NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Idelalisib for treating follicular lymphoma refractory to 2 treatments [ID1379]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Idelalisib for treating follicular lymphoma refractory to 2 treatments [ID1379]

Contents:

The following documents are made available to consultees and commentators:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology Appraisal

Idelalisib for treating follicular lymphoma refractory to 2 treatments [ID1379]

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

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Evaluation Determination (FED). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Evaluation Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ECD separately from the organisations that nominated them. They do not have the right of appeal against the FED other than through the nominating organisation.

Commentators – Organisations that engage in the evaluation process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FED. These organisations include manufacturers of comparator technologies, Welsh Government, Healthcare Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council); other groups (for example, the NHS Confederation, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ECD 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 evaluation committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

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.

Comments received from consultees

Consultee	Comment	Response
Bloodwise	1- Although there are 'potential serious adverse affects' for people having idelalisib, we know there are often serious adverse effects associated from chemotherapy. People living with blood cancer may therefore tolerate the side-effects of idelalisib better than chemotherapy, in some cases. 2- We are disappointed that the data provided does not facilitate a reliable estimate of idelalisib's cost-effectiveness. However, we welcome NICE's proposals for the model to be improved. We hope that this could enable NICE to make a full assessment of its cost-effectiveness in future. 3- We do not agree with the decision not to recommend idelalisib on the NHS. We note, for example, the potential value of idelalisib as a treatment to the 'double-refractory' population, even if that benefit is only for a very short period of time, or the possibility that it could be used as a bridge to transplant. We therefore hope that the manufacturer will be able to provide sufficient further evidence to enable the treatment to be made available via routine commissioning.	Thank you for your comment. The appraisal consultation document (ACD) and final appraisal document (FAD) note that idelalisib and chemotherapy have different safety profiles and that idelalisib is generally well tolerated (see sections 3.2 and 3.21 of the FAD). The committee heard from the clinical experts that the different toxicity profiles for idelalisib and chemotherapy meant that people may not tolerate the specific adverse events of chemotherapy, but might tolerate those of idelalisib (section 3.3 of the FAD). The committee noted that the company's decision not to pursue a confirmatory randomised controlled trial after DELTA had resulted in an important gap in the evidence base, making it more difficult to carry out an informed assessment of the effectiveness of idelalisib (FAD section 3.6). In the absence of head-to-head comparisons, the committee took into account the indirect matching analyses presented by the company. However, it identified a number of concerns with all indirect analyses (FAD sections 3.11 to 3.14), including sparse data, matching on

Consultee	Comment	Response
		variables defined differently (FAD section 3.13) and analyses that did not censor patients having a transplant (FAD section 3.8). The committee therefore agreed that the evidence presented by the company lacked robustness and concluded that idelalisib was not a cost-effective use of NHS resource because of the range of ICERs presented (between £16,481 and £86,161 per QALY gained) and because of its concerns with the quality of the evidence.
Lymphoma Action	1- Has sufficient consideration been given to the fact patients might prefer an oral therapy with possibly different side effects than more intensive chemotherapy after several treatments? 2- Has sufficient consideration been given to the different mechanism of action of idelalisib compared with chemotherapy, and the psychological advantage this offers patients who might be reluctant to undergo more chemotherapy after failing this type of treatment in the past? 3- Have frailer patients who are unable to have chemotherapy been given sufficient consideration?	Thank you for your comment. 1- Clinical experts explained that some patients may tolerate specific adverse events from idelalisib when they may not tolerate those from chemotherapy (see section 3.3 of the FAD). 2- The committee noted that idelalisib had a different mechanism of action to other available treatments, which might bring psychological benefits for people reluctant to have more chemotherapy after it had previously failed, but it was also aware that no evidence had been submitted to support this (see section 3.29 of the FAD). 3- Committee concluded that best supportive care is an option for those who cannot have chemotherapy, and it was therefore an appropriate comparator (see section 3.3 of the FAD). However, the committee was not presented with clinical data for best supportive care (sections 3.8 and 3.16

Consultee	Comment	Response
		of the FAD)
Royal College of Pathologists/ British Society for Haematology	Thanks for these documents. They are extensive, detailed and give clear conclusions. My only comment is that the overall outcome is disappointing as this is an active agent that would be useful to use in some patients with difficult Follicular lymphoma and it's a shame that the non-randomised nature of the data sets assessed hasn't provided the adequate data necessary to enable access to this treatment.	Comment noted. The committee noted that the company's decision not to pursue a confirmatory randomised controlled trial after DELTA had resulted in an important gap in the evidence base, making it more difficult to carry out an informed assessment of the effectiveness of idelalisib (FAD section 3.6). In the absence of head-to-head comparisons, the committee took into account the indirect analyses presented by the company. However, it identified a number of concerns with all indirect analyses (FAD sections 3.11 to 3.14), including sparse data, matching on variables defined differently (FAD section 3.13) and analyses that did not censor patients having a transplant (FAD section 3.8). The committee therefore agreed that the evidence presented by the company lacked robustness and concluded that idelalisib was not a cost-effective use of NHS resource because of the range of ICERs presented (between £16,481 and £86,161 per QALY gained) and because of its concerns with the quality of the evidence.

Consultee	Comment	Response
Consensus of 15 clinical experts	Dear Sir / Madam, We are writing to encourage the NICE STA committee to approve the use of idelalisib in double refractory follicular lymphoma. Although follicular lymphoma is an indolent lymphoma with excellent survival for the majority of patients, it is increasingly recognised that there are a group of patients who have poor outcomes and will die of their disease. Much recent work has identified the so-called 'Progression of disease within 24 months of treatment initiation' or POD24 risk factor as a critical determinant for survival. For these patients the 5-year overall survival rate is only approximately 50%. This emphasises the consistent finding in follicular lymphoma that short remissions following R-chemo are associated with high risk disease. The 101-09 study (which included a significant number of patients from England) investigated idelalisib in a very high-risk group of patients – those who were refractory to both rituximab and an alkylating agent. As these patients were a high-risk relapsed group, one would expect them to be higher risk that the POD24 group described above, who were a group of patients at first relapse. They therefore represent a small group of patients with high unmet need. However, the long-term follow-up from the 101-09 study shows a median overall survival of 5 years which is much better than expected. Furthermore, the median PFS for the participants receiving idelalisib was longer than their prior line of treatment which is unusual in follicular lymphoma where remissions are usually thought to shorten with time. Furthermore, we collected the real-world results from UK patients treated with idelalisib when it was available on a named patient basis. Although the baseline characteristics of the patients were of course different from those in the 101-09 study, the results were very similar, suggesting that there was benefit outside of a clinical trial setting. We	Thank you for your comment. Within its decision making, the committee took into account the association of disease progression within 24 months of first relapse with an increased risk of death (see section 3.26 of the FAD), the improved overall survival of the latest DELTA (also known as 101-109 study) data cut (see section 3.5 of the FAD) and the comparison between DELTA and the real-world UK data (CUP) (see section 3.7 of the FAD). The committee noted that the company's decision not to pursue a confirmatory randomised controlled trial after DELTA had resulted in an important gap in the evidence base, making it more difficult to carry out an informed assessment of the effectiveness of idelalisib (FAD section 3.6). In the absence of head-to-head comparisons, the committee took into account the indirect analyses presented by the company. However, it identified a number of concerns with all indirect analyses (FAD sections 3.11 to 3.14), including sparse data, matching on variables defined differently (FAD section 3.13) and analyses that did not censor patients having a transplant (FAD section 3.8). The committee therefore agreed that the evidence presented by the company lacked robustness and concluded that idelalisib was not a cost-effective use of NHS resource because of the range of ICERs presented (between £16,481 and

Consultee	Comment	Response
	are also very concerned that England is the only country in Europe which cannot access this agent. Although we are aware NICE only covers England, there is clearly a UK wide inequality of access for this agent, which is of great concern as it seems deeply unfair that, for example, a patient living in Edinburgh can be treated with idelalisib whereas as a patient in Newcastle cannot be. We are very grateful for your time in reading this letter and considering our arguments. We are also very grateful for the excellent work of NICE and its committees.	£86,161 per QALY gained) and because of its concerns with the quality of the evidence. (FAD section 3.25).

Gilead Sciences Response to:

National Institute for Health and Care Excellence

Appraisal Consultation Document – Idelalisib for treating refractory follicular lymphoma [ID1379]

May 2019

Dear Committee B,

We thank you for affording us this opportunity to respond to the September 2018 draft Appraisal Consultation Document (ACD) for the ongoing single technology appraisal (STA) for idelalisib to treat refractory follicular lymphoma [ID1379].

In this response, as discussed in ongoing dialogue with NICE since September, we present additional data from an updated database lock of the DELTA study (Study 101-09) and updated data from the Haematological Malignancy Research Network (HMRN) database. We use these data to present an updated case for the cost-effectiveness of idelalisib in this small patient group of fewer than 50 patients with high unmet need, responding to the committee's ACD statements of preferences for further data and analyses.

We acknowledge and appreciate the committee for clearly and fairly documenting the evidence available to them on 6 September 2018 in the ACD. In general, we consider the ACD summaries of clinical and cost effectiveness to be reasonable interpretations of this evidence.

However, we are concerned by a few, key statements. In ACD 1.2, the committee state:

"*Idelalisib has not been compared directly with current chemotherapy treatments. So, it is unclear whether it is better, and if so by how much, than what the NHS currently offers.*

"It is therefore not possible to reliably estimate the cost effectiveness of idelalisib. Because of this, idelalisib cannot be recommended for routine use in the NHS or for inclusion in the Cancer Drugs Fund."

It is disappointing that the committee are unclear as to whether idelalisib is a better option than current care for this patient group. Chemotherapy-*refractory* follicular lymphoma (FL) patients, and specifically those who have failed to respond or have relapsed within 6 months of an anti-CD20 monoclonal antibody and an alkylating agent (termed 'double-refractory'), face a bleak prognosis if all that is left for them is treatment options that are not evidenced standard of care in this setting, mostly comprising chemotherapy-based regimens. Median PFS of 11.0 months in DELTA study patients is notable.

Enough so clinicians with whom we have informally engaged hope for access to idelalisib for late-stage, refractory FL patients, and enough so for the European Medicines Agency to license use of idelalisib in this 'double-refractory' setting based on non-randomised, Phase 2 data.

If there can be little doubt that idelalisib does offer a benefit versus current chemotherapy regimens in chemotherapy-refractory FL patients, we recognise that *how much* better is less clear. The lack of a direct comparison versus current chemotherapy treatments is doubtless an obstacle to quantifying the improvement in quality and quantity of life offered by idelalisib to this treatment group. However, each clinical and cost-effectiveness comparison we presented in our June 2018 submission was inherently conservative, to varying degrees, and whether idelalisib in this indication represents a cost-effective use of NHS England resources is far less uncertain. The cost-effectiveness case we present in this response, using committee-preferred assumptions and underpinned by more mature clinical effectiveness data, is compelling.

From reasonable interpretation of NICE decision-making criteria, we are convinced that the availability of idelalisib for NHS FL patients refractory to two prior treatments in Scotland and Wales should be extended to the small group of these patients under the care of NHS England. Disconnect between NHS care availability between the devolved national branches of the NHS can arise owing to the different HTA processes in each country, but can be emotionally difficult for patient and clinical communities; a negative societal wellbeing effect that the separate HTA processes can fail to capture in decision-making. It is however notable that both the Scottish Medicines Consortium and the All Wales Medicines Strategy Group recommended idelalisib as cost-effective in its FL indication, based on less mature (2014 DBL) DELTA data, based on poorer projections of survival than those afforded based on the latest available data.

As recently as February, NICE Committee C recommended the routine availability of brentuximab vedotin for patients with CD30-positive cutaneous T-cell lymphoma (CTCL), with effectiveness data based primarily on subgroup data (n=97) from an n=128 randomised, controlled trial and important long-

term assumptions about the probability and success of subsequent stem-cell transplants (NICE TA577).[1] Cost-effectiveness estimates were naturally highly uncertain, yet Committee C chose to make this treatment available to the high-need CTCL patient population in England with a most plausible ICER of £29,613 in a non-end-of-life (EOL) patient population.[1] This recommendation was even extended to a subgroup of the most severe CTCL patients, those with Sezary Syndrome, despite such patients being excluded from the pivotal study.[1] We hope, with the updated case we present in this response, for a similar approach to decision-making from a sister committee to Committee C.

One other passage from the September 2018 ACD highlights a key concern over the committee's interpretation of the evidence. In consideration of whether EOL criteria should be applied to this appraisal decision, the committee "*concluded that the median overall survival from the HMRN cohort was the most relevant, but likely underestimated the mean life expectancy.*" (ACD 3.23). We draw the opposite conclusion from comparison of observable prognostic characteristics in this response, which we revisit in this response as we present updates from DELTA and HMRN datasets. Further, clinical expectations for survival in patients who are refractory to chemotherapy are low, from our informal communications with the clinical community. We sadly hear that FL patients are likely to survive for less than a year once they become refractory to chemotherapy. This is a poorly evidenced and small population, but we feel the case for the two EOL criteria being met is strong.

To give the committee independent and informed perspective on this and other issues, we hope a practicing NHS Consultant can be invited to the 2nd ACM.

The remainder of this response is structured as follows. Part 1 presents updated clinical effectiveness data from DELTA and HMRN samples and matching-adjusted comparisons of OS and PFS between these patient groups. Part 2 responds to ACD-highlighted areas of uncertainty in turn and presents results from updated cost-effectiveness analyses incorporating the latest available clinical data and committee-preferred assumptions, from our interpretation of ACD wording. Part 3 contains supplementary cost-effectiveness materials; Part 4 contains references.

In short, we hope and believe, with the clinical and patient community that this appraisal decision directly affects in mind, that the evidence we provide in this document is sufficient for the committee to reconsider the September 2018 decision, and recommend that idelalisib be made available for the small group of NHS patients with follicular lymphoma whose disease is refractory to two prior treatments.

