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


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**Please note that:**

Sections highlighted in yellow are 'academic in confidence'.

Sections highlighted in aqua are 'commercial in confidence'.

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# List of Abbreviations

| | |
|---|---|
| AC | Appraisal Committee |
| AE | Adverse Events |
| AIC | Akaike Information Criterion |
| BID | Twice daily |
| BSC | Best Supportive Care |
| CI | Confidence Interval |
| CLL | Chronic Lymphocytic Leukaemia |
| CR | Complete Response |
| CT | Computerised Tomography |
| DH | Department of Health |
| ECOG | Eastern Cooperative Oncology Group |
| EMA | European Medicines Agency |
| EPAR | European Public Assessment Report |
| ESMO | European Society for Medical Oncology |
| ERG | Evidence Review Group |
| EU | European Union |
| F | Fludarabine |
| FACIT | Functional Assessment of Chronic Illness Therapy |
| FACT-Leu | Functional Assessment of Cancer Therapy - Leukemia |
| FCR | Fludarabine, Cyclophosphamide and Rituximab |
| Hb | Haemoglobin |
| HR | Hazard Ratio |
| HRQoL | Health Related Quality of Life |
| HS | Health States |
| HSC | Hematopoietic Stem Cell |
| I | Idelalisib |
| IR | Idelalisib with Rituximab |
| ICER | Incremental Cost-Effectiveness Ratio |
| ITT | Intention To Treat |
| IgVH | Immunoglobulin Variable Region Heavy Chain |
| IV | Intravenous |
| IWCLL | International Workshop on Chronic Lymphocytic Leukemia |
| IWRS | Interactive Web Response System |
| KME | Kaplan-Meier Estimate |
| LDH | Lactate Dehydrogenase |

| | |
|---|---|
| M-CLL | Mutated Chronic Lymphocytic Leukaemia |
| MBL | Monoclonal B-cell Lymphocytosis |
| mg | Milligram |
| MCCN | National Comprehensive Cancer Network |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NMA | Network Meta-analysis |
| ORR | Overall Response Rate |
| OR | Odds Ratio |
| OS | Overall Survival |
| PAS | Patient Assess Scheme |
| PFS | Progression-Free Survival |
| PICO | Population, Intervention, Comparator, Outcome |
| PR | Partial Response |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| QALY | Quality Adjusted Life Years |
| QoL | Quality of Life |
| R | Rituximab |
| RCT | Randomised Controlled Trial |
| RR | Relative Risk |
| RB | Risk of Bias |
| RPSFT | Rank Preserving Structural Failure Time |
| SACT | Systemic Anti-Cancer Therapy |
| SAE | Serious Adverse Event |
| SD | Standard Deviation |
| SE | Standard Error |
| SLL | Small Lymphocytic Lymphoma |
| SR | Systematic Review |
| STA | Single Technology Assessment |
| ToT | Time on Treatment |
| U-CLL | Unmutated Chronic Lymphocytic Leukaemia |
| UK | United Kingdom |
| WTP | Willingness To Pay |

# 1 SUMMARY

### *1.1 Scope of the submission and Critique of the decision problem in the manufacturer's submission*

The NICE scope for the submission was:

i) Adults with chronic lymphocytic leukaemia who have received at least one therapy and
ii) Adults with untreated chronic lymphocytic leukaemia associated with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable

What is the clinical and cost-effectiveness of idelalisib in combination with rituximab compared with:

- Fludarabine in combination with cyclophosphamide and rituximab (FCR)
- Bendamustine (with or without rituximab)
- Chlorambucil (with or without rituximab)
- Corticosteroids (with or without rituximab)
- Ofatumumab
- Best supportive care (including but not limited to, regular monitoring, blood transfusions, infection control and psychological support)

for adults with chronic lymphocytic leukaemia who have received at least one prior therapy?

What is the clinical and cost-effectiveness of idelalisib in combination with rituximab compared with:

- Bendamustine (with or without rituximab)
- Chlorambucil (with or without rituximab)
- Alemtuzumab
- Best supportive care (including but not limited to regular monitoring, blood transfusions, infection control and psychological support)
- Ofatumumab in combination with bendamustine or chlorambucil (subject to ongoing NICE technology appraisal)
- Obinutuzumab in combination with chlorambucil (subject to ongoing NICE technology appraisal)

for adults with untreated chronic lymphocytic leukaemia associated with 17p deletion or TP53 mutation?

The outcome measures to be considered included:

- Overall survival
- Progression-free survival
- Response rates
- Adverse effects of treatment

- Health-related quality of life

And

- Cost-effectiveness of treatments expressed in terms of incremental cost per quality-adjusted life year.

**Decision problem in the manufacturer's submission**

The company submission statement on current service provision is appropriate, relevant, and up-to-date.

The company submission provided a detailed description of the previously treated CLL population by highlighting the heterogeneous nature of this population as comprising patients with varying degree of responsiveness and prognosis depending on frailty, age, comorbidities, and tolerance to cytotoxic agents. The NICE scope focused on the previously treated CLL population in a wider population context, whereas the focus of the company submission rests mostly on a single pivotal RCT of idelalisib (study 116; Furman et al., 2014),[1] which was conducted in a higher risk subgroup of refractory or relapsed CLL patients who were unsuitable for immune chemotherapy (e.g., due to being frailer, older, and with multiple comorbidities).

In addition the CLL patients with 17p deletion or TP53 mutation included in the pivotal study 116 (Furman et al., 2014)[1] were heavily pre-treated as opposed to the untreated population as specified in the NICE scope.

The company submission indicated that idelalisib with rituximab provides a relatively well-tolerated treatment option for relapsed or refractory CLL patients (regardless of 17p deletion and TP53 mutation) who are unsuitable for chemo-immunotherapy and who have limited options in the current treatment landscape. The company submission notes that idelalisib helps to address unmet needs for specific subgroups of patients (typically those who are elderly, frail, with multi-comorbidities, intolerant and/or refractory to chemo immunotherapy as well as high-risk untreated CLL patients with 17p deletion or TP53 mutation).

The company submission presented the decision problem issued by NICE and the rationale for deviation from the decision problem transparently. The ERG provides information on adherence to the scope using the population, intervention, comparator, outcome (PICO) framework.

**Population**

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 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 (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.

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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.

NICE technology appraisal guidance 193[2] recommends fludaribine, cyclophosphamide and rituximab as an option for people with relapsed or refractory CLL (i.e., a wider CLL population) unless their disease is refractory to fludarabine or has been previously treated with rituximab. According to the NICE scope, 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 also states that in UK clinical practice, 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's exclusion of bendamustine and chlorambucil (with or without rituximab) was justified stating that both agents belong to a chemo-immunotherapy class of drugs unsuitable for CLL patients with 17p deletion or T53 mutation.

The company's choice of rituximab as a comparator for relapsed or refractory CLL patients was based on the US and German guidelines: the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO), respectively, both of which recommend the use of rituximab in such patients. 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.

Due to a lack of sufficient 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). However, the company did submit inferences based on baseline risk adjusted indirect comparisons between study 116[1] and other trial arms. However the validity of these comparisons is difficult to establish, given the lack of a common comparator and the clinical heterogeneity in populations across trials.
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.

In summary, the relevance and importance of the selected primary comparator (rituximab monotherapy) to the current decision problem is problematic in the absence of direct or formal indirect evidence comparing rituximab to the interventions described as comparators in the decision problem or to any standard or commonly used treatment (bendamustine or chlorambucil with/without

rituximab, alemtuzumab, or ofatumumab). The ERG concur that a network meta-analysis to remedy some of these problems was not possible but do not deem

i) the use of ofatumumab in and its comparison with rituximab in Diffuse large B cell lymphoma or
ii) 'adjustment' factors to survival curves drawn from a variety of arms from a number of different studies

appropriate methods from which to extrapolate the relative benefits of their use in CLL..

**Outcomes**

All reported outcomes listed in the NICE scope were reported in the company submission (progression-free survival, overall survival, overall response rate, lymph node response rate, adverse effects of treatment, health-related quality of life, and incremental cost per quality-adjusted life year). 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.

### *1.2 Summary of clinical effectiveness evidence submitted by the manufacturer*

The company submission provided two systematic reviews (SRs) which evaluated the clinical effectiveness and safety of idelalisib plus rituximab compared to other treatments in: a) adult patients with CLL who had received at least one treatment (SR#1) and b) untreated adults with CLL associated with 17p deletion or TP53 (SR#2).

**Searches**

The company undertook four sets of searches for: 1) RCTs in relapsed or refractory CLL patients (13th January 2014; updated 7th January 2015), 2) non-RCTs in relapsed or refractory CLL patients (12th February 2014; updated 7th January 2015), 3) targeted search for steroid monotherapy (7th January 2015), 4) clinical studies in untreated CLL patients with 17p deletion or TP53 mutation (29th July 2014). Conference abstracts were initially only sought from two sources, but a further search of additional conferences was undertaken in 2015 at the request of the ERG.

The ERG conducted searches to verify the manufacturer's searches and to check for missing studies.

**Inclusion criteria**

The eligibility criteria for study inclusion were defined in terms of patient, intervention, comparators, outcomes (PICOS) and study design. The eligibility criteria for SR#1 was modified by adding rituximab as a relevant comparator and for SR#2 (treatment naïve CLL patients with 17p deletion or TP53 mutation) by deleting bendamustine and chlorambucil. The eligibility criteria for both SRs (#1 and #2) excluded non-English publications.

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**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] and there was some imbalance in baseline quality of life measured by the EQ-5D (better quality of life reported in the idelalisib arm), 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]

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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=6.5; 95% CI: 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

(OR) for idelelisib with rituximab compared to rituximab was OR=27.76 (95% CI: 13.4, 57.49), which favoured the idelalisib group of patients. The lymph node response was also in favour of idelalisib recipients compared to rituximab alone (OR=225.83; 95% CI: 65.56, 777.94).[1] According to the company submission, patients allocated to the experimental arm had a better baseline health related quality of life measures (generic EQ-5D utility index) compared to the rituximab monotherapy arm. The ERG cannot confirm whether or not this observed difference might occur by chance.

Adverse effects and withdrawals were more frequent in the idelalisib arm compared to rituximab monotherapy arm owing to longer exposure to the former. For example idelalisib was associated with a greater incidence of severe adverse events ((73.6% versus 53.7%) including for example neutropenia, pneumonia and diarrhoea. This led to idelalisib dose reduction (from 150 mg/d to 100 mg/d) in 18 patients. Generally, idelalisib was well tolerated and had a manageable safety profile when administered in combination with rituximab.

***Untreated CLL patents with 17p deletion (SR #2):*** 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] 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 alemtuzumab, respectively. Since this trial did not evaluate idelalisib, the results are not covered in this ERG report. The uncontrolled (single-arm) phase-II non-RCT (Study 101-08; O'Brien et al., 2014; Coutre et al., 2013)[25, 26] included 64 untreated patients consisting of a small subgroup (n=9) of patients with a 17p deletion or TP53 mutation who received the combination of idelalisib and rituximab for 48 weeks. Treatment with idelalisib plus rituximab in this subgroup of patients resulted in an overall response rate of 100% (95% CI: 66.4, 100). No patient progressed or died by 36 months. Data on adverse events were provided only for the overall trial population and not for the subgroup of patients with 17p deletion or TP53 mutation.

### *1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted*

Search strategies were well constructed and updated on request. The ERG does not believe that any important trials of the clinical effectiveness and safety of idelalisib have been omitted. Searches included all comparators from the NICE scope for relapsed or refractory CLL patients (except best supportive care). The search for clinical studies in untreated CLL patients with 17p deletion or TP53 mutation included only the company's choice of comparators. All searches were limited to English language publications.

The ERG verified the company's updated searches which were provided (from February 2014 onwards) in response to clarification questions. The ERG identified additional publications which were picked up by searches but which were not included in the company submission update, comprising five publications of idelalisib (4 describing an RCT[27-30] and 1 describing a non-RCT[31]). All four RCT publications[27-30] referred to study 116, of which only two (Xenakis at al., 2014 and Eradat et al., 2014)[29, 30] provided additional information beyond the clinical study 116.[1] One non-RCT (Zelenetz et al., 2014)[31] was a new single-arm study of untreated elderly patients with CLL (14% with 17p deletion/T53 mutation) who had received idelalisib monotherapy.

As we have seen, none of the included RCTs compared idelalisib plus rituximab directly with the appropriate comparators specified in the NICE scope in patients with relapsed or refractory CLL. Furthermore, idelalisib was used only in one phase-III RCT (study 116; Furman et al., 2014)[1] and three single-arm non-RCTs by Furman et al. (2013),[12] Study 101-08 (O'Brien et al., 2014; Coutre et al., 2013),[25, 26] and Zelenetz et al. (2014).[31]

Study 116[1] is the single source of evidence most relevant to the decision problem, however the ERG believes that its study sample was overly selective and overrepresented older, frailer, and more difficult to treat patients with multiple co-morbidities who were unsuitable for immune chemotherapy. About half of the participants were CLL patients with 17p deletion and TP53 mutation, a subgroup with a worse CLL prognosis, for whom standard cytotoxic therapy was not suitable. Also, in the study this subgroup of patients had already been treated which was not in line with the NICE scope. Given all the above issues, the representativeness of the study 116 sample in reference to the CLL population as outlined in the NICE scope may be questionable. Another concern refers to the choice of rituximab monotherapy as a relevant comparator in study 116. The ERG notes that rituximab is not standard therapy in the UK. The NICE scope does not include this drug as a comparator. Study 116 was terminated early for benefit based on results suggested by interim analysis.[1] There has been accumulation of evidence showing that trials terminated early for benefit tend to overestimate beneficial treatment effects.[7] Moreover, in study 116,[1] baseline quality of life (EQ-5D) was higher in the idelalisib as compared to the control arm which may also have overestimated the true benefit of idelalisib.

The ERG are in agreement with the company submission in that the available evidence does not permit a network meta-analysis to be conducted. Specifically, it was not possible to link idelalisib plus rituximab with other relevant comparators (as specified in the NICE scope) due to insufficient evidence, lack of relevant comparators, and heterogeneity across the trial populations. For treatment naive 17p/TP53 mutation sub-group analysis, lack of data precluded formal synthesis, instead other published evidence with a number of assumptions was adduced. The ERG considers that these

estimates tended to favour idelalisib in combination with rituximab in terms of PFS and overall survival. In the absence of formal modelling and data availability for this sub-group of patients it is unclear what data underlies the effectiveness estimates of idelalisib plus rituximab to feed into the economic model.

Idelalisib appears to be beneficial in it use in CLL as described in the pivotal study, but the ERG have considerable concerns about the populations and the comparators discussed in the submission. The evidence-base for idelalisib is limited in terms of the amount of relevant evidence and its potential applicability to other populations, comparators, and settings.

### *1.4 Summary of cost-effectiveness evidence submitted by the manufacturer*

The company submitted a de novo Markov model with a one week cycle length and a 25 year time horizon. The model defined states of progression-free survival (on treatment) (PFS), progression-free survival (off treatment) (PFS), post progression, terminal care and death. Patients in the progression-free survival state were further subdivided by whether they had or had not responded to initial treatment.

The initial patient cohort in the model represents the average patient from the Study 116 population,[1] with a starting age of 71 years. Overall survival, progression-free survival (PFS) and time on treatment (ToT) for idelalisib with rituximab and rituximab monotherapy are all derived from parametric survival curves fitted to data from Study 116 under the assumption that the benefits of treatment persist both after the time horizon of the trial, and after treatment discontinuation. Response rates to initial treatment are taken directly from Study 116.

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) 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.

Since the company found it impossible to construct a connected network of trials for other possible comparators, no formal evidence synthesis was conducted via a network meta-analysis. Therefore, estimates of the cost-effectiveness of idelalisib versus other treatments relied on viewing data on those comparators as individual, single arm studies, and then attempting to adjust for baseline population differences between those studies, using published data on the links between overall survival, progression-free survival and baseline patient characteristics. While these analyses are necessarily less robust than those based on trial data, they are nonetheless important as they provide the only means of

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

Superseded see erratum

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. Treatments other than idelalisib with rituximab and rituximab monotherapy were all assumed to have the same 'on-treatment' quality of life as rituximab monotherapy.

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. 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. 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 ICERs for idelalisib with rituximab versus ofatumumab monotherapy and best supportive care were respectively £1,527 per QALY and £20,461 per QALY.

From the exploratory analyses looking at comparing idelalisib with other, more UK relevant comparators, the ICERs were:

- £26,215 per QALY versus FCR
- £36,424 per QALY versus bendamustine monotherapy
- £21,910 per QALY versus bendamustine with rituximab
- £33,224 per QALY versus chlorambucil monotherapy
- £35,082 per QALY versus chlorambucil with rituximab
- £17,106 per QALY versus steroids with rituximab

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.

### *1.5 Summary of ERG critique on the robustness of cost-effectiveness evidence submitted*

#### 1.5.1 Strengths

The model constructed by the company is clearly explained and logical. It has a one week cycle length and a 25 year time horizon.

The model developed appears to capture the main important features of the disease (progression-free survival, overall survival and response rates), and the cycle length (1 week) is sufficiently short to allow accurate modelling of changes over short time periods.

The perspective, time horizon and discount rates chosen by the company all follow NICE recommendations, and are appropriate to the decision problem.

There were no discrepancies found between the models reported in the company submission and the copy of the model given to the ERG, nor were there any discrepancies between the results obtained by re-running analyses from the submitted model and those reported in the manuscript. Changes made by

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

Superseded see erratum

### 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. 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.

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.

viii. 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*

The ERG made a number of modifications 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 ICERs calculated by the ERG were:

- £16,947 per QALY versus rituximab monotherapy
- £26,058 per QALY versus best supportive care
- £5,355 per QALY versus ofatumumab monotherapy
- £24,065 per QALY versus steroids plus rituximab
- £29,548 per QALY versus bendamustine with rituximab
- £33,795 per QALY versus FCR
- £44,315 per QALY versus chlorambucil monotherapy
- £45,445 per QALY versus chlorambucil with rituximab
- £52,815 per QALY versus bendamustine monotherapy

There were, however, significant unquantifiable sources of uncertainty remaining in the model, all of which have the capacity to make the true ICERs considerably higher than those reported. These were:

- 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.
- The benefits of treatment on overall survival (OS) and progression-free survival (PFS) were assumed to last for 5 years (approximately 4 years after the mean follow up period for Study 116). Any reduction in the length of treatment benefit will reduce the cost-effectiveness of idelalisib.
- In adjusting for crossover between the two arms of the trial, the manufacturers assumed that idelalisib monotherapy has the same efficacy as idelalisib with rituximab. If idelalisib monotherapy has a lower efficacy, then idelalisib with rituximab will be less cost-effective than the current results imply.
- The model is highly sensitive to resource use parameters based on clinical judgement rather than data (section 5.3), in particular the frequency of IVIG therapy for responders and non-responders. The baseline model assumes that 45% of non-responders will require 1.24 cycles of IVIG therapy each month, whilst no responders will. Changing this to 1.14 for non-responders and 0.25 for responders, and leaving all other parameters in the model unchanged,

increases the ICER for idelalisib with rituximab versus rituximab from **£16,947** per QALY to **£34,438** per QALY.

***Conclusions***

Judging from the only pivotal trial (Study 116), the clinical effectiveness of idelalisib, when administered in combination with rituximab in a relatively unwell population is not in doubt. Estimates of clinical and cost-effectiveness in the UK population depend on a number of assumptions and data are not available to allow for robust assessments. Questions therefore remain about the use of idelalisib in the UK in comparison to the standard therapies currently used for adults with chronic lymphocytic leukaemia (CLL) and in the management of those patients with a 17p deletion or TP53 mutation who are treatment naive.

# 2 BACKGROUND

### *2.1 Critique of manufacturer's description of underlying health problem*

In section 3 (3.1 Disease overview and 3.2 Effects of the disease on patients, carers and society), the company submission provides a description of the underlying health problem, the number of patients affected by the condition in England and Wales, the aetiology/pathogenesis of CLL, and its prognosis and survival. The description of the underlying health problem provided in the company submission is relevant to the decision problem under consideration.

The company report the following (please note that from this point onwards, quotations from the company report do not include reference numbers):

- **Epidemiology (prevalence, incidence)** – "*CLL accounts for 1% of all new cancer cases in the UK and is the most common type of adult leukaemia in the UK, accounting for 38% of all leukaemias. A total of 2,712 people were diagnosed with CLL in England in 2011, with the highest incidence rates being in older people. Between 2009 and 2011, an average of 43% of cases was diagnosed in the UK in those aged 65 and over.*"
  "*As most patients have early-stage disease at diagnosis, they are observed for several years under a watch and wait strategy in line with guidelines before starting treatment. As such, while the median age at diagnosis is 72 years, the median age at treatment initiation is closer to 75 years.* "

- **Aetiology/Pathogenesis** – "*CLL is a B-cell chronic lymphoproliferative disorder (i.e. a cancer of the white blood cells) characterised by the proliferation and accumulation of functionally incompetent monoclonal B-cells. The World Health Organisation (WHO) criteria define CLL as greater than $5.0x10^9$/L monoclonal B-cells with a characteristic appearance (CLL immunophenotype) in peripheral blood. In the WHO classification, CLL is always a disease of neoplastic B-cells. The molecular pathogenesis of CLL is a complex process involving many stages, and the precise cell of origin of CLL is currently unknown. CLL is characterised by the clonal proliferation and accumulation of usually mature, typically CD5-positive B-cells within the blood, bone marrow, lymph nodes and spleen.*"

- **Disease severity, prognosis, survival and genetic subtypes** – "*CLL is an incurable disease, with a heterogeneous clinical course. While some patients have a highly stable disease with prolonged survival, other patients may have a more aggressive disease with a poorer outcome. Within the current treatment landscape, the median survival from diagnosis of CLL varies between 2 years and >10 years depending on disease stage.*"

Table 10 in the company submission (Table 1 in the ERG report), presented median survival (in years) of CLL patients according to the two disease staging systems by Binet et al. (Table 1)[33] and Rai et al. (Table 1)[34]

**Table 1. Median survival by Rai and Binet stage**

| Stage | Median survival (years) |
|---|---|
| ***Rai stage[34]*** | |
| Low risk (lymphocytosis with leukaemia cells in the blood and/or marrow [lymphoid cells >30%]) | 11.4 |
| Intermediate risk (lymphocytosis, enlarged nodes in any site, and splenomegaly and/or hepatomegaly) | 8.8 |
| High risk (disease-related anaemia [Hb <110g/L] or thrombocytopenia [platelet count <100x$10^9$/L]) | 5.2 |
| ***Binet stage[14]*** | |
| Stage A (Hb ≥100g/L, platelets ≥100x$10^9$/L, and ≤2 areas involved) | 9 |
| Stage B (Hb ≥100g/L, platelets ≥100x$10^9$/L, and ≥3 areas of nodal or organ enlargement) | 5 |
| Stage C (all patients with Hb <100g/L and/or platelet count <100x$10^9$/L) | 2 |
| **Key**: Hb: haemoglobin. | |

The company submission stated the following:
"*Mutated HSCs may result in B-cells with modest growth/survival advantages, which may progress to monoclonal B-cell lymphocytosis (MBL), a related but distinct haematological malignancy. Such cytogenic abnormalities include the following:*

a) *17p deletion (i.e. deletion of the short arm of chromosome 17), which usually includes band 17p13, where the prominent tumour suppressor gene TP53 is located. Approximately 5% to 10% of patients with CLL have 17p deletions in the first-line setting, but this increases to up to 50% in the refractory population.*
b) *Mutations of TP53; in patients with confirmed 17p deletion, more than 80% show mutations in the remaining TP53 allele, whereas in patients with CLL, 4% to 37% have TP53 mutations, reflective of the increase in the incidence of TP53 mutations as patients relapse or become refractory.*
c) *Mutations of the IgVH gene.*

*"The presence of a 17p deletion, TP53 mutation and unmutated IgVH are all associated with rapid progression of disease, poorer response to therapy and shorter survival. However, more specifically, presence of a 17p deletion and/or TP53 mutation impacts on treatment choice for these patients because these patients do not respond to chemo-immunotherapy regimens*."

The company submission reported on effects of the disease on patients, carers and society:

- **Disease symptoms** – "*Patients with CLL present with various symptoms as a result of the accumulation of lymphocytes in the lymph nodes, spleen, liver, blood and bone marrow. Common symptoms associated with CLL include abnormal enlargement of the lymph nodes (lymphadenopathy); enlargement of the liver and spleen (hepatosplenomegaly); autoimmune cytopenias; a wide range of systemic symptoms such as night sweats, dyspnoea, abdominal pain, weight loss, sleep disturbances and fatigue; and symptoms of anaemia and recurrent infections. Symptoms worsen as CLL progresses*."
- **Impact on patients** – "*CLL has a significant negative impact on HRQL, even in patients without clinical symptoms. The uncertainty as to how rapidly the disease will progress, the risk of complications, the toxicity of available therapies and the shortened life expectancy can have profound implications on patients' HRQL. Several studies have assessed HRQL in patients with CLL in comparison with the general population and with patients with other malignancies. Patients with CLL had a significantly lower emotional well-being (P<0.001) and significantly lower scores on the physical functioning (P<0.001) and role functioning (P<0.01) scales of the EORTC-QLQ-C30. Patients in one study also reported significantly worse symptoms such as fatigue (P<0.001), nausea/vomiting (P<0.001), dyspnoea (P<0.01), appetite loss (P<0.001) and constipation (P<0.001) on the EORTC-QLQ-C30 Symptom Scale. Patients in the higher risk category have a lower HRQL, and patients with progression have a lower HRQL compared with those in remission*.
- **Impact on carers** – "*The impact of CLL on caregivers and the wider society is poorly documented in the literature. However, one study on the economic burden of CLL in Germany reported that patients with CLL took a greater number of sick days than those without the disease within one year (7.6 vs. 3.1 days; p<0.001), and as a result, overall indirect costs were far greater for patients with CLL. Although there is no UK-specific data that we are aware of, it is likely that the same will be true in the UK, and CLL will have a substantial impact on the wider society and, potentially, caregivers if patients are taking time off work. As the disease progresses, it is likely that the need for caregiver support and the impact on the wider society will both increase*."

In addition, the company submission could have included the following points in this section:

- More details on the natural history of the disease (e.g., heterogeneity in age at onset, clinical presentation and course, and geographical/historical trends in the natural history)
- Diagnostic criteria for CLL (e.g., most patients are diagnosed incidentally through routine blood count; clinical evaluation, lymphocyte morphology, or immunophenotyping)

**ERG summary**

- The company submission provides an adequate description of the underlying health problem. The description of the underlying health problem is relevant to the decision problem under consideration.
- It would have been valuable for the company submission to report more details on the natural history and diagnosis of CLL.

### *2.2 Critique of manufacturer's overview of current service provision*

The company's overview of current service provision is provided in section 3.3 (page 38) of the company submission (Current treatment landscape and anticipated positioning of idelalisib). A summary of NICE technology appraisals in CLL (Table 11, Page 40-41) appears to be up to date and correct. In summary, the ERG agrees with the company submission statement, which is in line with the NICE scope, that it addresses two distinct patient populations for which idelalisib has a marketing authorisation. These are:

- ***Adults with CLL who have received at least one prior therapy:*** This patient population is highly heterogeneous and includes relatively fit patients who have received one prior cytotoxic therapy that induced a good response but eventually led to relapse, who have numerous treatment options, as well as much frailer patients who are refractory to, or have a rapid relapse following, cytotoxic agents, with/without rituximab, and/or with multiple comorbidities, and who have few if any active treatment options remaining.
- ***Adults with CLL and 17p deletion or TP53 mutation who are unsuitable for chemo-immunotherapy:*** Patients with these poor prognostic markers do not respond well to chemo-immunotherapy since this is toxic to sensitive cells but not cells that are resistant due to 17p deletion or TP53 mutation.

