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Title: Idelalisib Single Technology Appraisal - Idelalisib for relapsed chronic lymphocytic leukaemia [ID764]

Produced by	Warwick Evidence
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None

compared to rituximab monotherapy in previously treated CLL patients who had relapsed and/or been refractory to previous treatment. One notable deviation from the NICE scope was that study 116[1] 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. Almost half of the study 116 sample (43.2%) 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.

Another feature not in line with the NICE scope was that all CLL patients with 17p deletion and TP53 mutation in the study 116[1] had already been treated. Thus, the study 116 sample may have been too selective and over-representative of higher risk CLL patents who would not have been reflected in the more broadly defined population of 'all pre-treated CLL patients' as specified in the NICE scope. The ERG believes that the degree of applicability of the evidence provided on idelalisib to routine UK practice is limited in light of the lack of applicable evidence and the discrepancies between the pivotal trial population and the populations specified in the NICE scope.

Intervention

The company submission provided a description of the technology and its proposed marketing authorisation. There was no discrepancy in the described technology and its indication between the NICE scope and the company submission. Idelalisib was granted a UK marketing authorisation on 19th September 2014 and is indicated in combination with rituximab for the treatment of adult patients with CLL who have received at least one prior therapy, or as first-line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy. The recommended dose is 150 mg twice daily (BID) orally. During study 116, the dose of idelalisib was reduced from 150 mg to 100 mg for 18 patients owing to the occurrence of adverse events. The dose reduction in these participants took place at a mean of 130.6 (SD=89.7) days post randomisation. Also, the duration of patients' exposure to the drugs in the experimental arm (idelalisib plus rituximab) was longer compared to that in the rituximab arm alone (8.1 months vs. 4.6 months) which possibly led to a higher rate of discontinuation of the former in the experimental study group.

Comparator

The company submission relies mainly on a single RCT (Study 116)[1] which uses rituximab monotherapy as comparator. The company submission states that rituximab monotherapy is a recommended treatment option for patients with CLL in the US. The ERG note that rituximab is not standard therapy in the UK. The NICE scope does not include this drug as a comparator either. Our expert clinical advisor confirmed that rituximab alone is not an appropriate choice of treatment for relapsed/refractory CLL patients in the UK.

Study selection

Two independent reviewers screened studies using the same eligibility criteria applied to abstract/title level as well as full text screen level. Disagreements in opinion regarding eligibility of any given publication was resolved through discussion with a third independent reviewer.

Data extraction

The methodology of data extraction was not reported in the company submission. For the study 116, the accuracy of data extraction between the full submission and the final clinical study report was verified and found to be adequate. Data extracted for other included studies was also accurate.

Quality assessment

The included RCTs were appraised using an adapted tool by the Centre for Reviews and Dissemination, which consists of the following domains of bias: randomisation, allocation concealment, balance in baseline characteristics, blinding, sample attrition and losses to follow-up, and selective outcome reporting. The company submission assessed non-RCTs using the Downs and Black et al. (1998) modified tool.[3] The ERG verified the risk of bias assessment on RCTs using the Cochrane risk of bias tool.[4] Generally, the risk of bias assessment for the RCTs repeated by the ERG were in agreement with those of the company's submission except for study 116.[1]

Refractory or relapsed CLL population (SR #1): The company submission rated study 116[1] to be at low risk of bias. Two other RCTs of relevant comparators (Robak et al., 2010,[5] Niederle et al., 2013[6]) had a preponderance of 'unclear ROB' ratings owing to poor reporting quality of the publications. Most of the ERG's ROB assessments were rated either as 'unclear' or 'high risk' depending on the source of bias domain. Since study 116[1] was terminated early for benefit,[7] the ERG rated the domain of 'other bias' as at high risk for study 116.[1]

Untreated CLL patents with 17p deletion (SR #2): The review included one RCT (Hillmen et al., 2007)[8] and one non-RCT (Study 101-08). For the study by Hillmen et al. (2007),[8] the company submission rated three domains of 'method of randomisation,' 'treatment allocation concealment' and 'blinding' as unclear, two domains of 'similar distribution in baseline prognostic factors' and 'ITT analysis' were rated as 'Yes,' and two domains of 'imbalance due to dropouts' and 'selective outcome reporting' were rated as 'No.' The ERG could not confirm the quality of the Study 101-08, as this was not in the public domain.

