

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation [ID749]

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

1. [Response to consultee, commentator and public comments on the Appraisal Consultation Document \(ACD\)](#)
2. [Consultee and commentator comments on the Appraisal Consultation Document](#) from:
 - [Janssen](#)
 - [Chronic Lymphocytic Leukaemia Support Association and Leukaemia CARE](#)
 - [United Kingdom Chronic Lymphocytic Leukaemia Forum](#)
 - [Royal College of Physicians \(RCP\) on behalf of the NCRI-ACP-RCP](#)
 - [Royal College of Pathologists](#)
 - [NHS England](#)
The Department of Health indicated that they had no comments
3. [Comments on the Appraisal Consultation Document received through the NICE website](#)
4. [Letter from Janssen sent to NICE after the 4 August Committee meeting](#)

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

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SingleTechnology Appraisal

**Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation
Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

Definitions:

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

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

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

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

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Janssen	<p>1. Overview</p> <p>The main points we wish to address in this response are as follows:</p> <p>Magnitude of ibrutinib’s treatment effect</p> <p>The Committee appears to inadvertently conclude that the clinical benefits of ibrutinib and idelalisib in combination with rituximab (IR) are similar (4.14, 4.26 of 2nd ACD). We request that these data be reconsidered:</p> <ul style="list-style-type: none"> • By the Committee’s own acknowledgement, the IR regimen still only presents patients with a median life expectancy of 21.6 months (4.29 of 2nd ACD). • The latest results for ibrutinib (presented at the previous meeting), report that 77.8% of patients are still alive at median 30 month follow-up. • Extrapolation by any of the parametric functions previously considered (by Janssen or the ERG), suggest median overall survival (OS) will be at least 5 years. • Whilst the committee may consider the clinical evidence of ibrutinib immature, it is the ONLY treatment option available with demonstrable clinical OS that offers patients and physicians the ability to look beyond the “End of Life” timeframe. It is the fact that it continues to keep patients alive that continues to make the ongoing clinical data ‘uncertain’. <p>Comparators</p> <p>We recognise the desire of the Committee to compare ibrutinib to IR. Whilst we have tried to undertake as robust an analysis as feasible, we request the Committee consider:</p> <ul style="list-style-type: none"> • At the time of our submission, IR had not been approved for use on the NHS; in fact, final NICE guidance for IR was only released 7 days after ibrutinib was submitted to NICE • The most robust data comes from our Phase III head to head study, versus ofatumumab, a treatment which was available and used in the NHS during ibrutinib’s development, and was only displaced when the newer drugs, and especially ibrutinib itself, became available • The inability to provide a more robust comparative analysis against IR is driven by the paucity of clinical data on the IR combination in the public domain, particularly beyond published 6 month follow-up (Furman et al, 2014), rather than our modelling assumptions. 	<p>Thank you for your comment. Please see detailed responses for the individual issues below.</p>

Consultee	Comment [sic]	Response
	<ul style="list-style-type: none"> • The assumptions preferred by the Committee for the indirect comparison of ibrutinib versus IR lack face validity, given the short OS for IR, and the ongoing significant OS expected for patients receiving ibrutinib, as described above. We refer the Committee to our detailed discussion on this matter in our previous response (Section 4.1, Janssen Response to the 1st ACD, 23rd March 2016). • In light of the ongoing safety investigations into idelalisib by the European Medicines Agency (EMA), that its market share has never risen above 20%, and that (excluding ibrutinib) there is still significant variation in the treatment options used within the NHS, supports the assumption that there is currently no single standard of care for the treatment of CLL in England and Wales. It is therefore appropriate for the Committee to consider all four comparisons presented in the original submission, and identified in the scope (including Physician’s Choice [PC] which encapsulates all treatments listed in the scope for which data were not available to conduct one-to-one comparisons to). • The multiple comparisons to the various treatment options available for CLL provide greater certainty to the Committee’s consideration of the evidence. <p>Cross-over adjustment In light of the significant demonstrable benefits observed in the clinical trials and ongoing longer term follow-up, we request that the Committee reconsider our original approach to conduct an ITC based on cross-over adjustment to the RESONATE data:</p> <ul style="list-style-type: none"> • We maintain the cross-over adjusted RESONATE trial data is the most appropriate data set to use to represent the true efficacy of ibrutinib • To not adjust for cross-over raises questions on the face validity of the analysis; the unadjusted ofatumumab arm from RESONATE (including the 61% who crossed-over to ibrutinib and thus gained substantial benefit) would likely have a better OS than IR. The 30 month datacut of RESONATE, as presented within the previous ACD response, shows the ITT ofatumumab arm to have an OS of [REDACTED] at 30 months, which is in excess of the IR median OS of 21.6 months (4.29 of the 2nd ACD). <p>CLL patients with 17p deletion/TP53 mutation We are disappointed that NICE have invited us to apply to the CDF for the 17p deletion patient subgroup, for the following specific reasons:</p> <ul style="list-style-type: none"> • Given the ongoing safety concerns surrounding idelalisib and that EMA is now recommending that treatment-naïve patients with 17p deletion are not started on idelalisib. 	

Consultee	Comment [sic]	Response
	<ul style="list-style-type: none"> Given the breadth of data continuously becoming available on 17p deletion patients treated with ibrutinib (n = 243 from a pooled analysis of trial data and n = 428 from a real-world study of French patients), especially in light of the fact that IR received a positive recommendation based upon far less data (n = 9) in this same patient population; <p>A detailed response to each of these key issues is provided on the following pages.</p>	
Janssen	<p>2. Magnitude of ibrutinib’s treatment effect</p> <p>The committee considered the company’s extrapolation of data from RESONATE for progression-free survival and overall survival over the 20-year time horizon of the model. The committee and the ERG noted that data were immature (notably, median progression-free survival and overall survival had not been reached in the ibrutinib arm of RESONATE), which the committee acknowledged may reflect a successful treatment effect, but which led to uncertainty [para 4.16]</p> <p>The committee recognised that idelalisib plus rituximab has only recently become available, so differences between idelalisib plus rituximab and ibrutinib in efficacy estimates, utility values and longterm outcomes are unknown [para 4.26]</p> <p>The committee agreed that the uncertain benefits of ibrutinib compared with idelalisib plus rituximab was unlikely to warrant the significant additional acquisition cost of ibrutinib compared with idelalisib plus rituximab even when applying the current patient access schemes [para 4.26]</p> <p>At a median of 30 months follow-up in the RESONATE trial, patients treated with ibrutinib have not yet reached median OS and █████ of patients remain alive. These results are impressive and unprecedented, and represent a true step change for patients in the r/r CLL treatment setting.</p> <p>In contrast, NICE recommended IR, with a reported a median OS of 21.6 months (Section 2.1, Janssen Response to the 1st ACD, 23rd March 2016). Janssen therefore contends that the modelling assumptions preferred by the Committee simply cannot hold, given the considerable difference in survival that has been observed at the longest follow-up data cut for both treatments. This, coupled with the ongoing safety restrictions on the use of idelalisib issued on 18th March 2016 by EMA, is further compelling evidence of the differences between these two treatment requirements. Taken together, there is no justifiable basis for concluding that the two treatments are comparable in terms of clinical efficacy or tolerability. To illustrate this point, extrapolation by any of the parametric functions, presented in our original submission and our response to the first ACD (Section 4.2.1, Janssen Response to</p>	<p>The committee considered that comments from patient and clinical experts on the meeting and also the comments submitted by consultees, which suggested that ibrutinib provides progression-free survival benefits and well tolerated by patients. It also heard from clinicians that, because of the risks associated with idelalisib, their preference would be to offer ibrutinib. I therefore concluded that ibrutinib offered a more preferable toxicity profile, and was likely to offer progression-free and overall survival benefits compared with idelalisib plus rituximab, but was mindful that the extent of this benefit was uncertain. Please see section 4.14 of the FAD.</p>

Consultee	Comment [sic]	Response
	<p>the 1st ACD, 23rd March 2016), shows that median OS would not be reached for over 5 years for patients receiving ibrutinib, compared to the figure of less than 2 years reported for IR.</p>	
<p>Janssen</p>	<p>3. Comparators <i>“The committee heard that ibrutinib ‘replaced’ ofatumumab in the Cancer Drug Fund. However, the committee was clear that, in line with NICE’s Guide to the methods of technology appraisal 2013, ofatumumab was not an appropriate comparator because it was not considered a cost-effective use of NHS resources in NICE’s technology appraisal guidance on ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab” [para 4.3]</i> <i>“The committee concluded that, for the population relevant to the decision problem, idelalisib plus rituximab was the most relevant comparator in clinical practice for patients who had relapsed within 2 years. It further concluded that, for patients for whom idelalisib was not an option (those who relapsed beyond 2 years, or those for whom idelalisib was not appropriate), bendamustine plus rituximab was most likely to be used” [para 4.3]</i></p> <p>Janssen maintains that all comparators presented in the submission (that is, PC, ofatumumab, bendamustine in combination with rituximab [BR], and IR) are relevant to the appraisal of ibrutinib for the following key reasons:</p> <ul style="list-style-type: none"> • Ibrutinib was submitted to NICE seven days prior to the final NICE guidance for IR being released, which means at the time of submission, no treatments in this setting had formal NICE positive guidance. • The final NICE scope for ibrutinib included a broad range of treatment options, supporting our conclusion that there is no standard of care in R/R CLL. • Clinicians agree that there is no standard of care, and that both PC and ofatumumab are relevant comparators (Section 3.1-3.3, Janssen Response to the 1st ACD, 23rd March 2016). • Even since the introduction of the idelalisib and ibrutinib, authoritative UK and international clinical guidelines continue to support and recommend a broad range of treatments for this patient population (Section 3.3, Janssen Response to the 1st ACD, 23rd March 2016). • UK data, which we presented in our last ACD response, clearly shows that there are a range of treatments used in patients with relapsed CLL. This situation has only changed since the introduction of ibrutinib into the UK market (listed on the CDF in January 2015), from which point it has displaced several treatments. The IMS and OncoAnalyzer studies both clearly demonstrate that a variety of treatments are currently prescribed in r/r CLL within NHS baseline commissioning. It is incorrect to focus on the CDF notification data as this simply shows that ibrutinib has become 	<p>The committee thoroughly discussed the issue of comparators. It considered the statements from the clinical experts that both ibrutinib and idelalisib have been available on the Cancer Drugs Fund and, wherever possible, treatment with ibrutinib is strongly preferred because of its effectiveness and because of the adverse effects associated with idelalisib. However, the experts agreed that, in the absence of ibrutinib, clinicians would offer idelalisib plus rituximab.</p> <p>It also discussed whether other comparators would be relevant and in light of the evidence and based on what it heard from clinical experts on the meeting, it concluded that idelalisib plus rituximab was the most relevant comparator in clinical practice for patients who had relapsed within 2 years, and for those who cannot take idelalisib plus rituximab, best supportive care was the best comparator. Please also see sections 4.7-7.8.</p>

Consultee	Comment [sic]	Response
	<p>the dominant agent for these patients, being by far the most requested treatment, followed by idelalisib (at a ratio of close to 9:1). It makes no sense to disregard comparators to ibrutinib that have been displaced by ibrutinib, as this is the very definition of a comparator. For this reason it is important to look across baseline commissioning (as the CDF only represents a proportion of all funding provided by NHS England for cancer treatment) and to look at the treatment landscape before the introduction of ibrutinib. Doing so clearly shows that UK patients, in the absence of ibrutinib, receive a range of treatments that align to the original scope of the appraisal (see Table 1). The latest market research data from May 2016 shows ■ of patients receiving IR, ■ BR and the remainder a mix of chemoimmunotherapy regimens that we have previously described as physicians' choice. It should be noted that usage of IR has decreased slightly in the most recent data, almost certainly as a result of the ongoing safety concerns.</p> <ul style="list-style-type: none"> • Ofatumumab and BR were only removed from the CDF when ibrutinib was listed on the CDF; we would argue that this displacement represents the very definition of a comparator. We would also like to highlight that the final NICE scope of the IR appraisal included ofatumumab as a relevant comparator. It is deeply inconsistent to apply such different perspectives for these two appraisals that have been conducted within a matter of months of one another. Of note, 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. Lastly, NICE accepted rituximab monotherapy as the key comparator in the IR submission, even though it has never been recommended by NICE and was not included in the final NICE scope for IR. Thus, in order to be consistent, if rituximab monotherapy was accepted as a comparator for the IR submission, ofatumumab should be accepted for the ibrutinib submission. • The strongest and most relevant evidence to evaluate the comparative treatment effectiveness of ibrutinib is the randomised, phase III head-to-head trial against ofatumumab, RESONATE. The trial was designed to compare against ofatumumab as it was the only licensed treatment in this setting at the time of trial initiation, which was accepted by the EMA (European Medicines Agency, 2014). • Whilst Janssen recognises that IR is a relevant comparator, it is only one of a range of comparators. Furthermore, it is unreasonable for the committee to expect Janssen to have been able to generate evidence against IR, given that ibrutinib and IR came to market at roughly the same time. It is therefore unfair to use the methodological inability to conduct a robust analysis against IR as a reason not to approve this medicine. Importantly, Janssen was hampered in trying to establish 	

Consultee	Comment [sic]	Response
	<p>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 as we do not have access to comparative data that allows us to make a robust comparison against IR.</p> <ul style="list-style-type: none"> We maintain that when you take into account the very extensive set of analyses we have presented to the committee, against a range of relevant comparators, the totality of the evidence is compelling. ICERs against these comparators are consistently below £50K/QALY and are robust across different assumptions. There is a remarkable degree of consistency in the relative treatment effect of ibrutinib across a range of analytical methods and comparators and in the cost-effectiveness results they drive. <p>In short, Janssen has made the fullest possible use of all available data and, wherever possible, provided two estimates of ibrutinib's comparative efficacy versus comparators to address concerns regarding uncertainty. Estimates for comparing ibrutinib vs. ofatumumab and PC suggested a consistency in treatment effect. In the case of BR, where traditional comparative approaches could not be used and estimates differed somewhat, a range of estimates was far more valuable than a single estimate could be. However, the Committee has rejected nearly all of the comparative evidence Janssen has provided, including 30 months of comparative follow-up data from RESONATE, instead relying on a single ITC vs. IO and a single multivariate Cox model vs. BR to establish ibrutinib's relative efficacy. This contributes significantly to the uncertainty that the Committee cites on numerous occasions. The data submitted by Janssen as well as the Committee's decision regarding what data to consider are summarised in Table 1.</p> <p><i>Table has been presented but not replicated here.</i></p>	
Janssen	<p>4. Cross-over adjustment <i>The committee discussed how best to account for the effect of treatment switching, following the Jones et al trial, on the relative effectiveness of ibrutinib and idelalisib. The Committee recognised the company did not have access to the data from Jones et al, and therefore could not adjust this trial. The Committee therefore considered the options available, which were to either adjust the RESONATE trial only, or adjust neither trial. The Committee recognised that adjusting 1 trial, but not the other, would exaggerate the benefit of ibrutinib over idelalisib plus ofatumumab. It recognised that if crossover and treatment switching occurred more often in RESONATE than in Jones et al, then adjusting neither trial would underestimate the treatment effect of ibrutinib. Similarly, if the crossover or</i></p>	<p>The committee considered the options available to account for the effect of the treatment switching that occurred after the 119 trial on the relative effectiveness of ibrutinib and idelalisib and concluded that the true estimates of the clinical benefit of ibrutinib compared with idelalisib plus rituximab would likely be weaker than, but closer to, the company's estimates of clinical effectiveness when adjusting only the RESONATE data for crossover, compared with estimates based on not</p>