Yours sincerely,

Gordon Lundie

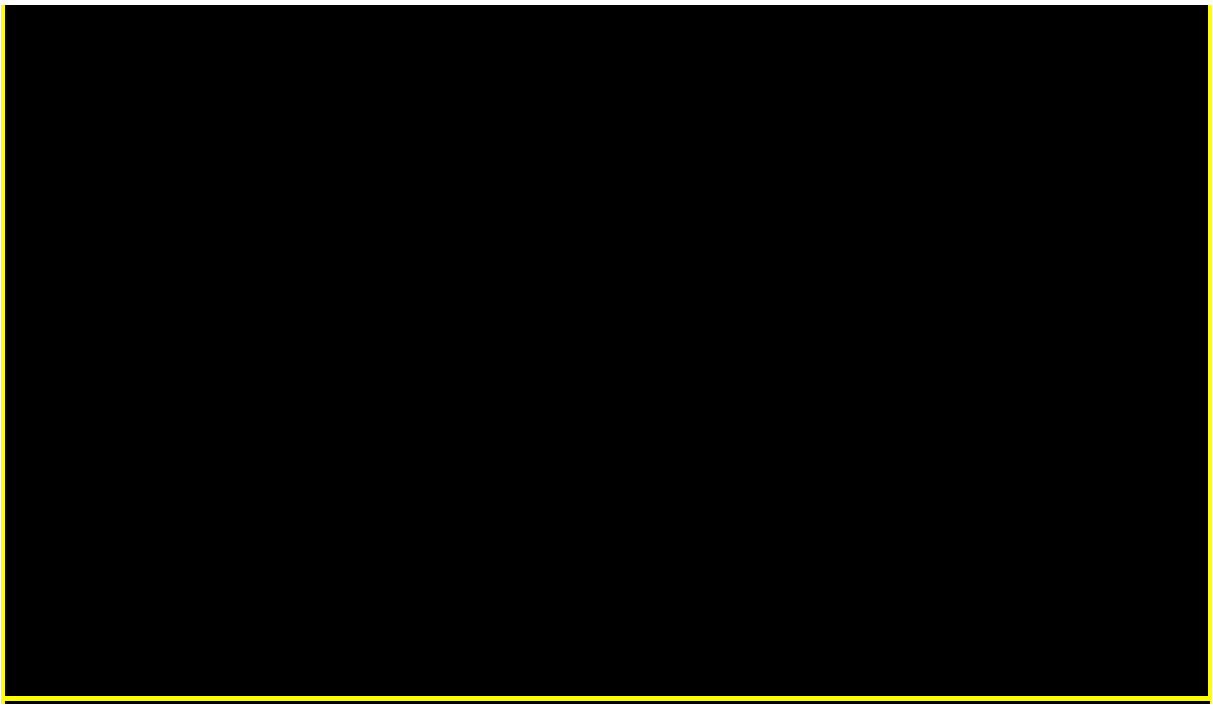
1 Latest clinical effectiveness data

1.1 Updated DELTA data

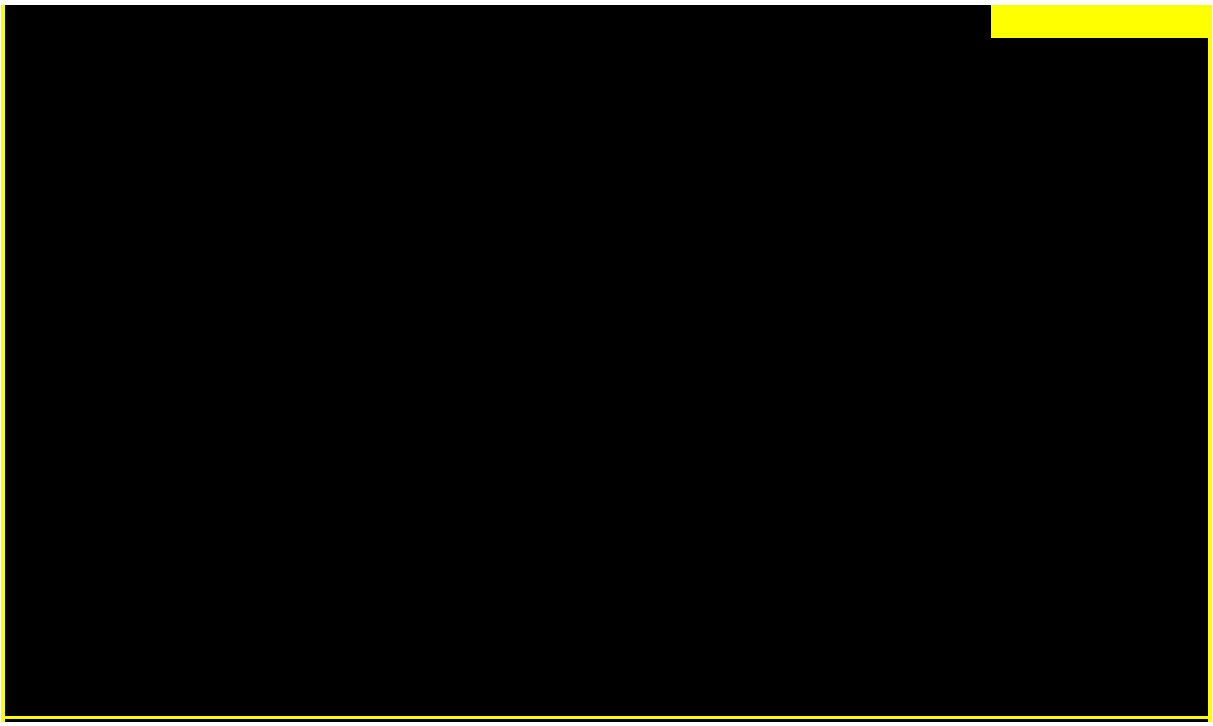
Our original June 2018 submission of evidence was based on the latest DELTA study data available at that time, from June 2015. With the patience of the committee and the patient and clinical community, we have since been able to obtain data from a far more recent cut-off: 22 August 2018. These August 2018 database lock (DBL), currently academic-in-confidence, data demonstrate an improved survival benefit to that estimated from earlier DBLs, suggesting a notable post-progression survival (PPS) benefit for FL patients who have received at least two prior treatments and were refractory to both rituximab and an alkylating agent, who go on to receive idelalisib.

Figure 1 shows Kaplan-Meier (KM) overall survival (OS) data for the FL population in DELTA, from the August 2018 DBL. Figure 2 shows these data alongside the June 2015 DBL OS data used to inform this appraisal up to the 6 September 2018 Appraisal Committee Meeting (ACM). Improved follow-up has shown more promising survival than the more optimistic among us had hoped for, versus the previous June 2015 results. Though as we stress evidence is scarce in this small and high unmet-need group, in a cohort of 588 Stage II to IV FL patients who received first-line rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), of the 22 patients whose disease progressed within 6 months, only 20% survived a further 2 years (Kaplan-Meier analysis).[2]

Figure 1: KM plot of OS, DELTA, FL population, August 2018 DBL



Key: CI, confidence interval; DBL; database lock; FL, follicular lymphoma; KM, Kaplan-Meier; OS, overall survival.

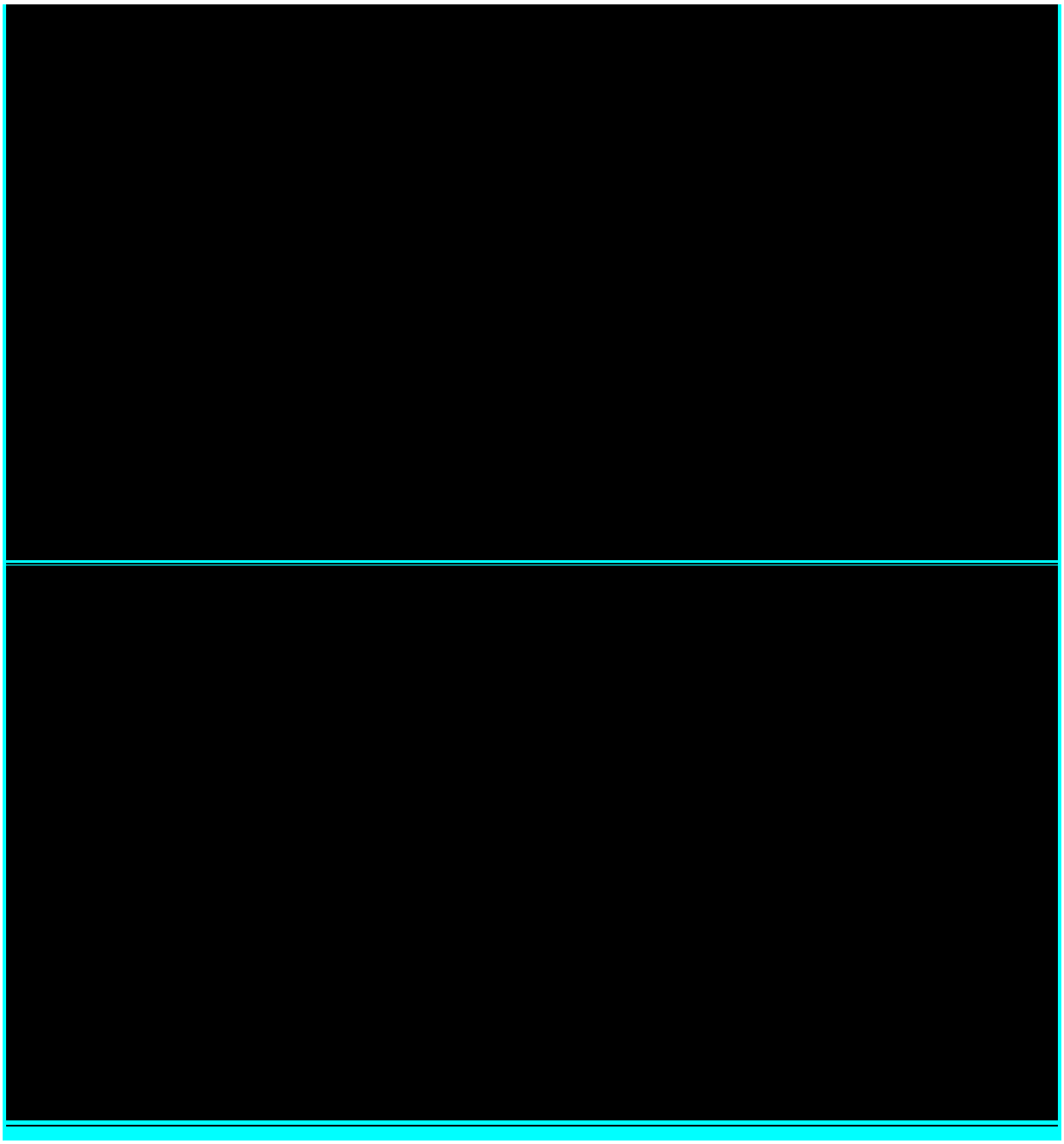


Key: DBL; database lock; FL, follicular lymphoma; KM, Kaplan-Meier; OS, overall survival.

Not only do these latest data represent an unprecedented survival benefit for patients with FL refractory to both rituximab and an alkylating agent, they suggest that this benefit is in large part a PPS benefit. Figure 3 shows DELTA KM data for

OS, progression-free survival (PFS) and time on treatment (ToT), across June 2015 and August 2018 databases, and illustrates this point. In this highly pre-treated and patient group (median 4, maximum 12 prior lines of treatment), survival expectations post-idelalisib were low, and yet half of the FL patients in 101-09 survived beyond 5 years, from median PFS of 11.0 months and median ToT of 6.6 months.

Figure 3: DELTA FL OS PFS and ToT KM data, August 2018 DBL vs June 2015 DBL



Key: DBL; database lock; FL, follicular lymphoma; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; ToT, time on treatment.

Whether the PPS trajectory observed in DELTA is due to a direct treatment benefit; for example, an extended treatment effect related to the idelalisib mechanism of action; or an indirect treatment benefit; for example, restoration of health to allow more effective subsequent treatment; is not fully understood.

A similar benefit has been observed in another haematological cancer patient cohort: chronic lymphocytic leukaemia (CLL) patients who received idelalisib in the Phase III RIAltO study. The RIAltO trial opened in December 2011 to compare ofatumumab plus chlorambucil with ofatumumab plus bendamustine in patients with previously untreated CLL considered unfit for a regimen of fludarabine-cyclophosphamide-rituximab.[3] A protocol amendment was introduced in September 2014 to investigate the addition of idelalisib or placebo. In early 2016, recruitment was suspended and idelalisib/placebo treatment withdrawn,[3] owing to a now better-understood safety profile. In June 2017, investigators published preliminary results from the investigation,[3] followed by presentation of updated results at the June 2018 European Hematology Association Congress.[4] Figure 5 shows a further year's PFS data, to be presented at the 15th International Conference on Malignant Lymphoma in June 2019. From a median treatment exposure of 2.5 months (Figure 4; 3.3 months in the latest Figure 5 PFS data), a trend for superior progression-free survival (PFS) and OS can be observed. As in DELTA, the OS improvement observed is not completely explained by the observed PFS benefit; there is a suggestion of post-treatment and post-progression OS benefit associated with idelalisib treatment.

Figure 4: Updated overall and progression-free survival results from the RIAltO trial, presented in June 2018

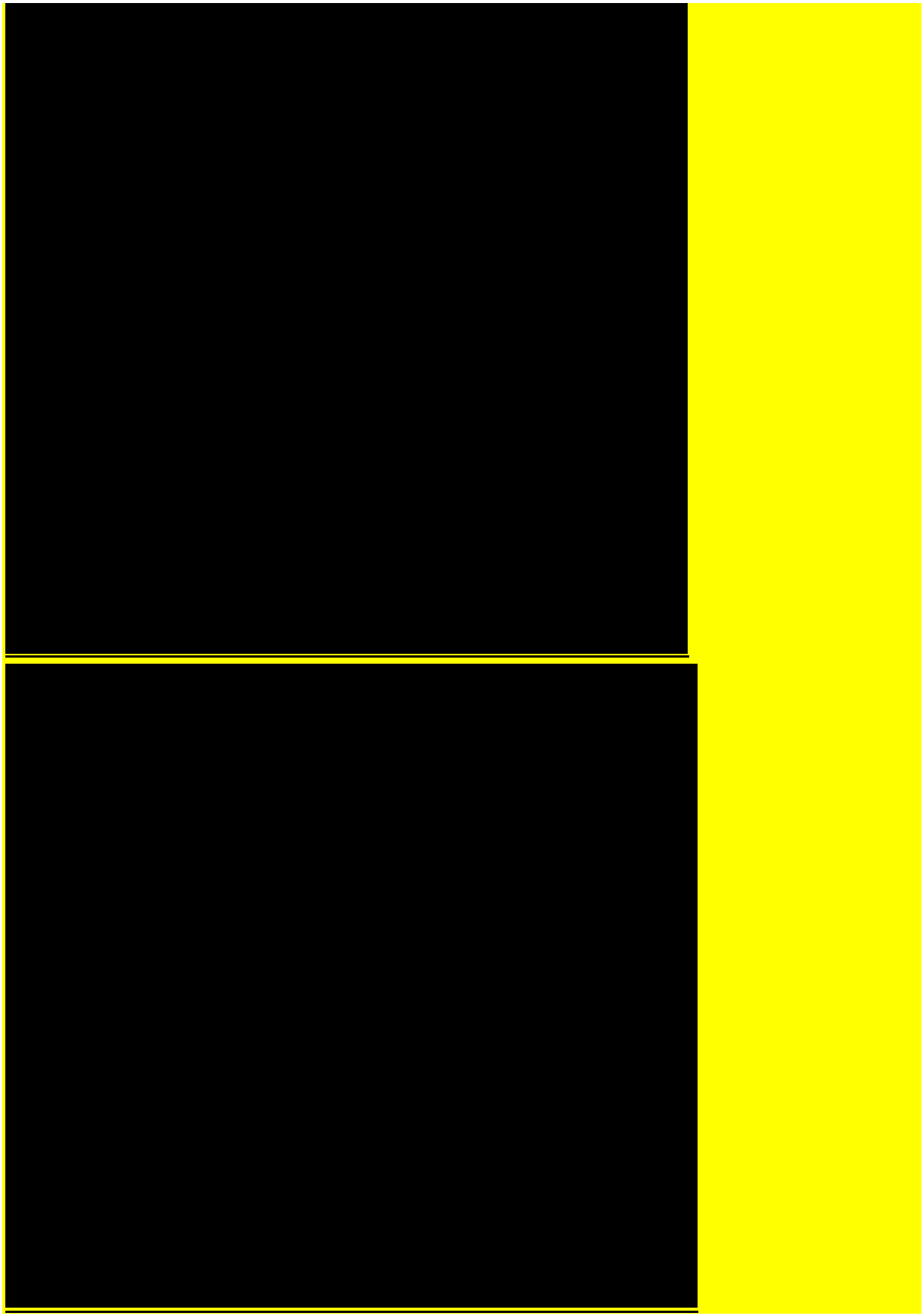
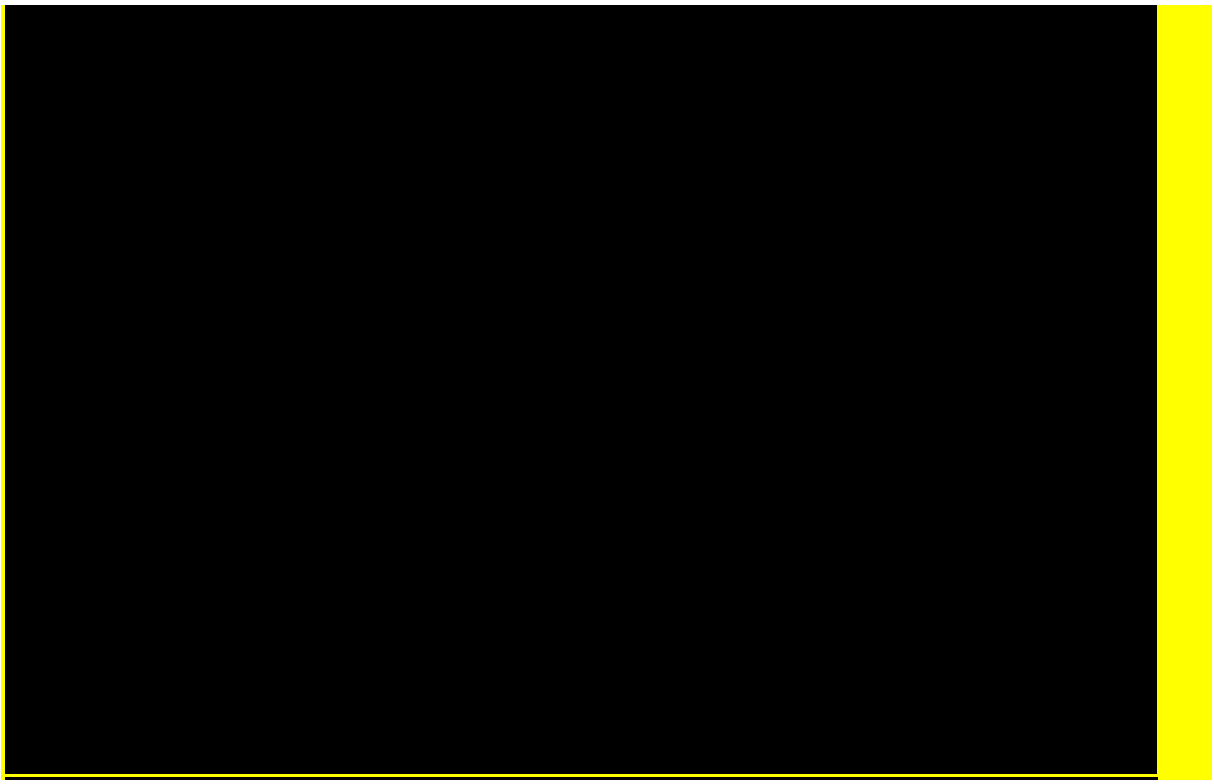


Figure 5: Further updated progression-free survival results from the RIAltO trial



1.2 Updated HMRN data

Of the relative clinical- and cost-effectiveness comparisons presented in our June 2018 company submission (CS), the Appraisal Committee (AC) found the most merit in the comparisons to patients in the HMRN database (ACD 3.7, 3.9).