For the wider CLL population, the company submission provides a more detailed description than the NICE scope by highlighting the heterogeneous nature of this population, which is composed of previously treated refractory/relapsed CLL patients with varying degree of responsiveness/prognosis depending on frailty, age, comorbidities, and tolerance to cytotoxic agents. Therefore, unlike the

NICE scope, which focuses on a previously treated CLL population in a wider population context (denoted with the first bullet), the focus of the company submission is on a higher risk subgroup of refractory/relapsed CLL patients who are unsuitable for immune chemotherapy (e.g., frailer, older, and with multiple comorbidities). This is the population reported in the single RCT of idelalisib (study 116;[1] see section 3.1 of ERG report). Another deviation from the NICE scope was that rather than focussing on "adults with 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").

NICE appraisal guidance 193[2] recommends repeat administration of fludaribine, cyclophosphamide and rituximab for patients with relapsed/refractory CLL unless they are refractory to fludarabine or have been previously treated with rituximab. The company submission highlights on page 39 that NICE recommends the same treatment (bendamustine or chlorambucil with or without rituximab) to patients for whom chemo immunotherapy is unsuitable - whether they are pre-treated with refractory or relapsed disease or whether they are treatment naïve patients with a 17p deletion or TP53 mutation. The NICE scope states to this effect (page 1) that in people with relapsed and/or refractory CLL (i.e., 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 also states (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.*" Notwithstanding its recommendations for the same treatment pathway, in the current scope NICE still requests separate evaluation of the efficacy and safety of idelalisib in patients with a 17p deletion or TP53 mutation and in the wider CLL population.

In describing the place of idelalisib in the treatment pathway for UK patients, the company submission suggests that used with rituximab, idelalisib provides an efficacious and well tolerated treatment option for relapsed or refractory CLL patients (regardless of 17p deletion and TP53 mutation) who do not respond well to chemo-immunotherapy and who have limited treatment options in the current treatment landscape (page 30). According to the company submission, idelalisib helps to address unmet needs for specific populations who are typically elderly, frail, with multi-comorbidities, or who are intolerant and/or refractory to chemo immunotherapy, or who are high-risk previously untreated CLL patients with 17p deletion or TP53 mutation.

**ERG summary**

- The company submission statement is in line with the NICE scope in addressing two distinct patient populations for which idelalisib has been granted a marketing authorisation: a) adults with CLL who have received at least one prior therapy and b) adults with CLL and 17p deletion or TP53 mutation who are unsuitable for chemo-immunotherapy.
- The company suggested that idelalisib's place in the treatment pathway for UK patients is to address unmet need for specific populations: those who are typically elderly, frail, with multi-comorbidities, intolerant and/or refractory to chemo immunotherapy, and those who have high-risk previously untreated CLL with 17p deletion or TP53 mutation.

# 3 Critique of manufacturer's definition of decision problem

The company submission presents the decision problem issued by NICE included in the final scope and the rationale for any deviation from the decision problem in the Executive Summary (section 1.1 Statement of decision problem) and Table 1 of the submission (on pages 24-26). For convenience, the table has been reproduced below (see Table 2):

**Table 2. The decision problem**

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope |
|---|---|---|---|
| **Population** | • Adults with chronic lymphocytic leukaemia who have received at least one therapy<br>• Adults with untreated chronic lymphocytic leukaemia associated with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable | As per the final scope | Not applicable |
| **Intervention** | • Idelalisib in combination with rituximab | As per the final scope | Not applicable |
| **Comparator(s)** | For adults with chronic lymphocytic leukaemia who have received at least one prior therapy:<br>• Fludarabine in combination with cyclophosphamide and rituximab (FCR)<br>• Bendamustine (with or without rituximab)<br>• Chlorambucil (with or without rituximab)<br>• Corticosteroids (with or without rituximab)<br>• Ofatumumab<br>• Best supportive care (including but not limited to, regular monitoring, blood transfusions, infection control and psychological support).<br><br>For adults with untreated chronic lymphocytic leukaemia associated with 17p deletion or TP53 mutation:<br>• Bendamustine (with or without rituximab)<br>• Chlorambucil (with or without rituximab) | For adults with chronic lymphocytic leukaemia who have received at least one prior therapy:<br>• FCR<br>• Bendamustine (with or without rituximab)<br>• Chlorambucil (with or without rituximab)<br>• Corticosteroids (with or without rituximab)<br>• Ofatumumab<br>• Rituximab<br>• Best supportive care<br><br>For adults with untreated | For adults with chronic lymphocytic leukaemia who have received at least one prior therapy:<br>• Rituximab has been added because it is assumed that it has equivalent efficacy to ofatumumab, another anti-CD20, based on a study comparing these treatments in relapsed or refractory diffuse large B-cell lymphoma; the US NCCN guidelines included dose-dense rituximab monotherapy as a treatment option for frail patients with relapsed CLL; and rituximab monotherapy is used in clinical practice to some extent in the UK. Further details on this rationale are provided in Section 3.3<br><br>For adults with untreated chronic lymphocytic leukaemia associated with 17p deletion or TP53 mutation:<br>• Bendamustine and chlorambucil have both been |

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope |
|---|---|---|---|
| | • Alemtuzumab<br>• Best supportive care (including but not limited to regular monitoring, blood transfusions, infection control and psychological support)<br>• Ofatumumab in combination with bendamustine or chlorambucil (subject to ongoing NICE technology appraisal)<br>• Obinutuzumab in combination with chlorambucil (subject to ongoing NICE technology appraisal) | chronic lymphocytic leukaemia associated with 17p deletion or TP53 mutation:<br>• Alemtuzumab<br>• Ofatumumab<br>• Best supportive care including steroids | excluded as relevant comparators because these are considered to be cytotoxic chemotherapy, which is not suitable for this high-risk patient population.<br>• Ofatumumab in combination with bendamustine or chlorambucil and obinutuzumab in combination with chlorambucil have been excluded as a relevant comparators because these treatments have not yet been appraised by NICE and are not part of standard care; in addition, these are chemo-immunochemotherapy, which is not suitable for this high-risk patient population, and are outside of the licensed indication. |
| **Outcomes** | The outcome measures to be considered include:<br>• overall survival<br>• progression-free survival<br>• response rates<br>• adverse effects of treatment<br>• health-related quality of life. | As per the NICE scope | Not applicable |
| **Economic analysis** | The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any | As per the NICE scope | Not applicable |

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope |
|---|---|---|---|
| | differences in costs or outcomes between the technologies being compared.<br>Costs will be considered from an NHS and Personal Social Services perspective.If appropriate, the appraisal should include consideration of the costs and implications of additional testing for genetic markers, but will not make recommendations on specific diagnostic tests or devices.<br>Where comparator technologies are available through the Cancer Drugs Fund, the cost incurred by the Cancer Drugs Fund should be used in economic analyses. | | |
| **Subgroups to be considered** | If the evidence allows, the following subgroup will be considered for adults with chronic lymphocytic leukaemia who have received at least one prior therapy:<br>• Presence or absence of 17p deletion. | • Presence or absence of 17p deletion.<br>• Presence or absence of 17p deletion and/or TP53 mutation. | The wider subgroup of patients with 17p deletion and/or TP53 mutation has been included as both are cytogenetic abnormalities that are associated with lower efficacy with chemotherapy, but for whom idelalisib can benefit, as per the EMA license for treatment-naïve patients. |
| **Special considerations equity & equality** | The current, most effective treatments available for treatment of CLL are most suited to young and fit patients. However, idelalisib is suitable for a wider patient population, including older patients, and its addition into the treatment landscape may address some of the equality issues regarding the availability of suitable treatments for an older, frailer population. | | Introduction of idelalisib may alleviate a potential equality issue. |
| **Key:** CLL, chronic lymphocytic leukaemia; NCCN, NCCN, National Comprehensive Cancer Network; NHS, National Health Service; NICE, National Institute for Health and Care Excellence. | | | |

### *3.1 Population*

The scope of the current company submission includes an appraisal of idelalisib when used in combination with rituximab in two patient populations:

- Adults with chronic lymphocytic leukaemia (CLL) who have received at least one therapy
- Adults with untreated CLL associated with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable

The main evidence provided in the company submission rests on a single pivotal RCT (study 116)[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.

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. 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 (vs. naïve as specified in the scope). Thus, the study 116[1] 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.

The company submission attests this fact on page 38 of the submission:

[the] "*pre-treated CLL patient population is highly heterogeneous and includes relatively fit patients who have received one prior cytotoxic therapy that induced a good response but eventually led to relapse, who have numerous treatment options, as well as much frailer patients who are refractory to, or have a rapid relapse following cytotoxic agents, with/without rituximab, and/or with multiple comorbidities, and who have few if any active treatment options remaining*."

The other evidence on idelalisib in addition to besides study 116,[1] described in the company submission's systematic review concerned two uncontrolled (single cohort) trials, one phase 1 (Furman et al., 2013)[12] and one phase 2 (Coutre et al., 2013; O'Brien et al., 2014).[25, 26] The trial by Furman et al. (2013)[12] included 40 patients with refractory/relapsed CLL who received idelalisib in

combination with either rituximab or ofatumumab (Furman 2013).[12] In the other trial, idelalisib plus rituximab was evaluated in 64 treatment-naïve patients (age≥ 65 years) with CLL or SLL, of whom, nine patients had 17p deletion or TP53 mutation (Coutre et al., 2013; O'Brien et al., 2014).[25, 26]

The company's response to an ERG clarification question on the representativeness of the patient population in study 116 (including the number of patients from the UK centres) was provided in Sections A12-A13 (Table 14):

"*As detailed further in Section 4.13 of the original submission, in general, patients included in Study 116 were representative of the wider population of patients with relapsed or refractory CLL treated in the clinical setting.*

- *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.*
- *A similar proportion of patients were female in Study 116 (35%), compared with the other studies (25-42%).*
- *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.*
- *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).*
- *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 TP53 mutation.*

*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.*

*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."*

Given the information provided in the company submission and responses to the clarification questions (study 116 patient characteristics 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.

### *3.2 Intervention*

The description of the technology and its proposed marketing authorisation are provided in the Executive Summary (page 14; Table 2) and sections 2.1-2.3 in the company submission (pages 25-28; Table 9). There is no discrepancy between the technology as described and in the submission and in the NICE scope. 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) given orally. In case of adverse events, the treatment is withheld and then resumed at 100 mg twice daily, and this can be re-escalated to 150 mg twice daily.

According to the company submission (page 67, Table 21) and their response to the ERG clarification questions (Sections A8-A10), the study dose of idelalisib was reduced from 150 mg to 100 mg for a total of 18 patients in the experimental arm 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 to rituximab alone (8.1 months vs. 4.6 months) which possibly led to a higher rate of discontinuation in the experimental study group.

### *3.3 Comparators*

In reporting the evidence on idelalisib, the company submission relies mainly on a single RCT with rituximab monotherapy as a comparator arm (Study 116). Although the company submission states that rituximab monotherapy is recommended by the US National Comprehensive Cancer Network (NCCN) as an appropriate treatment option in the US for patients with CLL aged ≥70 years, without 17p deletion, this is not standard therapy in the UK (it is not included in any UK guidance). Also, the NICE scope does not include rituximab monotherapy as a comparator. The ERG has received

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.

Superseded see erratum

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.*" 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)[35] and this is in agreement with the NICE scope.

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 difficult to compare the clinical effectiveness of idelalisib with rituximab in relapsed CLL with relevant comparators due to the scarcity of evidence in similar patient populations for comparator therapies, the vast heterogeneity in the patient populations for comparators where there is evidence available, and the fact that it is not possible to construct a network meta-analysis*."

This statement draws into question the validity of the company's inferences, which are based on informal naïve indirect comparisons between study 116 and other trial arms, included as if they were comparators in study 116.[1] This is questionable given the lack of a common comparator and the clinical heterogeneity in populations between trials (company submission page 32).

The company's response to the ERG clarification question regarding the choice of rituximab monotherapy as the comparator is provided in section A6:

"*In addition to the comparators listed in the scope, monotherapy with the anti-CD20, rituximab is also used in clinical practice in England to a limited extent. In particular, rituximab monotherapy is used for the management of complications such as auto-immune haemolytic anaemia and idiopathic thrombocytopenic purpura. However, clinical advisors suggested that it is more likely to be used in combination with other agents than on its own, and in district general hospitals rather than large trial/teaching hospitals and assumed that rituximab monotherapy comprises <10% of all rituximab regimen use across England.*

*For the phase III trial in relapsed CLL patients (Study 116), on which the idelalisib licence and the subsequent NICE submission is based, rituximab monotherapy was chosen as the comparator for idelalisib with rituximab, based on the NCCN guidelines, which included dose-dense rituximab monotherapy as a treatment option for frail patients with relapsed CLL. In addition, the ESMO guidelines also recommend the use of rituximab or ofatumumab with high-dose steroids as one option for patients if relapse occurs within 12–24 months after monotherapy or 24–36 months after chemo-immunotherapy. Rituximab monotherapy is also a potential treatment option recommended in the recent German CLL guidelines for patients with poor performance status. Some clinical use data published in 2014 also showed how rituximab monotherapy is a commonly prescribed treatment in the United States for patients with relapsed CLL and is increasingly being prescribed in Europe, particularly in Germany.*

*Overall we suggest that rituximab monotherapy can be used to treat CLL within the UK; that rituximab monotherapy can be assumed to represent anti-CD20 efficacy in the treatment of CLL within the UK; and that both of these facts, together with the need to most appropriately utilise the Phase III data available for idelalisib, all provide rationale for use of rituximab as the main*

*comparator for people with relapsed or refractory CLL. Although rituximab monotherapy is not a recognised comparator within the scope, it is assumed that it has a similar efficacy to ofatumumab in patients with CLL, as supported by clinical opinion from an advisory board of six UK clinicians. There are no data directly comparing rituximab and ofatumumab in CLL patients; however, one study, the ORCHARRD study, found no difference in efficacy between ofatumumab compared with rituximab, when used in combination with cisplatin, cytarabine, and dexamethasone in 447 patients with relapsed or refractory diffuse large B-cell lymphoma within a phase III, randomised, controlled trial.*

*In addition, work conducted by PenTAG ERG as part of the NICE appraisal for ofatumumab in combination with chlorambucil or bendamustine for CLL supports the conclusion of equal efficacy of rituximab and ofatumumab. A network meta-analysis was conducted that reported no significant difference between ofatumumab with chlorambucil and rituximab with chlorambucil, with the ERG recommending a PFS hazard ratio between rituximab with chlorambucil versus ofatumumab with chlorambucil of 1 and an alternative estimate indicating rituximab with chlorambucil to be more effective than ofatumumab with chlorambucil (HR=0.7). Similar results were found for overall survival.*

*The rationale for inclusion of rituximab monotherapy as a comparator is discussed further in Section 3.3 and Section 4.13 of the submission. This rationale is also further discussed in the response to question B5."*

The company's response to the ERG clarification question regarding the exclusion of bendamustine and chlorambucil from the list of potentially relevant comparators for untreated CLL adults associated with 17p deletion and TP53 mutation is provided in section A7:

"*Bendamustine (with or without rituximab) and chlorambucil (with or without rituximab) are both chemo-immunotherapy regimens, and as such they would not be suitable for patients with a 17p deletion or TP53 mutation, as was confirmed by clinical advisors20 and highlighted at the initial NICE scoping meeting. Furthermore, these are outside of the licensed indication for first line idelalisib (given that the licence for first-line use of idelalisib is for patients who are unsuitable for chemo-immunotherapy). We have provided this rationale in Table 1.1 in Section 1.1, and again in Table 14 in Section 3.3 of the original submission.*

*Rituximab monotherapy is not a relevant comparator for the untreated population with a 17p deletion or TP53 mutation and has not been included as such. The relevance of rituximab monotherapy in the treated CLL population has been discussed in response to question A6.*"

The company's response to the ERG clarification question regarding not considering alemtuzumab as a potentially relevant comparator for untreated CLL adults associated with 17p deletion and TP53 mutation is provided in section A11:

"*On page 114 of the submission, we state that "Alemtuzumab plus steroids is not a listed comparator" as this was not included in the NICE scope. However, we recognise that alemtuzumab monotherapy is a relevant comparator for these patients, as listed in the decision problem table (Table 1). As such, alemtuzumab was included in the systematic review searches and all identified evidence was presented. Only one study, a randomised controlled trial, was identified that reported data for alemtuzumab (versus chlorambucil) in untreated patients with 17p deletion or TP53 mutation (Hillmen, 2007), and these data were presented in Section 4.7 of the original submission. The results of the alemtuzumab study were compared with those of the idelalisib single-arm study (Study 101-08 18) in this patient population in Section 4.11 of the original submission*."

### *3.4 Outcomes*

All of the reported outcomes in the NICE scope were measured and reported in the company submission (progression-free survival, overall survival, overall response rate, lymph node response rate, adverse effects of treatment, health-related quality of life, and incremental cost per quality-adjusted life year).

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 (page 102; section 4.8).

### *3.5 Other relevant factors*

The company submission states the following on equity (section 3.4):

"*The current, most effective treatments available for treatment of CLL are most suited to young and fit patients. For example, an age threshold of approximately 70 years is often considered the upper limit for administering FCR as very few patients have adequate renal function or lack comorbidities to allow it (e.g., the ongoing FLAIR study, supported by Cancer Research UK, in untreated CLL has an absolute age cut off of 75 years). However, idelalisib is suitable for a wider patient population as it can provide effective therapy to all relapsed CLL patients, especially those who cannot receive cytotoxic therapies because of their mutation status, older age or fitness. As such, the addition of idelalisib into the treatment landscape may address some of the equality issues regarding the availability of suitable treatments for an older, frailer population*."

There is no reference to a Patient Access Scheme application in the main text. However, in Appendix 2, Pages 2-9 the company state the following:

*"As per dialogue with NICE colleagues and the DH Pricing team during 2014 and 2015, Gilead Sciences has provided a submission utilising within its basecase the nationally available discounted price for idelalisib of* [redacted] *per 60 tablets which is already available (via the CDF) and will become more broadly available upon any receipt of a positive NICE Technology Appraisal Guidance. A copy of a letter explaining the situation, to be provided to both NHS England and NHS in Wales, together with the draft local Trust agreement, is provided below. We understand from our interactions with NICE to date that this should meet the requirements to allow such a discount to be considered 'in the spirit of the Methods Guide' and understand that NICE is currently reviewing this applicability. Given the fact that this nationally available discounted price is already available within the NHS in England and will continue to be transparently, nationally and consistently provided for a fixed number of years, it has been utilised within the basecase even whilst DH is still exploring the applicability of a formal patient access scheme (or PAS) under the statutory scheme."*

*During clarification stage, NICE state: "please remove Appendix 2 from the submission and submit it as part of a patient access scheme submission template. The patient access scheme submission template should also include the impact of the anticipated discounted price on clinical and cost-effectiveness analyses." However, it was* decided that no update was required as per dialogue with NICE Project Team on 17 March 2015.

On presenting the costs of idelalisib (page 27, Table 9) the company submission provided the following information (see Table 3):

**Table 3. Costs of the technology being appraised**

| | Cost | Source |
|---|---|---|
| **Acquisition cost (excluding VAT) *** | £3,114.75 for 60 tablets of either 100mg or 150mg at list price<br>[redacted] for 60 tablets of either 100mg or 150mg with the NHS price<br>£1.75 per mg for rituximab | Gilead pricing information[37] please see Appendix 2 for further documentation<br>See section 5.5 |

* Indicate whether this acquisition cost is list price or includes an approved patient access scheme. When the marketing authorisation or anticipated marketing authorisation recommends the

intervention in combination with other treatments, the acquisition cost of each intervention should be presented.

**ERG summary**

- The main evidence 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 CLL patients who had relapsed and/or been refractory to the previous treatment.
- Notable deviations from the NICE scope include:
    - Study 116 included relatively older and frailer CLL patients with multiple comorbidities who had been intolerant and therefore not suitable to standard treatment with chemo immunotherapy agents. Thus, the study sample may have been too selective and over-represented by higher risk CLL patents who would not have been representative of the CLL patients as specified in the NICE scope
    - Almost half of the study 116 sample 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
    - CLL patients with 17p deletion and TP53 mutation were pre-treated
    - The company excluded bendamustine and chlorambucil, specified by the NICE as relevant comparators for the given disease. Study 116 used rituximab monotherapy comparator which is not a standard therapy in the UK and the NICE scope does not list it as a relevant comparator. The company explained that bendamustine and chlorambucil belong to chemo-immunotherapy class of drugs unsuitable for CLL patients with 17p deletion or T53 mutation

# 4 CLINICAL EFFECTIVENESS AND SAFETY

## *4.1 Critique of the methods of review(s)*

The company submission reported two systematic reviews (SR#1 and SR#2) that evaluated the clinical effectiveness and safety of idelalisib plus rituximab compared to other treatments in:

*a) Adult patients with CLL who had received at least one treatment (SR#1)*
*b) Treatment-naïve adults with CLL associated with 17p deletion or TP53 (SR#2)*

The design and scope of the SRs are in line with the NICE scope. The ERG does not consider that any important trials of the clinical effectiveness and safety of idelalisib have been omitted.

Critiques of the systematic review methods are provided below by section.

### 4.1.1 Searches

The company submission reported four sets of searches for:

- RCTs in relapsed or refractory CLL patients. Undertaken 13th January 2014; updated 7th January 2015.
- Non-RCTs in relapsed or refractory CLL patients. Undertaken 12th February 2014; updated 7th January 2015.
- Targeted search for steroid monotherapy. Undertaken 7th January 2015.
- Clinical studies in untreated CLL patients with 17p deletion or TP53 mutation. Search 29th July 2014.

The first two sets of searches were well-constructed and included all comparators from the NICE scope for relapsed or refractory CLL patients (except best supportive care). However, they were limited to only English language publications.

The fourth set was also well-constructed, but included only the company's choice of comparators. The company submission justifies why they didn't include all the comparators listed in table 1 of the NICE scope. This search was run in July 2014 and has not been updated. The first set of searches may have captured other RCTs in this population, but they are likely to have been excluded during screening due to tighter inclusion/exclusion criteria.

Conference abstracts were initially only sought from two sources, but a further search of additional conferences was undertaken in 2015 at the request of the ERG. The updated conference abstract

searches for the 2014 American Society of Hematology (ASH) and the 2014 European Hematology Association (EHA) conferences are provided in the company response to clarification questions report (Section A2, Page 2). Searches for the other listed conferences such as American Society of Clinical Oncology (ASCO), European Society of Medical Oncology, International Workshop on Chronic Lymphocytic Leukaemia, and International Conference on Malignant Lymphoma and pre-2012 searches for ASH, ASCO and EHA were conducted. More details are presented in the company's response to ERG clarification questions (iwCLL 2013; Appendix 1, Page 45-50). The 2013 conference proceedings were also searched and presented in appendix 1 (i.e., iwCLL 2011 was not available).

The ERG also undertook the following focussed independent searches to verify the company's searches and check for missing studies:

- Auto alerts were set up in Medline, Embase and Google for new RCTs, systematic reviews or meta-analyses on Idelalisib for CLL patients. The search included meeting abstracts.
- Search in Medline and Embase for all study types on Idelalisib for CLL patients post January 2014. The search was undertaken in March 2015 and included meeting abstracts.
- Search in Medline and Embase for RCTs and other clinical trials post January 2010 on the comparator Bendamustine for CLL patients. The search was undertaken in March 2015 and included meeting abstracts.

### 4.1.2 Inclusion criteria

The eligibility criteria for study inclusion were defined in terms of patient, intervention, comparators, outcomes and study design – PICOS criteria (company submission: Table 17 and Table 19). Misleadingly, the titles of both tables (Tables 17 and 19) suggest that the study eligibility criteria were those used for searches as opposed to study selection process.

As mentioned above, the eligibility criteria for SR#1 was modified from that of the NICE scope by adding rituximab as a relevant comparator. Moreover, 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:

a) Bendamustine (with/without rituximab): cytotoxicity and unsuitability for a high risk population
b) Chlorambucil (with/without rituximab): cytotoxicity and unsuitability for a high risk population
c) Ofatumumab plus bendamustine (or chlorambucil): not yet appraised by NICE
d) Obinutuzumab plus chlorambucil: not yet appraised by NICE

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

Superseded see erratum

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. 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).[9] According to the Leblond report, these numbers are 58 and 68, respectively. The data extracted for the remaining two trials by 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). For untreated CLL patients with 17p deletion (SR #2), [8]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)[8] and the company submission (Table 15; appendix; page 60).

**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 and there was some imbalance in baseline summary quality of life measure EQ-5D by dimension (better quality of life occurred in the idelalisib arm), the ERG rated the domain of 'other bias' as high risk (ERG report Appendix A; Table 59, Table 60, Table 61, Table 62). In general, ERG assessments of risk of bias (ERG report Appendix A; Table 59, Table 60, Table 61, Table 62) 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 (Table 62).

*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



Superseded see erratum

for the Study 101-08 (company submission Appendix 9, page 71, Table 21) is reproduced in Appendix A of this report (Table 63).

#### 4.1.5 Evidence synthesis

The company submission reported two systematic reviews (SR#1 and SR#2) which evaluated the clinical effectiveness and safety of idelalisib plus rituximab compared to other treatments in:

a) Adult patients with CLL who had received at least one treatment (SR#1)

b) Treatment-naïve adults with CLL associated with 17p deletion or TP53 (SR#2)

The evidence was synthesised narratively as the available evidence did not permit formal quantitative synthesis (e.g., meta-analysis and network meta-analysis). The ERG considered this narrative synthesis to be appropriate.

### *4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)*

The PRISMA diagrams of SR #1 (patients with elapsed or refractory CLL) and SR #2 (CLL patients with 17p deletion or TP53 mutation) are provided in the company submission in Figure 4 and Figure 5, respectively. The studies identified by any of the SRs as potentially eligible but then deemed as not relevant to the decision problem, are presented (with reasons for exclusion) in the company submission Appendix 3. Update searches were only performed for SR #1 (patients with elapsed or refractory CLL) and the corresponding PRISMA diagram is presented in the company report for responses to clarification questions (Section A2, Page 4, Figure 1). The ERG report provides the results of included studies separately by the type of population as in the company submission review.

#### 4.2.1 SR#1 [Patients with relapsed or refractory CLL] - included RCTs

This review, as presented in the company submission (Table 18, page 59), included four RCTs (from the main searches). These have been reproduced by the ERG report in Table 4.

