NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ibrutinib for treating chronic lymphocytic leukaemia [ID749]

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

1. **Consultee and commentator comments on the Appraisal Consultation Document from:**
   - Janssen
   - Leukaemia Care and CLL Support Association
   - Royal College of Pathologists
   - UK CLL Forum
   - Gilead

   The Department of Health and the Royal College of Nursing indicated that they had no comments on the ACD

2. **Comments on the Appraisal Consultation Document from experts:**
   - Professor Peter Hillmen - clinical expert, nominated by Janssen

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

4. **Evidence Review Group critique of the company's additional evidence**

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

Response to the Appraisal Consultation Document (ACD)

Ibrutinib for treating chronic lymphocytic leukaemia [ID749]

March 23rd 2016

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1. Overview

Janssen welcomes the opportunity to comment on the preliminary recommendation made by the Appraisal Committee detailed in the appraisal consultation document (ACD). We are extremely disappointed the Appraisal Committee's preliminary decision is that ibrutinib is not recommended for patients with relapsed or refractory chronic lymphocytic leukaemia (CLL); however, we are committed to working with NICE in order to address all of the Committee's key concerns outlined in the ACD.

Ibrutinib, with its unprecedented efficacy and safety, has quickly established itself as a new standard of care in the relapsed/refractory (R/R) CLL setting, offering a step-change to patients with few effective treatment options. The clinical demand for ibrutinib in this setting is high, as evidenced by the fact that it is by far the most requested CLL treatment on the Cancer Drugs Fund (CDF) (NHS England, 2016).

The main points we wish to address are as follows:

- The patient population appraised for treatment with ibrutinib in CLL is similar to the population recently considered in the appraisal of idelalisib plus rituximab (IR), which has met the **end of life** (EoL) criteria and Janssen therefore strongly believes that the same criteria hold for ibrutinib. We have also provided further evidence in this response to support this assertion.
- The comparison of ibrutinib to **multiple comparators** is a representation of the fact that there is currently no single standard of care for the treatment of CLL in England and Wales. To simply only compare against a newly licensed treatment that has only very recently received NICE approval, has less than 20% of all CDF notifications for CLL in the period January to September 2015 (NHS England, 2016), and that has various ongoing safety concerns that are being investigated by the European Medicines Agency (EMA), is not due process, and puts ibrutinib at a significant disadvantage. We believe it is not only vital and representative of current clinical practice for the Committee to consider all four comparisons presented in the original submission (vs. physician's choice, ofatumumab, bendamustine plus rituximab, and IR) but additionally, the multiple comparisons provide greater certainty to the Committee's consideration of the evidence. We have provided additional evidence to support the inclusion of all comparators.
- **Comparative efficacy** of ibrutinib relative to key comparators was established based upon a hierarchy of evidence generation methodologies, and careful consideration was given to ensure data were analysed in the most appropriate way. As such, we believe the cross-over adjusted RESONATE trial data is the most appropriate data set to use to represent the true efficacy of ibrutinib. Additionally, where multiple analyses of comparative efficacy are available for a given comparator, we ask the Committee to consider all in conjunction, as this aims to reduce uncertainty. We believe the evidence presented in this response will explain these considerations clearly.
- The Kaplan-Meier data from RESONATE is used to **extrapolate** both PFS and OS. We urge the Committee to consider our presentation of statistical goodness of fit, clinical plausibility, and visual inspection in conjunction with longer-term follow-up data from additional ibrutinib trials to support the selected extrapolations. As presented in Appendix 1 with permission from NICE, longer term data from RESONATE that has only just become available, which continue to support the extrapolations proposed in the original submission.
- The **utility data** has been age-adjusted as per the Committee's suggestion. Additionally, in response to comments from clinical experts that the PFS utility input may be an underestimation, alternative inputs have been considered to capture the benefits of being on-treatment (as opposed to off-treatment) and of taking an oral therapy (as opposed to IV

therapy) in line with other submissions to NICE in the CLL setting. Alternative inputs for the PPS utility input have also been considered as per the Committee's concerns.

- Data in treatment-naïve (TN) CLL patients with **17p deletion** remain limited and therefore, the Committee accept that the data in R/R CLL patients with 17p deletion is an acceptable proxy for the TN patients. To address any remaining concern around uncertainty in this patient group, we have provided additional evidence to help the Committee reach the conclusion that ibrutinib is a cost-effective option for these patients. Of note, idelalisib was granted a positive NICE recommendation in the same patient population with less data than that which exists for ibrutinib. Last week, the EMA issued a recommendation that idelalisib should not be started in previously untreated patients with CLL whose cancer cells have certain genetic mutations (17p deletion or TP53 mutation), due to the ongoing safety concerns. This change in recommendation from EMA for idelalisib only serves to further highlight the significant clinical need in this difficult to treat population.
- Differences in how **costing considerations** were applied to ibrutinib vs. comparators in the original submission were due to the fact that ibrutinib is the only purely oral, daily treatment included in the model. To be conservative and consistent across treatments, Janssen has accepted a number of the Committee's recommendations and these revisions are explained in detail with updated results provided for the Committee's consideration.

Importantly, with the proposed **modelling amendments** from the ERG, excluding those suggestions that Janssen would contest, and with consideration of the confidential PAS, ibrutinib remains cost-effective against all four comparators.

A detailed response to each of these key issues is provided on the following pages.

2. End of life (EoL) criteria

"The committee was aware that before idelalisib had been recommended as a treatment option, patients lived for a shorter length of time. In the current treatment landscape, the committee was unsure whether the life expectancy for patients with CLL would be less than 24 months" [para 4.28].

"*The company had not provided sufficient evidence to confirm the first criteria, and therefore the committee did not discuss end of life further. The committee concluded that the end-of-life criteria had not been met, mainly because the company did not provide sufficient evidence to support it being applied*" [para 4.28].

"The committee noted that the company's evidence about life expectancy for people who had previously been treated with fludarabine plus cyclophosphamide and rituximab was from a cohort of Swedish patients on therapies comprising physician's choice, which the committee noted did not represent the treatments in the NHS. The committee noted that the source of this life-expectancy estimate was unpublished data held by the company. During the meeting, the committee queried how many patients had died in the cohort, which the company could not provide" [para 4.28].

The following reasons outline why Janssen strongly believes that ibrutinib does meet the life expectancy criterion of the EoL criteria.

2.1 NICE precedence

Firstly, recent NICE precedence in the case of IR and preponderance of data strongly demonstrate that current life expectancy is less than 24 months in the populations being appraised. Specifically, a mean OS of less than 24 months has been established for the populations being appraised within this submission by the recent IR NICE recommendation. The median OS was established as 20.8 months based upon the comparative rituximab arm of the ITT population in the pivotal phase 3 IR trial, Study 116 (Sharman et al., 2014). Furthermore, clinical experts estimated life expectancy to be 12 to 24 months for patients with high-risk relapsed disease and less than 12 months for people with refractory disease during that appraisal (NICE, 2015a and Gilead Science Limited, 2015).

[redacted]. This is confirmed by the idelalisib plus ofatumumab (IO) trial, Study 119, which showed a median OS for IO of 20.9 months, compared with a median OS for ofatumumab of 19.4 months (Jones et al., 2015).

Ibrutinib is being evaluated in a similar patient population as IR, and Janssen firmly believes it is not reasonable to conclude that life expectancy for these patients would have increased significantly between 24 September 2015 (when IR was recommended by NICE) and 21 October 2015 (when ibrutinib was submitted for review). Janssen would request that ibrutinib and idelalisib are treated with equal consideration in terms of application of the EoL criteria, given that both treatments came to market in close succession. We believe it is prejudicial against ibrutinib to not afford the same designation and to not use the same standard upon which to compare against.

2.2 Swedish cohort study

Secondly, evidence from a cohort of Swedish R/R CLL patients was submitted to support the EoL criterion that life expectancy with R/R CLL remains less than 24 months. The therapies these patients were exposed to (alemtuzumab, chlorambucil, ofatumumab, BR, steroids with rituximab and steroids with chlorambucil; note that patients exposed to fludarabine- and lenalidomide-based therapies, ibrutinib, IR, and experimental treatments were excluded) are reflective of the final NICE scope and therapies used in current UK practice; therefore, it is inaccurate for the Committee to state that the treatments covering the Swedish patient cohort did not represent treatments used in the NHS. Furthermore, the baseline characteristics of the Swedish patient cohort closely match those in the ibrutinib pivotal phase 3 trial, RESONATE (see Appendix 2 for details) further supporting the notion that the patient population reflects those in the UK, and there is no reason to believe outcomes with the NICE scope drugs would be different in these Swedish patients compared to UK patients.

2.3 Further life expectancy data in the R/R CLL population

Third, it is important to clarify that data from the comparator arm of RESONATE (i.e. the ofatumumab arm) cannot be used in support of the life expectancy criterion because the trial was stopped early due to the impressive outcomes, resulting in 61% of patients in the ofatumumab arm switching to ibrutinib at the 16-month median follow-up ([redacted]). This high degree of cross-over renders ofatumumab's ITT OS data meaningless for determining whether this population meets the end of life criterion of expected survival of less than 24 months.

Consequently, data from other ofatumumab trials in the R/R CLL setting were reviewed not only as a proxy for the data from RESONATE which cannot be used, but also given ofatumumab was accepted as a relevant comparator for R/R CLL by NICE in the IR submission. The data collected from all relevant ofatumumab clinical trials strongly support that life expectancy is less than 24 months in patients with R/R CLL. These data are presented in Table 1.

Table 1: Median OS outcomes from ofatumumab R/R CLL trials

Trial	Comparator	Comparator median OS
Österborg et al., 2016 Study OMB114242	Ofatumumab	19.2 months (all ofatumumab patients)
Jones et al., 2015	Ofatumumab	19.4 months
Wierda et al., 2010	Ofatumumab	17.3 months (all ofatumumab patients) 13.9 months (double refractory) 17.4 months (bulky nodes refractory)
Österborg et al., 2012	Ofatumumab	18 months

3. Comparators

"*The ERG considered that the only relevant comparators to include in the incremental analysis are bendamustine plus rituximab and idelalisib plus rituximab because ofatumumab is no longer available through the Cancer Drugs Fund and physician's choice is problematic as a blended comparator*" [para 3.35].

Janssen strongly contends that all comparators presented in the submission (that is, PC, ofatumumab, bendamustine in combination with rituximab [BR] and IR) are all relevant to the appraisal of ibrutinib for the following key reasons (outlined in detail in subsections 3.1 – 3.6 below):

1. The NICE scope included a broad range of comparators, encompassing the full spectrum of treatment options, thereby supporting the contention that there is no standard of care in R/R CLL
2. Clinicians agree that there is no standard of care, and that PC is the best representation of this lack of standard
3. UK and international clinical guidelines support the broad range of comparators
4. Since the introduction of ibrutinib into the UK market (listed on the CDF in January 2015), it has displaced several treatments
5. Ofatumumab and BR were removed from the CDF when ibrutinib was listed on the CDF, which is the very definition of a comparator
6. IR cannot be the only relevant comparator, given that it was only recommended by NICE one month prior to the submission of ibrutinib to NICE, it has ongoing safety concerns, and has less than 20% market share in January 2016 for R/R CLL (Table 3).

3.1 NICE scope

The final NICE scope for ibrutinib included a broad range of comparators which represented the full spectrum of potential treatment options, given the lack of standard of care in CLL. In our submission, we followed the NICE scope by including all comparative treatments which are currently used in clinical practice within the UK, and where there were credible data upon which to base a comparison. Including multiple relevant comparators demonstrates the consistency in ibrutinib's treatment effect, and increases the robustness of ibrutinib's estimated cost-effectiveness in R/R CLL. Not only are PC, ofatumumab, BR and IR all relevant comparators to UK clinical practice, but including them in the submission makes fuller use of available comparative data, including direct RCT data (in the case of ofatumumab) and Bucher ITC (in the case of PC).

Given that the final NICE scope included a broad range of comparators which represented the full spectrum of potential treatment options and demonstrated the clear lack of standard of care, we are confused as to why the Committee has now asked us to narrow down the number of comparators to

those which represent less than [redacted] of treatments used in UK clinical practice in 2015 (i.e., IR and BR) (Janssen, 2016a).

3.2 Clinical opinion

"*The committee was aware the company had presented a comparison with physician's choice, which is a blended comparator… The committee also had concerns about using a blended comparator because this approach averages the cost effectiveness of the treatments included, masking the cost effectiveness of the individual treatments. Therefore there is a risk of displacing effective and cost effective treatment options that are included within the blended comparator…The committee concluded that the blended comparator physician's choice was not an appropriate comparator*" [para 4.3].

Janssen respectfully disagrees with PC being classified as a blended comparator and consequently discarded. Janssen asserts that PC is an appropriate and key comparator within this appraisal for the reasons explained below:

The NICE DSU TA Method Review Supporting Documents (Ciani and Taylor, 2011) describes that in situations where standard NHS practice is unclear with high variation, it can be argued that the additional costs and benefits of the new technology can be calculated against some form of "average" costs and benefits associated with the mix of current therapies, sometimes referred to as a blended comparator. The NICE DSU document also acknowledges that the approach of a comparator which captures the variability in treatments is appropriate if the goal of the NICE appraisal is to identify whether a single technology is more efficient compared to the current NHS practice as a whole.

Further to the NICE DSU document, the "averaging" approach to create a blended comparator appears in the respective NICE appraisals of teriflunomide (NICE, 2014), lapatinib (NICE, 2009a), and ledipasvir-sofobuvir (Thokala et al., 2015); NICE criticised the blended comparator approach in all three appraisals. It also appears in the appraisals of azacitidine (NICE, 2011) and fingolimod (NICE, 2012) but in these cases, the blended comparator was accepted because the Committee took into account the limitations of the available evidence, the absence of a satisfactory alternative, and variation in current practice.

In contrast to the DSU statements and the five appraisals mentioned here, if the definition of a blended comparator is the "averaging" of data, the PC comparator presented in this appraisal does not fit that definition and therefore should not be discarded. The PC clinical data presented in this appraisal was taken from a single trial, OMB114242, which compared patients who were given ofatumumab with patients who were given a therapy based on the physician's choice (Österborg et al., 2016). The clinical data for the PC arm are therefore only available as an amalgamated Kaplan Meier curve. Individual datasets for multiple comparators are not used to create a single weighted average efficacy (and cost) dataset.

In line with the DSU statements, standard NHS practice in CLL does indeed have high variation and there is use of a wide mix of therapies (and not simply one single standard of care). This situation has been demonstrated by the discussion of clinical guidelines and market share and therefore, PC is very much a relevant comparator which more accurately captures the cost and efficacy of the various CLL treatment options currently available. In an effort to fully address the NICE scope and to reflect the very real variability in CLL treatment options, Janssen included PC as a comparator to ensure the Committee had a full representation of all relevant comparators and all relevant data for their consideration. An incremental analysis versus each component of PC would not be possible due to a lack of data.

PC, as presented in this appraisal, accurately reflects the efficacy mix of commonly used therapies in the UK and should be considered a true proxy for standard of care. The composition and relative efficacy of PC (as demonstrated in OMB114242 and used in the economic model), was defined based upon input from practicing clinicians (Janssen Advisory Board, 2015), and is thus reflective of

therapies used in UK clinical practice. The efficacy of PC used in the economic model was derived from a single HR (used as an input in the ITC) from a head-to-head RCT (and not a blend of efficacy measures from different sources).

For these reasons, Janssen request that PC is considered along with the other three comparators as it aims to appropriately and robustly represent treatment practice in the UK.

3.3 Clinical guidelines

In addition to BR and IR, ofatumumab (an anti-CD20 antibody) and PC are appropriate comparators according to British Committee for Standards in Haematology (BCSH) guidelines. For ease of reference, Table 2 below provides a summary of the treatments recommended by the BCSH for patients with CLL and clearly demonstrates the various treatment options (Follows et al., 2015 and Oscier et al., 2012). It is important to note that these guidelines are interim with a revised full guideline expected this year.

International guidelines also support the clear lack of standard of care. The guidelines issued by the European Society of Medical Oncology (ESMO) for the management of CLL in Europe and the National Comprehensive Cancer Network (NCCN) guidelines for the management of CLL in the US also recommend a wide range of strategies for managing relapsed CLL (Eichhorst et al., 2011; Zelenetz et al., 2015; NCCN, 2015), the details of which were presented in our submission.

Table 2: Summary of BCSH guidelines updated with the interim 2015 statement

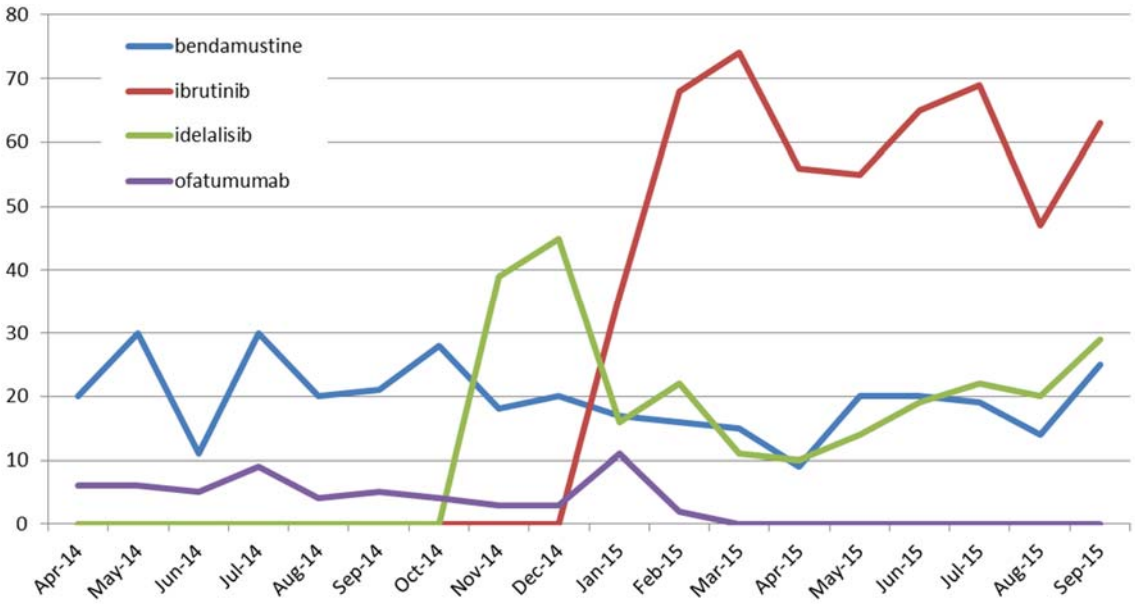
Patient population	Summary of guidance
First-line treatment of patients without TP53 abnormality who are fit enough to receive fludarabine	• FCR is recommended • Bendamustine plus rituximab is an alternative option in patients in whom FCR is contraindicated
First-line treatment of patients without TP53 abnormality who are not fit enough to receive fludarabine	• Chlorambucil in combination with ofatumumab or obinutuzumab • Chlorambucil in combination with rituximab is an alternative treatment if access to ofatumumab or obinutuzumab is restricted. • In particularly frail patients, chlorambucil is the treatment of choice for palliating frail patients, but bendamustine monotherapy is an option
First-line treatment of patients with TP53 abnormality	• Ibrutinib monotherapy or IR. • If not available, alemtuzumab with or without corticosteroids are preferable to chemotherapy
R/R CLL	• Patients relapsing ≥2 years after fludarabine-containing regimens who remain fit enough to receive fludarabine, should receive FCR. • Bendamustine plus rituximab is an alternative option • Patients relapsing after chlorambucil who are fit enough to receive fludarabine-based therapy should be considered for FCR. • Patients relapsing after chlorambucil can be retreated with chlorambucil, with/without an anti-CD20 antibody. • For patients refractory to chlorambucil and unable to tolerate myelosuppressive therapy, options include high-dose steroids, alone or in combination with rituximab and alemtuzumab.
High risk (TP53 mutation/17p deletion or failing fludarabine combination therapy within 2 years) patients	• Ibrutinib monotherapy or IR. • If not available, alemtuzumab with or without corticosteroids are preferable to chemotherapy

CLL with autoimmune cytopenias as a complication	• Steroids as first-line treatment • cyclosporine, intravenous immunoglobulin, thrombopoietin mimetic agents, low-dose cyclophosphamide, rituximab, alemtuzumab and splenectomy for patients unable to take steroids
CLL with infections as a complication	• Anti-microbial prophylaxis in patients at high risk of infection • Immunoglobulin replacement therapy may be considered to reduce bacterial infections in patients with a low serum IgG level with previous infection despite prophylaxis

3.4 Dynamic market share data

From market research data and the high uptake of ibrutinib on the CDF, it is clear that ibrutinib has become the new standard of care, by displacing everything else on the market. Following its addition to the CDF in January 2015, ibrutinib rapidly became the most requested item for R/R CLL, greater than idelalisib, BR and ofatumumab notifications combined (Figure 1). Data for the fourth quarter of 2015 are not yet available, but the observed trend is expected to continue.

Figure 1: Cancer Drug Fund notifications for R/R CLL from April 2014 to September 2015



Source: Table 16 and NHS England, 2016

In addition, Oncology Analyzer ™ market research data ([redacted]), which includes treatments in baseline funding as well as the CDF, show that, following listing on the CDF, ibrutinib took market share from a range of treatments including BR, chlorambucil and the chemotherapy regimens that Janssen would suggest also make up the PC comparator.

[redacted]

[redacted]

Source: [redacted] in Appendix 3

Lastly, the most recent snapshot of market share data from IMS Health (Table 3) suggests ibrutinib has the largest share of R/R CLL in second and subsequent lines of therapy, at [redacted] of patients in January 2016, compared to a market share of [redacted] for idelalisib.

[redacted]

Together, these data show that ibrutinib has displaced multiple comparators following its listing on the CDF. This strongly suggests that within the NICE appraisal there should not be one single comparator against which to compare the cost-effectiveness of ibrutinib. The data also support the

inclusion of the PC comparator, given that multiple chemotherapy regimens have been displaced by ibrutinib. Further details on these datasets are provided in Appendix 3.

3.5 Definition of a comparator

"*The committee was aware that ofatumumab was the control treatment in the main ibrutinib trial and that the company included ofatumumab in the decision problem, even though it had not been recommended by NICE and is no longer available on the CDF. The clinical experts confirmed that since the availability of idelalisib and ibrutinib, clinicians no longer offer ofatumumab monotherapy to patients*" [para 4.3].

Clinical experts advocated strongly for the inclusion of ofatumumab in the economic model due to its relevance in clinical practice at both our advisory board and during the first NICE Appraisal Committee meeting on 3 February 2016. Of note, the clinicians stated that they felt that ofatumumab was a relevant comparator as it being delisted from the CDF coincided with ibrutinib being introduced (Advisory Board, October 2015).

Furthermore, as per the NICE Guide to the methods of technology appraisal 2013, Section 5.1.6 "*When selecting comparators for assessment, give particular consideration to the scope (see section 2), and to the evidence to allow a robust assessment of relative clinical and cost effectiveness*". Furthermore, Section 6.2.2 states "w*hen selecting the most appropriate comparator(s), the Committee will consider: established NHS practice in England, the natural history of the condition without suitable treatment existing, NICE guidance, cost effectiveness, [and] the licensing status of the comparator*". The comparators selected for consideration in this appraisal were done so with the above points in mind (NICE, 2013).

Lastly, the NICE 2009 Guide to the single technology appraisal process defines a comparator as follows: a technology that is competing with the one under appraisal (NICE, 2009b). To this point, Janssen strongly believes it is important to bear in mind that both ofatumumab and BR were removed from the CDF upon the introduction of ibrutinib and IR. Given that ibrutinib was *instrumental in displacing* ofatumumab from the market, it is *by definition a relevant comparator*. Ofatumumab and BR directly competed with ibrutinib for funding through the CDF (and as a result, lost funding). In addition, the NICE appraisal of IR concluded that "rituximab, ofatumumab and best supportive care were appropriate comparators for people with refractory disease" (NICE, 2015b). If ofatumumab was an appropriate comparator for IR and IR is an appropriate comparator for ibrutinib, logic dictates that ofatumumab is an appropriate comparator for ibrutinib.

3.6 Relevance of idelalisib plus rituximab (IR) as a comparator

IR has not been on the market long enough to become a standard of care and it will not be appropriate for all R/R patients, particularly given its AE profile and recent provisional recommendations from the EMA to use in idelalisib in conjunction with antibiotics, and to not start treatment in patients with treatment naïve CLL with 17p deletion / TP53 mutation (see Appendix 4 for a detailed comparison of the ibrutinib and idelalisib EPARs as well as further data on AEs). This assertion is supported by the dynamic market share data presented in subsection 3.4 above. Put simply, to only compare against a newly licensed treatment that has only very recently received NICE approval, has less than 20% of all CDF notifications for CLL in January to September 2015, and has various ongoing safety concerns that are being investigated by the EMA, is not due process, and puts ibrutinib at a significant disadvantage. Janssen strongly asserts that ibrutinib should be compared against the same standard as idelalisib.

4. Comparative efficacy

4.1 Cross-over adjustment

"*The ERG also noted that the only information about the Jones trial came from an abstract, and that the company only adjusted the RESONATE trial, used to compare overall survival for ibrutinib compared with idelalisib, for cross-over*" [para 3.17].

"*The committee heard from the company that this was because the Jones trial did not allow cross-over to idelalisib. However, it heard from clinical experts that they considered it very likely that, after progression, patients leaving the trial would go on to receive other life-extending therapies. The committee appreciated that adjusting one trial, but not the other, would exaggerate the benefit of ibrutinib over idelalisib plus ofatumumab…The evidence review group (ERG) commented, and the committee agreed, that this was inconsistent and that it would have been more appropriate for the company to use the intention-to-treat analysis from RESONATE to conduct its indirect comparisons. The committee concluded that adjusting for the effect of treatment crossover on overall survival was appropriate, but it was not appropriate to do so for only 1 trial in the indirect comparison network*" [para 4.10].

"*…the company did not justify its use of the rank preserving structural failure time method for adjusting for crossover over other methods, for example, the inverse probability of censoring weighted method*" [para 4.10].

The Committee argues that RESONATE OS data should not be adjusted for cross-over given that cross-over adjustment was not conducted for the other trials included in the indirect treatment comparisons (ITC). Janssen strongly maintains that adjusting for cross-over within RESONATE is justified and appropriate given the particular circumstances relating to cross-over in the other studies included in the ITC (Study 119 representing IR and Study OMB114242 representing PC).

With respect to RESONATE, not correcting for 61% cross-over (and instead using the ITT hazard ratios) would introduce a great bias to the ITCs, notably underestimating ibrutinib's overall survival benefit.

In the case of OMB114242, patients were allowed to receive ofatumumab salvage therapy after progression. Whilst it is unclear whether the effect of salvage therapy was adjusted for, two factors make this question insignificant. First, patients who crossed over in RESONATE received monotherapy ibrutinib, a step-changing therapy. Patients in OMB114242 received ofatumumab salvage therapy, which does not have the impressive survival gains that novel agents do. Second, and more importantly, if the cross-over to the ofatumumab salvage therapy was not adjusted for, the relative efficacy of ofatumumab vs. PC would have been underestimated in OMB114242, which would serve to underestimate ibrutinib's relative treatment effect vs. PC. That is, not correcting for cross-over makes the PC arm look more effective, which makes ibrutinib appear less effective by comparison. Thus, the inability to adjust for cross-over in OMB114242 results in a conservative ITC for ibrutinib.