Consultee	Comment [sic]	Response
	<p><i>treatment switching occurred more often in Jones et al, this would overestimate the treatment effect of ibrutinib. The committee agreed that, of the options available, adjusting neither trial would be the most appropriate approach [para 4.11].</i></p> <p>Janssen urges the Committee to follow NICE DSU guidance, the ERG’s revised opinion, and good statistical practice (Ishak et al., 2014; Jonsson et al., 2014; Latimer et al., 2014; Watkins et al., 2013) by accepting that adjustment for cross-over must be taken into account under these circumstances.</p> <p>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 huge bias to the ITCs, dramatically underestimating ibrutinib’s OS benefit. If cross-over is not taken into account, it is estimated that the OS associated with the ofatumumab arm of the trial would be [REDACTED] at 30 months, which is clearly implausible, given that in all other trials of ofatumumab published in this area, median OS was less than 20 months (Table 2). Moreover, given that the NICE guidance for ofatumumab determined that median OS was 13.7 months, assuming no cross-over with a resultant OS of [REDACTED] at 30 months of follow up in the ofatumumab arm in the current appraisal is wholly inconsistent.</p> <p><i>Table has been presented, but not replicated here.</i></p> <p>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.</p> <p>Prof. Peter Hillmen has confirmed that no crossover occurred from the idelalisib + ofatumumab arm to the ofatumumab arm in Jones, 2015 (Study 119). Thus, the only</p>	<p>adjusting data from either trial. Please see section 4.13 of the FAD.</p>

Consultee	Comment [sic]	Response
	<p>treatment switching that may be relevant for consideration is subsequent treatment that could have affected OS outcomes that patients went on to receive outside the trial. In a recent poster publication of Study 119, the non-significant OS results comparing IO vs. ofatumumab were attributed in part to “control group transition to newly available active agents at or near disease progression” (see below). There is nothing in the trial methods or results to suggest that patients on the IO arm did not also go on to receive novel agents and may have also received survival benefits from subsequent treatment. Without knowing the specific subsequent treatments received by patients in both arms of the trial, there is no reason to assume that the ofatumumab control arm received greater OS benefit post-progression than did the IO arm. There is, therefore, no reason to consider a crossover adjustment.</p> <p>In contrast, the subsequent treatments for patients who progressed while on ibrutinib or ofatumumab in the RESONATE trial were very similar in the two trial arms <i>except for the crossover from the ofatumumab arm to the ibrutinib arm</i>. The most common subsequent treatment for both arms (again, excluding ibrutinib in the case of the ofatumumab arm) was rituximab, with neither arm receiving novel agents post-progression in any meaningful numbers (see Table 4). In the case of RESONATE, it is very clear that the OS of ofatumumab is contaminated by post-progression ibrutinib use, with no other differences in subsequent treatment between the ibrutinib and ofatumumab arms. Thus, crossover introduces significant bias in the RESONATE trial.</p> <p>As a result of the above, Janssen maintains that crossover adjustment must be included for the RESONATE trial in the ITCs to establish comparative efficacy. Of note, the ERG has agreed with this and based its ICERs in the second ACD on crossover-adjusted hazard ratios for ibrutinib vs. ofatumumab.</p>	
Janssen	<p>5. CLL patients with 17p deletion <i>“The appraisal committee is minded not to recommend ibrutinib as an option for treating chronic lymphocytic leukaemia in adults with a 17p deletion or TP53 mutation. The committee invites the company to submit a proposal for inclusion in the Cancer Drugs Fund” [para 1.2]</i></p> <p>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-naïve 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</p>	<p>The committee was aware that no data were available for patients with a 17p deletion or TP53 mutation who have not had treatment. To improve evidence related to patients with the 17p deletion or TP53 mutation, the committee had invited the company to submit a proposal for its use in the CDF. The committee understood that the company chose not to apply to the CDF, stating that data exceeding 2 years already exist. In support of this, the company submitted data from a study of 243 patients with the 17p deletion (both treatment naïve and relapsed/refractory) that showed both median</p>

Consultee	Comment [sic]	Response
	<p>ibrutinib data from the Farooqui trial, which demonstrated efficacy in 35 patients [33 evaluable] patients).</p> <p>The Committee continues to assert that IR remains a relevant comparator in patients with 17p deletion. Janssen would continue to contest this assertion, particularly given the ongoing safety concerns and recommendation from the EMA that patients with this mutation not be started on idelalisib.</p> <p>Lastly, Janssen is unclear as to how applying to the new CDF would help to reduce much uncertainty for the Committee in both the treatment-naïve and r/r 17p deletion subgroup. At the recent European Haematology Association (EHA) Congress, data were presented that demonstrated that in a study of 243 patients with 17p (both treatment naïve and RR), median PFS and OS were not yet met at 30 month follow-up. By applying to the CDF and by nature of the disease, it is unlikely that data “certainty” in terms of reaching median PFS or median OS would be attainable over a short time period (e.g. two years). We believe the efficacy and safety data associated with ibrutinib in 17p deletion patients is the strongest evidence base available in this patient group and the treatment benefit is clear. We do not believe that better data than this already available data source could be obtained through the CDF.</p> <p><i>Figure has been presented, but not replicated here.</i></p>	<p>progression-free survival and overall survival were not met at 30 month follow-up. The committee agreed with this.</p> <p>Please see section 4.6 of the FAD.</p>
Janssen	<p>6. Conclusion</p> <p>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 trial 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, has been fully reimbursed in 49 countries globally, and is the most requested drug for the treatment of CLL on the CDF (NHS England, 2016). In addition, the following was demonstrated by the 30-month data cut of the pivotal RESONATE trial:</p> <ul style="list-style-type: none"> • Robustness and maturity of data <p>The number of patients and the length of follow-up far exceeds prior trials in R/R CLL; 391 patients were randomised into RESONATE the median duration of follow up is now 30 months. This contrasts with the two idelalisib trials, where 220 and 261 patients were randomised to studies 116 and 119 with duration of follow up of ■ and 13.6 months, respectively (Sharman et al., 2014 and Jones et al., 2015).</p> <ul style="list-style-type: none"> • Impressive and unprecedented efficacy 	<p>The committee considered all the evidence presented to it. It agreed that ibrutinib represented an important and effective treatment in CLL. It was satisfied that in both populations of this appraisal, the ICERs for ibrutinib fell within the range normally considered as cost-effective use of NHS resource for a treatment that fulfils the end-of-life criteria, when incorporating the confidential updated patient access scheme for ibrutinib and the existing patient access scheme for idelalisib.</p> <p>Please see section 4.31 of the FAD.</p>

Consultee	Comment [sic]	Response
	<p>Of note, the median PFS has still not been met; [REDACTED] of patients remain on ibrutinib at this new median follow up of 30.4 months. In addition, the median OS has still not been met; [REDACTED] of ibrutinib patients are still alive at 30 months. These results are unprecedented in the treatment of R/R CLL.</p> <ul style="list-style-type: none"> Safety and tolerability At this new median follow-up of 30.4 months, only [REDACTED] of patients have discontinued treatment with ibrutinib for AEs or unacceptable toxicity. This further supports the notion that ibrutinib is a safe and well tolerated drug. <p>The current recommendation is most certainly not in the best interest of patients, given the ongoing safety concerns surrounding idelalisib, and the lack of any alternative licensed therapy funded in the UK in this setting. Janssen urges the Committee to reconsider their recommendation, taking into account the full evidence base, including clinical and patient opinion, which clearly demonstrates that ibrutinib is highly clinically effective, safe, and cost-effective against all relevant comparators.</p> <p>We recognize the Committee is keen to ensure ibrutinib is only made available within the NHS at a price that is cost-effective. We believe that the extensive analyses we have presented the committee with demonstrate that our existing Patient Access Scheme (PAS) would provide access to patients at a level deemed value for money for the NHS. However, of major concern to Janssen is the fact that the committee does not appear to recognize the step change in effectiveness that ibrutinib offers patients with r/r CLL. Our view is that to move forward in a constructive manner, we must first achieve a closer alignment on the interpretation of the relative clinical benefits of ibrutinib (as discussed previously in this response).</p> <p><i>References and Appendices have been presented, but not replicated here.</i></p>	
NHS England	<p>Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</p> <p>No – In March 2016 the European Medicines Agency recommended new safety monitoring procedures for idelalisib, which include close monitoring and antibiotics to prevent pneumonia. Idelalisib should not be started in people with previously untreated chronic lymphocytic leukaemia whose cancer cells have certain genetic mutations (17p deletion or TP53 mutation). These are provisional recommendations issued while idelalisib is being reviewed by the European Medicines Agency. Whilst this review is underway, and dependent on its outcome, idelalisib may not be a valid comparator in patients with previously untreated CLL who have a 17p deletion or TP53 mutation.</p>	<p>Thank you for your comment. After the announcement of new safety monitoring procedures for idelalisib, in July 2016 CHMP has confirmed that the benefits of idelalisib outweigh the risk of side effects and that idelalisib ‘can again be initiated in these patients provided they cannot take any alternative treatment and that the measures agreed to prevent infection are followed’.</p> <p>The committee therefore agreed that the relevant comparators for the untreated 17p deletion or TP53 mutation population were idelalisib plus rituximab or</p>

Consultee	Comment [sic]	Response
		best supportive care. Please see section 4.10 of the FAD.
NHS England	<p>1. The CDF previously considered the two new drugs in CLL for relapsed/refractory disease in 2014 and again in 2015. For ibrutinib, it was aware that the key clinical trial compared ibrutinib with one of the then standard options in such patients, ofatumumab. For idelalisib given in combination with rituximab, it was aware too that the main clinical trial compared idelalisib plus rituximab with single agent (s/a) rituximab. The CDF then considered both comparators (s/a ofatumumab, a/s rituximab) as being correct comparators (ofatumumab then being available via the CDF, s/a rituximab being available via baseline commissioning). The CDF considered that the two relevant phase 3 clinical trials recruited broadly similar populations of patients ie the populations had reasons for not being best treated with further cytotoxic chemotherapy.</p> <p>2. The CDF assessed these two new interventions at times when the follow-up data were immature. It recognised that both were very active, both represented a step change in the treatment in CLL but both had differing toxicities and certain contraindications (for ibrutinib, no patients on warfarin or CYP3A4/5 inhibitors or having severe pancytopenia; for idelalisib plus rituximab, no past history of colitis). There was an impression that ibrutinib might be the more promising of the two drugs as the progression free survival data potentially looked greater (but these were different trials, there was relatively immature follow-up, see the CDF decision summaries) and the toxicity of ibrutinib seemed more predictable. There was no data presented to the CDF of the activity of one drug following the other.</p> <p>3. The CDF approved both ibrutinib and idelalisib plus rituximab as it could not reliably conclude that one was better than the other. It recognised that certain patients were best treated with one rather than the other and thus gave the patients/clinicians the choice to use one but not both (unless toxicity prevented continued use of one and so switching for these patients was allowed). The CDF thus prevented sequential use of these two drugs.</p> <p>4. CDF use of ibrutinib was far greater than the use of idelalisib plus rituximab. This was partly because it was an entirely oral regimen whereas idelalisib plus rituximab requires the intravenous administration of rituximab (ie is less convenient for patients), partly because of the view that CLL clinicians favoured the toxicity profile of ibrutinib and partly because, within the confines of the evidence, many clinicians considered it to be the better drug.</p> <p>5. Since the CDF considered the entry of ibrutinib and idelalisib plus rituximab in 2014, the CDF removed ofatumumab from funding. Nevertheless, it still retained ibrutinib as it considered the control arms in the two key phase 3 trials to represent broadly similar benefits to patients (note the median PFS for ofatumumab was 8.1</p>	<p>Thank you for your comments. The Committee considered the comments received for consultation and all the evidence presented to it. It agreed that ibrutinib represented an important and effective treatment in CLL. It was satisfied that in both populations of this appraisal, the ICERs for ibrutinib fell within the range normally considered as cost-effective use of NHS resource for a treatment that fulfils the end-of-life criteria, when incorporating the confidential updated patient access scheme for ibrutinib and the existing patient access scheme for idelalisib.</p> <p>Please see section 4.31 of the FAD.</p>

Consultee	Comment [sic]	Response
	<p>mo in the ibrutinib trial and for s/a rituximab was 6.5 mo in the idelalisib plus rituximab trial). Thus it considered the benefits of ibrutinib to be similar versus an NHSE comparator, hence the decision to retail ibrutinib in the CDF.</p> <p>6. NHSE regards the comparator (ofatumumab) in the ibrutinib trial as being an international standard at the time but of course ofatumumab can no longer be considered as a comparator in England as it was removed from the CDF in 2015. NHSE also regards s/a rituximab as being an international standard too, this being used in the idelalisib plus rituximab study as the control arm and was the comparator in the idelalsib NICE TA. The CDF regarded at the time in 2014-15 that both these comparators were appropriate but also delivered broadly similar outcomes to patients (as has already been stated above). NHSE notes that the TAC also came to the same conclusion. NHSE therefore would regard the ibrutinib clinical trial as giving the best current evidence base for assessment of the clinical effectiveness of ibrutinib.</p> <p>7. Bendamustine was removed from the CDF in 2015 for use in previously treated CLL and so the combination of bendamustine plus rituximab should not be regarded as a comparator either in this appraisal.</p> <p>8. The core issue is whether NHSE thus regards the main comparator for ibrutinib being the combination of idelalisib plus rituximab as this has recently gained NICE approval.</p> <p>9. The current CDF notifications for ibrutinib remain high for ibrutinib despite the combination of idelalisib plus riximab having been in baseline since early 2016. In the event that ibrutinib was concluded to be cost effective when compared with the combination of idelalisib plus rituximab, NHSE would still like to have idelalisib plus rituximab as an option as it recognises that some patients are still best treated with idelalisib plus rituximab rather than ibrutinib.</p> <p>10. In a scenario in which NICE recommends both ibrutinib and idelalsib plus rituximab as options for treatment in relapsed/refractory CLL and on the current evidence bases for the two drugs, NHSE would wish to commission an either-or option for patients and clinicians although would allow the other drug to be used if there is unacceptable toxicity and the patient has not progressed.</p> <p>11. The situation appears to be akin to the years during which various TNF alpha inhibitors were coming through for NICE appraisal with similar comparators in the various trials but not in trials compared against each other. NICE in its STAs assessed each on its own merits and only much later has it appraised them together once head to head information became available. The difference as regards ibrutinib vs idelalisib plus rituximab if both are approved now is that NHSE would commission use of one or the other in individual patients until such time as the evidence base changes. It thus seems reasonable for NICE to use the s/a ofatumumab data as a</p>	

