# National Institute for Health and Care Excellence
# Centre for Health Technology Evaluation

## Pro-forma Response

## ERG report

### Idelalisib for previously treated chronic lymphocytic leukaemia [ID764]

You are asked to check the ERG report from Warwick Evidence to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm**, **Thursday 30 April**. Using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

**Issue 1 Overall comment: Summary of key issues of factual inaccuracy in the ERG report (please note that any responses provided by the ERG that are detailed in the erratum are highlighted in red)**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| We thank the ERG for their balanced and thorough review of our submission of evidence for idelalisib within its licensed indication for chronic lymphocytic leukaemia. There are however key issues of misinterpretation which have resulted in factual inaccuracies throughout the ERG report. These are detailed within this document by section and page number, and summarised here. | | Correct representation of, and inference from, the Gilead submission and idelalisib licence in the ERG report. | |
| **Patient population**<br>We are concerned that the ERG has misinterpreted the evidence from Study 116 and Study 101-08 and its relevance for the licensed indication. The patient group in Study 116 are representative of a subset of CLL patients who have received at least one prior therapy; a heavily pre-treated group for whom chemotherapy is unsuitable. The ERG has interpreted this group instead as *different* to the relapsed indication, which is not the case. | | | We agree with the statement that the patient group in Study 116 'are representative of a subset of CLL patients who have received at least one prior therapy; a heavily pre-treated group for whom chemotherapy is unsuitable.'<br>Given this, we state several times in our report that study 116 may not be representative of the whole CLL population seen in the UK practice (i.e., the previously treated CLL population in a wider context as specified in the scope). |
| Evidence from the subgroup of patients in Study 101-08 whose CLL was associated with 17p deletion or TP53 mutation comprises the key clinical evidence for idelalisib in its untreated licensed indication; it was on the basis of these data and supportive evidence from trials in relapsed patients that the EMA licence for idelalisib with rituximab for untreated CLL patients with 17p deletion or TP53 mutation was granted. Little reference is made to these data. Instead, the | | | Study 101-08 was considered very carefully by the ERG. This study was mentioned or described 19 times throughout the report.<br>However we do not consider a small single arm (uncontrolled) study which included only 9 patients (with 17p deletion or TP53 mutation) 'the key clinical evidence for idelalisib in its untreated |

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| ERG base their conclusions on the likely cost-effectiveness of idelalisib for this patient group upon incorrect inference from the subgroup of patients in Study 116 whose disease is associated with 17p deletion or TP53 mutation. These patients are heavily pre-treated and have high rates of comorbidities in comparison to the average untreated population, and careful consideration of these factors is required when using results from these patients to make inference for untreated patients with 17p deletion or TP53 mutation. | | | licensed indication'. Given the limitations in the design, sample size, and completeness of reported data (especially AEs), the findings of this study are questionable in allowing us to gauge the clinical effectiveness of idelalisib in this subpopulation. |
| **Manufacturer's choice of comparators**<br>In several places in the ERG report, the choice of comparators is questioned. In particular, the ERG report criticises the absence of alemtuzumab and of ibrutinib as comparators for the relapsed population, despite neither of these being included in the NICE scope. Furthermore, the ERG has also questioned the manufacturer's removal of the chemo-immunotherapy regimens as relevant comparators from the NICE scope for the untreated 17p deletion/TP53 mutation without providing the full context and rationale as to why these comparators are not appropriate. We request that this further detail is provided as without it the report is misleading. | | | The company submission relies mainly on a single RCT (Study 116)[1] which uses rituximab monotherapy as a comparator. Rituximab is not standard therapy in the UK and the NICE scope does not include it as a comparator. Our expert clinical advisor confirmed that rituximab alone is not an appropriate choice of treatment for relapsed/refractory CLL patients in the UK, even when they are heavily pre-treated.<br><br>Our clinical expert considered that alemtuzumab and ibrutinib are relevant comparators in the UK context. For example, although alemtuzumab was withdrawn for this indication at the request of the company manufacturing it, it is currently available in England through a patient access programme.<br><br>Alemtuzumab is one of the comparators in the NICE scope (for patients with 17p deletion).<br><br>The ERG states: (page 37): "*The relevance and importance of rituximab monotherapy to the current decision problem may be problematic and questionable in the absence of direct evidence comparing rituximab to any standard or commonly used treatment (bendamustine or chlorambucil* |

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| | | | *with/without rituximab, alemtuzumab, or ofatumumab)*." |
| **Health-related quality of life evidence**<br>The ERG is critical of the use of Study 116 EQ-5D data in the model, largely due to inference that baseline utility was worse in the comparator arm of Study 116 ERG report. This is incorrect, and a consequence of misinterpretation of the data presented in the submission document. The ERG have also misinterpreted health-related quality of life assumptions in pre-progressive health states.<br><br>**Treatment acquisition cost assumptions**<br>The ERG has misinterpreted the approach used to apply comparator treatment costs in the Gilead submission. | | | We noted a possible discrepancy in baseline quality of life between control and intervention groups in the trial. We welcome the further data which the company has now provided in a subsequent erratum note (see below). The issue of a potential imbalance was not, however, the primary reason why the ERG decided to primarily focus on utility data from outside of Study 116 (see issue 21)<br><br>See response to issue 54 |

## Issue 2 Section 1.1: Scope of the submission

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| The ERG report states (page 11):<br>"*In addition the CLL patients with 17p deletion or TP53 mutation included in the pivotal study 116 (Furman et al., 2014) were heavily pre-treated as opposed to the untreated population as specified in the NICE scope."*<br>No reference is made to the inclusion of Study 101-08 in untreated CLL patients with 17p deletion or TP53 mutation. It seems the ERG | Please clarify that there are two populations of interest for idelalisib, both of which are supported by evidence for idelalisib:<br>• Adults with CLL who have received at least one therapy, supported by evidence form | The populations and supporting evidence for idelalisib need to be clarified as the ERG report is confusing to the reader at present, and also inaccurate with its reporting of the populations and related evidence. | Please see response to: Issue 1 line 3 which states:<br>Study 101-08 was considered very carefully by the ERG. This study was mentioned or described 19 times throughout the report.<br>However we do not consider a small single arm (uncontrolled) study which included only 9 patients (with 17p deletion or TP53 mutation) 'the key clinical evidence for idelalisib in its untreated |

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| report is confusing the two distinct populations of interest that are described in the submission (and are as per the NICE scope):<br>"*Adults with chronic lymphocytic leukaemia who have received at least one therapy and;*<br>*"Adults with untreated chronic lymphocytic leukaemia associated with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable"* | Study 116, which consists of a heterogeneous population, some of which have a 17p deletion or TP53 mutation.<br>• Adults with untreated CLL with a 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable, supported by evidence from the single arm study 101-08, which is an untreated population of CLL patients, but includes a subgroup of patients with a 17p deletion TP53 mutation. | | licensed indication'. Given the limitations in the design, sample size, and completeness of reported data (especially AEs), the findings of this study are questionable in allowing us to gauge the clinical effectiveness of idelalisib in this subpopulation. |

## Issue 3 Section 1.1: Scope of the submission

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| The ERG report states (page 11): | Please delete the statement that the | The NICE scope for the previously treated group of | We would welcome evidence to demonstrate the ways in which the relative severity of the patients |

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| "*One notable deviation from the NICE scope was that study 116 included relatively older and frailer CLL patients with multiple comorbidities who had been intolerant and therefore less suitable to standard treatment with chemo immunotherapy agents.*"<br><br>Again, there seems to be some confusion over the populations of interest. It is true that Study 116 did include older and frailer patients who were considered unsuitable for standard treatment with chemotherapy agents; however, this is not a deviation from the NICE scope. | population of Study 116 represents a deviation from the population of the NICE scope. | patients states: *"Adults with CLL who have received at least one therapy*", without reference to any level of severity, or specific indication of patient characteristics. However, patients who have been previously treated with at least one therapy have failed or cannot tolerate that therapy. These patients are by their nature, going to be frailer and older. Indeed these are major factors as to why they cannot tolerate or fail the treatments they receive in the first place as they are unsuitable for the most efficacious regimens like FCR.<br><br>Furthermore, patients become frailer because of exposure to ineffective chemotherapy/chemo-immunotherapy regimens (they suffer the toxicity of chemotherapy such as myleosuppression for relatively little benefit). The proportion of patients who have mutations such as a 17p deletion or TP53 mutation increases with | included in study 116 is representative of the likely UK population for whom the NICE appraisal is being undertaken. In the absence of such evidence and on the advice of our clinical advisor we felt it important to notify NICE that the patients under consideration in the submission may not be representative of the full population in the scope. |

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| | | each line of therapy because they are resistant to chemotherapy and increase in prevalence with each line of therapy as a result of "clonal evolution."[1] Because 17p deletion/TP53 mutations convey resistance to chemotherapy, treatment with chemotherapy will thereby reduce/eliminate subclones sensitive to chemotherapy, and lead to the emergence of "fitter" and more aggressive subclones resistant to chemotherapy.[2] Therefore, the frailer, older and higher risk nature of patients included in Study 116 are fully representative of patients that have already received at least one therapy and therefore, by definition, are within scope. | |

## Issue 4 Section 1.1: Scope of the submission

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| The ERG report states (page 12): | The figure "42.6" is incorrect | The data presented in the ERG | We are happy to change the figure from "42.6" to |

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| "*Almost half of the study 116 sample (42.6%) was composed of CLL patients with 17p deletion and TP53 mutation…*"<br><br>[This incorrect figure was also mentioned on page 16] | and should be changed to "43.2". Furthermore, stating "*Almost half of the study"* is factually inaccurate. Rounding 43.2% to 50% misleads and exaggerates as to the proportion of patients with these mutations in the study. Please correct to read "*43.2% of the Study 116 sample was composed of CLL patients with 17p deletion and TP53 mutation…*" | report are factually incorrect and also the interpretation is misleading. | "43.2". (P12)<br><br>We consider that 'almost half' and 43.2% are equivalent. We did not 'round' we gave a verbal descriptor. |