In the case of Study 119, the Committee has further stated that while no cross-over from the control arm (ofatumumab) to the experimental arm (IO) occurred, progressed patients may have left the trial and received other life-extending therapies. Adjustment for this type of "cross-over" (to treatment arms outside of the study) is not recommended by NICE DSU guidance, which states that the key factor to adjust for is "the switch from control treatment to experimental treatment by patients randomised to the control group of an RCT" (Latimer & Abrams, 2014). Given that no cross-over of this nature occurred, adjusting for cross-over in RESONATE (and not in Study 119 as there was no cross-over of this nature) is appropriate, and indeed warranted, given that to not adjust for cross-over in RESONATE introduces significant bias against ibrutinib (with 61% of ofatumumab patients crossing over to the ibrutinib arm).

Lastly, the Committee argues that the method used to adjust for cross-over in RESONATE (the rank preserving structural failure time [RPSFT] method) was not justified. Janssen respectfully refer the Committee to the original submission (Section 4.4 and Appendix 4) as well as the responses to the clarification questions (response to priority question A3) where not only was it explained that multiple methods to adjust for cross-over were tested (RPSFT method, inverse probability of censoring weights [IPCW] method, the iterative parameter estimation [IPE] algorithm, and novel two-stage methods) as well as why RPSFT was selected as the base case adjust method, but there is also further explanation of how the IPCW method was also tested as an alternative scenario analysis. The HRs adjusted for cross-over resulting from both the RPSFT ([redacted]) and IPCW ([redacted]) methods were essentially similar and as such, either method can be used with minimal impact to the analysis and unquestionably demonstrates the certainty in the HR adjusted for cross-over.

4.2 Magnitude of ibrutinib's treatment effect

"*The committee noted that the company's model predicted that 10 times as many patients who take ibrutinib would be alive at 20 years compared with patients taking idelalisib plus rituximab. The committee considered this improbable and could be due to the indirect comparison generating biased results. The committee concluded that the degree of benefit estimated by the company's model was not supported by the data or clinical experience*" [para 4.16].

"*The ERG also noted that, because the company had chosen an MAIC as its preferred approach to comparing ibrutinib with bendamustine plus rituximab, it may also have been possible for the company to have done an MAIC analysis to compare ibrutinib with idelalisib using the Jones et al. trial*" [para 3.19].

"*Although the company stated that disease severity in the RESONATE trial population was greater than in the HELIOS trial, the committee concluded that the Cox multivariate analysis provided a statistically more robust analysis with which to compare ibrutinib with bendamustine plus rituximab*" [para 4.12].

Comparative efficacy data in the R/R CLL setting is extremely limited, given the clear lack of standard of care. In developing comparative efficacy estimates for modelling, Janssen considered a hierarchy of evidence favouring direct, comparative RCT evidence, followed by ITC analyses, then MAIC or Cox models. Wherever possible, we submitted not one, but two sources of comparative efficacy to provide more robust estimates of ibrutinib's benefit and to address uncertainty. In this way, we believe that we have provided the most robust and complete estimates possible of ibrutinib's treatment effect versus relevant comparators.

Table 4 summarises the data sources available and the analyses that were possible. Justifications of each analysis follow.

Table 4: Data Availability and Comparative Efficacy Methods

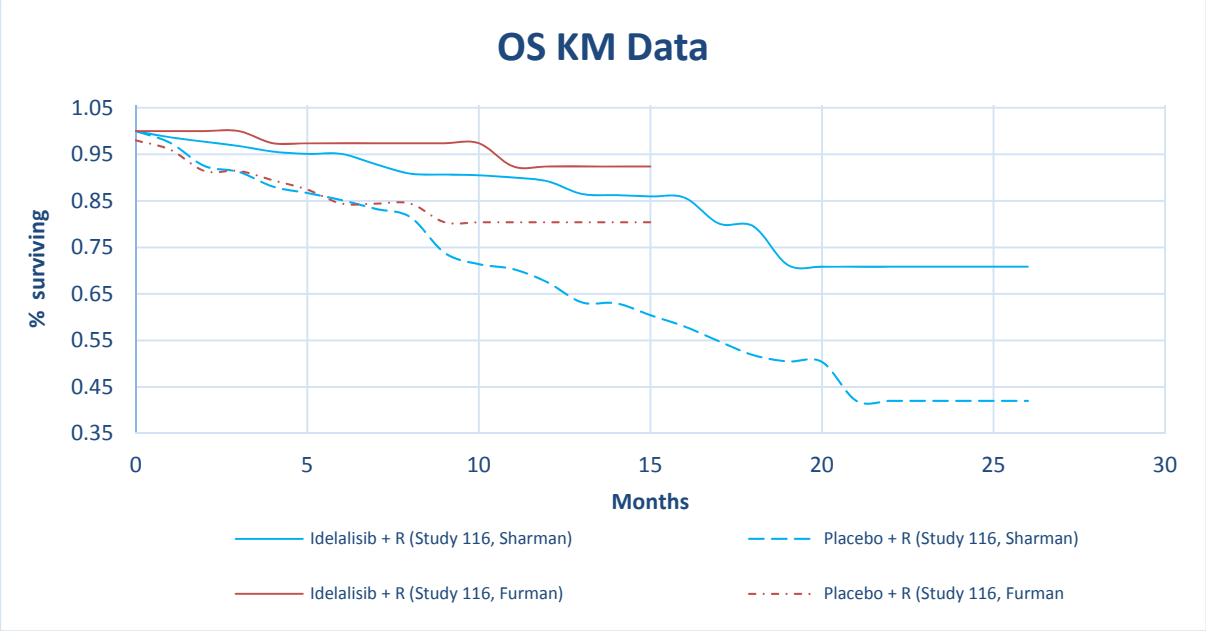
Ibrutinib vs.	Data available	Comparative efficacy method	Notes
Ofatumumab	RESONATE	Direct RCT evidence	Most rigorous data source
IR	Jones, 2015 (Study 119; IO used as a proxy for IR)	ITC	Best proxy in absence of direct RCT; see subsection 4.2.1 for additional details
	Sharman, 2015 (Study 116)	MAIC considered; found to be unfeasible	Trial design differences impossible to address in MAIC to generate an estimate for OS; see subsection 4.2.1 for additional details
BR	Fischer, 2015	MAIC	Trial found to be similar/patient

			population found to have sufficient overlap with RESONATE; see subsection 4.2.2 for additional details
	HELIOS	Multivariate Cox model	Leveraged patient-level data from two trials, however severely limited due to very small overlap between trial populations and no correction to OS for cross-over to ibrutinib in the BR arm; see subsection 4.2.2 for additional details
PC	Österborg, 2015 (OMB114242)	ITC	Best proxy in absence of direct RCT; see subsection 3.2 for additional details

4.2.1 Ibrutinib vs. Idelalisib + Rituximab

Janssen was hampered in trying to establish ibrutinib's relative efficacy versus IR due to the dearth of publically available data on IR trials. This reflects a lack of publicly available evidence on the longer term safety and efficacy of IR, and represents uncertainty that we as Janssen cannot address. Two publications were available from Study 116 which compared IR to rituximab. The Furman, 2014 publication of Study 116 reported outcomes based on a median of only 3.8 months of time on treatment. The Sharman, 2014 publication of Study 116 reported outcomes based on longer follow-up (an estimated median of 13 months); however, in this data cut, patients who progressed while on treatment with idelalisib were given the option to continue receiving idelalisib at double the dose. This renders it impossible to compare OS outcomes with those from the RESONATE trial. Figure 3, which illustrates the KM data from the two Study 116 publications, clearly demonstrates that the short-term follow-up survival data reported in Furman (red lines) dramatically over predicted survival compared to the longer-term follow-up reported in Sharman (blue lines).

Figure 3: Short- and long-term OS data from Study 116



Janssen explored conducting an MAIC to compare ibrutinib (RESONATE) to IR (Study 116 - Sharman, 2014). The patient populations in RESONATE and Study 116 differed on key factors (e.g. age, proportion with 17p deletion), which could have been adjusted for using MAIC. The fact that patients who progressed on IR in Study 116 were allowed to continue receiving a double dose of

idelalisib post-progression, however, compromises OS outcomes from Sharman, 2014. An MAIC on the outcome of OS is therefore meaningless. An ITC assuming the rituximab arm of Study 116 to be equivalent to the ofatumumab arm in RESONATE would have been similarly meaningless as the rituximab arm of Study 116 was contaminated with cross-over to idelalisib.

An ITC comparing ibrutinib (RESONATE) to Idelalisib plus ofatumumab (IO; Study 119 – Jones, 2015) was therefore considered the only robust analysis available. ITC is preferred over MAIC as a method of establishing comparative efficacy. Moreover, the study populations in RESONATE and Study 119 were markedly similar, providing a strong basis upon which to conduct an ITC.

There are numerous reasons why the magnitude of ibrutinib's efficacy versus IR would be superior. First, whether using Study 116 (IR vs R) or Study 119 (IO vs O), projections of IR's or IO's long-term outcomes are based upon a combination regimen, which in reality patients will receive for only a short duration (approximately 6 months as per the dosing regimen of both anti-CD20s, rituximab and ofatumumab). The only data available for idelalisib monotherapy are from a single-arm trial (Brown, 2014) in which idelalisib dosing ranged from 50 mg BID to 350 mg BID; only 20% of patients received the same dosing regimen (150 mg bid) as in Study 116 and as per the license, and the efficacy of idelalisib monotherapy was poor. These data are therefore entirely inconclusive in helping to understand idelalisib's relative efficacy as a monotherapy. By basing estimates of idelalisib's efficacy as a monotherapy on long term extrapolation of short term IR combination therapy data, it is likely that the long-term effectiveness will be overestimated. This will in turn lead to an overestimation of the cost-effectiveness of IR, as estimates will be extrapolated from the efficacy of IR combination with the cost of idelalisib monotherapy, once the rituximab component is discontinued after six months. This issue further confounds MAIC as a method for estimating comparative efficacy and places the ITC using the Jones publication of Study 119 as the most reliable source of comparative efficacy.

Second, OS data from Study 119 (the only trial of idelalisib plus an anti-CD20 antibody in which OS is not contaminated) demonstrated no survival benefit for IO (HR=0.74, CI: 0.44–1.25). As outlined above, expected median OS in both Study 116 and 119 for IR and IO regimens, respectively, were below 24 months whereas observed OS for ibrutinib in RESONATE is still 85% at the 16-month data cut [redacted].

Third, ibrutinib has a manageable and consistent tolerability profile. Treatment-emergent AEs tend to decrease over time (Byrd et al., 2015) and do not tend to lead to treatment discontinuation, allowing patients to remain on and benefit from treatment. In contrast, treatment discontinuation due to AEs is high for idelalisib combination therapies. The discontinuation due to AEs were 8% as reported for IR in the earlier data cut from Study 116 (Furman et al., 2014) and 31% for IO as reported in Study 119 (Jones et al., 2015), which will limit the long-term treatment benefit patients can derive from therapy. Furthermore, the likelihood of grade 3 or higher diarrhoea or colitis was shown to *increase* over the first 2 years of treatment. A more detailed account of the safety data publicly available for idelalisib has been summarised in Appendix 4.

The safety of idelalisib is currently under review by the EMA, and in the past few weeks, EMA's Pharmacovigilance Risk Assessment Committee (PRAC) issued preliminary guidance to use idelalisib in combination with antibiotics, and that it should not be started in previously untreated patients 17p deletion or TP53 mutation. At the same time, Gilead, the manufacturer of idelalisib, has announced that they are terminating the idelalisib trials in frontline CLL as well as indolent NHL. These recent developments only serve to highlight the key safety differences between ibrutinib and idelalisib. Appendix 5 provides a discussion on the immune differences between idelalisib and ibrutinib which underpin the superior safety profile of ibrutinib, and provide biologically plausible reasons as to why the toxicity issues observed with idelalisib have not been observed with ibrutinib.

Nonetheless, in light of the Committee's uncertainty regarding the magnitude of ibrutinib's treatment effect, we have provided the following two alternative analyses to demonstrate that all possible avenues of establishing relative efficacy have been explored:

1) *ITC in which the OS HR from RESONATE is not adjusted for cross-over*
   Whilst we strongly argue that adjusting for cross-over in RESONATE is appropriate and necessary, Janssen offers this scenario to demonstrate that, even when cross-over is not adjusted for, the resulting ITC OS HR and ICER do not change dramatically. This supports the assertion that the magnitude of differences in the base case model is robust.
2) *MAIC comparing ibrutinib (RESONATE) vs. IR (Sharman, 2014) – PFS only*

Table 5 summarises the various comparisons which are possible in order to establish the most robust estimate of comparative efficacy between ibrutinib and IR.

Table 5: PFS and OS HRs of Ibrutinib vs. IR

Comparison	PFS HR [95% CI]	OS HR [95% CI]	ICER (updated base case, without PAS)	Modelled mean PFS	Modelled mean survival
ITC ibrutinib (RESONATE) vs. IO (Study 119) (submitted base case; RESONATE OS HR adjusted for cross-over)	0.39 [0.23, 0.67]	0.50 [0.24, 1.05]	£50,827	Ibrutinib: 2.95 IR: 1.48	Ibrutinib: 6.31 IR: 3.72
ITC ibrutinib (RESONATE) vs. IO (Study 119) (RESONATE OS HR **not** adjusted for cross-over)	0.39 [0.23, 0.67]	0.58 [0.26, 1.30]	£60,374	Ibrutinib: 2.95 IR: 1.48	Ibrutinib: 6.31 IR: 4.21
MAIC of ibrutinib (RESONATE) vs. IR (Sharman, 2014), PFS outcome only	0.20 [0.10, 0.44]	NA*	£60,007*	Ibrutinib: 2.95 IR: 0.88	Ibrutinib: 6.31 IR: 3.71

*assume OS HR of 0.50

4.2.2 Ibrutinib vs. BR

Janssen provided two analyses estimating ibrutinib's relative efficacy vs. BR – an MAIC comparing ibrutinib (RESONATE) vs. BR (Fischer, 2011) and a multivariate Cox model comparing ibrutinib (RESONATE) vs. BR (HELIOS) - to provide a range of potential efficacies where data were sparse. The Committee preferred to disregard the Fischer MAIC, which we believe only serves to increase uncertainty, as all available data should be considered.

The Committee states that "the Cox multivariate analysis provided a statistically more robust analysis with which to compare ibrutinib with bendamustine plus rituximab" [para 4.12]. Whilst the Cox methodology leverages two sets of patient-level data, which from a theoretical perspective is advantageous, the robustness of the analysis depends entirely on the data sets used. A key requirement for both MAIC and multivariate Cox modelling is that there is significant enough overlap

in the trial populations to allow the populations to be reweighted. As demonstrated in Table 6, the RESONATE population was more severe than either comparator trial. However, the difference in severity is much more pronounced comparing RESONATE vs. HELIOS. The HELIOS trial excluded patients with 17p deletion, a known treatment effect modifier. Furthermore, cross-over from the BR arm to the ibrutinib + BR arm occurred in HELIOS (90 of 289 [31%] crossed over). The effects of this cannot be accounted for in the Cox model, which severely limits the validity of the results. All of these factors indicate that the Cox model will underestimate the difference between ibrutinib versus BR.

Alternatively, the overlap (in terms of 17p deletion especially) between the RESONATE and Fischer populations is much greater. Furthermore, as Fischer, 2011 was a single-arm trial, no cross-over occurred, which removes a confounding factor from the analysis.

Table 6: Comparison of RESONATE, HELIOS, and Fischer trial populations

	Ibrutinib	**Ibrutinib+BR**	**Placebo+BR**	**BR**
Trial / Author (year)	RESONATE	HELIOS		Fischer (2011)
Design	Phase III comparative	Phase III comparative	Phase III comparative	Phase II single arm
Sample size	195	289	289	78
Median age (range)	67 (30 to 86)	64 (31-86)	63 (36–83)	66.5 (42-86)
17p deletion, n (%)	63 (32.3%)	Excluded	Excluded	14 (17.9%)
Median prior therapies (range)	3 (1 to 12)	2 (1–11)	2 (1–9)	2 (1 - 5)
≥3 prior therapies (%)	52.8%	77 (26.6%)	72 (25.0%)	23.1%

4.2.3 Ibrutinib vs. PC

"*The committee recognised the comments from the clinical experts and the ERG that the composition presented by the company did not reflect the treatments offered in the UK…*" [para 4.3].

The Committee had reservations that the results vs PC modelled using the ITC vs. the Österborg trial (OMB114242) is not reflective of the UK composition of PC, despite this composition being amended based upon UK clinical opinion. Janssen would like to clarify that when using the data from OMB114242, the amended composition of PC solely impacted the cost applied to PC, whereas the efficacy of PC was not adjusted in any way, as UK clinical opinion stated that the efficacy from the trial was representative of PC in the UK (see subsection 3.2 for discussion on this point). The Committee also had concerns that the OMB114242 trial itself was not a representative population for the UK despite the majority of the trial being based in the EU (81 patients of a total of 122). Due to these concerns, the Committee preferred the alternative pooled Cox regression analysis based on the Karolinska patient-level data.

Janssen believe that both analyses vs PC remain relevant, and therefore both should be considered based on points discussed in subsection 3.2. However, in order to alleviate the Committee's concern and provide further clarity and certainty around the cost-effectiveness results of ibrutinib vs. PC, a revised estimate of the comparative efficacy of PC vs. ibrutinib was obtained by returning to the Karolinska patient-level data and more accurately re-weighting it to reflect what the most recent market research data shows as the current UK PC mix (Janssen, 2016a). Treatments listed in the Karolinska dataset not representative of PC in the UK market research (i.e. fludarabine-containing regimens, ibrutinib, and idelalisib) were not included in the analysis. The PC mix used in this revised analysis is show in Table 7.

Table 7: Revised composition of PC

Treatment	Proportion (weight)
Chlorambucil	14%
Alemtuzumab	10%
BR	41%
Chlorambucil + rituximab	13%
Ofatumumab	5%
Bendamustine	2%
Other	15%

Re-running the Cox regression analysis for this re-weighted PC dataset generates the following data:

[redacted]

- The alternative ICER is estimated to be £62,072 at list price and [redacted] with the PAS

Therefore, with an alternative measure of comparative efficacy that aims to address uncertainty around the PC treatment mix, ibrutinib remains cost-effective. Janssen strongly assert that all analyses vs PC (e.g. based on the Österborg trial, the original Karolinska pooled analysis, and the revised Karolinska pooled analysis) should be considered as this reduces the uncertainty in the cost-effectiveness assessment.

4.3. Equivalence of IR and IO

"*The committee [heard] from the company and clinical experts that idelalisib plus ofatumumab and idelalisib plus rituximab could be considered equivalent in terms of efficacy"* [para 4.11].

"The company also stated that in the appraisal of idelalisib, the committee had accepted that rituximab and ofatumumab were interchangeable in terms of efficacy. However, the committee noted that in the idelalisib appraisal, it was rituximab and ofatumumab monotherapy that were accepted as having equal efficacy, due to a lack of available evidence, rather than each in combination with idelalisib" [para 4.11].

Janssen strongly maintains that IO can be used as a proxy for IR to establish comparative efficacy relative to ibrutinib in the absence of head-to-head trial data. Clinical opinion supports this assumption and NICE's recent recommendation of IR in R/R CLL *relied specifically* on the equivalence of rituximab and ofatumumab monotherapy. There is no biological plausibility to assume that two CD20 monoclonal antibodies would be equivalent in monotherapy and not in combination therapy.

Secondly, to the Committee's latter concern quoted above, head-to-head RCT evidence comparing ofatumumab + DHAP and rituximab + DHAP (ORCHARRD study, GSK, NCT01014208) in relapsed or refractory diffuse large B cell lymphoma showed no statistical differences in ORR, PFS, or OS outcomes. Therefore, this RCT supports interchangeability of ofatumumab and rituximab

combination therapy. While these data were used in the IR appraisal to establish the interchangeability of monotherapy rituximab and ofatumumab, it supports the interchangeability between rituximab and ofatumumab *combination therapy.*

For these reasons and with the support of clinical opinion, Janssen maintains that robust data and precedence exist in establishing equal efficacy between rituximab and ofatumumab (whether in monotherapy or combination therapy) and therefore, the interchangeability of IR and IO stands. This ultimately supports the strength of the ITC comparing ibrutinib to IO (proxy for IR) as discussed in subsection 4.2.1.

5. PFS and OS extrapolation

"*The ERG recognised that the immature trial data meant that the company had to extrapolate both progression-free survival and overall survival to a greater degree than is usual for cancer drugs, which increased uncertainty. The ERG observed that there was little difference between parametric curves during the trial period but, during the extrapolation period they diverged, in some cases 'quite dramatically'*" [para 3.36].

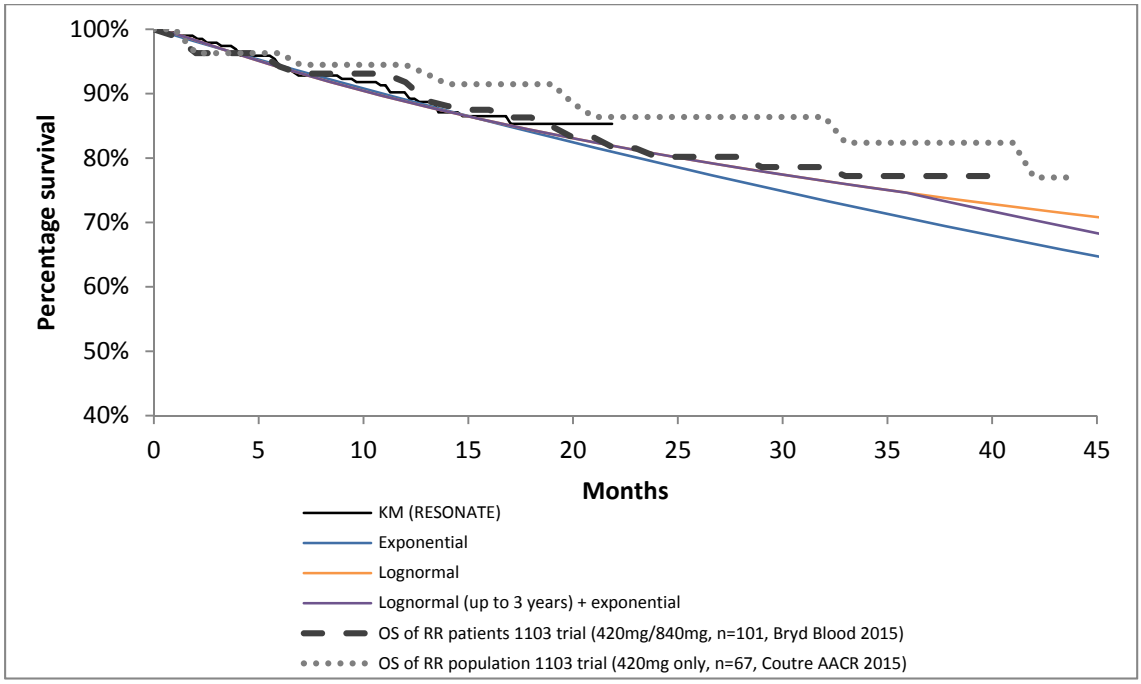
"*For overall survival, the ERG did not agree with the company's use of the log-normal function for 3 years followed by the exponential function because the goodness-of-fit statistics favoured the exponential distribution*" [para 3.36].

"*For progression-free survival, a key determinant of costs, the ERG acknowledged that the goodness-of-fit statistics did not provide any clear guidance as to which curve was best, but the ERG preferred an exponential curve while the company preferred a Weibull curve. The ERG interpreted the Weibull curve as predicting that too many people live for too long between disease progression and dying. ERG expert opinion suggested that the exponential curve provided a more credible proportion of patients remaining progression free given the anticipated survival*" [para 3.36].

5.1 OS extrapolation

Janssen maintains that the lognormal + exponential projection of OS provides the best fit for the short-term data and it appears to be the best fit when validated by longer-term OS data collected in 1102/1103, the ibrutinib phase 2 trials. Validation with 1102/1103 OS data suggests that an exponential fitting will underestimate ibrutinib's long-term survival (Figure 4). However, the difference between these projection approaches is minor. Janssen accepts the Committee's more conservative recommendation of an exponential fitting for OS KM data from RESONATE.

Figure 4: Validation of OS projections



5.2 PFS extrapolation

Janssen strongly maintains that the Weibull fitting for ibrutinib's PFS KM data used in the base case submission is the most appropriate projection approach and does not agree with the Committee's recommendation of an exponential fitting. The Weibull fitting was selected as per the NICE Decision Support Unit document on survival analysis (Latimer, 2011), e.g. considering goodness-of-fit statistics, visual inspection, clinical validation, and consistency with the disease area.

Weibull had the lowest AIC statistics, while exponential has the lowest BIC. Weibull is more appropriate in this case, as models based on the BIC criteria have a risk of under-fitting (not capturing the underlying trend in the data) (Kuha, 2004). Furthermore, the Weibull scale parameter (or shape parameter per SAS code) is significantly different from 1 (mean 0.77, SE 0.11) and fits RESONATE KM data well based upon visual inspection (note here that the exponential fit is a form of Weibull with the scale parameter = 1). Finally, Weibull projections were found to be clinically plausible, while an exponential fitting simulates >10% of patients to remain in PFS at 10 years, which is a likely overestimation.

Few progression events were captured in the ibrutinib arm of RESONATE, making a trend towards a best fit option less obvious. It is therefore useful to consider that a Weibull fit has been shown to be the best fit for other R/R CLL PFS KM data where more events were captured. A Weibull had the lowest goodness-of-fit statistics for the ofatumumab arm (RESONATE trial). In the NICE appraisal of IR, a Weibull was best fit for both the IR and rituximab arms of Study 116, while exponential was the worst fit. NICE accepted the Weibull fit as the base case. The argument in the IR submission that parametric function (in this case the Weibull) could be held constant between different treatments for R/R CLL (Gilead Science Limited, 2015), with only the scale of the Weibull varied was accepted by the ERG and NICE Committee. This makes the argument that PFS function should be disease-specific rather than treatment-specific. Given that the Weibull function has the best fit for PFS in the ofatumumab arm of RESONATE, and also consistently shown to be best fit in previous appraisals in CLL, including IR (Gilead Science Limited, 2015), ofatumumab (NICE, 2010 and NICE, 2015c) and the CLL8 trial (Papadakis K et al., 2008), Janssen would argue that this lends further support to the most appropriate parametric function for ibrutinib to be the Weibull.

"ERG expert opinion suggested that the exponential curve provided a more credible proportion of patients remaining progression free given the anticipated survival" [para 3.36].

