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

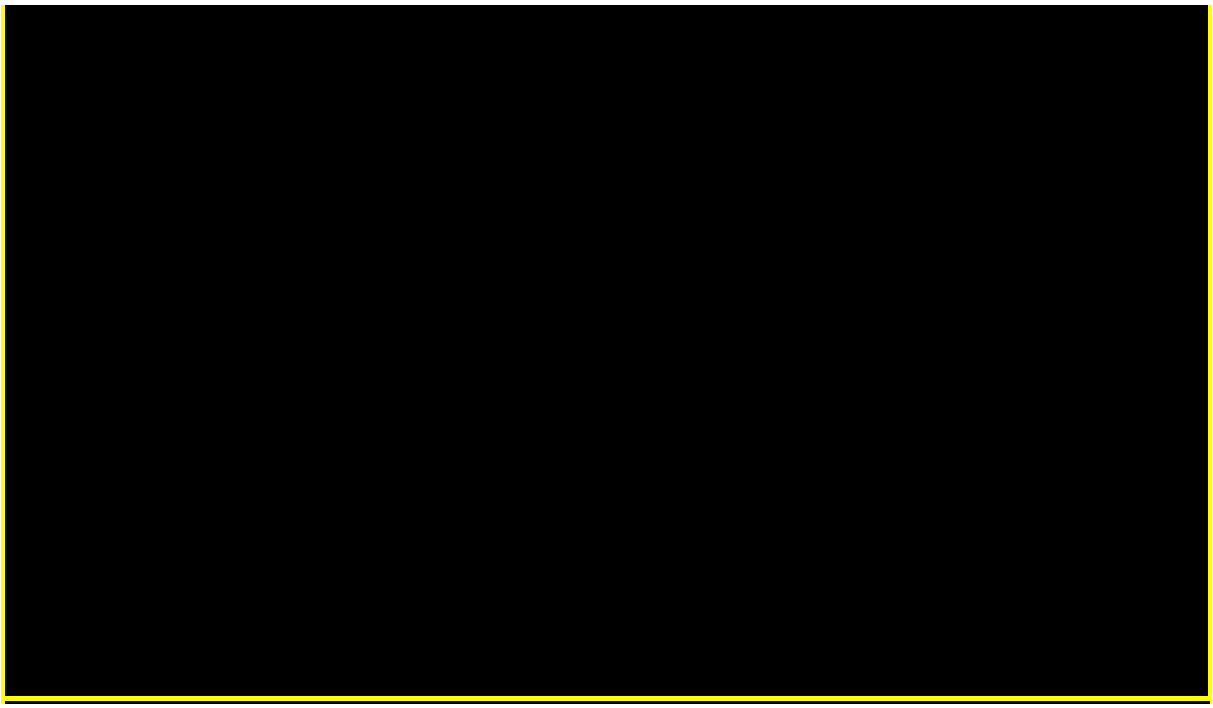
1 Latest clinical effectiveness data

1.1 Updated DELTA data

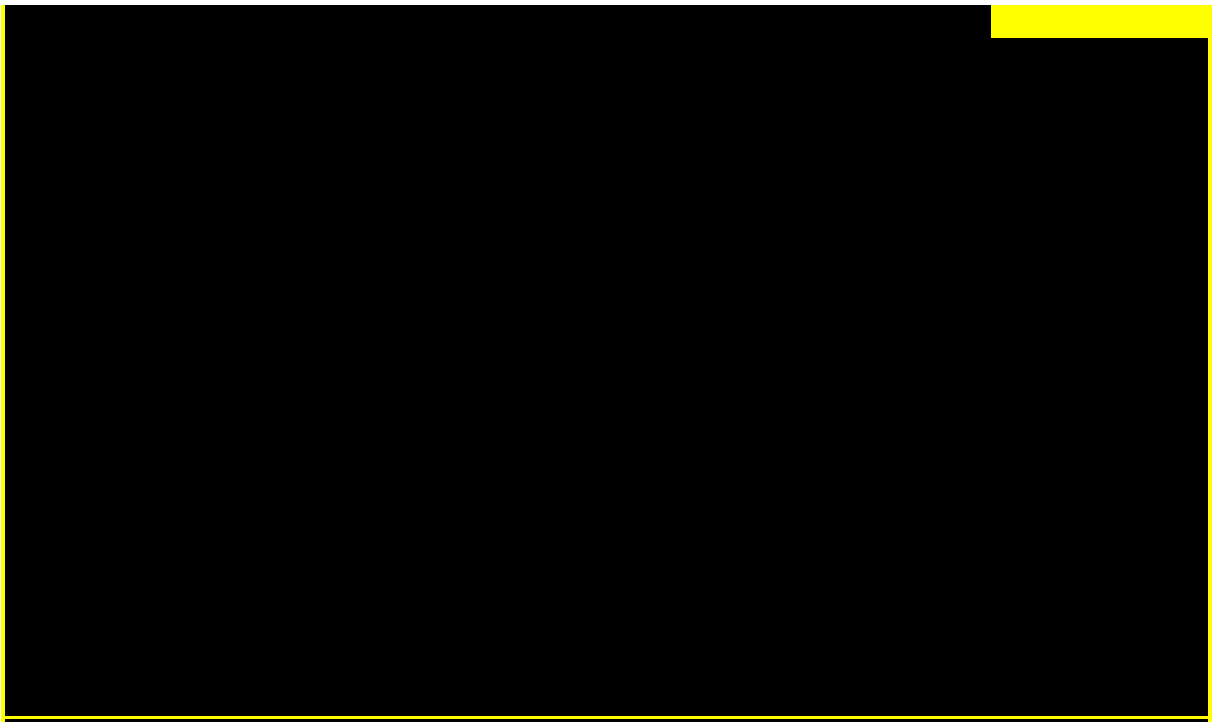
Our original June 2018 submission of evidence was based on the latest DELTA study data available at that time, from June 2015. With the patience of the committee and the patient and clinical community, we have since been able to obtain data from a far more recent cut-off: 22 August 2018. These August 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.