## Issue 5 Section 1.1: Scope of the submission

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| The ERG report states (page 12) "*Another feature not in line with the NICE scope was that all CLL patients with 17p deletion and TP53 mutation in the study 116 had already been treated.*"<br><br>Again, there is some confusion over the population. It is true that all of the CLL with 17p deletion and TP53 mutation in the study 116 had already been treated. However, the key evidence for the untreated population with a 17p deletion or TP53 mutation is the subgroup of patients from the | Reiterate the two populations of interest and which evidence for idelalisib is used to support the populations. | The populations of interest and their supporting evidence need correcting and clarifying to the reader. Data from 101-08 are within the scope population whilst data from study 116 are provided as supportive only for this population. | We consider that the company should have clarified that Study 116 provides evidence mainly for pre-treated adults with CLL and that the small single arm study 101-08 was their main evidence source for the 'untreated 17p deletion and TP53 mutation population.'<br><br>We also consider that the company submission should make it clear that evidence from Study 116 was used in support of results for the pre-treated patient subgroup with 17p deletion and TP53 from study 116. |

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| untreated population within Study 101-08.<br><br>Evidence from the subgroup of previously treated patients with 17p deletion/TP53 mutation from Study 116, are used as supporting evidence only, i.e., to demonstrate that idelalisib, in contrast to chemotherapy, has good efficacy in disease with these markers. | | | |

## Issue 6 Section 1.1: Choice of comparator

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| The ERG states (page 13):<br><br>"*Other explanation justifying this choice is an assumption that rituximab is representative of anti-CD20 efficacy and it has similar efficacy to ofatumumab in CLL patients. However, the ERG note that no direct or indirect comparison of rituximab vs. ofatumumab was adduced to support this assertion*."<br><br>This is not correct – the Gilead submission referred to the ERG report conducted for the ofatumumab NICE STA (page 141, Section 4.13):<br><br>"*Furthermore a recently conducted network meta-analysis (in combination with bendamustine or chlorambucil) showed that rituximab has a similar or slightly improved efficacy compared to ofatumumab in* | The report currently omits reference to the network meta-analysis conducted and the top-line findings (i.e., similar efficacy of rituximab and ofatumumab) – this should be provided within the ERG report. | The current ERG report is factually incorrect in stating that the Gilead submission does not provide evidence (i.e. ITC) to support the assumption that rituximab has similar efficacy to ofatumumab in CLL patients, because the Gilead submission does provide a | No evidence of the equivalence of ofatumuab and rituximab in the populations under consideration has been presented to us. Circumstantial evidence only, of such equivalence has been offered.<br><br>If the company refers to the citation by Hoyle et al. (Ofatumumab in combination with chlorambucil or bendamustine for *previously untreated* chronic lymphocytic leukaemia: a critique of the submission from GSK), this was based on previously untreated patients. This is not in line with the NICE scope for this appraisal – which includes a population of previously treated CLL patients, nor is it comparable to study 116 in which the population was pre-treated. |

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| *untreated CLL.*”[3] | | summary of previous analyses and data in the literature to suggest that there is a similarity in the efficacy of both antibodies. | |

## Issue 7 Section 1.1: Comparators in the scope

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| The ERG report states (page 13): *“Our clinical advisor mentioned that ibrutinib might be a useful drug in the population under consideration and the ERG were disappointed at the scant mention of ibrutinib in the submission.”* | Gilead asks for removal of the reference to ibrutinib as a relevant comparator – it was not included in the NICE scope and therefore should not be referenced here. | Ibrutinib is not a standard of care in the patient populations of interest and is not included in the NICE scope. | We acknowledge that ibrutinib is not a standard care in the populations of interest and that it is not included in the NICE scope. We did not give it equivalent consideration in our ERG report for those reasons. However our clinical advisor considered that this may be an important intervention for this population and this is why we were disappointed at the attention offered to it. |

## Issue 8 Section 1.1: Choice of outcomes

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| When discussing the outcomes reported in the | The outcome, “overall | The ERG report | Overall response rate in this context is described |

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| submission, the ERG report states (page 14): "*The NICE scope suggested a subgroup analysis by the presence of 17p deletion or TP53 mutation. The company submission reported this analysis for overall survival, progression-free survival, and lymph node response rate*."<br><br>The Gilead submission also provided the outcome, "overall response rate" but this was not listed in the ERG report. | response rate", should be added as this was reported for the subgroup of patients with 17p deletion/TP53 in Study 116. | is factually incorrect at present due to omission of the additional 'overall response rate' outcome for this population. | on page 18. |

## Issue 9 Section 1.2: Evidence synthesis

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| The ERG report states (page 16):<br><br>*"In addition small numbers of UK patients were involved in study 116*."<br><br>Study 116 actually included 32 (14.5%) patients from the UK, which is a relatively high proportion for an international study. This also represented the greatest number of patients enrolled from any of the EU countries involved in Study 116. | Please add the number and percentage of patients included from the UK into Study 116 when talking about the enrolment of the UK patients in the study | It is currently misleading to state that this is a small number. The number of UK patients is relatively high for an international study. | The ERG here is discussing the overall numbers in *absolute not relative terms*. In this respect we mean that the number of UK patients – at an overall UK total of 32 individuals – is not large. |

## Issue 10 Section 1.2: Evidence synthesis

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| The ERG report states (page 16):<br>"*Time to response was similar between the groups (no 95% CI or p-values reported).*"<br>This statement would benefit from clarification of the numerical difference between the arms. | Please add the supportive data after this statement, as follows: "*Mean (SD) time to response: IR= 3.0 (2.05); R=3.5 (2.14)*" | If these data are added here, the reader can draw their own conclusions from the data presented, and see the numerical difference between the treatment arms. | The reader can find the actual numbers in the company's own report, We did not report these because the results are not statistically significant and confidence intervals are not given. |

## Issue 11 Section 1.3: Summary of the ERG's critique of clinical effectiveness evidence

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| The ERG states (page 17): "*The search for clinical studies in untreated CLL patients with 17p deletion or TP53 mutation included only the company's choice of comparators*."<br>Although this is correct, it does not provide details as to why the search only included the company's choice of comparators. The other comparators were not considered relevant because they are chemo-immunotherapy | Further detail should be added to provide more context to this statement, i.e., to list the comparators excluded by the Gilead submission and the rationale as to why.<br>We recommend adding the following text to provide further context: "*The excluded* | The statement is incorrect as it is misleading without this additional clarification. The additional clarification would give a more | Our statement is correct and the company explains the reasons in its own submission.<br>The ERG report did mention the results of the study by Hillmen et al (2007) 24 times in total.<br>However because this RCT did not evaluate the drug of interest, our description is not as detailed as that for other trials which tested the drug of |

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| regimens that are not appropriate for this population. It is also worth noting that the ERG report did not mention the results of the study by Hillmen et al (2007)[4] in section 1.2. This was a randomised controlled trial of alemtuzumab vs chlorambucil in front line CLL, the results of which illustrate very well why chemotherapy is not appropriate for patients with 17p deletion or TP53 mutation because of its very poor efficacy. Chlorambucil led to a response rate of only 20% and a median PFS of only 2.2 months.[4] Furthermore, data and guidelines such as BCSH,[5] do not support use of chemotherapy or immunochemotherapy in patients with 17p deletion/TP53 mutation CLL because chemotherapy has such poor efficacy in this group. | *comparators were: bendamustine (with or without rituximab), chlorambucil (with or without rituximab), and obinutuzumab with chlorambucil. All of these are chemo-immunotherapy regimens, which are not suitable for this high-risk patient population, and are outside of the licensed indication*."<br><br>For further details, see Issue 3 for an explanation of why chemo-immunotherapy is not appropriate or effective in this population. | complete picture to the reader and allow understanding as to the reasons for exclusion for these comparators in this population. | interest. |

## Issue 12 Section 1.4: Description of the comparison to best supportive care

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| Page 19, ERG report, the following paragraph should mention the time on treatment assumption for best supportive care, for completeness:<br><br>*"Additional comparison are made to ofatumumab monotherapy and best supportive care, with ofatumumab monotherapy assumed to have the same overall survival (OS), progression-free survival (PFS), time on treatment (ToT)* | Please amend the text, to the following:<br><br>*"Additional comparison are made to ofatumumab monotherapy and best supportive care, with ofatumumab monotherapy assumed to have the same overall survival (OS), progression-free survival (PFS), time* | Section 1.4 and its description of the economic approach is important for the reader's initial understanding of the approach. The assumption of zero treatment cost for best | We consider that the phrase *with no time on treatment* does not add any additional clarity to the text. |

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| *and response rates (RR) as rituximab monotherapy, and best supportive care modelled as having the same overall survival and progression-free survival as rituximab monotherapy, with a response rate of zero."* | *on treatment (ToT) and response rates (RR) as rituximab monotherapy, and best supportive care modelled as having the same overall survival and progression-free survival as rituximab monotherapy, with no time on treatment and a response rate of zero.".* | supportive care is conservative, and this should be stated. Without this additional clarification the reader could be left confused. | |

## Issue 13 Section 1.4: Description of HRQL assumptions for treatments other than IR and R

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| Page 20, ERG report, the following sentence is factually incorrect:<br><br>*"Treatments other than idelalisib with rituximab and rituximab monotherapy were all assumed to have the same 'on-treatment' quality of life as rituximab monotherapy."* | Please replace the current text with the following which accurately describes the approach:<br><br>*"Patients receiving BSC or ofatumumab were assumed to have the same 'on-treatment' health-related quality of life as rituximab monotherapy. In comparisons to other treatments, progression-free survival health-related quality of life was assumed to be 0.8, the progression-free survival utility estimate from Dretzke et al.[6]. In these comparisons to other treatments, the health-related quality of life consequences of adverse effects associated with comparator chemotherapy treatments were not incorporated."* | The amendment corrects an important factual inaccuracy, and allows the reader to understand accurately the health-related quality of life assumptions in the approach. | This section has been expanded to include the explanation of utility sources for other treatment comparisons (P20).<br><br>Information on adverse event utility decrements is given on P86 of the ERG report, but since this assumption makes very little difference to the ICER, is not considered in the summary. |

## Issue 14 Section 1.4: Description of treatment cost assumptions for treatments other than IR and R

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| Page 20, ERG report, the following sentence is factually incorrect:<br><br>*"For ofatumumab monotherapy, patients were assumed to spend the same time on treatment as for rituximab monotherapy, whilst for all other treatments all patients were assumed to fully complete the maximum dosing duration, with none discontinuing early."* | Please replace the current text with the following which accurately describes the approach<br><br>*"The estimated time on treatment curve for rituximab monotherapy was assumed for ofatumumab monotherapy. In each comparison, treatment costs were applied to the proportion of patients remaining in the 'progression-free, on treatment' health states in the model, but only up to maximum treatment durations (8 treatment cycles over 21 weeks for rituximab; 12 treatment cycles over 24 weeks for ofatumumab).*<br><br>*For the exploratory comparisons to other treatments, treatment costs were applied to the proportion of patients with progression-free disease in the model, but only up to maximum treatment durations."* | The amendment corrects an important factual inaccuracy, and allows the reader to understand the approach taken by the company to capture comparator treatment costs. | The text has been modified to clarify the various assumptions made around the costs of different treatments. |