There were little data on the expected or "reasonable" proportion of long-term survivors who remain in PFS. The NICE appraisal of IR suggests that patients can in fact experience considerable post-progression survival. Furthermore, a DSU publication examining the relationship between PFS and OS cautioned that *"any cost-effectiveness analysis which makes a strong assumption regarding the relationship between PFS and OS should be treated with caution"* (Davies et al., 2012). Janssen thus restates its position that the Weibull function is the best fit for extrapolating PFS, and that any relationship between PFS and OS extrapolation should not be used to predict parametric function for PFS extrapolation.

5.3 Relationship of PFS and OS

"The committee noted that the model predicted that some patients live with progressed disease for an improbably long time before dying, recalling that the clinicians observed that patient do not live long periods with progressed disease" [para 4.15].

It is known that due to clonal evolution and impact on the patient of toxic chemotherapy that the duration of remission lessens with each line of therapy. Consistent with the hypothesis that ibrutinib does not select for more aggressive subclones (Landau et al., 2013) and that it has a benign toxicity profile, a multi-centre study in the US (Mato et al., 2015) showed that PFS subsequent to ibrutinib or idelalisib was not decreased. The median PFS of patients treated with ibrutinib (n=93) or IR (n=30) was 10.5 months. The median PFS of the treatment received subsequent to this was 11.9 months. This increases confidence that survival following discontinuation of ibrutinib is not shortened and increases the plausibility of the increased survival seen in the modelling.

6. Utility data

"*The committee concluded that the EQ-5D may not have fully captured the experience of patients with CLL, and the quality of life benefit with ibrutinib may have been underestimated in the model*" [para 4.21].

"*The committee concluded that the company's choice of utilities in the post-progression health state were likely to be overestimated and should have been age adjusted*" [para 4.22].

Janssen agrees that the EQ-5D data in the trial likely missed an important aspect of utility given limitations in the instrument to pick up key features of improvement such as fatigue (Garau et al., 2011). Assuming utility is the same for ibrutinib and comparators in PFS is a conservative approach, as other novel agents have included utility increments for treatment benefit. In the NICE appraisal of IR, a 0.07 utility increment was added to patients while on IR therapy and an increment of 0.05 was added for patients in PFS "off treatment." Oral therapies have also been modelled to have higher utility than IV therapies (difference of 0.04 in the NICE appraisal of obinutuzumab + chlorambucil for first line CLL [NICE, 2015d]).

Furthermore, a clinical advisory board recently hosted by Janssen (25 January 2016) advised that ibrutinib is expected to be associated with both a treatment-specific and an oral administration

utility benefit. In the current model, this has been excluded and is therefore a conservative scenario for ibrutinib.

In line with the suggestion from the Committee that utilities "*should have been age adjusted*" [para 4.22], Janssen are in agreement and age adjustment to the utility values has been applied to the revised base case. In a study by Ara and Brazier (2010), age was found to have a negative association with EQ-5D utility; the coefficient was -0.0002587 for age and -0.0000332 for age^2. The revised base case results are presented in section 9.

Finally, whilst demonstrating minor impact, the following scenarios exploring alternative utility assumptions are presented in Appendix 6:

- Applying a utility increment to patients on ibrutinib
- Applying a utility increment to patients on ibrutinib and IR
- Applying utilities from the idelalisib submission
- Applying a lower PPS utility (0.60, from obinutuzumab + chlorambucil NICE submission) per ERG's preference

7. CLL patients with 17p deletion

"*The committee concluded the only comparator for this population was idelalisib plus rituximab*" [para 4.5].

"*The committee concluded that there was considerable uncertainty when generalising the treatment effect of ibrutinib in the RESONATE trial from the previously treated population with 17p deletion to the previously untreated population with 17p deletion*" [para 4.8].

"*The committee took note of the unmet need for treatment options in these populations. It was aware of the lack of evidence available for these subgroups and agreed this data was the best available and could be used to support decision making in the untreated and TP53 population. The committee concluded that, because the data for the 17p deletion or TP53 mutation populations were uncertain and that the data did not include evidence for the untreated 17p deletion population or the TP53 mutation population, the results from the model were associated with uncertainty*" [para 4.17]

The Committee accepts that data on the 17p deletion subgroup in R/R CLL can serve as a proxy for a treatment-naïve 17p deletion subgroup. In the NICE FAD for IR in R/R CLL, IR was recommended for the subgroup of patients with treatment-naive 17p deletion with less data than Janssen has already submitted for ibrutinib (IR presented data from a total of 9 patients in Study 101-08, compared to the ibrutinib data from the Farooqui trial, which demonstrated efficacy in 35 patients [33 evaluable] patients).

The Committee considers that IR is the only relevant comparator in patients with 17p deletion. Janssen would context this assertion, particularly given that the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has recently issued a provisional precautionary recommendation that IR "*should…not be started in previously untreated patients with CLL whose cancer cells have certain genetic mutations (17p deletion orTP53 mutation*)", due to emerging safety concerns, including death (EMA, 2016a). Nonetheless, Janssen have explored the possibility of a naïve, indirect comparison to IR and the resulting ICER is £44,364 at list price and [redacted] with the PAS applied. The results are detailed in section 9 and an explanation of the analysis is provided in Appendix 7.

8. Costing considerations

The Committee indicated that the following costing decisions created a more favourable situation for ibrutinib vs. comparators:

- ***Use of time to treatment discontinuation curve for the ibrutinib arm, but not for the ofatumumab arm***

- ***Applying the dose intensity proportions to drug administration costs, which would reduce the costs of comparators, but not ibrutinib due to ibrutinib having zero administration costs***
- ***Applying half cycle correction and immediate discounting to the ibrutinib drug costs but not to the comparator drug costs.***

The Committee noted that there was some uncertainty in the response rates used in the models and that they may not reflect the proportion of PR and CR outcomes in the comparator trials.

In nearly all cases, the differences in how costing considerations were applied to ibrutinib versus comparators were due to the fact that ibrutinib was the only purely oral, daily treatment included in the model. Due to ibrutinib's unique route of administration, half-cycle correction and discounting, application of dosing intensity to administration costs, and the relevance of time until treatment discontinuation were considered differently for ibrutinib.

To be conservative and consistent across treatments, Janssen accepts the Committee's recommendation to apply half cycle correction, discounting and dose intensity in the same manner for all treatments in the model. Janssen also accepts the recommendation to use PFS as a more conservative estimate of time on treatment for ibrutinib rather than time to treatment discontinuation. For a full list of costing revisions to the base case, refer to Appendix 8.

Differentiating costs by response level adds clinical validity to the economic modelling and is supported by both clinical expert opinion and previous NICE precedent (including recently recommended IR). However, if the Committee maintains that such stratification is not appropriate, Janssen asserts that the routine care for partial responders should be used to characterise the medical resource use for all patients, as opposed to the routine care for non-responders, as the ERG and Committee have suggested. Using non-responder resource use to characterise an all-patient population will result in an overestimation of costs.

9. Revised economic analyses

Updated economic analyses comparing to all relevant comparators in both the overall R/R CLL population and the TN CLL population with 17p deletion are summarised in this section.

Following the concerns raised by the Committee, we have applied amendments to the model base case to reflect the changes suggested by the ERG, and with consideration to the main points discussed in the preceding sections. For ease of reference, the revised base case incorporates the following major changes:

- Correction to dose intensity of ibrutinib
- Alternative extrapolation of the OS data
- Age-adjustment of the utility data
- Amendment to the costing assumptions
- Treatment discontinuation curve

Please refer to Appendix 8 for a detailed table of all the suggested changes while Appendix 9 summarises minor points on factual accuracy.

With the amendments to the base case model made as described above (and further detailed in Appendix 8), at list price the ICERs are relatively consistent between the four comparators, ranging from £49,023 vs. BR to £53,644 vs. IR (Table 8). With the PAS applied to the cost of ibrutinib, ICERs are below £50,000/QALY when compared against all four comparators (Table 9), demonstrating that ibrutinib is a cost-effective use of NHS resources.

Table 8: Revised Janssen base case results in R/R CLL population at list price

Comparator	Total Costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (LYs)	ICER incremental (QALYs)
Ibrutinib	[redacted]	[redacted]	[redacted]					
Physician's Choice	[redacted]	[redacted]	[redacted]	[redacted]	4.33	3.07	37,483	52,787
IR	[redacted]	[redacted]	[redacted]	[redacted]	2.60	1.82	37,484	53,644
BR	[redacted]	[redacted]	[redacted]	[redacted]	4.79	3.36	34,393	49,023
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	3.47	2.48	38,127	53,245

Table 9: Revised Janssen base case results in R/R CLL population with PAS

Comparator	Total Costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (LYs)	ICER incremental (QALYs)
Ibrutinib	[redacted]	[redacted]	[redacted]					
Physician's Choice	[redacted]	[redacted]	[redacted]	[redacted]	4.33	3.07	[redacted]	[redacted]
IR	[redacted]	[redacted]	[redacted]	[redacted]	2.60	1.82	[redacted]	[redacted]
BR	[redacted]	[redacted]	[redacted]	[redacted]	4.79	3.36	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	3.47	2.48	[redacted]	[redacted]

Revised subgroup analyses for the 17p deletion population (including additional naïve comparison to IR) showed that ibrutinib is also cost-effective. ICERs at both list price and with the PAS were all below £50,000/QALY (Table 10 and Table 11).

Table 10: Results in TN CLL population with 17p deletion at list price

Comparator	Total Costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (LYs)	ICER incremental (QALYs)
Ibrutinib	[redacted]	[redacted]	[redacted]					
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	3.63	2.57	31,290	44,166
IR	[redacted]	[redacted]	[redacted]	[redacted]	2.33	1.59	30,237	44,364

Table 11: Results in TN CLL population with 17p deletion with PAS

Comparator	Total Costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (LYs)	ICER incremental (QALYs)
Ibrutinib	[redacted]	[redacted]	[redacted]					
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	3.63	2.57	[redacted]	[redacted]
IR	[redacted]	[redacted]	[redacted]	[redacted]	2.33	1.59	[redacted]	[redacted]

10. Conclusion

The Committee has made an initial decision to reject ibrutinib as they believe it does not represent a cost-effective option for the treatment of CLL. Janssen urges the Committee to consider the additional evidence presented in our response to the ACD, which strongly supports the following:

- The patient population appraised for treatment with ibrutinib in CLL meets the **end of life** (EoL) criteria
- The comparison of ibrutinib to **multiple comparators** is a representation of the fact that there is currently no single standard of care for the treatment of CLL in England and Wales.
- **Comparative efficacy** of ibrutinib relative to key comparators was established based upon a hierarchy of evidence generation methodology, and careful consideration was given to ensure data were analysed in the most appropriate way. As such, the cross-over adjusted RESONATE trial data is the most appropriate data set to use to represent the true efficacy of ibrutinib.
- The Kaplan-Meier data from RESONATE is used to **appropriately extrapolate** both PFS and OS.
- Ibrutinib is both a **safer and more efficacious treatment** option than the recently NICE approved regimen of IR. The ongoing safety concerns associated with idelalisib only serves to further highlight the significant clinical need that remains.

Ibrutinib has demonstrated a consistent and unprecedented survival benefit, with more than 50% of patients still alive and free of progression at the end of all published clinical trials, including one with a follow-up of up to 44 months (Coutre et al., 2015a). As a result of this unprecedented efficacy, ibrutinib was granted FDA breakthrough status and accelerated approval in February 2014, closely followed by the European Medicines Agency (EMA) in October 2014. It is a highly potent, highly effective, and safe drug that represents a step change in the treatment of CLL, and is the most requested drug for the treatment of CLL on the CDF (NHS England, 2016).

In our revised base case, upon taking into account the Committee's concerns and the confidential PAS, ibrutinib is a consistently cost-effective treatment option for use in the NHS against all four relevant comparators. Janssen therefore urges the Committee to reverse their initial decision, to allow patients routine access to this important new treatment.

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Appendix 1 RESONATE 30-month data cut

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Appendix 2 Comparison of RESONATE vs Karolinska Institute dataset

In support of subsection 2.2, the baseline characteristics of the Swedish patient cohort are presented alongside those of the RESONATE trial population in Table 14.

Table 14: Baseline characteristics of RESONATE vs Karolinska dataset

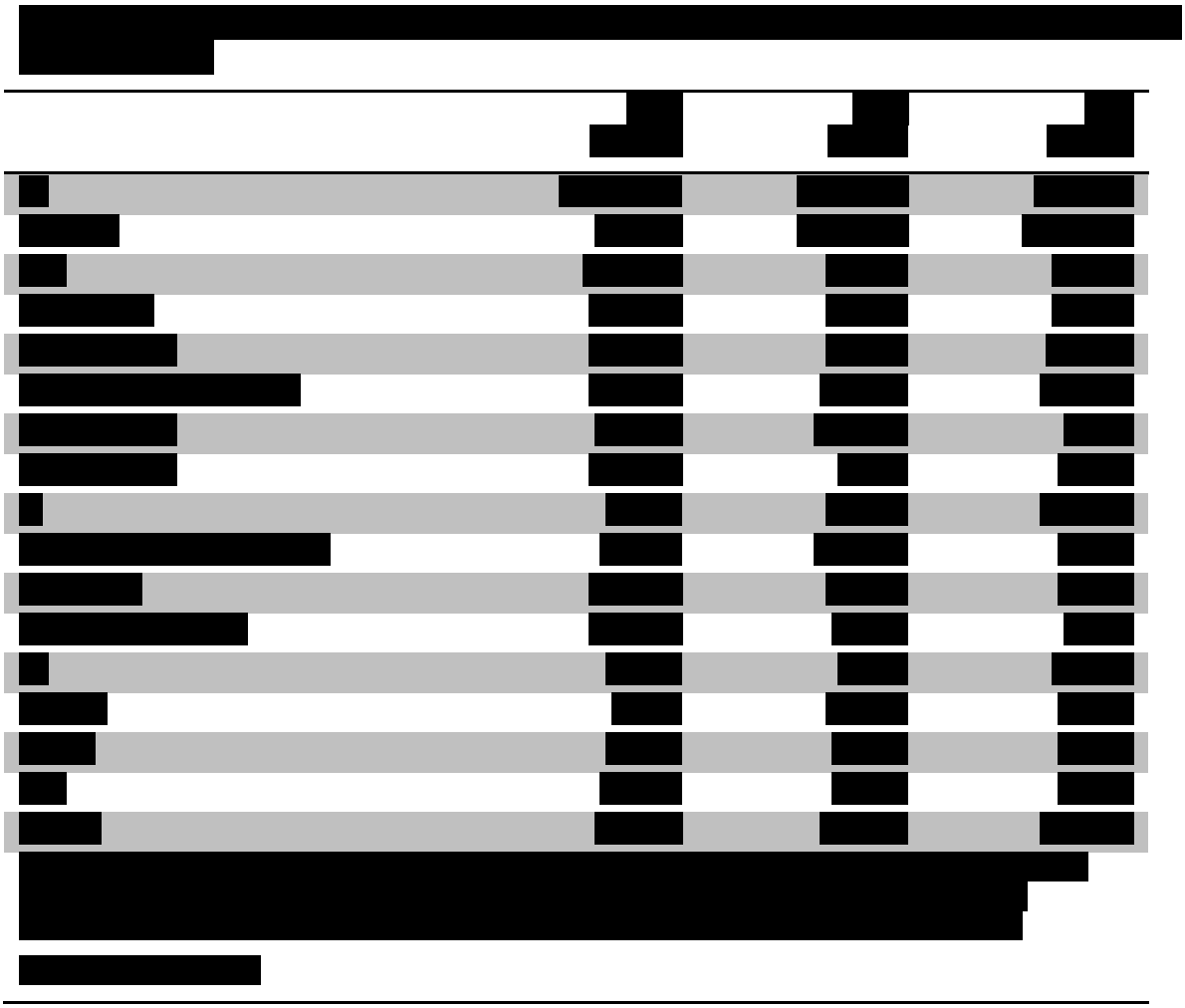
Characteristic	**Ibrutinib (n=195)**	**Ofatumumab (n=196)**	**PC (n = 203)**
Dataset	RESONATE		Karolinska Institute (Swedish registry)
Median age (range), year	67 (30–86)	67 (37–88)	71
Male sex, number (%)	129 (66%)	137 (70%)	64.7%
Cumulative Illness Rating Scale score >6, number (%)	38 (32%)	39 (32%)	NR
Creatinine clearance <60 ml/min, number (%)	62 (32%)	61 (31%)	NR
Median haemoglobin (range) g/l	110 (70–160)	110 (60–160)	105 (56-183)
Median platelet count (range), per mm^3	116,500 (20,000–441,000)	122,000 (23,000–345,000)	NR
Median lymphocyte count (range), per mm^3	29,470 (90–467,700)	29,930 (290–551,030)	NR
ECOG performance status 0, number (%)	79 (41%)	80 (41%)	22.4%
ECOG performance status 1, number (%)	116 (59%)	116 (59%)	49.9%
Bulky disease ≥5 cm, number (%)	124 (64%)	101 (52%)	NR
Interphase cytogenetic abnormalities, number (%)			
Chromosome 11q22.3 deletion	63 (32%)	59 (30%)	NR
Chromosome 17p13.1 deletion	63 (32%)	64 (33%)	NR
β2-microglobulin >3.5 mg/l, number (%)	153 (78%)	145 (74%)	NR
Previous therapies			
Median number (range)	3 (1–12)	2 (1–13)	2 (1-7)
≥3, number (%)	103 (53%)	90 (46%)	31.9%
Median time from last therapy (range), months	8 (1–140)	12 (0–184)	8.5 (0-84)
Resistance to purine analogues, number (%)	87 (45%)	88 (45%)	30%

Appendix 3 Market research for R/R CLL treatment uptake

Oncology Analyzer ™

IMS Oncology Analyzer ™ is a syndicated cross-sectional survey that covers major markets of Europe and Asia. It reports on patient case information relating to the treatment of patients across all cancer types and stages. It is updated on a quarterly basis.

Case histories are provided via online questionnaire. Information is sourced from patient records. Only senior grade clinicians can participate in the survey and they must be board-certified in target specialty. The clinician recruitment must meet a statistically set patient cap during the reporting period. Clinicians must have personally treated these patients within past three months.



Harmony data

Harmony data is collected by means of web-based interviews which are approximately 45 minutes duration, administered by the IMS Health Primary Market Research Centre of Excellence. In each wave of research, interviews are conducted with 50 specialists recruited from nationally representative panels of physicians who are responsible for the treatment of CLL and / or MCL. In order to qualify for participation physicians must have been practicing for more than 3 and less than 35 years and have seen a minimum of 6 patients with CLL or a minimum of 3 patients with MCL who they had personally treated with active treatment involving drug therapy in the previous month. Each physician completes 4 patient record forms and when doing so they are asked to refer

to actual patient records relating to CLL / MCL patients seen in the last 30 days. This enables IMS to capture detailed treatment information for patients at each line of therapy, excluding those on a clinical trial.

Table 16: Cancer Drug Fund Notifications for R/R CLL from April 2014 to September 2015

Molecule	CDF indication	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15
Bendamustine	2nd or subsequent line treatment of CLL for patients whom fludarabine combination therapy is not a therapeutic option	20	30	11	30	20	21	28	18	20	17	16	15	9	20	20	19	14	25
Ibrutinib	Treatment of R/R CLL	0	0	0	0	0	0	0	0	0	36	68	74	56	55	65	69	47	63
Idelalisib	In combination with rituximab for the treatment of adult patients with relapsed CLL not eligible for cytotoxic therapies	0	0	0	0	0	0	0	39	45	16	22	11	10	14	19	22	20	29
Ofatumumab	2nd line treatment of CLL in patients who are refractory to fludarabine and ineligible/unsuitable for alemtuzumab	2	2	1	3	1	2	2	2	2	10	0	0	0	0	0	0	0	0
	2nd line treatment of CLL in patients with p53 mutation who relapse or progress on first line alemtuzumab and are not suitable for fludarabine	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	3rd line treatment of CLL in patients refractory to fludarabine and alemtuzumab regimens	4	4	4	6	3	3	2	1	1	1	2	0	0	0	0	0	0	0

Source: NHS England, 2016

Appendix 4 EPAR comparison of ibrutinib vs idelalisib

The ibrutinib EPAR reported that "*AE incidence generally decreased over time*" (EMA, 2014a).

In contrast, high discontinuation rates (overall, approximately 20%), active management of AE by dose interruption and reduction, and the late occurrence of side-effects (primarily colitis) have led to an action in the idelalisib Risk Management Plan. This stipulated that long-term safety data be provided from ongoing or future studies which could lead to an update of labelling (EMA, 2014b).

Within the last two weeks, the EMA have initiated a review of idelalisib following an increased rate of serious adverse events (SAE), including deaths and mostly due to infections, in ongoing clinical trials (EMA, 2016b). This has been followed by an interim announcement which now requires all patients currently on treatment to receive antibiotics to prevent *Pneumocystis jirovecii* pneumonia as well as monitoring for infection and regular blood tests (EMA, 2016a). Additionally the recommendations state that whilst idelalisib is being investigated, treatment-naïve CLL patients with 17p deletion or TP53 mutation should not be initiated on idelalisib.

To further demonstrate the significant differences between ibrutinib vs idelalisib, a comparison of the respective EPARs is summarised:

Ibrutinib	**Idelalisib**
Discussion on clinical safety P123 Importantly, AE incidence generally decreased over time, and with relatively low discontinuation rates and dose reductions due to AEs, side effects overall seem clinically manageable by dose modifications as described in the SmPC Section 4.2. **Importance of favourable and unfavourable effects** P137 The results from studies conducted in the CLL indication are of high clinical relevance. The activity of ibrutinib was demonstrated across trials. The positive results in the high risk patients with 17p deletion / TP53 mutations are of particular importance and support an indication in first line for those patients who are unsuitable for chemo-immunotherapy. The most frequent adverse reactions related to the use of the ibrutinib are infections, neutropenia, and diarrhoea. However, discontinuation due to toxicity was infrequent and overall the toxicity was considered	**Discussion on clinical safety** P116 Response to therapy occurred early, whilst time to progression was long, meaning that the incentive to continue therapy probably decreases over time and might be reflected in the rather high discontinuation rates, overall about 20%. P117 As the idelalisib clinical program progressed from Phase 1 and 2 Studies (101-07 and 101-08) to the Phase 3 Study (312-0116), the approach for management of AEs by dose interruption and reduction was developed and Investigators gained experience in treating subjects with idelalisib, thus likely leading to a lower rate of discontinuation due to AEs in Study 312-0116. P118 Diarrhoea/colitis, sometimes severe, is the most obvious and clinically important side effect of idelalisib therapy. Of note, cases of colitis occurred sometimes after months of treatment and were in only 30% of cases preceded by grade 1/2 diarrhoea.

manageable. **Discussion on the benefit risk-balance** P138 Of major importance in the assessment of benefit is the consistently shown dramatic activity of ibrutinib irrespective of refractoriness to prior therapy or unfavourable prognostic factors in patients with MCL and CLL. P138 The high response rates and long durations of response at acceptable toxicity are acknowledged, although the long-term data are not yet available.	**Risk Management Plan/Safety concerns/Missing information** P120 and P126 Long-term safety (NB There is no equivalent statement for ibrutinib) Update of labelling as appropriate based on analysis of safety data that may arise from any ongoing or future studies. **Importance of favourable and unfavourable effects** P130 The results from studies conducted in the CLL indication are of high clinical relevance. The activity of idelalisib was demonstrated across trials. The positive results in the high risk patients with 17p deletion / TP53 mutations are of particular importance and support an indication in first line for those patients who are unsuitable for chemo-immunotherapy. Discontinuation due to toxicity was infrequent and overall the toxicity was considered manageable. **Discussion on the benefit-risk balance** P130 Of major importance in the assessment of benefit is the consistently shown high activity of idelalisib irrespective of refractoriness to prior therapy or unfavourable prognostic factors in patients with FL and CLL. The high response rates and long durations of response at acceptable toxicity are acknowledged, although the long-term data are not yet available. As a consequence, efficacy

	and safety data from ongoing studies will be regularly updated to provide additional information about long-term benefits and risks.
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003791/WC500177777.pdf	http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003843/WC500175379.pdf

Appendix 5 Immune difference between idelalisib and ibrutinib

Idelalisib

Idelalisib's mode of action affects phosphoinositide 3-kinase (PI3K), which are a family of enzymes involved in cellular functions such as cell growth, proliferation, differentiation, motility, survival and intracellular trafficking, which in turn are involved in cancer. While potentially important in multiple cell types, PI3K p110δ (PI3Kδ) shows an expression pattern that is particularly prominent in cells of hematopoietic origin (Vanhaesebroeck et al., 2005).

Whilst idelalisib has activity in CLL and other B cell malignancies, it has been shown that toxicities, particularly hepatic toxicity/transaminitis, pneumonitis and colitis occur following 7-9 months on therapy (Coutre et al., 2015b). Often these events are grade ≥3 severity. In treatment-naïve patients treated with idelalisib and ofatumumab (IO), it was recently reported that these toxicities are more common in less heavily pre- treated patients (Lampson et al., 2015). This toxicity is an on-target effect on lymphocytes, in particular T-regulatory lymphocytes. In the Lampson analysis, it was shown that there were severe cases of fulminant hepatitis (with lymphocyte infiltrates) as well as a decrease in T-regulatory cells in patients on idelalisib. Furthermore, over time, whilst patients are on treatment with idelalisib, these cells (which help prevent autoimmune disease) continued to decrease (Lampson et al., 2015). Moreover, in the treatment of patients with idelalisib and rituximab (I + R) in the treatment naïve setting , similar observations were made with the later onset of diarrhoea and inflammatory colitis (median time to onset 9 months), the hypothesis being that this is related to the effects on T-regulatory function by inhibiting PI3Kδ (O' Brien et al., 2015). These observations have also been made in R/R CLL patients with the development of transaminitis, colitis and pneumonitis ≥ grade 3 in severity, frequently requiring the discontinuation of therapy with idelalisib (Barrientos et al., 2015).

In summary, in earlier lines of therapy, toxicity with idelalisib is worse, and tends to increase over time. The effects of idelalisib on T-regulatory cells may be the reason for these autoimmune side effects.

Ibrutinib

In contrast, ibrutinib inhibits Bruton Tyrosine Kinase (BTK) with some activity on interleukin-2-inducible T-cell kinase (ITK). Due to this activity, the effects of ibrutinib are predominantly on B-lymphocytes. AEs with ibrutinib tend to be mild and reduce over time, with no increased toxicity in earlier lines of treatment (Byrd et al., 2015). Furthermore, there are positive effects of ibrutinib on the immune system, resulting in a partial reconstitution of humoral immunity. In a study of patients receiving ibrutinib, Sun and colleagues noted that IgA immunoglobulin levels improve over time (consistent with the same observation in other ibrutinib studies (Byrd et al., 2014). Patients who have improving IgA levels have also been shown to have decreased rates of infection (Sun et al., 2015). Moreover, in a review of clinical cases of autoimmune cytopenia, it was demonstrated that autoimmune hemolytic anaemia and autoimmune thrombocytopenia improved; in fact, patients receiving autoimmune cytopenia treatment were able to discontinue their immune suppressive therapy. It is thought that this is due to the activity of inhibiting BTK, removing auto antigen producing B cells. In addition to this, it is also hypothesised that due to inhibition of ITK, there is a shift in T-cell activity towards a Th1 response (a proinflammatory response), making an immune environment less favourable for the development of autoimmune haemolytic anaemia (Rogers et al., 2015).

