# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single technology appraisal

## Idelalisib for treating chronic lymphocytic leukaemia [ID764]

## Company evidence submission

**February 2015**

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## Abbreviation List

| | |
|---|---|
| A | alemtuzumab |
| Ag | antigen |
| AIC | Akaike Information Criterion |
| ASCT | allogeneic stem cell transplant |
| B | bendamustine |
| BCR | B-cell receptor |
| BCSH | British Committee for Standards in Haematology |
| BID | twice daily |
| BSC | best supportive care |
| C | cyclophosphamide |
| CDF | Cancer Drugs Fund |
| CE | cost effectiveness |
| Chl | chlorambucil |
| CI | confidence interval |
| CIRS | cumulative illness rating scale |
| CLL | chronic lymphocytic leukaemia |
| CR | complete response |
| CT | computerised tomography |
| CSR | clinical study report |
| ECOG | Eastern Cooperative Oncology Group |
| EMA | European Medicines Agency |
| EPAR | European Public Assessment Report |
| ESMO | European Society for Medical Oncology |
| 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 |
| FDA | Food and Drug Administratiion |
| Hb | haemoglobin |
| HRQL | health-related quality of life |
| HSC | hematopoietic stem cell |

| | |
|---|---|
| I | idelalisib |
| IRC | independent review committee |
| IR | Idelalisib with rituximab |
| ITT | intent to treat |
| ICER | incremental cost-effectiveness ratio |
| IgVH | immunoglobulin variable region heavy chain |
| IV | intravenous |
| IWCLL | International Workshop on Chronic Lymphocytic Leukemia |
| IWRS | interactive web response system. |
| LDH | lactate dehydrogenase |
| M-CLL | mutated chronic lymphocytic leukaemia |
| MBL | monoclonal B-cell lymphocytosis |
| mg | milligram |
| N | number |
| NA | not applicable |
| NCCN | National Comprehensive Cancer Network |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NR | not reported |
| Of | ofatumumab |
| ORR | overall response rate |
| OS | overall survival |
| PAS | patient access scheme |
| PFS | progression-free survival |
| PO | Per oral |
| PR | partial response |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| PS | performance status |
| PSA | probabilistic sensitivity analysis |
| QALY | quality-adjusted life year |
| R | rituximab |
| RCT | randomised controlled trial |
| RPSFT | rank preserving structural failure time |

| | |
|---|---|
| SACT | Systemic Anti-Cancer Therapy |
| SAE | serious advers event |
| SCT | stem cell therapy |
| SD | standard deviation |
| SE | standard error |
| SLL | small lymphocytic lymphoma |
| ToT | time on treatment |
| U-CLL | unmutated chronic lymphocytic leukaemia |
| UK | United Kingdom |
| WHO | World Health Organization |

# 1 Executive summary

## *1.1 Statement of decision problem*

Table 1 presents the decision problem for this submission, including the final scope provided by the National Institute for Health and Care Excellence (NICE), the scope of this submission dossier, and the rationale for any differences between the NICE scope and what is presented within this dossier. In summary, the scope of the current submission is a health technology 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

## Table 1: 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)<br>• 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 | 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 chronic lymphocytic leukaemia associated with 17p deletion or TP53 mutation:<br>• Alemtuzumab<br>• Ofatumumab<br>• Best supportive care including steroids | 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 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 |

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope |
|---|---|---|---|
| | to ongoing NICE technology appraisal) | | 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 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. | As per the NICE scope | Not applicable |
| **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.[1] 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. | | | |

## 1.2 Description of the technology being appraised

**Table 2: Technology being appraised**

| | |
|---|---|
| **UK approved name and brand name** | UK approved name: Idelalisib<br>Brand name: Zydelig® |
| **Marketing authorisation/CE mark status** | Marketing authorisation granted 19th September 2014 |
| **Indications and any restriction(s) as described in the summary of product characteristics** | Idelalisib is indicated in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL):<br>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. |
| **Method of administration and dosage** | Recommended dose is 150mg twice daily (BID) orally. 100mg tablets are available for retreatment if required after side-effect management. |
| **Key:** BID, twice daily; CLL, chronic lymphocytic leukaemia | |

## 1.3 Summary of the clinical effectiveness analysis

**Disease burden**

CLL is an incurable disease that accounts for 1% of all new cancer cases in the UK.[2, 3] Currently, the median survival from diagnosis of CLL varies between 2 years and >10 years depending on disease stage and the presence of cytogenetic abnormalities such as 17p deletion or TP53 mutation.[4, 5] Patients with CLL experience various symptoms, including abnormal enlargement of the lymph nodes, liver and spleen; autoimmune cytopenias; 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.[6-8] As a result, CLL has a substantial negative impact on patients' health-related quality of life (HRQL).

**Idelalisib**

Idelalisib is a first-in-class, oral, highly selective treatment that has a marketing authorisation for two CLL patient populations:[9]

- Adult patients with CLL who have received at least one prior therapy. This is a heterogeneous patient population that includes frailer patients who are refractory to, or have quick relapse following, cytotoxic agents, with/without rituximab, and/or with multiple comorbidities, and who have few if any active treatment options remaining.
- Adult patients with CLL who have 17p deletion or TP53 mutation who are unsuitable for chemo-immunotherapy. This patient group do not respond well to chemo-immunotherapy since this is toxic to sensitive cells but not to cells that are resistant due to 17p deletion or TP53 mutation.[7, 10-12] The reason for this is that the normal function of the p53 protein is to detect DNA damage and initiate repair, cell-cycle arrest, senescence, or apoptosis, and conventional chemotherapy agents induce a p53-dependent DNA damage response. As a result, these agents are much less effective in patients with an absence of normal functioning p53 as a result of 17p deletions or TP53 mutations.

**UK treatment pathway**

Guidance is limited regarding the choice of the NICE-recommended treatments for patients with relapsed/refractory CLL. As such, NICE recommends repeat administration of fludarabine, cyclophosphamide and rituximab (FCR) unless the patient is refractory to fludarabine or has been previously treated with rituximab outside of the context of a clinical trial. Alternatively, NICE recommends oral fludarabine for patients who have failed on or are intolerant to first-line chemotherapy who would otherwise have received standard combination chemotherapy. In addition, in UK clinical practice, bendamustine or chlorambucil may be administered with rituximab in fitter patients, although this is unlikely to be used in patients with 17p deletion or TP53 mutation.[13] Furthermore, anti-CD20s such as rituximab and ofatumumab (although the latter is not recommended by NICE), or best supportive care (BSC) (which includes outpatient review, platelet transfusion for anaemia, inpatient stays, blood transfusion for thrombocytopenia, and/or immunoglobulin replacement) may also be used.

Currently, a wide range of treatments are used for the management of patients with relapsed/refractory CLL according to different clinician practices and individualised treatment approaches, and it is clear that there is no existing standard of care for these patients.[12] For example, in Study 116 (the pivotal, phase III clinical trial for idelalisib [NCT01539512]), a total of 46 unique treatment regimens were identified as being used in previous therapy lines for the enrolled patients who had been treated according to current guidelines.[14]

For the patients with poor prognostic markers, (i.e., with 17p deletion or TP53 mutation), current treatment choices are very limited because patients do not respond well to chemo-immunotherapy.[10, 12, 13] Both the British Committee for Standards in Haematology (BCSH) and European Society for Medical Oncology (ESMO) guidelines recommend that first-line treatment of the patients with CLL and a 17p deletion or TP53 mutation consist of alemtuzumab with or without high-dose pulsed steroids followed by allogeneic stem cell transplant (ASCT).[7, 10] However, alemtuzumab does not have a marketing authorisation in the European Union (EU) and is only available via a patient access scheme agreed between the European Medicines Agency (EMA) and the manufacturer, and there is uncertainty regarding is unclear how long alemtuzumab will be available in this manner, and alemtuzumab tolerability can be challenging with a toxicity considered similar to that of fludarabine.[12] Furthermore, the majority of CLL patients are not suitable for ASCT due to fitness or availability of donor. Management of these patients is clearly an area of high unmet need.

**Available clinical evidence for idelalisib with rituximab and treatments used in UK current care**

For relapsed or refractory CLL patients, the key evidence for idelalisib with rituximab is from Study 116, which is a robust, double-blind, phase III, randomised, controlled trial (RCT) versus placebo with rituximab, in older, heavily pre-treated patients from the US and Western Europe, with almost half (42.6%) of the patients with a 17p deletion or TP53 mutation[14]. 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. Given the scarcity of data available for comparator therapies, an extensive clinical consultation was conducted to inform assessment of the current UK treatment pathway and clinical and cost-effectiveness analysis.[1, 13 15]

Of note, Study 116 used rituximab monotherapy as a comparator to idelalisib with rituximab, which was based on the National Comprehensive Cancer Network (NCCN) guidelines that list dose-dense rituximab monotherapy as a treatment option for frail patients with relapsed CLL.[16] 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 chemoimmunotherapy,[10] However, rituximab monotherapy is not considered to be a standard of care for this patient population as it is not included in any UK guidance and is rarely used in England; as such, it is also not included in the NICE scope for this submission. Despite this, rituximab monotherapy is still relevant and important to the decision problem as it has a similar efficacy to another anti-CD20 agent, ofatumumab, which is used frequently in UK patients with CLL, as supported by clinical opinion from the advisory board.[13]

An indirect comparison of rituximab with chlorambucil versus ofatumumab with chlorambucil performed and reported by the Evidence Review Group (ERG) in the ongoing appraisal of ofatumumab in combination with chlorambucil or bendamustine for untreated CLL (ID642), suggested that PFS outcomes for rituximab with chlorambucil and ofatumumab with chlorambucil are similar.[17] Furthermore, although there are no data directly comparing rituximab and ofatumumab in CLL patients, a phase III RCT in patients with relapsed/refractory diffuse large B-cell lymphoma (previously treated with rituximab) found no difference in efficacy between ofatumumab and rituximab in combination with a standard chemotherapy regimen.[18] Finally, in reference to Study 116 and the comparator arm used, the European Public Assessment Report (EPAR) for idelalisib states "…the effect shown is convincing compared to what can be expected with available chemotherapy options with minimal toxicity. Therefore, the control arm in the pivotal study is considered

acceptable."[12] Furthermore, the EPAR states "the high activity [of idelalisib] observed allows concluding that the benefits are expected to exceed any of the available options and are at least of similar magnitude than rituximab in the salvage setting."[12] Taking these factors into consideration, rituximab monotherapy can be considered as an anti-CD20 comparator arm in Study 116 and assumed to have a similar efficacy to ofatumumab, which is listed as a comparator in the NICE scope.

**Clinical trial outcomes for idelalisib with rituximab in patients with relapsed/refractory CLL**

Idelalisib, when used in combination with rituximab, results in unprecedented and highly statistically significant survival benefits in a frail, elderly population of patients with relapsed/refractory CLL:

- Statistically significant increase in progression free survival (PFS), for idelalisib with rituximab vs. placebo with rituximab (idelalisib with rituximab: 19.4 months [12.3, not reached] vs. placebo with rituximab: 6.5 months [4.0, 7.3]; hazard ratio (HR) 0.15; $p=1.6\times10^{-16}$).[14] These highly statistically significant PFS results warranted termination of the study after the first prespecified interim analysis.[19]
- Statistically significant increase in overall survival (OS) (idelalisib with rituximab: not reached [not reached, not reached] vs. placebo with rituximab: 20.8 [14.8, not reached]; HR: 0.34 [95% CI: 0.19, 0.60]; p=0.0001).[14]
- PFS and OS results favoured idelalisib with rituximab compared with placebo with rituximab across all predefined subgroups, including in high-risk patients with 17p deletion, TP53 mutation or unmutated immunoglobulin variable region heavy chain (IgVH); the treatment effect across these subgroups was similar, indicating that idelalisib is highly effective regardless of genetic mutational status.

Patient HRQL was also assessed in Study 116 by means of the EQ-5D utility index. Patients with relapsed CLL treated with idelalisib with rituximab consistently showed greater symptom improvement compared with patients receiving placebo with rituximab throughout the study, with a significant treatment effect (p=0.002). To put this into context, significant changes in HRQL based on a generic instrument are very rare in oncology conditions. This is likely to be linked, among other factors, to

the meaningful and fast response seen with idelalisib which induces a profound shrinkage of the lymph nodes as seen by the very high lymph node response (LNR) rate (96.2% vs. 6.7% for rituximab alone).[14]

Idelalisib was generally well tolerated and had a manageable safety profile when administered in combination with rituximab.[12, 14] Most adverse events (AEs) were consistent with those expected for a heavily pre-treated, relapsed/refractory CLL population, and discontinuation due to toxicity was infrequent.[12] Idelalisib was not found to be associated with the AEs observed with traditional cytotoxic chemotherapy regimens, meaning that it can be administered to those with comorbidities, poor bone marrow function, poor kidney function or cytopenias that would make chemotherapy unsuitable.[19] As such, idelalisib represents a step change in the management of patients with CLL who are typically an elderly, frail population.

**Clinical trial outcomes for idelalisib with rituximab in treatment naïve patients with a 17p deletion or TP53 mutation**

For previously untreated patients with a 17p deletion or TP53 mutation, the key evidence for idelalisib with rituximab is derived from a subgroup of patients from the single-arm study, 101-08, and supported by the larger subgroup of patients with a 17p deletion or TP53 mutation in the relapsed or refractory population.[20] Overall, the development programme for idelalisib in CLL has to date reported on clinical outcomes from 153 patients with a 17p deletion or TP53 mutation (including those in the Study 116).[12] As with the relapsed CLL population, evidence for potential comparators in this population is also very scarce.

In a subgroup of untreated CLL patients with a 17p deletion or TP53 mutation in Study 101-08, treatment with idelalisib with rituximab resulted in an overall response rate (ORR) of 100%.[21] At 36 months, none of these patients had progressed or died.[21] Only a single relevant comparator study was identified from the systematic literature review, which reported a median PFS of 10.7 months with alemtuzumab and 2.2 months with chlorambucil, and an ORR of 64% with alemtuzumab and 20% with chlorambucil.[22] As such, idelalisib compares favourably with the results in this comparator trial, despite the fact that the patient population in Study 101-08 was much sicker at baseline. Indeed, the EMA identified the activity of idelalisib in patients with CLL and a 17p deletion or TP53 mutation as an area of special interest

based upon the consistent results seen across studies at all lines of treatment in patients with a 17p deletion or TP53 mutation.[12] Recognising the high unmet need in this patient population, the EMA accordingly provided a license for idelalisib for this indication.

**Benefits of idelalisib with rituximab compared to UK current care**

Idelalisib, when administered in combination with rituximab, should be considered under end-of-life criteria in the relapsed or refractory CLL population because the mean overall survival of patients in Study 116 as determined by a restricted means analysis in the intention to treat (ITT) population was 21.6 months (95% CI: 20.0, 23.1) for idelalisib with rituximab, compared with 16.7 months (95% CI: 14.8, 18.6) for placebo with rituximab.[14] Idelalisib with rituximab offers an extension to life of more than an additional 3 months (4.9 months), compared with current treatment for a population with an expected life expectancy of less than 24 months.

Idelalisib, when administered in combination with rituximab, also 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, and consequently, the patients have a poor prognosis and a high unmet need.[10, 12] In accordance with the EPAR for idelalisib, the evidence provided in this submission demonstrated the consistently observed high activity of idelalisib irrespective of refractoriness to prior therapy or presence of a 17p deletion or TP53 mutation in patients with CLL.[12]

It is important to highlight that the patients included in Study 116 are representative of relapsed CLL patients seen in UK clinical practice, and furthermore 32 patients (15%) were recruited across UK centers.

## *1.4 Summary of the cost-effectiveness analysis*

To appraise idelalisib with rituximab for patients who have received at least one prior therapy, a Markov model was constructed. The pivotal study to inform this analysis was Study 116, which compared idelalisib with rituximab versus rituximab plus placebo in patients who were unfit to receive cytotoxic therapy. Clinical outcomes from Study 116 were pertinent to estimate the cost-effectiveness of idelalisib with rituximab versus rituximab monotherapy, and based on clinically justified assumptions, versus best supportive care (BSC) and ofatumumab monotherapy, in

this group of patients unfit to receive cytotoxic therapy, who meet end-of-life criteria. To appraise idelalisib with rituximab versus the other listed comparators, in previously treated patients fitter than those in Study 116, was highly challenging. Section 4 demonstrates the poorly connected network of RCT evidence in this disease area. Formal evidence synthesis to robustly compare survival outcomes across relevant studies was not possible. Nevertheless, in an effort to harness the evidence base to make cautious comparisons to other regimens used in practice, additional assumptions were made, and exploratory analysis results are presented in section 5.

Idelalisib with rituximab is shown to be highly cost-effective as an end-of-life therapy versus (i) rituximab monotherapy, (ii) BSC and (iii) ofatumumab monotherapy, in patients similar to those in Study 116, with base case incremental cost-effectiveness ratios (ICERs) of (i) £13,634, (ii) £20,461 and (iii) £1,527 per quality-adjusted life year (QALY) gained, as shown in Table 3 , Table 4 and Table 5, respectively. Probabilistic sensitivity analyses showed idelalisib with rituximab to be cost-effective at an end-of-life willingness to pay threshold of £50,000 per QALY gained in over 95% of probabilistic model iterations versus each of these comparators. Exploratory comparisons to other available treatments suggest that idelalisib with rituximab is preferable to its range of comparators in patients similar to those in Study 116, and may be beneficial for the wider group of patients who have received at least one prior therapy.

Subgroup analysis of the patients in Study 116 with 17p deletion or TP53 mutation, presented in Table 6, Table 7 and Table 8, confirms that idelalisib with rituximab is a cost-effective option for those patients with high unmet need and who currenlty have few if any effective treatment options available.

Given the very limited, but nonetheless compeling, data on the clinical effectiveness of idelalisib in CLL treatment-naïve patients with 17p deletion or TP53 mutation, conducting a formal cost-utility-analyis was not possible. However given the patho-physiological reason behind the unmet need of those patients, it is plausible that both the clinical effectiveness and cost-effectiveness seen for relapsed patients will be, at least, equivalent for treatment naïve patients.

**Base case results for CLL patients who have received at least one therapy**

**Table 3: Incremental cost-effectiveness results, base case results vs. rituximab monotherapy**

| *Technology (and comparators)* | *Total costs* | *Total life years* | *Total QALYs* | *Incremental costs* | *Incremental life years* | *Incremental QALYs* | *ICER versus baseline (A)* | *Incremental analysis* |
|---|---|---|---|---|---|---|---|---|
| **Rituximab monotherapy** | [redacted] | 1.39 | 0.89 | | | | | |
| **IR** | [redacted] | 4.63 | 2.81 | £26,128 | 3.24 | 1.92 | £13,634 | £13,634 |
| **Key:** IR, idelalisib with rituximab; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years. | | | | | | | | |

**Table 4: Incremental cost-effectiveness results, base case results vs. best supportive care**

| *Technology (and comparators)* | *Total costs* | *Total life years* | *Total QALYs* | *Incremental costs* | *Incremental life years* | *Incremental QALYs* | *ICER versus baseline (A)* | *Incremental analysis* |
|---|---|---|---|---|---|---|---|---|
| **BSC** | [redacted] | 1.39 | 0.89 | | | | | |
| **IR** | [redacted] | 4.63 | 2.81 | £39,211 | 3.24 | 1.92 | £20,461 | £20,461 |
| **Key:** IR, idelalisib with rituximab; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years. | | | | | | | | |

**Table 5: Incremental cost-effectiveness results, base case results vs. ofatumumab monotherapy**

| *Technology (and comparators)* | *Total costs* | *Total life years* | *Total QALYs* | *Incremental costs* | *Incremental life years* | *Incremental QALYs* | *ICER versus baseline (A)* | *Incremental analysis* |
|---|---|---|---|---|---|---|---|---|
| **Ofatumumab monotherapy** | [redacted] | 1.39 | 0.89 | | | | | |
| **IR** | [redacted] | 4.63 | 2.81 | £2,926 | 3.24 | 1.92 | £1,527 | £1,527 |
| **Key:** IR, idelalisib with rituximab; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years. | | | | | | | | |

**Subgroup analysis results for CLL patients with 17p deletion or TP53 mutation, using Study 116 data**

**Table 6: Subgroup results, IR versus rituximab monotherapy, patients with 17p deletion or TP53 mutation**

| *Technology (and comparators)* | *Total costs* | *Total life years* | *Total QALYs* | *Incremental costs* | *Incremental life years* | *Incremental QALYs* | *ICER versus baseline (A)* | *Incremental analysis* |
|---|---|---|---|---|---|---|---|---|
| **Rituximab monotherapy** | [redacted] | 0.98 | 0.64 | | | | | |
| **IR** | [redacted] | 3.57 | 2.31 | £33,653 | 2.59 | 1.67 | £20,200 | £20,200 |
| **Key:** IR, idelalisib with rituximab; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years. | | | | | | | | |

**Table 7: Subgroup results, IR versus BSC, patients with 17p deletion or TP53 mutation**

| *Technology (and comparators)* | *Total costs* | *Total life years* | *Total QALYs* | *Incremental costs* | *Incremental life years* | *Incremental QALYs* | *ICER versus baseline (A)* | *Incremental analysis* |
|---|---|---|---|---|---|---|---|---|
| **BSC** | [redacted] | 0.98 | 0.64 | | | | | |
| **IR** | [redacted] | 3.57 | 2.31 | £45,887 | 2.59 | 1.67 | £27,543 | £27,543 |
| **Key:** IR, idelalisib with rituximab; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years. | | | | | | | | |

**Table 8: Subgroup results, IR versus ofatumumab monotherapy, patients with 17p deletion or TP53 mutation**

| *Technology (and comparators)* | *Total costs* | *Total life years* | *Total QALYs* | *Incremental costs* | *Incremental life years* | *Incremental QALYs* | *ICER versus baseline (A)* | *Incremental analysis* |
|---|---|---|---|---|---|---|---|---|
| **Ofatumumab monotherapy** | [redacted] | 0.98 | 0.64 | | | | | |
| **IR** | [redacted] | 3.57 | 2.31 | £11,772 | 2.59 | 1.67 | £7,066 | £7,066 |
| **Key:** IR, idelalisib with rituximab; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years. | | | | | | | | |

# 2 The technology

## *2.1 Description of the technology*

Brand name: Zydelig®

UK approved name: Idelalisib

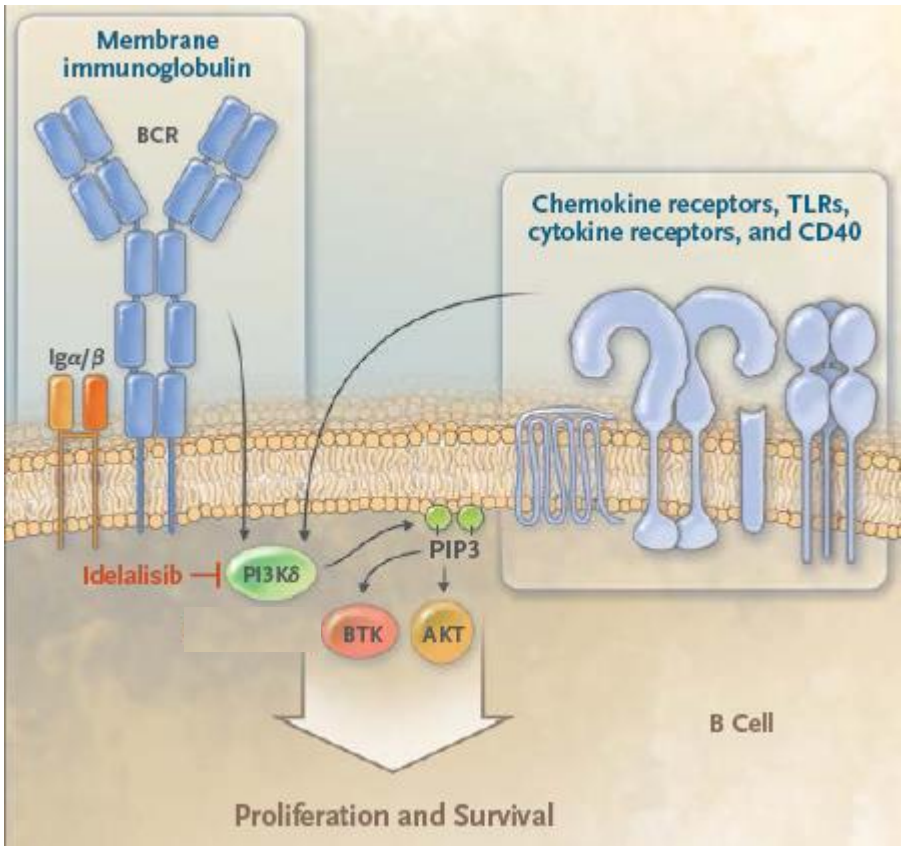
**Pharmacotherapeutic group:** antineoplastic agents, other antineoplastic agents, Anatomical Therapeutic Chemical (ATC) code: L01XX47.

**Mechanism of action:** Idelalisib inhibits the delta isoform of the phosphatidylinositol 3-kinase p110δ (PI3Kδ), which is hyperactive in B-cell malignancies and is central to multiple signalling pathways that drive the growth, differentiation, proliferation, survival, migration and metabolism of malignant cells in lymphoid tissues and bone marrow.[9] Idelalisib is a selective inhibitor of adenosine-5'-triphosphate (ATP) binding to the catalytic domain of PI3Kδ, resulting in inhibition of the phosphorylation of the key lipid second messenger phosphatidylinositol and the prevention of Akt (protein kinase B) phosphorylation.[9].

Idelalisib induces apoptosis and inhibits proliferation in cell lines derived from malignant B-cells and in primary tumour cells.[9] Through inhibition of signalling by the chemokine receptors CXCR4 and CXCR5, induced by the chemokines CXCL12 and CXCL13, respectively, idelalisib inhibits proliferation, survival, homing and retention, and promotes apoptosis of malignant B-cells in the tumour microenvironment, including lymphoid tissues and bone marrow.[9]

The high specificity of idelalisib for inhibiting the PI3K P110δ catalytic domain makes it a promising treatment option for prolonging efficacy and reducing toxicity compared to chemotherapy-containing regimens.[23] Furthermore, the mode of action of idelalisib is independent of p53 so idelalisib shows good efficacy even in patioents with defects in this pathway (e.g. 17p deletion or TP53 mutation). Figure 1 provides an overview of the mechanism of action of idelalisib.[24]

**Figure 1. Mechanism of action of idelalisib**




**Key:** BCR, B-cell receptor; BTK, Bruton's tyrosine kinase; Ig, immunoglobulin; PI3K, phosphoinositide 3-kinase; PIP3, phosphatidylinositol 3,4,5-trisphosphate; TLR, toll-like receptor

Source: Fruman and Cantley, 2014.[24]

## *2.2 Marketing authorisation/CE marking and health technology assessment*

**Marketing authorisation:** Idelalisib has received a UK marketing authorisation, which was granted on 19th September 2014.

**Indication:** Idelalisib 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.

In addition, idelalisib is also indicated as monotherapy for the treatment of adult patients with follicular lymphoma that is refractory to two prior lines of treatment.

However, this indication is beyond the scope of this submission and is not addressed here.

**Anticipated restrictions or contraindications:**

Hypersensitivity to the active substance or to any of the excipients.

**Anticipated date of availability:**

Idelalisib was made commercially available from 22nd September 2014.

**Regulatory approval outside of the UK:**

**EU:** On 19th September 2014, the European Commission has granted idelalisib a marketing authorisation for the EU.

**US:** Idelalisib was approved by the Food and Drug Administration (FDA) on 23rd July 2014 for the treatment of patients with relapsed CLL, in combination with rituximab, for whom rituximab alone would be considered appropriate therapy due to other co-morbidities.

**Australia:** Idelalisib was approved via a Category 1 Application (CAT 1) on the 30th January 2015 for use in combination with rituximab, for the treatment of patients with CLL/small lymphocytic lymphoma (SLL) for whom chemo-immunotherapy is not considered suitable, either: upon relapse after at least one prior therapy; or as first-line treatment in the presence of 17p deletion or TP53 mutation.

**Canada:** A submission was made on 28th February 2014 via the national procedure in Canada, and approval is anticipated in March/April 2015

**Switzerland:** Regulatory approval was obtained from Swissmedic on 22nd January, 2015.

**Any other UK health technology assessment:**

Idelalisib has been submitted to the SMC for review. This process is currently ongoing, and the advice from this is expected to be released on 9th March 2015.

There is no planned submission to AWMSG.

## *2.3 Administration and costs of the technology*

Table 9 summarises the anticipated costs of treatment with idelalisib.

**Table 9: Costs of the technology being appraised**

| | Cost | Source |
|---|---|---|
| **Pharmaceutical formulation** | Orange, oval-shaped, film-coated tablet of dimensions 9.7 mm by 6.0 mm, debossed on one side with “GSI” and “100” on the other side; or pink, oval-shaped, film-coated tablet of dimensions 10.0 mm by 6.8 mm, debossed on one side with “GSI” and “150” on the other side. | SPC[9] |
| **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[25]<br>please see Appendix 2 for further documentation<br>See section 5.5 |
| **Method of administration** | Oral tablet, administered in conjunction with IV rituximab for 8 cycles | SPC[9] |
| **Doses** | 100mg; 150mg | SPC[9] |
| **Dosing frequency** | 100mg or 150mg twice daily (BID) | SPC[9] |
| **Average length of a course of treatment** | Until disease progression or unacceptable toxicity. Mean time on treatment is expected to be [redacted] years | See section 5.3 |
| **Average cost of a course of treatment** | [redacted] idelalisib acquisition cost plus [redacted] rituximab acquisition cost) is the anticipated discounted cost for entire regimen at the NHS price based on extrapolation of time on treatment data from the clinical trial | See section 5.7 |
| **Dose adjustments** | • Treatment with idelalisib must be withheld in the event of a Grade 3 or 4 aminotransferase elevation (alanine aminotransferase [ALT]/aspartate aminotransferase [AST] > 5 x upper limit of normal [ULN]). Once values have returned to Grade 1 or below (ALT/AST ≤ 3 x ULN), treatment can be resumed at 100 mg twice daily. If the event does not recur, the dose can be re-escalated to 150 mg twice daily at the discretion of the treating physician. If the event recurs, treatment with idelalisib must be withheld until the values return to Grade 1 or less, after which re-initiation at 100 mg twice daily may be considered at the discretion of the physician.<br>• Treatment with idelalisib must be withheld in the event of Grade 3 or 4 diarrhoea/colitis. Once diarrhoea/colitis has returned to Grade 1 or below, treatment can be resumed at 100 mg twice daily. If diarrhoea/colitis does not recur, the dose can be re-escalated to 150 mg twice daily at the discretion of | SPC[9] |

| | Cost | Source |
|---|---|---|
| | the treating physician.<br>• Treatment with idelalisib must be withheld in the event of suspected pneumonitis. Once pneumonitis has resolved and if re-treatment is appropriate, resumption of treatment at 100mg twice daily can be considered. Treatment with idelalisib must be withheld in the event of Grade 3 or 4 rash. Once rash has returned to Grade 1 or below, treatment can be resumed at 100 mg twice daily. If rash does not recur, the dose can be re-escalated to 150 mg twice daily at the discretion of the treating physician. | |
| **Anticipated care setting** | Treatment with idelalisib should be conducted by a physician experienced in the use of anti-cancer therapies.<br>We would expect the rituximab element of the idelalisib regimen to be administered in a day case hospital setting. Idelalisib is an oral therapy. | SPC[9] |
| **Key:** IV, intravenous; mg, milligram; SPC, summary of product characteristics.<br>**Notes:** * 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. | | |

## *2.4 Changes in service provision and management*

No additional tests are anticipated to be required for the use of idelalisib over and above standard tests currently performed by the National Health Service (NHS) in this patient population.

The indication includes mention of the cytogenetic “classification” of 17p deletion or TP53 mutation. The outcome of both 17p deletion and TP53 mutation is the loss of TP53 function. Patients without TP53 function will relapse rapidly and thus fulfil the short remission criteria for consideration of an alternative to a chemoimmunotherapy-based treatment.

Fluorescence *In Situ* Hybridisation (FISH) testing is used to test for presence of a 17p deletion, whilst TP53 mutation is detected by PCR screening assays and defined by direct sequencing. The current recommendation issued in the BCSH guidelines for CLL management is that patients should be screened for the presence of a TP53 abnormality prior to initial and subsequent treatment. The guidelines

specify that currently, TP53 loss should be assessed by FISH, but patients should also be screened for TP53 mutations when this assay becomes routinely avaliable.[7]

No change to the English standard of care testing is proposed or expected with this application, i.e. no new companion diagnostic is required.

Caution is recommended when administering idelalisib in patients with impaired hepatic function; as such, an intensified monitoring of adverse reactions is recommended.

Elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been reported during the first 12 weeks of treatment, and as such, all patients should be monitored for ALT and AST every 2 weeks for the first 3 months of treatment.[9] Such elevations were generally asymptomatic and were reversible with dose interruption. If Grade 2 or higher elevations in ALT and/or AST are observed, patients must be monitored weekly until the values return to Grade 1 or below. However, no additional monitoring above usual clinical practice is required.

It is anticipated that patients will self-administer idelalisib at home. Since idelalisib will be used in combination with rituximab, the cost of rituximab must also be considered. We do not anticipate any change in rituximab administration compared with that currently used in clinical practice. A full evaluation of the resource use and costs associated with treatment can be found in section 6.

## *2.5 Innovation*

**Rationale for idelalisib representing a "step-change" in the management of CLL**

Idelalisib is a first-in-class, oral, highly selective PI3Kδ inhibitor that offers a step change in the management of CLL and meets the five criteria for step-change in innovation as listed in the Kennedy Report (2009):[26]

***Significantly and substantially improves the way that a current need is met***

- Idelalisib, when administered in combination with rituximab, represents a step-change in the management of CLL since it provides an efficacious and generally well-tolerated option for relapsed or refractory CLL patients who have limited treatment options in the current treatment landscape in which there is no

consistently accepted standard of care. After each subsequent regimen, fewer patients obtain responses, and patients become increasingly resistant to available therapy.[12]

- Idelalisib can be administered until progression of disease and thereby continues to deliver disease control, unlike traditional chemotherapy regimens, which are generally in short courses. This improved control can be seen in the substantial and highly significant gains in PFS demonstrated in Study 116: 19.4 months versus 6.5 months ($p<0.001$).
- Idelalisib was generally well tolerated and had a manageable safety profile when administered in combination with rituximab.[12, 14] Idelalisib is not associated with the AEs observed with traditional cytotoxic chemotherapy regimens, meaning that it can be administered to those with comorbidities, poor bone marrow function, poor kidney funtion or cytopenias that would make chemotherapy unsuitable.[19]
- As such, idelalisib represents a step change in the management of patients with CLL who are typically an elderly, frail population.
- In addition, idelalisib, when administered in combination with rituximab, also represents a step-change in the management of the high-risk population of previously untreated CLL patients with 17p deletion or TP53 mutation, where chemoimmunotherapy has very poor efficacy.[12] According to the ESMO guidelines,[10] there is no standard treatment for these patients, who currently have a median life expectancy of 2–3 years from front-line treatment and, consequently, a high unmet need. The EMA identify the activity of idelalisib in patients with CLL and a 17p deletion/TP53 mutation as an area of special interest based upon the consistent results seen across studies: Study 116 (total 95/220 subjects, n=46 in the idelalisib with rituximab arm and n=49 in the placebo with rituximab arm), Study 101-07 (n=24), Study 101-02 (dose finding) and Study 101-08 (n=9).[12]
- In accordance with the EPAR for idelalisib, the evidence provided in this submission demonstrated the consistently shown high activity of idelalisib irrespective of refractoriness to prior therapy or a 17p deletion/TP53 mutation in patients with CLL.[12]

***Idelalisib meets a need which the NHS has identified as being important***

Idelalisib meets an important need as evidenced by the recent NHS Outcomes Framework that reflects the government commitment to reducing mortality due to cancer.

***Idelalisib has a robust evidence base providing research on the populations in which the product is effective***

- For relapsed or refractory CLL patients, the key evidence for idelalisib with rituximab in these patients is from Study 116, a robust, phase III RCT versus placebo with rituximab, in older, heavily pretreated patients with almost half (42.6%) of the patients in high-risk categories (such as those with 17p deletion or TP53 mutation).[14]
- In contrast, the evidence base for the relevant comparators within this population that are used in UK practice, identified via a rigorous and comprehensive systematic literature review (see Section 4.1), is rather scarce.
- For the previously untreated patients with a 17p deletion or TP53 mutation, the key evidence for idelalisib with rituximab is derived from a small subgroup of patients from the single-arm study 101-08 and is supported by the much larger subgroup of patients with a 17p deletion or TP53 mutation in the relapsed or refractory population.[20] Again, evidence for the comparators in this population is also very scarce.
- Overall, the development programme for idelalisib in CLL has to date reported on clinical outcomes from 153 patients with either 17p deletion or TP53 mutation (including those in the Study 116), and as such, the EMA identified the activity of idelalisib in patients with CLL and a 17p deletion or TP53 mutation as an area of special interest based upon the consistent results seen across studies at all lines of treatment in patients with a 17p deletion or TP53 mutation.[12]

***Idelalisib has demonstrated an appropriate level of effectiveness***

- Idelalisib, when used in combination with rituximab, results in unprecedented survival benefits in a frail, elderly population of patients with relapsed CLL:

  - In terms of PFS (HR: 0.15 [95% CI: 0.09, 0.24] for idelalisib with rituximab vs. placebo with rituximab).[14] These unprecedented PFS results warranted termination of the study after the first prespecified interim analysis.[19]
  - In terms of OS (HR: 0.34 [95% CI: 0.19, 0.60] for idelalisib with rituximab vs. placebo with rituximab).[14]

- Furthermore, median PFS and OS in patients treated with idelalisib with rituximab in Study 116 were very similar to those reported for much fitter patients included in the published RCTs for the comparators. For example, in the RCT reported by Robak (2010), which included younger patients and fewer patients with high-risk mutations, who had received fewer prior therapies (median of 1 compared with 3 for idelalisib), the median PFS was 27.0 months with FCR, and 21.9 in the FC arm.[27] Similarly, median OS was not reached with FCR, compared with 52 months with FC.[27]
- Idelalisib demonstrates substantial clinical benefit in the hard-to-treat population of previously untreated patients with a 17p deletion or TP53 mutation. Idelalisib with rituximab demonstrated positive outcomes in these patients, with a 100% overall response rate (97% in overall population) and no progression or death at 36 months (n=9 patients).[21]
- Although no formal indirect comparisons could be made because of the limited evidence base, one RCT was identified from a rigorous systematic literature review that presented data for comparators in untreated patients with a 17p deletion/TP53 mutation. In an RCT comparing alemtuzumab with chlorambucil in a subgroup of patients with a 17p deletion, median PFS in the alemtuzumab arm (n=11) was 10.7 months, compared with 2.2 months with chlorambucil (n=10).[22] Overall response rate was 64% with alemtuzumab and 20% with chlorambucil.[22] As such, idelalisib compares favourably with the results in this comparator trial, despite the fact that the patients in Study 101-08 were much sicker.
- Patient HRQL was also assessed in Study 116 by means of the EQ-5D utility index. Patients with relapsed CLL treated with idelalisib with rituximab consistently showed greater symptom improvement compared with patients receiving placebo with rituximab throughout the study, with a statistically

significant treatment effect (p=0.002 for the overall treatment effect). To put this into context, significant changes in HRQL based on a generic instrument are very rare in oncology conditions.

- In addition, patients receiving idelalisib with rituximab consistently showed greater symptom improvement than subjects receiving placebo with rituximab based on the Additional Concerns (Leukemia subscale), FACT-Leu Total, and the Trial Outcome Index scores of the HRQL FACT-Leu Questionnaire, throughout the study.

***Idelalisib has a marketing authorisation for relevant indication***

Idelalisib, when used in combination with rituximab, has a marketing authorisation for two populations: adult patients with CLL who have received at least one prior therapy; and adult patients with CLL with 17p deletion/TP53 mutation who are unsuitable for chemo-immunotherapy.

**Benefits of idelalisib not captured in the QALY calculation**

Due to the very limited evidence base for the comparators, it has not been possible to construct a network analysis to allow formal comparisons between idelalisib and relevant comparators to inform the economic model. However, this submission provides some qualitative comparisons between the results for idelalisib in Study 116 compared with comparator trials, consistently favour idelalisib (see sections 4.7 and 4.11). Given the qualitative nature of these comparisons, these impacts cannot be accounted for within the standard QALY calculation.

In addition, as CLL has been associated with more sick leave in patients compared with the general population,[28] it is assumed that CLL will also impact on carers and the wider society as a result of patients with CLL taking time off work, although this is poorly documented in the literature. The impact is likely to increase as the disease progresses. Such impacts will not be captured in the QALY calculation.

# 3 Health condition and position of the technology in the treatment pathway

## *3.1 Disease overview*

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.[3] A total of 2,712 people were diagnosed with CLL in England in 2011, with the highest incidence rates being in older people.[3] Between 2009 and 2011, an average of 43% of cases were diagnosed in the UK in those aged 65 and over.[3]

CLL is an incurable disease,[2] with a heterogeneous clinical course.[6, 29] While some patients have a highly stable disease with prolonged survival, other patients may have a more aggressive disease with a poorer outcome.[6, 29] 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). [4, 5]

**Table 10: Median survival by Rai and Binet stage**

| Stage | Median survival (years) |
|---|---|
| ***Rai stage[9]*** | |
| 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. | |

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,[10] the median age at treatment initiation is closer to 75 years. [30]

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.[6] The World Health Organisation (WHO) criteria define CLL as greater than $5.0 \times 10^9$/L monoclonal B-cells with a characteristic appearance (CLL immunophenotype) in peripheral blood.[5, 31, 32] In the WHO classification, CLL is always a disease of neoplastic B-cells.[31, 32]

The molecular pathogenesis of CLL is a complex process involving many stages, and the precise cell of origin of CLL is currently unknown.[29]

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.[16, 32, 33]

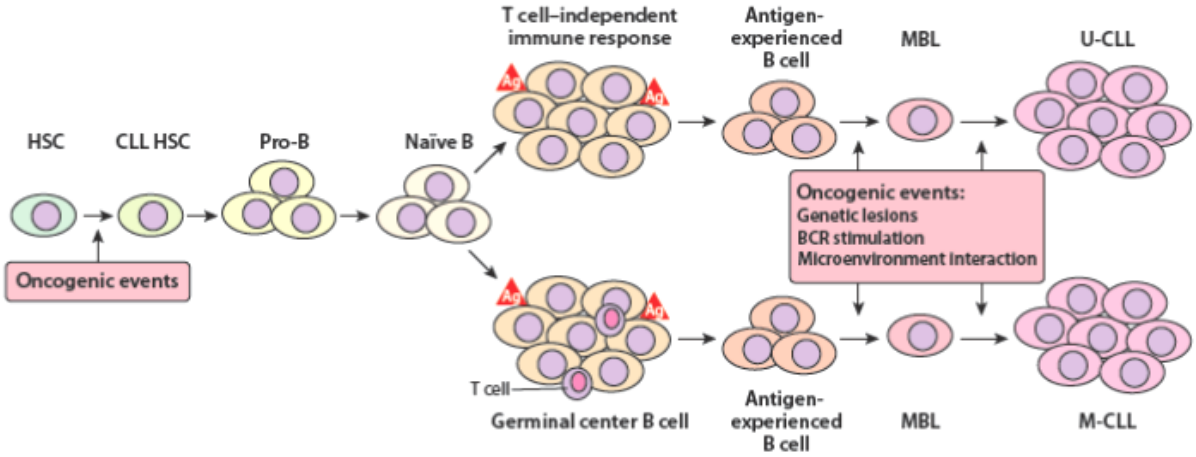
Figure 2 presents a schematic of the development of CLL. Cytogenic abnormalities and mutations may occur at any stage of B-cell development, including in hematopoietic stem cells (HSCs). Mutated HSCs may result in B-cells with modest growth/survival advantages, which may progress to monoclonal B-cell lymphocytosis (MBL), a related but distinct haematological malignancy.[34] Such cytogenic abnormalities include the following:

- 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.[11] 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.[2, 11 35, 36]
- Mutations of TP53; in patients with confirmed 17p deletion, more than 80% show mutations in the remaining TP53 allele,[11] 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.[11]
- Mutations of the IgVH gene.[10]

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.[37] 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.[10 7 11]

As stated within the idelalisib EPAR, it is accepted that patients with poor prognostic markers (i.e., 17p deletion and/or TP53 mutation) respond poorly to fludarabine-based therapy and that this cytogenetic abnormality is an important prognostic factor.[12] As shown in the CLL8 trial comparing FC with FCR in previously untreated CLL patients, some of which had 17p deletions or TP53 mutations, cytotoxic chemotherapy regimens with or without rituximab are very ineffective for these patients in terms of PFS, OS, and response rates.[38] CLL8 patients with a 17 deletion or TP53 mutation showed significantly poorer outcomes with both FC and FCR, compared with patients without these mutations, in terms of OS, PFS, and ORR (all $p<0.001$).[38]

**Figure 2: Development of CLL[34]**




**Key:** Ag, antigen; BCR, B-cell receptor; HSC, hematopoietic stem cell; MBL, monoclonal B-cell lymphocytosis; M-CLL, mutated chronic lymphocytic leukaemia; U-CLL, unmutated chronic lymphocytic leukaemia.

Source: Zhang and Kipps, 2014 [34]

## *3.2 Effects of the disease on patients, carers and society*

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.[6-8]

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.[39]

Several studies have assessed HRQL in patients with CLL in comparison with the general population and with patients with other malignancies.[39, 40] 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.[40] Patients in the higher risk category have a lower HRQL,[39] and patients with progression have a lower HRQL compared with those in remission.[41 42]

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.[28] 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.

## 3.3 *Current treatment landscape and anticipated positioning of idelalisib*

This submission addresses two patient populations for which idelalisib has a marketing authorisation:

- **Adult patients 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.
- **Adult patients with CLL who have 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.[11]

The primary goals of therapy in both of these populations are to improve survival and patient HRQL.[7]

**NICE Guidance**

A series of technology appraisals have already been conducted by NICE in CLL, and these are summarised in Table 11 and have been summarised in a pathway issued by NICE.[43]

For first-line treatment of CLL, NICE recommends FCR for patients who are able to take fludarabine-containing regimens. For patients who are unsuitable for fludarabine-containing regimens, bendamustine is recommended as an option.[44]

Guidance is limited as to the choice of NICE-recommended treatments for patients with relapsed/refractory CLL. As such, NICE recommends repeat administration of FCR unless the patient is refractory to fludarabine or has been previously treated with rituximab outside of the context of a clinical trial. As an alternative, NICE recommends oral fludarabine for patients who have failed on or are intolerant to first-

line chemotherapy who would otherwise have received standard combination chemotherapy (i.e. CHOP, CAP or CVP).

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. However, for this submission, NICE does not assume that patients with a17p deletion or TP53 mutation are the same as the wider CLL population and as such, recognises the need to address this patient population specifically.

**Table 11: Summary of NICE technology appraisals in CLL**

| Technology appraisal | Summary of guidance |
|---|---|
| ***First-line treatment of CLL*** | |
| Rituximab for first-line treatment of chronic lymphocytic leukaemia. TA174, June 2009.[45] | Rituximab in combination with fludarabine and cyclophosphamide is recommended as an option for the first-line treatment of CLL in people for whom fludarabine in combination with cyclophosphamide is considered appropriate.<br>Rituximab in combination with chemotherapy agents other than fludarabine and cyclophosphamide is not recommended for the first-line treatment of CLL. |
| Bendamustine for the first-line treatment of chronic lymphocytic leukaemia. TA216, February 2011[44] | Bendamustine is recommended as an option for the first-line treatment of CLL (Binet Stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate. |
| Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia. TA119, February 2007.[46] [46] | Fludarabine monotherapy is not recommended for first-line treatment of CLL. |
| Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia (ID650)[47] | Currently in preparation. Appraisal Committee's preliminary recommendations were released on 2nd December 2014, but these are subject to change and are not presented here.<br>Earliest anticipated publication TBC. |
| Ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia (ID642)[48] | Currently in preparation. Appraisal Committee's preliminary recommendations were released on 4th November 2014, but these are subject to change and are not presented here.<br>Earliest anticipated publication TBC. |
| ***Treatment of relapsed/refractory CLL*** | |
| Rituximab for the treatment of relapsed chronic lymphocytic leukaemia. TA193, July 2010.[49] | Rituximab in combination with fludarabine and cyclophosphamide is recommended as a treatment option for people with relapsed or refractory CLL except when the condition is one of the following:<br>• Refractory to fludarabine (i.e. not responding to fludarabine or has relapsed within 6 months of treatment)<br>• Has previously been treated with rituximab, unless in the context of a clinical trial: at a dose lower than |

| | |
|---|---|
| | that currently licensed for CLL, or in combination with chemotherapy other than fludarabine and cyclophosphamide. |
| Guidance on the use of fludarabine for B-cell chronic lymphocytic leukaemia. TA29, September 2001.[50] | Oral fludarabine is recommended as second-line therapy for CLL for patients who have either failed, or are intolerant of, first-line chemotherapy, and who would otherwise have received combination chemotherapy with any of the following:<br>• Cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP),<br>• Cyclophosphamide, doxorubicin and prednisolone (CAP) or,<br>• Cyclophosphamide, vincristine and prednisolone (CVP).<br>Intravenous fludarabine should only be used when oral fludarabine is contra-indicated. |
| Ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab. TA202, October 2010.[51] | Ofatumumab is not recommended for the treatment of CLL that is refractory to fludarabine and alemtuzumab. |
| Ibrutinib for treating relapsed or refractory chronic lymphocytic leukaemia and small lymphocytic leukaemia (ID749).[52] | Currently in preparation. Earliest anticipated publication is December 2015. |
| **Key:** CLL, chronic lymphocytic leukaemia; NICE, National Institute for Health and Care Excellence; TBC, to be confirmed | |

***UK Guidance***

The BCSH has issued UK-wide guidance regarding the management of CLL.[7] The guidance is summarised by patient populations, and a wide range of treatment options are provided based on fitness to tolerate FCR chemo-immunotherapy and whether patients are previously untreated or have relapsed or high-risk disease (Table 12).

The ESMO guidelines for the management of CLL in Europe also recommend a wide range of strategies for managing relapsed CLL.[10] For late relapses (≥12-24 months after monotherapy or ≥24-36 months after chemotherapy-containing regimens), first-line treatment should be repeated. If no response with first-line treatment or if relapse occurs within <12–24 months after monotherapy or <24–36 months after chemotherapy-containing regimens, a range of treatments/regimens are recommended, depending on fitness and other patient characteristics:

- For physically fit patients, alemtuzumab then ASCT is recommended.
- For patients relapsing or refractory to first-line treatment with an alkylating agent, FCR is recommended.
- For physically non-fit patients without 17p deletion, bendamustine- or alemtuzumab-containing regimens are recommended first, and then high-dose ofatumumab or rituximab with high-dose steroids for subsequent relapses.
- For patients with 17p deletion, an alemtuzumab-containing regimen is recommended, and may be combined with fludarabine or steroids in bulky disease.

In line with the BCSH guidelines, ESMO recommends that first-line treatment of patients with a 17p deletion or TP53 mutation consists of alemtuzumab followed by ASCT. However, alemtuzumab does not have a marketing authorisation in the EU and is only available via a patient access scheme agreed between EMA and the manufacturer. It is unclear how long alemtuzumab will be available in this manner. Furthermore, alemtuzumab tolerability can be challenging.

**Table 12: Summary of British Committee for Standards in Haematology guidance on management of CLL**

| Patient population | Summary of guidance |
|---|---|
| First-line treatment of patients without TP53 abnormality who are fit enough to receive fludarabine | FCR is recommended |
| First-line treatment of patients without TP53 abnormality who are not fit enough to receive fludarabine | Chlorambucil or bendamustine is recommended, with/without anti-CD20 antibodies (rituximab and ofatumumab) |
| Relapsed CLL without TP53 abnormality | • Patients relapsing ≥2 years after fludarabine-containing regimens who remain fit enough to receive fludarabine, should receive FCR.<br>• Patients relapsing after chlorambucil who are fit enough to receive fludarabine-based therapy should be considered for FCR.<br>• Patients relapsing after chlorambucil can be retreated with chlorambucil, with/without an anti-CD20 antibody. Alternatively, bendamustine in combination with rituximab should be considered.<br>• For patients refractory to chlorambucil and unable to tolerate myelosuppressive therapy, options include high-dose steroids, alone or in combination with rituximab, and alemtuzumab. |
| High risk (TP53 mutation/17p deletion or failing fludarabine combination therapy within 2 years) patients | The management of this high-risk population is challenging. Outside of trials:<br>• In patients who are able to receive ASCT, subcutaneous alemtuzumab in combination with pulsed high-dose glucocorticoids is recommended, followed by ASCT.<br>• In patients for whom ASCT is not an option, re-treatment with alemtuzumab should be considered in patients who relapse >12 months after initial treatment. For high-risk patients failing on alemtuzumab, ofatumumab is recommended (although not currently recommended by NICE, but available on the CDF until 12th March 2015). Other options include high-dose or conventional-dose glucocorticoids, lenalidomide (although not appraised by NICE for this indication or available via CDF) or radiotherapy. |
| **Key:** ASCT, allogeneic stem cell transplant; CLL, chronic lymphocytic leukaemia; CDF, Cancer Drugs Fund; FCR; fludarabine, cyclophosphamide and rituximab; NICE, National Institute for Health and Care Excellence. | |

Guidance on the management of CLL in the US has also been issued by the NCCN.[16] As with the other guidance, there are no clear standards for treatment of relapsed CLL, and a range of regimens are recommended for this group of patients, dependent on the fitness and age of patients and the length of time to relapse. Of note, rituximab monotherapy is recommended by the NCCN as an appropriate treatment option for patients with CLL aged ≥70 years, without 17p deletion.[16] For patients with 17p deletion, the NCCN acknowledges that there is no existing standard treatment and recommends enrolment in clinical trials. In the absence of clinical trials, the NCCN recommend a wide range of treatment options for these patients, again highlighting the unmet need for these patients and the need for a standard of care.