Consultee	Comment [sic]	Response
	<p>proxy for s/a rituximab (see above re equivalence) as the comparator in this appraisal.</p> <p>12. The issue of NHSE restricting use could also apply to reflect the trial population as the expert clinicians at the appraisal affirmed that the trial population in RESONATE was the relevant population in England. The MA is much wider than the trial population and hence it would be vital for NICE to comment on the absence of any other robust information for comparative purposes in terms of the populations examined in the evidence base and thus the recommendation should reflect the population (as the current CDF availability does) and the fact that this population had not received previous idelalisib.</p> <p>13. NHSE would also like to comment as regards crossover in the ibrutinib study. Censoring the patients that have crossed over brings one kind of bias and thus one kind of uncertainty. Trying to allow for crossover with various statistical methods brings assumptions and thus other uncertainties (as NICE TACs very well know). Given that there is longer term follow up in some of the ibrutinib phase 2 trials, NHSE hopes that there is sufficient follow up to help at least test the earlier part of the modelled survival curve for ibrutinib in the economic model.</p> <p>14. NHSE notes that the idelalisib appraisal considered the expense of subsequent intravenous immunoglobulin therapy which, depending on assumptions as to use, assisted the cost effectiveness of idelalisib plus rituximab. It is unclear from the ibrutinib ACD whether such consideration was given in the economic model in the ibrutinib appraisal.</p> <p>15. NHSE regards the generalisability of previously treated pats with del 17p/TP53 mutation as being robust enough for the assessment of treatment of naïve patients with the same molecular profile.</p>	
<p>National Cancer Research Institute- Association of Cancer Physicians- Royal College of Physicians</p>	<p>Summary</p> <p>The second ACD continues to make several fundamental errors in the interpretation of the data. Many of these were highlighted from the first draft ACD and have not been either acknowledged or changed. In addition, since the first draft of the ACD there has been very important safety data emerging for one of the possible comparators, idelalisib plus rituximab, with the revelation of a doubling of toxicity related deaths associated with this combination in three randomised trials, the amendment of the EMA approval to remove the use of the drug in previously untreated patients with CLL due to a high death rate and a change in the use of this combination due to the fear of complications. None of this appears to be considered in the current draft of the ACD. The main issues that really have to be challenged are:</p>	<p>Thank you for your comment. After the announcement of new safety monitoring procedures for idelalisib, in July 2016 CHMP has confirmed that the benefits of idelalisib outweigh the risk of side effects and that idelalisib ‘can again be initiated in these patients provided they cannot take any alternative treatment and that the measures agreed to prevent infection are followed’.</p> <p>The committee therefore agreed that the relevant comparators for the untreated 17p deletion or TP53 mutation population were idelalisib plus rituximab or best supportive care. Please see section 4.10 of the FAD.</p>

Consultee	Comment [sic]	Response
	<p>1. The use of idelalisib plus rituximab as a comparator for patients with untreated CLL who have a 17p deletion or TP53 mutation is entirely inappropriate as the licence for this indication has been withdrawn and clinicians have been instructed by the MHRA not to use idelalisib plus rituximab for this indication.</p> <p>2. Ofatumumab has to be allowed as an appropriate comparator for ibrutinib in this appraisal. At the time of the trials it was the only approved and funded drug for relapsed, refractory patients with CLL (one of the patient populations being considered) and funding for ofatumumab in England was only withdrawn because it was inferior to ibrutinib in the Resonate trial and was replaced on the CDF by ibrutinib. The only reason that ofatumumab is not being considered as an appropriate comparator is that it is no longer funded in England for this indication.</p> <p>3. The new information on the toxicity issues for idelalisib with a high rate of severe colitis, pneumonitis and hepatic toxicity and, more recently, of life-threatening and fatal infections must be considered. These problems are not observed with ibrutinib. The inevitable conclusion of this ACD would be that patients would have to be treated with idelalisib rather than ibrutinib leading to a marked increase in resource utilization to manage complications (including prolonged acute hospital admissions and intensive care unit admissions) and to deaths due to treatment. Ultimately this will undermine the whole process as the patient and expert voice will have been unheeded.</p>	<p>Regarding the previously treated population the committee concluded that idelalisib plus rituximab was the most relevant comparator in clinical practice for patients who had relapsed within 2 years, and for those who cannot take idelalisib plus rituximab, best supportive care was the best comparator. Please see section 4.8 of the FAD.</p>
NCRI-ACP-RCP	<p>Specific Points:</p> <p>2.1 line 4: In first line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemoimmunotherapy.</p> <p>All patients with 17p deletion or TP53 mutation are 'unsuitable' for chemoimmunotherapy as this is ineffective. The only approved therapy in this group of patients is now ibrutinib (since the licence was withdrawn for idelalisib plus rituximab). There is no effective approved alternative to ibrutinib in this group</p>	<p>Thank you for your comment. The wording of the marketing authorisation for ibrutinib has been updated. Please see the summary of product characteristics.</p>
NCRI-ACP-RCP	<p>3.4 line 1: Patients randomised to ofatumumab were permitted to switch to ibrutinib on progression of disease, as defined by a protocol amendment by the independent data monitoring committee.</p> <p>This statement is incorrect. It is important to highlight that initially patients were not permitted to switch from ofatumumab to ibrutinib until the DMC mandated that this should happen after IRC assessed progression. This only occurred after recruitment was complete.</p>	<p>This section has been removed, please see the FAD.</p>
NCRI-ACP-RCP	<p>3.10 idelalisib + rituximab</p> <p>The inclusion of idelalisib as a direct comparator for ibrutinib is unreasonable. Idelalisib plus rituximab was not available until 15 months after enrollment in the Resonate (ibrutinib) trial was complete. Idelalisib was only approved by the FDA on</p>	<p>Idelalisib for treating chronic lymphocytic leukaemia has been approved by NICE and it has been available on the CDF. The committee however heard from clinical experts, that treatment with ibrutinib is strongly preferred because of its</p>

Consultee	Comment [sic]	Response
	23/7/14 and CHMP positive recommendation 24/7/14 (Resonate completed recruitment on 18/4/13)	effectiveness and because of the adverse effects associated with idelalisib. However, the experts also stated that in the absence of ibrutinib, clinicians would offer idelalisib plus rituximab. The committee agreed that idelalisib plus rituximab is a comparator. Please see section 4.7 of the FAD.
NCRI-ACP-RCP	3.14 The comparison with idelalisib plus ofatumumab is reasonably clinically as Idelalisib plus ofatumumab will be at least as effective as idelalisib plus rituximab. Most haematologists with an interest in CLL regard these two therapies as at least comparable. There is no evidence (either clinical or basic research) to suggest that ofatumumab is inferior to rituximab.	The committee heard from the clinical experts that idelalisib plus ofatumumab and idelalisib plus rituximab could be considered equivalent in terms of efficacy. Therefore it concluded that although there were uncertainties around the assumptions when comparing ibrutinib with idelalisib plus rituximab. On balance, the company's assumption that idelalisib plus rituximab is equivalent to idelalisib plus ofatumumab was reasonable. Please see section 4.15 of the FAD.
NCRI-ACP-RCP	3.16 line 3: However, the ERG noted that the control treatment, ofatumumab, is not a relevant comparator for English NHS practice because NICE did not recommend it for relapsed or refractory CLL and it has been removed from the Cancer Drugs Fund. This is not a reasonable position to take. At the time of the Resonate trial ofatumumab was the only approved therapy for this group of patients. On the 8 August 2012 the European marketing authorisation for alemtuzumab for CLL was withdrawn. The Resonate trial recruited between June 2012 and April 2013. Idelalisib was only approved in July 2014. At the time ofatumumab was the only approved therapy and was funded in the UK through the CDF. It was only withdrawn from the CDF in January 2015 as ibrutinib proved to be superior in the Resonate trial. So ofatumumab was the only relevant comparator for ibrutinib until it was beaten by ibrutinib.	The committee heard from the clinical experts, that since the availability of idelalisib and ibrutinib, clinicians no longer offer ofatumumab monotherapy to patients. The committee also considered the comments from consultees that that ibrutinib replaced ofatumumab in the CDF and ofatumumab should therefore be considered an appropriate comparator in this appraisal. However, in line with NICE's Guide to the methods of technology appraisal 2013, the committee concluded that ofatumumab was not an appropriate comparator because it was not considered a clinically effective or a cost-effective use of NHS resources in NICE's technology appraisal guidance on ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab. See section 4.8 of the FAD.
NCRI-ACP-RCP	3.18 line 5: The ERG noted the differences in populations between the trials, particularly in the proportion of patients with a 17p deletion in each trial (32.3% randomised to ibrutinib and 32.7% randomised to ofatumumab in RESONATE,	The committee considered that for the population with untreated CLL and a 17p deletion or TP53 mutation there are no treatment options available

Consultee	Comment [sic]	Response
	<p>compared with 26.4% randomised to idelalisib plus ofatumumab and 21.8% randomised to ofatumumab plus placebo in Jones et al.) The proportion of 17p del patients is higher in Resonate and therefore would bias the comparison against ibrutinib in favour of idelalisib. This does not seem to be acknowledged in the ACD.</p>	<p>other than idelalisib plus rituximab or best supportive care. Please see section 4.10 of the FAD.</p>
NCRI-ACP-RCP	<p>3.21, second bullet point: ibrutinib compared with ofatumumab (not in the scope) Our experts question why ofatumumab monotherapy was not in the scope. Rituximab alone (for refractory disease) was in the scope and is not approved for CLL, is not used and will be less (or at best equally) effective as ofatumumab. Ofatumumab or rituximab as a comparator with no danger of bias except to the disadvantage of ibrutinib given the much higher dose of ofatumumab used in Resonate compared to rituximab in practice. From a clinical perspective the scope is clearly incorrect.</p>	<p>Please see response above and also section 4.8 of the FAD.</p>
NCRI-ACP-RCP	<p>3.26, line 4: It used the results of the indirect treatment comparisons to model ibrutinib compared with physician's choice, the company's base-case comparator, and with idelalisib plus ofatumumab, which the company equated to idelalisib plus rituximab. This is a very fair assumption from a clinical perspective. (see answer to 3.21)</p>	<p>The committee heard from the clinical experts that idelalisib plus ofatumumab and idelalisib plus rituximab could be considered equivalent in terms of efficacy. Therefore it concluded that although there were uncertainties around the assumptions when comparing ibrutinib with idelalisib plus rituximab. On balance, the company's assumption that idelalisib plus rituximab is equivalent to idelalisib plus ofatumumab was reasonable. Please see section 4.15 of the FAD.</p>
NCRI-ACP-RCP	<p>3.37 line 3: Because ofatumumab is no longer available through the Cancer Drugs Fund... This is inappropriate as ofatumumab was only removed from the CDF as ibrutinib beat it in Resonate. If ibrutinib was not available ofatumumab would still be (see answer to 3.16)</p>	<p>Please see response above and section 4.8 of the FAD.</p>
NCRI-ACP-RCP	<p>3.38 line 13: Expert clinical opinion sought by the ERG suggested that the exponential curve provided a more credible estimate of the proportion of patients remaining progression free, given the anticipated survival, and so a more credible estimate of patients in the post-progression state. The ERG failed to acknowledge the expert opinion given that it was very unlikely that patients would remain on ibrutinib therapy for years as other novel agents are currently well on the way to approval and these are highly likely to yield very high responses and potentially stopping of therapy. This is a strategy being pursued in the front-line FLAIR trial of ibrutinib in the UK.</p>	<p>Thank you for your comment. The committee looked at the evidence presented by the company and its critique by the ERG and noted that the choice of model to extrapolate progression-free survival from RESONATE was a key driver of the cost-effectiveness results. The committee agreed that the Weibull function resulted in implausibly long survival after disease progression (estimates marked commercial in confidence by the company). The committee concluded that it preferred the</p>

Consultee	Comment [sic]	Response
		exponential distributions. Please see section 4.19 of the FAD.
NCRI-ACP-RCP	<p>4 Committee discussion:</p> <p>The appraisal committee reviewed the data available on the clinical and cost effectiveness of ibrutinib, having considered evidence on the nature of chronic lymphocytic leukaemia (CLL) and the value placed on the benefits of ibrutinib by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.</p> <p>The evidence given by the patient voice and the experts was uniform and compelling. There is no evidence that the appraisal committee seriously considered this evidence.</p>	The committee fully considered all the evidence put forward by the company and stakeholders, and the ERG critique of this evidence. Please see how the evidence from people with the condition, those who represent them, and clinical experts have been taken into account in sections 4.1, 4.14 and 4.28 of the FAD.
NCRI-ACP-RCP	<p>4.2 line 9: The clinical experts also explained that, in practice, clinicians would not offer patients another round of fludarabine containing chemo-immunotherapy because of significant adverse effects, and because it was unlikely to work well; so, RESONATE was reflective of clinical practice.</p> <p>This sentence should read 'do not' rather than 'would not'.</p>	Comment noted, the FAD has been updated, please see section 4.3.
NCRI-ACP-RCP	<p>4.3 line 4: The committee noted that NICE's technology appraisal on idelalisib for treating chronic lymphocytic leukaemia recommends idelalisib plus rituximab for CLL in adults with treated disease that has relapsed within 24 months.</p> <p>The appraisal for idelalisib was based on a randomised trial that recruited at the same time as Resonate.</p>	The committee concluded that idelalisib plus rituximab was the most relevant comparator in clinical practice for patients who had relapsed within 2 years, and for those who cannot take idelalisib plus rituximab, best supportive care was the best comparator. Please see section 4.8 of the FAD.
NCRI-ACP-RCP	<p>4.3 line 8: The clinical experts stated that both ibrutinib and idelalisib have been available on the Cancer Drugs Fund (CDF) and, wherever possible, treatment with ibrutinib is preferred because of the unpredictable adverse effects associated with idelalisib. The experts agreed that, in the absence of ibrutinib, clinicians would offer idelalisib plus rituximab.</p> <p>This was before the doubling of the death rate for patients randomised to idelalisib in a number of Phase III trials that re-enforced our comment. Our experts would be very reticent to offer idelalisib plus rituximab now due to the excessive infection-related deaths (at the time of the first ACD meeting this was not apparent) as well as the high incidence of severe autoimmune complications with idelalisib.</p>	The committee was aware of the safety concerns raised by the EMA, however it noted that the EMA's Committee for Medicinal Products for Human Use had confirmed that the benefits of idelalisib outweigh the risk of side effects and had now concluded that idelalisib 'can again be initiated in these patients provided they cannot take any alternative treatment and that the measures agreed to prevent infection are followed'. Please see section 4.10 of the FAD.
NCRI-ACP-RCP	<p>4.3 bullet point 1: It [bendamustine] has therefore become more difficult to obtain, but it is still offered alongside rituximab for some patients</p> <p>This is incorrect - bendamustine is not available in the England for relapsed CLL.</p>	The committee, at its third meeting, concluded that bendamustine is not routinely available and is therefore not an appropriate comparator. Please see section 4.8 of the FAD.
NCRI-ACP-RCP	<p>4.3 bullet point 4: The clinical experts confirmed that, since the availability of idelalisib and ibrutinib, clinicians no longer offer ofatumumab monotherapy to patients.</p>	The committee was clear that, in line with NICE's Guide to the methods of technology appraisal 2013, ofatumumab was not an appropriate comparator