**Table 4. Included RCTs – main searches (from the company's main submission)**

| Primary reference | Secondary references | Interventions |
|---|---|---|
| Furman (2014)[1]<br>Study 116 CSR | Sharman 2014[39] | I + R vs. placebo + R |
| Robak (2010)[5] | Dufour 2013[40] | FCR vs. FC |
| Leblond (2012)[9] | NA | B + R vs. CH + R |
| Niederle (2013)[6] | NA | B vs. F |
| I= idelalisib; C=cyclophosphamide; CSR=clinical study report; F=fludarabine; NA=not applicable; | | |

| |
|---|
| R=rituximab; CH=chlorambucil; B=bendamustine; RCT=randomised controlled trial; CLL=chronic lymphocyte leukemia |

The company's response to ERG clarification questions (Section A2, Pages 2-10, Tables 1-7) stated that through the update searches for SR #1, two RCTs were identified, which were deemed as potentially eligible for inclusion (Byrd et al., 2014 and Awan et al., 2014).[10, 11] Moreover, the authors identified four non-RCTs (#173;#174;#175;#176). These studies (RCTs and non-RCTs) are not covered in detail by the ERG since none of these studies evaluated idelalisib and the comparators used were not relevant to the decision problem (see Table 5).

**Table 5. Included RCTs and non-RCTs – update searches (from the company's response to clarification questions report)**

| Primary reference | Secondary references | Interventions |
|---|---|---|
| **RCTs** | | |
| Byrd 2014[10] | Hillmen EHA 2014[41]<br>Brown ASH 2014[42] | IBR vs. OFA |
| Awan 2014[11] | NA | FCR vs. FCR + Lum |
| **Non-RCTs** | | |
| Donnellan ASH 2014[21] | NA | OFA |
| Sanhes EHA 2014a [22] | NA | B + R (or CH) |
| Zagoskina EHA 2014[23] | NA | B + R |
| Smolej ASH 2014b[24] | NA | FCR |
| IBR=ibrutinib; OFA=Ofatumumab; FCR=fludarabine + cyclophosphamide + rituximab; Lum= lumiliximab | | |

Table 5 indicates that none of the included RCTs compared idelalisib plus rituximab directly with the appropriate comparators specified in the NICE scope in patients with relapsed or refractory CLL. Furthermore, in this population, idelalisib was used only in one phase-III RCT (study 116; Furman et al., 2014)[1] and one uncontrolled (single-arm) non-RCT phase-I study (Furman et al., 2013).[12] The latter study included 40 patients with refractory/relapsed CLL who received idelalisib in combination with either rituximab or ofatumumab (Furman et al. 2013).[12] The eight other non-RCT studies (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; and Pileckyte et al., 2011)[13-20] which were identified as having relevant comparators are described in Table 15 and Tables 41-42 of the company submission (page 53 and pages 111-113).

Results from two studies (study 116 and Furman et al., 2013)[1, 12] which evaluated idelalisib are of most relevance to the decision in question, and therefore, are provided below in this report. Details on trials which did not evaluate idelalisib are not covered in this report.

Study 116 CSR (Furman 2014)[1]: The single pivotal trial on idelalisib (Study 116) is described in the company submission (section 4.3, Tables 21-24). For convenience, the summary methodology of this trial (the company submission: Table 21) has been reproduced in Table 6 below:

**Table 6. Study 116 - Summary of the methodology**

| **Trial number (acronym)** | **Study 116/NCT01539512** |
|---|---|
| **Location** | 90 centres in the US and Europe (France, United Kingdom, Italy, and Germany) |
| **Trial design** | Phase III, multicentre, 2-arm, randomised, double-blind, parallel-group study |
| **Duration of study** | The blinded phase of the study was stopped early after the first prespecified interim efficacy analysis, on the recommendation of the Data Monitoring Committee, because of overwhelming efficacy in the idelalisib arm. In accordance with the discussion with the FDA on 07 October 2013, a second analysis of the blinded-phase was conducted based on a data cut-off date of 09 October 2013. A public announcement of stopping the trial due to overwhelming efficacy observed from the first interim analysis was made on 09 October 2013. Results presented herein reflect the final analysis of Study 116 |
| **Method of randomisation** | Fixed block centralised randomisation |
| **Method of blinding (care provider, patient and outcome assessor)** | Method of blinding (care provider, patient and outcome assessor) |
| **Stratification** | Randomisation was stratified according to the following prognostic factors:<br>• 17p deletion and/or p53 mutation in CLL cells: either vs. neither<br>• Immunoglobulin heavy chain variable region (IgVH) mutation: unmutated (or IgVH3-21) vs. mutated<br>• Any prior therapy with an anti-CD20 therapeutic antibody: yes vs. no |
| **Intervention and comparator** | Patients were randomised 1:1 to receive either IR arm or placebo + rituximab (R arm). Study treatment comprised:<br>• Rituximab (both arms): 375 mg/m$^2$, i.v., followed by 500 mg/m$^2$ every 2 weeks for 4 doses and then every 4 weeks for 3 doses, for a total of 8 infusions<br>• Idelalisib: 150 mg tablet, twice daily, until progression. (Dose modification to 100 mg/day was permitted in response to adverse events, using |

| Trial number (acronym) | Study 116/NCT01539512 |
|---|---|
| | recommendations given in the protocol)<br>• Placebo: matching tablet, twice daily, until progression.<br>Rationale for the rituximab dose: the dose and schedule that was approved in combination with fludarabine and cyclophosphamide in the rituximab product label was used, with two additional doses (Weeks 2 and 6) to provide more intensive anti-CD20 therapy early in treatment (intensified dose regimen) |
| **Cross-over** | Patients receiving placebo + rituximab were allowed to cross over to idelalisib upon confirmation of progression by the independent review committee |
| **Definitions of response and progression** | Response and progression were defined using the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria, as modified to exclude lymphocytosis as an isolated criterion for disease progression in patients treated with agents inhibiting the B-cell receptor |
| **Centralised diagnostic assessment and independent blinded response/progression review** | Centralised reference diagnostic procedures were carried out at Ulm University (Ulm, Germany) or Cancer Genetics (Rutherford, NJ, US), using fluorescence in situ hybridisation for genomic aberrations (e.g. del17p), DNA sequencing for IgVH mutation status, and WAVE DNA fragment analysis and confirmatory Sanger sequencing for TP53 analyses.<br>Response and disease progression for each patient, and the dates of occurrence, were reviewed by an independent committee whose members (including two radiologists and a haematologist or oncologist) were blinded to study-group assignments. The review committee's findings were used for the primary efficacy analyses |
| **Primary outcome (including scoring methods and timings of assessments)** | The primary endpoint was PFS, defined as the interval from randomisation to first documentation of definitive disease progression or death from any cause SEE ABOVE COMMENT (whichever is the earlier). Definitive disease progression was defined as CLL progression based on standard criteria (IWCLL) and occurring for any reason (i.e. increasing lymphadenopathy, organomegaly or bone marrow involvement; decreasing platelet count, haemoglobin, or neutrophil count; or worsening of disease-related symptoms) other than lymphocytosis.<br>Timing of assessment: clinic visits, including laboratory testing, were scheduled every 2 weeks for the first 12 weeks, then every 4 weeks for 12 weeks, and then every 6 weeks for 24 weeks, then visits every 12 weeks |
| **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. |

| Trial number (acronym) | Study 116/NCT01539512 |
|---|---|
| | 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. | |

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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 Table 7). Time to response was similar between the groups (no 95% CI or p-values reported). The odds ratio for overall response (OR) for idelelisib with rituximab compared to rituximab was OR=27.76 (95% CI: 13.4, 57.49), which favoured the idelalisib

group of patients. The lymph node response was also in favour of the idelalisib recipients compared to rituximab alone (OR=225.83; 95% CI: 65.56, 777.94).[1]

**Table 7. Study 116 - efficacy outcomes**

| Outcome | Overall sample | | Subgroup (17p deletion T53 mutation) | |
|---|---|---|---|---|
| | I + R | R + P | I + R | R + P |
| Median PFS months (95% CI) | 19.4 (12.3, not reached) | 6.5 (4.0, 7.3) | Not reached (12.3, not reached) | 4.0 (3.7, 5.7) |
| PFS (95% CI) | HR=0.15 (0.09, 0.24) | | HR=0.13 (0.07, 0.27) | |
| OS (95% CI) | HR=0.34 (0.19, 0.60) | | # median months Not reached (18.8; not reached) | # median months 14.8 (8.4, not reached) |
| Overall response rate (95% CI) | OR=27.76 (13.4, 57.49) | | OR=39.93 (12.35, 129.09) | |
| Lymph node response rate (95% CI) | OR=225.83 (65.56, 777.94) | | OR=924.5 (80.79, 10579.16) | |
| Median # months to response (Q1, Q3) | 2.1 (1.9, 3.7) | 2.8 (2.0, 3.9) | - | - |
| Median duration of response in # months (95% CI) | Not reached (12.0, not reached) | 6.2 (2.8, 6.5) | - | - |
| OR=odds ratio; HR=hazard ratio; PFS=progression-free survival; OS=overall survival; I= idelalisib; R=rituximab; P=placebo; Q1=first quartile; Q3=third quartile | | | | |

In addition, patients allocated to the experimental arm showed significantly better improvements from baseline compared to rituximab monotherapy arm in generic (e.g., EQ-5D utility index) as well as disease-specific (Leukemia FACT-Leu) health related quality of life measures (the company submission; pages: 93-96; Figure 11; Table 32). For example, the proportion of subjects in Levels 1 (no problems), 2 (some problems), and 3 (extreme problems) of the 5 dimensions of the EQ-5D questionnaire (i.e. mobility, self-care, usual activities, pain/discomfort, anxiety/depression) by treatment arm are provided in Table 8 (Table 32 reproduced from the company submission).

The mean (SD) EQ-5D score change from the baseline for both treatment groups is depicted in Figure 1 (Figure 11 reproduced from the company submission).

**Table 8. Summary of EQ-5D Results by Dimension (%)**

| | | Baseline | | Week 24 | | Week 48 | |
|---|---|---|---|---|---|---|---|
| | **Level** | **IR** | **R** | **IR** | **R** | **IR** | **R** |
| Anxiety/ Depression | 1 | 70.4 | 59.0 | 81.5 | 68.2 | 78.8 | 72.7 |
| | 2 | 28.7 | 40.4 | 17.3 | 29.5 | 18.2 | 27.3 |
| | 3 | 0.9 | 0 | 1.2 | 2.3 | 3.0 | 0 |
| Mobility | 1 | 60.2 | 55.8 | 70.4 | 68.2 | 60.6 | 72.7 |
| | 2 | 39.8 | 44.2 | 29.6 | 31.8 | 39.4 | 27.3 |
| | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pain/ Discomfort | 1 | 53.3 | 52.9 | 61.7 | 55.8 | 66.7 | 90.9 |
| | 2 | 39.3 | 43.3 | 35.8 | 37.2 | 30.3 | 9.1 |
| | 3 | 7.5 | 3.8 | 2.5 | 7.0 | 3.0 | 0 |
| Self-Care | 1 | 90.7 | 87.4 | 92.6 | 93.0 | 93.9 | 90.9 |
| | 2 | 9.3 | 12.6 | 6.2 | 7.0 | 6.1 | 9.1 |
| | 3 | 0 | 0 | 1.2 | 0 | 0 | 0 |
| Usual Activities | 1 | 56.5 | 44.2 | 70.0 | 65.1 | 75.8 | 63.6 |
| | 2 | 36.1 | 51.0 | 27.5 | 32.6 | 18.2 | 27.3 |
| | 3 | 7.4 | 4.8 | 2.5 | 2.3 | 6.1 | 9.1 |

**Key:** I, idelalisib; R, rituximab; **Source:** Study 116 CSR

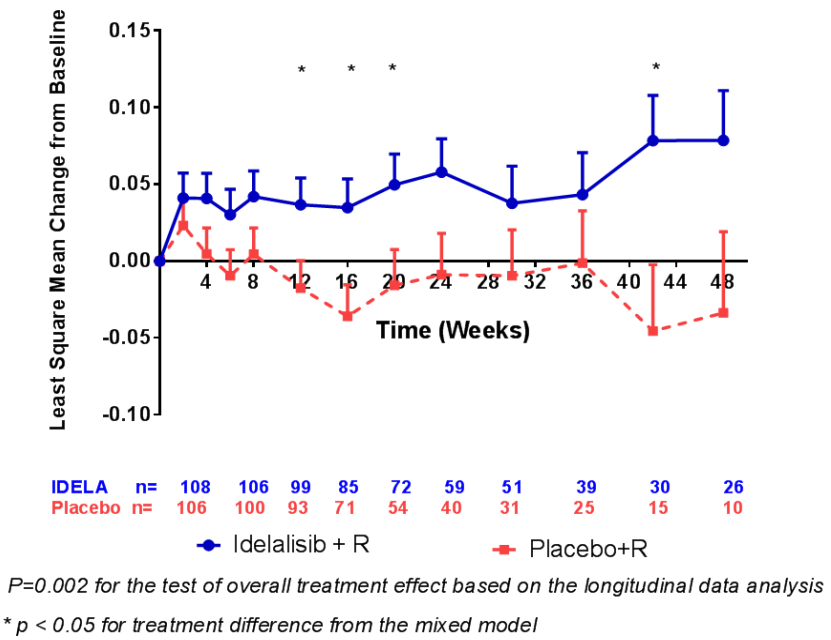


**Figure 1. Mean (±SE) change from baseline in the EQ-5D utility index (Study 116 ITT analysis set)**

**Key:** EQ-5D, EuroQol 5 dimensions; ITT, intention to treat; R, rituximab; SE, standard error; **Source:** Study 116 CSR

Subjects in the idelalisib arm experienced greater symptom improvement compared to those in the rituximab monotherapy arm at different follow-up time points for the Additional Concerns (Leukemia), FACT-Leu Total, and the Trial Outcome Index. Subjects in the experimental treatment arm reached the MID for Additional Concerns at Week 4, and their improvement was sustained, whereas subjects receiving rituximab reached the MID only at Week 72. In the mixed effects model analysis of the changes from baseline in subscale score, the main Additional Concerns was statistically significant in favour of the idelalisib group (p=0.0003). Subjects treated with idelalisib plus rituximab also showed rapid and sustained improvements in the FACT-Leu Total and Trial Outcome Index scores vs. those treated with rituximab alone. The main effect of treatment was statistically significant for the FACT-Leu Total score and the Trial Outcome Index score, p=0.0039 and p=0.0023, respectively. The proportion of patients with 5 point improvement in the Additional Concerns (Leukemia) Subscale score was greater in the idelalisib group compared to the rituximab alone group (76.9% vs. 66.7%).

The ERG notes the absence of point estimates and corresponding 95% CIs for the EQ-5D proportions by dimension and tabular presentation of FACT-Leu in the company submission (Table 32) which would help gauging whether the differences observed between the two treatment groups represented a true benefit or might be due to the play of chance.

Adverse events data for study 116 are presented in the company submission (Section 4.12; pages 121-128; Tables 48-50). Specifically, the summary data on duration of exposure to drugs, length of follow-up, and overall adverse events are reproduced in Table 9. According to the company submission, idelalisib generally was well tolerated and had a manageable safety profile when administered in combination with rituximab.

**Table 9. Study 116 – Drug exposure and overall adverse events**

| Outcome | Overall sample | |
|---|---|---|
| | I + R (n=110) | R + P (n=108) |
| Median duration of exposure (Q1, Q3) in months | 8.1 (5.6, 11.1) | 4.6 (3.3, 7.3) |
| Median duration of follow-up (range) in months | 12.5 (0.3-25.1) | 11.1 (0.2-24.6) |
| Any AE (%) | 98.2 | 98.1 |
| ≥ Grade 3 AE (%) | 73.6 | 53.7 |
| Study Drug-Related AE (Idelalisib or Placebo) (%) | 55.5 | 24.1 |
| ≥ Grade 3 Study Drug-Related AE (Idelalisib or Placebo) (%) | 32.7 | 7.4 |
| Rituximab-Related AE (%) | 64.5 | 58.3 |
| ≥ Grade 3 Rituximab-Related AE (%) | 22.7 | 15.7 |
| AE Related to both Study Drug and Rituximab (%) | 32.7 | 13.0 |

| | | |
|---|---|---|
| Any SAE (%) | 59.1 | 39.8 |
| Study Drug-Related SAE (Idelalisib or placebo) (%) | 20.0 | 6.5 |
| Rituximab-Related SAE (%) | 10.0 | 3.7 |
| AE That Led to Study Drug Dose Reduction (%) | 6.4 | 0 |
| AE That Led to Study Drug Discontinuation (%) | 17.3 | 12.0 |
| AE That Led to Death (%) | 3.6 | 10.2 |
| I= idelalisib; R=rituximab; P=placebo; Q1=first quartile; Q3=third quartile | | |

Most adverse events (Table 10) were numerically more frequent in the treatment arm compared to the control arm. For example, the idelalisib arm experienced more frequent AEs that led to idelalisib dose reduction (in 18 patients from 150 mg/d to 100 mg/d in the experimental arm) or drug discontinuation compared to rituximab monotherapy arm (17.3% vs. 12.0%). In contrast, the occurrence of AEs leading to death was more frequent in the rituximab monotherapy arm. Results of tests of statistical significance which would allow to gauge whether these differences were real or due to sampling variability were not provided.

Data on the occurrence of specific adverse events in ≥10% of patients is provided in Table 10. The most frequently reported AE overall in idelalisib arm vs. rituximab monotherapy arm was fatigue (30.9% vs. 33.3%). The most common AE in the idelalisib arm was pyrexia (40.0% vs.18.5%).

**Table 10. Study 116 – adverse events occurring in ≥10% of patients**

| **Outcome (% patients)** | **Overall sample** | |
|---|---|---|
| | I + R (n=110) | R + P (n=108) |
| Subjects with any adverse events | 98.2 | 98.1 |
| General Disorders and Administration Site Conditions | 73.6 | 61.1 |
| Fatigue | 30.9 | 33.3 |
| Pyrexia | 40.0* | 18.5 |
| Chills | 24.5 | 15.7 |
| Oedema peripheral | 10.9 | 9.3 |
| Gastrointestinal Disorders | 69.1 | 59.3 |
| Nausea | 27.3 | 23.1 |
| Diarrhoea | 29.1 | 17.6 |
| Constipation | 14.5 | 14.8 |
| Vomiting | 15.5 | 8.3 |
| Abdominal Pain | 9.1 | 10.2 |
| Gastrooesophageal Reflux Disease | 10.0 | 0 |
| Infections and Infestations | 72.7 | 53.7 |

| | | |
|---|---|---|
| Pneumonia | 14.5 | 13.9 |
| Upper Respiratory Tract Infection | 8.2 | 13.9 |
| Respiratory, Thoracic, and Mediastinal Disorders | 59.1 | 61.1 |
| Cough | 24.5 | 31.5 |
| Dyspnoea | 15.5 | 20.4 |
| Skin and Subcutaneous Tissue Disorders | 48.2 | 38.0 |
| Night Sweats | 10.9 | 12.0 |
| Rash | 14.5 | 4.6 |
| Injury, Poisoning, and Procedural Complications | 38.2 | 40.7 |
| Infusion Related Reaction | 20.0 | 30.6 |
| Blood and Lymphatic System Disorders | 40.0 | 37.0 |
| Neutropenia | 25.5 | 19.4 |
| Anaemia | 12.7 | 11.1 |
| Nervous System Disorders | 34.5 | 28.7 |
| Headache | 10.0 | 9.3 |
| Metabolism and Nutrition Disorders | 30.9 | 24.1 |
| Decreased Appetite | 16.4 | 11.1 |
| Investigations | 33.6 | 13.9 |
| Weight Decreased | 10.0 | 8.3 |

I=idelalisib; R=rituximab; P=placebo; Q1=first quartile; Q3=third quartile; *Statistically significant ($p \leq 0.1$)

**Notes**: AEs were classified by SOC, high level term (HLT), and PT using Medical Dictionary for Regulatory Activities (MedDRA) version 17. Subjects who experienced multiple events within the same PT (or HLT, SOC) were counted once per PT (or HLT, SOC) in the highest severity grade. For subjects in the placebo + R group, summary included data up to the first dosing of open-label IDELA

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. Data on the occurrence of ≥ Grade 3 specific adverse events in ≥2% of patients is provided in Table 11. The most common of these more severe AEs for the idelalisib arm were neutropenia (22.7%), pneumonia (10.0%), and diarrhoea (9.1%). The most commonly reported ≥ Grade 3 AEs for rituximab were neutropenia (16.7%), pneumonia (9.3%), and anaemia (6.5%). Idelalisib was not associated with the AEs observed with the use of traditional cytotoxic chemotherapy regimens.

**Table 11. Study 116 – Adverse events ≥ Grade 3 occurring in ≥ 2% of patients**

| System Organ Class<br>Preferred Term, % | Overall sample | |
|---|---|---|
| | I + R (n=110) | R + P (n=108) |
| Blood and Lymphatic System Disorders | 33.6 | 28.7 |
| Neutropenia | 22.7 | 16.7 |
| Anaemia | 7.3 | 6.5 |
| Febrile Neutropenia | 4.5 | 4.6 |
| Thrombocytopenia | 3.6 | 3.7 |
| Infections and Infestations | 32.7 | 23.1 |
| Pneumonia | 10.0 | 9.3 |
| Sepsis | 5.5 | 2.8 |
| Pneumocystis jirovecii pneumonia | 3.6 | 0.9 |
| Lung infection | 2.7 | 1.9 |
| Lower respiratory tract infection | 2.7 | 0.9 |
| General Disorders and Administration Site Conditions | 12.7 | 13.0 |
| Fatigue | 5.5 | 3.7 |
| Asthenia | 1.8 | 3.7 |
| Pyrexia | 2.7 | 0.9 |
| Oedema peripheral | 0 | 2.8 |
| Respiratory, Thoracic, and Mediastinal Disorders | 13.6 | 9.3 |
| Dyspnoea | 4.5 | 2.8 |
| Pneumonitis | 3.6 | 0.9 |
| Investigations | 11.8 | 4.6 |
| Alanine Aminotransferase Increase | 3.6 | 0 |
| Transaminases Increase | 2.7 | 0.9 |
| Gastrointestinal Disorders | 13.6 | 1.9 |
| Diarrhoea | 9.1 | 0 |
| Colitis | 4.5 | 0 |
| Metabolism and nutrition disorders | 9.1 | 6.5 |
| Dehydration | 2.7 | 0 |
| Vascular Disorders | 2.7 | 5.6 |
| Hypotension | 1.8 | 2.8 |
| Injury, Poisoning, and Procedural Complications | 0 | 5.6 |
| Infusion Related Reaction | 0 | 3.7 |

I= idelalisib; R=rituximab; P=placebo; Q1=first quartile; Q3=third quartile; * Statistically significant ($p \leq 0.1$)

Notes: AEs were classified using MedDRA version 17. Subjects who experienced multiple events within the same PT (or SOC) were counted once per PT (or SOC) in the highest severity grade. Severity of AEs was graded according to the CTCAE, version 4.03. For subjects in the placebo + R group, summary included data up to the first dosing of open-label IDELA

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**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
- Baseline imbalance in EQ-5D ratings potentially benefiting the intervention (idelalisib) arm.

*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 12.

**Table 12. 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<br>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

alemtuzumab, respectively. Since this trial did not evaluate idelalisib, its results are not covered by the ERG.

The uncontrolled (single-arm) phase-II non-RCT (Study 101-08; O'Brien et al., 2014; Coutre et al., 2013)[25, 26] included 64 untreated patients consisting of a small subgroup (n=9) of patients with a 17p deletion or TP53 mutation who received the combination of idelalisib and rituximab for 48 weeks during the study period (company submission: page 62). Treatment with idelalisib plus rituximab in this subgroup of patients resulted in an overall response rate of 100% (95% CI: 66.4, 100). No patient progressed or died by 36 months (the company submission: pages 114-121; Tables 43-47). Data on adverse events were provided only for the overall trial population and not for the subgroup of patients with 17p deletion or TP53 mutation (the company submission: pages 128-131; Tables 51-53). The median duration of exposure to the drugs was 22.4 months (range: 0.8-45.8) (O'Brien 2014).[25] More detailed data on adverse events from this interim CSR is presented in the company submission (the company submission: Appendix 11).

**4.2.3 Additional relevant studies not discussed in the submission and identified by the ERG**

According to the ERG specialist clinical advisor, the trial by Goede et al. (2013)[43] should have been identified and included in the company submission. This phase III trial of obinutuzumab plus chlorambucil versus rituximab plus chlorambucil versus chlorambucil alone in patients with chronic lymphocytic leukaemia (CLL) does not appear to have been identified during the searching. In the absence of other evidence, the trial may provide useful data on some of the comparators which are listed in the final scope issued by NICE. This trial was also not in the list of excluded trials in the company submission (Appendix 3).

The company's response to clarification questions explained why the trial by Goede et al (2013)[43] was not considered:

"*Obinutuzumab and idelalisib are licensed for different CLL populations and as such, obinutuzumab was not considered as part of the searches. Obinutuzumab was not used as a search term in the SLR for the untreated 17pDel/TP53 population, because at the time of performing the literature searches obinutuzumab was not licensed in the EMA. In addition, obinutuzumab in combination with chlorambucil (as per the NICE final scope for idelalisib December 2014) (and rituximab plus chlorambucil) were not considered to be relevant comparators as these are not routinely used in the NHS and not a part of standard of care for these first-line patients. Although obinutuzumab in combination with chlorambucil has obtained a positive final appraisal determination from NICE, the recommendation is specifically as an option for adults with previously untreated CLL who have*

*comorbidities that make fludarabine-based therapy unsuitable (as per the licensed indication), and also only where bendamustine is unsuitable and the company provides obinutuzumab with the discount agreed in the patient access scheme. The recommendation does not mention high-risk patients or patients specifically with a 17p deletion/TP53 mutation so obinutuzumab with chlorambucil would not be considered an option in these patients. Furthermore, these treatments are chemo-immunotherapies and given that the licence for first-line use of idelalisib is for patients who are unsuitable for chemo-immunotherapy, obinutuzumab with chlorambucil is outside of the licensed indication for idelalisib. In addition, because they are chemo-immunotherapies, these treatments would have limited effectiveness for this untreated CLL population with 17p deletion and/or TP53 mutation. Indeed chemo-immunotherapies are not recommended as a treatment option in the BCSH guidelines for front-line patients with TP53 mutations as chemotherapy depends on functioning p53 for efficacy and efficacy. This was confirmed by data presented in the supplementary appendix to the Goede et al publication showing relatively poor hazard ratios for the antibody-containing regimens compared with chlorambucil alone in patients with 17p deletion, and the lack of a benefit of the obinutuzumab over the rituximab combination is noted in the obinutuzumab SmPC. Chlorambucil alone is has little effectiveness in patients with TP53 mutations (the least effective of the three regimens used in the CLL4 study). Therefore obinutuzumab with chlorambucil would not be an appropriate choice of therapy for front line patients with a 17p deletion or TP53 mutation CLL.*"

Another trial worthy of consideration was a phase-II study conducted in the UK in which 39 relapsed or refractory CLL patients with 17p deletion or TP53 mutation (17 of them untreated) received alemtuzumab with methylprednisolone for 16 weeks (Pettitt et al., 2012).[35] 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). The ERG specialist clinical advisor agreed with the NICE scope (pages 2-3) in noting that alemtuzumab is one of the currently available relevant comparators and used treatments for this population of patients in the UK. Although the company withdrew alemtuzumab in this indication from the market for commercial reasons, the drug is still available in England under a patient access scheme (PAS) (Table 13).