Although the treatment recommendations for first-line CLL patients are fairly clear and consistent, the situation for relapsed CLL patients is more complex with a range of treatment regimens being recommended and an even wider range being used in clinical practice. For example, in Study 116, a total of 46 unique treatment regimens were identified as being used in these patients who were being treated to current guidelines.[14] In view of the wide range of unique treatment regimens being used, it is clear that there is no existing standard of care for patients with relapsed CLL, which is also likely to be the case for England.

Patients with a 17p deletion or TP53 mutation do not respond well to chemo-immunotherapy, and as such, current treatment choices are very limited for these patients.[13] Alemtuzumab tolerability can be challenging,[12] and the majority of CLL patients are not suitable for ASCT. Management of these patients is clearly an area of high unmet need.

Despite the existence of UK recommendations for the management of CLL, these are not entirely reflective of the actual situation in current clinical practice. Guidelines from the BCSH were published in 2012, and the most recent NICE technology appraisal to be published was in 2011; since then clinical practice in this area has further developed.[1, 13, 35] Table 13 and Table 14 present the treatments within the scope of this submission, in which patients these treatments are used, the extent of use of these treatments in the UK, and any issues associated with them.

**Table 13: Treatments in NICE scope and use in clinical practice: Relapsed CLL**

| Class of treatment | Treatment in scope | Patients who receive treatment | Use in clinical practice | Issues |
|---|---|---|---|---|
| Cytotoxic therapies for patients fit enough to receive fludarabine | Fludarabine in combination with cyclophosphamide and rituximab | Patients relapsing after fludarabine or chlorambucil within 2 years who are fit enough to receive fludarabine | Most commonly used regimen in England, over all lines of treatment combined, as reported by SACT.[53] | Clinical advisors suggested that FCR would not be used to treat for early relapse (within 2 years) and is not an option in older patients and those with significant comorbidities.[13]<br>Advisors agreed that chemo-immunotherapy regimens such as this would not be suitable for relapsed patients with a 17p deletion or TP53 mutation. |
| Cytotoxic therapies for patients unable to receive fludarabine | Bendamustine (with or without rituximab) | Patients relapsing after chlorambucil treatment, with or without an anti-CD20 | B+R is the second most commonly used regimen in England[a], over all lines of treatment combined, as reported by SACT.[53] Bendamustine monotherapy is also used. | Clinical advisors suggested that B±R is an appropriate option in relapsed CLL, but there are very limited data on the efficacy of bendamustine in the relapsed/refractory setting.[13] Advisors found it difficult to contemplate using B±R in relapsed patients with a 17p deletion or TP53 mutation. |
| | Chlorambucil (with or without rituximab) | Patients relapsing after chlorambucil treatment, with or without an anti-CD20 | Chlorambucil monotherapy is the third most commonly used regimen in England, over all lines of treatment combined, as reported by SACT.[53] Chlorambucil in combination with rituximab is also used. | Clinical advisors suggested that chlorambucil±R is an appropriate option in relapsed CLL, but the data are very limited in the relapsed setting.[13] Advisors estimated that, in the absence of robust data in the relapsed setting, chlorambucil±R would be around half as effective as in the first-line setting in terms of PFS and responses.<br>Advisors found it difficult to contemplate using it in patients with a 17p deletion or TP53 mutation. |
| Anti-CD20s | Ofatumumab | Patients relapsing after fludarabine, or patients who cannot tolerate myelosuppressive therapy | Ofatumumab is the seventh most commonly used regimen in England[b], when all lines of treatment combined, as reported by SACT.[53]<br>Clinical advisors accepted that this is | Not recommended by NICE |

| Class of treatment | Treatment in scope | Patients who receive treatment | Use in clinical practice | Issues |
|---|---|---|---|---|
| | | | a relevant comparator, which would be expected to have a similar efficacy to rituximab in Study 116. [13] | |
| Supportive therapies | Corticosteroids (with or without rituximab) | Patients refractory to chlorambucil and unable to tolerate myelosuppressive therapy | Steroid use is not captured in the SACT data.[53] | Not assessed by NICE in this population. |
| | Best supportive care (including but not limited to regular monitoring, blood transfusions, infection control and psychological support) | In patients not fit enough to receive any of the above treatments, or where all other treatment options have been exhausted. | Best supportive care consists of a wide range of therapies. Clinical advisors felt that BSC included the following:[13]<br>• Outpatient review (100%)<br>• Blood/red cell transfusion for anaemia (82%)<br>• Inpatient stays (40%)<br>• Platelet transfusion for thrombocytopenia (27%)<br>• Immunoglobulin replacement (17%)<br>• Plasmaphoresis (1%)<br>In addition, advisors reported the likely use of anti-infective agents:<br>• Antimicrobial (91.3%)<br>• Antifungals (13.3%)<br>• Antivirals (63.8%) | Not assessed by NICE in this population. |

**Key:** B, bendamustine; CLL, chronic lymphocytic leukaemia; FCR, fludarabine, cyclophosphamide and rituximab; NICE, National Institute for Health and Care Excellence; R, rituximab; SACT, Systemic Anti-Cancer Therapy

[a]Bendamustine is currently used outside its marketing authorisation by means of the Cancer Drugs Fund.[54]

[b]Ofatumumab is used via the Cancer Drugs Fund, although it will be removed on 12th March 2015.[54]

**Table 14: Treatments in NICE scope and use in clinical practice: Untreated patients with 17p deletion or TP53 mutation**

| Class of treatment | Treatment in scope | Patients who receive treatment | Use in clinical practice | Issues |
|---|---|---|---|---|
| Cytotoxic therapies for patients unable to receive fludarabine | Bendamustine (with or without rituximab) | Patients with poor prognostic markers for whom chemo-immunotherapy is not appropriate | No data available in this patient group | Clinical advisors agreed that such chemoimmunotherapy regimens would not be suitable for patients with a 17p deletion or TP53 mutation, and therefore not relevant comparators for this group.[13] |
| | Chlorambucil (with or without rituximab) | Patients with poor prognostic markers for whom chemo-immunotherapy is not appropriate | No data available in this patient group | Clinical advisors agreed that such chemoimmunotherapy regimens would not be suitable for patients with a 17p deletion or TP53 mutation, and therefore, not relevant comparators for this group.[13] |
| Anti-CD20s | Alemtuzumab | Patients for whom chemo-immunotherapy is not an option, but who are able to receive ASCT, used in combination with pulsed high-dose glucocorticoids. | No data available in this patient group | Clinical advisors recognise alemtuzumab as a relevant comparator,[13] but it does not have a marketing authorisation in the EU and is only available via a patient access scheme agreed between EMA and the manufacturer. It is unclear how long alemtuzumab will be available in this manner.<br>Alemtuzumab is associated with considerable toxicity as a result of immunosuppression such as reactivation of cytomegalovirus[13] and is not suitable for unfit patients. |

| Class of treatment | Treatment in scope | Patients who receive treatment | Use in clinical practice | Issues |
|---|---|---|---|---|
| | Ofatumumab in combination with bendamustine or chlorambucil (subject to ongoing NICE technology appraisal) | Indication: Patients with CLL who have not received prior therapy and who are not eligible for fludarabine-based therapy | No data available in this patient group. | NICE assessment ongoing but not specifically focusing on this patient group. NICE assessment is for all patients with previously untreated CLL for whom fludarabine combination chemotherapy is unsuitable.<br>Clinical advisors felt that ofatumumab+chlorambucil is not a relevant comparator for these high-risk patients as it is a chemo-immunotherapy regimen.[13] |
| | Obinutuzumab in combination with chlorambucil (subject to ongoing NICE technology appraisal) | Indication: Adult patients with previously untreated CLL with comorbidities, making them unsuitable for full-dose fludarabine-based therapy | Not used (not yet available) | NICE assessment ongoing but not specifically focusing on this patient group. NICE assessment is for all patients with previously untreated CLL for whom fludarabine combination chemotherapy is unsuitable.<br>Clinical advisors felt that this is not a relevant comparator for these high-risk patients as it is a chemo-immunotherapy regimen.[13] |
| Supportive therapies | Best supportive care (including but not limited to regular monitoring, blood transfusions, infection control and psychological support) | In patients not fit enough to receive any of the above treatments or where all other treatment options have been exhausted. | No data available for this patient group. Likely to consist of similar treatments to those noted above. | Not assessed by NICE in this population. |

**Key:** CLL, chronic lymphocytic leukaemia; EMA, European Medicines Agency; EU, European Union; FCR, fludarabine, cyclophosphamide and rituximab; NICE, National Institute for Health and Care Excellence

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.[53] In particular, rituximab monotherapy is used for the management of complications such as auto-immune haemolytic anaemia and idiopathic thrombocytopenic purpura.[13] 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 regimen use across England.[13]

For the phase III trial in relapsed CLL patients (Study 116), on which this 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.[16]

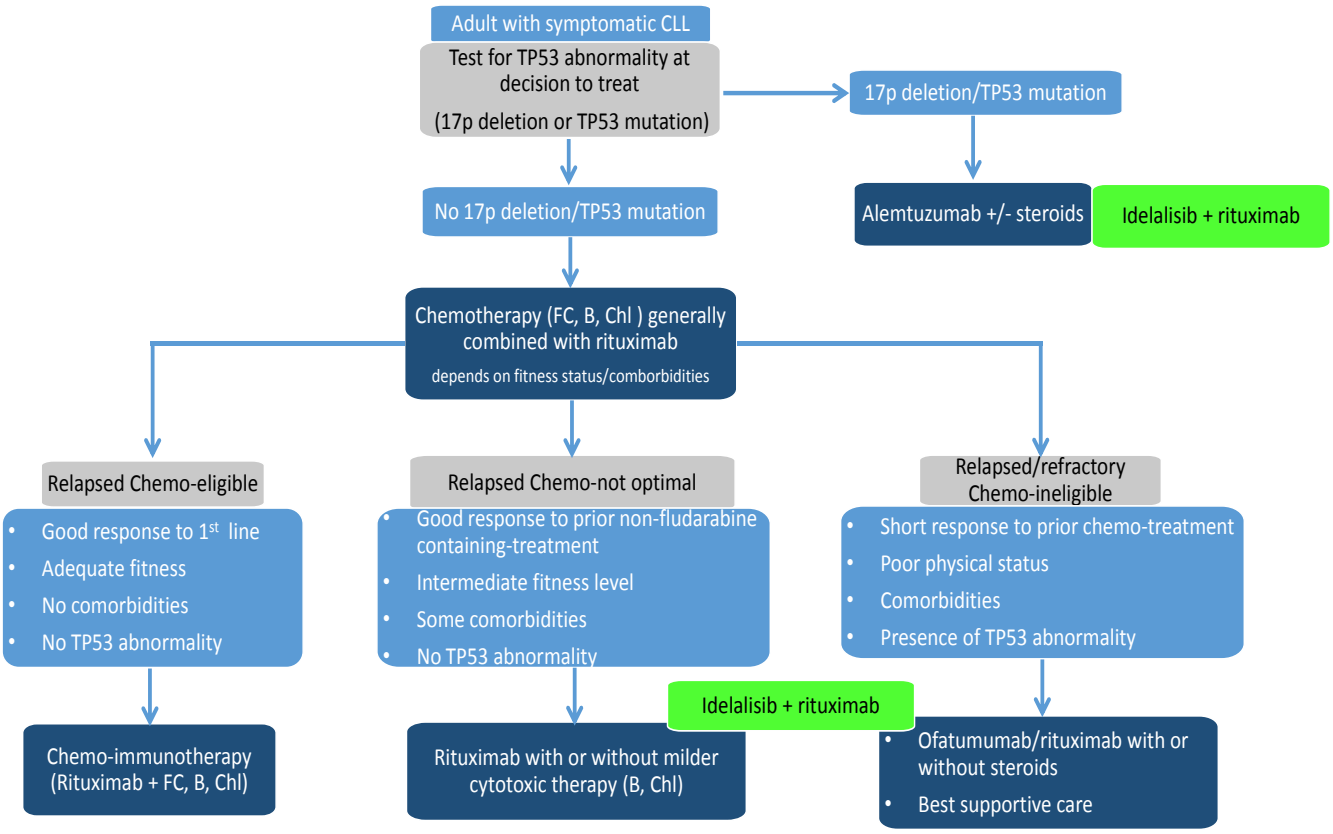
Although rituximab monotherapy is not a recognised comparator within the scope, it is assumed that it has a similar efficacy to ofatumumab in patients with CLL, as supported by clinical opinion from an advisory board of UK clinicians.[13] There are no data directly comparing rituximab and ofatumumab 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.[18]

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. A network meta-analysis was conducted that indicated 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.[17]

As described earlier, idelalisib, when used in combination with rituximab, has a marketing authorisation for two populations: adult patients with CLL who have received at least one prior therapy and for whom cytotoxic-based therapy will not be indicated; and adult patients with CLL with a 17p deletion/TP53 mutation who are

unsuitable for chemo-immunotherapy. The anticipated positioning for idelalisib within the existing treatment landscape is presented in Figure 3. For both of the populations, idelalisib represents a clear step-change as it addresses a high unmet need and provides a well tolerated and 'patient-friendly' treatment.

**Figure 3: Anticipated place of idelalisib in the treatment pathway for CLL**




**Key:** B, bendamustine; Chl, chlorambucil; CLL, chronic lymphocytic leukaemia; FC, fludarabine and cyclophosphamide.

## *3.4 Equality issues*

The current, most effective treatments available for treatment of CLL are most suited to young and fit patients.[1] 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).[55] 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.

# 4 Clinical effectiveness

The methods for the identification of relevant studies are presented in section 4.1 for the following:

- the relapsed or refractory CLL population,
- the untreated CLL population with 17p deletion or TP53 mutation.

A summary of all of the identified RCTs are presented together. Following this, the results are presented in detail for the identified RCTs of idelalisib with rituximab and any relevant comparators from the decision problem for the following:

- the relapsed or refractory CLL population,
- the untreated CLL population with a 17p deletion or TP53 mutation.

Only one RCT and one non-RCT were identified for the untreated population with a 17p deletion or TP53 mutation, and therefore, the majority of the presented evidence will be for the relapsed or refractory population. Table 15 and Table 16 present a summary of the evidence available for each treatment related to the decision problem, for relapsed or refractory and untreated CLL with a 17p deletion or TP53 mutation, respectively, and where this evidence is presented in this submission.

**Table 15: Summary of available evidence for relapsed or refractory CLL**

| Treatment in NICE scope | Available evidence | Comparator(s) | Trial(s) | Section |
|---|---|---|---|---|
| IR (idelalisib with rituximab) | RCT | Rituximab monotherapy | Study 116 | Section 4.1 through Section 4.8 |
| | Single-arm study | NA | Furman (2013) | Section 4.11 |
| FCR | RCT | FC | Robak (2010) | Section 4.1, 4.2, and 4.7 |
| | Single-arm studies | NA | Tam (2006), Badoux (2011) and Smolej (2013) | Section 4.11 |
| | Observational studies | Bendamustine + rituximab and chlorambucil + rituximab | Lopez (2013) | Section 4.11 |
| Bendamustine | RCT | Fludarabine | Niederle (2013) | Section 4.1, 4.2, and 4.7 |
| Bendamustine + rituximab | RCT | Chlorambucil + rituximab | Leblond (2012) | Section 4.1, 4.2, and 4.7 |
| | Single-arm study | NA | Fischer (2011) | Section 4.11 |
| | Observational study | FCR and chlorambucil + rituximab | Lopez (2013) | Section 4.11 |
| Chlorambucil | No evidence | | | |
| Chlorambucil + rituximab | RCT | Bendamustine + rituximab | Leblond (2012) | Section 4.1, 4.2, and 4.7 |
| | Observational study | FCR and bendamustine + chlorambucil | Lopez (2013) | Section 4.11 |
| Corticosteroids | No evidence | | | |
| Corticosteroids + rituximab | Single-arm study | NA | Pileckyte (2011) | Section 4.11 |
| Ofatumumab | Single-arm studies | NA | Coiffier (2010) and Wierda (2010) | Section 4.11 |
| Best supportive care | No evidence | | | |

**Key:** C, cyclophosphamide; CLL, chronic lymphocytic leukaemia; F, fludarabine; FCR, fludarabine and cyclophosphamide; FCR, fludarabine, cyclophosphamide and rituximab; NA, not applicable; NICE, National Institute for Health and Care Excellence; R, rituximab; RCT, randomised, controlled trial.

**Table 16: Summary of available evidence for untreated CLL with a 17p deletion or TP53 mutation**

| Treatment in NICE scope | Available evidence | Comparator(s) | Trial(s) | Section |
|---|---|---|---|---|
| IR | Single-arm study | NA | O'Brien (2014) | Section 4.11 |
| Bendamustine | No evidence | | | |
| Bendamustine + rituximab | No evidence | | | |
| Chlorambucil | Subgroup of RCT | Alemtuzumab | Hillmen (2007) | Section 4.1, 4.2, and 4.7 |
| Chlorambucil + rituximab | No evidence | | | |
| Alemtuzumab | Subgroup of RCT | Chlorambucil | Hillmen (2007) | Section 4.1, 4.2, and 4.7 |
| Best supportive care | No evidence | | | |
| **Key:** CLL, chronic lymphocytic leukaemia; NA, not applicable; NICE, National Institute for Health and Care Excellence; RCT, randomised, controlled trial. | | | | |

## *4.1 Identification and selection of relevant studies*

**Relapsed or refractory CLL patients**

**Search strategy for RCTs in relapsed or refractory CLL**

The final NICE scope was available in December 2014 but was not available at the time the searches were conducted. Therefore, selection of the comparators was performed by reviewing international guidelines and expert opinion. A targeted review of the clinical guidelines for the treatment of relapsed and refractory CLL was carried out. The following guidelines were searched:

- American Journal of Haematology CLL: 2013 update on diagnosis, risk stratification and treatment[11]
- European Society for Medical Oncology (ESMO 2011)[10]
- National Comprehensive Cancer Network (NCCN Version 2.2013 was searched but this version is no longer available online)
- Recommendations from the German Society for Diagnosis and Therapy of Haematological and Oncological Diseases (2012)[56]
- British Committee for Standards in Haematology(2012)[7]
- Alberta Health Services – Clinical Practice Guideline (2013)[57]

If a treatment was recommended by two or more guidelines, it was selected for inclusion as a comparator in the systematic literature review. To validate the list of comparators, clinical opinion was sought, and a one day advisory meeting was held with the aim of refining the list of comparators to those pertinent to current clinical practice. The discussions led to the selection of the comparators outlined in Table 17. The wide variety of comparators identified as used for treatment of this population despite the lack of evidence within clinical studies further demonstrates that there is a high unmet need within this population.

The following databases were searched from their inception date on 14 January 2014:

- MEDLINE and MEDLINE in Process (OVID SP)
- EMBASE (OVID SP)
- Cochrane Central Register of Controlled Trials (CENTRAL)

These databases are regarded as the most important sources to search for reports of controlled trials.[58]

The search strategies combined free text and controlled vocabulary terms (MeSH in MEDLINE and CENTRAL and EMTREE terms in EMBASE). Search filters to identify RCTs were used in MEDLINE and EMBASE. The searches were limited to English-language papers pertaining to humans. The search strategies are provided in Appendix 3.

In addition, conference abstracts from the 2012 and 2013 annual meetings of the European Hematology Association (EHA) and American Society of Hematology (ASH) were searched. These conference proceeding searches were restricted to the last 2 years as any studies that were presented at previous conferences would be expected to have been subsequently reported in full papers.

**Study selection for RCTs in relapsed or refractory CLL**

The eligibility criteria were defined in terms of patient, intervention, comparators, outcomes and study design – PICOS criteria (Table 17).

**Table 17: Eligibility criteria used in search strategy**

| | |
|---|---|
| Patients | Adult patients with relapsed or refractory CLL |
| Intervention | IR |
| Comparators[a] | Fludarabine + cyclophosphamide + rituximab<br>Fludarabine + cyclophosphamide<br>Bendamustine<br>Bendamustine + rituximab<br>Alemtuzumab<br>Alemtuzumab + methylprednisolone<br>Alemtuzumab + fludarabine<br>Rituximab<br>Ofatumumab<br>Chlorambucil<br>Ibrutinib[b] |

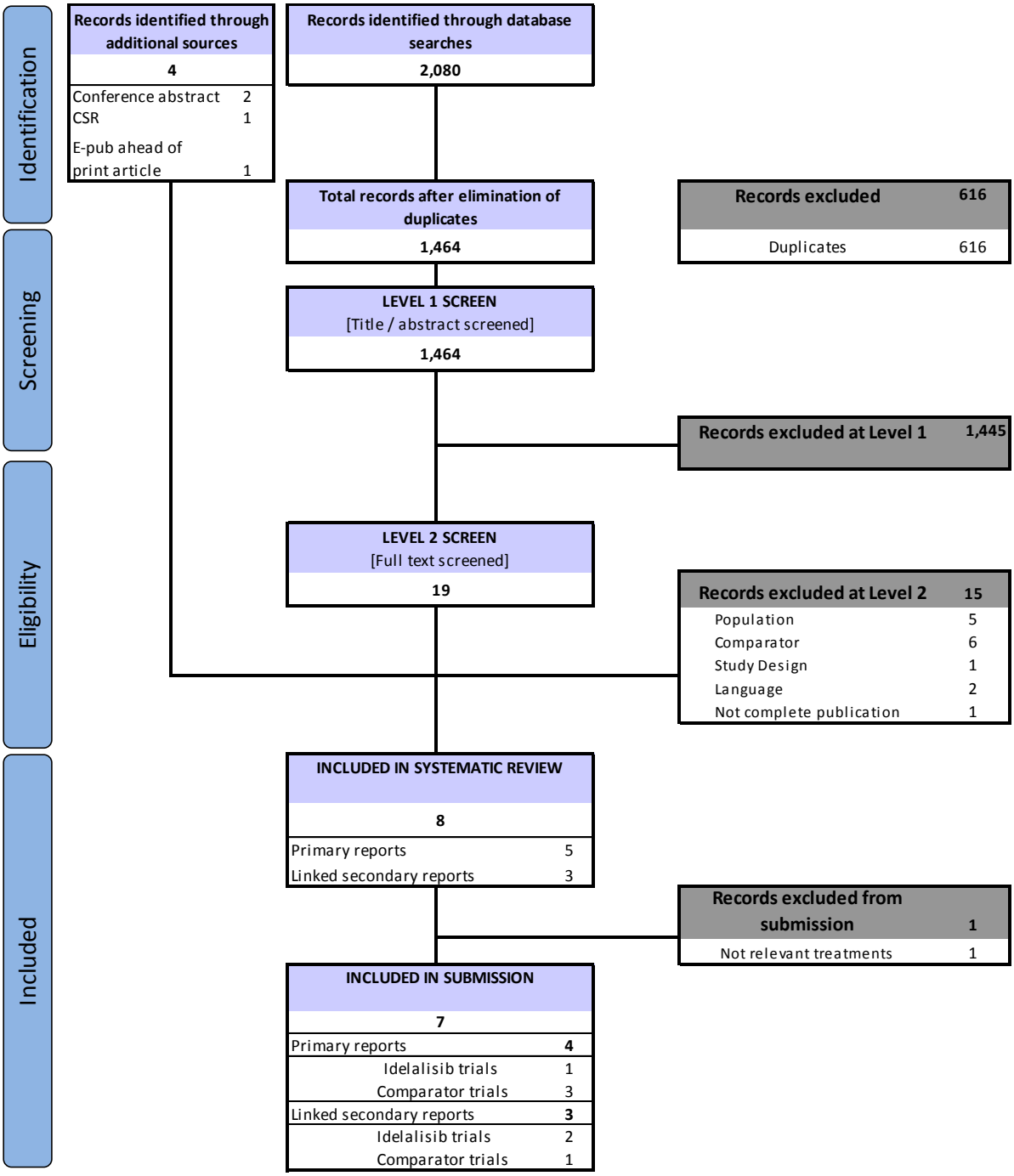
| | |
|---|---|
| Outcomes | Progression-free survival<br>Overall survival<br>Response<br>Grade 3/4 adverse events |
| Study design | Randomised controlled trials only |
| Language | English-language studies only |
| **Key:** CLL**,** chronic lymphocytic leukaemia.<br>**Notes**: a. Any study that contained treatment combinations including one of the listed comparators was included in the systematic literature review.<br>b. the Bruton kinase inhibitor ibrutinib was included as a comparator because it was mentioned as a treatment option in the NCCN guidelines.[16] | |

Abstracts were assessed against the eligibility criteria by two independent reviewers, and any difference in opinion regarding eligibility was resolved through discussion with a third independent reviewer. The same selection process was also applied to the subsequent review of full papers.

**PRISMA diagram for RCTs in relapsed or refractory CLL**

Figure 4 presents the PRISMA diagram for the systematic literature review to identify RCTs of idelalisib with rituximab and relevant comparators. The systematic literature review identified seven relevant publications relating to five trials. One of these trials did not include any relevant comparators from the final NICE scope and was therefore excluded from the submission. This submission includes RCT data from two publications relating to one trial of idelalisib with rituximab and from four publications relating to three trials of relevant comparators. The references of studies identified by any of the systematic literature reviews used to inform this submission that were considered not to be relevant to the decision problem are presented in Appendix 3, alongside the reason for their exclusion.

**Figure 4: PRISMA diagram for IR and comparators**




**Key:** CSR, clinical study report; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Table 18 presents the primary and secondary references for the trials that were identified by the systematic literature review and were identified as being relevant to the NICE scope for this submission:

- Study 116 – RCT of idelalisib with rituximab vs. placebo with rituximab (rituximab monotherapy) in relapsed or refractory CLL patients

- Robak et al., 2010 – RCT of FCR vs. FC in relapsed or refractory CLL patients
- Leblond et al., 2012 – RCT of bendamustine with rituximab vs. chlorambucil with rituximab in relapsed or refractory CLL patients
- Niederle et al., 2013 – RCT of bendamustine vs. fludarabine in relapsed or refractory CLL patients

**Table 18: Relevant references identified by the systematic literature review**

| Primary reference | Secondary references | Interventions |
|---|---|---|
| Furman 2014[19] (Study 116 CSR[14]) | Sharman 2014[59] | IR vs. placebo + rituximab |
| Robak 2010[27] | Dufour 2013[60] | FCR vs. FC |
| Leblond 2012[61] | NA | Bendamustine+rituximab vs. chlorambucil+rituximab |
| Niederle 2013[62] | NA | Bendamustine vs. fludarabine |
| **Key**: C, cyclophosphamide; CSR, clinical study report; F, Fludarabine; NA, Not applicable; R, rituximab. | | |

As corticosteroids were not included in the draft NICE scope, the systematic literature reviews were not designed to identify any evidence for steroid therapy. However, a single-arm study of steroid + rituximab was identified through the search for non-RCT evidence [63] but no evidence for steroid monotherapy was identified. Therefore, a small, targeted search was performed to identify evidence for steroid monotherapy. The methods of this search are described in Appendix 7.

This search did not identify any relevant trials that investigated the use of steroid monotherapy in this patient population. Details of this search are presented in Appendix 7.

**Untreated CLL patients with a 17p deletion or TP53 mutation**

The evidence base for the untreated CLL patients with 1poor prognostic markers is based on a systematic literature review of clinical studies (RCTs and non-RCT studies) specifically investigating idelalisib and relevant comparators for first-line treatment of previously untreated patients with CLL and a 17p deletion or TP53 mutation.

### Search strategy

Searches were performed on 29th July 2014 on the same databases and conference websites as those used for the searches for the relapsed refractory CLL population and using the same search methods. The search strategies are presented in Appendix 3.

### Study selection

The eligibility criteria were defined in terms of patient, intervention, comparators, outcomes and study design (i.e. the PICOS criteria, Table 19).

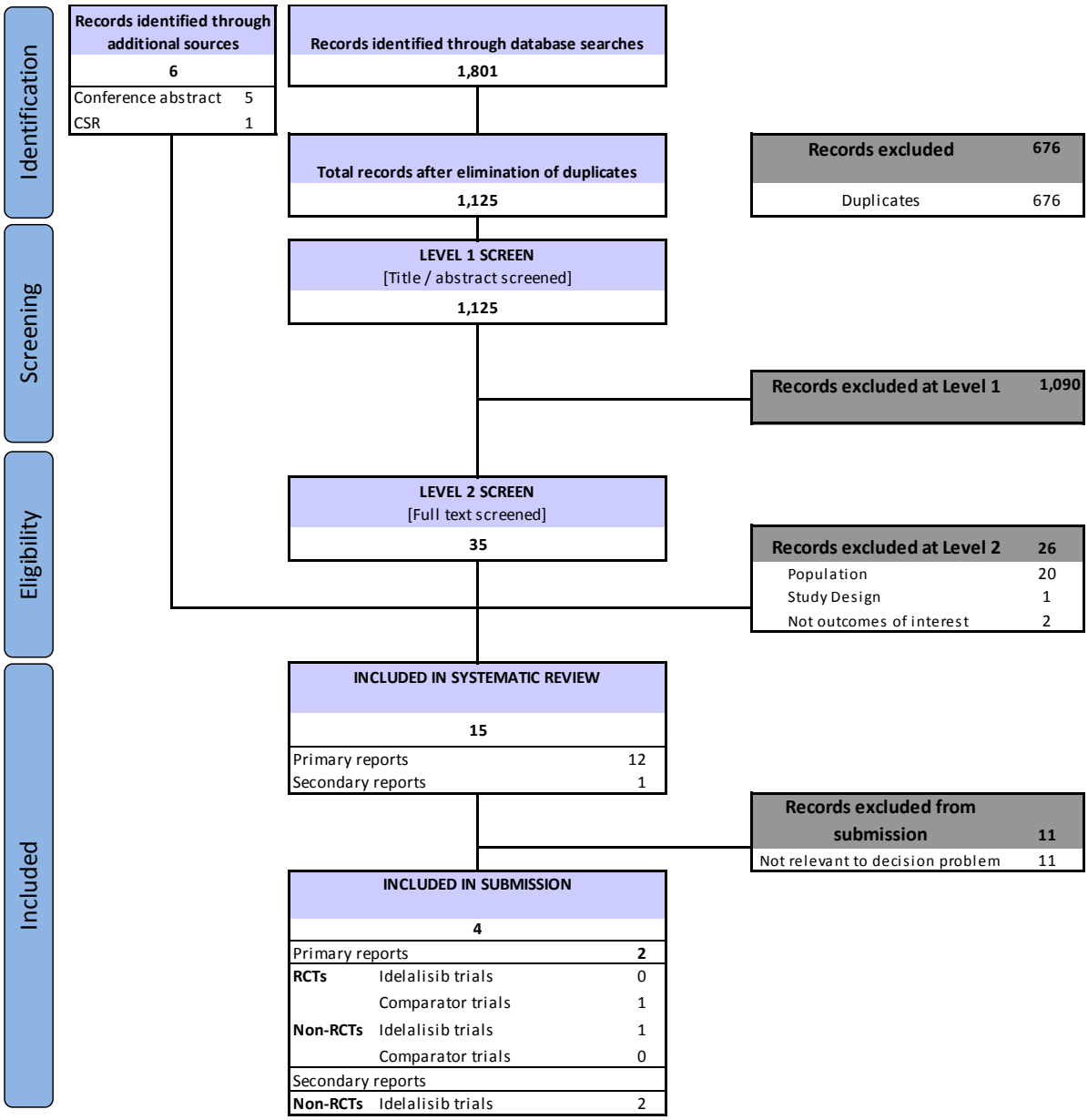
**Table 19: Eligibility criteria used in the search strategy for untreated CLL patients with a 17p deletion or TP53 mutation**

| Clinical effectiveness | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **Population** | Adult patients (age ≥18 years) with treatment naïve CLL and 17p deletion or TP53 mutation | None specified |
| **Intervention** | Idelalisib | None specified |
| **Comparators** | Ofatumumab<br>High-dose methylprednisolone<br>Alemtuzumab | SCT |
| **Outcomes** | Overall survival<br>Progression-free survival<br>Response<br>Grade 3/4 adverse events | None specified |
| **Study design** | Randomised and non-randomised studies<br>Prospective studies only | Retrospective analyses<br>Case studies or case series not designed to compare clinical effectiveness<br>Reviews<br>Commentaries |

| Language restrictions | English language | Non-English language |
|---|---|---|
| **Key**: CLL, chronic lymphocytic leukaemia; SCT, stem cell therapy | | |

Figure 5 presents the PRISMA flow diagram, showing the flow of studies through the systematic literature review and inclusion/exclusion at each stage. The references of studies identified by any of the systematic literature reviews used to inform this submission that were considered not to be relevant to the decision problem are presented in Appendix 3, alongside the reason for their exclusion.

**Figure 5: PRISMA diagram for systematic literature review for untreated CLL patients with a 17p deletion or TP53 mutation**




**Key:** CLL, chronic lymphocytic leukaemia; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial.

Only two studies were identified within the systematic literature review that were strictly relevant to the decision problem:

- Hillmen (2007)[22] – RCT of alemtuzumab vs. chlorambucil in untreated patients containing a small subgroup (n=11 vs. n=10) of patients with a 17p deletion or TP53 mutation
- Study 101-08 [21,64] – single-arm study of idelalisib with rituximab in untreated patients containing a small subgroup (n=9) of patients with a 17p deletion or TP53 mutation

In summary, there are no RCTs of idelalisib identified for this population of untreated CLL patients with a 17p deletion or TP53 mutation. The single-arm study of idelalisib in this untreated patient population [64] will be discussed further within the section describing non-RCT studies (Section 4.11).

The RCTs comparing treatments relevant to the decision problem in this untreated patient population[22] will be described in more detail under the relevant headings in section 4.2 through section 4.7.

The scarcity of evidence for effective treatment options in this population further demonstrates that there is a high unmet need within this population.

## *4.2 List of relevant randomised controlled trials*

Table 20 summarises the RCTs that were identified by the systematic literature review as being relevant to the decision problem.

**Relapsed or refractory CLL**

None of the trials identified in the systematic literature review compared idelalisib with rituximab directly with the appropriate comparators identified in the NICE scope for relapsed or refractory CLL. Only one idelalisib with rituximab trial was identified and this compared with rituximab monotherapy. This systematic literature review also identified three RCTs that investigated treatments relevant to the decision problem; one comparison of FCR with FC,[65] one comparison of bendamustine with rituximab with chlorambucil with rituximab[61] and one comparison of bendamustine with fludarabine.[62] These 3 studies are not conducted in the same population as the main idelalisib with rituximab trial, and they do not provide any links for a treatment

network. The Leblond (2012) study[61] also does not report any PFS or OS outcomes that were of interest. These studies of comparator trials are summarised in Appendix 7.

**Untreated CLL with a 17p deletion or TP53 mutation**

No RCTs were identified that investigated idelalisib in untreated CLL patients with CLL and a 17p deletion or TP53 mutation. However, one single-arm study of idelalisib with rituximab, which included patients within this population was identified (Coutre et al., 2013). This study will be described in further detail in the section describing non-RCT studies (Section 4.11). The EMA identified the activity of idelalisib in patients with CLL and a 17p deletion or TP53 mutation as an area of special interest based upon this study and the consistent results seen across studies at other lines of treatment in the patients with a 17p deletion or TP53 mutation: Study 116 total 95/220 subjects, (n=46 in the idelalisib with rituximab arm and n=49 in the placebo with rituximab arm), Study 101-07 (n=24), Study 101-02 (dose finding).[12]

One RCT was identified that investigated treatments relevant to the decision problem; a comparison of alemtuzumab with chlorambucil.[22] A summary of this trial is presented in Appendix 7.

**Table 20: List of relevant RCTs**

| Trial no. (acronym) | Population | Intervention | Comparator | Patient characteristics |
|---|---|---|---|---|
| NCT01539512 [14, 19, 59] | Relapsed or refractory CLL | IR:<br>I 150mg BID (could be reduced to 100mg); R 375mg/m$^2$ week 0 then 500mg/m$^2$ at weeks 2, 4, 6, 8, 12, 16, 20<br>[N=110] | R 375mg/m$^2$ week 0 then 500mg/m$^2$ at weeks 2, 4, 6, 8, 12, 16, 20<br>[N=110] | • ≥18 years<br>• Had CLL that had progressed within 24 months after their last treatment<br>• Were not able to receive cytotoxic agents<br>• Had a Karnofsky PS of ≥40<br>• Previously treated with either a CD20 antibody-based regimen or at least two previous cytotoxic regimens<br>• Were not able to receive cytotoxic agents |
| Robak et al., 2010[27] | Relapsed or refractory CLL | FCR: F 25mg/m$^2$ daily for 3 days; C 250mg/m$^2$ daily for 3 days; R 375mg/m$^2$ on day 1 of cycle 1 then 500mg/m$^2$ in subsequent cycles<br>[N=276] | FC: F 25mg/m$^2$ daily for 3 days; C 250mg/m$^2$ daily for 3 days<br>[N=276] | • ≥18 years<br>• Patients with CD20+ CLL<br>• Patients had received one prior line of therapy, which could be single-agent chlorambucil (± prednisone/prednisolone), single-agent fludarabine (or other nucleoside analog), or an alkylator-containing combination regimen, but not an alkylator/nucleoside analog combination<br>• Patients could be sensitive or refractory to prior alkylating agents but had to be sensitive to fludarabine (defined as achieving a response that lasted ≥6 months)<br>• Patients with adequate hepatic, renal and bone marrow function and an ECOG performance status ≤1; and a life expectancy more than 6 months |
| Leblond et al., 2012[61] | Relapsed or refractory CLL | BR: B 70mg/m$^2$; R 375mg/m$^2$ on day 1 of cycle 1 then 500mg/m$^2$ in cycles 2-6<br>[N=18] | ChR: Chl 10mg/m$^2$ days 1-7; R 375mg/m$^2$ on day 1 of cycle 1 then 500mg/m$^2$ in cycles 2-6 | • ≥18 years<br>• Patients ineligible for fludarabine treatment as a result of age or greater number of comorbidities<br>• Patients undergoing first- or second-line treatment in whom relapse had occurred no earlier than 12 months since their |

| Trial no. (acronym) | Population | Intervention | Comparator | Patient characteristics |
|---|---|---|---|---|
| | | | [N=23] | last dose of first-line treatment |
| Niederle et al., 2013[62] | Relapsed or refractory CLL | B 100mg/m$^2$ days 1 and 2<br>[N=50] | F 25mg/m$^2$ days 1-5<br>[N=46] | • ≥18 years<br>• Patients with histologically or immunologically confirmed chronic B-cell leukaemia in refractory (no response or progression during initial chemotherapy) or relapsed situation after first-line treatment regimen<br>• Patients exhibiting disease statuses II-IV according to Rai or B/C according to Binet staging system, respectively. ECOG PS ≥3 |
| Hillmen et al., 2007[22] | Untreated CLL with a subgroup of patients with 17p deletion | Alemtuzumab iv: escalated daily 3, 10, and 30 mg until tolerated at 30mg, three times per week, for up to 12 weeks | Chlorambucil 40 mg/m$^2$ PO, daily for 28 days for no more than 12 cycles | • ≥18 years<br>• Flow cytometry-confirmed CLL, Rai Stage I to IV<br>• No previous chemotherapy for CLL<br>• A life expectancy of at least 12 weeks<br>• WHO performance status of 0 to 2 and adequate renal and liver function. |

**Key:** B, bendamustine; BID, twice daily; C, cyclophosphamide; Chl, chlorambucil; CLL, chronic lymphocytic leukaemia; ECOG, Eastern Cooperative Oncology Group; F, fludarabine; I, idelalisib; iv, intravenous; PO, per oral; PS, performance status; R, rituximab; RCT, randomised controlled trial; WHO, World Health Organisation.

## *4.3 Summary of methodology of the relevant randomised controlled trials*

**Relapsed or refractory CLL**

**Study 116**

Study 116 was a phase III, double-blind, randomised controlled trials of idelalisib 150mg BID with rituximab compared to rituximab monotherapy, conducted in the US, France, UK, Italy and Germany. The study used the International Workshop on CLL (IWCLL) (2008) guidelines for their diagnostic criteria.

Patients who had disease progression while on rituximab monotherapy could crossover to an extension study (Study 117) to receive idelalisib 150mg BID. Table 21 presents a summary of the methods used in Study 116.

**Table 21: Summary of the Methodology of Study 116**

| **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 |

| Trial number (acronym) | Study 116/NCT01539512 |
|---|---|
| | 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 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.[11] |
| **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** | The primary endpoint was PFS, defined as the interval |

| Trial number (acronym) | Study 116/NCT01539512 |
|---|---|
| **(including scoring methods and timings of assessments)** | from randomisation to first documentation of definitive disease progression or death from any cause (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. 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. | |

The main inclusion and exclusion criteria for the idelalisib with rituximab study are reported in Table 22. They specified that participants had to be aged ≥18 years, were eligible after at least one treatment line (either an anti-CD20 or two prior regimens with at least one cytotoxic chemotherapy) and reported performance status criteria; specifying a Karnofsky PS ≥40.

Patients were only included if they were ineligible to receive cytotoxic chemotherapy, due to the presence of cytopenias, creatinine clearance and the number of comorbidities (a cumulative illness rating scale (CIRS) score

>6) and had disease progression within 24 months. They excluded patients with transformation of CLL to more aggressive malignancies.

In general the patient population in Study 116 included high risk patients, with high CIRS scores, that were difficult to treat. More details on the patient characteristics are presented in section 4.5.

The full inclusion and exclusion criteria for the comparator RCTs are presented in Appendix 7.

**Table 22: Inclusion/exclusion criteria – Study 116**

| Main inclusion criteria | Main exclusion criteria |
|---|---|
| ≥18 years<br>Diagnosis of B-cell CLL that warranted treatment according to IW-CLL criteria<br>Presence of radiographically measurable lymphadenopathy previously treated with either an anti-CD20 antibody-based regimen or at least two previous cytotoxic regimens<br>In a subject whose last prior therapy contained an anti-CD20 antibody evidence of disease improvement during that therapy or documentation of CLL progression ≥6 months after completion of that therapy had CLL that had progressed within 24 months after their last treatment<br>Discontinuation of all therapy ≥3 months before randomisation<br>All acute toxic effects of any prior anti-tumour therapy resolved to Grade ≤1 before randomization (with the exception of alopecia [Grade 1 or 2], neurotoxicity [Grade 1 or 2], or bone marrow parameters [Grades 1, 2, 3, or 4] )<br>Were not able to receive cytotoxic agents<br>Had a Karnofsky PS of ≥40<br>Willingness to use contraceptives<br>Required baseline laboratory data within 4 weeks of randomisation<br>In the judgment of the investigator, participation in the protocol offered an acceptable benefit-to-risk ratio when considering current CLL disease status, medical condition, and the potential benefits and risks of alternative treatments for CLL<br>Willingness to comply with study requirements<br>Evidence of a personally signed consent form | Known histological transformation from CLL to an aggressive lymphoma<br>Presence of intermediate- or high-grade myelodysplastic syndrome<br>History of a non-CLL malignancy except for the following: adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate specific antigen for ≥1 year prior to randomization, other adequately treated Stage 1 or 2 cancer currently in complete remission, or any other cancer that has been in complete remission for ≥ 5 years<br>Evidence of ongoing systemic infection at the time of initiation of randomisation<br>Ongoing drug-induced liver injury, chronic active HCV, chronic active HBV, alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver, or portal hypertension<br>Ongoing drug-induced pneumonitis, inflammatory bowel disease, alcohol or drug addiction<br>Pregnancy or breastfeeding<br>History of prior allogenic bone marrow progenitor cell or solid organ transplant<br>Ongoing immunosuppressive therapy other than corticosteroids<br>Prior therapy with any inhibitor of AKT (a serine/threonine protein kinase), Bruton tyrosine kinase (BTK), Janus kinase (JAK), mammalian target of rapamycin (mTOR), phosphatidylinositol 3 kinase (PI3K) (including IDELA), or spleen tyrosine kinase (SYK)<br>History of anaphylaxis in association with previous admin. of monoclonal antibodies<br>Concurrent participation in another therapeutic clinical trial<br>Prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, electrocardiogram (ECG) finding, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the subject or impair the assessment of study results |
| **Key**: CLL, chronic lymphocytic leukaemia; HBV, hepatitis B virus; HCV, hepatitis C virus; IW-CLL, IWCLL, International Workshop on Chronic Lymphocytic Leukemia; PS, performance score; WHO, World Health Organisation. | |

## *4.4 Statistical analysis and definition of study groups in the relevant RCTs*

**Prespecified statistical analysis in Study 116**

Two interim analyses were prespecified at ~50% and ~75% of the planned 119 PFS events and were to be tested at a 2-sided significance level of 0.001 and 0.005, respectively. These analyses offered the opportunity to assess for evidence of substantial clinical benefit early. A decision was made to stop the blinded-phase of the study after the first interim analysis as the 2 sided p-value for the primary PFS analysis crossed the prespecified alpha boundary of 0.001. 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. The significance level of the second analysis was prespecified at 0.005 for the PFS endpoint and 0.05 for the secondary endpoints. 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.

Table 23 presents the primary and secondary outcomes of Study 116. HRQL was included as a tertiary outcome. Table 24 summarises the statistical analyses used in this trial to assess these outcomes.

**Table 23: Primary and secondary outcomes of Study 116**

| Trial no. (acronym) | Primary outcome(s) and measures | Reliability/validity/ current use in clinical practice | Secondary outcome(s) and measures | Reliability/validity/ current use in clinical practice |
|---|---|---|---|---|
| NCT01539512[14] | PFS | Tumour control assessments were based on standardised IWCLL criteria [32], modified for this study considering the pharmacology of idelalisib and rituximab. The individual and composite endpoints of response and progression (considering changes in lymph node area, liver and spleen size, bone marrow, platelet counts, haemoglobin, neutrophil counts, and peripheral blood lymphocyte counts) were determined. The efficacy and safety measurements used in this study followed standard medical practice guidelines and were acceptable measurements that provided health assessments for this study population. These measurements were generally recognized as reliable, accurate, relevant, and appropriate. Primary analyses were assessed by IRC for increased validity. | OS<br>ORR – defined as the proportion of patients who receive a CR or a PR<br>CR rate<br>Lymph Node Response rate – the proportion of patients who achieve a ≥50% decrease from baseline in the sum of the products of the greatest perpendicular diameters of index lymph nodes | Tumour control assessments were based on standardised IWCLL criteria [32], modified for this study considering the pharmacology of idelalisib and rituximab. The individual and composite endpoints of response and progression (considering changes in lymph node area, liver and spleen size, bone marrow, platelet counts, haemoglobin, neutrophil counts, and peripheral blood lymphocyte counts) were determined. The efficacy and safety measurements used in this study followed standard medical practice guidelines and were acceptable measurements that provided health assessments for this study population. These measurements were generally recognized as reliable, accurate, relevant, and appropriate. Primary analyses were assessed by IRC for increased validity. |

**Key**: CR, complete response; IRC, independent review committee; IWCLL, International Workshop on Chronic Lymphocytic Leukemia ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

**Table 24: Summary of statistical analyses in Study 116**

| | |
|---|---|
| **Hypothesis/objective** | Objective: To evaluate the effect of the addition of idelalisib to rituximab on progression-free survival in subjects with previously treated CLL.<br>Statistical hypothesis: H0: hazard ratio (between Arm A [IR] and Arm B [placebo + rituximab]) equals 1 versus H1: hazard ratio is less than 1 |
| **Statistical analysis: general and analysis populations** | A sequential testing procedure was used to adjust for the overall type I error rate (i.e. if the primary endpoint was significant, the secondary endpoints of rates of overall response, lymph-node response, and overall survival would be tested sequentially).<br>Two interim analyses were prespecified after approximately 50% and 75% of the anticipated 119 events had occurred, at alpha levels of 0.001 and 0.005, respectively.<br>All efficacy analyses, including the primary analysis, were based on the ITT population unless stated otherwise, defined as all subjects who were randomised, regardless of whether they received any study drug(s) or received a different regimen from the one they were randomised to. Treatment assignments were designated according to randomisation. This analysis set was also used in the analyses of subject characteristics.<br>The Per Protocol analysis set was used as a sensitivity analysis: this included subjects in the ITT analysis set who met the general criteria defining the target population for this study, were adherent to the protocol, were compliant with study drug treatment, and were evaluable for relevant efficacy endpoints. Study drug assignment was designated according to the actual treatment received.<br>The Safety analysis set included all subjects who received at least 1 dose of study treatment, with treatment assignments designated according to the actual treatment received. This analysis set was used in the analyses of safety variables, study treatment administration, post-study therapy, and health economic variables.<br>For the ITT analysis all patients who crossed over from Study 116 were analysed according to the treatment that they were randomised to. An additional Rank Preserving Structural Failure Time (RPSFT) analysis was performed for overall survival to evaluate the effect of IR on OS to account for the crossover effect. |
| **Statistical analysis: endpoints** | Primary endpoint (PFS): PFS was calculated using the Kaplan-Meier method and rates compared using a stratified log-rank test. A Cox model with adjustment for stratification was used to calculate hazard ratios.<br>Binary response endpoints: the Cochran–Mantel–Haenszel chi-square test, adjusted for stratification, was used to assess between-group differences.<br>HRQL: FACT-Leu was scored based on the FACIT3 scoring guideline and user manual. Repeated measures |

| | |
|---|---|
| | mixed-effects models were used to assess mean change from baseline within and between treatment arms. Least squares of mean change from baseline over time were plotted for each arm, and the FACT-Leu questionnaire compliance and completion rates for each study arm and at each time point were calculated. |
| **Sample size, power calculation** | Based on previous studies it was assumed that the rituximab arm would have a median PFS of approximately 6 months. An improvement to 10.5 months due to the addition of idelalisib would correspond to a benefit ratio of 1.75 (hazard ratio [HR] 0.57). With HR=1 under the null hypothesis of no difference between treatment arms, and HR=0.57 under the alternative hypothesis of superiority of the idelalisib containing combination, 119 events (definitive CLL progressions) are required to achieve a power of > 0.85 based on a stratified log-rank test with a 2-sided significance level of 0.05.<br>Assuming a planned accrual period of 12 months, a minimum follow-up of 12 months, and that 10% of subjects would be lost to follow-up, 100 subjects per arm (200 total) were to be enrolled to achieve the expected number of events by 12 months. |
| **Data management, patient withdrawals** | In general, values for missing data were not imputed unless methods for handling missing data were specified. No data were excluded from the analyses, including any outliers. |
| **Subgroup analyses** | Primary and secondary efficacy endpoints were examined in the following prespecified subgroups:<br>• 17p deletion and/or *TP53* mutation in CLL cells: either versus neither (or indeterminate)<br>• *IgVH* mutation: unmutated (or *IgVH*3-21) versus mutated (or indeterminate)<br>• 17p deletion (Yes or No [including indeterminate])<br>• Sex (Male or Female)<br>• Age group (< 65 or ≥ 65)<br>• Race (White or Non-White) |
| **Key:** CLL, chronic lymphocytic leukaemia; FACIT, Functional Assessment of Chronic Illness Therapy; FACT-Leu, Functional Assessment of Cancer Therapy – Leukemia; HRQL, health-related quality of life; PFS, progression free survival. | |

**Accounting for crossover**

According to the protocol, patients in Study 116 could crossover from rituximab monotherapy to idelalisib 150mg BID (in the extension Study 117) if they had disease progression confirmed by IRC. Additionally, based on results from the first interim analysis, the decision was made to stop the trial early because of overwhelming efficacy and to perform a second interim analysis on blinded data. Patients randomised to rituximab monotherapy were then given the option to cross over to idelalisib with rituximab without confirmed disease progression.

For the ITT analysis, patients were analysed according to the treatment that they were randomised to, and this included patients who had crossed over to receive idelalisib with rituximab in Study 117.

According to the study protocol for the blinded phase, following disease progression confirmed by IRC, subjects randomised to the rituximab plus placebo arm were given the opportunity to receive idelalisib 150 mg twice daily. Forty-two of 110 patients randomised to rituximab plus placebo patients (38%) switched to idelalisib monotherapy following disease progression.

Based on results from the first interim efficacy analysis, the data monitoring committee (DMC) recommended stopping the trial for overwhelming efficacy, and Gilead agreed. On 07 October 2013, a decision was made in consultation with the US FDA to stop the study early and to perform a second interim analysis on blinded data up to 09 October 2013. The database for the blinded portion of the study was finalised on 08 November 2013, and the subjects randomised to the rituximab plus placebo arm were given the opportunity to receive idelalisib 150 mg without confirmed disease progression. Forty-three of the 110 patients randomised to rituximab plus placebo (39%) switched to idelalisib monotherapy at this point, before disease progression.

Three statistical methods were considered to attempt to account for bias due to cross-over, and evaluate OS in line with DSU guidance [66]:

1. Inverse Probability of Censoring Weighing (IPCW)
2. Two-stage Weibull
3. Rank Preserving Structural Failure Time (RPSFT)

Considering the level of cross-over (i.e. 86 patients, 78% of the control arm, switched to the intervention arm), no probability or propensity score could be determined through the IPCW method. The IPCW was non-informative in trying to adjust for the cross-over.

The two-stage model requires the definition of a clinical secondary baseline, for example, progression. This would require that all, or at least the majority, of switches occur at treatment progression. In Study 116, there was not much difference in the number of patients switching prior to progression, therefore this method was inappropriate.

For these reasons, the adjusted OS data presented here and used in the model were estimated using the RPSFT method. The RPSFT method assumes that the treatment effect of idelalisib with rituximab is equal for all patients no matter when the treatment is received.

Using the RPSFT method, for patient i, the counterfactual event time is estimated as follows:

- Time to event while patient is on the control is $TX_i$, and on treatment it is $TY_i$. Therefore, the ITT time to observed event $T_i$ is: $T_i = TX_i + TY_i$.
- The RPSFT method calculates counterfactual survival times based on $\phi$, the value for which $U_i$ (counterfactual survival times) are balanced across treatment groups on a specified test.

The exponential of $-\phi$ represents the acceleration factor – the relative speed at which life is 'used up' – on the control compared to the treatment. The counterfactual event time for patients who switched treatment is then given as $U_i = TX_i + 1/F * TY_i$. $= TX_i + \exp(\phi)\, TY_i$.