Evidence synthesis

Refractory or relapsed CLL population (SR #1): This review included six RCTs: study 116 (Furman et al., 2014),[1] Robak et al. (2010),[5] Niederle et al. (2013)[6] Leblond et al. (2012)[9] Byrd et al. (2014),[10] and Awan et al. (2014).[11]

The review also included 13 non-RCTs as having relevant comparators: Furman et al. (2013),[12] Coiffier et al. (2008),[13] Wierda et al. (2010),[14] Tam et al. (2006),[15] Badoux et al. (2011),[16] Smolej et al. (2012),[17] Lopez et al. (2013),[18] Fischer et al. (2011),[19] Pileckyte et al. (2011),[20] Donnellan et al. (2014),[21] Sanhes et al. (2014a),[22] Zagoskina et al. (2014),[23] and Smolej et al. (2014b).[24]

The main bulk of evidence provided in the company submission rests on a single pivotal RCT (study 116; Furman et al., 2014)[1] which evaluated the efficacy and safety of idelalisib plus rituximab compared to rituximab monotherapy in previously treated CLL patients who had relapsed and/or been refractory to the previous treatment. 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. In addition small numbers of UK patients were involved in study 116. Evidence from studies other than study 116 (Furman et al., 2014)[1] was deemed less relevant because none of them compared idelalisib to a relevant to the decision problem comparator. Network meta-analysis could not be performed by the company due to the lack of relevant data.

Progression-free survival (PFS), overall survival, response rate (overall, lymph node), median time to and duration of response (in # of months) were improved for the idelalisib plus rituximab arm compared to the rituximab monotherapy arm. For example, median PFS was longer in the idelalisib (19.4 in months; 95% CI: 12.3, not reached) compared to rituximab monotherapy arm (6.5 months; 95% CI: 4.0, 7.3). The adjusted hazard ratio (HR) also indicated a significant improvement in PFS for patients who received idelalisib with rituximab compared to rituximab monotherapy (HR=0.15; 95% CI: 0.09, 0.24). The 12-month PFS rates were greater with idelalisib plus rituximab compared to rituximab alone (70.4% vs. 9.2%; 95% CI not reported). Neither of the study arms reached the 24-month PFSs. The median overall survival (OS) was not reached in the idelalisib arm when in the rituximab monotherapy arm it was 20.8 months (95% CI: 14.8 not reached). The adjusted HR for OS favoured idelalisib with rituxumab compared to rituximab (HR=0.34; 95% CI: 0.19, 0.60). The 12-month OS for the idelalisib was better than the rituximab monotherapy group (89.3% vs. 49.2%; test of statistical significance results no reported). The Kaplan-Meier estimate (KME) of median duration of response was longer in the idelalisib with rituximab arm (Not reached; 95% CI: 12.0, not reached) compared to the rituximab alone arm (KME=6.2; 95% CI: 2.8, 6.5). Time to response was similar between the groups (no 95% CI or p-values reported). The odds ratio for overall response

comparison to treatments more relevant to the UK CLL population than the rituximab monotherapy used in Study 116.

Quality of life values for the pre-progression on treatment state were calculated from EQ-5D data collected during Study 116 (0.813 for idelalisib, 0.748 for rituximab). The EQ-5D was only administered to patients who were in the pre-progression states and still on therapy, so it was not possible to use this trial to calculate utility values for the other states in the model. Data for the pre-progression (off treatment) and post progression states were taken from Dretzke et al.,[32] and the terminal care state was assumed to have the same utility as the post progression state. Since the quality of life losses associated with treatment related adverse events should be captured by EQ-5D data collected in the trial, no additional disutilities for treatment related adverse events were included in the base case. Patients receiving BSC or ofatumumab were assumed to have the same 'on-treatment' health-related quality of life as rituximab monotherapy. For other treatments, health-related quality of life for the progression-free survival state was assumed to be 0.8, derived from Dretzke et al.

Costs of treatment for idelalisib with rituximab and rituximab monotherapy were calculated by combining time on treatment data from Study 116 with reference prices for the drugs, including an agreed price discount for idelalisib, with treatment costs applied to patients in the 'pre-progression, on treatment' health state, up to the maximum treatment duration. For ofatumumab monotherapy, the same ToT curve was assumed as for rituximab monotherapy. For all other treatments, patients remaining in the pre-progression state were assumed to complete the full maximum dosing duration, with none discontinuing early. Best supportive care was assumed to have a treatment cost of zero. Costs of managing adverse events were calculated by multiplying trial data on events with NHS reference costs for the treatment of those events. Ofatumumab was assumed to have the same adverse event profile as rituximab monotherapy, with other treatments outside the trial incurring no costs for treatment related adverse events.

Disease management costs were stratified into pre progression, post progression and terminal care costs, with additional one-time costs when patients moved from the pre-progression to the post-progression state. Costs in the pre-progression state were further stratified according to whether patients had or had not responded to treatment. Costs associated with disease progression came principally from NHS reference costs but, although some of the resource use frequencies came from published data, a large number of them were based on clinical assumptions.

Base case results

The company base case results indicate that idelalisib with rituximab provides an additional 1.92 QALYs versus rituximab monotherapy and costs an additional £26,128, with an ICER of £13,634 per QALY. The parameters included in sensitivity analyses to which this estimate is most sensitive are those used to extrapolate progression-free and overall survival.

the ERG to the company's base case assumptions moderately increased the ICERs for idelalisib versus the various treatment alternatives.