Consultee	Comment [sic]	Response
	This is incorrect. It should read that 'The clinical experts confirmed that since the availability of ibrutinib clinicians no longer offer ofatumumab monotherapy to patients.' Grouping idelalisib and ibrutinib together in this way is inappropriate given the excessive toxicity associated with idelalisib.	because it was not considered a clinically effective or a cost-effective use of NHS resources in NICE's technology appraisal guidance on ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab. It was also not available through the CDF. Please see section 4.8 of the FAD.
NCRI-ACP-RCP	4.3 Final line:bendamustine plus rituximab was most likely to be used. This is incorrect. Bendamustine is not available for this population	The committee concluded that idelalisib plus rituximab was the most relevant comparator in clinical practice for patients who had relapsed within 2 years, and for those who cannot take idelalisib plus rituximab, best supportive care was the best comparator. Please see section 4.8 of the FAD.
NCRI-ACP-RCP	4.6 The comparators listed are inappropriate because: First bullet point for patients with refractory or relapsed CLL - Idelalisib plus rituximab (for those whose disease progresses within 2 years after the end of previous treatment) Idelalisib is too toxic with a doubling in treatment related deaths - Bendamustine plus rituximab (for those whose disease progresses 24 months after the end of previous treatment) Bendamustine is not available in England for this indication Second bullet point for patients with untreated CLL who have a 17p deletion or TP53 mutation. - idelalisib plus rituximab Inappropriate as the licence for this indication for idelalisib has now been withdrawn by the EMA on 17 March 2016.	The committee was aware of the safety concerns raised by the EMA, however it noted that the EMA's Committee for Medicinal Products for Human Use had confirmed that the benefits of idelalisib outweigh the risk of side effects and had now concluded that idelalisib 'can again be initiated in these patients provided they cannot take any alternative treatment and that the measures agreed to prevent infection are followed'. Please see section 4.10 of the FAD.
NCRI-ACP-RCP	4.7 line 10: The committee considered that the results from RESONATE were immature and uncertain in the longer term This is not the case. There is an overall survival benefit in favour of ibrutinib. How can an excess of deaths mean that the trial is 'immature'? There are no uncertainties in 'longer term' if the control arm patients are dying. ...and that the comparison with ofatumumab was not directly relevant to UK clinical practice as this is not used in UK clinical practice. As listed above ofatumumab is now only not available in England because ibrutinib was shown to be better in the Resonate trial leading to ofatumumab's removal from the CDF. How can it be correct to not look at ofatumumab as an appropriate comparator because it is worse than the drug (ibrutinib) that is being compared with	The committee was clear that the 'immaturity' of the data reflected the effectiveness of ibrutinib and viewed this positively. However, the committee was mindful that it did mean that a greater proportion of the modelled time horizon depended on extrapolations. The committee agreed that the trial showed ibrutinib extended progression-free survival compared with ofatumumab. Please see section 4.11 of the FAD.

Consultee	Comment [sic]	Response
	it. In this case, all high quality evidence would be immediately discounted. Ofatumumab was the only approved and funded drug when the Resonate trial was being carried. It was, in fact, the only reasonable comparator to use.	On the appropriateness of ofatumumab as a comparator please see response above and section 4.8 of the FAD.
NCRI-ACP-RCP	Innovation - Section 4.27 This seems to be the only part of the ACD that has been significantly changed from the original draft. Our expert are delighted that the appraisal committee recommended the end of life designation.	Comment noted.
Royal College of Pathologists	<p>General comments:</p> <p>1) Point 1.1</p> <p>“Ibrutinib is not recommended for treating chronic lymphocytic leukaemia in adults without a 17p deletion or TP53 mutation.”</p> <p>The data in the literature and emerging from the literature are showing overwhelming efficacy and reduced toxicity in the RESONATE and RESONATE-2 trials. The committee is not taking into any consideration the results of the RESONATE-2 study.</p>	<p>Thank you for your comments.</p> <p>The committee was not presented with any evidence from RESONATE-2, therefore it could not take it into consideration during the appraisal.</p>
RCPath	<p>2) Point 1.2</p> <p>"The appraisal committee is minded not to recommend ibrutinib as an option for treating chronic lymphocytic leukaemia in adults with a 17p deletion or TP53 mutation. The committee invites the company to submit a proposal for inclusion in the Cancer Drugs Fund."</p> <p>I have a concern that CDF is not going to be funded anymore hence ibrutinib becomes not accessible to patients with CLL in the UK. If CDF is going to close, I would like to argue as RCPath that the committee should strongly encourage the Company to propose ibrutinib to NICE for 17p-/TP53mut asap and/or favour studies.</p>	<p>The committee understood that the company chose not to apply to the CDF, stating that data exceeding 2 years already exist.</p> <p>Please see section 4.6 of the FAD.</p>
RCPath	<p>3) Although Resonate study have immature data (9.4 months follow-up) and inappropriate comparison for UK standards (ofatumomab), 17p-/TP53mut CLL remains a clinical unmet need and no right comparison exist"</p>	<p>The committee was aware that, in the absence of idelalisib, people with untreated CLL and a 17p deletion or TP53 mutation have no treatment options, and recognised the unmet need in this population. The committee therefore agreed that the relevant comparators for this group were idelalisib plus rituximab or best supportive care.</p> <p>Please see section 4.10 of the FAD.</p>
RCPath	<p>4) If the toxicity profile is considered acceptable, indication of Ibrutinib in the 17p-/TP53mut CLL setting should be considered, particularly in light of the toxicity of</p>	<p>Please see response above and also section 4.10 of the FAD.</p>

Consultee	Comment [sic]	Response
	idelalisib+rituximab, which does not remain an option for 17p-/TP53 CLL at least in the UK.	
RCPath	Cost-effectiveness: I convene that costs of the treatment are very expensive and believe that the company should make any major effort to accommodate patients' needs in the UK.	Before the fourth meeting, the company proposed and updated patient access scheme, which reduced the ICER results substantially to the point where the committee considered that ibrutinib reflected a cost-effective use of scarce NHS resources. Please see section 4.27 of the FAD.
RCPath	The recommendation at point 6.2 that research proposals "should include data collection to support the company's assumption that people with a 17p deletion and TP53 mutation whose CLL has been previously treated is a reasonable proxy for data in people with untreated disease, in terms of overall survival, progression-free survival and quality of life" is biased by the existence of a no profit collection of currently 304 patients in the NPS scheme. The collection has been a spontaneous initiative of many academic and non academic hospitals in the UK under the egidy of the UK CLL Forum. Careful attention of avoiding any interference by the company should be made, or viceversa an independent data monitoring committee and revision should be supported to review the effects of ibrutinib in real-life patients.	The research recommendation has been deleted from the FAD.
RCPath	<p>Specific comments: I copy and paste Prof. Hillmen reports that should be highlighted further plus my comments in red.</p> <p>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. Also RESONATE-2 trial has not been considered.</p> <p>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.</p> <p>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.</p>	Please see specific responses above.

Consultee	Comment [sic]	Response
	<p>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.</p>	
UK CLL Forum	<p>The UK CLL Forum has passed detailed comments on the previous ACD for ibrutinib for patients with relapsed / refractory CLL.</p> <p>Reading this second ACD, our major concern is that the clinician's vote of confidence in this drug and the patient's desire for access to it seem to have been lost in the various pharmacokinetic arguments. What we know for certain is that this is the most effective drug for treating relapsed / refractory CLL with an excellent side effect profile. The toxicity profile of its main NICE-approved competitor, idelalisib, is of significant concern, leading to the suspension of its EMA marketing authorisation for first line use, and we do not think this has been adequately considered in this review.</p> <p>We fully appreciate that it is very challenging to project long-term estimates as to how long patients will stay on this drug, owing to its efficacy, which makes it even more challenging to calculate true costs of the drug for the NHS population. However, the UK experience with using this drug to treat relapsed / refractory CLL is now extensive and the results from across the UK, which the UK CLL Forum have collated are remarkable. It is simply unimaginable to envisage managing CLL without access to this drug in 2016 and beyond and we implore NICE to come to a negotiated agreement with Janssen that permits our patients access to this drug. Lack of access to ibrutinib will unfortunately be literally a fatal blow to many patients with CLL in the UK.</p>	<p>Thank you for your comments.</p> <p>The committee concluded that the updated patient access scheme for ibrutinib reduced the ICER to the point where the committee considered that ibrutinib reflected a cost-effective use of scarce NHS resources. Please see section 4.27 and 4.31 of the FAD.</p>
Leukaemia CARE - Chronic Lymphocytic Leukaemia Support Association	<p>We are writing on behalf of chronic lymphocytic leukaemia (CLL) patients in response to the recently published second ACD for the appraisal of ibrutinib (Imbruvica®) – ID 749. We previously submitted a joint response to the initial ACD, which may provide additional information to supplement our response.</p> <p>We are extremely disappointed that the committee has invited the company to submit a proposal to the Cancer drugs fund for adults with a 17p deletion or TP53 mutation only. We feel that this recommendation would create an inequitable situation for adults who have had at least one prior therapy but without a 17p deletion or TP53 mutation. We feel that ibrutinib should be made available to both groups for the following reasons:</p> <ol style="list-style-type: none"> 1. Similar patient needs - both populations share a number of similarities in patient need, including a significant symptom burden, limited alternative treatment 	<p>The committee understood that the company chose not to apply to the CDF. It agreed with the company that data collection through the CDF would not resolve this uncertainty. Please see section 4.6 of the FAD.</p>

Consultee	Comment [sic]	Response
	<p>options and consequently poor survival prospects. Ibrutinib is a very well tolerated treatment offering improved symptom control for both populations. As both groups have a similar symptom burden, it is unfair that they will be unable to benefit from access to this treatment. We feel that ibrutinib should be available to both groups.</p> <p>2. Quality of life benefits - we do not feel that the quality of life benefits reported by patients have been adequately captured in the model. As such, the cost-effectiveness of ibrutinib is likely to have been underestimated.</p> <p>3. CLL is a heterogeneous disease – so there is a need for multiple options in every situation. Some patients may not respond to, be unable to tolerate or be otherwise unsuitable for alternative treatments such as idelalisib. As such, there is a clear need for access to ibrutinib to enable patient and clinician choice, so that treatment can be tailored to meet patients' individual clinical needs.</p> <p>4. 'Uncertainty' - throughout the ACD there are numerous references to the 'uncertainty' of the data relating to ibrutinib. The data is 'uncertain' because 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 means that after 30 months of follow-up, over 50% of patients are still alive and responding to treatment (compared with only 8.1 months progression-free for the comparator treatment option in the trial, ofatumumab). We do not consider it appropriate that this is being viewed as 'uncertainty', instead of a significant step forward for patients.</p> <p>5. Patient in Wales – would a recommendation for entry into the Cancer Drugs Fund (for patients in England only) create a health inequity, penalising against patients in Wales?</p> <p>As such, we feel the recommendations are an unreasonable conclusion in light of the evidence submitted.</p> <p>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 make it available to all of those who could benefit from it.</p>	

Comments received from clinical experts and patient experts

None

Comments received from commentators

None

Comments received from members of the public

Role*	Section	Comment [sic]	Response
Patient		<p>CLL experts are clear on the value of Ibrutinib which provides a paradigm shift in the treatment of CLL. An enlightened approach of immune-based strategies maintaining remissions, minimizing toxicities, and preserving immune functions offers preferential patient outcomes.</p> <p>The role of chemotherapy in this incurable chronic cancer is diminished and has moved to a targeted therapy approach, giving CLL patients the possibility to live a normal life span. You cannot seriously treat this chronic cancer continuously with chemotherapy with out directly reducing the patients overall survival.</p> <p>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.</p> <p>Has all of the relevant evidence been taken into account?</p> <p>Any trial comparison would be positive for Ibrutinib, regardless of which CLL treatment was used in comparison.</p> <p>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. Ibrutinib and Idelalisib are both required options for 17p deleted patients.</p> <p>In general Ibrutinib is considered to be more benign than idelalisib and offers a different toxicity profile for those patients unable to use idelalisib. Some patients will be resistant to Idelalisib. Both the options of idelalisib and ibrutinib is required in this setting.</p> <p>The trial data has been approved by EMA ,FDA and the CDF in favour of Ibrutinib.</p>	<p>Thank you for your comment. The committee considered all the evidence presented by the company and the ERG and also the comments received during consultation. It concluded that the updated patient access scheme for ibrutinib reduced the ICER results substantially to the point where the committee considered that ibrutinib reflected a cost-effective use of scarce NHS resources. Please see section 4.31 of the FAD.</p>

* When comments are submitted via the Institute’s web site, individuals are asked to identify their role by choosing from a list as follows: ‘patient’, ‘carer’, ‘general public’, ‘health professional (within NHS)’, ‘health professional (private sector)’, ‘healthcare industry (pharmaceutical)’, ‘healthcare industry’(other)’, ‘local government professional’ or, if none of these categories apply, ‘other’ with a separate box to enter a description.