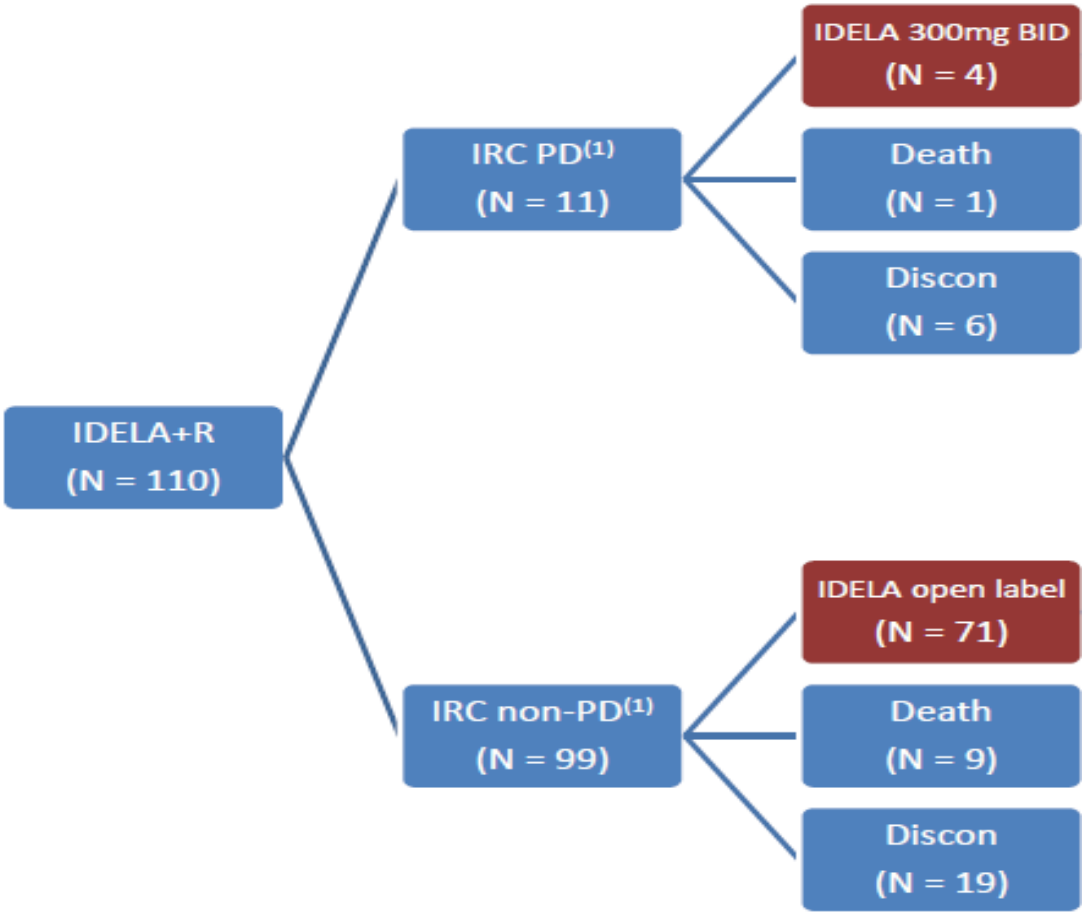
The "grid" search method was used to obtain the RPSFT acceleration factor. After adjusting the time on-treatment for rituximab plus placebo subjects ([redacted]).

## 4.5 Participant flow in the relevant randomised controlled trials

**Participant flow in Study 116**

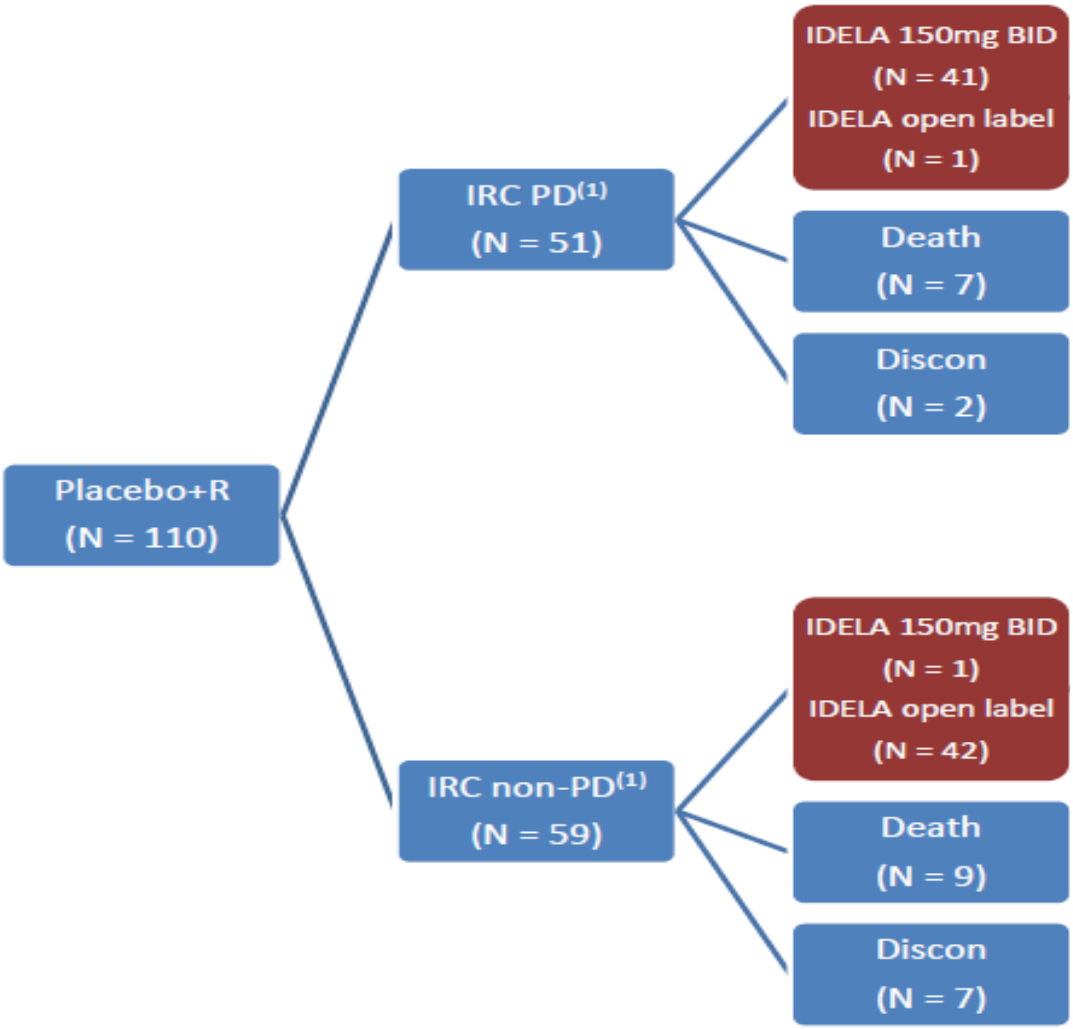
Figure 6 and Figure 7 present the CONSORT diagrams of the patient disposition details for Study 116.

**Figure 6: CONSORT Diagram for the IR Arm of Study 116**




**Key:** BID, twice daily; discon, discontinued; Idela, idelalisib; IRC, independent review committee; R, rituximab; PD, progressive disease
**Notes:** (1) As of 2nd interim datacut (9 October 2013)
Out of 32 subjects who discontinued study, 17 subjects agreed to continue in the 5-year long-term follow-up

**Figure 7: CONSORT Diagram for the Placebo with Rituximab Arm of Study 116**




**Key:** BID, twice daily; discon, discontinued; Idela, idelalisib; IRC, independent review committee; R, rituximab; PD, progressive disease
**Notes:** (1) As of 2nd interim datacut (9 October 2013)
Out of 20 subjects who discontinued study, 10 subjects agreed to continue in the 5-year long-term follow-up

## Baseline characteristics of Study 116[14,19]

The baseline characteristics of study participants are reported in Table 25. The numbers of patients randomised were the same as the numbers of patients in the ITT population. The size of the ITT population was 110 in both arms. The mean age was 71 in the idelalisib with rituximab arm and 70 in the rituximab monotherapy arm, and the median age was 71 years for both. The proportion of female participants in study arms was well balanced. Patients in Study 116 had received an average of three previous treatments.

The genetic characteristics of participants in each treatment group are also reported in Table 25. In total, 41.8% to 44.5% of patients had 17p deletion and/or TP53 mutation, and 82.7% to 84.5% were IgVH unmutated.

CLL can be described by a number of staging systems, including Binet stage and Rai stage. Binet stage was the most widely reported classification in this review and is most commonly used in the UK and Europe. The majority of patients had Stage C disease. Some patients with Stage A disease were included; 3.6% in the rituximab monotherapy arm and 6.4% in the idelalisib with rituximab arm.

Rai stage was also reported in Study 116 and most patients had Stage III or IV disease. This is consistent with Binet staging (Table 25).

The Karnofsky score for the patient population was required to be ≥40 in order for patients to be included in Study 116. The majority of patients had a Karnofsky score of ≤80.

Patients in Study 116 also had a large number of comorbidities, as is indicated by their CIRS scores; with median scores of 8.5 and 8.0 for the idelalisib with rituximab and rituximab arms, respectively. Over 90% of patients had a total CIRS score of >6 and a score of >0 in at least 3 organ systems (Table 25).

In general, patients in Study 116 were considered to be more severe, sicker, and therefore more difficult to treat patients than patients in other clinical trials in the relapsed or refractory setting. However, the patient population in this clinical trial is more reflective of patients in real clinical practice.

**Table 25: Baseline characteristics of participants in Study 116**

| Baseline characteristic | IR | Placebo + R |
|---|---|---|
| Patients | n=110 | n=110 |
| ITT population | n=110 | n=110 |
| ITT definition | All randomised patients regardless of whether they received study drug or a different regimen to the one to which they were randomised | |
| Age (years), mean (SD) | 71 (7.7) | 70 (8.1) |
| Age (years), median (range) | 71 (48-90) | 71 (47-92) |
| Gender, female (%) | 30.9 | 38.2 |
| Rai Stage, %… 0 | 0 | 0.5 |

| Baseline characteristic | IR | Placebo + R |
|---|---|---|
| I | 16.4 | 17.3 |
| II | 14.5 | 10.0 |
| III | 20.0 | 15.5 |
| IV | 43.6 | 49.1 |
| Missing | 5.5 | 7.3 |
| Binet Stage, %… A | 6.4 | 3.6 |
| B | 226.4 | 30.0 |
| C | 57.3 | 54.5 |
| Missing | 10.0 | 11.8 |
| Time since diagnosis, median (range), months | 94.2 (7.6, 318.7) | 103.1 (8.6, 248.8) |
| Time since diagnosis, mean (SD) months | 108.3 (62.28) | 106.4 (52.73) |
| Prior therapies, median (range) | 3 (1-12) | 3 (1-9) |
| Prior therapy, regimen, % | | |
| BR | 46 | 43 |
| FCR | 33 | 36 |
| R | 32 | 31 |
| FR | 16 | 18 |
| Ch | 18 | 14 |
| Karnofsky score, % | | |
| 40 | 0.9 | 0.9 |
| 50 | 2.7 | 3.6 |
| 60 | 5.5 | 4.5 |
| 70 | 18.2 | 11.8 |
| 80 | 38.2 | 40.9 |
| 90 | 20.9 | 26.4 |
| 100 | 13.6 | 11.8 |
| ≤80 | 65.5 | 61.8 |
| Platelet count <100 x $10^9$/L, % | 45.5 | 50.0 |
| Haemoglobin <12.5g/dL, % | 79.1 | 82.7 |
| Absolute Neutrophil Count ≤1.5 x $10^9$/L, % | 24.5 | 26.4 |
| **Creatinine clearance, mL/min** | | |
| Mean (SD) | 67.9 (24.38) | 68.9 (22.01) |
| Median (range) | 61.5 (32.4, 160.8) | 66.3 (22.8, 198.6) |
| <30, % | 0 | 0.9 |
| 30≤ creatinine clearance <60, % | 43.6 | 35.5 |
| 60≤ creatinine clearance <90, %) | 37.3 | 52.7 |

| Baseline characteristic | IR | Placebo + R |
|---|---|---|
| ≥90, % | 19.1 | 10.9 |
| Missing, % | 0 | 0 |
| **CIRS Score** | | |
| Median (Q1, Q3) | 8.5 (7.0, 10.0) | 8.0 (7.0, 10.0) |
| Total CIRS score >6, % | 88.2 | 82.7 |
| CIRS score of 3 or 4 for any organ system, % | 35.5 | 39.1 |
| CIRS score of >0 in at least 3 organ systems, % | 98.2 | 90.9 |
| **CLL genetics** | | |
| IgVH unmutated, % | 82.7 | 84.5 |
| 17p deletion and/or TP53 mutation, % | 41.8 | 44.5 |
| 17p deletion, % | 24 | 28 |
| **Key:** B, bendamustine; C, cyclophosphamide; Chl, chlorambucil; CIRS, cumulative illness rating scale; CLL, Chronic lymphocytic leukaemia; F, fludarabine; FCR, fludarabine, cyclophosphamide and rituximab; I, idelalisib; IgVH, immunoglobulin variable region heavy chain; ITT, intent to treat; N, Number; NR, not reported; R, rituximab; SD, WHO, World Health Organisation.<br>**Notes:** Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee | | |

**Baseline characteristics for the trials of relevant comparators are presented, with their results, alongside the same data from Study 116 in**

**Table 33 and**

Table 34, in section 4.7.

## *4.6 Quality assessment of the relevant randomized controlled trials*

Table 26 presents the quality assessment for Study 116.

**Table 26: Quality assessment results for Study 116**

| Trial no. (acronym) | NCT01539512[14] |
|---|---|
| Was randomisation carried out appropriately? | Yes<br>IWRS was used |
| Was the concealment of treatment allocation adequate? | Yes<br>IWRS was used |
| Were the groups similar at the outset of the study in terms of prognostic factors? | Yes |
| Were the care providers, participants and outcome assessors blind to treatment allocation? | Yes<br>Double blind. Maintained by identical appearance, packaging, labelling and scheduling of placebo |
| Were there any unexpected imbalances in drop-outs between groups? | No |
| Is there any evidence to suggest that the authors measured more outcomes than they reported? | No<br>All prespecified outcomes reported |
| Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data? | Yes<br>ITT of all randomised patients |
| **Key**: ITT, intent to treat; IWRS, interactive web response system.<br>**Notes**: Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination | |

Information was provided regarding the method of randomisation and the method of allocation concealment, which are interpreted as indicating a low risk of bias due to the interactive voice-/web-response system used. The risk of bias in the blinding of participants, personnel and outcome assessment was assessed as being low due to the methods used. The risk of bias due to incomplete data and for selective reporting was assessed and interpreted as being low for both. Overall, Study 116 was considered to be at low risk of bias for all items considered.

Quality appraisals for the RCTs of relevant comparators are presented in Appendix 7. Overall, there was a lot of unclear risk assessment across the trials due to the poor reporting in the publications.[62, 65] The Niederle study could be considered to be at high risk of bias due to the potential bias in the assessment of PFS.[62]

## 4.7 Clinical effectiveness results of the relevant randomised controlled trials

Final endpoint data has not yet been published and was therefore taken from the clinical study report provided by Gilead Sciences, as described in section 4.3.[14]

**Study 116 progression-free survival**

PFS results are presented in Table 27. Median PFS was 19.4 months (95% CI: 12.3, not reached) in the idelalisib with rituximab arm and was 6.5 months (95% CI: 4.0, 7.3) in the rituximab arm.[14] The Sharman (2014) ASH poster[59] presents the PFS for rituximab patients at 7.3 months. However, this data included patients who had crossed over to receive idelalisib in the open label extension (Study 117) and was therefore not strictly for patients who received rituximab monotherapy. Therefore, the evidence presented in the clinical study report (CSR)[14] is more appropriate to use.

Idelalisib with rituximab was superior to rituximab, with an adjusted hazard ratio of 0.15 (95% CI: 0.09, 0.24; 2-sided p-value based on a stratified log rank test: $1.6 \times 10^{-16}$). The unadjusted hazard ratio was 0.16 (95% CI: 0.10, 0.25; p-value of 1.8 × 10-17 based on the unstratified log-rank test). The 12-month PFS rates were 70.4% and 9.2% for idelalisib with rituximab and rituximab, respectively. The 24-month PFS has not yet been reached. The Kaplan-Meier curves of PFS are presented in Figure 8.Figure 8

**Study 116 overall survival**

OS results are presented in Table 27. Median OS was not reached in the idelalisib with rituximab arm of the trial. In the rituximab arm, median OS was 20.8 months (95% CI: 14.8, not reached). The adjusted hazard ratio for idelalisib with rituxumab compared to rituximab was 0.34 (95% CI: 0.19, 0.60), which favoured idelalisib with rituximab compared with rituximab (p-value from stratified log-rank test = 0.0001; p-value from unstratified log-rank test = 0.0001).

An additional RPSFT analysis was performed to adjust for patients within the trial that had disease progression on rituximab and crossed over to idelalisib.[67] This analysis showed even more favourable results for patients treated with idelalisib with rituximab compared with rituximab (hazard ratio: [redacted]. The

crossover adjusted 12- and 24-month OS rates were the same as the ITT analysis for the idelalisib with rituximab arms and were 89.3% and 71.0%, respectively. In the rituximab arm, for the ITT analysis, the 12- and 24-month OS rates were 66.8% and 41.7%, respectively. In the crossover adjusted analysis, the 12- and 24-month OS rates were 49.2% and not reached, respectively. The Kaplan-Meier curves of OS are presented in Figure 9 and Figure 10. There was a statistically significantly greater improvement with idelalisib with rituximab compared to rituximab monotherapy for both PFS and OS.

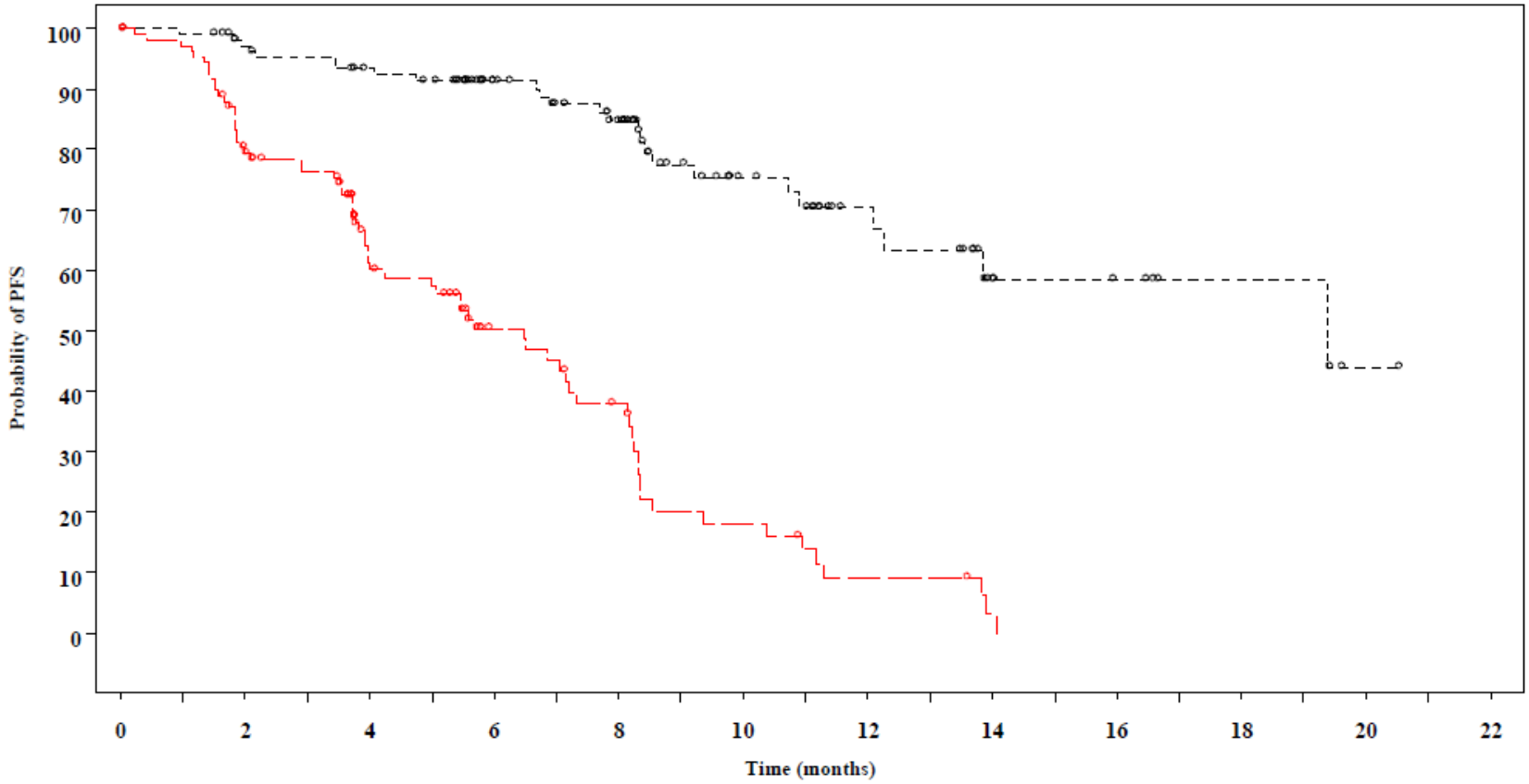
**Table 27: Progression-free survival and overall survival**

| | **IR (N=110)** | **Placebo + R (N=110)** |
|---|---|---|
| **Progression-Free Survival[a]** | | |
| % of Subjects with Events | 22.7 | 63.6 |
| Disease Progression | 15.5 | 56.4 |
| Death | 7.3 | 7.3 |
| % of Subjects Censored | 77.3 | 36.4 |
| Completed Study/Crossed over to Open-Label IDELA | 62.7 | 30.0 |
| Discontinued Study | 14.5 | 6.4 |
| Received Another Antitumor Treatment | 0 | 0 |
| Missed ≥ 2 Consecutive Tumour Measurements | 0 | 0 |
| KM Estimate of PFS[b] (Months) | | |
| Q1 (95% CI) | 10.7 (8.3, 13.9) | 3.5 (1.8, 3.8) |
| Median (95% CI) | 19.4 (12.3, not reached) | 6.5 (4.0, 7.3) |
| Q3 (95% CI) | Not reached (19.4, not reached) | 8.3 (8.1, 10.9) |
| Adjusted Hazard Ratio (95% CI)[c] | 0.15 (0.09, 0.24) | |
| P-value[d] | $1.6 \times 10^{-16}$ | |
| 12-month PFS | 70.4% | 9.2% |
| 24-month PFS | Not reached | Not reached |
| **Overall Survival[e] [ITT analysis]** | | |
| % of Subjects Who Died | 15.5 | 36.4 |
| % of Subjects Censored | 84.5 | 63.6 |
| Ongoing | 54.5 | 34.5 |

| | IR (N=110) | Placebo + R (N=110) |
|---|---|---|
| Discontinued Study | 30.0 | 29.1 |
| KM Estimate of OS (Months) [f] | | |
| Q1 (95% CI) | 19 (16.6, not reached) | 9.2 (7.3, 12.6) |
| Median (95% CI) | Not reached (not reached, not reached) | 20.8 (14.8, not reached) |
| Q3 (95% CI) | Not reached (not reached, not reached) | Not reached (20.8, not reached) |
| Adjusted Hazard Ratio (95% CI) | 0.34 (0.19, 0.60) | |
| P-value From Stratified Log-Rank Test[g] | 0.0001 | |
| P-value From Unstratified Log-Rank Test | 0.0001 | |
| 12-month OS | 89.3% | 66.8% |
| 24-month OS | 71.0% | 41.7% |
| **Overall Survival [Crossover Adjusted RPSFT analysis]** | | |
| Median (95% CI) | Not reached (not reached, not reached) | [redacted] |
| Adjusted Hazard Ratio (95% CI) | [redacted] | |
| 12-month OS | 89.3% | 49.2% |
| 24-month OS | 71.0% | NR |

**Key:** CI, confidence interval; IDELA, idelalisib; ITT, intent to treat; KM, Kaplan-Meier; NR, not reported; OS, overall survival; PFS, progression-free survival; R, rituximab; RPSFT, rank preserving structural failure time.
**Notes:**
a For subjects in Placebo + R, summary includes data up to the first dosing of open-label IDELA.
b PFS (months) = (minimum [date of PD, date of death] - date of randomization +1)/30.4375.
c Hazard ratio and 95% CIs are calculated using the Cox proportional hazards model, adjusted for randomization stratification factors (17p deletion/TP53 mutation and IgVH mutation).
d P-value is from stratified log-rank test, adjusted for randomization stratification factors (17p deletion/TP53 mutation and IgVH mutation).
e Analysis is based on data from Study GS-US-312-0116 and its extension study, GS-US-312-0117.
f OS (months) = (date of death – date of randomization + 1)/ 30.4375.
g P-value is from stratified log-rank test, adjusted for randomization stratification factors (17p deletion/*TP53* mutation and *IgVH* mutation).

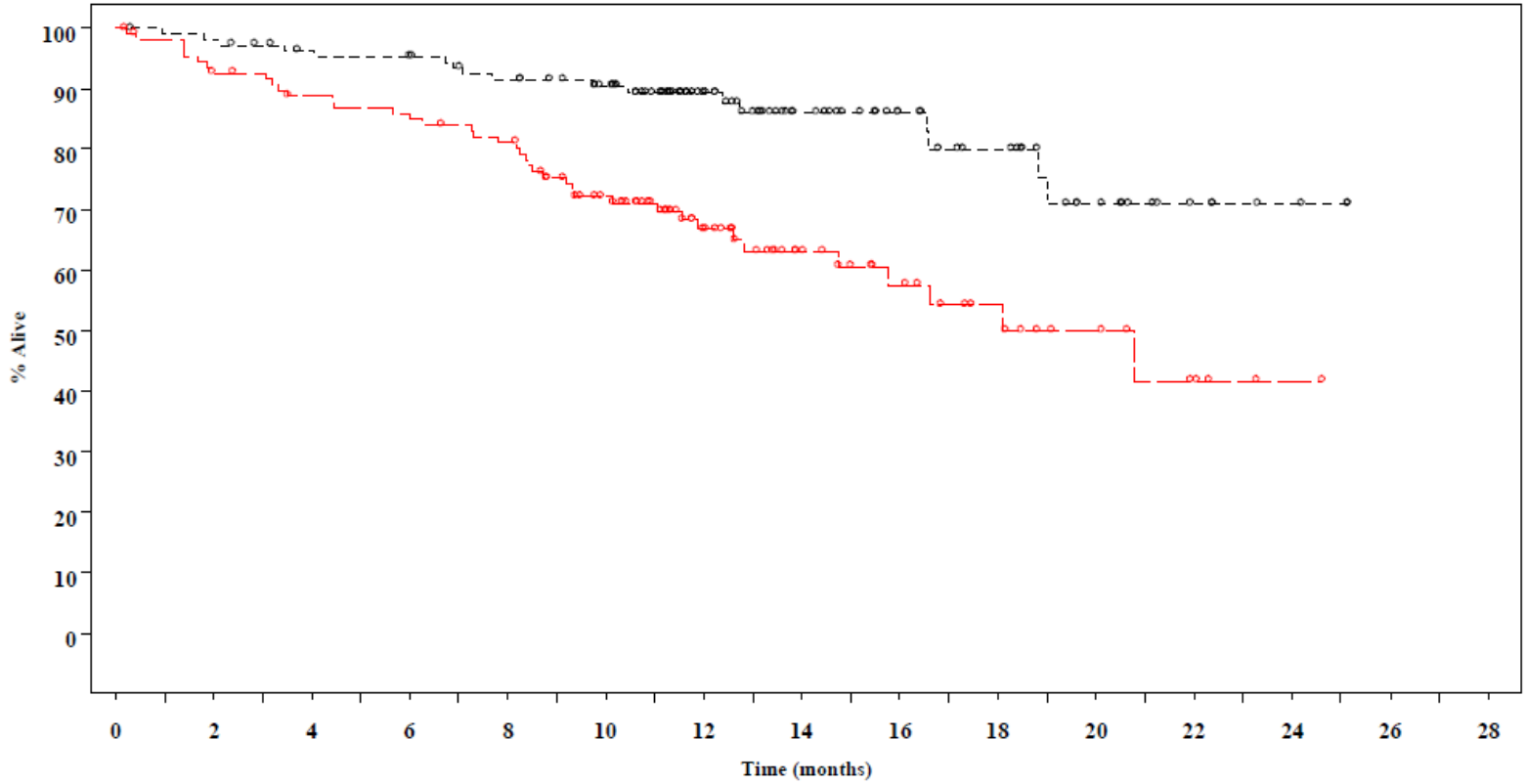
**Figure 8: Kaplan-Meier curves of PFS**




| N at Risk (Events) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| IDELA + R | 110 (0) | 101 (3) | 93 (7) | 73 (9) | 59 (14) | 31 (19) | 20 (21) | 9 (24) | 7 (24) | 4 (24) | 1 (25) | 0 (25) |
| Placebo + R | 110 (0) | 84 (21) | 48 (38) | 29 (46) | 20 (53) | 9 (63) | 4 (67) | 1 (69) | 0 (70) | 0 (70) | 0 (70) | 0 (70) |

**Notes**: For subjects in the Placebo + R group, summary includes data up to the first dosing of open-label IDELA.
**Key:** IDELA, idelalisib; PFS, progression-free survival; R, rituximab. **Source:** Study 116 CSR[14]

**Figure 9: Kaplan-Meier curves of OS [ITT analysis]**




| N at Risk (Events) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| IDELA + R | 110 (0) | 107 (2) | 101 (4) | 99 (5) | 93 (9) | 85 (10) | 60 (11) | 41 (13) | 30 (13) | 23 (15) | 13 (17) | 6 (17) | 3 (17) | 0 (17) | 0 (17) |
| Placebo + R | 110 (0) | 99 (8) | 93 (12) | 90 (15) | 84 (20) | 66 (29) | 42 (33) | 27 (35) | 19 (37) | 13 (38) | 8 (39) | 4 (40) | 1 (40) | 0 (40) | 0 (40) |

**Notes**: Analysis is based on data from Study GS-US-312-0116 and its extension study, GS-US-312-0117.
**Key:** IDELA, idelalisib; ITT, intention to treat; OS, overall survival; R, rituximab. **Source:** Study 116 CSR[14]

**Figure 10: Kaplan-Meier curves of OS [RPSFT analysis]**

[redacted]

[redacted]

**Study 116 Response**

Response was assessed using the IWCLL 2008 criteria by an independent review committee in the ITT population. The overall response rates assessed by independent review committee (IRC) are reported in Table 28.

The ORRs, as assessed by IRC, were 83.6% compared to 15.5% for idelalisib with rituximab compared to rituximab, respectively. No patients in either treatment arm experienced a complete response; therefore, all of the ORR was made up of partial responders. For idelalisib with rituximab and rituximab patients, SD rates were 11.8% and 64.5%, and 0.9% and 14.5% of patients presented with progressive disease, respectively.[14] The odds ratio for overall

response for idelelisib with rituximab compared to rituximab is 27.76 (95% CI: 13.4, 57.49), which favoured IR (p-value: 1.3 x $10^{-23}$).

Minimal residual disease (MRD) status was not documented in Study 116.

**Table 28: Overall response rate by IRC Assessment**

| | **IR (N=110)** | **Placebo + R (N=110)** |
|---|---|---|
| Best Overall Response, % | | |
| Complete Response (CR) | 0 | 0 |
| Partial Response (PR) | 83.6 | 15.5 |
| Stable Disease (SD) | 11.8 | 64.5 |
| Progressive Disease (PD) | 0.9 | 14.5 |
| Not Evaluable (NE) | 3.6 | 5.5 |
| No Disease | 0 | 0 |
| ORR[a], n (%) | 83.6 | 15.5 |
| 95% CI[b] | 75.4, 90.0 | 9.3, 23.6 |
| Odds Ratio for Overall Response[c] | 27.76 | |
| 95% CI for Odds Ratio | 13.4, 57.49 | |
| P-value | $1.3 \times 10^{-23}$ | |

**Key:** CI, confidence interval; IRC, independent review committee; ORR, overall response rate; R, rituximab.
**Notes:** For subjects in placebo + rituximab, summary includes data up to the first dosing of open-label idelalisib.
a ORR is the percentage of subjects that had best overall response of CR or PR.
b 95% CI for ORR is based on the exact method.
c Odds ratio, 95% CI, and p-value are calculated from the CMH Chi-square test stratified by stratification factors (17p deletion and/or TP53 mutation and IgVH mutation).

Median duration of response and time to response are presented in Table 29. Duration of response was longer in the idelalisib with rituximab arm compared to the rituximab arm, and idelalisib with rituximab patients responded more rapidly. The first measurement took place at 1.9 months, which is why the Q1 time to response is reported as 1.9 months. However, in practice, the clinicians saw these responses much earlier (e.g. after a few days of treatment).

**Table 29: Time to response and duration of response**

| | IR (N=110) | Placebo + R (N=110) |
|---|---|---|
| **Time to Response (months)[a]** | | |
| N | 92 | 17 |
| Mean (SD) | 3.0 (2.05) | 3.5 (2.14) |
| Median | 2.1 | 2.8 |
| Q1, Q3 | 1.9, 3.7 | 2.0, 3.9 |
| Min, Max | 1.5, 14.1 | 1.9, 8.5 |
| **Duration of Response (months)** | | |
| % of Subjects with CR or PR | 83.6 | 15.5 |
| % of Subjects with Events | 14.1 | 47.1 |
| Disease Progression | 10.9 | 47.1 |
| Death | 3.3 | 0 |
| % of Subjects Censored | 85.9 | 52.9 |
| Completed Study/Crossed over to Open-Label IDELA | 70.7 | 52.9 |
| Discontinued Study | 15.2 | 0 |
| Received another Antitumor Treatment | 0 | 0 |
| Missed ≥ Consecutive Tumour Measurements | 0 | 0 |
| KM Estimate of DOR[b] (Months) | | |
| Q1 (95% CI) | 10.4 (6.5, not reached) | 4.0 (2.7, 6.2) |
| Median (95% CI) | Not reached (12.0, not reached) | 6.2 (2.8, 6.5) |
| Q3 (95% CI) | Not reached (not reached, not reached) | 6.5 (5.6, not reached) |

**Key:** CI, confidence interval; CR, complete response; DOR, duration of response; IDELA, idelalisib; PR, partial response; R, rituximab; SD, standard deviation.
**Notes:** Analysis included only subjects who achieved a CR or PR.
For subjects in the Placebo + R, summary includes data up to the first dosing of open-label IDELA.
a TTR (months) = (date of first PR/CR – date of randomization + 1)/30.4375.
b DOR (months) = (minimum [date of PD, date of death] - date of first documented CR or PR + 1)/ 30.4375

## Study 116 Lymph node response rate

Lymph node response (LNR) rate was assessed using an independent review committee in the ITT population that had at least one postbaseline summary product of diameters (SPD). The LNR rate (95% CI) was 96.2% (90.6, 99.0) for subjects in the IR group and 6.7% (2.7, 13.4) for subjects in the R group (Table 30). The stratified odds ratio (95% CI) for the LNR rate was 225.83 (65.56, 777.94), which favoured IR compared with R ($p=8.5\times10^{-38}$).

**Table 30: Lymph node response rate**

| | **IR (N=110)** | **Placebo + R (N=110)** |
|---|---|---|
| LNR Rate[a] | 102/106 (96.2%) | 7/104 (6.7%) |
| 95% CI for LNR Rate[b] | 90.6, 99.0 | 2.7, 13.4 |
| Odds Ratio[c] | 225.83 | |
| 95% for Odds Ratio | 65.56, 777.94 | |
| P-value | $8.5 \times 10^{-38}$ | |

**Key:** CI, confidence interval; LNR, lymph node response; R, rituximab
**Notes:** Analysis only included subjects in the ITT Analysis Set that had both baseline and at least 1 evaluable postbaseline SPD.
For subjects in Placebo + R, summary includes data up to the first dosing of open-label IDELA.
a LNR rate was defined as the percentage of subjects who achieved a ≥50% decreased from baseline in the SPD of index lymph nodes.
b 95% CI for response rate was based on the exact method.
c Odds ratio, 95% CI, and p-value were calculated from the Cochran-Mantel-Haenszel Chi-square test stratified by 17p deletion/TP53 mutation and IgVH mutation

## Other endpoints in Study 116

Table 31 presents the other endpoints reported in Study 116. All of the results favoured patients treated with IR compared to R; with IR patients achieving a better percentage change in SPD, a better change from baseline in Karnovsky performance status and better responses as assessed by splenomegaly, hepatomegaly, absolute lymphocyte count (ALC), platelets, haemoglobin and absolute neutrophile count (ANC).

**Table 31: Other endpoints reported in Study 116**

| | IR (N=110) | Placebo + R (N=110) |
|---|---|---|
| **Best percentage change in SPDa, b** | N=106 | N=104 |
| Mean (SD) | -74.6 (11.20) | -7.3 (28.82) |
| Median (range; Q1, Q3) | -76.8 (-92.0 to -36.6; -82.9, -68.7) | -6.9 (-68.7 to 105.8; -25.4, 7.8) |
| **Other Response Rates** | | |
| Splenomegaly Response Rate [c], % (95% CI[d]) | 76.6 (65.6, 85.5) | 21.9 (12.5, 34.0) |
| Hepatomegaly Response Rate [e], % (95% CI[d]) | 54.5 (40.6, 68.0) | 18.3 (9.5, 30.4) |
| ALC Response Rate[f], % (95% CI[d]) | 92.0 (84.3, 96.7) | 85.9 (76.6, 92.5) |
| Platelet Response Rate[g], % (95% CI[d]) | 93.8 (82.8, 98.7) | 52.1 (37.2, 66.7) |
| Haemoglobin Response Rate[h], % (95% CI[d]) | 78.0 (65.3, 87.7) | 42.9 (29.7, 56.8) |
| ANC Response Rate[i], % (95% CI[d]) | 81.5 (61.9, 93.7) | 69.2 (48.2, 85.7) |
| **Karnofsky performance status (best change from baseline)j** | N=108 | N=105 |
| Mean (SD) | 10.7 (10.39) | 4.2 (11.91) |
| Median (range; Q1, Q3) | 10.0 (-10.0 to 40.0; 0.0, 20.0) | 0.0 (-70.0 to 30.0; 0.0, 10.0) |

**Key:** ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CI, confidence interval; SD, standard deviation; SPD, Sum of Products Dimensions; R, rituximab
**Notes:** For subjects in the Placebo + R, summary includes data up to the first dosing of open-label IDELA.
a The tumour measurement from radiographic reader A was used unless the adjudicator chose reader B.
b The best percent change from baseline was defined as the largest decrease in SPD postbaseline. For subjects who had SPD increases only, the smallest increase was considered the best change from baseline. Baseline was defined as the last measurement before randomisation.
c Analysis included only subjects in the ITT Analysis Set who had splenomegaly at baseline and had at least 1 evaluable postbaseline spleen measurement. Responders were subjects with a 50% decrease (minimum 2 cm) from baseline in the enlargement of the spleen in its LVD or to ≤ 12 cm by imaging.
d 95% CI for the response rate was based on the exact method.

e Analysis only included subjects who had hepatomegaly at baseline and at least one evaluable postbaseline liver measurement. Hepatomegaly response rate was the percentage of subjects with a 50% decrease (minimum 2 cm) from baseline in the enlargement of the spleen in its LVD or to ≤ 18 cm by imaging.
f Analysis only included subjects who had lymphocytosis (ALC ≥ 4 × 109/L) at baseline and ALC values 28 days postbaseline. Responders were subjects with baseline lymphocytosis who achieved on-study ALC < 4 × 109/L or ≥ 50% decreased in ALC from baseline.
g Analysis only included subjects who had thrombocytopenia (platelet count < 100 × 10^9/L) at baseline and platelet values 28 days postbaseline. Responders were subjects with baseline thrombocytopenia who achieved on-study platelet count of ≥ 100 × 109/L or ≥ 50% increase in platelet count from baseline.
h Analysis included subjects who had anaemia (hemoglobin < 110 g/L [11 g/dL]) at baseline and hemoglobin values 28 days postbaseline. Responders were subjects with baseline anaemia who achieved on-study hemoglobin ≥ 110 g/L (11 g/dL) or ≥ 50% increase in hemoglobin from baseline.
i Analysis only included subjects in the ITT Analysis Set who had neutropenia (ANC ≤ 1.5 × 109/L) at baseline. Responders were subjects with baseline neutropenia who achieved on-study ANC of > 1.5 × 109/L or ≥ 50% increase in ANC from baseline.
j Best change from baseline = (highest value among all postbaseline visits - baseline value).

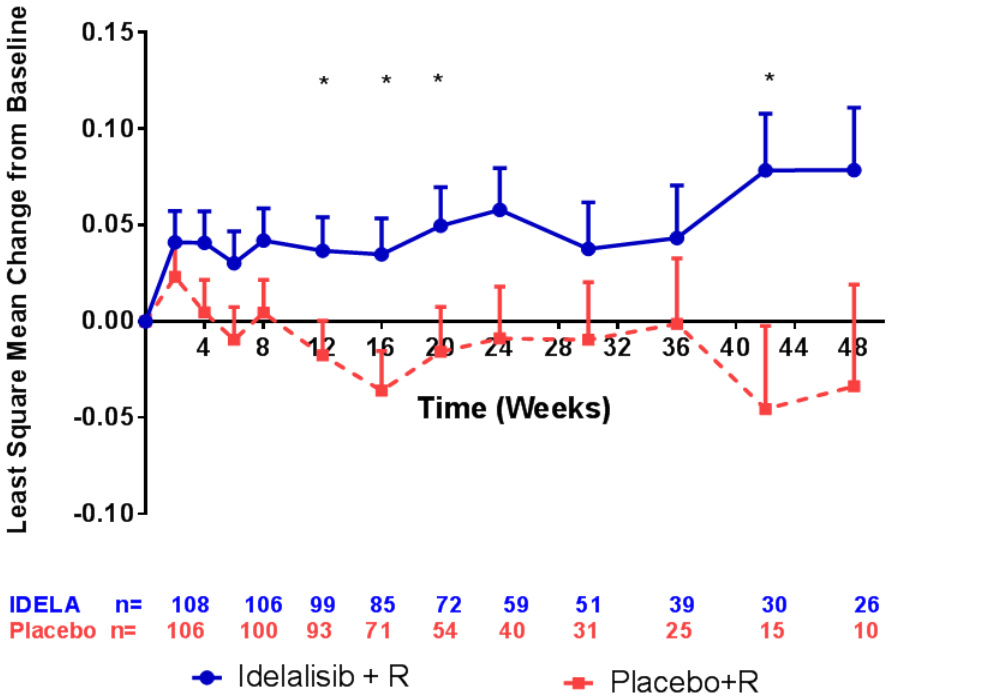
## Study 116 Health-Related Quality of Life

### EQ-5D Results

Mean (±SE) change from baseline in the EQ-5D utility index is presented in Figure 11. As assessed by the EQ-5D utility index, subjects on IR showed improvement over baseline and consistently showed greater symptom improvement than subjects on R throughout the study, with a statistically significant treatment effect for patients treated with IR (Figure 11).

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) are presented by treatment arm in Table 32.

**Figure 11: Mean (±SE) change from baseline in the EQ-5D utility index (Study 116 ITT analysis set)**




*P=0.002 for the test of overall treatment effect based on the longitudinal data analysis*

** p < 0.05 for treatment difference from the mixed model*

**Key:** EQ-5D, EuroQol 5 dimensions; ITT, intention to treat; R, rituximab; SE, standard error
**Source:** Study 116 CSR[14]

**Table 32: 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<br>**Source:** Study 116 CSR[14] | | | | | | | |

**Functional Assessment of Cancer Therapy: Leukemia (FACT-Leu) Questionnaire Results**

The Functional Assessment of Cancer Therapy: Leukemia (FACT-Leu) questionnaire includes subscales for physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), functional well-being (FWB), and additional concerns (Leukemia subscale).[68] In addition, the following composite scores are derived from the subscale total scores: Trial Outcome Index = PWB + FWB + Additional Concerns and FACT-Leu Total Score = PWB + SWB + EWB + FWB + Additional Concerns. For the PWB, SWB, EWB, and FWB subscales, the minimally important difference (MID) was an increase of at least 3 points from baseline and this was considered to be symptom improvement. For the Additional Concerns subscale, the MID is defined as an increase of at least 5 points from baseline.

Subjects treated with IR consistently showed greater symptom improvement than subjects on R at each time point throughout the study for the Additional Concerns (Leukemia), FACT-Leu Total, and the Trial Outcome Index. Subjects treated with IR reached the MID for Additional Concerns rapidly (Week 4), and their improvement was sustained, whereas subjects on R reached the MID at Week 72. In the mixed effects model analysis of the changes from baseline in the Additional Concerns subscale score, the main effect of treatment was statistically significant (p=0.0003). Subjects treated with IR also showed rapid and sustained improvements in the FACT-Leu Total and Trial Outcome Index scores compared to subjects treated with R. 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.

A total of 80 subjects (76.9%) in the IR treatment group showed MID improvement from baseline (i.e. 5 point improvement) in the Additional Concerns (Leukemia) Subscale score compared to only 66 subjects (66.7%) subjects in the R treatment group. This shows a massive improvement in symptoms for patients treated with idelalisib with rituximab compared to those treated with rituximab alone.

**Comparator RCTs in relapsed or refractory CLL**

Table 33 presents the baseline characteristics of the RCTs of relevant comparators alongside Study 116. Patients in Study 116 were generally older, had received more prior therapies and had a larger proportion of patients in Binet disease Stage C, i.e. were more severe patients. They also included more patients with 17p deletion or TP53 mutation than the Robak (2010) study, which was the only other study to report this data. The most important factors that influence PFS are age, comorbidities (CIRS scores), serum creatinine levels, platelets, LDH, albumin, number of prior treatments, the proportion of patients that are fludarabine refractory and the presence of 17p deletion or TP53 mutation. [69] The differences between Study 116 and the identified comparator RCTs indicate that patients in Study 116 were generally sicker than their counterparts in the other trials. There were also differences in the methods and the criteria used to assess PFS and response outcomes. Therefore, in light of these limitations, comparability of effectiveness between these studies should be interpreted with caution.

Table 34 presents the results of the relevant comparator trials. Despite clear differences in patient characteristics, with Study 116 being conducted in a

much sicker patient population, PFS results are similar across trials. Given these differences, the overall response rates and partial response rates for IR-treated patients in Study 116 look very compelling.

**Table 33: Baseline characteristics of participants in the relevant RCTs**

| Study | Study 116 | | Robak (2010) | | Leblond (2012) | | Niederle (2013) | |
|---|---|---|---|---|---|---|---|---|
| **Treatment arm** | **IR** | **R** | **FCR** | **FC** | **BR** | **ChR** | **B** | **F** |
| Patients (N) | 110 | 110 | 276 | 276 | 18[a] | 23[a] | 50 | 46 |
| ITT population | 110 | 110 | 276 | 276 | 18 | 23 | 49 | 43 |
| Age (years), median (range) | 71 (48-90) | 71 (47-92) | 63 (35-83) | 62 (35-81) | NR | NR | 68 (44-84) | 69 (52-83) |
| Gender, female, % | 30.9 | 38.2 | 32 | 34 | NR | NR | 37[a] | 37[a] |
| Prior therapies, median (range) | 3 (1-12) | 3 (1-9) | 1 | 1 | 1 | 1 | 1 | 1 |
| Binet Stage, % | | | | | NR | NR | | |
| A | 6.4 | 3.6 | 9 | 11 | | | 0 | 0 |
| B | 26.4 | 29.1 | 60 | 58 | | | 45 | 49 |
| C | 57.3 | 55.5 | 31 | 31 | | | 55 | 51 |
| Unmutated IgVH, % | 82.7 | 84.5 | 61 | 65 | NR | NR | NR | NR |
| 17p deletion, % | 24 | 28 | 7 | 9 | NR | NR | NR | NR |

**Key:** B, bendamustine; C, cyclophosphamide; Chl, chlorambucil; CLL, chronic lymphocytic leukaemia; ECOG, Eastern Cooperative Oncology Group; F, fludarabine; I, idelalisib; TT, intent to treat; NR, not reported; PS, performance status; RCT, randomised controlled trial; R, rituximab; SD, standard deviation;
**Notes:** a Calculated.
b The numbers of patients with ECOG performance status 0 /1 in the FC arm do not add up to 276 but are as reported in the paper.

**Table 34: Results of the relevant RCTs**

| Study | Study 116 | | Robak (2010) | | Leblond (2012) | | Niederle (2013) | |
|---|---|---|---|---|---|---|---|---|
| **Treatment arm** | **IR** | **R** | **FCR** | **FC** | **BR** | **ChR** | **B** | **F** |
| **PFS[a]** | | | | | | | | |
| PFS definition | From randomisation to first documentation of definitive PD (based on standard criteria) or death from any cause | | From day of random assignment until first documented disease progression, relapse after response, or death from any cause | | NR | | From the date of randomisation to the time of progressive disease or to death from any cause | |
| PFS assessed by | IRC | | IRC [IA] | | NR | | IA | |
| Median, months (95% CI) | 19.4 (12.3, not reached) | 6.5 (4.0, 7.3) | 27.0 [30.6] | 21.9 [20.6] | NR | NR | 20.1 | 14.8 |
| Hazard ratio (95% CI) | 0.15 (0.09, 0.24) | | 0.76 (0.60, 0.96)<br>[0.65 (0.51, 0.82)] | | NR | NR | 0.87 (0.6, 1.27) | |
| 12-month PFS, % | 70.4 | 9.2 | 75 [80] | 72 [74] | NR | NR | 71 | 60 |
| 24-month PFS, % | NR[b] | NR[b] | 54 [61] | 44 [45] | NR | NR | 37 | 23 |
| **OS[c]** | | | | | | | | |
| Median, months (95% CI) | Not reached<br>[Not reached] | 20.8 (14.8, not reached)<br>[redacted] | Not reached | 52 | NR | NR | 43.8 | 41 |
| Hazard ratio (95% CI) | 0.34 (0.19,0.60)<br>[0.20 (0.10, 0.35)] | | 0.83 (0.59, 1.17) | | NR | | 0.82 (0.47, 1.43) | |
| 12-month OS, % | 89.3 [89.3] | 66.8 [49.2] | 89 | 91 | NR | NR | 87 | 88 |

| Study | Study 116 | | Robak (2010) | | Leblond (2012) | | Niederle (2013) | |
|---|---|---|---|---|---|---|---|---|
| **Treatment arm** | **IR** | **R** | **FCR** | **FC** | **BR** | **ChR** | **B** | **F** |
| 24-month OS, % | 71.0 [71.0] | 41.7 [NR[b]] | 81 | 81 | NR | NR | 70 | 76 |
| **Response[d]** | | | | | | | | |
| Response criteria | IWCLL 2008[32] | | NCI-WG 1996[70] | | NR | | NCI-WG 1996[70] | |
| Response assessed by | IRC | | IRC [IA] | | NR | | IA | |
| ORR, % | 83.6 | 15.5 | 61 [69.9] | 49 [58] | 89 | 83 | 76 | 62 |
| CR, % | 0 | 0 | 9 [24.3] | 3 [13] | 11 | 4 | 27 | 9 |
| PR, % | 83.6 | 15.5 | [45.7] | [44.9] | NR | NR | 49 | 53 |
| SD, % | 11.8 | 64.5 | [17] | [22.1] | NR | NR | 8 | 16 |
| PD, % | 0.9 | 14.5 | [2.5] | [5.4] | NR | NR | NR | NR |
| NE, % | 3.6 | 5.5 | [10.5] | [14.5] | NR | NR | NR | NR |
| Duration of response, months, median (95% CI) | 10.4 (7.1, not reached) | 6.4 (4.5, 7.4) | 39.6 | 27.7 | NR | NR | NR | NR |

**Key:** B, bendamustine; C, cyclophosphamide; Chl, chlorambucil; CI, confidence interval; CLL, chronic lymphocytic leukaemia; CR, complete response; ECOG, Eastern Cooperative Oncology Group; F, fludarabine; I, idelalisib; IA, investigator assessed; IRC, independent review committee; ITT, intent to treat; NE, not evaluable; NR, not reported; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PS, performance status; R, rituximab; RCT, randomised controlled trial; SD, stable disease; WHO, World Health Organization.

**Notes:**

a PFS outcomes are primarily presented as assessed by an independent review committee (IRC) where this was available. Niederle (2013) only presented PFS as assessed by the investigator, the other studies all presented PFS as assessed by an IRC. Robak (2010) also presented investigator-assessed PFS, and these results are presented in square brackets.

b The maximum observation time is <24 months.

c OS outcomes presented in square brackets for the 116 study are the crossover adjusted RPSFTM results.

d Response outcomes are primarily presented as assessed by an independent review committee (IRC) where this was available. Niederle (2013) only presented response as assessed by the investigator, Leblond (2012) did not report their methods in the abstract, and the other studies all presented response as assessed by an IRC. Robak (2010) also presented investigator-assessed response, and these results are presented in square brackets.

**Comparator RCTs in untreated CLL with a 17p deletion or TP53 mutation**

The baseline characteristics of patients included in the Hillmen (2007) study[22] are presented in Table 35. Patient characteristics were not reported for this subgroup separately.

This was the only RCT identified in untreated patients. The population of interest is presented as a subgroup of patients with 17p deletion (n=11 vs. n=10). Patient characteristics were not reported for this subgroup separately.

