F., HIRT, C., LAKNER, V. & NAUMANN, R. 2015. Long-term follow-up of rituximab plus first-line mitoxantrone, chlorambucil, prednisolone and interferon-alpha as maintenance therapy in follicular lymphoma. *J Cancer Res Clin Oncol,* 141**,** 1689-95.

KAHL, B. S., BARTLETT, N. L., LEONARD, J. P., CHEN, L., GANJOO, K., WILLIAMS, M. E., CZUCZMAN, M. S., ROBINSON, K. S., JOYCE, R., VAN DER JAGT, R. H. & CHESON, B. D. 2010. Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma: results from a Multicenter Study. *Cancer,* 116**,** 106-14.

LATIMER, N. R. 2013. Survival analysis for economic evaluations alongside clinical trials--extrapolation with patient-level data: inconsistencies, limitations, and a practical guide. *Med Decis Making,* 33**,** 743-54.

MCNAMARA, C., DAVIES, J., DYER, M., HOSKIN, P., ILLIDGE, T., LYTTELTON, M., MARCUS, R., MONTOTO, S., RAMSAY, A., WONG, W. L. & ARDESHNA, K. 2012. Guidelines on the investigation and management of follicular lymphoma. *Br J Haematol,* 156**,** 446-67.

MOSSNER, E., BRUNKER, P., MOSER, S., PUNTENER, U., SCHMIDT, C., HERTER, S., GRAU, R., GERDES, C., NOPORA, A., VAN PUIJENBROEK, E., FERRARA, C., SONDERMANN, P., JAGER, C., STREIN, P., FERTIG, G., FRIESS, T., SCHULL, C., BAUER, S., DAL PORTO, J., DEL NAGRO, C.,

DABBAGH, K., DYER, M. J., POPPEMA, S., KLEIN, C. & UMANA, P. 2010. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. *Blood,* 115**,** 4393-402.

PAPAIOANNOU, D., RAFIA, R., RATHBONE, J., STEVENSON, M., BUCKLEY WOODS, H. & STEVENS, J. 2012. Rituximab for the first-line treatment of stage III-IV follicular lymphoma (review of Technology Appraisal No. 110): a systematic review and economic evaluation. *Health Technol Assess,* 16**,** 1-253, iii-iv.

POTT C, HOSTER E, KEHDEN B, UNTERHALT M, HEROLD M, VAN DER JAGT, R. H., JANSSENS A, KNEBA M, MAYER J, POCOCK C, DANESI N, FINGERLE-ROWSON G, HARBRON C, MUNDT K, MARCUS R & W, H. Minimal residual disease in patients with follicular lymphoma treated as first-line with obinutuzumab or rituximab-based immunochemotherapy in the Phase III GALLIUM study. American Society of Hematology, 2016.

SCHULZ, H., BOHLIUS, J., SKOETZ, N., TRELLE, S., KOBER, T., REISER, M., DREYLING, M., HEROLD, M., SCHWARZER, G., HALLEK, M. & ENGERT, A. 2007. Chemotherapy plus Rituximab versus chemotherapy alone for B-cell non-Hodgkin's lymphoma. *Cochrane Database Syst Rev***,** CD003805.

VIDAL, L., GAFTER-GVILI, A., SALLES, G., BOUSSETA, S., OBERMAN, B., RUBIN, C., VAN OERS, M. H., FORTPIED, C., GHIELMINI, M., PETTENGELL, R., WITZENS-HARIG, M., DREGER, P., VITOLO, U., GOMES DA SILVA, M., EVANGELISTA, A., LI, H., FREEDMAN, L., HABERMANN, T. M. & SHPILBERG, O. 2017. Rituximab maintenance improves overall survival of patients with follicular lymphoma-Individual patient data meta-analysis. *Eur J Cancer,* 76**,** 216-225.

WILD D, WALKER M, PETTENGELL R & LEWIS G 2006. Utility Elicitation in Patients with Follicular Lymphoma. *Value Health,* 9**,** A294.

WILD D, T. M. 2005. Utility values in Follicular Lymphoma. Oxford Outcomes.

**NHS England submission on the NICE appraisal of the combination of obinutuzumab plus chemotherapy and then followed by maintenance obinutuzumab in the 1st line systemic treatment of follicular lymphoma (FL): response following ACD**

[redacted]