Role*	Section	Comment [sic]	Response
		<p>Ibrutinib offers an easy to administer treatment that has lower toxicity and provides a targeted approach which will according to trials and extensive clinical practice deliver a better outcomes.</p> <p>Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</p> <p>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.</p> <p>Ibrutinib is a superior targeted oral treatment with low toxicity frees up resources and in combination may offers extended remissions.</p> <p>48 countries globally which have opted to fund Ibrutinib</p> <p>USA have also approved the use of Ibrutinib as a front line treatment for all CLL patients</p> <p>Are the provisional recommendations sound and a suitable basis for guidance to the NHS?</p> <p>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. The extensive clinical data now available for Ibrutinib is overwhelming and refusal to look at this along with all the additional trial data is wrong.</p> <p>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.</p>	

Role*	Section	Comment [sic]	Response
		<p>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?</p> <p>The role of chemotherapy in this incurable chronic cancer is diminished and has moved to a targeted therapy approach, giving CLL patients the possibility to live a normal life span. You cannot seriously treat a chronic cancer continuously with chemotherapy with out directly reducing the patients overall survival, the objective for young CLL patients should not be how someone is doing in ten years, but how they are doing in 20-30 years. Not providing the targeted drug therapy full options discriminates against CLL patients, reducing there potential life span.</p> <p>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 (rare cancers).</p> <p>The CLL patient community deserve to have the full resource and support of the NHS. Applying standard assessment methods to small groups of patients (such as rare cancers) “would result in us always recommending against their use. This would be unfair.” These are the words of Andrew Dillon, the Chief Executive of NICE.</p> <p>The use of ibrutinib in clinical practice has proved the effectiveness and safety profile of the drug and established it as the best non-chemo CLL drug currently approved for CLL. As a 57 year old CLL English patient I have no doubt that the prospect of continual NHS chemotherapy treatments will not offer me the prospect of a healthy life and normal life span.</p>	

Response to the Second Appraisal Consultation Document (ACD) Ibrutinib for treating chronic lymphocytic leukaemia [ID749]

June 22nd 2016

Thank you for the opportunity to comment on the above ACD. Despite the disappointing decision, Janssen remains committed to finding a mutually agreeable way to make ibrutinib available to appropriate patients within England and Wales. Janssen prides itself on our long history of collaborative working with NICE. We have always managed to find a way to allow access to our treatments at a price that is acceptable to both NICE and the NHS. We are therefore extremely disappointed that we have been unable, thus far, to find a mutually agreeable way forward for the current appraisal.

Janssen delayed this submission, in agreement with NICE in February 2015, in good faith. We delayed our submission as we made our initial European Medicines Agency (EMA) submission based upon single arm, Phase II trial data, and we were waiting for our Phase III trial (RESONATE) to report. NICE agreed to this request, to allow the Committee to assess ibrutinib based upon the most complete evidence base available. The following statement can be viewed on the NICE website, dated February 2015: *The manufacturer of ibrutinib, Janssen, has requested that this STA is rescheduled to start later this year, so that more mature data can be included in the appraisal. Because it is important that the most robust evidence available is considered by the Appraisal Committee, we have agreed to this request.*

Janssen is therefore disappointed that the current appraisal of ibrutinib has not been consistent with the recent appraisal of idelalisib in combination with rituximab (IR), due to the timing of the two appraisals and due to disregard of the scope of the current ibrutinib appraisal. In the IR appraisal, the full scope of comparators was considered, whereas in the current ibrutinib appraisal, the Committee has decided that IR is the main relevant comparator despite the fact that it is not an established standard of care in current clinical practice (nor was it at the time of Janssen's submission), dismissing the rest of the comparators (and resultant evidence base) in the scope.

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, across Europe and globally. The clinical demand for ibrutinib 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).

Our concerns and comments on this draft decision are summarised in the overview below and detailed in the following sub-sections. We respectfully request a consideration of our response and a fair, balanced and equitable clinical assessment that is consistent with the approach taken in the IR appraisal.

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1. Overview

The main points we wish to address in this response are as follows:

Magnitude of ibrutinib's treatment effect

The Committee appears to inadvertently conclude that the clinical benefits of ibrutinib and idelalisib in combination with rituximab (IR) are similar (4.14, 4.26 of 2nd ACD). We request that these data be reconsidered:

- By the Committee's own acknowledgement, the IR regimen still only presents patients with a median life expectancy of 21.6 months (4.29 of 2nd ACD).
- The latest results for ibrutinib (presented at the previous meeting), report that 77.8% of patients are still alive at median 30 month follow-up.
- Extrapolation by any of the parametric functions previously considered (by Janssen or the ERG), suggest median overall survival (OS) will be at least 5 years.
- Whilst the committee may consider the clinical evidence of ibrutinib immature, it is the ONLY treatment option available with demonstrable clinical OS that offers patients and physicians the ability to look beyond the "End of Life" timeframe. It is the fact that it continues to keep patients alive that continues to make the ongoing clinical data 'uncertain'.

Comparators

We recognise the desire of the Committee to compare ibrutinib to IR. Whilst we have tried to undertake as robust an analysis as feasible, we request the Committee consider:

- At the time of our submission, IR had not been approved for use on the NHS; in fact, final NICE guidance for IR was only released 7 days after ibrutinib was submitted to NICE
- The most robust data comes from our Phase III head to head study, versus ofatumumab, a treatment which was available and used in the NHS during ibrutinib's development, and was only displaced when the newer drugs, and especially ibrutinib itself, became available
- The inability to provide a more robust comparative analysis against IR is driven by the paucity of clinical data on the IR combination in the public domain, particularly beyond published 6 month follow-up (Furman et al, 2014), rather than our modelling assumptions.
- The assumptions preferred by the Committee for the indirect comparison of ibrutinib versus IR lack face validity, given the short OS for IR, and the ongoing significant OS expected for patients receiving ibrutinib, as described above. We refer the Committee to our detailed discussion on this matter in our previous response (Section 4.1, Janssen Response to the 1st ACD, 23rd March 2016).
- In light of the ongoing safety investigations into idelalisib by the European Medicines Agency (EMA), that its market share has never risen above 20%, and that (excluding ibrutinib) there is still significant variation in the treatment options used within the NHS, supports the assumption that there is currently no single standard of care for the treatment of CLL in England and Wales. It is therefore appropriate for the Committee to consider all four comparisons presented in the original submission, and identified in the scope (including Physician's Choice [PC] which encapsulates all treatments listed in the scope for which data were not available to conduct one-to-one comparisons to).
- The multiple comparisons to the various treatment options available for CLL provide greater certainty to the Committee's consideration of the evidence.

Cross-over adjustment

In light of the significant demonstrable benefits observed in the clinical trials and ongoing longer term follow-up, we request that the Committee reconsider our original approach to conduct an ITC based on cross-over adjustment to the RESONATE data:

- We maintain the cross-over adjusted RESONATE trial data is the most appropriate data set to use to represent the true efficacy of ibrutinib
- To not adjust for cross-over raises questions on the face validity of the analysis; the unadjusted ofatumumab arm from RESONATE (including the 61% who crossed-over to ibrutinib and thus gained substantial benefit) would likely have a better OS than IR. The 30 month datacut of RESONATE, as presented within the previous ACD response, shows the ITT ofatumumab arm to have an OS of [REDACTED] at 30 months, which is in excess of the IR median OS of 21.6 months (4.29 of the 2nd ACD).

CLL patients with 17p deletion/TP53 mutation

We are disappointed that NICE have invited us to apply to the CDF for the 17p deletion patient subgroup, for the following specific reasons:

- Given the ongoing safety concerns surrounding idelalisib and that EMA is now recommending that treatment-naïve patients with 17p deletion are not started on idelalisib.
- Given the breadth of data continuously becoming available on 17p deletion patients treated with ibrutinib (n = 243 from a pooled analysis of trial data and n = 428 from a real-world study of French patients), especially in light of the fact that IR received a positive recommendation based upon far less data (n = 9) in this same patient population;

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

2. Magnitude of ibrutinib's treatment effect

The committee considered the company's extrapolation of data from RESONATE for progression-free survival and overall survival over the 20-year time horizon of the model. The committee and the ERG noted that data were immature (notably, median progression-free survival and overall survival had not been reached in the ibrutinib arm of RESONATE), which the committee acknowledged may reflect a successful treatment effect, but which led to uncertainty [para 4.16]

The committee recognised that idelalisib plus rituximab has only recently become available, so differences between idelalisib plus rituximab and ibrutinib in efficacy estimates, utility values and longterm outcomes are unknown [para 4.26]

The committee agreed that the uncertain benefits of ibrutinib compared with idelalisib plus rituximab was unlikely to warrant the significant additional acquisition cost of ibrutinib compared with idelalisib plus rituximab even when applying the current patient access schemes [para 4.26]

At a median of 30 months follow-up in the RESONATE trial, patients treated with ibrutinib have not yet reached median OS and ████████ of patients remain alive. These results are impressive and unprecedented, and represent a true step change for patients in the r/r CLL treatment setting.

In contrast, NICE recommended IR, with a reported a median OS of 21.6 months (Section 2.1, Janssen Response to the 1st ACD, 23rd March 2016). Janssen therefore contends that the modelling assumptions preferred by the Committee simply cannot hold, given the considerable difference in survival that has been observed at the longest follow-up data cut for both treatments. This, coupled with the ongoing safety restrictions on the use of idelalisib issued on 18th March 2016 by EMA, is further compelling evidence of the differences between these two treatment requirements. Taken together, there is no justifiable basis for concluding that the two treatments are comparable in terms of clinical efficacy or tolerability. To illustrate this point, extrapolation by any of the parametric functions, presented in our original submission and our response to the first ACD (Section 4.2.1, Janssen Response to the 1st ACD, 23rd March 2016), shows that median OS would not be reached for over 5 years for patients receiving ibrutinib, compared to the figure of less than 2 years reported for IR.

3. Comparators

“The committee heard that ibrutinib ‘replaced’ ofatumumab in the Cancer Drug Fund. However, the committee was clear that, in line with NICE’s Guide to the methods of technology appraisal 2013, ofatumumab was not an appropriate comparator because it was not considered a cost-effective use of NHS resources in NICE’s technology appraisal guidance on ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab” [para 4.3]

“The committee concluded that, for the population relevant to the decision problem, idelalisib plus rituximab was the most relevant comparator in clinical practice for patients who had relapsed within 2 years. It further concluded that, for patients for whom idelalisib was not an option (those who relapsed beyond 2 years, or those for whom idelalisib was not appropriate), bendamustine plus rituximab was most likely to be used” [para 4.3]

Janssen maintains that all comparators presented in the submission (that is, PC, ofatumumab, bendamustine in combination with rituximab [BR], and IR) are relevant to the appraisal of ibrutinib for the following key reasons:

- Ibrutinib was submitted to NICE seven days prior to the final NICE guidance for IR being released, which means at the time of submission, no treatments in this setting had formal NICE positive guidance.
- The final NICE scope for ibrutinib included a broad range of treatment options, supporting our conclusion that there is no standard of care in R/R CLL.
- Clinicians agree that there is no standard of care, and that both PC and ofatumumab are relevant comparators (Section 3.1-3.3, Janssen Response to the 1st ACD, 23rd March 2016).
- Even since the introduction of the idelalisib and ibrutinib, authoritative UK and international clinical guidelines continue to support and recommend a broad range of treatments for this patient population (Section 3.3, Janssen Response to the 1st ACD, 23rd March 2016).
- UK data, which we presented in our last ACD response, clearly shows that there are a range of treatments used in patients with relapsed CLL. This situation has only changed since the introduction of ibrutinib into the UK market (listed on the CDF in January 2015), from which point it has displaced several treatments. The IMS and OncoAnalyzer studies both clearly demonstrate that a variety of treatments are currently prescribed in r/r CLL within NHS baseline commissioning. It is incorrect to focus on the CDF notification data as this simply shows that ibrutinib has become the dominant agent for these patients, being by far the most requested treatment, followed by idelalisib (at a ratio of close to 9:1). It makes no sense to disregard comparators to ibrutinib that have been displaced by ibrutinib, as this is the very definition of a comparator. For this reason it is important to look across baseline commissioning (as the CDF only represents a proportion of all funding provided by NHS England for cancer treatment) and to look at the treatment landscape before the introduction of ibrutinib. Doing so clearly shows that UK patients, in the absence of ibrutinib, receive a range of treatments that align to the original scope of the appraisal (see Table 3). The latest market research data from May 2016 shows █████ of patients receiving IR, █████ BR and the remainder a mix of chemoimmunotherapy regimens that we have previously described as physicians’ choice. It should be noted that usage of IR has decreased slightly in the most recent data, almost certainly as a result of the ongoing safety concerns.
- Ofatumumab and BR were only removed from the CDF when ibrutinib was listed on the CDF; we would argue that this displacement represents the very definition of a comparator. We would also like to highlight that the final NICE scope of the IR appraisal included ofatumumab as a relevant comparator. It is deeply inconsistent to apply such different perspectives for these two appraisals that have been conducted within a matter of months of one another. Of note, 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. Lastly, NICE accepted rituximab monotherapy as the key comparator in the IR submission, even though it has never been recommended by NICE and was not included in the final NICE scope for IR. Thus, in order to be consistent, if rituximab monotherapy was accepted as a comparator for the IR submission, ofatumumab should be accepted for the ibrutinib submission.

- The strongest and most relevant evidence to evaluate the comparative treatment effectiveness of ibrutinib is the randomised, phase III head-to-head trial against ofatumumab, RESONATE. The trial was designed to compare against ofatumumab as it was the only licensed treatment in this setting at the time of trial initiation, which was accepted by the EMA (European Medicines Agency, 2014).
- Whilst Janssen recognises that IR is a relevant comparator, it is only one of a range of comparators. Furthermore, it is unreasonable for the committee to expect Janssen to have been able to generate evidence against IR, given that ibrutinib and IR came to market at roughly the same time. It is therefore unfair to use the methodological inability to conduct a robust analysis against IR as a reason not to approve this medicine. Importantly, 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 as we do not have access to comparative data that allows us to make a robust comparison against IR.
- We maintain that when you take into account the very extensive set of analyses we have presented to the committee, against a range of relevant comparators, the totality of the evidence is compelling. ICERs against these comparators are consistently below £50K/QALY and are robust across different assumptions. There is a remarkable degree of consistency in the relative treatment effect of ibrutinib across a range of analytical methods and comparators and in the cost-effectiveness results they drive.