In summary, adverse events decrease with ibrutinib over time. During treatment with ibrutinib, it appears there is a partial reconstitution in humoral immunity, with improvements in immune functioning. This results in an increase in IgA, decreasing rates of infection, and an improvement in autoimmune mediated cytopenias.

Appendix 6 Exploratory analyses of alternative utility data

Table 17 presents results for the overall R/R CLL population considering a number of alternative utility inputs as listed in section 6. Despite these alternative inputs, the ICERs remain consistent, ranging only between £44,144 and £52,595 per QALY (at list price).

Table 17: Results in R/R CLL population considering alternative utility data at list price

Comparator	Total Costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (QALYs)	ICER incremental (LYs)
Scenario 1: Applying a utility increment to patients on ibrutinib (0.07)								
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]				
Physician's Choice	[redacted]	[redacted]	[redacted]	[redacted]	4.33	3.44	47,206	37,483
IR	[redacted]	[redacted]	[redacted]	[redacted]	2.60	2.13	45,682	37,484
BR	[redacted]	[redacted]	[redacted]	[redacted]	4.79	3.73	44,144	34,393
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	3.47	2.83	46,775	38,127
Scenario 2: Applying a utility increment to patients on both ibrutinib and IR (0.07)								
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]				
Physician's Choice	[redacted]	[redacted]	[redacted]	[redacted]	4.33	3.44	47,206	37,483
IR	[redacted]	[redacted]	[redacted]	[redacted]	2.60	2.03	48,023	37,484
BR	[redacted]	[redacted]	[redacted]	[redacted]	4.79	3.73	44,144	34,393
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	3.47	2.83	46,775	38,127
Scenario 3: Applying utilities from the idelalisib submission (Utility increment applied to both ibrutinib and IR)								
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]				
Physician's Choice	[redacted]	[redacted]	[redacted]	[redacted]	4.33	3.20	50,800	37,483
IR	[redacted]	[redacted]	[redacted]	[redacted]	2.60	1.88	51,743	37,484
BR	[redacted]	[redacted]	[redacted]	[redacted]	4.79	3.45	47,688	34,393
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	3.47	2.63	50,340	38,127
Scenario 4: Applying a lower PPS utility (0.60, from obinutuzumab + chlorambucil NICE submission) per ERG's preference								
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]				
Physician's Choice	[redacted]	[redacted]	[redacted]	[redacted]	4.33	3.12	52,016	37,483
IR	[redacted]	[redacted]	[redacted]	[redacted]	2.60	1.85	52,594	37,484
BR	[redacted]	[redacted]	[redacted]	[redacted]	4.79	3.38	48,767	34,393
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	3.47	2.55	51,924	38,127

Appendix 7 Exploratory analysis vs idelalisib plus rituximab in patients with 17p deletion

As discussed in section 7, the exploratory naïve comparison of ibrutinib vs IR is explained further here with the following caveats:

- Ibrutinib was compared to idelalisib plus ofatumumab (IO), a proxy for efficacy of idelalisib plus rituximab (IR). The comparative efficacy of ibrutinib vs. IO in the 17p deletion population was estimated via an indirect treatment comparison (ITC) comparing ibrutinib (RESONATE) vs. IO (Study 119).

- The analysis was conducted using data from R/R CLL patients with 17p deletion, a proxy for treatment-naïve CLL patients with 17p deletion. The cost-effectiveness of ibrutinib for treatment of R/R CLL in the presence of 17p deletion (based on the subgroup data from RESONATE and Study 119) provides the best available estimate of efficacy associated with treatment-naïve CLL patients with 17p deletion.

The PFS hazard ratio (HR) comparing ibrutinib vs. ofatumumab in the RESONATE 17p deletion population was 0.116 (95% confidence interval [CI] 0.063-0.213). The Jones et al. publication on Study 119 reported a PFS HR for IO vs. ofatumumab for the Study 119 17p deletion population as 0.21 (95% CI 0.09 – 0.49).

Study 119 did not report an OS HR for the 17p deletion population. Therefore, the ITC in the 17p deletion population relied on the OS HR for the all-patient R/R population from both trials as the best available proxy.

Table 18 below presents the results of the ITC analyses for PFS and OS. Model results based on the subgroup ITC are presented in section 9. Regardless, given the recent announcements from the EMA, which provisionally recommend against starting idelalisib in patients with treatment-naïve CLL with 17p deletion/TP53 mutation, Janssen believes there is now an even stronger unmet medical need in this difficult to treat population.

Table 18: Results of ITC Analyses

Outcome	**Source**	**HR ibrutinib vs. IO (95% CI)**
PFS (all R/R CLL patients)	RESONATE INV 16 months (all patients) vs. Jones et al., 2015 (all patients)	0.39 (0.23 – 0.67)
PFS (R/R CLL with 17p deletion)	RESONATE INV 16 months (17p deletion population) vs. Jones et al., 2015 (17p deletion population)	[redacted]
OS (all R/R CLL patients, used as proxy for 17p deletion population)	RESONATE INV 16 months (all patients) vs. Jones et al., 2015 (all patients)	0.50 (0.24-1.05)

Appendix 8 Details of revised base case and supporting sensitivity analyses

Summary of revised base case

Table 19 below provides a detailed summary, including justifications, on the Committee's preferred base case and the revised base case presented by Janssen in section 9.

Table 19: Summary of revised base case

Parameters	Committee's preferred base case	Janssen revised base case	Justification / notes
Cost calculation	Corrections made to cost calculations	Accept ERG suggestion	Corrections – please see section 8 for details.
Ibrutinib OS curve	Exponential	Accept ERG suggestion	Likely underestimates OS
Ibrutinib PFS curve	Exponential	Weibull	Please refer to section 5 for details.
Ibrutinib treatment discontinuation	PFS	Accept ERG suggestion	Since similar data are not available for IR, using PFS for both is considered appropriate
HR for OS ibrutinib vs. IR	HR unadjusted for cross-over	HR adjusted for cross-over	Please refer to subsection 4.1 for details.
HR for OS ibrutinib vs. PC	HR unadjusted for cross-over	HR adjusted for cross-over	Please refer to subsection 4.1 for details.
Administration costs for PFS on-treatment	Apply dosing intensity to administration costs	Accept ERG suggestion	As this is not a major driver of cost-effectiveness, Janssen concedes this point.
Half cycle correction for ibrutinib cost	Removed half cycle correction	Accept ERG suggestion	As this is not a major driver of cost-effectiveness, Janssen concedes this point.
Dose intensity for BR	Alternative dose intensity of 84.2% to inform BR.	Accept ERG suggestion	As this is not a major driver of cost-effectiveness, Janssen concedes this point.
Terminal care cost	Include terminal care costs for patients that remain alive at the end of the time horizon	Do not include terminal care costs for patients that remain alive at the end of the time horizon.	The ERG preferred case included terminal care costs for those alive at the end of the time horizon. This is not reasonable as those patients have not experienced terminal care. An alternative suggestion to fully capture this would be to extend the modelling horizon to 30 years so that both costs and benefits are fully captured.

BSA	1.79 based on general population estimates	1.85 which takes into account the gender distribution	BSA must be weighted to take into account the gender distribution in RESONATE. The average BSA of 1.79 was reported Sacco et al., 2010 for a UK population with cancer. The population was 60% female, whereas RESONATE had only 32% female. If we reweight the BSA based on the RESONATE gender distribution, the resulting BSA is 1.85.
Utility values	Age-adjust utility values	Accept ERG suggestion	Please see section 6 for details.
PPS utility value	Reduce QoL input	Accept ERG suggestion	Using the alternative 0.6 PPS utility value has minimal impact on the ICER.
Utility for 17p deletion subgroup	Use subgroup-specific utility estimates	Do not use subgroup-specific utility estimate	The sample size for 17p deletion population is very limited to allow for reliable utility estimate for this subgroup.
PC composition	Alternative PC composition excluding R-CHOP	Retain original composition and consider additional evidence.	The original composition was informed by UK clinical opinion. Please see subsections 3.2 and 4.2.3 for details.
Biopsy cost	Remove ongoing biopsy costs	Accept ERG suggestion	No further comment.
Routine follow up cost during PFS	No stratification by responding status. Use stable disease cost for the entire PFS.	Retain the stratification by response	Differentiating costs by response level adds clinical validity to the economic modelling and is supported by both clinical expert opinion and previous NICE precedent (including recently recommended idelalisib plus rituximab).
Infusion cost	Differentiate cost of first infusion and subsequent infusion	Accept ERG suggestion	No further comment.

Sensitivity analysis at list price

Probabilistic sensitivity analysis

Figure 9: ICER scatter plot for ibrutinib at list price vs. PC

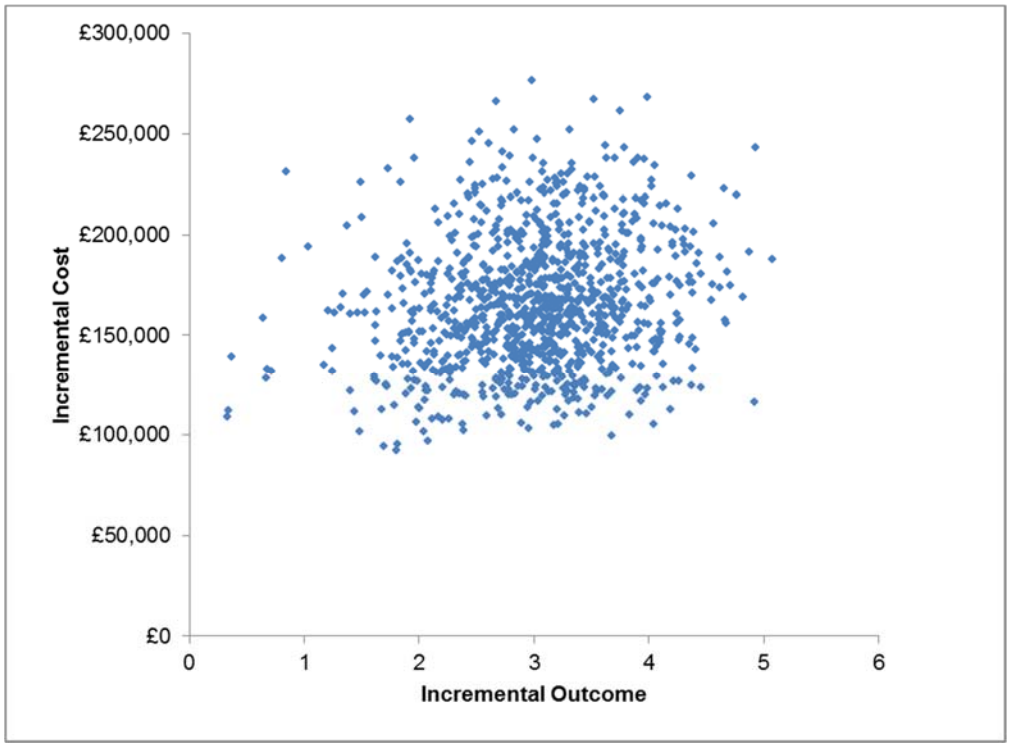


Figure 10: Cost effectiveness acceptability curve for ibrutinib at list price vs. PC

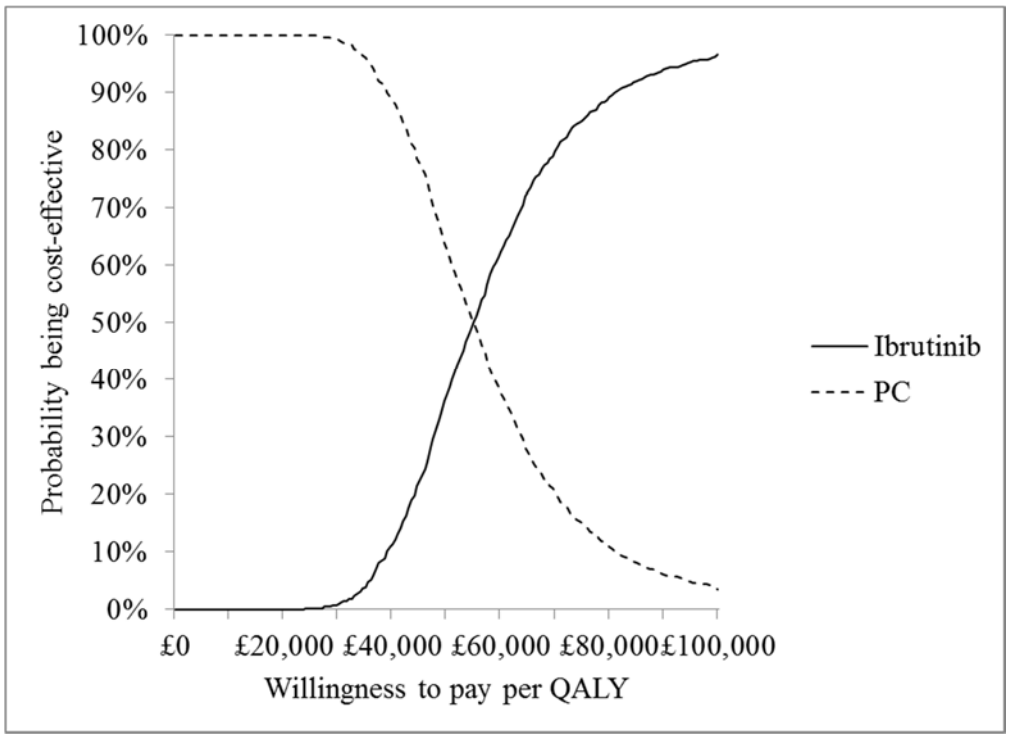


Figure 11: ICER scatter plot for ibrutinib at list price vs. IR

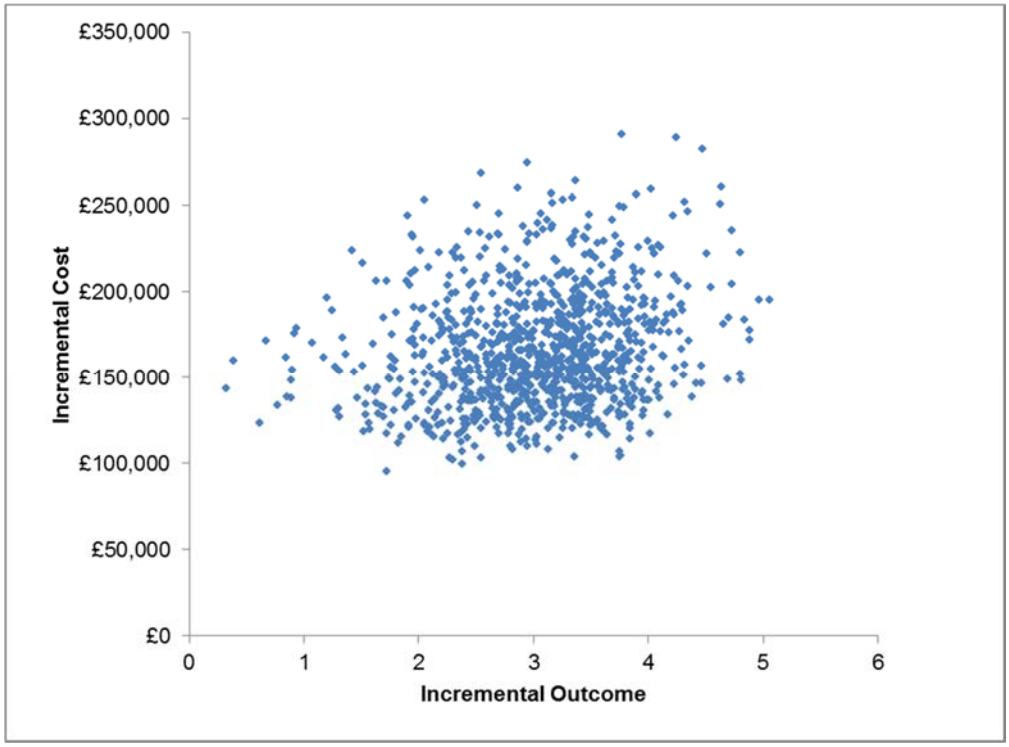


Figure 12: Cost effectiveness acceptability curve for ibrutinib at list price vs. IR

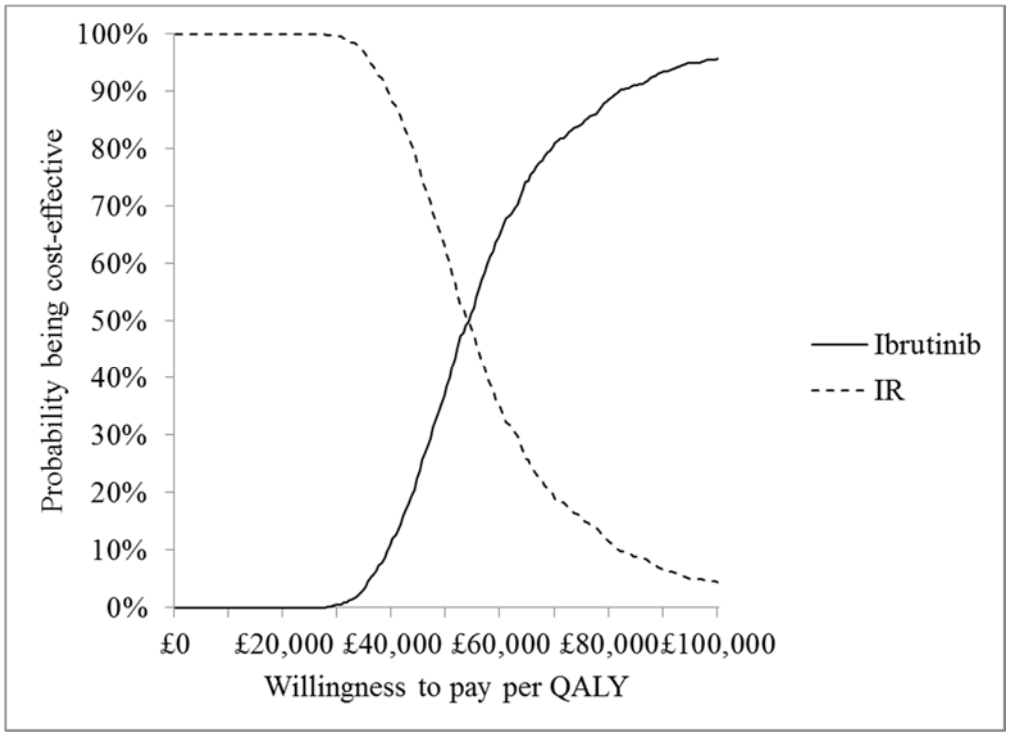


Figure 13: ICER scatter plot for ibrutinib at list price vs. BR

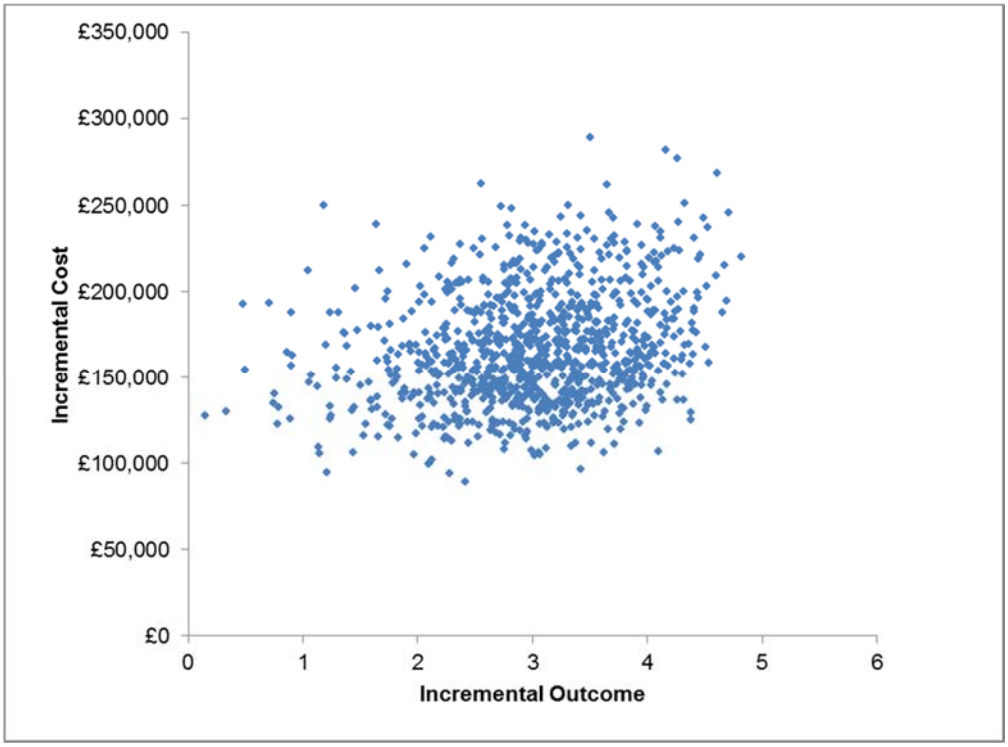


Figure 14: Cost effectiveness acceptability curve for ibrutinib at list price vs. BR

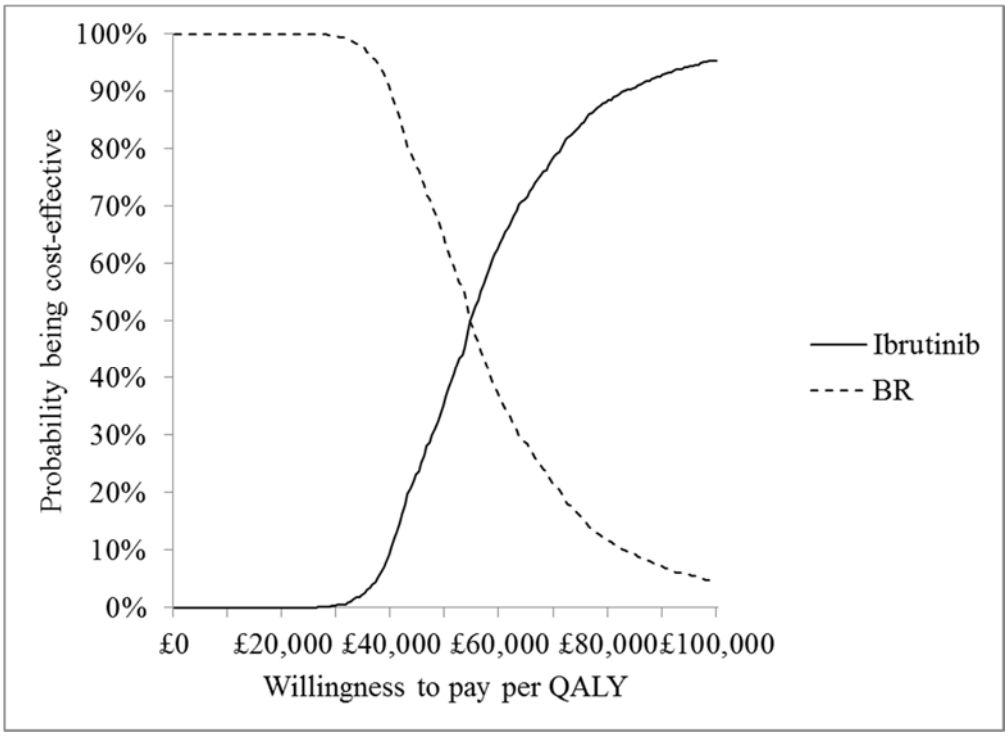


Figure 15: ICER scatter plot for ibrutinib at list price vs. ofatumumab

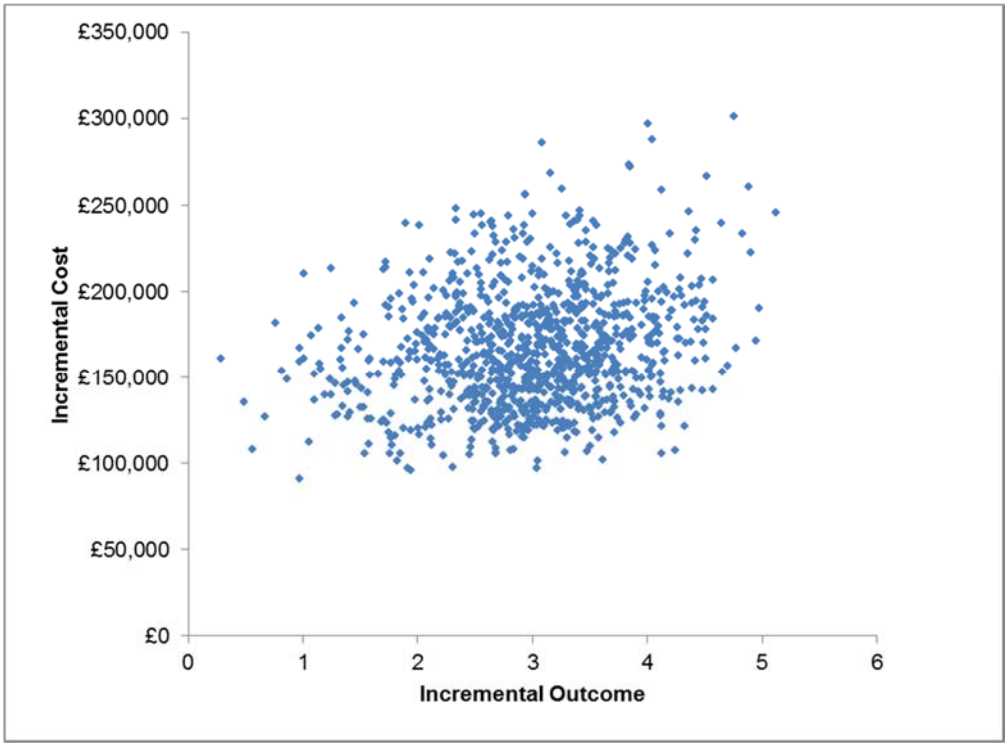
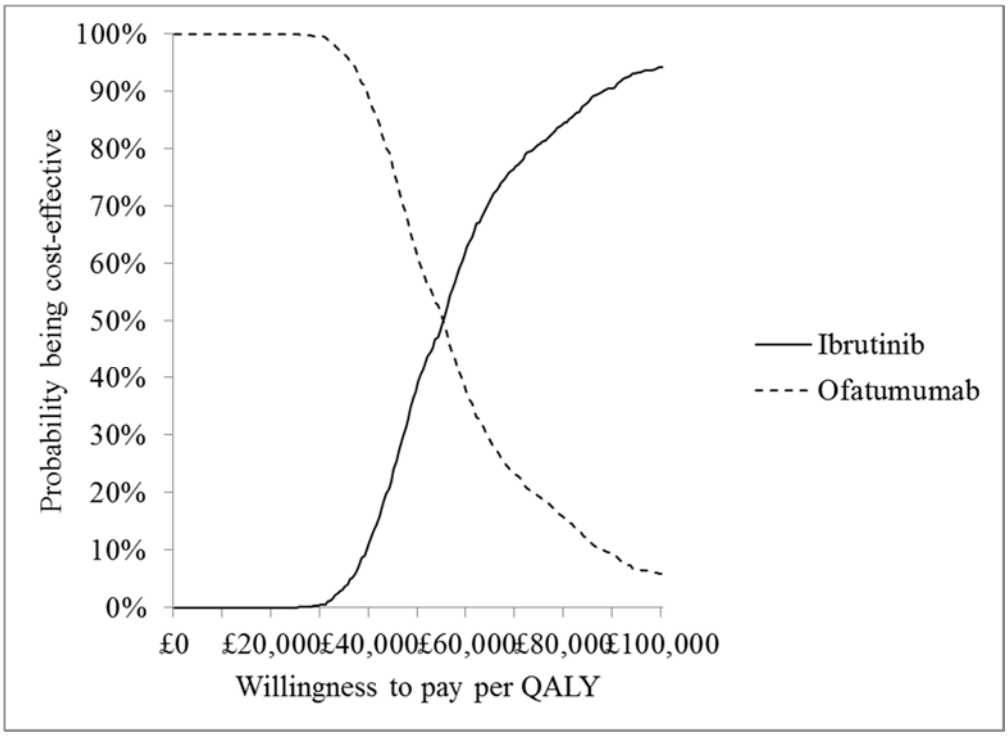