The HMRN population comprises all patients diagnosed with a haematological malignancy within the Yorkshire and Humber region since its creation, in 2004. For our CS, University of York researchers accessed data for patients in their sample diagnosed with FL between 1 September 2004 and 31 August 2013 who had received ≥2 prior lines of chemotherapy/immuno-chemotherapy/rituximab maintenance and were refractory to both rituximab and an alkylating agent; or who had a relapse within 6 months after receipt of those therapies, and were subsequently treated. Only 26 such patients were identified, highlighting the small patient numbers in this high unmet-need group. The 31 August 2013 diagnosis cut-off was determined by the data cut-off available to University of York researchers. Following the 6 September 2018 ACM, University of York researchers informed us that an updated DBL had become available, including patients diagnosed with FL up

to 31 August 2016. This allows further follow-up data on those 26 patients included in the CS, and data on any further patients who met selection criteria between 31 August 2013 and 31 August 2016. At the request of the University of York research team, HMRN data are treated as academically sensitive.

In this updated HMRN DBL, 34 FL patients met pre-treatment criteria similar to those in DELTA.[5] Table 1 describes the characteristics of these 34 patients at closest equivalent to trial baseline, alongside baseline characteristics of the 72 FL patients in DELTA. We note, these characteristics were not selected by Gilead, rather by University of York researchers based on variable availability across the two databases.

[redacted]

Overall, the treatment history of the two groups suggests that the DELTA patient sample had worse expected prognosis at baseline[redacted]

Table 1: DELTA and HMRN FL sample characteristics at time of reaching eligibility criteria

Key: FL; follicular lymphoma; HMRN, Haematological Malignancy Research Network

We acknowledge that there may be unobserved differences across the datasets. As well as differences in measurement for the variables in Table 1 across samples, we note the other factors considered by the Committee as potentially important for prognosis: "*serum beta 2 microglobulin levels, bone marrow involvement, size of the largest involved lymph node, haemoglobin levels, time in previous remission, time since completing the last therapy, comorbid conditions, and which chemotherapeutic agents the patient has had previously*". (ACD 3.10) We did not restrict the University of York researchers in their approach to effectiveness comparisons, and as noted below, provided the University of York patient-level DELTA data in order to undertake matching analysis; further matching-adjusted indirect comparison and patient-level propensity score matching analyses; as per ACD preferences.

Figure 6 shows the OS KM data from the latest DBL of DELTA alongside similar data for the 34 patients in the updated HMRN sample. Consistent with CS DBLs, OS from start of treatment was poorer in the HMRN sample than in the DELTA sample (2-year overall survival [redacted] though further follow-up indicates that some of the heavily pre-treated HMRN sample, like the DELTA sample, are surviving 3, 4, 5 years post treatment-initiation. Given the heavier pre-treatment history of the DELTA sample, these results suggest a substantial survival benefit attributable to idelalisib.

Figure 7 shows PFS KM data across DELTA FL patients and the 34 HMRN sample patients. These projections remain contra to expectations: patients receiving late-

stage combination chemotherapy and R-chemotherapy have improved projected PFS from ~12 months, compared to idelalisib patients. This is counter-intuitive even considering the EMA licensing terms for idelalisib in this indication; median PFS of 11 months was sufficiently notable in the DELTA FL patient sample to warrant a license based on Phase 2 data.

Aside from observed and unobserved differences across the DELTA and HMRN samples, differences in how disease progression is measured across the two datasets may provide some explanation for these results. Across both samples, PFS was defined as time from initiation of treatment to date of first disease progression or death from any cause. However, according to the study protocol, trial subjects were subject to regular imaging-based tumour assessments, performed at ~8- to 12-week intervals at Visits 1, 6, 9, 11, 13, and 15 (corresponding to baseline, Weeks 8, 16, 24, 36, and 48) and every 12 weeks thereafter and at an end-of-treatment. By contrast, HMRN patients, as is the NHS standard of care, may have an interim treatment scan, but be routinely scanned only at the end of treatment or if they become symptomatic and disease progression is suspected. As such, the HMRN dataset will systematically overpredict PFS in comparison to DELTA. Along with other issues of comparability across the two datasets, PFS comparison is rendered almost meaningless.

Figure 6: KM OS, HMRN August 2016 diagnosis DBL sample versus DELTA August 2018 DBL sample

Key: DBL, database lock; HMRN, Haematological Malignancy Research Network; KM, Kaplan-Meier; OS, overall survival

Figure 7: KM PFS, HMRN August 2016 diagnosis DBL versus DELTA August 2018 DBL

Key: DBL, database lock; HMRN, Haematological Malignancy Research Network; KM, Kaplan-Meier; PFS, progression-free survival

1.3 Matched comparisons between updated DELTA and HMRN datasets

The CS clinical- and cost-effectiveness comparison to HMRM sample outcomes as a proxy for late-stage chemotherapy (CS Comparison B) was based on an unanchored, matching-adjusted, indirect comparison (MAIC), as described in CS B.2.9, B.3.2 and B.3.3, and as critiqued in ACD 3.9 and 3.10. One key criticism of the CS MAIC was the effective sample size of the adjusted HMRN sample, n=6.9, and the implicit reliance of outcome projections on few patients. Table 2 shows the sample characteristics of the updated DELTA and HMRN patients as shown in Table 1, alongside MAIC-adjusted HMRN sample characteristics (matched to DELTA sample characteristics). The effective sample size in this update to Comparison B is slightly increased, but remains small at 8.4 patients. Table 2 also shows 2-year OS and 1-year PFS estimates across samples.

Figure 8 shows unadjusted KM OS data for the 2018 and 2015 DBLs of DELTA, alongside both (i) the CS MAIC-adjusted HMRN data (diagnoses up to 31 August 2013), and (ii) updated MAIC-adjusted HMRN data (diagnoses up to 31 August 2016). Chemotherapy survival projections in the updated analysis are broadly consistent with the submitted MAIC, with a lower median survival but greater proportion of patients alive at the end of adjusted sample follow-up in the updated analysis.

Table 2: Updated DELTA and HMRN sample characteristics and outcomes before and after MAIC using IPD from DELTA and summary data from the HMRN sample, otherwise consistent with CS Comparison B

[redacted]

* Effective sample size calculated as the square of the summed weights divided by the sum of the squared weights

Figure 8: Company submission (2015 DELTA versus 2013 HMRN) OS comparisons, HMRN MAIC-adjusted, alongside updated (2018 DELTA versus 2016 HMRN) OS comparisons, MAIC-adjusted

[redacted]

Key: DBL, database lock; HMRN, Haematological Malignancy Research Network; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival.

MAIC-adjusted PFS comparisons, a "reverse MAIC" in which DELTA sample outcomes are weighted to match the sample characteristics of the 34 HMRN patients, and sensitivity analyses around MAIC results using different matching variables, are all contained within the latest University of York report,[5] but not

discussed further here. As described in Part 1.2, the PFS comparison is considered almost meaningless given the differences in progression status data collection across the two samples. Further sensitivity analyses around MAIC results, including a “reverse MAIC”, was noted as of merit in ACD 3.9. However, the committee comment that given data availability, patient-level propensity score matching could be performed (ACD 3.9). This required us to both (i) share our patient-level data files with the University of York research team (we cannot access HMRN IPD) and (ii) engage this team to undertake such analyses. This has taken time and financial commitment. We are equally grateful to the committee for allowing a pause in the process and glad to commit the resources, given the importance of access to idelalisib for double-refractory FL patients.

The University of York research team had academic control over the propensity score matching analysis, as they did for all MAIC analyses. Their chosen approach was to use three-nearest-neighbour matching to exclude poor matches.[5] Where the nearest neighbours were not close matches in terms of baseline characteristics, a caliper width of 0.2 was chosen so that controls were only matched where they were within 0.2 standard deviations of the propensity score of the treated subjects.[5] Additionally, a common support was used so that treated subjects with a propensity score outside the range of the control group were excluded.[5]

The research team note: “[redacted]”[5]

Propensity score matching analyses were run first treating the DELTA sample as the “treated” group, whereby HMRN patients who match DELTA patients in terms of baseline characteristics are found, and then repeated treating the HMRN sample as the treated group. Table 3 shows sample characteristics and selected outcomes before and after propensity-score matching, with the DELTA sample as the “treated” group. Table 4 shows similar data for the reverse case, where the HMRN sample are the “treated” group. The sample sizes are here far more balanced across treatment arms than in the MAICs in Table 2 and Figure 9. Table 3 shows matching results are

based on 26 patients from the HMRN sample and 39 from the DELTA sample when the DELTA patients are the “treated” group (total n=65), while Table 4 shows all 34 patients in the HMRN sample are matched to 35 patients in the DELTA sample in the reverse analysis (total n=69). Unlike the MAIC, the process does not lead to balanced sample characteristics across arms.

Figure 9 shows propensity-score-matching OS KM curves consistent with the data in Table 3. Figure 10 shows these curves alongside the unadjusted DELTA OS KM curves and MAIC-adjusted HMRN OS curves shown in Figure 8. Idelalisib OS is improved versus unadjusted KM data in the propensity-score-matching-adjusted analysis, while HMRN chemotherapy OS is much improved versus the MAIC analysis, and notably no events are observed in the chemotherapy arm of the matched analysis after 13.62 months.

Figure 11 shows “reverse” propensity-score-matching OS KM curves, consistent with the data in Table 4, though we note mis-labelling of 2-year OS as 1-year OS and of 1-year PFS and 2-year PFS in this table, confirmed by the University of York team in response to an email query. Figure 12 shows the “reverse” propensity-score-matching OS KM curves alongside the unadjusted DELTA OS KM curves and MAIC-adjusted HMRN OS curves shown in Figure 8. In comparison to the propensity-score-matching-adjusted analysis where DELTA patients are the “treated” group, idelalisib OS is slightly less optimistic, as is HMRN chemotherapy OS, though it remains improved versus the MAIC analysis.

In Part 2 we present deterministic and probabilistic results from cost-effectiveness analyses based on each of the updated DBL OS comparisons presented here: (i) updated MAIC; (ii) propensity-score-matching-adjusted comparison with DELTA patients as “treated”; (iii) “reverse” propensity-score-matching-adjusted comparison with HMRN patients as “treated”. Results across reaffirm the suggestion that idelalisib is a cost-effective treatment option for the high-unmet need group the appraisal directly affects.

Table 3: Sample characteristics and outcomes before and after propensity-score matching, DELTA patients as "treated" group

[redacted]

Figure 9: Propensity-score-matching-adjusted OS KM curves, DELTA patients as "treated" group

Key: HMRN, Haematological Malignancy Research Network; KM, Kaplan-Meier; OS, overall survival.

Figure 10: Figure 9 KM data alongside Figure 8 KM data

Key: HMRN, Haematological Malignancy Research Network; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival.

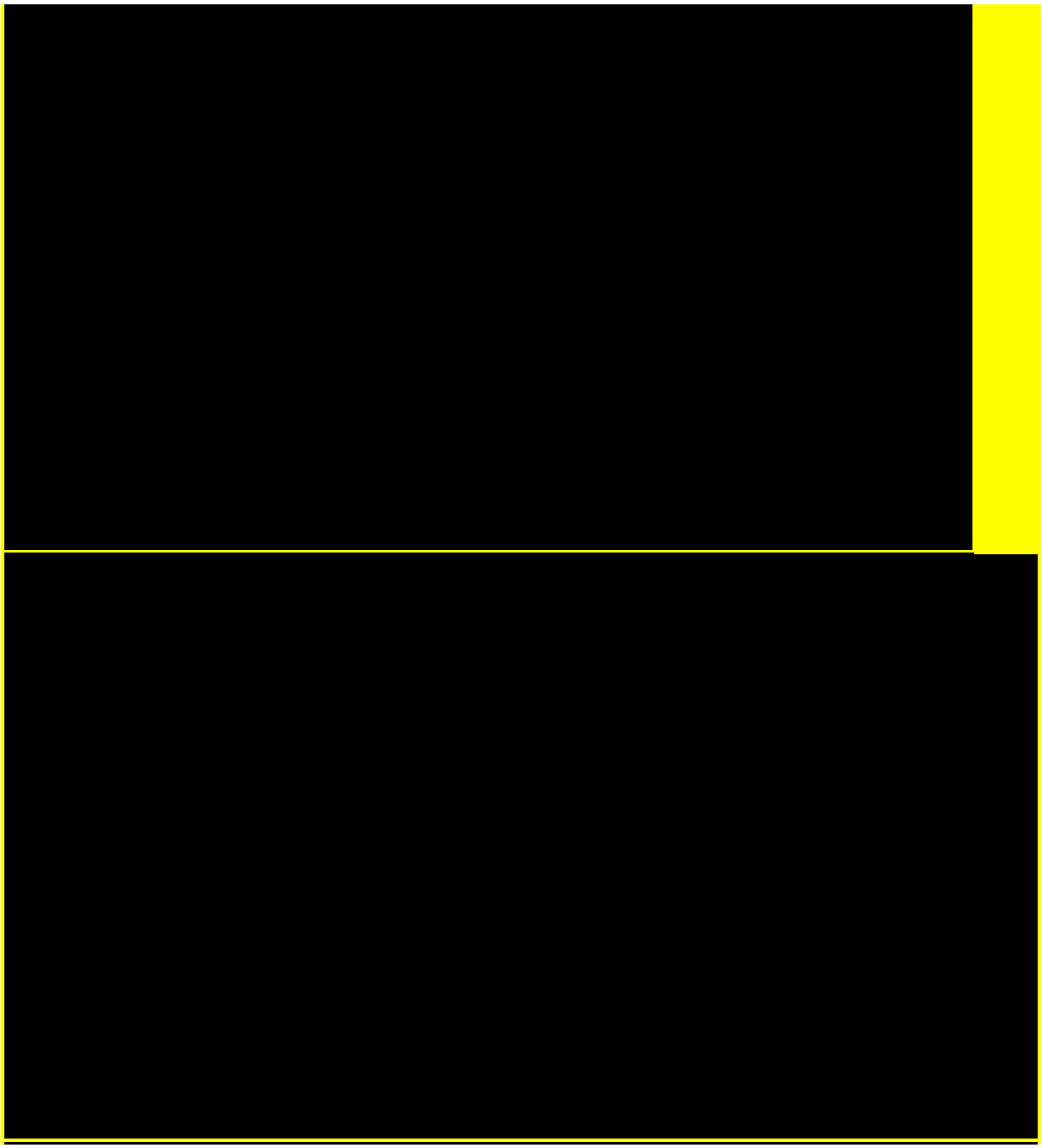
Table 4: Sample characteristics and outcomes before and after propensity-score matching, HMRN patients as "treated" group

Key: CI, confidence interval; HMRN, Haematological Malignancy Research Network.