**Table 35: Characteristics of participants in the RCT reported by Hillmen (2007)**

| Baseline characteristic | Alemtuzumab (n=149) | Chlorambucil (n=148) |
|---|---|---|
| **Age, years (median [range])** | 59.0 (35-86) | 60.0 (36-83) |
| **Male gender (%)** | 71.1 | 72.3 |
| **Rai stage group (IRRP), %** | | |
| 0 or missing* | 4.0 | 2.0 |
| I-II | 62.4 | 64.9 |
| III/IV | 33.6 | 33.1 |
| **Time since initial diagnosis to random assignment, months (median [range])** | 9.38 (-0.5-167.4†) | 7.85 (0.1-224.8) |
| **Maximum lymph node size, cm. %** | | |
| <5 | 71.8 | 70.3 |
| ≥5 | 22.1 | 23.0 |
| No enlarged lymph nodes | 5.4 | 6.8 |
| **Palpable hepatomegaly, %** | 28.9 | 18.2 |
| **Palpable splenomegaly, %** | 35.6 | 37.8 |
| **WHO performance status, %** | | |
| 0-1 | 96.0 | 96.6 |
| 2 | 3.4 | 3.4 |
| **Night sweats, %** | 43.0 | 46.6 |
| **Weight loss > 10%, %** | 9 (6.0) | 10.8 |
| **Fever, %** | 0.7 | 1.4 |
| **Hierarchical cytogenetic subgroups‡, %** | | |
| 17p13.1 (p53) mutation | 7.7 | 7.2 |

| Baseline characteristic | Alemtuzumab (n=149) | Chlorambucil (n=148) |
|---|---|---|
| Any 11q del | 16.1 | 22.3 |
| Trisomy 12 (no 11p or 17p del) | 16.8 | 7.2 |
| Normal | 17.5 | 18.7 |
| Sole 13q del | 23.1 | 24.5 |
| Various other combinations | 18.9 | 20.1 |

**Key:** IRRP, independent response review panel; CLL, chronic lymphocytic leukaemia; del, deletion; RCT, randomised controlled trial; WHO, World Healkth Organisation.
**Notes:** *These patients were assessed as Rai Stage 0 (n=5) and unconfirmed for B-cell CLL diagnosis (n=4) by the IRRP.
†One patient was inadvertently randomly assigned prior to completion of CLL diagnosis.
‡According to the hierarchical Döhner et al method, n=43 for the alemtuzumab group and n=139 for the chlorambucil group.
**Source:** Hillmen (2007)

Outcomes reported in the Hillmen (2007) study[22] are presented in Table 36. A comparison of these results versus the results from the idelalisib non RCT is presented in section 4.11.

**Table 36: Outcomes reported for untreated CLL patients with 17p deletion**

| | Alemtuzumab | Chlorambucil |
|---|---|---|
| **Median PFS, months** | 10.7 | 2.2 |
| P-value | 0.4066 | |
| **Overall response rate** | 7/11 (64%) | 2/10 (20%) |
| P-value | 0.0805 | |
| Overall survival | Not reached | Not reached |

**Key:** PFS, progression-free survival.

## 4.8 Subgroup analysis

**Relapsed or refractory CLL with a 17p deletion or TP53 mutation**

Baseline characteristics for the subgroup of patients with a 17p deletion or TP53 mutation within Study 116 are presented in Table 37.

**Table 37: Characteristics of the subgroup of patients with a 17p deletion or TP53 mutation in Study 116 across treatment groups**

| | IR (N=110) | Placebo + Rituximab (N=110) |
|---|---|---|
| Either, % | 41.8 | 44.5 |
| Neither, % | 58.2 | 55.5 |
| 17p deletion, % | | |
| Presence, % | 23.6 | 28.2 |
| Absence, % | 76.4 | 71.8 |
| **Key:** | | |
| **Source**: Study 116 CSR[14] | | |

A summary of all relevant outcomes reported during Study 116 for this subgroup of patients is provided in Table 38.

**Table 38: Outcomes reported for relapsed CLL patients with and without a 17p deletion or TP53 mutation in Study 116**

| | IR (N=46) | Placebo + Rituximab (N=49) |
|---|---|---|
| **PFS - 17p deletion/TP53 mutation** | | |
| Median (95% CI) PFS, months | Not reached (12.3, not reached) | 4.0 (3.7, 5.7) |
| Hazard ratio (95% CI) | 0.13 (0.07, 0.27) | |
| **PFS - no 17p deletion/TP53 mutation** | | |
| Median (95% CI) PFS, months | 19.4 (10.7, not reached) | 8.1 (5.1, 8.2) |
| Hazard ratio (95% CI) | 0.20 (0.11, 0.39) | |
| **Overall survival, hazard ratio (95% % CI)** | | |
| 17p deletion/TP53 mutation | Not reached (18.8; not reached) | 14.8 (8.4, not reached) |

| | | |
|---|---|---|
| | 0.31 (0.15, 0.65) | |
| No 17p deletion/TP53 mutation | Not reached (not reached, not reached) | 20.8 (16.6, not reached) |
| | 0.38 (0.16, 0.93) | |
| **Overall response rate, odds ratio (95% CI)** | | |
| 17p deletion/TP53 mutation | 84.8% | 12.2% |
| | 39.93 (12.35, 129.09) | |
| No 17p deletion/TP53 mutation | 82.8% | 18.0% |
| | 21.9 (8.72, 55.0) | |
| **Lymph node response rate, odds ratio (95% CI)** | | |
| 17p deletion/TP53 mutation | 924.5 (80.79, 10579.16) | |
| No 17p deletion/TP53 mutation | 212.4 (48.44, 931.37) | |
| **Key:** CI, confidence interval; CLL, chronic lymphocytic leukaemia; PFS, progression-free survival.<br>**Source**: CSR, Dec 2014[14]. | | |

For PFS, the results robustly favoured idelalisib with rituximab compared with placebo with rituximab in patients with or without either 17p deletion and/or TP53 mutation. For overall survival and response rates, the results also favoured idelalisib with rituximab compared with placebo with rituximab in both subgroups of patients (i.e. with or without 17p deletion and/or TP53 mutation).

**Relapsed or refractory CLL with 17p deletion only**

The smaller subgroup of relapsed or refractory CLL patients with 17p deletion is listed as an important consideration in the decision problem. Where reported, the subgroup analyses for the relapsed or refractory CLL patients with 17p deletion are presented in Appendix 5. However as explained in Section 3, outcomes for CLL patients with 17p deletion or TP53 mutations are similar, since both cytogenetic abnormalities impact the P53 pathway, and lead to chemo-resistance.

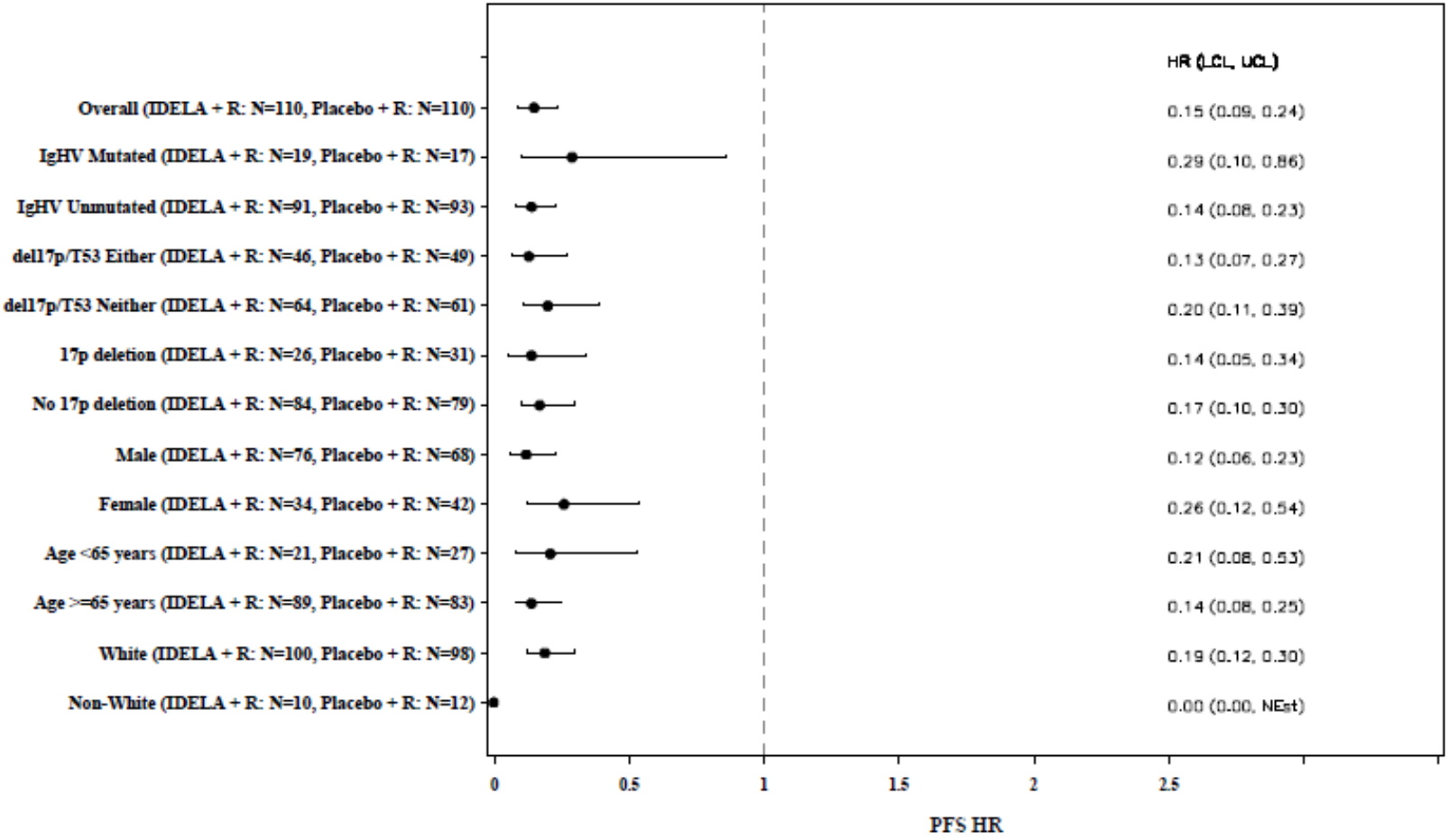
**Other subgroups in relapsed or refractory CLL**

In addition to the del17p/TP53 subgroups, Study 116 also investigated outcomes across the following subgroups:

- IgVH mutated and IgVH unmutated patients
- Male or female patients
- Patients aged <65 or ≥65 years
- Patients who were white or non-white

Results for primary and secondary outcomes were consistent across these subgroups; with similar treatment effects on PFS, OS, response, and lymph node response. Figure 12 shows the forest plot for PFS across all subgroups and results are consistent for them all. This shows that the combination of idelalisib with rituximab works equally well across all of these subgroups.

**Figure 12: Forest Plot of PFS by IRC Assessment by Subgroup (ITT Analysis)**




**Key:** HR, hazard ratio; IDELA, idelalisib; IRC, independent review committee; ITT, intention to treat; LCL, lower confidence limit; PFS, progression free survival; R, rituximab; UCL, upper confidence limit.
**Source:** Study 116 CSR[14]
**Notes:** For subjects in the placebo with rituximab group, summary includes data up to the first dosing of open-label idelalisib.

## 4.9 Meta-analysis

Only a single idelalisib RCT was available at this time, and therefore, it was not possible to conduct a meta-analysis.

## 4.10 Indirect and mixed treatment comparisons

**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.

## 4.11 Non-randomised and non-controlled evidence

**Relapsed or refractory CLL**

Searches were performed on 12th February 2014 on the same databases and conference websites and using the same search methods as presented in section 4.1. The search strategies are presented in Appendix 3.

A more detailed description of the methods and the eligibility criteria is presented in Appendix 7.

A detailed PRISMA diagram is presented in Appendix 7. Twelve publications reporting on 9 trials were identified. A summary of the included trials, their methods and their inclusion and exclusion criteria are presented in Appendix 7. The references of studies identified by any of the systematic literature reviews used to inform this submission that were considered not to be relevant to the decision problem are presented in Appendix 3, alongside the reason for their exclusion.

**IR (Furman, 2013)**

**Study design**

Only one non-randomised study (NRS) was identified that assessed idelalisib.[71] This was a phase I, two-arm trial in patients with relapsed or refractory CLL. It studied different combination of idelalisib with various agents including anti-CD20s (rituximab and ofatumumab) in patients with heavily pre-treated CLL and other B-cell malignancies (Rai Stage III/IV; median number of previous lines of therapy 2, range 0–9). Information from this study was only available as a conference abstract and is therefore very limited.

**Baseline characteristics**

The participant demographics reported in the Furman study are detailed in Table 39. The majority of patients had received one prior therapy containing rituximab (98%). Prior therapies also included alkylating agents (78%) and purine analogues (78%).

The baseline WHO/ECOG performance status (PS) for all patients in the Furman study is summarised in Table 39 . In this study, 60% of patients had a PS of 0 (activity levels same as before) with the remainder of patients scoring 1 (cannot carry out heavy physical work but can do anything else).

The study only reported data on IgVH status and 17p deletion and/or TP53 mutations. Evidence of other chromosomal deletions/mutations was not discussed. As can be seen in Table 39, three-quarters (75%) of patients had evidence of unmutated IgVH and just over a quarter (28%) had 17p deletion and/or TP53 mutation.

**Table 39: Baseline characteristics of participants in Furman (2013)**

| Baseline characteristic | IR/IO |
|---|---|
| Patients | n=40 |
| Age (years), median (range) | 66 (43-87) |
| Gender, female, % | 30 |
| WHO Performance Score, n (%)<br>0<br>1<br>≥2<br>Missing | <br>24 (60)<br>16 (40)<br>0 (0)<br>0 (0) |
| **CLL Genetics, n (%)** | |
| IgVH unmutated | 30 (75) |
| 17p deletion and/or TP53 mutation | 11 (28) |

**Key**: CLL, chronic lymphocytic leukaemia; I, idelalisib; IgVH, immunoglobulin heavy chain; ITT, intent to treat; O, ofatumumab; PS, performance status; R, rituximab; WHO, World Health Organization.
**Notes**: Adapted from the Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.
**Source**: Furman (2013)[71]

## Results

### *Progression-free survival*

PFS results are presented in Table 40. Median PFS in the Furman study was 26 months, but little further information was provided.

### Overall survival

Median OS was not reached at the time of the publication, and 14 (35%) of patients were still continuing therapy.

### Response

Response was assessed using both the IWCLL (2008) and Cheson (2012) criteria for all enrolled patients.

An overall response rate of 83% and a complete response rate of 8% are reported for the two treatment arms together.

The median duration of response for 33 of the participants was 24 months.

**Table 40: Results from Furman (2013)**

| | IR/IO (N=40) |
|---|---|
| Progression-free survival, median (months) | 26 |
| Overall survival, median (months) | Not reached |
| Response | |
| Overall response rate (n=40), % | 83 |
| Overall response rate 17pDel patients (n=11), % | 73 |
| Complete response, % | 8 |
| Duration of response, median (months) [N=33] | 24 |
| **Key:** I, idelalisib; O, ofatumumab; R, rituximab.<br>**Source**: Furman (2013)[71] | |

**Relevant comparator non RCTs in relapsed or refractory CLL**

Table 41 presents the baseline characteristics of the non-RCTs of relevant comparators alongside the single-arm trial of idelalisib with rituximab and Study 116.

Patients in the idelalisib with rituximab trials (Study 116 and Furman (2013)) were generally older, had received more prior therapies, had a larger proportion of patients in more severe disease states and had larger proportions of patients with 17p deletion and/or TP53 mutation than the majority of the non-RCTs that were identified. These are all important factors that influence PFS and other outcomes in CLL patients and indicate that the patients in these idelalisib with rituximab trials are generally sicker than in the comparator trials. There are also differences in the criteria used to assess patient response between the trials. The majority of the papers do not report the methods used for the other outcomes, and therefore, there are potentially some additional differences between the reporting of these outcomes. Therefore, in light of these limitations, comparability of effectiveness between these studies should be interpreted with caution.

The results for the non-RCTs of relevant comparators alongside the single-arm trial of idelalisib with rituximab and Study 116 are presented in Table 42.

The trials with the most similar patient populations to the idelalisib with rituximab trials (Study 116 and Furman (2013)) are Coiffier (2008) and Wierda (2010).

Compared to these trials, idelalisib with rituximab shows greater PFS and a higher ORR. The PFS rates for ofatumumab in the Coiffier (2008) and Wierda (2010) trials are similar to the PFS rates reported for the rituximab monotherapy arm in Study 116.

Despite clear differences in patient characteristics between the other studies, with Study 116 being conducted in a much sicker patient population, PFS and ORR results are broadly similar when compared to the FCR trials and show some improvements when compared to bendamustine with rituximab and methylprednisolone with rituximab.

## Table 41: Baseline characteristics of the relevant non-RCTs

| | Study 116 | | Furman (2013) | Coiffier (2008) | Wierda (2010) | | Tam (2006) | Badoux (2011) | Smolej (2013) | Lopez (2013) | Fischer (2011) | Pileckyte (2011) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment** | **IR** | **R** | **IR/IO** | **O** | **O [FA-ref]** | **O [BF-ref]** | **FCR** | **FCR** | **FCR[a]** | **FCR, BR, ChR** | **Benda-R** | **MpR** |
| Patients (N) | 110 | 110 | 40 | 33 | 59 | 79 | 34 | 284 | 97[b] | 110 | 83 | 29 |
| ITT population | 110 | 110 | | | | | | 284 | | | 78 | |
| Age (years), median (range) | 71 (48-90) | 71 (47-92) | 66 (43-87) | 61 (27-82) | 64 (41-86) | 62 (43-84) | 59 (30-89) | 60 | 71 (58-87) | 69 (29-87) | 66.5 (42-86) | 59 (45-76) |
| Gender, female, % | 30.9 | 38.2 | 30 | 42 | 25 | 28 | 35 | NR | 41 | NR | 34.6 | 41 |
| Prior therapies, median (range) | 3 (1-12) | 3 (1-9) | NR | 3 (1-9) | 5 (1-14) | 4 (1-16) | NR | 2 (1-10)[c] | NR | NR | [c] | NR |
| Rai Stage, % | | | | | | | | 0-II: 154/284 III-IV: 130/284 | | NR | NR | |
| 0 | 0 | 0.9 | | 3 | 2 | 0 | 3 | | | | | 0 |
| I-II | 30.9 | 26.4 | | 84 | 44 | 30 | 50 | | | | | 24 |
| III-IV | 73.6 | 65.5 | | 12 | 51 | 70 | 47 | | 66[d] | | | 76 |
| Binet Stage, % | | | NR | | | | NR | NR | NR | | | NR |
| A | 6.4 | 3.6 | | 21 | 10 | 5 | | | | 11 | 18.7 | |
| B | 26.4 | 29.1 | | 67 | 39 | 30 | | | | 42 | 32.1 | |
| C | 57.3 | 55.5 | | 12 | 51 | 65 | | | | 46 | 48 | |
| CLL Genetics, % | | | | | | | | | | | | |
| Unmutated IgVH, % | 82.7 | 84.5 | 75 | NR | NR | NR | NR | 68.6[e] | 72 | 9 | 67 | 86 |
| 17p deletion, % | 24 | 28 | NR | NR | 129 | 118 | NR | NR | 9 | 10 | 18 | 41 |
| 17p deletion and/or TP53 mutation, % | 41.8 | 44.5 | 128 | NR | NR | NR | NR | NR | NR | NR | NR | NR |

**Key**: BF-ref, fludarabine refractory with bulky (>5 cm) lymphadenopathy; C, cyclophosphamide; Chl, chlorambucil; CI. confidence interval; CLL, chronic lymphocytic leukaemia; FA-ref, fludarabine and alemtuzumab refractory; I, idelalisib; IgVH, immunoglobulin heavy chain; ITT, intention to treat; Mp, methlyprednisone; NE, not evaluable; NR, not reported;
**Notes**: **a** Reduced dose regimen; **b** Includes treatment naïve patients; **c** Fischer (2011) only presents prior therapies by treatment line: 1 – 36 (46.2%); 2 – 22 (28.2%); 3 – 18 (23.1%). Badoux (2011) also presents prior therapies by treatment line: 1;(n=116); 2 (n=80); 3 (n=46); ≥4 (n=42); **d** Reported as patients in "advanced Rai stages"; **e** 59/86

**Table 42: Results of the relevant non-RCTs**

| Study | Study 116 | | Furman (2013) | Coiffier (2008) | Wierda (2010) | | Tam (2006) | Badoux (2011) | Smolej (2013) | Lopez (2013) | Fischer (2011) | Pileckyte (2011) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment** | **IR** | **R** | **IR/IO** | **O** | **O [FA-ref]** | **O [BF-ref]** | **FCR** | **FCR** | **FCR[a]** | **FCR, BR, ChR** | **BR** | **MpR** |
| **PFS** | | | | | | | | | | | | |
| PFS definition | Randomisation to first documentation of definitive PD or death from any cause | | NR | NR | NR | | NR | NR | NR | NR | NR | Study entry to PD or death |
| Assessed by | IRC | | NR | NR | NR | | NR | NR | NR | NR | IA and verified by IRC | NR |
| Median, months (95% CI) | 19.4 (12.3, not reached) | 6.5 (4.0, 7.3) | 20 | 4.4 (3.4, 5.2) | 5.7 (4.5, 8) | 5.9 (4.9, 6.4) | NR | 20.9 (18.8, 27.6) | 15 | NR | 15.2 (12.5, 17.9) | 12 (8, 16) |
| 12-month PFS, % | 70.4 | 9.2 | NR | 8 | 8 | 6 | NR | 64 | NR | NR | 57 | 41 |
| 24-month PFS, % | NR[b] | NR[b] | NR | 8 | NR | NR | 3-year PFS: 25% | 47 | NR | NR | 22 | 14 |
| **OS[c]** | | | | | | | | | | | | |
| Median, months (95% CI) | Not reached [Not reached] | 20.8 (14.8, not reached) [redacted] | Not reached | NR | 13.7 (9.4, not reached) | 15.4 (10.2, 20.2) | NR | 46.7 (41.2, 53.4) | 31 | NR | 33.9 (25.5, 42.1) | 31 (20, 42) |
| 12-month OS, % | 89.3 [89.3] | 66.8 [49.2] | NR | NR | 54 | 61 | NR | 81 | NR | NR | 81 | 83 |
| 24-month OS, % | 71.0 [71.0] | 41.7 [NR[f]] | NR | NR | NR | NR | 3-year OS: 64% | 69 | NR | NR | 72 | 61 |

| Study | Study 116 | | Furman (2013) | Coiffier (2008) | Wierda (2010) | | Tam (2006) | Badoux (2011) | Smolej (2013) | Lopez (2013) | Fischer (2011) | Pileckyte (2011) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment** | **IR** | **R** | **IR/IO** | **O** | **O [FA-ref]** | **O [BF-ref]** | **FCR** | **FCR** | **FCR[a]** | **FCR, BR, ChR** | **BR** | **MpR** |
| **Response[d]** | | | | | | | | | | | | |
| Response criteria | IWCLL 2008[32] | | IWCLL (2008)[32] | Cheson (1988) and NCIWG (1996) | NCIWG (1996)[70] | | NCIWG (1996) | i) NCIWG (1996) and ii) IWCLL (2008) | NR | NR | NCIWG (1996) | NCIWG (1996) |
| Assessed by | IRC | | NR | NR | IRC | | NR | NR | NR | NR | IA[e] | NR |
| ORR, % | 83.6 | 15.5 | 83 | 50 | 58 | 47 | 95 | i) 74 | 64 | FCR: 43<br>ChR: 55 | 59 | 62 |
| CR, % | 0 | 0 | 8 | 0 | 0 | 1/79 | 14 | i) 30<br>ii) 28 | 29 | NR | 9 | 0 |
| PR, % | 83.6 | 15.5 | NR | 44.4[f] | 58 | NR | 54 | i) 30[f] | NR | NR | 50 | 62 |
| SD, % | 11.8 | 64.5 | NR | NR | 31 | 41 | 27 | NR | 21 | NR | 26 | 28 |
| PD, % | 0.9 | 14.5 | NR | NR | NR | NR | NR | NR | 6 | NR | 6 | NR |
| NE, % | 3.6 | 5.5 | NR | NR | NR | NR | NR | NR | 9 | NR | 9 | NR |
| Duration of response, months, median (95% CI) | 10.4 (7.1, not reached) | 6.4 (4.5, 7.4) | 19 | 4.4 (3.7, 5.7) | 7.1 (3.7, 7.6) | 5.6 (3.6, 7) | NR | NR | NR | NR | 15.2 (12.1, 18.3) | NR |

**Key**: B, bendamustine; BF-ref, fludarabine refractory with bulky (>5 cm) lymphadenopathy; C, cyclophosphamide; Chl, chlorambucil; CI, confidence interval; CR, complete response; FA-ref, fludarabine and alemtuzumab refractory; IA, investigator assessed; IRC, independent review committee; IWCLL, International Workshop on Chronic Lymphocytic Leukemia; Mp, methylprednisone; NCIWG, ; NE, not evaluable; NR, not reported; O, ofatumumab; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; R, rituximab; RCT, randomised controlled trial; SD, stable disease

**Notes:**

a Reduced dose regimen

b The maximum observation time is <24 months

c OS outcomes presented in square brackets for Study 116 are the crossover adjusted RPSFTM results

d Badoux (2011) also reported nodular partial response: i) 14% as assessed by NCIWG (1996) criteria and ii) 11% as assessed by IWCLL (2008) criteria

e Verified by IRC f One additional patient achieved a nodular partial response

**Untreated CLL with a 17p deletion or TP53 mutation**

The systematic literature review of untreated patients identified one single-arm idelalisib trial (Study 101-08), which is summarised in Table 43. No evidence was identified for any comparator treatments.

It is worth mentioning that although there were no alemtuzumab monotherapy studies identified, there was a phase II trial for alemtuzumab and streroids conducted in the UK,[72] which included 17 previously untreated relatively fit patients with a median age of 62 (n=39, including previously treated patients). The BCSH guidelines recommend combination therapy with alemtuzumab and pulsed high-dose glucocorticoids. However, the guidelines also recognise that this regimen is associated with a significant risk of infection and advise to administer with caution.[7] Alemtuzumab plus streroids is not a listed comparator and therefore this study will not be discussed further in this submission.

**Table 43: List of relevant non-randomised and non-controlled evidence**

| Study number (acronym) | Objective | Population | Intervention | Comparator | Primary study reference | Justification for inclusion |
|---|---|---|---|---|---|---|
| Study 101-08/ NCT01203930 | Evaluate the safety and clinical activity of idelalisib alone and in combination with rituximab in patients with CLL or SLL | 64 previously untreated patients with CLL or small lymphocytic lymphoma; aged age≥ 65 yrs; of these, 9 patients had 17p deletion or TP53 mutation | Idelalisib 150 mg bid with rituximab 375 mg/m$^2$ weekly x 8, continuously for 48 weeks | None | O'Brien et al (2014)[21] [Secondary ref: Coutre et al., 2013[20]] | This study represents the only currently available evidence for idelalisib conducted in an untreated population of CLL patients, a proportion of which have 17p deletion or TP53 mutation and was used in the EMA's determination of licensed indication |
| **Key:CLL, chronic lymphatic leukaemia; EMA, European Medicines Agency; SLL, small lymphocytic lymphoma** | | | | | | |

### Study design

Study 101-08 was a phase II, single-arm study of idelalisib and rituximab combination therapy, conducted in the US. Patients were treated for 48 weeks in the primary study, and the patients who completed 48 weeks without progression could continue to receive idelalisib in an extension study. A summary of the trial methodology is provided in Table 44.

**Table 44: Summary of trial methodology**

| **Trial number (acronym)** | **Study 101-08/ NCT01203930** |
|---|---|
| **Location** | US |
| **Trial design** | Phase II, single arm |
| **Eligibility criteria for participants** | Key inclusion criteria<br>• Histologically or cytologically confirmed CLL or SLL<br>• Age ≥ 65<br>• Presence of measurable lymphadenopathy (defined as the presence of ≥1 nodal lesion that measures ≥ 1.5 cm in the longest diameter [LD] and ≥ 1.0 cm in the longest perpendicular diameter [LPD] as assessed by physical exam, computed tomography [CT] or magnetic resonance imaging [MRI]).<br>• CLL or SLL - Binet Stage C or Rai Stage III or IV or has active disease<br>• World Health Organization (WHO) Performance Status of ≤ 2<br>**Exclusion criteria**<br>• Prior therapy for CLL or SLL, except corticosteroids for symptom relief<br>• Treatment with a short course of corticosteroids for symptom relief within 1-week prior to Visit 1<br>• Known active central nervous system involvement of the malignancy<br>• Ongoing active, serious infection requiring systemic therapy. Patients may be receiving prophylactic antibiotics and antiviral therapy at the discretion of the treating physician<br>• Serum creatinine ≥ 2.0 mg/dL<br>• Serum bilirubin ≥ 2 mg/dL (unless due to Gilbert's syndrome) or serum transaminases (i.e. aspartate aminotransferase [AST], alanine aminotransferase [ALT]) ≥ 2 x upper limit of normal |
| **Settings and locations where the data were collected** | Multiple sites in the US |
| **Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered)**<br>**Idelalisib (n=64)**<br>**Permitted and** | Idelalisib 150 mg oral tablets bid with iv rituximab 375 mg/m$^2$ weekly x 8, continuously for 48 weeks (n=48)<br><br>Details of permitted and disallowed medications are provided within the exclusion criteria listed above |

| | |
|---|---|
| **disallowed concomitant medication** | |
| **Primary outcomes (including scoring methods and timings of assessments)** | Overall response rate (ORR), defined as the proportion of participants who achieve a complete response (CR) or partial response (PR) as evaluated according to standard criteria |
| **Secondary/tertiary outcomes (including scoring methods and timings of assessments)** | • Type, frequency, severity, and relationship to study therapy of any adverse events (AEs) or abnormalities of physical findings, laboratory tests, drug discontinuations due to AEs or serious adverse events (SAEs). This composite endpoint will measure the safety profile of idelalisib<br>• Lymphadenopathy response rate, defined as the proportion of participants with a ≥ 50% reduction from baseline in the sum of the perpendicular diameters of all measurable lesions while receiving study therapy<br>• Change from baseline in the sum of the perpendicular diameters of all measurable lesions<br>• Duration of response (DOR) is defined as the interval from the first documentation of CR or PR to the first documentation of definitive disease progression or death from any cause<br>• Progression-free survival (PFS) is defined as the interval from the first dose of study drug to the first documentation of definitive disease progression or death from any cause<br>• Overall survival (OS) is defined as the interval from the start of study treatment to death from any cause<br>• Trough and 1.5 hour post-dose plasma concentrations of idelalisib<br>• Changes in potential pharmacodynamic markers of drug activity in plasma and whole blood |
| **Pre-planned subgroups** | Efficacy endpoints (PFS, duration of response and time to response) were examined in the following subgroups of patients:<br>• With or without 17p deletion and/or TP53 mutation<br>Disease history, exposure to study drug, overall summary of AEs, all treatment-emergent adverse events (TEAEs), Grade ≥3 TEAEs, and SAEs were examined in the following subgroups of patients:<br>• Sex (male or female)<br>• Age group (<70 or ≥70 years) |
| **Key: CLL, chronic lymphatic leukaemia; SLL, small lymphocytic lymphoma** | |

## Baseline characteristics

Baseline characteristics of the patients within Study 101-08 are reported in Table 45. This study included 64 patients. 62 of these patients completed the first 8 weeks of treatment and 43 patients completed 48 weeks. 21 patients discontinued treatment; 17 due to AEs, 3 due to deaths and 1 withdrawn consent.

A total of 9 of the 64 patients included in Study 101-08 had 17p deletion or TP53 mutation. Although all patients are presented here, this submission is only interested in these 9 patients with 17p deletion or TP53 mutation, as per the final scope and the license for idelalisib.

**Table 45: Baseline characteristics of participants in Study 101-08**

| **Baseline characteristic** | |
|---|---|
| Patients | n=64 |
| Age (years), median (range) | 71 (65-90) |
| Gender, female, % | 37.5 |
| Diagnosis: CLL; SLL | 59/5 |
| WHO Performance Score 0-1 / 2 | 63/1 |
| Rai Stage I-II / III-IV | 33/27 |
| Binet Stage A/B/C | 14/22/28 |
| β2 Microglobulin, mg/L, median [range] | 4.0 (1.9-15.8) |
| Haemoglobin < 11 g/dl | 27% |
| Platelets < 100 x103/µl | 27% |
| B-symptoms | 41% |
| Bulky adenopathy (≥5 cm) | 11% |
| 17 deletion or TP53 mutation: presence; absence | 9; 52 |
| IgVH: non-mutated; mutated | 37; 23 |
| 11q deletion: presence; absence | 10; 51 |
| NOTCH 1: mutation; wild type | 8; 51 |
| **Notes**: Adapted from the Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee. | |
| **Key: IgVH, immunoglobulin variable region heavy chain** | |

### Quality assessment

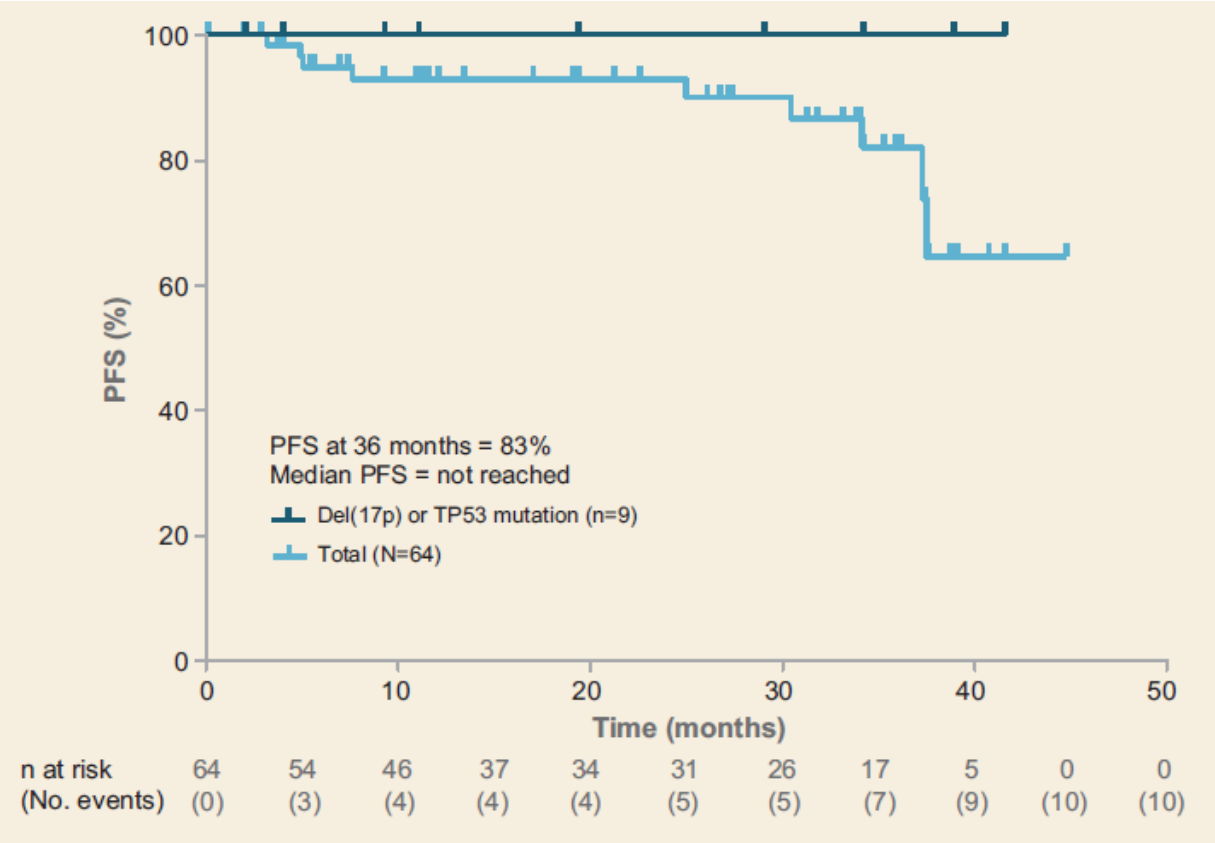
The quality assessment of Study 101-08 is provided in Appendix 9.

### Clinical effectiveness results

Progression-free survival data for the whole population in Study 101-08 and for the subgroup of patients with 17p deletion and/or TP53 mutation are presented in Figure 13. Median PFS, including patients who continued into the extension study, was not reached for the overall population nor for patients with 17p deletion/TP53 mutation.

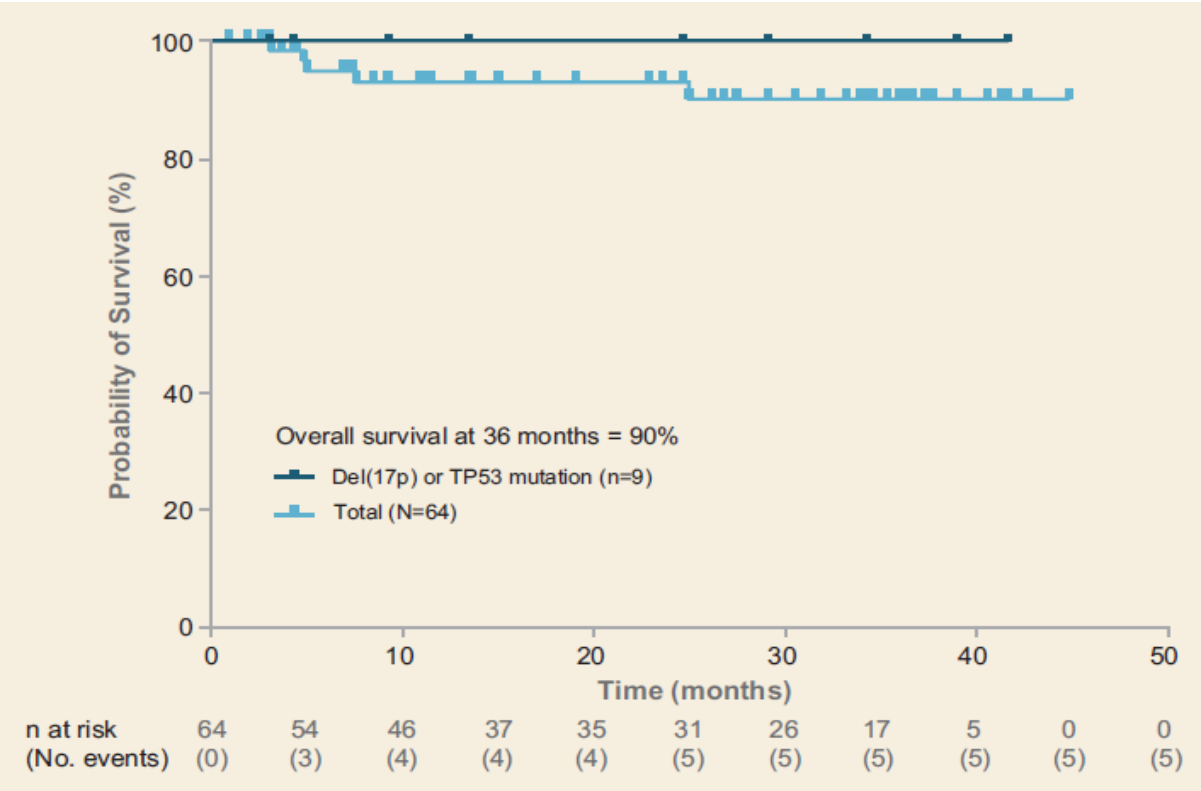
PFS for the overall population at 36 months was 83%, compared with 100% for the 17p deletion/TP53 mutation patients.

**Figure 13: Progression-free survival for patients receiving idelalisib and rituximab in Study 101-08**




Overall survival data for the whole population in Study 101-08 and for the subgroup of patients with 17p deletion and/or TP53 mutation are presented in Figure 14. Overall survival for the whole study population at 36 months was 90%. None of the patients with 17p deletion and/or TP53 mutation had died at this point.

**Figure 14: Overall Survival in Study 101-08**




In Study 101-08, the ORR for all treatment-naive patients with CLL was 96.9%: 53 patients (82.8%) had a PR, and 9 patients (14.1%) had a CR. The ORR for patients with 17p deletion/TP53 mutation was 100%; 3 patients (33.3%) had a CR, and 6 patients (66.7%) had a PR (Table 46), and at 24 months, none of these patients had progressed (Figure 13).

**Table 46: Response data for Study 101-08**

| Response assessment | All patients (n=64) | Patients with 17p deletion and/or TP53 mutation (n=9) |
|---|---|---|
| Complete Response | 18.8% | 33.3% |
| Partial Response | 78.1% | 66.7% |
| Stable Disease | 0 | 0 |
| Progressive Disease | 0 | 0 |
| Not Evaluable | 3.1% | 0 |
| Overall Response Rate[a] | 96.9% | 100% |
| 95% CI[b] | 89.2 – 99.6 | 66.4 – 100 |

**Key**: CI, confidence interval; CR, complete response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.
**Notes:**
a Patients who had a CR or PR fall in best overall response category.
b 95% exact binomial confidence interval of overall response rate.

The median duration of response for Study 101-08, including patients who continued into the extension study, were not reached for the overall population nor for patients with 17p deletion/TP53 mutation. The median time to response was 1.9 months (range: 1.6-5.7).

Figure 15 presents the haematologic response in patients with cytopenias at baseline. Seventeen out of 17 patients with anaemia, 16 out of 17 patients with thrombocytopenia, and 5 out of 5 patients with neutropenia showed a haematologic response.

**Figure 15: Improvement in Cytopenias**

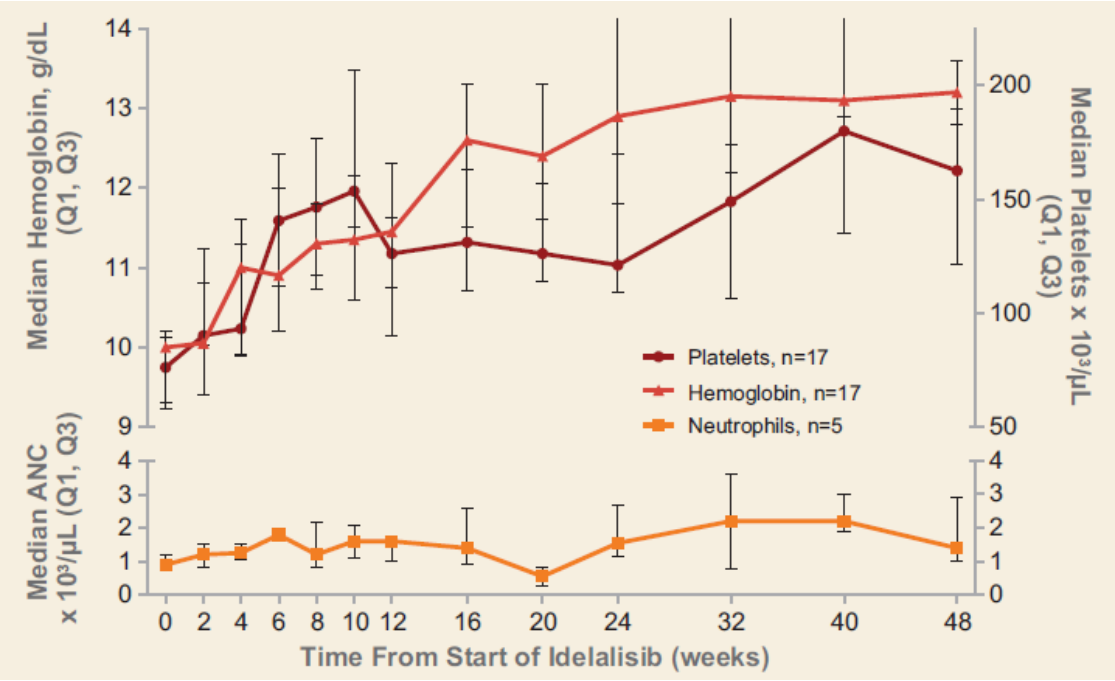



Table 47 presents a comparison of the patients with 17p deletion and/or TP53 mutation in Study 101-08 with the patients in Hillmen (2007)[22] who had 17p deletion. The evidence available from these trials was scarce, and the populations were not really comparable; with patients in Study 101-08 being generally sicker than the patients in Hillmen (2007). However, the massive improvement in ORR in Study 101-08 shows a large benefit of treatment with idelalisib with rituximab for this patient population.

**Table 47: Response data for Study 101-08 compared to Hillmen (2007)**

| | Study 101-08 | Hillmen (2007) | |
|---|---|---|---|
| | IR | Alemtuzumab | Chlorambucil |
| | Patients with 17p deletion and/or TP53 mutation (n=9) | Patients with 17p deletion (n=11) | Patients with 17p deletion (n=10) |
| **Median PFS, months** | Not reached | 10.7 | 2.2 |
| p-value | | 0.4066 | |
| **Overall response rate n (%) [95% CI]** | 100% [66.4, 100] | 64% | 20% |
| p-value | | 0.0805 | |
| **Overall survival** | Not reached | Not reached | Not reached |

**Key:** CI, confidence interval; IR, idelalisib with rituximab
**Notes:**
a Patients who had a complete response or partial response in best overall response category.
b 95% exact binomial confidence interval of overall response rate.

## *4.12 Adverse reactions*

**Relapsed or refractory CLL**

A summary of the overall adverse events reported in Study 116 are presented in Table 48. In total 218 patients received at least one dose of the study drug to which they were assigned and were included in the safety analysis. Median duration of exposure for patients assigned to idelalisib with rituximab was 8.1 months (Q1 5.6, Q3 11.1) with a range of 0.3 to 19.5 months. Median duration of exposure for patients assigned to rituximab monotherapy was 4.6 months (Q1 3.3, Q3 7.3), with a range of 0.1 to 14.6 months. Median follow-up for patients treated with idelalisib with rituximab was 12.5 months (range: 0.3-25.1; 95% CI: 11.5, 13.5) compared to 11.1 months (range: 0.2-24.6; 95% CI: 10.1, 11.8) for patients treated with placebo with rituximab.

**Table 48: Overall summary of adverse events in Study 116 (Safety Analysis Set)**

| Adverse Event Category, % | IR (N=110) | Placebo + R (N=108) |
|---|---|---|
| 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 |

**Key:** AE, adverse event; IR, idelalisib rituximab; R, rituximab; SAE, serious adverse event
**Notes:** Relationship to study drug was determined by investigator; AEs with missing relationships were considered to be related.
For subjects in the placebo + R group, summary included data up to the first dosing of open-label IDELA.
**Source:** Study 116 CSR[14]

Thirty-two subjects (idelalisib with rituximab: 17.3%, 19 subjects; placebo with rituximab: 12%, 13 subjects) discontinued study drug due to an AE. Infections and infestations were the most common type of AE that led to discontinuation, occurring in 11 of the 32 subjects (idelalisib with rituximab: 5 subjects; placebo with rituximab: 6 subjects). Gastrointestinal disorders accounted for events in 6 of the subjects with AEs leading to discontinuation. Respiratory, thoracic, and mediastinal disorders accounted for events in 6 of the subjects with AEs leading to discontinuation (idelalisib with rituximab: 3 subjects; placebo with rituximab: 3 subjects). Investigations accounted for events in 3 subjects in the idelalisib with rituximab group and 0 subjects in the placebo group. All other SOCs accounted for only 1 or 2 subjects who discontinued study drug in either treatment group.

In the idelalisib with rituximab group, the most common AEs leading to discontinuation were diarrhoea (3.6%, 4 subjects) and pneumonitis, colitis, and transaminases increase (each 1.8%, 2 subjects). In the placebo with rituximab group, AEs that led to discontinuation in more than 1 subject were sepsis and pneumonia (each 1.9%, 2 subjects).

No subject in the placebo with rituximab group had AEs that led to a reduction in study drug. A total of 7 subjects (6.4%) in the idelalisib with rituximab group had AEs that led to a reduction in study drug. One subject each (0.9%) had a dose reduction for the following AEs: ALT increase, transaminases increase, diverticulitis, pneumonitis, rash, maculo-papular rash, and skin disorder.

A total of 15 patients had treatment-emergent adverse events (TEAEs) that led to death (4 with idelalisib and rituximab; 11 with placebo and rituximab). Causes of death were consistent with advanced CLL and the underlying frailty, age, and poor prognosis of the study population. TEAEs leading to the death of more than 1 subject in either treatment group were sepsis and pneumonia, each occurring in 2 subjects in the placebo with rituximab group. Sepsis led to death in 1 subject in the idelalisib with rituximab group, and pneumonia led to death in no subjects in the idelalisib with rituximab group, although one patient died as a result of fungal pneumonia, and one patient died as a result of *Pneumocystis jirovecii* pneumonia. (Pneumocystis prophylaxis was not mandatory under the protocol but clinical advisors held the opinion that prophylaxis for pneumocystis would be considered mandatory in UK practice for such a heavily treated, relapsed population.[13]) One patient in each treatment group died as a result of acute respiratory failure. The remaining six deaths in the patients receiving placebo and rituximab were as a result of the following AEs: cardiac failure, COPD, general physical health deterioration, pulmonary oedema and left ventricular failure, bacteraemia, and multi-organ failure.

Table 49 reports the treatment-emergent AEs for ≥10% of subjects in either treatment group and are summarised by system organ class (SOC) and preferred term (PT) by decreasing frequency for the safety analysis population. The three most frequent AEs were consistent with those expected for a heavily pretreated, relapsed or refractory CLL population having received prior chemoimmunotherapeutic agents and on study immunotherapy. Fatigue was the most common event overall,

occurring in 34 subjects (30.9%) in the idelalisib with rituximab group and 36 subjects (33.3%) in the placebo with rituximab group.

The most commonly reported AEs in the idelalisib with rituximab groups were pyrexia (40.0%, 44 subjects), fatigue (30.9%, 34 subjects), diarrhoea (29.1%, 32 subjects), nausea (27.3%, 30 subjects), and neutropenia (25.5%, 28 subjects). The most commonly reported AEs in the placebo with rituximab group were fatigue (33.3%, 36 subjects), cough (31.5%, 34 subjects), and infusion related reaction (30.6%, 33 subjects).

**Table 49: Adverse events occurring in ≥10% of patients in Study 116**

| Adverse Event, % | IR (N=110) | Placebo + R (N=108) |
|---|---|---|
| Subjects with any AEs | 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 |

| Adverse Event, % | IR (N=110) | Placebo + R (N=108) |
|---|---|---|
| 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 |

**Key:** AE, adverse event; IR idelalisib with rituximab
**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.
**Source:** Study 116 CSR[14]

Table 50 reports the incidence of AEs ≥ Grade 3 that occurred in ≥ 2% of patients in either treatment group.

The most commonly reported ≥ Grade 3 AEs for idelalisib with rituximab patients were neutropenia (22.7%, 25 subjects), pneumonia (10.0%, 11 subjects), and diarrhoea (9.1%, 10 subjects). The most commonly reported ≥ Grade 3 AEs for rituximab patients were neutropenia (16.7%, 18 subjects), pneumonia (9.3%, 10 subjects), and anaemia (6.5%, 7 subjects). Clinical advisors felt that the rate of pneumonia in the study was not overly concerning as it is generally high in such a heavily pre-treated CLL population.[13]

**Table 50: Adverse events ≥ Grade 3 occurring in ≥ 2% of patients in Study 116**

| System Organ Class<br>Preferred Term, % | IR (N=110) | Placebo + R (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 |

| System Organ Class<br>Preferred Term, % | IR (N=110) | Placebo + R (N=108) |
|---|---|---|
| **Key:** AE, adverse event; IR idelalisib with rituximab<br>**Notes:** AEs were classified using MedDRA version 17.<br>Subjects who experienced multiple events within the same PT (or SOC) were counted once per PT (or SOC) in the highest severity grade.<br>Severity of AEs was graded according to the CTCAE, version 4.03.<br>For subjects in the placebo + R group, summary included data up to the first dosing of open-label IDELA.<br>**Source:** Study 116 CSR[14] | | |

## AEs of special interest

*Diarrhoea/colitis*

Thirty-two subjects (29.1%) in the idelalisib with rituximab group had an AE of diarrhoea (any grade), and 10 subjects (9.1%) had events that were ≥ Grade 3 in severity (9 subjects with Grade 3 and 1 subject with Grade 4). In the placebo with rituximab group, 19 subjects (17.6%) had diarrhoea of any grade, and no subjects had diarrhoea events that were ≥ Grade 3 in severity. Adverse events of colitis were reported for 8 subjects (7.3%) in the idelalisib with rituximab group and 1 subject (0.9%) in the placebo with rituximab group. Five of the 8 subjects in the idelalisib with rituximab group with AEs of colitis also were reported to have AEs of diarrhoea (3 of which were concurrent), and the 2 AE terms may have been used interchangeably for these subjects. Colitis AEs of Grade 3 in severity were reported for 5 subjects (4.5%) in the idelalisib with rituximab group; no subjects had Grade 4 colitis. No subject in the placebo with rituximab group had ≥ Grade 3 colitis. In the majority of such cases, regardless of the preferred term reported, subjects presented after several months of idelalisib administration with several weeks of high volume watery diarrhoea that was poorly responsive to antidiarrhoeals or to empiric treatment with antimicrobials. With idelalisib interruption, and symptomatic measures including antidiarrhoeals and anti-inflammatory agents such as budesonide, resolution has been documented in almost all cases within approximately 1 month from the discontinuation of idelalisib. In subjects with ≥ Grade 3 diarrhoea who were rechallenged with idelalisib, diarrhoea has recurred in some but not all subjects.

*Rash*

Sixteen subjects (14.5%) in the idelalisib with rituximab group had rash of any grade, and 1 subject (0.9%) had rash of ≥ Grade 3 in severity (there were no events that

were Grade 4). In the placebo with rituximab group, 5 subjects (4.6%) had rash, with no events of ≥ Grade 3 in severity. Maculo-papular rash was reported for 4 subjects (3.6%) in the idelalisib with rituximab group (1 event [0.9%] of Grade 3) and for no subjects in the placebo with rituximab group. To further characterise the occurrence of rash in the idelalisib development program, a review of all AE preferred terms potentially related to rash was conducted for the safety population. A search of MedDRA preferred terms (including the terms: dermatitis exfoliative, drug eruption, exfoliative rash, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash morbiliform, rash papular, and rash pruritic was conducted). Twenty-seven subjects (24.5%) in the idelalisib with rituximab arm had an event within this medical search term (MST) rash classification, compared to 7 subjects (6.5%) in the placebo with rituximab arm. This included 4 subjects (3.6%) in the idelalisib with rituximab arm with events that were Grade 3, compared to 1 subject (0.9%) in the placebo with rituximab arm (there were no subjects in either arm with an event of Grade 4). In the idelalisib with rituximab group, 2 subjects (1.8%) discontinued due to one of the rash MST terms, compared to no subjects in the placebo with rituximab group.

*Pneumonitis*

Six subjects (5.5%) in the idelalisib with rituximab group had pneumonitis of any grade, and 4 subjects (3.6%) had pneumonitis of ≥ Grade 3 in severity. In the placebo with rituximab group, 1 subject (0.9%) had pneumonitis, and the event was of ≥ Grade 3 severity. There were no Grade 4 events of pneumonitis in either treatment group.