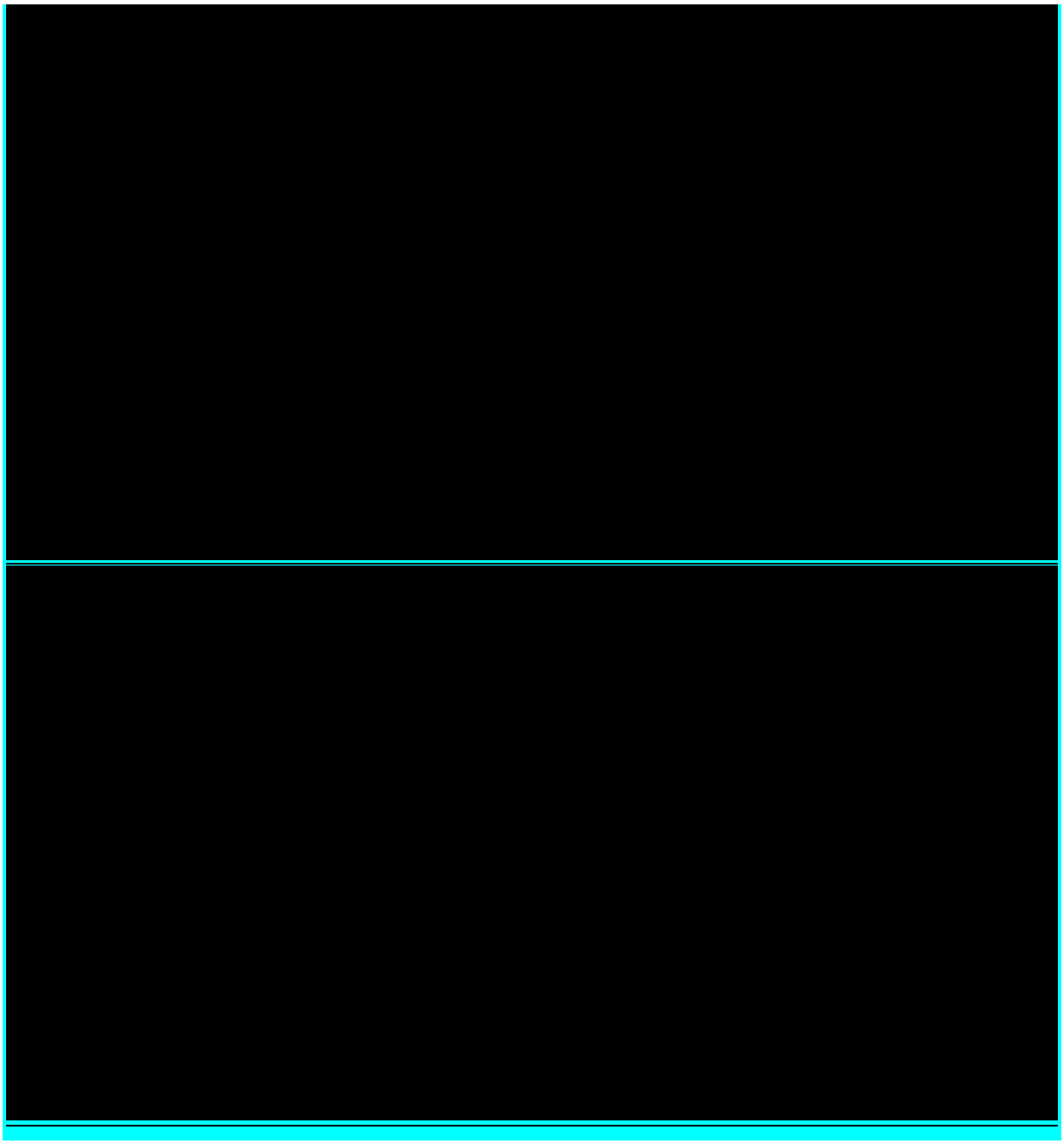


Key: DBL; database lock; FL, follicular lymphoma; KM, Kaplan-Meier; OS, overall survival.