**Table 13. Idelalisib studies not included in the company submission or updated searches provided in the response to clarification questions**

| First Author (year) | Title | Source of publication | Study design |
|---|---|---|---|
| Xenakis (2014)[29] | A decision-analytic model of idelalisib and rituximab combination therapy versus rituximab monotherapy in relapsed, unfit CLL | J Clin Oncol 32:5s, 2014 (suppl; abstr 7101) | RCT |
| Hallek (2014)[28] | 2nd analysis of a phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of Idelalisib and Rituximab for previously treated patients with CLL | Oncology Research and Treatment 37: 183 | RCT |
| Eradat (2014)[30] | Health-related quality of life impact of idelalisib in patients with relapsed CLL: Phase 3 results | Haematologica 99: 63 | RCT |
| Coutre (2014)[27] | Second interim analysis of a phase 3 study evaluating idelalisib and rituximab for relapsed CLL | Haematologica 99: 249-250 | RCT |
| Zelenetz (2014)[31] | A phase 2 study of idelalisib monotherapy in previously untreated patients >65 years with CLL or SLL | Blood 124 (21) | Single-arm uncontrolled trial |
| RCT=randomised controlled trial; CLL=chronic lymphocyte leukemia; LeuS= leukemia-specific concerns | | | |

The ERG verified the company's searches (2014 February and onwards) updated in response to clarification questions. The ERG identified additional publications which were picked up by searches but not included in the company submission update, comprising five publications of idelalisib (4 describing an RCT and 1 describing a non-RCT).[27-31] All four RCT publications (Table 13), referred to study 116, of which only two (Xenakis at al., 2014 and Eradat et al., 2014)[29, 30] provided additional

information beyond the clinical study report for 116 or the Furman 2014 publication.[1] The remaining 2 RCTs (Hallek et al., 2014 and Coutre et al., 2014)[27, 28] did not provide any additional information to that already reported in the company's submission or their response to clarification questions (Table 14). One phase-II non-RCT (Zelenetz et al., 2014)[31] was a new single-arm study of untreated elderly patients with CLL (14% with 17p deletion/T53 mutation) who had received idelalisib monotherapy.

**Table 14. Idelalisib studies providing additional information to the one already reported in the company submission**

| First author (year) design | Treatments compared | Findings |
|---|---|---|
| | | |
| Xenakis (2014)[29]<br>Study 116[1]<br>RCT | I + R vs. R | Treatment with I+R vs. R resulted in better health outcomes, increasing LYs by 1.0 to 9.7 mos, increasing PFLYs by 4.6 to 11.6 mos, and improving QALYs by 0.1 to 0.7, while decreasing AEs by 46% to 2% and reducing hospitalizations by 48% to 5% over a 1 to 5 year time horizon<br><br>I+R vs. R was projected to yield better health outcomes in relapsed, unfit CLL patients largely driven by and improved PFS and OS |
| Eradat (2014) [30]<br>Study 116[1]<br>RCT | I + R vs. R | Leukemia (FACT-Leu) scale was used to measure PWB, FWB, SWB and EWB and LeuS<br><br>TOI is the sum of PWB, FWB and LeuS. Higher scores reflect better HRQL. Repeated measures mixed-effects models assessed change from baseline within and between arms. Results: I+R compared to R was superior for OS (HR=0.28; 95% CI: 0.09, 0.86), PWB (p=0.015), FWB (p=0.014), LeuS (p=0.001), TOI (p=0.002), and FACT-Leu total (p=0.006)<br><br>EWB/SWB scores did not change significantly over time |

| | | |
|---|---|---|
| | | I+R vs. R had clinically significant improvements in HRQL and symptom control by 8 weeks |
| Zelenetz (2014)[31]<br>Non-RCT | I | The median idelalisib exposure was 4.8 mos (range 0.9-8.5). There has been one discontinuation at 3 mo for respiratory distress, assessed as related to a prior condition. The median absolute lymphocyte count was 59.7 K/mul (range: 0.8-294) at baseline peaking at 100 K/mul (range: 2-385) at week 4. 27 pts were evaluable for response, having reached the first evaluation time point of 8 weeks. Of these 27, the ORR was 81% with 9 (33%) PR and 13 (48%) PR with lymphocytosis. Splenomegaly has responded in 88% of 17 evaluable pts and hepatomegaly in 75% of 4 evaluable pts. The most TEAE (Grade >3) were rash (27/3), URI (16/0), constipation (14/0), cough (14/0), nausea (11/0), pyrexia (11/0), arthralgia (8/0), back pain (8/0), diarrhea (8/3), and pneumonia (8/5). Pneumonitis was observed in 2 pts (5%), Gr >3 in 1(3%) |
| I= idelalisib; R=rituximab; RCT=randomised controlled trial; TEAE= treatment emergent adverse events; LYs= life-years; PFLYs=progression-free life-years; QALYs=quality-adjusted life-years; AEs=adverse events; pts=patients; months=mos.; CLL=chronic lymphocyte leukaemia; PFS=progression-free survival; OS=overall survival; ORR= overall response rate; PR=partial response; URI= upper respiratory infection; PWB=physical well-being; FWB=functional well-being; SWB=social well-being; EWB=emotional well-being; LeuS= leukaemia-specific concerns; TOI=trial outcome index | | |

A search for studies with potential relevant comparators to enable a NMA resulted in no additional studies identified. Therefore, this corroborates with the company's submission and response to the ERG clarification questions that there is insufficient comparative evidence to undertake an NMA.

The company submission provided an update of abstracts from other relevant conferences not already included in the submission (the company response to clarification questions, Appendix 1). The ERG confirmed that all additional abstracts from the conferences were relevant. Furthermore, any information provided in these conference abstracts related of idelalisib data was superseded by the published evidence for study 116.[1]

**ERG summary**

The ERG considers that although not all the relevant evidence was elicited and critiqued by the company, no other studies identified added substantially to the information provided by the pivotal RCT.

### *4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison*

Network meta-analysis (indirect treatment/mixed treatment comparison) could not be performed due to the lack of relevant data (see the company submission, section 4.10, page 106). Specifically, the company submission states the following:

*"Relapsed or Refractory CLL: Evidence for relevant comparators was obtained from the same systematic literature review to identify trials of idelalisib using the methods described in section 4.1. The only RCT data, other than for Study 116, that was identified was for cytotoxic chemotherapy regimens; no RCT data was identified for any anti-CD20 treatments. The relevant RCTs are discussed in section 4.1 through section 4.7. It was not possible to construct a connected treatment network as the evidence base did not provide any links between the treatments of interest. Therefore, it was not possible to conduct an indirect/mixed treatment comparison.*

*Untreated CLL with a 17p deletion or TP53 mutation: A systematic literature review of untreated CLL patients with poor prognostic markers was conducted as described in section 4.1. This systematic literature review searched for both idelalisib studies and relevant comparator studies. Given that only one single-arm study was identified for idelalisib, and only one RCT was identified for the comparators (alemtuzumab vs. chlorambucil), it was not possible to construct a network and therefore not possible to perform an indirect/mixed treatment comparison."*

Update searches did not identify any RCTs with a relevant comparator to conduct a network meta-analysis.

### *4.4 Critique of the indirect comparison and/or multiple treatment comparison*

See above Section 4.3 of the ERG report.

### *4.5 Additional work on clinical effectiveness undertaken by the ERG*

See above Section 4.2 of the ERG report.

### *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.

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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] There was an imbalance in the baseline summary quality of life measure EQ-5D on each dimension which may have overestimated idelalisib treatment beneficial effect.

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

patients with CLL who had received at least one treatment and b) untreated adults with CLL associated with 17p deletion or TP53.

- The evidence included seven RCTs (6 in refractory CLL and 1 in 17p deleted or T53 mutation patients) of which only one evaluated idelalisib (study 116). Neither of the trials compared idelalisib to a relevant to the decision problem comparator.
- In study 116, PFS, OS, RR (overall, lymph node), median time to and duration of response (in # of months) were all significantly improved in the idelalisib plus rituximab arm compared to the rituximab monotherapy arm. Adverse effects and withdrawals were more frequent in the idelalisib arm compared to rituximab monotherapy arm owing to longer exposure to the former.
- The study 116 findings warrant cautious interpretation. The study was terminated early for benefit and baseline quality of life measure favoured the idelalisib arm. These may have resulted in an overestimate of effect of the drug.
- It was not possible to indirectly link idelalisib plus rituximab with other relevant comparator (as specified in NICE scope) due to insufficient evidence, lack of relevant comparators, and heterogeneity between trial populations.

# 5 COST-EFFECTIVENESS

## *5.1 ERG comment on manufacturer's review of cost-effectiveness evidence*

The company has provided an appropriate description of the cost-effectiveness systematic review undertaken including the search strategy, inclusion/exclusion criteria and description of included and excluded studies.

In brief, the company searched MEDLINE, EMBASE, EconLit and the NHS Economic Evaluation Database for cost-effectiveness analyses of idelalisib for patients who have received at least one prior therapy. A summary of the eligibility criteria are given in Table 15, below.

**Table 15. Eligibility criteria for the cost-effectiveness search**

| Category | Definition |
|---|---|
| Patient population | Adults with B-cell chronic lymphocytic leukaemia (B-CLL), also known as CLL or small lymphocytic lymphoma (SLL) |
| Interventions | Idelalisib |
| Indication | Relapsed / refractory CLL |
| Study type | Full economic evaluations: cost utility analyses (CUAs), cost-effectiveness analyses (CEAs), cost-benefit analyses (CBAs), cost-minimisation analyses (CMAs) and cost-consequence studies. |
| Limitations | English language studies pertaining to humans |

CLL: chronic lymphocytic leukaemia.

This search was carried out on the 10th June 2014. The search criteria used were fairly restrictive, looking only at cost-effectiveness studies including idelalisib, not those comparing multiple potentially relevant non-idelalisib treatments, and excluding conference abstracts. No studies meeting the eligibility criteria were found by this search, nor were any identified from an additional PudMed search undertaken by the manufacturer, for economic evaluations of idelalisib for patients with previously untreated CLL with a 17p deletion or TP53 mutation.

Despite these fairly narrow searches, the ERG does not believe that any important cost-effectiveness evidence was missed, mainly due to the established scarcity of evidence in this area. The only additional study found by the ERG was a 2014 American Society of Clinical Oncology conference abstract, which contained a decision-analytic model comparing idelalisib with rituximab versus rituximab monotherapy.[12] However, since this model was based on the same data as the company

submission (primarily Study 116[1]), its inclusion in the review is unlikely to have added any useful additional data to the submission.

**ERG summary**

- Despite the cost-effectiveness review undertaken being rather narrow (excluding conference abstracts and studies comparing non-idelalisib treatments), there is no evidence that any important information which would improve the cost-effectiveness analysis has been missed.

## *5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG*

### 5.2.1 NICE reference case checklist

| **Attribute** | **Reference case and TA Methods guidance** | **Does the *de novo* economic evaluation match the reference case** |
|---|---|---|
| **Comparator(s)** | Therapies routinely used in the NHS, including technologies regarded as current best practice for the two populations | Idelalisib in combination with rituximab is being compared primarily with rituximab monotherapy, but additional comparisons are made with ofatumumab monotherapy and best supportive care.<br><br>In scenario analyses, comparisons are also made with:<br>• Fludarabine, cyclophosphamide and rituximab<br>• Bendamustine<br>• Bendamustine and rituximab<br>• Chlorambucil<br>• Chlorambucil and rituximab<br>• Steroids and rituximab<br><br>Alemtuzumab was not considered. |
| **Patient group** | • As per NICE final scope, two populations: | Population from study 116, which is argued to be representative of |

| | | |
|---|---|---|
| | 1. Adults with chronic lymphocytic leukaemia who have received at least one prior therapy<br><br>2. Adults with untreated chronic lymphocytic leukaemia associated with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable. | the UK treatment population. |
| **Perspective costs** | NHS & Personal Social Services | Yes. |
| **Perspective benefits** | All health effects on individuals | Yes. |
| **Form of economic evaluation** | Cost-effectiveness analysis | Cost-utility analysis. |
| **Time horizon** | Sufficient to capture differences in costs and outcomes | Yes (25 years). |
| **Synthesis of evidence on outcomes** | Systematic review | As the sole source of data on idelalisib, overall survival, progression-free survival, response rates, adverse effects of treatment, and health-related quality of life are drawn from a single trial (Study 116[1]). |
| **Outcome measure** | Quality adjusted life years | Yes. |
| **Health states for QALY** | Described using a standardised and validated instrument | Yes.<br>CLL health states are evaluated using EQ-5D data collected during the study 116,[1] as well as values from the literature. |
| **Benefit valuation** | Time-trade off or standard gamble | The standard UK EQ-5D tariff is used, which is based upon time-trade off. |
| **Source of preference data for valuation of changes in HRQL** | Representative sample of the public | Yes. |
| **Discount rate** | An annual rate of 3.5% on both costs and health effects | Yes. |
| **Equity** | An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit | Yes. |

| | | |
|---|---|---|
| **Probabilistic modelling** | Probabilistic modelling | Yes. |
| **Sensitivity analysis** | | A range of sensitivity and scenario analyses are presented. |

To appraise idelalisib with rituximab for patients who have received at least one prior therapy, the company constructed a de novo Markov model with a one week cycle length and a 25 year time horizon. The model assumes that treatment benefit continues both beyond the length of the trial and after treatment discontinuation.

The pivotal study to inform this analysis was Study 116, which compared idelalisib with rituximab versus rituximab plus placebo, in patients who had received a median of three prior therapies and were not eligible to receive cytotoxic therapy.[1] Data on PFS and OS for idelalisib with rituximab and rituximab monotherapy were drawn directly from Study 116 patient level data.

A full economic analysis was not undertaken for patients with 17p deletion or TP53 mutation, due to the shortage of data. Instead, a subgroup analysis of patients from Study 116,[1] together with data from Study 101-08/99 was used to argue that there would be substantial benefits for patients in this group, who have poor prognoses and a current lack of effective treatment options.

### 5.2.2 Model structure

The company constructed a de novo cost-utility Markov model with a one week cycle length. The model defines 5 health states, based on disease progression, treatment, discontinuation and death (Figure 2).

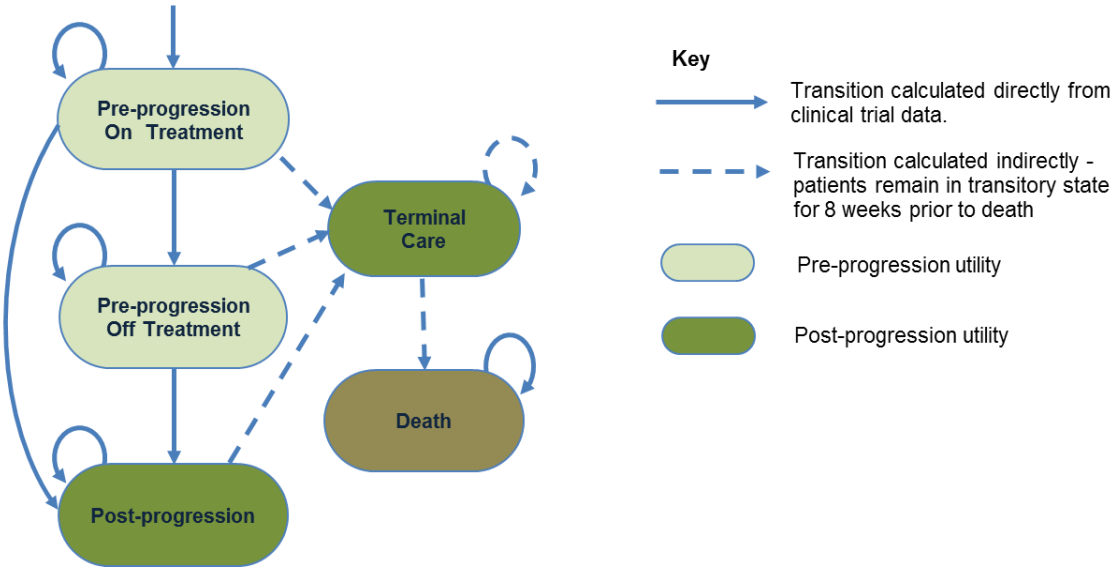

**Figure 2. Economic model health states and structure**

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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. 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

impact this may have on treatment efficacy and thus cost-effectiveness, should be borne it mind when interpreting any of the results in this report.

### 5.2.4 Interventions and comparators

In the company's base-case analysis, idelalisib in combination with rituximab is compared with rituximab monotherapy. Additional comparisons are also made to ofatumumab monotherapy and best supportive care, under the assumption that these have equal efficacy to rituximab.

For other listed comparators, the company argued that based on the lack of current evidence, it was challenging to appraise idelalisib with rituximab versus these alternatives, in previously treated patients fitter than those in Study 116. An attempt was made by the company to formally compare these alternatives using an indirect comparison, but a connected network of clinical evidence could not be formed, precluding formal synthesis of the available evidence to control for study and patient differences across the evidence base. However, the company has performed scenario analyses comparing idelalisib and rituximab with these alternative treatments, attempting to adjust for baseline differences in the populations between the different studies.

**ERG summary**

- The base case comparison of idelalisib with rituximab versus rituximab monotherapy is not necessarily a clinically relevant one in the UK. Nevertheless, the choice of rituximab as the comparator in Study 116 means this is the only treatment comparison that can be modelled in a fully robust way.
- 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. Therefore, the plausibility of the results obtained depends entirely on whether one believe this assumption of equal efficacy.
- Comparisons with other agents rely on much less statistically robust techniques, and the results generated are therefore necessarily less reliable than those from a formal evidence synthesis. Nevertheless, since many of these agents are in use in the UK and thus represent important comparators, results from this analysis (with appropriately conservative assumptions) may represent important additional information for understanding the cost-effectiveness of idelalisib versus other available treatments.

### 5.2.5 Perspective, time horizon and discounting

The perspective is as per the NICE 2013 *Guide to the methods of technology appraisal*,[44] with benefits from a patient perspective and costs from an NHS/PSS perspective.

The time horizon of the model is 25 years, which is effectively a lifetime time horizon given that the mean baseline age of patients in Study 116 was 71 years.[1] Over 99.9% of patients in both arms of the base-case model are in the death state by the end of this 25 year horizon. In the base-case, costs and benefits are discounted at an annual rate of 3.5%.

**ERG summary**

- The perspective, time horizon and discount rates chosen by the manufacturer all follow NICE recommendations, and are appropriate to the decision problem.

### 5.2.6 Treatment effectiveness and extrapolation

*Idelalisib with rituximab versus rituximab monotherapy*

Four clinical outcomes defined in Study 116[1] were used to inform transition probabilities in the model. There are:

- Overall survival (OS)
- Progression-free survival (PFS)
- Time on treatment (ToT)
- Overall response rates (ORR)

*Overall survival*

Overall survival was extrapolated from Kaplan-Meier survival data derived from Study 116.[1] Since a large proportion of patients randomised to rituximab switched to idelalisib monotherapy (86/110) during the course of the trial, it was deemed necessary to control for cross-over bias in overall survival estimates for those individuals randomised to rituximab. The HR for the OS data in the ITT analysis (i.e. without adjustment for treatment cross-over) versus the crossover adjusted analysis is provided in Table 16 below. 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 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).

**Table 16. Cox proportional hazards analysis of OS across treatment arms**

| | **Cox PH Model** | | **Log-Rank Test** | **IR Median OS in Months** | **Rituximab Median OS in Months** |
|---|---|---|---|---|---|
| | **Hazard ratio** | **HR 95%CI** | **p-value** | **(95% CI)** | **(95% CI)** |

| | Cox PH Model | | Log-Rank Test p-value | IR Median OS in Months (95% CI) | Rituximab Median OS in Months (95% CI) |
|---|---|---|---|---|---|
| | **Hazard ratio** | **HR 95%CI** | | | |
| ITT | 0.34 | 0.19-0.60 | 0.0001 | Not reached (not reached, not reached) | 20.8 (14.8, not reached) |
| Crossover adjusted | [redacted] | [redacted] | <0.0001 | Not reached (not reached, not reached) | [redacted] |

**Notes:** Data source: final analysis of Study 312-0116 and Study 312-0117 with a data-cut off on July 1, 2014.
**Key:** CI, confidence interval; PH, proportional hazards; SLL, small lymphocytic lymphoma

In the unadjusted analysis, idelalisib plus rituximab still has significantly better rates of overall survival than rituximab monotherapy, but the magnitude of the benefit is smaller. All of the future analyses undertaken by the company make use of the crossover adjusted hazard ratio. The crossover adjusted Kaplan-Meier overall survival data for the two trial arms are shown in Figure 3.

REDACTED

**Figure 3. Model KM curves for OS, IR versus R**

Parametric survival curves were then fitted to the adjusted data. Various functional forms were tested (exponential, Weibull, log-logistic and log-normal), with the preferred curve chosen by a combination of model fit (assessed using the Akaike Information Criterion (AIC)), and clinical judgement as to whether the curves represented plausible clinical scenarios (visual inspection by an NHS clinical haematologist). The AIC suggested the exponential model as being the best fit to the data, but this was rejected as clinically unrealistic since it projected over 5% of patients to be alive after 20 years, when the age of the cohort would be 91 years. Thus, the second best fitting model (Weibull), which did not suffer this problem, was selected instead.

The chosen fitted overall survival curves, together with the trial Kaplan-Meier data, are shown in Figure 4.

REDACTED

**Figure 4. KM OS R and IR and selected (Weibull) curve fits**

It is important to note that the use of such parametric survival curves as the sole basis for transitions relies upon the assumption that the benefits of treatment persist both after the time horizon of the trial, and after treatment discontinuation. In response to a clarification question from the ERG, the company gave the following explanation as to why they believe this to be a plausible assumption.

*"Biologically there are plausible explanations for why the treatment benefit of idelalisib with rituximab will continue beyond treatment with idelalisib: its impact on clonal evolution and on regulatory immune mechanisms."*

*Clonal heterogeneity and evolution during treatment are key features of CLL. A number of driver mutations including, but not restricted to, TP53 mutation are recognised. TP53 mutation conveys resistance to chemotherapy. Thus treatment with chemotherapy will reduce/eliminate subclones sensitive to chemotherapy, allowing emergence of "fitter" and more aggressive subclones resistant to chemotherapy. This is reflected in the increasing incidence of 17pdel/TP53 mutation with each line of therapy in CLL. On the other hand, treatment with an agent such as idelalisib with broad efficacy across subclones, including those with TP53 mutations, will maintain clonal equilibrium and not allow chemotherapy resistant subclones to emerge and become dominant. Thus after use of idelalisib and rituximab, chemotherapy will have a greater efficacy.*

*Immune dysfunction is also a feature of CLL. Inhibition of PI3Kδ has potential immune and anticancer effects through inhibition of T regulatory cells. Enhanced immune function could, for example, play a role in CLL reducing disease progression and contrasts with the immune suppression seen with fludarabine and bendamustine.*

*In addition, the side effect profile of idelalisib is different to that of conventional chemotherapy. Chemotherapy leads to cumulative effects on bone marrow, whereas idelalisib does not. An alternative approach other than chemotherapy could lead to better bone marrow function later in the course of the disease, allowing other options and further lines of treatment, and thus better outcomes."*

It is important to note that all analyses undertaken by the company rely on this assumption of long-term treatment benefit, and no sensitivity analyses are undertaken to test the sensitivity of the ICER to alternative assumptions, such as that the treatment benefit lasts either for the trial time horizon, or until treatment discontinuation, but from that point forward future progression rates are the same in the idelalisib and rituximab groups. In the opinion of the ERG, whilst it seems plausible the benefits of idelalisib would persist beyond the time horizon of the trial, assuming they last for the whole of a patient's life seems overly optimistic. The ERG therefore looked at remodelling this assumption, with different cut-off values for the duration of treatment benefit post discontinuation.

*Progression-free survival*

Progression-free survival, as with overall survival, was estimated with parametric survival curves fitted to Kaplan-Meier data from Study 116.[1] However, in this case, no adjustment was made for

crossover bias as the main reason for treatment switching from rituximab to idelalisib (in the rituximab monotherapy arm of the trial) was disease progression. This assumption can be considered a conservative one as a number of trial participants did switch treatment pre-progression (34/110). AIC based model selection gave the Weibull model as the best fit to the data, and the curves generated were also deemed to be clinically plausible. Fitted PFS curves for the two treatment options, together with Kaplan-Meier data from the trial, are shown in Figure 5. Again, as with overall survival, an assumption was made that the benefit of treatment will persist post treatment discontinuation and after the time horizon of the trial. The assumption is, however, somewhat less important in this case than with overall survival, as a considerably lower proportion of patients remained in the progression-free survival state at the conclusion of the trial.

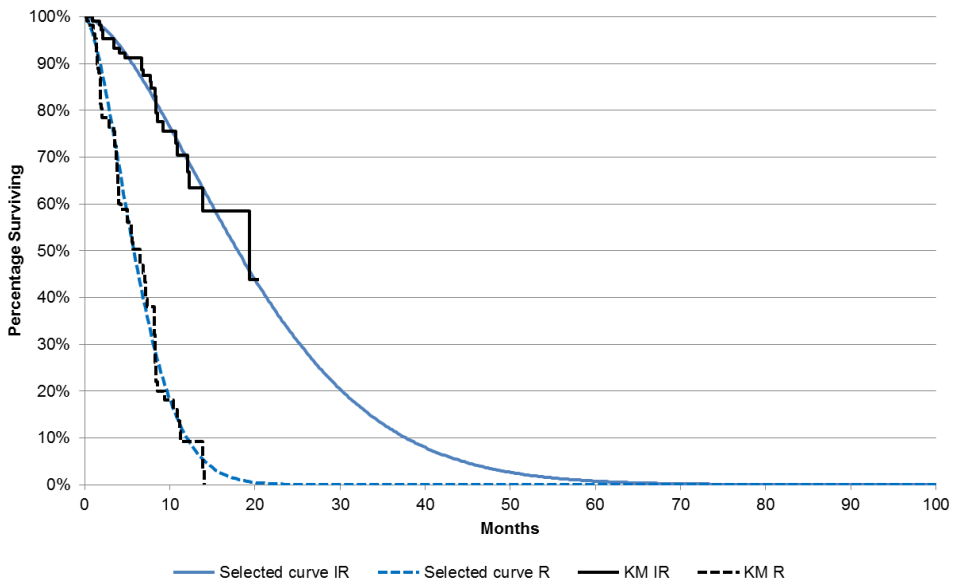


**Figure 5. KM PFS R and IR and selected (Weibull) curve fits**

*Time-on treatment*

Since idelalisib is indicated to be taken until either disease progression or unacceptable toxicity, ToT curves were fitted to estimate treatment costs for idelalisib. A proportional hazards model was fitted to ToT and PFS to estimate time on treatment for those individuals who had not progressed. A hazard ratio of 1.31 was estimated for ToT versus PFS, and this was applied to the modelled PFS curve for idelalisib with rituximab. This fitted curve, together with Kaplan-Meier data on ToT, are shown in Figure 6.