1.5.2 Weaknesses and areas of uncertainty

i. The company's base case comparison of idelalisib with rituximab versus rituximab monotherapy is not necessarily a clinically relevant one in the UK.

ii. Survival curves were fitted to data from Study 116, assuming that the benefits of treatment (gains both in overall survival and progression-free survival) persist both after the time horizon of the trial, and after treatment discontinuation. No convincing justification was given to support this optimistic assumption.

iii. Modelling of idelalisib with rituximab versus ofatumumab and best supportive care both rely on the assumption of equal efficacy to rituximab monotherapy for these alternatives. The justification for assuming equal efficacy for ofatumumab and rituximab is not based on data in CLL, but in diffuse large B-cell lymphoma.

iv. Cost-effectiveness of idelalisib for the group of treatment naïve patients with 17p deletion or TP53 mutation unsuitable for chemo-immunotherapy was not modelled. A subgroup analysis was conducted on patients in Study 116 with 17p deletion of TP53 mutation, but these were not treatment naive.

v. 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.

vi. 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.

vii. 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.

1.6 Summary of exploratory and sensitivity analyses undertaken by the ERG

specialist clinical advice which confirms that the Study 116 comparator arm (rituximab alone) is not a recommended choice of treatment for relapsed/refractory CLL patients in the UK.

NICE technology appraisal guidance 193[2] recommends fludaribine, cyclophosphamide and rituximab as an option for people with relapsed or refractory CLL (i.e., wider CLL population) unless their disease is refractory to fludarabine or has previously been treated with rituximab. According to the NICE scope (page 1), in people with relapsed and/or refractory CLL (i.e., the wider CLL population) for whom chemo immunotherapy is unsuitable, bendamustine (with or without rituximab) or chlorambucil (with or without rituximab) is used.

The NICE scope states the following (page 2):

"*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.*"

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):

"*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*."

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 with/without rituximab, alemtuzumab, or ofatumumab). Due to a lack of or /insufficient comparator evidence, the company was unable to conduct a formal indirect treatment comparison (i.e., network meta-analysis) to compare rituximab monotherapy with any other standard treatment (e.g., ofatumumab, chlorambucil plus rituximab, alemtuzumab with methylprednisolone). Also, NICE does not recommend ofatumumab for treating CLL refractory to fludarabine (NICE technology appraisal guidance 202; NICE scope page 1).[36]
The company submission stated the following (page 16-17):

It is important to note that the eligibility criteria for both SRs (#1 and #2) excluded non-English publications.

Study selection (Figures 4-5) was performed by two independent reviewers using the same eligibility criteria applied to abstract/title level as well as full text screen level. Disagreements in opinion regarding eligibility of any given publication were resolved through discussion with a third independent reviewer (company submission: Section 4.1 Identification and selection of relevant studies; page 57).

4.1.3 Critique of data extraction

The methodology of data extraction was not reported in the company submission. For the refractory or relapsed CLL population (SR #1), data from Study 116 reported in the Furman et al. (2014)[1] publication is based on an earlier analysis as opposed to the company submission. Also, the latter describes the same trial in more detail. Therefore, these two sources of study 116[1] are not directly comparable in terms of extracted data. For study 116, the accuracy of data extraction between the full submission and the Final Clinical Study Report was verified and it was adequate. The data extracted for the remaining three trials LeBlond et al (2012)[9], Robak et al. (2010)[5] and Niederle et al. (2013)[6] were in agreement with that reported in the company submission (Appendix pages-57-60; Tables 9-14).

4.1.4 Quality assessment

Quality assessment of included RCTs for both clinical SRs (SR #1 and #2) was done using an adapted tool from the Centre for Reviews and Dissemination.[38] The instrument consists of the following domains of sources of bias: randomisation, allocation concealment, balance in baseline characteristics, blinding, sample attrition/losses to follow-up, and selective outcome reporting.

*For **refractory or relapsed CLL population (SR #1)**,* the company submission provided the ROB assessment of the single RCT of the study drug (study 116; Furman et al., 2014)[1] (Table 26, page 82). The ROB assessment for two other RCTs of relevant comparators is presented in Appendix 7 of the company submission (pages 56-57, Table 12) (Robak et al., 2010; Niederle et al., 2013).[5, 6] The ROB assessment for one remaining RCT (Leblond et al., 2012)[9] could not be carried out because the report in question was an abstract.

RCTs

In the company's submission, study 116 (Furman et al., 2014)[1] was rated to be at low risk of bias. Two other RCTs of relevant comparators assessed in the company's submission (Robak et al., 2010, Niederle et al., 2013)[5, 6] had a preponderance of 'unclear ROB' ratings, perhaps owing to poor reporting quality (company submission Appendix 7, pages 56-57, Table 12).

The ERG assessed the risk of bias in Study 116 (Furman et al., 2014,[1] and in Robak et al., 2010, and Niederle et al., 2013)[5, 6] using the Cochrane risk of bias tool.[4] Since study 116 was terminated early, the ERG rated the domain of 'other bias' as high risk (ERG report Appendix A; **Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**). In general, ERG assessments of risk of bias (ERG report Appendix A; **Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**) were in agreement with those of the company submission (Appendix A, Table 59, Table 60, Table 61).