## Issue 15 Section 1.4: Description of applicability of end of life criteria

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| Page 21, ERG report, the ERG state the following:<br><br>*"The company discussed 'end of life.' (Criteria include i) treatment indicated for patients with a short life expectancy, normally less than 24 months; ii) sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment; iii) treatment licensed or otherwise indicated for small patient populations). We considered that criteria ii) and iii) above were probably met. However if we take into account the considerably healthier UK CLL population and make use of the best available comparator evidence rather than suboptimal rituximab monotherapy, it seems highly unlikely that criterion i) - a short baseline life expectancy would be met for this group."* | We propose the following amendment: *"The company discussed 'end of life.' (Criteria include i) treatment indicated for patients with a short life expectancy, normally less than 24 months; ii) sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment; iii) treatment licensed or otherwise indicated for small patient populations). We considered that criteria ii) and iii) above were probably met. ~~However if we take into account the considerably healthier UK CLL population and make use of the best available comparator evidence rather than suboptimal rituximab monotherapy, it seems highly unlikely that criterion i) - a short baseline life expectancy would be met for this group.~~ However in patients with better survival prospects than those in Study 116, who may respond to* | While we agree that for younger, fitter patients eligible for chemotherapy, normal life expectancy may exceed 24 months, the patients in study 116 represent a subset of the licensed population for whom life expectancy is short. This should not be presented as a result of the sub-optimality of rituximab; for these patients there is no effective | We would argue that the population in Study 116 is not representative of the full UK population for whom this appraisal is being undertaken, and therefore consider that our statement should stand as written. |

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| | *chemotherapy, criterion i) - a short baseline life expectancy – may not be met."* | treatment currently available. | |

## Issue 16 Section 1.4: Description of justification of assuming equal efficacy between rituximab and ofatumumab

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| Page 22, ERG report, the ERG state the following:<br><br>*"The justification for assuming equal efficacy for ofatumumab and rituximab is not based on data in CLL, but in diffuse large B-cell lymphoma."*<br><br>This statement only describes one selective justification and does not accurately describe the full justification. | Please amend to the following, to accurately describe the full justification rather than selecting just one aspect of it:<br><br>*The justification for assuming equal efficacy for ofatumumab and rituximab is six-fold:*<br><br>• The results of the ORCHARRD study, which found no significant differences in OS or PFS between rituximab and ofatumumab, although not in the same population as Study 116.[7] The ORCHARRD study was not conducted in CLL, but in diffuse large B-cell lymphoma.<br>• The use of the two treatments interchangeably as a class of therapies in clinical trials.[8] | The amendment describes the full justification for assuming equal efficacy between ofatumumab and rituximab, as opposed to one selective justification. The full justification is as provided within the Gilead submission. | We describe fully the sources of data that the company suggest indicate equivalence in the ERG report (P40 and P79). |

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| | • Conclusions from a meta-analysis conducted as part of an appraisal and accepted by NICE for ofatumumab in combination with bendamustine and Chlorambucil.[9]<br>• The single-arm study of ofatumumab from Wierda et al [10], which was the identified study with the patient characteristics arguably most similar to Study 116, reported a median OS of 15.4 months for fludarabine-refractory patients who are less suited to alemtuzumab due to bulky lymph nodes, with a life expectancy of 6 months or more. Comparison with the median predicted OS for rituximab, 13.6 months, suggests that survival outcomes for rituximab and ofatumumab are similar.<br>• The exploratory economic comparison to ofatumumab using data from Weirda et al produced results suggestive both (i) that idelalisib with rituximab is relatively cost effective (ICER versus ofatumumab =£4,254 (company model assumptions)) and (ii) that assumptions in the base case comparison to ofatumumab were reasonable (ICER versus ofatumumab=£1,527 (company model assumptions))<br>• Expert clinical advice. | | |

## Issue 17 Section 1.4: Description of crossover analysis assumptions

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| Page 22, ERG report, the ERG state the following:<br><br>*"Adjustment made for crossover between trial arms in Study 116 relied on the assumption of equal efficacy for idelalisib monotherapy and idelalisib with rituximab. A lower efficacy for idelalisib monotherapy will result in a lower treatment benefit for IR versus R."*<br><br>This is incorrect. | Please amend the text to the following:<br><br>*"Adjustment made for crossover between trial arms in Study 116 relied on the assumption of equal efficacy for idelalisib with rituximab and idelalisib monotherapy in patients who are pre-treated with rituximab monotherapy. ~~A lower efficacy for idelalisib monotherapy will result in a lower treatment benefit for IR versus R.~~ While it is not possible to quantify the implications of this assumption, there is clinical rationale supporting patients not being re-treated with rituximab."* | The amendment accurately describes the implicit assumption in the cross-over adjustment. | We consider that adjustment made for crossover between trial arms in Study 116 relied on the assumption of equal efficacy for idelalisib with rituximab and idelalisib monotherapy (as administered in Study 116). |

## Issue 18 Section 1.4: Criticism of the use of EQ-5D data collected in Study 116

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| Page 22, ERG report, the ERG | We ask that this is removed from the list of | The ERG base their inference on data presented in Table 32 of the Gilead submission document, which shows Study | We thank the company for supplying this information, which has not previously been |

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<td>state the following:<br><br>“It is unclear if the baseline imbalance in utility values from Study 116 was appropriately adjusted for when calculating pre-progression on treatment utilities for the two treatments in the economic model. If not, this would introduce a clear bias in favour of idelalisib. In addition, it was not possible to use the pivotal trial to calculate utility values for any of the other health states in the model”<br><br>This is false inference from selective analysis of the data presented in the</td>
<td>‘weaknesses and areas of uncertainty’, along with all other descriptions of baseline utility being worse in the intervention arm of Study 116 ERG report, as this is false inference from selective analysis of the data presented in the submission document.</td>
<td>116 EQ-5D data results by dimension. From Table 32, the ERG observe that at baseline, a higher proportion of patients report Level 1 results in the intervention arm of Study 116 than in the comparator arm, across all 5 dimensions of health, and infer from this that baseline HRQL was higher at baseline in the intervention arm versus the comparator arm. While the mean EQ-5D utility values at baseline were not reported by treatment arm in the submission document, Table 32 also showed the proportions of patients in each treatment arm reporting the worst level of HRQL at baseline (Level 3), and this proportion is not lower in the comparator arm versus the intervention arm in any of the 5 dimensions of health.<br><br>The true implication of the data in Table 32 of the submission document is that HRQL was consistent across Study 116 treatment arms at baseline, as would be expected in a randomised controlled trial. Mean baseline utility was 0.7507 (to 4 decimal places) for patients randomised to receive idelalisib and 0.7510 (to 4 decimal places) for patients randomised to receive placebo, as shown in Table 1.<br><br>Table 1: Baseline EQ-5D utility in Study 116, by treatment arm
<table>
<tr><th>Planned Treatment Arm</th><th>N</th><th>Mean</th><th>Std D</th></tr>
<tr><td>Idelalisib 150mg BID</td><td>107</td><td>0.750738318</td><td>0.258</td></tr>
<tr><td>Placebo</td><td>103</td><td>0.750990291</td><td>0.214</td></tr>
</table>
<br>The generalised estimating equation regression analysis</td>
<td>presented.<br><br>Whilst this is not an erratum – since this is the first time these data have been made available to us - we have nevertheless adjusted the ERG report to take this into account, with references to baseline imbalances in EQ-5D removed. (P15,P22,P46,P58,P65,P87).</td>
</tr>
</table>

| | | | |
|---|---|---|---|
| submission document. | | used to estimate utility values for model health states from Study 116 EQ-5D data did not control for baseline HRQL differences across treatment arms, as justified by the results in Table 1. Table 2 shows alternative generalised estimation equation (GEE) results to those used in the model (summarised in Table 69 of the submission document), in which baseline utility has been included as a covariate. As expected, results are almost identical. The treatment effect estimate is equivalent to that used in the submission, to 4 decimal places.<br><br>**Table 2: GEE regression results including baseline EQ-5D utility as additional covariate** | |

| **Parameter** | | **Estimate** | **Standard Error** | **95% Confidence Limits** | |
|---|---|---|---|---|---|
| **Intercept** | | 0.3858 | 0.0278 | 0.3313 | 0.44 |
| **Baseline EQ-5D score** | | 0.4796 | 0.0331 | 0.4149 | 0.54 |
| **Treatment with idelalisib** | IDELA | 0.0652 | 0.0160 | 0.0339 | 0.09 |

## Issue 19 Section 1.4: Assessment of the importance of uncertainty around pre-progression, off treatment utility assumptions

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 22, ERG report, the ERG state the following:<br><br>*"Vii Patient's discontinuing from idelalisib in the model maintain a considerably higher quality of life than those still being treated with rituximab, an assumption not justified in the submission"*<br><br>It is incorrect to list this as a weakness /area of uncertainty | We request that this is removed from the list of weaknesses and areas of uncertainty. | We request that this is removed from the list of weaknesses and areas of uncertainty, as it is not a key area of uncertainty. Instead, it is an area of uncertainty that was highlighted by the ERG as an issue for clarification (question B10), and which the company therefore explored. The response to question B10 is replicated below, for reference. Given this further analysis, it should be clear that the practical assumption made in the submission document, about HRQL for patients whose disease has not progressed but have withdrawn from treatment, is not key in terms of driving the cost-effectiveness.<br><br>*EQ-5D data were not collected post treatment in either arm of Study 116. While robust health-related quality of life (HRQL) estimates were available from the gold-standard source for patients in the 'PFS, on treatment' health state, it was necessary to rely on the literature for other model health states. For the 'PFS, off treatment' health state, it seemed most reasonable to use the best available utility estimate for pre-progressive patients: 0.80, as reported by Dretzke et al [6]. That this approach implies that patients who receive anti-CD20 monotherapy* | We welcome the explanation by the company about patients maintaining a higher quality of life after treatment discontinuation in the model. Nevertheless we consider that this is an area where the evidence is not available to support the assumption of continuing benefit made. |