**Untreated CLL with 17p deletion/TP53 mutation**

All 64 patients in Study 101-08 received at least one dose of the study drug and were included in the safety analysis. The median duration of exposure was 22.4 months (range: 0.8-45.8; Q1, Q3: 8.3, 35.4). Table 50 through Table 52 present a summary of the adverse event data in Study 101-08. These data are only presented for the overall trial population and not specifically for those patients with 17p deletion or TP53 mutation. Evidence for adverse event data from Study 101-08 is taken from a poster presented at the 2014 ASH conference,[21] as this presented data from a later time point than the interim CSR.[64] More detailed AE data from this interim CSR

is presented in Appendix 11. The final CSR for Study 101-08 is expected to be available in April.

The most frequently occurring TEAEs of any grade were diarrhea/colitis (77%), rash (58%) and pyrexia (42%). The most frequent Grade ≥3 AE was diarrhea/colitis, which developed in 27 patients (42%), occurred at a median of 9.5 months (range 3–29) and led to dosing interruption or discontinuation in 21 patients. Eleven of these patients received a corticosteroid (budesonide or prednisone) to treat this. Twenty-one patients were rechallenged following idelalisib dose interruption or had dose reduced to 100 mg BID and 12 of these (44% of 27 affected) were subsequently able to maintain dosing for minimum of 120 days.

**Table 51: Treatment-Emergent Adverse Events (ITT Analysis)**

| **Patients, %** | **All Patients, N = 64** | |
|---|---|---|
| | **Any Grade AE** | **Grade ≥3 AE** |
| Any AE | 100 | 89 |
| Diarrhea/colitis | 77 | 42 |
| Pyrexia | 42 | 3 |
| Nausea | 38 | 2 |
| Rash | 58 | 13 |
| Chills | 36 | 0 |
| Cough | 33 | 2 |
| Fatigue | 31 | 0 |
| Pneumonia | 28 | 19 |
| Dyspnea | 25 | 6 |
| Headache | 23 | 0 |
| Vomiting | 22 | 3 |
| Insomnia | 20 | 0 |
| **Laboratory Abnormalities** | | |
| Transaminase elevation | NR | 23 |
| Neutropenia | NR | 28 |
| Anemia | NR | 3 |
| Thrombocytopenia | NR | 2 |
| **Key:** AE, adverse event; NR, not reported | | |

The most frequent serious AEs were diarrhea/colitis (38%) and pneumonia (17%). 5 patients died while on treatment; 1 from pneumonia/sepsis, 1 from pneumonia/metastatic melanoma, 2 from pneumonitis and 1 myocardial infarction.

**Table 52: Serious Adverse Events Occurring in >1 Patient (ITT Analysis)**

| **Patients, %** | **All Patients, N = 64** |
|---|---|
| Any SAE | 66) |
| Diarrhea/colitis | 38 |
| Pneumonia | 17 |
| Death | 8 |
| Dyspnea | 3 |
| Febrile neutropenia | 3 |
| Hypoxia | 3 |
| Pneumonitis | 3 |
| Pulmonary fibrosis | 3 |
| Pyrexia | 3 |
| Respiratory failure | 3 |
| **Key:** SAE, serious adverse event<br>**Notes:** Patients may have ≥1 SAE | |

**Table 53: Adverse Events Leading to Discontinuation (ITT Analysis)**

| **Patients, n (%)** | **Treatment Duration** | | | |
|---|---|---|---|---|
| | **<24 week, n=10** | **24-48 week, n=6** | **>48 weeks, n=11** | **Total, n=23** |
| Diarrhea/colitis | 0 | 4 | 8 | 12 (19) |
| Respiratory disorders | 6 | 0 | 1 | 7 (11) |
| Rash | 3 | 0 | 0 | 3 (5) |
| Infection | 1 | 2 | 0 | 3 (5) |
| Anemia | 1 | 1 | 0 | 2 (3) |
| ALT/AST | 1 | 0 | 0 | 1 (2) |
| Other | 2 | 4 | 2 | 8 (13) |
| **Notes:** Patients may have ≥1 AE | | | | |

Rates of diarrhoea and colitis were much higher in Study 101-08 than in Study 116. Study 101-08 was one of the first trials performed for this treatment and indication, and investigators were not aware of the potential for late-onset diarrhoea in patients. Similarly, at this time there was not the guidance in place within the protocol that currently exists. Therefore, investigators that encountered these events did not stop

treatment soon enough and allowed their patients to continue, which caused the diarrhoea side effects to worsen. This was mentioned publically by the lead author at the presentation of an abstract at ASH in 2014.[21] One clinical advisor felt that the worsened toxicity might be a result of the intensity of the dose-dense rituximab regimen included in this trial.[13]

This is in contrast to Study 116 where the rituximab dosing regimen was spaced out over a number of months. As the idelalisib clinical program progressed from phase I and II Studies (Study 101-07 and Study 101-08) to the phase 3 Study (Study 116), the approach for management of AEs by dose interruption and reduction was developed and investigators gained further experience in treating subjects with idelalisib.[12]

**Overview of Comparator Safety**

Table 54 summarises adverse events associated with idelalisib with rituximab, and all the relevant comparator treatments or regimen components, as reported in the Summary of Product Characteristics for each. In general, idelalisib with rituximab is associated with fewer common and very common AEs than any of the other comparators or combinations. The main AEs associated with comparators are those associated with the cytotoxic effects of myelosuppression, such as neutropenia, leukopenia, anaemia, thrombocytopenia, and bone marrow suppression (Table 54).[19] Additionally, patients are less able to receive cytotoxic therapies if they have reduced kidney function, or multiple comorbidities.[19]. Further to the similar efficacy observed with the anti-CD20s, rituximab and ofatumumab, as reported in a network meta-analysis (in combination with bendamustine),[17] (described further in section 4.13), these treatments also have a similar safety profile, particularly in terms of infections, neutropenia, nausea and and a range of infusion-related reactions (e.g., rash)(Table 54).

**Table 54: Summary list of very common and common adverse events by treatment**

| Intervention | Key adverse events | |
|---|---|---|
| | **Very common (≥1/10)** | **Common (≥1/100 to <1/10)** |
| IR [9] | Infections; neutropenia; diarrhoea/colitis; transaminase increase; rash (includes the preferred terms dermatitis exfoliative, drug eruption, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash morbilliform, and exfoliative rash); pyrexia; increased triglycerides | Pneumonitis |
| Fludarabine [73] | Infections /opportunistic infections (like latent viral reactivation, e.g. progressive multifocal leukoencephalopathy, Herpes zoster virus Esptein-Barr-virus), pneumonia; neutropenia, anaemia, thrombocytopenia; cough; vomiting, diarrhoea, nausea; fever, fatigue, weakness | Myelodysplastic syndrome and acute myeloid leukaemia (mainly associated with prior, concomitant or subsequent treatment with alkylating agents, topoisomerase inhibitors or irradiation); myelosuppression; anorexia; peripheral neurophathy; visual disturbances; stomatitis; rash; oedema, mucositis, chills, malaise |
| Cyclophosphamide [74] | Myelosuppression (manifested as bone marrow failure, pancytopenia, neutropenia, agranulocytosis, granulocytopenia, thrombocytopenia [complicated by bleeding], leukopenia, anaemia), leukopenia, neutropenia; immunosuppression; alopecia (may progress to baldness); cystitis, microhaematuria; fever | Infections (an increased risk for and severity of pneumonias (including fatal outcomes), other bacterial, fungal, viral, protozoal, and parasitic infections; reactivation of latent infections, including viral hepatitis, tuberculosis, JC virus with progressive multifocal leukoencephalopathy (including fatal outcomes), pneumocystis jiroveci, herpes zoster, strongyloides, sepsis and septic shock (including fatal outcomes)); febrile neutropenia; mucosal inflammation; hepatic function abnormal; haemorrhagic cystitis, macrohaematuria; impairment of spermatogenesis; chills, asthenia, malaise |
| Rituximab [75] | Bacterial infections, viral infections, bronchitis, neutropenia, leucopenia, febrile neutropenia, thrombocytopenia; infusion related reactions, angioedema; nausea; pruritus, rash, alopecia*; fever, chills, asthenia, headache; decreased IgG levels | Pneumonia*, febrile infection*, herpes zoster*, respiratory tract infection*, fungal infections, infections of unknown aetiology, acute bronchitis*, sinusitis*, hepatitis B1; anaemia, pancytopenia*, granulocytopenia*; hypersensitivity; hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia; paraesthesia, hypoaesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety; lacrimation disorder, conjunctivitis; tinnitus, ear pain; myocardial infarction*, arrhythmia, atrial fibrillation*, tachycardia, cardiac disorder*; hypertension, orthostatic hypotension, hypotension; bronchospasm, respiratory disease, chest pain, dyspnoea, increased cough, rhinitis; vomiting, diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, |

| Intervention | Key adverse events | |
|---|---|---|
| | **Very common (≥1/10)** | **Common (≥1/100 to <1/10)** |
| | | anorexia, throat irritation; urticaria, sweating, night sweats, skin disorder*; hypertonia, myalgia, arthralgia, back pain, neck pain, pain; tumour pain, flushing, malaise, cold syndrome, fatigue*, shivering*, multi-organ failure*<br>Clinical advisors also mentioned that rituximab, when administered in combination with high-dose methylprednisone, is associated with a high rate of fungal infection[13] |
| Ofatumumab [76] | Lower respiratory tract infection, including pneumonia, upper respiratory tract infection; neutropenia, anaemia; nausea (likely infusion reaction), rash (likely infusion reaction), pyrexia (likely infusion reaction) | Sepsis, including neutropenic sepsis and septic shock, herpes virus infection, urinary tract infection; febrile neutropenia, thrombocytopenia, leukopenia; anaphylactoid reactions (likely infusion reaction), hypersensitivity (likely infusion reaction); tachycardia (likely infusion reaction); hypotension (likely infusion reaction), hypertension (likely infusion reaction); bronchospasm (likely infusion reaction), hypoxia (likely infusion reaction), dyspnoea (likely infusion reaction), chest discomfort (likely infusion reaction), pharyngolaryngeal pain (likely infusion reaction), cough (likely infusion reaction), nasal congestion (likely infusion reaction); diarrhoea (likely infusion reaction); urticarial (likely infusion reaction), pruritus (likely infusion reaction), flushing (likely infusion reaction); back pain; cytokine release syndrome (likely infusion reaction), rigors (likely infusion reaction), chills (likely infusion reaction), hyperhidrosis (likely infusion reaction), fatigue (likely infusion reaction) |
| Bendamustine [77] | Infection NOS*; leukopenia NOS*, thrombocytopenia; nausea, vomiting; mucosal inflammation, fatigue, pyrexia; haemoglobin decrease, creatinine increase, urea increase | Tumour lysis syndrome; haemorrhage, anaemia, neutropenia; hypersensitivity NOS*; insomnia; cardiac dysfunction, such as palpitations, angina pectoris, arrhythmia; hypotension, hypertension; pulmonary dysfunction; diarrhoea, constipation, stomatitis; alopecia, skin disorders NOS*; amenorrhoea; pain, chills, dehydration, anorexia; AST increase, ALT increase, alkaline phosphatase increase, bilirubin increase, hypokalemia; |
| Chlorambucil [78] | Leucopenia, neutropenia, thrombocytopenia, pancytopenia or bone marrow suppression | Acute secondary haematologic malignancies (especially leukaemia and myelodysplastic syndrome), particularly after long term treatment; anaemia; seizures in children with nephrotic syndrome; gastro-intestinal disturbances such as nausea and vomiting, diarrhoea and oral ulceration |
| Corticosteroids (methylprednisolone used as a proxy) [79] | None listed | Infection (including increased susceptibility and severity of infections with suppression of clinical symptoms and signs); cushingoid; sodium retention, fluid retention; psychiatric reactions including affective disorders (such as irritable, euphoric, depressed and labile moods psychological dependence and suicidal thoughts), psychotic reactions (including mania, delusions, hallucinations and aggravation of schizophrenia), behavioural disturbances , irritability, anxiety, sleep disturbances, cognitive dysfunction including confusion and amnesia have been reported for all corticosteroids. Reactions are common |

| Intervention | Key adverse events | |
|---|---|---|
| | **Very common (≥1/10)** | **Common (≥1/100 to <1/10)** |
| | | and may occur in both adults and children. In adults, the frequency of severe reactions was estimated to be a 5-6%. Psychological effects have been reported on withdrawal of corticosteroids; the frequency is unknown; posterior subcapsular cataracts; hypertension; peptic ulcer (with possible peptic ulcer perforation and peptic ulcer haemorrhage); peripheral oedema; ecchymosis; skin atrophy (thin fragile skin); acne; growth retardation (in children); osteoporosis; muscular weakness; impaired wound healing; blood potassium decreased (potassium loss) |
| Alemtuzumab [80] | Upper respiratory tract infection, urinary tract infection; lymphopenia, leukopenia; infusion-associated reactions (specifically flushing, nausea, urticaria, rash, pruritus, pyrexia, fatigue) | Lower respiratory tract infections, herpes zoster, gastroenteritis, oral herpes, oral candidiasis, vulvovaginal candidiasis, influenza, ear infection; lymphadenopathy; cytokine release syndrome; Basedow's disease, hyperthyroidism, autoimmune thyroiditis, hypothyroidism, goitre, antithyroid antibody positive; insomnia (infusion-related reaction), anxiety; MS relapse, dizziness (infusion-related reaction), hypoaesthesia, paraesthesia, tremor, dysgeusia (infusion-related reaction); vision blurred; vertigo; tachycardia (infusion - related reaction), bradycardia, palpitations; hypotension (infusion-related reaction), hypertension; dyspnoea (infusion-related reaction), cough, epistaxis, oropharyngeal pain; abdominal pain, vomiting, diarrhoea, dyspepsia (infusion-related reaction), stomatitis; generalised rash (infusion-related reaction), erythema, ecchymosis, alopecia, hyperhidrosis, acne; myalgia, muscle weakness, arthralgia, back pain, pain in extremity, muscle spasms, neck pain; proteinuria, haematuria; menorrhagia, irregular menstruation; chest discomfort (infusion-related reaction), chills (infusion-related reaction), pain (infusion-related reaction), oedema peripheral, asthenia, influenza-like illness, malaise, infusion site pain; contusion |
| Obinutuzumab + chlorambucil[a] [81] | Neutropenia, thrombocytopenia, anaemia; diarrhoea; pyrexia; infusion related reactions | Urinary tract infection, nasopharyngitis, oral herpes, rhinitis, pharyngitis; squamous cell carcinoma of the skin; leukopenia; tumour lysis syndrome, hyperuricaemia; atrial fibrillation; hypertension; cough; constipation; alopecia; arthralgia, back pain, musculoskeletal chest pain; white blood cell count decreased, neutrophil count decreased, weight increased |

**Key:** IV, NR, not reported; NOS = not otherwise specified; *frequency count was based only on severe (≥ Grade 3 NCI common toxicity criteria) reactions
**Sources:** (Aspen Pharma, 2014)[79], (Beacon, 2014)[79], (Genzyme Therapeutics, 2013)[80], (Gilead, 2014)[4, 9, 73, 74, 77], (GlaxoSmithKline, 2015)[76], (Napp, 2014)[77], (Roche, 2014)[81], (Roche, 2014)[75], (Sandoz, 2014)[74], (Sanofi, 2011)[73]
[a]reported with a higher incidence in patients receiving obinutuzumab plus chlorambucil versus chlorambucil alone/ rituximab plus chlorambucil (higher incidence = difference between treatment arms of ≥2%)

## *4.13 Interpretation of clinical effectiveness and safety evidence*

**Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology**

*Survival and response rates*

In Study 116, which included heavily pretreated patients with relapsed or refractory CLL with significant comorbidities and a poor prognosis PFS, the primary efficacy endpoint was statistically significant and greatly favoured idelalisib with rituximab compared with placebo with rituximab (hazard ratio 0.15; $p=1.6\times10^{-16}$). Furthermore, the PFS results favoured idelalisib with rituximab compared with placebo with rituximab across all predefined subgroups, including in high-risk patients with 17p deletion, TP53 mutation or unmutated IgVH; the treatment effect across these subgroups was similar, indicating that idelalisib is highly effective regardless of cytogenetic status.

Idelalisib with rituximab also demonstrated a statistically significant improvement in overall survival compared with placebo with rituximab (hazard ratio [95% CI]: 0.34 [0.19, 0.60]; p=0.0001). An additional RPSFT analysis was performed to adjust for patients within the trial that had disease progression on placebo with rituximab and crossed over to idelalisib with rituximab. This analysis showed even more favourable results for patients treated with idelalisib with rituximab compared with placebo with rituximab (hazard ratio: [redacted]

Idelalisib, when used in combination with rituximab, results in unprecedented survival benefits:

- In terms of PFS (HR: 0.15 [95% CI: 0.09, 0.24] for idelalisib with rituximab vs. placebo with rituximab)[14] compared with data from comparator RCTs from the literature (HR: 0.76 [95% CI: 0.60, 0.96] for FCR vs. FC;[27] and HR: 0.87 [95% CI: 0.6, 1.27] for bendamustine vs. fludarabine).[62] These unprecedented PFS results warranted termination of the study after the first prespecified interim analysis.[19]
- In terms of OS (HR: 0.34 [95% CI: 0.19, 0.60] for idelalisib with rituximab vs. placebo with rituximab)[14] compared with data from comparator RCTs from the

literature (HR: 0.83 [95% CI: 0.59, 1.17] for FCR vs. FC;[27] and HR: 0.82 [95% CI: 0.47, 1.43] for bendamustine vs. fludarabine.[62]

In addition to substantially and significantly improved PFS and OS both the overall response rate and lymph node response rates were significantly greater with idelalisib with rituximab compared with placebo with rituximab (83.6% vs. 15.5%; OR: 27.8; p=1.3×10-23 and stratified odds ratio: 225.83; p=8.5×10-38). As with PFS and OS, both lymph node and overall response rate results favoured idelalisib with rituximab over placebo with rituximab across all predefined subgroups.

*Health-related quality of life*

Regarding HRQL, subjects treated with idelalisib with rituximab consistently showed greater symptom improvement than subjects receiving placebo with rituximab based on the Additional Concerns (Leukemia subscale), FACT-Leu Total, and the Trial Outcome Index scores of the HRQL FACT-Leu Questionnaire, throughout the study. Patients treated with idelalisib with rituximab reached the minimal important difference for Additional Concerns much more rapidly compared with patients receiving placebo with rituximab (Week 4 vs. Week 72) and their improvement was sustained. In a mixed effects model analysis of changes from baseline in the Additional Concerns, FACT-Leu Total and Trial Outcome Index scores, the main effect of treatment was statistically significant (p=0.0003, p=0.0039, p=0.0023, respectively).

Patient HRQL was also assessed in Study 116 by means of the EQ-5D utility index. Patients treated with idelalisib with rituximab showed improvement over baseline and consistently showed greater symptom improvement compared with patients receiving placebo with rituximab throughout the study, with a statistically significant treatment effect for patients treated with idelalisib with rituximab (p=0.002 for the overall treatment effect based on the longitudinal data analysis).

Additionally, patients treated with idelalisib with rituximab had a greater median improvement on the Karnofsky Performance Status compared with patients receiving placebo with rituximab (10.0 vs. 0.0; p-value not reported).

*Safety*

Idelalisib was generally well tolerated and had a manageable safety profile when administered in combination with rituximab.[14 12] Most AEs were consistent with those expected for a heavily pretreated, relapsed/refractory CLL population. The most frequently reported AE overall was fatigue (30.9% for idelalisib with rituximab; 33.3% for placebo with rituximab). The most common AE with idelalisib with rituximab was pyrexia (40.0% for idelalisib with rituximab; 18.5% for placebo with rituximab).

Adverse events that occurred more frequently with idelalisib with rituximab (p-value of relative risk ≤ 0.1) were pyrexia, GERD, increased ALT, increased AST, dehydration, rash, colitis, pain, diarrhoea, chest discomfort, fall, sinus congestion, and stomatitis.

The most commonly reported ≥ Grade 3 AEs for idelalisib with rituximab were neutropenia (22.7%, 25 subjects), pneumonia (10.0%, 11 subjects), and diarrhoea (9.1%, 10 subjects). The most commonly reported ≥ Grade 3 AEs for rituximab were neutropenia (16.7%, 18 subjects), pneumonia (9.3%, 10 subjects), and anaemia (6.5%, 7 subjects). Clinical advisors felt that the rate of pneumonia in the study was not overly concerning as it is generally high in such a heavily pre-treated CLL population.[13] Idelalisib was not found to be associated with the AEs observed with traditional cytotoxic chemotherapy regimens.

*Data for comparators*

It is difficult to compare the clinical effectiveness of idelalisib with rituximab in relapsed CLL with relevant comparators in the NICE scope due to the scarcity of evidence for the comparators in similar patient populations, the vast heterogeneity in the patient populations for the comparators where there is evidence available, and the fact that it is not possible to construct a network meta-analysis due to lack of common comparators within studies.

Despite the large differences in the patient populations between the trials with the majority of other studies including younger and less heavily pretreated populations with less high risk patients, the median PFS for patients treated with idelalisib with rituximab in Study 116 is similar or improved compared to the other treatments. The one exception is the median PFS for FCR (27 months vs. 19.4 months for idelalisib

withrituximab, respectively); however, the Robak trial included much fitter, younger patients with a lower incidence of del17p and IgVH mutation than the patients in Study 116 and patients that had only received one prior line of therapy. As discussed previously, FCR is the standard of care in the fittest patients who are able to tolerate fludarabine and the patient population in this trial is not comparable to the patients included in Study 116. Taking all these factors into consideration in the context of the comparator trials, a median PFS of 19.4 months for idelalisib with rituximab demonstrates a clinically significant result in patients that have few treatment options available. Furthermore, the PFS benefit is supported by the high ORR observed in the idelalisib with rituximab arm and compares favourably to the ORRs reported for other comparators.

Compared to the two non-RCTs that were conducted in a similar patient population to that of Study 116:[65, 82] idelalisib with rituximab was associated with a considerably longer median PFS (19.4 months [95% CI: 12.3, not reached]) and OS (not reached [not reached]) than that reported for the comparator of ofatumumab within these two studies as presented in Table 55.

**Table 55. Key results of Study 116 compared with selected non-RCTs**

| Study | PFS (months) | OS (months) | ORR (%) |
|---|---|---|---|
| Coiffier (2008) [84] | 4.4 | Not reported | 50 |
| Wierda (2010) [66]<br>Refractory to fludarabine unsuitable for alemtuzumab | 5.9 | 13.7 | 47 |
| Wierda (2010) [66]<br>Refractory to fludarabine and alemtuzumab | 5.7 | 15.4 | 58 |
| R placebo arm Study 116 | 6.5 | 20.8 ([redacted] adjusted for cross-over) | 15.5 |
| IR arm Study 116[14] | 19.4 | Not reached | 83.6 |
| **Key:** ORR, overall response rate; OS, overall survival; PFS, progression-free survival; non-RCT, non-randomised control trial | | | |

The overall response rate was also better for idelalisib with rituximab (83.6%) than most of the comparator data from the non-RCTs,[65, 82] including the two ofatumumab non-RCTs that were conducted in a similar patient population (50%;[82] 58%;[65] 47%.[65]).

The rituximab arm from Study 116 was in line with the PFS and OS data for ofatumumab (PFS for rituximab: 6.5 [95% CI: 4.0, 7.3]; PFS for ofatumumab: 4.4 [95% CI: 3.4, 5.2];[82] 5.7 [95% CI: 4.5, 8]; [65] 5.9 [95% CI: 4.9, 6.4];[65] OS for rituximab: 20.8 [95% CI: 14.8, not reached]; OS for ofatumumab: not reported;[82] 13.7 [95% CI: 9.4, not reached];[65] 15.4 [95% CI: 10.2, 20.2].[65]).

In the small subgroup of untreated CLL patients with 17p deletion or TP53 mutation, from Study 101-08, treatment with idelalisib with rituximab resulted in an ORR of 100%, including 3 patients (33.3%) with a CR and 6 patients (66.7%) with a PR.[21] At 36 months, none of these patients had progressed or died.[21] Only a single relevant comparator study was identified from the systematic literature review, which was an RCT comparing alemtuzumab (n=11) with chlorambucil (n=10), which can help put these idelalisib results into context.[22] This RCT reported a median PFS of 10.7 months with alemtuzumab, and 2.2 months with chlorambucil,[22] compared with a median PFS not reached at 36 months.[21] Overall response rate was 64% with alemtuzumab and 20% with chlorambucil,[22] compared with 100% in Study 101-08.[21] As such, idelalisib compares favourably with the results in this comparator trial, despite the fact that the patient population in Study 101-08 were much sicker at baseline.

Study 116 demonstrated a benefit with idelalisib with rituximab regardless of whether or not patients presented with 17p deletion/TP53 mutation. The same has not been demonstrated with available alternatives with the only robust available evidence demonstrating significantly poorer outcomes with both FC and FCR, in patients with TP53 mutation and 17p deletion compared with patients without these abnormalities in terms of OS, PFS, and ORR (all $p<0.001$).[38]

To put into context the results with idelalisib, the median PFS for these patients with TP53 mutations when treated with ineffective fludarabine-containing regimens was 12.1-15.4 months (compared with not reached at 36 months), ORR was 51.6-75.0% (compared with 100%), and OS was 30.4-42.2 months.[38] Similar results were observed for patients with a 17p deletion.[38]

**Strengths and limitations of the clinical evidence base: idelalisib**

*The evidence presented in this submission is relevant to the populations within the decision problem.*

This submission presents an evidence base in support of idelalisib with rituximab in the two patient populations presented within the NICE final scope:

- Adult patients with CLL who have received at least one prior therapy
- Adult patients with CLL who have 17p deletion or TP53 mutation and who are unsuitable for chemo-immunotherapy

Evidence is presented for both of these populations. Study 116 is an RCT that presents efficacy, safety and HRQL data for idelalisib with rituximab compared with placebo with rituximab in 220 patients with CLL who have received at least one prior therapy; and Study 101-08 presents data for a small sub-population of patients receiving idelalisib with rituximab in a single-arm study with 17p deletion or TP53 mutation who have been previously untreated.

*Robust evidence from a randomised controlled trial*

The key evidence for this submission comes from Study 116, which is a double-blind RCT with a robust design, comparing idelalisib and rituximab with rituximab and placebo. Randomisation was carried out appropriately using an Interactive Web Response System, and allocation of treatment was concealed by use of a matched placebo for the idelalisib comparison. The trial used a double-blind design so that care providers, participants and outcome assessors were all blinded to treatment. An independent review committee was used to assess disease progression and response outcomes. Baseline disease and demographic characteristics were well balanced between the treatment groups. There were no unexpected imbalances in terms of drop-outs between treatment groups.

*Rituximab comparator arm – relevant and similar efficacy profile to ofatumumab*

Study 116 used rituximab monotherapy as a comparator to idelalisib with rituximab, which was based on the NCCN guidelines that list dose-dense rituximab monotherapy as a treatment option for frail patients with relapsed CLL.[16] 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 chemoimmunotherapy,[10] and 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.[19]

However, based on an advisory board with UK clinicians experienced in CLL management, rituximab monotherapy is not considered to be a standard of care for this patient population and is not widely used in England (<10%); as such, it is also not included in the NICE scope for this submission.[13] Despite this, evidence from this comparator is still relevant and important to the decision problem as rituximab has a similar efficacy to another anti-CD20 agent, ofatumumab, which is used frequently in UK patients with CLL, as supported by clinical opinion from the advisory board.[13] Although in vitro ofatumumab is shown to have more potent complement-dependent cytotoxicity than rituximab, there has been no data to suggest or support that this is reflected in terms of efficacy in the clinical setting. Furthermore a recently conducted network meta-analysis (in combination with bendamustine or chlorambucil) showed that rituximab has a similar or slightly improved efficacy compared to ofatumumab in untreated CLL.[17] Trials with an ofatumumab monotherapy arm reported median PFS values of 5.8, and 4.4 months (Wierda,[66] and Coiffier,[84] respectively) and included heavily pre-treated patients. Although there are no direct comparisons of these trials to Study 116, the median PFS of 6.5 months for rituximab is in the same range, indicating that this is a reasonable assumption. Furthermore, although there are no data directly comparing rituximab and ofatumumab in CLL patients, a phase III RCT in patients with relapsed/refractory diffuse large B-cell lymphoma (previously treated with rituximab), found no difference in efficacy between ofatumumab and rituximab in combination with a standard chemotherapy regimen.[18] Finally, in reference to Study 116 and the comparator arm used, the EPAR for idelalisib states "…the effect shown is convincing compared to what can be expected with available chemotherapy options with minimal toxicity. Therefore, the control arm in the pivotal study is considered acceptable."[12] The EPAR also states "the high activity [of idelalisib] observed allows concluding that the benefits are expected to exceed any of the available options and are at least of similar magnitude than rituximab in the salvage setting."[12] It is important to mention that over 10 sites recruited 32 patients in the UK

(15% of the total patients in the trial) and given the blinded trial design this would suggest that UK clinicians did indeed consider rituximab as an appropriate treatment for these patients or they are unlikely to have participated in the trial.

Taking these factors into consideration, the limitation of rituximab monotherapy in Study 116 can be addressed by considering this arm as an anti-CD20 comparator arm and assuming a similar efficacy to ofatumumab, which is listed as a comparator in the NICE scope.

*Dosing for idelalisib consistent with the SPC*

The idelalisib dosing used in Study 116 and Study 101-08 was in line with the dosing guidance in the SPC. Patients received 150mg twice daily in both studies unless they needed any dose adjustments, in which case their dose was lowered to 100mg twice daily, as per the SPC. The rituximab dosing schedule for Study 116 (detailed in section 4.2) is based on the US NCCN guidelines and is in line with the idelalisib SmPC given that no rituximab dose is specified. Any potential differences between the idelalisib dosing schedule used in Study 116, Study 101-08 and those used in clinical practice in England are not anticipated to bias the trial results. Note that the dose of rituximab used in Study 116 was different from the dose and schedule that was approved in combination with fludarabine and cyclophosphamide in the rituximab SPC; two additional doses (weeks 2 and 6) were administered to provide more intensive anti-CD20 therapy early in treatment (intensified dose regimen). This intensified dose regimen of rituximab monotherapy is recommended by the NCCN guidelines in frail patients.[16]

*Evidence to support the cohort of front-line patients with 17p deletion/TP53 mutation*

This submission presents data for the relapsed or refractory CLL population for all the outcomes of interest listed in the NICE scope, including PFS, OS, response rates, AEs and HRQL. The efficacy of idelalisib has been demonstrated in Study 116 using endpoints that are directly relevant to the clinical benefits experienced by patients in practice (i.e. PFS and OS). Supportive evidence from Study 116 included data on response rates and the impact on the patient in terms of HRQL endpoints.

For the subgroup of patients with a 17p deletion or TP53 mutation who were previously untreated, the key evidence comes from Study 101-08, which is a phase

II, single-arm study in 64 patients, of which, a subgroup of 9 patients had 17p deletion or TP53 mutation. However, despite this being a non-randomised study in a small group of patients, the high unmet need in these difficult-to-treat patients, coupled with the unprecedented efficacy of idelalisib being demonstrated (PFS not reached at 36 months), idelalisib was granted marketing authorisation for this patient population. Supportive data on response rates were also provided. Clinical advisors agreed that these patients should not be considered in isolation and behave clinically similar to the patients with 17p deletion/TP53 mutation in the relapsed setting.[13] As such, the subgroup of patients with 17p deletion/TP53 mutation in Study 116 can be considered as supportive evidence for idelalisib in the untreated subgroup too. As reported in the subgroup analysis in section 4.8, PFS, OS and response rate results favoured idelalisib with rituximab compared with placebo with rituximab in patients with 17p deletion and/or TP53 mutation. In summary, idelalisib with rituximab was also efficacious in the subgroup of relapsed CLL patients with 17p deletion/TP53 mutation, as well as the whole relapsed CLL population, which can be used as further supportive evidence for the efficacy of idelalisib in patients with 17p deletion or TP53 mutation.

Indeed, the EMA identified the activity of idelalisib in patients with CLL and 17p deletion/TP53 mutations as an area of special interest based upon the consistent results seen across studies at all lines of treatment in 153 patients with 17p deletion or TP53 mutations.[12]

**Strengths and limitations of the clinical evidence base: comparators**

Although systematic literature reviews were conducted to gather evidence for both populations of interest in this submission, there were few sources identified that were deemed relevant to the decision problem. Table 15 and Table 16, presented at the start of section 4, summarise all the available evidence for all comparators included within the NICE scope for this submission.

For the relapsed CLL populations, only 3 RCTs were identified for the comparators in the scope (FCR vs. FC;[27] bendamustine vs. fludarabine;[62] bendamustine with rituximab vs. chlorambucil vs. rituximab[61]); only non-RCT evidence was identified for the comparators corticosteroids with rituximab and ofatumumab; and no evidence

was identified for the comparators chlorambucil monotherapy, corticosteroids monotherapy, and best supportive care (BSC).

For the previously untreated CLL population with a 17p deletion or TP53 mutation, evidence was even sparser. Only one RCT was identified (chlorambucil vs. alemtuzumab[22]), and no evidence was found for any of the other comparators considered relevant to this submission. No evidence from non-RCT studies was identified for any of the comparators. Of note, however, although there were no alemtuzumab monotherapy studies identified, there was a phase II trial for alemtuzumab and steroids conducted in the UK,[72] which included 17 previously untreated relatively fit patients with a median age of 62 (n=39, including previously treated patients). This is the basis of the BCSH guidelines recommendation of combination therapy with alemtuzumab and pulsed high-dose glucocorticoids.[7] However, the BCSH guidelines also recognise that this regimen is associated with a significant risk of infection and advise to administer with caution.[7] Alemtuzumab plus steroids is not a listed comparator and therefore this study will not be discussed further in this submission.

Because of the limited evidence available, lack of a connecting network and the fact that the populations within the comparator RCTs are not comparable to the older, more pre-treated patients included in Study 116, it was not possible to construct a network meta-analysis. Therefore, in the absence of head-to-head data or the possibility to conduct any formal indirect comparisons with the comparators, it was only possible to conduct qualitative comparisons between Study 116 and comparator studies with similar patient populations.

The RCTs that were identified represent a younger population than in Study 116, with a lower proportion of high-risk patients who had not been heavily pretreated. Despite the clear differences in patient characteristics, with Study 116 being conducted in a much sicker patient population, PFS results were similar across trials. Given these differences, the overall response rates and partial response rates for IR-treated patients in Study 116 look very positive compared with the other treatments in the comparator RCTs.

**Generalisability**

**In general, patients included in Study 116 were representative of the wider population of patients with relapsed or refractory CLL treated in the clinical 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 71 years across the studies;**

Table 33; Table 41). Given a median age at diagnosis of 72 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 chemoimmunotherapy resistant group of patients with a 17p deletion or TP53 mutation. [63]

Furthermore, 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 (15% of all recruited patients) were enrolled from the UK, which represents a relatively high proportion of patients in a global study.[14]

**End of life criteria**

Table 56 demonstrates that idelalisib with rituximab should be considered under end of life criteria in the relapsed or refractory population.

**Table 56: 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][83]<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][83]<br>**For untreated patients**<br>Mean OS (restricted means analysis): [redacted] months (SE: [redacted][83]<br>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.[10] |
| 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][83]<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][83] |
| 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.[84] The number requiring treatment at third line and subsequent settings is 384.[85] |

**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

## 4.14 Ongoing studies

Details on all of the ongoing studies of idelalisib in patients with CLL that are due to report within the next 12 months are presented in Table 57.

**Table 57: List of ongoing trials of idelalisib that are due to report data within the next 12 months**

| Trial no. (Acronym) Phase | Interventions | Population | Primary outcome | Status | Primary reference |
|---|---|---|---|---|---|
| NCT01088048; Phase I | IR<br>IR + Bendamustine<br>Idelalisib + Bendamustine<br>Idelalisib + Ofatumumab<br>Idelalisib + Fludarabine<br>Idelalisib + Everolimus<br>Idelalisib + Bortezomib<br>Idelalisib + Chlorambucil<br>Idelalisib + Rituximab + Chlorambucil<br>Idelalisib + Lenalidomide + Rituximab | 224 patients aged ≥ 18 with relapsed or refractory CLL, indolent B-Cell Non-Hodgkin Lymphoma (NHL) or Mantle Cell Lymphoma | Safety data | Ongoing; estimated primary completion: April 2015 | NA |
| NCT01539291; Phase III [extension study to NCT01539512] | Idelalisib 300mg BID<br>Idelalisib 150mg BID | 160 adult patients with previously treated, recurrent CLL who have measurable lymphadenopathy from the 116 study (NCT01539512) | Safety data | Ongoing; estimated primary completion: December 2015 | NA |
| NCT01796470; | GS-9973 + Idelalisib [dose-ranging study] | 66 patients aged ≥ 18 with relapsed or refractory CLL, | Objective response rate | Ongoing; estimated | NA |

| Trial no. (Acronym) Phase | Interventions | Population | Primary outcome | Status | Primary reference |
|---|---|---|---|---|---|
| Phase II | | follicular lymphoma, mantle cell lymphoma, indolent B-cell NHL, diffuse large B-cell lymphoma, SLL or marginal zone lymphoma | | primary completion: December 2014 | |
| NCT02136511; Expanded Access Protocol | Idelalisib 150mg BID + Rituximab | Patients aged ≥ 18 with previously treated, recurrent B-cell CLL | NA | Ongoing; estimated primary completion: unknown | NA |

**Key:**BID, twice daily; CLL, chronic lymphocyticleukaemia; IR, idelalisib with rituximab; SLL, small lymphocytic lymphoma
**Source:** www.clinicaltrials.gov

# 5 Cost-effectiveness

This section presents evidence for the cost-effectiveness of idelalisib with rituximab within its licensed indication to treat chronic lymphocytic leukaemia.

To appraise idelalisib with rituximab for patients who have received at least one prior therapy, a Markov model was constructed. The pivotal study to inform this analysis was Study 116, described in section 4. Study 116 compared idelalisib with rituximab versus rituximab plus placebo, in patients who were not eligible to receive cytotoxic therapy. Clinical outcomes from Study 116 were useful to estimate the cost-effectiveness of idelalisib with rituximab versus rituximab monotherapy, and also, using clinically justified assumptions, versus best supportive care and ofatumumab monotherapy, in the end-of-life group of patients unfit to receive cytotoxic therapy. To appraise idelalisib with rituximab versus its other listed comparators, and in previously treated patients fitter than those in Study 116, was highly challenging. Section 4 demonstrated the poorly connected network of RCT evidence in this disease area. Formal evidence synthesis to robustly compare survival outcomes across relevant studies was not possible. Nevertheless, in an effort to harness the evidence base to make cautious comparisons to other regimens used in practice, additional assumptions were made, and exploratory analysis results are presented.

Idelalisib with rituximab is shown to be highly cost-effective as an end-of-life therapy, versus (i) rituximab monotherapy, (ii) best supportive care and (iii) ofatumumab monotherapy, in patients similar to those in Study 116, with base case incremental cost-effectiveness ratios of (i) £13,634, (ii) £20,461 and (iii) £1,527 per QALY gained. Probabilistic sensitivity analyses showed that idelalisib with rituximab is cost-effective at a willingness to pay threshold of £50,000 per QALY gained in over 95% of probabilistic model iterations versus each of these comparators. Exploratory comparisons to other available treatments suggest idelalisib with rituximab is preferable to its range of comparators in patients similar to those in Study 116, and may be beneficial for the wider group of patients who have received at least one prior therapy.

In treatment-naïve patients who have CLL in the presence of 17p deletion or TP53 mutation, effective treatment options are scarce. The evidence for idelalisib with

rituximab for these patients, and even more so for its comparators, is however limited and precluded robust economic analysis. Subgroup analysis of patients in Study 116 with of 17p deletion or TP53 mutation nevertheless supports the clinical evidence for idelalisib with rituximab in this patient group, who currently have few if any effective treatment options available.

## *5.1 Published cost-effectiveness studies*

The search strategy to identify previous cost-effectiveness analyses of idelalisib for patients with CLL who have received at least one prior therapy combined free text and controlled vocabulary terms, using the databases MEDLINE and MEDLINE in Process, EMBASE, EconLit and NHS Economic Evaluation Database (NHS EED). The search strategy is detailed in Appendix 11.

The process of assessing the relevance of each reference for data extraction was based on the *a priori* definition of eligibility criteria, including patient population, indication and study type. The eligibility criteria used are summarised in Table 58.

**Table 58: 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 |
| **Key:** CLL, chronic lymphocyticleukaemia; | |

No studies met the pre-defined eligibility criteria. Appendix 12 provides details of this result.

The systematic literature search for evidence of clinical effectiveness of treatments for previously untreated CLL with a 17p deletion or TP53 mutation, described in

section 4.1 revealed that evidence for this population is scarce. A targeted PubMed search for economic evaluations of idelalisib for this patient group identified no such studies.

## *5.2 De novo analysis*

**Patient population**

Idelalisib in combination with rituximab has market authorisation for use in adults with CLL who have received at least one prior therapy. This patient group is highly heterogeneous and includes relatively fit patients who have numerous treatment options; as well as much frailer patients who are refractory to cytotoxic agents or ineligible to receive them because of multiple comorbidities, and who have few if any active treatment options remaining.

The key clinical data available for the submission are from Study 116, described in detail in section 4, which assessed idelalisib with rituximab versus rituximab (plus placebo) in patients who had received a median 3 prior therapies and who were not suited to receive cytotoxic-containing therapies because of either their fitness or lack of previous response to those treatments. Furthermore a large proportion of these patients were 17pDel or TP53 mutated rendering their CLL insensitive to chemotherapy-based treatment.

These data, from a robustly designed double-blind control study, are useful to inform the economic comparison of idelalisib with rituximab versus rituximab alone for patients unsuited to cytotoxic therapy, to make inferences regarding the relative effect versus other anti-CD20 monotherapy regimens in this patient group, and to make conservative assumptions to compare to BSC.

To extend the comparison of idelalisib with rituximab to other CLL treatment regimens for relapsed patients with more options is challenging. This is not least owing to the absence of a connected network of clinical evidence, as described in section 4, which precludes formal synthesis of evidence to control for study and patient differences across the evidence base. Nevertheless, the best available methods are employed herein to make cautious exploratory economic comparisons between idelalisib with rituximab and the range of treatment regimens used in clinical

practice in England, to treat CLL patients who have received at least one prior therapy.

Idelalisib with rituximab has also received market authorisation for patients with treatment-naïve CLL that is associated with 17p deletion or TP53 mutation, for whom chemo-immunotherapy is not suitable [11].

As described in section 4, patients whose CLL is associated with 17p deletion or TP53 mutation do not respond well to chemo-immunotherapy, which is toxic to sensitive cells but not cells that are resistant due to 17p deletion or TP53 mutation [11 7, 10].

Approximately 135 to 270 of the 2,700 people who are diagnosed with CLL in England each year have disease associated with 17p deletion or TP53 mutation (Final Scope) [3]. As described in section 4, in this small patient group with high unmet need the evidence for idelalisib with rituximab, and even more so for comparators, is highly limited and precludes robust economic analysis. Nevertheless, as is argued in section 4, the clinical benefits shown in Study 101-08/99 suggests that idelalisib with rituximab will provide a substantial benefit to patients with an otherwise poor prognoses with a lack of effective treatment options while having a small and predictable impact on the NHS budget. This argument is developed further later.

**Model structure**

A *de novo* Markov model was constructed to evaluate the cost-effectiveness of idelalisib with rituximab; its structure and possible patient transitions are represented diagrammatically by Figure 16. Health states were used to distinguish between pre- and post-progressive disease.

Idelalisib with rituximab is indicated for use until disease progression or unacceptable toxicity as reflected in the Summary of Product Characteristics [86] and Study 116. Patients may withdraw from active treatment before disease progression, due to adverse effects. For this reason, model states were also used to distinguish between costs for those pre-progressive disease patients receiving active treatment and those not receiving active treatment.

Treatment efficacy also influences cost outcomes in the model via overall response rate (ORR; OR defined as patients achieving either complete response or partial

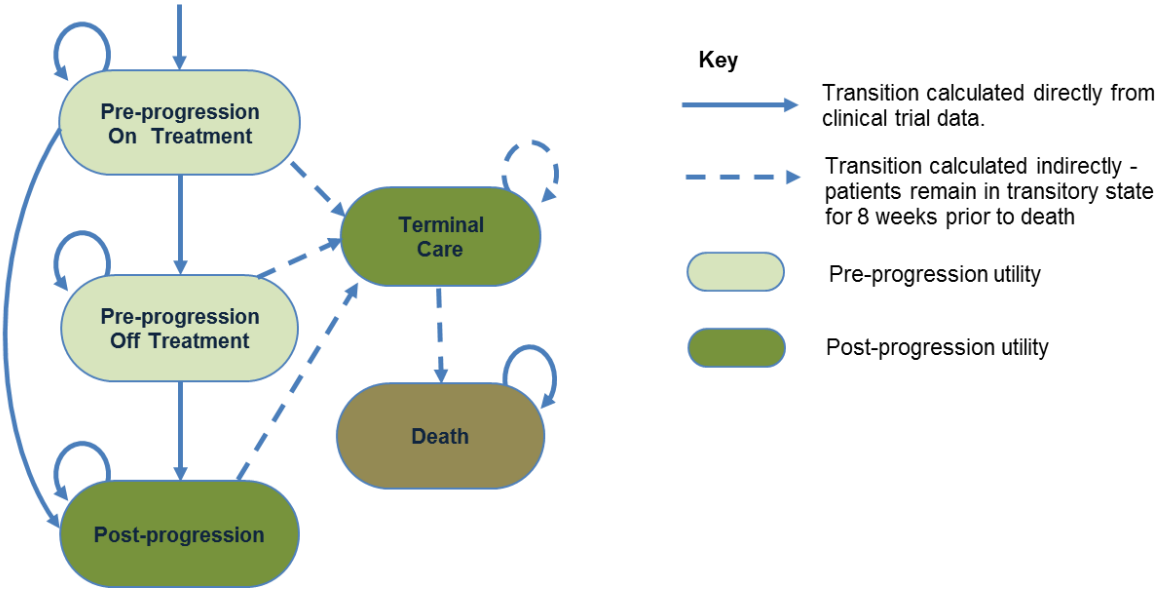
response) with treatment-specific OR profiles used to inform background resource use allocation before disease progression, as described in section 5.5.

It is possible to transition to death from any of the disease-related health states, via the transitory palliative care health state.

Research from The King's Fund [87] has estimated the economic burden of palliative care in the 8 weeks preceding death; this estimate has been used in previously, for example in NICE TA268, as a relevant data source. To account for this cost, the proportion of patients in "Pre-progression On Treatment", "Pre-progression Off Treatment", and "Post-progression" is adjusted in the model to account for the proportion of patients expected to be receiving palliative care (defined in line with the period over which palliative care costs were estimated [87] as 8 weeks prior to death). Transitions to the "Palliative Care" model state are described as "indirect" in Figure 16.

As described in section 5.3, the proportion of the patient cohort in the "Pre-progression On Treatment" health state was determined over time by the area under parametric time-on-treatment curves estimated from trial data. Similarly, the proportions of the patient cohort in "Pre-progression Off Treatment" and "Post-progression" health states were informed by parametric survival curve analysis of progression-free and overall survival data.

**Figure 16: Economic model health states and structure**




The model health states capture treatment status and disease progression and are consistent with the care pathway and treatment-dependent costs and outcomes associated with each component. As patients receive active therapy, they incur treatment-specific drug, administration, resource use and adverse event, costs.

Evidence from the analysis of patient-level EQ-5D data from Study 116, presented in section 5.4, suggests that patient HRQL differed across treatment arms; the model allows for this in the "Pre-progression On Treatment" health state, where Study 116 clinical outcomes are modelled. Study 116 did not collect HRQL data for patients who were no longer on treatment.

Upon disease progression, patients receive disease and relapse management and, eventually, palliative care costs. Evidence from published literature [42, 88, 89] suggests that patients will also suffer a substantial fall in HRQL upon progression, and this is reflected in the model.

Additional key features of the economic model are described and justified in Table 59.

**Table 59: Key features of the economic analysis**

| Factor | Chosen values | Justification | Reference |
|---|---|---|---|
| Time horizon | 25 years | Mean age of patients in Study 116 was 71 years; over 99.9% of patients in either arm of the base case model are dead at 25 years | Extrapolation of OS from Study 116 |
| Cycle length | 1 week | Sufficiently short to accurately capture clinical outcomes in Study 101-09 and fit with dosing schedules | Sections 5.3 and 5.5 |
| Half-cycle correction | Applied to costs and health effects | NICE reference case | NICE (2013)[90] |
| Were health effects measured in QALYs; if not, what was used? | QALYs | NICE reference case | NICE (2013)[90] |
| Discount of 3.5% for utilities and costs | 3.5% per annum | NICE reference case | NICE (2013)[90] |
| Perspective (NHS/PSS) | NHS/PSS | NICE reference case | NICE (2013)[90] |
| **Key:** NHS, National Health Service; NICE, national institute for health and care excellence; PSS, personal social services; QALYs, quality-adjusted life years. | | | |

**Intervention technology and comparators**

Idelalisib with rituximab (IR) and rituximab monotherapy (R) are implemented in the model as per the dosing schedule in Study 116. In both arms of the model, 375mg/m$^2$ rituximab is administered intravenously in the first model cycle (Week 1), followed by 500mg/m$^2$ rituximab in Weeks 3, 5, 7, 9, 13, 17 and 20. In the idelalisib with rituximab model arm, 150mg oral idelalisib is given twice daily. This is in line with the marketing authorisation for idelalisib in CLL.

Time-on-treatment data from the clinical study were used to inform the model. Parametric survival curves estimated from Study 116 data show the duration of treatment to be systematically lower than PFS across both study arms (see Figure 26, section 5.3).

To compare to ofatumumab, fludarabine with cyclophosphamide and rituximab (FCR), bendamustine with or without rituximab (B or BR), chlorambucil with or without rituximab (Chl or Chl+R), and corticosteroids with rituximab (Steroids+R),

costs for these treatments were applied to the proportion of patients in the pre-progression stage of the model according to available dosing information, as reported in section 5.5.

This approach was taken in preference to using time on treatment (ToT) data from Study 116 as a proxy for time on treatment for external comparators. Available dosing information for these comparators recommended maximum dose durations, rather than treatment to progression, as indicated for idelalisib (section 5.5). It was reasoned that ToT data from Study 116 was likely unrepresentative of ToT for treatments outside of the study, particularly when maximum dose durations are applied. It is plausible that mild adverse reactions would lead to delaying one or two treatment cycles for a treat-to-progression therapy, when the same adverse reactions would not interrupt the treatment pattern when the therapy is applied for a maximum of 6 to 10 treatment cycles.

## *5.3 Clinical parameters and variables*

**Clinical evidence from Study 116**

As described in section 5.2, the pivotal study used to inform the cost-effectiveness analysis was Study 116, described in detail in section 4.

The primary objective of the study was to assess idelalisib with rituximab versus rituximab (with placebo), for key outcomes including efficacy and safety in 220 subjects with previously treated CLL who were not able to receive cytotoxic therapy. Data from Study 116 are used to make inferences regarding comparative clinical outcomes for idelalisib with rituximab versus (i) rituximab monotherapy; (ii) ofatumumab monotherapy; and (iii) BSC, as described in section 5.2. Equal efficacy is assumed for the anti-CD20s rituximab and ofatumumab, as described in Section 3, based upon the results of the ORCHARRD study [18], the use of the two interchangeably within clinical trials as a class of therapies, the network meta-analysis conducted as part of ongoing appraisal for ofatumumab in combination with bendamustine or chlorambucil and clinical expert advice. [18 13, 71 17] The conservative assumption of equal efficacy for rituximab and BSC (no active therapy) is made in order to provide a comparison to BSC where no data is available and provide a

sensible upper bound incremental cost-effectiveness ratio (ICER) in the Study 116 patient population, this comparison assumes the survival benefits of rituximab are received by BSC patients with none of the associated costs or adverse events.

The clinical outcomes assessed were the following:

- overall survival (OS),
- IRC-assessed progression-free survival (PFS),
- time on treatment (ToT), and
- IRC-assessed response status
- health-related quality of life (HRQL) (reported in section 5.4)

Extrapolated OS, PFS and ToT data inform the proportion of patients in each model health state in each cycle.

**Overall survival**

The OS benefit of idelalisib with rituximab is extrapolated from Kaplan–Meier (KM) data from those who were randomised to receive idelalisib in Study 116. To estimate the OS benefit of rituximab monotherapy for relapsed / refractory patients unsuited to cytotoxic therapy, it was necessary to attempt to control for cross-over bias in OS estimates for those randomised to receive rituximab instead of idelalisib with rituximab. As described in section 4, patients randomised to rituximab treatment could switch to idelalisib monotherapy with a large proportion of patients switching treatment (86 out of 110; 78%).

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 60. Full methodology for selection and production of the crossover analysis is provided in section 4.7.

**Table 60: 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 (95% CI)** |
|---|---|---|---|---|---|
| | **Hazard ratio** | **HR 95%CI** | **p-value** | **(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

The KM data for OS of patients randomised to rituximab in Study 116, adjusted for cross-over bias, are shown alongside ITT KM OS data for patients randomised to idelalisib with rituximab, in **Figure 17**.

**Figure 17: Model KM curves for OS, IR versus R**

[redacted]

Parametric curves were fitted to these KM data, to extrapolate OS estimates over the model time horizon. Curves fitted to standard parametric model forms were estimated (exponential, Weibull, log-logistic and log-normal), and the fit of each parametric model was compared with the observed data. The most appropriate

functional form was assessed using Akaike Information Criterion (AIC) statistics. These measures provide an indication of the statistical fit between the observed KM data and the parametric model estimates throughout the trial period. The use of AICs in the selection of the most appropriate curve has been criticised on the basis that they do not provide any measure of the relative merits of each functional form when used for extrapolation [91]. This is a valid criticism, and the appropriateness of curve fits was therefore further assessed by visual inspection by a clinical haematologist currently practising within the NHS in England [1], and economists, to ensure the predicted extrapolations were credible.

Figure 18 and Figure 19 show parametric curve fits to KM OS data for the idelalisib with rituximab and rituximab arms of Study 116, respectively.

Table 61 shows AIC statistics for these curve fits. AIC statistics suggest that the exponential model provides the best fit to the data, followed by the Weibull curve. However, visual inspection of the idelalisib with rituximab exponential curve beyond the trial data cut-off shows over 5% of patients to be alive after 20 years, when this sick patient cohort are 91 years of age. This was considered unrealistic at clinical review, and the Weibull model was selected as the only clinically plausible curve fit to the OS KM data.