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

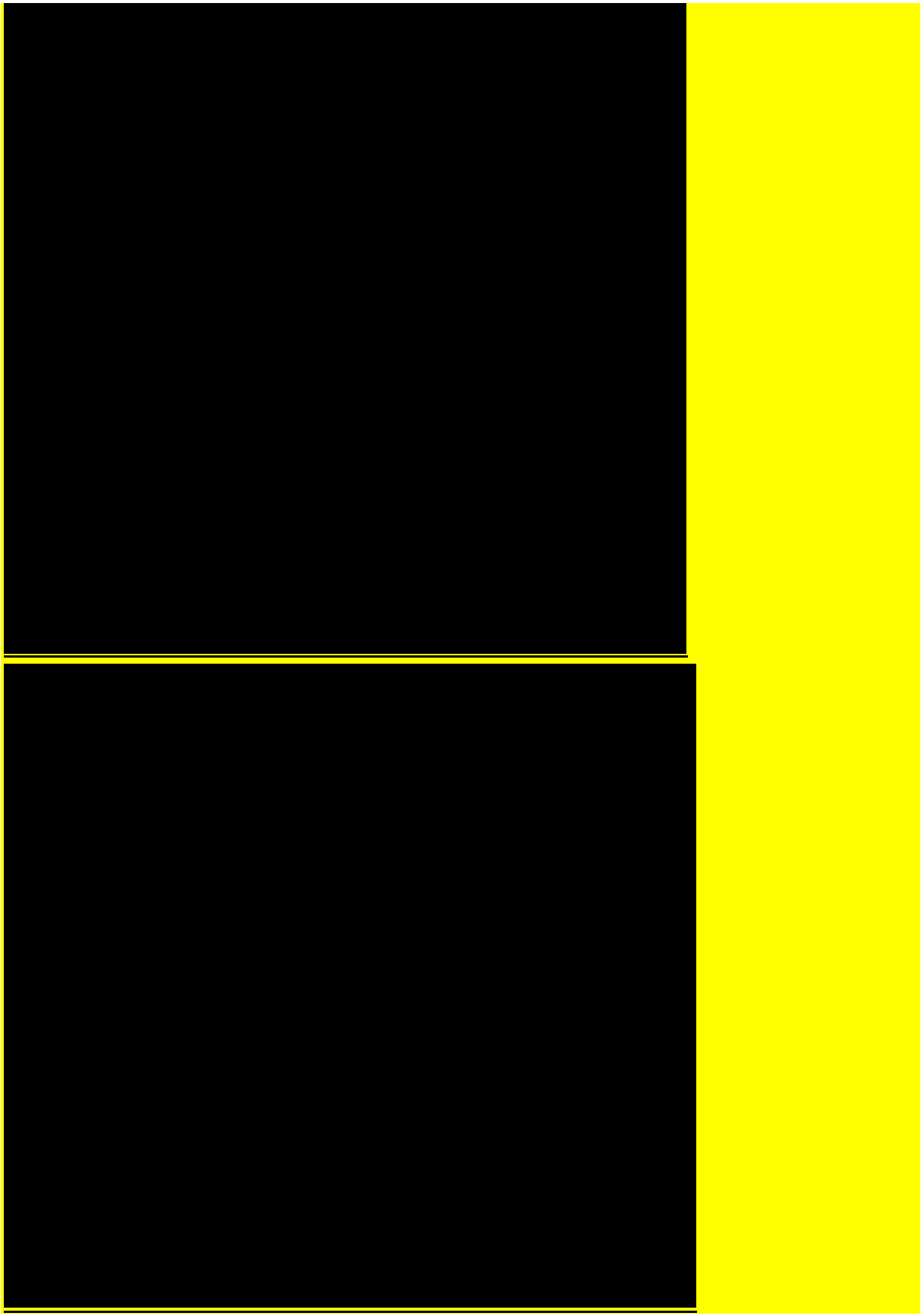
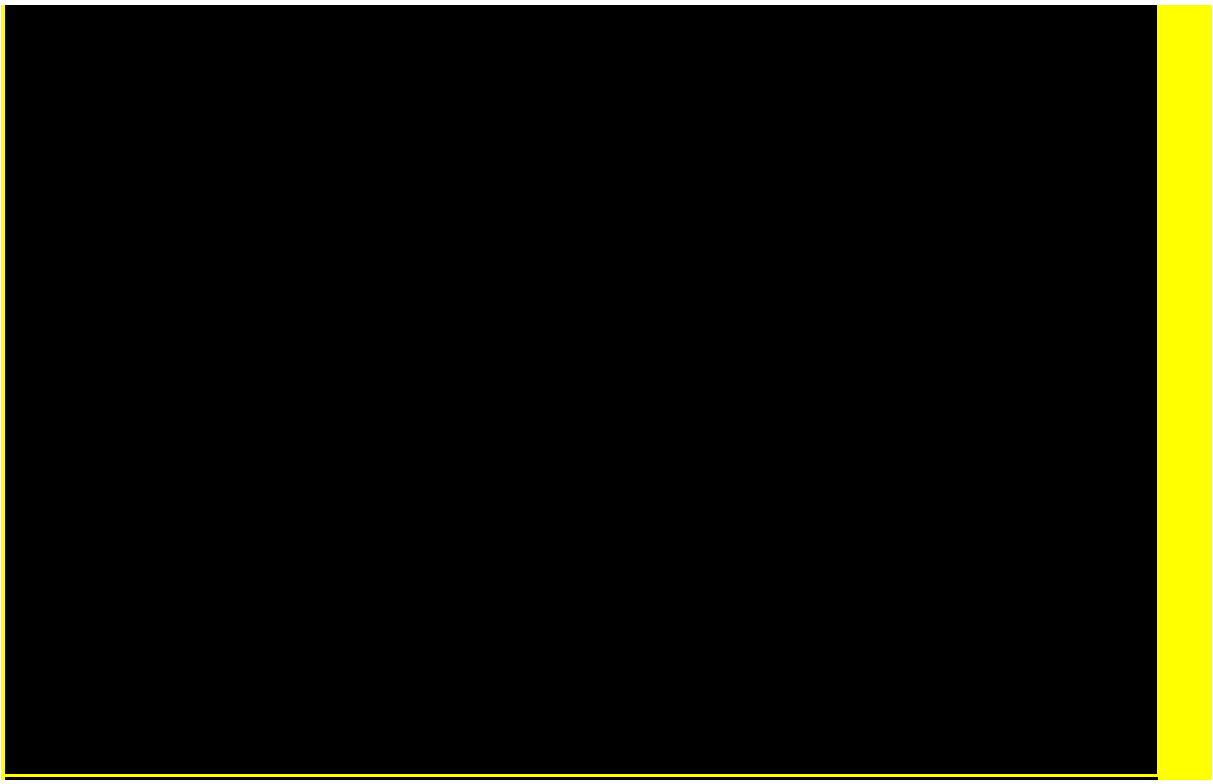