In short, Janssen has made the fullest possible use of all available data and, wherever possible, provided two estimates of ibrutinib's comparative efficacy versus comparators to address concerns regarding uncertainty. Estimates for comparing ibrutinib vs. ofatumumab and PC suggested a consistency in treatment effect. In the case of BR, where traditional comparative approaches could not be used and estimates differed somewhat, a range of estimates was far more valuable than a single estimate could be. However, the Committee has rejected nearly all of the comparative evidence Janssen has provided, including 30 months of comparative follow-up data from RESONATE, instead relying on a single ITC vs. IO and a single multivariate Cox model vs. BR to establish ibrutinib's relative efficacy. This contributes significantly to the uncertainty that the Committee cites on numerous occasions. The data submitted by Janssen as well as the Committee's decision regarding what data to consider are summarised in Table 1.

Table 1: Summary of comparative data submitted and the Committee’s response

Population	Comparison	Analysis type	Data sources	HR PFS (95% CI)	HR OS (95% CI)	Committee’s Response
R/R CLL	Ibrutinib vs. Ofatumumab	Direct RCT	RESONATE, 16-month data	0.11 (0.07-0.15)		Discarded; ofatumumab deemed not relevant to UK clinical practice
	Ibrutinib vs. PC	ITC, Bucher method	RESONATE vs. Osterborg, 2014			Discarded; PC’s composition not relevant to UK clinical practice
		ITC, multivariate Cox model	RESONATE vs. Karolinska Institute			Discarded; PC’s composition not relevant to UK clinical practice
		ITC, multivariate Cox model (revised PC composition)	RESONATE vs. Karolinska Institute			Discarded; PC’s composition not relevant to UK clinical practice despite being further re-weighted based on more recent UK market research data
	Ibrutinib vs. IO	ITC, Bucher method	RESONATE vs. Jones, 2015 (Study 119)	0.39 (0.23-0.66)	0.50 (0.24-1.04)	Accepted*
	Ibrutinib vs. BR	MAIC	RESONATE vs. Fischer, 2011			Discarded; MAIC not considered robust
		ITC, multivariate Cox model	RESONATE vs. HELIOS			Accepted
17p deletion	Ibrutinib vs. Ofatumumab	Direct RCT	RESONATE	0.25 (0.14-0.45) median follow-up of 5.8 mo.		Discarded; ofatumumab deemed not relevant to UK clinical practice
	Ibrutinib vs. IO	ITC, Bucher method	RESONATE vs. Jones, 2015 (Study 119)	 17pdel population	0.50 (0.24-1.05) all patients used as proxy for 17pdel population	Accepted*

* However, the Committee has not accepted the equivalence of ofatumumab and rituximab when in combination with idelalisib.

4. Cross-over adjustment

The committee discussed how best to account for the effect of treatment switching, following the Jones et al trial, on the relative effectiveness of ibrutinib and idelalisib. The Committee recognised the company did not have access to the data from Jones et al, and therefore could not adjust this trial. The Committee therefore considered the options available, which were to either adjust the RESONATE trial only, or adjust neither trial. The Committee recognised that adjusting 1 trial, but not the other, would exaggerate the benefit of ibrutinib over idelalisib plus ofatumumab. It recognised that if crossover and treatment switching occurred more often in RESONATE than in Jones et al, then adjusting neither trial would underestimate the treatment effect of ibrutinib. Similarly, if the crossover or treatment switching occurred more often in Jones et al, this would overestimate the treatment effect of ibrutinib. The committee agreed that, of the options available, adjusting neither trial would be the most appropriate approach [para 4.11].

Janssen urges the Committee to follow NICE DSU guidance, the ERG’s revised opinion, and good statistical practice (Ishak et al., 2014; Jonsson et al., 2014; Latimer et al., 2014; Watkins et al., 2013) by accepting that adjustment for cross-over must be taken into account under these circumstances.

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 huge bias to the ITCs, dramatically underestimating ibrutinib’s OS benefit. If cross-over is not taken into account, it is estimated that the OS associated with the ofatumumab arm of the trial would be █████ at 30 months, which is clearly implausible, given that in all other trials of ofatumumab published in this area, median OS was less than 20 months (Table 2).

Moreover, given that the NICE guidance for ofatumumab determined that median OS was 13.7 months, assuming no cross-over with a resultant OS of █████ at 30 months of follow up in the ofatumumab arm in the current appraisal is wholly inconsistent.

Table 2: 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

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.

Prof. Peter Hillmen has confirmed that no crossover occurred from the idelalisib + ofatumumab arm to the ofatumumab arm in Jones, 2015 (Study 119). Thus, the only treatment switching that may be relevant for consideration is subsequent treatment that could have affected OS outcomes that patients went on to receive outside the trial. In a recent poster publication of Study 119, the non-significant OS results comparing IO vs. ofatumumab were attributed in part to “control group transition to newly available active agents at or near disease progression” (see below). There is nothing in the trial methods or results to suggest that patients on the IO arm did not also go on to receive novel agents and may have also received survival benefits from subsequent treatment. Without knowing the specific subsequent treatments received by patients in both arms of the trial, there is no reason to assume that the ofatumumab control arm received greater OS benefit post-progression than did the IO arm. There is, therefore, no reason to consider a crossover adjustment.

In contrast, the subsequent treatments for patients who progressed while on ibrutinib or ofatumumab in the RESONATE trial were very similar in the two trial arms *except for the crossover from the ofatumumab arm to the ibrutinib arm*. The most common subsequent treatment for both arms (again, excluding ibrutinib in the case of the ofatumumab arm) was rituximab, with neither arm receiving novel agents post-progression in any meaningful numbers (see Table 4). In the case of RESONATE, it is very clear that the OS of ofatumumab is contaminated by post-progression ibrutinib use, with no other differences in subsequent treatment between the ibrutinib and ofatumumab arms. Thus, crossover introduces significant bias in the RESONATE trial.

As a result of the above, Janssen maintains that crossover adjustment must be included for the RESONATE trial in the ITCs to establish comparative efficacy. Of note, the ERG has agreed with this and based its ICERs in the second ACD on crossover-adjusted hazard ratios for ibrutinib vs. ofatumumab.

5. CLL patients with 17p deletion

“The appraisal committee is minded not to recommend ibrutinib as an option for treating chronic lymphocytic leukaemia in adults with a 17p deletion or TP53 mutation. The committee invites the company to submit a proposal for inclusion in the Cancer Drugs Fund” [para 1.2]

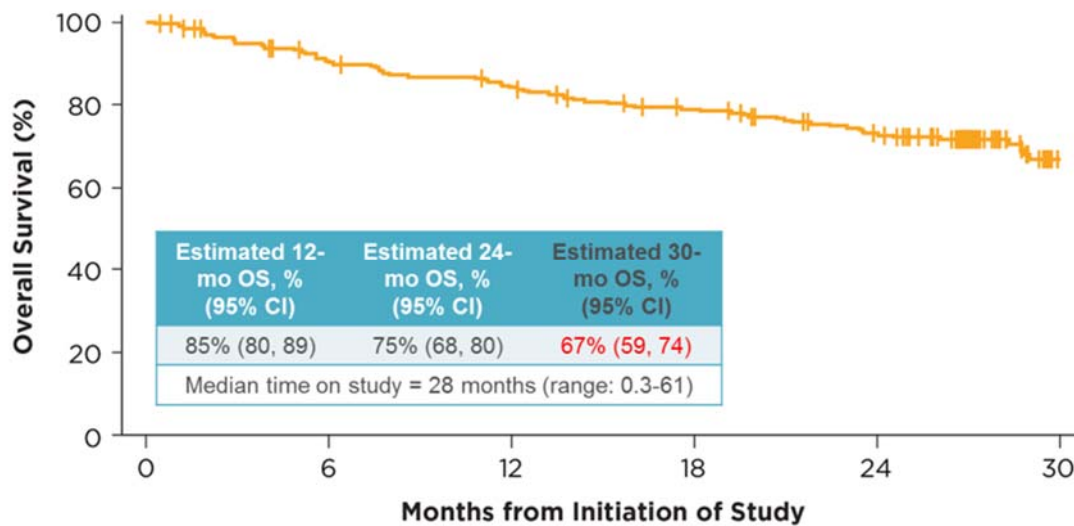
The Committee accepts that data on the 17p deletion subgroup in R/R CLL can serve as a proxy for a treatment-naïve 17p deletion subgroup. In the NICE FAD for IR in R/R CLL, IR was recommended for the subgroup of patients with treatment-naïve 17p deletion with less data than Janssen has already submitted 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 continues to assert that IR remains a relevant comparator in patients with 17p deletion. Janssen would continue to contest this assertion, particularly given the ongoing safety concerns and recommendation from the EMA that patients with this mutation not be started on idelalisib.

Lastly, Janssen is unclear as to how applying to the new CDF would help to reduce much uncertainty for the Committee in both the treatment-naïve and r/r 17p deletion subgroup. At the recent European Haematology Association (EHA) Congress, data were presented that demonstrated that in a study of 243 patients with 17p (both treatment naïve and RR), median PFS and OS were not yet met at 30 month follow-up (Jones et al, 2016). By applying to the CDF and by nature of the disease,

it is unlikely that data “certainty” in terms of reaching median PFS or median OS would be attainable over a short time period (e.g. two years). We believe the efficacy and safety data associated with ibrutinib in 17p deletion patients is the strongest evidence base available in this patient group and the treatment benefit is clear. We do not believe that better data than this already available data source could be obtained through the CDF.

Figure 1: Overall survival of 17p deletion patients treated with ibrutinib (n = 243)



6. Conclusion

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 trial 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, has been fully reimbursed in 49 countries globally, and is the most requested drug for the treatment of CLL on the CDF (NHS England, 2016).

In addition, the following was demonstrated by the 30-month data cut of the pivotal RESONATE trial:

- **Robustness and maturity of data**

The number of patients and the length of follow-up far exceeds prior trials in R/R CLL; 391 patients were randomised into RESONATE and the median duration of follow up is now 30 months. This contrasts with the two idelalisib trials, where 220 and 261 patients were randomised to studies 116 and 119 with duration of follow up of [redacted] and 13.6 months, respectively (Sharman et al., 2014 and Jones et al., 2015).

- **Impressive and unprecedented efficacy**

Of note, the median PFS has still not been met; [redacted] of patients remain on ibrutinib at this new median follow up of 30.4 months. In addition, the median OS has still not been met; [redacted] of ibrutinib patients are still alive at 30 months. These results are unprecedented in the treatment of R/R CLL.

- **Safety and tolerability**

At this new median follow-up of 30.4 months, only [redacted] of patients have discontinued treatment with ibrutinib for AEs or unacceptable toxicity. This further supports the notion that ibrutinib is a safe and well tolerated drug.

The current recommendation is most certainly not in the best interest of patients, given the ongoing safety concerns surrounding idelalisib, and the lack of any alternative licensed therapy funded in the UK in this setting. Janssen urges the Committee to reconsider their recommendation, taking into account the full evidence base, including clinical and patient opinion, which clearly demonstrates that ibrutinib is highly clinically effective, safe, and cost-effective against all relevant comparators.

We recognize the Committee is keen to ensure ibrutinib is only made available within the NHS at a price that is cost-effective. We believe that the extensive analyses we have presented the committee with demonstrate that our existing Patient Access Scheme (PAS) would provide access to patients at a level deemed value for money for the NHS. However, of major concern to Janssen is the fact that the committee does not appear to recognize the step change in effectiveness that ibrutinib offers patients with r/r CLL. Our view is that to move forward in a constructive manner, we must first achieve a closer alignment on the interpretation of the relative clinical benefits of ibrutinib (as discussed previously in this response).

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Appendix 1 Other issues, factual inaccuracies in the ACD, and additional data

“The committee noted that a scenario analysis done by the company (see section 3.33), which reduced the duration of ibrutinib’s benefit to 5 years, increased the ICER for ibrutinib compared with IR. The committee agreed to consider this analysis as part of its decision-making” (para 4.15)

The scenarios presented in the original submission (which tested reducing the duration of ibrutinib’s benefit to 6 or 7 years, not 5) were presented to highlight ibrutinib’s cost-effectiveness even if its efficacy continued for a brief duration. Based on the fact that median PFS has not been reached after a median of 30 months (RESONATE) and 3 years (1102/1103) of treatment with ibrutinib, limiting ibrutinib’s benefit to only 6 years is not reasonable. The ERG for the IR submission chose to limit the treatment benefit of IR to 5 years in an effort to reduce uncertainty. A five-year treatment benefit was arguably justified in that case given that median PFS was met in Study 116 at 19.4 months. It does not seem reasonable to use essentially the same duration of treatment benefit (6 years vs. 5 years) when one drug has a median PFS more than 50% greater than the other.

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 3.32, page 18	“The company explored another scenario in which ibrutinib’s treatment benefit was maintained for 5 years instead of indefinitely”	We provided scenario analyses limiting treatment benefit to 6 and 7 years.
Section 3.20, page 13	“The ERG noted the Österborg trial was not supported by a peer-reviewed publication.”	Österborg has now been published in <i>Leukemia & Lymphoma</i> ; published data aligns with the data used in the ITC (Österborg et al, 2016)
Section 4.3, page 26	The committee argues that PC is indeed a blended comparator	PC is not a blended comparator; the HR is estimated based on a single trial (and not a number of HRs averaged together and blended diluting or highlighting treatment effects).
Section 4.10, page 31	Typo: “The committee noted that the company adjusted the trial results of RESONATE (which compared ibrutinib with ofatumumab) to account for cross over, but did not adjust the hazard ratio from the Jones et al. (2015) trial (which compared idelalisib plus ofatumumab with ofatumumab) to account for treatment switching to ibrutinib.”	The sentence should end with “idelalisib”; “ibrutinib” is an error.
Section 4.16, page 36	Typo: “The committee considered how overall survival was modelled. It recognised that during consultation	“Weibull” is incorrect; it should state “exponential”.