Figure 16: Cost effectiveness acceptability curve for ibrutinib at list price vs. ofatumumab



Deterministic sensitivity analysis

Table 20: Sensitivity analysis results for ibrutinib vs. PC at list price

Parameter	Base case value	Alternative value	ICER (£/QALY)
Base case			52,787
Time horizon	20 years	10 years	65,250
		30 years	51,047
Health discount	3.5%	1.5%	46,206
Cost discount	3.5%	1.5%	56,290
Probability of death during PFS per 4 weeks cycle	0.6%	0.5%	52,869
		0.7%	52,706
% of patients receive subsequent treatment for all comparators	41.90%	33.5%	52,907
		50.3%	52,668
Dosing intensity of ibrutinib	94.8%	100%	50,168
		90%	55,625
Dosing intensity of PC	95.2%	100%	52,614
Cost of routine care and follow up during PFS (£)	Ibrutinib: 416 Physician's choice: 831	20% decrease	51,975
		20% increase	53,600
Cost of routine care and follow up during PPS (£)	845	20% decrease	52,430
		20% increase	53,145
Cost of routine care and follow up for BSC(£)	250	20% decrease	52,412
		20% increase	53,163
Terminal care cost (£)	7,360	20% decrease	52,883
		20% increase	52,692
Baseline utility and utility during PFS	Baseline utility: [redacted] Utility during PFS: [redacted]	Baseline utility and utility during PFS Lower 95% CI	53,851
		Baseline utility and utility during PFS Upper 95% CI	51,765
Utility decrement due to progression	-0.098	20% decrease	52,221
		20% increase	53,367
Duration of AE disutility	14 days	0 day	52,787

Figure 17: Tornado diagram of deterministic sensitivity analysis

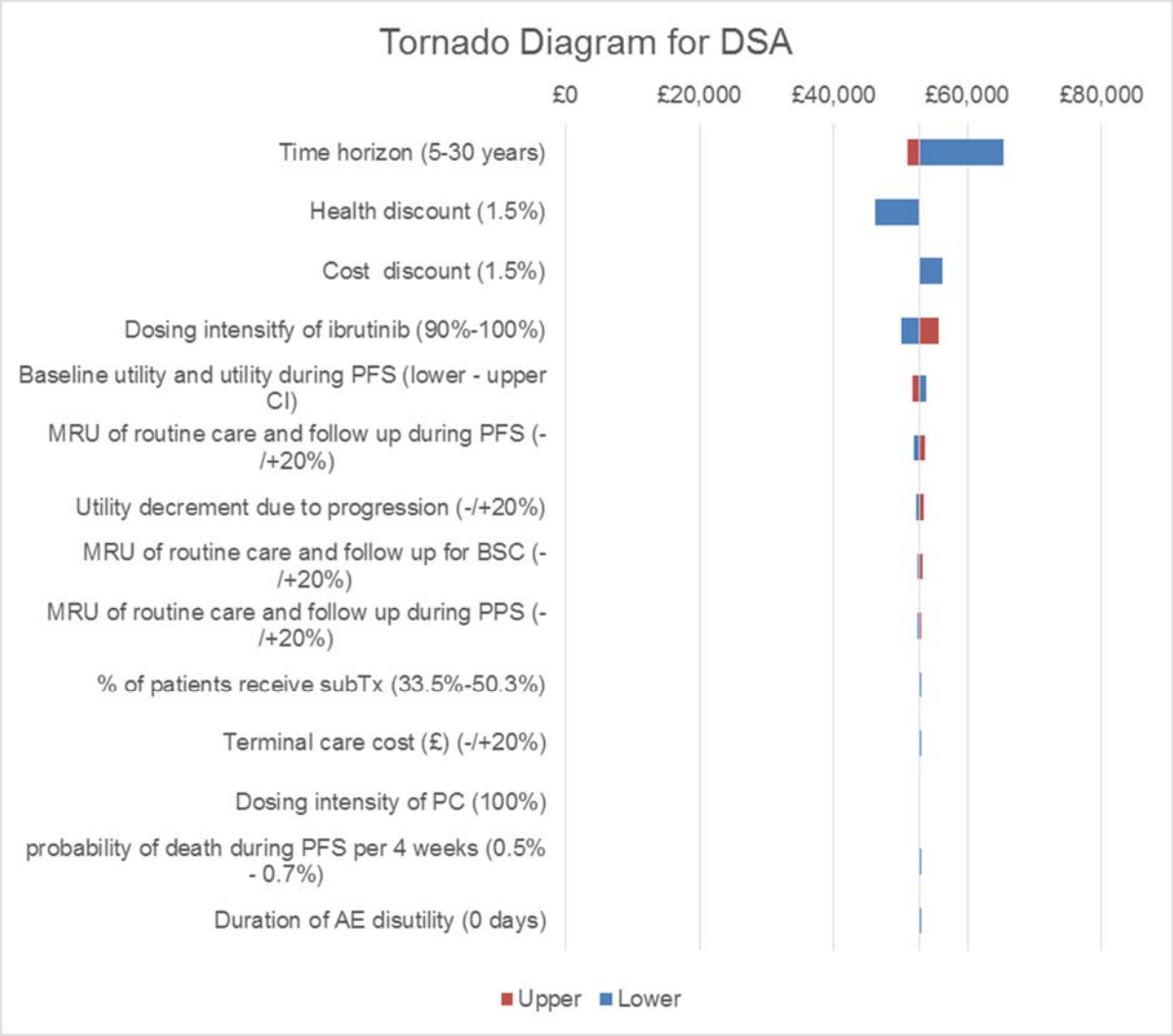


Table 21: Sensitivity analysis results for idelalisib and ofatumumab discount

Variable	Base case	Price discount	ICER (£)
Ibrutinib vs. IO (as a proxy for IR)			
Base case			53,644
Idelalisib price	£51.91 per 150 mg tablet	5% discount	55,154
		10% discount	56,663
		15% discount	58,173
		20% discount	59,683
		25% discount	61,192
		30% discount	62,702
		35% discount	64,211
		40% discount	65,721
		45% discount	67,231
		50% discount	68,740
Base case			53,245
Ofatumumab price	£182 per 20 mg/ml vial of 5 ml	5% discount	53,966
		10% discount	54,687
		15% discount	55,408
		20% discount	56,128
		25% discount	56,849
		30% discount	57,570
		35% discount	58,291
		40% discount	59,011
		45% discount	59,732
		50% discount	60,453

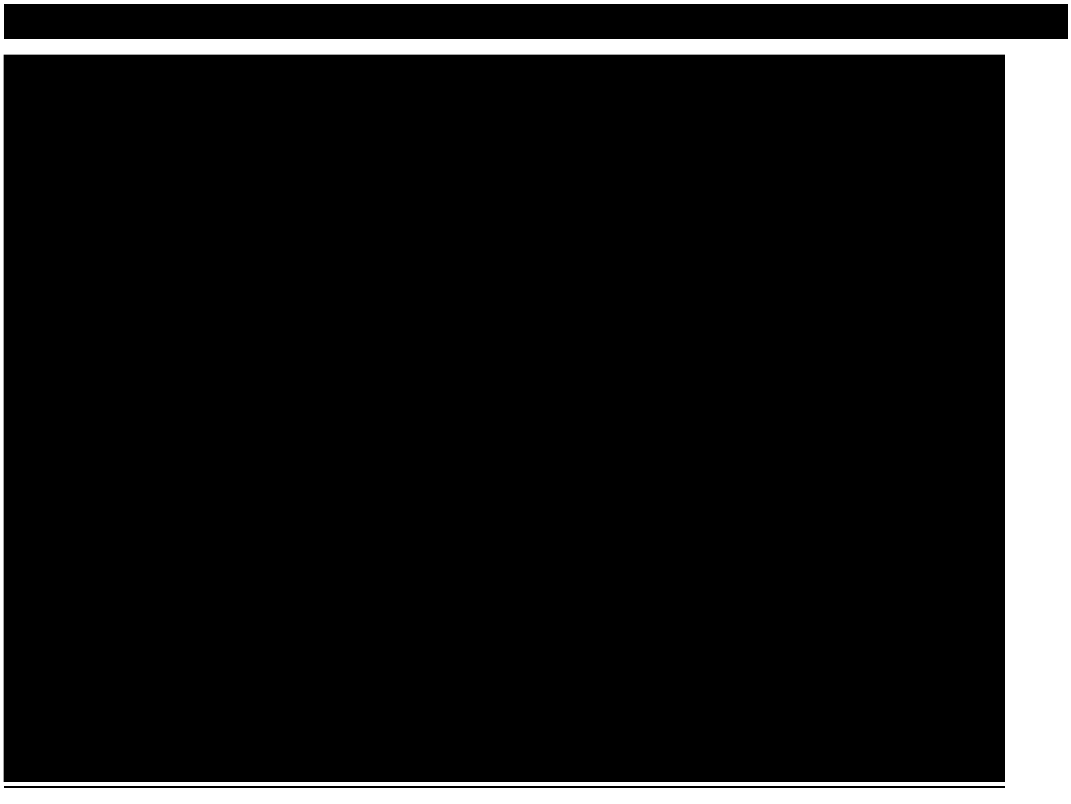
Sensitivity analysis with ibrutinib PAS applied

Probabilistic sensitivity analysis

[redacted]

[redacted]

[redacted]



Deterministic sensitivity analysis

Table 22: Sensitivity analysis results for ibrutinib vs. PC with PAS

Parameter	Base case value	Alternative value	ICER (£/QALY)
Base case			[redacted]
Time horizon	20 years	10 years	[redacted]
		30 years	[redacted]
Health discount	3.5%	1.5%	[redacted]
Cost discount	3.5%	1.5%	[redacted]
Probability of death during PFS per 4 weeks cycle	0.6%	0.5%	[redacted]
		0.7%	[redacted]
% of patients receive subsequent treatment for all comparators	41.90%	33.5%	[redacted]
		50.3%	[redacted]
Dosing intensity of ibrutinib	94.8%	100%	[redacted]
		90%	[redacted]
Dosing intensity of PC	95.2%	100%	[redacted]
Cost of routine care and follow up during PFS (£)	Ibrutinib: 416 Physician's choice: 831	20% decrease	[redacted]
		20% increase	[redacted]
Cost of routine care and follow up during PPS (£)	845	20% decrease	[redacted]
		20% increase	[redacted]
Cost of routine care and follow up for BSC(£)	250	20% decrease	[redacted]
		20% increase	[redacted]
Terminal care cost (£)	7,360	20% decrease	[redacted]
		20% increase	[redacted]
Baseline utility and utility during PFS	Baseline utility: [redacted] Utility during PFS: [redacted]	Baseline utility and utility during PFS Lower 95% CI	[redacted]
		Baseline utility and utility during PFS Upper 95% CI	[redacted]
Utility decrement due to progression	-0.098	20% decrease	[redacted]
		20% increase	[redacted]
Duration of AE disutility	14 days	0 day	[redacted]

Table 23: Sensitivity analysis results for idelalisib and ofatumumab discount with ibrutinib PAS

Variable	Base case	Price discount	ICER (£)
Ibrutinib vs. IO (as a proxy for IR)			
Base case			[redacted]
Idelalisib price	£51.91 per 150 mg tablet	5% discount	[redacted]
		10% discount	[redacted]
		15% discount	[redacted]
		20% discount	[redacted]
		25% discount	[redacted]
		30% discount	[redacted]
		35% discount	[redacted]
		40% discount	[redacted]
		45% discount	[redacted]
		50% discount	[redacted]
Base case			[redacted]
Ofatumumab price	£182 per 20 mg/ml vial of 5 ml	5% discount	[redacted]
		10% discount	[redacted]
		15% discount	[redacted]
		20% discount	[redacted]
		25% discount	[redacted]
		30% discount	[redacted]
		35% discount	[redacted]
		40% discount	[redacted]
		45% discount	[redacted]
		50% discount	[redacted]

Appendix 9 Factual inaccuracies in the ACD

Major discussion points have been addressed in the main body of this response. Minor factual inaccuracies and/or errors are tabulated here:

Section & page of ACD	Issue	Correction
Section 2.1; Page 3	Ibrutinib is "a monoclonal antibody"	Factually inaccurate. Ibrutinib is an oral, once-a-day, covalent Bruton's tyrosine kinase inhibitor.
Section 3.1; Page 4	"No people with the TP53 mutation were included in the trial."	Factually inaccurate. Patients enrolled in RESONATE were not explicitly tested for the TP53 mutation; therefore, there most certainly would have been TP53 mutations amongst the 391 patients.
Section 3.3; Page 5	"The trial protocol permitted patients randomised to switch to ibrutinib on progression of disease."	Factually inaccurate. Cross-over was only permitted following a protocol amendment.
Section 3,4; page 5	"The company also explored adjusting for crossover by XXX"	Typographical error. Should this state "RPSFT"?
Section 3.4 and 3.7; pages 5 and 7	"116 patients crossed over" "(120 of 196 patients crossed over)"	Factually inaccurate. At the 16-month data cut, 120 of 196 patients had crossed over (61.2%).
Section 3.8; page 7	"overall infection rates were higher with ibrutinib"	Factually incorrect. As it is a rate, it should be corrected for drug exposure.
Section 3.13; page 10	"which limited the sample size to 30 patients"	Factually inaccurate. This is the *effective* sample size which is an important distinction in MAIC methodology.
Section 3.13; page 10	"HELIOS, an unpublished trial"	Factually inaccurate. This trial has now been published.
Section 3.18; page 11	"Osterborg trial was not supported by a peer-reviewed publication"	Factually inaccurate. This trial has now been published.
Section 4.7; page 28	"the committee acknowledged that the company had re-analysed the data at 16 months in November 2014 (approximately 11 months before the company submitted its evidence to NICE"	Factually inaccurate. As explained by the clinical expert during the first appraisal committee meeting, neither companies nor investigators can ad hoc request new data cuts of trials due to the statistical rigour this would require. The data cut upon which the interim analysis for RESONATE was conducted had a median follow-up of 9.4 months (and therefore, the interim data is often referred to as the 9.4-month data); the subsequent data cut upon which updated analysis of RESONATE was conducted had a median follow-up of 16 months (and therefore, this data if often referred to as the 16-month data).
Section 4.18; page 35	"with a median age of 70 years, a time horizon of	Factually incorrect. Median age was 67 years at model start.

	20 years might be too long"	
Section 4.22; page 37	"clinical experts…would not expect the utility values in the post-progression health state to be as high"	Factually inaccurate. The Committee presented the incorrect utility value to the clinical experts during the first appraisal committee meeting (the baseline utility rather than the baseline with the utility decrement applied was presented) and hence the views of the clinicians were of the incorrect value and this point should be disregarded.
Section 4.28; page 40	"the committee was aware that the company itself manages a CLL registry"	Factually inaccurate. The registry mentioned by the Committee – CLL Inform – started enrolment in September 2015, one month before the submission to NICE. Therefore, there were no suitable analyses from this registry to inform the submission.

Dear NICE Technology Appraisal Committee B,

RE: ibrutinib (Imbruvica®) – ID 749 – chronic lymphocytic leukaemia

We are writing on behalf of chronic lymphocytic leukaemia (CLL) patients in response to the recently published appraisals consultation document relating to ibrutinib (Imbruvica®) – ID 749 - for treating chronic lymphocytic leukaemia.

We are extremely disappointed by the committee's preliminary decision not to recommend ibrutinib for treating chronic lymphocytic leukaemia, that is either: for people who have had at least 1 prior therapy or, for people with 17p deletion or TP53 mutation in whom chemo-immunotherapy is unsuitable[1].

We ask you to reconsider your preliminary recommendation for the following reasons:

1) **Comparators and limited treatment options**

The committee discussed the relevant comparators for each of the two populations and concluded that for people who have had at least one prior therapy idelalisib plus rituximab was the most relevant comparator[2] and that bendamustine was most likely to be used in those for whom this was not appropriate. Bendamustine has recently been withdrawn from the cancer drugs fund (CDF) in this setting, although we understand it is still available in some parts of the NHS, access is inconsistent and is now restricted in some areas. The committee also concluded that the only comparator in the '17p deletion or TP53 mutation' population was idelalisib plus rituximab[3]. We therefore strongly recommend that ibrutinib is made available to extend the very limited options available to treat both populations.

We would also like to raise our concerns regarding the committee's decision not to allow comparison to ofatumumab as part of this appraisal[4], which was the control arm of the RESONATE trial. Whilst it is true to say that ofatumumab is now rarely used as a monotherapy in UK clinical practice, this has happened since the availability of ibrutinib and idelalisib. Ofatumumab was removed from the CDF in March 2015[5], after the analysis of the trial data by Janssen in November 2014. As such, at the point that ibrutinib had "demonstrated extended progression-free survival compared with ofatumumab"[6], this was a relevant part of UK clinical practice. The decision by the committee not to accept ofatumumab as a comparator has created a great deal of uncertainty as the remaining data is extrapolations and estimates. The fact that the availability of ibrutinib and idelalisib has since led to ofatumumab not being used in UK clinical practice should not penalise this appraisal.

[1] Ibrutinib ACD, pg. 3
[2] Ibrutinib ACD, pg. 27
[3] Ibrutinib ACD, pg. 27
[4] Ibrutinib ACD, pg. 28
[5] https://www.england.nhs.uk/wp-content/uploads/2015/01/ncdf-summ-ofatumb-relps-rfrct-cll.pdf
[6] Ibrutinib ACD, pg. 28

As such, in this situation there are limited treatment options, particularly for patients unsuitable for, or unable to tolerate, treatment with idelalisib plus rituximab. Clinical experts commented that wherever possible treatment with ibrutinib is preferred because of the unpredictable adverse events associated with idelalisib[7]. Since the committee meeting additional information regarding the incidence and severity of adverse events have come to light. This has resulted in the European Medicines Agency (EMA) issuing new safety measures for the use of idelalisib[8] while the medicine is being reviewed. If the EMA licence for idelalisib is revoked then options for patients will be further limited, leaving a void in treatment options for the appraisal indication. In light of the emerging toxicity issues of idelalisib there is a clear need for multiple options to ensure that clinicians and patients can access the treatment which is most clinically appropriate. This need is further emphasised by the suspension of ongoing idelalisib clinical trials (due to concerns over toxicity and infection-related death), with a consequent limitation in treatment options for patients.

During a 2015 CLL PAG and LLS Canada survey, carers were asked about the challenges of adverse effects of treatment and commented that: "Dealing with their patient's often-serious treatment induced side effects was mentioned as major reasons for stress." One patient commented that ibrutinib offered "Better remissions. Less side effects. A more hopeful future." Access to Ibrutinib is therefore of great importance to offer effective alternative treatment options for these patients.

2) A Need for Additional Treatment Options

We would also like to emphasise the importance of access to additional effective treatment options. As recognised in the ACD document[9], once treatment is stopped because of disease progression, if no other treatment is available, survival is poor and additional treatment options are very valuable. Patients who have received idelalisib and have progressed or experienced a severe adverse event, for which ibrutinib would be the appropriate follow-up therapy would have extremely limited options. It is important that CLL patients whose disease is extremely heterogeneous have a number of options as the disease tends to respond less well to each line of therapy, with shorter subsequent remissions. Whilst the committee has drawn attention to uncertainty around the benefits of ibrutinib, it is clear that at the very least it would provide an additional option for those who have exhausted, or are unsuitable for, currently available options.

During the 2015 CLL PAG and LLS Canada survey; patients and caregivers were asked what was important to them in any new treatment, 95% of patients indicated they wanted longer remissions with less toxicity, with the remainder referencing having treatment choices and more knowledge on the treatments. In the same survey 96% of patients indicated it was important to have choices available for CLL treatment. Assigning a rating of 5, 6 or 7 on a scale of 1-7, where 1 indicates not important and 7 indicates very important - 84% of responses rated this 7. Patients said: "Each 'flavour' of CLL is different, it needs to be a patient by patient decision" as "CLL is very complex

[7] Ibrutinib ACD, pg. 25 and 33

[8] www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Zydelig_20/Procedure_started/WC500203473.pdf

[9] Ibrutinib ACD, pg. 24

and you need a range of treatments to meet all complexities." One patient said that the "most important thing is to treat the CLL from the perspective that treatment is tailored to my version of the disease - better a scalpel than a chainsaw."

3) End of Life

Criteria:

1. The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
2. There is sufficient evidence to show that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
3. The treatment is licensed or otherwise indicated for small patient populations.

We believe that ibrutinib satisfies the criteria for end of life classification for the following reasons:

Ibrutinib appears to overcome biological disease characteristics such as 17p deletion/ TP53 and unmutated igVH status that limit effective treatment with chemotherapy and therefore considerably extend life for a patient group with few options available to them. Treatment options are very limited for this group and patients relapsing early from previous chemo–immunotherapy have survival predictions that are poor and under 24 months. The Tam paper in Blood, 2014[10] evidences poor survival for those who relapse early from FCR in a population that was predominantly young. Those relapsing under one year had a 13 month median OS, while those relapsing after 1-3 years had a median OS of 27 months. This indicates that a significant majority of the patients who are relapsing early in this group have predicted survivals of fewer than 24 months. As these patients were predominantly younger fitter patients, older or less fit patients who relapse within 3 years will have a predicted life expectancy of fewer than 24 months, as per 'end of life' criteria 1.

It is also clear that ibrutinib and idelalisib are evidencing great improvements in survival for these groups and indicates that there are OS improvements in excess of three months as per 'end of life' criteria 2 'There is sufficient evidence to show that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.' In light of the toxicity concerns being raised regarding idelalisib[11], which have caused alarm and anxiety in the patient community, the OS benefit of ibrutinib should be compared against treatments other than idelalisib (as it will not be an appropriate comparator if the EMA licence is revoked). As recognised in the ACD "before idelalisib had been recommended as a treatment option, patients lived for a shorter length of time"[12]. In its absence, ibrutinib therefore clearly satisfies this criteria. If ibrutinib is not made available for this group and patients relapsing within 3 years of FCR, then patients will die within 24 months. A positive FAD that makes Ibrutinib available will extend survival of patients

[10] http://www.bloodjournal.org/content/124/20/3059?sso-checked=true
[11] http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Zydelig_20/Procedure_started/WC500203473.pdf
[12] Ibrtuinib ACD, pg. 40

relapsing after previous treatments and will also offer improvements to QOL, giving patients the ability to carry out tasks of daily living and not just extend life. For younger patients this may also include a return to work.

With regards to the requirement that the treatment is licensed or otherwise indicated for small patient populations (criteria 3), as ibrutinib received orphan designation from the EMA[13], we believe it satisfies this criteria.

We strongly believe there is sufficient evidence and argument that confirms ibrutinib fulfils these requirements. Therefore we urge the committee to reconsider your preliminary recommendation and apply the end of life criteria to this appraisal.

4) Toxicity and Quality of Life

We would also like to draw attention to the potential quality of life benefits associated with ibrutinib, which we feel has a number of potential advantages that ought to be highlighted. CLL is a chronic and incurable condition that impacts greatly on the physical and emotional health of patients who are living with a significant symptom burden and the complications of treatment.

Ibrutinib is a very well tolerated treatment that has a preferable toxicity profile (compared to the comparator - idelalisib plus rituximab), with "minimal, "mild" and "manageable" side effects. It offers improved symptom control (often "immediately") and patients report an "amazing quality of life". It is also an easily administered oral treatment offering convenience, reduced travel to hospital, reduced hospital time, independence and avoids the need for infusions (and potential infusion reactions). Patients who have been treated with ibrutinib have described it as "remarkable", "life-saving", a "miracle pill" that has "given my life back" so that they can live their life "as if I had no disease whatsoever". As this quality of life information is not appropriately captured by the EQ-5D it is likely that these benefits have been underestimated in the model. It is imperative that the QALY is adjusted to take into account these considerations and ensure that these quality of life benefits are not overlooked.

In the survey carried out by CLL PAG and LLS Canada, 42/45 (93.3%) of the patients and carers reported their experience of ibrutinib as 'positive'. Of the remaining 3, one stated "too soon to tell", one thought they were "not experiencing the full effects of the drug" at the 3-month point and one stated "nothing positive or negative". Patient comments include:

- "Saved my life. The remarkable thing about most patients in my early trial for relapsed and refractory patients was how rapidly we all felt so much better".
- "Preserving quality of life while being treated is important...if the treatment is worse that the disease it makes it hard to be optimistic."
- "I started to feel better immediately and it impacted my lymph nodes very quickly. The side effects so far are minimal and most of my blood counts are in the normal range after a year".

[13] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/003791/WC500177778.pdf

- “It has been an incredibly positive experience.”
- “Amazing quality of life for more than last 3 yrs & no chemo infusions!!”
- “Currently available treatments put me at risk of further reductions in my already badly compromised immunity, both during treatment and after treatment.”
- “No side effects. I had been actively dying. I am alive and active. At this point, my CBCw diff is very near normal. I am not taking Rituxin with ibrutinib. To my eyes, my ibrutinib pill sparkle. I'm very thankful for them. 78 yrs. of age”.
- “It has been a miracle pill for me. My lymph nodes have reduced as much as 50%, I have reduced pain, breathing better, have more energy than before and I am no longer at death's door. My biggest negative is that my white cell count has increased from 4 to 60. I still have fatigue, but I am so much better. Overall it is far easier than any chemotherapy or biologic that I have had before”.

Survey respondents noted that the ibrutinib drug regime has changed their long-term health and wellbeing with these comments:

- “Regained my health to where I hardly think of having leukaemia. I am living my life as if I had no disease whatsoever.”
- “I was diagnosed with three cancers at once…. breast, fallopian tube and CLL. CLL was the cancer without a hopeful outcome until ibrutinib was available.”
- “Ibrutinib has taken me from an actively dying man to a man who is increasingly active - both physically and mentally. I have hope. I don't see the pain in my wife's eyes. I see joy and hope.”
- “Prolonging my life so I can continue to pay taxes and keep the economy going.”
- “I feel like I've been given my life back. I'm not limited in any physical way. What an extraordinary drug this has been.”