Figure 5: Further updated progression-free survival results from the RIAltO trial



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

[redacted]

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

[redacted]

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

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

[redacted]

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

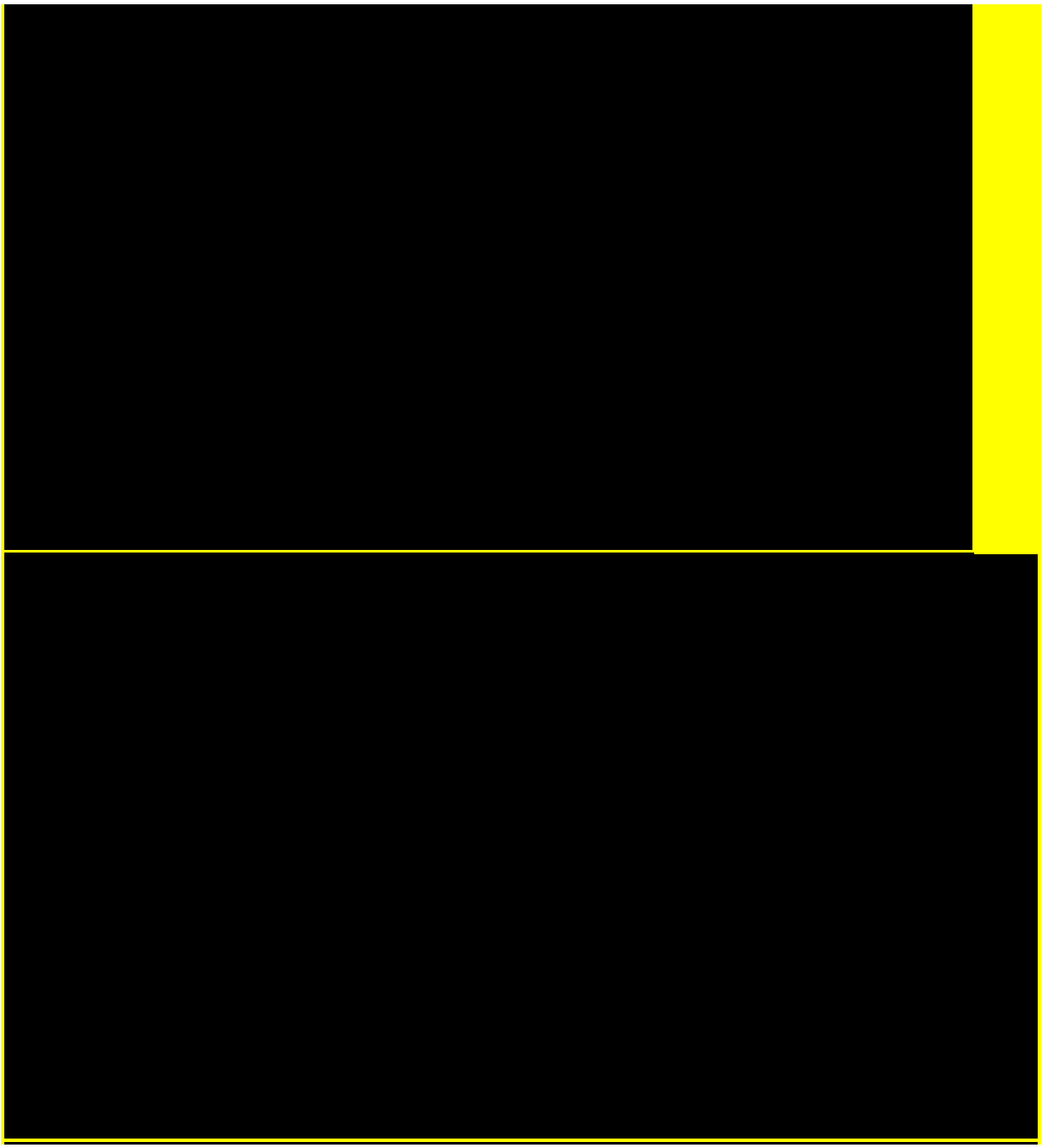
[redacted]