Non-RCTs

The company submission (e.g., see page 111, Table 41; Appendix 7, Tables 18-20) did not provide risk of bias assessments for eight non-RCTs (Coiffier et al., 2008, Wierda et al., 2010, Tam et al., 2006, Badoux et al., 2011, Smolej et al., 2013, Lopez et al., 2013, Fischer et al., 2011, Pileckyte et al., 2011).[13-20]

For ***untreated CLL patents with 17p deletion or T53 mutation (SR #2)***, the review included one RCT (Hillmen et al., 2007)[8] and one non-RCT (Study 101-08).

RCTs

The company submission provides the quality assessment for the RCT by Hillmen et al. (2007)[8] in Appendix 7 (Page 60, Table 16) and for the non-RCT (Study 101-08) in Appendix 9 (page 71, Table 21). [8]The company submission (page 60, Table 16) rated three domains of 'method of randomisation,' 'treatment allocation concealment' and 'blinding' as unclear in the study by Hillmen et al. (2007),[8], two domains of 'similar distribution in baseline prognostic factors' and 'ITT analysis' were rated as 'Yes,' and two domains of 'imbalance due to dropouts' and 'selective outcome reporting' were rated as 'No.' The ERG assessment of the RCT (Hillmen et al., 2007)[8] is provided in this report in Appendix A (**Error! Reference source not found.**).

Non-RCTs

The company submission assessed the non-RCT [Study 101-08] using the Downs and Black et al. 1998 modified tool (the company submission Appendix 9, page 71, Table 21).[3] The ERG could not confirm the quality of the Study 101-08, as this was not in the public domain. The ROB assessment

Secondary outcomes (including scoring methods and timings of assessments)	Secondary efficacy endpoints were rates of overall (complete + partial) and complete response, lymph-node response (decrease of ≥50% in lymphadenopathy), and overall survival. Responses were by IWCLL criteria. Time to response and duration of response were measured as tertiary endpoints. Various other tertiary disease control endpoints were also measured but will not be described here as they do not inform the decision problem
Health-related quality of life (HRQL)	HRQL was assessed using change in domain and symptom scores from the Functional Assessment of Cancer Therapy: Leukaemia (FACT-Leu) instrument, and using the EQ-5D instrument. These were administered at baseline and at each study visit. Changes in Karnofsky Performance Status were also assessed
Key: CLL, chronic lymphocytic leukaemia; EQ-5D, EuroQoL 5 dimensions; FACT-Leu, Functional Assessment of Cancer Therapy - Leukemia; FDA, Food and Drug Administration; HRQL, health-related quality of life; IWCLL, International Workshop on Chronic Lymphocytic Leukemia; US, United States.	

Efficacy outcomes for study 116 are provided in the company Final Clinical Study Report, the company submission (Section 4.7; pages 82-96; Figures: 8-10; Tables 27-32), and the journal publication.[1] Progression-free survival (PFS), overall survival (OS), response rate (overall, lymph node), median time and duration of response (in # of months) significantly favoured the idelalisib plus rituximab arm compared to the rituximab monotherapy arm (Table 2).

Median PFS was longer in the idelalisib arm (19.4 in months; 95% CI: 12.3, not reached) compared to the rituximab monotherapy arm (6.5 months; 95% CI: 4.0, 7.3). The adjusted hazard ratio (HR) also indicated a significant improvement in PFS for patients who received idelalisib with rituximab compared to rituximab monotherapy (HR=0.15; 95% CI: 0.09, 0.24). The 12-month PFS rates were greater with idelalisib plus rituximab compared to rituximab alone (70.4% vs. 9.2%; 95% CI not reported). Neither of the study arms reached the 24-month PFSs. The median overall survival (OS) was not reached in the idelalisib arm when in the rituximab monotherpay arm it was 20.8 months (95% CI: 14.8, not reached). The adjusted HR for OS favoured idelalisib with rituxumab compared to rituximab (HR=0.34; 95% CI: 0.19, 0.60). The 12-month OS for the idelalisib was better than the rituximab monotherapy group (89.3% vs. 49.2%; test of statistical significance results no reported).

The Kaplan-Meier (KM) estimate of median duration of response was longer in the idelalisib with rituximab arm (Not reached; 95% CI: 12.0, not reached) compared to the rituximab alone arm (KME=6.5; 95% CI: 6.2; 95% CI: 2.8, 6.5; see **Error! Reference source not found.**). Time to response was similar between the

ERG summary

In summary Study 116 was an international phase III trial of idelalisib with rituximab versus rituximab alone. Benefits were shown in all the main outcomes measures and the trial was stopped early because of the benefits in the primary outcome measure (PFS; HR = 0.15, 95% CI: 0.09, 0.24). The ERG considers that this pivotal trial was on the whole well conducted. Our principal concerns are:

- Applicability to the decision problem questions
- Greater incidence of mild, moderate and severe adverse events particularly an excess of severe neutropenia and diarrhoea in idelalisib treated patients

Study by Furman et al. (2013): efficacy and safety[12]

This phase-I single-arm study by Furman et al. (2013) included 40 previously treated patients with refractory/relapsed CLL who received idelalisib in combination with either rituximab or ofatumumab (the company submission; pages 107-109, Tables 39-40).[12] Median PFS was 26 months and median OS was not reached at the time of the publication, and 14 (35%) of patients were still continuing therapy. The cohort experienced an overall response rate of 83% and a complete response rate of 8%. The overall response rate in patient subgroup with 17p deletion was 73%. The median duration of response for 33 of the participants was 24 months.