*experience an improvement in HRQL after treatment withdrawal above that explained by the absence of key adverse events appears illogical, but these data are from different sources, and such differences can be expected.*

*This base case approach assumes that the higher HRQL observed in the intervention arm of Study 116 versus the comparator arm while patients received treatments disappears following treatment withdrawal. In reality, the HRQL of patients who receive idelalisib with rituximab may continue to outperform that of patients receiving anti-CD20 monotherapy after treatment withdrawal; therefore, the base case approach can be viewed as conservative.*

*Regardless, model results are robust to assumptions regarding HRQL in the 'PFS, off treatment' health state, as demonstrated in Table 3 and Table 4. Table 3 shows model results for the comparison to rituximab, assuming utility in this health state is 0.6, the best available estimate from the literature for post-progressive disease, which is also from Dretzke et al [6]. Table 4 shows base case results versus rituximab, for comparison.*

**Table 3: Alternative PFS off-treatment utility estimate, IR versus R**

| | Costs | Life Years | QALYs | Incremental | | | ICER |
|---|---|---|---|---|---|---|---|
| | | | | Co | Lif | QA | |

| | | | | sts | e Ye ars | LY s | |
|---|---|---|---|---|---|---|---|
| Rituxi mab | [redacted] | 1.3 9 | 0.8 8 | | | | |
| Idelalis ib with rituxim ab | [redacted] | 4.6 3 | 2.7 6 | £26 ,12 8 | 3.2 4 | 1.8 8 | £13 ,86 5 |

**Key:** ICER, incremental cost-effectiveness ratio; IR, idelalisib with rituximab; PFS, progression-free survival; QALYs, quality adjusted life year; R, rituximab

**Table 4: Base case results, IR versus R**

| | | | | Incremental | | | |
|---|---|---|---|---|---|---|---|
| | **Co sts** | **Lif e Ye ars** | **QA LY s** | **Co sts** | **Lif e Ye ars** | **QA LY s** | **ICE R** |
| Rituxi mab | [redacted] | 1.3 9 | 0.8 9 | | | | |
| Idelalis ib with rituxim ab | [redacted] | 4.6 3 | 2.8 1 | £26 ,12 8 | 3.2 4 | 1.9 2 | £13 ,63 4 |

**Key:** ICER, incremental cost-effectiveness ratio; IR, idelalisib with rituximab; QALYs, quality adjusted life year; R, rituximab

## Issue 20 Section 1.4: Uncertainty around intravenous immunoglobulin therapy resource use

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 22, ERG report, the ERG state the following:<br><br>*"Although some of the resource use frequencies came from published data, a large number were based on clinical assumptions. One of the most important of these is the assumption around the need for IVIG therapy in the different groups. If the model's base case assumption that patients who initially respond to treatment will never need IVIG therapy, however long they remain in the PFS state, is not justified, then idelalisib will appear considerably less cost-effective than it currently does."* | Please amend to reflect clinical rationale for assumptions.<br><br>As stated within BSCH guidance response to treatment suggests a recovery in B-cell function and improvement in immunoglobulin levels, eliminating the need for IVIG therapy.[11] | The amendment adds balance and clinical rationale to the description of the assumption and its validity. | The reference provided by the company is to guidelines, not to data on actual resource use.<br><br>The ERG has not made any modifications to the company's base case analysis. Nevertheless, since differences in IVIG requirements are a key driver of the model it is important to understand the impact of uncertainty in this parameter. The ERG has attempted to do this by providing additional sensitivity analyses |

## Issue 21 Section 1.4: Modifications to company model assumptions for the ERG base case

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 23, ERG report, the ERG state the following:<br><br>*"The ERG made a number of modifications* | We suggest that the ERG base case should use the company's HRQL data assumptions, and request that | We suggest that the ERG base case should follow the | There are two key issues with the use of trial utility values:<br><br>1) considerably higher utilities for post- |

| | | | |
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| *to the model assumptions made by the company, including the use of external data rather than Study 116 data for pre-progression utilities, using ToT data to estimate drug costs for all treatments, rather than assuming all patients would complete the maximum course, the use of a more realistic survival curve for FCR therapy and reducing the benefits of treatment to a 5 year rather than lifetime horizon."* | the ERG's modifications to drug costing assumptions are clarified. | company's HRQL data assumptions with reference to 0 (above) and the NICE Reference Case.<br><br>With reference to Issue 14, it is unclear to the company how using ToT data to estimate drug costs for rituximab and ofatumumab in the base case comparisons is a modification to company model assumptions, and given the absence of ToT data for chemotherapy regimens, it is unclear how the ERG used ToT data to estimate drug costs for these treatments. | discontinuation IR patients than for on-treatment R ones<br><br>2) higher on-treatment utilities for IR than other (non R, ofatumumab, BSC) comparators (e.g. FCR, B)<br><br>A robust justification has been provided for neither of these. The ERG believes the use of consistent HRQoL estimates across all arms of the model to be the most sensible assumption.<br><br>Using ToT data for drug costs is not a modification for rituximab and ofatumumab. For other comparators, in the absence of data, the same proportion of patients in the PFS state were assumed to be on treatment as for rituximab, with costs then applied to the maximum dosing duration for those still on treatment. Whilst this is still an assumption, we consider that it is more justified than assuming that all patients in the PFS state complete the full course of treatment for these additional comparators. |

## Issue 22 Section 1.4: Interpretation of subgroup analyses

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 23, ERG report, the ERG state the following:<br><br>*"All analyses were based on the Study 116 population, which was considerably less healthy than the UK CLL population, and which does not match with either of the populations listed in the NICE scope. Analyses already undertaken by the company suggest idelalisib to be less cost-effective in the 17p deletion and TP53 mutation population (see section 5.2.12), and idelalisib may well prove to be less cost-effective in the UK population than that from Study 116."*<br><br>The ERG's inference from the subgroup analysis results (requested in the NICE scoping document) is | We request this text is amended, to the following:<br><br>*"All analyses were based on the Study 116 population, ~~which was considerably less healthy than the UK CLL population, and which does not match with either of the populations listed in the NICE scope. Analyses already undertaken by the company suggest idelalisib to be less cost-effective in the 17p deletion and TP53 mutation population (see section 5.2.12), and idelalisib may well prove to be less cost-effective in the UK population than that from Study 116.~~ which is representative of a subset of the licensed population, who are heavily pre-treated, with few if any remaining effective treatment options, and unable to receive cytotoxic therapy."* | As described in Issue 15, the patient group in Study 116 are a subgroup of the licensed population, and are more clearly described as such, rather than *different to* the licensed population. This is an important distinction when considering the value of idelalisib for CLL patients.<br><br>The ERG's inference from the subgroup analysis results (requested in the NICE scoping document) is inaccurate. These results suggest that idelalisib with rituximab is less cost-effective in heavily pre-treated CLL patients who cannot receive cytotoxic therapy and whose CLL is associated with 17p deletion or TP53 mutation than in heavily pre-treated CLL patients who cannot receive cytotoxic therapy in general, as survival prospects are so poor for the former group.<br><br>This is not suggestive that idelalisib is less cost-effective in the 17p deletion and TP53 mutation population as a whole. For treatment-naïve patients with 17p deletion or TP53 mutation, the mechanism of action of idelalisib is likely to prolong survival substantially, as | Please see responses to issue 1, line 2 and to issue 5 section 1.1. |

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| inaccurate. | | described at length in the submission document, and represent a cost-effective treatment option for these patients, who currently have high unmet need. To suggest otherwise is incorrect and this text should be deleted. | |

## Issue 23 Section 2.2: Population

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Population – the ERG report has misinterpreted the population (Page 28-29). | See responses to 0 and Issue 3 above. | See responses to 0 and Issue 3 above. | See above corresponding responses of ERG. |

## Issue 24 Section 2.2: Decision Problem

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states that the submission deviates from the NICE scope for the population of untreated CLL with 17p deletion and/or TP53 mutation. (Page 29):<br>*"Another deviation from the NICE scope was that rather than focussing on "adults with* | Study 101-08 is the study that provides the main evidence for the population of untreated CLL patients with 17p deletion and/or TP53 mutation, and this evidence is supported by the subgroup of treated patients with 17p deletion and/or TP53 mutation from Study 116. This is stated throughout the submission, including page 19 in the executive summary: | The submission is factually correct in stating that there was no deviation from the NICE scope in the evidence for untreated CLL population with 17p deletion and/or TP53 mutation; as the key | Please see responses to Issue 1, line 2 and to issue 5, section 1.1. |

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| *untreated chronic lymphocytic leukaemia associated with 17p deletion or TP53 mutation who are unsuitable for chemo-immunotherapy," the patients referred to in Study 116 were not "untreated", and in fact were "heavily pre-treated patients from the US and Western Europe" (page 16). This contradicts the company submission (Table 1, page 12), which states that no deviation had been made from the decision problem (i.e., "as per the final scope")."*<br><br>This is incorrect. [This is also mentioned in the conclusions – page 119] | *"For previously untreated patients with a 17p deletion or TP53 mutation, the key evidence for idelalisib with rituximab is derived from a subgroup of patients from the single-arm study, 101-08, and supported by the larger subgroup of patients with a 17p deletion or TP53 mutation in the relapsed or refractory population"* (Study 116).<br><br>This is a fundamental misunderstanding and should be amended in the ERG report. | evidence came from a sub-group of patients with 17p deletion and/or TP53 mutation in a study of untreated CLL patients. This is a fundamental misunderstanding by the ERG and should be clarified throughout the ERG Report | |