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.

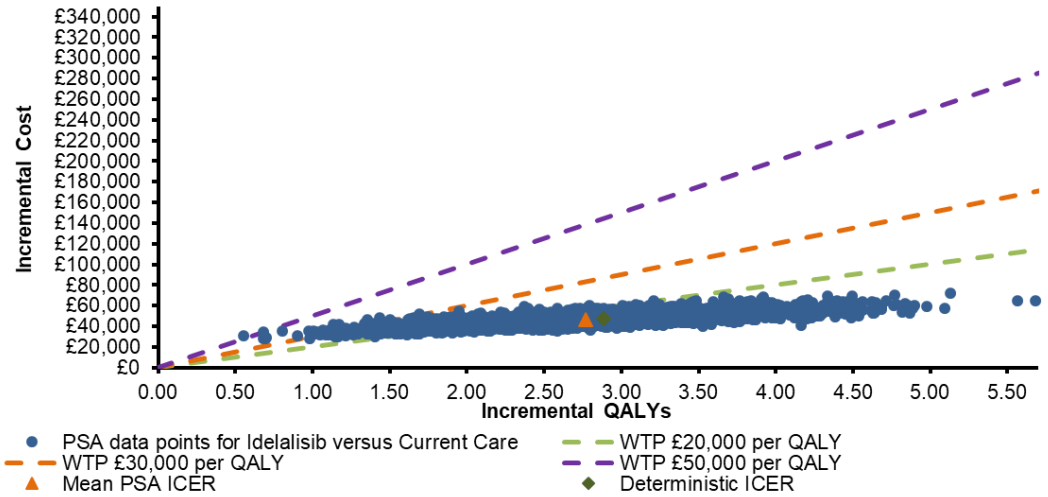
Table 7: Comparison B1: Updated MAIC-informed deterministic cost-effectiveness results, including idelalisib CCD

	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

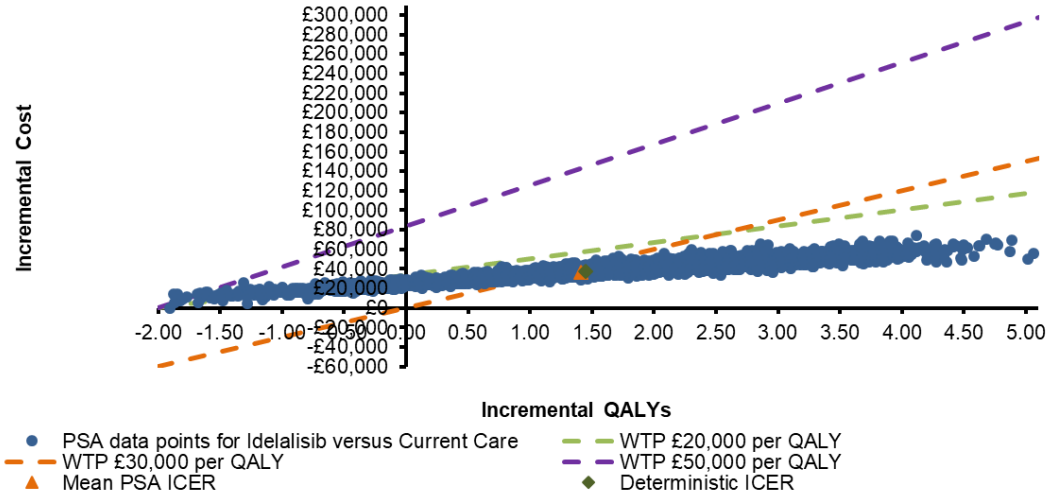
Key: CCD, confidential commercial discount; ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusted indirect comparison; PSM, propensity-score-matching; QALYs, quality-adjusted life years.