1. Roche wishes to narrow the use of obinutuzumab in combination with chemotherapy to the subgroup of patients scoring 2 or more using the Follicular Lymphoma International Prognostic Index (FLIPI). The manufacturer states that the trial was not designed to explore differences in outcome according to FLIPI subgroups (albeit a stratified outcome), yet then proceeds to use the subgroup data in this appraisal as a way of seeking an optimised NICE recommendation. A lack of follow-up duration in the trial in the better prognosis FLIPI 0-1 group could easily explain the apparent lack of difference so far between obinutuzumab and rituximab. NHS England is wary of such retrospective analyses being used in this way, just as it would not accept retrospective subgroup analyses which favoured seeking recommendations of obinutuzumab to women (HR 0.49 in the NEJM paper) but not men (HR 0.82) or to those without B symptoms (HR 0.57) but not those with B symptoms (HR 0.86).
2. NHS England also notes that Roche states in its post-ACD submission that 'FLIPI does not yet have a role in determining treatment selection since no differential benefit for currently available therapies has been demonstrated on FLIPI score'. It therefore seems strange for Roche then to retrospectively use a scoring system that is validated for prognosis but not for treatment selection.
3. NHS England notes that Roche has used incorrect figures for the HRG chemotherapy administration tariffs. Use of the correct figures may not make a large difference to the ICER but would increase the ICER for obinutuzumab. Rituximab infusion times can be shortened very significantly (there is published evidence to shorten the durations of infusion stated in the rituximab SPC) whereas those of obinutuzumab will remain significantly longer and in keeping with the SPC as obinutuzumab causes more infusion reactions and thus infusion times will remain prolonged. The HRG administration cost of R-CVP/R-CHOP for the first cycle would be £449 and for subsequent cycles would be £299. The cost of B-R for the first cycle would be £748 and for subsequent cycles would be £598. The tariff cost of subcutaneous rituximab is £150. The cost of Ob-CVP/Ob-CHOP for the first cycle would be £1047 and then for subsequent cycles would be £449. The tariff cost of B-Ob for the first cycle would be £1352 and for subsequent cycles would be £748. The cost of maintenance Ob would be £449.
4. Roche's base case uses the comparator of its own branded rituximab and Roche provides a scenario analysis that it regards as being unlikely in which there is an 80%

uptake of biosimilar rituximab which carries a 60% discount. Uptake in NHS England of biosimilar rituximab is currently rapid and faster than anticipated and much faster than previous biosimilars. Use of biosimilar rituximab is subject to a CQUIN. NHS England expects a [redacted] uptake of biosimilar rituximab to be in place by Q3/2018 and [redacted]

Prof Peter Clark

NHS England Chemotherapy Lead and National Clinical Lead for the Cancer Drugs Fund

October 2017

# Comments on the ACD Received from the Public through the NICE Website

| | |
|---|---|
| **Name** | [redacted] |
| **Role** | NHS Professional |
| **Other role** | Consultant Haematologist |
| **Organisation** | |
| **Location** | England |
| **Conflict** | No |
| **Notes** | |
| **Comments on the ACD:** | |
| The PFS benefit of 30% is significant for all patients as clinically their concern is time to next treatment. This is significant for younger patients who want to delay 2nd treatments as long as possible. NICE has also previously approved single agent rituximab for asymptomatic advanced patients in order to delay time to next treatment based on economic benefit in older patients. This would be in concordance with a benefit in older people having obinutuzumab first line and an additional 30% PFS benefit and having non-lymphoma mortality prior to need for next treatment. | |


in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

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# Obinutuzumab for untreated advanced follicular lymphoma

## 2nd ADDENDUM

## Critique on the additional evidence submitted in response to the ACD

**Produced by** Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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## 1. Critique on the additional clinical effectiveness evidence

The company changed the eligible patient population from ITT to the subgroup of patients with intermediate or high FLIPI score. The company considered that these patients are at greater risk of relapse and therefore they have the highest clinical unmet need.

The patient characteristics of this subgroup and the complete ITT population are presented in Table 2 of the new submission (appendix to the ACD response). Based on the information provided in this table, nothing seems to suggest that these two populations are not comparable.

However, the subgroup data presented in the new submission are from the September 2016 data-cut, whereas the original subgroup data reported in the company submission were from the January 2016 data-cut. Therefore, the ERG could not validate any of these numbers against the original data presented by the company.

Furthermore, there was no information about the distribution of the background therapy (CVP, CHOP or bendamustine) in the 'higher risk' subgroup.

It was also unclear to the ERG if a change in a patient's FLIPI score (from low/moderate risk to intermediate/high risk or vice versa) would lead to a change in the initially assigned anti-lymphoma treatment, even though the patient was still progression-free.

Finally, it should be emphasised that the uncertainty was high in the original analyses. Choosing the subgroup of intermediate or high FLIPI score resulted in excluding 20% of the trial population from the updated analyses, which will only increase the uncertainty.

## 2. Critique on the additional cost-effectiveness evidence

### *2.1 Model structure*

The company did not revise the model structure, however argued that the existing model structure can address the following concerns expressed by the committee.

1. Disease progression is more frequently assessed in clinical trials than clinical trials
2. The response (to determine whether people were offered maintenance therapy) was not modelled explicitly
3. Time between disease progression and subsequent treatments was not taken into the account
4. The model structure may not accurately reflect the patient's experience during disease expression.

Due to lack of enough data and time, the ERG could not assess the validity of the arguments provided by the company to the concerns expressed by the committee. Regarding the second concern, the ERG considers using time to off treatment data from the trial might be plausible to determine the patients that were offered maintenance therapy due to response. About the third point, the ERG would like to draw attention to the fact that the company based its argumentation that using PFS instead of TTNALT would be more conservative based on the high/intermediate risk TTNALT data (Figure 7 in the Appendix to the ACD response).

### *2.2 Duration of treatment effect for anti-CD20 treatments*

The company provided some additional evidence for the long-term effect of anti-CD20 treatments.