Figure 11: Propensity-score-matching-adjusted OS KM curves, HMRN patients as "treated" group

Key: HMRN, Haematological Malignancy Research Network; KM, Kaplan-Meier; OS, overall survival.

Figure 12: Figure 11 KM data alongside Figure 8 KM data



Key: HMRN, Haematological Malignancy Research Network; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival.

2 Exploration of committee-highlighted areas of uncertainty

We are grateful to the committee for clearly summarising the ways in which they feel the clinical evidence could be improved in ACD 3.13, and for going on to similarly

summarise their view of key modelling uncertainties and additional analyses that could better inform decision-making, in ACD 3.22. Throughout Part 2, we attempt to address specific concerns highlighted by the committee.

2.1 The (un)availability of further clinical effectiveness datasets on relevant patient outcomes in this refractory population

In ACD 3.13, the committee note the evidence base could be improved by "*better (larger, better characterised) populations from other registries*", as well as updated data from the HMRN registry. Potential datasets to provide clinical effectiveness evidence relevant to the decision problem were sought as part of the evidence generation activities undertaken prior to submission. These datasets were sought through systematic review of the clinical evidence base in line with recommended approaches to evidence identification.

As reported in the original CS, no trials outside of those investigating idelalisib were identified for the double-refractory FL group. When extending the population of interest to patients with refractory FL, three further studies were identified (as highlighted to the Evidence Review Group [ERG] during clarification). These studies, and an assessment of their potential suitability for decision-making are summarised in Table 5.

Table 5: Studies investigating patients with refractory FL

Study overview	Suitability for decision-making in the double-refractory FL setting
Aviles et al. 2001[6]	
- Single-arm pilot study - Rituximab 375mg/m2 qw for 6 weeks - Refractory FL patients (n=17)	- Small sample size - Rituximab is unlikely to be re-administered in the R-refractory setting - Rituximab was not a named comparator of interest in the appraisal scope - Patient level data unavailable
Tinmouth et al. 2001[7]	
- Observational study - Fludarabine 25mg/m2 qid for 5 days (repeated as needed) - Alkylator-resistant FL (n=17)	- Small sample size - Retrospective study design - Patient level data unavailable

Witzig et al. 2002[8]	
- Single-arm study - Ibritumomab tiuextan RI - Rituximab-refractory FL (n=57)	- Ibritumomab tiuextan RI is not routinely used in the refractory setting - Ibritumomab tiuextan RI was not a named comparator of interest in the appraisal scope - Patient level data unavailable
Key: R, rituximab; RI, radioimmunotherapy; qw, once per week	

If we extend the population further to those patients with relapsed FL or relapsed/refractory FL/indolent non-Hodgkin's lymphoma (iNHL), there are several more studies available. However, these have similar limitations to those outlined in Table 5 as well as the added limitation of diminished applicability to the patient group of interest considering the differences in treatment choice and prognosis across the relapsed versus refractory populations. Of important note, no studies providing data on best supportive care (either as a comparator arm in a controlled chemotherapy trial or an uncontrolled single arm study) were identified in either extension.

Aside from clinical trial data, we remain convinced that no available registry data could improve upon those patient-level data we have engaged University of York researchers to access from the HMRN registry, and since the September ACM, compare to patient-level DELTA data. Beyond patient-level data access considerations, as described in relation to HMRN data collection in Part 1.2, data collection is inherently different and limited in any registry in comparison to a clinical trial. The emphasis on primary source information; data from radiology reports, blood tests, clinical examination, and clinician summaries; from patients receiving NHS England care, surely makes the HMRN the best available comparator dataset available for this decision problem. Beyond geographical considerations, the challenge of accurately identifying patients sufficiently refractory to be comparable to DELTA FL patients will be great in any registry dataset. We understand the approach of the HMRN registry, based on NHS England standards of data collection, to be world-leading.

Further to discussions in the first ACM on the potential availability of additional observational data for idelalisib, we can confirm that Gilead have no sponsored compassionate use programmes open that may provide access to additional outcome data. Idelalisib was made available reactively on compassionate use basis

following authorisation in several markets, but unfortunately data collection and ownership was not a provision of these compassionate use programmes, and our understanding is that no data have been collected that could be used to help inform decision-making (outside of that presented in the original CS that have been published and were thus identified through systematic review).

2.2 Exploration of committee-highlighted uncertainty around cost-effectiveness results

Table 6 summarises the analyses highlighted as potentially useful in the ACD and how and where this response has sought and seeks to address each. The remainder of Part 2.2 addresses those issues not yet addressed in Part 2, as indicated within Table 6.

Table 6: ACD-highlighted areas for further cost-effectiveness exploration and summary of our approach

#	Analysis proposed in ACD	Summary of our response approach
1	Exploration of uncertainty around hazard ratio applied to prior therapy outcomes, relevant for Comparison A, C and D analyses (ACD 3.15)	No further exploration of Comparisons A, C and D beyond #5, in light of implications from the survival data from the latest DBL of Study 101-09, as described in Part 2.2
2	Calibration of Comparison A, C and D analyses to better match model predictions of observed data (ACD 3.22)	No further exploration of Comparisons A, C and D in this response beyond #5, in light of implications from the survival data from the latest DBL of Study 101-09, as described in Part 2.2
3	Exploration of different match-adjusted comparisons to chemotherapy data, including number of matched characteristics and population (Comparison B) (ACD 3.22)	Addressed in Part 2.2; further analyses presented
4	Exploration of uncertainty around the cost-effectiveness of individual chemotherapy regimens (Comparisons A, B and C) (ACD 3.22)	Addressed in Part 2.2; no further analyses presented
5	PSA for all Comparisons (ACD 3.22)	Addressed in Part 2.2; PSA for updated Comparison B scenarios presented
6	Exploration of trial-based utility values for all Comparisons (ACD 3.22)	Addressed in Part 2.2; no further analyses presented
Key: ACD, Appraisal consultation document; PSA, probabilistic sensitivity analysis		

Updated cost-effectiveness results

The long-term benefit of idelalisib treatment observed in the DELTA study supports an approach to economic modelling that represents this survival profile (that is, has

capacity to accommodate expected incremental PPS benefit). In the CS, we provided four comparisons utilising all available clinical evidence for idelalisib and current care: two of these comparisons (Comparison A and Comparison C) looked at prior line of treatment outcomes to estimate chemotherapy effect, and one of these comparisons (Comparison D) assumed equal PPS effect between idelalisib and best supportive care (BSC). In light of updated DELTA study survival estimates, the clinical validity of these approaches (which do not adequately allow for differences in PPS time across treatments) is increasingly debatable. We have therefore focused additional economic analyses presented in Part 2 on updates to, and sensitivity analyses around, Comparison B, which uses a partitioned survival modelling approach typical to oncology HTA to capture the clinical comparison between DELTA FL patients and the HMRN FL sample.

Our updates to Comparison B use the latest 2018 DELTA OS, PFS and TTD individual patient data, presented in Part 1.1. Updated HMRN OS data presented in Part 1.2, and the matching-adjusted OS data presented in Part 1.3, have been similarly incorporated, with the extra step of digitisation required to create pseudo-patient data from the University of York report.[5] As in the CS, *GetData Graph Digitizer* software were used for digitisation.[9] The six standard parametric survival models fitted to 2015 DBL time-to-event data were fitted to these updated data, and incorporated into the cost-effectiveness model update we submit alongside this response.

Our approach to recreating the ERG base case is described in Part 3, for completeness. The cost-effectiveness model retains 2015 DBL data and functionality for the user to intuitively set assumptions to our recreation of the ERG base case, and the results presented in Part 3, for transparency.

We present the three updated versions of cost-effectiveness Comparison B, which we believe to be in line with the stated preferences of the committee, and collectively improve upon CS Comparison B, in terms of both clinical effectiveness data maturity and range of matching approaches. We define the three comparisons as follows:

- Comparison B1: Consistent with our recreation of ERG Comparison B, updated using the latest DELTA and HMRN data shown in Part 1

- Comparison B2: Consistent with B1, but using propensity-score-matching-adjusted comparative analysis assuming the DELTA patients are the “treated” group, shown in Part 1, and conservatively assuming patients who receive chemotherapy-based treatment will have PFS equal to patients treated with idelalisib
- Comparison B3: Consistent with B2, except using propensity-score-matching-adjusted comparative analysis assuming the HMRN patients are the “treated” group, shown in Part 1

The assumption of PFS equivalence across treatment arms in B2 and B3 definitively biases against idelalisib and is seen as a practical conservative assumption in the absence of robust comparative PFS data. The critical limitations of HMRN PFS data were described in Part 1. Irrespective of this assumption, each comparison is thought to be definitively conservative in comparing OS across DELTA and HMRN samples, given (i) the greater number of prior treatments in the DELTA sample, (ii) the longer time since diagnosis in the DELTA sample and (iii) the informal clinical expectation that life expectancy in this patient group in the absence of idelalisib is less than two year.

Table 7 to Table 12 and Figure 13, Figure 14 and Figure 15 present deterministic and probabilistic results from Comparisons B1, B2 and B3. Consistent with CS analyses, each probabilistic analysis is based on 4,000 random draws from uncertain input parameter distributions.

Despite the inherently conservative nature of each comparison, cost-effectiveness results across Comparisons B1, B2 and B3 suggest idelalisib is a highly cost-effective EOL treatment option for the small, high-need patient group of FL patients who are refractory to two prior treatments.

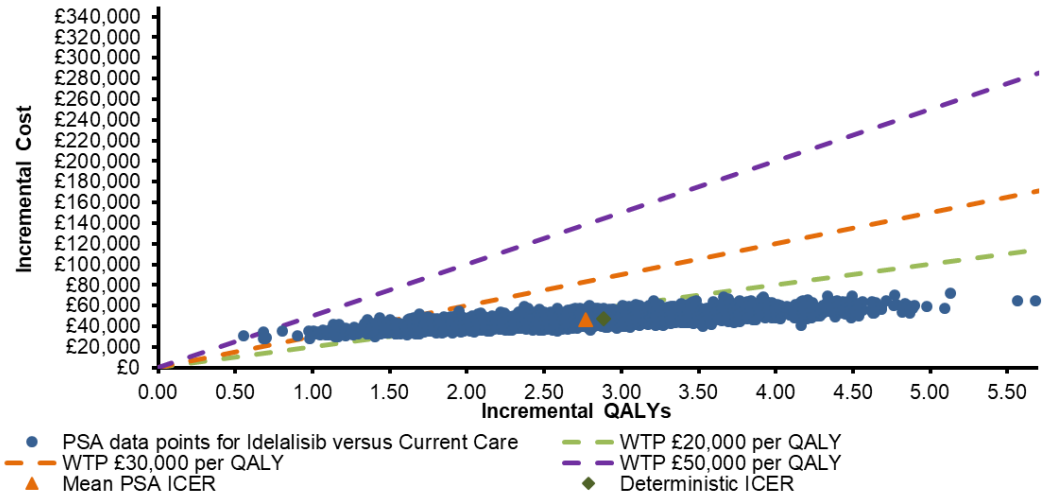
Table 7: Comparison B1: Updated MAIC-informed deterministic cost-effectiveness results, including idelalisib CCD

	Costs	Life Years	QALYs	Incremental			ICER
				Costs	Life Years	QALYs	
Chemotherapy	[redacted]	1.66	1.01	-	-	-	-
Idelalisib	[redacted]	7.47	3.89	£47,500	5.81	2.88	£16,481
Key: CCD, confidential commercial discount; ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusted indirect comparison; QALYs, quality-adjusted life years.							

Table 8: Comparison B1: Updated MAIC-informed probabilistic cost-effectiveness results, including idelalisib CCD

	Costs	Life Years	QALYs	Incremental			ICER
				Costs	Life Years	QALYs	
Chemotherapy	[redacted]	2.02	1.14	-	-	-	-
Idelalisib	[redacted]	7.61	3.91	£46,552	5.59	2.77	£16,802
Key: CCD, confidential commercial discount; ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusted indirect comparison; QALYs, quality-adjusted life years.							

Figure 13: Comparison B2: PSA scatterplot, Updated MAIC-informed cost-effectiveness results, including idelalisib CCD



Key: CCD, confidential commercial discount; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.

Table 9: Comparison B2: Updated PSM-informed deterministic cost-effectiveness results, DELTA patients as "treated", including idelalisib CCD

	Costs	Life Years	QALYs	Incremental			ICER
				Costs	Life Years	QALYs	
Chemotherapy	[redacted]	5.97	2.97	-	-	-	-
Idelalisib	[redacted]	8.94	4.42	£37,160	2.97	1.45	£25,605

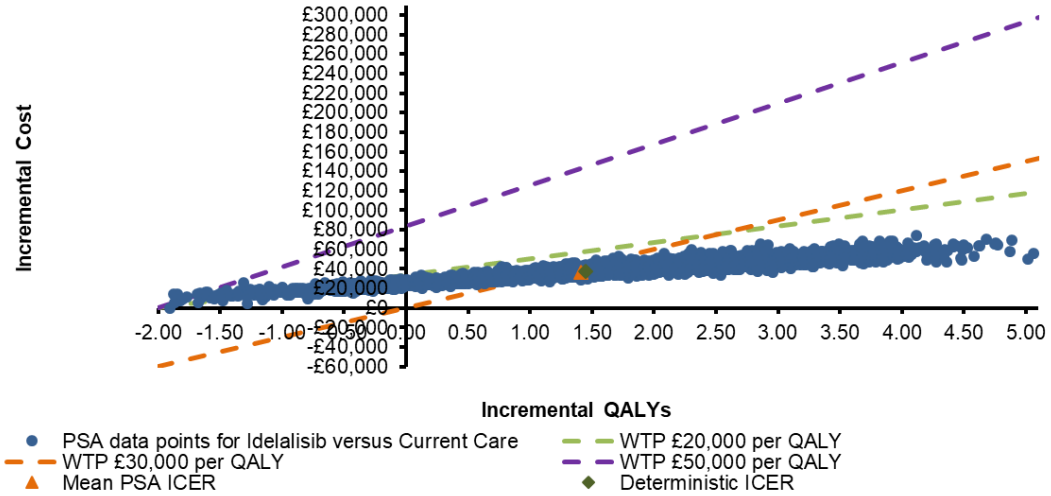
Key: CCD, confidential commercial discount; ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusted indirect comparison; PSM, propensity-score-matching; QALYs, quality-adjusted life years.

Table 10: Comparison B2: Updated PSM-informed probabilistic cost-effectiveness results, DELTA patients as "treated", including idelalisib CCD

	Costs	Life Years	QALYs	Incremental			ICER
				Costs	Life Years	QALYs	
Chemotherapy	[redacted]	6.30	3.03	-	-	-	-
Idelalisib	[redacted]	9.16	4.43	£36,788	2.86	1.41	£26,147

Key: CCD, confidential commercial discount; ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusted indirect comparison; PSM, propensity-score-matching; QALYs, quality-adjusted life years.

Figure 14: Comparison B2: PSA scatterplot, Updated PSM-informed cost-effectiveness results, DELTA patients as "treated", including idelalisib CCD



Key: CCD, confidential commercial discount; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; PSM, propensity-score-matching; QALYs, quality-adjusted life years.