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.

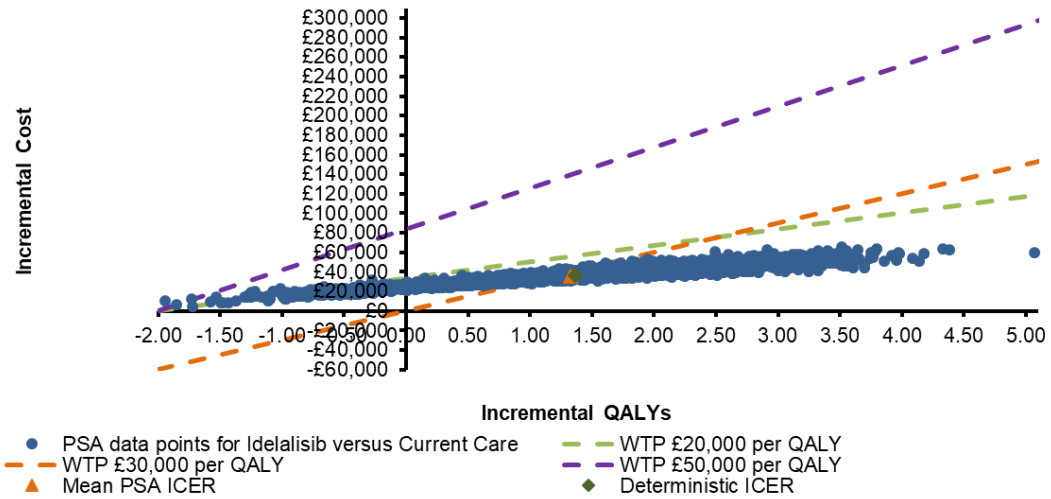
Table 11: Comparison B3: Updated PSM-informed deterministic cost-effectiveness results, HMRN patients as "treated", including idelalisib CCD

	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		

4 References

1. National Institute for Health and Care Excellence. Final appraisal document: Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma. 2019. (Updated: February 2019) Available at: https://www.nice.org.uk/guidance/ta577/documents/final-appraisal-determination-document. Accessed: 1 May 2019.

2. 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):2516-22.

3. Pettitt AR, Kalakonda N, Polydoros F, et al. EFFECT OF ADDING IDELALISIB TO FRONTLINE OFATUMUMAB PLUS EITHER CHLORAMBUCIL OR BENDAMUSTINE IN LESS FIT PATIENTS WITH CLL: PRELIMINARY RESULTS FROM THE NCRI RIALTO TRIAL. *Hematol Oncol*. 2017; 35(S2):88-9.

4. Pettitt AR, Kalakonda N, Polydoros F, et al. Effect of adding idelalisib to frontline ofatumumab plus either chlorambucil or bendamustine in less fit patients with CLL: Updated Results from the NCRI RIALTO Trial. European Hematology Association 23rd Congress. Stockholm, Sweden. 14-17 June 2018 2018.

5. Smith A and Bagguley T. Clinical management and outcome of follicular lymphoma (FL) with a focus on relapsed/refractory disease. (Version 3.1) 15 March 2019 2019. (Updated: 01 April 2019)

6. Aviles A, Leon MI, Diaz-Maqueo JC, et al. Rituximab in the treatment of refractory follicular lymphoma -- six doses are better than four. *J Hematother Stem Cell Res*. 2001; 10(2):313-6.

7. Tinmouth A, Zanke B and Imrie KR. Fludarabine in alkylator-resistant follicular non-Hodgkin's lymphoma. *Leuk Lymphoma*. 2001; 41(1-2):137-45.

8. Witzig TE, Flinn IW, Gordon LI, et al. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. *J Clin Oncol*. 2002; 20(15):3262-9.

9. Digitizer GG. GetData Graph Digitizer. 2013. Available at: http://getdata-graph-digitizer.com/index.php. . Accessed: 2 May 2019.