Due to the similar mechanisms of action, the company suggested that the long-term treatment duration effect seen for rituximab maintenance treatment observed in (Bachy et al. 2013 and Herold et al. 2015) would hold true for obinutuzumab, as well. However, it should be noted that the long-term duration of treatment effect of rituximab was observed against chemotherapy, it is unclear to the ERG how the long-term treatment duration effect of rituximab (against chemotherapy) would inform the long-term duration effect of obinutuzumab (against rituximab, another anti-CD20).

The company suggested that there is no evidence of a finite duration of treatment effect in CLL11 study (Goede et al. 2015), however the ERG considers that the long-term treatment effect (obinutuzumab vs rituximab) is still unclear, since the treatment effect in (Goede et al. 2005) study was in a different indication (chronic lymphocytic leukemia) and furthermore, the study report the PFS results up to 40 months follow-up at most.

### *2.3 Extrapolation of PFS for rituximab and obinutuzumab*

The company updated its assumptions on the PFS extrapolation. Following changes were applied when compared to the company base-case assumptions:

1. The company used PFS data based on IRC assessment instead of PFS data based on investigator assessment.
2. The company followed an independent modelling approach (for the PFS of rituximab and obinituzumab arms) instead of a joint modelling approach for both arms, using treatment as a covariate in parametric survival regressions.
3. The company selected log-logistic distribution for the extrapolation of the PFS curves instead of the Weibull distribution.

4. The company assumed that the treatment effect (defined on PFS) is maintained instead of assuming no treatment effect after a certain point in time (e.g. 108 months)

The ERG considers the change explained in the first bullet point above concerning the PFS data choice of the company (i.e. IRC) as plausible. However, the ERG has concerns about the consequences of the other changes explained in the second, third and fourth bullet points.

The ERG considers implementing independent models might be plausible, as the visual assessments for the proportional hazards assumption in the original submission could be deemed as inconclusive. The company argued that independent modelling of PFS curves would lead to more conservative estimates, based on the results given in Table 6 of the Appendix to the ACD response. The ERG would like to point out that the data in Table 6 were only for the intermediate/high FLIPI subgroup, and under the maximum treatment duration assumption of 9 years. It is unclear to the ERG if independent modelling approach would be always more conservative than joint modelling approach under all subgroup/assumption possibilities.

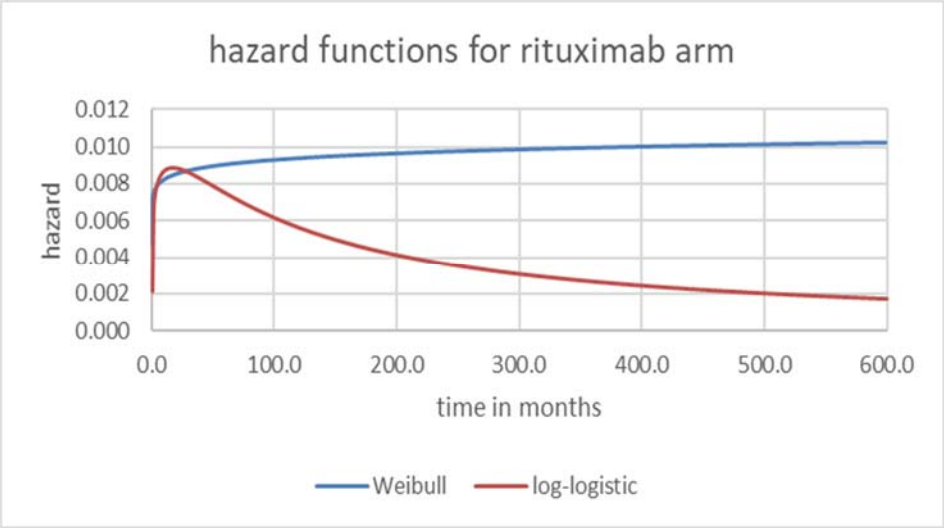
The company chose log-logistic distribution for the extrapolation of the independent models fitted to the higher FLIPI subgroup PFS data. The steps and the logic that led to the final choice of extrapolation distribution were not clear to the ERG. The AIC/BIC figures given in Table 5 of the Appendix to the ACD response suggested that Log-normal distribution would give the best statistical fit. However, the company did not base its decision of distribution on AIC/BIC results, but rather on the expected behaviour of hazard of progression in time. The company, based on long-term follow-up data from rituximab & chemotherapy induction studies and clinical opinion, suggested that the hazard of progression should be a declining or a constant function, which is in conflict with the use of Weibull function for extrapolation having an increasing hazard of progression.

The ERG can confirm that using Weibull function would result in a slowly increasing hazard for progression (can be seen in Figure 1), however, the ERG is not sure if log-logistic distribution is the only distribution that would have a decreasing/constant hazard. Furthermore, the ERG is not aware if there is a clinical consensus on the expected hazard rate behaviour for the PFS of the follicular lymphoma patients under anti-lymphoma treatment. Also, the ERG realised that not all the distribution results were presented (e.g. Gompertz distribution). As it can be seen in Table 1, using Gompertz distribution for extrapolation would lead to smaller mean life years in PFS for patients receiving obinutuzumab when independent modelling approach was followed.