4.2.2 SR#2 [CLL patients with 17p deletion or TP53 mutation] – included RCTs and non-RCTs

This review included one RCT (Hillmen et al., 2007)[8] and one uncontrolled (single-arm) phase-II non-RCT (Study 101-08; O'Brien et al., 2014; Coutre et al., 2013)[25, 26] These studies are provided in Table 1.

Table 1. Included RCTs and non-RCTs (CLL patients with 17p deletion or TP53 mutation)

Primary reference	Study design	Secondary references	Interventions
Hillmen (2007)[8]	RCT	NA	CH vs. A
Study 101-08 CSR O'Brien (2014)[25]	Non-RCT (single-arm)	Coutre (2013)[26]	I + R
I= idelalisib; CSR=clinical study report; NA=not applicable; R=rituximab; CH=chlorambucil; A=alemtuzumab; RCT=randomised controlled trial; CLL=chronic lymphocyte leukemia			

The study by Hillmen et al. (2007)[8] randomised 297 untreated CLL patients to receive either chlorambucil (148 patients) or alemtuzumab (149 patients). There was a subgroup of 21 patients with 17p deletion or TP53 mutation, of whom 10 and 11 were allocated to receive chlorambucil and

4.6 Conclusions of the clinical effectiveness section

The evidence identified showed that Idelalisib was investigated in one phase-III RCT (study 116)[1] and in three uncontrolled (single cohort) trials (one phase-I (Furman et al. 2013)[12] and two phase-II trials Study 101-08 (Coutre et al., 2013; O'Brien et al., 2014))[25, 26] and Zelenetz et al., 2014[31] Thus, none of the trials identified in the systematic review compared idelalisib plus rituximab directly with the appropriate comparators as specified in the NICE scope in patients with relapsed or refractory CLL.

No formal indirect comparison was possible to link idelalisib plus rituximab with other relevant comparator (as specified in NICE scope). The company was unable to construct a connected treatment network (using indirect/mixed treatment comparison) as the evidence base did not provide any links between the treatments of interest (submission, page 106).

The only RCT of idelalisib (study 116)[1] 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 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.

Moreover, 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.

Study 116[1] was terminated early because of the benefit desmontrated in the results suggested by interim analysis. There has been accumulation of evidence showing that trials terminated early for benefit tend to overestimate beneficial treatment effects.[7]

Finally, the evidence-base for idelalisib is limited in terms of the amount of relevant evidence and the applicability of its findings to relevant populations, comparators, and settings.

ERG summary

The company submission conducted two systematic reviews which evaluated the clinical effectiveness and safety of idelalisib plus rituximab compared to other treatments in: a) adult

Figure 1. Economic model health states and structure

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, risks of progression/death do not differ between these states; based on the assumption that treatment efficacy remains the same post treatment discontinuation. Treatment efficacy also influences cost outcomes in the model via the ORR (overall response rate; defined as achieving either complete or partial response), with different costs for patients who have/have not responded.

As described in section 5.2.6 below, proportions of people in the pre-progression on treatment, pre-progression off treatment and post-progression states were calculated using parametric extrapolations of data from Study 116[1]. The terminal care state is an indirectly modelled state, meaning transition probabilities are not defined from prior states to terminal care, and then terminal care to death. Rather, transitions are calculated from the pre-progression and post-progression states to death, and then people who die are retrospectively assumed to have spent the 8 weeks prior to death in this state.

ERG summary

- The model developed appears to capture the main important features of the disease (PFS, OS and RR), and the cycle length (1 week) is sufficiently short to allow accurate modelling of changes over short time periods.

5.2.3 Population

The population modelled in this submission is that from Study 116,[1] which is argued to be sufficiently similar to the UK treatment population as to provide a valid comparison. The population consists of patients who had received a median of 3 prior therapies and who were not eligible to receive cytotoxic-containing therapies. Further, many of these patients were 17pDel or TP53 mutated rendering their CLL insensitive to chemotherapy-based treatment. All patients are assumed to begin the model in the pre-progression on treatment state.

ERG summary

- All the results presented by the company are based on modelling the Study 116 population, and no attempt was made to extrapolate to a population more representative of the UK clinical population.