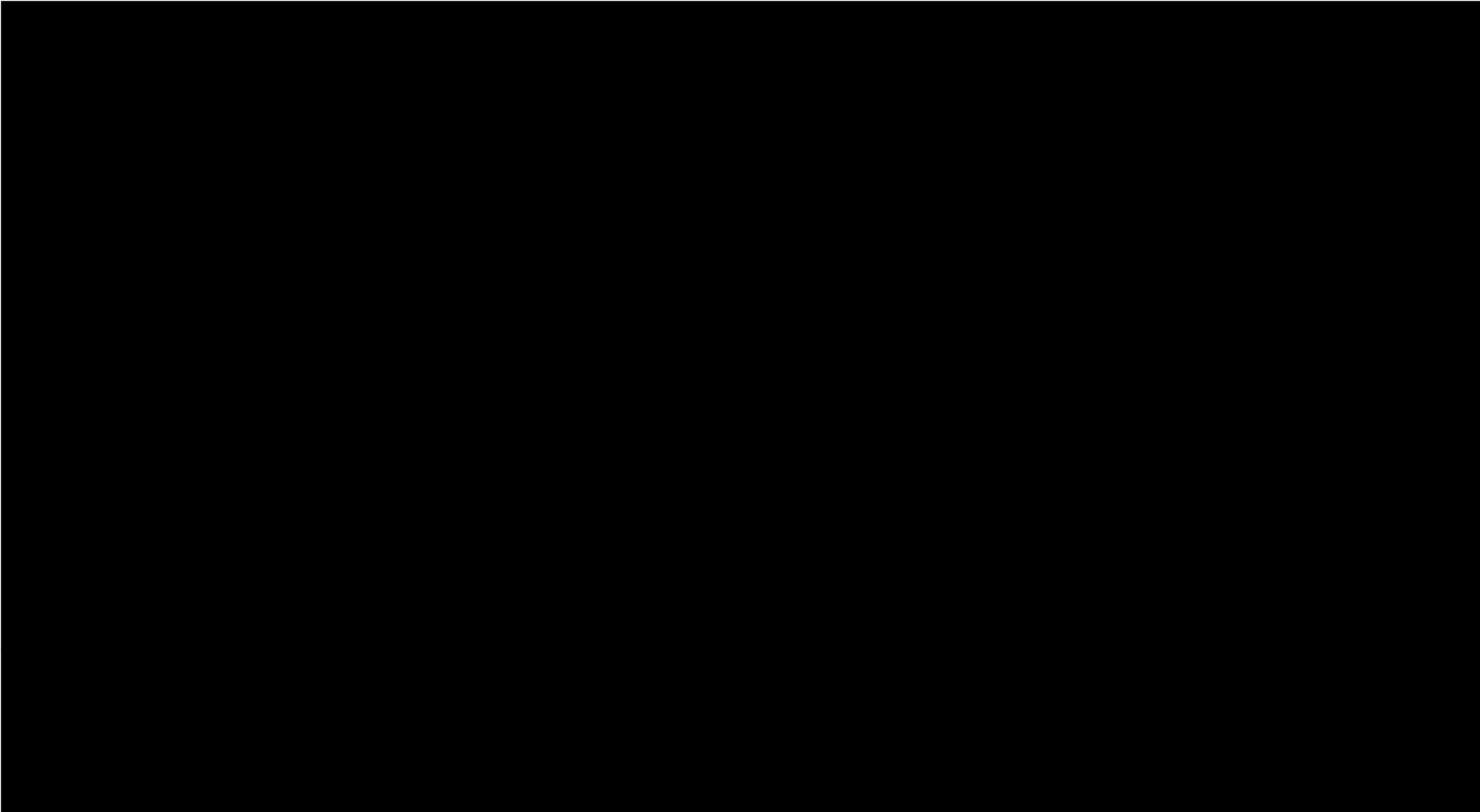
	the company had agreed with the committee that Weibull function provided the best fit of the options presented.”	
Section 4.8, page 30; Summary of appraisal committee’s key conclusions, page 50 and 52.	“The committee was aware that no data were available for patients with a 17p deletion or TP53 mutation who have not had treatment”	There are data available for patients with a 17p deletion or TP53 mutation who have not had treatment; Janssen presented this data in our original submission dated October 2015 for n = 35 patients from the Farooqui trial (please see Section 4.11 of the Janssen submission).
Summary of appraisal committee’s key conclusions, pages 48 and 51.	“The treatment options currently used in England in the NHS for CLL are:... for patients with untreated CLL who have a 17p deletion or TP53 mutation: idelalisib plus rituximab”	This statement is not accurate as the statement issued by the European Medicines Agency dated 18 th March 2016 clearly states “ <i>[idelalisib] should also not be started in previously untreated patients with CLL whose cancer cells have certain genetic mutations (17p deletion or TP53 mutation)</i> ” - EMA/201814/2016. Therefore, there is currently no treatment option used in England in the NHS for these patients.

Additional detailed data

Table 3: IMS Harmony market share data, excluding ibrutinib prescriptions

	Aug-14	Nov-14	Feb-15	May-15	Jul-15	Sep-15	Oct-15	Nov-15	Jan-16	Mar-16	May-16
	n= 27	n=25	n=32	n=59	n=67	n=60	n=75	n=56	n=61	n=60	n=50
Idelalisib + rituximab	■	■	■	■	■	■	■	■	■	■	■
BR	■	■	■	■	■	■	■	■	■	■	■
Ofatumumab regimen	■	■	■	■	■	■	■	■	■	■	■
FCR	■	■	■	■	■	■	■	■	■	■	■
R-CHOP	■	■	■	■	■	■	■	■	■	■	■
Obinutuzumab regimen	■	■	■	■	■	■	■	■	■	■	■
Bortezomib regimen	■	■	■	■	■	■	■	■	■	■	■
Lenalidomide regimen	■	■	■	■	■	■	■	■	■	■	■
Rituximab + chlorambucil	■	■	■	■	■	■	■	■	■	■	■
Other bendamustine regimen	■	■	■	■	■	■	■	■	■	■	■
Other chlorambucil regimen	■	■	■	■	■	■	■	■	■	■	■
Other fludarabine regimen	■	■	■	■	■	■	■	■	■	■	■
Other rituximab regimen	■	■	■	■	■	■	■	■	■	■	■
Other regimen	■	■	■	■	■	■	■	■	■	■	■

Table 4: Subsequent antineoplastic medicine (please treat as AIC)



Source: Table 14.1.5.6 of the RESONATE CSR

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 second ACD for the appraisal of ibrutinib (Imbruvica®) – ID 749. We previously submitted a joint response to the initial ACD, which may provide additional information to supplement our response.

We are extremely disappointed that the committee has invited the company to submit a proposal to the Cancer drugs fund for adults with a 17p deletion or TP53 mutation only. We feel that this recommendation would create an inequitable situation for adults who have had at least one prior therapy but without a 17p deletion or TP53 mutation. We feel that ibrutinib should be made available to both groups for the following reasons:

1. Similar patient needs - both populations share a number of similarities in patient need, including a significant symptom burden, limited alternative treatment options and consequently poor survival prospects. Ibrutinib is a very well tolerated treatment offering improved symptom control for both populations. As both groups have a similar symptom burden, it is unfair that they will be unable to benefit from access to this treatment. We feel that ibrutinib should be available to both groups.
2. Quality of life benefits - we do not feel that the quality of life benefits reported by patients have been adequately captured in the model. As such, the cost-effectiveness of ibrutinib is likely to have been underestimated.
3. CLL is a heterogeneous disease – so there is a need for multiple options in every situation. Some patients may not respond to, be unable to tolerate or be otherwise unsuitable for alternative treatments such as idelalisib. As such, there is a clear need for access to ibrutinib to enable patient and clinician choice, so that treatment can be tailored to meet patients' individual clinical needs.
4. 'Uncertainty' - throughout the ACD there are numerous references to the 'uncertainty' of the data relating to ibrutinib. The data is 'uncertain' because 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 means that after 30 months of follow-up, over 50% of patients are still alive and responding to treatment (compared with only 8.1 months progression-free for the comparator treatment option in the trial, ofatumumab). We do not consider it appropriate that this is being viewed as 'uncertainty', instead of a significant step forward for patients.
5. Patient in Wales – would a recommendation for entry into the Cancer Drugs Fund (for patients in England only) create a health inequity, penalising against patients in Wales?

As such, we feel the recommendations are an unreasonable conclusion in light of the evidence submitted.

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 make it available to all of those who could benefit from it.

Kind Regards,

A black rectangular redaction box covering the signature of the representative from Leukaemia CARE.

Leukaemia CARE

A black rectangular redaction box covering the signature of the representative from CLL Support Association.

CLL Support Association

The UK CLL Forum has passed detailed comments on the previous ACD for ibrutinib for patients with relapsed / refractory CLL.

Reading this second ACD, our major concern is that the clinician's vote of confidence in this drug and the patient's desire for access to it seem to have been lost in the various pharmacokinetic arguments. What we know for certain is that this is the most effective drug for treating relapsed / refractory CLL with an excellent side effect profile. The toxicity profile of its main NICE-approved competitor, idelalisib, is of significant concern, leading to the suspension of its EMA marketing authorisation for first line use, and we do not think this has been adequately considered in this review.

We fully appreciate that it is very challenging to project long-term estimates as to how long patients will stay on this drug, owing to its efficacy, which makes it even more challenging to calculate true costs of the drug for the NHS population. However, the UK experience with using this drug to treat relapsed / refractory CLL is now extensive and the results from across the UK, which the UK CLL Forum have collated are remarkable. It is simply unimaginable to envisage managing CLL without access to this drug in 2016 and beyond and we implore NICE to come to a negotiated agreement with Janssen that permits our patients access to this drug. Lack of access to ibrutinib will unfortunately be literally a fatal blow to many patients with CLL in the UK.

Professor Anna Schuh
Oxford
Chair, UK CLL Forum

Dr George Follows
Cambridge
Former Chair, UK CLL Forum

June 2016

National Institute for Health and Care Excellence
10 Spring Gardens
London
SW1A 2BU
jeremy.powell@nice.org.uk



27 June 2016

Dear Jeremy

Re: Ibrutinib for treating chronic lymphocytic leukaemia ID749

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 32,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

The NCRI-ACP-RCP are grateful for the opportunity to respond to the above consultation. We would like to make the following comments.

Summary

The second ACD continues to make several fundamental errors in the interpretation of the data. Many of these were highlighted from the first draft ACD and have not been either acknowledged or changed. In addition, since the first draft of the ACD there has been very important safety data emerging for one of the possible comparators, idelalisib plus rituximab, with the revelation of a doubling of toxicity related deaths associated with this combination in three randomised trials, the amendment of the EMA approval to remove the use of the drug in previously untreated patients with CLL due to a high death rate and a change in the use of this combination due to the fear of complications. None of this appears to be considered in the current draft of the ACD. The main issues that really have to be challenged are:

1. The use of idelalisib plus rituximab as a comparator for patients with untreated CLL who have a 17p deletion or TP53 mutation is entirely inappropriate as the licence for this indication has been withdrawn and clinicians have been instructed by the MHRA not to use idelalisib plus rituximab for this indication.
2. Ofatumumab has to be allowed as an appropriate comparator for ibrutinib in this appraisal. At the time of the trials it was the only approved and funded drug for relapsed, refractory patients with CLL (one of the patient populations being considered) and funding for ofatumumab in England was only withdrawn because it was inferior to ibrutinib in the Resonate trial and was replaced on the CDF by ibrutinib. The only reason that ofatumumab is not being considered as an appropriate comparator is that it is no longer funded in England for this indication.
3. The new information on the toxicity issues for idelalisib with a high rate of severe colitis, pneumonitis and hepatic toxicity and, more recently, of life-threatening and fatal infections must be considered.

These problems are not observed with ibrutinib. The inevitable conclusion of this ACD would be that patients would have to be treated with idelalisib rather than ibrutinib leading to a marked increase in resource utilization to manage complications (including prolonged acute hospital admissions and intensive care unit admissions) and to deaths due to treatment. Ultimately this will undermine the whole process as the patient and expert voice will have been unheeded.

Specific points:

2.1 line 4: In first line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemoimmunotherapy.

All patients with 17p deletion or TP53 mutation are 'unsuitable' for chemoimmunotherapy as this is ineffective. The only approved therapy in this group of patients is now ibrutinib (since the licence was withdrawn for idelalisib plus rituximab). There is no effective approved alternative to ibrutinib in this group of patients.

3.4 line 1: Patients randomised to ofatumumab were permitted to switch to ibrutinib on progression of disease, as defined by a protocol amendment by the independent data monitoring committee.

This statement is incorrect. It is important to highlight that initially patients were not permitted to switch from ofatumumab to ibrutinib until the DMC mandated that this should happen after IRC assessed progression. This only occurred after recruitment was complete.

3.10 idelalisib + rituximab

The inclusion of idelalisib as a direct comparator for ibrutinib is unreasonable. Idelalisib plus rituximab was not available until 15 months after enrollment in the Resonate (ibrutinib) trial was complete. Idelalisib was only approved by the FDA on 23/7/14 and CHMP positive recommendation 24/7/14 (Resonate completed recruitment on 18/4/13)

3.14

The comparison with idelalisib plus ofatumumab is reasonably clinically as Idelalisib plus ofatumumab will be at least as effective as idelalisib plus rituximab. Most haematologists with an interest in CLL regard these two therapies as at least comparable. There is no evidence (either clinical or basic research) to suggest that ofatumumab is inferior to rituximab.

3.16 line 3: However, the ERG noted that the control treatment, ofatumumab, is not a relevant comparator for English NHS practice because NICE did not recommend it for relapsed or refractory CLL and it has been removed from the Cancer Drugs Fund.

This is not a reasonable position to take. At the time of the Resonate trial ofatumumab was the only approved therapy for this group of patients. On the 8 August 2012 the European marketing authorisation for alemtuzumab for CLL was withdrawn. The Resonate trial recruited between June 2012 and April 2013. Idelalisib was only approved in July 2014. At the time ofatumumab was the only approved therapy and was funded in the UK through the CDF. It was only withdrawn from the CDF in January 2015 as ibrutinib proved to be superior in the Resonate trial. So ofatumumab was the only relevant comparator for ibrutinib until it was beaten by ibrutinib.

3.18 line 5: The ERG noted the differences in populations between the trials, particularly in the proportion of patients with a 17p deletion in each trial (32.3% randomised to ibrutinib and 32.7% randomised to ofatumumab in RESONATE, compared with 26.4% randomised to idelalisib plus ofatumumab and 21.8% randomised to ofatumumab plus placebo in Jones et al.)

The proportion of 17p del patients is higher in Resonate and therefore would bias the comparison against ibrutinib in favour of idelalisib. This does not seem to be acknowledged in the ACD.

3.21, second bullet point: ibrutinib compared with ofatumumab (not in the scope)

Our experts question why ofatumumab monotherapy was not in the scope. Rituximab alone (for refractory disease) was in the scope and is not approved for CLL, is not used and will be less (or at best equally) effective as ofatumumab. Ofatumumab or rituximab as a comparator with no danger of bias except to the disadvantage of ibrutinib given the much higher dose of ofatumumab used in Resonate compared to

rituximab in practice. From a clinical perspective the scope is clearly incorrect.

3.26, line 4: It used the results of the indirect treatment comparisons to model ibrutinib compared with physician's choice, the company's base-case comparator, and with idelalisib plus ofatumumab, which the company equated to idelalisib plus rituximab.