Patients sharing their personal story**:**

- “At ibrutinib focus group meeting, I was surprised as to all the patients with previous treatments who are now leading normal sick-free lives.... thanks to Ibrutinib”.
- “Getting ibrutinib on a clinical trial before it was approved was life saving”
- “3 1/2 yrs ago when I relapsed after achieving a CR with FCR treatment, I thought my only real chance at seeing any long term remission was a stem cell transplant with a 50/50 shot of dying. Ibrutinib gave me my life back.”

5) Carers

Impact on carers are rarely publicised, the 2015 CLL PAG and LLS Canada caregivers and patients survey elicited comments from carers that may aid the with understanding carers challenges:

Respondents cited financial concerns, mental stress and emotional turmoil brought on by their exhausting care-taking duties. 15/19 who responded to the LLSC caregiver survey cited depression, 8/19 cited fear and 13/19 cited anxiety. Seven of nineteen (36.8%) experienced financial difficulties, 6/19 specifically suffered loss of income due to their partner's cancer diagnosis and treatment, 4/19 cited transportation costs.

Caregiver duties included doing research online in journal articles, online postings and interviews to discover potentially available treatments for their ailing partners, becoming familiar with side effects of various therapies and how to deal with those. Caregivers have to ensure patients attend their medical appointments, accompany them during often very time consuming therapy sessions, ensure that the patients followed their physicians' instructions and monitor their condition round the clock. "I try to keep abreast of developing therapies such as the targeted treatments and to provide such information as my husband might want".

The survey also noted the impact of treatment on carers. This noted that caregivers had to take on all previously shared household duties including meal preparation, shopping, etc. Their own careers suffered because caregivers were too exhausted to fully concentrate on their own careers and sometimes had to give up their jobs to take care of their partners or parents. "I quit my job to take care of parent with CLL". Thirteen of nineteen caregiver respondents cited fear of recurrence and 6/19 feared that another family member would be diagnosed. "Unfortunately CLL never truly goes away so we're constantly on edge wondering when it will return again and what treatment will be available to him when it does."

As such, the benefits of ibrutinib felt by patients will be equally felt by caregivers, who will also experience a significant improvement in their quality of life.

6) Equalities

In addition, we would also like to highlight the potential equality issue relating to the improved tolerability of ibrutinib. Patients unable to tolerate alternative treatments are mostly older, less fit and high-risk patients. Age is a characteristic protected by the equality legislation, with older patients more likely to be unable to tolerate alternative options, any decision not to recommend ibrutinib could unduly impact on older patients contrary to the equality legislation.

7) Uncertainties

Throughout the ACD there are numerous references to the 'uncertainty' of the data relating to ibrutinib. As highlighted by the fact that new information has recently come to light regarding adverse events associated with idelalisib (see point 1 above), the data of other comparators is also uncertain.

In addition, we must also consider the wider landscape to indicate why the ibrutinib data remains 'uncertain'. Ibrutinib is an innovative treatment that has been licenced on phase 2 clinical trial data, so the data available from the ongoing phase 3 trial RESONATE is immature with median PFS and OS yet to be reached in the ibrutinib arm of the study. This data is not available because at the

point of data collection, patients in this arm were still receiving and responding to treatment. We do not consider it appropriate that this is being viewed as 'uncertainty' which is preventing NICE from being able to recommend ibrutinib as a cost-effective use of NHS resources.

We hope that you will bear our comments in mind when considering your final recommendation.

Ibrutinib has the potential to improve and extend the lives of CLL patients. We urge you to reconsider your recommendation and make it available so that patients can benefit from it.

Kind Regards,

[redacted]

Leukaemia CARE **CLL Support Association**

Blood and Lymphatic cancers
Leukaemia CARE
supporting a quality of life
Registered charity 259483 and SC039207

CLLSA

Points for revision – [redacted]:

2.1
“Ibrutinib (Imbruvica, Janssen) is a monoclonal antibody that inhibits B-cell proliferation,…….”

Ibrutininb is NOT a monoclonal antibody but it is part of the category of “small molecule kinase inhibitors” by inhibiting BTK function.

It is not clear if Ibrutinib inhibits B-cell “proliferation” nor to promote cell death in VIVO. It acts by inhibiting BTK mediated cell signalling with consequences on survival and homing of the tumour CLL cells. I would suggest to reformulate the sentence by saying that inhibits B-cell proliferation in vitro

3.2
Response assessment of resonate-2 was according to the “revised” IWCLL criteria (Kipps, Cheson, JCO), which includes PR+L, which is a category not previously described in the original IWCLL 2008 criteria.

3.3
“The company also explored adjusting for crossover by XXX” what does it mean?

3.8
“The company presented crossover adjusted hazard ratios using the rank-preserving structural failure time approach for the overall population and for the 17p deletion subgroup, but these were academic-in-confidence.” Should the committee not be allowed to review those data?

3.10
Company did not mention Ibrutinib+Rituximab as comparator R/R CLL patients (Burger JA, Lancet Oncol. 2014 Sep;15(10):1090-9.)

3.10
did company presented data in relation to recent toxicity reported by idelalisb based study? This is relevant because 17p- CLL is an unmet clinical need and no effective medications are now available.

3.15
The company did not present RESONATE-2 data for 17p- CLL requiring first treatment (Burger JA, N Engl J Med. 2015 Dec 17;373(25):2425-37.) and did not detail results from Farooqui MZ, Lancet Oncol. 2015 Feb;16(2):169-76. Or Burger JA, Lancet Oncol. 2014 Sep;15(10):1090-9.

Summary of appraisal committee’s key conclusions:

these are likely inaccurate in light of the recent EMA findings on Idelalisib based treatments and on the likely withdrawal of licence/indication for 17p- CLL requiring treatment for the first time.
In particular “The committee concluded that there was considerable uncertainty around the progression free and overall survival benefits of ibrutinib compared idelalisib plus rituximab…” may be incorrect.

Also point 4.2, “….CLL who have received at least 1 prior therapy with fludarabine”. Literature data does not point to identifying R/R CLL benefiting from ibrutinib solely in the category of previously treated with fludarabine-based therapies, but any R/R patient following any combination of (immuno)chemotherapy.

・ Has all of the relevant evidence been taken into account?

Please see above for specific comments. Overall, the data presented are from Resonate study with ibrutinib versus ofatumomab. Ofatumomab single agent is not ideal comparator for R/R CLL patients in Europe.

The committee may benefit from evidence from the following publications

1: Burger JA, et al; RESONATE-2 Investigators. Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia. N Engl J Med. 2015 Dec 17;373(25):2425-37. doi: 10.1056/NEJMoa1509388. Epub 2015 Dec 6. PubMed PMID: 26639149; PubMed Central PMCID: PMC4722809.

2: Jaglowski SM, et al. Safety and activity of BTK inhibitor ibrutinib combined with ofatumumab in chronic lymphocytic leukemia: a phase 1b/2 study. Blood. 2015 Aug 13;126(7):842-50. doi: 10.1182/blood-2014-12-617522. Epub 2015 Jun 26. PubMed PMID: 26116658; PubMed Central PMCID: PMC4536539.

3: Brown JR, et al. The Bruton tyrosine kinase inhibitor ibrutinib with chemoimmunotherapy in patients with chronic lymphocytic leukemia. Blood. 2015 May 7;125(19):2915-22. doi: 10.1182/blood-2014-09-585869. Epub 2015 Mar 9. PubMed PMID: 25755291; PubMed Central PMCID: PMC4424415.

4: Farooqui MZ, et al. Ibrutinib for previously untreated and relapsed or refractory chronic lymphocytic leukaemia with TP53 aberrations: a phase 2, single-arm trial. Lancet Oncol. 2015 Feb;16(2):169-76. doi: 10.1016/S1470-2045(14)71182-9. Epub 2014 Dec 31. PubMed PMID: 25555420; PubMed Central PMCID: PMC4342187.

5: Hallek M, et al. The HELIOS trial protocol: a phase III study of ibrutinib in combination with bendamustine and rituximab in relapsed/refractory chronic lymphocytic leukemia. Future Oncol. 2015;11(1):51-9. doi: 10.2217/fon.14.119. PubMed PMID: 24901734.

6: Burger JA, et al. Safety and activity of ibrutinib plus rituximab for patients with high-risk chronic lymphocytic leukaemia: a single-arm, phase 2 study. Lancet Oncol.

2014 Sep;15(10):1090-9. doi: 10.1016/S1470-2045(14)70335-3. Epub 2014 Aug 20. PubMed PMID: 25150798; PubMed Central PMCID: PMC4174348.

7: Byrd JC, et al; RESONATE Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014 Jul 17;371(3):213-23. doi: 10.1056/NEJMoa1400376. Epub 2014 May 31. PubMed PMID: 24881631; PubMed Central PMCID: PMC4134521.

8: O'Brien S, et al. Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: an open-label, multicentre, phase 1b/2 trial. Lancet Oncol. 2014 Jan;15(1):48-58. doi: 10.1016/S1470-2045(13)70513-8. Epub 2013 Dec 10. PubMed PMID: 24332241; PubMed Central PMCID: PMC4134524.

9: Byrd JC, et al. N Engl J Med. 2013 Jul 4;369(1):32-42. doi: 10.1056/NEJMoa1215637. Epub 2013 Jun 19. Erratum in: N Engl J Med. 2014 Feb 20;370(8):786. PubMed PMID: 23782158; PubMed Central PMCID: PMC3772525.

・ Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

As a non expert economist on cost effectiveness , I find the interpretations reasonable, based on the current literature.

・ Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

Please see comment above re summary at point 4.2 (“….CLL who have received at least 1 prior therapy with fludarabine”.) Literature data does not point to identifying R/R CLL benefiting from ibrutinib solely in the category of previously treated with fludarabine-based therapies, but any R/R patient following any combination of (immuno)chemotherapy.

・ Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

no

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE
Appraisal consultation document

Ibrutinib for treating chronic lymphocytic Leukaemia

February 2016

Comments from Dr G Follows on behalf of the UK CLL Forum

Cambridge, March 2016

As clinicians with large CLL practices we are clearly disappointed with the NICE draft recommendation not to approve ibrutinib for use in the NHS to treat chronic lymphocytic leukaemia.

We are encouraged that the review committee has taken on board key messages from the clinical experts and patient experts that ibrutinib is an efficacious drug in CLL with a better toxicity profile than idelalisib/rituximab (section 4.13). The committee has also noted the excellent quality of life noted by the majority of CLL patients taking ibrutinib (section 4.21) and acknowledged that where clinicians / patients have an appropriate clinical choice between ibrutinib and idelalisib/rituximab, then with the majority of cases, the choice would be for ibrutinib (section 4.13). This decision is primarily driven by concerns about the idelalisib side effect profile and is further emphasised by the recent suspension of idelalisib clinical trials because of concerns over toxicity and infection related death.

Concerns from a clinical perspective:

1. **<u>The entry criteria for the key RESONATE trial appear to be incorrectly noted.</u>**

To clarify from the original paper:

RESONATE inclusion criteria from Byrd et al NEJM 2014

1. Must have received at least one prior therapy for CLL/SLL and not be appropriate for treatment or retreatment with purine analog–based therapy, defined by at least one of the following criteria:

a. Failure to respond (stable disease or disease progression on treatment), or a progression-free interval of less than 3 years from treatment with a purine analog– based therapy and anti-CD20–containing chemoimmunotherapy regimen after at least two cycles.

b. Age ≥70 years, or age ≥65 and the presence of comorbidities (Cumulative Illness Rating Scale [CIRS] ≥6 or creatinine clearance<70 ml/min) that might place the patient at an unacceptable risk for treatment-related toxicity with purine analog–based therapy, provided they have received one or more prior treatment including at least two cycles of an alkylating agent–based (or purine analog–based) anti-CD20 antibody–containing chemoimmunotherapy regimen. CIRS score can be determined using a web-based tool.

c. History of purine analog–associated autoimmune anemia or autoimmune thrombocytopenia.

d. Fluorescent hybridization showing del17p in ≥20% of cells (either at diagnosis or at any time before study entry) either alone or in combination with other cytogenetic abnormalities, provided the patient has received at least one prior therapy.

Clearly the RESONATE trial is the major prospective randomised trial upon which this appraisal is based. It is therefore important to realise that:

1. While the majority of RESONATE patients would have been treated previously with chemotherapy+anti-CD20, this was not restricted to fludarabine + chemotherapy (section 4.2 incorrectly states this, and incorrectly states that *'clinical experts ….would wish to offer ibrutinib to patients who had had at least 1 round of fludarabine-containing chemo-immunotherapy'*). Older patients / less fit may have been treated with other combinations such as an alkylator + anti-CD20, and as clinical experts we would very much like to use ibrutinib for patients following alkylator + anti-CD20. This is very important going forward, as NICE-approved first line therapy for less fit CLL patients is either ofatumumab+ chlorambucil or obinutuzumab + chlorambucil, i.e. alkylator+ anti-CD20.

2. Patients with 17p deletion could be included in RESONATE as long as they had received one prior line of therapy, i.e. there was no requirement for chemotherapy + anti-CD20 in the presence of 17p deletion.

We believe that the majority of UK clinicians would still prefer to use ibrutinib broadly within the resonate trial entry criteria rather than the marketing authorisation (which does not have any specification of prior treatment or time restrictions on remission duration)

2. Ofatumumab as a control arm in RESONATE

From our perspective, it appears unfairly biased against ibrutinib to state that ofatumumab (the control arm of the RESONATE trial) is not an appropriate comparator reflective of UK practice (section 4.3). Please remember that it was the introduction of ibrutinib that led directly to the removal of ofatumumab from the CDF. When RESONATE was recruiting, ofatumumab was the only licensed therapy in this indication and of note, NICE have previously accepted the control arm of the idelalisib 116 trial, which was rituximab monotherapy. This antibody does not have monotherapy license in CLL and has never been used by UK clinicians as monotherapy in R/R CLL.

3. Concern regarding access to bendamustine

In the summary part of the document it states that:

'The treatment options currently used in England in the NHS for CLL are:

- *Bendamustine plus rituximab for patients with refractory or relapsed CLL whose disease progresses 24 months after the end of previous treatment and in whom further treatment with a fludarabine containing compound is inappropriate.'*

Bendamustine has been withdrawn from the CDF. I understand the drug is now generically available, but there is very inconsistent access to the drug in different parts of the NHS. I would very much welcome some simple clarity from commissioners regarding access to bendamustine for patients with R/R CLL.

4. Defining end of life criteria

We do not have a full understanding as to how NICE define 'end of life' criteria. The appraisal lists 3 criteria:

1. The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
2. There is sufficient evidence to show that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
3. The treatment is licensed or otherwise indicated for small patient populations.

When assessing against these criteria it is important to remember that certain biological characteristics such as 17p deletion / TP53 mutation or IgvH mutational status have less impact on outcomes for patients treated with ibrutinib / idelalisib compared with a major impact on outcomes for patients treated with chemotherapy. Hence, assessing all R/R CLL patients homogeneously for end of life criteria is very challenging.

Criteria 1

There are actually few good datasets defining OS in different R/R CLL populations. However, it is clear that patients relapsing early after previous therapy have a shorter life span that those relapsing later. From the Tam paper (Blood, 2014), young patients (in this paper, only 20% were older than 65) had poor survivals post FCR. Relapsing <1 year = 13 months median OS, while relapsing 1-3 years post had median OS 27 months. However, these were young relatively fit patients (median age 56 at relapse), so it remains highly likely that older patients relapsing within 3 years of FCR have a median life-expectancy less than 2 years. However, there is further uncertainty, as I am not aware of any data presenting survival duration after relapse post less intensive treatments such as alkylator+anti-CD20. On the one hand, these patients are generally older and more commonly less fit, so survivals are likely shorter. On the other hand, we know that relapsing early after very intensive therapy (such as FCR) selects a particularly poor risk group of patients. I am not sure we know whether the same statement is true for less intensively treated patients.

How will ibrutinib fit criteria 1 in the context of the current idelalisib / rituximab approvals? Clearly both idelalisib and ibrutinib were not available when the patients reported in the Tam paper were relapsing. Either of these drugs will highly likely prolong the survivals of patients relapsing early post FCR. However, the toxicity of idelalisib remains a major concern (a further global safety announcement was made with regards to this drug in March 2016). If ibrutinib is not available, a patient who relapses within 3 years of FCR and cannot tolerate idelalisib, will more than likely die within 2 years, i.e. meeting criteria.

Criteria 2

For patients to meet criteria 1, then they must have relapsed within 2 to 3 years of previous immno-chemotherapy. If within 2 years, then is the evidence sufficient to support a 3 month OS benefit compared with 'NHS standard treatment' i.e. idelalisib / rituximab? By my interpretation of the data, the key determining factor here would be whether the patient suffers idelalisib toxicity requiring therapy termination. Unfortunately ibrutinib monotherapy has not been trialled against chemotherapy / immuno-chemotherapy in the relapsed setting making it harder to assess criteria 2 in the late-relapsing patients, where standard treatment remains immuno-chemotherapy (although these patients are less likely to meet criteria 1)

Criteria 3
We don't know how NICE assess 'small'

5. First Line treatment in 17p- / TP53 mutated patients

In the pre-ibrutinib / pre-idelalisib era, the survival of 17p deleted CLL patients was poor. Median OS of these patients in the UK phase 2 campath trial (Pettitt et al *JCO*, 2012) was 38 months, but toxicity was very significant and treatment related mortality was 5%, limiting this therapy to the very fittest patients. Campath is no longer licensed for this indication. In the German CLL8 trial, around 50% of 17p deleted patients treated with FCR relapsed within a year. By 5 years only 18% of 17p- patients were still in remission after FCR and of the patients who relapsed, only 20% survived - the majority of these having had an allogeneic stem cell transplant. (Fischer et al *Blood*, 2016). Although idelalisib/rituximab and ibrutinib have not been compared against other therapies in first line 17p deleted CLL, they were granted licenses for this indication based on limited data in a very poor risk group of patients.

However, more evidence has recently been presented concerning significant toxicity when idelalisib is used as first line therapy. This appears exaggerated in 1st line treatment when a patient's T-cell network (which mediates the toxicity – colitis / pneumonitis / transaminitis / rash) is relatively intact.

Now that RESONATE2 has been published (Burger et al, *NEJM* Dec 2015), there is significantly more very encouraging data on the safety and efficacy of first line ibrutinib in CLL. Although the first line efficacy data in 17p deleted patients is still relatively limited, with this very difficult to treat group of patients, we would very strongly support the use of ibrutinib rather than idelalisib/rituximab in this patient group.

6. There are some minor errors in the documents:

2.1 – ibrutinib is a kinase inhibitor, not a monoclonal antibody

3.1 – 'no people with TP53 mutated CLL were treated in resonate'. This is a factually incorrect statement. They were not tested in the trial. Almost inevitably, due to frequency of TP53 mutation in a R/R CLL population, some patients in RESONATE would have had TP53 mutation

3.3 There was no cross-over permitted in the original RESONATE protocol. The option for patients to cross over was introduced to the trial after interim data analysis identified a highly significant difference in PFS between the arms. A trial amendment was required before cross-over could be considered

Conclusions

In this appraisal, NICE have recognised that ibrutinib is an innovative therapy for CLL. They have listened to the patient and clinical experts and documented the expert opinion that ibrutinib is a drug of major importance in the management of CLL. Generally, the drug has an excellent toxicity profile and proven efficacy in relapsed / refractory CLL. As a Forum, we have no expertise or training in pharmaco-economics so we have not expressed an opinion on these aspects of the appraisal document. It is clear, however, that if NICE approve ibrutinib within the current licensing

authorisations, ibrutinib would be prescribed to a significant number of patients in England and Wales which will inevitably bring additional cost pressures for the NHS. However, it will be a tragedy for CLL patients in England and Wales if Janssen and NICE cannot work out a way forward to permit approval for ibrutinib in CLL.

London, 23/03/2016

Response to the first Appraisal Consultation Document on Leukaemia (chronic lymphocytic) - ibrutinib [ID749]

Dear Jeremy Powell

Gilead appreciates the opportunity to comment on the Appraisal Consultation Document (ACD).

Our comments will be limited only to the evidence taken into consideration regarding idelalisib (Zydelig®), with the aim of contributing to the appraisal by providing information regarding idelalisib and its clinical development.

The Committee has already highlighted uncertainties regarding the chosen comparison to the idelalisib plus ofatumumab combination (study 119). Gilead would like to provide additional information regarding the 119 trial.

Idelalisib plus ofatumumab is currently undergoing regulatory review and Gilead has not submitted to NICE for this indication.

Additional information regarding the 119 study

The 119 trial was open label and patients receiving ofatumumab monotherapy were likely to switch to other available therapies. During the time of the study RESONATE was un-blinded and a compassionate use programme for ibrutinib was made available. Early discontinuation in the ofatumumab arm was 39% (34 out of 87 patients) and in the idelalisib plus ofatumumab arm was 20% (34 out of 174 patients).

	idelalisib +ofatumumab, n=174	**ofatumumab, n=87**	**Total, N=261**
Early discontinuation from study, n (%)[†]	34 (20)	34 (39)	68 (26)
AE[‡]	2 (1)	3 (3)	5 (2)
Withdrew consent[§]	12 (7)	14 (16)	26 (10)
Physician decision	19 (11)	16 (18)	35 (13)
Other	1 (<1)	1 (1)	2 (<1)

[†]Ended study participation prior to PFS event (does not preclude participation in long-term follow-up). [‡]Per early amendment, AE was disallowed as valid reason for study discontinuation. [§]Withdrawal from long-term follow-up: n=9, IDELA + OFA; n=14, OFA.

Patients that did not respond well to ofatumumab may have withdrawn from the study prior to their PFS assessment (because they had knowledge of the treatment they were receiving). This may have

biased the ofatumumab PFS curve, with responding patients making a higher contribution to the curve; this does not affect the two arms in the same way.

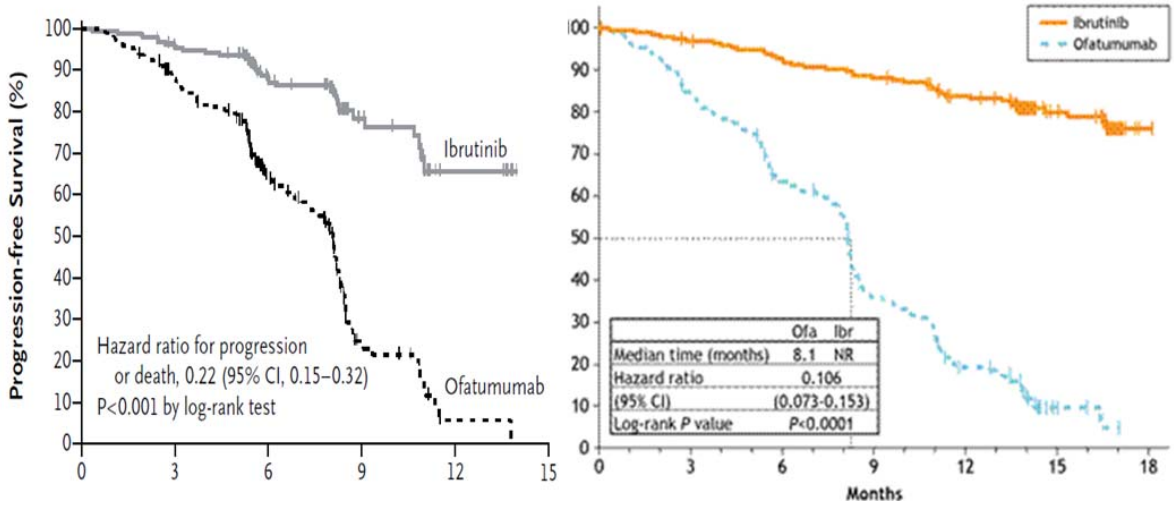
This would explain the similar shape of the ofatumumab curves between RESONATE and the 119 trial, even though the population recruited may have been different.

The 119 trial, as opposed to RESONATE:

1. 49% of patients were refractory, defined as **relapsed <6months**, as opposed to 45% refractory, but defined as **relapsed <12 months**
2. Recruited patients relapsed <24 months, as opposed to relapsed <36 months in RESONATE
3. excluded patients refractory to ofatumumab, as opposed to excluding any patient with prior exposure to ofatumumab

In addition, the median follow-up (FU) was 5.3 months in the ofatumumab arm and 11.1 months in the idelalisib plus ofatumumab arm and progression free survival (PFS) was assessed by an independent review committee (IRC). Comparing across trials is fraught with challenge. In this case the very different follow-up times also contribute to the uncertainty. Eliminating any differences related to the populations in the studies by considering the RESONATE trial alone illustrates the issue effectively; when comparing data from different follow up times as illustrated in the PFS curves below the hazard ratio for PFS was 0.22 at 9.4 month FU (IRC assessed) and 0.106 at 16 months (investigator assessed).

RESONATE trial – 9.4month vs. 16month follow up



Additionally, all of the issues described above from the 119 trial are equally relevant when one is looking to utilise the 119 trial data to represent idelalisib efficacy as has already been demonstrated within the 116 trial – i.e. we believe that the biases inherent in 119 trial make it a much less robust dataset than the double blind randomised controlled trial that is the 116 trial (the data upon which

the idelalisib CLL indication is based). To illustrate this point, in the 116 trial 71% of patients were still alive at 24 months even with a short median FU of 13 months in the intervention arm and median OS was not reached; this is remarkably different from that seen within the 119, ofatumumab trial.

In conclusion, it is highly uncertain that the 119 trial, idelalisib plus ofatumumab, is comparable to the RESONATE trial and it is even more doubtful that the 119 trial can be used as a proxy to represent the efficacy of the idelalisib + rituximab combination.

Yours faithfully

[redacted]
[redacted]
Gilead UK&Ireland

NB Additional information for reference

In the interests of transparency we would also like to draw your attention to the recent recommendation regarding idelalisib. For the relapsed CLL indication there is a recommendation for routine PJP (Pneumocystis jirovecii pneumonia) prophylaxis and monitoring of patients receiving idelalisib. There is an interim recommendation that idelalisib should not be initiated as first line treatment for CLL until an EMA review is completed. Further information is available on the EMA website:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/03/news_detail_002490.jsp&mid=WC0b01ac058004d5c1

REFERENCES

RESONATE: Byrd JC, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukaemia. N Engl J Med 2014;371:213-223

RESONATE follow up: Brown JR, et al. Updated efficacy including genetic and clinical subgroup analysis and overall safety in the Phase 3 RESONATE trial of ibrutinib versus ofatumumab in previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma. Abstract presented at ASH 2014; Abstract #3331

Study 116: Furman et al. N Engl J Med 2014;370:997-1007

Study 119: Jones et al. Abstract presented at ASCO 2015; Abstract #7023

Comments regarding NICE ACD for ibrutinib (ID: 749) from Professor Peter Hillmen (Clinical Expert at the Appraisal Committee Meeting, 3rd February 2016)

Summary:
There are several major criticisms of the draft ACD for ibrutinib. These are as follows:
1) The draft ACD indicates that ofatumumab is an inappropriate comparator as this is no longer funded in England due to it's removal from the Cancer Drug Fund (CDF) in November 2015. However the only reason for ofatumumab's removal was the clear demonstration that ibrutinib was superior to ofatumumab in the RESONATE Trial and therefore ofatumumab was replaced by ibrutinib on the CDF. The draft guidance, if implemented, would mean that neither would be available for patients in England.
2) Ibrutinib is a safer drug than idelalisib. At the time of the NICE Appraisal Meeting the experts and patients highlighted the potential toxicity of idelalisib in terms of potentially life-threatening autoimmune complications, particularly colitis and pneumonitis. Since the meeting the European Medicines Agency has issued a press release entitled "EMA recommends new safety measures for Zydelig" which highlighted the increased rate of infections including deaths observed in several Phase III trials. The EMA also state that "It [idelalisib] should also not be started in previously untreated patients with CLL whose cancer cells have certain genetic mutations (17p deletion or *TP53* mutation)." (http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/03/news_detail_002490.jsp&mid=WC0b01ac058004d5c1). Therefore idelalisib is no longer considered safe for previously untreated patients with 17p deletion and is associated with an even higher risk than previously thought in all other patients. Most experts now believe that idelalisib should be reserved for patients who are unsuitable for ibrutinib (either due to intolerance or refractoriness). The Committee's view that idelalisib is the most appropriate comparator for ibrutinib is inappropriate and with the new safety data indicates that ibrutinib is clearly a preferable drug.
3) The decision that ibrutinib does not qualify as an end-of-life designation is inappropriate as the idelalisib trials that led to both the European licence and NICE approval was based on a median follow-up of 13 months. This assumes that patients receiving idelalisib will remain on therapy for a prolonged period but most patients stop treatment early due to progression or toxicity. To not allow end-of-life designation because of idelalisib is unreasonable. In patients relapsing in less than 3 years after FCR chemotherapy the median overall survival is less then 24 months. The end-of-life criteria should apply to ibrutinib both for frontline 17p deleted CLL and for patients relapsing within 3 years of previous chemotherapy.