Whilst it was not possible to quantitatively assess the impact of modelling a more UK appropriate population, differences between the modelled and real populations, and the

Table 2. Cycle probability of AE and cycle QALY decrement, R

Grade 3/4 AE	AE event QALY decrement	Cycle probability	Cycle QALY decrement
Anaemia	-0.006	0.004	-0.00002
Febrile Neutropenia	-0.012	0.003	-0.00004
Sepsis	-0.012	0.002	-0.00002
Neutropenia	-0.007	0.011	-0.00007
Pneumonia	-0.010	0.006	-0.00006
Thrombocytopenia	-0.007	0.002	-0.00002
Diarrhoea + Colitis	0.000	0.000	0.00000
Total cycle QALY decrement due to AEs, R			**-0.00023**

Key: AE, adverse event; R, rituximab; QALY, quality adjusted life year

The ERG has some concerns about the use of Study 116 data as the primary data source for pre-progression utilities. Firstly, the utilities for patients who have discontinued treatment (taken from Dretzke et al.[32]) 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. Secondly, all other treatment options considered (ofatumumab, best supportive care, FCR etc.) are assumed to have lower on-treatment pre-progression utilities than idelalisib (ofatumumab and BSC assumed to be the same as rituximab, other treatments the value from Dretzke et al.). No justification is given for assuming these utilities to be considerably lower than those for idelalisib.

Many of these issues arise from the use of utilities from different data sources, which do not appear in this case to 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.[32] 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.

ERG summary

- In the company's base case analysis, utilities for the pre-progression on treatment state are taken from Study 116,[1] and utilities for the pre-progression off treatment and post-progression states are taken from a separate literature source.[32]. Treatments other than idelalisib and rituximab are assumed to have the same utilities as rituximab.
- In the company's analysis 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.
- In the ERGs preferred analysis, utilities for the different health states are taken from a single source[32], with adverse event disutilities then applied to these, according to data from Study 116.

5.2.8 Resource use and costs

Intervention costs

As per the dosing protocol for Study 116,[1] in both arms of the model, 375mg/m^2 of rituximab was administered in the first model cycle, followed by 500mg/m^2 in week 3, 5, 7, 9, 13, 17 and 20. In the idelalisib with rituximab arm, 150mg of oral idelalisib is given twice daily. For the idelalisib and rituximab monotherapy arms, ToT curves (see section 5.2.6) were used to estimate how long patients in the progression-free survival state would be on treatment, and therefore for how long treatment costs would be applied in the model, up to the maximum dosing duration for rituximab monotherapy. The same time on treatment curve was used for ofatumumab monotherapy as rituximab monotherapy whilst, for all other comparators, treatment costs were applied to patients in the progression-free survival state 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. Specifically, mild adverse reactions, which could result in fewer treatment cycles for a treat-to-progression therapy (i.e. idelalisib) would merely lead to delays, rather than fewer cycles, in a maximum dose duration treatment (i.e. all those modelled except idelalisib). Drug costs were taken from the Monthly Index of Medical Specialties, and administration costs from 2012-13 NHS references costs,[54] with the calculated per cycle treatment and administration costs given in **Error! Reference source not found.**.

		Rituximab	£3,351		£660	
	Subsequent cycles	Methylprednisolone	£1,367	£3,043	£642	£972
		Rituximab	£1,676		£330	
Ofatumumab	Initial cycle	Ofatumumab	£546	£546	£214	£214
	Subsequent cycles	Ofatumumab	£3,640	£3,640	£214	£214

Key: B, bendamustine; Chl, chlorambucil; FCR, fludarabine, cyclophosphamide and rituximab; IR, idelalisib with rituximab; R, rituximab

The ERG is not convinced by the assumption that, for treatments other than idelalisib with rituximab, rituximab monotherapy and ofatumumab monotherapy, all patients in the progression-free survival state would complete the full course of treatment. The current approach almost certainly overestimates the drug treatment costs for these 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 with rituximab, rituximab monotherapy and ofatumumab monotherapy, all patients in the progression-free survival state complete the full treatment course was replaced by an assumption that patients in the progression-free survival state complete the same proportion of the treatment course as was so for rituximab monotherapy in Study 116.

Health state costs

The costs associated with each model health state are calculated as a combination of adverse events and disease management. The unit costs associated with the seven treatment-emergent AEs considered in the model were sourced from NHS Reference Costs[54] (Table 3).

Table 3. Costs associated with treatment-emergent AEs

Grade 3/4 AE	**Event Cost**	**Source**
Anaemia	£439	NHS Reference Costs 2012-13; Total - HRGs, SA04L
Febrile Neutropenia	£5,993	NHS Reference Costs 2012-13; Total- HRGS, PA45Z
Sepsis	£955	NHS Reference Costs 2012-13; Total- HRGS, PA17B
Neutropenia	£179	NHS Reference Costs 2012-13; Total - HRGs, XD25Z
Pneumonia	£1,252	NHS Reference Costs 2012-13; Total - HRGs, DZ23G
Thrombocytopenia	£470	NHS Reference Costs 2012-13; Total - HRGs, SA12K
Diarrhoea + Colitis	£140	NHS Reference Costs 2012-13; Total - Outpatient Attendances, 301

Key: AE, adverse event; NHS, National Health Service.