Table 11: Comparison B3: Updated PSM-informed deterministic cost-effectiveness results, HMRN patients as "treated", including idelalisib CCD

	Costs	Life Years	QALYs	Incremental			ICER
				Costs	Life Years	QALYs	
Chemotherapy	[redacted]	5.71	2.78	-	-	-	-
Idelalisib	[redacted]	8.52	4.14	£36,364	2.81	1.37	£26,627

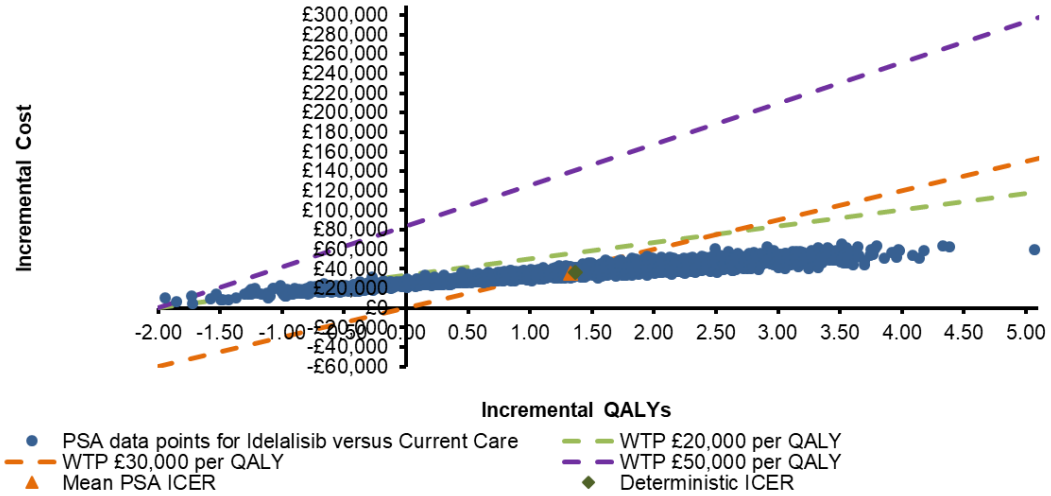
Key: CCD, confidential commercial discount; HMRN, Haematological Malignancy Research Network; ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusted indirect comparison; PSM, propensity-score-matching; QALYs, quality-adjusted life years.

Table 12: Comparison B3: Updated PSM-informed probabilistic cost-effectiveness results, HMRN patients as "treated", including idelalisib CCD

	Costs	Life Years	QALYs	Incremental			ICER
				Costs	Life Years	QALYs	
Chemotherapy	[redacted]	5.94	2.83	-	-	-	-
Idelalisib	[redacted]	8.65	4.15	£35,978	2.71	1.33	£27,108

Key: CCD, confidential commercial discount; HMRN, Haematological Malignancy Research Network; ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusted indirect comparison; PSM, propensity-score-matching; QALYs, quality-adjusted life years.

Figure 15: Comparison B3: PSA scatterplot, Updated PSM-informed cost-effectiveness results, HMRN patients as "treated", including idelalisib CCD



Key: CCD, confidential commercial discount; HMRN, Haematological Malignancy Research Network; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; PSM, propensity-score-matching; QALYs, quality-adjusted life years.

In their consistency with previous iterations of Comparison B, Comparisons B1, B2 and B3 assume the most appropriate parametric model structure for previous DBLs remains the most appropriate with updated data, for each time-to-event endpoint captured in the cost-effectiveness model. Table 13 shows results from scenario analysis that tests these assumptions for the most pessimistic update of Comparison B; B3. The deterministic estimated ICER for idelalisib remains below £30,000 per QALY gained across different specifications.

Table 13: Scenario analysis, Comparison B3: Robustness of cost-effectiveness estimates and decision uncertainty to time-to-event parametric model selection, for the most conservative updated cost-effectiveness scenario

OS model	PFS model	ToT model	ICER
Generalised Gamma	Lognormal	Exponential	£25,193
Exponential	Lognormal	Exponential	£21,717
Weibull	Lognormal	Exponential	£26,627
Loglogistic	Lognormal	Exponential	£23,567
Lognormal	Lognormal	Exponential	£22,305
Gompertz	Lognormal	Exponential	£25,686
Weibull	Generalised Gamma	Exponential	£26,255
Weibull	Exponential	Exponential	£27,030
Weibull	Weibull	Exponential	£26,978
Weibull	Loglogistic	Exponential	£26,337
Weibull	Lognormal	Exponential	£26,627
Weibull	Gompertz	Exponential	£26,786
Weibull	Lognormal	Generalised Gamma	£26,973
Weibull	Lognormal	Exponential	£26,627
Weibull	Lognormal	Weibull	£26,572
Weibull	Lognormal	Loglogistic	£29,006
Weibull	Lognormal	Lognormal	£27,625
Weibull	Lognormal	Gompertz	£26,796

Key: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; ToT, time on treatment.

Exploration of uncertainty around the cost-effectiveness of individual chemotherapy regimens

In Sections 3.11 and 3.18 of the ACD, the committee highlight the limitations of a blended comparator arm and conclude that the cost effectiveness of idelalisib needs to be considered against each chemotherapy treatment individually. We hope on reflection that the committee agree informative comparison to the individual chemotherapy options defined in the scope is far beyond the reach of the available comparator data. The conclusions of ACD Section 3.18 as written imply that any newly available treatment for a small patient population with poorly defined current care will have insufficient data for a positive NICE recommendation based on cost-effectiveness. In December 2017, this committee recommended daratumumab monotherapy to treat relapsed and refractory multiple myeloma through the CDF, based on broadly similar evidence (single-arm pivotal Phase II trial, unanchored non-randomised comparison to blended comparator data from the HMRN database) in TA510. We wonder the extent to which the committee have considered this issue, and the implications for equity principles and consistency with historical decisions.

Exploration of trial-based utility values for all Comparisons

In ACD Section 3.19 the committee concur with the ERG's assessment that there is value in utility estimates derived through mapping of Functional Assessment of Cancer Therapy – General (FACT-G) elements of Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym) responses in Study 101-09 to EuroQol-5 Dimension-3 Level (EQ-5D-3L) estimates, using one of the existing mapping algorithms identified by the ERG.

We understand that to evaluate how useful such estimates would be, it would be useful to have the estimates. We remain however, highly skeptical of the usefulness of such work, for the reasons described in our response to ERG Clarification Question B17, on top of the limitations that would apply to EQ-5D-3L data if such data had been collected alongside FACT-Lym data in Study 101-09.

3 Supplementary materials

Recreating the ERG-preferred approach to cost-effectiveness analysis

Although the ERG-amended model was shared with us upon request, in absence of the functionality to work between ERG and CS results in the ERG-amended model (described in Issue 2 of our proforma response to the ERG report), we have amended our submitted model to meet ERG preferences. A key reason for this was the expansion of the PPS health state into weekly tunnel states in the ERG-amended model. As highlighted in Issue 2 of our proforma response, the ERG's creation of tunnel states hampered the functionality of a previously functional model, and substantially increased model execution time. While the PPS health state informs Comparisons A, C and D results, the ERG's move to tunnel states is not (theoretically) consequential when the (company and ERG) base case extrapolation of PPS data assumes an exponential distribution. Further, the use of tunnel states improves the estimated cost-effectiveness of idelalisib across Comparisons A, C and D if any of the alternative parametric survival distributions modelled (Weibull, Gompertz, log-normal, log-logistic, generalised gamma) are assumed for PPS. As such, please be assured that our preference to capture PPS as one health state is motivated solely by maintaining a functional decision-analytic model, and not by more favourable results.

Table 14 shows the ERG's preferred deterministic base case incremental cost-effectiveness ratios (ICERs) for Comparisons A to D, alongside the results from our recreation of the ERG's preferences within our submitted economic model.

Our recreated ERG base case results differ slightly from the base case results in the ERG-amended model and ERG report, as shown in Table 14. While these differences have not been explored further, at least some of the small differences across Comparisons A, C and D results are explained by the introduction of tunnel states and implications for calculations, in the ERG-amended model.

The estimated ERG-preferred ICER for Comparison B differs by only £2 across the ERG-amended model and our recreation of the ERG base case. Given the implication of the updated Study 101-09 survival estimates for the usefulness of comparisons to previous treatment as a proxy for current care and the resultant primacy of Comparison B, we hope the committee share our confidence that our recreation of the ERG base case is sufficient as a basis from which to explore the outstanding uncertainties around cost-effectiveness.

Table 14: ERG base case and company recreation of ERG base case: deterministic mean ICERs (idelalisib versus current care), Comparisons A to D

Comparison	ERG base case ICER (ERG Report, Section 5.3)	Company recreation of ERG base case ICER
A	£32,822	£32,859
B	£21,559	£21,561
C	£58,745	£58,741
D	£29,639	£29,822
Key: ERG, Evidence Review Group, ICER, incremental cost-effectiveness ratio		

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20/05/2019

Letter in support of NICE approval for idelalisib in double refractory follicular non-Hodgkin Lymphoma

Dear Sir / Madam,

We are writing to encourage the NICE STA committee to approve the use of idelalisib in double refractory follicular lymphoma. Although follicular lymphoma is an indolent lymphoma with excellent survival for the majority of patients, it is increasingly recognised that there are a group of patients who have poor outcomes and will die of their disease. Much recent work has identified the so-called 'Progression of disease within 24 months of treatment initiation' or POD24 risk factor as a critical determinant for survival. For these patients the 5-year overall survival rate is only approximately 50% [1]. This emphasises the consistent finding in follicular lymphoma that short remissions following R-chemo are associated with high risk disease.

The 101-09 study (which included a significant number of patients from England) investigated idelalisib in a very high-risk group of patients – those who were refractory to both rituximab and an alkylating agent. As these patients were a high-risk relapsed group, one would expect them to be higher risk that the POD24 group described above, who were a group of patients at first relapse. They therefore represent a small group of patients with high unmet need. However, the long-term follow-up from the 101-09 study shows a median overall survival of 5 years which is much better than expected. Furthermore, the median PFS for the participants receiving idelalisib was longer than their prior line of treatment which is unusual in follicular lymphoma where remissions are usually thought to shorten with time[2].

Furthermore, we collected the real-world results from UK patients treated with idelalisib when it was available on a named patient basis [3]. Although the baseline characteristics of the patients were of course different from those in the 101-09 study, the results were very similar, suggesting that there was benefit outside of a clinical trial setting. We are also very concerned that England is the only country in Europe which cannot access this agent. Although we are aware NICE only covers England, there is clearly a UK wide inequality of access for this agent, which is of great concern as it seems deeply unfair that, for example, a patient living in Edinburgh can be treated with idelalisib whereas as a patient in Newcastle cannot be.

We are very grateful for your time in reading this letter and considering our arguments. We are also very grateful for the excellent work of NICE and its committees.

Yours faithfully,

Dr Graham Collins, lymphoma lead, Oxford University Hospitals NHS Foundation Trust
Dr Kim Linton, senior lecturer and honorary consultant in oncology, Christie NHS Foundation Trust and chair of the NCRI low grade lymphoma subgroup
Dr Rebecca Auer, Consultant haemato-oncologist, St Bartholomew's Hospital, London
Dr Mary Gleeon, Consultant Haemaologist, Guys and St Thomas' Hospital, London
Dr Nick Morley, Consultant Haematologist, Sheffield Teaching Hospital
Dr Paul Fields, Consultant Haematologist, Guys and St Thomas' Hospital
Dr Rob Lown, Consultant Haemaologist, Southampton University Hospital
Dr Dima El-Sharkawai, Consultant Haematologist, Royal Marsden Hospital, London
Dr Sunil Iyengar, Consultant Haematologist, Royal Marsden Hospital, London
Dr Cathy Burton, Consultant Haematologist, Leeds Teaching Hospital
Dr Rod Johnson, Consultant Haematologist, Leeds Teaching Hospital
Dr Kate Cwynarski, Consultant Haematologist, University College Hospital, London
Dr Tobias Menne, Consultant Haematologist, Freeman Hospital, Newcastle
Professor Andy Davies, Honorary consultant medical oncologist, Southampton University Hospital
Professor Simon Rule, Professor of Haematology, Peninsula Medical School, Plymouth

References:

1. Casulo C, Byrtek M, Dawson KL, et al. 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. *Journal of Clinical Oncology*. 2015;33(23):2516–2522.
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3. Eyre TA, Osborne WL, Gallop-Evans E, et al. Results of a multicentre UK-wide compassionate use programme evaluating the efficacy of idelalisib monotherapy in relapsed, refractory follicular lymphoma. *Br. J. Haematol.* 2017;181(4):555–559.

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Idelalisib for treating follicular lymphoma refractory to 2 treatments [ID1379]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Bloodwise
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments
	Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Although there are 'potential serious adverse affects' for people having idelalisib, we know there are often serious adverse effects associated from chemotherapy. People living with blood cancer may therefore tolerate the side-effects of idelalisib better than chemotherapy, in some cases.
2	We are disappointed that the data provided does not facilitate a reliable estimate of idelalisib's cost-effectiveness. However, we welcome NICE's proposals for the model to be improved. We hope that this could enable NICE to make a full assessment of its cost-effectiveness in future.
3	We do not agree with the decision not to recommend idelalisib on the NHS. We note, for example, the potential value of idelalisib as a treatment to the 'double-refractory' population, even if that benefit is only for a very short period of time, or the possibility that it could be used as a bridge to transplant. We therefore hope that the manufacturer will be able to provide sufficient further evidence to enable the treatment to be made available via routine commissioning
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5	

Insert extra rows as needed

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- 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.
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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

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transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Lymphoma Action**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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Example 1	We are concerned that this recommendation may imply that ……..
1	Has sufficient consideration been given to the fact patients might prefer an oral therapy with possibly different side effects than more intensive chemotherapy after several treatments?
2	Has sufficient consideration been given to the different mechanism of action of idelalisib compared with chemotherapy, and the psychological advantage this offers patients who might be reluctant to undergo more chemotherapy after failing this type of treatment in the past?
3	Have frailer patients who are unable to have chemotherapy been given sufficient consideration?
4	
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6	

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Royal College of Pathologists/British Society for Haematology**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**Insert disclosure here**]
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Thanks for these documents. They are extensive, detailed and give clear conclusions. My only comment is that the overall outcome is disappointing as this is an active agent that would be useful to use in some patients with difficult Follicular lymphoma and it's a shame that the non-randomised nature of the data sets assessed hasn't provided the adequate data necessary to enable access to this treatment.
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Insert extra rows as needed

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Idelalisib for treating follicular lymphoma refractory to 2 treatments [ID1379]

Appraisal Committee Meeting – 25 June 2019

The NICE technical team asked the clinical experts for answers to a number of questions. The responses from one of the clinical experts and from the company are given below.

Response from Professor Andrew Pettitt
Honorary Consultant Haematologist, University of Liverpool & Clatterbridge Cancer Centre NHS Foundation Trust – clinical expert, nominated by the NCRI-ACP-RCP-RCR

1. Sections 3.2 of the Appraisal Consultation Document states that the committee heard that some chemotherapeutic agents offered third line for double refractory follicular lymphoma are more effective than others.
    a. Can the you please expand on this?

To be defined as double refractory, patients need to have failed (i.e. no response or relapse within 6 months of responding) rituximab (R) and at least one chemotherapy regimen. Since R is nowadays always given in combination with chemotherapy, the definition effectively means failing at least one R-chemo regimen. In the frontline setting, 3 different R-chemo regimens are used depending on circumstance: BR (bendamustine + R), R-CHOP and R-CVP. To complicate things, ofatumumab (O) can now be used an alternative to R, meaning that there are 6 different chemoimmunotherapy regimens from which to choose. BR/O+B is more effective than O/R-CHOP which, in turn, is more effective than O/R-CVP. On the other hand, O/R-CVP is better tolerated than O/R-CHOP and BR/O+B. The choice of chemotherapy regimen depends on several factors including patient age, fitness and co-morbidity and the clinical behaviour of the lymphoma. O/R-CHOP is used if there is any suspicion of high-grade transformation but is contraindicated in patients with cardiac comorbidity, while BR/O+B depletes T cells an can cause life-threatening infection especially in older patients. Patients who don't respond to or progress after CIT currently receive a different CIT regimen as second-line treatment. Younger, fitter patients may a receive "salvage" regimen followed by autologous stem-cell transplantation (ASCT) if they respond. There are number of different salvage regimens but they are all more intensive than the 3 main frontline options and not suitable for older or less fit patients. In general, patients will progressive through progressively stronger treatment regimens. Older and less fit patients are likely to start with R-CVP and stop at R/O-CHOP or BR/O+B due to intolerance, whereas younger fitter patients are likely to start with R/O-CHOP or BR/O+B and move through to salvage CIT/ASCT. Consequently, most patients run out of credible treatment options after 1-3 lines of CIT. There are currently no credible treatment options for patients who are refractory to BR or R-CHOP as salvage CIT is unlikely to be effective in this setting.