**Table 1 PFS extrapolation results when treatment effect is assumed to be maintained.**

| Model | Time in PFS | Incremental LY in PFS (undiscounted) Obinutuzumab vs. Rituximab | |
|---|---|---|---|
| | | Joint Modelling | Independent Modelling |
| Gompertz (intermediate/high FLIPI score subgroup) | Mean | 2.69 | -2.05 |
| | Median | 2.58 | 0.42 |
| Gompertz (ITT) | Mean | 2.45 | -2.04 |
| | Median | 2.33 | 0.33 |

**Figure 1: Hazard functions for the fitted Weibull and log-logistic distributions fitted to the IRC PFS data from the ITT population from the rituximab arm of the GALLIUM trial**




By implementing independent models for the rituximab and the obinutuzumab arms, the company argued that they implemented the potential decline in the treatment effect in the long-term PFS extrapolation and therefore any assumption on the finite treatment effect duration was unnecessary.

The ERG agrees that with the independent log-logistic extrapolation for the PFS, treatment effect (e.g. hazard ratio between the obinutuzumab and rituximab arms) tends to decline over time without any further assumptions on treatment effect duration, however, the ERG has concerns whether this would result in a more conservative estimate on the treatment effect as the company suggested. In Figure 2 and Figure 3, the hazard ratios as a function of time, under the new company base-case assumptions (independent log-logistic extrapolation) as well as under previous ERG preferred base-case assumptions (joint Weibull extrapolation with 5-year treatment effect duration) are plotted for the PFS of the ITT population and for the PFS of the intermediate/high FLIPI score subpopulation, respectively.

**Figure 2: PFS hazard ratios in time (obinituzumab vs. rituximab) from the new company base-case (red) and the previous ERG preferred base-case (blue) based on ITT GALLIUM population**

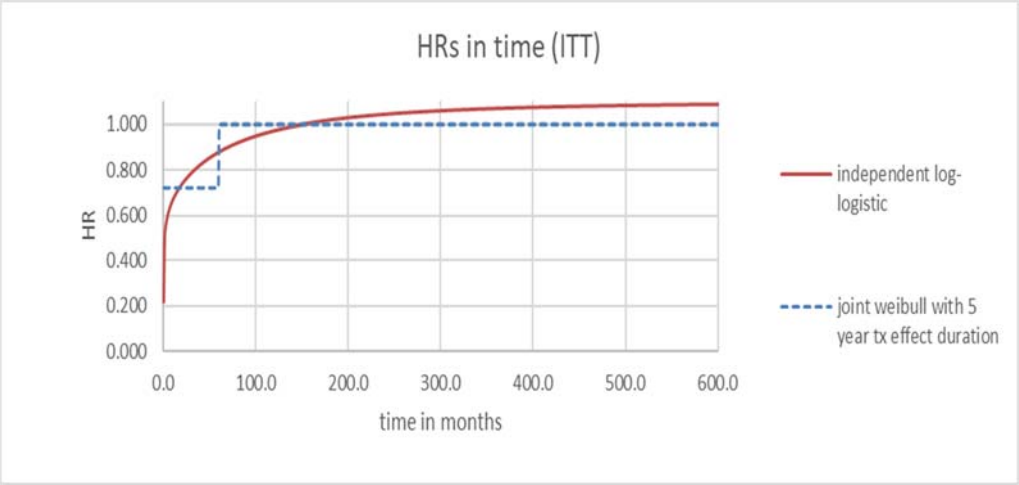
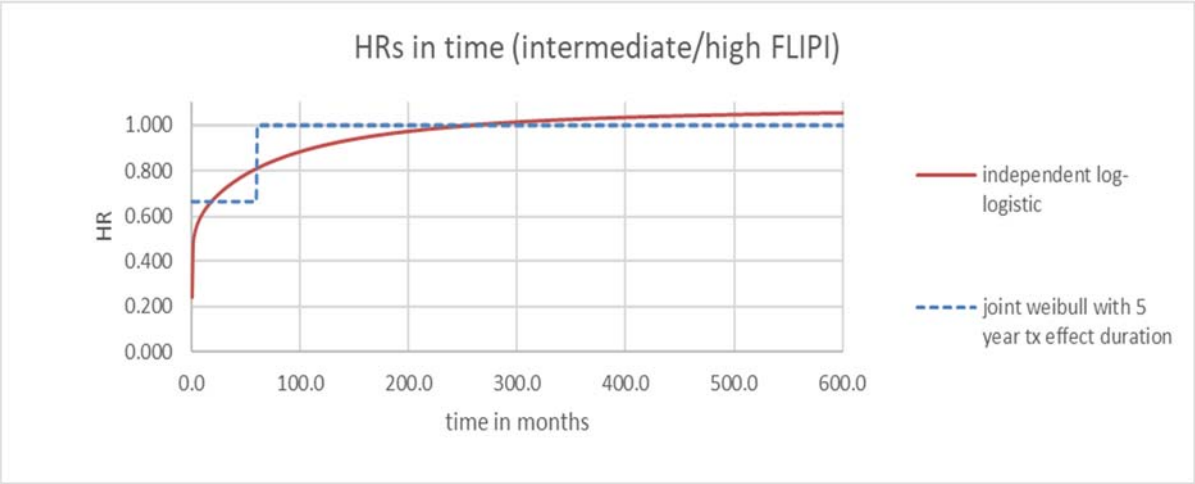


**Figure 3: PFS hazard ratios in time (obinituzumab vs. rituximab) from the new company base-case (red) and the previous ERG preferred base-case (blue) based on intermediate/high FLIPI score subpopulation from GALLIUM**




As it can be seen from Figure 2 and Figure 3, assumptions in the new company base-case might lead to less conservative treatment effect duration realisations compared to the ERG base-case. For ITT population, PFS hazard ratio is less than one for longer than ten years, whereas for the intermediate/high FLIPI score subpopulation, it takes almost 20 years until the PFS hazard ratio reaches one.