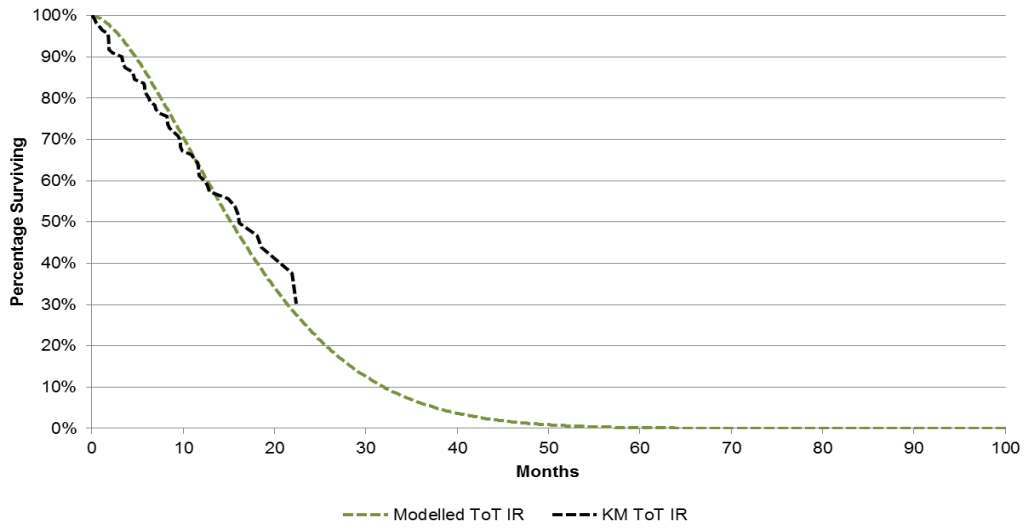


**Figure 6. KM ToT IR and parametric curve fit**

*Response rates*

Overall response rates (complete or partial response) were taken directly from Study 116[1] and applied to the model. ORR in the idelalisib arm of the trial was 84%, and in the rituximab arm was 15%. Response rates do not impact on disease progression or quality of life, but are used to inform resource use, and thus costs. These four pieces of data (OS, PFS, ToT and ORR) make up all the clinical transitions in the model, to which data on costs and quality of life are applied.

*Comparisons with ofatumumab and best supportive care*

Ofatumumab was assumed to have equal clinical efficacy to rituximab monotherapy, and therefore the same parameters were used for OS, PFS and ORR. Thus, life years and QALYs calculated for this treatment option will be the same as for rituximab, with the cost of treatment the only difference between the two. The company submission gives four justifications for this assumption. Specifically:

- 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.[45] The ORCHARRD study was not conducted in CLL, but in diffuse large B-cell lymphoma.
- The use of the two treatments interchangeably as a class of therapies in clinical trials.[9]
- Conclusions from a meta-analysis conducted as part of an appraisal for ofatumumab in combination with bendamustine and Chlorambucil.[46]
- Expert clinical advice.

The company submission states that to provide an upper bound on the ICER for best supportive care, it was modelled as having the same clinically efficacy (OS and PFS) as rituximab monotherapy, and having a treatment cost of £0. ORRs for best supportive care were assumed to be zero.

*Comparisons with other agents*

No connected network of RCT evidence was found for other CLL treatments, which precluded formal evidence synthesis using a network meta-analysis. As an exploratory alternative, RCTs and single-arm trials in which median OS and PFS data were reported for treatment regimens within the scope were identified. PFS and OS curves were then fitted to these median OS and PFS data, assuming a Weibull distribution with the same shape parameter as the rituximab monotherapy OS and PFS curves. This means that the fitted curves will follow the same shape as the rituximab curve, but will be scaled differently according to differences in median OS and PFS. These curves were then validated by visual inspection against Kaplan-Meier data reported from these studies, where available. A summary of the additional treatments for which comparisons were made based on this approach is shown in Table 17.

**Table 17. Summary of key external trial and Study 116 data**

| Treatment Regimen | Median OS (months) | Median PFS (months) | Median age | Median no of prior trts | %17p deleted | Eligibility criteria [1] | No. of patients | Study Design |
|---|---|---|---|---|---|---|---|---|
| FCR | 47 | 21 | 59 | 2 | 7% | ECOG<3<br>Able to receive cytotoxic agents | 284 | Open-label, phase II study[16] |
| B | 44 | 20 | 68 | 1 | NR | No prior fludarabine or bendamustine<br>Able to receive cytotoxic agents | 49 | Open label RCT[6] |
| B+R | 34 | 15 | 67 | 2 | 18% | ≥1 but ≤3 previous treatments<br>WHO PS 0-2<br>Life expectancy of ≥12 weeks<br>Able to receive cytotoxic agents | 78 | Open-label, phase II study[19] |
| Steroids+R | 31 | 12 | 59 | 1 | 31% | Progressive or stable disease while on F treatment, or relapse within 12 months after F treatment and/or at least one of: 17p deletion, 11q deletion, or trisomy 12 | 29 | Single arm open label study[20] |
| Ofa | 15 | 6 | 62 | 4 | 18% | CLL refractory to at least one F regimen and either refractory to at least one A regimen or considered less suitable for A as a result of bulky lymphadenopathy<br>Life expectancy ≥6 months | 79 | Single arm open label study[14] |
| R | [redacted] | 7 | 71 | 3 | 28% | Unable to receive cytotoxic agents<br>ECOG unrestricted | 110 | Study 116 Double-blind RCT[1] |
| IR | 45 (model) | 18 | 71 | 3 | 24% | | 110 | |

**Key:** B, bendamustine; ECOG, eastern cooperative oncology group; FCR, fludarabine, cyclophosphamide and rituximab; IR, idelalisib with rituximab; NR, not reported; ofa, ofatumumab; R, rituximab; RCT, randomised control trial

**1**: These eligibility criteria, alongside other patient characteristics reported in this table, suggest Study 116 patients were relatively unfit in comparison to other studies, and analyses ignoring cross-study heterogeneity would be biased against evidence for idelalisib with rituximab from Study 116

An additional step was then undertaken to adjust for differences in baseline characteristics between the different studies, as the participants in Study 116 were generally less healthy at baseline than those from other studies. In the analysis of clinical outcomes for FCR in relapsed CLL patients presented by Badoux et al,[16] the authors performed Cox proportional hazards regression analyses of associations between pre-treatment patient characteristics and clinical outcomes (OS and PFS). Hazard ratios for OS and PFS associated with different patient characteristics are shown in Table 18 and Table 19.

**Table 18. Patient characteristics hazard ratios for OS, from Badoux et al.**

| **Pre-treatment characteristic** | **Hazard Ratio** |
|---|---|
| Age | 1.03 |
| Serum creatinine (mg/L) | 2.30 |
| ln(platelets*10^9/L) | 0.59 |
| Abnormality of chromosome 17 | 5.20 |
| Complex karyotype, not chromosome 17 | 1.90 |
| >3 prior treatments % | 1.70 |
| Fludarabine refractory % | 1.80 |
| **Key:** OS, overall survival | |

**Table 19. Patient characteristics hazard ratios for PFS, from Badoux et al.**

| **Pre-treatment characteristic** | **Hazard Ratio** |
|---|---|
| Serum creatinine (mg/L) | 2.00 |
| ln(platelets*10^9/L) | 0.66 |
| Abnormality of chromosome 17 | 4.60 |
| Complex karyotype | 2.60 |
| 11q deletion | 3.00 |
| Median no of prior treatments | 1.12 |
| **Key:** PFS, progression-free survival | |

These hazard ratios can then be used to calculate an adjustment factor for each of the studies included in this analysis (based on baseline differences in population characteristics between those studies and Study 116), which is then applied to the calculated OS and PFS hazard ratios for these treatment options. Whilst this will account for some of the between study variation, the company make it clear that these comparisons should still be regarded as exploratory, as it is never possible to adjust for all between trial variation, and such single arm comparisons are necessarily less robust than those from a trial or formal indirect comparison. Estimates of to what extent it was possible to adjust for baseline differences in each additional study (essentially, how many of the characteristics in the Badoux et al. proportional hazard model were reported for that study) are given in Table 20. The lower the ability to adjust for these baseline differences, the more exploratory the comparison must be regarded as being.

**Table 20. Comparability of external studies**

| Treatment | N patients | Similarity of patients to Study 116 | Ability to adjust for patient characteristics determining OS | Ability to adjust for patient characteristics determining PFS | Study 1st author and year |
|---|---|---|---|---|---|
| FCR | 284 | Low | High | High | Badoux 2011[16] |
| B | 49 | Low | Low | Low | Niederle 2013[6] |
| BR | 78 | Low | Medium | Medium | Fischer 2011[19] |
| Steroids+R | 29 | Low | Medium | Medium | Pileckelyte 2011[20] |
| Ofa | 79 | Medium | Low | Low | Wierda 2010[14] |

**Key:** B, bendamustine; FCR, fludarabine, cyclophosphamide and rituximab; ofa, ofatumumab; OS, overall survival; PFS, progression free survival

Response rates for these alternative comparators were again taken from published RCTs and single arm studies but, unlike data on OS and PFS, were not adjusted for differences in baseline population (Table 21).

**Table 21. Overall response rates**

| Treatment | Sample size | Number overall response | Overall response rate | Source |
|---|---|---|---|---|
| FCR | 284 | 210 | 74% | Badoux et al 2011[16] |
| B | 49 | 37 | 76% | Niederle et al 2013[6] |
| B+R | 78 | 46 | 59% | Fischer et al 2011[19] |
| Chl | 123 | 59 | 48% | Knauf et al 2010[47] |
| Chl+R | 68 | 56 | 83% | Leblond et al 2012[9] |
| Steroids+R | 29 | 18 | 62% | Pileckyte et al 2011[20] |
| Ofatumumab | 79 | 37 | 47% | Wierda et al 2010[14] |
| **Study 116 data** | | | | |
| IR | 110 | 92 | 84% | Study 116[1] |
| R | 110 | 17 | 15% | Study 116[1] |
| BSC | NA | NA | 0% | Assumption |

**Key:** B, bendamustine; BSC, best supportive care; Chl, chlorambucil; FCR, fludarabine, cyclophosphamide and rituximab; IR, idelalisib with rituximab; R, rituximab

The use of a constant shape parameter for the survival curves for these alternative treatments was justified by the company as being necessary as full Kaplan-Meier data were not available. However, digitised Kaplan-Meier plots were used to validate the fitted models, and hence could have been used to fit survival models directly, removing the need for the constant shape assumption. This is particularly important for FCR, where the fitted model (assuming a constant shape) had a very poor fit to the data. Following a clarification question from the ERG, the company refitted the survival curve for FCR using a more appropriate distribution (section 5.2.11), and this more appropriate model is used in the ERGs further analyses.

Further, no justification was given by the company for using hazard ratios from the Badoux et al. study to adjust for baseline differences, rather than a model from any other trial, and no sensitivity analyses were conducted looking at the impact of this assumption. The ERG undertook additional sensitivity analyses to look at the impact the hazard ratios used for adjustment have on the ICERs for these comparators.

### ERG summary

- 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.
- OS and PFS extrapolation all rely on the untested and unexplored assumption that the benefit of treatment persists, both after the time horizon of the trial and after treatment discontinuation. Any reduction in treatment benefit following either of those events will result in a smaller treatment benefit for idelalisib with rituximab over its comparators than is currently the case.
- The crossover adjustment for the rituximab monotherapy arm of Study 116 relies 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, though the magnitude of this change will only be substantial if idelalisib monotherapy is thought to be considerably inferior to idelalisib with rituximab.
- The company’s primary comparisons with ofatumumab and best supportive care both model the assumption these have the same OS and PFS values as rituximab monotherapy, with ofatumumab having the same ORR as rituximab, and best supportive care an ORR of 0. If the assumption of equal efficacy for ofatumumab and rituximab is thought to be implausible, then the results of the scenario analysis with ofatumumab efficacy estimated from external data should be preferred to those from the analysis assuming equal efficacy.

### 5.2.7 Health-related quality of life

The base case model makes use of EQ-5D data collected during Study 116.[1] Participants who had not progressed and were still on treatment were administered the EQ-5D at 2, 4, 6, 8, 12, 16, 20, 24, 30, 36, 42 and 48 weeks post baseline, and every 12 weeks thereafter. A generalised estimating equation (accounting for autocorrelations caused by repeated measurements from the same participants) was then fitted to these data to estimate health state utilities for the pre-progression on treatment health state for both treatment alternatives (Table 22).

**Table 22. EQ-5D estimates for patients receiving treatment in Study 116**

| Treatment arm | Estimate | Standard Error |
|---|---|---|
| R utility | 0.7475 | 0.0159 |
| IR treatment effect vs. R | 0.0652 | 0.0216 |
| IR utility | 0.8127 | |
| **Key:** IR, idelalisib with rituximab; R, rituximab | | |

Since EQ-5D data were not collected during the trial for individuals post-progression or post treatment discontinuation, these values were instead estimated from a systematic review of the literature, looking for studies reporting utilities for different CLL health states. Six studies were identified, and the utility values extracted from them are given in Table 23.

**Table 23. Health state utility values, HRQL studies**

| First author | Description of health state | Values (SE) |
|---|---|---|
| Beusterien [48] | Complete response | 0.91 (0.11)* |
| | Partial response | 0.84 (0.14)* |
| | No change | 0.78 (0.14)* |
| | 2nd-line treatment | 0.71 (0.17)* 0.65 |
| | 3rd-line treatment | (0.22)* |
| | Progressive disease | 0.68 (0.20)* |
| Dretzke [32] | Progression-free | 0.80 |
| | Progressive disease | 0.60 |
| Hoyle [49] | 1st-line treatment with alemtuzumab | 0.62 (0.03) |
| | 1st-line treatment with chlorambucil | 0.62 (0.03) |
| | 1st-line treatment: progression-free | 0.78 (0.02) |
| | Following 1st-line treatment: progressive disease | 0.54 (0.03) |
| | Following 2nd-line treatment: progression-free | 0.65 (0.03) |
| | Following 2nd-line treatment: progressive disease | 0.47 (0.03) |
| | Following 3rd-line treatment: progression-free | 0.43 (0.03) |
| | Following 3rd-line treatment: progressive disease | 0.28 (0.03) |

| | | |
|---|---|---|
| Hyde [50] | CLL in remission<br>CLL<br>CLL during 6-month treatment with fludarabine<br>CLL during 6-month treatment with CAP | 0.96<br>0.81<br>0.81<br>0.79 |
| Pashos [51] | Utility mean index score, males<br>Utility mean index score, females | 0.9<br>0.8 |
| Tolley [52] | Anchor state<br>Progression-free; responding to treatment<br>Progression-free; not responding to treatment<br>Disease progression | 0.55 (0.23)*<br>0.67 (0.24)*<br>0.39 (0.22)*<br>0.21 (0.18)* |
| **Key:** CLL, chronic lymphocytic leukaemia; SE, standard error; * standard deviation, not SE. | | |

In the base-case, the company chose to use utilities from the Dretzke study[32] for the post-progression and pre-progression off treatment states. The justification used for this is that it was one of only two of the above studies (the other being Pashos et al.) that elicited utilities directly from the CLL population, and the only one to do both that and report separate health states for pre and post-progressive disease. The utility values from this study were also validated as being realistic by an NHS clinical haematologist. Utilities in the terminal care state are assumed to be equal to those in the post-progression state. The full set of utility values and sources used in the base case model are shown in Table 24.

**Table 24. Summary of utility values for cost-effectiveness analysis**

| State | Utility value | Confidence interval | Justification |
|---|---|---|---|
| Progression-free, comparator | 0.75 | (0.72, 0.78) | Study 116 EQ-5D data[1] |
| IR treatment utility effect | 0.07 | (0.03, 0.11) | |
| PFS Off treatment | 0.80 | (0.63, 0.93) | Most robust literature estimate, used in NICE TA 193[32] |
| PPS | 0.60 | (0.48, 0.71) | |
| **Adverse Event** | **Utility Decrement** | **Confidence interval** | **Justification** |
| Anaemia | -0.09 | (-0.07, -0.11) | NICE TA 216[53] |
| Febrile Neutropenia | -0.20 | (-0.16, -0.23) | Assumed equal to infection disutility[52] |
| Sepsis | -0.20 | (-0.16, -0.23) | Assumed equal to infection disutility[52] |
| Neutropenia | -0.16 | (-0.13, -0.2) | Tolley et al.[52] |
| Pneumonia | -0.20 | (-0.16, -0.23) | Assumed equal to infection disutility[52] |

| | | | |
|---|---|---|---|
| Thrombocytopenia | -0.11 | (-0.09, -0.13) | Tolley et al.[52] |
| Diarrhoea + Colitis | -0.20 | (-0.16, -0.23) | Assumed to be the same as febrile neutropenia (clinical advice) |

Since the impact of treatment related adverse events should be included in the utilities calculated from Study 116 data, in the base case model no additional decrements were included for adverse events. However, the company also conducted sensitivity analyses using values from the literature instead of trial data for pre-progression on treatment utilities, and in this case it is important to include disutilities associated with adverse events. On treatment adverse event frequencies were derived from Study 116,[1] and these were combined with utility decrements for these events taken from the literature (Table 25) to give per cycle QALY decrements associated with each event, for each treatment (Table 25 and Table 26). All adverse events observed in the rituximab arm were assumed to occur whilst the individual was still on treatment. Total per cycle on treatment adverse event QALY decrements were calculated to be 0.00013 for idelalisib with rituximab, and 0.00023 for rituximab monotherapy, and these were applied in all models which used literature rather than Study 116 data for pre-progression on treatment health state utilities. When other comparators are considered ofatumumab is assumed to have the same adverse event QALY decrements as rituximab, whilst other comparators are assumed to incur no utility decrement as a result of adverse events.

**Table 25. Cycle probability of AE and cycle QALY decrement, IR**

| Grade 3/4 AE | AE event QALY decrement | Cycle probability | Cycle QALY decrement |
|---|---|---|---|
| Anaemia | -0.006 | 0.001 | -0.00001 |
| Febrile Neutropenia | -0.012 | 0.001 | -0.00001 |
| Sepsis | -0.012 | 0.001 | -0.00001 |
| Neutropenia | -0.007 | 0.004 | -0.00003 |
| Pneumonia | -0.006 | 0.002 | -0.00001 |
| Thrombocytopenia | -0.007 | 0.001 | 0.00000 |
| Diarrhoea + Colitis | -0.020 | 0.003 | -0.00005 |
| **Total cycle QALY decrement due to AEs, IR** | | | **-0.00013** |
| **Key:** AE, adverse event; IR, idelalisib with rituximab; QALY, quality adjusted life year | | | |

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**Table 26. 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 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.

Secondly, 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. 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.

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.[32] paper, and then apply adverse event disutilities from the trial. This approach is tested in one of

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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 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. 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 Table 27.

**Table 27. Summary of drug and administration costs for each modelled treatment regimen**

| Regimen | Cycle type | Drug | Active Cycle Drug Costs | | Active Cycle Administration Costs | |
|---|---|---|---|---|---|---|
| | | | *Each Component* | *Total by cycle type* | *Each Component* | *Total by cycle type* |
| IR | Initial cycle | Idelalisib | [redacted] | [redacted] | £0 | £330 |
| | | Rituximab | £1,257 | | £330 | |
| | Subsequent cycles | Idelalisib | [redacted] | [redacted] | £0 | £330 |
| | | Rituximab | £1,676 | | £330 | |
| R | Initial cycle | Rituximab | £1,257 | £1,257 | £330 | £330 |
| | Subsequent cycles | Rituximab | £1,676 | £1,676 | £330 | £330 |
| FCR | Initial cycle | Fludarabine | £446 | £1,727 | £428 | £758 |
| | | Cyclophosphamide | £24 | | £0 | |
| | | Rituximab | £1,257 | | £330 | |
| | Subsequent cycles | Fludarabine | £446 | £2,145 | £428 | £758 |
| | | Cyclophosphamide | £24 | | £0 | |
| | | Rituximab | £1,676 | | £330 | |
| B | All cycles | Bendamustine | £1,062 | £1,062 | £428 | £428 |
| B+R | Initial cycle | Bendamustine | £744 | £2,000 | £214 | £544 |
| | | Rituximab | £1,257 | | £330 | |
| | Subsequent cycles | Bendamustine | £744 | £2,419 | £214 | £544 |
| | | Rituximab | £1,676 | | £330 | |
| Chl | | Chlorambucil | £113 | £113 | £0 | £0 |
| Chl+R | Initial cycle | Chlorambucil | £109 | £1,366 | £0 | £330 |
| | | Rituximab | £1,257 | | £330 | |
| | Subsequent cycles | Chlorambucil | £109 | £1,785 | £0 | £330 |
| | | Rituximab | £1,676 | | £330 | |
| Steroids+R | Initial cycle | Methylprednisolone | £1,367 | £3,881 | £642 | £1,302 |
| | | Rituximab | £2,513 | | £660 | |
| | Second cycle | Methylprednisolone | £1,367 | £4,719 | £642 | £1,302 |
| | | Rituximab | £3,351 | | £660 | |
| | Subsequent cycles | Methylprednisolone | £1,367 | £3,043 | £642 | £972 |
| | | Rituximab | £1,676 | | £330 | |

| Regimen | Cycle type | Drug | Active Cycle Drug Costs | | Active Cycle Administration Costs | |
|---|---|---|---|---|---|---|
| | | | *Each Component* | *Total by cycle type* | *Each Component* | *Total by cycle type* |
| 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 and rituximab; IR, idelalisib with rituximab; R, rituximab

The ERG is not convinced by the justification given for 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.

Superseded see erratum

*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 28).

**Table 28. 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.

Applying these costs to the cycle probability of each event, calculated from Study 116 data and reported in section 4, produces cycle costs of £9.86 for idelalisib with rituximab and £22.02 for rituximab alone, as shown in Table 29. Ofatumumab monotherapy is assumed to produce equivalent AE rates to rituximab monotherapy whilst, in the absence of data, no costs for AEs are included for the other comparators. The ERG had concerns that the costs of some of these adverse events were underestimated. For example, the cost for diarrhoea and colitis was assumed to be that of a single outpatient gastroenterology attendance, which may underestimate the costs for severe cases of this adverse event. However, the model ICERs were not sensitive to changes in these parameters, and therefore there is no concern that this possible underestimate has any meaningful impact on the results of the model.

**Table 29. Weekly costs attributable to treatment-emergent AEs**

| **Grade 3/4 AE** | **IR** | | **Rituximab or Ofatumumab** | | **All other comparators** | |
|---|---|---|---|---|---|---|
| | **Cycle Probability** | **Cost per cycle** | **Cycle Probability** | **Cost per cycle** | **Cycle Probability** | **Cost per cycle** |
| Anaemia | 0.001 | £0.62 | 0.004 | £1.86 | 0.000 | £0.00 |
| Febrile Neutropenia | 0.001 | £5.25 | 0.003 | £18.13 | 0.000 | £0.00 |
| Sepsis | 0.001 | £1.00 | 0.002 | £1.73 | 0.000 | £0.00 |
| Neutropenia | 0.004 | £0.78 | 0.011 | £1.94 | 0.000 | £0.00 |
| Pneumonia | 0.002 | £2.41 | 0.006 | £7.56 | 0.000 | £0.00 |
| Thrombocytopenia | 0.001 | £0.33 | 0.002 | £1.14 | 0.000 | £0.00 |
| Diarrhoea + Colitis | 0.003 | £0.37 | 0.000 | £0.00 | 0.000 | £0.00 |
| **Total Cycle Cost** | | **£10.76** | | **£32.37** | | **£0.00** |
| **Key:** AE, adverse events; IR, idelalisib with rituximab | | | | | | |

Disease management costs were stratified by response status, with individuals requiring different amounts of each service depending on whether they had or had not responded to treatment. Some of these frequencies were derived from the literature, but most were clinical assumptions, and as such are subject to considerable uncertainty. Usage was calculated as frequency per month both pre and post progression, and there were also one off costs associated with disease progression. Resource use is shown in Table 30 and Table 31, with the associated costs (most of which are derived from NHS reference costs) shown in Table 32.

**Table 30. Monthly resource use estimates, pre- and post-disease progression**

| Resource | Pre-progression | | | Post-progression | |
|---|---|---|---|---|---|
| | **Frequency per month, responders** | **Frequency per month, non-responders** | **Source** | **Frequency per month** | **Source** |
| Haematologist-led outpatient visit | 0.00 | 1.00 | NICE TA216[53] | 1 | NICE TA216[53] |
| LDH test | 0.33 | 1.00 | NICE TA216[53] | 1 | NICE TA216[53] |
| Full blood test | 0.33 | 1.00 | NICE TA216[53] | 1 | NICE TA202[36] |
| Blood cell transfusion | 0.00 | 1.00* | Clinical validation | 0.5 | NICE TA216[53] |
| Platelet transfusion | 0.00 | 2.17** | Clinical validation | 0 | Clinical validation |
| IVIG therapy | 0.00 | 1.24* | Clinical validation | 0 | Clinical validation |
| Chest X-ray | 0.00 | 0.33 | Clinical validation | 0.33 | NICE TA202[36] |
| prophylactic antibiotics* | 1.00 | 1.00*** | Clinical validation | 0 | Clinical validation |
| prophylactic antivirals* | 1.00 | 1.00**** | Clinical validation | 0 | Clinical validation |

**Key:** IVIG, immunoglobulin variable region heavy chain; LDH, lactate dehydrogenase; NICE, national institute of health and care excellence

**Notes:** * applied to 45% of patients; ** applied to 15% of patients; *** applied to 60% of patients; **** applied to 50% of patients.

**Table 31. One-off resource use estimates, upon disease progression**

| Resource | Proportion of patients |
|---|---|
| G-CSF usage | 50% |
| Cytogenetic testing | 100% |
| Bone marrow biopsy | 90% |
| Radiographic MRI scan | 0% |
| CT scan | 50% |

**Key:** G-CSF, granulocyte colony-stimulating factor; MRI, magnetic resonance imaging; CT, computerised tomography

**Table 32. Resource costs**

| Resource | Cost | Source |
|---|---|---|
| Haematologist-led visit | £143 | NHS Reference Costs 2012-13; Consultant Led Outpatient Attendance; WF01A 303 |
| Nurse-led visit | £91 | NHS Reference Costs 2012-13; Non-Consultant Led Outpatient Attendance; |

| Resource | Cost | Source |
|---|---|---|
| | | WF01A 303 |
| Cytogenetic testing | £372 | NHS Reference Costs 2012-13; Total - Outpatient Attendances; 311 |
| LDH test | £3 | NHS Reference Costs 2012-13; Directly Accessed Pathology Services; DAPS05 |
| Full blood test | £3 | NHS Reference Costs 2012-13; Directly Accessed Pathology Services; DAPS05 |
| Blood cell transfusion | £122 | NHS Blood and Transplant: Standard red cells, item code N12 |
| Platelet transfusion | £197 | NHS Blood and Transplant: Platelets (1.0 ATD), item code N32 |
| IVIG therapy | £13,706 | IVIG therapy costs (£7,529) plus administration cost (£6,177) |
| Bone marrow biopsy | £234 | NHS Reference Costs 2012-13; Total HRG data; Clinical Haematology, HRG SA33Z, Procedures in Outpatients |
| MRI scan | £246 | NHS Reference Costs 2012-13; Diagnostic Imaging, clinical haematology, RA07Z |
| Chest X-ray | £28 | NHS Reference Costs 2012-13; Directly Accessed Diagnostic Services, DAPF |
| CT scan | £91 | NHS Reference Costs 2012-13; Computerised Tomography Scan, one area, no contrast, 19 years and over, RA08A |
| Prophylactic antibiotics | £12 | NICE TA202[36] |
| Prophylactic antiviral | £89 | Zidovudine, 100mg white cap marked GSYJU, 100, MIMS online[37] |
| G-CSF support | £311 | NICE TA202[36] |

**Key**: NICE, national institute for health and care excellence; NHS, National Health Service; IVIG, Intravenous immunoglobulin therapy; LDH, lactate dehydrogenase; CT, computerised tomography; G-CSF, Granulocyte-colony stimulating factor.