2. Section 3.23 of the Appraisal Consultation Document, NICE's provisional guidance, discusses whether the treatment meets 'end of life criteria' (according to our methods guide section 6.2.10, the population has to have a short life expectancy of normally <24 months, and there should be sufficient evidence that the treatment could offer an extension of life of normally > 3 months vs standard NHS treatment). The Appraisal Consultation Document states that there is some uncertainty about whether these criteria had been demonstrated.

a. What are your thoughts on:
    i. the life expectancy for the population considered in this appraisal (that is, patients with follicular lymphoma with disease refractory to rituximab and an alkylating agent who would be fit enough to receive chemotherapy third line),

As explained above, being refractory to an alkylating agent (CVP, CHOP or bendamustine) and rituximab effectively means being refractory to CVP, CHOP or bendamustine in combination with rituximab. This situation might arise after the first, second or third line of CIT depending on the sequencing of treatment. Patients who are resistant to R-CVP might respond to R-CHOP or BR if they are able to tolerate these regimens, but patients who are resistant to R-CHOP or BR (irrespective of whether the regimens are given as first, second or third line treatment) are unlikely to respond to salvage CIT/ASCT and have no other credible treatment options. In the absence of effective treatment, survival is likely to be substantially less than 24 months (I would estimate somewhere in the order of 6 months on average if pushed). The situation is likely to be very similar for patients who are refractory to O+B or O-CHOP, as well as for those patients who are refractory to R-CVP and unable to tolerate BR/O+B or R/O-CHOP.

    ii. how much would you expect idelalisib to extend life vs existing chemotherapeutic treatments, on average? We recognise that your clinical experience with idelalisib long term is likely to be limited.

Compared to further (ineffective) CIT, idelalisib is likely to prolong life for substantially longer than 3 months. If pushed, I would estimate somewhere in the order of 12 months on average, although it could be much longer than this for some patients.

3. The company presented data that suggests that, compared with chemotherapy, idelalisib is superior for overall survival, but inferior for progression free survival. The company recognise that this is counterintuitive, but argue that “Across both samples, PFS was defined as time from initiation of treatment to date of first disease progression or death from any cause. However, according to the study protocol, trial subjects were subject to regular imaging-based tumour assessments, performed at ~8- to 12-week intervals at Visits 1, 6, 9, 11, 13, and 15 (corresponding to baseline, Weeks 8, 16, 24, 36, and 48) and every 12 weeks thereafter and at an end-of-treatment. By contrast, HMRN patients, as is the NHS standard of care, may have an interim treatment scan, but be routinely scanned only at the end of treatment or if they become symptomatic and disease progression is suspected. As such, the HMRN dataset will systematically overpredict PFS in comparison to DELTA. Along with other issues of comparability across the two datasets, PFS comparison is rendered almost meaningless”.
    a. Is this rationale plausible?

Yes. Regular imaging-based assessments are likely to identify progression at an earlier stage than clinically based assessments. This is a particular issue for those patients with predominantly abdominal disease that cannot be detected by physical examination.

    b. In your experience, could this data reflect a true difference, i.e. might idelalisib make people live longer while making the disease progress sooner vs standard NHS treatment?

No, I think this is highly unlikely. I’ve never heard of such a thing.

c. Because the of the counterintuitive relationship described above, the company present cost-effectiveness analyses that assume progression free survival is the same in both intervention and comparator arms (rather than being superior in the comparator arm, as suggested by clinical data). Is this assumption realistic?

If overall survival is superior in idelalisib-treated patients compared to CIT-treated patients in the HMRN dataset, I would expect PFS to show a similar pattern. Consequently, I think the company's assumptions are actually quite conservative.

If you have any questions, please let me know. We are currently preparing slides for the June meeting so the earlier you can reply the better. Thank you for your time.

I would like to take this opportunity to emphasise that idelalisib fulfils a genuine unmet need in patients with relapsed or refractory FL who have exhausted CIT options.

Questions for clinical experts – June 2019

1. Sections 3.2 of the Appraisal Consultation Document states that the committee heard that some chemotherapeutic agents offered third line for double refractory follicular lymphoma are more effective than others.

a. Can the you please expand on this?

- Selection of chemotherapy regimens in 1st and 2nd lines in the UK consists largely of R-CVP, R-bendamustine, R-CHOP or single-agent rituximab; with clinician- and patient-choice based ultimately on the goal of treatment (either maximise activity/disease control [e.g. R-CHOP or R-bendamustine] OR maximise tolerability/QoL [e.g. R-CVP or R])

- For example, trial data suggests a lower risk of progressive disease following R-CHOP versus R-CVP in long-term follow-up of front-line symptomatic FL patients (https://ascopubs.org/doi/10.1200/JCO.2017.74.1652), although consideration of the potential cardiotoxic effects of R-CHOP may favour R-CVP in patients with previous history of cardiac disease, thus necessitating use of R-CHOP for second or later lines in some patients

- This is consistent with HMRN real-world dataset, whereby ~42% of patients received R-CVP front-line versus ~18% R-CHOP

- As noted in the NICE ACD (Sept 2018) (Section 3.2), the current lack of an evidence-based standard of care in third-line treatment of follicular lymphoma (FL) limits the choice of a suitable chemotherapy regimen to that which the patient has not already received, and progressed or failed to respond to, in previous lines

- [redacted] – refractoriness in particular to the intensive R-CHOP or R-bendamustine regimens is commonly accepted by clinicians as reflective of a high-risk, poor-prognostic group of patients

- Having potentially exhausted the availability of the most effective chemotherapeutic options in earlier lines, this very high-risk subgroup of double-refractory FL patients is currently limited to conventional single-agent or combination chemotherapy in 3rd line (or, in some cases, best-supportive care for those patients who can no longer tolerate chemotherapy) with increasingly shorter remissions for each subsequent line of treatment owing to the relapsing/remitting nature of the disease

2. Section 3.23 of the Appraisal Consultation Document, NICE's provisional guidance, discusses whether the treatment meets 'end of life criteria' (according to our methods guide section 6.10, the population has to have a short life expectancy of normally <24 months, and there should be sufficient evidence that the treatment could offer an extension of life of normally > 3 months vs standard NHS treatment). The Appraisal

Consultation Document states that there is some uncertainty about whether these criteria had been demonstrated.

a. What are your thoughts on:

i. the life expectancy for the population considered in this appraisal (that is, patients with follicular lymphoma with disease refractory to rituximab and an alkylating agent who would be fit enough to receive chemotherapy third line),

ii. how much would you expect idelalisib to extend life vs existing chemotherapeutic treatments, on average? We recognise that your clinical experience with idelalisib long term is likely to be limited.

- It will be important to understand the opinion of the clinical experts on this based on their experiences with idelalisib alongside other chemo-therapeutic options in the treatment of double-refractory FL. This is what prompted the clinical community to compile their independent clinical consensus letter (*uploaded to NICE docs*) in support of this appraisal given the absence of a current, evidence-based standard of care for these patients

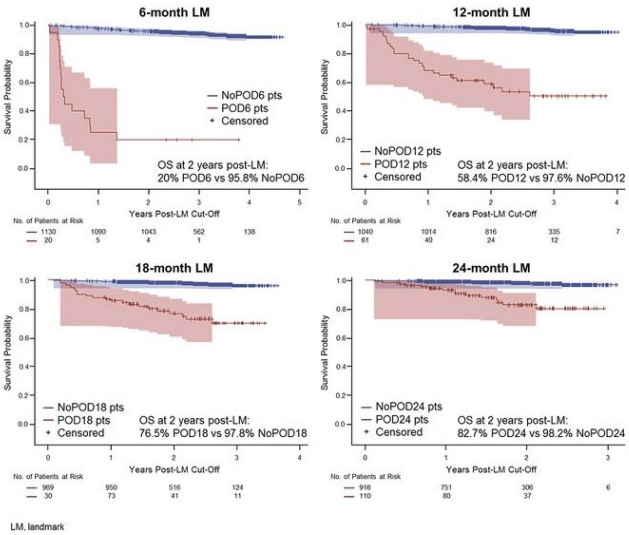
- The letter also points out the analysis around progression of disease within 24 months of treatment initiation (or 'POD24') as a critical determinant of survival for FL patients at first relapse. Casulo *et al* (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4879714/) was one of the first publications to look at the significance of POD24

- The GALLIUM study (http://www.bloodjournal.org/content/130/Suppl_1/1490) went one step further and performed landmark (LM) analyses on POD24 looking at the post-progression mortality rates for all POD24 patients on study, and looked specifically at those progressing within 6 months compared to <12 months, <18 months, and <24 months

- Estimated 2-year OS KM analyses for these patients is captured below, and shows a particularly dire prognosis for those relapsing within 6 months (i.e. rituximab-refractory). This 6-month cut-off for refractoriness is now used in many study protocols

- The letter written by the clinical community acknowledges further that the patients in this POD24 analysis were a group of patients at first relapse, whereas patients in the DELTA study were refractory to both rituximab and an alkylating agent, thus it would very reasonable to assume the DELTA study patients are even higher risk relapsed group than in the POD24 analysis

Figure 1. LM Analysis per POD Time



LM, landmark

Table 1. Post-Progression Mortality Rates Stratified by Time of Progression

Time of Progression, Months	N	OS Events	Pt Years at Risk	Deaths/100 Pt-Yrs (95% CI)
0–6	22	18	22.2	81.0 (51.2–100)
6–12	58	27	111.6	24.2 (16.6–35.3)
12–18	46	9	102.2	8.8 (4.6–16.9)
18–24	29	2	52.5	3.8 (1–15.2)

Table 2. PFS and POD Events at 24 Months by Treatment Arm

	R-Chemo (n=601)	G-Chemo (n=601)
Absolute risk of a PFS event before 24 months, %	18.94 (95% CI: 15.94–22.42)	12.53 (95% CI: 10.06–15.55)
Relative risk reduction, G-chemo vs R-chemo (95% CI)	33.85 (12.76–49.84)	
PFS events at 24 months		
All	107	71
POD24 events (PD or death due to PD)	98	57
noPOD24 events (death not due to PD)	9	14

3. The company presented data that suggests that, compared with chemotherapy, idelalisib is superior for overall survival, but inferior for progression free survival. The company recognise that this is counterintuitive, but argue that "Across both samples, PFS was defined as time from initiation of treatment to date of first disease progression or death from any cause. However, according to the study protocol, trial subjects were subject to regular imaging-based tumour assessments, performed at ~8- to 12-week intervals at Visits 1, 6, 9, 11, 13, and 15 (corresponding to baseline, Weeks 8, 16, 24, 36, and 48) and every 12 weeks thereafter and at an end-of-treatment. By contrast, HMRN patients, as is the NHS standard of care, may have an interim treatment scan, but be routinely scanned only at the end of treatment or if they become symptomatic and disease progression is suspected. As such, the HMRN dataset will systematically overpredict PFS in comparison to DELTA. Along with other issues of comparability across the two datasets, PFS comparison is rendered almost meaningless".

a. Is this rationale plausible?
b. In your experience, could this data reflect a true difference, i.e. might idelalisib make people live longer while making the disease progress sooner vs standard NHS treatment?
c. Because the of the counterintuitive relationship described above, the company present cost-effectiveness analyses that assume progression free survival is the same in both intervention and comparator arms (rather than being superior in the comparator arm, as suggested by clinical data). Is this assumption realistic?

- The interpretation implied by NICE in this question is surprising – the rationale explained in our ACD response is clear in that, owing to significant differences in the way in which progressive disease is monitored in a clinical trial versus clinical practice, there is a likely systematic over-prediction of the timing of true disease progression events observed in clinical practice (i.e. HMRN cohort) compared to the rigorous, routine clinical assessment performed in the DELTA study

- Put simply, the disease progression events seen in the DELTA study will have been identified sooner due to more rigorous patient follow-up versus the HMRN cohort, making comparisons between the two cohorts very challenging, if not impossible with regards to PFS – hence our recommendation not to draw such comparison

- To infer from these data that idelalisib is somehow making the actual disease progress sooner than current chemotherapy options in the third-line FL setting is certainly not our interpretation, and is contrary to the licensing terms of the FDA and EMA who deemed the OS and PFS outcomes of the DELTA study a sufficient gain compared with current treatment options in the 3rd line setting to warrant a license based on Phase 2 data – this was even at the earlier data-cut, to which we now present further consistent and compelling evidence from longer follow-up (Aug 2018 data-cut

- Given these considerations, we believe that our assumption of equal PFS in comparisons B2 and B3 is, in fact, highly conservative against idelalisib.

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Idelalisib for treating refractory follicular lymphoma

ERRATUM

This document contains errata in respect of the ERG report in response to the company's factual accuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page nr:	**Change:**
14	Sentence amended
18	Sentence deleted
36	Factual inaccuracy (carried over from the CS) amended: WHO PFS ≤ 2 for study 101-02/99
40-41	Baseline characteristics of CUP and HMRN patients amended in Table 4.4 of Page 40-41.
52	Baseline characteristics of HMRN adjusted population amended in Table 4.11 of Page 52
101	Sentence amended
102	Caption of Table 5.18 amended
107	Sentence deleted
113	Sentence amended
115	Typo amended
116	Sentence deleted
120	Sentence deleted

Table 4.3: Summary of methodology of included clinical effectiveness studies

Study	101-09[33]	101-02/99[34]	Compassionate use programme[35]
Location	41 sites in the US and Europe	Eight sites in the US	46 sites in UK and Ireland
Trial design	Single group, open label, Phase II study	Phase Ib dose escalation and extension study	Retrospective cohort study
Eligibility criteria for participants	Key criteria for eligibility included: • Confirmed diagnosis of B cell iNHL without evidence of histological transformation • Histological types included FL Grade 1, 2 or 3a; small lymphocytic lymphoma; splenic, nodal or extranodal marginal zone lymphoma; LPL/WM • Radiographically measurable disease (defined as ≥1 lymph node with perpendicular dimensions measuring ≥2.0 x ≥1.0cm) • Received at least two prior systemic therapies for iNHL • Refractory to both rituximab and an alkylating agent, whether administered together or in successive treatment regimens. Refractory was defined as less than a partial response or progression of disease within 6 months after completion of a prior therapy • Karnofsky performance score of 60 or higher (on a scale of 0=death and 100=complete absence of symptoms) Exclusion criteria included: • Central nervous system lymphoma • Known histological transformation from iNHL to diffuse large B cell lymphoma • History of a non-lymphoma malignancy except for the following: adequately treated local basal cell or	Key criteria for eligibility included: • Histologically confirmed diagnosis of iNHL • Histologic types included follicular lymphoma Grade 1, 2 or 3a; small lymphocytic lymphoma; marginal zone lymphoma; lymphoplasmacytic lymphoma with or without WM • Measurable disease (defined as ≥1 lesion measuring >2cm in a single dimension by computed tomography • World Health Organization performance status ≤2 • Received at least 1 prior chemotherapy and prior rituximab Exclusion criteria included: • Active central nervous system lymphoma • Active serious infection requiring systemic therapy • Prior stem cell transplantation with active graft-versus-host disease	Refractory or relapsed FL: • Refractory defined as stable disease or progressive disease to the prior treatment, or relapse <6 months following a previous partial/complete response • Relapse defined as progressive disease followed a remission >6 months

Table 4.4: Baseline characteristics of patients in included studies

Baseline characteristic	Study 101-09[33]		Study 101-02/99 (n=64)[34]	CUP cohort (n=79)[35]	HMRN Patients ([redacted])[14]
	Overall population (n=125)	FL population (n=72)			
Median age, years (range)	64 (33–87)	62 (33–84)	64 (32–91)	64 (29–86)	[redacted]
Sex, male, n (%)	80 (64%)	39 (54.2%)	44 (69%)	40 (51%)	[redacted]
Performance status/Disease stage, n (%)	KPS 60: 2 (1.6%) KPS 70: 6 (4.8%) KPS 80: 27 (21.6%) KPS 90: 44 (35.2%) KPS 100: 46 (36.8%)	ECOG 2: 6 (8.3%) ECOG 1: 35 (48.6%) ECOG 0: 31 (43.1%)	NR	ECOG 2-4: 20 (25%) ECOG 0-1: 59 (75%)	Stage III or IV (%): [redacted]
Median time since diagnosis, years (range)	5.3 (0.4–18.4)	4.7 (0.8–18.4)	NR	NR	[redacted]
Disease subtype, n (%)					
Follicular lymphoma	72 (57.6%)	72 (100%)	38 (59%)	79 (100%)	[redacted]
Small lymphocytic lymphoma	28 (22.4%)	Not applicable	11 (17%)	NR	NR
Marginal zone lymphoma	15 (12.0%)	Not applicable	6 (9%)	NR	NR
Lymphoplasmacytic lymphoma with or without Waldenström's macroglobulinaemia	10 (8.0%)	Not applicable	9 (14%)	NR	NR
Health assessment, n (%)					
Disease Stage III or IV	111 (88.8)	60 (83.3)	NR	NR	NR
Elevated LDH	38 (30.4)	21 (29.2)	24 (38%)	NR	NR
Bulky disease (one or more nodes with at least one dimension of 7cm or more)	33 (26.4)	16 (22.2)	28 (44%)	NR	[redacted]
Baseline neutropenia (ANC <1,500 per mm^3)	17 (13.6)	9 (12.5)	7 (11%)	NR	NR
Baseline anaemia (haemoglobin <10 g/dL)	19 (15.2)	8 (11.1)	41 (64%)	NR	NR
Baseline thrombocytopenia (platelet count <75,000 per mm^3)	10 (8.0)	5 (6.9)	36 (56%)	NR	NR
High FLIPI risk score at baseline	Not applicable	39 (54.2)	NR	0-2: 19/78 (25%)	NR