Finally, in the new company base case, (IRC data, independent modelling and log-logistic distribution extrapolation with indefinite treatment duration assumption), at the end of 10 years, 45% of the patients receiving rituximab are still expected to be progression free and alive. The ERG would like to emphasize that this figure overestimates the 10-year PFS expected figures (between 30% and 40%) which were provided by the clinical experts that were communicated by the company in the original submission. Note that these figures were used in the PFS extrapolation choice in the original company submission (i.e. a candidate distribution was excluded if it generated a 10-year PFS estimate outside this margin).

### *2.4 Overall survival*

The company used differentiated death rates for both arms from GALLIUM trial in the PFS and early progressed disease (PD) states. For the late PD states, a pooled death rate from PRIMA trial was assumed. These inputs resulted in a mean overall survival benefit of 0.94 years in the new company base-case for the ITT population and 1.27 years for the intermediate/high FLIPI subgroup. The ERG deems including OS benefit for obinutuzumab without any mature OS comparative data (obinutuzumab vs. rituximab in follicular lymphoma patients) would be speculative. The studies mentioned in the new submission were either for rituximab vs. chemotherapy or for obinutuzumab vs. chemotherapy for rituximab refractory patients.

### *2.5 HRQOL*

The company reconsidered the approach presented in the original submission for modelling utilities in the PD health states. In particular, the company proposed using different values for early (0.62) and late (0.77) progression (both based on Wild et al. 2006). In addition, GALLIUM utility estimates per arm for PFS were implemented as suggested by the ERG and to be consistent with the implementation of pre- and post-progression mortality rate estimates per arm preferred by the committee.

The ERG agrees with the approach of the company of considering different utility values for early and late progressed-disease. Actually, the ERG already asked the company whether this was a reasonable assumption in the clarification letter (question B21). In their response, the company argued that, while this was plausible, they were not aware of any study reporting different utilities for patients progressing early or late. Therefore, it remains uncertain whether the new proposed utility values are representative for the health states. The company provided the report from Wild et al. (2005) from where the PD utilities were sourced and the ERG could verify their values. However, some of the limitations mentioned in the ERG report are still present. The study was unpublished (it is a company's internal report) and it is inconsistent with the results of the GALLIUM trial. Furthermore, the ERG questions to what extent utility values from 2006 can be seen as representative of UK patients currently suffering with advanced FL.

In addition, in its new base case, the company used treatment specific utility values from the GALLIUM trial instead of pooled utility values. These treatment-specific and pooled utility estimates can be seen in Table 2.

**Table 2: Pooled and treatment specific utility estimates for the PFS health states used in the model**

| PFS health states | Treatment arm | Pooled Utility | Treatment-specific Utility |
|---|---|---|---|
| Induction - off tx | Obinutuzumab | 0.772 | 0.765 |
| | Rituximab | 0.772 | 0.779 |
| Maintenance & follow-up - off tx | Obinutuzumab | 0.818 | 0.826 |
| | Rituximab | 0.818 | 0.810 |
| Induction - On tx | Obinutuzumab | 0.823 | 0.823 |
| | Rituximab | 0.823 | 0.824 |
| Maintenance & follow-up - on tx | Obinutuzumab | 0.831 | 0.834 |
| | Rituximab | 0.831 | 0.828 |

Actually, the ERG suggested using treatment specific estimates for PFS state utilities in its previous critique, in terms of consistency with the approach followed for PFS/early progression death rates. However, since treatment specific disutility for adverse events are also incorporated in the model, the ERG thought this would lead to a double counting issue. Furthermore, the ERG had difficulty in interpreting the additional utility benefit of the obinutuzumab treatment in the PFS health states, despite more frequent side effects.

As EQ5D measures were taken only at certain points of time (e.g. last assessment before progression and first assessment after progression), and the utility estimates are obtained from a mixed level statistical analysis with some baseline covariate adjustments, without seeing the details of the treatment-specific analysis, the ERG suspects that the uncertainty around the treatment-specific utility estimates might be higher than the treatment-specific death estimates. Furthermore, the ERG noticed that the PFS

utility estimates do not change when intermediate/high risk FLIPI score subgroup is selected. Due to these uncertainty and double counting issues related with the utility estimates, the ERG is in favour of using pooled utility estimates instead of treatment specific utility estimates.

### *2.6 Costs*

The company updated its administration costs with the latest 2017 codes, which were given in the Table 12 from the Appendix to the response to the ACD document. The ERG deems using the updated administration costs as plausible.