Finally, the data on adverse events, disease management and maximum dosing duration were combined to give per cycle costs for each treatment and health state in the mode (Table 33).

**Table 33. Summary of health state costs**

| Health states | Items | Value | Reference in submission |
|---|---|---|---|
| Pre-progression, On Treatment | Technology | As described in | Section 5.5 |
| | AE management | IR: £11 per week<br>R: £32 per week*<br>Ofa: £32 per week<br>All other comparators: £0 per week** | Section 5.5 |
| | Disease management | IR: £319 per week for 3 months, then £307 per week<br>R: £1,551 per week for 3 months, then £1,539 per week<br>FCR: £493 per week for 3 months, then £481 per week<br>B: £457 per week for 3 months, then £445 per week<br>BR: £764 per week for 3 months, then £752 per week<br>Chl: £461 per week for 3 months, then £450 per week<br>Chl+R: £330 per week for 3 months, then £319 per week<br>Steroids+R: £710 per week for 3 months, then £698 per week<br>Ofa: £981 per week for 3 months, then £969 per week | Section 5.5 |
| | Total excluding technology | IR: £330 per week for 3 months, then £318 per week<br>R: £1,632 per week for 3 months, then £1,620 per week<br>FCR: £493 per week for 3 months, then £481 per week<br>B: £457 per week for 3 months, then £445 per week<br>BR: £764 per week for 3 months, then £752 per week<br>Chl: £461 per week for 3 months, then £450 per week<br>Chl+R: £330 per week for 3 months, then £319 per week<br>Steroids+R: £710 per week for 3 months, then £698 per week<br>Ofa: £1,113 per week for 3 months, then £1001 per week | |
| Pre-progression, Off Treatment | Disease management (total) | IR: £319 per week for 3 months, then £307 per week<br>R: £1,551 per week for 3 months, then £1,539 per week<br>FCR: £493 per week for 3 months, then £481 per week<br>B: £457 per week for 3 months, then £445 per week<br>BR: £764 per week for 3 months, then £752 per week<br>Chl: £461 per week for 3 months, then £450 per week<br>Chl+R: £330 per week for 3 months, then £319 per week<br>Steroids+R: £710 per week for 3 months, then £698 per week<br>Ofa: £981 per week for 3 months, then £969 per week | Section 5.5 |
| Upon | Disease | £784 (one off) | Section 5.5 |

Superseded see erratum

| Health states | Items | Value | Reference in submission |
|---|---|---|---|
| progression | management | | |
| 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 and rituximab; IR, idelalisib with rituximab; ofa, ofatumumab; R, rituximab<br>* AE cost for R > AE cost for IR per cycle despite higher toxicity for IR, due to shorter time on treatment for R<br>** 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 are accrued until treatment discontinuation, whilst for other comparators patients are assumed to complete the full maximum dosing indicated for that product.

- 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.
- 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.
- The model ICERs are sensitive to resource use parameters derived not from data but from estimation by clinicians, and therefore particular attention should be paid to sensitivity analyses looking at the impact of these assumptions.

### 5.2.9 Cost-effectiveness results

For the comparisons of idelalisib with rituximab against rituximab monotherapy, ofatumumab and best supportive care, the company's deterministic base case results are presented below.

**Table 34. Company Base case results, IR versus R**

| | Costs | Life Years | QALYs | Incremental | | | ICER |
|---|---|---|---|---|---|---|---|
| | | | | Costs | Life Years | QALYs | |
| Rituximab | [redacted] | 1.39 | 0.89 | | | | |
| IR | [redacted] | 4.63 | 2.81 | £26,128 | 3.24 | 1.92 | £13,634 |
| **Key:** ICER, incremental cost effectiveness ratio; IR, idelalisib with rituximab, QALYs, quality adjusted life year | | | | | | | |

**Table 35. Company Base case results, IR versus BSC**

| | Costs | Life Years | QALYs | Incremental | | | ICER |
|---|---|---|---|---|---|---|---|
| | | | | Costs | Life Years | QALYs | |
| BSC | [redacted] | 1.39 | 0.89 | | | | |
| IR | [redacted] | 4.63 | 2.81 | £39,211 | 3.24 | 1.92 | £20,461 |
| **Key:** ICER, incremental cost effectiveness ratio; IR, idelalisib with rituximab, QALYs, quality adjusted life year | | | | | | | |

**Table 36. Company Base case results, IR versus ofatumumab**

| | Costs | Life Years | QALYs | Incremental | | | ICER |
|---|---|---|---|---|---|---|---|
| | | | | Costs | Life Years | QALYs | |
| Ofatumumab | [redacted] | 1.39 | 0.89 | | | | |
| IR | [redacted] | 4.63 | 2.81 | £2,926 | 3.24 | 1.92 | £1,527 |
| **Key:** ICER, incremental cost effectiveness ratio; IR, idelalisib with rituximab, QALYs, quality adjusted life year | | | | | | | |

The corresponding results from the means of the probabilistic analyses are very similar, with ICERs of £13,680, £20,021 and £1,692 per QALY for idelalisib with rituximab versus rituximab monotherapy, best supportive care and ofatumumab monotherapy, respectively. Cost-effectiveness

planes and cost-effectiveness acceptability curves (calculated from the same probabilistic model) are shown below. These show the proportion of these simulations for which the ICER falls below a given willingness to pay threshold.

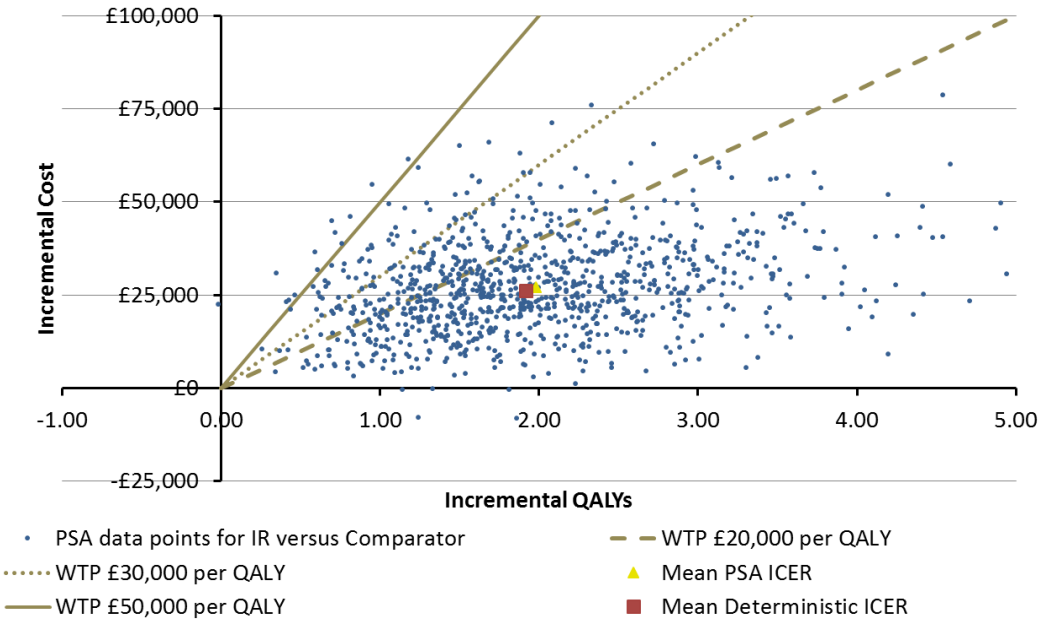


**Figure 7. PSA scatter plot, IR versus R**

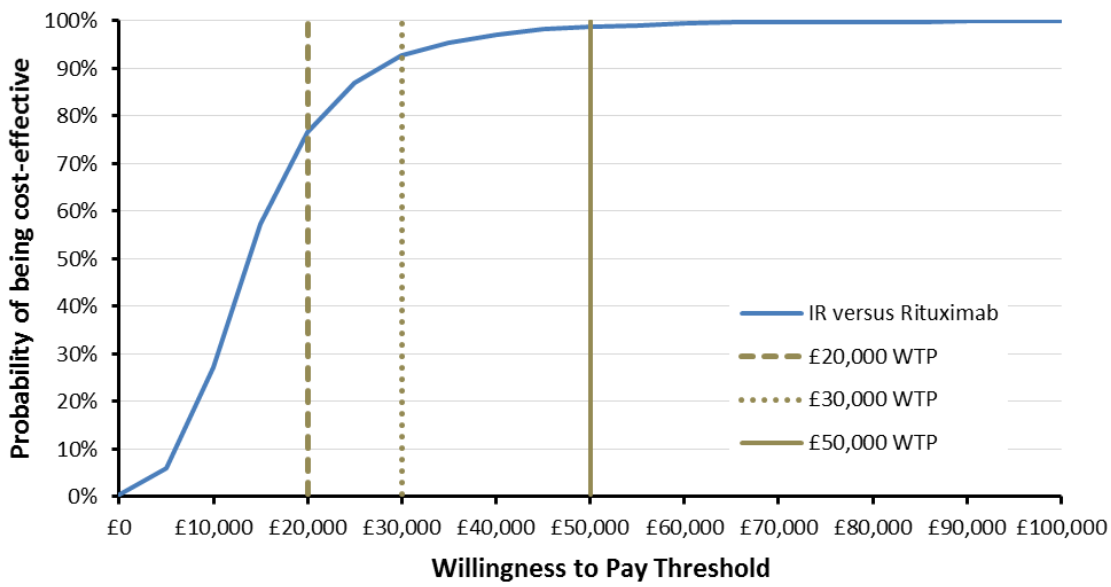


**Figure 8. Cost-effectiveness acceptability curve, IR versus R**

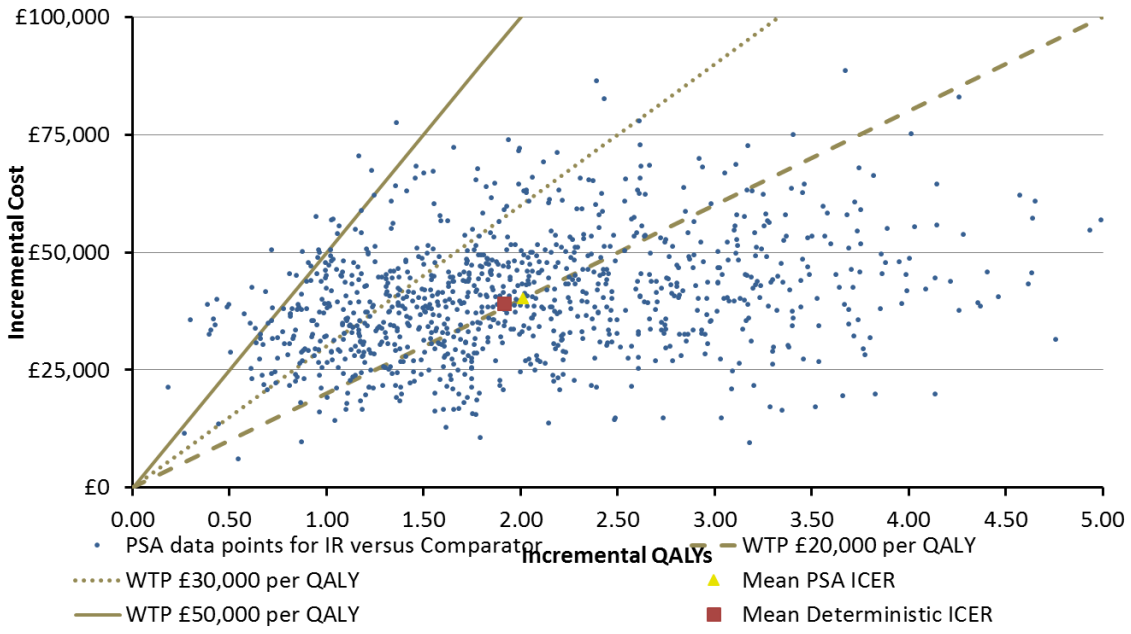


**Figure 9. PSA scatter plot, IR versus BSC**

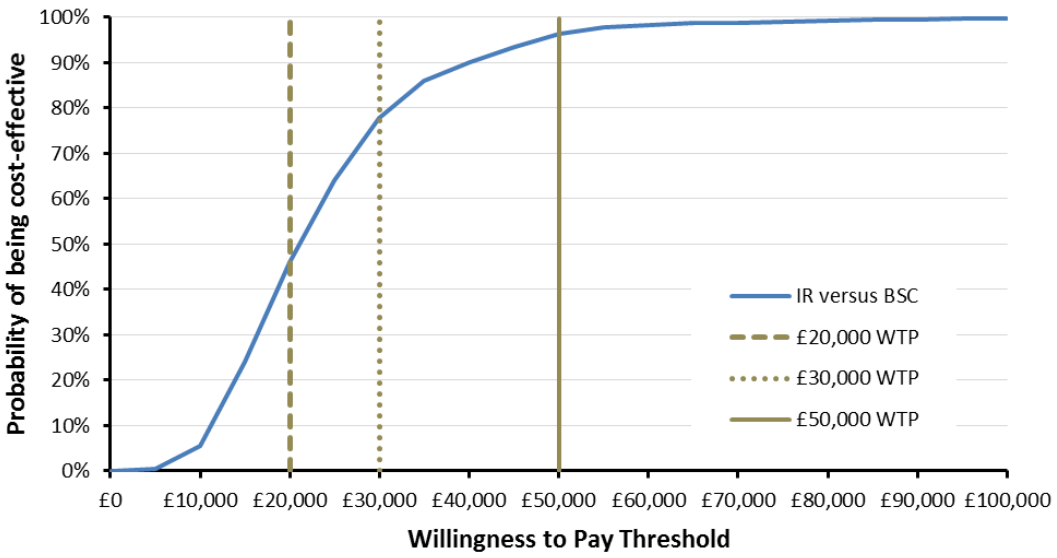


**Figure 10. Cost-effectiveness acceptability curve, IR versus BSC**

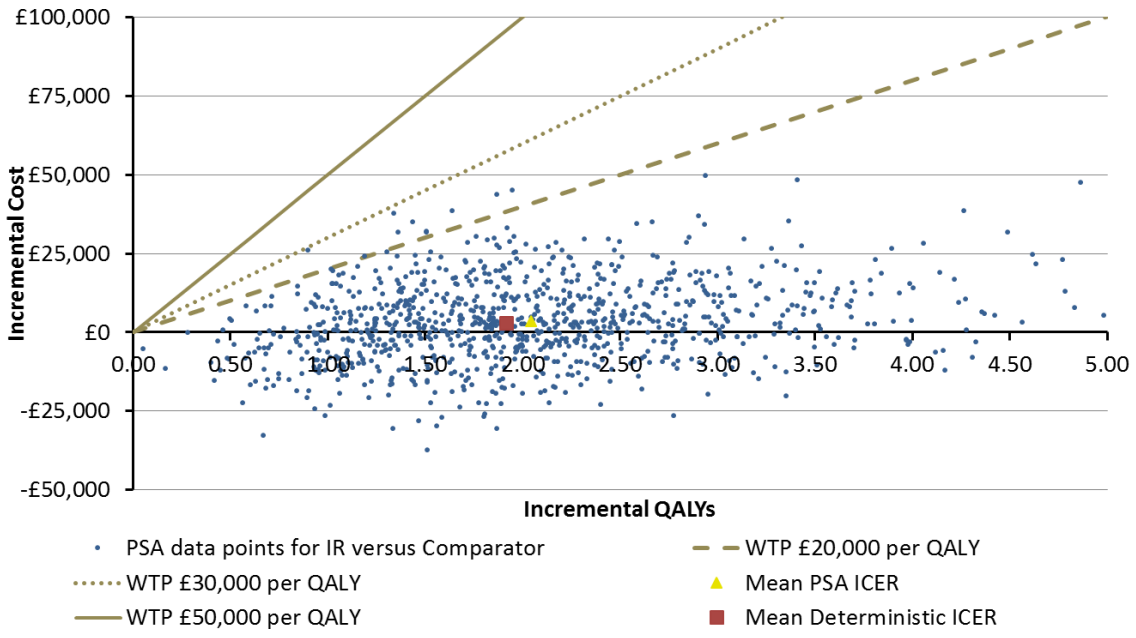


**Figure 11. PSA scatter plot, IR versus ofatumumab**

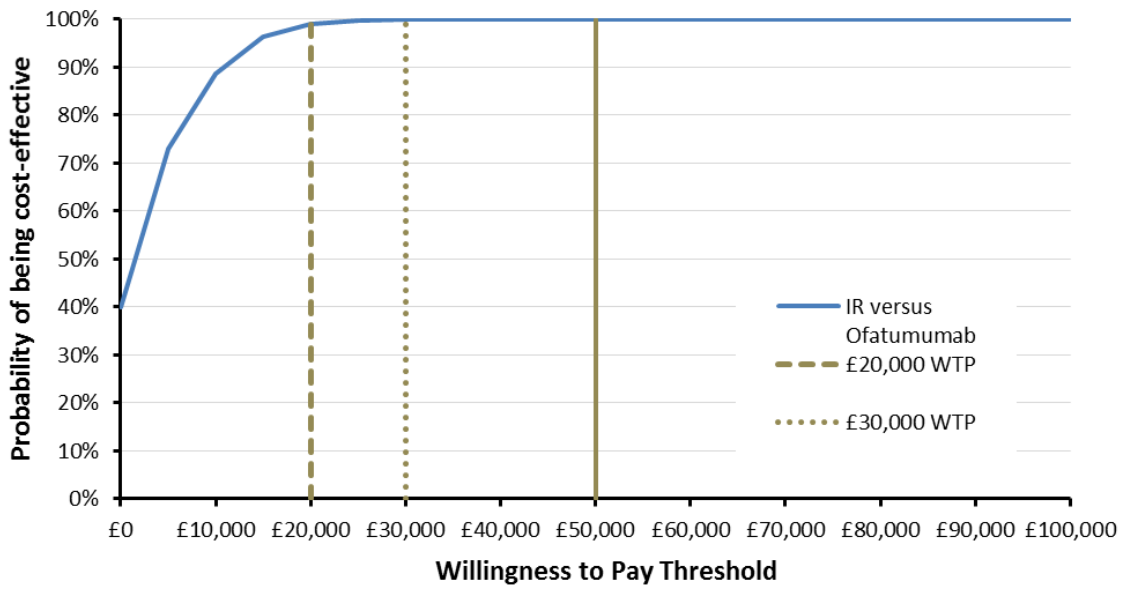


**Figure 12. Cost-effectiveness acceptability curve, IR versus ofatumumab**

### 5.2.10 Sensitivity analyses

One-way sensitivity analyses were undertaken for each of the three main treatment comparisons, and are reported as the impact on the ICER when a particular parameter value is varied to the lower and upper bounds of the 95% confidence interval for that parameter (Figure 13, Figure 14, Figure 15). Uncertainties around estimation of the survival curves and the ORR for rituximab monotherapy are shown to have the largest impact on the ICER. It is important to note, however, that these analyses only consider the impact of varying one single parameter at a time, and are therefore less informative as to the overall level of uncertainty in the model than the results from the full probabilistic sensitivity analysis.

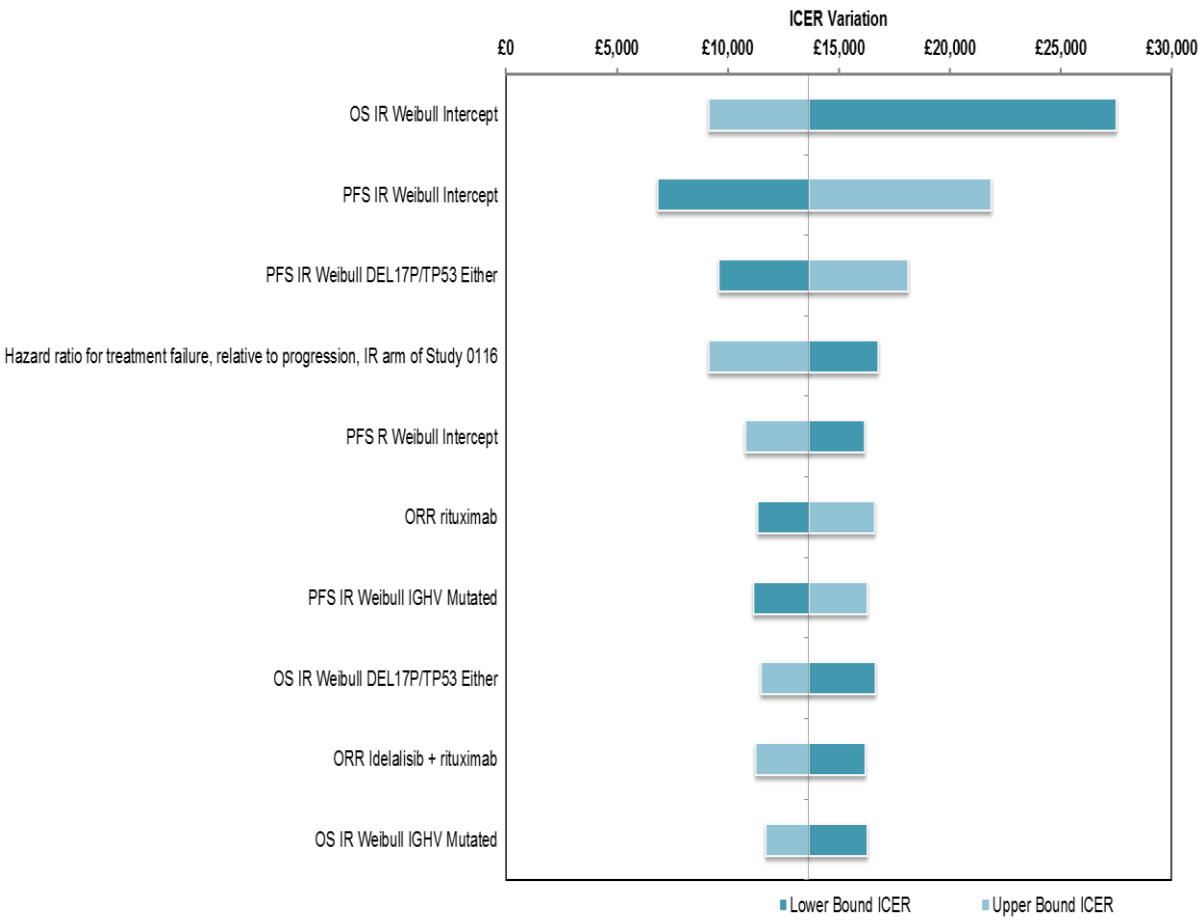


**Figure 13. Tornado diagram showing OWSA results, IR versus R**

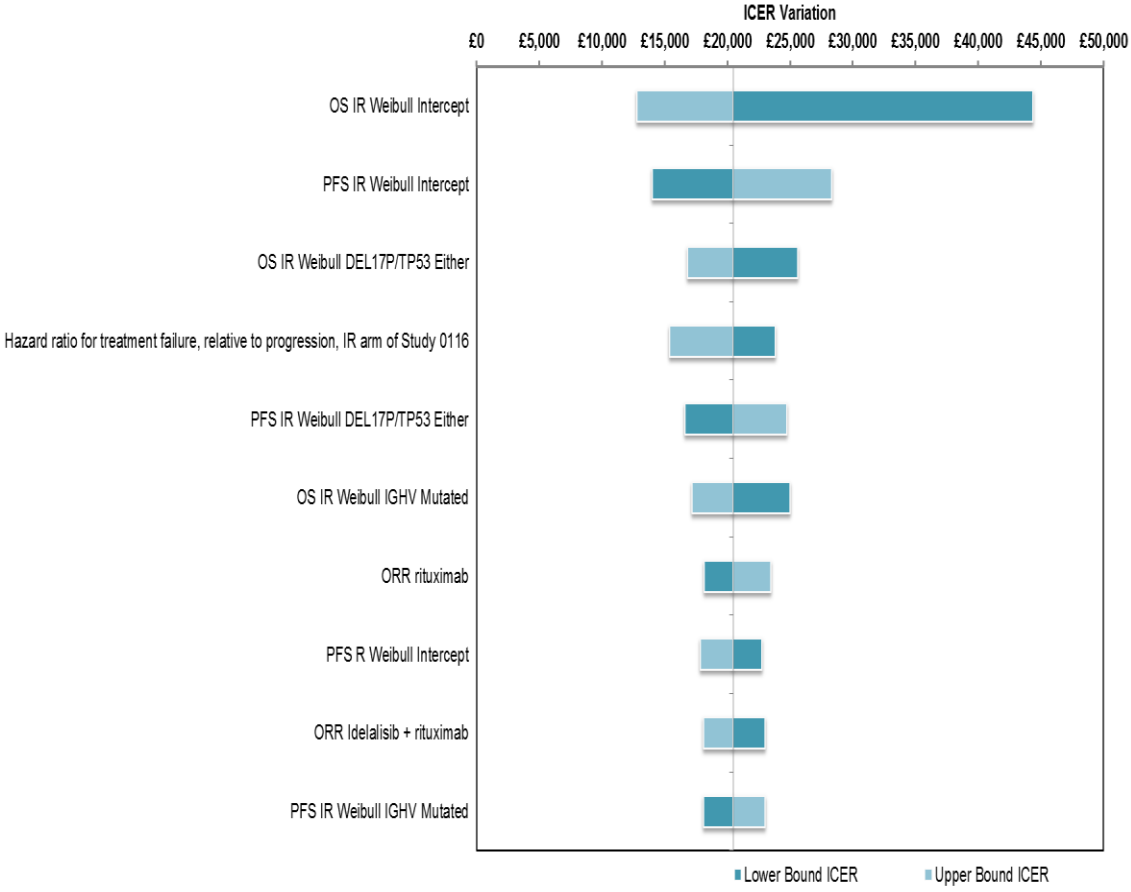


**Figure 14. Tornado diagram showing OWSA results, IR versus BSC**

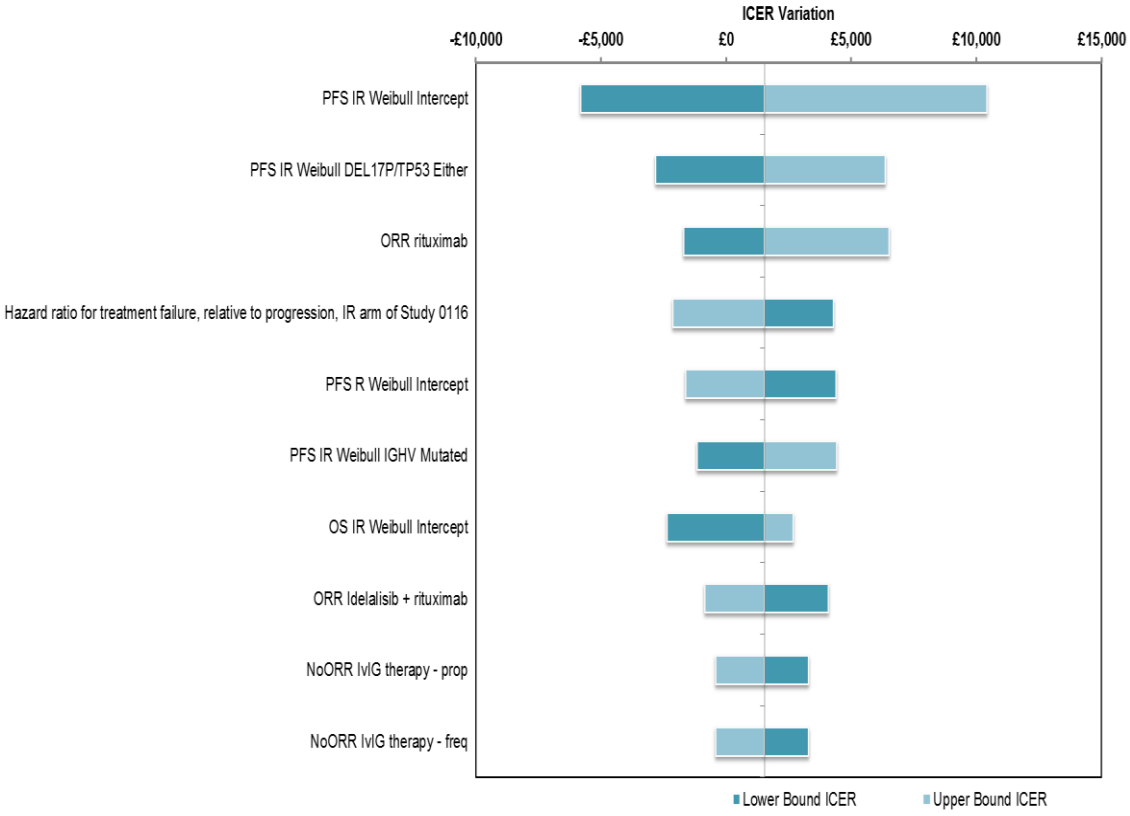


**Figure 15. Tornado diagram showing OWSA results, IR versus ofatumumab**

Additional sensitivity analyses were also taken, looking at the impact of varying the time horizon, source of health state utility estimates, functional form of the overall survival extrapolation curve, and various assumptions around costs. The key results of these additional analyses are summarised below.