Health states	Items	Value	Reference in submission
Upon progression	Disease management	£784 (one off)	Section 5.5
Progressive disease	Disease management (total)	£50 per week	Section 5.5
Eight weeks to death	Palliative care (total)	£763 per week	Section 5.5

Key: AE, adverse event; BSC, best supportive care; B, bendamustine; Chl, chlorambucil; FCR, fludarabine, cyclophosphamide and rituximab; IR, idelalisib with rituximab; ofa, ofatumumab; R, rituximab

* AE cost for R > AE cost for IR per cycle despite higher toxicity for IR, due to shorter time on treatment for R

** Conservative assumption

The ERG has no concerns about the unit costs chosen for disease management. However, there is an issue with many of the frequency parameters, including some which make a considerable impact on the ICER, being estimated by clinical experts rather than being based on data.

In particular, the costs of IVIG therapy have a considerable impact on the model ICERs, and the values given by the clinical experts utilised give very high resource use for non-responders, and none for responders. This is particularly important as the greatest difference in clinical outcomes between idelalisib with rituximab and rituximab monotherapy is in the ORR, and thus the clinical assumptions made result in considerably higher disease management costs for patients on rituximab than those on idelalisib. In order to try and quantify the impact of these assumptions on the ICER, the ERG undertook additional sensitivity analyses looking at the impact of changes in the assumed frequency of IVIG therapy for responders and non-responders.

It should also be noted than the differences in resource use between responders and non-responders are assumed to remain for as long as patients are in the pre-progressive state, including beyond the time horizon of the trial. If it were believed that these differences would instead reduce over time, then the impact would be an increase in the relative costs of idelalisib versus all other treatment alternatives.

ERG summary

- In the company's base case, costs for idelalisib, rituximab monotherapy and ofatumumab monotherapy are accrued until treatment discontinuation, whilst for other comparators patients in the progression-free survival state are assumed to complete the full maximum dosing indicated for that product.

- Costs of disease management were stratified by response status, with increased costs for non-responders assumed to continue for the entire time patients are in the pre-progressive state.

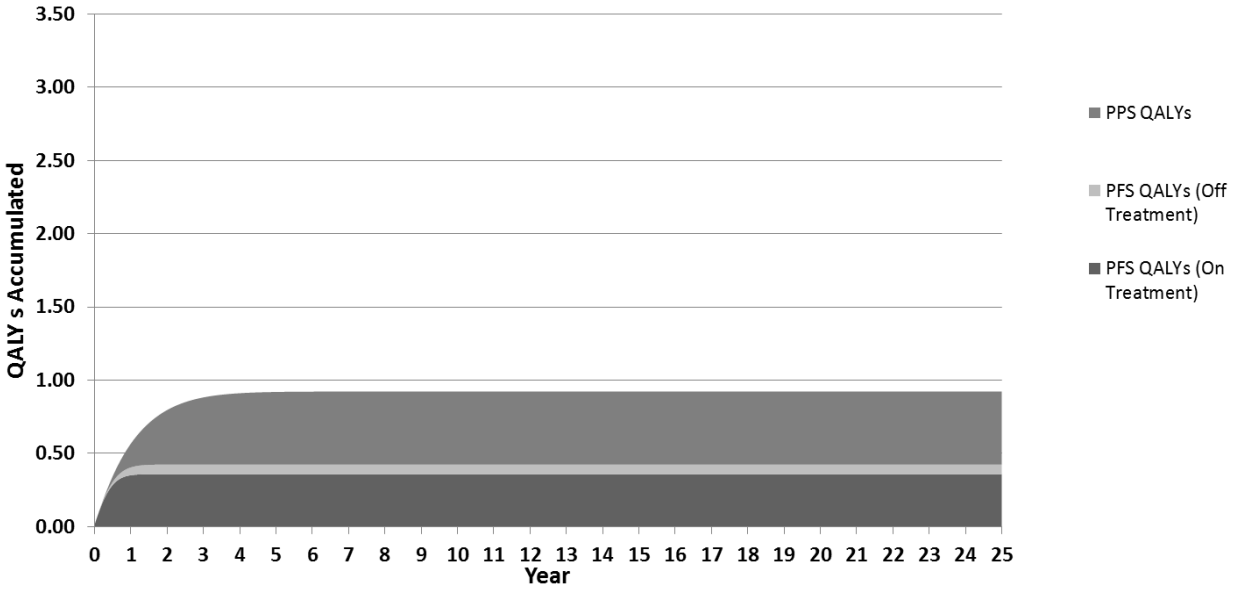

Figure 2. QALY accumulation over time, R

ERG summary

- The model supplied by the company matches that described in the submitted manuscript, and results derived from that model accurately match those reported in the manuscript.
- The model results obtained are reasonable given the expected clinical progression of the disease, and have good agreement with comparable results taken directly from the trial.