## Issue 25 Section 3.1: Idelalisib Evidence Base

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states that:<br><br>*"The main evidence provided in the company submission rests on a single pivotal RCT (study 116) which evaluated the efficacy and safety of idelalisib plus rituximab compared to rituximab monotherapy in previously treated* | Study 116 is the main evidence for the previously treated (relapsed or refractory) CLL population, but the main evidence for the untreated CLL patients with 17p deletion and/or TP53 mutation came from a subgroup of Study 101-08, which was conducted in untreated CLL patients. The sub-group of 17p deletion and/or TP53 mutation patients who had been previously treated in Study 116 is provided as | The main evidence for the untreated CLL with 17p deletion and/or TP53 mutation appears to have been overlooked. Note that Study 101-08 formed the basis of the evidence base for the EMA | The underlying rationale for the EMA approval is different to the NICE process.<br><br>This is why there are two different processes. We have not overlooked Study 101-08.<br><br>Please see responses to issue 1, line 2 and to issue 5, section 1.1. |

| | | | |
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| *CLL patients who had relapsed and/or been refractory to the previous treatment."* (Page 34)<br><br>This is incorrect. [This is also mentioned in the conclusions – page 119] | supporting evidence only.<br><br>"*For previously untreated patients with a 17p deletion or TP53 mutation, the key evidence for idelalisib with rituximab is derived from a subgroup of patients from the single-arm study, 101-08, and supported by the larger subgroup of patients with a 17p deletion or TP53 mutation in the relapsed or refractory population"* (Study 116). (Company submission, page 19) | approval of idelalisib.[12] Furthermore, the EMA identified the activity of idelalisib in patients with CLL and a 17p deletion or TP53 mutation as an area of special interest based upon the consistent results seen across studies at all lines of treatment in patients with a 17p deletion or TP53 mutation, including the subgroup from 101-08.[12] | |

## Issue 26 Section 3.1: 17p Deletion and/or TP53 Mutation in Study 116

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states that 42.6% of patients in Study 116 had 17p deletion and TP53 mutation. (Page 34):<br>"*Almost half of the study 116 sample (42.6%) was composed of CLL patients with 17p deletion and TP53 mutation*"<br>This is factually incorrect. | In Study 116 43.2% of the population had 17p deletion and/or TP53 mutation. | The data presented in the ERG report are factually incorrect. | Please see response to Issue Section 4 1.1. |

## Issue 27 Section 3.1: Population

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Population – the ERG report has misinterpreted the population (Page 34)<br>*"One feature not in line with the NICE scope was that the study sample was composed of relatively older and frailer CLL patients with multiple comorbidities who had been intolerant and therefore less suitable to standard treatment with chemo immunotherapy agents. Moreover, almost half of the study 116 sample (42.6%) was composed of CLL patients with 17p deletion and TP53 mutation, a distinct subgroup known to have a worse CLL prognosis, for whom standard cytotoxic therapy is not suitable."*<br>[This is also mentioned in the conclusions – page 119] | See responses to 0 and Issue 3 above. | See response to 0 above. | Please see response to Issue Section 4 1.1. |

## Issue 28 Section 3.1: Population in the NICE Scope

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states that the submission is not in line with the NICE scope because the 17p deletion/TP53 mutation population in Study 116 had been previously treated. (Page 34): | The main evidence for the untreated CLL patients with 17p deletion and/or TP53 mutation comes from a subgroup of Study 101-08, which was conducted in untreated CLL patients. Therefore this evidence is in line with the NICE scope. | The main evidence for the population of untreated CLL patients with 17p deletion and/or TP53 mutation appears to have been overlooked and it is factually | Please see responses to issue 1, line 2 and to issue 5, section 1.1. |

| | | | |
|---|---|---|---|
| *"Another feature not in line with the NICE scope was that all CLL patients with 17p deletion and TP53 mutation in the study 116 had already been treated (vs. naïve as specified in the scope). Thus, the study 116 sample may have been overly selective and probably over-represented by higher risk (i.e., harder to treat) CLL patents who would not be representative of the more broadly defined all pre-treated CLL patients specified in the NICE scope."*<br><br>This is incorrect. [This is also mentioned in the conclusions – page 119] | The subgroup of patients with 17p deletion and/or TP53 mutation who had been previously treated in Study 116 is provided as supporting evidence only. The Gilead submission (page 19) states:<br><br>*"For previously untreated patients with a 17p deletion or TP53 mutation, the key evidence for idelalisib with rituximab is derived from a subgroup of patients from the single-arm study, 101-08, and supported by the larger subgroup of patients with a 17p deletion or TP53 mutation in the relapsed or refractory population*" (Study 116).<br><br>Please add this text to clarify and please remove mention of this population not being in line with the NICE scope. | incorrect that the evidence presented for the untreated CLL population with 17p deletion and/or TP53 mutation differs from the NICE scope.<br><br>The populations of interest and their supporting evidence need correcting and clarifying to the reader. Data from 101-08 are within the scope population whilst data from study 116 are provided as supportive evidence only for this population. | |

## Issue 29 Section 3.1: Generalisability of Idelalisib Evidence

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG states that:<br><br>*"Given the information provided in the company submission and responses to the clarification questions (study 116 patient characteristics* | This conclusion seems to ignore the evidence presented by the company submission which has been copied in above this statement (page 35-36), and does not provide any explanation for why it has been discounted. The following is stated:<br><br>*"As detailed further in Section 4.13 of the Gilead submission, in general, patients included in Study* | The ERG report does not seem to take into account the explanation in the company submission for why the population in Study 116 is representative of the patient population likely to be seen in clinical practice and | We consider given the evidence, that the Study 116 sample is not representative of the whole CLL adult pre-treated patient population as specified in the NICE scope. The Study 116 sample is comprised of [or over-represented by] frailer, older, chemo immunotherapy intolerant and |

| | | | |
|---|---|---|---|
| *compared to those from other trials), the ERG considers that the evidence provided on idelalisib is of limited applicability to routine UK practice as outlined in the NICE scope, in light of the lack of or insufficient evidence and the discrepancies in the trial and scope populations."* (Page 36)<br><br>[This is also mentioned in the conclusions – page 119]<br><br>This is misleading as it ignores evidence included in the company submission. | *116 were representative of the wider population of patients with relapsed or refractory CLL treated in the clinical setting.*<br><br>*Patients in Study 116 were older than patients in the other RCT and non-RCT studies of comparator treatments (median age of 71 years vs. median age of 59 to 71 years across the studies). Given a median age at diagnosis of 71 years, this patient population is much more likely to represent actual patients seen in clinical practice.*<br><br>*A similar proportion of patients were female in Study 116 (35%), compared with the other studies (25-42%).*<br><br>*Patients included in Study 116 had received a median of 3 prior therapies compared with a median of 1 in all RCTs and 2-5 prior therapies across the other non-RCT studies that reported these data.*<br><br>*Patients in Study 116 were of a similar disease severity compared with the other studies, according to the proportion of patients in Binet Stage C (56% vs. 12-65% across the other studies).*<br><br>*In general, the proportion of patients with 17p deletion was greater in Study 116 (26%) when compared with six other studies reporting such data (9%, 10%, 7-9%, 18%, 41%, 18- 29%). This is perhaps not surprising given that the patients in Study 116 were heavily pretreated and therefore will have a higher proportion of this subgroup as they progress through treatment lines and undergo clonal selection of the chemo-immunotherapy resistant group of patients with a 17p deletion or* | doesn't provide any explanation for why this evidence has been ignored, even though it has been presented and clinically validated. | refractory/relapsed patients.<br><br>Please see our previous responses to this issue.<br><br>Our concern is about the precise relevance of the Study 116 sample to the English population for whom NICE will be making a decision. |

| | | | |
|---|---|---|---|
| | *TP53 mutation.*<br><br>*Study 116 was a multinational, multicentre study, which included representative centres from the US, France, Germany, Italy and UK. Of the 220 patients randomised in Study 116, 32 patients (14.5% of all recruited patients) were enrolled from the UK, which represents a relatively high proportion of patients in a global study.*<br><br>*Overall Study 116 is expected to be highly representative of the relapsed or refractory CLL population that would be found in general clinical practice. As such, the meaningful clinical effectiveness demonstrated with idelalisib with rituximab in Study 116 is expected to be replicated in clinical practice."* | | |

## Issue 30 Section 3.3: Evidence Base for Idelalisib

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states that:<br><br>*"In reporting the evidence on idelalisib, the company submission relies mainly on a single RCT with rituximab monotherapy as a comparator arm (Study 116)."* (Page 36)<br><br>[This is also mentioned in the conclusions – page 119]<br><br>Clarification is required. | While this is correct for the previously treated CLL population, this overlooks Study 101-08, which is the main evidence for the untreated CLL population with 17p deletion and/or TP53 mutation. | It is important to distinguish between the main evidence that is presented for each of the populations in the NICE scope. | Please see responses to issue 1, line 2 and to issue 5, section 1.1. |

## Issue 31 Section 3.3: Population

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report has confused the patient populations of interest (Page 37).<br><br>"*The NICE scope states the following (page 2):*<br><br>*"**In clinical practice in England, patients with untreated CLL associated with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable are treated with bendamustine (with or without rituximab), chlorambucil (with or without rituximab) or alemtuzumab."** According to our specialist clinical adviser, alemtuzumab with methylprednisolone (but not rituximab monotherapy) is a common treatment for relapsed/refractory CLL patients with 17p deletion or TP53 mutation in UK practice (Pettitt et al., 2012) and this is in agreement with the NICE scope."* | The sentence talks about the untreated CLL population with 17p deletion and/or TP53 mutation and then refers to the relapsed/refractory population with 17p deletion and/or TP53 mutation. In the NICE scope, alemtuzumab is not listed as a relevant comparator for the previously treated patient population.<br><br>However, alemtuzumab monotherapy (not in combination with steroids) is listed in the NICE scope as a relevant comparator for the untreated CLL population with 17p deletion and/or TP53 mutation. | The section needs clarification on which specific populations are being referred to. | The ERG have deleted the following sentence (P37):<br><br>*According to our specialist clinical adviser, alemtuzumab with methylprednisolone (but not rituximab monotherapy) is a common treatment for relapsed/refractory CLL patients with 17p deletion or TP53 mutation in UK practice (Pettitt et al., 2012) and this is in agreement with the NICE scope."* |

## Issue 32 Section 3.3: Comparators

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report (page 39) states that bendamustine and chlorambucil (with or without rituximab) were excluded as relevant comparators for the relapsed/refractory CLL population with 17p deletion and/or TP53 mutation. This is factually incorrect.<br><br>"*The company submission deleted bendamustine and chlorambucil (with or without rituximab) as relevant comparators for relapsed/refractory CLL patients with 17p deletion or TP53 mutation and stated (page 39):*<br><br>*"NICE currently does not provide any specific treatment pathways for patients with a 17p deletion or TP53 mutation; therefore, these patients are treated using the same treatment pathway as the wider CLL patient population, suggesting a poorly-addressed patient population and a high unmet need in this area."* | Bendamustine and chlorambucil (with or without rituximab) were included as relevant comparators for the previously treated (relapsed or refractory) CLL population. However, these treatments were not considered to be relevant comparators in the untreated CLL population with 17p deletion and/or TP53 mutation. We ask that the ERG report is amended as follows:<br><br>The Gilead submission (page 12) states: *"Bendamustine and chlorambucil have both been excluded as relevant comparators because these are considered to be cytotoxic chemotherapy, which is not suitable for this high-risk patient population."* | The statement in the ERG report is factually incorrect. | Our statement is not factually incorrect. |