**Table 37. Time horizon of model limited to 20 years**

| | | | | Incremental | | | |
|---|---|---|---|---|---|---|---|
| | **Costs** | **QALYs** | **Life Years** | **Costs** | **QALYs** | **Life Years** | **ICER** |
| Rituximab | [redacted] | 0.89 | 1.39 | | | | |
| IR | [redacted] | 2.81 | 4.63 | £26,116 | 1.91 | 3.23 | £13,638 |
| **Key:** ICER, incremental cost effectiveness ratio; IR, idelalisib with rituximab; QALY, quality adjusted life year | | | | | | | |

**Table 38. Time horizon of model limited to 10 years**

| | | | | Incremental | | | |
|---|---|---|---|---|---|---|---|
| | **Costs** | **QALYs** | **Life Years** | **Costs** | **QALYs** | **Life Years** | **ICER** |
| Rituximab | [redacted] | 0.89 | 1.39 | | | | |
| IR | [redacted] | 2.71 | 4.38 | £25,374 | 1.82 | 2.99 | £13,952 |

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

**Table 39. Time horizon of model limited to 5 years**

| | Costs | QALYs | Life Years | Incremental | | | ICER |
|---|---|---|---|---|---|---|---|
| | | | | Costs | QALYs | Life Years | |
| Rituximab | [redacted] | 0.89 | 1.39 | | | | |
| IR | [redacted] | 2.24 | 3.38 | £21,959 | 1.35 | 2.00 | £16,272 |
| **Key:** ICER, incremental cost effectiveness ratio; IR, idelalisib with rituximab; QALY, quality adjusted life year | | | | | | | |

**Table 40. Dretzke et al utility estimates[32] used instead of Study 116 values[1]**

| | Costs | QALYs | Life Years | Incremental | | | ICER |
|---|---|---|---|---|---|---|---|
| | | | | Costs | QALYs | Life Years | |
| Rituximab | [redacted] | 0.91 | 1.39 | | | | |
| IR | [redacted] | 2.78 | 4.63 | £26,128 | 1.87 | 3.24 | £13,972 |
| **Key:** ICER, incremental cost effectiveness ratio; IR, idelalisib with rituximab; QALY, quality adjusted life year | | | | | | | |

**Table 41. Exponential curve fits for OS rather than Weibull**

| | Costs | QALYs | Life Years | Incremental | | | ICER |
|---|---|---|---|---|---|---|---|
| | | | | Costs | QALYs | Life Years | |
| Rituximab | [redacted] | 1.15 | 1.89 | | | | |
| IR | [redacted] | 3.88 | 7.23 | £29,505 | 2.73 | 5.35 | £10,809 |
| **Key:** ICER, incremental cost effectiveness ratio; IR, idelalisib with rituximab; QALY, quality adjusted life year; OS, overall survival | | | | | | | |

**Table 42. Assume treatment until progression or maximum treatment duration rather than use ToT curve**

| | Costs | QALYs | Life Years | Incremental | | | ICER |
|---|---|---|---|---|---|---|---|
| | | | | Costs | QALYs | Life Years | |
| Rituximab | [redacted] | 0.89 | 1.39 | | | | |
| IR | [redacted] | 2.81 | 4.63 | £32,270 | 1.92 | 3.24 | £16,775 |
| **Key:** ICER, incremental cost effectiveness ratio; IR, idelalisib with rituximab; QALY, quality adjusted life year | | | | | | | |

**Table 43. Assume zero terminal care costs**

| | Costs | QALYs | Life Years | Incremental | | | ICER |
|---|---|---|---|---|---|---|---|
| | | | | Costs | QALYs | Life Years | |
| Rituximab | [redacted] | 0.89 | 1.39 | | | | |
| IR | [redacted] | 2.81 | 4.63 | £26,613 | 1.92 | 3.24 | £13,887 |
| **Key:** ICER, incremental cost effectiveness ratio; IR, idelalisib with rituximab; QALY, quality adjusted life year | | | | | | | |

Decreases in the time horizon, the use of alternative utilizes estimates, the exclusions of ToT data from Study 116 and removal of terminal care costs all increased the ICER for idelalisib with rituximab versus rituximab, whilst the use of the exponential model for overall survival reduced the ICER.

### 5.2.11 Additional comparators

The results of the exploratory comparisons versus other treatment options are given in the table below (see Table 44). Whilst these comparisons are necessarily less robust than the main idelalisib with rituximab versus rituximab monotherapy analysis reported above, they do nonetheless represent the most plausible way to try and obtain estimates versus these other agents, and therefore may provide valuable information if these comparisons were thought to be necessary in understanding the true cost-effectiveness of idelalisib versus current best or standard care. These results include a second evaluation of the cost-effectiveness of idelalisib versus ofatumumab, this time using data from a study of ofatumumab, rather than the assumption of equal efficacy to rituximab monotherapy used in the base case analyses.

**Table 44. Exploratory comparison to treatments outside of Study 116, using external clinical data**

| | | | | **Incremental (IR versus comparator)** | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Regimen** | **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** |
| FCR | [redacted] | 0.53 | 0.40 | £63,232 | 4.10 | 2.41 | £26,215 | 284 | Low | High |
| B | [redacted] | 2.08 | 1.44 | £49,677 | 2.55 | 1.36 | £36,424 | 49 | Low | Low |
| BR | [redacted] | 1.68 | 1.17 | £35,910 | 2.95 | 1.64 | £21,910 | 78 | Low | Medium |
| Chl | [redacted] | 1.72 | 1.14 | £55,471 | 2.91 | 1.67 | £33,224 | 0 | Assumption - no evidence available | |
| Chl+R | [redacted] | 1.38 | 0.92 | £66,267 | 3.25 | 1.89 | £35,082 | 0 | Assumption - no evidence available | |
| Steroids+R | [redacted] | 2.08 | 1.42 | £23,689 | 2.55 | 1.38 | £17,106 | 29 | Low | Medium |
| Ofatumumab | [redacted] | 1.17 | 0.85 | £8,323 | 3.46 | 1.96 | £4,254 | 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<br>* Study 116 rituximab plus placebo survival data used as a proxy in the absence of external data for corticosteroids |

Following correspondence with the company, they undertook additional modelling for the FCR arm of this comparison, relaxing the assumption of a common shape parameter with the rituximab monotherapy arm of Study 116 (Table 45). This was particularly important for the FCR comparison as the fixed shape assumption led to a very poor fit between the model and data. This more appropriate distributional assumption led to an increase in the ICER for IR versus FCR, though this increase was not substantial.

**Table 45. Different approaches to exploratory comparison to FCR**

| Survival curve estimation method | Costs | QALYs | Incremental Costs | Incremental QALYs | ICER (IR versus comparator) |
|---|---|---|---|---|---|
| Common shape to Study 116 IR survival assumed | [redacted] | 0.40 | [redacted] | 2.41 | £26,215 |
| Best statistical model fit to KM data from Badoux et al. | [redacted] | 0.24 | [redacted] | 2.57 | £28,242 |
| Weibull model fit to KM data from Badoux et al. | [redacted] | 0.19 | [redacted] | 2.61 | £29,350 |

In the view of the ERG, the model with the best statistical fit to the Kaplan-Meier data is the most appropriate one to use, and the ERGs additional analyses all made used of this functional form for the FCR overall survival data, rather than the original models assuming a constant shape parameter.

### 5.2.12 Subgroup analysis

The company also present a subgroup analysis, focusing only on those patients from Study 116 who have 17p deletions or TP53 mutations. This involves calculating OS, PFS and ORRs specific to this subgroup, but leaving all other elements of the model unchanged.

**Table 46. Subgroup results, IR versus rituximab monotherapy, patients with 17p deletion or TP53 mutation**

| | | | | Incremental | | | |
|---|---|---|---|---|---|---|---|
| | Costs | Life Years | QALYs | Costs | Life Years | QALYs | ICER |
| Rituximab | [redacted] | 0.98 | 0.64 | | | | |
| IR | [redacted] | 3.57 | 2.31 | £33,653 | 2.59 | 1.67 | £20,200 |
| **Key:** ICER, incremental cost effectiveness ratio; IR, idelalisib with rituximab; QALY, quality adjusted life year | | | | | | | |

**Table 47. Subgroup results, IR versus BSC, patients with 17p deletion or TP53 mutation**

| | Costs | Life Years | QALYs | Incremental | | | ICER |
|---|---|---|---|---|---|---|---|
| | | | | Costs | Life Years | QALYs | |
| BSC | [redacted] | 0.98 | 0.64 | | | | |
| IR | [redacted] | 3.57 | 2.31 | £45,887 | 2.59 | 1.67 | £27,543 |
| **Key:** BSC, best supportive care; ICER, incremental cost effectiveness ratio; IR, idelalisib with rituximab; QALY, quality adjusted life year | | | | | | | |

**Table 48. Subgroup results, IR versus ofatumumab monotherapy, patients with 17p deletion or TP53 mutation**

| | Costs | Life Years | QALYs | Incremental | | | ICER |
|---|---|---|---|---|---|---|---|
| | | | | Costs | Life Years | QALYs | |
| Ofatumumab | [redacted] | 0.98 | 0.64 | | | | |
| IR | [redacted] | 3.57 | 2.31 | £11,772 | 2.59 | 1.67 | £7,066 |
| **Key:** ICER, incremental cost effectiveness ratio; IR, idelalisib with rituximab; QALY, quality adjusted life year | | | | | | | |

Idelalisib with rituximab maintains a clear clinical improvement over the three alternative treatments considered in this subgroup, but the ICERs for this subgroup are somewhat higher than those for the full trial population. It is important to note that this Study 116 subgroup comprises patients with 17p deletions or TP53 mutations who have received prior treatment, and not the treatment naive population specified in the NICE scope, and therefore care should be taken when interpreting these results.

### 5.2.13 Model validation and face validity check

The company present validity checks for their model, comprising comparisons of model predicted OS, PFS and ToT with data from Study 116 (Table 49). Results from the model and trial are similar, with the model seeming to slightly underestimate PFS for both arms of the trial, but since the magnitude of this underestimate is greater in the idelalisib arm, this discrepancy can be regard as a conservative one.

**Table 49. Summary of model results compared with clinical data (months)**

| Outcome | IR Clinical trial result | IR Model result | R Clinical trial result | R Model result |
|---|---|---|---|---|
| Median ToT | 16.1 | 15.4 | Not reported | 5.1 |
| Median PFS | 19.4 | 18.2 | 6.5 | 6.0 |
| Median OS | Not reached | 45.1 | [redacted] | 13.6 |
| **Key:** IR, idelalisib with rituximab; OS, overall survival; PFS, progression free survival; ITT, intent to treat; R, rituximab; | | | | |

| | | |
|---|---|---|
| RPSFT, rank preserving structural failure time; ToT, time on treatment | | |

Also reported are Markov model traces, which shown proportions of people in each state of the model over time (Figure 16 and Figure 17) and QALY accumulation plots, which show how QALYs are accumulated in both of the models over time, stratified by state (Figure 18 and Figure 19). These results are consistent with trial data from Study 116, the model described by the company and the expected clinical course of the disease. Similar trace plots were not presented for the other treatment alternatives but can be derived from model supplied by the company, and the same broad patterns occur in each model, scaled according to the PFS and OS parameters estimated for that treatment.

There were no discrepancies found between the models reported in the company submission, and the copy of the model given to the ERG, nor were there any discrepancies between the results obtained by re-running analyses from the submitted model and those reported in the manuscript.

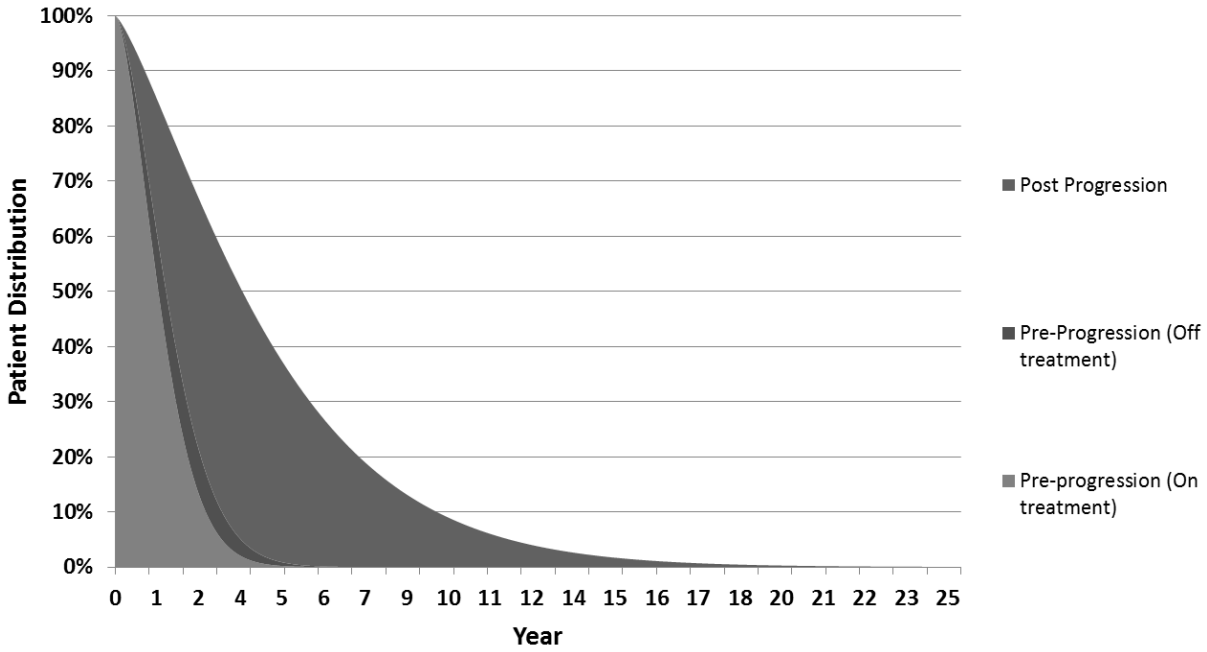


**Figure 16. Markov Trace, IR**

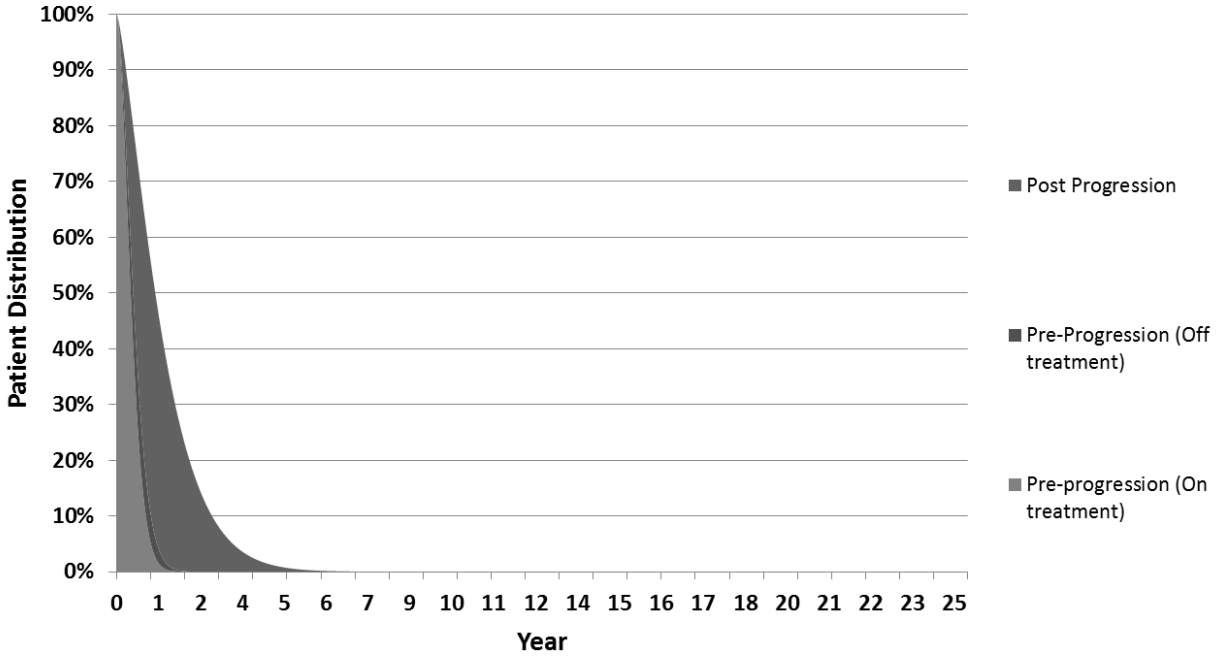


**Figure 17. Markov Trace, R**

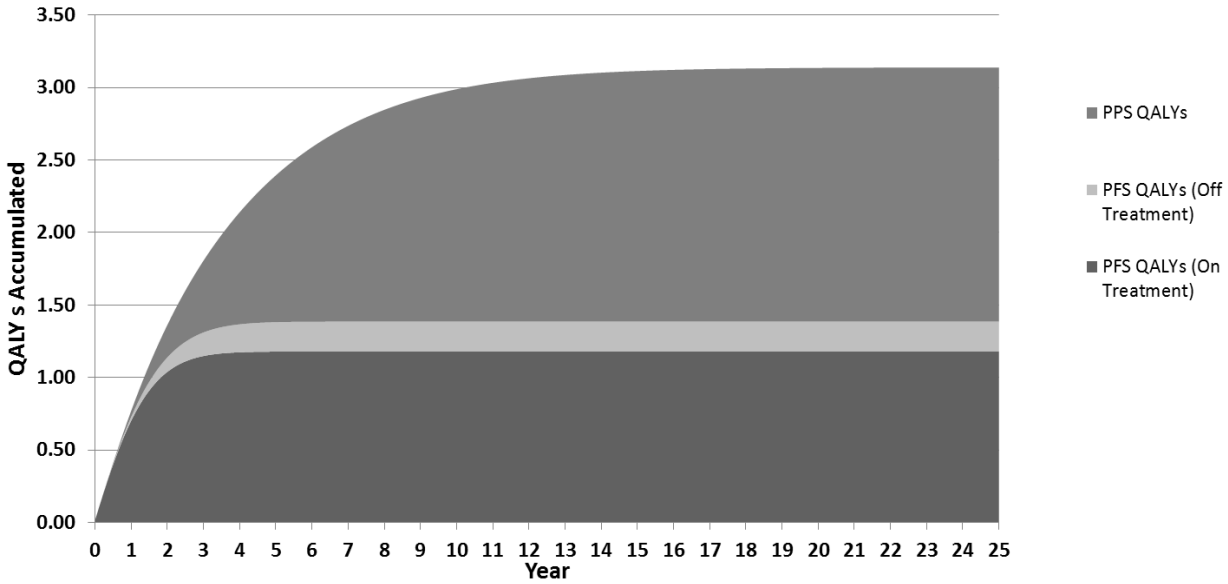


**Figure 18. QALY accumulation over time, IR**

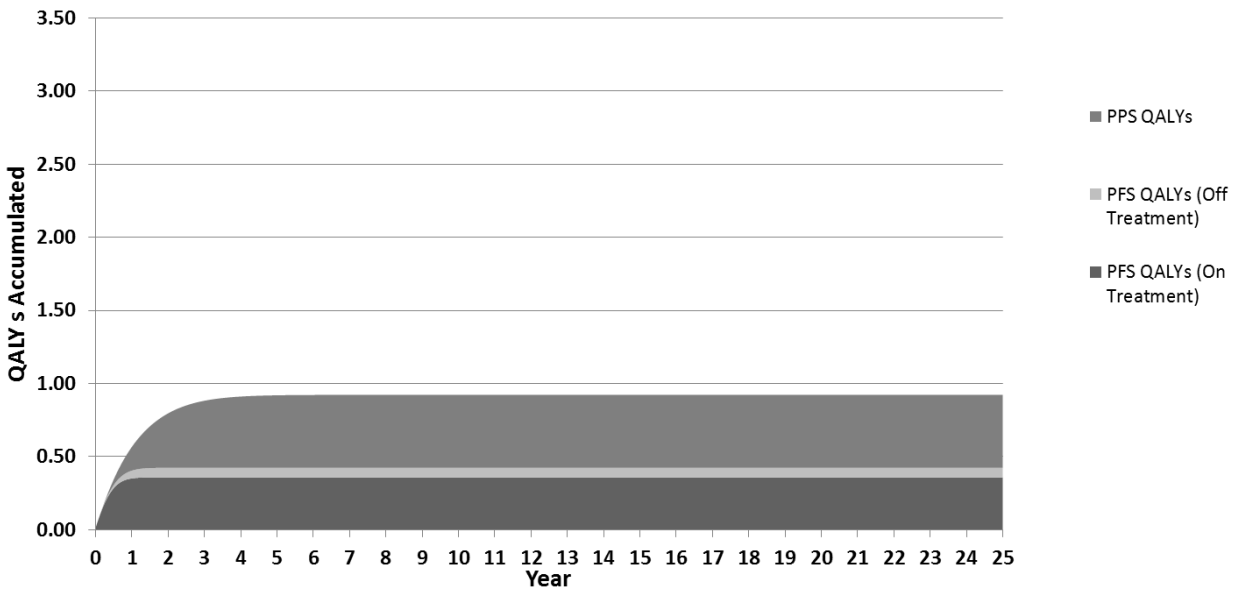


**Figure 19. QALY accumulation over time, R**

Superseded see erratum

**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, rather than assuming all patients complete the full course. For treatments other that IR and R, patients 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.

Results, comparable to those reported in section 5.2.9 for the company's base case model are given below.

**Table 50. ERG Base case results, IR versus R**

| | Costs | Life Years | QALYs | Incremental | | | ICER |
|---|---|---|---|---|---|---|---|
| | | | | Costs | Life Years | QALYs | |
| Rituximab | [redacted] | 1.39 | 0.91 | | | | |
| IR | [redacted] | 3.66 | 2.35 | £24,335 | 2.27 | 1.44 | £16,947 |
| **Key:** ICER, incremental cost effectiveness ratio; IR, idelalisib with rituximab, QALYs, quality adjusted life year | | | | | | | |

**Table 51. ERG Base case results, IR versus BSC**

| | Costs | Life Years | QALYs | Incremental | | | ICER |
|---|---|---|---|---|---|---|---|
| | | | | Costs | Life Years | QALYs | |
| BSC | [redacted] | 1.39 | 0.91 | | | | |
| IR | [redacted] | 3.66 | 2.35 | £37,418 | 2.27 | 1.44 | £26,058 |
| **Key:** ICER, incremental cost effectiveness ratio; IR, idelalisib with rituximab, QALYs, quality adjusted life year<br>This model assumes equal efficacy of rituximab to best supportive care | | | | | | | |

**Table 52. ERG Base case results, IR versus ofatumumab**

| | Costs | Life Years | QALYs | Incremental | | | ICER |
|---|---|---|---|---|---|---|---|
| | | | | Costs | Life Years | QALYs | |
| Ofatumumab | [redacted] | 1.39 | 0.91 | | | | |
| IR | [redacted] | 3.66 | 2.35 | £1,132 | 2.27 | 1.44 | £788 |
| **Key:** ICER, incremental cost effectiveness ratio; IR, idelalisib with rituximab, QALYs, quality adjusted life year<br>This model assumes equal efficacy of rituximab to ofatumumab | | | | | | | |

**Table 53. Exploratory comparison to treatments outside of Study 116, using external clinical data**

| | | | | Incremental (IR versus comparator) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Regimen** | **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** |
| FCR | [redacted] | 0.32 | 0.24 | £71,177 | 3.34 | 2.11 | £33,795 | 284 | Low | High |
| B | [redacted] | 2.04 | 1.42 | £48,821 | 1.61 | 0.92 | £52,815 | 49 | Low | Low |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 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 |
| Ofatumu mab | [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.

Superseded see erratum

**Table 54. 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 55. 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 initially respond 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.

Superseded see erratum

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 56. 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, | 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.

**ERG summary**

- The changes made by the ERG to the company's base case assumptions slightly increased the ICERs for idelalisib versus the various treatment alternatives, but this increase was not substantial.

- Uncertainty in the adjustment factors used for comparisons other than rituximab monotherapy, ofatumumab monotherapy and best supportive care do not appear to lead to uncertainties in the outputs generated.
- The model is highly sensitive to the levels of IVIG therapy needed in the model, particularly for responders. If the models 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.

### *5.4 Conclusions of the cost-effectiveness section*

The company submission is based around an economic analysis of idelalisib with rituximab versus rituximab monotherapy, based primarily on a single trial, Study 116.[1] With the exception of some specific sources of uncertainty that are not quantified by the company (discussed below), the model submitter seems to provide a relatively unbiased estimate of the ICER for this comparison, in the Study 116 population. Alterations made by the ERG to some of the company's base case assumptions did not result in substantial changes to the ICER for this comparison.

There are several important sources of uncertainty which are not adequately discussed or justified in the company submission. First, the model contains an assumption that the benefits of treatment persist both after the time horizon of the trial and post treatment discontinuation. No attempt is made to assess the impact of this assumption, which must be considered a very optimistic one, and one which maximises the treatment benefit of idelalisib. Secondly, 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.

Also, there are a number of resource use parameters which are based not on data but clinical judgment and the model ICERs are extremely sensitive to changes in these parameters, in particular the frequency of IVIG therapy in patients who initially respond to treatment. The base case assumption used in the model once again appears to favour idelalisib, with an assumption of no IVIG therapy being needed for responders for the entire time they remain in the PFS state. When interpreting the results, it is important to consider the impact of these three key sources of uncertainty in the ICER, and the impact any alternative assumptions would make.