Baseline characteristic	Study 101-09[33]		Study 101-02/99 (n=64)[34]	CUP cohort (n=79)[35]	HMRN Patients ([redacted])[14]
	Overall population (n=125)	FL population (n=72)			
				3-5: 59/78 (75%)	
FL grade	Not applicable	1: 21 (29.2) 2: 39 (54.2) 3A: 12 (16.7)	NR	NR	NR
Treatment history					
Median prior regimens (range)	4 (2–12)	4 (2–12)	4 (1–10)	3 (1–13)	[redacted]
Median time since completion of last treatment, months (range)	3.9 (0.7–41.4)	4.3 (0.7–39.1)	NR	8.6 (0.9–99.2)	NR
Prior therapy, n (%)					
Rituximab	125 (100)	72 (100)	62 (97%)	78 (99%)	[redacted]
Alkylating agent	125 (100)	72 (100)	58 (91%)	78 (99%)	[redacted]
Bendamustine	81 (64.8)	50 (69.4)	17 (27%)	NR	NR
Anthracycline	79 (63.2)	51 (72.2)	33 (52%)	NR	NR
Purine analogue	42 (33.6)	17 (23.6)	27 (42%)	NR	NR
Stem cell transplantation	14 (11.2)	12 (16.7)	NR	21 (27%)	[redacted]
Prior therapy to which the disease was refractory, n/total n (%)					
Rituximab	125/125 (100)	72/72 (100)	NR	NR	[redacted]
Alkylating agent	124/125 (99)[a]	72/72 (100)	NR	NR	[redacted]
R-bendamustine	47/60 (78.3)	23/36 (72.2)	NR	NR	NR
R-CHOP	40/56 (71.4)	23/35 (65.7)	NR	NR	NR
R-CVP	29/36 (80.6)	15/20 (75.0)	NR	NR	NR
Bendamustine	61/81 (75.3)	32/50 (64.0)	NR	NR	NR
Refractory to ≥2 regimens	99/125 (79.2)	57/72 (79.2)	NR	NR	NR
Refractory to most recent regimen	112/125 (89.6)	62/72 (86.1)	37 (58%)	NR	NR

Summary data for the FL population of Study 101-09 (June 2014 database lock), were compared with individual patient data (IPD) from HMRN. All variables which were common to both datasets were considered for inclusion in the MAIC. However, several variables were subsequently excluded. The variables included in the MAIC were therefore:

[redacted]

Patient characteristics pre- and post-matching are summarised in Table 4.11.

Table 4.11: Baseline characteristics of Study 101-09 patients and HMRN patients (pre- and post-matching), FL population with disease refractory to rituximab and an alkylating agent

Characteristic	Study 101-09 (n=72)	HMRN (n=[redacted])	Adjusted HMRN ([redacted])
Male, n (%)	39 (54.2)	[redacted]	[redacted]
Median age, years (range) Age ≥ 62 years (%)	62 (33–84) NR	NR [redacted]	[redacted]
Stage III or IV, n (%)	60 (83.3)	[redacted]	[redacted]
Bulky disease, n (%)	16 (22.2)	[redacted]	[redacted]
Median time since diagnosis, years (range) Time from diagnosis >=4.7 (%)	4.7 (0.8–18.4) NR	NR [redacted]	NR [redacted]
Median lines of prior therapy (range)	4 (2–12)	[redacted]	NR
Prior ASCT, n (%)	12 (16.7)	[redacted]	NR

Source: CS, Table 16, page 59, and Table 17, page 61.
ASCT = autologous stem cell transplantation; HMRN = Haematological Malignancy Research Network; FL = follicular lymphoma.

[redacted][37] The results for two-year OS and one-year PFS for the idelalisib patients in Study 101-09 and the HMRN patients before and after MAIC adjustment are summarised in Table 4.12.

Table 4.12: OS and PFS results for Study 101-09 patients and HMRN patients after adjustment, FL population with disease refractory to rituximab and an alkylating agent

Outcome	Study 101-09 (n=72)	Unadjusted HMRN (n=[redacted])	Adjusted HMRN [redacted]	Adjusted HMRN excluding time to diagnosis [redacted]
Two-year OS	69.8%	[redacted]	[redacted]	[redacted]
One year PFS	43%	[redacted]	[redacted]	[redacted]

Source: CS, Table 17, page 61; HMRN report, Tables 18 and 19
ASCT = autologous stem cell transplantation; HMRN = Haematological Malignancy Research Network; FL = follicular lymphoma.
*effective MAIC sample size calculated as the square of the summed weights divided by the sum of the squared weights.

Table 5.17: Comparison D: Study 101-09 vs. Study 101-09 (BSC) results, including idelalisib CCD

	Costs	QALYs	Life years	Incremental			ICER
				Costs	QALYs	Life years	
BSC	[redacted]	2.50	4.62	-	-	-	£25,272
Idelalisib	[redacted]	3.71	6.34	£30,473	1.21	1.72	

Source: Table 63 in the CS.[1]
BSC = best supportive care; CCD = confidential commercial discount; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years.
*Note that the "Life years" results provided in the table are undiscounted

Other scenario analyses: alternative assumptions on Comparison A

Detailed cost effectiveness results for the remaining set of scenarios were not presented in the CS. However, based on the ICER change figures shown in Table 5.14 above, the ICER results from Comparison A did not change drastically with the scenarios tested by the company. The largest positive difference with respect to the base-case ICER was found in the scenario when the time horizon of 10 years was used (instead of a time horizon of 38 years in the base-case, using 10 years of time horizon resulted in an ICER increase of £5,462). The largest negative difference with respect to the base-case ICER was found in the scenario, which assumes a generalised gamma distribution for TTP (instead of using lognormal distribution for TTP in the base-case, using generalised gamma distributed TTP would lead to an ICER decrease of -£7,117).

ERG comments: Even though the results were presented in an appropriate way, the ERG discovered and corrected several errors in the model as described in Section 5.3.1. This had an impact on the results, as shown in sections 5.3.2 and 5.3.3. In the PSA, the ERG noted that normal distribution was used to sample cost related model inputs, and considers that using normal distribution has a probability, albeit small, to generate implausible (negative) sampled values, and therefore the ERG would have preferred gamma or lognormal distribution used while sampling for logically positive parameters. The ERG doubts if correlated variables like the survival coefficients should have been included in the one-way sensitivity analysis, since changing one parameter to its upper/lower bound while keeping the other correlated variable unchanged might lead to unrealistic combination of parameters.

Several structural uncertainties were tested by the company as scenario analyses. However, the ERG considered that the company could have conducted more scenario analyses, especially considering the substantial uncertainty in some of the model inputs related to resource use and utilities. Furthermore, in all scenario analyses, the uncertainties were explored individually and therefore a combined effect of changing multiple assumptions in the model on the ICER, is missing. This will be explored by the ERG in Section 5.3.

5.2.12 Model validation and face validity check

In the CS (on page 152), it was mentioned that the inputs and assumptions of the cost effectiveness analyses were reviewed during a meeting with Dr Robert Marcus. The meeting report was enclosed in the submission. Furthermore, it was stated that the economic model was reviewed for coding errors, inconsistencies, and the plausibility of inputs by an economist not involved in model building. In addition, in the CS, it was mentioned that a checklist of known modelling errors and questioning of assumptions was used to review the model. The details and results of the technical validation of the economic model were not reported.

The ERG has serious concerns on the lack of the reporting of the model validation efforts. The company declined to provide these, even this was requested. This, in combination with the spotted programming errors and the gap between trial outcomes and the model outcomes decreased our level of confidence in the economic model.

The ERG incorporated several changes to the comparisons provided in the CS: 1) fixing programming errors 2) Incorporating half cycle correction 3) Using the mean ToT estimate from the most recent data cut-off date while calculating AE cycle probabilities 4) Implementing wastage costs for idelalisib (i.e. when patients stop the treatment before the package is finished completely) 5) Implementing idelalisib mean dose intensity from Study 101-09 for chemotherapy (as a conservative estimate, as it was reported that the MDI for chemotherapy is expected to be lower) 6)Implementing age adjusted utility decline from Ara et al. 2010.[57]

After the ERG changes were implemented, in Comparison A, idelalisib resulted in [redacted] total (discounted) costs and 3.43 total QALYs, while chemotherapy resulted in [redacted] total (discounted) costs and 2.71 total QALYs, as presented in Table 5.19. Therefore, idelalisib produced 0.72 additional QALYs at an incremental cost of £23,599 when compared to chemotherapy, leading to an ICER of £32,882. This is higher than the company base-case ICER.

For Comparison B, after ERG changes, idelalisib resulted in [redacted] total (discounted) costs and 3.10 total QALYs, while chemotherapy resulted in [redacted] total (discounted) costs and 1.38 total QALYs, as presented in Table 5.20. Therefore, idelalisib produced 1.72 additional QALYs at an incremental cost of £37,164 when compared to chemotherapy, leading to an ICER of £21,559.

After the ERG changes were implemented, in Comparison C, idelalisib resulted in [redacted] total (discounted) costs and 3.21 total QALYs, while chemotherapy resulted in [redacted] total (discounted) costs and 2.82 total QALYs, as presented in Table 5.21. Therefore, idelalisib produced 0.39 additional QALYs at an incremental cost of £22,712 when compared to chemotherapy, leading to an ICER of £58,754.
For the chemotherapy ineligible patients, after ERG changes are implemented in Comparison D, idelalisib resulted in [redacted] total (discounted) costs, and 3.43 total QALYs, same as in Comparison A, while BSC resulted in [redacted] total (discounted) costs and 2.43 total QALYs, as presented in Table 5.22. Therefore, idelalisib produced 0.99 additional QALYs at an incremental cost of £29,426, when compared to BSC, leading to an ICER of £29,639.

The ERG conducted following additional scenario analyses: 1) 50% price reduction rituximab (due to biosimilar availability) 2) HR=1 for adjusting prior line treatment outcomes 3) Alternative utility inputs from Bec et al. 2014 or GADOLIN trial 4) 100% increase in CMV monitoring frequency 5) CHOP regimen costs for the chemotherapy costs 6) Applying minimum function instead of maximum to operationalise logical constraints on time to event extrapolation curves 7) Using alternative TTP (PFS for Comparison B), ToT and PPS (OS for Comparison B) extrapolations

In Comparison A, the ICER values range between £30,000 to £40,000. Incremental costs are between £22,500 to £27,500 and incremental QALYs are between 0.59 and 0.84. The scenarios that had the most impact on the ICER seems to be using an alternative distribution for TTP extrapolation (scenario 7a), assuming cheaper (i.e. similar to the CHOP regimen) chemotherapy costs (scenario 5) and using utility inputs from Bec et al. 2014 (Scenario 3a).

When we look at Comparison B, the ICER values range between £16,800 to £26,000. Incremental costs are between £36,000 to £46,000 and incremental QALYs are between 1.42 and 2.73. The scenarios that had the most impact on the ICER seem to be using an alternative distribution for OS extrapolation (scenario 7c) and using utility inputs from Bec et al. 2014 (Scenario 3a). Total LYs, QALYs and costs associated with the chemotherapy seem to be lower in Comparison B than those in Comparisons A, C and even comparison D (for chemotherapy ineligible patients, receiving BSC). This gap can be due to the difference in model inputs used (e.g. MAIC adjusted HMRN dataset) as well as the different underlying modelling assumptions made in comparison B (e.g. area under the curve approach).

In Comparison C, besides the one outlier (Scenario 7c), which generated rather implausible estimates in terms of LYs and QALYs, the ICER values range between £58,000 to £95,000. Incremental costs are between £21,500 to £26,500 and incremental QALYs are between 0.23 and 0.39. The scenarios that had the most impact on the ICER seem to be using an alternative distribution for TTP extrapolation (scenario 7a), and assuming an HR=1 to adjust for the prior-line treatment time-to-event outcomes (scenario 2). Less than these two scenarios, the other scenarios that still had a substantial impact on the ICER are assuming less expensive (i.e. same as the CHOP regimen) estimates for the chemotherapy costs (scenario 5) and using utility inputs from Bec et al. 2014 (Scenario 3a). The only difference of comparison C from comparison A was the TTP inputs, therefore, as expected, total LYs, QALYs and cost outcomes from comparison C seem to be in line with the outcomes from comparison A. The QALYs from the idelalisib arm are a bit lower and the QALYs from the chemotherapy arm are a bit higher than those in comparison A, which led to a higher ICER. The ERG considers that the TTP data used in comparison C might be more reflective of the UK population, as it was from a compassionate use program conducted in the UK and Ireland.

Finally, in Comparison D, the cost-effectiveness results are relatively robust. Incremental QALYs are around 0.99 and incremental costs are around £29,000, which lead to an ICER value around £30,000 per QALY gained in all scenarios. Scenarios that had some impact on the ICER are using an alternative distribution for TTP extrapolation (scenario 7a) and using utility inputs from Bec et al. 2014 or GADOLIN trial (Scenario 3a and 3b). However, one should interpret these comparison D results with caution since in this comparison, it is assumed that patients receiving BSC progress immediately, which leads to an underestimation for the BSC related outcomes.

In conclusion, the ERG analyses resulted in a range of ICERs between £16,800 and £95,000 per QALY gained. Most of the ICER estimates are larger than the £30,000 per QALY threshold. Especially in Comparison C, where the TTP data are potentially the most reflective of the UK clinical practice, the ICER estimates are all above the £50,000 per QALY threshold. These ranges are indicative of the substantial uncertainty inherent in the cost-effectiveness estimates, and with the inherent uncertainty, especially on the clinical effectiveness evidence, the ERG is doubtful whether idelalisib can be considered as cost-effective for the population it was indicated for.

5.3.3. Results from the ERG additional exploratory scenario analyses

The additional scenarios listed in Section 5.3.1 were performed after the ERG changes were implemented to all four comparisons. The results of these additional scenarios are going to be summarised from Table 5.23 to Table 5.26, for Comparisons A, B, C and D, respectively.

It can be seen that there is a substantial uncertainty surrounding the cost effectiveness of idelalisib.

When we look at Comparison A, the ICER values range between £30,000 to £40,000. Incremental costs are between £22,500 to £27,500 and incremental QALYs are between 0.59 and 0.84.

The scenarios that had the most impact on the ICER seems to be using an alternative distribution for TTP extrapolation (scenario 7a), assuming cheaper (i.e. similar to the CHOP regimen) chemotherapy costs (scenario 5) and using utility inputs from Bec et al. 2014 (Scenario 3a).

When we look at Comparison B, the ICER values range between £16,800 to £26,000. Incremental costs are between £36,000 to £46,000 and incremental QALYs are between 1.42 and 2.73.

The scenarios that had the most impact on the ICER seems to be using an alternative distribution for OS extrapolation (scenario 7c) and using utility inputs from Bec et al. 2014 (Scenario 3a).

Total LYs, QALYs and costs associated with the chemotherapy seem to be lower in Comparison B than those in Comparisons A, C and D (for chemotherapy ineligible patients receiving BSC).

In Comparison C, besides the one outlier (Scenario 7c), which generated rathe implausible estimates in terms of Lys and QALYs, the ICER values range between £58,000 to £95,000. Incremental costs are between £21,500 to £26,500 and incremental QALYs are between 0.23 and 0.39.