Specific comments requested by the Appraisal Committee:

The appraisal committee is interested in receiving comments on the following:
Has all of the relevant evidence been taken into account? No. The new emerging data from several of the idelalisib trials indicates that idelalisib is associated with a high risk of potentially life-threatening infections. It is probably that the EMA approval for idelalisib will be amended possibly to exclude previously untreated patients.
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? No. They are based on idelalisib being safe and effective. This is not a safe assumption and in light of very recent toxicity reported with idelalisib is untrue.
Are the provisional recommendations sound and a suitable basis for guidance to the NHS? No. Ibrutinib is a major step forward in the treatment of CLL and is clearly superior both interms of toxicity and efficacy when compared to idelalisib plus rituximab. Patients in the NHS being unable to access ibrutinib will create a major problem resulting in inferior survival for patients with CLL in the NHS compared to countries where ibrutinib is available.
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? CLL is more common in males and therefore a lack of access to ibrutinib will affect men more then women. Also the majority of patients

with CLL are elderly and cannot receive conventional fludarabine-based therapy. Ibrutinib is safer in the elderly and so this draft guidance will discriminate against elderly patients with CLL compared to younger patients.

Specific comments regarding the Draft Appraisal "Ibrutinib for treating chronic lymphocytic Leukaemia (ID:749). Dated February 2016

1.1 Given the accepted efficacy of ibrutinib it is difficult to understand how ibrutinib cannot be approved. It is the most effective drug in CLL and significantly safer than idelalisib.

2.1 **"Ibrutinib (Imbruvica, Janssen) is a monoclonal antibody that inhibits B-cell proliferation, and promotes cell death. "** Ibrutinib is not a monoclonal antibody it is a small molecule which inhibits B-cell receptor signaling.

2.2 This list of AE's are mainly due to the underlying disease and there is no increased frequency of them with ibrutinib over comparators in randomized controlled trials. The exception being bruising as an adverse reaction.

3.1 **"No people with the TP53 mutation were included in the trial."** This is technically incorrect because most of the patients with 17p deletion would also have TP53 mutations. A more accurate statement would be that "TP53 mutation was not an inclusion criteria in the trial."

3.3 The statement **"The trial protocol permitted patients randomised to ofatumumab to switch to ibrutinib on progression of disease."** is incorrect. Cross-over from ofatumumab was not permitted originally in the RESONATE Trial and was mandated by the independent data monitoring committee (iDMC) only when there was clear evidence that denying cross-over was unethical. Also cross-over was only initially allowed at Independent Review Committee (IRC) confirmation of progression. The statement as it stands would clearly undermine the rigor of the RESONATE trial.

3.4 It is very important to highlight that the cross-over from ofatumumab to ibrutinib after progression was mandated by the iDMC because they saw inferior survival in patients randomized to ofatumumab. Not allowing cross-over would have been unethical at this stage. The wording of paragraphs 3.3 and 3.4 undermines the highly clinical relevance of the findings in RESONATE with the implication that this undermined the trial – it certainly didn't and as an Investigator on the trial this cross-over was essential! Many of the patients who cross-over are still alive and undoubtedly wouldn't have been without the iDMC taking this action.

3.7 The draft ACD implies criticism of the company for censoring the survival data at cross-over. However there was a similar advantage in overall survival for ibrutinib over ofatumumab if the data was not censored as is described in the manuscript of the RESONATE Trial. The following statement is the relevant sentence from the manuscript. "At 12 months, the survival effect was also observed in the uncensored sensitivity analysis (hazard ratio for death, 0.39; P = 0.001), with an overall survival rate of 90% in the ibrutinib group and 79% in the ofatumumab group." (Byrd *et al.,* N Engl J Med 2014;371:213-23.)

3.8 **The statement "The adverse events were generally grade 1 or 2 in severity, managed with standard treatment, and resulted in only a few patients stopping treatment (less than15%)." whilst correct is misleading.** The quote directly from the RESONATE manuscript is "Discontinuation of treatment because of adverse events

occurred in 4% of the patients in each study group." Indicates that only 4% of patients stopped therapy due to adverse events and that this was the same for ofatumumab as for ibrutinib. In fact the adverse events were mostly not related to drug but more underlying disease. The statement in Section 3.8 as worded suggests that up to 15% of patients stop ibrutinib due to adverse reactions which is not true. It should say "less than 5%". In addition the statement in 3.8 "In comparison with ofatumumab in the RESONATE trial, overall infection rates were higher with ibrutinib (70% compared with 54%)," ignores the fact that the cause of infections is the underlying disease and that the exposure to ibrutinib was longer than to ofatumumab (in the manuscript "(median duration, 8.6 months [range, 0.2 to 16.1] (exposure to ibruutinib) vs. 5.3 months [range, 0 to 7.4] (exposure to ofatumumab)." This explains the apparent difference in infections. Again this statement is misleading suggesting that ibrutinib leads to infections which it doesn't!

3.12 In my opinion data comparing rituximab with ofatumuamb in diffuse large B-cell lymphoma cannot be used as evidence to indicate comparability between the antibodies when used in CLL. In CLL when used as a single agent in the doses used in CLL (ofatumumab is used at a significantly higher dose) ofatumumab leads to higher response rates in separate Phase I and II trials. However there is no direct head-to-head data to support this statement.

3.16 **The statement "However, the ERG noted that the control treatment, ofatumumab, was not a relevant comparator for English NHS practice because it is not recommended for relapsed or refractory CLL and has been removed from the Cancer Drugs Fund." is inappropriate.** When the Resonate trial was designed (I was the international Chief Investigator of RESONATE) the only approved drug in this patient group was ofatumumab and therefore was the only realistic comparator. In addition ofatumumab was only removed from the CDF in England when ibrutinib was put on the CDF and it was removed <u>because</u> RESONATE so clearly demonstrated that ibrutinib was superior to ofatumumab. It cannot be legitimate to criticize the RESONATE Trial on this basis. It clearly penalizes ibrutinib because it is such an effective and safe drug! In addition there is an inconsistency within the ERG's draft guidance in that bendamustine+rituximab is still considered an appropriate comparator but this was also withdrawn from the CDF at the same time as ofatumumab and is no longer available for patients with CLL in England.

3.17 **At the time the RESONATE Trial was run idelalisib plus rituximab was not available.** In fact since then it has not been available as the CDF and NICE do not allow cross-over from ibrutinib to idelalisib. Therefore cross-over to idelalisib could not have confounded the overall survival advantage seen in RESONATE.

3.19 **The statement "The ERG noted the differences in populations between the trials, particularly in the proportion of patients with 17p deletion in each trial, which is associated with poorer outcomes (32.3% of people randomised to ibrutinib and 32.7% randomised to ofatumumab in RESONATE, compared with 26.4% of people randomised to idelalisib plus ofatumumab and 21.8% of people randomised to ofatumumab plus placebo in Jones et al.)."** fails to make the point that this means that the RESONATE population were a worse prognostic group than the Jones et al. trial and that not adjusting for this can only hurt ibrutinib in the comparison.

3.35 I believe that ofatumumab is a relevant comparator for ibrutinib as it is licensed in this patient group and was only removed from the CDF because the RESONATE Trial demonstrated it's inferiority to ibrutinib. (see comment on 3.16).

4.3 **The statement "The committee heard from the clinical experts that bendamustine is no longer available through the CDF. It has therefore become more difficult to obtain, but it is still offered alongside rituximab for some patients,**

particularly those whose disease had been treated but relapsed after 24 months." Is incorrect. Bendamustine is no longer funded for patients with relapsed CLL in England.

4.3 **The statement "It further concluded that for those for whom idelalisib was not appropriate (the population outside of the NICE recommendation), bendamustine was most likely to be used."** is factually incorrect as bendamustine is no longer available.

4.5 "The committee concluded the only comparator for this population (17p deleted CLL) was idelalisib plus rituximab." Recent experience indicates that the toxicity to idelalisib is significantly higher in previously untreated patients and as things stand there is considerable doubt over this therapy in previously untreated patients with 17p deleted CLL as the EMA has indicated such front-line patients should not be treated with idelalisib. (http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/03/news_detail_002490.jsp&mid=WC0b01ac058004d5c1). Undoubtedly ibrutinib is the drug of choice for this population.

4.6 Bendamustine plus rituximab is no longer available on the CDF.

4.7 Fails to accept that ofatumumab is only no longer available because of RESONATE. Also that the trial was sopped by the independent Data Monitoring Committee because ibrutinib was so much more effective than the only approved therapy in this patient population. **The statement that "The committee concluded that the results from RESONATE were immature and uncertain and that the comparison with ofatumumab was not directly relevant to UK clinical practice."** Is inappropriate because there was a clear overall survival advantage for ibrutinib in RESONATE and obviously further maturity of the data will not alter this end-point!

4.8 The recommendation to approve idelalisib plus rituximab in previously untreated patients with 17p deleted CLL (Idelalisib for treating chronic lymphocytic leukaemia NICE technology appraisal guidance [TA359] Published date: October 2015) was based on only 9 patients. There is more experience of ibrutinib in this group of patients as there were 35 such patients in the Farooqui et al study. It seems strange that almost 4 times the number of patients is considered to be "no data".

4.10 **The comment that " However, it (the Committee) heard from clinical experts that they considered it very likely that, after progression, patients leaving the trial would go on to receive other life-extending therapies."** is of interest because the other life-extending therapies would almost certainly be ibrutinib!

4.14 **The statement "The committee heard from clinical experts that the benefits of ibrutinib were likely to decrease over time."** Is a mis-representation of the clinical experts opinion. Contrary to this statement the benefits of ibrutinib are sustained for individual patients now beyond 4 years and are likely to continue. The point that the clinical experts made was that the development of therapies in CLL and related diseases in progressing rapidly. It is very likely that ibrutinib monotherapy will not remain the standard of care for long and will be replaced by therapies or combinations of therapies that will lead to the discontinuation of ibrutinib and similar therapies for patients in deep remissions. So the statement was to say that continuous therapy with ibrutinib will be replaced by short duration treatment with a different pharmaco-economic impact.
Furthermore the same impact will be apparent for idelalisib plus rituximab and so **the statement "which reduced the duration of benefits with ibrutinib to 5 years increased the ICER for ibrutinib compared with idelalisib plus rituximab."** is not sustainable.

Comments regarding NICE ACD for ibrutinib (ID: 749) from Professor Peter Hillmen (Clinical Expert at the Appraisal Committee Meeting, 3rd February 2016)

4.19 This needs clarification. When there is a true progression of CLL on ibrutinib then patients will not remain on therapy for a prolonged period. A small proportion of patients who have to stop ibrutinib due to operations, etc. may technically progress whilst off ibrutinib for a short period but then come back under control when the ibrutinib is re-started. Patients do not spend prolonged periods with progressive disease on ibrutinib.

4.25 As we highlighted at the toxicity of idelalisib will impact significantly on the efficacy of the drug. Ibrutinib is much better tolerated and therefore more effective.

4.28 Idelalisib has recently been associated with an increase in infections including a doubling of infection-related deaths in 3 large randomized clinical trials. Idelalisib is now no longer recommended for previously untreated patients with CLL including those with 17p deletion. Therefore the end of life criteria for front-line 17p deleted patients with CLL is in my opinion appropriate for ibrutinib. The toxicity of idelalisib in relapsed and refractory patients is increasingly a concern both in terms of autoimmune complications, such as colitis and pneumonitis, and life-threatening infections. Idelalisib plus rituximab is now being positioned for patients who are intolerant or resistant to ibrutinib, which is clearly a safer and more effective agent. I believe that given the concerns over the tolerability of idelalisib then it is unlikely many patients will remain on this therapy and therefore the end of life criteria is appropriate for ibrutinib in pstients with relapsed and refractory CLL.

General Comments:

The committee seems to have failed to accept that the clinical experts consider ibrutinib a preferable therapy compared to idelalisib plus rituximab because there is clearly considerably more toxicity that is not infrequently life-threatening with idelalisib. Such severe toxicities are simply not seen with ibrutinib. This clinical expert finds it intolerable to have patients die as a direct complication of a therapy when safe alternatives are available. In addition the requirement to use intravenous rituximab with idelalisib adds both a financial and day case burden that is not seen with ibrutinib.

The committee has applied double standards by excluding ofatumumab as a suitable comparator because it is no longer available after being de-listed by the CDF whereas bendamustine plus rituximab is considered an appropriate comparator despite it also being removed from the CDF at the same time as ofatumumab.

Conclusion

The following changes should be made to the ACD:

1) Ofatumumab is an appropriate comparator for ibrutinib
2) The end-of-life criteria are met for ibrutinib
3) Idelalisib plus rituximab is no longer available for front-line patients with 17p deleted CLL and there is no other alternative for these patients except for ibrutinib.
4) The increased toxicity of idelalisib including fatal infections should be recognized.

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

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	Scotland
Conflict	No
Notes	
Comments on the ACD	
Please consider the widely published data of the efficacy of this drug. ibrutinib [ID749 As a stage 3 patient options for treatment of CLL are evidently rare. Given 50 experience years of processing engineering and scientific data negative pushbacks are considered counterproductive. Where more data and or evidence is required simply make the request (stating why if necessary) dont throw away opportunities. A silver bullet solution is desperately required to shut down the horrors of CLL and this plea is for the NICE Committee to do all within its power to expedite solutions to implement possible acceptance of this drug Thank you for considering this request [redacted]	

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on the ACD	
I have commented on each of your consultation questions to get you to reconsider the preliminary appraisal of Ibrutinib. Has all of the relevant evidence been taken into account? --- All the relevant evidence supports the approval of Ibrutinib, CLL experts see Ibrutinib as the a key component in the treatment of this cancer. The evidence has been approved by EMA ,FDA and the CDF. 17p Patients have a more aggressive form of CLL and it is essential that clinicians have a range of treatment options available to suit individual patient need - this is due to the variable course and nature of the disease, the toxicity profile of the therapies and the comorbidities which are more prevalent in this patient population. In general Ibrutinib is considered to be more benign than idealisib (ie. the only other treatment for 17p deleted patients) and offers a different toxicity profile for those patients unable to use idealisib. As stated in the NICE preliminary decision treatment ibrutinib is preferred because of the unpredictable adverse effects associated with idelalisib. The recent EMA/FDA review of trials using Idelalisib in combination with other cancer drugs is further evidence of the need for Ibrutinib.	

The trial evidence used Ofatumumab as a comparison for Ibrutinib, this antibody has efficacy for 17p deleted patients and is a legitimate comparison for Ibrutinib. The NHS has very little to offer these patients, ofatumumab is approved in the USA and EU for fludarabine- and alemtuzumab-refractory CLL patients. Certainly Ofatumumab is an effective treatment for these patients and as such is a good trial comparison. Any trial comparison would be positive for Ibrutinib, regardless of which CLL treatment was used in comparison. Ofatumumab is superior to rituximab and as such provides a good comparison when assessing Ibrutinib against Idelalisib + rituximab (ie. using the indirect comparison of Idelalisib + Ofatumumab).

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The costs of non targeted toxic treatments are high in terms of patients health and the economy.

The medical argument for ibrutinib is clear, if CLL patients are not treated efficiently then they will require further resources over decades and ultimately require extensive resources due poor health and further serious secondary infections / malignancies. In many cases they deny patients the ability to work and contribute fully to family life due to poor health. A superior targeted oral treatment with low toxicity frees up resources and in combination may offer extended remissions. The new oral drugs offer an easy to administer treatment that has lower toxicity and provides a targeted approach which will according to trials and clinical practice deliver a better outcome. An enlightened approach of immune-based strategies maintaining remissions, minimizing toxicities, and preserving immune functions offers preferential patient outcomes and overall savings.

As the 5th largest economy in the world the NHS should lead and move with developments in world medicine. The draft recommendation from NICE for ibrutinib sits in stark contrast to the recommendations of 48 countries globally which have opted to fund or reimburse the medicine including 27 European countries, most recently in Greece. Other countries fast track these targeted treatments and the USA have also approved the use of Ibrutinib as a front line treatment for all CLL patients. If this preliminary decision stands NHS England will be out of step with many European countries and the United States where these drugs are routinely available and have a significant impact on life expectancy and also on quality of life. Ibrutinib is seen by both clinical experts and the CLL patient community as fundamental to the treatment of this rare cancer.

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

Ibrutinib is regarded by patients and clinical specialists around the world as the single most important treatment for Chronic Lymphocytic Leukemia and more specifically essential for 17p deleted patients.

Given the great clinical success of Ibrutinib some trials have yet to reach Statistical completion, some have been so successful that the trial has had to cut over. The Approval should take account of these superior results irrespective of the statistical completion.

I believe the NICE preliminary recommendation is not sound.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

If such a game changing drug and widely approved treatment such as ibrutinib is refused by the NHS then something is very wrong. Patients will pay the price with their lives. If the NHS cannot approve Ibrutinib like 48 other countries have already done, then our health system which we have supported is inferior.

World experts are clear on the value of Ibrutinib, which provides a paradigm shift in the treatment of CLL. I feel CLL patients are being discriminated against as this rare cancer has historically been given poor service from the NHS, only now is the condition being given the required attention with targeted treatments.

The facts talk for themselves New analysis shows lower survival from all cancers in Denmark, the UK and Eastern Europe than in neighbouring countries September 2015. The health of English CLL patients is being discriminated against by poor decision policies and a health system not actively doing the best for its patients. CLL is a rarer cancer with orphan status. Ibrutinib is used in the treatment of both relapsed CLL and now in the USA as a frontline treatment. I believe that CLL patients will be severely disadvantaged and discriminated against by the NICE preliminary findings, in particular that the assessment for overall survival and progression free survival have been applied unfairly to trial data for these small populations.

At 57 years old I feel unlucky to have been diagnosed with CLL and it is a struggle dealing with this incurable cancer on a daily basis. As CLL patients we need a health system that delivers a varied and best of class treatment for one of the rarer cancers. My struggle and overall survival is closely linked to having access to novel but proven agents such as Ibrutinib.

Evidence Review Group critique of the company's additional evidence presented in response to the Appraisal Consultation Document for Ibrutinib for treating relapsed or refractory chronic lymphocytic leukaemia [ID 749]

Produced by: Aberdeen HTA Group

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Date completed: 01 April 2016

Version 0

This document contains a critique of the Company's additional evidence for the single technology appraisal of Ibrutinib for treating relapsed or refractory chronic lymphocytic leukaemia (dated March 23rd 2016).

CIC and AIC mark-up

The ERG has had very limited time to appraise the Company submission of the 23rd March and to provide additional analyses. Time pressures have meant that it has followed the AIC and CIC mark-up of the original ERG report, which may be too restrictive. During the first AC the Company agreed that certain elements such as the mean and incremental gains in undiscounted progression free survival and overall survival could be presented and discussed during part 1.

The document is structured in the following manner:

Section 1 **Summary**
Section 2 **Additional data to support end of life criteria**
Section 3 **Additional data to support relevant comparators**
Section 4 **Additional data to support comparative efficacy**
Section 5 **Extrapolation of OS and PFS**
Section 6 **Utility data**
Section 7 **Costing considerations**
Section 8 **Revised economic analyses: company**
Section 9 **Revised economic analyses: ERG**

Section 1 Summary

The Company March 23rd submission can be briefly summarised along the following lines.

- The new 30 month data provides further evidence for the continued safety and efficacy of ibrutinib.
- The Company market analysis data suggests ofatumumab is currently very little used and that most treatment is with bendamustine or the KIs, with the KIs on a strong upward path.
- The ERG accepts the Company arguments that the base case should adjust the OS HRs for cross-over during RESONATE.
- Company still argues for 3 years log-normal OS prior to switching to the exponential, but applies the exponential throughout its revised modelling.
- Company still argues for the Weibull PFS, but has provided little additional information that is useful for deciding between the Weibull and the exponential.
- Company provides sensitivity analyses that increase the quality of life gain from ibrutinib during PFS. The ERG thinks that any sensitivity analyses should rather apply a decrement to the comparator treatments. The ERG does not see the argument for this for the comparison with ofatumumab or with idelalisib+rituximab. If there is an argument for the comparison with bendamustine+rituximab the decrement that should be applied is unclear.
- Company argues that costing ibrutinib in a number of different ways from the way the comparators should be costed is due to ibrutinib being the only *purely* oral therapy. This does not explain any of the asymmetries. Company has also not provided any credible account of why the double 5.2% discount for just ibrutinib should be seen as accidental.
- The Company modelling has accepted many of the recommendations of the ACD and the ERG report, most notably the age weighting of utilities and removing the drug costing asymmetries.
- The Company modelling has not applied some of the AC preferences for the base case, most notably retaining the Weibull PFS curve and the Fischer MAIC HRs for bendamustine+rituximab.

The revised cost effectiveness estimates of Company and the ERG are presented below. They have not been summarised here due to time constraints.

Section 2 Additional data to support end of life criteria

In section 2 of the Company response, the EoL criteria are contested. Much of the Company argument relates to NICE precedence rather than new data. In section 2.2 the Company have provided some further information on the Swedish Cohort that the ERG has not seen before. A list of the therapies used in the cohort have been provided:

"(alemtuzumab, chlorambucil, ofatumumab, BR, steroids with rituximab and steroids with chlorambucil; note that patients exposed to fludarabine- and lenalidomide-based therapies, ibrutinib, IR, and experimental treatments were excluded)"

But no details were given on relative usage of each of the therapies in the cohort.

In addition a Table comparing RESONATE to the Karolinska dataset was provided in Appendix 2 of the Company response. The Company state that the characteristics provide evidence that the two study populations were similar. The ERG are not as confident as the Company about the strength of the evidence for similarity of the baseline characteristics. The ERG are uncertain given that several of the characteristics appear to be different (e.g. ECOG status of zero were fewer in the Karolinska dataset (22% v 41%), proportion of patients with greater than two previous therapies was also lower (32% v 49%). Secondly, of the 17 baseline characteristics included in the characteristics table from the RESONATE trial, 8 were not reported in the Karolinska dataset.

Section 3 Additional data to support relevant comparators

The Company in section 3.4 and appendix 3 of its March 23rd submission presents three estimates of market share for the various treatments: cancer drug fund notifications, the oncology analyser and the IMS Harmony market research data. These all confirm that there is little to no current use of ofatumumab. They also confirm that the sizeable majority of current treatment is ibrutinib, idelalisib or bendamustine, with the KIs on a strong upward path.

It should also be borne in mind that physician choice is assumed to be composed of 35% bendamustine+rituximab. From a purely modelling point of view this complicates having physician choice as a comparator alongside bendamustine+rituximab.

Section 4 Comparative efficacy

4.1 Cross-over adjustment

The Company consider that the cross-over adjustment OS data for switching treatment in the RESONATE trial should be used in the indirect treatment comparison (ITC) instead of the committee preferred approach of using the intention to treat estimate. The company argument is as follows:

"In the case of OMB114242 [Osterberg trial of OF v PC], patients were allowed to receive ofatumumab salvage therapy after progression. Whilst it is unclear whether the effect of salvage therapy was adjusted for, two factors make this question insignificant. First, patients who crossed over in RESONATE received monotherapy ibrutinib, a step-changing therapy. Patients in OMB114242 received ofatumumab salvage therapy, which does not

have the impressive survival gains that novel agents do. Second, and more importantly, if the cross-over to the ofatumumab salvage therapy was not adjusted for, the relative efficacy of ofatumumab vs. PC would have been underestimated in OMB114242, which would serve to underestimate ibrutinib's relative treatment effect vs. PC. That is, not correcting for cross-over makes the PC arm look more effective, which makes ibrutinib appear less effective by comparison. Thus, the inability to adjust for cross-over in OMB114242 results in a conservative ITC for ibrutinib."

The ERG have considered this argument carefully. The first point is not compelling, but the second argument, which may appear counter intuitive (i.e. one may think that because the hazard ratio is too conservative in the *OMB114242* trial if the ITT estimate is used that the ibrutinib effect is overestimated when the ITT estimate is used in the ITC), does in fact imply that the ITC estimate is not overstating the effect of ibrutnib versus PC. The ERG suggests that the RESONATE crossover adjusted HR OS estimate of effect ([redacted] 95%CI [redacted]) should be retained in the ITC for the comparison with PC.

For the ITC comparison with IO, the Company state that:

"In the case of Study 119, the Committee has further stated that while no cross-over from the control arm (ofatumumab) to the experimental arm (IO) occurred, progressed patients may have left the trial and received other life-extending therapies. Adjustment for this type of "cross-over" (to treatment arms outside of the study) is not recommended by NICE DSU guidance, which states that the key factor to adjust for is "the switch from control treatment to experimental treatment by patients randomised to the control group of an RCT" (Latimer & Abrams, 2014)."

The ERG could not identify any recommendation in the NICE DSU guidance that discouraged adjustment for this type of crossover.

4.2 Ibrutinib efficacy versus IR

In response to the committee (and ERG) comment querying whether an MAIC analysis could have been undertaken to compare ibrutinib versus IR (instead of assuming the IR effect was the same as the IO effect), the Company did undertake an MAIC analysis for progression free survival using the Sharman 2014 trial. The resultant MAIC estimate of effect was [redacted]. This estimate is smaller than the original submission estimate of [redacted]. However, there are no statistical details provided for the new MAIC analysis so the ERG cannot comment on the robustness of the new MAIC values.

4.3 Hazard ratios

The Company March 23rd submission uses the following hazard ratios for its base cases in Table 1.