The company investigated several scenarios with costs from subsequent lines of treatment, using time to next anti-lymphoma treatment KM data. The company suggested that the gap between PFS and TTNALT is higher for the patients receiving obinutuzumab compared to the patients receiving rituximab, therefore using PFS instead of TTNALT was a more conservative approach. The ERG can verify that using TTNALT with different extrapolations under the new company base-case, for both ITT and intermediate/high risk subgroup populations, would result in lower ICERs, however it could not check the correctness of the implementation of the TTNALT, and could not check if using TTNALT would always lead to a lower ICER in all possible scenarios due to time limitation.

The company discussed the biosimilar uptake for rituximab would not reach 100% based on other biosimilar uptake examples for anti-tumour necrosis factor agents (e.g. etanercept and infliximab). However, the ERG considers the 100% biosimilar uptake scenario might be plausible, as etanercept and infliximab were agents used in other indications and the originator prices were also decreased after biosimilars were in the market.

Finally, in the new submission model, the vial sharing assumption was assumed for both rituximab and obinutuzumab. Furthermore, the actual dose data for obinutuzumab given during induction in addition to CVP chemotherapy was lacking in the model.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# Obinutuzumab for untreated advanced follicular lymphoma

## 3rd ADDENDUM

## Exploratory analyses undertaken by the ERG

**Produced by** Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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## 1. ERG preferred base-case

After the new evidence submitted by the company before the ACD meeting, the ERG revised its preferred base-case. The additional assumptions made by the ERG on the new company base-case model are as follows:

1. In the new company submission, pooled utility estimates from the GALLIUM trial was used for both arms instead of treatment specific utility estimates. Even though the ERG suggested the use of treatment specific utility estimates in its previous critique (of the original company submission), it is then realised that incorporating both treatment specific utility estimates and adverse event (AE) related disutilities in the model might cause double counting. Furthermore, not sufficient detail of the statistical analysis (for the treatment specific utility estimates) was provided by the company; therefore, the ERG cannot judge the plausibility of using these estimates. Furthermore, the ERG is uncertain about the clinical relevance of the differences between the utility estimates of the PFS health states of two arms in the GALIUM trial (as can be seen in Table 2 in the 2nd Addendum to the ERG report).
2. As discussed in its critique to the new evidence, the ERG considers the evidence on the maintenance of the treatment effect for obinutuzumab vs. rituximab in follicular lymphoma patients as inconclusive, therefore, a duration of five years was assumed for the treatment effect of obinutuzumab vs. rituximab (follow up of GALLIUM trial).
3. Vial sharing is not assumed for obinutuzumab.

The results of the new ERG preferred base-case are shown below for both ITT and intermediate/high FLIPI populations in Table 1 and Table 2, respectively.

**Table 1: ITT population, IRC PFS dataset, independent log-logistic models for PFS with no treatment effect after 5 years**

| | Total Costs (£) | Tot LYG | Tot QALYs | Inc Costs (£) | Inc LYG | Inc QALYs | ICER (£) |
|---|---|---|---|---|---|---|---|
| Obin-Chemo+Obin | [redacted] | 13.03 | 9.85 | [redacted] | 0.54 | 0.44 | [redacted] |
| R-Chemo+R | [redacted] | 12.49 | 9.42 | - | - | - | - |
| ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY = quality adjusted life year | | | | | | | |

**Table 2: Intermediate/high FLIPI population – IRC PFS dataset, independent log-logistic models for PFS with no treatment effect after 5 years**

| | Total Costs (£) | Tot LYG | Tot QALYs | Inc Costs (£) | Inc LYG | Inc QALYs | ICER (£) |
|---|---|---|---|---|---|---|---|
| Obin-Chemo+Obin | [redacted] | 12.82 | 9.70 | [redacted] | 0.69 | 0.56 | [redacted] |
| R-Chemo+R | [redacted] | 12.14 | 9.14 | | | | |
| ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY = quality adjusted life year | | | | | | | |

## 2. ERG exploratory scenarios

A number of additional scenarios were explored by the ERG on its updated preferred base-case. The main idea behind these scenarios was to explore the sensitivity of the ICER to the assumptions on the PFS modelling method (independent vs. joint modelling), the choice of the PFS extrapolation probability distribution and the duration of the obinutuzumab treatment effect. The results for both ITT and intermediate/high FLIPI populations are presented in Table 3 and Table 4, respectively.

**Table 3: Scenario analyses: ITT population – IRC PFS dataset**

| | | Independent modelling | | | Joint modelling | | |
|---|---|---|---|---|---|---|---|
| **Treatment effect duration** | **PFS distribution** | **Incremental Costs (£)** | **Incremental QALYs** | **ICER (£)** | **Incremental Costs (£)** | **Incremental QALYs** | **ICER (£)** |
| 5 years | Exponential | [redacted] | 0.42 | [redacted] | [redacted] | 0.42 | [redacted] |
| | Weibull | [redacted] | 0.41 | [redacted] | [redacted] | 0.40 | [redacted] |
| | Log-logistic | [redacted] | 0.44 | [redacted] | [redacted] | 0.44 | [redacted] |
| | Log-normal | [redacted] | 0.45 | [redacted] | [redacted] | 0.47 | [redacted] |
| | Gompertz | [redacted] | 0.40 | [redacted] | [redacted] | 0.40 | [redacted] |
| Maintained | Exponential | [redacted] | 0.59 | [redacted] | [redacted] | 0.59 | [redacted] |
| | Weibull | [redacted] | 0.46 | [redacted] | [redacted] | 0.59 | [redacted] |
| | Log-logistic | [redacted] | 0.47 | [redacted] | [redacted] | 0.55 | [redacted] |
| | Log-normal | [redacted] | 0.51 | [redacted] | [redacted] | 0.55 | [redacted] |
| | Gompertz | [redacted] | 0.15 | [redacted] | [redacted] | 0.58 | [redacted] |