**Figure 18: KM OS IR and parametric curve fits**

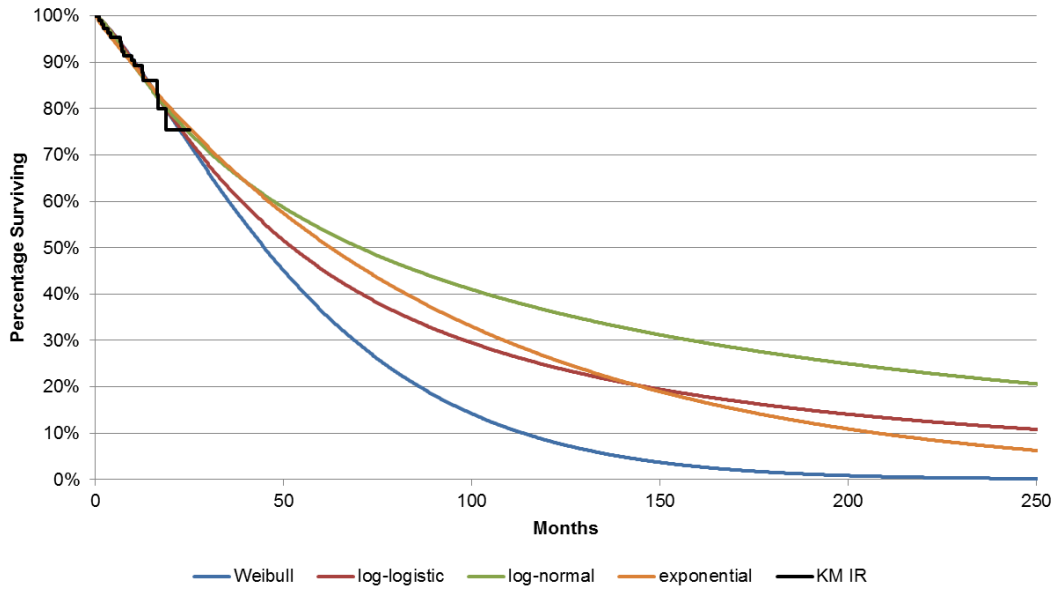



**Figure 19: KM OS R and parametric curve fits**

[redacted]

**Table 61: AIC statistics, parametric curve fits to OS KM curves**

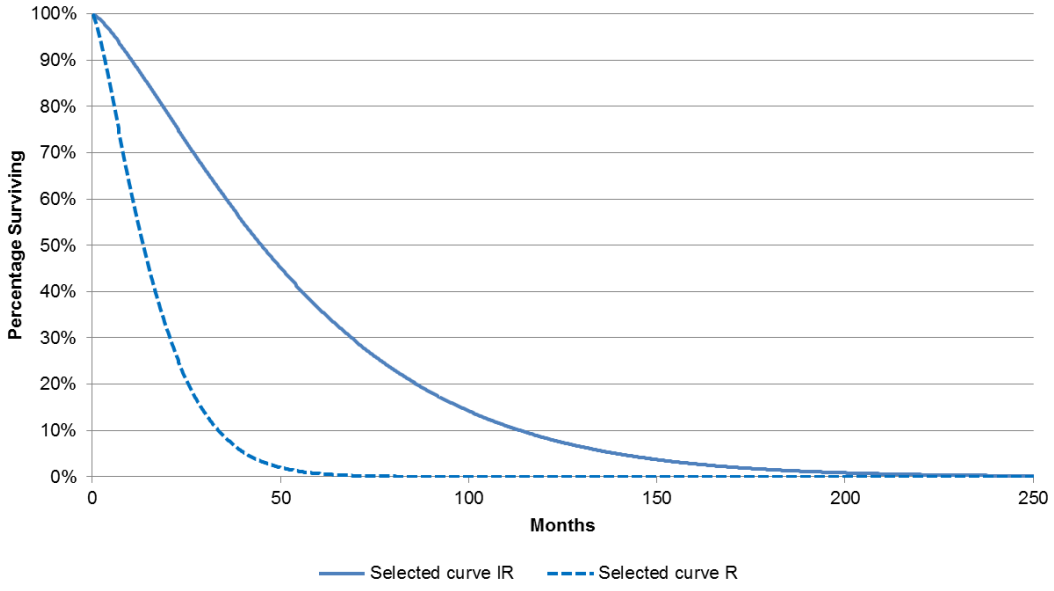
| Model | AIC – IR arm | AIC – R arm |
|---|---|---|
| Weibull | 189.388 | 317.769 |
| log-logistic | 189.949 | 317.749 |
| log-normal | 190.388 | 318.734 |
| exponential | 188.616 | 319.491 |
| **Key:** AIC, Akaike Information Criterion; IR, idelalisib with rituximab; R, rituximab plus placebo | | |

**Figure 20** shows the Weibull parametric curve fits to OS data, which determine survival in the base case model.

**Figure 20: KM OS R and IR and selected (Weibull) curve fits**

[redacted]

**Figure 21: Selected (Weibull) curve fits, OS R and IR**




## Progression-free survival

Disease progression was the key driver of patient switches to idelalisib treatment in the rituximab plus placebo arm of Study 116; for this reason, these PFS KM data were not adjusted to account for cross-over bias. Nevertheless, as many rituximab

patients did switch to idelalisib monotherapy before disease progression (34 of 110 patients), the relative difference in PFS between idelalisib with rituximab treatment and rituximab treatment will most likely be greater in clinical practice than suggested here. The parametric curves are fitted to unadjusted PFS KM data to inform the analysis, which is highly conservative.

Figure 22 and Figure 23 show the respective parametric curve fits to idelalisib with rituximab and rituximab KM PFS data. Table 62 shows AIC statistics for these curve fits. The AIC statistics suggest the Weibull model is the best fit to the data. This is visually clear, particularly for the rituximab monotherapy arm of the study, where the KM data are complete, and the choice of Weibull curves to inform PFS in the model was validated at clinical review.

**Figure 22: KM PFS IR and parametric curve fits**

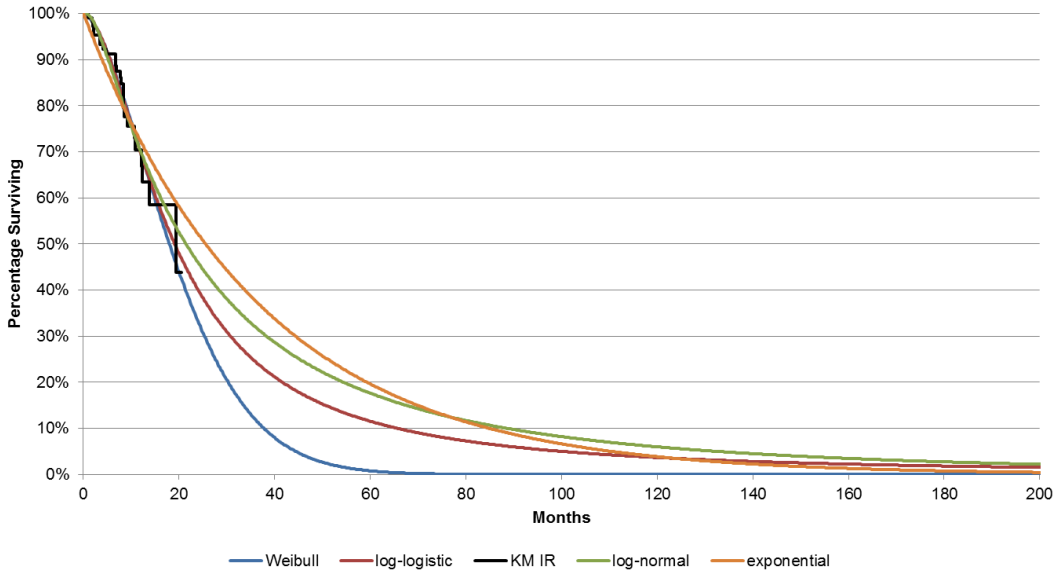
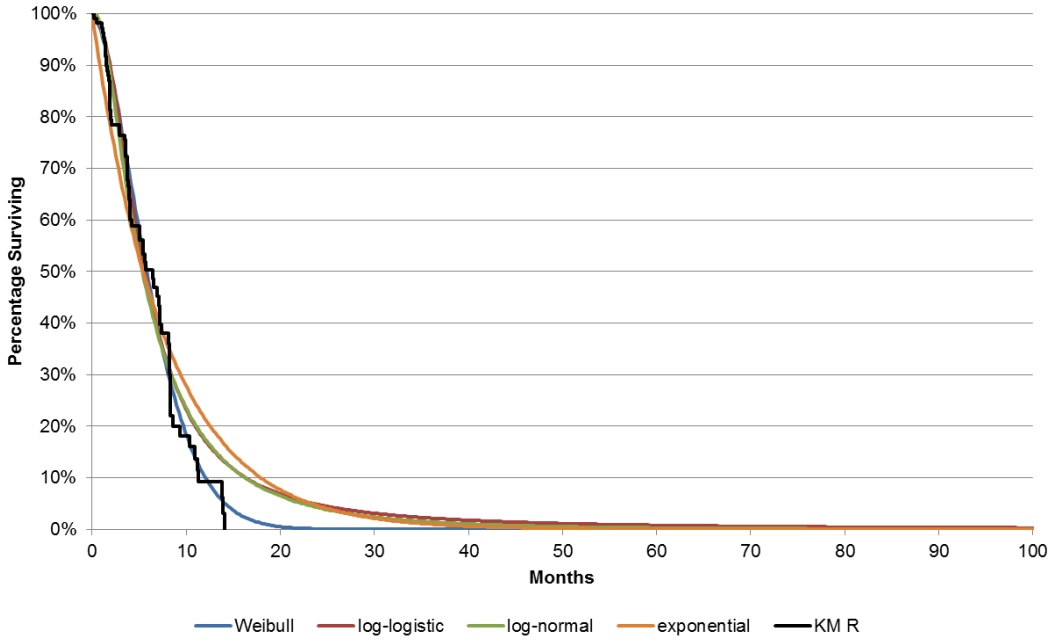


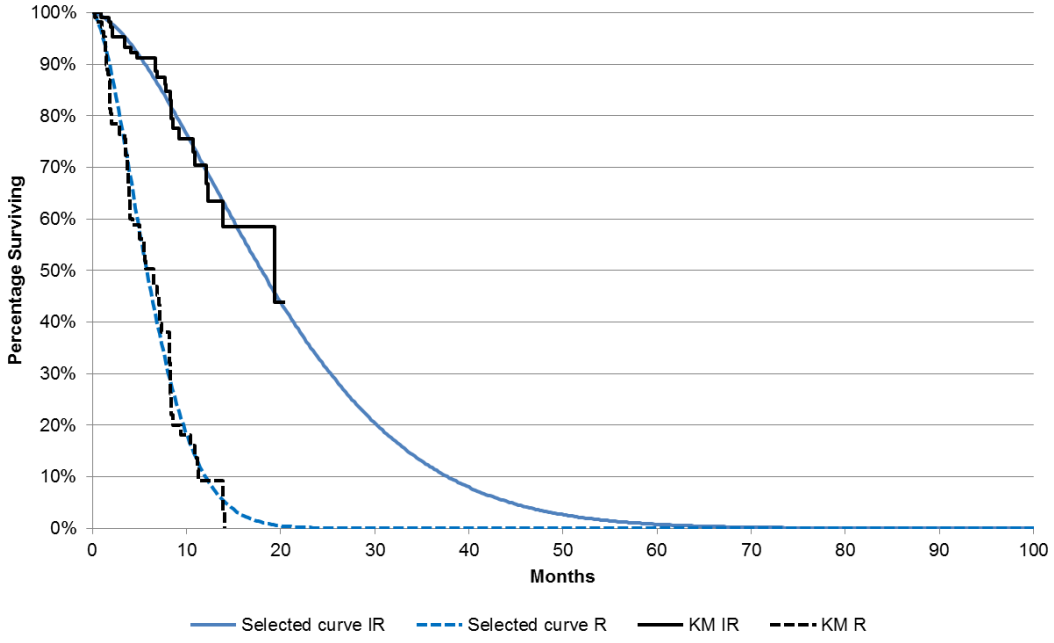
**Figure 23: KM PFS R and parametric curve fits**



| Table 62: AIC statistics, parametric curve fits to PFS KM curvesModel | AIC – IR arm | AIC – R arm |
|---|---|---|
| Weibull | 231.434 | 401.573 |
| Log-logistic | 231.845 | 412.341 |
| Log-normal | 232.704 | 413.127 |
| Exponential | 236.175 | 421.488 |
| **Key:** AIC, akaike information criterion; IR, idelalisib with rituximab; R, rituximab | | |

Figure 24 shows the Weibull parametric curve fits to KM PFS data for both treatment arms of Study 116. These curves determine PFS in the base case model.

**Figure 24: KM PFS R and IR and selected (Weibull) curve fits**



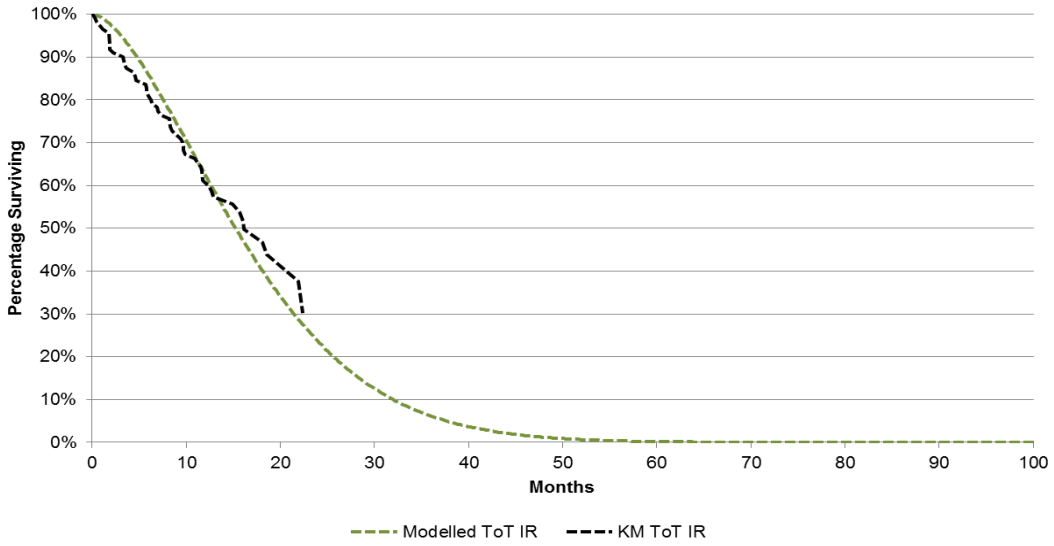

## Time on treatment

To accurately estimate the costs for treating patients with idelalisib, which should be continued until disease progression or unacceptable toxicity [92], ToT information from Study 116 has been utilised. These data are selected in preference to the

assumption that idelalisib is administered until progression, to account for patients who discontinued idelalisib before disease progression in Study 116 due to toxicity.

Figure 26 shows ToT compared to PFS for patients randomised to receive idelalisib with rituximab. ToT follows a similar course to PFS, as would be expected, with a small proportion of patients discontinuing earlier. A Schoenfeld residual test was conducted that determined that proportional hazards can be assumed between ToT and PFS (rho=-0.157, p= 0.156). This being the case, a Cox proportional hazards (PH) model was used to derive a hazard ratio for ToT versus PFS (HR = 1.31). This HR was applied to the modelled PFS curve for idelalisib, to derive a modelled ToT curve for idelalisib that could inform drug costing for idelalisib across the model time horizon. This modelled ToT curve and its fit to idelalisib with rituximab KM ToT data are shown in Figure 25.

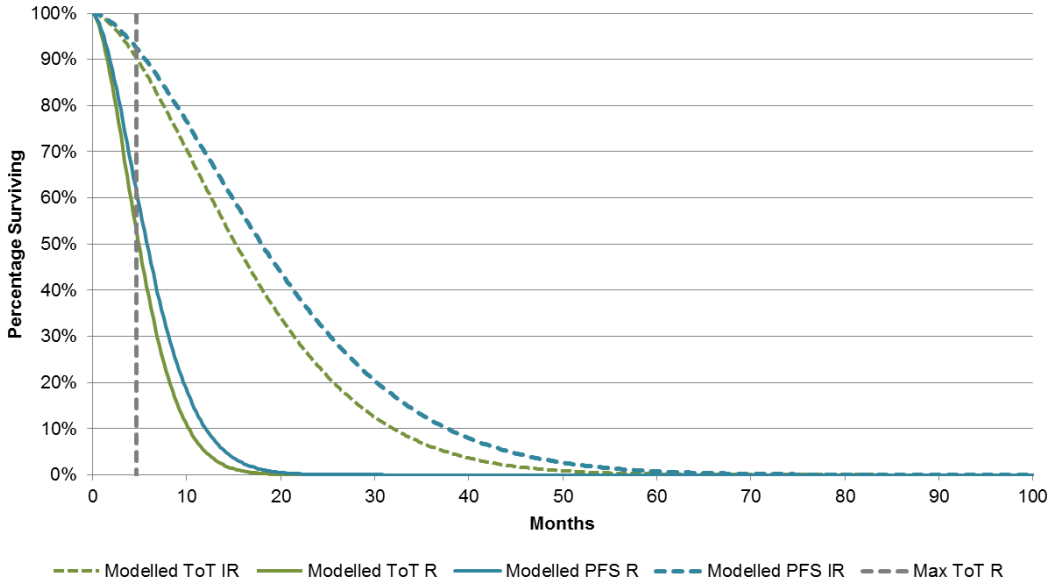
**Figure 25: KM ToT IR and parametric curve fit**




For consistency across comparators, the same HR was applied to estimate a ToT curve for the rituximab monotherapy arm of Study 116. As described in section 5.2, drug costs for base case comparators are applied up to a fixed number of weeks, according to treatment regimens described in section 5.5 (until Week 21 for rituximab monotherapy; until Week 48 for ofatumumab monotherapy; not at all for BSC). Modelled ToT for the comparator arm is close to modelled PFS, as shown in Figure 26, which shows the PFS and ToT curves applied in the base case model. Using the

rituximab monotherapy ToT curve rather than the rituximab monotherapy PFS curve to inform comparator drug cost assumptions allows early discontinuation of rituximab monotherapy due to toxicity to be accounted for and is more consistent with the assumptions made for idelalisib with rituximab; however, the assumption does not have a large impact on cost-effectiveness, as is clear from the difference between the respective areas under the ToT and PFS curves for rituximab monotherapy up to the maximum duration of rituximab treatment, shown in Figure 26.

**Figure 26: Modelled PFS and ToT curves applied in the base case analysis**




## Response rates

Results from Study 116 showed an overall response (complete or partial response) in 92 patients on the idelalisib with rituximab arm, yielding an ORR of 84%, but an overall response was observed in only 17 patients on the rituximab arm, yielding an ORR of 15%. These results are used to inform resource use assumptions in the model, as described in section 5.5.

For the base case comparison to BSC, patients were assumed to have no overall response. For the base case comparison to ofatumumab, the ORR observed for rituximab plus placebo patients in Study 116 was applied.

**Clinical evidence from the wider literature**

While it was possible to use Study 116 data to make inferences regarding the effectiveness of idelalisib with rituximab in comparison to ofatumumab monotherapy and BSC, to compare idelalisib with rituximab to other treatment regimens within the scope was more challenging. This is primarily due to the sparse and unconnected network of RCT evidence for treatments in relapsed or refractory CLL, as described in section 4, which precluded formal evidence synthesis.

In an effort to harness the evidence base to make cautious comparisons to the full range of regimens used in practice to treat relapsed or refractory CLL, an alternative methodology was used.

Section 4 identified a handful of RCT and single-arm trials in which median OS and PFS data were reported for treatment regimens within the scope [62, 63, 65, 69, 93, 94]. For the Weibull model (as well as the log-logistic and log-normal models[1]), there are two parameters: the shape and the scale. Median outcome data informs the scale parameter; if the shape parameter is known, it is possible to calculate the scale parameter if the median outcome is known. For the Weibull model, this relationship is described as follows:

$$scale = -\left[ {\ln(0.5)}/{median\ outcome^{shape}} \right]$$

Assuming constant shape between (i) the selected parametric curves for OS and PFS in the idelalisib with rituximab arm of Study 116 (selected over the rituximab monotherapy arm data, which was affected by cross-over bias as described) and (ii) OS and PFS for treatments outside of Study 116, it was therefore possible to derive survival curves for treatments not considered in the key trial.

However, this involves key assumptions and limitations. As mentioned, a common shape must be assumed across treatments. This assumption may be important for cost-effectiveness estimates, although it is possible to test the visual validity of this assumption where KM data have been reported, and the importance of uncertainty

[1] the exponential model is a one-parameter model with a fixed shape; it is also possible to apply the methodology described here to the exponential model

around survival parameters can to a degree be measured and reflected in sensitivity analyses.

Digitised KM curves from external studies were compared to parametric curves estimated with the assumption of constant shape across studies, as reported in Appendix 17. The constant shape assumption appears to hold for comparisons to bendamustine monotherapy, bendamustine plus rituximab, ofatumumab monotherapy and steroids with rituximab, supporting the validity of these comparisons. For FCR however, the constant shape assumption does not appear to hold, with survival over-predicted before the median and under-predicted after the median, for both OS and PFS. This is not entirely surprising given that FCR is targeted to a very different population to the other treatments noted here; i.e. the youngest and fittest patients who are able to receive the most toxic chemotherapy regimen; for this reason FCR is most commonly used first-line in the UK as described in Section 3.

Perhaps more important than the assumption of constant shape, the approach does not control for study-level differences between evidence sources. One treatment could appear to produce superior outcomes to another, when these differences are driven not by treatment, but by differences in patient characteristics and study design across trials. This is crucial as results produced using this method could be misleading for this reason.

Table 63 summarises data from key previous studies identified in section 4[61 69 62, 63, 65, 69, 93]. There are studies to provide median OS and PFS data for FCR, bendamustine, bendamustine with rituximab, steroids with rituximab and ofatumumab monotherapy. From the data presented in Table 63, it is clear that there are patient differences across study samples that could influence OS and PFS. The median age in Study 116 was higher than in any other study. The proportion of patients with del(17p), which is known to impact prognosis, was higher in Study 116 than in all the other trials reporting such information bar the Pileckyte study for steroids with rituximab[63]. In addition, the median number of prior treatments was higher than in Study 116 only in the ofatumumab trial reported by Wierda et al [65]. These data suggest clear differences across trial patient samples, which would be

more likely to bias any cautionary exploratory analysis against idelalisib with rituximab.

For chlorambucil, chlorambucil with rituximab, steroids without rituximab and BSC, studies reporting median OS and PFS estimates were not identified. To compare idelalisib to these treatment regimens, additional assumptions are required.

Evidence identified in section 4 suggests superior outcomes for bendamustine with rituximab versus chlorambucil with rituximab in terms of response [61]. [61]Elsewhere, Knauf et al have reported a phase III RCT comparing bendamustine monotherapy and chlorambucil monotherapy in previously untreated CLL patients [95]. This study showed results favouring bendamustine over chlorambucil; hazard ratios were reported as 1.30 for OS and 2.83 for PFS, chlorambucil versus bendamustine. To attempt to capture outcomes for chlorambucil with and without rituximab despite there being no reported information in the correct population (i.e. relapsed/refractory CLL), these hazard ratios were applied to the estimated survival curves for bendamustine with and without rituximab.

Due to the additional layer of assumptions required to analyse chlorambucil and chlorambucil with rituximab, comparisons between idelalisib with rituximab and chlorambucil with or without rituximab should be interpreted with extreme caution. For steroid monotherapy, there were insufficient data to make any meaningful economic comparison.

For BSC, the conservative assumption of equivalent survival outcomes to the rituximab monotherapy arm of Study 116, presented in the base case analysis, is the only viable comparison available and no further data are presented. These assumptions were validated as conservative an NHS England clinical haematologist at clinical review [1].

**Table 63: 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[69] |
| B | 44 | 20 | 68 | 1 | NR | No prior fludarabine or bendamustine<br>Able to receive cytotoxic agents | 49 | Open label RCT[62] |
| 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[93] |
| 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[63] |
| 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[65] |
| R | 20.8; *[redacted] | 7 | 71 | 3 | 28% | Unable to receive cytotoxic agents<br>ECOG unrestricted | 110 | Study 116<br>Double-blind RCT |
| IR | 45 (model) | 18 | 71 | 3 | 24% | | 110 | |

**Key:** B, bendamustine; ECOG, eastern coraprative 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 heretrogeniety would be biased against evidence for idelalisib with rituximab from Study 116

In the analysis of clinical outcomes for FCR in relapsed CLL patients presented by Badoux et al [69], the authors performed Cox PH regression analyses of associations between pre-treatment patient characteristics and clinical outcomes (OS and PFS). Incorporation of results from these analyses allow some adjustment of survival data from external OS and PFS estimates to account for study-level patient characteristics, albeit subject to assumptions. Hazard ratios for OS and PFS associated with different patient characteristics were reported by Badoux et al [69] and are reproduced in Table 64 and Table 65.

**Table 64: 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, overal survival | |

**Table 65: 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 | |

To use these results to partially account for patient differences across the trials informing the comparisons reported here, ‘adjustment factors’ were estimated as follows:

$$adjustment\ factor = exp\left[\sum_{pat\ char=1}^{P} \{\ln(Hazard\ Ratio_{pat\ char}) * (pat\ char_{Study\ 116} - pat\ char_{ext\ study})\}\right]$$

where $pat\ char$ is a pre-treatment characteristic associated with OS or PFS, as reported in Table 64 or Table 65, $P$ is the total number of patient characteristics to be considered for the clinical outcome under consideration, $Hazard\ Ratio_{pat\ char}$ is the hazard ratio associated with the patient characteristic, $pat\ char_{Study\ 116}$ is the value of the patient characteristic in Study 116, and $pat\ char_{ext\ study}$ is the value of the patient characteristic in the external study.

These adjustment factors are applied to survival curves informed by external study data, as hazard ratios. Importantly, this makes survival estimates for interventions outside of Study 116 more appropriate for the Study 116 patient group, rather than adapting Study 116 data so that it is more representative of patients comprising external study samples.

While accounting for some of the confounding effects of sample differences in comparisons between trials, this approach should not be viewed as equivalently robust as established methods for evidence synthesis. The ability to infer from comparisons across studies depends on (i) the degree of similarity between Study 116 patients and external study patients, (ii) the robustness of external studies (quality and sample size) and (iii) the ability to adjust for known confounders, which is intrinsically linked to the level of reporting of patient characteristics in external studies.

Table 66 summarises the comparability of external studies according to these criteria. Only 29 patients inform survival estimates for steroids with rituximab; only 49 inform survival estimates for B monotherapy (also used indirectly to inform chlorambucil monotherapy survival). To characterise the similarity of external study patients to the patients in Study 116, a qualitative “High/Medium/Low” system was applied. The survival data from Wierda et al [65] were from patients who were refractory to fludarabine; regarding the suitability to cytotoxic treatments, Wierda et al [65] is the only external study that can be considered to have even a moderately similar patient sample to Study 116. The subgroup of patients who were less-suited to, rather than refractory to, alemtuzumab, were used as these were more

representative of Study 116 patients. Patients in Wierda et al were however required to have a life expectancy of at least 6 months to enrol. As shown in Table 63, patients in Study 116 are the eldest of the studies incorporated, and only the patients presented by Wierda et al [65] had a higher median number of prior therapies. On the other hand, a lower proportion of patients had 17p deletion in Wierda et al versus patients in Study 116 randomised to idelalisib with rituximab (18% versus 24%). These factors have been shown by Badoux et al [69] to be important for survival outcomes, and while the similarity of the Wierda et al sample merits the classification of “Medium” similarity, for the remaining studies, the similarity to the Study 116 patient sample is low.

The ability to adjust for patient characteristics determining OS and PFS was determined by the proportion of pre-treatment characteristics listed in Table 64 and Table 65 that were discernible from each study publication. For characteristics determining OS, possessing at least 6 of the 7 characteristics in Table 64 was considered to indicate “High” ability to adjust, and possessing either 4 or 5 of the 7 characteristics was considered to indicate “Medium” ability to adjust. For characteristics determining PFS, possessing at least 5 of the 6 characteristics in Table 65 was the criterion for “High” ability to adjust, and possessing 3 or 4 of the 6 characteristics was considered to indicate “Medium” ability to adjust. The ability to adjust for characteristics important for PFS and OS varied; for the comparison to FCR, which utilised survival data the study from which the Cox PH model was reported [69], it was possible to trace data for all sample characteristics of importance. For comparisons to bendamustine monotherapy and ofatumumab monotherapy, levels of reporting in Neiderle et al [62] and Wierda et al [65] meant the ability adjust for patient characteristics was low.

Overall, the ability to compare to external studies is demonstrated to be limited, subject to numerous key assumptions, and the exploratory comparisons presented using these data in section 6.8 should be interpreted with these limitations in mind.

**Table 66: 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 |
| B | 49 | Low | Low | Low | Niederle 2013 |
| BR | 78 | Low | Medium | Medium | Fischer 2011 |
| Steroids+ R | 29 | Low | Medium | Medium | Pileckelyte 2011 |
| Ofa | 79 | Medium | Low | Low | Wierda 2010 |

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

Figure 27 and Figure 28 show the final modelled survival curves across the range of comparators for refractory/relapsed CLL, for OS and PFS respectively. Idelalisib in combination with rituximab is shown to have the highest projected OS and PFS. Given the inability to fully account for the relatively elderly, weak and refractory patients in Study 116 in comparison to external studies, the evidence strongly suggests that idelalisib with rituximab provides the greatest OS and PFS benefits of available comparators, for highly refractory and ageing patients in particular, but even perhaps for the relapsed/refractory patient population as a whole.

Figure 27 and Figure 28 also serve to demonstrate the limitations of comparisons to external study data in this submission. Bendamustine monotherapy is projected to have superior outcomes to bendamustine with rituximab – a projection which lacks clinical credibility – and this is highly likely attributable to differences in study design and patient profiles across trials. Additionally FCR (the comparator where the highest ability to adjust was present) is projected to have the worst outcomes despite being generally acknowledged as more effective in fit patients that bendamustine with rituximab or chlorambucil with rituximab. Projections for OS for ofatumumab, the

most similar trial to Study 116, are similar to (slightly worse than) rituximab in Study 116 as would be expected based upon the NMA conducted by PenTAG. [17]

**Figure 27: Modelled OS curves, full range of comparators**

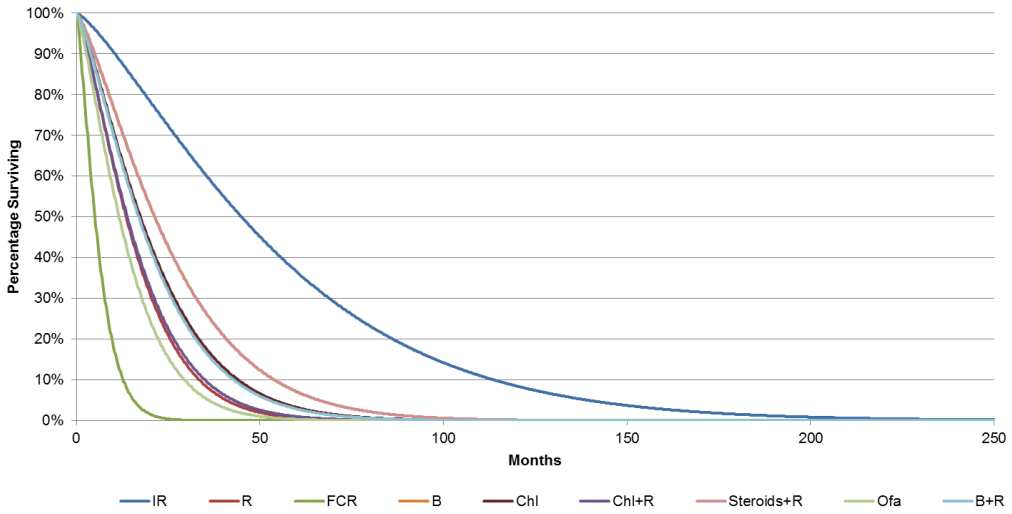
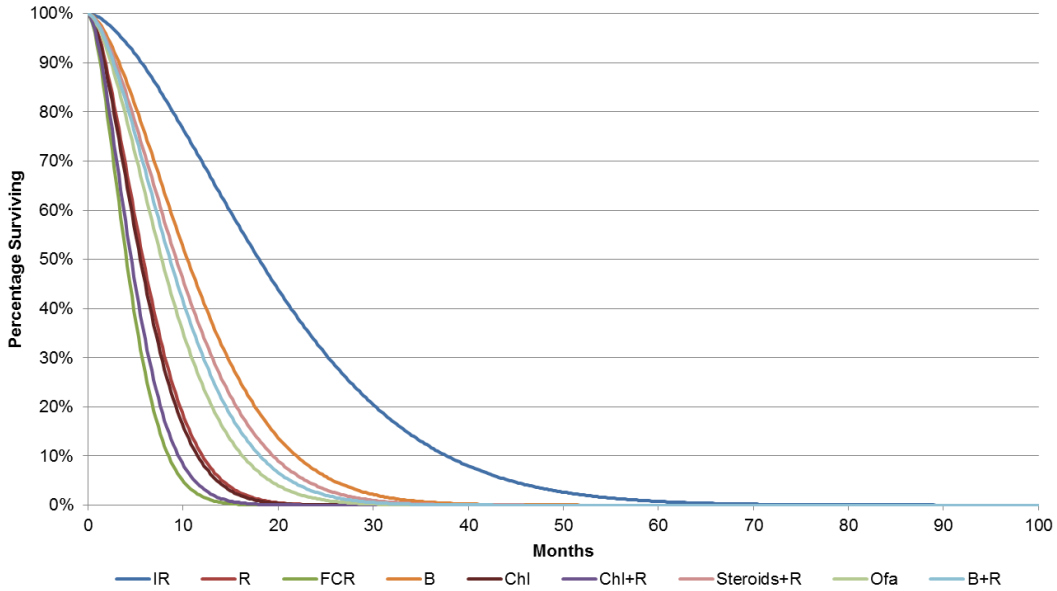



**Figure 28: Modelled PFS curves, full range of comparators**




<u>Response rates</u>

ORR data were sourced from the external studies, to inform resource use assumptions for comparators outside of the base case, as described in section 5.5. These response rates are shown in Table 67. For chlorambucil with rituximab, a study, identified in section 4, from Leblond et al [61], which did not report OS or PFS

data but did report response rates for previously treated patients, was used. Again these comparisons should be interpreted with caution due to both differences in patient populations, which could not be adjusted for across the studies, and differences in the reporting of response rates. ORRs from Study 116, for idelalisib with rituximab and rituximabplus placebo, and assumed for BSC, are also presented here for comparison.

**Table 67: Overall response rates**

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

## *5.4 Measurement and valuation of health effects*

Due to the accumulation of non-functional lymphocytes in a patient's lymph nodes, spleen, liver, blood and bone marrow, patients with CLL experience recurrent infections. Disease-related symptoms for CLL include fatigue, dyspnoea, abdominal pain, weight loss, lymphadenopathy and sleep disturbances, which all have an impact on quality of life. Holzner et al [8] have reported results from both the EORTC QLQ-C30 and the FACT-G functioning scales from a sample of 81 CLL patients. Holzner et al conducted their study to determine the differences between the two instruments [8]; however, both sets of results showed emotional functioning to be affected by the disease.

Elsewhere, Beusterien et al [96] have described CLL symptoms worsening as a patient's disease progresses. The health-related quality of life of a patient is a

function of their disease status; the data from previous HRQL studies reviewed here and clinical opinion attest to the importance of postponing disease progression for patient wellbeing.

Idelalisib with rituximab has a role in improving patient HRQL, both by postponing disease progression and extending life, as suggested in section 5.3, and by improving patient wellbeing while on active treatment, as suggested by data from Study 116, presented in this section.

**Health-related quality of life data from clinical trials**

The EQ-5D was used as a tertiary endpoint in Study 116. Measurements were taken at baseline, at Weeks 2, 4, 6, 8, 12, 16, 20, 24, 30, 36, 42, and 48, at every 12 weeks thereafter prior to progression and at the end of treatment. EQ-5D data were not collected post progression in either arm. Compliance rates for EQ-5D completion were good across all time points, as shown in Table 68.

**Table 68: EQ-5D compliance in Study 116**

| Visit | Treatment | N | Compliance Rate |
|---|---|---|---|
| Week 2 | Idelalisib | 110 | 96% |
| | Placebo | 108 | 94% |
| Week 4 | Idelalisib | 108 | 95% |
| | Placebo | 106 | 93% |
| Week 6 | Idelalisib | 107 | 90% |
| | Placebo | 106 | 90% |
| Week 8 | Idelalisib | 106 | 89% |
| | Placebo | 100 | 92% |
| Week 12 | Idelalisib | 99 | 84% |
| | Placebo | 93 | 85% |
| Week 16 | Idelalisib | 85 | 82% |
| | Placebo | 71 | 75% |
| Week 20 | Idelalisib | 72 | 85% |
| | Placebo | 54 | 76% |
| Week 24 | Idelalisib | 59 | 86% |
| | Placebo | 40 | 78% |
| Week 30 | Idelalisib | 51 | 77% |
| | Placebo | 31 | 81% |

| Visit | Treatment | N | Compliance Rate |
|---|---|---|---|
| Week 36 | Idelalisib | 39 | 80% |
| | Placebo | 25 | 72% |
| Week 42 | Idelalisib | 30 | 90% |
| | Placebo | 15 | 67% |
| Week 48 | Idelalisib | 26 | 81% |
| | Placebo | 10 | 70% |
| **Key:** N, number of patients | | | |

A generalised estimation equation (GEE) regression was carried out to determine whether there was a difference in quality of life between idelalisib with rituximab and rituximab monotherapy while patients were receiving treatment. GEE regression was used as this method accounts for potential autocorrelation of patient quality of life scores. Using the 1,667 observations over both treatments arms, a significant treatment effect was found (p=0.031), with patients receiving idelalisib with rituximab having a better quality of life than those receiving rituximab monotherapy alone (absolute difference of 0.0652).

Table 69 shows resulting mean EQ-5D estimates for patients on treatment in Study 116, across treatment arms. These estimates are the most appropriate to describe the experience of patients receiving idelalisib with rituximab and rituximab monotherapy and are used in the base case model. To inform utility estimates for patients after treatment discontinuation, both during PFS and PPS, data from the literature were sought.

**Table 69: 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 | | |

## Health-related quality of life studies

A systematic literature search for HRQL studies was performed alongside the search for previous economic evaluation studies. Six studies were identified [88, 89, 96-99]. Details of the search strategy, inclusion and exclusion criteria, as well as the study filtering and data extraction processes, are reported in Appendix 18.

Table 70 shows size and characteristics of the samples from which utility estimates were elicited in the six identified studies. In only two studies [88, 99] were HRQL estimates elicited from patients with CLL; a major limitation of existing HRQL data

**Table 70: Sample size and characteristics, HRQL studies**

| Identified Study | Sample size | Sample characteristics |
|---|---|---|
| Beusterien et al 2010 [96] | 89 | General population |
| Dretzke et al 2010 [88] (data originally from Holzner et al [8] 2001) | 81 | CLL patients |
| Hoyle et al 2011 [97] (data originally from Ferguson et al [100]) | 60 | General population |
| Hyde et al 2002 [98] (data reported as originally from Best 1995; Best study could not be found) | NR | Not clear; experts |
| Pashos et al 2013 [99] | 1140 | CLL patients |
| Tolley et al 2013 [89] | 110 | General population |
| **Key:** CLL, chronic lymphocytic lymphoma; HRQL, health realted quality of life | | |

Three of the six identified studies are associated with UK Health Technology Assessments. [88, 97, 98] Dretzke et al reported a summary of the Evidence Review Group (ERG) report from NICE TA193 [88]; the utility data used were from an earlier study [101], which had calculated health state utility values from the Holzner et al study of CLL patients [8], although the method of transformation from EORTC-QLQ-C30/FACT-Lym data to health state utility estimates is not clear. Hoyle et al [97] reported a critique of the manufacturer's submission in NICE TA 202. [102] Utility data in this submission were originally from structured interviews with 60 members of the UK general public, published only as an abstract for a conference poster [100]. The study from Hyde et al comprises an NHS-funded TA of fludarabine for relapsed/refractory CLL patients [98]; a copy of the 1995 study in which the utility data were originally reported could not be found; based on Hyde et al, it is probable that

the Wessex Development and Evaluation Committee used experts to estimate the impact of fludarabine treatment on HRQL, *"based on gauging where patients might be on the Index of Health-related Quality of Life"* [98].

Of the remaining three studies in the review, Pashos et al have recently reported baseline results from a large-sample prospective observational study of CLL patients currently underway in the US [99]. This study is currently collecting longitudinal EQ-5D data in over 1000 patients and could be of great use in informing utility estimates in economic evaluations of CLL treatments in future. However, the paper presented by Pashos et al only reports associations between baseline HRQL and gender in the baseline sample [99]; the results are therefore of little use for this submission. Elsewhere, Beusterien et al conducted a cross-sectional study of members of the general population to elicit preferences for different CLL disease state descriptions, using the standard gamble technique [96]. Lastly, Tolley et al have reported a preference-elicitation study of 110 members of the UK general public, using the time trade-off method to elicit utility values for various CLL disease states [89].

Table 71 shows the health states and corresponding HRQL estimates reported in each study. The patient-reported EQ-5D data presented in this section, which meet the NICE reference case, are the most informative data to inform assumed HRQL in the 'pre-progression, on treatment' model disease state. Nevertheless, data from the literature are required (i) to inform the utility estimate for the 'pre-progression, on treatment' and 'post-progression' model health states, (ii) for comparisons to clinical data outside of Study 116, and (iii) to inform scenario analyses. The estimate for progressive disease from Dretzke et al [88] matches the 'post-progression' model state and is the only such estimate to be derived from patient-reported outcomes; a utility of 0.6 is assumed for post-progressive disease in the base case.

Furthermore, the utility values reported by Dretzke et al [88] were validated by an NHS England clinical haematologist as appropriate for both pre-progression and post-progression health states in the model [103]. However, these values are high compared to the (albeit less robust) estimates derived recently in the GlaxoSmithKlyne-sponsored study by Tolley et al [89]. Estimates from the preference-elicitation study [89] of 0.67 for progression-free disease for responders and 0.21 for disease progression

can be used in scenario analyses for pre-progression and progressive disease health states, to test the robustness of results to extremely low utility estimates. It should be noted that such a low utility is not considered clinically plausible for this population upon progression and was most likely obtained due to the description of severity used within the Tolley study, (e.g. a patient “could no longer walk a short distance”), which was designed for late stage CLL rather than after only one prior treatment.

**Table 71: Health state utility values, HRQL studies**

| Study ID | Description of health state | Values (SE) |
|---|---|---|
| Beusterien et al [96] | Complete response<br>Partial response<br>No change<br>2nd-line treatment<br>3rd-line treatment<br>Progressive disease | 0.91 (0.11)*<br>0.84 (0.14)*<br>0.78 (0.14)*<br>0.71 (0.17)*<br>0.65 (0.22)*<br>0.68 (0.20)* |
| Dretzke et al [88] | Progression-free<br>Progressive disease | 0.80<br>0.60 |
| Hoyle et al [97] | 1st-line treatment with alemtuzumab<br>1st-line treatment with chlorambucil<br>1st-line treatment: progression-free<br>Following 1st-line treatment: progressive disease<br>Following 2nd-line treatment: progression-free<br>Following 2nd-line treatment: progressive disease<br>Following 3rd-line treatment: progression-free<br>Following 3rd-line treatment: progressive disease | 0.62 (0.03)<br>0.62 (0.03)<br>0.78 (0.02)<br>0.54 (0.03)<br>0.65 (0.03)<br>0.47 (0.03)<br>0.43 (0.03)<br>0.28 (0.03) |
| Hyde et al [98] | 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 et al [99] | Utility mean index score, males<br>Utility mean index score, females | 0.9<br>0.8 |
| Tolley et al [89] | 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. | | |

**Adverse reactions**

In the base case analysis, where Study 116 EQ-5D data are used, the HRQL effects of treatment-emergent AEs are captured by these data. For scenario analyses of different utility sources, however, accounting for the HRQL effects is important, and the methods and data used to do so in the model are described here. The description of AE rates and cycle probabilities also serves to inform the description of AE-related costs in the model in section 5.5.

Section 4.12 reported incidence of grade III or IV AEs in Study 116. Te adverse events considered in the model are those grade III or IV AEs that occurred in at least 3% of patients on either treatment arm of Study 116. These AEs and their assumed disutility values are shown in Table 72. The study from Tolley et al was useful in informing disutility estimates for three AEs; three of the health states for which preferences were elicited were “PFS responder + thrombocytopenia”, “PFS responder + AE: neutropenia”, and “PFS responder + severe infection” [89]. Vignette descriptions of these states corresponded to Grade 3/4 experiences [89]. For other AEs, information from previous studies and NICE TAs were targeted, and assumptions were made, as reported in Table 72.

**Table 72: AE utility decrement estimates**

| Grade 3/4 AE | Disutility | Source |
|---|---|---|
| Anaemia | -0.09 | NICE TA 216 |
| Febrile Neutropenia | -0.20 | Assumed equal to infection disutility |
| Sepsis | -0.20 | Tolley et al (2013) infection disutility |
| Neutropenia | -0.16 | Tolley et al (2013) |
| Pneumonia | -0.20 | Tolley et al (2013) infection disutility |
| Thrombocytopenia | -0.11 | Tolley et al (2013) |
| Diarrhoea + Colitis | -0.20 | Similar to Febrile Neutropenia decrement: advice from NHS England clinical haematologist |
| **Key:** AE, adverse events; NHS, national health service; NICE, national institute for health and care excellence; TA, technology appraisal | | |

To capture the effect of these AEs on HRQL in the model, assumptions regarding the durations of AEs were required. Average duration of event information was recorded for

pneumonia and diarrhoea in Study 116. For neutropenia and thrombocytopenia, data from the manufacturer's submission in NICE TA 306 were used. For anaemia and febrile neutropenia, AE duration was assumed equal to thrombocytopenia. These data and the resulting AE QALY decrement attributable to each event are shown in Table 73, for both the intervention and the comparator in Study 116.

Finally, the cycle probability of each event, from Study 116 incidence and time on treatment data, can be multiplied by the QALY decrement for each event to produce the cycle QALY decrement attributable to each AE for patients receiving treatment. These data are shown in Table 74 and
Table 75. The resulting cycle QALY decrement is small for each arm of the trial; -0.00010 QALYs for the intervention arm and -0.00021 for the comparator arm. Event QALY decrements are similar across treatment arms, as are event rates. Differences in duration of treatment over which adverse events are applied drive the higher cycle QALY decrements observed on the rituximab arm (rituximab is given for a fixed treatment length and time-on-treatment is substantially less than for idelalisib).

**Table 73: Durations of AEs and event QALY decrements**

| Grade 3/4 AE | Disutility | IR | | Rituximab | |
|---|---|---|---|---|---|
| | | Duration (weeks) | AE QALY decrement | Duration (weeks) | AE QALY decrement |
| Anaemia | -0.090 | 3.314 | -0.006 | 3.314 | -0.006 |
| Febrile Neutropenia | -0.195 | 3.314 | -0.012 | 3.314 | -0.012 |
| Sepsis | -0.195 | 3.314 | -0.012 | 3.314 | -0.012 |
| Neutropenia | -0.163 | 2.157 | -0.007 | 2.157 | -0.007 |
| Pneumonia | -0.195 | 1.600 | -0.006 | 2.600 | -0.010 |
| Thrombocytopenia | -0.108 | 3.314 | -0.007 | 3.314 | -0.007 |
| Diarrhoea + Colitis | -0.195 | 5.300 | -0.020 | 0.000 | 0.000 |
| **Key:** AE, adverse event; IR, idelalisib with rituximab; QALY, quality adjusted life year | | | | | |

The total cycle QALY decrement reported in Table 74 is applied to the intervention arm of the model in scenarios exploring the use of HRQL from the literature. In comparisons between idelalisib with rituximab and ofatumumab, the total cycle QALY decrement reported in

Table 75 is applied to the comparator arm of the model. For all other comparisons, in the absence of data, the comparator arm is assumed to incur no utility decrement as a result of treatment-emergent AEs. This is a conservative assumption and can be viewed as such in consideration of the corresponding results presented in sections 5.7 and 5.8.

**Table 74: 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 | | | |

**Table 75: 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 | | | |

**Health-related quality of life data used in cost-effectiveness analysis**

**Table 76: Summary of utility values for cost-effectiveness analysis**

| State | Utility value | Confidence interval | Reference in submission | Justification |
|---|---|---|---|---|
| **Base case comparisons** | | | | |
| Progression-free, comparator | 0.75 | (0.72,0.78) | Section 5.4 Table 69 | Study 116 EQ-5D data |
| IR treatment utility effect | 0.07 | (0.03,0.11) | | |
| PFS Off treatment | 0.80 | (0.63,0.93) | Section 5.4 Table 71 | Most robust literature estimate, used in NICE TA 193 [104] |
| PPS | 0.60 | (0.48,0.71) | | |
| **Comparisons to external study data** | | | | |
| Progression-free | 0.80 | (0.63,0.93) | Section 5.4 Section 5.4 | Most robust literature estimate |
| Progressive disease | 0.60 | (0.48,0.71) | | |
| **Adverse event decrements– excluded in the base case to avoid double counting** | | | | |
| **Adverse Event** | **Utility Decrement** | **Confidence interval** | **Reference in submission** | **Justification** |
| Anaemia | -0.09 | (-0.07,-0.11) | Section 5.4 Table 72 | Most robust literature estimate or validated assumption |
| Febrile Neutropenia | -0.20 | (-0.16,-0.23) | | |
| Sepsis | -0.20 | (-0.16,-0.23) | | |
| Neutropenia | -0.16 | (-0.13,-0.2) | | |
| Pneumonia | -0.20 | (-0.16,-0.23) | | |
| Thrombocytopenia | -0.11 | (-0.09,-0.13) | | |
| Diarrhoea + Colitis | -0.20 | (-0.16,-0.23) | | |
| **Key:** IR, idelalisib with rituximab; PFS, progression free survival; PPS, post progression survival | | | | |

## *5.5 Cost and healthcare resource use identification, measurement and valuation*

### Resource identification, measurement and valuation studies

The systematic literature search for resource identification, measurement and valuation studies was run alongside the search for previous economic evaluation and HRQL studies, as described in Appendix 14.

Two studies were identified for inclusion [97, 105]. Hoyle et al [97] report a critique of the manufacturer's submission for ofatumumab for refractory CLL in NICE TA202 [102]; Woods et al present results from a cost-utility analysis of bendamustine versus chlorambucil for untreated CLL [105], used to support the manufacturer's submission in NICE TA216 [106]. Data from these submissions were useful in informing resource use assumptions in the economic model.

**Intervention and comparators' costs and resource use**

Table 77 summarises the drug acquisition and administration costs associated with idelalisib with rituximab and its comparators. The price presented within this submission for idelalisib incorporates the discount agreed with the NHS. Including the discount and relative dose intensity figures observed in Study 116 (93.25% for idelalisib; 100% for rituximab assumed in absence of data), the total drug acquisition cost for the intervention is [redacted] in the first week of treatment and [redacted] in subsequent weeks in which rituximab is also administered. In weeks in which rituximab is not administered, the weekly acquisition cost for the intervention is [redacted].

Data reported in Table 78, Table 79 and Table 80 inform the estimates shown in Table 77. Table 80 describes the applied dosing regimens for each treatment. Table 78 shows drug acquisition costs for each intervention and each comparator considered. To calculate the required weekly dose for regimens whose dose is determined by a patient's body surface area (BSA), the mean pre-treatment BSA of Study 116 patients was used. Mean pre-treatment BSA was calculated using Mosteller's approximating equation [107] as 1.92m$^2$, from mean observed height and weight figures of Table 79. Table 79 shows administration costs for intravenous (IV) therapies.

Importantly, the total drug acquisition and administration costs reported in Table 77 are applied only up to the maximum length of treatment for each drug therapy. For example, Table 80 shows FCR to be administered in 4-weekly cycles for a total of 6 cycles. The active cycle drug acquisition and administration costs for FCR reported in Table 77 are therefore applied in model Weeks 1, 5, 9, 13, 17 and 21 only.

For all regimens except idelalisib with rituximab, where idelalisib is taken until disease progression barring complications including unacceptable toxicity, patients

are assumed not to be treated beyond the maximum number of treatment cycles recommended by guidance documents. For comparators outside of the base case, treatment costs are applied to the pre-progressive disease proportion of the model cohort up to the maximum treatment duration.