Table 1 Company March 23rd base case hazard ratios

	PFS	OS	Source
PHYS	[redacted]	[redacted]	Company ITC Osterborg trial
OFAT	[redacted]	[redacted]	Company RESONATE OS adjusted for X-over using RPSFT text of page 64
IDEL	[redacted]	[redacted]	Company ITC with RESONATE OS adjusted for X-over using RPSFT Table 33
BEND	[redacted]	[redacted]	Fischer MAIC

As described in section 4.1 above, the ERG is of the opinion that the hazard ratios for overall survival for the base case should be adjusted for cross-over.

The AC also had a preference for the HELIOS Cox HRs for the comparison with bendamustine+rituximab. Note that for these the values of the Company electronic model which correspond with those of the Company appendix 6 of its original submission have been applied. The values of Table 39 of the Company submission appear to be incorrect, since the central estimate for the HR for OS falls outside the reported 95% CI.

For completeness for the comparison with physician choice the ERG has also applied the Company March 23rd revised HRs for the Swedish registry data of Karolinska.

This results in the following base case hazard ratios.

Table 2 ERG base case hazard ratios

	PFS	OS	Source
PHYS	[redacted]	[redacted]	Company revised ITC Karolinska section 4.2.3 Company revised submission
OFAT	[redacted]	[redacted]	Company RESONATE OS adjusted for X-over using RPSFT text of page 64
IDEL	[redacted]	[redacted]	Company ITC with RESONATE OS adjusted for X-over using RPSFT Table 33
BEND	[redacted]	[redacted]	HELIOS Cox model of appendix 6 of Company submission and electronic model

The additional hazard ratios that will be explored as sensitivity analyses are:

Table 3 Additional hazard ratios explored as sensitivity analyses

	PFS	OS	Source
PHYS	[redacted]	[redacted]	Company original ITC Karolinska
PHYS	[redacted]	[redacted]	Company ITC Osterborg trial
IDEL	[redacted]	[redacted]	ITC with no OS cross-over adjustment
IDEL	[redacted]	[redacted]	Naïve indirect comparison 17p subgroup
BEND	[redacted]	[redacted]	HELIOS Cox model as reported in Table 39 of Company submission
BEND	[redacted]	[redacted]	Fischer MAIC

The Company March 23rd submission also provides a 17p depleted subgroup specific estimate for the PFS hazard ratio for idelalisib+rituximab compared to ibrutinib of [redacted] compared to [redacted] for the all patient group. It should be borne in mind that worse PFS HRs for ibrutinib tend to improve its cost effectiveness since this will increase the costs in the comparator arm while having no corresponding impact of an increase in overall survival in the comparator arm. As a consequence, the ERG only applies this as a sensitivity analysis due to there being no corresponding estimate for the HR for overall survival.

Section 5 Extrapolation of OS and PFS

5.1 OS extrapolation

Company plots the 1102 and 1103 data as an argument for using the ibrutinib log-normal OS curve. In the opinion of the ERG these are of limited usefulness without the numbers at risk also being plotted. The ERG report Figure 23 did so for the 1102 study and is reproduced here for ease of reference.

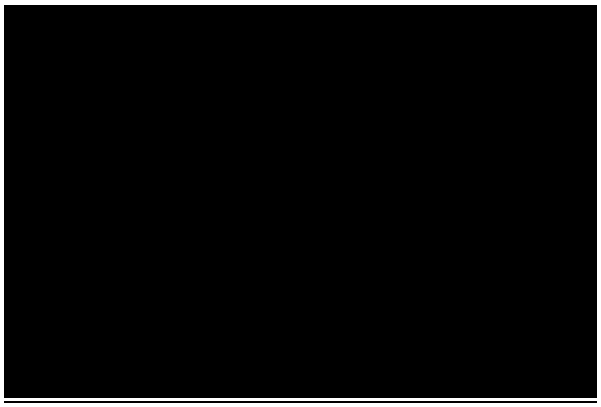

Figure 1 OS: Ibrutinib 1102 KM and RESONATE parameterised curves: all patients

The Company March 23rd submission maintains that the log-normal for three years followed by a switch at three years to the exponential is the best fit. When arguing this the Company does not cite the information criteria as being important. The information criteria suggest the exponential is the natural choice during the period of RESONATE.

Table 4 OS: Ibrutinib RESONATE parameterisations goodness of fit

	Ibrutinib: All		Ibrutinib: 17p	
	AIC	BIC	AIC	BIC
Weibull	214.63	221.18	215.68	225.50
Log-Normal	214.21	220.76	214.43	224.25
Log-Logistic	214.46	221.01	215.33	225.15
Exponential	**212.66**	**215.93**	**213.70**	**220.25**

But in its revised modelling the Company has applied the exponential throughout.

5.2 PFS extrapolation

The Company present 1102 and 1103 data as a means of justifying the log-normal assumption for three years followed by the exponential for overall survival, but have not presented the parallel data to justify its preference for the Weibull PFS curve over the exponential PFS curve. Figure 35 of the original ERG report presents this data and is reproduced here for ease of reference.

Figure 2 1102 and 1103 PFS KM curves and RESONATE parameterised curves

In contrast to the Company arguments about the OS curves, the Company places strong emphasis on the information criteria for the choice of the Ibrutinib PFS curve.

Table 5 PFS: RESONATE parameterisations goodness of fit statistics

	Ibrutinib: All		Ibrutinib: 17p	
	AIC	BIC	AIC	BIC
Weibull	**267.64**	274.19	**268.78**	278.60
Log-Normal	269.31	275.86	269.09	278.91
Log-Logistic	267.85	274.39	268.70	278.52
Exponential	268.43	**271.71**	269.52	**276.07**

The ERG argument is that the extrapolation of the PFS curve is crucial to the cost effectiveness estimates and that the information criteria on goodness of fit during the RESONATE trial may not be the best guide for this given the degree of extrapolation that is required. The exponential and the Weibull show little practical difference during the period of RESONATE when numbers at risk were still reasonable, though as the Company notes the Weibull scale parameter is significantly different from unity with a mean of 0.77 and a standard error of 0.11.

In the opinion of the ERG given the degree of extrapolation that is require for both OS and PFS these need to be viewed for reasonableness and general clinical validity.

The exponential OS curve estimates an undiscounted overall survival for ibrutinib of [redacted] years.

- The Weibull PFS curve suggests that only [redacted] years of this occurs during PFS, with a majority of [redacted] years occurring after treatment cessation and during PPS.
- The exponential PFS curve suggests that more of this survival occurs during PFS, [redacted] years, with the PPS survival being [redacted] years.

ERG expert opinion suggests that anticipating even [redacted] years survival subsequent to cessation of ibrutinib may be optimistic, and that [redacted] years seems unlikely to occur on average.

Using the OS HR adjusted for cross-over of [redacted] for idelalisib+rituximab compared to ibrutinib the undiscounted net overall survival gain from ibrutinib is [redacted] years.

- The Weibull PFS estimates that the net gain during PFS is [redacted] years, with a [redacted] majority of the net gain compared to idelalisib+rituximab actually occurring after treatment cessation and during PPS.
- The exponential PFS estimates that the majority of the net gain is during PFS at [redacted] years, with the net gain in PPS being [redacted] years.

5.3 30 month data cut

The Company have estimated parameterised curves for OS and PFS using the RESONATE 30 month data cut for ibrutinib but does not appear to have used them in any of the economic modelling. The parameters of these curves have not been presented and as a consequence the ERG cannot explore what effect they might have upon the cost effectiveness estimates. The data that is presented does not help with the choice of curves – there is still a considerable amount of extrapolation necessary.

The 30 month data does provide further evidence for the continued safety and efficacy of ibrutinib compared with ofatumumab.

Section 6 Utility data

The Company undertakes some sensitivity analyses which apply the estimated quality of life difference between idelalisib+rituximab and rituximab of that STA.

The base case PFS QoL of [redacted] is based upon the mean post baseline PFS of the RESONATE trial which already suggests a reasonable improvement over the RESONATE mean baseline value of [redacted]. In the opinion of the ERG any exploration of the differences in QoL while patients remain on the various treatments should be implemented as decrements from the ibrutinib PFS QoL. There does not seem to be an argument for further increasing the ibrutinib PFS QoL, which is how Company has implemented it in its sensitivity analyses.

Given that the Company does not appear to be arguing that RESONATE demonstrated a quality of life difference between ibrutinib and ofatumumab during PFS the ERG assumption is that the Company accepts that there was no difference during RESONATE. The Company repeated measure analysis of Model 1 as outlined in Table 56 of the ERG report did estimate a coefficient of 0.022 for ibrutinib treatment compared to ofatumumab treatment, but the p-value for this was 0.895. The question then seems to be whether those in PFS while on the comparators would have QoL decrement compared to those in PFS while on ibrutinib. The Company in its scenario analyses largely appears to imply that there is no evidence for or any real expectation of a QoL decrement for PFS while on idelalisib+rituximab compared to PFS while on ibrutinib. The remaining question would seem to be whether there should be a QoL decrement for PFS while on bendamustine+rituximab,

The Company applies the 0.07 difference estimated between idelalisib+rituximab and rituximab during the idelalisib STA. The ERG for this assessment noted that mean baseline responses in the idelalisib plus rituximab arm were somewhat better than those in the rituximab arm, and questioned whether the GEE analysis would or could have sufficiently adjusted for this. In other words the estimated decrement for rituximab may have been too large. The 0.07 difference is also compared to rituximab and not to bendamustine+rituximab.

An alternative interpretation of the ACD is that the main focus should be upon the gains from remaining on treatment and in PFS as compared to having progressed into PPS. The PPS health state is based upon the RESONATE baseline of [redacted] conditioned by a 13% fall from Beusterein et al (2010) to yield a quality of life of [redacted]. This was assumed to be constant during the 20 year time horizon of the model, but is now age weighted along the lines of Ara & Brazier (2010). The [redacted] may still be felt too high, and the Company provides sensitivity analyses that apply the 0.600 PPS QoL of Dtetzke et al (2010).

The ERG has cross checked that the age weighting of quality of life in the Company 23rd March submission corresponds with Ara & Brazier, and agrees with it.

Company rejects using the 17p specific QoL values of RESONATE. There may be a priori reasons for anticipating 17p depleted patients to typically have a worse quality of life over the course of their PFS while on ibrutinib treatment and during their PPS. The number of post baseline EQ-5D values for the 17p depleted subgroup based upon Table 37 of the ERG report is n=[redacted] for the [redacted] patients in the ibrutinib arm and n=[redacted] for the [redacted] patients in the ofatumumab arm. In the opinion of the ERG this is quite a reasonable number of observations across a fairly reasonable number of patients. Company have not provided any formal analysis of whether 17p was a determinant of QoL during the RESONATE trial. The ERG provides a sensitivity analysis which applies the all patient QoL values.

Section 7 Costing considerations

In all previous STA reviews that the ERG economic reviewer has been involved in it is relatively common for the submitting company to make assumptions about how drug costs should be handled. But the key here is that the assumptions made are usually applied equally to the company drug and the comparator drugs. The Company submission here assumed that the costs of ibrutinib should be handled in one way and the costs of the comparators handled in another way.

It would have been reasonable for the Company to have presented these asymmetries in a transparent manner and argued the reasons for their inclusion but Company did not do so. The Company has never explained why these asymmetries should be applied. The Company in its March 23rd submission on page 23 asserts that:

> *"In nearly all cases, the differences in how costing considerations were applied to ibrutinib versus comparators were due to the fact that ibrutinib was the only purely oral, daily treatment included in the model. Due to ibrutinib's unique route of administration, half-cycle correction and discounting, application of dosing intensity to administration costs, and the relevance of time until treatment discontinuation were considered differently for ibrutinib."*

But it is not then explained why this should lead to any of the asymmetries that the Company chose to apply. The *purely* oral administration justification seems rather specious given that the vast majority of the drug costs in the idelalisib+rituximab arm arise from the costs of idelalisib which is also administered orally on a daily basis. Ibrutinib is not unique in this.

Then there is the additional Company asymmetry of the double application of the drug utilisation discount for ibrutinib but not for any of the other comparators. As per the original ERG report, the ERG explained why it found it extremely difficult to see how this double discount for ibrutinib can have been accidental. The Company modelling of its 23rd March submission accepts the ERG proposals and removes the asymmetries in the calculation of the direct drug costs.

The Company submission of March 23rd argues that costs during PFS should be differentiated by the Company estimates of treatment specific response rates. But it does not add anything to the debate on this point other than to argue that if costs are equalised they should be equalised at the partial response level.

The ERG remains concerned about the lack of detail underlying the indirect comparison estimates of complete response and partial response, the times to peak response and the durations of peak response as outlined on page 122 and 157 of the ERG report. The Company has not addressed these points during error check or in its March 23rd submission. If the Company response rate estimates of Table 35 of the ERG report are reasonable to apply, the IP admission rates differentiated by response status as outlined in Table 41 of the ERG report need to be assessed for reasonableness. Expert opinion suggests that routine follow-up would not be differentiated by response status.

The ERG accepts that it is more reasonable to equalise costs at the partial response level.

Section 8 Revised economic analyses: company

Company has revised its original model along the following lines:

- Exponential OS curve throughout.
- Age weight PFS and PPS utilities.
- Mean BSA of 1.85m^2 in the light of the gender balance of RESONATE being largely male.
- Remove the asymmetries and double discount for ibrutinib drug costs.
- Assumed the same dosing intensity for idelalisib as for ibrutinib.
- 84.2% treatment holidays for bendamustine+rituximab.
- Remove the costs of biopsy.
- Revise the subsequent infusion unit cost.

Company has retained:

- The Weibull PFS curve.
- The Osterborg HRs for physician choice.
- The Fischer MAIC HRs for bendamustine+rituximab.
- The differentiation of PFS routine follow-up and IP costs by response status.

- The all patient QoL for 17p patients.
- R-CHOP as an element of physician choice.

There are a number of more minor model revisions outlined in the ERG report section 5.4 some of which it appears Company has implemented, others not.

The revised base case estimates of Company presented below are taken from the Company March 23rd electronic model. There are discrepancies for the 17p modelling with those presented in Table 10 of the Company 23rd March submission.

Table 6 Company revised base case: All patients: Ex PAS

	IBRU	PHYS	OFAT	IDEL	BEND
PFS total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS Drug cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS Administration cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS Routine follow up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS AE cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS SubTx Tx cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS BSC cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS SubTx Routine follow up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Terminal cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost vs comparator		£162,314	£132,214	£97,425	£164,690
Total undisc LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS undisc LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS undisc LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net undisc LY		[redacted]	[redacted]	[redacted]	[redacted]
net PFS LY		[redacted]	[redacted]	[redacted]	[redacted]
net PPS LY		[redacted]	[redacted]	[redacted]	[redacted]
QALYs PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net QALY vs comparator		3.075	2.483	1.816	3.359
ICER vs comparator		£52,787	£53,245	£53,644	£49,023

Company has chosen not to submit any probabilistic modelling in its March 23rd submission despite the NICE TAPs methods guide.

It should be borne in mind that the central probabilistic estimates of the cost effectiveness of ibrutinib are worse than those of the deterministic modelling. For instance, the ERG revised base case estimate for the all patients modelling of section 5.4 of the ERG report had a deterministic cost effectiveness estimate for ibrutinib compared to idelalisib+rituximab of £88,484 per QALY compared to £92,562 per QALY for the probabilistic modelling.

Table 7 Company revised base case: 17p patients: Ex PAS

	IBRU	OFAT	IDEL
PFS total	[redacted]	[redacted]	[redacted]
PFS Drug cost	[redacted]	[redacted]	[redacted]
PFS Administration cost	[redacted]	[redacted]	[redacted]
PFS Routine follow up	[redacted]	[redacted]	[redacted]
PFS AE cost	[redacted]	[redacted]	[redacted]
PPS total	[redacted]	[redacted]	[redacted]
PPS SubTx Tx cost	[redacted]	[redacted]	[redacted]
PPS BSC cost	[redacted]	[redacted]	[redacted]
PPS SubTx Routine follow up	[redacted]	[redacted]	[redacted]
Terminal cost	[redacted]	[redacted]	[redacted]
Total Costs	[redacted]	[redacted]	[redacted]
Net cost vs comparator		£113,617	£84,178
Total undisc LY	[redacted]	[redacted]	[redacted]
PFS undisc LY	[redacted]	[redacted]	[redacted]
PPS undisc LY	[redacted]	[redacted]	[redacted]
Net undisc LY		[redacted]	[redacted]
net PFS LY		[redacted]	[redacted]
net PPS LY		[redacted]	[redacted]
QALYs PFS	[redacted]	[redacted]	[redacted]
QALYs PPS	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Net QALY vs comparator		2.573	1.636
ICER vs comparator		£44,161	£51,464

Company has not submitted any probabilistic modelling for the 17p patient population. As noted in the original ERG report, it appeared that the model did not apply 17p specific variance-covariance matrices for the 17p specific RESONATE curves. The ERG has not had time to check whether this remains the case, but assumes that it does.

8.1 Cross check of revised company base cases

Within the revised model submitted by Company which includes the revised 17p depleted PFS HR for idelalisib+rituximab setting the patient population to 17p in cell H9 of the *Settings* worksheet results in the following ERG estimates which differ from those of the Company Table 10.

Table 8 17p base case model ICERs using 23rd March revised company model

	OFAT	IDEL
ERG ICER vs	£44,161	£44,357
Company ICER vs	£44,213	£51,647

The main discrepancy is in terms of the cost effectiveness estimate compared to idelalisib+rituximab. The text of the Company submission states that this applies the 17p specific naïve PFS HR of [redacted], but it appears that the Company estimate actually applies the all patient PFS HR of [redacted].

8.2 Additional model error and ERG error

The first cycle IV administration costs are calculated as the number of administrations during the cycle multiplied by the cost per subsequent IV administration minus the net lower cost of a first administration. But the cost per subsequent IV administration minus the net lower cost of a first administration does not have brackets around it as it should. All models needs to be corrected for this[1].

When revising the second cycle and beyond IV administration costs the ERG incorrectly copied the first year IV administration costs formulae into these cells. The combination of these errors resulted in negative administration costs over a number of cycles, most notably for ibrutinib. This is most easily seen in Table 59 of the original ERG report where the administration costs for ibrutinib during PFS are -£2,641. The ERG revised model that underlies section 5.4 of the original ERG report needs to be corrected for this[2].

[1] Implemented by bracketing the administration cost elements in the *Drug_Cost* worksheet cells AZ10:BC10, the *PC_Drug_Costs* worksheet cells CF12:CJ12 and the *SubTx_Drug_Costs* cells AI10:AJ10.
[2] Corrected by removing the reference to *C_admin_IV_d1extra* in the Drug_Costs worksheet cells A11:BC410, in the PC_Drug_Costs worksheet cells CF13:CJ412 and the SubTx_Drug_Costs worksheet cells AI11:AJ410, and setting the Drug_Costs worksheet cells AY10:AY410 and the PC_Drug_Costs cells CI12:CI412 equal to zero.

Section 9 Revised economic analyses: ERG

The ERG has corrected the errors outlined above and further changed the ERG revised model of section 5.4 of the original ERG report along the following lines:

- Apply the HRs outlined above, accepting that the cross-over adjustment is suitable for the base case
- 1.85m^2 BSA
- Age weighted utilities as per the Company revised model[3]
- Apply PD rather than SD ongoing costs during PFS[4]

The ERG also presents the following deterministic sensitivity analyses:

- SA01: Restricting the OS HR benefit for ibrutinib to 5 years
- SA02: Applying the Weibull PFS curve
- SA03: The OS HR of [redacted] for idelalisib+rituximab not adjusted for cross-over
- SA04: The 17p specific PFS HR of [redacted] for idelalisib+rituximab
- SA05: The HELIOS Cox Table 39 OS HR of [redacted] and PFS HR of [redacted] for bendamustine+rituximab
- SA06: The Fischer MAIC OS HR of [redacted] and PFS HR of [redacted] for bendamustine+rituximab
- SA07: The original Swedish registry OS HR of [redacted] and PFS HR of [redacted] for physician choice
- SA08: The Osterborg OS HR of [redacted] and PFS HR of [redacted] for physician choice
- SA09: A 0.600 QoL for PPS
- SA10: Applying the all patient QoL in the 17p analysis
- SA11: Differentiating PFS costs by the response status estimates of the Company ITC

9.1 ERG: all patient modelling

The deterministic estimates for the all patient modelling are as below.

[3] Note that this requires that the relatively minor ERG revision of applying the 2nd line QoL decrement of Beusterein (2010) for those receiving further treatment subsequent to progression be removed. This has minimal impact upon results.

[4] Implemented in the Micro_Costs worksheet by having cells L42:46 refer to cell S37 rather than cell S35

Table 9 ERG: all patients deterministic estimates: Ex PASs

	IBRU	PHYS	OFAT	IDEL	BEND
PFS total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS Drug cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS Administration cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS Routine follow up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS AE cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS SubTx Tx cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS BSC cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS SubTx Routine follow up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Terminal cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost vs comparator		£227,266	£202,111	£152,933	£223,469
Total undisc LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS undisc LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS undisc LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net undisc LY		[redacted]	[redacted]	[redacted]	[redacted]
net PFS LY		[redacted]	[redacted]	[redacted]	[redacted]
net PPS LY		[redacted]	[redacted]	[redacted]	[redacted]
QALYs PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net QALY vs comparator		2.773	2.638	1.937	2.123
ICER vs comparator		£81,966	£76,612	£78,936	£105k

Running the PSA over 10,000 iterations results in the following central pairwise cost effectiveness estimates.

Table 10 ERG: all patients PSA central estimates: Ex PASs

	IBRU	PHYS	OFAT	IDEL	BEND
Costs	£262,691	£34,444	£59,579	£110,261	£38,285
QALYs	4.579	1.870	1.995	2.734	2.534
ICER		£84,231	£78,609	£82,608	£109,729

The corresponding CEAFs are as below.

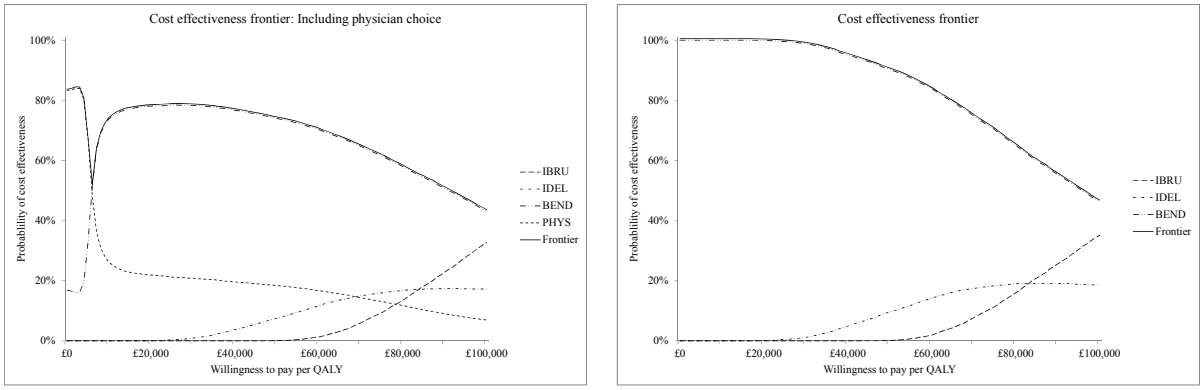

Figure 3 ERG: all patients CEAFs: Ex PASs

The pairwise probabilities of ibrutinib being the most cost effective are as below.

Table 11 ERG: all patients pairwise probabilities of cost effectiveness: Ex PASs

WTP	PHYS	OFAT	IDEL	BEND
£0	0%	0%	0%	0%
£10,000	0%	0%	0%	0%
£20,000	0%	0%	0%	0%
£30,000	0%	0%	0%	0%
£50,000	1%	3%	12%	0%
£100,000	73%	78%	66%	43%

9.2 ERG: all patient modelling: univariate sensitivity analyses

Table 12 ERG All patient modelling sensitivity analyses: Ex PASs

	PHYS	OFAT	IDEL	BEND
Base case	£81,966	£76,612	£78,936	£105k
SA01: OS HR benefit only 5 years	£85,751	£78,319	£83,356	£125k
SA02: Weibull PFS curve	£61,783	£53,739	£54,193	£80,131
SA03: IDEL OS HR no x-over adjustment			£93,293	
SA04: IDEL PFS HR 17p naïve comparison				
SA05: BEND OS HR & PFS HR Table 39				£81,252
SA06: BEND OS HR & PFS HR Fischer MAIC				£65,936
SA07: PHYS OS HR & PFS HR previous reg.	£85,682			
SA08: PHYS OS HR & PFS HR Osterborg	£71,490			
SA09: PPS QoL 0.600	£82,259	£76,567	£79,541	£103k
SA10: All patient QoL for 17p patients				
SA11: PFS costs differentiated by Tx response	£81,630	£76,271	£78,499	£105k

9.3 ERG: 17p patient modelling: base case

The deterministic estimates for the all patient modelling are as below.

Table 13 ERG: 17p deterministic estimates: Ex PASs

	IBRU	PHYS	OFAT	IDEL	BEND
PFS total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS Drug cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS Administration cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS Routine follow up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS AE cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS SubTx Tx cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS BSC cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS SubTx Routine follow up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Terminal cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost vs comparator		£191,537	£168,866	£128,948	£188,422
Total undisc LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS undisc LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS undisc LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net undisc LY		[redacted]	[redacted]	[redacted]	[redacted]
net PFS LY		[redacted]	[redacted]	[redacted]	[redacted]
net PPS LY		[redacted]	[redacted]	[redacted]	[redacted]
QALYs PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net QALY vs comparator		2.318	2.561	1.650	1.812
ICER vs comparator		£82,630	£65,927	£78,140	£104k

9.4 ERG: 17p patient modelling: univariate sensitivity analyses

Table 14 ERG 17p patient modelling sensitivity analyses: Ex PASs

	PHYS	OFAT	IDEL	BEND
Base case	£82,630	£65,927	£78,140	£104k
SA01: OS HR benefit only 5 years	£87,569	£65,199	£83,672	£121k
SA02: Weibull PFS curve	£64,316	£47,253	£55,072	£81,694
SA03: IDEL OS HR no x-over adjustment			£91,251	
SA04: IDEL PFS HR 17p naïve comparison			£68,688	
SA05: BEND OS HR & PFS HR Table 39				£82,041
SA06: BEND OS HR & PFS HR Fischer MAIC				£67,966
SA07: PHYS OS HR & PFS HR previous reg.	£86,042			
SA08: PHYS OS HR & PFS HR Osterborg	£73,086			
SA09: PPS QoL 0.600	£82,783	£66,258	£78,403	£103k
SA10: All patient QoL for 17p patients	£78,696	£62,621	£74,304	£99,635
SA11: PFS costs differentiated by Tx response	£82,293	£65,631	£77,708	£104k

9.5 End of life

As summarised in the cost effectiveness estimates base case, the ERG base case mean overall survival estimates that the model outputs are:

- [redacted] years for ibrutinib
- [redacted] years for physician choice
- [redacted] years for ofatumumab
- [redacted] years for idelalisib+rituximab
- [redacted] years for bendamustine+rituximab

Revising the HR for bendamustine+rituximab to that of of Table 39 of the Company submission reduces its estimated mean overall survival from [redacted] years to [redacted] years, while that of the Fischer MAIC further reduces it to [redacted] years.