The scenarios that had the most impact on the ICER seems to be using an alternative distribution for TTP extrapolation (scenario 7a), and assuming an HR=1 to adjust for the prior-line treatment time-to-event outcomes (scenario 2). Less than these two scenarios, the other scenarios that had still a substantial impact on the ICER are assuming cheaper (i.e. similar to the CHOP regimen) chemotherapy costs (scenario 5) and using utility inputs from Bec et al. 2014 (Scenario 3a).

Total LYs, QALYs and costs associated with the chemotherapy in Comparison C seem to be in line with the results from Comparison A. The QALYs from the idelalisib arm is a bit lower and the QALYs from the chemotherapy arm is a bit higher than those in Comparison A.

Finally, in Comparison D, the cost effectiveness results are relatively robust. Incremental QALYs are around 0.99 and incremental costs are around £29,000, which lead to an ICER value around £30,000 per QALY gained.

The scenarios that had some impact on the ICER are to be using an alternative distribution for TTP extrapolation (scenario 7a) and using utility inputs from Bec et al. 2014 or GADOLIN trial (Scenario 3a and 3b). However, one should interpret the results with caution since in this comparison, it is assumed that patients receiving BSC progress immediately, which is an underestimation for the BSC related outcomes.

When we look at Comparison B, the ICER values range between £16,800 to £26,000. Incremental costs are between £36,000 to £46,000 and incremental QALYs are between 1.42 and 2.73. The scenarios that had the most impact on the ICER seems to be using an alternative distribution for OS extrapolation (scenario 7c) and using utility inputs from Bec et al. 2014 (Scenario 3a). Total LYs, QALYs and costs associated with the chemotherapy seem to be lower in Comparison B than those in Comparisons A, C and D (for chemotherapy ineligible patients receiving BSC).

In Comparison C, besides the one outlier (Scenario 7c), which generated rather implausible estimates in terms of LYs and QALYs, the ICER values range between £58,000 to £95,000. Incremental costs are between £21,500 to £26,500 and incremental QALYs are between 0.23 and 0.39. The scenarios that had the most impact on the ICER seems to be using an alternative distribution for TTP extrapolation (scenario 7a), and assuming an HR=1 to adjust for the prior-line treatment time-to-event outcomes (scenario 2). Less than these two scenarios, the other scenarios that had still a substantial impact on the ICER are assuming cheaper (i.e. similar to the CHOP regimen) chemotherapy costs (scenario 5) and using utility inputs from Bec et al. 2014 (Scenario 3a). Total LYs, QALYs and costs associated with the chemotherapy in Comparison C seem to be in line with the results from Comparison A. The QALYs from the idelalisib arm is a bit lower and the QALYs from the chemotherapy arm is a bit higher than those in Comparison A.

Finally, in Comparison D, the cost effectiveness results are relatively robust. Incremental QALYs are around 0.99 and incremental costs are around £29,000, which lead to an ICER value around £30,000 per QALY gained. The scenarios that had some impact on the ICER are using an alternative distribution for TTP extrapolation (scenario 7a) and using utility inputs from Bec et al. 2014 or GADOLIN trial (Scenario 3a and 3b). However, one should interpret the results with caution since in this comparison, it is assumed that patients receiving BSC progress immediately, which is an underestimation for the BSC related outcomes obviously.

In conclusion, the ERG analyses resulted in a range of ICER between £16,800 and £95,000 per QALY gained. Most of the ICER estimates are larger than the £30,000 per QALY threshold. Especially in Comparison C, where the TTP data that is potentially the most reflective of the UK clinical practice, the ICER estimates are above £50,000 per QALY threshold. These ranges are indicative of the substantial uncertainty inherent in the cost effectiveness estimates.

In the total population, 72 patients (57.6%) reported a serious adverse event (SAE); in the FL population, 36 patients (50.0%) reported an SAE. The most frequent SAEs in the total population (reported in ≥10% of patients) were pyrexia and pneumonia (both reported in 14 [11.2%] patients); pyrexia was also the only SAE reported in ≥10% of patients in the FL population (reported in 8 [11.1%] patients). In total, 13 (10.4%) patients had an AE that resulted in death.

No adverse events were reported for comparators. Therefore, it is not possible to say anything about the relative safety profile in comparison to usual care.

The base-case cost effectiveness analysis for Comparison A showed that idelalisib resulted in a total cost of [redacted] and 3.75 QALYs, whereas chemotherapy regimens as used in the previous line of treatment as observed in Study 101-09 resulted in a total cost of [redacted] and 2.81 QALYs, resulting in an ICER of £26,076 per QALY gained. In Comparison B, idelalisib treatment resulted in a total cost of [redacted] and 3.19 QALYs, whereas chemotherapy regimens as observed in the HMRN database resulted in a total cost of [redacted] and 1.44 QALYs. In Comparison C idelalisib treatment resulted in a total cost of [redacted] and 3.41 QALYs, whereas chemotherapy regimens as used in the previous line of treatment as observed in the UK and Ireland compassionate use programme resulted in a total cost of [redacted] and 2.92 QALYs. Lastly, in Comparison D idelalisib treatment resulted in a total cost of [redacted] and 3.71 QALYs, best supportive care in a total cost of [redacted] and 2.50 QALYs.

The company submission presented a probabilistic sensitivity analysis (PSA) and deterministic sensitivity analysis for Comparison A, and a number of scenario analyses covering all comparisons. The estimated probability of idelalisib being cost effective compared to chemotherapy regimens as used in the previous line of treatment as observed in Study 101-09 was 68% at a threshold of £30,000 per QALY gained. The deterministic sensitivity analysis showed that model outcomes were most sensitive to changes in the time to progression under idelalisib treatment.

In the scenario analyses, the published survival data used in Comparison B and C was digitised, and parametric survival models were subsequently fitted and incorporated into the economic analysis. This scenario resulted in a reduced ICER in Comparison B (£19,872), but a large increase in the ICER in Comparison C (£47,011). Other scenarios assessed the impact of choosing different parametric survival models for TTP, PPS and ToT in Comparison A. These resulted in moderate changes in the ICER, changes ranging from -£7,117 to +£3,785.

In Comparison A, the ICER values range between £30,000 to £40,000. Incremental costs are between £22,500 to £27,500 and incremental QALYs are between 0.59 and 0.84. The scenarios that had the most impact on the ICER seems to be using an alternative distribution for TTP extrapolation (scenario 7a), assuming cheaper (i.e. similar to the CHOP regimen) chemotherapy costs (scenario 5) and using utility inputs from Bec et al. 2014 (Scenario 3a).

When we look at Comparison B, the ICER values range between £16,800 to £26,000. Incremental costs are between £36,000 to £46,000 and incremental QALYs are between 1.42 and 2.73. The scenarios that had the most impact on the ICER seems to be using an alternative distribution for OS extrapolation (scenario 7c) and using utility inputs from Bec et al. 2014 (Scenario 3a). Total LYs, QALYs and costs associated with the chemotherapy seem to be lower in Comparison B than those in Comparisons A, C and D (for chemotherapy ineligible patients receiving BSC).

The base-case cost effectiveness analysis for Comparison A showed that idelalisib resulted in a total cost of [redacted] and 3.75 QALYs, whereas chemotherapy regimens as used in the previous line of treatment as observed in Study 101-09 resulted in a total cost of [redacted] and 2.81 QALYs, resulting in an ICER of £26,076 per QALY gained. In Comparison B, idelalisib treatment resulted in a total cost of [redacted] and 3.19 QALYs, whereas chemotherapy regimens as observed in the HMRN database resulted in a total cost of [redacted] and 1.44 QALYs. In Comparison C idelalisib treatment resulted in a total cost of [redacted] and 3.41 QALYs, whereas chemotherapy regimens as used in the previous line of treatment as observed in the UK and Ireland compassionate use programme resulted in a total cost of [redacted] and 2.92 QALYs. Lastly, in Comparison D idelalisib treatment resulted in a total cost of [redacted] and 3.71 QALYs, best supportive care in a total cost of [redacted] and 2.50 QALYs.

The company submission presented a probabilistic sensitivity analysis (PSA) and deterministic sensitivity analysis for Comparison A, and a number of scenario analyses covering all comparisons. The estimated probability of idelalisib being cost effective compared to chemotherapy regimens as used in the previous line of treatment as observed in Study 101-09 was 68% at a threshold of £30,000 per QALY gained. The deterministic sensitivity analysis showed that model outcomes were most sensitive to changes in the time to progression under idelalisib treatment.

In the scenario analyses, the published survival data used in Comparison B and C was digitised, and parametric survival models were subsequently fitted and incorporated into the economic analysis. This scenario resulted in a reduced ICER in Comparison B (£19,872), but a large increase in the ICER in Comparison C (£47,011). Other scenarios assessed the impact of choosing different parametric survival models for time to progression (TTP), post-progression survival (PPS) and time on treatment (ToT) in Comparison A. These resulted in moderate changes in the ICER, changes ranging from -£7,117 to +£3,785.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The model structure in the CS can be considered in line with other, commonly used, Markov models used in oncology. The population considered in the company's economic analyses is in line with the NICE scope. It was not obvious to the ERG to what extent the population from Study 101-09 was reflective of the double refractory FL population in the UK.

The comparators included in the cost effectiveness analyses were in line with the final scope. However, the ERG considered that obinutuzumab with bendamustine should have been one of the chemotherapy options constituting the umbrella treatment, as comparator in the model. The company did not consider this comparator based on the lack of evidence and the opinion of one clinical expert.

The company generated comparative clinical effectiveness inputs for the economic model from non-randomised evidence. This non-randomised evidence was obtained either from different single arm studies, or obtained from the same study but using data from different time-points. The ERG considered that the analyses conducted to derive these comparative effectiveness inputs were not fully in line with the recommendations outlined in NICE DSU TSD 17, which could have led to biased estimates. In line with the recommendations, the ERG considered that a covariate adjusted survival analysis might have provided a less biased, sounder and confounder-adjusted treatment effect of idelalisib for the relevant time-to-event endpoints. Additionally, the ERG had some concerns regarding the use of a hazard ratio (HR) of 0.75 for the chemotherapy arm, to adjust for the additional number of prior treatments received. The evidence source for this parameter value could not be verified, and it is not clear to the ERG why one HR should be used for all time-to-event outcomes.

Different health utilities were assigned to the pre- and post-progression health states. Input for utilities was derived from previously published poster using the EQ-5D questionnaire in FL patients. Utility decrements were applied to account for adverse events.

The model included the costs of treatment, drug administration costs, costs for monitoring and prophylaxis, costs for healthcare use in the form of visits, tests, and procedures, and costs for the treatment of adverse events. Chemotherapy proportions from Study 101-09 were used in the model. Separate estimates of healthcare utilisation for pre- and post-progressive disease are used. A separate cost estimate for the last eight weeks of life (palliative care phase) is used. Resource use was based on a combination of clinical sources and published literature, and NHS reference costs were used.

The base-case cost effectiveness analysis for Comparison A showed that idelalisib resulted in a total cost of [redacted] and 3.75 QALYs, whereas chemotherapy regimens as used in the previous line of treatment as observed in Study 101-09 resulted in a total cost of [redacted] and 2.81 QALYs, resulting in an ICER of £26,076 per QALY gained. In Comparison B, idelalisib treatment resulted in a total cost of [redacted] and 3.19 QALYs, whereas chemotherapy regimens as observed in the HMRN database resulted in a total cost of [redacted] and 1.44 QALYs. In Comparison C idelalisib treatment resulted in a total cost of [redacted] and 3.41 QALYs, whereas chemotherapy regimens as used in the previous line of treatment as observed in the UK & Ireland compassionate use programme resulted in a total cost of [redacted] and 2.92 QALYs. Lastly, in Comparison D idelalisib treatment resulted in a total cost of [redacted] and 3.71 QALYs, best supportive care in a total cost of [redacted] and 2.50 QALYs.

The company submission presented a probabilistic sensitivity analysis (PSA) and deterministic sensitivity analysis for Comparison A, and a number of scenario analyses covering all comparisons. The estimated probability of idelalisib being cost effective compared to chemotherapy regimens as used in the previous line of treatment as observed in Study 101-09 was 68% at a threshold of £30,000 per QALY gained. The deterministic sensitivity analysis showed that model outcomes were most sensitive to changes in the time to progression under idelalisib treatment.

In the scenario analyses, the published survival data used in Comparison B and C was digitised, and parametric survival models were subsequently fitted and incorporated into the economic analysis. This scenario resulted in a reduced ICER in Comparison B (£19,872), but a large increase in the ICER in Comparison C (£47,011). Other scenarios assessed the impact of choosing different parametric survival models for TTP, PPS and ToT in Comparison A. These resulted in moderate changes in the ICER, changes ranging from -£7,117 to +£3,785.

The model structure in the CS can be considered in line with other, commonly used, Markov models used in oncology. The population considered in the company's economic analyses is in line with the NICE scope. It was not obvious to the ERG to what extent the population from Study 101-09 was reflective of the double refractory FL population in the UK.

The comparators included in the cost effectiveness analyses were in line with the final scope. However, the ERG considered that obinutuzumab with bendamustine should have been one of the chemotherapy options constituting the umbrella treatment, as comparator in the model. The company did not consider this comparator based on the lack of evidence and the opinion of one clinical expert.

The company generated comparative clinical effectiveness inputs for the economic model from non-randomised evidence. This non-randomised evidence was obtained either from different single arm studies, or obtained from the same study but using data from different time. The ERG considered that

The company also provided an internal validation check (Table 35 in the Appendices), where the model base-case outcomes for mean PFS and mean OS were compared with median trial PFS and OS outcomes from Study 101-09. The ERG replaced the reported mean values from the model with the median PFS and OS outcomes from the model, which is given in Table 5.18 below.

Table 5.18: Comparison A: mean PFS and OS – model predictions vs. observed data

	Idelalisib		Chemotherapy	
	Median from base-case model	**Median from the trial**	**Median from base-case model**	**Median from the trial (prior line)**
PFS (months)	12.46	11.0	3.69	4.60
OS (months)	57.46	38.10	43.38	NA
Source: Table 35 in the Appendix of the CS and the electronic model submitted in the CS[1] PFS = progression free survival; OS = overall survival;				

From Table 5.18 above, a gap between the trial and model outcomes can be seen, especially in the idelalisib arm. The gap between model and trial PFS outcomes is less pronounced in the chemotherapy arm, especially considering the HR=0.75 applied to adjust the trial PFS. The median OS for the prior line therapy was not reported from the Study 101-09, but it is expected to be higher than the median OS from the idelalisib, since no patient has reported dead during the prior line therapy. The potential causes for this gap were not discussed in the CS.

Also, in Table 27 of the CS, the features of the economic analysis were justified in comparison to the corresponding features of the NICE appraisal of obinutuzumab with bendamustine for treating follicular lymphoma refractory to rituximab, completed in August 2017 (TA472).[50]

According to this table, the time horizon, utility source and resource use features of the CS of this appraisal and the CS of the TA472 appraisal seemed to be in line with each other.

ERG comments: The ERG requested the company to provide all details of the validation methods, using the AdvisHE validation tool.[75] In the response to the clarification letter, the company stated that the details of the model quality control process were confidential commercial property of the company and declined to provide these details.[29] It was not clear to the ERG why the company did not submit the reporting of their quality control efforts as a "commercial in confidence" document. Without any documentation of these efforts, the ERG considers that the validation section of the CS is clearly inadequate. The lack of the documenting of the validation efforts, the trust level of the ERG on the results of the cost effectiveness analyses is very low, which is reinforced by the gap between the median OS from the economic model and median trial OS from Study 101-09 for idelalisib, as depicted in Table 5.18.

Finally, in Table 27 of the CS, "the treatment effect waning" features were compared between the CS model and the TA472 model. It was not clear how the company handles the "treatment effect waning" in its model. The separate modelling of time to event outcomes for idelalisib and prior line therapy does not assume a constant HR between two treatment arms (unless exponential distribution is chosen), however there is some level of OS surrogacy, as the gain in TTP is transferred into a gain in OS, since the PPS of both arms were modelled identically. This OS surrogacy issue was reviewed in Davis et al. 2012, and was discussed thoroughly in previous cancer appraisals (e.g. TA496).[76, 77]