ICER = incremental cost effectiveness ratio; PFS = progression-free survival; QALY = quality adjusted life year

**Table 4: Scenario analyses: high/intermediate FLIPI population– IRC PFS dataset**

| | | Independent model | | | Joint model | | |
|---|---|---|---|---|---|---|---|
| **Treatment effect duration** | **PFS distribution** | **Incremental Costs (£)** | **Incremental QALYs** | **ICER (£)** | **Incremental Costs (£)** | **Incremental QALYs** | **ICER (£)** |
| 5 years | Exponential | [redacted] | 0.52 | [redacted] | [redacted] | 0.52 | [redacted] |
| | Weibull | [redacted] | 0.52 | [redacted] | [redacted] | 0.50 | [redacted] |
| | Log-logistic | [redacted] | 0.56 | [redacted] | [redacted] | 0.56 | [redacted] |
| | Log-normal | [redacted] | 0.58 | [redacted] | [redacted] | 0.58 | [redacted] |
| | Gompertz | [redacted] | 0.51 | [redacted] | [redacted] | 0.49 | [redacted] |
| Maintained | Exponential | [redacted] | 0.75 | [redacted] | [redacted] | 0.75 | [redacted] |
| | Weibull | [redacted] | 0.62 | [redacted] | [redacted] | 0.74 | [redacted] |
| | Log-logistic | [redacted] | 0.63 | [redacted] | [redacted] | 0.69 | [redacted] |
| | Log-normal | [redacted] | 0.69 | [redacted] | [redacted] | 0.68 | [redacted] |
| | Gompertz | [redacted] | 0.17 | [redacted] | [redacted] | 0.72 | [redacted] |

ICER = incremental cost effectiveness ratio; PFS = progression-free survival; QALY = quality adjusted life year

Finally, the ERG conducted one final additional scenario analysis on the new ERG preferred base-case. In this scenario analysis, instead of using treatment specific death rate estimates for PFS and early progression health states derived from the GALLIUM trial, the ERG incorporated pooled death rate estimates from the GALLIUM trial, for both arms. The results for both ITT and intermediate/high FLIPI populations are presented in Table 5 and Table 6, respectively.

**Table 5: ITT population, IRC PFS dataset, independent log-logistic models for PFS with no treatment effect after 5 years, pooled death rates**

| | Total Costs (£) | Tot LYG | Tot QALYs | Inc Costs (£) | Inc LYG | Inc QALYs | ICER (£) |
|---|---|---|---|---|---|---|---|
| Obin-Chemo+Obin | [redacted] | 13.03 | 9.86 | [redacted] | 0.53 | 0.44 | [redacted] |
| R-Chemo+R | [redacted] | 12.50 | 9.42 | | | | |
| ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY = quality adjusted life year | | | | | | | |

**Table 6: Intermediate/high FLIPI population, IRC PFS dataset, independent log-logistic models for PFS with no treatment effect after 5 years, pooled death rates**

| | Total Costs (£) | Tot LYG | Tot QALYs | Inc Costs (£) | Inc LYG | Inc QALYs | ICER (£) |
|---|---|---|---|---|---|---|---|
| Obin-Chemo+Obin | [redacted] | 12.84 | 9.72 | [redacted] | 0.72 | 0.59 | [redacted] |
| R-Chemo+R | [redacted] | 12.13 | 9.12 | | | | |
| ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY = quality adjusted life year | | | | | | | |


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# Obinutuzumab for untreated advanced follicular lymphoma

## 4th ADDENDUM

## Administration costs

**Produced by** Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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NHS England noted that the company used incorrect figures for the HRG chemotherapy administration tariffs. The HRG administration cost of R-CVP/R-CHOP for the first cycle would be £449 and for subsequent cycles would be £299. The cost of Benda-R for the first cycle would be £748 and for subsequent cycles would be £598. The tariff cost of subcutaneous rituximab is £150. The cost of Obin-CVP/Obin-CHOP for the first cycle would be £1047 and then for subsequent cycles would be £449. The tariff cost of Benda-Obin for the first cycle would be £1352 and for subsequent cycles would be £748. The cost of maintenance with Obin would be £449.

The results of the new ERG preferred base-case after correcting the administration costs are shown below for both ITT and intermediate/high FLIPI populations in Table 1 and Table 2, respectively.