## Issue 33 Section 4.1.2: Reasons for exclusion of comparators

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states that ofatumumab plus bendamustine, and obinutuzumab plus | The additional reasons that these treatment combinations were not | The current text incorrectly infers the | Our statement is correct. |

| | | | |
|---|---|---|---|
| chlorambucil were excluded from the eligibility criteria for the single reason that they were not yet appraised by NICE (page 44), as follows:<br>"*The eligibility criteria of SR#2 (treatment naïve CLL patients with 17p deletion or TP53 mutation) was modified from those of the NICE scope by deleting the following comparators:*<br>*a) Bendamustine (with/without rituximab): cytotoxicity and unsuitability for a high risk population*<br>*b) Chlorambucil (with/without rituximab): cytotoxicity and unsuitability for a high risk population*<br>*c) Ofatumumab plus bendamustine (or chlorambucil): not yet appraised by NICE*<br>*d) Obinutuzumab plus chlorambucil: not yet appraised by NICE*" | considered to be relevant need to be stated: neither were part of standard care and they are both chemo-immunotherapies, which are not suitable for this patient population and are outside of the licensed indication for idelalisib. (Table 1 in the Gilead submission dossier). These additional reasons should be re-stated here. | reason for exclusion of ofatumumab and obinutuzumab. As such, the addition of these additional reasons will more accurately capture the fact that these treatment combinations are not relevant comparators for the licensed population of idelalisib. | |

## Issue 34 Section 4.1.3: Critique of data extraction

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report quoted the baseline number of patients in the LeBlond (2012) study using the total population values and not the number of patients being treated as second-line, as is appropriate for the relapsed or refractory CLL population for which this study was included | The initial numbers that were presented were correct for the relapsed or refractory population only; therefore the ERG correction should be removed and the original numbers should remain. | The correction made by the ERG was factually incorrect and the data specific to the patients treated as second-line should be kept | We have removed this from the report, as we agree with the company's argument about the correct numbers. |

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| (Page 45)<br>"*Data extraction for the Leblond study was inaccurate in presenting the baseline numbers of patients by the treatment groups (bendamustine plus rituximab: 18 vs. chlorambucil plus rituximab: 23) (Leblond et al., 2012). According to the Leblond report, these numbers are 58 and 68, respectively*."<br><br>This is factually incorrect. | | as it was. | |

## Issue 35 Section 4.1.3: Critique of data extraction

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report (page 45) states that there were numerical discrepancies across outcomes between the study report, Hillmen et al (2007) and the company submission:<br>"*For untreated CLL patients with 17p deletion (SR #2), there were numerical discrepancies across outcomes (e.g., median PFS, overall response rate) between the study report (Table 2, Figure 1) Hillmen et al. (2007) and the company submission (Table 15; appendix; page 60)*."<br>This is incorrect. | The data presented in the submission were for the subgroup of untreated patients with 17p deletion and/or TP53 mutation, as was relevant to the decision problem, whereas the ERG quoted numbers for the overall population of these studies. Therefore the correction should be removed. | The correct data was originally presented in the submission for the untreated 17p and/or TP53 mutation population, as was relevant to the decision problem. | ERG will delete this sentence. |

## Issue 36 Section 4.2.1: Description of duration of response in key idelalisib trial

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states that the Kaplan-Meier median duration of response for the rituximab arm in Study 116 is;;<br>"*KME=6.5; 95% CI: 6.2; 95% CI: 2.8, 6.5; see Table 7*".(page 51)<br>The first part "*6.5; 95% CI:*" is a typographical error. (Page 51)<br>[This error is also seen on page 16 in section 1.2] | The Kaplan-Meier median duration of response should be: 6.2; 95% CI: 2.8, 6.5. | The reader may be confused as to what the actual point estimate is for median survival; 6.5 vs 6.2 months. The report should confirm that it should be 6.2 months. | Thank you for noting this typo – we will change this in the report. (P16, P51). |

## Issue 37 Section 4.2.1: Description of time to response in key idelalisib trial

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states that: "*Time to response was similar between the groups (no 95% CI or p-values reported)*." (Pages 51-52). This requires clarification. | While this is true (IR median: 2.1, 95% CI 1.9, 3.7; R median: 2.8, 95% CI 2.0, 3.9) it should also be noted that the first scan measurement took place at 1.9 months, which is why the Q1 time to response is reported as 1.9 months in the IR group. In practice, however, the clinicians saw these clinical responses to idelalisib and rituximab such as shrinkage of lymph nodes much earlier (e.g. after a few days of treatment). (Page 89 of Gilead submission). | This caveat suggests that had response been measured earlier, the median response for these patients may have been lower. | We thank the company for pointing out the clinicians' views, which are also stated in the company's submission. |

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| | We recommend adding this clarification. | | |

## Issue 38 Section 4.2.1: Inclusion of results from additional PFS/OS analysis in key idelalisib trial

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report presents the results for Study 116, but does not present the results of the crossover adjusted RPSFT analysis for OS. (Page 51-52; Table 7). This is misleading/requires additional clarification. | The crossover adjusted RPSFT analysis for OS results should be presented:<br>IR median: Not reached (95% CI: not reached, not reached)<br>[redacted]<br>IR 12-month OS: 89.3%; R 12-month OS: 49.2%<br>IR 24-month OS: 71.0% | This analysis provides useful additional data for Study 116, adjusting for crossover from the placebo arm of the trial onto idelalisib. The rationale for this analysis and a description of the methods used is provided on page 75 of the original company submission. | The ERG has already included these data in Table 16 P74 of the report. |

## Issue 39 Section 4.2.1: Significant differences in AEs in idelalisib key trial

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report mentions a number of specific AEs that occurred statistically more frequently in the idelalisib arm of Study 116 (Page 56 and Table 10): | All AEs listed also show a significant difference between the groups should also be marked up in the | To correctly and fully report the data. | The ERG is pleased to note that the differential occurrence of AEs is noted. |

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| "*Specific AEs that occurred significantly more frequently (p-value for relative risk ≤ 0.1) in the idelalisib arm were pyrexia, GERD, increased ALT, increased AST, dehydration, rash, colitis, pain, diarrhoea, chest discomfort, fall, sinus congestion, and stomatitis*."<br><br>Currently only pyrexia is marked up in the table as being statistically significant. | table with an asterisk. | | |

## Issue 40 Section 4.2.3: Rationale for excluding one study from literature review

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states that a study by Pettitt et al (2012) was excluded from the submission due to an irrelevant comparator (Page 60):<br><br>"*Although the company submission identified this study, it was excluded from the review synthesis, owing to a comparator deemed as irrelevant (company submission: Appendix 3)*."<br><br>Clarification is required. | It should be noted that this study is discussed on page 144 of the submission and was excluded from discussion as alemtuzumab in combination with steroids was not listed as a comparator in the final NICE scope. Although alemtuzumab was listed as a relevant comparator in the NICE scope, alemtuzumab with steroids was not listed as a comparator so was therefore, not considered in this submission, Despite this, the manufacturer did make mention of this study and the rationale for not including:<br><br>"*Of note, however, although there were no alemtuzumab monotherapy studies identified, there was a phase II trial for alemtuzumab and steroids conducted in* | This provides further clarification for the exclusion of this study from the submission. | The ERG consider that the text in the report is clear. |

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| | *the UK,(Pettitt, 2012) which included 17 previously untreated relatively fit patients with a median age of 62 (n=39, including previously treated patients). This is the basis of the BCSH guidelines recommendation of combination therapy with alemtuzumab and pulsed high-dose glucocorticoids. However, the BCSH guidelines also recognise that this regimen is associated with a significant risk of infection and advise to administer with caution. Alemtuzumab plus steroids is not a listed comparator and therefore this study will not be discussed further in this submission*." | | |

## Issue 41 Section 4.6: Population

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG statement that previously treated population in Study 116 is not representative of the broader population specified in the NICE scope (Page 65) is incorrect.<br>"*The only RCT of idelalisib (study 116) was conducted in the subgroup of previously treated relapsed and/or refractory CLL patients who were also relatively older and frailer with multiple comorbidities and intolerant or not suitable to chemo immunotherapy agents. Moreover, almost half of the study 116 sample (42.6%) included CLL* | See responses to 0 and Issue 3 above | See responses to 0 and Issue 3 above | Please see our previous responses. |

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| *patients with 17p deletion and TP53 mutation for whom standard cytotoxic therapy is not suitable. Thus, study 116 sample was overly selective, and probably over-represented higher risk (i.e., harder to treat) CLL patents who would not be representative of the more broadly defined 'all pre-treated CLL patients' specified in the NICE scope*." | | | |

## Issue 42 Section 4.6: Conclusions of the clinical effectiveness section

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| In the ERG report it states that: "*All CLL patients with 17p deletion and TP53 mutation in the study 116 had already been treated unlike naïve patients as specified in the NICE scope*." (Page 65)<br><br>This section is misleading and does not mention Study 101-08, which was the main trial used to provide evidence for the population of untreated CLL patients with 17p deletion and/or TP53 mutation, as specified as the second population of interest in the NICE scope. | The 17p deletion and/or TP53 mutation subgroup from Study 116 is only used as supporting data for the population of untreated patients with 17p deletion and/or TP53 mutation.<br><br>It should be stated that the primary trial of interest for the population of untreated CLL patients with 17p deletion and/or TP53 mutation is Study 101-08, which should be referenced here instead. | The current statement is misleading and fails to mention all the data presented. It is important to note that the relapsed or refractory (previously treated) patients with 17p deletion and/or TP53 mutation are not the only source of data that are being used to address the untreated 17p deletion/TP53 mutation population that is specified in the NICE scope. It should be clarified that the subgroup of patients from Study 116 with 17p deletion and/or TP53 mutation should only be used to support the evidence presented in Study 101-08 for the untreated patients with 17p deletion/TP53 mutation. Note that Study 101-08 formed the basis of the evidence base for the EMA approval of idelalisib.[12] Furthermore, the EMA | Please see our previous responses about use of evidence from the single arm Study 101-08. |