**Table 77: 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 |

| Regimen | Cycle type | Drug | Active Cycle Drug Costs | | Active Cycle Administration Costs | |
|---|---|---|---|---|---|---|
| | | | Each Component | Total by cycle type | Each Component | Total by cycle type |
| 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 | |
| Ofatumumab | Initial cycle | Ofatumumab | £546 | £546 | £214 | £214 |
| | Subsequent cycles | Ofatumumab | £3,640 | £3,640 | £214 | £214 |

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

**Table 78: Drug acquisition costs**

| Drug | Unit | Measure | Unit Cost | Measures per Unit | Cost per mg | Source |
|---|---|---|---|---|---|---|
| Idelalisib (list) | tab | 150mg | £3,114.75 | 60 | £0.35 | Gilead data on file. |
| Idelalisib (post-discount) | tab | 150mg | [redacted] | 60 | [redacted] | Gilead data on file. |
| Rituximab | concentrate | 100mg | £174.63 | 1 | £1.75 | MIMS online (accessed Jan 2015) |
| | concentrate | 500mg | £873.15 | 1 | £1.75 | MIMS online (accessed Jan 2015) |
| Fludarabine | concentrate | 50mg | £155.00 | 1 | £3.10 | MIMS online (accessed Jan 2015) |
| Cyclophosphamide | tab | 50mg | £82.00 | 100 | £0.02 | MIMS online (accessed Jan 2015) |
| Bendamustine | concentrate | 25mg | £347.26 | 5 | £2.78 | MIMS online (accessed Jan 2015) |
| | concentrate | 100mg | £1,379.04 | 5 | £2.76 | MIMS online (accessed Jan 2015) |
| Chlorambucil | tab | 2mg | £40.51 | 25 | £0.81 | MIMS online (accessed Jan 2015) |
| Dexamethasone | concentrate | 40mg | £1.58 | 1 | £0.04 | MIMS online (accessed Jan 2015) |
| | concentrate | 125mg | £4.75 | 1 | £0.04 | MIMS online (accessed Jan 2015) |
| | concentrate | 500mg | £9.60 | 1 | £0.02 | MIMS online (accessed Jan 2015) |
| | concentrate | 1000mg | £17.30 | 1 | £0.02 | MIMS online (accessed Jan 2015) |
| Ofatumumab | concentrate | 100mg | £546.00 | 3 | £1.82 | MIMS online (accessed Jan 2015) |
| | concentrate | 1000mg | £1,820.00 | 1 | £1.82 | MIMS online (accessed Jan 2015) |

**Key:** mg, milligram; MIMS, Monthly Index of Medical Specialties

**Table 79: Administration costs**

| Administration costs for IV Therapies | Unit Cost | Source |
|---|---|---|
| Administration of intravenous R-chemotherapy | £330 | NHS Reference Costs 2012-13; Total HRGs, SB14Z: deliver complex chemotherapy, including prolonged infusional treatment, at first attendance, Daycase [108] |
| Administration of other intravenous chemotherapy | £214 | NHS Reference Costs 2012-13; Total HRGs, SB12Z: deliver simple parenteral chemotherapy at first attendance, Daycase [108] |
| **Key:** NHS, national health service; HRG, healthcare resource group; R, rituximab | | |

**Table 80: Dosing regimens**

| Regimen | Drug | Dosing Cycle | Dose | Cycle length (days) | Max number of cycles | Admins per dosing cycle | Admin type | Source |
|---|---|---|---|---|---|---|---|---|
| IR | Idelalisib | all | 2100mg | 7 | Until disease progression | 7 | oral | Study 116 |
| | Rituximab | Cycle 1 | 375mg/m$^2$ | 14 | 8 | 1 | IV complex | Study 116 |
| | Rituximab | Cycle 2-5 | 500mg/m$^2$ | | | 1 | IV complex | Study 116 |
| | Rituximab | Cycle 6+ | 500mg/m$^2$ | 28 | | 1 | IV complex | Study 116 |
| R | Rituximab | Cycle 1 | 375mg/m$^2$ | 14 | 8 | 1 | IV complex | Study 116 |
| | Rituximab | Cycle 2-5 | 500mg/m$^2$ | | | 1 | IV complex | Study 116 |
| | Rituximab | Cycle 6+ | 500mg/m$^2$ | 28 | | 1 | IV complex | Study 116 |
| FCR | Fludarabine | Cycle 1 | 25mg/m$^2$ | 28 | 6 | 3 | IV | Robak et al 2010 [27] |
| | Cyclophosphamide | Cycle 1 | 250mg/m$^2$ | | | 3 | oral | Robak et al 2010 [27] |
| | Rituximab | Cycle 1 | 375mg/m$^2$ | | | 1 | IV complex | Robak et al 2010 [27] |
| | Fludarabine | Cycle 2+ | 25mg/m$^2$ | | | 3 | IV | Robak et al 2010 [27] |

| Regimen | Drug | Dosing Cycle | Dose | Cycle length (days) | Max number of cycles | Admins per dosing cycle | Admin type | Source |
|---|---|---|---|---|---|---|---|---|
| | Cyclophosphamide | Cycle 2+ | 250mg/m$^2$ | | | 3 | oral | Robak et al 2010 [27] |
| | Rituximab | Cycle 2+ | 500mg/m$^2$ | | | 1 | IV complex | Robak et al 2010 [27] |
| B | Bendamustine | all | 100mg/m$^2$ | 28 | 8 | 2 | IV | Niederle et al 2013 [62] |
| B+R | Bendamustine | Cycle 1 | 70mg/m$^2$ | 28 | 6 | 2 | IV | Fischer 2011 [93] |
| | Rituximab | Cycle 1 | 375mg/m$^2$ | | | 1 | IV complex | Fischer 2011 [93] |
| | Bendamustine | Cycle 2+ | 70mg/m$^2$ | | | 2 | IV | Fischer 2011 [93] |
| | Rituximab | Cycle 2+ | 500mg/m$^2$ | | | 1 | IV complex | Fischer 2011 [93] |
| Chl | Chlorambucil | all | 10mg | 28 | 12 | 14 | oral | East Midlands Cancer Network 2011 [109] |
| Chl+R | Chlorambucil | all | 10mg/m$^2$ | 28 | 6 | 7 | oral | Hillmen et al 2014 [110] |
| | Rituximab | Cycle 1 | 375mg/m$^2$ | | | 1 | IV complex | Hillmen et al 2014 [110] |
| | Rituximab | Cycle 2+ | 500mg/m$^2$ | | | 1 | IV complex | Hillmen et al 2014 [110] |
| Steroids+R | Methylprednisolone | all | 5000mg/m$^2$ | 21 | 6 | 5 | IV | Pileckyte et al 2011 [63] |
| | Rituximab | Cycle 1 | 375mg/m$^2$ | | | 2 | IV complex | Pileckyte et al 2011 [63] |
| | Rituximab | Cycle 2 | 500mg/m$^2$ | | | 2 | IV complex | Pileckyte et al 2011 [63] |
| | Rituximab | Cycle 3+ | 500mg/m$^2$ | | | 1 | IV complex | Pileckyte et al 2011 [63] |
| Ofa | Ofatumumab | Cycle 1 | 300mg | 7 | 12 | 1 | IV | Wierda 2010 [65] |
| | Ofatumumab | Cycle 2-8 | 2000mg | | | 1 | IV | Wierda 2010 [65] |
| | Ofatumumab | Cycle 9+ | 2000mg | 28 | | 1 | IV | Wierda 2010 [65] |

**Key:** B, bendamustine; Chl, chlorambucil; FCR, fludarabine, cyclophosphamideand and rituximab; IR, idelalisib with rituximab; ofa, ofatumumab; R, rituximab; IV, intravenous; m, metre

**Health-state unit costs and resource use**

The costs associated with each model health state are set out in Table 81 and include treatment and disease-management costs as well as costs associated with adverse events and palliative care.

The resource use and unit cost estimates attributed to disease management are described in Table 82, Table 83 and

Table 84. All resource use assumptions were validated at clinical review an NHS England clinical haematologist [1]. Table 82 shows the monthly resource use estimates attributed to disease management for responders and non-responders with pre-progressive disease and attributed to all patients with progressive disease. Table 83 shows the one-off resource use estimates associated with disease progression; these were informed by clinical guidance [15].

Table 84 reports unit cost estimates for resources associated with disease management.

**Table 81: Summary of health state costs**

| Health states | Items | Value | Reference in submission |
|---|---|---|---|
| Pre-progression, On Treatment | Technology | As described in Table 77 | 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 | Disease management | IR: £319 per week for 3 months, then £307 per week | Section 5.5 |

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

**Key:** AE, adverse event; BSC, best supportive care; B, bendamustine; Chl, chlorambucil; FCR, fludarabine, cyclophosphamideand and rituximab; IR, idelalisib with rituximab; ofa, ofatumumab; R, rituximab
* AE cost for R > AE cost for IR per cycle despite higher toxicity for IR, due to shorter time on treatment for R
** Conservative assumption

**Table 82: 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 [106] | 1 | NICE TA216 [106] |
| LDH test | 0.33 | 1.00 | NICE TA216 [106] | 1 | NICE TA216 [106] |
| Full blood test | 0.33 | 1.00 | NICE TA216 [106] | 1 | NICE TA202 [102] |
| Blood cell transfusion | 0.00 | 1.00* | Clinical validation [1, 15] | 0.5 | NICE TA216 [106] |
| Platelet transfusion | 0.00 | 2.17** | Clinical validation [1, 15] | 0 | Clinical validation [1, 15] |
| IvIG therapy | 0.00 | 1.24* | Clinical validation [1, 15] | 0 | Clinical validation [1, 15] |
| Chest X-ray | 0.00 | 0.33 | Clinical validation [1, 15] | 0.33 | NICE TA202 [102] |
| prophylactic antibiotics* | 1.00 | 1.00*** | Clinical validation [1, 15] | 0 | Clinical validation [1, 15] |
| prophylactic antivirals* | 1.00 | 1.00**** | Clinical validation [1, 15] | 0 | Clinical validation [1, 15] |

**Key:** IvIG, immunoglobulin variable region heavy chain; LDH, lactate dehydrogenase; NICE, national insitue 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 83: 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 84: Resource costs**

| Resource | Cost | Source |
|---|---|---|
| Haematologist-led visit | £143 | NHS Reference Costs 2012-13 [108]; Consultant Led Outpatient Attendance; WF01A 303 |
| Nurse-led visit | £91 | NHS Reference Costs 2012-13 [108]; Non-Consultant Led Outpatient Attendance; WF01A 303 |
| Cytogenetic testing | £372 | NHS Reference Costs 2012-13 [108]; Total - Outpatient Attendances; 311 |
| LDH test | £3 | NHS Reference Costs 2012-13 [108]; Directly Accessed Pathology Services; DAPS05 |
| Full blood test | £3 | NHS Reference Costs 2012-13 [108]; 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 | Average of IvIG therapy costs (£7,529, see Table 85) plus administration cost (£6,177, see text) |
| Bone marrow biopsy | £234 | NHS Reference Costs 2012-13 [108]; Total HRG data; Clinical Haematology, HRG SA33Z, Procedures in Outpatients |
| MRI scan | £246 | NHS Reference Costs 2012-13 [108]; Diagnostic Imaging, clinical haematology, RA07Z |
| Chest X-ray | £28 | NHS Reference Costs 2012-13 [108]; Directly Accessed Diagnostic Services, DAPF |

| Resource | Cost | Source |
|---|---|---|
| CT scan | £91 | NHS Reference Costs 2012-13 [108]; Computerised Tomography Scan, one area, no contrast, 19 years and over, RA08A |
| Prophylactic antibiotics | £12 | NICE TA202 [102]: Composite of ciprofloxacin 750mg (£8.00 for 10-tab pack, assumed cycle length of 28 days and dosage of 500mg bid); azithromycin 250mg (£1.86 for 4-tab pack, assumed cycle length of 3 days and dosage of 500mg qd); phenoxymethyl penicillin 250mg (£1.19 for 28-tab pack, assumed cycle length of 3 days and dosage of 500mg q6h); co-trimoxazole 960mg (£23.46 for 100-tab pack, assumed cycle length of 3 days and dosage of 960mg bid). Drug costs updated from MIMS [25] |
| Prophylactic antiviral | £89 | Zidovudine, 100mg white cap marked GSYJU, 100, MIMS online [25] |
| G-CSF support | £311 | NICE TA202 [102]; 300µg filgrastim MIMS online [25] |

**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.

Table 84 reports a cost of £13,706 for IV immunoglobulin-based (IvIG) therapy used to prevent infections in patients with no functional antibodies, applied to 45% of non-responders in the pre-progression health state of the model. There are numerous such therapies available, and in the absence of market share data, the average cost of a range of appropriate therapies was used to inform cost assumptions. Table 85 shows the cost of 0.4g of compound for 10 therapies listed on MIMS online [25]; assuming a dose of 0.4g/kg five times for one active treatment week, and given an average weight of 77.4kg in Study 116, the average cost of IvIG drug acquisition is £7,529. The IV administration cost for immunoglobulin (band 1) is £1,235 per infusion (NHS Reference Costs 2012/2013 [108], XD34Z); for five infusions the weekly administration cost is £6,177. Combining drug acquisition and administration costs, the model cost for IvIG therapy is £13,706.

**Table 85: Estimated IV immunoglobulin-based drug acquisition cost**

| Treatment | 0.4g cost, MIMS online [25] | Total therapy cost (154.8g) |
|---|---:|---:|
| Aragam | £23 | £8,978 |
| Flebogamma | £24 | £9,288 |
| Gammagard | £16 | £6,207 |
| Gammaplex | £17 | £6,471 |
| Gamunex | £20 | £6,471 |
| Intratect | £18 | £9,288 |
| Kiovig | £20 | £7,585 |
| Octagam | £19 | £7,430 |
| Privigen | £18 | £7,105 |
| Vigam | £17 | £6,471 |
| **Average cost** | **£19** | **£7,529** |
| **Key:** | | |

### Adverse reaction unit costs and resource use

The unit costs associated with the seven treatment-emergent AEs considered in the model, as described in section 5.4, were sourced from NHS Reference Costs and are shown in Table 86.

**Table 86: 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 87. Ofatumumab monotherapy is assumed to produce equivalent AE rates to rituximab monotherapy (section 4). In the absence of data, and in line with HRQL assumptions reported in section 5.4, the highly conservative assumption of no costs for AEs is made for all other comparators.

**Table 87: 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 | | | | | | |

### Miscellaneous unit costs and resource use

The cost of care immediately prior to death is taken from a King's Fund report into improving choice at end of life [87], and is the average cost of community and acute care for patients with cancer in the last eight weeks of their life reported by the authors, inflated to 2013/2014 levels [111].

The cost for 8 weeks of care is £6,105. Assumed to be spread evenly across the last 8 weeks of a patient's life, this is applied as a cost of £763 per week to the proportion of patients in the "Palliative care" health state.

Not all of these costs are direct NHS costs, some falling on 'third sector' healthcare organisations; however, their inclusion is relevant to the disease, and does not introduce any bias, as all patients die within the model time horizon.

## *5.6 Summary of base case de novo analysis inputs and assumptions*

### Summary of base case *de novo* analysis inputs

Table 88 summarises the base case economic model variables, in terms of their point estimate value and their assumed distribution, and guides the reader towards the sections of the submission in which the different variables are described. The scale of uncertainty around estimates was informed by data and not arbitrary assumptions for key parameters, including all survival parameters, ORRs, and utility estimates for the "PFS, on Treatment" health state.

**Table 88: Summary of variables applied in the economic model**

| Variable | Value | CI (distribution) | See Section |
|---|---|---|---|
| **Response Rates** | | | |
| ORR IR | 84% | Beta (0.8,0.87) | 5.2 |
| ORR BSC | 0% | Not included in SA | 5.2 |
| ORR Rituximab | 15% | Beta (0.07,0.26) | 5.2 |
| ORR Fludarabine with cyclophosphamide and rituximab | 74% | Beta (0.69,0.79) | 5.2 |
| ORR Bendamustine | 76% | Beta (0.71,0.8) | 5.2 |
| ORR Bendamustine with rituximab | 59% | Beta (0.51,0.67) | 5.2 |
| ORR Chlorambucil | 48% | Beta (0.38,0.58) | 5.2 |
| ORR Chlorambucil with rituximab | 83% | Beta (0.8,0.86) | 5.2 |
| ORR Steroids with rituximab | 62% | Beta (0.55,0.69) | 5.2 |
| ORR Ofatumumab | 47% | Beta (0.37,0.57) | 5.2 |
| **Adverse Events** | | | |
| IR anaemia rate | 7% | Beta (0,0.31) | 5.4 |
| IR febrile neutropenia rate | 5% | Beta (0,0.3) | 5.4 |
| IR sepsis rate | 5% | Beta (0,0.3) | 5.4 |
| IR neutropenia rate | 23% | Beta (0.1,0.38) | 5.4 |
| IR pneumonia rate | 10% | Beta (0,0.31) | 5.4 |
| IR thrombocytopenia rate | 4% | Beta (0,0.3) | 5.4 |
| IR diarrhoea +colitis rate | 14% | Beta (0.02,0.33) | 5.4 |
| Rituximab anaemia rate | 6% | Beta (0,0.31) | 5.4 |
| Rituximab febrile neutropenia rate | 5% | Beta (0,0.3) | 5.4 |
| Rituximab sepsis rate | 3% | Beta (0,0.29) | 5.4 |
| Rituximab neutropenia rate | 16% | Beta (0.04,0.34) | 5.4 |
| Rituximab pneumonia rate | 9% | Beta (0,0.31) | 5.4 |
| Rituximab thrombocytopenia rate | 4% | Beta (0,0.3) | 5.4 |

| Variable | Value | CI (distribution) | See Section |
|---|---|---|---|
| Rituximab diarrhoea + colitis rate | 0% | Beta (0,0) | 5.4 |
| **Pre-progression Background Resource Use** | | | |
| ORR Visit Haematologist led - prop | 1.00 | Gamma (0.81,1) | 5.5 |
| ORR Visit Nurse led - prop | 1.00 | Gamma (0.81,1) | 5.5 |
| ORR Visit Haematologist led - freq | 0.08 | Gamma (0.06,0.09) | 5.5 |
| ORR Visit Nurse led - freq | 0.00 | Gamma (0,0) | 5.5 |
| ORR Cytogenetic testing - prop | 1.00 | Gamma (0.81,1) | 5.5 |
| ORR LDH test - prop | 1.00 | Gamma (0.81,1) | 5.5 |
| ORR Full blood test - prop | 1.00 | Gamma (0.81,1) | 5.5 |
| ORR Cytogenetic testing - freq | 0.00 | Gamma (0,0) | 5.5 |
| ORR LDH test- freq | 0.08 | Gamma (0.06,0.09) | 5.5 |
| ORR Full blood test - freq | 0.08 | Gamma (0.06,0.09) | 5.5 |
| ORR Blood cell transfusion - prop | 1.00 | Gamma (0.81,1) | 5.5 |
| ORR Platelet transfusion - prop | 1.00 | Gamma (0.81,1) | 5.5 |
| ORR IvIG therapy - prop | 1.00 | Gamma (0.81,1) | 5.5 |
| ORR CT scan - prop | 1.00 | Gamma (0.81,1) | 5.5 |
| ORR MRI scan - prop | 1.00 | Gamma (0.81,1) | 5.5 |
| ORR Chest X-ray - prop | 1.00 | Gamma (0.81,1) | 5.5 |
| ORR Blood cell transfusion - freq | 0.00 | Gamma (0,0) | 5.5 |
| ORR Platelet transfusion - freq | 0.00 | Gamma (0,0) | 5.5 |
| ORR IvIG therapy - freq | 0.00 | Gamma (0,0) | 5.5 |
| ORR CT scan - freq | 0.00 | Gamma (0,0) | 5.5 |
| ORR MRI scan - freq | 0.00 | Gamma (0,0) | 5.5 |
| ORR Chest X-ray - freq | 0.00 | Gamma (0,0) | 5.5 |
| ORR prophylactic antibiotics - prop | 0.60 | Gamma (0.49,0.72) | 5.5 |
| ORR prophylactic antiviral - prop | 0.50 | Gamma (0.41,0.6) | 5.5 |

| Variable | Value | CI (distribution) | See Section |
|---|---|---|---|
| ORR prophylactic antibiotics - freq | 0.23 | Gamma (0.19,0.28) | 5.5 |
| ORR prophylactic antiviral - freq | 0.23 | Gamma (0.19,0.28) | 5.5 |
| NoORR Visit Haematologist led - prop | 1.00 | Gamma (0.81,1) | 5.5 |
| NoORR Visit Nurse led - prop | 1.00 | Gamma (0.81,1) | 5.5 |
| NoORR Visit Haematologist led - freq | 0.23 | Gamma (0.19,0.28) | 5.5 |
| NoORR Visit Nurse led - freq | 0.00 | Gamma (0,0) | 5.5 |
| NoORR Cytogenetic testing - prop | 1.00 | Gamma (0.81,1) | 5.5 |
| NoORR LDH test - prop | 1.00 | Gamma (0.81,1) | 5.5 |
| NoORR Full blood test - prop | 1.00 | Gamma (0.81,1) | 5.5 |
| NoORR Cytogenetic testing - freq | 0.00 | Gamma (0,0) | 5.5 |
| NoORR LDH test- freq | 0.23 | Gamma (0.19,0.28) | 5.5 |
| NoORR Full blood test - freq | 0.23 | Gamma (0.19,0.28) | 5.5 |
| NoORR Blood cell transfusion - prop | 0.45 | Gamma (0.37,0.54) | 5.5 |
| NoORR Platelet transfusion - prop | 0.15 | Gamma (0.12,0.18) | 5.5 |
| NoORR IvIG therapy - prop | 0.45 | Gamma (0.37,0.54) | 5.5 |
| NoORR CT scan - prop | 1.00 | Gamma (0.81,1) | 5.5 |
| NoORR MRI scan - prop | 1.00 | Gamma (0.81,1) | 5.5 |
| NoORR Chest X-ray - prop | 1.00 | Gamma (0.81,1) | 5.5 |
| NoORR Blood cell transfusion - freq | 0.23 | Gamma (0.19,0.28) | 5.5 |
| NoORR Platelet transfusion - freq | 0.50 | Gamma (0.41,0.6) | 5.5 |
| NoORR IvIG therapy - freq | 0.28 | Gamma (0.23,0.34) | 5.5 |
| NoORR CT scan - freq | 0.00 | Gamma (0,0) | 5.5 |
| NoORR MRI scan - freq | 0.00 | Gamma (0,0) | 5.5 |
| NoORR Chest X-ray - freq | 0.08 | Gamma (0.06,0.09) | 5.5 |
| NoORR prophylactic antibiotics - prop | 0.60 | Gamma (0.49,0.72) | 5.5 |
| NoORR prophylactic antiviral - prop | 0.50 | Gamma (0.41,0.6) | 5.5 |

| Variable | Value | CI (distribution) | See Section |
|---|---|---|---|
| NoORR prophylactic antibiotics - freq | 0.23 | Gamma (0.19,0.28) | 5.5 |
| NoORR prophylactic antiviral - freq | 0.23 | Gamma (0.19,0.28) | 5.5 |
| **Upon- and post-progression Background Resource Use** | | | |
| PPS Visit Haematologist led - freq | 0.23 | Gamma (0.19,0.28) | 5.5 |
| PPS Visit Nurse led - freq | 0.00 | Gamma (0,0) | 5.5 |
| PPS Cytogenetic testing - freq | 0.00 | Gamma (0,0) | 5.5 |
| PPS LDH test- freq | 0.23 | Gamma (0.19,0.28) | 5.5 |
| PPS Full blood test - freq | 0.23 | Gamma (0.19,0.28) | 5.5 |
| PPS Blood cell transfusion - freq | 0.11 | Gamma (0.09,0.14) | 5.5 |
| PPS Platelet transfusion - freq | 0.00 | Gamma (0,0) | 5.5 |
| PPS IvIG therapy - freq | 0.00 | Gamma (0,0) | 5.5 |
| PPS bone marrow - freq | 0.00 | Gamma (0,0) | 5.5 |
| PPS MRI scan - freq | 0.00 | Gamma (0,0) | 5.5 |
| PPS Chest X-ray - freq | 0.08 | Gamma (0.06,0.09) | 5.5 |
| PPS prophylactic antibiotics - freq | 0.00 | Gamma (0,0) | 5.5 |
| PPS prophylactic antiviral - freq | 0.00 | Gamma (0,0) | 5.5 |
| Percentage of pts. incurring terminal cost | 1.00 | Gamma (0.81,1) | 5.5 |
| upon PPS one-off G-CSF usage | 0.50 | Gamma (0.41,0.6) | 5.5 |
| upon PPS one-off Cytogenetic testing | 1.00 | Gamma (0.81,1) | 5.5 |
| upon PPS one-off Bone marrow biopsy | 0.90 | Gamma (0.73,1) | 5.5 |
| upon PPS one-off Radiographic MRI scan | 0.00 | Gamma (0,0) | 5.5 |
| upon PPS one-off CT scan | 0.50 | Gamma (0.41,0.6) | 5.5 |
| **Unit Costs** | | | |
| Anaemia unit cost | £439 | Gamma (357.19,529.12) | 5.5 |
| Febrile Neutropenia unit cost | £5,993 | Gamma (4876.14,7223.3) | 5.5 |
| Sepsis unit cost | £955 | Gamma (777.03,1151.05) | 5.5 |

| Variable | Value | CI (distribution) | See Section |
|---|---|---|---|
| Neutropenia unit cost | £179 | Gamma (145.64,215.75) | 5.5 |
| Pneumonia unit cost | £1,252 | Gamma (1018.68,1509.02) | 5.5 |
| Thrombocytopenia unit cost | £470 | Gamma (382.41,566.49) | 5.5 |
| Diarrhoea unit cost | £140 | Gamma (113.91,168.74) | 5.5 |
| Visit Haematologist led unit cost | £143 | Gamma (116.35,172.36) | 5.5 |
| Visit Nurse led unit cost | £91 | Gamma (74.04,109.68) | 5.5 |
| Cytogenetic testing unit cost | £372 | Gamma (302.67,448.37) | 5.5 |
| LDH test unit cost | £3 | Gamma (2.44,3.62) | 5.5 |
| Full blood test unit cost | £3 | Gamma (2.44,3.62) | 5.5 |
| Blood cell transfusion unit cost | £122 | Gamma (99.14,146.86) | 5.5 |
| Platelet transfusion unit cost | £197 | Gamma (160.25,237.39) | 5.5 |
| IvIG therapy unit cost | £13,706 | Gamma (11151.89,16519.9) | 5.5 |
| bone marrow test unit cost | £234 | Gamma (190.65,282.42) | 5.5 |
| MRI scan unit cost | £246 | Gamma (200.16,296.5) | 5.5 |
| Chest X-ray unit cost | £28 | Gamma (22.78,33.75) | 5.5 |
| prophylactic antibiotics unit cost | £12 | Gamma (9.7,14.37) | 5.5 |
| prophylactic antiviral unit cost | £89 | Gamma (72.3,107.1) | 5.5 |
| CT scan cost | £91 | Gamma (74.04,109.68) | 5.5 |
| Rituximab administration cost | £330 | Gamma (268.5,397.75) | 5.5 |
| Simple chemotherapy administration cost | £214 | Gamma (174.12,257.93) | 5.5 |
| GCSF support unit cost | £311 | Gamma (253.25,375.15) | 5.5 |
| End of life care cost | £6,105 | Gamma (4967.29,7358.32) | 5.5 |
| **HRQL** | | | |
| Trial IR Utility | 0.81 | Beta (0,0) | 5.4 |
| Trial Rituximab plus Placebo Utility | 0.75 | Beta (0.72,0.78) | 5.4 |
| Trial IR Treatment Utility Effect | 0.07 | Beta (0.03,0.11) | 5.4 |

| Variable | Value | CI (distribution) | See Section |
|---|---|---|---|
| Assumed Utility for Trial Patients Post-Progression | 0.60 | Beta (0.48,0.71) | 5.4 |
| Dretzke PFS Utility | 0.80 | Beta (0.63,0.93) | 5.4 |
| Dretzke PPS Utility | 0.60 | Beta (0.48,0.71) | 5.4 |
| Tolley PFS Utility | 0.67 | Beta (0.63,0.71) | 5.4 |
| Tolley PPS Utility | 0.21 | Beta (0.18,0.25) | 5.4 |
| Utility decrement anaemia | -0.09 | Beta (-0.07,-0.11) | 5.4 |
| Utility decrement febrile neutropenia | -0.20 | Beta (-0.16,-0.23) | 5.4 |
| Utility decrement infection | -0.20 | Beta (-0.16,-0.23) | 5.4 |
| Utility decrement neutropenia | -0.16 | Beta (-0.13,-0.2) | 5.4 |
| Utility decrement pneumonia | -0.20 | Beta (-0.16,-0.23) | 5.4 |
| Utility decrement thrombocytopenia | -0.11 | Beta (-0.09,-0.13) | 5.4 |
| Utility decrement diarrhoea | -0.20 | Beta (-0.16,-0.23) | 5.4 |
| **Study 116 survival** | | | |
| OS IR Weibull Intercept | 4.20 | | 5.3 |
| OS IR Weibull DEL17P/TP53 Either | -0.45 | | 5.3 |
| OS IR Weibull IGVH Mutated | 0.43 | | 5.3 |
| OS IR Weibull Shape | 0.77 | | 5.3 |
| OS R Weibull Intercept | 3.04 | | 5.3 |
| OS R Weibull DEL17P/TP53 Either | -0.61 | | 5.3 |
| OS R Weibull IGVH Mutated | 0.57 | | 5.3 |
| OS R Weibull Shape | 0.75 | | 5.3 |

| | Intercept | DEL17P/TP53 Either | IGVH Mutated | Shape |
|---|---|---|---|---|
| Intercept | 0.20 | -0.12 | -0.01 | 0.06 |
| DEL17P/TP53 Either | -0.12 | 0.16 | -0.01 | -0.02 |
| IGVH Mutated | -0.01 | -0.01 | 0.35 | 0.01 |
| Shape | 0.06 | -0.02 | 0.01 | 0.03 |

| Variable | Value | CI (distribution) | See Section |
|---|---|---|---|
| | | | |
| PFS IR Weibull Intercept | 3.08 | | 5.3 |
| PFS IR Weibull DEL17P/TP53 Either | 0.08 | | 5.3 |
| PFS IR Weibull IGVH Mutated | -0.01 | | 5.3 |
| PFS IR Weibull Shape | 0.62 | | 5.3 |
| PFS R Weibull Intercept | 2.08 | | 5.3 |
| PFS R Weibull DEL17P/TP53 Either | -0.39 | | 5.3 |
| PFS R Weibull IGVH Mutated | 0.37 | | 5.3 |
| PFS R Weibull Shape | 0.61 | | 5.3 |
| OS IR exponential Intercept | 4.66 | | 5.3 |
| OS IR exponential DEL17P/TP53 Either | -0.60 | | 5.3 |
| OS IR exponential IGVH Mutated | 0.54 | | 5.3 |
| OS IR exponential Shape | 1.00 | | 5.3 |

| Variable | Value | CI (distribution) | See Section |
|---|---|---|---|
| | | [redacted] | |
| OS R exponential Intercept | 4.66 | | 5.3 |
| OS R exponential DEL17P/TP53 Either | -0.60 | | 5.3 |
| OS R exponential IGVH Mutated | 0.54 | | 5.3 |
| OS R exponential Shape | 1.00 | | 5.3 |
| **External studies survival** | | | |
| OS FCR patient characteristics adjustment hazard | 17.90 | Not included in SA | 5.3 |
| OS Bendamustine patient characteristics adjustment hazard | 2.54 | Not included in SA | 5.3 |
| OS Bendamustine + rituximab patient characteristics adjustment hazard | 2.46 | Not included in SA | 5.3 |
| OS Steroids + rituximab patient characteristics adjustment hazard | 1.62 | Not included in SA | 5.3 |
| OS Ofatumumab patient characteristics adjustment hazard | 1.44 | Not included in SA | 5.3 |
| OS FCR Weibull scale parameter | 0.00 | Not included in SA | 5.3 |
| OS Bendamustine Weibull scale parameter | 0.01 | Not included in SA | 5.3 |
| OS Bendamustine + rituximab Weibull scale parameter | 0.01 | Not included in SA | 5.3 |
| OS Steroids + rituximab Weibull scale parameter | 0.01 | Not included in SA | 5.3 |
| OS Ofatumumab Weibull scale parameter | 0.02 | Not included in SA | 5.3 |
| PFS FCR patient characteristics adjustment hazard | 14.32 | Not included in SA | 5.3 |
| PFS Bendamustine patient characteristics adjustment hazard | 2.89 | Not included in SA | 5.3 |
| PFS Bendamustine + rituximab patient characteristics adjustment hazard | 2.50 | Not included in SA | 5.3 |
| PFS Steroids + rituximab patient characteristics adjustment hazard | 1.52 | Not included in SA | 5.3 |

| Variable | Value | CI (distribution) | See Section |
|---|---|---|---|
| PFS Ofatumumab patient characteristics adjustment hazard | 0.64 | Not included in SA | 5.3 |
| PFS FCR Weibull scale parameter | 0.01 | Not included in SA | 5.3 |
| PFS Bendamustine Weibull scale parameter | 0.01 | Not included in SA | 5.3 |
| PFS Bendamustine + rituximab Weibull scale parameter | 0.01 | Not included in SA | 5.3 |
| PFS Steroids + rituximab Weibull scale parameter | 0.01 | Not included in SA | 5.3 |
| PFS Ofatumumab Weibull scale parameter | 0.04 | Not included in SA | 5.3 |

**Key:** CI, confidence interval; CT, computerised tomography; FCR, fludarabine, cyclophosphamide and rituximab; HRQL, health related quality of life;IR, idelalisib with rituximab; IvIG, Intravenous immunoglobulin therapy; LDH, lactate dehydrogenase; ORR, overall response rate; PFS, progression free survival; PPS, post prohression survival

**Assumptions**

The base case analysis, which uses data from Study 116 to infer about the relative economic value of idelalisib with rituximab versus (i) rituximab, (ii) BSC and (ii) ofatumumab, is subject to several key assumptions, described and discussed throughout section 5, but listed here for reference.

**Safety and effectiveness**

1. OS and PFS are best characterised by Weibull curves fitted to Study 116 data with only OS adjusted for crossover bias, due to patients switching from rituximab monotherapy to idelalisib with rituximab in Study 116
2. Subsequent therapy other than crossover is unimportant for economic outcomes. Subsequent therapy was recorded only in terms of tracking those patients who switched to idelalisib monotherapy. It would not be expected that other than crossover an imbalance in therapies would be seen across the arms and latter line therapies are unlikely to have much impact on this patient population due to the short survival experienced post progression.
3. Anti-CD20s rituximab and ofatumumab have equal efficacy and safety
4. BSC can conservatively be assumed to have equal efficacy to rituximab as observed within the clinical trial but with 0% response.

**Resource use and costs**

5. Patients are treated until the first of either progression, unacceptable toxicity, the maximum number of cycles of therapy recommended by guidance documents, or death
6. Resource use is dependent on response and progression status
7. BSC is associated with no treatment costs

**Quality of life**

8. Quality of life is dependent on treatment received and progression status
9. The most suitable sources to estimate utilities are Study 116 EQ-5D data for patients receiving treatment, and the literature values reported by Dretzke et al [88] for patients not receiving treatment
10. Quality of life effects of treatment-related adverse events are captured by Study 116 EQ-5D data

The exploratory comparisons to external study data are subject to additional key assumptions, as discussed in section 5.3, and results from these comparisons, presented in section 5.8, should be interpreted with caution. These key assumptions

are listed here for reference. Some of these assumptions are unlikely to be entirely met therefore these analyses are presented as exploratory work only.

1. Patients are treated until the first of either progression, the maximum number of cycles of therapy recommended by guidance documents, or death
2. Results from the Cox PH analysis reported by Badoux et al [69] are generalisable across CLL patients who have received at least one prior therapy
3. Study population heterogeneity can be accounted for using results from the Cox PH analysis reported by Badoux et al [69]
4. Response rates can be compared across the studies well enough to allow direct use of rates from trials with different designs and reporting
5. Proportional hazards can be assumed across all comparators for both OS and PFS
6. Applying hazard ratios reported by Knauf et al for chlorambucil versus bendamustine to OS and PFS curves estimated for bendamustine with and without rituximab can capture outcomes for chlorambucil with and without rituximab.

## *5.7 Base case results*

**Base case incremental cost-effectiveness analysis results**

Base case results of the economic comparison between idelalisib with rituximab and rituximab monotherapy are presented in Table 89. Corresponding results for the comparison between idelalisib with rituximab and BSC are shown in Table 90; these results for the comparison between idelalisib with rituximab and ofatumumab are shown in Table 91.

All results are presented using the NHS price for idelalisisb.

Idelalisib with rituximab is estimated to lead to 3.24 incremental life years (LYs) and 1.92 incremental QALYs versus the comparator in Study 116.

Applying rituximab monotherapy treatment costs to the comparator arm of the model leads to an incremental cost of under £26,500 for idelalisib with rituximab versus rituximab monotherapy and a base case ICER of under £14,000.

Applying no treatment costs to the comparator arm, in the conservative comparison to BSC, results in incremental costs of around £39,200 for idelalisib with rituximab and an estimated ICER of around £20,500 for idelalisib with rituximab.

When treatment costs for ofatumumab are applied to the comparator arm, incremental costs for idelalisib with rituximab are just under £3,000, owing to the high drug acquisition cost for ofatumumab. This results in an ICER of around £1,500 for idelalisib with rituximab versus ofatumumab.

From these results, idelalisib with rituximab is clearly cost-effective in comparison to rituximab monotherapy, ofatumumab monotherapy and BSC for CLL patients similar to those recruited into Study 116, i.e. for whom cytotoxic-based therapies are not indicated. The comparison to BSC assumed zero treatment costs and equivalent survival outcomes to rituximab monotherapy; these are highly conservative key assumptions, yet the results still show idelalisib with rituximab to be cost-effective in comparison to BSC within the usual £20,000 - £30,000 ICER threshold range, and therefore a highly economically viable therapy within and end-of-life setting where higher thresholds are likely to apply.

**Table 89: 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 90: 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 91: 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 | | | | | | | |

### Clinical outcomes from the model

Table 92 summarises median model results in comparison to median Study 116 results, for the key clinical outcomes. The model predicts median ToT and PFS for idelalisib with rituximab accurately if somewhat conservatively, and while median OS was not reached for idelalisib with rituximab in Study 116, at 12 months, the model accurately predicts idelalisib with rituximab OS (89% model; 88% Study 116). For the rituximab monotherapy arm of Study 116, the model again predicts PFS accurately, although conservatively, and marginally over-predicts OS compared to the crossover adjusted results in Table 92.

**Table 92: 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 | 20.8 (ITT) [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

Figure 29 and Figure 30 depict the Markov traces for the intervention and comparator arms of the base case model. Survival benefits are clear both pre- and post-progression for idelalisib with rituximab versus rituximab monotherapy (and, by inference, BSC and ofatumumab).

**Figure 29: Markov Trace, IR**

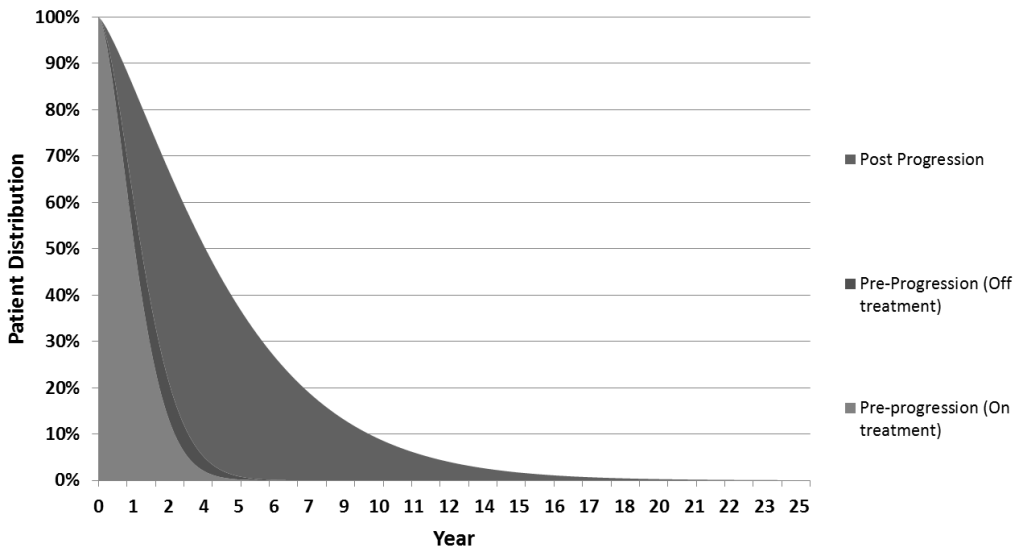



**Figure 30: Markov Trace, R**

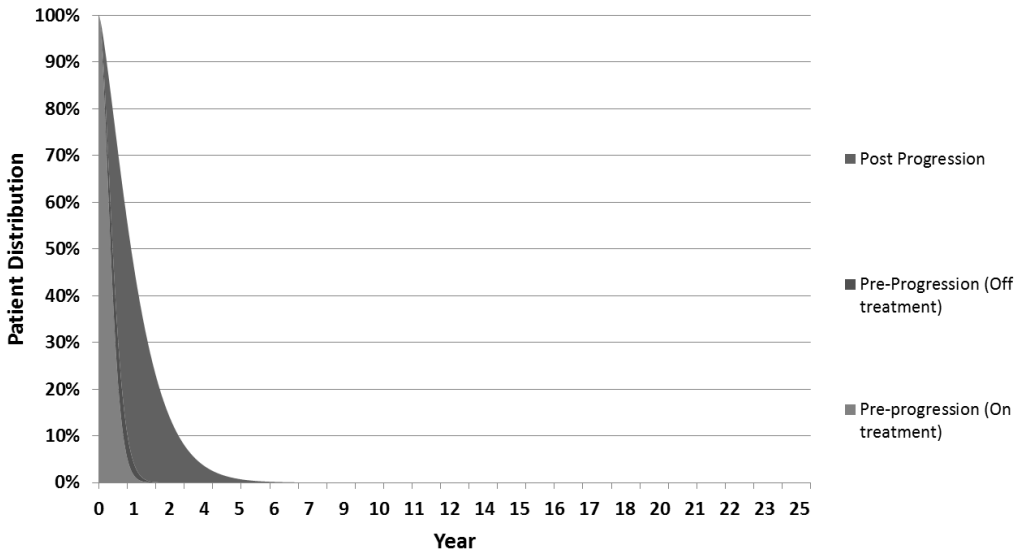



Figure 31 and Figure 32 demonstrate how QALYs are assumed to accrue for the simulated cohorts in each arm of the model. The incremental QALY benefit of idelalisib with rituximab versus rituximab monotherapy (and, by inference, BSC and ofatumumab) is clear from these figures.

**Figure 31: QALY accumulation over time, IR**

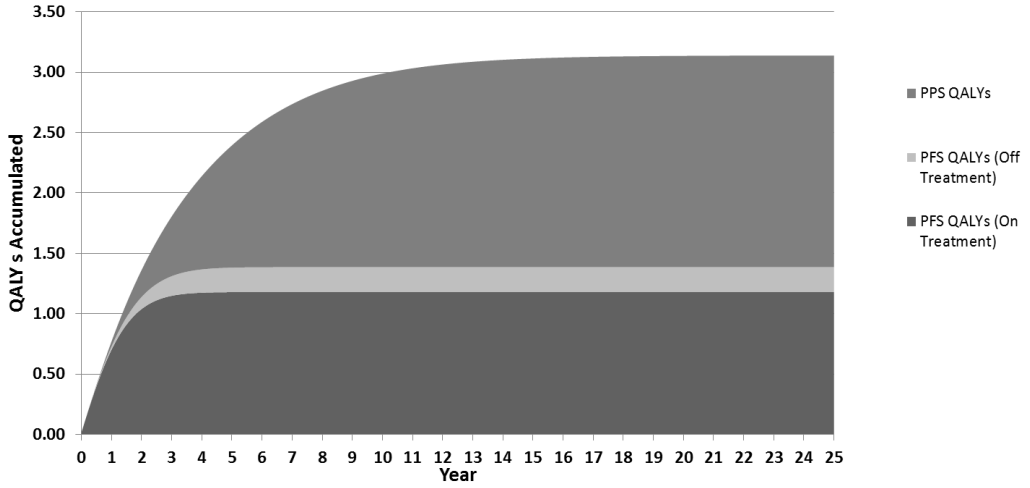
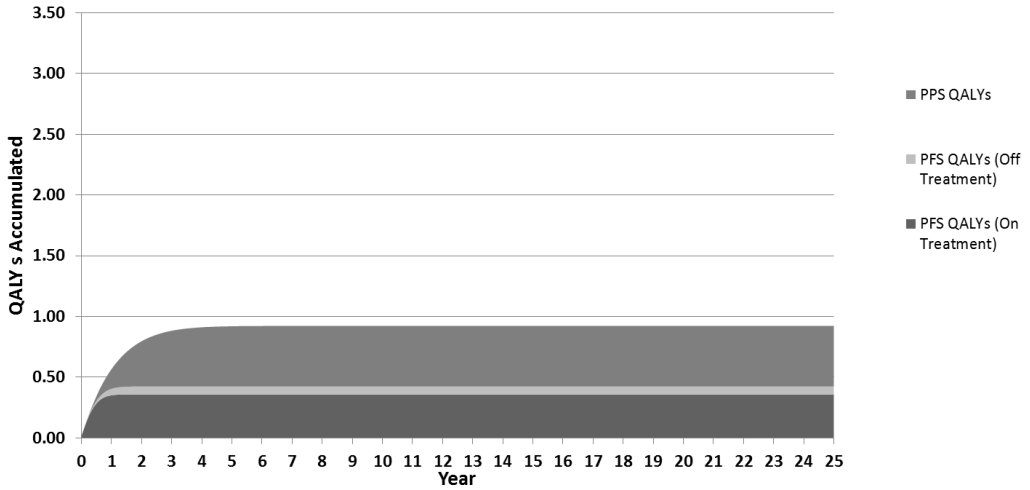



**Figure 32: QALY accumulation over time, R**



**Disaggregated results of the base case incremental cost-effectiveness analysis**

Table 93 summarises total QALYs for each arm of the base case model, disaggregated by model health states; Table 94 summarises total life years. Reflecting the inference from Figure 31 and Figure 32, the predicted incremental idelalisib with rituximab QALY gain is substantial both pre- and post-disease progression. This gain can be seen to be due to increases in overall survival above and beyond the increases seen in PFS and is therefore not surprising as this is reflective of Study 116 results.

**Table 93: Summary of QALY gain by health state**

| Health State | QALY IR | QALY R | Increment | Absolute Increment | % Absolute Increment |
|---|---|---|---|---|---|
| PFS On Treatment | 1.14 | 0.35 | 0.79 | 0.79 | 41% |
| PFS Off Treatment | 0.19 | 0.06 | 0.13 | 0.13 | 7% |
| PPS | 1.48 | 0.47 | 1.00 | 1.00 | 52% |
| Total | 2.81 | 0.89 | 1.92 | 1.92 | 100% |
| **Key:** IR, idelalisib with rituximab; PFS, progression free survival; PPS, post progression survival; R, rituximab; QALY, quality adjusted life year | | | | | |

**Table 94: Summary of life year gain by health state**

| Health State | QALY IR | QALY R | Increment | Absolute Increment | % Absolute Increment |
|---|---|---|---|---|---|
| PFS On Treatment | 1.45 | 0.48 | 0.97 | 0.97 | 30% |
| PFS Off Treatment | 0.26 | 0.08 | 0.18 | 0.18 | 5% |
| PPS | 2.92 | 0.83 | 2.09 | 2.09 | 65% |
| Total | 4.63 | 1.39 | 3.24 | 3.24 | 100% |
| **Key:** IR, idelalisib with rituximab; PFS, progression free survival; PPS, post progression survival; R, rituximab; QALY, quality adjusted life year | | | | | |

Table 95, Table 96 and Table 97 show predicted total incremental costs for idelalisib with rituximab versus each of the three base case comparators; R, BSC and ofatumumab. At least [redacted] of the incremental total cost of idelalisib with rituximab versus (i) rituximab monotherapy and (ii) BSC is attributable to differences across model arms in the "PFS, On Treatment" health state. For the comparison to ofatumumab, where incremental costs are far smaller, the cost differences across model arms are more evenly spread across health states. Table 98, Table 99 and Table 100 show these data further aggregated by different resource use categories. At least [redacted] of the incremental difference in costs accrued in the "PFS, On Treatment" health state in the model are attributable to the higher pre-progression (on treatment) disease management costs accrued in the idelalisib with rituximab arm, reflective of the estimated pre-progression survival benefit of idelalisib with rituximab versus R.

**Table 95: Disaggregated costs by health state, IR vs. R**

| Health State | IR | R | Increment | Absolute Increment | % Absolute Increment |
|---|---|---|---|---|---|
| PFS On Treatment | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PFS Off Treatment | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PPS | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Key: IR, idelalisib with rituximab; NHS, national health service; PFS, progression free survival; PPS, post progression survival; R, rituximab;

**Table 96: Disaggregated costs by health state, IR vs. BSC**

| Health State | IR | BSC | Increment | Absolute Increment | % Absolute Increment |
|---|---|---|---|---|---|
| PFS On Treatment | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PFS Off Treatment | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PPS | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

| Health State | IR | BSC | Increment | Absolute Increment | % Absolute Increment |
|---|---|---|---|---|---|
| **Key:** BSC, best supportive care; IR, idelalisib with rituximab; NHS, national healh service; PFS, progression free survival; PPS, post progression survival; R, rituximab | | | | | |

**Table 97: Disaggregated costs by health state, IR vs. ofatumumab**

| Health State | IR | Ofa | Increment | Absolute Increment | % Absolute Increment |
|---|---|---|---|---|---|
| PFS On Treatment | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PFS Off Treatment | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PPS | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Key:** IR, idelalisib with rituximab; NHS, national healh service; Ofa, ofatumumab; PFS, progression free survival; PPS, post progression survival; | | | | | |

**Table 98: Disaggregated predicted resource use costs, IR vs. R**

| | IR | R | Increment | Absolute Increment | % Absolute Increment |
|---|---|---|---|---|---|
| PFS (on treatment) Treatment Drug cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PFS (on treatment) Treatment Admin cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PFS (on treatment) AE cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PFS (on treatment) Disease Management cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PFS (off treatment) Disease Management cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PPS Disease Management cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Terminal Care cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Key:** AE, adverse event; IR, idelalisib with rituximab; NHS, national healh service; PFS, progression free survival; PPS, post progression survival; R, rituximab | | | | | |

**Table 99: Disaggregated predicted resource use costs, IR vs. BSC**

| | IR | BSC | Increment | Absolute Increment | % Absolute Increment |
|---|---|---|---|---|---|
| PFS (on treatment) Treatment Drug cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PFS (on treatment) Treatment Admin cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PFS (on treatment) AE cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PFS (on treatment) Disease Management cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PFS (off treatment) Disease Management cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PPS Disease Management cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Terminal Care cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Key:** AE, adverse events; BSC, best supportive care; IR, idelalisib with rituximab; NHS, national healh service; PFS, progression free survival; PPS, post progression survival; R, rituximab | | | | | |

**Table 100: Disaggregated predicted resource use costs, IR versus ofatumumab**

| | IR | Ofa | Increment | Absolute Increment | % Absolute Increment |
|---|---|---|---|---|---|
| PFS (on treatment) Treatment Drug cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PFS (on treatment) Treatment Admin cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PFS (on treatment) AE cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PFS (on treatment) Disease Management cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PFS (off treatment) Disease Management cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PPS Disease Management cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Terminal Care cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Key**: AE, adverse event**;** BSC, best supportive care; IR, idelalisib with rituximab; NHS, national healh service; PFS, progression free survival; PPS, post progression survival; R, rituximab | | | | | |

Figure 33 shows QALY accrual over time across model arms. Figure 34, Figure 35 and Figure 36 show total cost accrual over time across model arms, for the respective base case comparisons to rituximab monotherapy, BSC and ofatumumab monotherapy. Accrual of costs and QALYs is clearly driven by survival estimates. In the comparison to ofatumumab, the high treatment costs for ofatumumab compensate for the worse survival on the comparator arm to produce a similar accumulation of costs across model arms over time. In both model arms the majority of costs and QALYs are accrued within 10 years.