It is also important to note that neither the treatment comparators nor the modelled population are exactly as in the NICE scope. A lack of data precluded robust comparisons to many treatments currently used in the NHS, though attempts were made to produce such comparisons, using the best available methods, which are nevertheless considerably less robust than a formal indirect comparison

would have been, had one been possible. Despite the limitation in these comparisons, such as the difficulty in adjusting for differing trial designs and baseline patient populations, it may nonetheless be important to consider the results of these analyses, as otherwise decisions would be made on the basis of a comparison solely with rituximab monotherapy, not a relevant comparator in the UK.

Finally, the population modelled is considerably older and sicker than the UK CLL population, and has used a larger number of prior therapies at baseline. Whilst it is not possible to quantitatively adjust for the differences in patient population, consideration should be given to whether the same treatment benefit would be expected to occur in a younger and fitter population. 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.

### *5.5 Impact on the ICER of additional analyses undertaken by the ERG*

Alterations to the base case assumptions made by the ERG moderately increased many of the ICERs reported, with the ICER for IR versus R increasing from £13,634 per QALY to £16,947 per QALY. This change was primarily driven by reducing the duration of idelalisib treatment benefit from a lifetime to 5 years. The final best estimates of the ICERs for idelalisib with rituximab, accounting for uncertainty that could be quantitatively modelled were:

- £16,947 per QALY versus rituximab monotherapy
- £26,058 per QALY versus best supportive care
- £5,355 per QALY versus ofatumumab monotherapy
- £24,065 per QALY versus steroids plus rituximab
- £29,548 per QALY versus bendamustine with rituximab
- £33,795 per QALY versus FCR
- £44,315 per QALY versus chlorambucil monotherapy
- £45,445 per QALY versus chlorambucil with rituximab
- £52,815 per QALY versus bendamustine monotherapy

The equivalent ICERs, restricting to the subset of the Study 116 population with 17p deletion or TP53 mutation, were:

- £23,405 per QALY for idelalisib with rituximab versus rituximab monotherapy
- £32,182 per QALY for idelalisib with rituximab versus best supportive care

- £7,709 per QALY for idelalisib with rituximab versus ofatumumab monotherapy
- £34,062 per QALY for idelalisib with rituximab versus steroids plus rituximab
- £37,191 per QALY for idelalisib with rituximab versus FCR
- £38,861 per QALY for idelalisib with rituximab versus bendamustine with rituximab
- £56,811 per QALY for idelalisib with rituximab versus chlorambucil with rituximab
- £57,589 per QALY for idelalisib with rituximab versus chlorambucil monotherapy
- £75,925 per QALY for idelalisib with rituximab versus bendamustine monotherapy

Key sources of uncertainty in these estimates, together with the current assumptions utilised in the model and the likely impact of varying those assumptions, are summarised in the table below (see Table 57. Key sources of uncertainty in ICERs). These additional uncertainties should always be borne in mind when interpreting the ICERs given above.

**Table 57. Key sources of uncertainty in ICERs**

| **Parameter/model feature** | **Current assumption** | **Likely impact of varying assumption** |
|---|---|---|
| Patient population | 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 | 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 |
| OS and PFS extrapolation over time. | Treatment benefit persists for five years post treatment initiation | Any reduction in the treatment benefit after either of these events will result in idelalisib becoming less cost-effective than it currently is, versus all comparators. |
| Adjustment for crossover in rituximab monotherapy arm of Study 116. | Idelalisib monotherapy has the same efficacy as idelalisib with rituximab. | If idelalisib monotherapy is less effective than idelalisib with rituximab, idelalisib will become less cost-effective than it currently appears. |
| Clinical outcomes for ofatumumab monotherapy | Ofatumumab monotherapy has equal efficacy and safety to rituximab monotherapy | Unclear. Depend on whether ofatumumab is considered more or less effective than rituximab |
| Resource use frequency | Many items of resource use for the pre-progressive state were derived from estimates from clinical advisors, not data | See tables AE and AF, section 5.3 |

| | | |
|---|---|---|
| Adjustment for differences in baseline populations (comparisons outside Study 116) | The proportional hazards models from Badoux et al.[16] can adequately adjust for baseline population differences | Unclear. There is likely to be considerable error in the adjustment factors calculated, but it is unclear in which direction that error would lie. |

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.

# 6 End of life

The company provide a justification; again based primarily on Study 116, for why they believe that idelalisib with rituximab should be considered under end of life criteria in the relapsed or refractory population (Table 58).

**Table 58. End of life criteria**

| Criterion | Data available |
|---|---|
| The treatment is indicated for patients with a short life expectancy, normally less than 24 months | **For relapsed CLL patients:**<br>**ITT**: Mean OS in Study 116 (from restricted means analysis): IR: [redacted]months (95% CI: [redacted]; placebo + rituximab: [redacted]months (95% CI: [redacted]<br>**RPSFT analysis**: Mean OS in Study 116 (from restricted means analysis): IR: [redacted]months (95% CI: [redacted]; placebo + rituximab: [redacted]months (95% CI: [redacted]<br>**For untreated patients**<br>Mean OS (restricted means analysis): [redacted]months (SE: [redacted] Results not available for the 17p deletion / TP53 population as no deaths seen during the trial.<br>In standard clinical practice, patients with a 17p deletion or TP53 mutation are expected to survive for 2-3 years. |
| There is 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 | **For relapsed CLL patients:**<br>**ITT**: Mean OS in Study 116 (from restricted means analysis): IR: [redacted]months (95% CI: [redacted]; placebo + rituximab: [redacted]months (95% CI: [redacted]<br>**RPSFT analysis**: Mean OS in Study 116 (from restricted means analysis): IR: [redacted]months (95% CI: [redacted]; placebo + rituximab: [redacted]months (95% CI: [redacted] |
| The treatment is licensed or otherwise indicated for small patient populations | **CLL indications (See section 6):**<br>Patients with CLL who require treatment and who have received one prior treatment: 363<br>Patients with CLL who have 17p deletion or TP53 mutation: 203<br><br>**Follicular lymphoma:**<br>Idelalisib is also indicated as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment.<br><br>Based on data published by Cancer Research UK using the Haematological Malignancy Research Network (HMRN) the estimated yearly number of FL patients in England and Wales is 1,677. The number requiring treatment at third line and subsequent settings is 384. |
| **Key:** CLL, chronic lymphocytic leukemia; IR, idelalisib with rituximab; ITT, intent to treat; NHS, National Health Service; OS, overall survival; RPSFT, rank preserving structural failure time; SE, standard error | |

The second and third criteria, concerning an at least 3 months extension to life (versus rituximab monotherapy) and a small treatment population, seem likely to be met. However, it is much less clear

that the first criterion, a short initial life expectancy, is met. The company bases its argument on a restricted means analysis from Study 116, but it seems more consistent to look at the results of the cost-effectiveness model submitted, as these form the basis of the main arguments concerning the long term effectiveness of idelalisib. Mean undiscounted life years from this model are 1.39 years for rituximab monotherapy and 4.63 years for idelalisib. However, as elsewhere in this report, it must be borne in mind these are considerably sicker patients than the UK CLL population, with the control group given a treatment likely to be worse than UK standard care. The mean undiscounted life years for treatments potentially more relevant to the UK population (e.g. bendamustine) are considerably higher than rituximab monotherapy (2.08 life years for bendamustine monotherapy), and this is still in a much sicker population than the UK, implying that in the UK population baseline life expectancy would be considerably greater in 2 years.

**ERG summary**

- Considering only the study population and treatment from Study 116, idelalisib with rituximab appears to meet the end of life criteria set out by NICE.
- However, in the considerably healthier UK CLL population, making use of the best available comparators, rather than suboptimal rituximab monotherapy, it seems highly unlikely that the criteria for a short baseline life expectancy would be met for this group.

# 7 Overall conclusions

### *Clinical effectiveness evidence*

Search strategies were well constructed and updated on request. The ERG does not believe that any important trials of the clinical effectiveness and safety of idelalisib have been omitted. Searches included all comparators from the NICE scope for relapsed or refractory CLL patients (except best supportive care). The search for clinical studies in untreated CLL patients with 17p deletion or TP53 mutation included only the company's choice of comparators. All searches were limited to English language publications.

Idelalisib was used only in one phase-III RCT (study 116; Furman et al., 2014)[1] and this study is the single source of evidence most relevant to the decision problem, however the ERG believes that its study sample was overly selective and overrepresented older, frailer, and more difficult to treat patients with multiple co-morbidities who were unsuitable for immune chemotherapy. About half of the participants were CLL patients with 17p deletion and TP53 mutation, a subgroup with a worse CLL prognosis, for whom standard cytotoxic therapy was not suitable. Also, in the study this subgroup of patients had already been treated which was not in line with the NICE scope.

Given all the above issues, the representativeness of the study 116 sample in reference to the CLL population as outlined in the NICE scope may be questionable. Another concern refers to the choice of rituximab monotherapy as a relevant comparator in study 116. The ERG note that rituximab is not standard therapy in the UK. The NICE scope does not include this drug as a comparator. Study 116 was terminated early for benefit based on results suggested by interim analysis.[1] There has been accumulation of evidence showing that trials terminated early for benefit tend to overestimate beneficial treatment effects.[7] Moreover, in study 116,[1] baseline quality of life (EQ-5D was higher in the idelalisib as compared to the control arm which may also have overestimated the true benefit of idelalisib.

The ERG are in agreement with the company submission in that the available evidence does not permit a network meta-analysis to be conducted. Specifically, it was not possible to link idelalisib plus rituximab with other relevant comparators (as specified in the NICE scope) due to insufficient evidence, lack of relevant comparators, and heterogeneity across the trial populations. For treatment naive 17p/TP53 mutation sub-group analysis, lack of data precluded formal synthesis, instead other published evidence with a number of assumptions was adduced. The ERG consider that these estimates tended to favour idelalisib in combination with rituximab in terms of PFS and overall survival. In the absence of formal modelling and data availability for this sub-group of patients it is unclear what data underlies the effectiveness estimates of idelalisib plus rituximab to feed into the economic model.

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

### *Cost-effectiveness evidence*

Judging both from the model submitted by the manufacturer and the ERG's modified model, which includes more conservative assumptions, idelalisib with rituximab appears to provide substantial long-term benefits over rituximab monotherapy, in the Study 116 population. This conclusion appears to be robust to all the parameter uncertainties that were included in the model. Nevertheless, there are several difficulties in extrapolating the results from these analyses to the relevant decision problem in the UK. Specifically

- Will idelalisib with rituximab be as cost-effective in the generally healthier UK CLL population as it appears to be in the older and sicker population, who have taken more previous therapies, in Study 116?
- 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.
- 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 scope.
- The presented results are highly sensitive to clinical expert derived assumptions about treatment frequency, and in particular the considerably, and permanent, lower long term costs of managing responders than non-responders. Small changes to these parameter values make idelalisib much less cost-effective, but in the absence of data it is hard to know what the most plausible value for these parameters is.

In the absence of robust data to address these important uncertainties, it is difficult to provide robust estimates of the cost-effectiveness of idelalisib with rituximab, in the UK treatment population.

### *Implications for research*

Judging from the only pivotal trial (Study 116) , the clinical effectiveness of idelalisib, when administered in combination with rituximab is not in doubt and represents a step-change in the management of the high-risk patients with a 17p deletion or TP53 mutation, where chemo-

immunotherapy has very poor efficacy, but questions remain about the use of idelalisib in comparison to standard therapies currently used in the UK for adults with chronic lymphocytic leukaemia and in the management of patients with a 17p deletion or TP53 mutation who are treatment naive.

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# Appendix A

**Refractory or relapsed CLL population**

**Table 59. Risk of bias in study 116[1] - ERG assessment with Cochrane risk of bias tool**

| Bias domain | Source of bias | Support for judgment* | Authors' judgment** |
|---|---|---|---|
| Selection bias | **Random sequence generation**<br>• Low risk of bias (truly random process, random number table; computer random number generator)<br>• High risk of bias (non-random process, date of birth; hospital or clinic record number)<br>• Unclear risk of bias | Randomisation was carried out appropriately using an Interactive Web Response System (the company submission; page 140) – no concern | Low |
| | **Allocation concealment**<br>• Low risk of bias (telephone or central randomisation; consecutively numbered sealed opaque envelopes)<br>• High risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth)<br>• Unclear risk of bias | Fixed block centralised randomisation (the company submission; Table 21) – no concern<br><br>Allocation of treatment was concealed by use of a matched placebo for the idelalisib comparison (the company submission; page 140) – no concern | Low |
| Performance bias | **Blinding of participants and personnel**<br>Assessment of blinding separate for participants and staff<br>• Low risk of bias(blinded, or lack of blinding could not have affected the results)<br>• High risk of bias<br>• Unclear risk of bias | Placebo: matching tablet (the company submission; Table 21) – no concern<br><br>The trial used a double-blind design so that care providers, participants and outcome assessors were all blinded to treatment (the company submission; page 140) – no concern | Low |

| | | | |
|---|---|---|---|
| **Detection bias** | **Blinding of outcome assessors**<br>• Low risk of bias (blinded, or lack of blinding could not have affected the results; outcomes recorded by outcome assessors with no knowledge of group assignment; self-reported outcome data by mailed questionnaire)<br>• High risk of bias<br>• Unclear risk of bias | Response and disease progression for each patient, and the dates of occurrence, were reviewed by an independent committee whose members (including two radiologists and a haematologist or oncologist) were blinded to study-group assignments (the company submission; Table 21) – no concern<br><br>The trial used a double-blind design so that care providers, participants and outcome assessors were all blinded to treatment (the company submission; page 140) – no concern | Low |
| **Attrition bias** | **Incomplete outcome data**<br>• Low risk of bias (Reported numbers included in the analysis at each stage, withdrawals, dropouts, attrition and exclusions from the analysis, protocol deviations for the study, and for each outcome or class of outcomes, with reasons and high data completeness)<br>• High risk of bias (Did not report numbers included in the analysis at each stage, or reported numbers but high levels of missing data or imbalances between groups)<br>• Unclear risk of bias | Relevant information cannot be found – concern | Unclear |
| **Reporting bias** | **Selective reporting of the outcome, subgroups, or analysis**<br>• Low risk of bias (all of the study's pre-specified outcomes and all expected outcomes of interest were reported)<br>• High risk of bias (where not all the study's | Complete response rates specified in the Methods section are not reported – concern | High |

| | | | |
|---|---|---|---|
| | pre-specified outcomes were reported; one or more reported primary outcomes were not pre-specified; outcomes of interest were reported incompletely and so could be used; study failed to include results of a key outcome that would were expected to were reported)<br>• Unclear risk of bias | | |
| **Other bias** | **Any important concerns about other possible sources of bias**<br>• Low risk of other sources of bias (free of other problems that could put the study at risk of bias)<br>• High risk of other sources of bias (Funding source, adequacy of statistical methods used, type of analysis [Intention-to-treat; Per protocol], baseline imbalance in important characteristics)<br>• Unclear risk of other sources of bias | Baseline disease and demographic characteristics were more or less balanced between the treatment groups. There were no unexpected imbalances in terms of drop-outs between treatment groups (the company submission; page 140) – no concern<br><br>ITT used for primary outcomes (the company submission; Table 24) – no concern<br><br>Post-trial crossover of rituximab monotherapy recipients to idelalisib arm were not included in the main analysis of study 116[1] – no concern<br><br>Quality of life at baseline was higher in the idelalisib arm - concern<br><br>Early terminated trial may overestimate the treatment benefit[7] – concern | High |

[*] Statement, description or quote supporting the judgment. [**] Low, high, or unclear risk of bias

**Table 60. Risk of bias in Robak (2010)[5] - ERG assessment with Cochrane risk of bias tool**

| Bias domain | Source of bias | Support for judgment* | Authors' judgment** |
|---|---|---|---|
| **Selection bias** | **Random sequence generation**<br>• Low risk of bias (truly random process, random number table; computer random number generator)<br>• High risk of bias (non-random process, date of birth; hospital or clinic record number)<br>• Unclear risk of bias | Not reported – concern | Unclear |
| | **Allocation concealment**<br>• Low risk of bias (telephone or central randomisation; consecutively numbered sealed opaque envelopes)<br>• High risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth)<br>• Unclear risk of bias | Not reported – concern | Unclear |
| **Performance bias** | **Blinding of participants and personnel**<br>Assessment of blinding separate for participants and staff<br>• Low risk of bias(blinded, or lack of blinding could not have affected the results)<br>• High risk of bias<br>• Unclear risk of bias | Not reported – concern | Unclear |
| **Detection bias** | **Blinding of outcome assessors**<br>• Low risk of bias (blinded, or lack of blinding could not have affected the results; outcomes recorded by outcome assessors with no knowledge of group assignment; self-reported outcome data by mailed questionnaire)<br>• High risk of bias<br>• Unclear risk of bias | All CT scans and clinical efficacy data underwent an independent review (Perceptive Informatics, Boston, MA) – no concern | Low |

| | | | |
|---|---|---|---|
| **Attrition bias** | **Incomplete outcome data**<br>• Low risk of bias (Reported numbers included in the analysis at each stage, withdrawals, dropouts, attrition and exclusions from the analysis, protocol deviations for the study, and for each outcome or class of outcomes, with reasons and high data completeness)<br>• High risk of bias (Did not report numbers included in the analysis at each stage, or reported numbers but high levels of missing data or imbalances between groups)<br>• Unclear risk of bias | Although data for missing outcomes were imputed, there were high proportions of participants that differed between the study groups who discontinued the drug or withdrew from the study – concern | Unclear |
| **Reporting bias** | **Selective reporting of the outcome, subgroups, or analysis**<br>• Low risk of bias (all of the study's pre-specified outcomes and all expected outcomes of interest were reported)<br>• High risk of bias (where not all the study's pre-specified outcomes were reported; one or more reported primary outcomes were not pre-specified; outcomes of interest were reported incompletely and so could be used; study failed to include results of a key outcome that would were expected to were reported)<br>• Unclear risk of bias | All pre-specified outcomes were reported in the Results section – no concern | Low |
| **Other bias** | **Any important concerns about other possible sources of bias**<br>• Low risk of other sources of bias (free of other problems that could put the study at risk of bias)<br>• High risk of other sources of bias (Funding source, adequacy of statistical methods used, type of analysis [Intention-to-treat; Per protocol], baseline imbalance in important characteristics) | No other serious issues– no concern | Low |

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|---|---|---|---|
| | • Unclear risk of other sources of bias | | |

[*] Statement, description or quote supporting the judgment

[**] Low risk of bias, high risk of bias, or unclear risk of bias

**Table 61. Risk of bias in Niederle (2013)[6] - ERG assessment with Cochrane risk of bias tool**

| Bias domain | Source of bias | Support for judgment* | Authors' judgment** |
|---|---|---|---|
| Selection bias | **Random sequence generation**<br>• Low risk of bias (truly random process, random number table; computer random number generator)<br>• High risk of bias (non-random process, date of birth; hospital or clinic record number)<br>• Unclear risk of bias | Computer-generated randomization lists, created by a block randomization method with variable block size, were used – no concern | Low |
| | **Allocation concealment**<br>• Low risk of bias (telephone or central randomisation; consecutively numbered sealed opaque envelopes)<br>• High risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth)<br>• Unclear risk of bias | Not reported – concern | Unclear |
| Performance bias | **Blinding of participants and personnel**<br>Assessment of blinding separate for participants and staff<br>• Low risk of bias(blinded, or lack of blinding could not have affected the results)<br>• High risk of bias<br>• Unclear risk of bias | Open-label – concern | High |
| Detection bias | **Blinding of outcome assessors**<br>• Low risk of bias (blinded, or lack of blinding could not have affected the results; outcomes recorded by outcome assessors with no knowledge of group assignment; self-reported outcome data by mailed questionnaire)<br>• High risk of bias<br>• Unclear risk of bias | Not reported – concern | Unclear |

| | | | |
|---|---|---|---|
| **Attrition bias** | **Incomplete outcome data**<br>• Low risk of bias (Reported numbers included in the analysis at each stage, withdrawals, dropouts, attrition and exclusions from the analysis, protocol deviations for the study, and for each outcome or class of outcomes, with reasons and high data completeness)<br>• High risk of bias (Did not report numbers included in the analysis at each stage, or reported numbers but high levels of missing data or imbalances between groups)<br>• Unclear risk of bias | Low proportion of protocol violation: 4.0% – no concern | Low |
| **Reporting bias** | **Selective reporting of the outcome, subgroups, or analysis**<br>• Low risk of bias (all of the study's pre-specified outcomes and all expected outcomes of interest were reported)<br>• High risk of bias (where not all the study's pre-specified outcomes were reported; one or more reported primary outcomes were not pre-specified; outcomes of interest were reported incompletely and so could be used; study failed to include results of a key outcome that would were expected to were reported)<br>• Unclear risk of bias | All specified outcomes in the Methods section reported in Results section – no concern | Low |
| **Other bias** | **Any important concerns about other possible sources of bias**<br>• Low risk of other sources of bias (free of other problems that could put the study at risk of bias)<br>• High risk of other sources of bias (Funding source, adequacy of statistical methods used, type of analysis [Intention-to-treat; Per protocol], baseline imbalance in important characteristics) | No additional major issues – no concern | Low |

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|---|---|---|---|
| | • Unclear risk of other sources of bias | | |

[*] Statement, description or quote supporting the judgment

[**] Low risk of bias, high risk of bias, or unclear risk of bias

**Untreated CLL patents with 17p deletion or T53 mutation**

**Table 62. Risk of bias in Hillmen (2007)[8] - ERG assessment with Cochrane risk of bias tool**

| Bias domain | Source of bias | Support for judgment* | Authors' judgment** |
|---|---|---|---|
| **Selection bias** | **Random sequence generation**<br>• Low risk of bias (truly random process, random number table; computer random number generator)<br>• High risk of bias (non-random process, date of birth; hospital or clinic record number)<br>• Unclear risk of bias | Not reported – concern | Unclear |
| | **Allocation concealment**<br>• Low risk of bias (telephone or central randomisation; consecutively numbered sealed opaque envelopes)<br>• High risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth)<br>• Unclear risk of bias | Not reported – concern | Unclear |
| **Performance bias** | **Blinding of participants and personnel**<br>Assessment of blinding separate for participants and staff<br>• Low risk of bias(blinded, or lack of blinding could not have affected the results)<br>• High risk of bias<br>• Unclear risk of bias | The trial was open label (participants and personnel were aware of the assigned treatment) – concern | High |
| **Detection bias** | **Blinding of outcome assessors**<br>• Low risk of bias (blinded, or lack of blinding could not have affected the results; outcomes recorded by outcome assessors with no knowledge of group assignment; self-reported outcome data by mailed questionnaire)<br>• High risk of bias<br>• Unclear risk of bias | Outcome assessors were independent panel who were blind to the treatment assignment – no concern | Low |

| | | | |
|---|---|---|---|
| **Attrition bias** | **Incomplete outcome data**<br>• Low risk of bias (Reported numbers included in the analysis at each stage, withdrawals, dropouts, attrition and exclusions from the analysis, protocol deviations for the study, and for each outcome or class of outcomes, with reasons and high data completeness)<br>• High risk of bias (Did not report numbers included in the analysis at each stage, or reported numbers but high levels of missing data or imbalances between groups)<br>• Unclear risk of bias | Outcome data were available for all or most of the patients – no concern | Low |
| **Reporting bias** | **Selective reporting of the outcome, subgroups, or analysis**<br>• Low risk of bias (all of the study's pre-specified outcomes and all expected outcomes of interest were reported)<br>• High risk of bias (where not all the study's pre-specified outcomes were reported; one or more reported primary outcomes were not pre-specified; outcomes of interest were reported incompletely and so could be used; study failed to include results of a key outcome that would were expected to were reported)<br>• Unclear risk of bias | All pre-specified outcomes reported in the Results section – no concern | Low |
| **Other bias** | **Any important concerns about other possible sources of bias**<br>• Low risk of other sources of bias (free of other problems that could put the study at risk of bias)<br>• High risk of other sources of bias (Funding source, adequacy of statistical methods used, type of analysis [Intention-to-treat; Per protocol], baseline imbalance in important characteristics) | No additional important issues that would impact the risk of bias – no concern | Low |

| | | | |
|---|---|---|---|
| | • Unclear risk of other sources of bias | | |

[*] Statement, description or quote supporting the judgment

[**] Low risk of bias, high risk of bias, or unclear risk of bias

**Table 63. Quality Assessment of Study 101-08 (Downs and Black modified tool[6])**

| **Study Number/Acronym** | **Study 101-08** |
|---|---|
| **Reporting** | |
| Is the hypothesis/aim/objective of the study clearly described? | Yes: The purpose of the study is clearly outlined on Clinicaltrials.gov |
| Are the main outcomes to be measured clearly described in the Introduction or Methods section? | Yes: Clinicaltrials.gov and the ad board slides clearly describe the main outcomes of interest |
| Are the characteristics of the patients included in the study clearly described? | Yes: Clinicaltrials.gov and the ad board slides clearly describe the patient characteristics |
| Are the interventions of interest clearly defined? | Yes: Clinicaltrials.gov and the ad board slides clearly describe the treatments of interest |
| Are the distributions of principal confounders in each group of subjects to be compared clearly described? | Yes |
| Are the main findings of the study clearly described? | Yes |
| Does the study provide estimates of the random variability in the data for the main outcomes? | Yes |
| Have all important adverse events that may be a consequence of the intervention been reported? | Yes: The ad board slides capture all important AEs |
| Have the characteristics of patients lost to follow-up been described? | No |
| Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes, except where the probability value is <0.001? | No: No p-values are reported |
| **External Validity** | |
| Were the subjects asked to participate in the study representative of the entire population from which they were recruited? | No: In general patients were older and sicker than the representative patient in the overall population |
| Were those subjects who were prepared to participate representative of the entire population from which they were recruited? | Unclear |
| Were the staff, places and facilities where the patients were treated representative of the treatment the majority of patients receive? | Yes |
| **Internal Validity - bias** | |
| Was an attempt made to blind study subjects to the intervention they have received? | No: The study was single-arm and open-label |
| Was an attempt made to blind those measuring the | No: The study was single-arm and open-label |

| | |
|---|---|
| main outcomes of the intervention? | |
| If any of the results of the study were based on "data dredging" was this made clear? | Yes: All results were pre-planned |
| In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies is the time period between the intervention and outcome the same for cases and controls? | Unclear |
| Were the statistical tests used to assess the main outcomes appropriate? | Yes |
| Was compliance with the interventions reliable? | Yes |
| Were the main outcome measures used accurate (valid and reliable)? | Yes |
| **Internal validity – confounding (selection bias)** | |
| Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? | No: Patients were recruited from multiple hospitals |
| Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? | Yes |
| Were study subjects randomized to intervention groups? | No: Non-randomised, single-arm study |
| Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? | NA |
| Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? | Unclear |
| Were losses of patients to follow-up taken into account? | Yes |
| **Power** | |
| Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? | Yes |
| € Adapted from Downs and Black (1998) *The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions*[3] **Notes:** Quality assessment was based on the Coutre (2013) abstract from ASH, an advisory board presentation (Gilead, 2014), data available on www.clinicaltrials.gov and the CSR where not available from these sources. | |