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| | | identified the activity of idelalisib in patients with CLL and a 17p deletion or TP53 mutation as an area of special interest based upon the consistent results seen across studies at all lines of treatment in patients with a 17p deletion or TP53 mutation.[12] | |

## Issue 43 Section 5.2.1: Criticism for not comparing to alemtuzumab in the relapsed patient population

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Section 5.2.1, Page 68, states:<br><br>*"Alemtuzumab was not considered."*<br><br>This does not reflect the scope. | Please remove this sentence. | Alemtuzumab was not a listed comparator in the final scope determined by NICE. | Alemtuzumab is listed in the scope for ii) Adults with untreated chronic lymphocytic leukaemia associated with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable |

## Issue 44 Section 5.2.1: Description of the modelled patient group's adherence to the reference case

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 69, ERG report, Row 3, column 3 of the table summarising adherence to the NICE reference case, the ERG include the following: | Please amend this sentence to the following:<br><br>*"Population from study 116, which is a* | The Study 116 population are not argued to represent the entire UK treatment | The data from Study 116 is used as the main base of the company's submission for this decision problem. |

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| *"Population from study 116, which is argued to be representative of the UK treatment population."* | *subset of the population of adults with chronic lymphocytic leukaemia who have received at least one prior therapy"* | population; they are presented clearly and throughout as a patient group who represent a subset of relapsed patients who are heavily pre-treated and no longer suited to chemotherapy. | |

## Issue 45 Section 5.2.2: Description of utility assumption

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 71, ERG report, the ERG state the following:<br><br>*"Since patients may withdraw from active treatment or complete the full treatment course before disease progression, costs differ between the two pre-progression states. However, utilities and risks of progression/death do not differ between these states; based on the assumption that treatment efficacy remains the same post treatment discontinuation."*<br><br>This is factually incorrect. | Please amend the description of utility and transition probability assumptions in this text, with reference to 0 (Study 116 EQ-5D data were used to capture HRQL in the 'pre-progression, on-treatment' state, the estimate from Dretzke et al was assumed to capture HRQL in the 'pre-progression, off-treatment' state). | Corrects for a factual inaccuracy. | Reference to utilities has been removed from this sentence. P71. |

## Issue 46 Section 5.2.3: Description of company presentation of the modelled patient group

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 71, ERG report, the ERG state the following:<br><br>*"The population modelled in this submission is that from Study 116,[13] which is argued to be sufficiently similar to the UK treatment population as to provide a valid comparison."*<br><br>This is misleading | Please amend this text with reference to Issue 44. | An appropriate amendment here will correct for an important misinterpretation; the Study 116 population are not *different to* the UK treatment population; they are a patient group who represent a subset of relapsed patients who are heavily pre-treated and no longer suited to chemotherapy. | See response to issue 44, section 5.2.1 |

## Issue 47 Section 5.2.6: Description of crossover analysis assumptions

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 73, ERG report, the ERG state the following:<br><br>*"This analysis assumes that the treatment efficacy of idelalisib monotherapy is the same as that for idelalisib with rituximab. Assuming a lower treatment efficacy for idelalisib monotherapy than idelalisib with rituximab will* | Please amend this text with reference to Issue 16. | An appropriate amendment will correct for a slight factual inaccuracy. | Please see response to issue 17 |

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| *result in a lower treatment benefit for idelalisib with rituximab versus rituximab (the HR will fall somewhere between those for the ITT and crossover adjusted analyses below)"*<br><br>This is factually incorrect. | | | |

## Issue 48 Section 5.2.6: Criticism of the applicability of Study 116 patient group data for the UK treatment population

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 83, ERG report, the ERG summary states the following:<br><br>*"Overall survival, progression-free survival, time on treatment (for idelalisib) and overall response rates) were all calculated as extrapolations to data from Study 116, and therefore the applicability of these data to the UK treatment population needs to be carefully considered."* | Please amend this text with reference to Issue 44. | To provide clarification and avoid incorrect misinterpretation by the reader. | The ERG believes its statement is accurate. The company's reliance on evidence relating to a subgroup of the scope populations does not mean that issues of generalisability to the reference population in the NICE scope need not be considered. |

## Issue 49 Section 5.2.7: Misinterpretation of Study 116 EQ-5D data presented in the submission document

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 87, ERG report, the ERG state the following:<br><br>*"The ERG has a number of concerns about the use of Study 116 EQ-5D data as the primary source of pre-progression utilities. Firstly, patients in the IR arm of the trial appeared to have a better quality of life than those in the R arm at baseline. In the IR arm at baseline, 70.4%, 60.2%, 53.3%, 90.7% and 56.5% of participants were at level 1 (the best possible state) on the anxiety/depression, mobility, pain/discomfort, self-care and usual activities scales of the EQ-5D, respectively. The proportions for the R arm were uniformly lower, at 59.0%, 55.8%, 52.9%, 87.4% and 44.2%, implying a lower initial quality of life. Whilst a generalised estimating equation model can be used to attempt to adjust for these baseline imbalances, sufficient detail was not given to assess whether this was done. Even if this bias was appropriately corrected for, it would still introduce concerns about relying so heavily on a data source with such an obvious baseline imbalance."*<br><br>As described in 0, the ERG have wrongly inferred a lower initial quality of life on the comparator arm of Study 116. | Please remove or substantially amend this text, with reference to 0. | An appropriate amendment here will correct for an important misinterpretation; as described in 0, the ERG's concerns are unfounded and based on false inference from data presented in the submission document. | This paragraph has been removed as a result of the additional data now provided by the company. |

## Issue 50 Section 5.2.7: Criticism of model assumptions regarding HRQL

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 87, ERG report, the ERG state the following:<br><br>*"Secondly, the utilities for patients who have discontinued treatment (taken from Dretzke et al.[6]) were higher than those for people being treated with rituximab, and this difference was considerably more than could be explained by the adverse event disutilities calculated from Study 116. Thus, patients discontinuing from idelalisib maintain a considerably higher quality of life than those still being treated with rituximab, an assumption not justified in the submission. Finally, all other treatment options considered (ofatumumab, best supportive care, FCR etc.) are assumed to have the same pre-progression utilities as rituximab, and thus a lower on treatment utility than idelalisib. No justification is given for setting these utilities to be equal to the lower rituximab utility rather than the higher idelalisib utility."* | Please remove or amend this text, with reference to Issue 19. | Appropriate amendment to, or removal of, this text will correct for a factual inaccuracy and misrepresentation of the importance of another model assumption. | Text around the HRQoL assumptions made in the model has been clarified (P87). |

## Issue 51 Section 5.2.7: Criticism of the use of multiple sources for utility data

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page87-88, ERG report, the ERG state the following:<br><br>*"Many of these issues arise from the use of utilities from different data sources, which do not necessarily give consistent or comparable values. In the opinion of the ERG, a more reliable and robust approach would be to take utility values for the different health states solely from the Dretzke et al.[6] paper, and then apply adverse event disutilities from the trial. This approach is tested in one of the sensitivity analysis reported by the company, and is used as the base case in additional analyses undertaken by the ERG."* | Please amend or remove this text, with reference to 0 and the NICE methods guide. | Appropriate amendment to, or removal of, this text is warranted given the argument presented in 0. | We consider the use of the Dretzke utility values as a base case to be preferable (see issue 21). |

## Issue 52 Section 5.2.7: Interpretation of and inference from HRQL assumptions.

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| Page 88, ERG report, the ERG summary of HRQL data states the following:<br><br>*"In the company's analysis patients* | Please revise this text with reference to Issue 19. | Appropriate revision of this text corrects for misinterpretation of the Gilead submission document by the ERG (the false interpretation that patients on chemotherapy are assumed to be attributed the same HRQL as patients in the | Issues around this have been addressed above. However, this sentence itself remains accurate. |

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| *discontinuing from idelalisib maintain a considerably higher quality of life than those still being treated with rituximab, an assumption not justified in the submission."* | | comparator arm of Study 116), and inference that the company's utility assumptions for patients in the 'pre-progression, off-treatment' health state are important for model results. | |

## Issue 53 Section 5.2.7: Repeat of criticism of the use of multiple sources for utility data

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 88, ERG report, the ERG summary of HRQL data states the following:<br><br>*"In the ERGs preferred analysis, utilities for the different health states are taken from a single source[6], with adverse event disutilities then applied to these, according to data from Study 116."* | Please revise or remove this text with reference to 0 and the NICE reference case | Appropriate amendment to, or removal of, this text is warranted given the argument presented in 0. | The issue is not with the use of utility data from multiple sources, which is an entirely justifiable thing to do in general, but rather that in this particular case to do so produces, as the company themselves state, illogical results. Therefore, as per issue 21 above, the ERG maintains this statement is accurate. |

## Issue 54 Section 5.2.8: Misinterpretation of treatment cost assumptions

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 87 ERG report, the ERG state the following:<br><br>*"For the idelalisib arm, ToT treatment curves (see section 5.2.6) were used to estimate how long patients would be on treatment, and therefore for how long treatment costs would be applied in the model. For other comparators, treatment costs were applied for the full maximum dosing duration indicated for that product, under the assumption that all patients would take the full course, with none discontinuing early. The justification given for this is that ToT data in Study 116 were deemed to be unrepresentative of ToT outside of the study when maximum dose durations are applied."* | Please revise this text with reference to Issue 14. | Appropriate amendment to the text will correct for an important factual inaccuracy regarding the application of treatment costs to comparator treatments in the company submission. | Text has been clarified (P88). |

## Issue 55 Section 5.2.8: Misinterpretation and criticism of treatment cost assumptions

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 90, ERG report, the ERG state the following:<br><br>*"The ERG is not convinced by the justification given for* | Please revise or remove this text, with reference to | Appropriate amendment to, or removal of, this text is warranted, given the ERG's | Adjusted, as per issue 14. |