**Table 1: ITT population, IRC PFS dataset, independent log-logistic models for PFS with no treatment effect after 5 years**

| | Total Costs (£) | Tot LYG | Tot QALYs | Inc Costs (£) | Inc LYG | Inc QALYs | ICER (£) |
|---|---|---|---|---|---|---|---|
| Obin-Chemo+Obin | [redacted] | 13.03 | 9.85 | [redacted] | 0.54 | 0.44 | [redacted] |
| R-Chemo+R | [redacted] | 12.49 | 9.42 | - | - | - | - |
| ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY = quality adjusted life year | | | | | | | |

**Table 2: Intermediate/high FLIPI population – IRC PFS dataset, independent log-logistic models for PFS with no treatment effect after 5 years**

| | Total Costs (£) | Tot LYG | Tot QALYs | Inc Costs (£) | Inc LYG | Inc QALYs | ICER (£) |
|---|---|---|---|---|---|---|---|
| Obin-Chemo+Obin | [redacted] | 12.82 | 9.70 | [redacted] | 0.69 | 0.56 | [redacted] |
| R-Chemo+R | [redacted] | 12.14 | 9.14 | - | - | - | - |
| ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY = quality adjusted life year | | | | | | | |


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# Obinutuzumab for untreated advanced follicular lymphoma

## 5th ADDENDUM

## Clarification on the company submission model assumptions

**Produced by** Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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In this addendum, additional clarifications on the progression free survival (PFS) extrapolation from the new company submission model for the high and intermediate FLIPI subgroup are provided.

In the new company base-case, the company assumed treatment-specific utilities from the GALLIUM trial for the pre-progression health states, followed an independent modelling approach for PFS extrapolation and assumed no biosimilar uptake for IV rituximab.

In Table 1, proportion of patients in the rituximab arm, who are progression-free at 10 years for log-logistic, Gompertz, Weibull and exponential distributions for high and intermediate FLIPI subgroup are given.

**Table 1: Proportion of progression-free patients at 10 years in the rituximab arm for high and intermediate FLIPI subgroup**

| Distribution for PFS extrapolation | Proportion of patients that are progression-free at 10 years |
|---|---|
| Log-logistic | 41.3% |
| Gompertz | 36.7% |
| Weibull | 34.3% |
| Exponential | 36.7% |

By following an independent PFS extrapolation modelling approach, the company stated that there was no need for a finite treatment effect duration assumption. However, this approach leads to an "implied treatment effect duration", during which the hazard rate of the obinutuzumab arm is lower than the hazard rate of the rituximab arm. For high-intermediate FLIPI subgroup, when the exponential distribution is used for PFS extrapolation, the PFS hazard rate of the obinutuzumab arm is always lower than the rituximab arm. Similarly, when the log-logistic distribution is used for PFS extrapolation, the PFS hazard rate of the obinutuzumab arm is lower than that of the rituximab arm at any time point before 20 years; and when the Weibull distribution is used for PFS extrapolation, the PFS hazard rate of the obinutuzumab arm is lower than that of the rituximab arm at any time point before 33 years.


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# Obinutuzumab for untreated advanced follicular lymphoma

## 6th ADDENDUM

## ERG comments on the company submission

**Produced by** Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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In this addendum, the ERG provides a critique to the latest cost effectiveness results submitted by the company. These main analyses were performed for patients with intermediate or high follicular lymphoma international prognostic index (FLIPI) and they were based on the following (committee's preferred) assumptions:

1. PFS extrapolation with individual Weibull functions (non-proportional hazard model, declining effect)
2. Independent assessed PFS (PFS-IRC);
3. PFS utilities from GALLIUM, pooled between study arms;
4. PD utilities based on literature values.
5. Revised administration tariff schedule as per NHSE ACD response and corrected actual dosing for Obin-CVP.

Furthermore, the company assumed a rituximab BS uptake with a market share of currently up to 40% as considered by the committee. Moreover, the company assumed a 60% discount for BS rituximab net price.

The company made the following model revisions:

1. A revised patient access scheme (PAS) for obinutuzumab consisting of an increased discount from [redacted]% to [redacted]%, changing the net price to £[redacted] per 1000mg vial.
2. Revised administration tariff schedule.
3. Corrected dosing schedule for Obin-CVP.
4. Implementation of fixed dosing for obinutuzumab. In the revised model, a fixed 1,000mg dose for all Obin-chemo or maintenance doses was used as a default as obinutuzumab is given as a fixed dose. This assumes no vial sharing (fixed dose administration) and no missed doses.

The company investigated the following cost effectiveness scenarios:

1. Scenario 1: preferred committee's assumptions and a treatment effect duration of up to 9 year.
2. Scenario 2: preferred committee's assumptions using an Exponential function and a treatment effect of up to 9 years.
3. Scenario 3: preferred committee's assumptions and assuming a treatment effect of 5 years (no effect after GALLIUM follow up period).
4. Scenario 4: preferred committee's assumptions using an Exponential function and a treatment effect duration of 5 years.

**ERG comment:** In the previous addendum, the cycle costs were incorrectly calculated by the ERG, which resulted in an overestimation of the administration costs. The costs presented in Table 3 in the company's addendum are correct except for the SB14Z reference costs, where £449 instead of £499 should have been reported. Nevertheless, in the electronic model submitted by the company this is correct. Furthermore, the company used NHS reference costs (instead of a national tariff prices) to inform the administration costs implemented in the model. The ERG agrees with this choice. The ERG could reproduce the ICERs presented by the company. Finally, the ERG would like to emphasize that they do not share the view of the company in considering the choice of PFS-IRC data and the duration of treatment effect of 5 to 9 years as conservative assumptions.