**Figure 33: QALY accrual over time, base case comparison**

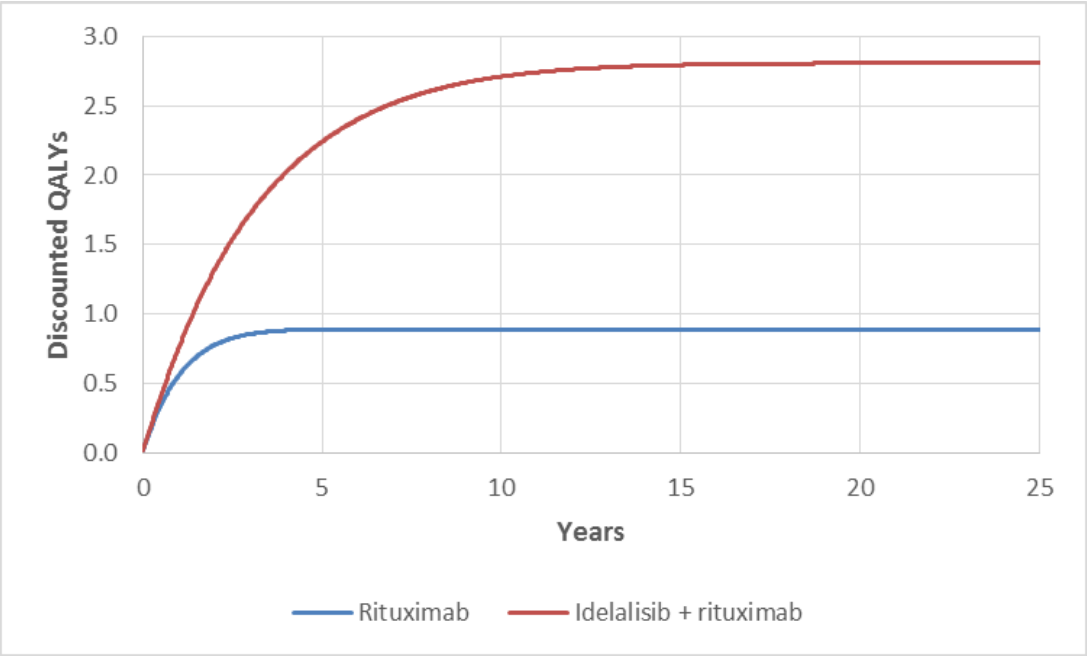


**Figure 34: Cost accrual over time, IR versus R**

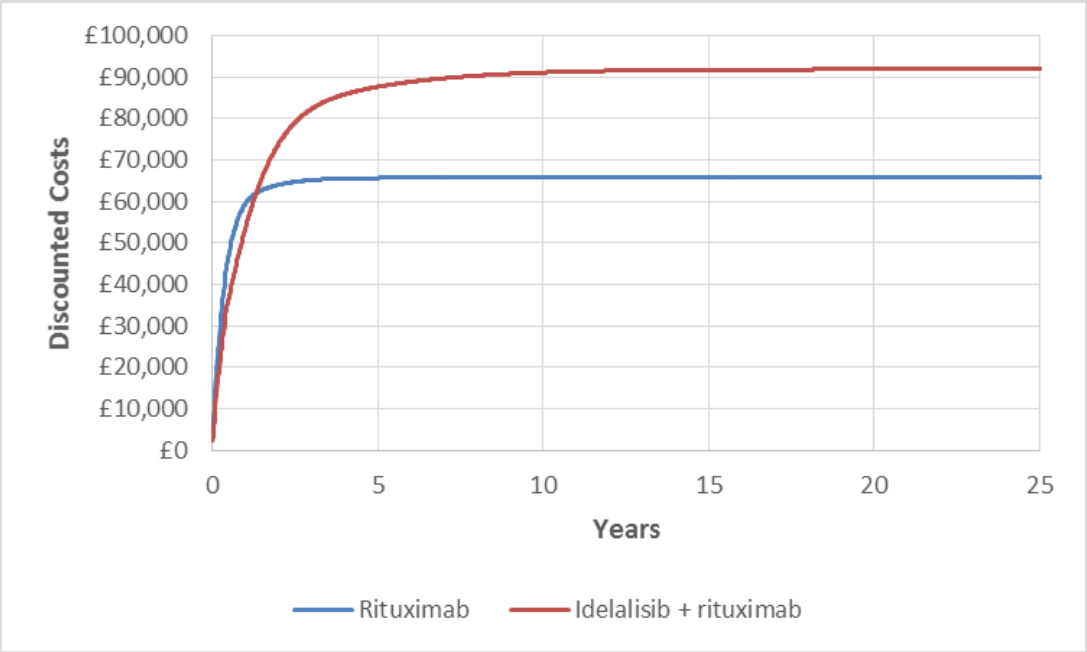



**Figure 35: Cost accrual over time, IR versus BSC**

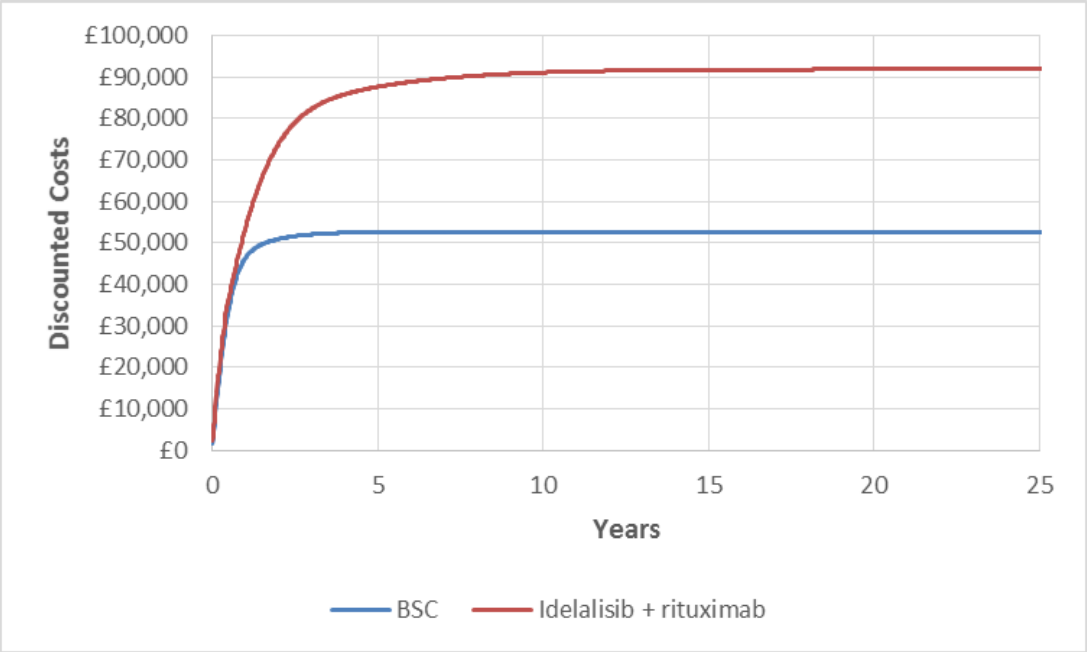
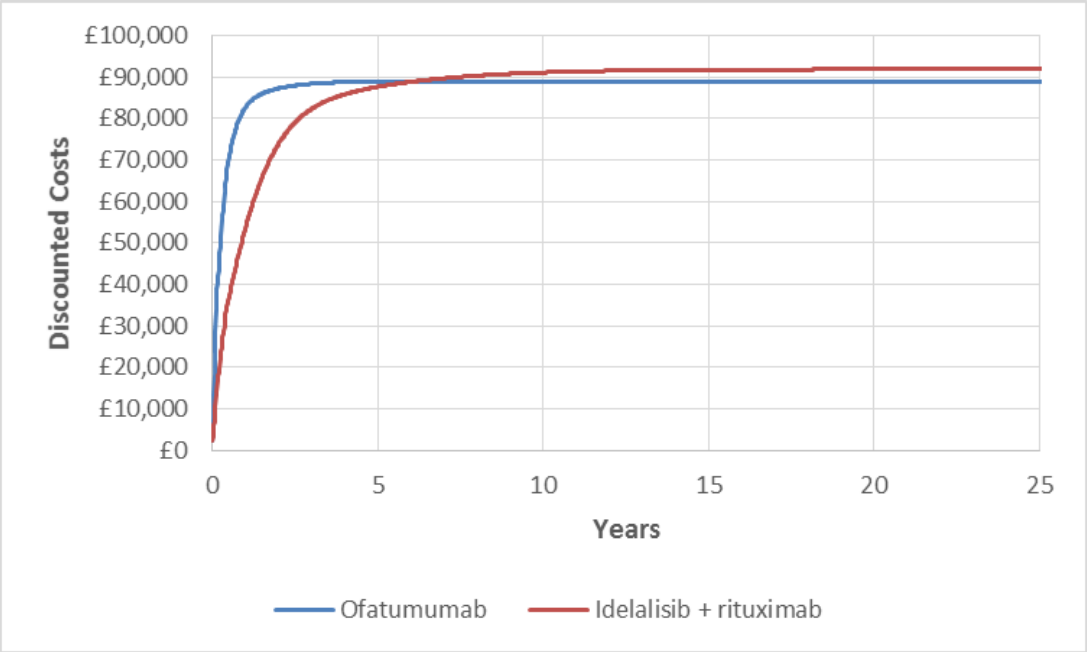


**Figure 36: Cost accrual over time, IR versus ofatumumab**




## *5.8 Sensitivity analyses*

**Probabilistic sensitivity analysis**

Mean probabilistic sensitivity analysis (PSA) results for the base case comparisons to rituximab monotherapy, BSC and ofatumumab monotherapy are shown in Table 101, Table 102 and Table 103. Figure 37 to Figure 42 show PSA scatterplots and cost-effectiveness acceptability curves (CEACs) for these comparisons.

The mean PSA ICER is a good approximation to the deterministic ICER in each comparison, and slightly lower than the deterministic ICER in each case. Scatterplots show that there is some parameter uncertainty around the mean ICER as there is some uncertainty which is inherent to the fitting of survival functions on relatively immature data. As demonstrated in section 5.6, the scale of uncertainty around parameter estimates was informed by data and not arbitrary assumptions for key parameters, including all survival parameters, ORRs, and utility estimates for the "PFS, on Treatment" health state. Every effort has been made to ensure the parameter uncertainty shown in scatterplots is reflective of true parameter

uncertainty. The majority of the uncertainty comes from the variability of QALY estimates due to the uncertainty in survival curve fits for the two modelled arms.

CEACs show around probabilities of 90%, 80% and close to 100% that idelalisib with rituximab is cost-effective versus rituximab monotherapy, BSC and ofatumumab monotherapy, respectively, at a willingness to pay threshold of £30,000 per QALY gained. These probabilities are all close to 100% at an end of life threshold of £50,000 per QALY gained.

**Figure 37: PSA scatterplot, IR versus R**

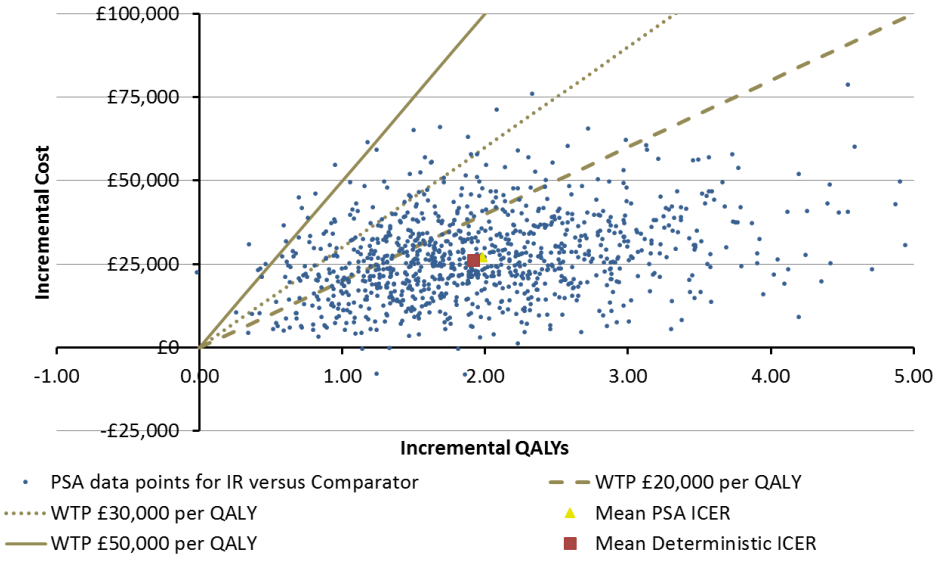



**Figure 38: CEAC, IR versus R**

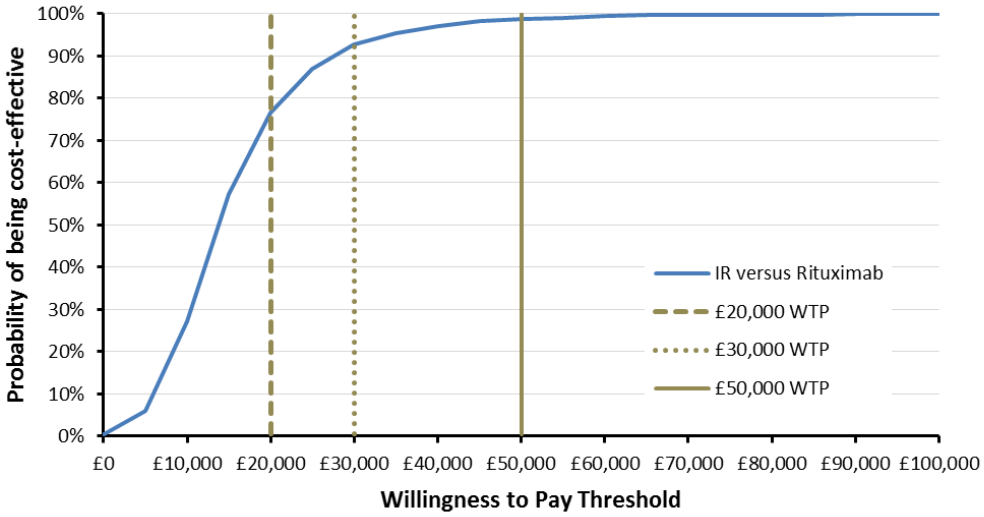


**Figure 39: PSA scatterplot, IR versus BSC**

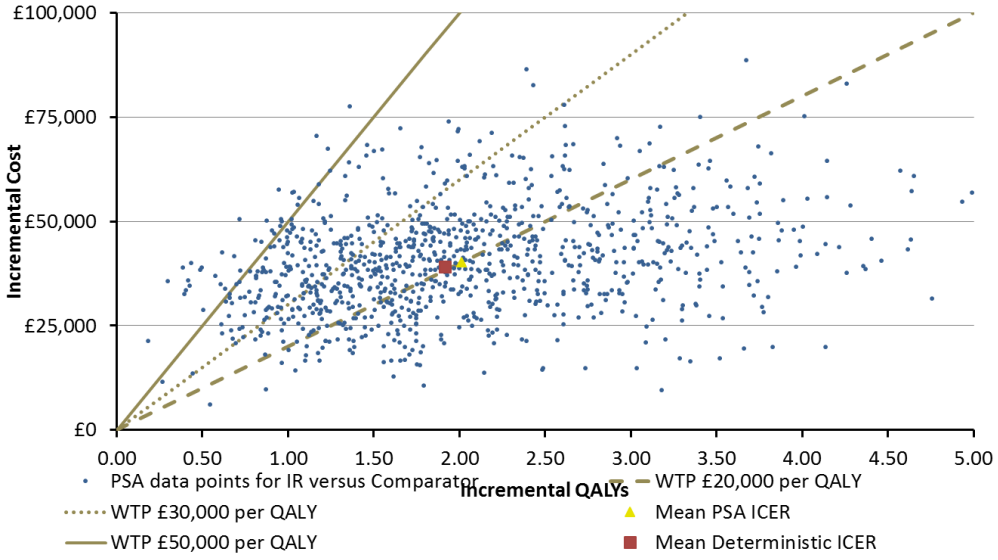



**Figure 40: CEAC, IR versus BSC**

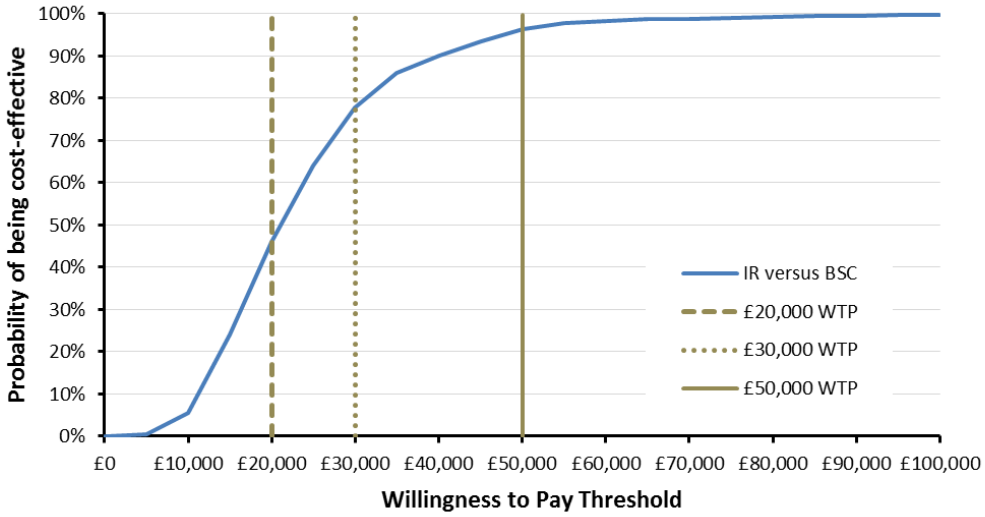


**Figure 41: PSA scatterplot, IR versus ofatumumab**

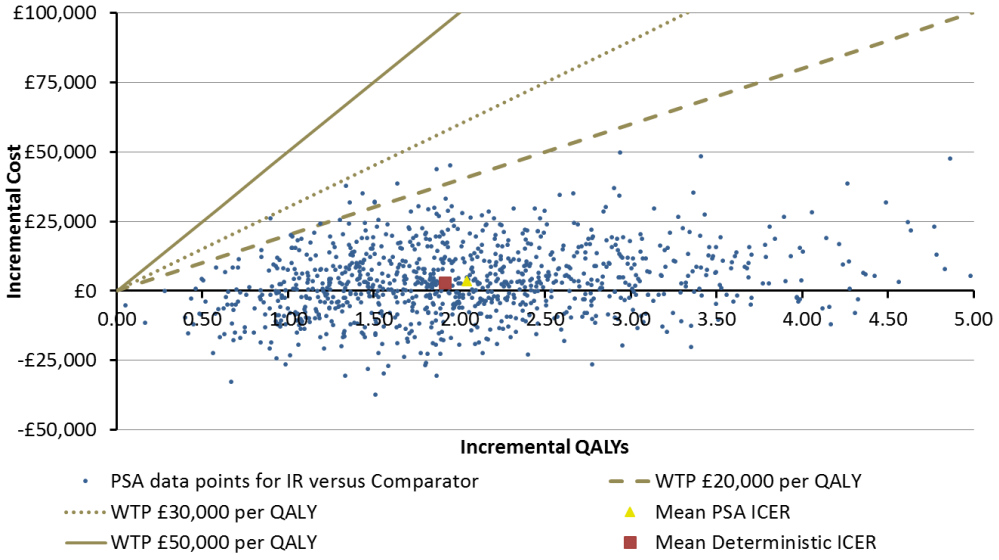



**Figure 42: CEAC, IR versus ofatumumab**

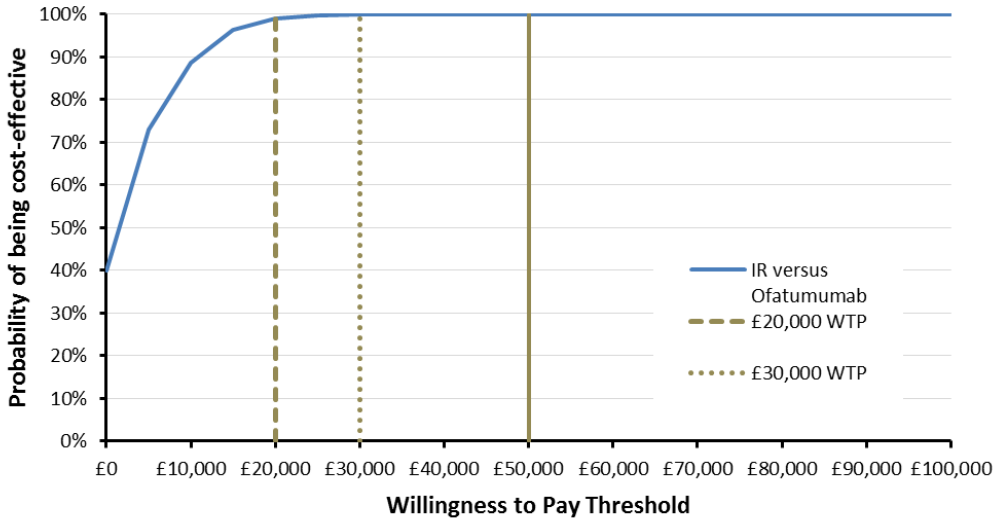


**Table 101: Mean PSA results, IR versus R**

| | Costs | QALYs | Life Years | Incremental | | | ICER |
|---|---|---|---|---|---|---|---|
| | | | | Costs | QALYs | Life Years | |
| Rituximab | [redacted] | 1.52 | 1.41 | | | | |
| IR | [redacted] | 2.88 | 4.89 | £27,063 | 1.98 | 3.48 | £13,680 |

**Key**: ICER, incremental cost-effectiveness ratio; IR, idelalisib with rituximab; NHS, National Health Service; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; R, rituximab.

**Table 102: Mean PSA results, IR versus BSC**

| | Costs | QALYs | Life Years | Incremental | | | ICER |
|---|---|---|---|---|---|---|---|
| | | | | Costs | QALYs | Life Years | |
| BSC | [redacted] | 1.52 | 1.43 | | | | |
| IR | [redacted] | 2.92 | 4.98 | £40,233 | 2.01 | 3.55 | £20,021 |

**Key:** ICER, incremental cost-effectiveness ratio; IR, idelalisib with rituximab; NHS, National Health Service; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.

**Table 103: Mean PSA results, IR versus ofatumumab**

| | Costs | QALYs | Life Years | Incremental | | | ICER |
|---|---|---|---|---|---|---|---|
| | | | | Costs | QALYs | Life Years | |
| Ofatumumab | [redacted] | 1.52 | 1.43 | | | | |
| IR | [redacted] | 2.95 | 5.02 | £3,452 | 2.04 | 3.59 | £1,692 |

**Key:** ICER, incremental cost-effectiveness ratio; IR, idelalisib with rituximab; NHS, National Health Service; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.

**Deterministic sensitivity analysis**

Figure 43, Figure 44 and Figure 45 show tornado diagrams depicting the ten parameters with the greatest influence upon the ICER estimate in the one-way sensitivity analysis (OWSA) and the influence they had upon the mean deterministic ICER estimate when varied to upper and lower 95% CI values, for the base case comparisons to R, BSC and ofatumumab.

Results are robust to isolated parameter changes to the vast majority of variables in the model. In line with PSA results, uncertainty around survival curve parameter estimates are shown to have the greatest influence on results, while uncertainty around the ORR for the rituximab monotherapy arm of the model is also highlighted as important due to its impact on resource use. Importantly, as described in section 5.6 and above, the scale of uncertainty around these parameter estimates was informed by robust data and not arbitrary assumptions.

**Figure 43: Tornado diagram showing OWSA results, IR versus R**

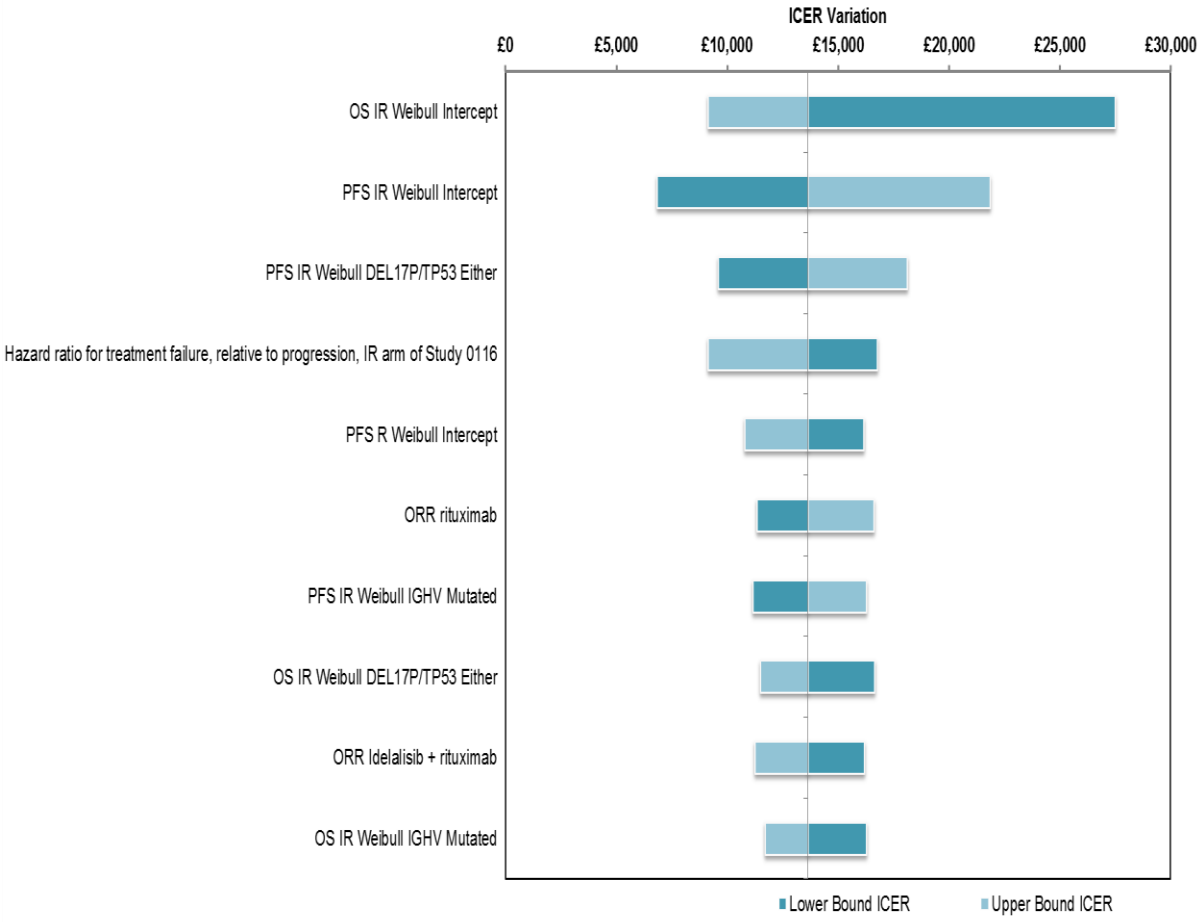


**Figure 44: Tornado diagram showing OWSA results, IR versus BSC**

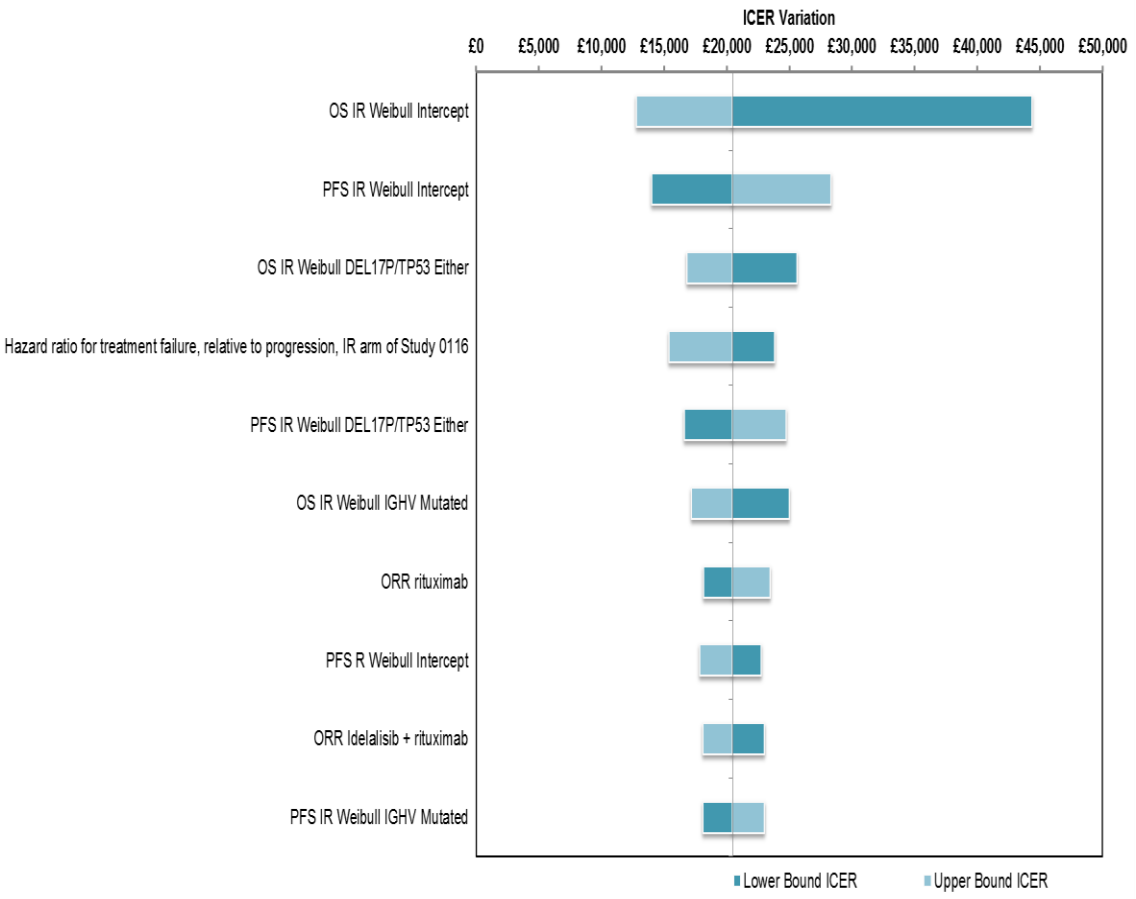
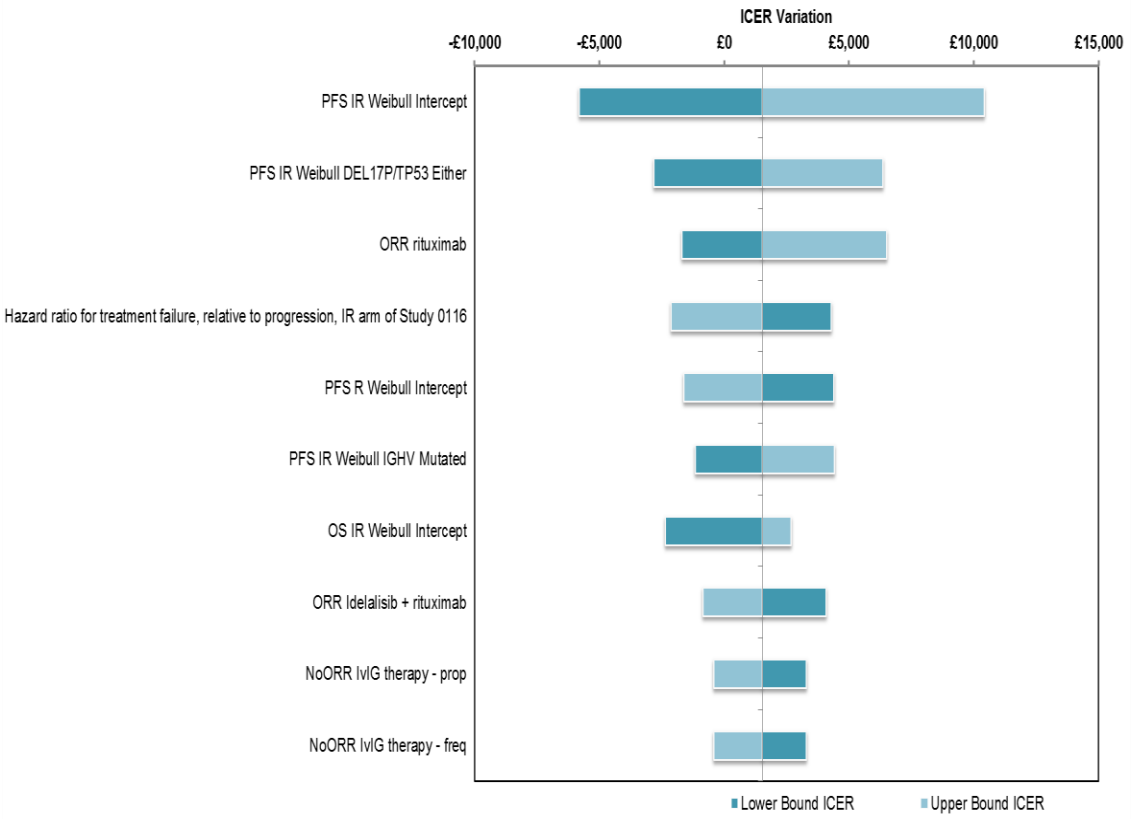


**Figure 45: Tornado diagram showing OWSA results, IR versus ofatumumab**




## Scenario analysis

Further parameter and methodological uncertainty around base case ICER estimates was explored through scenario analyses. The alternative scenarios explored are summarised in Table 104.

**Table 104: Alternative base case scenarios**

| Scenario | Description |
|---|---|
| Scenario 1 | Time horizon limited to 20 years |
| Scenario 2 | Time horizon limited to 15 years |
| Scenario 3 | Time horizon limited to 10 years |
| Scenario 4 | Time horizon limited to 5 years |
| Scenario 5 | Dretzke et al [88] utility estimates |
| Scenario 6 | Tolley et al [89] utility estimates |
| Scenario 7 | Dretzke et al [88] utility estimates, No AE HRQL decrement |
| Scenario 8 | Tolley et al [89] utility estimates, No AE HRQL decrement |

| | |
|---|---|
| Scenario 9 | Tolley et al [89] utility estimates PPS, Study 116 utility estimates PFS |
| Scenario 10 | Exponential curve fits for OS |
| Scenario 11 | Assume treatment until progression or maximum treatment duration |
| Scenario 12 | Assume zero terminal care costs |
| Scenario 13 | Use Wierda 2010 [65] ORR to calculate ofatumumab costs (comparison to ofatumumab only) |
| **Key:** AE, adverse event; HRQL, health realted quality of life; ORR, overall response rate, OS, overall survival; PFS progression free survival | |

Results for each scenario versus rituximab monotherapy are shown in Table 105 to Table 116. Scenario analysis results versus BSC and ofatumumab monotherapy are shown in Appendix 18.

Scenarios 1 to 4 test sensitivity of results to extrapolation assumptions with time horizons of 20, 15, 10 and 5 years, as opposed to the 25 year time horizon assumed in the base case. Scenario 1 to 4 results, versus rituximab, BSC and ofatumumab respectively, show the ICER to be robust to a reduction in the time horizon of at least 15 years.

Scenarios 5 to 9 test the sensitivity of results to HRQL assumptions. Scenarios 5 and 7 uses the HRQL estimates from Dretzke et al [88] in place of Study 116 EQ-5D data (0.80 pre-progression; 0.60 post-progression). The results are only very marginally different from base case results; it can be inferred the difference in utility across treatment arms observed in Study 116 is not critical in determining the cost-effectiveness of idelalisib with rituximab, and neither are HRQL effects associated with AEs.

Scenarios 6, 8 and 9 use HRQL estimates from Tolley et al [89] (0.67 pre-progression; 0.21 post-progression). This post-progression utility estimate is likely unrealistically low; nevertheless, idelalisib with rituximab is estimated to be cost-effective versus rituximab monotherapy, BSC and ofatumumab monotherapy as an end of life therapy.

The exponential model demonstrated the best fit to OS KM data according to AIC statistics, as shown in section 5.3, but the Weibull model was indicated as the only plausible OS curve by an NHS England clinical haematologist [1] and as such was

used in the base case. Scenario 10 explores the estimated base case results using the exponential curve fit to model OS data. The exponential model for OS and the Weibull model for PFS provided the best fitting curves to Study 116 KM data, according to AIC criteria. Predicted survival increases using the exponential curve to extrapolate Study 116 OS, and the estimated ICER falls versus each of the base case comparators.

Assuming treatment costs until disease progression or maximum treatment duration favours comparators to idelalisib with rituximab. Nevertheless, results from Scenario 11 show the cost-effectiveness of idelalisib with rituximab to be robust to assumptions about treatment duration. Results from Scenario 12 further show ICER estimates to be robust to assumptions around resource use associated with palliative care.

The base case comparison to ofatumumab assumed an ORR observed for rituximab plus placebo patients in Study 116. As opposed to using ORR estimates observed for ofatumumab monotherapy elsewhere, this was appropriate due to variation in both patient characteristics and definitions of response across trials. Scenario 13 tests the robustness of the ICER to ORR assumptions by using the ORR reported for ofatumumab in Wierda et al [65] (47% versus 15.5% in Study 116). This large increase in the ORR reduces the costs associated with PFS disease management for ofatumumab monotherapy, but idelalisib with monotherapy is still estimated to be highly cost effective versus ofatumumab.

The estimated optimality of idelalisib with rituximab versus base case comparators has been shown to be robust to a range of key assumptions.

**Table 105: Scenario 1, Time horizon limited to 20 years, vs. rituximab monotherapy**

| | Costs | QALYs | Life Years | Incremental | | | ICER |
|---|---|---|---|---|---|---|---|
| | | | | Costs | QALYs | Life Years | |
| 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 106: Scenario 2, Time horizon limited to 15 years, vs. rituximab monotherapy**

| | Costs | QALYs | Life Years | Incremental | | | ICER |
|---|---|---|---|---|---|---|---|
| | | | | Costs | QALYs | Life Years | |
| Rituximab | [redacted] | 0.89 | 1.39 | | | | |
| IR | [redacted] | 2.79 | 4.59 | £26,019 | 1.90 | 3.20 | £13,674 |
| **Key:** ICER, incremental cost effectiveness ratio; IR, idelalisib with rituximab; QALY, quality adjusted life year | | | | | | | |

**Table 107: Scenario 3, Time horizon limited to 10 years, vs. rituximab monotherapy**

| | Costs | QALYs | Life Years | Incremental | | | ICER |
|---|---|---|---|---|---|---|---|
| | | | | Costs | QALYs | Life Years | |
| 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 108: Scenario 4, Time horizon limited to 5 years, vs. rituximab monotherapy**

| | 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 109: Scenario 5, Dretzke et al [88] utility estimates, vs. rituximab monotherapy**

| | 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 110: Scenario 6, Tolley et al [89] utility estimates, vs. rituximab monotherapy**

| | Costs | QALYs | Life Years | Incremental | | | ICER |
|---|---|---|---|---|---|---|---|
| | | | | Costs | QALYs | Life Years | |
| Rituximab | [redacted] | 0.54 | 1.39 | | | | |
| IR | [redacted] | 1.65 | 4.63 | £26,128 | 1.10 | 3.24 | £23,652 |
| **Key:** ICER, incremental cost effectiveness ratio; IR, idelalisib with rituximab; QALY, quality adjusted life year | | | | | | | |

**Table 111: Scenario 7, Dretzke et al [88] utility estimates, no AE HRQL decrement, vs. rituximab monotherapy**

| | Costs | QALYs | Life Years | Incremental | | | ICER |
|---|---|---|---|---|---|---|---|
| | | | | Costs | QALYs | Life Years | |
| Rituximab | [redacted] | 0.92 | 1.39 | | | | |
| IR | [redacted] | 2.79 | 4.63 | £26,128 | 1.87 | 3.24 | £13,944 |

**Key:** AE, adverse event; HRQL, health related quality of life; ICER, incremental cost effectiveness ratio; IR, idelalisib with rituximab; QALY, quality adjusted life year

**Table 112: Scenario 8, Tolley et al [89] utility estimates, no AE HRQL decrement, vs. rituximab monotherapy**

| | Costs | QALYs | Life Years | Incremental | | | ICER |
|---|---|---|---|---|---|---|---|
| | | | | Costs | QALYs | Life Years | |
| Rituximab | [redacted] | 0.55 | 1.39 | | | | |
| IR | [redacted] | 1.66 | 4.63 | £26,128 | 1.11 | 3.24 | £23,573 |

**Key:** AE, adverse event; HRQL, health related quality of life; ICER, incremental cost effectiveness ratio; IR, idelalisib with rituximab; QALY, quality adjusted life year

**Table 113: Scenario 9, Tolley et al [89] utility estimates PPS, Study 116 utility estimates PFS, vs. rituximab monotherapy**

| | Costs | QALYs | Life Years | Incremental | | | ICER |
|---|---|---|---|---|---|---|---|
| | | | | Costs | QALYs | Life Years | |
| Rituximab | [redacted] | 0.59 | 1.39 | | | | |
| IR | [redacted] | 1.86 | 4.63 | £26,128 | 1.27 | 3.24 | £20,560 |

**Key:** ICER, incremental cost effectiveness ratio; IR, idelalisib with rituximab; PFS, progression free survival; PPS, post progression survival; QALY, quality adjusted life year

**Table 114: Scenario 10, Exponential curve fits for OS, vs. rituximab monotherapy**

| | 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 115: Scenario 11, Assume treatment until progression or maximum treatment duration, vs. rituximab monotherapy**

| | 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 116: Scenario 12, Assume zero terminal care costs, vs. rituximab monotherapy**

| | 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 | | | | | | | |

The base case comparison to ofatumumab uses the ofatumumab list price. In light of uncertainty around the real NHS price for ofatumumab, which was until recently available within the NHS through the Cancer Drugs Fund, the relationship between ofatumumab price and the ICER was analysed. Table 117 shows the sensitivity of the base case ICER for idelalisib with rituximab versus ofatumumab, to the price assumed for ofatumumab. Even assuming a 75% discount on the list price for ofatumumab, idelalisib with rituximab remains preferable at a willingness to pay threshold of £20,000 per QALY gained, and highly preferable as an end of life therapy.

**Table 117: Sensitivity of ICER versus ofatumumab to ofatumumab price**

| Ofatumumab Price Discount | ICER versus ofatumumab |
|---|---|
| 0% | £1,527 |
| 25% | £5,973 |
| 50% | £10,419 |
| 75% | £14,866 |
| **Key:** ICER, incremental cist effectiveness ratio | |

### Exploratory comparisons

Results from the exploratory economic analysis of idelalisib with rituximab versus those comparators within the scope for which base case results were not informative – fludarabine with cyclophosphamide and rituximab, bendamustine with rituximab, bendamustine, chlorambucil, chlorambucil with rituximab and corticosteroids with rituximab– as well as versus ofatumumab using external trial data, are reported in Table 118. The clinical data underpinning these comparisons are reported in section 5.3.

As highlighted in section 5.3 and in the rightmost columns of Table 118, these results should be interpreted with caution, as the constant shape assumption did not hold for the comparison to FCR (see Appendix 17), and it has not been possible to control through robust methods to formally account for differences across study patient samples. As noted in section 5.3, the superior survival benefit predicted for bendamustine versus bendamustine with rituximab is almost certainly partially driven by patient differences across studies.

Nevertheless, Study 116 patients have been demonstrated to have baseline characteristics indicative of poor survival relative to external studies considered; therefore, these comparative results are likely to be unfavourable to idelalisib with rituximab. Furthermore, highly conservative assumptions were made in ignoring the detrimental effects of AEs for comparator treatments in this cautious analysis. In this light, the results in Table 118 suggest that idelalisib with rituximab is an economically viable option in comparison to all available treatment options, and importantly, it is likely to produce the greatest patient QALY benefit for the patient group considered, and perhaps for relapsed/refractory CLL patients in general.

**Table 118: 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, fludaarabine, 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

**Summary of sensitivity analyses results**

Probabilistic and one-way sensitivity analysis results showed mean PSA ICER estimates to closely approximate mean deterministic ICER estimates and ICER estimates to be robust to changes in the majority of model parameters. Uncertainty around ICERs was largely driven by uncertainty around parametric curve fits to Study 116 survival data. Projections of clinical outcomes from Study 116 data have been validated at clinical review, following NICE DSU guidance [91], in an effort to be transparent and accurate in our clinical assumptions. In addition, despite parameter uncertainty around the base case ICER estimate, from PSA results, the probability that idelalisib with rituximab is cost-effective is 90% versus rituximab, 80% versus BSC and nearly 100% versus ofatumumab at a willingness to pay threshold of £30,000 per QALY gained. These probabilities are all close to 100% at an end of life threshold of £50,000 per QALY gained.

Base case ICER estimates were shown to be robust to further parameter and methodological assumptions explored in scenario analyses, in which the cost-effectiveness of idelalisib with rituximab versus ofatumumab was shown to be robust to uncertainty around the acquisition cost of ofatumumab.

The exploratory analysis of idelalisib with rituximab versus those comparators within the scope, but for which base case results were less informative due to the lack of a connected network of evidence, is limited due to the necessary and clearly detailed assumptions involved. However, given the analysis was largely biased against idelalisib with rituximab, the results suggest that idelalisib with rituximab is an economically viable option in comparison to all available treatment options, and importantly is likely to produce the greatest patient QALY benefit, for the patient group considered, and possibly for relapsed/refractory CLL patients in general.

## *5.9 Subgroup analysis*

It was possible to replicate base case results for the subgroup of patients with 17p deletion or TP53 mutation using survival analysis estimates of the effect of this characteristic upon OS and PFS, reported in section 5.6, and using ORRs specific to the subgroup of 17p deletion or TP53 mutation patients in Study 116 (85% IR; 12% R). In this way, the subgroup analysis accounts at least partially for the influence of

17p deletion or TP53 mutation survival upon survival and resource use, but no other factors important for cost-effectiveness. Results for each comparison are shown in Table 119, Table 120 and Table 121. Overall survival for this subgroup with a 17p deletion or TP53 mutation is reduced across model arms in comparison to the base case, and the incremental survival benefit is also reduced slightly across arms. This results in higher cost-effectiveness ratios, yet idelalisib with rituximab is estimated to be highly cost-effective as an end-of-life treatment option for this subgroup of relapsed patients with poor prognostic characteristics.

**Table 119: Subgroup results, IR versus rituximab monotherapy, patients with 17p deletion or TP53 mutation**

| | Costs | Life Years | QALYs | Incremental | | | ICER |
|---|---|---|---|---|---|---|---|
| | | | | Costs | Life Years | QALYs | |
| 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 120: 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 121: 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 | | | | | | | |

## 5.10 Validation

The limitations of the available clinical data to analyse the cost-effectiveness of idelalisib with rituximab versus its defined comparators for CLL patients who have received at least one prior therapy (FCR, bendamustine with or without rituximab, chlorambucil with or without rituximab, corticosteroids with or without rituximab, ofatumumab and BSC) were numerous. The economic approach in this submission was designed to harness the available data to make robust comparisons where possible, and exploratory comparisons where not possible. The overall economic approach was designed prior to and discussed at the NICE decision problem meeting of 26th November 2014, and validated as the best available approach given apparent data limitations. Throughout, every effort has been made to make conservative assumptions, and to be transparent in reporting of model assumptions and their implications.

The model was quality-assured by the internal processes of the external economists who adapted the economic model. In these processes, an economist not involved in model adaptation reviewed the model for coding errors, inconsistencies and the plausibility of inputs. The model was also put through a checklist of known modelling errors, and questioning of the assumptions.

Further to this, the conceptual model and key assumptions were validated at an advisory board with practising UK haematologists [15] and the detailed inputs and assumptions of the model were reviewed by a clinical haematologist currently practising within the NHS in England [1].

## 5.11 Interpretation and conclusions of economic evidence

As described in section 5.10, the methods and data used to analyse the cost-effectiveness of idelalisib with rituximab for CLL patients who have received at least one prior therapy have been validated and are believed to be the best available. The clarity, transparency and usefulness of the evidence presented are the main strengths of the economic evaluation. The main weakness of the evaluation are the limitations in available clinical data for core survival outcomes across all relevant comparators.

Analysis of results has shown estimates of overall and progression-free survival to be key model drivers. The methods used to analyse survival data from Study 116 have followed NICE DSU methods guidance documents [66, 91], including validation of results at clinical review. It is difficult to validate projections of survival from Study 116 with comparison to results from elsewhere in the literature, as (i) there are no other studies of idelalisib with rituximab for CLL patients and (ii) it is not possible to fully control for cross-study heterogeneity as discussed at length herein. However, the identified study with the patient characteristics arguably most similar to Study 116, the single-arm study of ofatumumab from Wierda et al [65], reported a median OS of 15.4 months for fludarabine-refractory patients who are less suited to alemtuzumab due to bulky lymph nodes, with a life expectancy of 6 months or more. The median predicted OS for rituximab, as reported in Table 92, at 13.6 months, suggests that survival outcomes for rituximab and ofatumumab are similar. This supports the assumption of equivalence between ofatumumab and rituximab in the base case analysis. In addition, an indirect comparison of rituximab with chlorambucil versus ofatumumab with chlorambucil, performed and reported by the ERG in the ongoing appraisal of ofatumumab in combination with chlorambucil or bendamustine for untreated CLL (ID642) [17], suggested PFS outcomes for rituximab with chlorambucil and ofatumumab with chlorambucil in untreated CLL patients are similar.

Overall, the economic analysis suggests that idelalisib with rituximab is a cost-effective treatment option for the NHS, for patients who are unsuited to cytotoxic therapies, including in the hardest to treat patients with a 17p deletion or TP53 mutation across all lines of therapies, and also possibly for relapsed/refractory CLL patients in general. This conclusion holds across both the base case comparators and those presented within exploratory analysis and is particularly important given the better safety profile of idelalisib compared to standard chemotherapies which allows its use in the frailest and hardest to treat patients.

It was not possible to robustly model the cost-effectiveness of idelalisib with rituximab for untreated CLL in the presence of 17p deletion or TP 53 mutation due to data scarcity. The data that have been reported for idelalisib with rituximab in this patient group, from Study 101-08/99, are, however, compelling. The case for

idelalisib with rituximab in this small patient group with unmet need was established in section 4, while the anticipated budgetary impact of making idelalisib with rituximab available for these patients will be shown to be small in section 6. Within the relapsed and refractory population, treatment of these hard to treat patients remains cost-effective as shown in section 5.9, at a time point in which there is perhaps less opportunity for idelalisib to have its full effect in improving survival.

Given this, it is highly likely that idelalisib with rituximab is the cost-effective option for treatment-naïve patients with CLL associated with 17p dleletion or TP53 mutation.

# 6 Assessment of factors relevant to the NHS and other parties

There are two patient groups for whom idelalisib with rituximab is licensed: treatment-naïve patients with del17p/TP53 mutation; and patients who have received one prior therapy. In 2011, there were 2,712 CLL patients in England who were eligible for treatment[3]. It is assumed that the incidence of CLL remains constant for the time horizon of the budget impact model. Of these patients, 67% (1817 patients) would be expected to require treatment based upon Dighiero 2003[112] which states: a third of patients have an initial indolent disease followed by progression of the disease; a third of patients have aggressive disease at the onset and require early treatment; and the remaining third never require treatment, have a long survival and die of causes unrelated to CLL.[102]

The Final Scope states that 5-10% of people diagnosed with CLL have 17p deletion or TP53 mutation. In the budget impact model, we have taken an average of this and used a value of 7.5%. Based upon this, 203 patients are expected to be eligible for treatment in the treatment-naïve patient group with CLL associated with 17p deletion or TP53 mutation.[35]

We have estimated the proportion of patients who would relapse on the standard cytotoxic first-line treatments each year (primarily FCR) and then receive non-cytotoxic treatments after 1st line to be 19% using IMS sales data on the proportion of patients currently receiving each line of therapy. There are expected to be 363 eligible patients in the prior therapy patient group.[113]

The acquisition cost and administration cost of treatment were added together to give the total treatment cost for patients in each of these patient groups. Unit costs have been sourced from MIMS online[25] and NHS Reference Costs 2012-2013[108] and are described in more detail in section 5.5.

The split of therapies received by each patient across both subgroups is taken from IMS sales data (Table 122).[113] For patients who have received one prior therapy the proportion of patients who could receive idelalisib and are currently receiving cytotoxic chemotherapies is assumed to be 0% because clinicians have indicated

that they would use idelalisib in patients who cannot tolerate cytotoxic chemotherapy. The proportion of patients in this patient group receiving alemtuzumab is also assumed to be 0% because this is not on the NICE scope. For treatment-naïve patients with 17p deletion or TP53 mutation, the proportion of patients receiving FCR, ofatumumab or steroids with rituximab is assumed to be 0% because these treatments are not included in the NICE scope. The proportions of patients in this patient group receiving bendamustine, bendamustine with rituximab, chlorambucil and chlorambucil with rituximab are also assumed to be 0% because patients with 17p deletion or TP53 mutation do not respond to cytotoxic chemotherapy and therefore should not receive it in current practice.

The market share of idelalisib with rituximab for the patient group who have received one prior therapy was estimated according to Gilead internal forecasts as [redacted] in year 1 and [redacted] in years 2 to 5. The market share of idelalisib with rituximab for the treatment-naïve patient group with 17p deletion or TP53 mutation is assumed to be [redacted] in year 1 and [redacted]in years 2-5.

Table 123 and Table 124 show the total budget impact of idelalisib with rituximab in both populations. In year 1 the budget impact in the 1 prior treatment population is expected to be £[redacted] million rising to £[redacted] million thereafter with increased uptake. In year 1, the budget impact for the treatment-naïve population with CLL associated with 17p deletion or TP53 mutation, if alemtuzumab remains at freely available, is expected to be £[redacted] million rising to £[redacted] million thereafter with increased uptake, if the EMA scheme were to be withdrawn and alemtuzumab costed at list price the use of idelalisib would save between £[redacted] million and £[redacted] million per year.

**Table 122: Make up of current care in the population who would receive treatment with idelalisib**

| | 1 prior treatment (%) | 17p deletion or TP53 mutation (%) |
|---|---|---|
| Fludarabine with cyclophosphamide and rituximab | 0% | 0% |
| Bendamustine | 0% | 0% |
| Bendamustine with rituximab | 0% | 0% |
| Chlorambucil | 0% | 0% |
| Chlorambucil with rituximab | 0% | 0% |
| Steroids with rituximab | 32% | 0% |
| Ofatumumab | 37% | 0% |
| Best supportive care | 32% | 75% |
| Alemtuzumab | 0% | 25% |

**Table 123: Annual and Overall Costs for the one prior treatment patient group**

| | 2015 | 2016 | 2017 | 2018 | 2019 |
|---|---|---|---|---|---|
| Total number of patients starting treatment | 363 | 363 | 363 | 363 | 363 |
| Patients expected to receive idelalisib | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Cost for total population without idelalisib available | £8,392,959 | £8,392,959 | £8,392,959 | £8,392,959 | £8,392,959 |
| Cost for total population of idelalisib | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Cost for total population of other treatments when idelalisib is available | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Cost for total population with idelalisib available | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Net budget impact** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Table 124: Annual and Overall Costs for the treatment-naive 17p deletion/TP53 mutation patient group**

| | 2015 | 2016 | 2017 | 2018 | 2019 |
|---|---|---|---|---|---|
| Total number of patients starting treatment | 203 | 203 | 203 | 203 | 203 |
| Patients expected to receive idelalisib | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Cost for total population without idelalisib available (assuming 0 cost for alemtuzumab) | £0 | £0 | £0 | £0 | £0 |
| Cost for total population of idelalisib | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Cost for total population of other treatments when idelalisib is available (assuming 0 cost for alemtuzumab) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Cost for total population with idelalisib available (assuming 0 cost for alemtuzumab) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Cost for total population without idelalisib available (alemtuzumab at list price) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Cost for total population of other treatments when idelalisib is available (assuming alemtuzumab at list price) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Cost for total population with idelalisib available (assuming alemtuzumab at list price) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Net budget impact (alemtuzumab at 0 cost)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Net budget impact (alemtuzumab at list price)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

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Appendices

Appendix 1: European public assessment report, SmPC/IFU, scientific discussion or drafts (section 2.2)

Appendix 2: Idelalisib national discounted pricing supply agreement.

Appendix 3: Search strategy for relevant studies (section 4.1.2)

Appendix 4: Quality assessment of randomised controlled trials (RCTs) (section 4.6)

Appendix 5: Subgroup analysis (section 4.8)

Appendix 6: Search strategy for indirect and mixed treatment comparisons (section 4.10.1)

Appendix 7: Methods, results, outcomes and quality assessment of the relevant trials in the indirect or mixed treatment comparison (section 4.10.9–10)

Appendix 8: Programming language used in the analysis (section 4.10.13)

Appendix 9: Quality assessment of the relevant non-randomised and non-controlled evidence (see section 4.11.6–9)

Appendix 10: Search strategy for adverse reactions (section 4.12.3)

Appendix 11: Quality assessment of adverse reaction data, and supplementary adverse reaction data (section 4.12)

Appendix 12: Search strategy for cost-effectiveness studies (section 5.1.1)

Appendix 13: Quality assessment of cost-effectiveness studies (section 5.1.3)

Appendix 14: Search strategy for measurement and valuation of health effects (section 5.4.3)

Appendix 15: Resource identification, measurement and valuation (section 5.5.2)

Appendix 16: Checklist of confidential information

Appendix 17: Validation of constant shape assumption for external study comparisons

Appendix 18: Scenario analysis for alternative comparators