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| *using two different methodologies for calculating the duration of treatment costs for the different treatment options. Specifically, if ToT data derived from the trial were not thought to be representative of standard practice for rituximab monotherapy, then it is unclear why they should be viewed as reliable for idelalisib therapy. The current approach almost certainly overestimates the drug treatment costs for all non-idelalisib regimens, as it is unlikely that all patients would complete the full course of treatment. A more realistic (and conservative) approach would appear to be to make use of ToT data from the rituximab monotherapy arm of Study 116. Therefore, in the ERG's base case analysis, the assumption that, for all treatments other than idelalisib, all patients complete the full treatment course was replaced by an assumption that patients complete the same proportion of the treatment course as was so for rituximab monotherapy in Study 116."* | Issue 14 and Issue 21. | misunderstanding of the approach to treatment costing in the submission, highlighted in Issue 14. | |

## Issue 56 Section 5.2.8: Repeat of misinterpretation and criticism of treatment cost assumptions

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 95-96, ERG report, the ERG summary of cost and resource use data states the following:<br><br>• *"In the company's base case, costs for idelalisib are* | Please revise or remove this text with reference to Issue 14 | Appropriate amendment to, or removal of, this text is warranted, given the ERG's misunderstanding of the | Adjusted, as above. |

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| *accrued until treatment discontinuation, whilst for other comparators patients are assumed to complete the full maximum dosing indicated for that product.*<br>• *"The ERG believe a more realistic approach is to use ToT data from Study 116 to estimate the proportion of the maximum number of doses actually administered for rituximab monotherapy, in the same way as was done for idelalisib, and apply costs to these estimated ToT data."* | and Issue 21. | approach to treatment costing in the submission, highlighted in Issue 14. | |

## Issue 57 Section 5.3: Description of the ERG's base case

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 109, ERG report, the ERG describe their base case as including the following changes to the company's base case model:<br><br>• *"Health state utilities for the pre-progression and post-progression states are taken from the Dretzke et al. paper,[6] with adverse events disutilities applied to the frequency of adverse events in Study 116.*<br>• *"ToT data for rituximab monotherapy are used to inform estimated drug costs, rather than assuming all patients complete the full course. For treatments other that IR and R, patients are assumed to take the same* | Please consider revising this text (and the ERG base case), with reference to Issue 14, 0, Issue 21 and the NICE reference case. | The ERG base case and criticism of the company's base case may warrant revision given Issue 14, 0, Issue 21 and the NICE reference case. | The text has been adjusted (see above). However, the ERG has not made any changes to the assumptions it has used for its own base-case analysis, as we believe they represent a set of plausible alternative assumptions with which to develop an ICER. |

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| *proportion of the maximum dosing duration as for rituximab monotherapy in Study 116."* | | | |

## Issue 58 Section 5.4: Conclusion regarding crossover analysis

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| Page 113, ERG report, the ERG state the following:<br><br>*"when adjusting for crossover in the rituximab arm of the trial (an entirely correct adjustment to make), equal efficacy is assumed for idelalisib monotherapy and idelalisib with rituximab, which is again an assumption which favours the idelalisib arm of the model"* | Please consider revising this text with reference to Issue 17. | Slight and appropriate revision of the text will more accurately describe the assumptions implicit in the crossover adjustment. | Please see response to issue 17. |

## Issue 59 Section 5.4: Conclusion regarding the modelled patient population

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| Page 114, ERG report, the ERG state the following:<br><br>*"It is also important to note that neither the treatment comparators nor the modelled population are* | Please consider revising this text with reference to Issue 22 and Issue 44. | Appropriate revision to this text can more accurately present the modelled population as a subgroup of adult patients with CLL who have received at least one treatment. | Please see responses to issues 22 and 45. |

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| *exactly as in the NICE scope."* | | | |

## Issue 60 Section 5.4: Conclusion making incorrect inference from subgroup analysis results

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| Page 114, ERG report, the ERG state the following:<br><br>*"No data was presented at all for a treatment naïve population with 17p deletions or TP53 mutations, with the closest being a subgroup of patients from Study 116, who did have a 17p deletion or TP53 mutation, but were not treatment naïve. Idelalisib therapy appeared to be somewhat less cost-effective in this population than the overall Study 116 population."* | Please amend this text with reference to Issue 22. | Appropriate amendment of this text will avoid misinterpretation of the subgroup analysis results requested in the final NICE scope. | See response to issue 22. |

## Issue 61 Section 5.4: Assessment of key sources of uncertainty in ICERs – Patient population

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 115, ERG report, the ERG state the following in consideration of 'key sources of uncertainty in ICERs': | Please revise or remove this text with reference to | At no point in the submission is the Study 116 population assumed | See our relevant responses to previous discussion of this issue above. |

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| ***"Parameter/model feature*** *Patient population*<br><br>***Current assumption*** *Study 116 population is modelled, which is assumed to be sufficiently similar to the UK CLL treatment population that results can be extrapolated to this group*<br><br>***Likely impact of varying assumption*** *If the treatment benefit of idelalisib is less in the populations in the scope than Study 116, then idelalisib would become less cost-effective than it currently appears"* | Issue 22. | to be sufficiently similar to the UK CLL treatment population that results can be extrapolated to this group. The Study 116 population is presented, accurately, as a subgroup of the relapsed population. | |

## Issue 62 Section 5.4: Assessment of key sources of uncertainty in ICERs – Adjustment for crossover

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| Page 115, ERG report, the ERG state the following in consideration of 'key sources of uncertainty in ICERs':<br><br>***"Parameter/model feature*** *Adjustment for crossover in rituximab monotherapy arm of Study 116*<br><br>***Current assumption*** *Idelalisib monotherapy has the same efficacy as idelalisib with rituximab.*<br><br>***Likely impact of varying assumption*** *If idelalisib monotherapy is less effective than idelalisib with* | Please consider revising this text with reference to Issue 17. | Slight and appropriate revision of the text will more accurately describe the assumptions implicit in the crossover adjustment. | The ERG raises a legitimate concern here since we are not presented with evidence to suggest the equivalent efficacy of the two groups. |

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| *rituximab, idelalisib will become less cost-effective than it currently appears."* | | | |

## Issue 63 Section 5.4: Overall assessment of bias introduced by model assumptions

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 116, ERG report, below the table of 'key sources of uncertainty in ICERs', the ERG state the following:<br><br>*"Since in general the assumptions chosen in the model appear to favour idelalisib over its comparators, it must be considered that the presented ICERs represent optimistic assessments for the cost-effectiveness of idelalisib. How optimistic the assessment of cost-effectiveness is depends on to what extent it is believed that the assumptions given in the table above are violated."* | Please consider revising this text, to reflect a more balanced assessment of model assumptions. | Of the key sources of uncertainty highlighted by the ERG, an unbiased observer may observe that two assumptions favour idelalisib: the assumption implicit in the crossover analysis and the assumption of persistent treatment effect in the absence of long-run data. There are numerous conservative assumptions in the model, which the ERG's conclusion ignores, including the use of ITT PFS data, which surely underestimates the time to progression benefit of idelalisib with rituximab versus rituximab monotherapy, the conservative assumptions underpinning the comparison to best supportive care, and the assumption that there are no adverse event costs or HRQL effects associated with chemotherapy treatments. | It is important to note that some of the optimistic assumptions in the model (e.g. permanent treatment benefit, choice of crossover adjustment etc.) have the potential to substantially impact the ICER, whilst the conservative ones (e.g. no HRQoL losses from adverse events for other chemotherapy regimens) make only a marginal difference to the ICER, so it is important to focus on these key assumptions. |

## Issue 64 Section 7: Criticism of choice of comparator in Study 116

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 120, ERG report, the ERG present the following as a difficulty in extrapolating the results from these analyses to the relevant decision problem in the UK:<br><br>*"Will idelalisib with rituximab be as cost-effective versus other, more relevant, comparators as it is versus rituximab monotherapy? The results presented seem to indicate that rituximab monotherapy is one of the two most favourable comparators that could have been selected (together with ofatumumab monotherapy), and that idelalisib with considerably less cost-effective versus other possible comparators."* | Please revise this text, with consideration of the feasible and ethical options for treatment comparators in Study 116. | The text suggests that rituximab was selected as a comparator in Study 116 in order to make idelalisib appear effective. The patients in Study 116 were not able to receive chemotherapy and rituximab monotherapy was chosen as a comparator in line with the NCCN Guidelines (as clarified within the Gilead submission / NICE Scoping meetings). | The text indicates the net result of the choice selected by the company. |

## Issue 65 Section 7: Inference from subgroup analysis

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| Page 120, ERG report, the ERG present the following as a difficulty in extrapolating the results from these analyses to the relevant decision problem in the UK: | Please revise this text, with reference to Issue 22 and with reconsideration of the implications of subgroup analysis results for patients with CLL associated with | As described in Issue 22, subgroup analysis results are not suggestive that idelalisib is less cost-effective in the 17p deletion and TP53 mutation patient population as a whole; indeed the inference would be the opposite – | Please see previous responses as per issue 22.<br><br>The ERG report does not state that idelalisib is not cost-effective in the group of patients with 17p deletion or |

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| *"Will idelalisib with rituximab be as cost-effective in patients with 17p deletions or TP53 mutations as those without? The results presented seem to indicate idelalisib is somewhat less cost-effective than in these groups, though these are based on a subgroup of pre-treated patients from Study 116, not the treatment naïve population specified in the sco."* | 17p deletion or TP53 mutation who are younger, less heavily pre-treated and have fewer comorbidities than the subgroup of patients with 17p deletion or TP53 mutation in Study 116. | that subgroup analysis results suggest idelalisib would be a cost-effective option for this group of patients. For treatment-naïve patients with 17p deletion or TP53 mutation, the mechanism of action of idelalisib is likely to prolong survival substantially, as described at length in the submission document, and represent a cost-effective treatment option for patients who are younger, less heavily pre-treated and have fewer comorbidities than the subgroup of patients with 17p deletion or TP53 mutation in Study 116, and who have high unmet need. | TP53 mutation, but merely that, for the subgroup of pre-treated patients with these characteristics, it appears less cost-effective (a higher ICER) than for the whole pre-treated population. |

**Additional comments**

| Comment | ERG response |
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| P1 Renata Walewska, Consultant in Haematology | "The Bournemouth Private Clinic" has been removed. |
| P103, table 44. Should total costs for additional comparators be CIC? | They are marked as such in the company's submission, therefore this question should probably be directed to them. |
| P111, tables 54/55. Should ICERs be CIC? | These ICERs should not be marked as CIC |
| P112, table 56. The ICER for an adjustment factor of 3.8 is missing | The correct ICER here is £34,337 |

## References


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