This is a very fair assumption from a clinical perspective. (see answer to 3.21)

3.37 line 3: Because ofatumumab is no longer available through the Cancer Drugs Fund...

This is inappropriate as ofatumumab was only removed from the CDF as ibrutinib beat it in Resonate. If ibrutinib was not available ofatumumab would still be (see answer to 3.16)

3.38 line 13: Expert clinical opinion sought by the ERG suggested that the exponential curve provided a more credible estimate of the proportion of patients remaining progression free, given the anticipated survival, and so a more credible estimate of patients in the post-progression state.

The ERG failed to acknowledge the expert opinion given that it was very unlikely that patients would remain on ibrutinib therapy for years as other novel agents are currently well on the way to approval and these are highly likely to yield very high responses and potentially stopping of therapy. This is a strategy being pursued in the front-line FLAIR trial of ibrutinib in the UK.

4 Committee discussion:

The appraisal committee reviewed the data available on the clinical and cost effectiveness of ibrutinib, having considered evidence on the nature of chronic lymphocytic leukaemia (CLL) and the value placed on the benefits of ibrutinib by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

The evidence given by the patient voice and the experts was uniform and compelling. There is no evidence that the appraisal committee seriously considered this evidence.

4.2 line 9: The clinical experts also explained that, in practice, clinicians would not offer patients another round of fludarabine containing chemo-immunotherapy because of significant adverse effects, and because it was unlikely to work well; so, RESONATE was reflective of clinical practice.

This sentence should read 'do not' rather than 'would not'.

4.3 line 4: The committee noted that NICE's technology appraisal on idelalisib for treating chronic lymphocytic leukaemia recommends idelalisib plus rituximab for CLL in adults with treated disease that has relapsed within 24 months.

The appraisal for idelalisib was based on a randomised trial that recruited at the same time as Resonate.

4.3 line 8: The clinical experts stated that both ibrutinib and idelalisib have been available on the Cancer Drugs Fund (CDF) and, wherever possible, treatment with ibrutinib is preferred because of the unpredictable adverse effects associated with idelalisib. The experts agreed that, in the absence of ibrutinib, clinicians would offer idelalisib plus rituximab.

This was before the doubling of the death rate for patients randomised to idelalisib in a number of Phase III trials that re-enforced our comment. Our experts would be very reticent to offer idelalisib plus rituximab now due to the excessive infection-related deaths (at the time of the first ACD meeting this was not apparent) as well as the high incidence of severe autoimmune complications with idelalisib.

4.3 bullet point 1: It [bendamustine] has therefore become more difficult to obtain, but it is still offered alongside rituximab for some patients

This is incorrect - bendamustine is not available in the England for relapsed CLL.

4.3 bullet point 4: The clinical experts confirmed that, since the availability of idelalisib and ibrutinib, clinicians no longer offer ofatumumab monotherapy to patients.

This is incorrect. It should read that 'The clinical experts confirmed that since the availability of ibrutinib clinicians no longer offer ofatumumab monotherapy to patients.' Grouping idelalisib and ibrutinib together in this way is inappropriate given the excessive toxicity associated with idelalisib.

4.3 Final line:bendamustine plus rituximab was most likely to be used.

This is incorrect. Bendamustine is not available for this population

4.6 The comparators listed are inappropriate because:

First bullet point for patients with refractory or relapsed CLL

- Idelalisib plus rituximab (for those whose disease progresses within 2 years after the end of previous treatment)

Idelalisib is too toxic with a doubling in treatment related deaths

- Bendamustine plus rituximab (for those whose disease progresses 24 months after the end of previous treatment)

Bendamustine is not available in England for this indication

Second bullet point for patients with untreated CLL who have a 17p deletion or TP53 mutation.

- idelalisib plus rituximab

Inappropriate as the licence for this indication for idelalisib has now been withdrawn by the EMA on 17 March 2016.

4.7 line 10: The committee considered that the results from RESONATE were immature and uncertain in the longer term

This is not the case. There is an overall survival benefit in favour of ibrutinib. How can an excess of deaths mean that the trial is 'immature'? There are no uncertainties in 'longer term' if the control arm patients are dying.

...and that the comparison with ofatumumab was not directly relevant to UK clinical practice as this is not used in UK clinical practice.

As listed above ofatumumab is now only not available in England because ibrutinib was shown to be better in the Resonate trial leading to ofatumumab's removal from the CDF. How can it be correct to not look at ofatumumab as an appropriate comparator because it is worse than the drug (ibrutinib) that is being compared with it. In this case, all high quality evidence would be immediately discounted. Ofatumumab was the only approved and funded drug when the Resonate trial was being carried. It was, in fact, the only reasonable comparator to use.

Innovation - Section 4.27

This seems to be the only part of the ACD that has been significantly changed from the original draft. Our expert are delighted that the appraisal committee recommended the end of life designation.

I would be grateful if you could confirm receipt.

Yours sincerely



Comments regarding NICE ACD for ibrutinib (ID: 749) from Francesco Forconi on behalf of the RCPATH 23rd June 2016

General comments:

1) Point 1.1

“Ibrutinib is not recommended for treating chronic lymphocytic leukaemia in adults without a 17p deletion or TP53 mutation.”

The data in the literature and emerging from the literature are showing overwhelming efficacy and reduced toxicity in the RESONATE and RESONATE-2 trials. The committee is not taking into any consideration the results of the RESONATE-2 study.

2) Point 1.2

“The appraisal committee is minded not to recommend ibrutinib as an option for treating chronic lymphocytic leukaemia in adults with a 17p deletion or TP53 mutation. The committee invites the company to submit a proposal for inclusion in the Cancer Drugs Fund.”

I have a concern that CDF is not going to be funded anymore hence ibrutinib becomes not accessible to patients with CLL in the UK. If CDF is going to close, I would like to argue as RCPATH that the committee should strongly encourage the Company to propose ibrutinib to NICE for 17p-/TP53mut asap and/or favour studies.

- 3) Although Resonate study have immature data (9.4 months follow-up) and inappropriate comparison for UK standards (ofatumomab), 17p-/TP53mut CLL remains a clinical unmet need and no right comparison exist”
- 4) If the toxicity profile is considered acceptable, indication of Ibrutinib in the 17p-/TP53mut CLL setting should be considered, particularly in light of the toxicity of idelalisib+rituximab, which does not remain an option for 17p-/TP53 CLL at least in the UK.

Cost-effectiveness: I convene that costs of the treatment are very expensive and believe that the company should make any major effort to accommodate patients’ needs in the UK.

The recommendation at point 6.2 that research proposals “should include data collection to support the company’s assumption that people with a 17p deletion and TP53 mutation whose CLL has been previously treated is a reasonable proxy for data in people with untreated disease, in terms of overall survival, progression-free survival and quality of life” is biased by the existence of a no profit collection of currently 304 patients in the NPS scheme. The collection has been a spontaneous initiative of many academic and non academic hospitals in the UK under the egidy of the UK CLL Forum. Careful attention of avoiding any interference by the company should be made, or viceversa an independent data monitoring committee and revision should be supported to review the effects of ibrutinib in real-life patients.

Specific comments: I copy and paste Prof. Hillmen reports that should be highlighted further plus my comments in red.

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.

Also RESONATE-2 trial has not been considered.

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 in terms 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.

NHS England Response to NICE ACD – Ibrutinib for treating chronic lymphocytic leukaemia

Please find NHS England's response to the ACD – Ibrutinib for treating chronic lymphocytic leukaemia

Has all of the relevant evidence been taken into account?
No comments.
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
<p>No – In March 2016 the European Medicines Agency recommended new safety monitoring procedures for idelalisib, which include close monitoring and antibiotics to prevent pneumonia. Idelalisib should not be started in people with previously untreated chronic lymphocytic leukaemia whose cancer cells have certain genetic mutations (17p deletion or TP53 mutation). These are provisional recommendations issued while idelalisib is being reviewed by the European Medicines Agency.</p> <p>Whilst this review is underway, and dependent on its outcome, idelalisib may not be a valid comparator in patients with previously untreated CLL who have a 17p deletion or TP53 mutation.</p>
Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
No comments.
Any other comments
No comments.

Contact details

Title (e.g. Dr, Mr, Ms, Prof)	████
Name	██████████
Job title or role	██████████
Email address	██████████

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

Role	Patient
Organisation	
Location	England
Conflict	No
Comments on the ACD:	
<p>CLL experts are clear on the value of Ibrutinib which provides a paradigm shift in the treatment of CLL. An enlightened approach of immune-based strategies maintaining remissions, minimizing toxicities, and preserving immune functions offers preferential patient outcomes.</p> <p>The role of chemotherapy in this incurable chronic cancer is diminished and has moved to a targeted therapy approach, giving CLL patients the possibility to live a normal life span. You cannot seriously treat this chronic cancer continuously with chemotherapy with out directly reducing the patients overall survival.</p> <p>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.</p> <p>Has all of the relevant evidence been taken into account?</p> <p style="padding-left: 40px;">Any trial comparison would be positive for Ibrutinib, regardless of which CLL treatment was used in comparison.</p> <p style="padding-left: 40px;">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. Ibrutinib and Idelalisib are both required options for 17p deleted patients.</p> <p style="padding-left: 40px;">In general Ibrutinib is considered to be more benign than idelalisib and offers a different toxicity profile for those patients unable to use idelalisib. Some patients will be resistant to Idelalisib. Both the options of idelalisib and ibrutinib is required in this setting.</p> <p style="padding-left: 40px;">The trial data has been approved by EMA ,FDA and the CDF in favour of Ibrutinib.</p> <p style="padding-left: 40px;">Ibrutinib offers an easy to administer treatment that has lower toxicity and provides a targeted approach which will according to trials and extensive clinical practice deliver a better outcomes.</p> <p>Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</p> <p style="padding-left: 40px;">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.</p>	

Ibrutinib is a superior targeted oral treatment with low toxicity frees up resources and in combination may offers extended remissions.

48 countries globally which have opted to fund Ibrutinib

USA have also approved the use of Ibrutinib as a front line treatment for all CLL patients

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

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. The extensive clinical data now available for Ibrutinib is overwhelming and refusal to look at this along with all the additional trial data is wrong.

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.

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?

The role of chemotherapy in this incurable chronic cancer is diminished and has moved to a targeted therapy approach, giving CLL patients the possibility to live a normal life span. You cannot seriously treat a chronic cancer continuously with chemotherapy with out directly reducing the patients overall survival, the objective for young CLL patients should not be how someone is doing in ten years, but how they are doing in 20-30 years. Not providing the targeted drug therapy full options discriminates against CLL patients, reducing there potential life span.

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 (rare cancers).

The CLL patient community deserve to have the full resource and support of the NHS. Applying standard assessment methods to small groups of patients (such as rare cancers) â€œwould result in us always recommending against their use. This would be unfair.â€ These are the words of Andrew Dillon, the Chief Executive of NICE.

The use of ibrutinib in clinical practice has proved the effectiveness and safety profile of the drug and established it as the best non-chemo CLL drug currently approved for CLL. As a 57 year old CLL English patient I have no doubt that the prospect of

continual NHS chemotherapy treatments will not offer me the prospect of a healthy life and normal life span.

Ibrutinib for treating chronic lymphocytic leukaemia [ID749]

Upon discussion with NICE and internally with our Global senior management team, Janssen will now revise the current simple discount for ibrutinib in relapsed/refractory chronic lymphocytic leukaemia (CLL).

Janssen proposes to increase the discount from [REDACTED]. This changes the net price to [REDACTED] per capsule. Cost-effectiveness analyses using the ERG's revised model¹ and preferred assumptions have been performed using the revised discount against the following comparators:

- The Committee's preferred comparator, idelalisib + rituximab (IR). The nationally agreed price reduction (NAPR) agreed for idelalisib remains confidential [REDACTED]
- Janssen's preferred comparator, Physician's choice (PC). Janssen presented two data sets for this comparator and as such, revised analyses using both the Österborg indirect treatment comparison (ITC) and the Karolinska Cox multivariate regression analysis have been conducted.

Table 1: Cost-effectiveness results with the revised ibrutinib discount, and assumed idelalisib NAPR of 35%

Comparator	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER vs. ibrutinib
Ibrutinib	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
IR	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	£48,190
PC (Österborg)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	£46,064
PC (Karolinska)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	£52,186

Key: QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio; IR, idelalisib+rituximab; PC, physicians' choice

Janssen proposes that the most important comparisons are vs. IR and PC (using the Österborg dataset), giving ICERs of £48,190 and £46,064, respectively (Table 1).

With respect to PC, given multiple data sources, the following hierarchy of evidence was considered in selecting the base case comparative efficacy estimate (as presented in the original company submission dated October 2015):

1. The most rigorous source of comparative efficacy is a head-to-head, RCT against the relevant comparator. This was not available for PC.
2. In the absence of RCT data, the NICE Methods Guide recommends establishing a network meta-analysis (NMA) or, if not all comparators can be included in one network, an ITC using common treatment arms². Such methods are considered to generate unbiased estimates of the relative treatment effect, under the assumption of relative treatment effects being similar across heterogeneity of trial characteristics. This was possible by using the Österborg study which allowed for ibrutinib and PC to be compared via the common ofatumumab comparator arm.

¹ version '(ID749) ibrutinib – IBRU model ERG revised sent to NICE 140616 (ACIC).xslm'

² National Institute for Health and Care Excellence. (2013). Guide to the methods of technology appraisal 2013. Available from: <http://publications.nice.org.uk/pmg9> (Accessed: 10 Jun 2016)

3. When indirect comparisons cannot be conducted due to lack of a common comparator, alternative statistical methods, such as matched-adjusted indirect comparison (MAIC) and pooled multivariate analysis, can be employed to estimate relative treatment efficacy between two treatments, adjusting for population differences between trials and therefore improving on naïve, unadjusted comparisons that can be introduce bias. A pooled multivariate analysis was possible using the Karolinska Swedish Registry dataset; however, given an ITC vs PC was possible, the ITC is the Janssen base case for PC while the pooled multivariate analysis with the Karolinska dataset as a scenario analysis.

In addition to the above, it is important to note that the Österborg dataset is derived from a randomised controlled trial, whereas the Karolinska comparison is from a real world observational dataset with the inherent biases this entails. For these two reasons, Janssen considers the Österborg PC comparison to be more robust than the Karolinska PC comparison.

Janssen have today notified the Department of Health regarding this revised simple discount. In conclusion, at this revised discount and based on the ERG preferred assumptions, ibrutinib is a cost-effective treatment option when compared to IR and PC, at the end of life threshold of £50,000 per QALY.