5.3 Additional analyses undertaken by the ERG

The ERG has run a modified version of the company's base case model, incorporating the following changes:

- Health state utilities for the pre-progression and post-progression states are taken from the Dretzke et al. paper,[32] with adverse events disutilities applied to the frequency of adverse events in Study 116.
- ToT data for rituximab monotherapy are used to inform estimated drug costs for all non-IR treatments, rather than assuming all patients in the PFS state complete the full course for treatments other than IR, R and ofatumumab. For treatments other that IR and R, patients in the PFS state are assumed to take the same proportion of the maximum dosing duration as for rituximab monotherapy in Study 116.
- The model for FCR uses the statistically best fitting survival curve, rather than relying on a constant shape parameter with the rituximab monotherapy curve.

- The duration of treatment benefit for agents other than rituximab was assumed to be 5 years. That is, after 5 years, future transition probabilities were set to be equal to those from the rituximab arm of the simulation.

BR	[redacted]	1.67	1.16	£34,921	1.99	1.18	£29,548	78	Low	Medium
Chl	[redacted]	1.71	1.13	£53,779	1.95	1.21	£44,315	0	Assumption - no evidence available	
Chl+R	[redacted]	1.38	0.92	£64,893	2.28	1.43	£45,445	0	Assumption - no evidence available	
Steroids+ R	[redacted]	2.04	1.40	£22,751	1.62	0.95	£24,065	29	Low	Medium
Ofatumumab	[redacted]	1.17	0.85	£8,006	2.48	1.49	£5,355	79	Medium	Low

Key: B, bendamustine; Chl, chlorambucil; FCR, fludarabine, cyclophosphamide and rituximab; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; R, rituximab

* Study 116 rituximab plus placebo survival data used as a proxy in the absence of external data for corticosteroids

There is a moderate increase in the ICER for idelalisib with rituximab versus rituximab compared to the company's base case, and more substantial increases in the ICER versus some other comparators. The ERG also undertook additional sensitivity analyses to look at uncertainty in key parameters not addressed in the company submission. The first is the frequency of IVIG therapy for responders and non-responders. In the company's model, no IVIG therapy is needed for responders, whilst 45% of non-responders require 1.24 cycles per month. The impact on the ICER for two comparators (rituximab monotherapy and bendamustine monotherapy) is shown in tables 54 and 55.

Table 4. Impact of frequency of IVIG therapy on ICER; IR versus R

	Frequency in responders (applied to 45% of patients)				
Frequency in non-responders (applied to 45% of patients		**0**	**0.1**	**0.25**	**0.5**
	1.00	19,381	25,978	35,875	52,369
	1.14	17,944	24,542	34,438	50,932
	1.24	16,947*	23,515	33,412	49,906
*model base case					

Table 5. Impact of frequency of IVIG therapy on ICER; IR versus B

	Frequency in responders (applied to 45% of patients)				
Frequency in non-responders (applied to 45% of patients		**0**	**0.1**	**0.25**	**0.5**
	1.00	52,181	57,185	64,692	77,204
	1.14	52,555	57,560	65,066	77,578
	1.24	52,815*	57,827	65,334	77,845
*model base case					

As can clearly be seen, the ICER is highly sensitivity to changes in the frequency of IVIG therapy, particularly to the frequency in patients who in 111 spond to treatment. The parameter used in the

base case model is based not on data but estimation by clinical experts, so it is important to be aware of the significant impact that uncertainty in this parameter has on the ICER.

The second additional sensitivity analysis undertaken by the ERG concerned the adjustment factor used to account for baseline differences in study populations, when comparing idelalisib with treatments not in Study 116. This adjustment factor was calculated from proportional hazards models reported by Badoux et al,[16] which report the association between baseline patient characteristics and OS and PFS. However, the company only make use of the mean parameter value, and do not consider the uncertainty in this model. As an illustration of the uncertainty in these values, two additional variations on the idelalisib versus FCR comparison are reported, which instead of using the mean values for all parameters instead set one particular parameter (serum creatinine for overall survival) to the upper and lower limit of its 95% confidence interval, to see what impact this has on the ICER for idelalisib versus FCR.

Table 6. Idelalisib with rituximab versus FCR; impact of varying adjustment factor

				Incremental (IR versus comparator)						
Serum creatinine adjustment factor	**Costs**	**Life Years**	**QALYs**	**Costs**	**Life Years**	**QALYs**	**ICER (IR versus comparator)**	**N patients informing comparator survival**	**Similarity of patients to Study 116**	**Ability to adjust for patient characteristics**
2.3*	[redacted]	0.32	0.24	£71,177	3.34	2.11	£33,795	284	Low	High
1.4	[redacted]	0.62	0.42	£69,953	4.01	1.93	£36,245	284	Low	High
3.8	[redacted]	0.16	0.13	£75,743	4.57	2.22	£34,337	284	Low	High
* Base case analysis										

In this case, is does not appear that uncertainty in the adjustment factors used has a great impact on the ICER. Whilst this does not detract from the many limitations these exploratory comparisons have, this does at least give us some confidence that one potential source of uncertainty in the input parameters (the adjustment factors used) will not cause similar uncertainty in the output.